

SECOND EDITION

Pharmaceutical Preformulation and Formulation

A Practical Guide from Candidate Drug Selection to Commercial Dosage Form



edited by

Mark Gibson

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IPR Petition – USP 12,128,039

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Pharmaceutical Preformulation and Formulation Second Edition

A Practical Guide from Candidate Drug Selection to Commercial Dosage Form

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New York London

Informa Healthcare USA, Inc.
52 Vanderbilt Avenue
New York, NY 10017

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Printed in the United States of America on acid-free paper
10 9 8 7 6 5 4 3 2 1

International Standard Book Number-10: 1-4200-7317-6 (Hardcover)
International Standard Book Number-13: 978-1-4200-7317-1 (Hardcover)

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Library of Congress Cataloging-in-Publication Data

Pharmaceutical preformulation and formulation: A practical guide from candidate drug selection to commercial dosage form / edited by Mark Gibson.
—2nd ed.

p. : cm. — (Drugs and the pharmaceutical sciences ; 199)

Includes bibliographical references and index.

ISBN-13: 978-1-4200-7317-1 (hb : alk. paper)

ISBN-10: 1-4200-7317-6 (hb : alk. paper) 1. Drugs—Dosage forms.

I. Gibson, Mark, 1957- II. Series: Drugs and the pharmaceutical sciences ; v. 199.

[DNLM: 1. Drug Compounding. 2. Biopharmaceutics—methods. 3.

Dosage Forms. 4. Drug Discovery. 5. Drug Evaluation. W1 DR893B v.199
2009 / QV 778 P53535 2009]

RS200.P425 2009

615'.1—dc22

2009012458

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5 | Early Drug Development: Product Design

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THE IMPORTANCE OF PRODUCT DESIGN

It may seem obvious to state that a new product should be adequately defined before any serious product development is undertaken. In many cases, the value of the design phase is often underestimated in the rush to start development and get products to the market quickly. This can result in much wasted time and valuable resources. It can also lead to reduced staff motivation if a product is developed that is not wanted or if the product definition is constantly changing during development. The quality of the design activities can strongly influence the success of development of the right product to the market and ultimate return on investment (ROI).

Several nonpharmaceutical industries have long realized the necessity of investing time and money in an initial product design phase. The automobile, aeroplane, or shipbuilding industries, for example, would not think of gearing up for large-scale manufacture of a new model until they were satisfied with the design phase. Thorough market research will have been completed to ensure customer requirements are being met. The product definition and technical specifications will have been agreed on, and the cost of goods (CoG) estimated, so that the company is satisfied that the venture will be commercially viable! What makes it more difficult in the pharmaceutical industry are the relatively longer timelines involved and the risks and complexity associated with the development of new medicines. However, the more progressive pharmaceutical companies seem to be finally realizing the value of the product design stage to achieve successful product development and marketing of a new product.

Unfortunately, some companies still do not seem to be getting the product design process right to their cost. The following recent example of inhalable insulin has been described as “one of the drug industry’s costliest failures ever,” estimated to be \$2.8 billion from the cost of development, closure of dedicated manufacturing plants, and unsold product (Johnson, 2007). Certain companies have invested more than 10 years and vast amounts of money on making insulin treatment more convenient for diabetes patients. The idea was that diabetics did not like to prick themselves with needles several times a day to deliver the insulin they need to balance their blood sugar. The biggest hurdle was to deliver insulin by inhaler as consistently as with a standard needle and syringe. It took a technological breakthrough to develop and launch the first inhalable insulin product in July 2006, only to abandon it in October 2007, after the product’s disappointing sales performance. The company predicted that inhalable insulin would be a \$2 billion-a-year product by 2010, but it only sold \$12 million in the first year. There were several reasons attributed to the poor sales performance.

- The device was unwieldy and drew unfavorable reviews from doctors and investors. Some patients likened it to a bong for smoking marijuana and were embarrassed to use the device in public.
- It was taking much longer to teach patients how to use the inhaler device compared with an insulin pen, and diabetic specialists said it was hard to use.
- There were concerns about safety as only 10% of the insulin reaches the bloodstream, raising the question about the long-term effects of the other 90% remaining in the lungs.
- The inhaled treatment was approximately twice as expensive per day as the injectable insulin and some payers refused to accept the inhaled product on costs alone.

From the above, it is questionable whether there was appropriate input to the product design process. Was adequate market research really undertaken to identify what the market would accept from different customer perspectives?

Studies have shown that the initial design phase actually requires a relatively small investment, which can greatly influence the nature of the product and its ultimate commercial success (Berliner and Brimson, 1988). The ROI of the conceptual design phase was shown to be five times greater than the ROI of later development work to develop and optimize the product and manufacturing process.

A simple definition of “product design” is “the initial stage of product development, where ‘global’ agreement is required about the nature of the product to be developed.” Figure 3 in chapter 1 illustrates where product design fits into the overall product development process. Effective product design is considered to have the following important benefits:

- To provide clear direction and objectives for the project team
- To gain buy-in and input from all the key functions at the start of development (such as pharmaceutical development, safety, clinical, manufacturing operations, quality assurance, regulatory, and commercial/marketing)
- To assess the feasibility of the project in commercial and technical terms
- To identify any risks early and hence manage them
- To avoid wasting valuable resources on developing a product that is not needed or wanted
- To provide a good reference source for the development plan

PRODUCT DESIGN CONSIDERATIONS

A useful outcome of the initial product design phase is a product design report. This should document the careful evaluation of the following key elements:

- Target product profile (TPP)/minimum product profile (MPP)
- Design specification and critical quality parameters
- Commercial and marketing considerations
- Technical issues and risk assessment
- Safety assessment considerations
- Environmental, health, and safety considerations
- Intellectual property considerations

Each of these elements is discussed in more detail below.

Target Product Profile/Minimum Product Profile

A TPP, which defines the product attributes, should be established for the intended marketed product based on all “customer” and “end-user” needs. Customers and end users include anyone in the supply chain, including both internal and external customers, such as those in manufacturing and in sales and marketing, distributors, doctors, nurses, pharmacists, and patients. Each customer wants the right product (meeting their quality expectations) at the right time and at the right price. Additionally, each customer will have his or her own specific requirements.

The TPP is often expressed primarily in clinical terms, but should also include the pharmaceutical, technical, regulatory, and commercial/marketing attributes required of the product. The TPP is based on the ideal product characteristics, which are considered to be desirable, whereas the MPP is based on the minimum product requirements, which must be met for the product to be viable and worth developing. For example, the TPP may stipulate an ideal dosing regimen of once daily. However, the MPP may state that the dosing regimen must be no more than twice daily for the product to be competitive.

The ideal attributes for a fictitious product profile example prepared for a product being developed to treat osteoarthritis is shown in Table 1.

The level of information on the dosage form and pack should provide sufficient clarity of detail to enable the pharmaceutical development group to plan their development. These

Table 1 Target Product Profile for a Fictitious Product to Treat Osteoarthritis

Key attributes	Target product profile
Disease to be treated	Osteoarthritis
Patient type (e.g., geriatric, pediatric)	Adults older than 40 years, including geriatrics
Route of administration	Oral
Efficacy	Analgesic and anti-inflammatory activity better than current "criterion standard" therapy
Safety/tolerability	No GI side effects No interactions with other agents
Pharmacoeconomics	Reduced health care costs by preventing disease progression
Dosage/presentation (type/size)	Immediate release tablet No more than two strengths
Dose and dose frequency	Once daily
Pack design/type	Blister calendar pack with moisture barrier Must be able to be opened by patient Tamper evident
Process	Use standard processing equipment for tablets
Aesthetic aspects (color, flavors, taste, etc.)	Color to differentiate tablet strengths Taste masked to reduce bitterness
Territories to be marketed	United States, Europe, Japan
Cost of goods	No more than 10% of commercial price
Commercial price	Equivalent or less than current criterion standard therapy

Table 2 Example of a Pharmaceutical Product Profile for an Intravenous Solution

Key attributes	Target product profile
Dosage form presentation	Single dose, non-preserved
Primary pack	Type I clear glass vial (10 mL) rubber stopper Aluminum overseal
Secondary pack	Carton with patient instruction leaflet
Product strength range	10–50 mg in 5 mL
Excipient to be evaluated	
Tonicity adjustment	Dextrose or saline
Buffer	Phosphate or citrate
Antioxidant	Sodium metabisulfite or acetylcysteine
Manufacturing process	Aseptic manufacture/sterile filtration (terminal sterilization by autoclaving not possible)

pharmaceutical attributes may be documented separately in a pharmaceutical product profile (PPP). A typical example of a PPP is shown in Table 2 for an intravenous injection product, illustrating the level of detail expected in a product design report. Similarly, a target clinical profile (TCP) can be developed by the clinical development group to document and capture the clinical characteristics required of the drug, which will meet the needs of patients, clinicians, and payers. Both the PPP and TCP can be used in conjunction with the TPP to provide a complete summary of the product design requirements.

It is clearly beneficial to conduct some early preformulation studies to characterize the candidate drug and to determine the physicochemical properties considered important in the development of the intended dosage form to support product design. Preformulation data from solubility, stressed stability, excipient compatibility, and other preformulation studies may influence the selection of the formulation dosage form and excipients. The results may also influence the choice of manufacturing process, as shown in the example in Table 2, where terminal sterilization by autoclaving has been shown not to be feasible. The preformulation data should also help to establish the critical quality parameters for the product. In chapter 6 of this book, Gerry Steele discusses in much greater detail the preformulation studies that may be undertaken to support product design.

The formulation developed for early clinical trials (phase 0 or I) is often a simple one and different from the intended commercial dosage form. A parallel development approach can significantly reduce development time by delinking early clinical supply with commercial formulation development. However, the product profile in the product design report is for the intended commercial product. This information is required at the start of development so that the final commercial product and simple clinical formulation can both be developed in parallel to avoid affecting the medical needs or timings. For example, the commercial formulation could be a film-coated tablet, but the early clinical formulation may be a simple oral solution or suspension or a hand-filled capsule. Regulatory authorities will be interested in the linkage between formulations used in early clinical studies and those used in the pivotal (phase III) studies and the final commercial product. The objective of many companies is to optimize and finalize the commercial product (formulation and process) for the start of the pivotal clinical studies to minimize any regulatory concerns.

Meeting Customer Needs

There are various methods and tools available for gathering information about customer needs to establish the product profile. It is not the intention of this book to cover this in great detail, and only an overview is given here.

A primary source of information is usually held within the pharmaceutical company, particularly if the company is already established with marketed products in a particular therapeutic area. Most companies will have a variety of information representing the voice of their customers. Much of this may be negative in the form of complaints and letters from users. These can be valuable sources of information to consider in the development of better products. It is important that all of the company's internal departments involved in product development are consulted. These internal departments include Pharmaceutical Development, Design Engineering, Manufacturing Operations, Quality Assurance, Safety/Toxicology, Medical, and Commercial/Marketing. They should be involved in the product design and product profile discussions, as they are also key internal customers. This is easier said than done because pharmaceutical organizations often lack the processes and structure to support their collaboration. The TPP should be used to facilitate joint development and "buy-in." Typically, research and development (R&D) "owns" or acts as if it owns the TPP, but ideally the process needs to be improved to incorporate real input into the TPP from all parties, or else it may become a dead document (Illert, 2007). The process needs to encourage constructive teamwork to ensure that the science, regulatory, and commercial functions' inputs are all reviewed and agreed upon. One way of doing this is to bring together all the stakeholders at one or more workshops to agree upon the development objectives and to optimize the TPP.

Once defined, the TPP provides details of the label claims that the company is seeking for the candidate drug, including the safety and efficacy requirements that should allow drug approval. Although it is not compulsory for the regulatory approval process, there are benefits of sharing the TPP with the regulators at an early stage in development as a discussion document to check with them whether the development plans are appropriate to support a marketing application.

It is important to recognize that these internal customers' perceptions and requirements may be far removed from those of external customers. If a company is venturing into a new therapeutic area, or is endeavoring to learn more about the changing needs of the market, external customers and end users in the supply chain need to be consulted for their views about current treatments and shortfalls. There are various ways of achieving this feedback. For example, surveys can be conducted by sending out questionnaires or by telephoning key customers and end users to gather perception data. Alternatively, clinics and focus groups can be set up to gain insight into customers' wants and perceptions. Clinicians, doctors, patients, or other customers may be asked to attend small focus groups, facilitated by medical, marketing, or pharmaceutical personnel, to discuss their likes and dislikes. This type of forum can be useful for demonstrating samples and prototypes of devices and drug delivery systems. Other ways of obtaining feedback include setting up individual interviews with opinion leaders in the field and generally listening to customers' comments at conferences, exhibitions, and trade

shows. Consultancy organizations are often hired to gather this type of information on behalf of the pharmaceutical company developing a new product. Customer insight studies can be conducted in conjunction with the pharmaceutical company to gain a deep and clear understanding of the needs and behaviors of its customers: prescribers, patients, and all other stakeholders involved in pharmaceutical decisions. The studies try to answer the key questions such as

- What are the barriers keeping our medicines from reaching patients who would benefit from them?
- Why would physicians not prescribe our products to patients?

For example, one obstacle to the uptake of a cholesterol lowering medicine was that some physicians do not conduct frequent diagnostic tests that would lead to prescriptions. This could be overcome by providing easy-to-use blood testing equipment to the physicians so that they can diagnose more patients and prescribe the cholesterol-reducing medication.

Information gained from such customer insight studies is used by the pharmaceutical company in the design of the new medicine. The pharmaceutical development group can play a leading role in determining the pharmaceutical requirements for a new product from key customers. Customers may want more specific packs or delivery systems, and different markets still have their own preferences for different dosage forms.

Quality function deployment (QFD), also referred to as “customer-driven engineering” and “matrix product planning,” is a useful quality and planning tool that uses a structured approach in defining all the customer needs or requirements and translates these into design requirements for product development. QFD seeks out both the “spoken” and “unspoken” customer requirements and maximizes “positive” quality (such as ease of use) that creates value, whereas traditional quality systems aim at minimizing negative quality (such as defects).

QFD originated in Japan in the late 1960s and was initially applied to shipbuilding, where large capital investments are made and design and planning needs to be thorough. Through the 1970s and 1980s, there was a rapid increase in the application of QFD to all industries in Japan, and in the 1980s and 1990s, it was accepted in the United States and Europe as a means of quality improvement (Akao, 1990; Day, 1993; Mizuno and Akao, 1994).

The QFD basic approach is to start with customer requirements, which are usually vague qualitative items such as easy to use, feels good, lasts a long time. These vague customer requirements are converted into internal company design requirements that are measurable and can be used objectively to evaluate the product. If the company requirements are properly introduced, the product should satisfy all the customer requirements. The company requirements must then be translated into specific parts of the product, and the characteristics of these specific parts should cause the essential functions to be performed.

Customer requirements → Company requirements (measures) → Design characteristics (specific parts)

QFD is accomplished through a series of charts, sometimes referred to as the “House of Quality” (HOQ) because the shape of the charts has a rooflike structure at the top (Fig. 1). Ideally, the chart should be developed by a cross-functional team made up of members of the core functions in product development. The first step in building the HOQ is to list the customer requirements, “the WHATs,” down the left-hand side of the matrix (area 1 in Fig. 1). Each of the WHATs is translated into one or more global customer characteristics or design requirements, “the HOWs,” and listed across the top of the matrix (area 2). The design requirements will usually be measurable characteristics, which can be evaluated on the completed product. The next step is to complete the relationship matrix in the center (area 3). The strength of the relationship between each customer requirement and technical requirement is depicted by using different symbols and weightings, for example, “strong” = 9, “medium” = 3, and “weak” = 1. A blank column in the relationships matrix could indicate a design requirement that is not really needed.

Next, the team completes area 4, comprising measurements for the design requirements (HOW MUCH). These objective target values should represent how good the product has to be

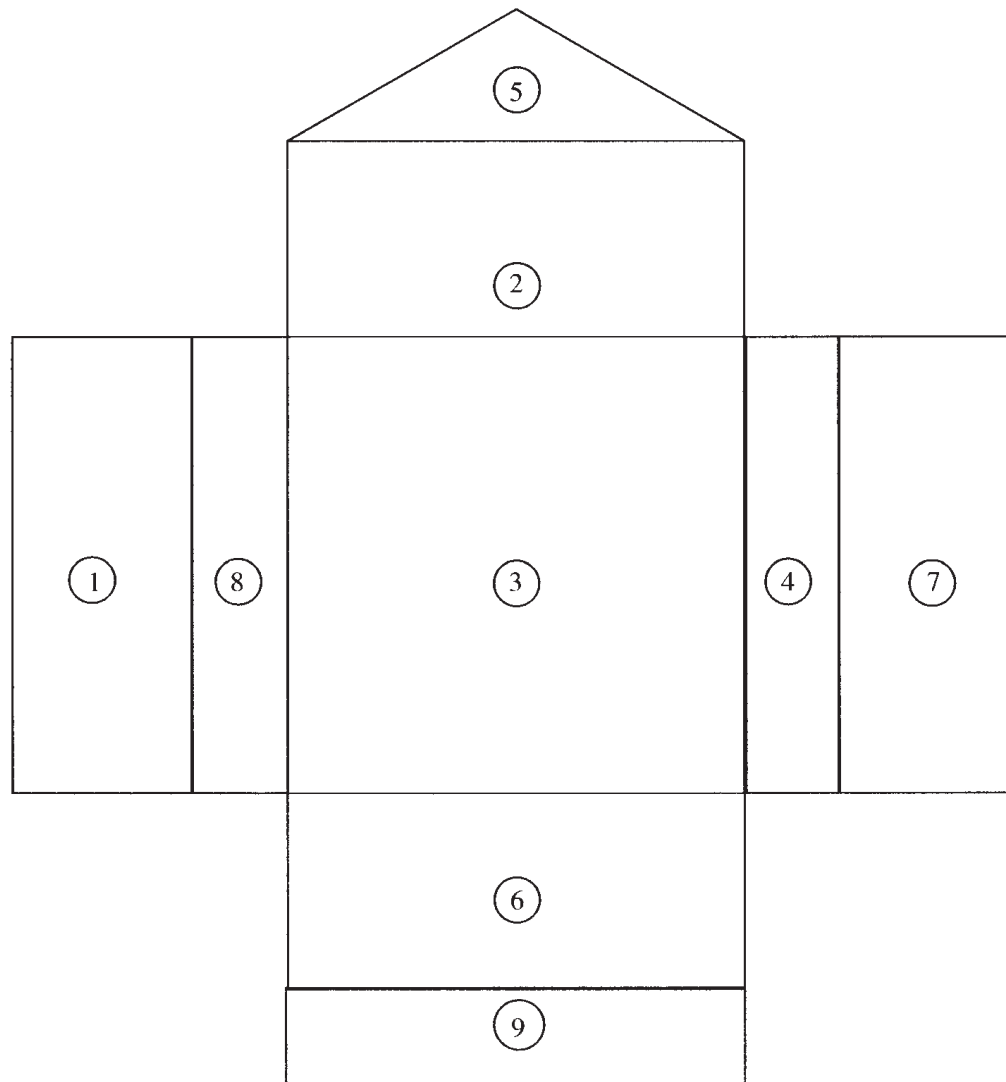


Figure 1 The QFD diagram: the House of Quality.

Key:

1. Customer requirements (WHATs)
2. Design requirements (HOWs)
3. Relationship matrix
4. Objective targets for customer's requirements (HOW MUCH)
5. Correlation matrix
6. Customer competitive assessment
7. Technical competitive assessment
8. Customer importance rating
9. Technical importance rating

to satisfy the customer and need not necessarily represent current performance levels. These values are required to provide an objective means of assuring that requirements have been met and to provide targets for further detailed development.

In area 5, the roof of the house, the correlation matrix establishes any potential synergies or conflicts between each design requirement (HOW). The purpose is to identify areas where trade-off decisions may be required. Symbols are often used to describe the strength of the relationship, for example, positive, strong positive, negative, and strong negative. From the matrix, it should be possible to identify which of the design requirements support one another and which are in conflict. Positive correlations are important because some resource

efficiencies may be gained by not duplicating efforts to attain the same result. Negative correlations are also important because they indicate conditions where trade-offs are suggested. There may be ways of eliminating trade-offs by introducing some degree of innovation, which may lead to competitive advantage and patent opportunities. Trade-off resolution is achieved by adjusting the values of the targets for customer requirements (HOW MUCH).

The competitive assessment is a pair of graphs (areas 6 and 7), which depict item for item how competitive products compare with current company products. This is completed for both the customer requirements (WHATs) and the design requirements (HOWs). The customer competitive assessment is important to understand the customer's perception of the product relative to the competition, whereas the technical competitive assessment is undertaken by the company's product development experts to gain an internal view.

The final step in constructing the QFD chart is to establish the importance ratings. The customer importance rating (area 8) is based on customer assessment and is expressed as a relative scale (typically 1 to 5), with the higher numbers indicating greater importance to the customer.

It is vital that these values represent the true customer needs and not just internal company perceptions. Importance ratings for the design requirements (HOWs) are calculated by multiplying the value of the symbols in the relationship matrix for each cell (9, 3, or 1) by the corresponding customer importance rating and summing the products down the columns (area 9). The importance ratings are useful for prioritizing efforts and making trade-off decisions. The values have no direct meaning but rank in relative importance the customer and technical requirements that have to be satisfied.

Figure 2 provides a typical example of a completed top-level QFD chart for a fictitious metered dose inhaler (MDI) product to be used for the treatment of asthma.

The QFD concept can be further utilized by cascading the Voice of the Customer through a series of matrices or phases. In the product development process, this involves taking the customer requirements and defining design requirements. Some of the design requirements are translated to the next chart to establish the optimum design characteristics. This is continued to define the optimum manufacturing process requirements and production requirements. In practice, this is achieved by creating new charts in which the HOWs of the previous chart become the WHATs of the new chart, as illustrated in Figure 3.

While the QFD charts are a good planning and documentation tool, the real value is in the process of communicating and decision-making within a company because the process encourages input from multiple functional disciplines involved in product development. The active participation of the various disciplines should lead to a more balanced consideration of the customer and design requirements and, ultimately, increased customer/end-user satisfaction. Having said that, the perceived complexity of the QFD charts, and getting buy-in from across the company, can be barriers to success. However, QFD should help maintain a focus on the true requirements and requires more time to be spent at the start of development, thereby ensuring that the company determines, understands, and agrees with what needs to be done before rushing into development activities.

When appropriately applied, QFD has demonstrated that design changes are less likely later in development and has shown a corresponding reduction in development time to market (Akao, 1990).

Like any good system, QFD has evolved over the years. Modern QFD now incorporates much advancement that was not in traditional QFD. For example, traditional QFD is centered on the "4-House" approach. Some companies that do their own design work have found that this approach does not integrate well into their new product development process and is too time consuming. Modern QFD is custom tailored to identify the minimum QFD effort required with the optimum tools and sequence, making QFD more efficient and sustainable in today's lean business environment. Large, complex tools such as the HOQ are now often replaced with smaller, faster ones that provide a level of analysis that is faster and easier. In some cases, the HOQ matrix may be still useful; however, the important thing is to know when HOQ is appropriate and when it is too much team effort for the value it delivers.

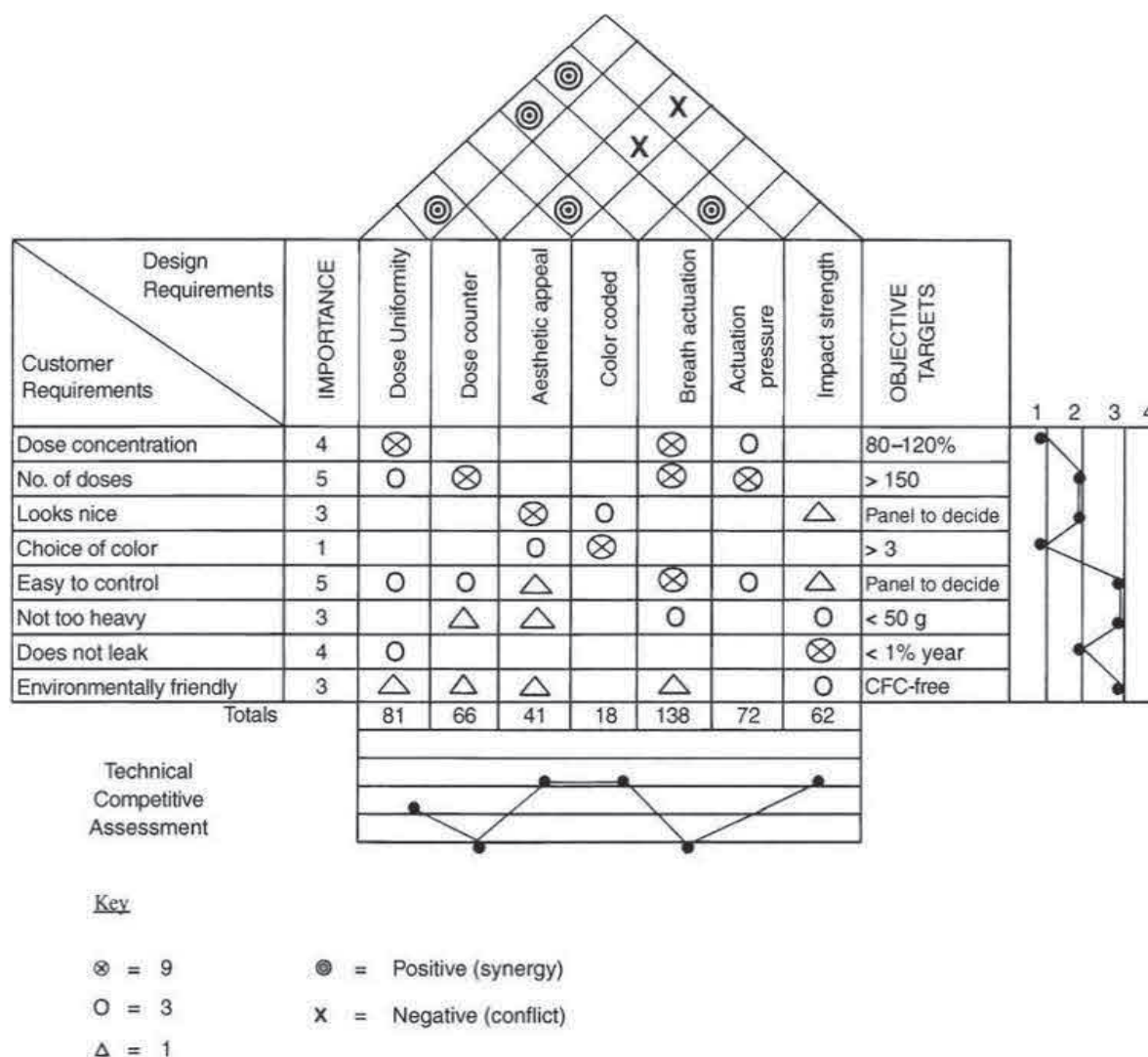


Figure 2 A fictitious QFD chart for metered dose inhaler.

Modern QFD also incorporates upgraded mathematics in the QFD matrices to meet the mathematical rigor demanded by Six Sigma precision. Traditional QFD often did not go deep enough into the Voice of the Customer to uncover unspoken needs because it began at the time when most design work was done by the customer's engineers. Modern QFD has a set of rigorous front-end tools to refine the Voice of the Customer into spoken and unspoken customer needs, leading to more innovative solutions. Additionally, Modern QFD includes psychological and lifestyle needs, not just functional needs. Today, consumers are making the purchase decision more and more on emotional needs and image issues. Lifestyle QFD (available at http://www.qfdi.org/workshop_kansei.htm) connects consumers' needs for psychological and lifestyle-enhancing solutions with product development and branding. Traditional QFD ignores bottlenecks caused by availability of certain experts. It assumed that experts were always available or would work overtime to finish the work. Modern QFD also has components for schedule deployment and project deployment based on Critical Chain Project Management to improve allocation of constrained resources and finish more projects on time. Overall, Modern QFD today provides a much better framework for integration of various innovative methods into the product development process (Mazur, 2007; Mazur, 2008).

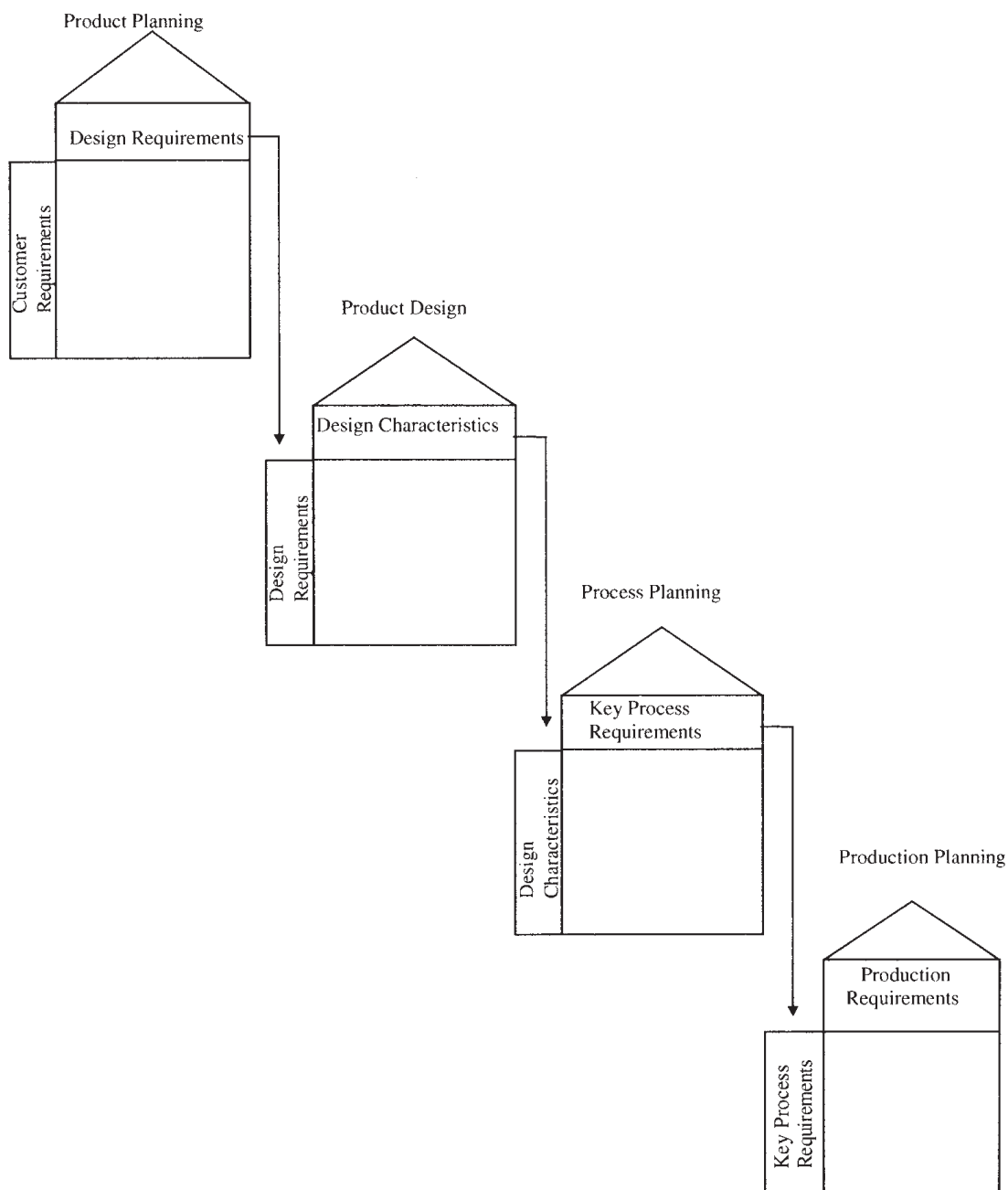


Figure 3 QFD: cascading the voice of the customer.

Design Specifications and Critical Quality Parameters

In addition to the preformulation information, there will be other considerations in the selection of the excipients and packaging components for the product. Taking the intravenous injection example in Table 2, it may be important to stipulate that any excipient used must be of parenteral grade, will comply with pharmacopoeial requirements, and be restricted to those known to be safe and acceptable to the regulatory authorities. This will reduce the risk, compared with using a novel excipient, which might be questionable to some regulatory authorities. It will also reassure the safety/toxicology department that no extra toxicological studies will be required to approve a new excipient.

Similarly, a list of requirements can be produced for the primary pack, such as the following:

- The pack will be acceptable to regulatory authorities in the countries to be marketed (other approved marketed products already use this type of pack).
- Only packs that can be multiple sourced from more than one supplier/country will be used.
- The pack must have consistency of dimensions and performance.
- The pack will meet function/user tests and specifications.

These dimensions, performance limits, and function/user test limits should be specified in the product design report.

Even though the product has not yet been developed, a high-quality product specification can be proposed with tests and limits that the product should meet at the time of manufacture and at the end of shelf life. For the intravenous product example, tests might include appearance (clear, particle free), pH, osmolality, particulate levels, sterility, and endotoxin levels. Appropriate standards or limits can also be proposed on the basis of the knowledge of similar types of products that have already been developed and from standard pharmacopoeial monographs.

Finally, in this section, it is useful to agree on what the minimum acceptable shelf life for the product should be. The product will need to be stable enough to allow time for quality control (QC) testing and quality assurance (QA) release after manufacture; distribution to wholesalers, pharmacists, and doctors; and with acceptable time for storage until prescribed and used by patients. Normally, a minimum three-year shelf life at room temperature (15–30°C) is targeted. However, if the treatment is very novel, it may be possible to justify a shorter shelf life and/or storage at lower temperatures, if stability is likely to be a problem.

Commercial and Marketing Considerations

Any pharmaceutical company's economic objective must be to maximize its ROI after launch. Therefore, the commercial viability of a new product to be developed needs to be commercially assessed at the product design stage to satisfy the company that it will achieve a satisfactory ROI. Some of the factors that should be considered in the evaluation are as follows:

- Development costs
- Timing to market
- Market size (disease prevalence, diagnosis and treatment rates, market value)
- Competition (current, developing, and impact on future market)
- Unmet medical need (effectiveness of current treatment, improvements required)
- Pricing and reimbursement (current and future)
- CoG (target)

The development costs are an estimate of the total costs of development of the product through the various stages of R&D, including preclinical, clinical, pharmaceutical (drug substance and product), and marketing costs. As a rule, the development costs will increase exponentially with development time (see Fig. 2, chap. 1), and the cost of conducting the phase III clinical studies are usually the most expensive element of the development program. Estimates of the total cost of all material, labor, and overhead costs should be included.

A major consideration for the development costs is whether to contract out some or all of the work (Spurlin et al., 1996). Contract research organizations (CROs) can offer a broad range of services covering all parts of the drug development process. In terms of product development, preformulation studies, including drug substance characterization, formulation development, stability testing, clinical trial manufacturing, and scale-up/technology transfer, are typically outsourced. In fact, most pharmaceutical companies have to contract out some aspect of R&D because of the diverse requirements and multidisciplinary nature of the work. Taken to the extreme, it is possible to create a “virtual” pharmaceutical company run by a

Table 3 Advantages and Disadvantages of Outsourcing

Advantages	Disadvantages
• More cost effective • Reduced overhead costs • Avoid capital expenditure • Reduced cost of good • Reduced training costs • Access to the best expertise, technology, and resources not available within company • Access to patented technology • Allows optimal use of internal resource (focus on company strengths) • Free up resource for other purposes • Management of peaks and troughs • Shorter time to achieve results-fast track to market • Shared risk-joint venture • Increased probability of success? • Convenient and efficient	• A big commitment and initial costs • Questionable quality and regulatory concerns; detailed audits required • Secrecy/loss of patent opportunities • Loss of technical expertise and product knowledge • Stagnation of in-house competence • Decreased flexibility moving resources between projects • Short-term gain—no future development of company • Dependability on partner

committee of project managers responsible for coordinating the outsourcing of every part of the development program (Stevenson, 1997). However, it is unlikely that major pharmaceutical companies would want to take this approach and not have any internal capability.

There are pros and cons to outsourcing, some of which are summarized in Table 3. Clearly, contracting out is not simply a commercial decision. The issues identified if outsourcing is done have to be carefully considered. One significant risk of outsourcing is if the relationship with the CRO goes sour or the CRO goes out of business. It may be difficult to find an alternative without having the detailed technical knowledge.

The outsourcing company should be aware of the potential additional costs to simply paying for a package of work. Someone from the parent company has to manage the process, and this can involve several stages such as

- selecting the CRO,
- auditing to ensure technical, commercial, and quality standards are acceptable,
- establishing a contract and agreement of the work program,
- attending reviews to discuss progress or technical issues, and
- accepting the end result.

These activities are likely to involve significant parent company investment in time, people, and costs if the outsourcing is to be successful. Some of these issues associated with using and controlling contractors are discussed further by Burton (1997).

An estimate of the timing to market is important to know to assess the positioning of the new product in relation to competitor products in development and those already marketed. The use of CROs should be able to speed up development by allowing activities to be conducted in parallel. It is also important to predict what the market size is likely to be at the time of launch on the basis of market trends. Being first to market with a new treatment can be very advantageous in determining a high commercial price. However, if other competitor products are already established, the market price may be restricted unless some significant benefit can be shown over existing treatments. For example, a novel delivery system or device that improves patient compliance might achieve a higher price than a conventional delivery system.

The potential market size can be estimated from current research data, showing the number of patients in the countries of interest and the total value of treatment. Trends in disease prevalence should be noted, whether the number of patients is increasing or decreasing. However, it should also be noted that market research can sometimes be

misleading and could result in missed opportunities. A good example to illustrate this point is the introduction of a new therapeutic class of drugs where there was no existing market. Before the introduction of the H₂-receptor antagonist cimetidine, there was little evidence that many people suffered from gastric ulcers. It was only after an effective treatment was available that people came forward, and an enormous market was established.

One way of assessing the commercial viability for a new product is to subtract the total development costs from the potential market share value. The potential market share value is estimated by multiplying the percentage of the potential number of patients by the potential commercial price for the new product. An alternative approach is to do the calculations based on the cost of the product or one course of treatment:

Estimated commercial return = (commercial price – cost of goods) × predicted sales volume

The commercial price that the company thinks it can obtain for the product, or for a course of treatment, will depend on some of the other factors mentioned above, such as the predicted time of market launch, the competitive positioning, and the relative cost of competitor products in the countries to be marketed. The CoG is an estimate of the sum of the cost of the drug substance, excipients, packaging materials, manufacture, labor, and overheads, among other things, that contribute to making the product.

It has been estimated that 85% of the future cost of a new product can be determined at the product design phase (Matthews, 1997). The industry average for the CoG has gradually increased over the last decade from about 10% to 20% of the commercial price. A CoG target of 5% to 10% is about the industry average, with a maximum of no more than 40%. Higher than this would be difficult to justify developing, as the margins would be too small. The choice of the commercial dosage form and manufacturing process can have a significant impact on the CoG. For example, if a product is freeze-dried, the processing costs will be extremely high because of the limited batch sizes and lengthy process involved. A less obvious example is the choice between tablets versus capsules. Cole (1998) compared the relative costs in the development and production of film-coated tablets with a dry-filled hard gelatin capsule for a new chemical entity (NCE). The relative costs in terms of development time, raw materials used, production equipment, facilities, and validation for the manufacture were considered. There is a general belief that tablets are easier and cheaper to produce than dry-fill capsules, but surprisingly, Cole found that a capsule-manufacturing facility is cheaper to build, validate, and operate than a tablet-manufacturing facility. Only when the costs of excipients are considered in isolation does the tablet process have an advantage, mainly because gelatin capsules are relatively expensive.

Technical Issues and Risk Assessment

There may be a variety of issues that should be documented in the product design report to highlight the perceived risks involved in developing the product. Some of these risks will be related to pharmaceutical development and others to clinical, safety/toxicology, or other areas.

For pharmaceutical development, risk may be associated with the technical challenges anticipated in developing a novel or complex drug delivery system or manufacturing process. Information from early preformulation and biopharmaceuticals studies should indicate the potential problems for drug delivery, formulation development, and manufacture.

There may be a lack of in-house expertise, resulting in the need to contract out the work or the need to develop an in-house capability. Alternatively, there may be a lack of in-house facilities or equipment to handle the candidate drug. These issues need to be resolved quickly or else time penalties could be incurred. Other areas of risk include the sources of excipients and packaging components. Some excipients or packaging components may only be available from one supplier, with the risk that the supplier could go out of business.

The importance of identifying these issues in a product design report is to make the company aware of the risks it is taking and to make effective plans to overcome problems and manage the risks.

Safety Assessment Considerations

In the interests of rapid product development, it is beneficial to select well-established excipients that already have regulatory approval in registered products. In the United States, specific requirements for “new” excipients are detailed in the U.S. Food and Drug Administration’s *Guidance for Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, published in May 2005.

According to ICH, an excipient is considered new or novel if it is used for the first time in a human drug product or by a new route of administration. In the United States, FDA maintains the Inactive Ingredient Database, which lists excipients used in approved drug products, their route of administration, and their maximum dosage. There may be situations where there are good reasons to use new excipients. There may be incompatibility problems with the candidate drug and existing excipients or there may be a need to use new excipients in a new drug delivery system. The replacement of chlorofluorocarbons (CFCs) with new hydrofluorocarbon (HFA) propellants in pressurized MDIs has been driven by environmental factors. The cost of safety testing HFA-134a and HFA-227 has been shared by a consortium of pharmaceutical companies who all had a vested interest. However, the search for novel surfactants required to suspend the drug in the new propellants has been left to individual companies, after it was discovered that none of the traditional surfactants were compatible with HFA propellants. This has resulted in many new surfactants being patented, but few have been successfully safety tested and used in marketed products.

The safety-toxicological testing of a new excipient for Europe or the United States is as extensive as that for an NCE and can take four to five years to complete. There are differences in the safety evaluation requirements for different types of formulations: oral, parenteral, and topical/transdermal. The International Pharmaceutical Excipients Council (IPEC Europe and IPEC Americas) have developed a protocol for the rational safety testing of excipients to aid the introduction of new chemical excipients (Table 4). IPEC is a federation of three independent regional industry associations based in Europe, the United States and Japan who are focused on the applicable law, regulations, and business practices of each region with respect to pharmaceutical excipients. Historically, new excipients were only reviewed by regulatory authorities in the context of new drug applications (NDAs). As a result, pharmaceutical companies were reluctant to include them in their formulations because any questions about the excipients could delay or reject their applications. To address this IPEC of the Americas has developed a New Excipient Evaluation Procedure (DeMerlis et al., 2008). The aim of this process is to provide independent evaluation of the regulatory acceptance of a new excipient before a regulatory filing of a new drug product. Although this process will not provide any type of regulatory approval, it should provide confidence to pharmaceutical companies that the excipient will be acceptable in their formulations. Supporting information for a new excipient can be provided in a drug application or in an appropriately referenced drug master file (DMF). This information includes full details of chemistry, manufacturing, and controls as well as supporting safety data. The information provided is similar in the level of detail to that provided for a drug substance. The level of information, however, may be less depending on the “newness” of the excipient.

Investment in a new excipient includes the cost of safety testing, investment in manufacturing facilities, and other development costs, including stability testing. Safety testing of a new excipient alone can be expensive. It is estimated that about \$40 million to \$50 million is required to allow for the cost of those materials that do not make it to the market. There is a big financial risk that the investment costs will not be recovered during the patent life of a new product. However, it may be possible to reduce these costs and timings. For example, if the new excipient is essential for the development of the new candidate drug, it may be possible to “piggyback” the safety evaluation of the new excipient onto the safety evaluation of the candidate drug itself. This approach could be particularly appropriate for parenteral products. Finally, there may be lesser considerations for excipient safety testing in novel treatments, where there is an overwhelming need to treat patients quickly and effectively, for example, for life-threatening diseases such as cancer.

Table 4 Summary of Excipient Safety Testing for Different Routes of Exposure for Humans (proposal by IPEC Europe and IPEC America)

Dermal/inhalation/tests	Oral	Mucosal	Transdermal	Topical	Parenteral	Intranasal	Ocular
Appendix 1—base set							
Acute oral toxicity	R	R	R	R	R	R	R
Acute dermal toxicity	R	R	R	R	R	R	R
Acute inhalation toxicity	C	C	C	C	C	R	C
Eye irritation	R	R	R	R	R	R	R
Skin irritation	R	R	R	R	R	R	R
Skin sensitization	R	R	R	R	R	R	R
Acute parenteral toxicity	—	—	—	—	R	—	—
Application site evaluation	—	—	R	R	R	—	—
Pulmonary sensitization	—	—	—	—	—	R	—
Phototoxicity/ photoallergy	—	—	R	R	—	—	—
Ames test	R	R	R	R	R	R	R
Micronucleus test	R	R	R	R	R	R	R
ADME-intended route	R	R	R	R	R	R	R
28-day toxicity (2 species)-intended route	R	R	R	R	R	R	R
Appendix 2							
90-day toxicity (most appropriate species)	R	R	R	R	R	R	R
Teratology (rat and rabbit)	R	R	R	R	R	R	R
Additional assays	C	C	C	C	C	C	C
Genotoxicity assays	R	R	R	R	R	R	R
Appendix 3							
Chronic toxicity (rodent, non-rodent)	C	C	C	C	C	C	C
1 Generation reproduction	R	R	R	R	R	R	R
Photocarcinogenicity	—	—	C	C	—	—	—

Abbreviations: R: required; C: conditional.

Environmental, Health, and Safety Considerations

There are increasing pressures on the pharmaceutical industry to use environmentally friendly materials in products, which are biodegradable or recyclable and do no harm to the environment. Examples are the replacement of CFCs in pressurized metered dose aerosols and the replacement of polyvinyl chloride (PVC) for alternative packaging materials in some countries. Any special restrictions on the use of materials in the product need to be identified at the product design stage. The choice of appropriate materials to suit product, customer, and environment may also have cost implications.

Another aspect is the nature of the candidate drug to be developed. Special handling requirements may be required for a very potent and potentially hazardous compound. There may be implications for the design and purchase of new facilities or equipment or the training of employees in new techniques.

Intellectual Property Considerations

Few pharmaceutical companies would venture into a long and expensive development program without a strategy for effective patent protection in place to ensure market exclusivity. Patents are legal property that prevents others using the invention (for 20 years in most countries) in exchange for a full public disclosure of information.

The pharmaceutical industry is one of the major users of the patent system, which requires that three criteria be met to grant a patent. These criteria are novelty, presence of an

inventive step, and industrial applicability. Although an invention might be novel, it might not be patentable if it could have been predicted from "prior art," that is, knowledge in the public domain. Hence, there is a need for an inventive step.

At the product design stage of development, the only patent filed is likely to be for the new candidate drug. There may be a patent for a candidate drug and further patents for a new indication or a new pharmaceutical use. For example, Minoxidil, originally developed as an antihypertensive, had been discovered subsequently to be useful for the treatment of male pattern baldness. Patent protection is stronger if multiple patents can be obtained; for example, a single product could have patents covering a range of features from the candidate drug itself to the method of treatment and the delivery system. These new discoveries may only become known during development. Polymorphs (e.g., cimetidine) and hydrates (e.g., amoxycillin trihydrate) have been patented, as they have shown to have therapeutic advantages. A new formulation of the drug, delivery device, or new pharmaceutical process might allow further patent cover to be granted, to extend the exclusivity beyond that of the primary patent.

The current patent status and potential for future patents to be obtained should be highlighted in the product design report to assess the overall strength of patent protection to cover future development, and, as long as possible, market exclusivity.

CONCLUDING REMARKS

The potential benefits of conducting an initial product design stage prior to commencing product development have been emphasized in this chapter. Experience shows that the most frequent reason for terminating a project in late phase development is not because of lack of efficacy or poor safety but because the product developed does not meet the market (customer) needs. This might have been avoided if more consideration had been given to product design.

The TPP and product design report can be very useful documents to focus the company on developing the right product at the right time to the market. Of course, to be of value it is essential that the correct input has been obtained from internal and external customers. For this to happen, a pharmaceutical company's senior management has to support this approach and ensure that time and resources are allowed for the design phase activities. The most successful pharmaceutical companies are effectively using this approach.

It is important that the TPP and product design report are reviewed by the project team at milestones in the project life and updated if necessary. It is imperative that some information will change with time, for example, competitor data and information gained from conducting development studies. The introduction of a new competitor product to the market with unexpected product attributes may result in a reevaluation of the desired product profile for the new product being developed. This, in turn, can result in subsequent modifications to the preformulation and formulation development program. It is hoped that this will not be a complete change in direction, but if it is, the product design review will have alerted the company sooner rather than later to address this, and not to develop a product that is not wanted or needed.

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6 | Preformulation as an Aid to Product Design in Early Drug Development

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INTRODUCTION

It is axiomatic that the physicochemical properties of candidate drugs can influence their subsequent development. The results of characterization studies carried out will influence their product design. However, in the interest of only doing necessary work, any detailed studies should only be carried out after the candidate drug has successfully overcome the safety and clinical trials performed in early development as many will fail at this stage. Since pharmaceuticals are formulated in a variety of dosage forms, the studies that should be undertaken include those of solid and solution state. In terms of solid-state evaluation, material science has assumed great importance (Cui, 2007), and this is especially true for compounds to be delivered via the inhalation route (Chow et al., 2007; Young et al., 2007). If the solid-state characteristics of the candidate drugs are less than desirable from a formulation perspective, then crystal engineering techniques can sometimes be employed to give them more amenable properties (Chow et al., 2008).

Variability of the drug candidate and excipients is the major cause of challenges in the formulation development of new compounds, and so methods for their characterization need to be available (Hagsten et al., 2008). While there are many traditional approaches to dosage form design, newer approaches based on expert systems that require knowledge of the physicochemical properties are being employed to speed up development (Rowe, 1998; Pérez et al., 2006; Branchu et al., 2007). Expert systems are discussed further in chapter 8 “Product Optimization.”

SOLID DOSAGE FORMS

Since tablets and capsules account for approximately 70% of pharmaceutical preparations, an investigation into the solid-state properties of candidate drugs is an important task to be undertaken during preformulation (Wells, 1988). Generally speaking, when dealing with high-strength solid dosage forms, this formulation will be more susceptible to any drug substance variability. However, other studies are also important since, for example, the same chemical compound can have different crystal structures (polymorphs), external shapes (habits), and hence different flow and compression properties.

Carstensen et al. (1993) have usefully, although briefly, reviewed the physicochemical properties of particulate matter dealing with the topics of cohesion, powder flow, micromeritics, crystallization, yield strengths, effects of moisture, and hygroscopicity. Buckton (1995) has reviewed the surface characterization of pharmaceuticals with regard to understanding sources of variability. A general overview of the methods available for the physical characterization of pharmaceutical solids has been presented by Brittain et al. (1991). York (1994) has also dealt with these issues and produced a hierarchy of testing techniques for powdered raw material. Finally, a book dealing with the physical characterization of pharmaceutical solids by Carstensen (2001) is recommended for additional reading on this subject. The importance of powder technology in pharmaceuticals has been emphasized by Muzzio et al. (2002), who have argued that particle technology strongly affects the time to market and the length of patent protection.

Table 1 Estimated Material Demands with Respect to Development Time

Months from CD nomination	Campaign	Typical amount (kg)	Use
4	1	0.2	7-day rat and dog toxicity + pharmaceutical studies
	2	1–20	1-mo toxicity studies Phase I trials
10 11	3	30	3 and 6 month toxicity and reproductive toxicity 12-mo dog study Phase II trials
17	4	125	Oncogenicity studies Phase III formulation development Phase III trial supply
25	5	210	Phase III trial supply

There are a number of other studies that can be enacted on a candidate drug to determine other important solid-state properties, for example, particle size, powder flow, compression, and polymorphism. Therefore, when a sample undergoes initial physicochemical testing, the following parameters should be measured: particle size, true, bulk, and tapped density, surface area and properties, compression properties, and powder flow properties. Pérez et al. (2006) have devised a new expert system for the control of batch powder properties. Some of these factors will be discussed in this chapter. However, others are dealt with in more detail in chapter 11, which deals specifically with solid oral dosage forms.

The production of drug substance is usually undertaken by the process research and development department (R&D) in a typical pharmaceutical company in so-called “campaigns.” The typical batch size of each campaign and its typical usage is shown in Table 1. As can be seen from this table, the output of crystallization processes employed by PR&D produces increasing quantities of drug substance material per campaign as drug development progresses (Desikan et al., 2000). It is these materials that the product development department will use for initial preformulation and continued pharmaceutical development studies. An assumption made when calculating the amount per campaign is that the maximum dose for safety assessment is 250 mg/kg. Campaign 1 material tends to be non-GMP (Good Manufacturing Practice) material and is used to support prenomination studies from a batch size of approximately 150 to 300 g.

The cost of drug substance (in raw material terms) in the early stages of development is typically in the range of US\$3000 to 7000 per kg. After transferring from R&D to manufacturing operations, the cost in raw material terms for a single batch of drug substance is typically US\$1 to 2 million. However, the cost per kg should be considerably reduced because of economy of scale and process optimization.

Depending on the method of crystallization (cooling crystallization, antisolvent crystallization), the subsequent isolation (filtration and drying) of the drug substance will have a specific presentation to the product development department. The crystals produced may be single crystals, but often the crystals are associated in some way with each other. Nichols et al. (2002) have defined the way crystals are associated with each other in two ways, that is, hard and soft agglomerates. They preferred this definition to aggregate and agglomerate and defined a hard agglomerate as an assemblage of crystals that is non-friable and not easily dispersed, with a soft agglomerate being the opposite.

Agglomeration, as defined by Brunsteiner et al. (2005), is the intergrowth of aggregates formed by particle collisions, through a cementation process that forms an agglomerative bond. As shown by Ålander et al. (2002), supersaturation, particle concentration, hydrodynamics, and the solvent all affect agglomeration processes. Results showed that the material crystallized from acetone showed higher levels and stronger agglomerates than samples recovered from IPA (isopropyl alcohol). This behavior was postulated to be due to IPA –OH group hydrogen bonding with H-bonding functional groups on the growing paracetamol surface; acetone being a H-bond acceptor could not partake in this process and hence agglomerated. In addition, the viscosity of acetone is approximately seven times less than that of IPA, which may also influence agglomeration. Agglomeration can be a problem since it can

lead to solvent inclusions. Agglomeration involves two steps. In the first step, crystals collide and are held together by attractive forces, giving a soft agglomerate (or aggregate). In the second step, the crystals cement together to form a hard agglomerate. Agglomeration increases with supersaturation, and small particles are more likely to agglomerate than large particles. Agglomeration is also more likely between a large particle and a small particle than between two particles of similar size (Brunsteiner et al., 2005). As a test, they suggested that the powders be placed on a microscope slide and some silicone oil added. If the powders readily dispersed under gentle shearing motion of the cover slip, then the powders could be classified as a soft agglomerate. Agglomerates can be further characterized using image analysis and strength measurements (Alander et al., 2003).

Kim et al. (2005) have discussed the control of the particle properties of a drug substance by crystal engineering and its effect on drug product. This work showed how, as part of a solid supply chain, a controlled crystallization produced large crystals with a narrow distribution, which were preserved during the drying process by utilizing low shear in the filter dryer. Drug substance produced by this method was found to have reproducible formulation properties. A more general review of crystal engineering is given by Chow et al. (2008).

Drug substance quality by design (QbD) is an important new aspect in the production of pharmaceuticals. The QbD concept describes developing a design space, establishing control strategies, and defining criticality for the drug substance. As an example of the use of QbD in the manufacture of the active pharmaceutical ingredient (API) torcetapid, see Am Ende et al. (2007). In this study, they employed design of experiments (DoEs) methodologies to examine the design space of the crystallization. In addition to DoEs, process analytical technologies (PAT) are used to monitor and control crystallization processes (Yu et al., 2004; Birch et al., 2005; Byrn et al., 2006). McKenzie et al. (2006) have pointed out that adoption of these manufacturing initiatives must be accompanied by the adoption of modeling tools and efficient information management systems.

Lionberger (2007) and Yu (2008) have summarized QbD into four areas. These are

- definition of the target product quality profile that describes the performance needed to get clinical benefit and meet consumer expectation,
- product and process design,
- identifying critical parameters, and
- process monitoring and control.

Drying of drug substances after crystallization is, perhaps, a neglected area, but one that can profoundly affect their properties. This is particularly true if a hydrate is involved, which was exemplified by a paper by Cypes et al. (2004), who described the drying of a compound that existed as an anhydrate, a monohydrate, and an isopropylalcohol solvate. They pointed out that drying filtration wet cakes and fixing a set time to dry a cake was dangerous, since variability in the process may cause overdrying of the monohydrate.

Impurities

Since unwanted impurities, for example, intermediates, degradation products, and products from side reactions may have deleterious pharmacological and toxicological activities, they must be removed from the final product. The identification of impurities is thus a crucial activity in drug substance PR&D (Huang et al., 2008). Indeed, it is a regulatory requirement that the level of impurities in the drug substance be controlled (see International Committee for Harmonization (ICH) Q3a, Müller et al., 2006; Jacobson-Kram and McGovern, 2007). In addition to regulatory requirements, the incorporation of impurities in the crystal lattice can lead to crystal defects, which in turn can lead to differences in, for example, mechanical properties, dissolution behavior, and stability, which may be the basis of batch-to-batch variation (Gu and Grant, 2002). One of the main objectives of crystallization is therefore to purge the compound of these impurities to make it fit for use as the active pharmaceutical ingredient in a medicine.

ICH classifies impurities into the following categories: organic impurities (process and drug related), inorganic impurities, and residual solvents. Organic impurities include, for

example, starting materials, by-products, intermediates, degradation products as well as reagents, ligands, and catalysts. Inorganic impurities can often result from the manufacturing process, and examples of these are reagents, ligands and catalysts, heavy metals, inorganic salts, and other process-related materials such as filtration aids and charcoal. Solvents are controlled through ICH guideline Q3C. In addition to these obvious impurities, polymorphs as well as enantiomeric impurities need to be considered.

Impurities can have effects on the size, shape, and polymorphic form of compounds, such that, as the synthetic chemists experiment with different synthetic routes to the drug substance, different impurities generated can alter the physical properties of the crystals generated. For example, Masui et al. (2003) found that a related substance to their drug substance, cefmatilen hydrochloride, acted as a habit modifier. During early work, it was found that the compound crystallized as fine needles. However, by controlling the reaction, the production of the impurity was reduced and the habit was modified to larger blade-like crystals. Interestingly, by crystallizing in the presence of hydroxycelluloses or polyvinyl derivatives, the habit could be modified, that is, the additives thus act as crystal engineering aids. See Hulse et al. (2008) for the effect of low levels of aluminum, at the parts per million (ppm) level, on the physical properties of paracetamol.

Impurities may also affect the polymorph that crystallizes from solution. For example, Gu et al. (2002) have reported how substances related to sulphamerazine stabilized the metastable form in a slurry experiment conducted in acetonitrile. Normally, in solution-mediated phase transformations, slurries of metastable forms will convert to the stable form. The sequence of events is dissolution of the metastable phase, nucleation of the stable phase, followed by crystal growth. The transformation of the metastable form I to form II is controlled by the crystallization of form II. However, in the presence of impurities, the nucleation and growth rates were significantly reduced in the rank order N4-acetylsulphamerazine (NSMZ) $\gg$ sulphadiazine > sulphamethazine (NSMZ $\gg$ SD > SM). Similarly, Okamoto et al. (2004) found that one of the impurities of AE1-923, a compound for pollakiuria and pain, inhibited a polymorphic transformation. The most important learning point of these studies is that the presence of impurities can affect the results of polymorph screens, since impurities can stabilize metastable forms and give a false sense of security that you are dealing with the stable form. Therefore, the use of pure material for polymorph screens is recommended, and the screen should be reconducted when route changes are made—especially if the impurity profile changes.

It should also be remembered that formulations also contain excipients that have their own crystal properties, which can be altered by the incorporation of impurities with the result that batch-to-batch variation can be experienced. For example, Garnier et al. (2002) determined the effect of supersaturation and the presence of structurally related additives on the crystal growth of α -lactose monohydrate [an important excipient used in dry-powder inhalers (DPIs)]. Contrary to expectation, the crystal size of α -lactose monohydrate increased with increasing supersaturation. This was explained to be due to β -lactose strongly inhibiting crystal growth at low supersaturation. With regard to the effect of the other impurities, it was found that some impurities were able to change the habit without being incorporated into the growing crystal lattice. Indeed, α -galactose, β -cellobiose, and maltitol were found to preferentially adsorb to two specific faces of the α -lactose, leading to a flattened morphology.

Particle Size Reduction

The particle size of the drug substance is important since it can affect such things as content uniformity in tablets (Rohrs et al., 2006), bioavailability (Rasenack and Müller, 2005; Jinno et al., 2006), sedimentation, and flocculation rates in suspensions. Moreover, the inhalation therapy of pulmonary diseases demands that particles of a small particle size (2–5 μ m) are delivered to the lung for the optimum therapeutic effect (Howarth, 2001; Pritchard, 2001). It is therefore important that the particle size is consistent throughout the development studies of a product to satisfy formulation and regulatory demands (Rohrs et al., 2006).

At the lead optimization stage, only small quantities (e.g., 50 mg) will be available to administer to the animal. Thus, to reduce the risk of dissolution rate limited bioavailability, the material can be ground with a mortar and pestle to reduce the particle size of the compound.

Table 2 Mill Selection Matrix

Criteria	Slurry	Fluid energy	Universal	Cone	Hammer
Particle size	Less than average	Very favorable	Very favorable	Less than average	Average
Particle distribution	Average	Very favorable	Very favorable	Favorable	Favorable
Cleaning	Less than average	Average	Average	Favorable	Less than average
Operating cost	Favorable	Unfavorable	Unfavorable	Very favorable	Favorable
Dust containment	Very favorable	Less than average	Less than average	Very favorable	Favorable
Temperature	Very favorable	Favorable	Less than average	Very favorable	Favorable
Flexibility	Average	Average	Very favorable	Favorable	Favorable

Source: From Spencer and Dalder, 1997, reproduced with permission.

However, there needs to be some caution because the process of grinding can induce a polymorphic change as shown by Lin et al. (2006). If larger quantities of drug substance are available, then ball milling or micronization can be used to reduce the particle size.

Taylor et al. (2007) have described a nanoindentation technique for predictive milling of compounds. Using a range of Pfizer compounds, they were able to calculate a fracture toughness of the material such that hardness could be calculated from the depth of the indentation. The brittleness index (BI) could then be calculated according to equation (1).

$$BI = \frac{H}{K_c} \quad (1)$$

where H is the hardness and K_c is the fracture toughness. For a sildenafil citrate (Viagra[®]), the BI is $27.8 \text{ km}^{-1/2}$ (very brittle), whereas voriconazole has a BI of less than 1 (very plastic). Zügner et al. (2006) have also used nanoindentation to calculate hardness and elastic modulus of a range of compounds, which are essential when determining the conditions under which a compound is micronized. Their results showed that the elastic-plastic properties of the crystals strongly influenced their breaking behavior.

The main methods of particle size reduction have been reviewed by Spencer and Dalder (1997), who devised the mill selection matrix shown in Table 2. Chickhalia et al. (2006) have examined the effect of crystal morphology and the mill type on the disorder induced by milling. Using β -succinic acid as a model compound, which can be crystallized in plate-and-needle morphologies, size reduction was carried out in a ball-and-jet mill. They showed that the plate crystals were more susceptible to disordering in the ball mill than that in the jet mill. Interestingly, they also found that some conversion to the α -form occurred. Wilfdong et al. (2006) have attempted to provide a theoretical framework of the disordering process induced by milling. It would appear from their investigations that disordering is a result of the crystal lattice being forced to accommodate a large number of dislocations with the net effect that, from an energetic perspective, it is effectively amorphous.

Nakach et al. (2004) have compared the various milling technologies for the particle size reduction of pharmaceutical solids. They investigated both air jet mills and impact mills. Using vitamin C (ascorbic acid) as a test substance, they concluded that the pancake mill was preferred for ultrafine grinding since it was simple to use, had a high feed rate, and was easy to clean.

Ball Milling

Ball milling is probably used most often at the preformulation stage to reduce the particle size of small amounts of a compound, especially for the preparation formulations to be administered to animals. It is also used for the preparation of co-crystals, as described in chapter 3. For a review of high-purity applications of ball milling, such as pharmaceuticals, see Vernon (1994).

Ball mills reduce the size of particles through a combined process of impact and attrition. Usually, they consist of a hollow cylinder that contains balls of various sizes, which are rotated

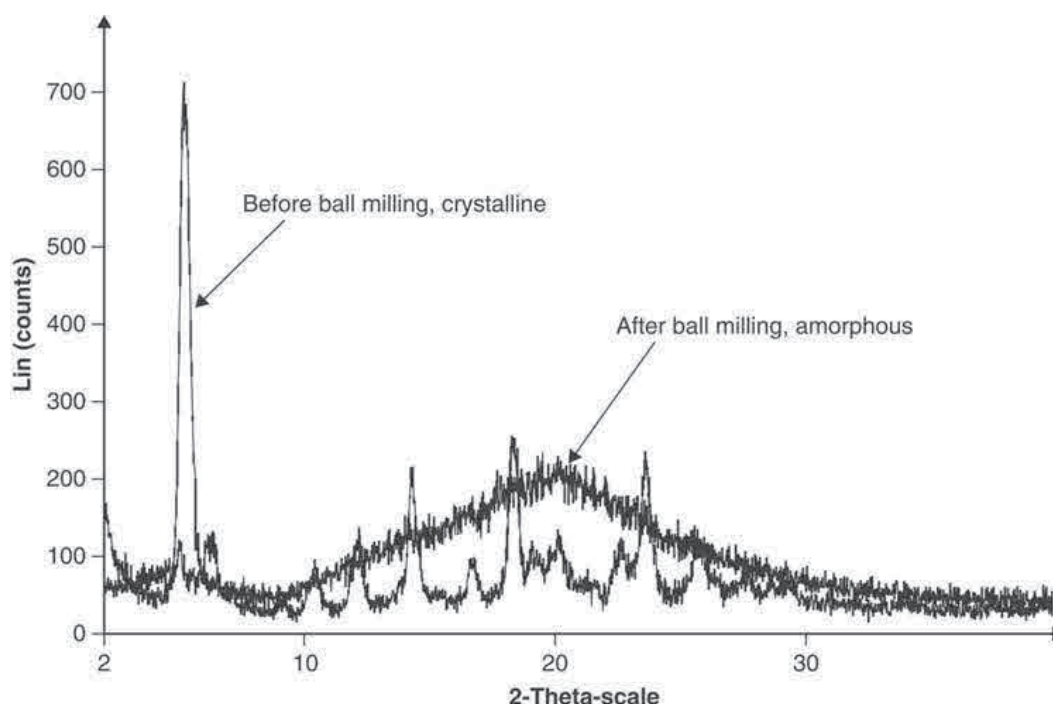


Figure 1 Effect of ball milling on a development compound.

to initiate the grinding process. There are a number of factors that affect the efficiency of the milling process, and these include rotation speed, mill size, wet or dry milling, and the amount of material to be milled.

Although ball milling can effectively reduce the particle size of compounds, prolonged milling may be detrimental in terms of its crystallinity and stability (Font et al., 1997). This was illustrated in a study that examined the effect of ball mill grinding on cefixime trihydrate (Kitamura et al., 1989). Using a variety of techniques, it was shown that the crystalline solid was rendered amorphous after four hours in a ball mill. The stability of the amorphous phase was found to be less than that of the crystalline solid, and in addition, the samples were discolored because of grinding. Thus, it is important to check this aspect of the milling process, since amorphous compounds can show increased bioavailability and possible pharmacological activity compared with the corresponding crystalline form. Ball milling may also change the polymorphic form of a compound as shown by the work conducted by Zhang et al. (2002) on the polymorphs of sulfamerazine. These workers found that when the metastable form II of this compound was milled, it resulted in a broadening and decrease in the intensities of the X-ray diffraction peaks. However, when form I (the stable form) was milled, it quickly transformed to form II. Descamps et al. (2007) have explored potential reasons why some compounds are rendered amorphous and why some may undergo a polymorphic change when milled. In particular, they pointed out that the position of the glass transition of the amorphous phase had an important bearing on the transformations that took place on milling. For example, they concluded that milling a crystalline compound well below its glass transition temperature (T_g) induced amorphization, whereas milling above the T_g caused polymorphic changes.

Figure 1 shows the X-ray Powder Diffraction (XRPD) patterns of a sample of a compound “as received” and after ball milling. After ball milling for one hour, the sample was rendered amorphous, and hence, a shorter milling period was used when preparing the sample for a suspension formulation. Polymorphic changes due to ball milling have also been followed by Raman spectroscopy (Cheng et al., 2007).

Micronization (Jet Milling)

If instrumentation and sufficient compound are available, then micronization can be undertaken. In this respect, Hosokawa has a small-scale air jet mill with a 1 in. screen, which can be used to

micronize small quantities of compound (down to ~500 mg) and is thus ideal for the preformulation stage where the amount of compound is restricted. Micronization is routinely used to reduce the particle size of active ingredients so that the maximum surface area is exposed to enhance the solubility and dissolution properties of poorly soluble compounds.

The micronization process involves feeding the drug substance into a confined circular chamber where the powder is suspended in a high-velocity stream of air. Interparticulate collisions result in a size reduction. Smaller particles are removed from the chamber by the escaping airstream toward the center of the mill where they are discharged and collected. Larger particles recirculate until their particle size is reduced. Micronized particles are typically less than 10 μm in diameter (Midoux et al., 1999). De Vegt et al. (2005a,b) have discussed some theoretical and practical aspects of the milling of organic solids in a jet mill. Zügner et al. (2006) have reported the influence of the nanomechanical crystal properties on jet milling, and the kinetics of jet milling of ethenzamide have been investigated by Fukunaka et al. (2006).

Because of the enhanced surface area, the oral bioavailability of compounds is often improved. For example, the absorption characteristics of both a micronized (8 μm) and a coarse fraction (125 μm) of felodipine were studied under two motility patterns (Scholz, 2002). The reduction in particle size led up to an approximately 22-fold increase in maximum plasma concentration and up to an approximately 14-fold increase in area under the curve, with a commensurate decrease in the time at which the maximum plasma concentration occurred. Although the absorption of felodipine from the solution and micronized suspension were not influenced by a change in the hydrodynamics, felodipine was absorbed from the coarse suspension almost twice as well in the “fed” state as under “fasted” conditions.

In addition to air jet milling, micronization by precipitation from supercritical fluids has received much attention as alternative particle size reduction method for pharmaceuticals (Martin and Cocero, 2008).

Nanoparticles

Typically, micronization can reduce the particle size of compounds to sizes in the micrometer range. However, increases in bioavailability can be obtained by further particle size reduction. To reduce the particle size into the colloidal range (10–1000 nm), other techniques such as precipitation processes, pearl milling, and high-pressure homogenization need to be employed (Gao et al., 2008). The colloidal particles produced by these processes are typically stabilized by surfactants. The precipitation technique is relatively straightforward and is usually reliant on the rapid generation of high supersaturation induced by adding an antisolvent to a solution of the compound. Pearl milling is essentially wet ball milling in the presence of a surfactant, which produces a colloidal dispersion of the compound within a few hours or days depending on the hardness of the compound and the desired particle size. High-pressure homogenization consists of passing a suspension (with a surfactant) of a compound through a narrow gap under a very high velocity. The high energy created in this region, coupled with the collisions between the particles, causes the particles to decrease in size into the colloidal region. As an alternative, Yang et al. (2008) have described the production of sumatriptan succinate nanoparticles by reactive crystallization of the two components of the salt followed by spray drying.

Effect of Milling and Micronization

Although micronization of the drug offers the advantage of a small particle size and a larger surface area, it can result in processing problems due to high dust, low density, and poor flow properties. Indeed, micronization may be counter-productive since the micronized particles may aggregate, which may decrease the surface area and compact on the surface of the equipment (Furunaka et al., 2005). In addition, changes in crystallinity of the drug can also occur, which can be detected by techniques such as microcalorimetry, dynamic vapor sorption (DVS) (Macklin et al., 2002), and inverse gas chromatography (IGC) (Buckton and Gill, 2007).

Ward and Schultz (1995) reported subtle differences in the crystallinity of salbutamol sulfate after micronization by air jet milling. They found that amorphous to crystalline conversions that were dependent on temperature and relative humidity (RH) occurred. It was suggested that particle size reduction of the powder produced defects on the surface that, if

enough energy was imparted, led to amorphous regions on the surface. In turn, these regions were found to have a greater propensity to adsorb water. On exposure to moisture, these regions crystallized and expelled excess moisture. This is illustrated in Figure 2, which shows the uptake of moisture, as measured by DVS of a micronized development compound. Note how the percent mass change increases and then decreases as the RH is increased between 40% and 60% during the sorption phase. This corresponds to crystallization of the compound and subsequent ejection of the excess moisture. The compound also exhibits some hysteresis.

This effect can be important in some formulations such as DPI devices, since it can cause agglomeration of the powders and variable flow properties (Steckel et al., 2006; Young et al., 2007). In many cases, this low level of amorphous character cannot be detected by techniques such as X-ray powder diffraction. Since microcalorimetry can detect less than 10% amorphous content (the limit of detection is 1% or less), it has the advantage over other techniques such as X-ray powder diffraction or differential scanning calorimetry (DSC) (Phipps and Mackin, 2000; Mackin et al., 2002). Using the ampoule technique, with an internal hygrostat, as described by Briggner et al. (1994) (Fig. 3), the amorphous content of a micronized drug can be determined

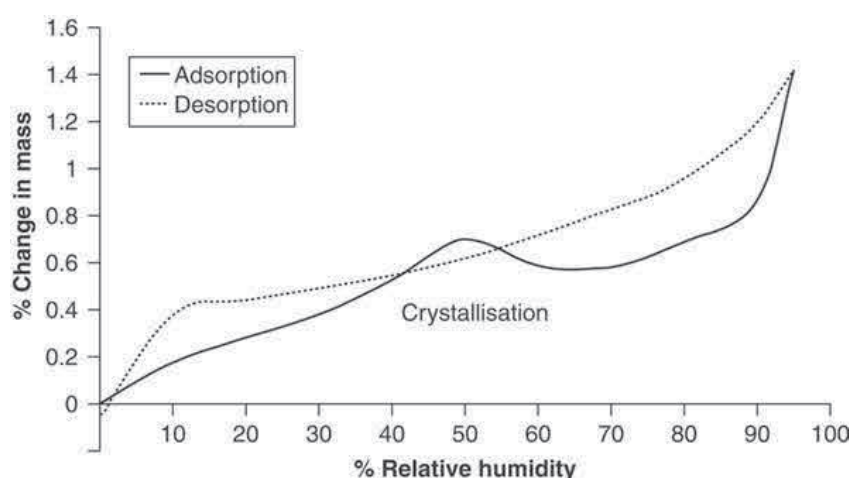


Figure 2 Dynamic vapor sorption showing crystallization effects due to moisture.

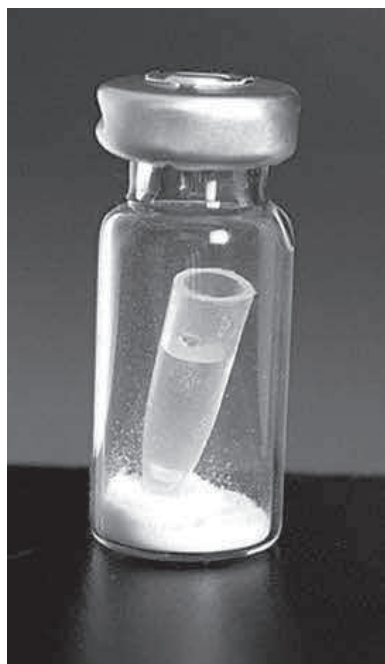


Figure 3 Internal hygrostat for microcalorimetric measurements of moisture sorption.

by measuring the heat output caused by the water vapor inducing crystallization of the amorphous regions (Fig. 4).

The crystallization of amorphous regions can cause changes to the surface of the micronized materials. For example, when Price and Young (2005) examined the effect of 70% RH on the surface of milled lactose crystals using atomic force microscopy (AFM), they found that it had undergone both morphological and physicochemical changes. RH is not the only variable that can affect the outcome of the recrystallization process. For example, Chieng et al. (2006) have shown that the temperature of milling has an effect on the form of ranitidine hydrochloride after milling. In particular, the temperature of ball milling was found to be important, for example, form I was converted to form II between 12°C and 35°C. If the milling was conducted under cold room conditions, form I was converted to the amorphous form. Another work reported by this group (Chieng et al., 2008) on the cryomilling of ranitidine polymorphs showed that both the forms were rendered amorphous by the ball mill but were found to crystallize back to the original polymorphs after two weeks.

Figure 5 shows the calibration curve of heat output versus amorphous content of a development compound. In this case, the technique is used to crystallize, or condition, these amorphous regions by exposure to elevated relative humidities. Thus, if authentic 100% amorphous and crystalline phases exist, it is possible to construct a calibration graph of heat output versus percent crystallinity so that the amount of amorphous character introduced by

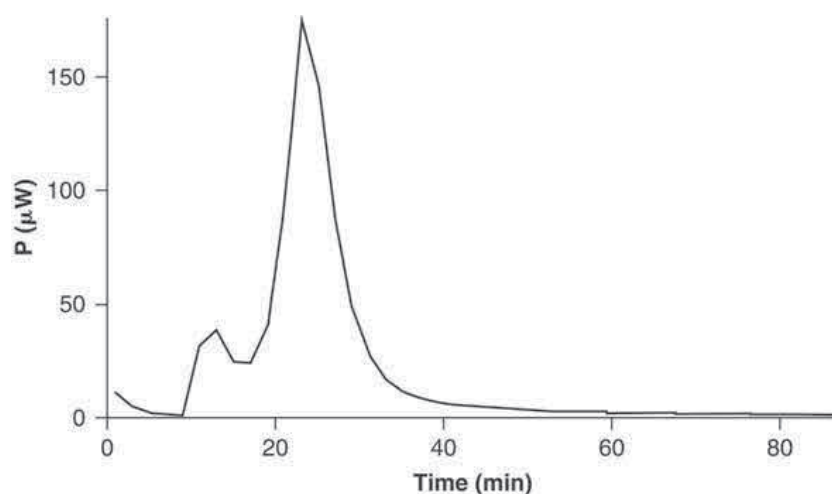


Figure 4 Crystallization peak energy versus time.

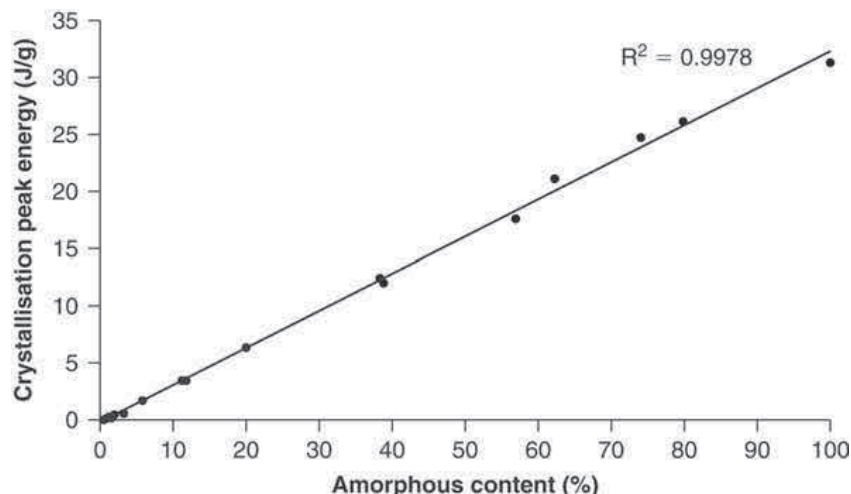


Figure 5 Crystallization peak energy versus amorphous content using microcalorimetry.

the milling process can be quantified. Ramos et al. (2005) have provided some guidance on the preparation of calibration curves when isothermal calorimetry is used in this mode.

Inverse Gas Chromatography

In addition to the DVS and microcalorimetric techniques for the characterization of surface properties of powders, another technique known as IGC can be employed (Telko and Hickey, 2007; Buckton and Gill, 2007). This technique differs from traditional gas chromatography in so far that the stationary phase is the powder under investigation. In this type of study, a range of nonpolar and polar adsorbates (probes), for example, alkanes from hexane to decane, acetone, diethyl ether, or ethyl acetate, are used. The retention volume, that is, the net volume of carrier gas (nitrogen) required to elute the probe, is then measured. The partition coefficient (K_s) of the probes between the carrier gas and surfaces of test powder particles can then be calculated. From this, a free energy can be calculated, which can show that one batch may more favorably adsorb the probes when compared with another, implying a difference in the surface energetics.

The experimental parameter measured in IGC experiments is the net retention volume, V_n . This parameter is related to the surface partition coefficient, K_s , which is the ratio between the concentration of the probe molecule in the stationary and mobile phases shown by equation (2).

$$K_s = \frac{V_n}{m} \times A_{sp} \quad (2)$$

where m is the weight of the sample in the column and A_{sp} is the specific surface of the sample in the column.

From K_s , the free energy of adsorption ($-\Delta G_A$) is defined by equation (3).

$$-\Delta G_A = RT \ln \left(K_s \times \frac{P_{sg}}{P} \right) \quad (3)$$

where P_{sg} is the standard vapor state (101 kN/m²) and P is the standard surface pressure, which has a value of 0.338 mN/m.

IGC and molecular modeling have been used to assess the effect of micronization on dl-propranolol (York et al., 1998). The samples were jet milled (micronized) to various particle sizes, and γ_s^D was measured and plotted against their median particle size. This showed that as the particle size decreased because of the micronization process, the surface of the particles became more energetic. Interestingly, it was pointed out that the plateau region corresponded to the brittle-ductile region of this compound, as previously reported by Roberts et al. (1991). This observation implied a change in the mechanism of milling from a fragmentation to an attrition process. The data for $-\Delta G_A^{SP}$ for the tetrahydrofuran (THF) and dichloromethane probes showed that the electron donation of the surface increased as the particle size decreased. Combining these data with molecular modeling, which was used to predict which surfaces would predominate, they showed that the electron-rich naphthyl group dominated the surface of the unmilled material. This led to the conclusion that as the particle size was reduced, this surface became more exposed, leading to a greater interaction with the THF and dichloromethane probes. However, as previously noted, as milling proceeded, the mechanism of size reduction changed, which might lead to exposure of the chloride and hydroxyl moieties. More recent work on how milling affects surface properties of crystals of paracetamol has been reported by Heng et al. (2006), who found that as the crystals were reduced in size, the surfaces became more hydrophobic. This was explained by reference to the crystal structure whereby the crystals fractured along the weakest attachment energy facet, which became progressively exposed as milling progressed.

In summary, using moisture sorption, microcalorimetry, IGC, molecular modeling, and other techniques, the consequences of the particle size reduction process can be assessed. Moreover, surface energetics can be measured directly and predictions made about the nature of the surface, which could ultimately affect properties such as the flow of powders or adhesion of particles. For example, Tong et al. (2006) used IGC measurements to measure the

interaction between salmeterol xinafoate powders and lactose carriers used in DPI formulations.

In addition to its use in the determination of surface properties after milling, IGC has also been used for such things as the determination of the solubility parameters of pharmaceutical excipients (Adamska et al., 2007) and determination of the of glass transitions (Surana et al., 2003; Ambarkhane et al., 2005).

Atomic Force Microscopy

AFM is a scanning probe microscopy technique that has been used in preformulation to study in great detail the surfaces of crystals (Turner et al., 2007). Imaging using AFM utilizes a sharp tip, typically made from silicon or silicon nitride (Si_3N_4), attached to a flexible cantilever that rasters across the surface using a piezoelectric scanner. This motion induced by the interaction of the tip and the surface is monitored using a laser beam that falls on photodiode detector. It can be used in a number of modes, that is, contact, "tapping," and noncontact. It has been used, for example, for characterizing polymorphs and amorphous phases and the effect of humidity on lactose (Price and Young, 2004). It has also been used to characterize crystal growth phenomena (Thomson et al. (2004).

Time-of-Flight Secondary Ion Mass Spectroscopy

Time-of-flight secondary ion mass spectroscopy (ToF SIMS) is a surface characterization technique. Surface mass spectrometry techniques measure the masses of fragment ions that are ejected from the surface of a sample to identify the elements and molecules present. ToF SIMS instruments with mass resolution of 10^{-3} to 10^{-4} amu are achievable. This enables ToF SIMS to be sensitive to ppm/ppb. ToF SIMS has been used in the pharmaceutical arena (Muster and Prestidge, 2002). In this study, face-specific surface chemistries of polymorphs I and III were characterized.

Particle Size Distribution Measurement

It is known that the particle size distribution of a pharmaceutical powder can affect the manufacturability, stability, and bioavailability of immediate-release tablets (Tinke et al., 2005). The Food and Drugs Administration (FDA) recommends that a suitable test method and acceptance criteria be established for the particle size distribution of a drug substance.

Snorek et al. (2007) has discussed the concepts and techniques of particle size analysis and its role in pharmaceutical sciences and gives the range of size measurement methods commonly used and the corresponding approximate useful size range (Snorek et al., 2007). The most readily available laboratory techniques include sieving (Brittain and Amidon, 2003), optical microscopy in conjunction with image analysis, electron microscopy, the Coulter counter, and laser diffraction (Xu et al., 2003). It is usual that a powder shows a distribution of particle sizes often represented as a Gaussian distribution (log normal).

Sieve Analysis

Sieving is a simple, well-established technique to determine the particle size distribution of powders whereby the particles pass through a set of screens of decreasing size due to agitation or sonication. The sample is introduced on the top sieve, and the agitation causes the powder to move through the rest of the sieves, and the particle size distribution is determined from the weight of compound remaining on each sieve. The particle size distribution data is then presented as a percentage of the material retained on each sieve. Like all techniques for particle size analysis, it has its strengths and weaknesses. The major strength of sieve analysis is its relative simplicity. However, the nature of the sieves is such that, for example, acicular crystals may pass through the sieve via their short axis.

Laser Diffraction and Scattering

Laser diffraction has become the most popular method of particle size analysis because of its ease of use, fast analysis times, and high reproducibility (Xu, 2000). The use of this technique is based on light scattered through various angles, which is directly related to the diameter of the

particle. Thus, by measuring the angles and intensity of scattered light from the particles, a particle size distribution can be deduced. It should be noted that the particle diameters reported are the same as those that spherical particles would produce under similar conditions.

Two theories dominate the theory of light scattering; the Fraunhofer and Mie theories. In the former, each particle is treated as spherical and essentially opaque to the impinging laser light. Mie theory, on the other hand, takes into account the differences in refractive indices between the particles and the suspending medium. If the diameter of the particles is above 10 μm , then the size produced by utilizing each theory is essentially the same. However, discrepancies may occur when the diameter of the particles approaches that of the wavelength of the laser source.

The following are the values reported from diffraction experiments:

$D[v,0.1]$ is the size of particles for which 10% of the sample is below this size.

$D[v,0.5]$ is the volume (v) median diameter for which 50% of the sample is below and above this size.

$D[v,0.9]$ gives a size of particle for which 90% of the sample is below this size.

$D[4,3]$ is the equivalent volume mean diameter calculated from equation (4), which is as follows:

$$D[4, 3] = \frac{\sum d^4}{\sum d^3} \quad (4)$$

where d is the diameter of each unit.

$D[3,2]$ is the surface area mean diameter; also known as the Sauter mean.

Log difference represents the difference between the observed light energy data and the calculated light energy data for the derived distribution.

Span is the measurement of the width of the distribution and is calculated from equation (5).

$$\text{Span} = \frac{D[v, 0.9] - D[v, 0.1]}{D[v, 0.5]} \quad (5)$$

The dispersion of the powder is important in achieving reproducible results. Ideally, the dispersion medium should have the following characteristics:

- Should have a suitable absorbency
- Should not swell the particles
- Should disperse a wide range of particles
- Should slow sedimentation of particles
- Should allow homogeneous dispersion of the particles
- Should be safe and easy to use

In terms of sample preparation, it is necessary to deaggregate the samples so that the primary particles are measured. To achieve this, the sample may be sonicated, although there is a potential problem of the sample being disrupted by the ultrasonic vibration. To check for this, it is recommended that the particle dispersion be examined by optical microscopy standards for laser diffraction given in the standard.

The Malvern Mastersizer (Malvern Instruments, Malvern, U.K.) is an example of an instrument that measures particle size by laser diffraction on the basis of the Mie theory, and the Helos laser diffraction instrument (Sympatec GmbH, Clausthal-Zellerfeld, Germany) represents a Fraunhofer-based system.

Although laser light diffraction is a rapid and highly repeatable method in determining the particle size distributions of pharmaceutical powders, the results obtained can be affected by particle shape. For example, Xu et al. (2003) compared the particle size distributions

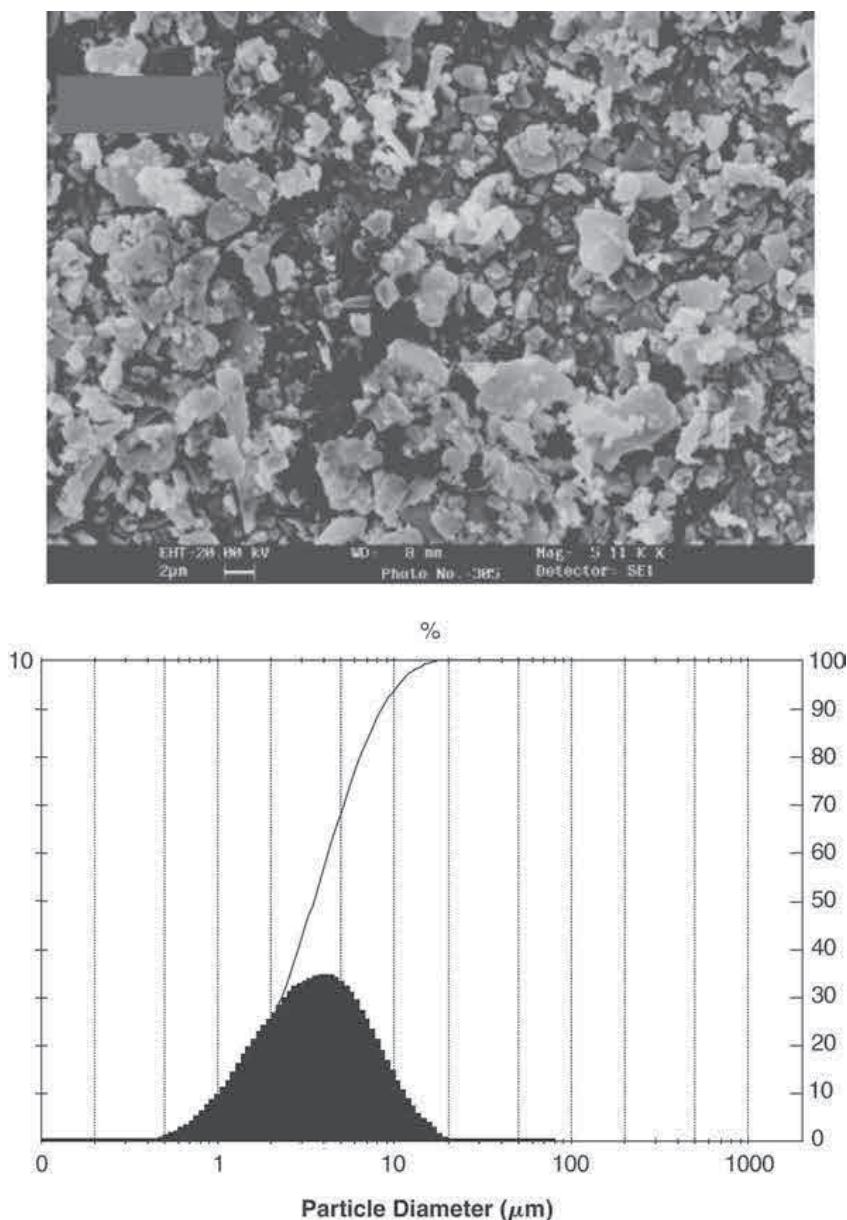


Figure 6 Scanning electron microscopy of a micronized powder and particle size measured by laser diffraction.

obtained from laser diffraction experiments, electrical zone sensing, and dynamic image analysis (DIA). They found that for spherical particles or particles with small aspect ratio, all instruments returned similar results. However, as the shape of the particle size distribution became more extreme, the laser diffraction instrument tended to overestimate the breadth of the size distribution. Thus, when dealing with anisotropic particle shape, caution should be exercised on the quotation of a particle size.

Figure 6 shows the particle size distribution of a micronized powder determined by scanning electron microscopy (SEM) and laser light scattering. Table 3 shows the data obtained from the laser diffraction analysis shown in Figure 6.

Another laser-based instrument, relying on light scattering, is the aerosizer. This is a particle-sizing method based on a time-of-flight principle as described by Niven (1993). The aerosizer with aero-disperser is specifically designed to carry deaggregated particles in an airstream for particle sizing. Mendes et al. (2004) have used this instrument to evaluate the Ventilan RotocapsTM and Bricanyl TubohalerTM DPIs.

Table 3 Particle Size Distribution of a Micronized Powder Measured by Using Laser Diffraction

Size (μm)	Volume under %	Size (μm)	Volume under %	Size (μm)	Volume under %	Size (μm)	Volume under %
0.05	0.00	0.65	1.09	4.30	60.67	28.15	100.00
0.12	0.00	0.81	2.58	5.29	71.18	34.69	100.00
0.15	0.00	1.00	5.08	6.52	80.61	42.75	100.00
0.19	0.00	1.23	8.90	8.04	88.21	52.68	100.00
0.23	0.00	1.51	14.24	9.91	93.69	64.92	100.00
0.28	0.00	1.86	21.22	12.21	97.18	80.00	100.00
0.35	0.00	2.30	29.72	15.04	99.08		
0.43	0.03	2.83	39.38	18.54	99.87		
0.53	0.34	3.49	49.86	22.84	100.00		
Range: 45 mm	Beam: 2.40 mm		Sampler: MS1				Obs': 15.8%
Presentation: 2\$D				Analysis: polydisperse		Residual: 0.117%	
Modifications: none							
Concentration = 0.0062% volume				Density = 1.427 g/cm ³		SSA = 1.6133 m ² /g	
Distribution: volume				D[4,3] = 4.34 μm		D[3,2] = 2.61 μm	
D[v,0.1] = 1.29 μm				D[v,0.5] = 3.50 μm		D[v,0.9] = 8.54 μm	
Span = 2.071E + 00				Uniformity = 6.515E - 01			

Photon Correlation Spectroscopy or Quasi-Elastic Elastic Light Scattering

For submicron materials, particularly colloidal particles, photon correlation spectroscopy (PCS) [quasi-elastic elastic light scattering (QELS)] is the preferred technique. This technique has been usefully reviewed by Phillies (1990). Often this technique is coupled with zeta potential measurements so that the dispersion stability can be assessed. Examples of the use of PCS in the literature include the characterization of nebulized buparvaquone nanosuspensions (Hernandez-Trejo et al., 2005) and the characterization of liposomes (Ruozi et al., 2005). PCS relies on the Doppler shift in the wavelength of the scattered laser light, and from the autocorrelation function, a z-average particle size is derived and can be used to measure particles in the size range 3 nm to 3 μm. In addition to the size of the particles, a polydispersity index (a measure of the width of the distribution) is also derived. An example of a commercial PCS is the Malvern Zetasizer manufactured by Malvern Instruments (U.K.) (Grau et al., 2000).

Image Analysis

Optical microscopy is a simple but powerful technique for the examination of crystal size and shape (Lerke and Adams, 2003). It can give a quick estimation of the average size of crystals, but for a more quantitative measure, the microscopic images need to be coupled with image analysis software to increase the accuracy, decrease the tediousness of manual counting, and minimize operator bias. Recent advances in high-speed camera and more powerful computers have been combined to such an extent that it is now possible to perform DIA. An example of DIA is Sympatec's QicPic, which can capture images of particles in an airstream (see Yu and Hancock, 2008 for details of this technique). In essence, the QicPic uses rear illumination with a visible pulsed (1–500 Hz) light source synchronized with a high-speed camera running at 500 frames per second. The sample is delivered to this detection system via a dry-powder feeder where air is flowing at 100 m/s. During the course of an experiment, approximately 10⁵ particle images are counted. Yu and Hancock compared the data obtained from samples that were spherical or rod-shaped and their mixtures with the measurements obtained from a laser diffraction instrument. The initial analysis indicated that the QicPic overestimated the amount of rod-shaped particles in the mixture, but when other data with respect to apparent density were taken into account, good agreement between the computed and experimental data was obtained.

In an interesting extension to image analysis is its use in following the recrystallization of, for example, amorphous cefadroxil (Parkkali et al., 2000).

Surface Area Measurements

The surface area of a solid pharmaceutical is an important parameter since such secondary properties such as dissolution and bioavailability (as predicted by the Noyes–Whitney equation) can be affected. Surface areas are usually determined by gas adsorption (nitrogen or krypton), and although there are a number of theories describing this phenomenon, the most widely used is the Bruner, Emmet, and Teller (BET) method. Adsorption methods for surface area determination have been reviewed in detail by Sing (1992). Two methods are used, that is, multipoint and single-point.

Without going into too much theoretical detail, the BET isotherm for type II (typical for pharmaceutical powders) adsorption processes is given by equation (6).

$$\left\{ \frac{z}{(1-z)V} \right\} = \frac{1}{cV_{\text{mon}}} + \frac{(c-1)z}{cV_{\text{mon}}} \quad (6)$$

where $z = P/P_o$, V the volume of gas adsorbed, V_{mon} the volume of gas at monolayer coverage, and c is related to the intercept. It can be seen that equation (6) is of the form of a straight line. Thus, by plotting $\{z/(1-z)V\}$ versus z , a straight line of slope $(c-1)/cV_{\text{mon}}$ and intercept $1/cV_{\text{mon}}$ will be obtained. According to the U.S. Pharmacopoeia (USP), the data are considered to be acceptable if, on linear regression, the correlation coefficient is not less than 0.9975, that is, r^2 is not less than 0.995.

Figure 7 shows the full adsorption isotherm of two batches of the micronized powder shown earlier in Figure 6.

It should be noted that, experimentally, it is necessary to remove gases and vapors that may be present on the surface of the powder. This is usually achieved by drawing a vacuum or purging the sample in a flowing stream of nitrogen. Raising the temperature may not always be advantageous. For example, Phadke and Collier (1994) examined the effect of degassing temperature on the surface area of magnesium stearate obtained from two manufacturers. In this study, helium at a range of temperatures between 23°C and 60°C was used in single and

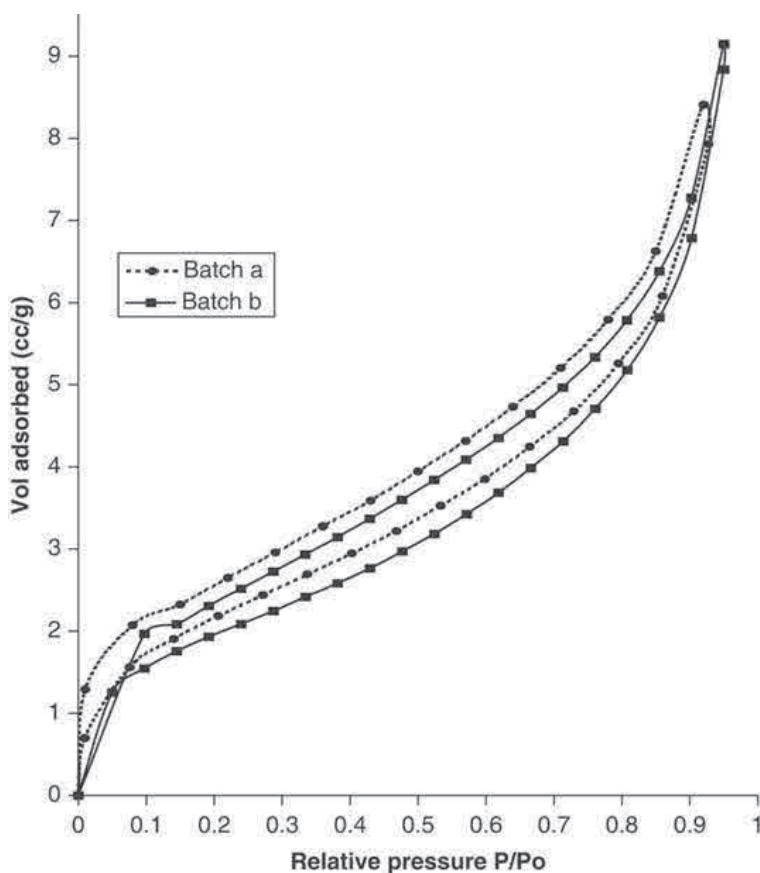


Figure 7 Full type IIb adsorption isotherm for two batches of a micronized powder.

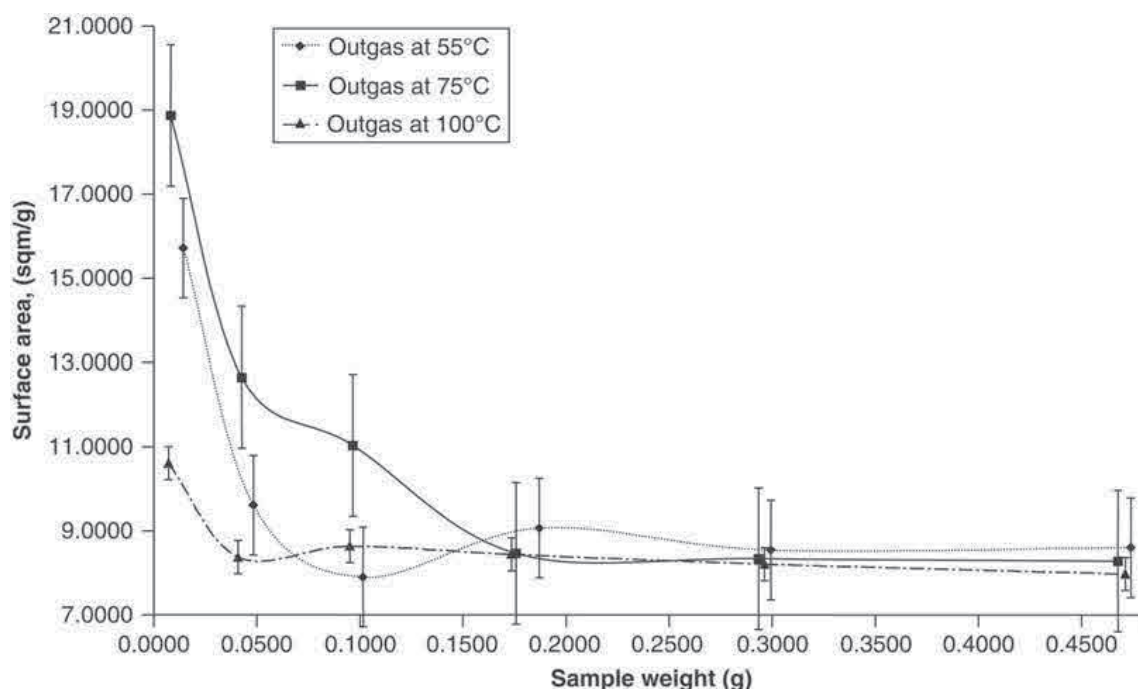


Figure 8 Effect of sample weight and degassing temperature on the surface area of micronized powder.

multipoint determinations. It was found that the specific surface area of the samples decreased with an increase in temperature. From other measurements using DSC and thermogravimetric analysis (TGA), it was found that raising the temperature changed the nature of the samples. Hence, it was recommended that magnesium stearate should not be degassed at elevated temperatures. Further work on the difficulty in measuring the surface area of magnesium stearate has been reported by Andr  s et al. (2001).

Figure 8 shows the effect of sample weight and temperature of degassing on a sample of a micronized powder using a Micromeritics Gemini BET analyzer. From this plot, it can be seen that the weight of the sample can have a marked effect on the measured surface area of the compound under investigation. Therefore, to avoid reporting erroneous surface areas, the sample weight should not be too low and in this case be greater than 300 mg.

In an interesting paper by Joshi et al. (2002a), they reported that after micronization, the specific surface area increased after storage at 25  C. This was attributed to postmicronization stress relief via intraparticle crack formation.

True Density

Density can be defined as the ratio of the mass of an object to its volume. Therefore, the density of a solid is a reflection of the arrangement of molecules in a solid. In pharmaceutical development terms, knowledge of the true density of powders has been used for the determination of the consolidation behavior. For example, the well-known Heckel relation [equation (7)] requires knowledge of the true density of the compound.

$$\ln \left[\frac{1}{(1 - D)} \right] = KP + A \quad (7)$$

where D is the relative density, which is the ratio of the apparent density to the true density, K is determined from the linear portion of the Heckel plot, and P is the pressure. Sun (2005) has pointed out that an inaccurate true density value can affect powder compaction data. Using a novel mathematical model (Sun, 2004), it was shown that to achieve 4% accuracy, a true density with less than 0.28% error was required. The densities of molecular crystals can be increased by compression. For example, while investigating the compression properties of

acetylsalicylic acid using a compaction simulator, increases in the true density were found (Pedersen and Kristensen, 1994).

- Information about the true density of a powder can be used to predict whether a compound will cream or sediment in a metered-dose inhaler (MDI) formulation. The densities of the hydrofluoroalkane (HFA) propellants, 227 and 134a, which have replaced chlorofluorocarbons (CFCs) in MDI formulations, are 1.415 and 1.217 g/cm³, respectively. Traini et al. (2007) have reported the true densities of the inhalation drugs budesonide and formoterol fumarate dihydrate as 1.306 and 1.240 g/cm³, respectively. Suspensions of compounds that have a true density less than these figures will cream (rise to the surface) and those that are denser will sediment. Those that match the density of the propellant will stay in suspension for a longer period (Williams et al., 1998). It should be noted, however, that the physical stability of a suspension is not merely a function of the true density of the material.

The true density is thus a property of the material and is independent of the method of determination. In this respect, the true density can be determined using three methods: displacement of a liquid, displacement of a gas (pycnometry), or floatation in a liquid. These methods of measuring true density have been evaluated by Duncan-Hewitt and Grant (1986). They concluded that whereas liquid displacement was tedious and tended to underestimate the true density, displacement of a gas was accurate but needed relatively expensive instrumentation. As an alternative, the floatation method was found to be simple to use, inexpensive, and, although more time consuming than gas pycnometry, accurate.

Gas pycnometry is probably the most commonly used method in the pharmaceutical industry for measuring true density. For details of the measurement of density by gas pycnometry, the reader should, for example, refer to Pharm Forum 20, 7222 (1994). All gas pycnometers rely on the measurement of pressure changes as a reference volume of gas, typically helium, is added to or deleted from the test cell. Experimentally, measurements should be carried out in accordance with the manufacturers' instructions. However, it is worth noting that artifacts may occur. For example, Figure 9 shows the measured true density of a number of tableting excipients as a function of sample weight. As can be seen, at low sample

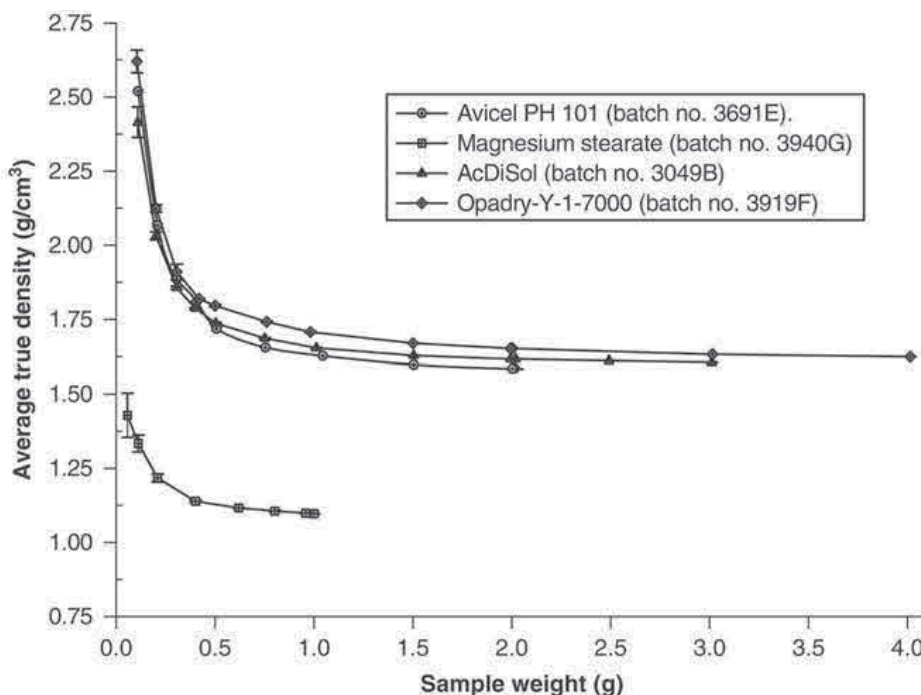


Figure 9 True density as a function of sample mass for some excipients.

weights, the measured true density was seen to increase, making the measurements less accurate. Viana et al. (2002) have systematically investigated pycnometry and showed that accuracies of the technique to the nearest 0.001% g/cm³ could not be guaranteed.

The true density of organic crystals can also be calculated from the crystal structure of the compound and can be accessed via the Mercury program supplied by the Cambridge Crystallographic Data Centre (CCDC). As a further sophistication, Sun (2007) has examined the variability of this value and found that, on average, a relative standard deviation (RSD) of ~0.4% is typical for a calculated crystal structure. He also found that the true density increased as the temperature decreased. The experiments carried out by Viana et al. (2002) pointed out that true densities determined by pycnometry appeared to be less than those calculated from the crystal structure.

Coa et al. (2008) have used two empirically derived predictive methodologies to estimate the true densities of some drug substances. Both the methods showed good agreement with measured values and thus may be valuable when very limited amounts of compound are available for experimental measurements.

Flow and Compaction of Powders

Although at the preformulation stage, only limited quantities of candidate drug are available, any data generated on flow and compaction properties can be of great use to the formulation scientist. The data provided can give guidance on the selection of the excipients to use, the formulation type, and the manufacturing process to use, for example, direct compression or granulation. It is important that once the habit and size distribution of the test compound have been determined, the flow and compaction properties are evaluated, if the intended dosage form is a solid dosage form. York (1992) has reviewed the crystal engineering and particle design for the powder compaction process, and Thalberg et al. (2004) has compared the flowability tests for inhalation powders (ordered mixtures). The techniques investigated include the poured bulk density, compressed bulk density, an instrument known as the AeroFlow, and a uniaxial tester. Other shear testing includes ring shear testers (Hou and Sun, 2008), the angle of repose, Carr's index, Hausner ratio, etc. (see Hickey et al., 2007a, b for a good review of the various methods available).

The European Pharmacopoeia (Ph Eur) contains a test on flowability of powders based on how a powder flows vertically out of a funnel. Using data from a range of excipients, Schüssele and Bauer-Brandl (2003) have argued that the powder flow using this technique should be expressed as volume per unit time rather than mass per unit time as recommended by the Ph Eur. Soh et al. (2006) have proposed some new indices of powder flow based on their avalanching behavior, that is, avalanche flow index (AFI) and cohesive interaction index (CoI), using the commercially available AeroFlowTM instrument.

The compaction properties of the API are critical in their formulation, and such parameters such as yield stress and strain rate sensitivity (SRS) and their measurement are important.

The compression of flow powders is dealt with in more detail in chapter 11 "Oral Solid Dosage Forms. With respect to the preformulation screening of candidate drugs for solid dosage forms, a protocol to examine their compression properties devised by Aulton and Wells (1988) can be carried out. Their scheme is shown in Table 4. Essentially, the compound is compressed using an IR and die set under 10 tons of pressure, and the resulting tablets are tested with regard to their crushing strength.

The interpretation of crushing strengths is as follows. If the crushing strengths are of the order $B > A > C$, the material probably has plastic tendencies. Materials that are brittle are usually independent of the scheme, while elastic material can behave in a variety of ways, for example,

1. A will cap or laminate,
2. B will probably maintain integrity but will be very weak, and
3. C will cap or laminate.

Figure 10 shows a scanning electron micrograph of a compound (remacemide HCl) that had poor compression properties. Notice how the top of the compact has partially detached

Table 4 Compression Protocol

	500 mg drug + 1% magnesium stearate		
	A	B	C
Blend in a tumbler mixer for	5 min	5 min	30 min
Compress in 13 mm die set	75 MPa	75 MPa	75 MPa
Compacts in a hydraulic press at dwell time of	2 sec	30 sec	2 sec
Store tablets in sealed container at room temperature to allow equilibration	24 hr	24 hr	24 hr
Perform crushing strength			

Source: From Aulton and Wells (1988).

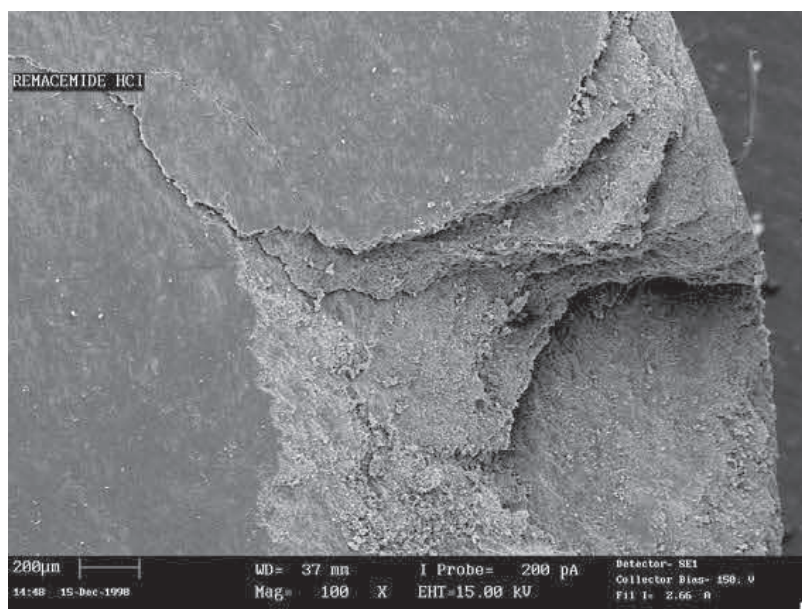


Figure 10 Scanning electron microscopy of a compound that undergoes capping and lamination.

(capping) and how the compact has separated into layers (lamination) (Yu et al., 2008). For further details on remacemide HCl, an *N*-methyl-D-aspartate (NMDA) antagonist that was investigated as a potential treatment of epilepsy, Parkinson's and Huntingdon's diseases (Schachter and Tarsy, 2000).

As shown by Otsuka et al. (1993), it is always worth checking the effect of compression on a powder if the compound is known to be polymorphic. Using the XRPD patterns of chlorpropamide forms A and C, they examined the effect of temperature and compression force on the deagglomerated powders and found that both the forms were mutually transformed.

Computational methods of predicting the mechanical properties of a powder from the crystal structure are now being explored. There appears to be a relationship between the indentation hardness and the molecular structure of organic materials. However, a prerequisite for predicting indentation hardness is knowledge of the crystal structure (Roberts et al., 1994). Payne et al. (1996) have used molecular modeling to predict the mechanical properties of aspirin and forms A and B of primidone. The predicted results of the Young's modulus were found to be in good agreement with those determined experimentally, and thus, compaction measurements might not always be necessary if they are difficult to perform.

Color

Color is a useful observation when describing different batches of drug substance since it can sometimes be used as an indicator of solvent presence, or, more importantly, an indication of degradation. In addition, subtle differences in color may be due to variations in the particle size distribution. Usually, color is subjective and is based on individual perception. However,

more quantitative measurements can be obtained by using, for example, reflectance spectroscopy (Berberich et al., 2002, Rhee et al., 2008). The method is based on the CIELAB color system, which gives a precise representation of the color perception of humans. For full details of the CIELAB system, the reader is referred to the paper by Rhee et al. (2008) or the USP. Rhee et al.'s conclusions were that spectrophotometry was a useful drug-excipient screening tool, particularly because it was cheaper and faster than other methods. However, they added a note of caution by stating that the values obtained were only comparable when the measurements were carried out on comparable instruments.

Stark et al. (1996) have observed color changes during accelerated stability testing of captopril tablets, flucloxacillin sodium capsules, cefoxitin sodium powder for injection, and theophylline CR (controlled release) tablets. Under ambient conditions, only the flucloxacillin sodium and cefoxitin were observed to show any significant coloring. However, under stress conditions of accelerated stability testing, a linear relationship between color formation and the drug content of the formulations was found except for the theophylline tablets, where discoloration occurred in the absence of any significant degradation. Interestingly, the rate of coloring was found to obey the Arrhenius equation. The authors proposed that the shelf life of the formulations could be specified using the Commission Internationale d'Eclairage or International Commission on Illumination (CIE) system for color.

Electrostaticity

Powders can acquire an electrostatic charge during processing, the extent of which is related to the aggressiveness of the process and the physicochemical properties (Lachiver et al., 2006). It is important since it has been shown that, for example, electrostatic deposition is among the most important factors in deposition of drug substances in the lung (Hinds, 1999). Table 5, from BS5958, gives the range of values that arise because of various processes. Static electrification of two dissimilar materials occurs by the making and breaking of surface contacts (triboelectrification) (Watanabe et al., 2007). Simply put, charge accumulation is due to electron transfer and depends on a number of factors such as surface resistivity of the materials in contact, the roughness of the surface, and contaminations (Elajna et al., 2007). Thus, the extent of the electrostatic charge accumulation will increase as the surfaces collide and contact, for example, by increasing the agitation time and intensity of a powder in a mixer. The net results will therefore increase the spot charge over the particle surfaces and adhesive characteristics. This technique has been used to prepare drug-carrier systems known as an interactive mixture.

The net charge on a powder may be either electropositive or electronegative. Although the process is not fully understood, it is generally accepted that charging occurs as a result of electron transfer between materials of different electrical properties. It has been shown that increased RH of the atmosphere has the effect of decreasing the electrostaticity of powders (Rowley and Macklin, 2007). The electrostatic charge of bulk solids can be measured using a Faraday pail (Carter et al., 1992).

The electrostatic charges on the surface of a powder can affect the flow properties of powders. An electric detector can determine the electric field generated by the electrostatic charges on the surface of the powder. This acts as a voltmeter and allows the direct determination of both polarity and absolute value of the electrostatic field. Rowley (2001) has reviewed the ways in which the electrostatic interactions in pharmaceutical powders can be quantified.

Table 5 Mass Charge Density Arising from Various Operations (BS5958)

Operation	Mass charge density ($\mu\text{C/kg}$)
Sieving	10^{-3} to 10^{-5}
Pouring	10^{-1} to 10^{-3}
Scroll feed transfer	1 to 10^{-2}
Grinding	1 to 10^{-1}
Micronizing	10^2 to 10^{-1}

Source: Reproduced from BS5958 with permission of BSI under licence number 2001SK/0091. Complete standards can be obtained from BSI Customer Services, 389 Chiswick High Road, London, W4 4AL.

Kwok et al. (2008) have investigated the electrostatic properties of DPI aerosols of Pulmicort® and Bricanyl® Turbuhalers®. In this study, they investigated the effect of RH on the performance of these inhalers and found that although both generated significant charge, different RHs did not affect their mass output. Bricanyl appeared to be more affected by the RH of the atmosphere, whereby the charge decreased with increasing RH. Pulmicort, on the other hand, showed a decrease in particle charge at 40% RH and then increased with increasing RHs. Young et al. (2007) also showed that the electrostaticity of micronized sulbutamol sulfate was reduced at RHs greater than 60%. In an interesting application of AFM, Bunker et al. (2007) observed the charging of a single particle of lactose as it was either dragged or tapped on a glass slide. They also showed that as the RH increased, the charge was dissipated.

Caking

Caking can occur after storage and involves the formation of lumps or the complete agglomeration of the powder. A number of factors have been identified that predispose a powder to exhibit caking tendencies. These include static electricity, hygroscopicity, particle size, and impurities of the powder, and, in terms of the storage conditions, stress temperature, RH, and storage time can also be important. The caking of 11-amino undeconoic acid has been investigated, and it was concluded that the most important cause of the observed caking with this compound was its particle size (Provent et al., 1993). The mechanisms involved in caking are based on the formation of five types of interparticle bonds. These are

- bonding resulting from mechanical tangling,
- bonding resulting from steric effects,
- bonds via static electricity,
- bonds due to free liquid, and
- bonds due to solid bridges.

The caking tendency of a development compound was investigated when it was discovered to be lumpy after storage. An experiment was performed on the compound whereby it was stored at different RHs (from saturated salt solutions) for four weeks in a dessicator. Results revealed that caking was evident at 75% RH, with the compound forming loosely massed porous cakes (Table 6). Thermogravimetric analysis of the samples showed that caked samples lost only a small amount of weight on heating (0.62% w/w), which indicated that only low levels of moisture were required to produce caking for this compound.

It is known that micronization of compounds can lead to the formation of regions with a large degree of disorder, which, because of their amorphous character, are more reactive compared with the pure crystalline substance. This is particularly true on exposure to moisture and can lead to problems with caking, which is detrimental to the performance of the product. It has been argued that these amorphous regions transform during moisture sorption because of surface sintering and recrystallization at relative humidities well below the critical RH. Fitzpatrick et al. (2007) have shown that when amorphous lactose is raised above its T_g , it becomes sticky, cohesive, and eventually cakes (Listiohadi et al., 2008).

Table 6 Effect of moisture on the caking of a development compound

% Relative humidity	Moisture content (%)	Appearance and flow properties
0	0.31	Free-flowing powder; passed easily through sieve
11.3	0.24	Ditto
22.5	0.27	Less-flowing powder
38.2	0.32	Base of powder bed adhered to petri dish, however, material above this flowed
57.6	0.34	Less free flowing
75.3	0.62	Material caked
Ambient	0.25	Base of powder adhered to petri dish

Polymorphism Issues

Because polymorphism can have an effect on so many aspects of drug development, it is important to fix the polymorph (usually the stable form) as early as possible in the development cycle and probably before campaign 3. The FDA has produced guidance for industry: ANDAs: Pharmaceutical Solid Polymorphism Chemistry, Manufacturing, and Controls Information (<http://www.fda.gov/cder/guidance/7590fnl.htm>). Raw et al. (2004) have reported this in the literature, but the reader should consult the FDA Web site for the most up-to-date guidance.

While it is hoped that the issue polymorphism is resolved during prenomination and early development, it can remain a concern when the synthesis of the drug is scaled up into a larger reactor or transferred to another production site. In extreme cases and despite intensive research, work may have only produced a metastable form and the first production batch produces the stable form. Dunitz and Bernstein (1995) have reviewed the appearance of and subsequent disappearance of polymorphs. Essentially, this describes the scenario whereby, after nucleation of a more stable form, the previously prepared metastable form could no longer be made.

The role of related substances in the case of the disappearing polymorphs of sulphathiazole has been explored (Blagden et al., 1998). These studies showed that a reaction by-product from the final hydrolysis stage could stabilize different polymorphic forms of the compound depending on the concentration of the by-product. Using molecular modeling techniques, they were able to show that ethamidodisulphthiazole, the by-product, influenced the hydrogen bond network and hence form and crystal morphology.

In the development of a reliable commercial recrystallization process for dirithromycin, Wirth and Stephenson (1997) proposed that the following scheme should be followed in the production of Candidate Drugs

1. Selection of the solvent system
2. Characterization of the polymorphic forms
3. Optimization of process times, temperature, solvent compositions, etc.
4. Examination of the chemical stability of the drug during processing
5. Manipulation of the polymorphic form, if necessary

While examples of disappearing polymorphs exist, perhaps more common is the crystallization of mixtures of polymorphs. Many analytical techniques have been used to quantitate mixtures of polymorphs, for example, XRPD has been used to quantitate the amount of cefepime: 2HCl dihydrate in cefepime, 2HCl monohydrate (Bugay et al., 1996). As noted by these workers, a crucial factor in developing an assay based on a solid-state technique is the production of pure calibration and validation samples. Moreover, while the production of the forms may be straightforward, production of homogeneously mixed samples for calibration purposes may not be so. To overcome this problem, a slurry technique was employed, which satisfied the NDA requirements, to determine the amount of one form in the other. The criteria employed are as follows:

1. A polymorphic transformation did not occur during preparation or analysis.
2. A limit of detection of 5% (w/w) of the dihydrate in monohydrate.
3. Ease of sample preparation, data acquisition, and analysis.
4. Ease of transfer to a quality control (QC) environment.

Calibration samples were limited to a working range of 1% to 15% w/w, and to prepare the mixes, samples of each form were slurried in acetone to produce a homogeneous mixture of the two.

With respect to solid dosage forms, there have been a few reports on how processing affects the polymorphic behavior of compounds (Morris et al., 2001). For example, the effect of polymorphic transformations that occurred during the extrusion-granulation process of carbamazepine granules has been studied by Otsuka et al. (1997). Results showed that granulation using 50% ethanol transformed form I into the dihydrate during the process. Wet

granulation (using an ethanol-water solution) of chlorpromazine hydrochloride was found to produce a phase change (Wong and Mitchell, 1992). This was found to have some advantage since form II (the initial metastable form) was found to show more severe capping and lamination compared with form I, the (stable) form produced on granulation. Using a range of compounds, Wikström et al. (2008) have studied factors that influence the anhydrate-to-hydrate conversion during wet granulation and concluded that the transformation was a function of such things as the compound's solubility, surface properties, seeds, and the shear forces involved in wet granulation. However, even this paper noted that better models were needed to understand the complexities of the transformations. Solvate formation may have some advantages. For example, Di Martino et al. (2007) showed that the desolvated dioxane solvate of nimesulide had better tableting properties than the known polymorphs of the compound, which appears to represent a viable method of improving the compression properties of drug substances.

Polymorphism is not only an issue with the compound under investigation, that is, excipients also show variability in this respect. For example, it is well known that the tablet lubricant magnesium stearate can vary depending on the supplier. In one study, Wada and Matsubara (1992) examined the polymorphism with respect to 23 batches of magnesium stearate obtained from a variety of suppliers. Using DSC they classified the batches into six groups—interestingly, the polymorphism was not apparent by XRPD, IR, or SEM observations. In another report, Barra and Somma (1996) examined 13 samples of magnesium stearate from three suppliers. They found that there was variation not only between the suppliers but also in the lots supplied by the same manufacturer.

It is well known that polymorphism is a function of temperature and pressure, thus under the compressive forces that compounds experience under tableting conditions phase transformations may be possible. However, Németh et al. (2005) have sounded a note of caution when conducting analysis of compressed samples. They reported that DSC measurements tended to amplify the transformation of form B to form A of famotidine.

SOLUTION FORMULATIONS

Development of a solution formulation requires a number of key pieces of preformulation information. Of these, solubility (and any pH dependence) and stability are probably the most important. As noted by Meyer et al. (2007), with over 350 parenteral products marketed worldwide, these probably represent the most common solution formulation type. The principles and practices governing the formulation development of parenteral products have been reviewed by Sweetana and Akers (1996). Strickley (1999, 2000, 2001) has produced a useful series of papers detailing the formulation of a large number of compounds delivered by the parenteral route. A further review by Strickley (2004) has detailed solubilizing excipients for both oral and injectable formulations. Rowe et al. (1995) have described an expert system for the development of parenteral products (see also chapter 9).

Solubility Considerations

One of the main problems associated with developing a parenteral or any other solution formulation of a compound is its aqueous solubility. For a poorly soluble drug candidate, there are several strategies for enhancing its solubility. These include pH manipulation, cosolvents, surfactants, emulsion formation, and complexing agents; combinations of these methods can also be used (Ran et al., 2005). More sophisticated delivery systems, for example, liposomes, can also be considered.

pH Manipulation

Since many compounds are weak acids or bases, their solubility will be function of pH. Figure 11 shows the pH-solubility curve for sibenadit HCl salt with pK_a s at 6.58 and 8.16. When the acid-base titration method (Serrajuddin and Mufson, 1985) was used, the solubility curve showed a minimum pH between 6 and 8. Below this pH region, the solubility increased

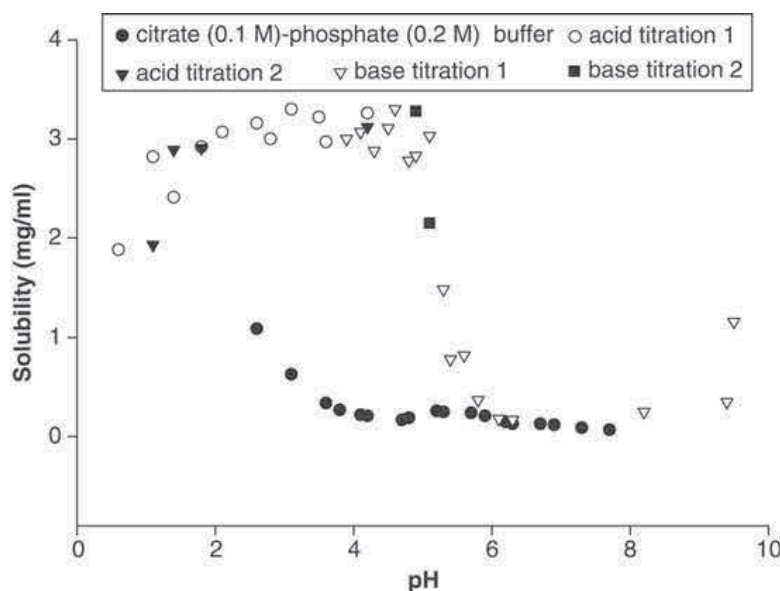


Figure 11 pH-solubility curve of sebenidet hydrochloride.

as the pK_a was passed to reach a maximum between pH 2 and 4 and then decreased because of the common ion effect. As the second pK_a was passed in the alkaline region, the solubility again increased. However, when the solubility experiments were performed in 0.2 M citrate-phosphate buffer, the solubility of the compound decreased, and this illustrates the effect that ionic strength can have on drug solubility. Clearly, the region between pH 2 and 5 represents the best area to achieve the highest solubility. However, caution should be exercised if the solution needs to be buffered, since this can decrease the solubility, as in this case. Myrdal et al. (1995) found that a buffered formulation of a compound did not precipitate on dilution and did not cause phlebitis. In contrast, the unbuffered drug formulation showed the opposite effects. These results reinforce the importance of buffering parenteral formulations instead of simply adjusting the pH.

Cosolvents

The use of cosolvents has been utilized quite effectively for some poorly soluble drug substances. It is probable that the mechanism of enhanced solubility is the result of the polarity of the cosolvent mixture being closer to the drug than in water. This was illustrated in a series of papers by Rubino and Yalkowsky (1984, 1985, 1987), who found that the solubilities of phenytoin, benzocaine, and diazepam in cosolvent and water mixtures were approximated by the log-linear equation (8).

$$\log S_m = f \log S_c + (1 - f) \log S_w \quad (8)$$

where S_m is the solubility of the compound in the solvent mix, S_w the solubility in water, S_c the solubility of the compound in pure cosolvent, f the volume fraction of cosolvent, and σ the slope of the plot of $\log (S_m/S_w)$ versus f . Furthermore, they related σ to indexes of cosolvent polarity such as the dielectric constant, solubility parameter, surface tension, interfacial tension, and octanol-water partition coefficient.

It was found that the aprotic cosolvents gave a much higher degree of solubility than the amphiprotic cosolvents. This means that if a cosolvent can donate a hydrogen bond, it may be an important factor in determining whether it is a good cosolvent. Deviations from log-linear solubility were dealt with in a subsequent paper (Rubino and Yalkowsky, 1987).

Figure 12 shows how the solubility of a development drug increases in a number of water-solvent systems.

Care must be taken when attempting to increase the solubility of a compound, that is, a polar drug might actually show a decrease in solubility with increasing cosolvent composition (Gould et al., 1984).

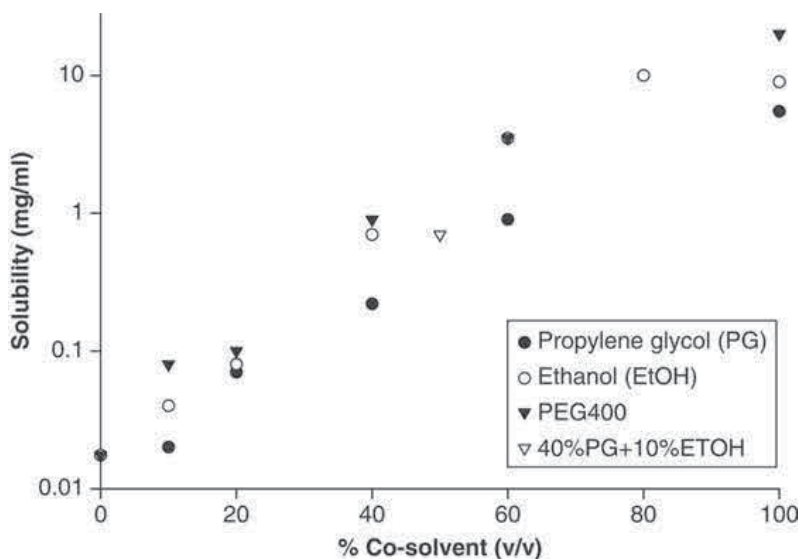


Figure 12 Solubility as a function of cosolvent volume for a development compound.

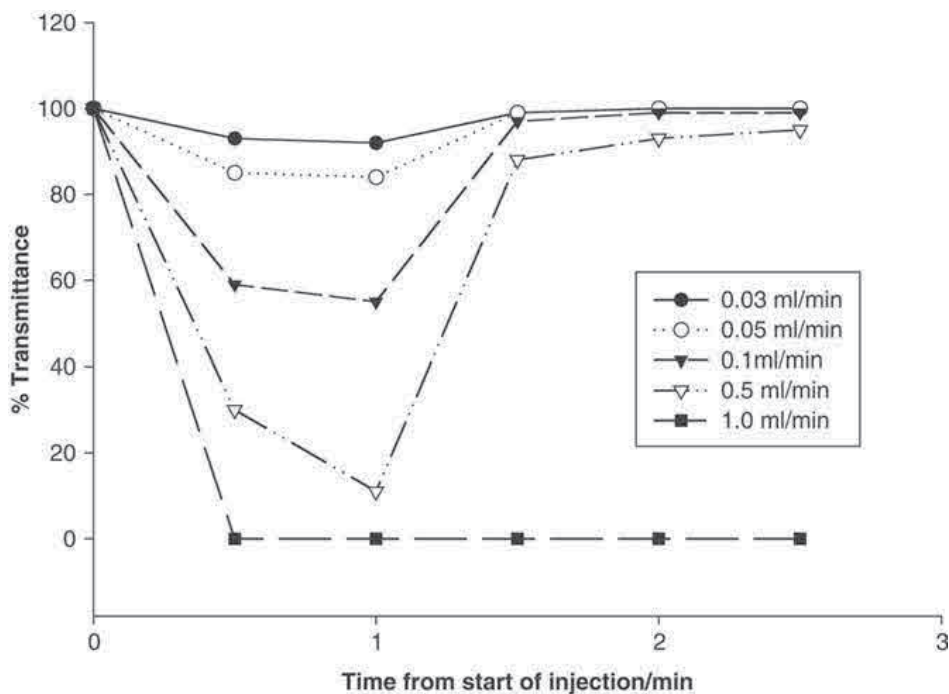


Figure 13 Effect of flow rate on the precipitation of a polyethylene glycol 400 solution of a drug.

It is often necessary to administer a drug parenterally at a concentration that exceeds its aqueous solubility. Cosolvents offer one way of increasing drug solubility, but the amount of cosolvent that can be used in a parenteral intravenous (IV) formulation is often constrained by toxicity considerations. It may cause hemolysis (Amin, 2006), or the drug may precipitate when diluted or injected, causing phlebitis (Johnson et al., 2003). Prototype formulations are often tested on animals, which is undesirable if a reliable *in vitro* technique can be employed.

Yalkowsky and coworkers (1983) have developed a useful *in vitro* technique based on UV spectrophotometry for predicting the precipitation of a parenteral formulations *in vivo* following injection. Figure 13 shows the effect of injection rate on the transmittance at 600 nm of a polyethylene glycol (PEG) 400 formulation of a compound being introduced into flowing saline. As shown, the faster the injection rate, the more precipitation was detected by the

spectrophotometer. This simple technique can be used to assess whether precipitation of a compound might occur on dilution or injection. Johnson et al. (2003) have now validated this approach for screening formulations.

Narazaki et al. (2007a,b) have developed equations for estimating the precipitation of pH-cosolvent solubilized formulations. The equation takes account of the effect of the cosolvent on the pK_a of the compound and any buffering components, which have determining effects on its solubility. In the case of the model compound used, phenytoin, more precipitation occurred on dilution when compared with a pH-controlled formulation.

While cosolvents can increase the solubility of compounds, on occasion, they can have a detrimental effect on their stability. For example, a parenteral formulation of the novel antitumor agent carzelsin (U80,244) using a PEG 400/absolute ethanol/polysorbate 80 (PET) formulation in the ratio 6:3:1 v/v/v has been reported (Jonkman-De Vries et al., 1995). While this formulation effectively increased the solubility of the compound, this work showed that interbatch variation of PEG 400 could affect the stability of the drug because of pH effects.

One point that is often overlooked when considering cosolvents is their influence on buffers or salts. Since these are conjugate acid-base systems, it is not surprising that introducing solvents into the solution can result in a shift in the pK_a of the buffer or salt. These effects are important in formulation terms, since many injectable formulations that contain cosolvents also contain a buffer to control the pH (Rubino, 1987).

Emulsion Formulations

Oil-in-water (o/w) emulsions have been successfully employed to deliver drugs with poor water solubility (Date and Nagarsenker, 2008). In preformulation terms, the solubility of the compound in the oil phase (often soybean oil) is the main consideration while using this approach. However, the particle size of the emulsion and its stability (physical and chemical) also need to be assessed (Tian et al., 2007). Ideally, the particle size of the emulsion droplets should be in the colloidal range to avoid problems with phlebitis. For example, Intralipid 10% (a soybean o/w emulsion) was found to consist of “artificial chylomicrons” (oil droplets) with a mean diameter of 260 nm and liposomes with a diameter of 43 nm (Férézou et al., 2001). To achieve this size, a microfluidizer should be used, since other techniques may produce droplets of a larger size, as shown in Table 7 (Lidgate, 1990). Emulsions are prepared by homogenizing the oil in water in the presence of emulsifiers, for example, phospholipids, which stabilize the emulsion via a surface charge and also a mechanical barrier. Intravenous emulsions can be sterilized by autoclaving, which gives a high level of assurance of sterility. However, careless aseptic techniques can compromise the patient. In this situation, the inclusion of antimicrobial additives could be considered. To this end, Han and Washington (2005) have investigated the effect of antimicrobial additives on the stability of Diprivan[®], an intravenous anesthetic emulsion.

The particle size and zeta potential of emulsions can be measured using instruments that combine PCS and surface charge measurements (Tian et al., 2007). Driscoll et al. (2001) have compared a light obscuration (LO) and laser diffraction to examine the stability of parenteral nutrition mixtures-based intravenous emulsions. From this study, they concluded that LO was a better technique for detecting globules greater than 5 μm in diameter. They recommended two key measurements, that is, the mean droplet size and the large droplet size, since without these it is impossible to guarantee the safety of the emulsion (large droplets can cause thrombophlebitis).

Table 7 Size of Emulsion Droplets Produced by Various Methods

Method of manufacture	Particle size (μm)
Vortex	0.03–24
Blade mixer	0.01–8
Homogenizer	0.02–2
Microfluidizer	0.07–0.2

Source: From Lidgate (1990), reproduced with permission.

Physical instability of emulsions can take a number of forms, for example, creaming, flocculation, coalescence, or breaking, while chemical instability can be due to hydrolysis of the stabilizing moieties. To assess the stability of the emulsion, heating and freezing cycles as well as centrifugation can be employed (Yalabik-Kas, 1985b). Chansiri et al. (1999) have investigated the effect of steam sterilization (121°C for 15 minutes) on the stability of o/w emulsions. They found that emulsions with a high negative zeta potential did not show any change in their particle size distribution after autoclaving. Emulsions with a lower negative value, on the other hand, were found to separate into two phases during autoclaving. Because the stability of phospholipids-stabilized emulsion is dependent on the surface charge, they are normally autoclaved at pH 8 to 9. Similarly, Han et al. (2001) found that when two formulations of propofol were shaken and subjected to a freeze-thaw cycle, the formulation that had a more negative zeta potential (−50 vs. −40 mV) was more stable. There was also a difference in pH of the formulations, with the less stable formulation having a pH between 4 and 5 compared with pH 8 for the more stable formulation (AstraZeneca's Diprivan).

An interesting extension of this approach of solubilizing a poorly soluble compound is the SolEmuls[®] technology described by Junghanns et al. (2007). In this technique, a nanosuspension of amphotericin was generated, mixed with a Lipofundin[®], a conventional lipidic emulsion, and then subjected to high-pressure homogenization. Results indicated that this formulation approach produced better antifungal effects when compared with the commercially available Fungizone[®].

In recent years, microemulsions have been investigated as a way of solubilizing drugs for intravenous delivery (Date and Nagarsenker, 2008). In contrast to the conventional emulsions described above, microemulsions are thermodynamically stable, complex dispersions consisting of micro domains of oil and water, which are stabilized by alternating films of surfactants and co-surfactants. The droplet size of microemulsions is generally less than 150 nm. One feature of microemulsions is that they are clear in contrast to the milk-like appearance of the conventional emulsions.

Stability Considerations

The second major consideration with respect to solution formulations is stability. The stability of pharmaceuticals, from a regulatory point of view, is usually determined by forced degradation studies. These studies provide data on the identity of degradants, degradation pathways, and the fundamental stability of the molecule. Guidance for the industry on how to conduct stability testing of new drug substances and products is given in the ICH guideline Q1A (R2). See Reynolds et al. (2002) and Alsante et al. (2007) for a detailed account on the regulatory requirements of forced degradation studies and recommended degradation conditions.

Notari (1996) has presented some arguments regarding the merits of a complete kinetic stability study. He calculated that with reliable data and no buffer catalysis, sixteen experiments were required to provide a complete kinetic stability study. If buffer ions contribute to the hydrolysis, then each species contributes to the pH-rate expression. Thus, for a single buffer, for example, phosphate, a minimum of six experiments were required. A stock solution of the compound should be prepared in an appropriate solvent and a small aliquot (e.g., 50 µL) added to, for example, a buffer solution at a set pH. This solution should be maintained at a constant temperature, and the ionic strength may be controlled by the addition of KCl (e.g., $I = 0.5$). After thorough mixing, the solution is sampled at various time points and assayed for the compound of interest. If the reaction is very fast, it is recommended that the samples be diluted into a medium that will stop or substantially slow the reaction, for example, a compound that is unstable in acid may be stable in an alkaline medium. Cooling the solution may also be useful. Slow reactions, on the other hand, may require longer-term storage at elevated temperature. In this situation, solutions should be sealed in an ampoule to prevent loss of moisture. If sufficient compound is available, the effect of, for example, buffer concentration should be investigated. Of course, such studies can be automated, for example, Symyx Technologies (Santa Clara, California, U.S.) offer their Automated Forced Degradation System for high-throughput forced degradation studies. This platform produces degradation libraries of stressed samples of liquid formulations, which are then heated and sampled over

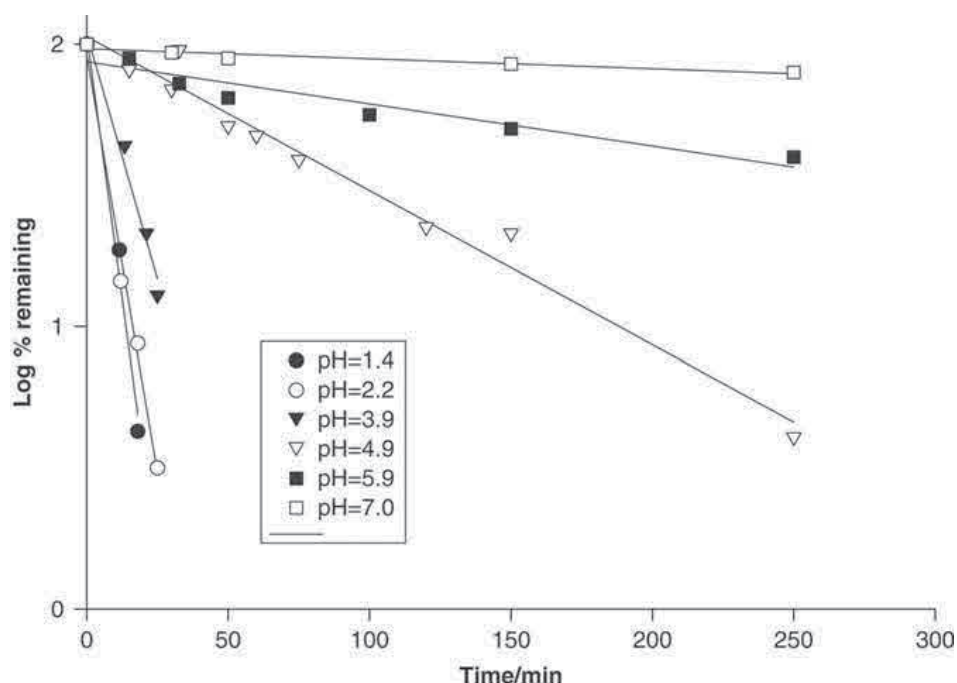


Figure 14 First-order hydrolysis decomposition of a compound (25°C).

time at 55°C, 70°C, and 85°C, and the compound degradation is followed with time. From these measurements, library arrays of first-order kinetic plots are generated, and predictions of room temperature stability of the compound are produced (Carlson et al., 2005).

The first-order decomposition plot of an acid-labile compound with respect to pH is shown in Figure 14. Clearly, this compound is very acid labile, and even at pH 7, some decomposition is observed. A stable solution formulation would, therefore, be difficult to achieve in this pH range. However, a solution formulation at lower pHs might be possible, depending on how long it needed to be stored. To get an estimate of how long this might be, Arrhenius experiments should be undertaken. As an example of this methodology, Jansen et al. (2000) followed the decomposition of gemcitabine, formulated as a lyophilized powder, at pH 3.2 at four different temperatures from which an Arrhenius plot was used to calculate the decomposition rates at lower temperatures. From the data generated, they concluded that a solution formulation of gemcitabine was feasible if the solution was stored in a refrigerator.

A detailed paper on the mechanistic interpretation of pH-rate profiles is that by Loudon (1991). Van der Houwen et al. (1997) have reviewed the systematic interpretation of pH degradation profiles. The rate profiles obtained when the pH is varied can take a number of forms. However, Loudon (1991) makes the point that they “usually consist of linear regions of integral slope connected by short curved segments.” Indeed, the linear regions generally have slopes of -1 , 0 , or $+1$, and “any pH-rate profile can be regarded as a composite of fundamental curves.”

It is also possible that compounds may be formulated in cosolvent systems for geriatric or pediatric use where administration of a tablet would be difficult (Chang and Whitworth 1984). In addition, cosolvents are routinely employed in parenteral formulations to enhance the solubility of poorly soluble drugs. For example, Tu et al. (1989) have investigated the stability of a nonaqueous formulation for injection based on 52% *N,N*-dimethylacetamide and 48% propylene glycol. By stressing the preparation with regard to temperature, they found that by using Arrhenius kinetics, the time for 10% degradation at 25°C would be 885 days. The solution also discolored when stressed. Furthermore, it is also sometimes useful to assess the effect of ethanol/acid on the stability of compounds that can be taken concurrently, for example, temazepam (Yang, 1994).

Stability to Autoclaving

For parenteral formulations, a sterile solution of the compound is required. According to Meyer et al. (2007), one-third of the 350 parenteral products on sale worldwide are multi-dose formulations, which require the inclusion of an antimicrobial preservative. The most commonly used preservatives are benzyl alcohol, chlorobutanol, m-cresol, phenol, phenox-yethanol, propylparaben, and thiomersal. Of these, benzyl alcohol and combinations of methyl and propylparaben are the most popular. See Meyer et al. (2007) for further details of the use of preservatives in parenteral formulations. Of course, one of the limiting factors of the use of a preservative is its compatibility with the active ingredient, and these studies should be undertaken during the preformulation stage of development. In addition, other formulation ingredients may affect the effectiveness of the antimicrobial agent (Meyer et al., 2007).

A terminal sterilization method is preferred, rather than aseptic filtration, because there is a greater assurance of achieving sterility. As noted by Moldenhauer (1998), the regulatory authorities will require a written justification to explain why a product is not terminally sterilized. Therefore, for a sterile formulation product, it is mandatory to assess whether it is stable to autoclaving as part of any preformulation selection process. Autoclaving (usually 15 minutes at 121°C) at various pHs is undertaken after which the drug solutions should be evaluated for impurities, color, pH, and degradation products. Clearly, if one compound shows superior stability after autoclaving, then this will be the one to take forward.

The effect of the autoclave cycle, that is, fill, heat-up, peak dwell, and cool-down on the theoretical chemical stability of compounds intended for intravenous injection, has been investigated by Parasrampur et al. (1993). Assuming first-order degradation kinetics, that is, hydrolysis, the amount of degradation was calculated for any point during the above process. Although the results were calculated for the first-order kinetics, the authors estimated that the calculations were applicable to other reaction orders, that is, zero and second.

Acceptable reasons for not proceeding with a terminally sterilized product are

- pH changes,
- color changes,
- carbonate buffering loss,
- container closure problems, and
- drug or excipient degradation.

Effect of Metal Ions and Oxygen on Stability

After hydrolysis, oxidation is the next most important way by which a drug can decompose in both the solid and liquid states. It is a complex process that can take place by way of such mechanisms as autoxidation, nucleophilic or electrophilic additions, and electron transfer reactions (Hovorka and Schneich, 2001). In addition, some excipients have been shown to contain impurities (such as peroxides and metal ions), which can promote oxidative degradation. Therefore, in formulation terms, the removal of oxygen and trace metal ions and the exclusion of light may be necessary to improve the stability of oxygen-sensitive compounds (Waterman et al., 2002). Formulation aids to this end include antioxidants and chelating agents and, of course, the exclusion of light where necessary. As an example, Li et al. (1998) showed that a formulation of AG2034 could be stabilized through using nitrogen in the ampoule headspace and the inclusion of an antioxidant. Antioxidants are substances that should preferentially react with oxygen and hence protect the compound of interest toward oxidation. A list of water- and oil-soluble antioxidants is given in Table 8 (Akers, 1982).

Reformulation screening of the antioxidant efficiency in parenteral solutions containing epinephrine has been reported by Akers (1979), who concluded that screening was difficult on the basis of the redo potential, and complicated by a complex formulation of many components. To assess the stability of compounds toward oxidation, a number of accelerated (forced) degradation studies need to be undertaken Alsante et al. (2007). As an example, Freed et al. (2008) examined the forced degradation of a number of compounds.

Caution should be exercised when including antioxidants, since a number of reports have pointed out that some antioxidants, for example, sulfites, can have a detrimental effect on

Table 8 List of Water- and Oil-Soluble Antioxidants

Water soluble	Oil soluble
Sodium bisulfite	Propyl gallate
Sodium sulfite	Butylated hydroxyanisole
Sodium metabisulfite	Butylated hydroxytoluene
Sodium thiosulfate	Ascorbyl palmitate
Sodium formaldehyde sulfoxylate	Nordihydroguaiaretic acid
L- and d-ascorbic acid	Alpha-tocopherol
Acetylcysteine	
Cysteine	
Thioglycerol	
Thioglycolic acid	
Thiolactic acid	
Thiourea	
Dithithreitol	
Glutathione	

Source: From Akers (1982), reproduced with permission.

the stability of certain compounds (Asahara et al., 1990). Thus, oxygen-sensitive substances should be screened for their compatibility with a range of antioxidants. It should also be noted that bisulphite has also been known to catalyze hydrolysis reactions (Munson et al., 1977).

Trace metal ions can affect stability and can arise from the bulk drug, formulation excipients, or glass containers (Allain and Wang, 2007). The effect of metal ions on the solution stability of fosinopril sodium has been reported (Thakur et al., 1993). In this case, the metal ions were able to provide, through complexation, a favorable reaction pathway. Metal ions can also act as degradation catalysts by being involved in the production of highly reactive free radicals, especially in the presence of oxygen. The formation of these radicals can be initiated by the action of light or heat, and propagate the reaction until they are destroyed by inhibitors or by side reactions that break the chain (Hovorka and Schöneich, 2001).

Ethylenediaminetetraacetic Acid and Chelating Agents

Because of the involvement of metal ions in degradation reactions, the inclusion of a chelating agent is often advocated (Pinsuwan et al., 1999). The most commonly used chelating agents are the various salts of ethylenediaminetetraacetic acid (EDTA). In addition, the use of hydroxyethylenediaminetriacetic acid (HEDTA), diethylenetriaminepentacetic acid (DPTA), and nitrilotriacetate (NTA) has been assessed for their efficiency in stabilizing, for example, isoniazid solutions (Ammar et al., 1982).

EDTA has pK_a values of $pK_1 = 2.0$, $pK_2 = 2.7$, $pK_3 = 6.2$, and $pK_4 = 10.4$ at 20°C . Generally, the reaction of EDTA with metal ions can be described by equation (9).



In practice, however, the disodium salt is used because of its greater solubility. Hence,



From equation (10), it is apparent that the dissociation (or equilibrium) will be sensitive to the pH of the solution. Therefore, this will have implications for the formulation.

The stability of the complex formed by EDTA–metal ions is characterized by the stability or formation constant, K . This is derived from the reaction equation and is given by equation (11).

$$K = \frac{[MY^{(n-4)+}]}{[M^{n+}][Y^{4-}]} \quad (11)$$

Stability constants (expressed as $\log K$) of some metal ion–EDTA complexes are shown in Table 9.

Table 9 Metal Ion–Ethylenediaminetetraacetic Acid Stability Constants

Ion	log <i>K</i>	Ion	log <i>K</i>	Ion	log <i>K</i>
Ag ⁺	7.3	Co ²⁺	16.3	Fe ³⁺	25.1
Li ⁺	2.8	Ni ²⁺	18.6	Y ³⁺	18.2
Na ⁺	1.7	Cu ²⁺	18.8	Cr ³⁺	24.0
Mg ²⁺	8.7	Zn ²⁺	16.7	Ce ³⁺	15.9
Ca ²⁺	10.6	Cd ²⁺	16.6	La ³⁺	15.7
Sr ²⁺	8.6	Hg ²⁺	21.9	Sc ³⁺	23.1
Ba ²⁺	7.8	Pb ²⁺	18.0	Ga ³⁺	20.5
Mn ²⁺	13.8	Al ³⁺	16.3	In ³⁺	24.9
Fe ²⁺	14.3	Bi ³⁺	27.0	Th ⁴⁺	23.2

Equation (11) assumes that the fully ionized form of EDTA^{4−} is present in solution. However, at low pH, other species will be present, that is, HEDTA^{3−}, H₂EDTA^{2−}, and H₃EDTA[−], as well as the undissociated H₄EDTA. Thus, the stability constants become conditional on pH.

The ratio can be calculated for the total uncombined EDTA (in all forms) to the form EDTA^{4−}. Thus, the apparent stability constant becomes K/α_L , and hence,

$$\alpha_L = \frac{[\text{EDTA}]_{\text{all forms}}}{[\text{EDTA}^{4-}]} \quad (12)$$

Thus,

$$K_H = \frac{K}{\alpha_L} \text{ Or } \log K_H = \log K - \alpha_L \quad (13)$$

where $\log K_H$ is known as the conditional stability constant.

Fortunately, α_L can be calculated from the known dissociation constants of EDTA, and its value can be calculated from equation (14).

$$\alpha_L = \left\{ 1 + \frac{[\text{H}^+]}{K_4} + \frac{[\text{H}^+]^2}{K_4 K_3} + \dots \right\} = 1 + 10^{(\text{p}K_4 - \text{pH})} + 10^{(\text{p}K_4 + \text{p}K_3 - \text{pH})} + \dots \quad (14)$$

Thus, at pH 4, the conditional stability constants of some metal-EDTA complexes are calculated as follows:

$$\begin{aligned} \log K_H \text{ EDTABa}^{2+} &= 0.6 \\ \log K_H \text{ EDTAMg}^{2+} &= 1.5 \\ \log K_H \text{ EDTACa}^{2+} &= 3.4 \\ \log K_H \text{ EDTAZn}^{2+} &= 9.5 \\ \log K_H \text{ EDTAFe}^{3+} &= 17.9 \end{aligned}$$

Thus, at pH 4, the zinc and ferric complexes will exist. However, calcium, magnesium, and barium will only be weakly complexed, if at all.

The inclusion of EDTA is occasionally not advantageous since there are a number of reports of the EDTA catalyzing the decomposition of drugs (Medenhall, 1984; Nayak et al., 1986). Citric acid, tartaric acid, glycerin, sorbitol, etc., can also be considered as complexing agents. However, these are often ineffective. Interestingly, some formulators resort to amino acids or tryptophan because of a ban on EDTA in some countries (Wang and Kowal, 1980).

Surface Activity

Many drugs show surface-active behavior because they have the correct mix of chemical groups that are typical of surfactants. The surface activity of drugs can be important since they show a greater tendency to adhere to surfaces or solutions may foam. The surface activity of compounds can be determined using a variety of techniques, for example, surface tension

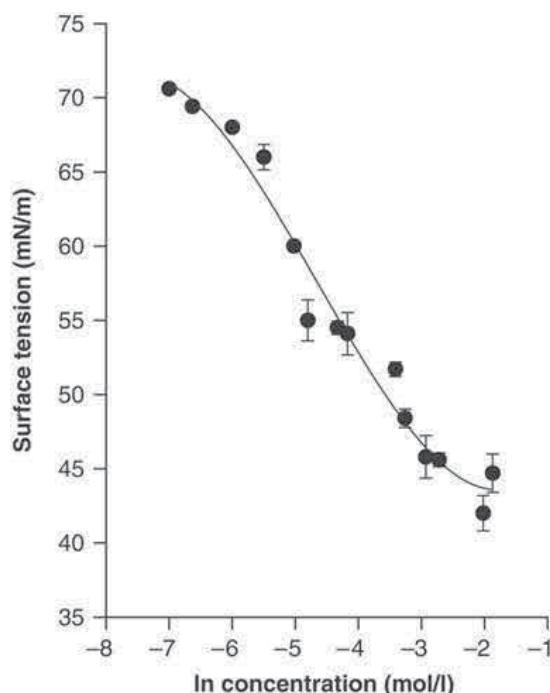


Figure 15 Plot of surface tension versus the natural log of the concentration for a primary amine hydrochloride.

measurements using a Du Nouy tensiometer, a Whilhelmy plate or conductance measurements. Figure 15 shows the surface tension as a function of concentration (using a Du Nouy tensiometer) of remacemide hydrochloride solutions in water. The surface tension of water decreased because of the presence of the compound. However, there was no break, which would have been indicative of micelle formation. Even when the pH of the solution was adjusted to 7, where a solubility “spike” had been observed, the surface tension was not significantly different to that observed for water alone. Thus, although the compound was surface active, it did not appear to form micelles, probably because of steric effects.

The surface-active properties of MDL 201346, a hydrochloride salt, have been investigated by a number of techniques including conductivity measurements (Streng et al., 1996). It was found that it underwent significant aggregation in water at temperatures greater than 10°C. Moreover, a break in the molar conductivity versus square root of concentration was noted, which corresponded to the critical micelle concentration (cmc) of the compound and aggregation of 10 to 11 molecules. In addition to surface-active behavior, some drugs are known to form liquid crystalline phases with water, for example, diclofenac diethylamine (Kriwet and Muller, 1993). Self-association in water (vertical stacking) of the novel anticancer agent brequiner sodium (King et al., 1989) has been reported.

Osmolality

Body fluids, such as blood, normally have an osmotic pressure, which is often described as corresponding to that of a 0.9% w/v solution of sodium chloride, and, indeed, a 0.9% w/v NaCl solution is said to be iso-osmotic with blood. Solutions with an osmotic pressure lower than 0.9% w/v NaCl are known as hypotonic, and those with osmotic pressure greater than this value are said to be hypertonic. The commonly used unit to express osmolality is osmol, and this is defined as the weight in grams per solute, existing in a solution as molecules, ions, macromolecules, etc., that is osmotically equivalent to the gram molecular weight of an ideally behaving nonelectrolyte.

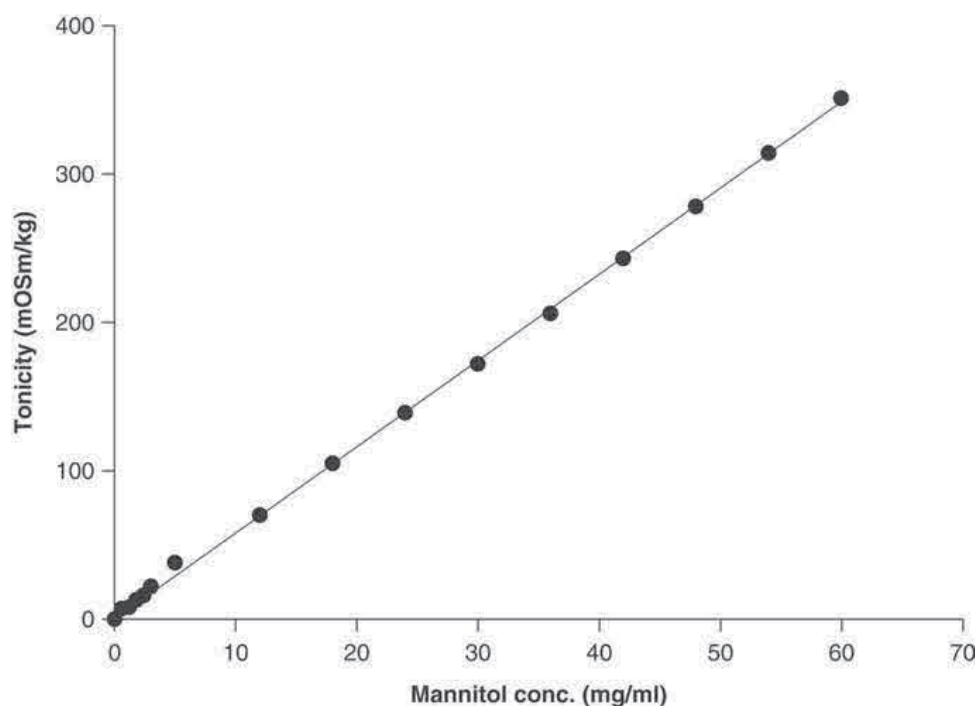
Pharmaceutically, osmotic effects are important in the parenterals and ophthalmic field, and work is usually directed at formulating to avoid the side effects or finding methods of administration to minimize them. The ophthalmic response to various concentrations of sodium chloride is shown in Table 10 (Flynn, 1979).

Osmolality determinations are usually carried out using a cryoscopic osmometer, which is calibrated with deionized water and solutions of sodium chloride of known concentration.

Table 10 Ophthalmic Response to Various Concentrations of Sodium Chloride

% NaCl	Ophthalmic response
0.0	Very disagreeable
0.6	Perceptibly disagreeable after 1 min
0.8	Completely indifferent after long exposure
1.2	Completely indifferent after long exposure
1.3	Perceptibly disagreeable after 1 min
1.5	Somewhat disagreeable after 1 min
2.0	Disagreeable after 0.5 min

Source: From Flynn (1979), reproduced with permission.

**Figure 16** Plot of tonicity versus concentration for mannitol in water.

Using this technique, the sodium chloride equivalents and freezing point depressions for more than 500 substances have been determined and reported in a series of papers by Hammarlund and coworkers (Hammarlund, 1981). Figure 16 shows the osmolality of mannitol-water solutions.

Cyclodextrins are used for the solubility enhancement of poorly soluble drugs, and Zannou et al. (2001) have determined the osmotic properties of the sulfobutyl and hydroxypropyl derivatives. In an interesting set of measurements to accompany the osmometry measurements, they conducted osmolality measurements on frozen solutions using DSC. Sodium chloride solutions of known osmolality were used as calibrants.

FREEZE-DRIED FORMULATIONS

If a drug in solution proves to be unstable, then an alternative formulation approach will be required, and freeze-drying is often used to produce the requisite stability. A common prerequisite for this method of production of a freeze-dried formulation is restricted to those that have enough aqueous solubility and stability over the time course of the process.

However, if the compound is unstable in water, then an alternative solvent such as *t*-butanol may be employed (Ni et al., 2001). Preformulation studies can be performed to evaluate this approach and to aid the development of the freeze-drying cycle. Briefly, freeze-drying consists of three main stages: (i) freezing of the solution, (ii) primary drying, and (iii) secondary drying (Tang and Pikal, 2004). In many cases, the inclusion of excipients is necessary, which act as bulking agents and/or stabilizing agents. Thus, production conditions should be evaluated to ensure that the process is efficient and that it produces a stable product (Schwegman et al., 2005). The first stage, therefore, is to characterize the freezing and heating behavior of solutions containing the candidate drug, and in this respect, DSC and freeze-drying microscopy can be used as described by Thomas and Cannon (2004). Schwegman et al. (2005) have produced some good advice with regard to the formulation and process development of freeze-dried formulations. Since mannitol is a common excipient used in the formulated product, the sub-ambient behavior of its solutions is of importance (Kett et al., 2003).

To understand the processes taking place during freezing a solution containing a solute, it is worth referring to the phase diagram described by Her and Nail (1994). This shows that as a solution of a compound is cooled, the freezing point is depressed because of the presence of an increasing concentration of the dissolved solute. If the solute crystallizes during freezing, a eutectic point is observed. If crystallization does not take place, the solution becomes super-cooled and thus becomes more concentrated and viscous. Eventually, the viscosity is increased to such an extent that a glass is formed. This point is known as the T_g .

Measurement of the glass transition of frozen solution formulation of the candidate drug is an important preformulation determination since freeze-drying an amorphous system above this temperature can lead to a decrease in viscous flow of the solute (due to a decrease in viscosity) after the removal of the ice. This leads to what is commonly known as "collapse," and for successful freeze-drying, it should be performed below the T_g . Consequences of collapse include high residual water content in the product and prolonged reconstitution times. In addition, the increase in the mobility of molecules above the T_g may lead to in-process degradation (Pikal and Shah, 1990).

Figure 17 shows the glass transition, as determined by DSC, of a trial formulation of a candidate drug. The glass transition was measured by freezing a solution of the compound in a DSC pan and then heating the frozen solution. It should be noted that T_g is usually a subtler event compared with the ice-melt endotherm, and so the thermogram should be examined

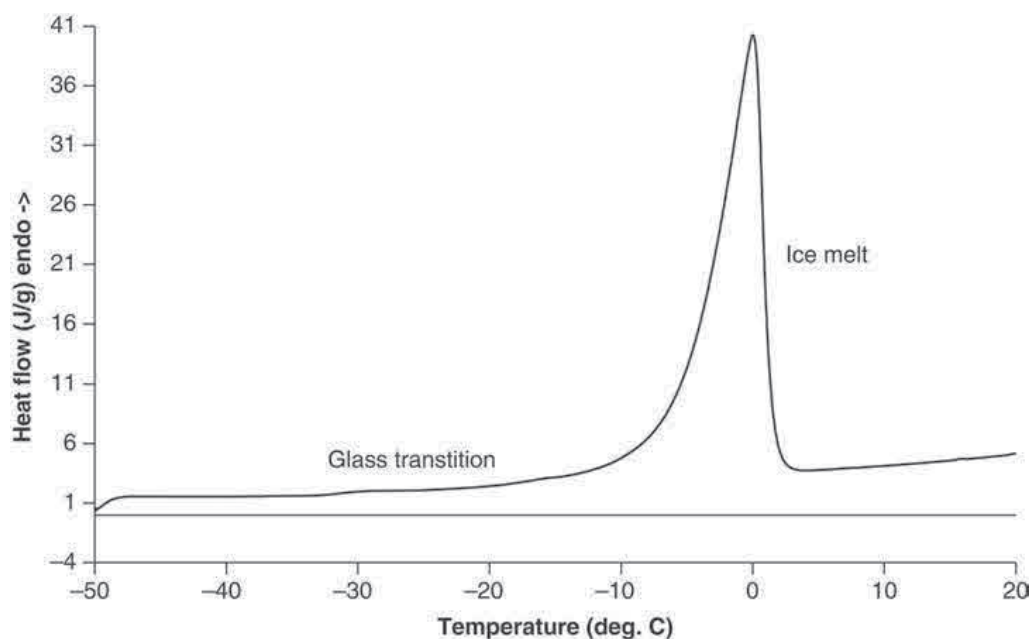


Figure 17 DSC thermogram showing a glass transition of heated frozen drug solution.

very carefully (Fig. 17). In some cases, an endotherm due to stress relaxation may be superimposed on the glass transition. It is possible to resolve these events by using the related technique, modulated DSC (MDSC) or dynamic DSC (DDSC) (Kett, 2001).

If during freezing the solutes crystallize, the first thermal event detected using DSC will be the endotherm that corresponds to melting of the eutectic formed between ice and the solute. This is usually followed by an endothermic event corresponding to the melting of ice. Figure 18 shows this behavior for a saline solution. Normally, freeze-drying of these systems are carried out below the eutectic melting temperature (Williams and Schwinke, 1994). Another way of detecting whether a solute or formulation crystallizes on freezing is to conduct sub-ambient X-ray diffractometry (Cavatur and Suryanarayanan, 1998).

If a lyophilized drug is amorphous, then knowledge of the glass transition temperature is important for stability reasons. Chemically, amorphous compounds are usually less stable than their crystalline counterparts. This is illustrated in Table 11, which shows some stability data for an amorphous compound (produced by lyophilization) and the crystalline hydrate form of the compound.

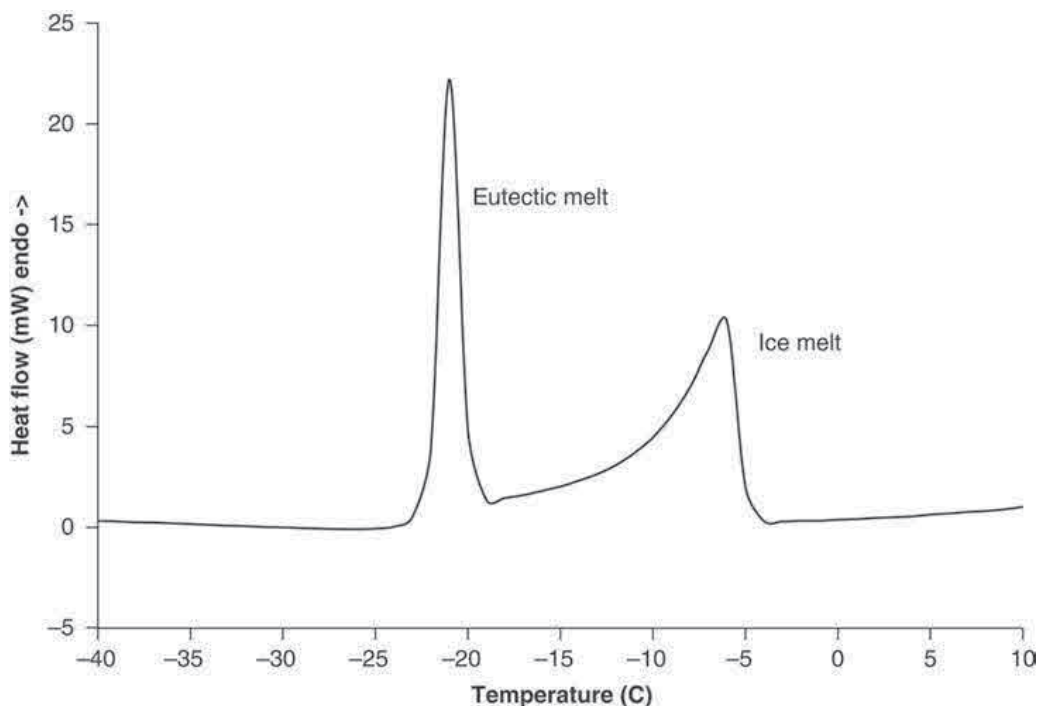


Figure 18 DSC thermogram of a frozen 9% w/v saline solution.

Table 11 Stability Data for an Amorphous (Lyophilized) and Crystalline Hydrate Form of a Compound

	Storage conditions	Time (mo)	Moisture content (% w/w)	Total impurities (% w/w)
Crystalline		Initial	15.98	0.53
	25°C/16% RH	1	15.78	0.54
	25°C/60% RH	1	15.50	0.56
	40°C/75% RH	1	15.76	0.59
Amorphous		Initial	4.83	0.47
	25°C/16% RH	1	8.31	0.57
	25°C/60% RH	1	12.55	0.69
	40°C/75% RH	1	12.72	1.44

Abbreviation: RH, relative humidity.

Although the moisture content of the amorphous form was increased, it did not crystallize. Other work showed that at relative humidities greater than 70%, the sample crystallized (O'Sullivan et al., 2002). It is important to note that moisture has the effect of lowering the glass temperature, which in turn increases the propensity of instability. This appears to be due to water acting as a plasticizer such that molecular mobility is increased, thus facilitating reactivity (Shalaev and Zografi, 1996).

Duddu and Weller (1996) have studied the importance of the glass transition temperature of an amorphous lyophilized aspirin-cyclodextrin complex. Using DSC, the glass transition was found to be 36°C followed by an exothermic peak, believed to be due to aspirin crystallization. The glass transition at this temperature was also observed by using dielectric relaxation spectroscopy. When the aspirin/hydroxypropylcyclodextrin (HPCD) loophole was exposed to higher humidities, the T_g was reduced to a temperature below room temperature and the product became a viscous gel. Craig et al. (1999) have reviewed the physicochemical properties of the amorphous state with respect to drugs and freeze-dried formulations, and Nail and Seales (2007) have discussed QdD (Quality by Design) aspects of their development and scale-up of freeze-dried formulations.

SUSPENSIONS

If the drug substance is not soluble, then the compound may be administered as a suspension. This might be the formulation approach used for oral administration of drugs to animals for safety studies, for early-phase clinical studies in humans, or for the intended commercial dosage form, for example, ophthalmic, nasal, oral, etc. Data considered to be important for suspensions at the preformulation stage include solubility, particle size, and propensity for crystal growth and chemical stability. Furthermore, during development, it will be important to have knowledge of the viscosity of the vehicle to obtain information with respect to settling of the suspended particles, syringibility, and physical stability (Akers, 1987). In a report on the preformulation information required for suspensions, Morefield et al. (1987) investigated the relationship between the critical volume fraction as a function of pH. They noted that "it is usually desirable to maximize the volume fraction of solids to minimize the volume of the dose."

It should be obvious that for a successful suspension, insolubility of the candidate drug is required. While for large hydrophobic drugs like steroids, this may not be a problem, weak acids or bases may show appreciable solubility. In this instance, reducing the solubility by salt formation is a relatively common way to achieve this end. For example, a calcium salt of a weak acid may be sufficiently insoluble for a suspension formulation. However, difficulties may arise because of hydrate formation, for example, with concomitant crystal growth. Hoelgaard and Møller (1983) found that metronidazole formed a monohydrate on suspension in water. Zietsman et al. (2007) have shown that this conversion can be prevented by using Avicel RC-591 as a suspending agent.

Another way crystals can grow in suspension that is not attributable to a phase change is by Ostwald ripening. This is the result of the difference in solubility between small and large crystals, as predicted by equation (15).

$$\frac{RT}{M} \ln\left(\frac{S_2}{S_1}\right) = \frac{2\sigma}{\rho} \left(\frac{1}{r_1} - \frac{1}{r_2}\right) \quad (15)$$

where R is the gas constant, T the absolute, S_1 and S_2 the solubilities of crystals of radii r_1 and r_2 , respectively, σ the specific surface energy, ρ the density, and M the molecular weight of the solute molecules. Ostwald ripening is promoted by temperature changes during storage, particularly if there is a strong temperature-solubility relationship. Therefore, as the temperature is increased, the small particles of the drug will dissolve, which is followed by crystal growth as the temperature is decreased. Ziller and Rupprecht (1988a) have reported the design of a control unit to monitor crystal growth. However, simple microscopic observation may be all that is necessary to monitor the growth of crystals. If a phase change occurs, then the usual techniques may be used to assess the solid-state form of the compound produced on

storage such as DSC, HSM (hot stage microscopy), or XRPD. Various polymeric additives may be employed to inhibit drug crystallization. Ziller and Rupprecht (1988b) found that polyvinylpyrrolidone (PVP) and bovine serum albumin inhibit crystal growth using a variety of compounds. Similarly, Douroumis and Fahr (2007) found that PVP and hydroxypropylmethylcellulose (HPMC) were effective in preventing the growth of carbamazepine nanosuspension.

It is a pharmacopoeial requirement that suspensions should be redispersible if they settle on storage. However, the pharmacopoeias do not offer a suitable test that can be used to characterize this aspect of the formulation. In an attempt to remedy this situation, Deicke and Süverkrüp (1999) have devised a mechanical redispersibility tester, which closely simulates the action of human shaking. The crystal habit may also affect the physical stability of the formulation. For example, Tiwary and Panpalia (1999) showed that trimethoprim crystals with the largest aspect ratio showed the best sedimentation volume and redispersibility.

If the suspension is for parenteral administration, it will need to be sterilized. However, terminal heat sterilization can affect both its chemical and physical stabilities, the latter usually observed as crystal growth or aggregation of the particles (Na et al., 1999). Another measure of suspension stability is the zeta potential, which is a measure of the surface charge. However, various studies have shown that it is only useful in some cases. For example, Biro and Racz (1998) found that the zeta potential of albendazole suspensions was a good indicator of stability, whereas Duro et al. (1998) showed that the electrical charge of pyrantel pamoate suspensions was not important for its stabilization.

As noted above, the particle size of suspensions is another important parameter in suspension formulations. The particle size distribution can be measured using a variety of techniques including laser diffraction. A point to note in laser diffraction is the careful selection of the suspending agent. This was illustrated by Akinson and White (1992), who used a Malvern Mastersizer to determine the particle size of a 1% methylcellulose in the presence of seven surface-active agents (Tween 80, Tween 20, Span 20, Pluronic L62, Pluronic F88, Cetomacrogol 100, and sodium lauryl sulfate). The particle size of the suspensions was measured as a function of time, and surprisingly, Tween 80, which is widely used in this respect, was found to be unsuitable for the hydrophobic drug under investigation. Other surfactants also gave poor particle size data, for example, Tween 20, Cetomacrogol 1000, Pluronic F88, and sodium lauryl sulfate. This arose from aggregation of the particles, and additionally, these suspensions showed slower drug dissolution into water. Span 20 and Pluronic L62 showed the best results, and the authors cautioned the use of a standard surface-active agent in preclinical studies.

Usually, suspensions are flocculated so that the particles form large aggregates that are easy to disperse—normally, this is achieved using potassium or sodium chloride (Akers et al., 1987). However, for controlled flocculation suspensions, sonication may be required to determine the size of the primary particles (Bommireddi et al., 1998).

Although high performance liquid chromatography (HPLC) is the preferred technique for assessing the stability of formulations, spectrophotometry can also be used. Girona et al. (1988) used this technique for assessing the stability of an ampicillin-dicloxacillin suspension. Rohn (2004) has reported that rheology could be used as a rapid screening technique for testing the stability of drug suspensions. He claims that by monitoring the tan delta parameter, the stability of the suspension could be predicted. Furthermore, the oscillation frequency sweep test gave information on the viscoelastic properties of the suspension, which could be used to screen potential suspending agents.

TOPICAL/TRANSDERMAL FORMULATIONS

Samir (1997) has reviewed preformulation aspects of transdermal drug delivery. This route of delivery offers several potential advantages compared with the oral route such as avoidance of fluctuating blood levels, no first-pass metabolism, and no degradation attributable to stomach acid. However, the transdermal route is limited because of the very effective barrier function of the skin. Large, polar molecules do not penetrate the stratum corneum well. The physicochemical properties of candidate drugs that are important in transdermal drug

delivery include molecular weight and volume, aqueous solubility, melting point, and log *P*. Clearly, these are intrinsic properties of the molecule and as such will determine whether or not the compounds will penetrate the skin. Furthermore, since many compounds are weak acids or bases, pH will have an influence on their permeation.

One way in which the transport of zwitterionic drugs through skin has been enhanced was to form a salt. This was demonstrated by Mazzenga et al. (1992), who showed that the rank order of epidermal flux of the salts of phenylalanine across the epidermis was hydrobromide > hydrochloride > hydrofluoride > phenylalanine. Thus, like most other delivery routes, it is worth considering salt selection issues at the preformulation stage to optimize the delivery of the compound via the skin.

The formulation in which the candidate drug is applied to the skin is another important factor that can affect its bioavailability. In transdermal drug delivery, a number of vehicles may be used, such as creams, ointments, lotions, and gels. The solubility of the compound in the vehicle needs to be determined. Problems can arise from crystal growth if the system is supersaturated; for example, phenylbutazone creams were observed to have a gritty appearance attributable to crystal growth (Sallam et al., 1986). Indeed, in matrix patches, crystals of estradiol hemihydrate or gestodene of up to 800 μm grew during three months of storage at room temperature (Lipp and Müller, 1999). Needle-like crystals of the hydrate of betamethasone-17 valerate were found by Folger and Muller-Goymann (1994) when creams were placed on storage.

Chemical and physical stability also needs to be considered. For example, Thoma and Holzmann (1998) showed that dithranol showed a distinct instability in the paraffin base due to light, but was stable when protected from light. In terms of kinetics, Kenley et al. (1987) found that the degradation in a topical cream and that in ethanol-water solutions were very similar in the pH range 2 to 6. This suggested that the degradation of this compound occurred in an aqueous phase or compartment that was undisturbed by the oily cream excipients. If the compound decomposes because of oxidation, then an antioxidant may have to be incorporated. In an attempt to reduce the photodegradation of a development compound, Merrifield et al. (1996) compared the free acid of compound with a number of its salts, each of which they incorporated into a white soft paraffin base. Their results (Table 12) showed that after a one-hour exposure in a SOL2 light-simulation cabinet, the disodium salt showed significant degradation.

Martens-Lobenhoffer et al. (1999) have studied the stability of 8-methoxypsoralen (8-MOP) in various ointments. They found that after 12 weeks of storage, the drug was stable in Unguentum Cordes and Cold Cream Naturel. However, the Unguentum Cordes emulsion began to crack after eight weeks. When formulated in a carbopol gel, 8-MOP was unstable.

The physical structure of creams has been investigated by a variety of techniques, for example, DSC, TGA, microscopy, reflectance measure, rheology, Raman spectroscopy, and dielectric analysis (Peramal et al., 1997). Focusing on TGA and rheology, Peramal et al. (1997) found that when aqueous BP creams were analyzed by TGA, there were two peaks in the derivative curve. It was concluded that these were attributable to the loss of free and lamellar water from the cream, and therefore TGA could be used as a quality-control tool. The lamellar structure of creams can also be confirmed using small-angle X-ray measurements (Niemi and

Table 12 Light Stability of the Salts of a Candidate Drug in a White Soft Paraffin Base

Salt/form	% Initial compound after 1-hr exposure in SOL2		
	0.1% concentration	0.5% concentration	2.0% concentration
Free acid (micronized)	51.0	80.0	85.9
Free acid (unmicronized)	69.4	nd	nd
Disodium (unmicronized)	9.9	3.6	nd
Ethylenediamine (unmicronized)	51.9	65.1	nd
Piperazine (unmicronized)	79.9	88.2	nd

Abbreviation: nd, not detected.

Source: From Merrifield et al. (1996).

Laine, 1991). For example, the lamellar spacings of a sodium lauryl sulfate, cetostearyl alcohol and liquid paraffin cream were found to increase in size as the water content of the cream increased until, at greater than 60% water, the lamellar structure broke down. This was correlated with earlier work that showed that at this point, the release of hydrocortisone was increased (Niemi et al., 1989).

Atkinson et al. (1992) have reported the use of a laser diffraction method to measure the particle size of drugs dispersed in ointments. In this study, they stressed the fact that a very small particle size was required to ensure efficacy of the drug. In addition, the size of the particles was especially important if the ointment was for ophthalmic use where particles must be less than 25 μm . While the particle size of the suspended particles can be assessed microscopically, laser diffraction offers a more rapid analysis.

INHALATION DOSAGE FORMS

As noted by Sanjar and Matthews (2001), delivering drugs via the lung is not new since the absorption of nicotine by smoking of tobacco has been known for centuries, and before inhalation drug delivery devices, some asthma medications were administered in cigarettes. In addition, anesthetic gases are routinely administered by inhalation. For many years now, however, respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD) have been treated by inhaling the drug from a pressurized metered-dose inhaler (pMDI), DPI, or a nebulizer solution. Although pMDIs remain the most popular devices for the delivery of drugs to the lungs, DPIs have gained in popularity over the years (Gonda, 2000). For example, Taylor and Gustafsson (2005) stated that in 2004, 292 million pMDIs and 113 million DPIs were sold worldwide: In another article, Colthorpe (2003) has estimated that, on a daily basis, 500 million people carry a pMDI. Smyth and Hickey (2005) have estimated that there are greater than 11 DPIs in use and a similar number under development. See this publication for a list of devices and compounds. Islam and Gladki (2008) have reviewed DPI device reliability.

Because of the large surface area available, drug delivery via the lung has a number of advantages over the oral route since the rate of absorption of small molecules from the lung is only bettered by the intravenous route, and thus the bioavailability is usually higher than that obtained from drug delivery by the oral route. This is particularly true for hydrophobic compounds, which can show extremely rapid absorption (Cryan et al., 2007). However, drug deposition in the lung can be problematic and requires the drug to be reduced in size to between 2 and 6 μm for optimal effect (Pritchard, 2001; Howarth, 2001). If the particle size is greater than 6 μm , the compound is deposited in the mouth and esophageal region, and there is no clinical effect apart from the part that is swallowed. Particles of size 2 μm , on the other hand, are deposited in the peripheral airways/alveoli.

Metered-Dose Inhalers

In pMDI technology, CFC propellants are being replaced with the ozone-friendly HFAs 134a and 227 (McDonald and Martin (2000). For an overview of the environmental hazards and exposure risk of hydrofluorocarbons (HFCs), see Tsai (2005). In pMDI drug delivery systems,



the drugs are formulated as a suspension or as a solution depending on the solubility of the drug in the propellant (or the addition of a cosolvent). Hoyer et al. (2008) have investigated the solubility of 36 organic solutes in HFA 134a, and it was found that calculations of solubility from an ideal solubility viewpoint did not agree well with experimental values. However, addition of other terms such as log P , molar volume, molecular weight, etc., showed a better

correlation and could provide an initial estimate of the solubility of a compound in HFA 134a. Traini et al. (2006) have described a novel apparatus for the determination of the solubility of salbutamol sulfate, budesonide, and formoterol fumarate dihydrate in propellant 134a. Their device allows the pMDI to be actuated into a collection vessel from which the amount that has been dissolved is assessed (using HPLC) after the propellant has evaporated. Another technique, based on direct injection from a pMDI into the injector port of an HPLC, for determining compound solubility in pMDIs has been described by Gupta and Myrdal (2004, 2005). An earlier method for determining the solubility of drugs in aerosol propellants has been described by Dalby et al. (1991). At room temperature, the propellants are gases, therefore, special procedures are required in separating the excess solid from the solution in the aerosol can; in this case, it is a simple filtration from one can to another. The propellant from the can containing the filtrate is then allowed to evaporate, and the residue is assayed for the drug using, for example, HPLC. Appreciable drug solubility may lead to particle growth, however, this may be overcome by the appropriate choice of salt if the compound is a weak acid or base. Thus, although suspensions offer the advantage of superior chemical stability (Tiwari et al. (1998), they may have problematic physical stability in terms of crystal growth or poor dispersion properties. In this respect, Tzou et al. (1997) examined whether the free base or the sulfate salt of albuterol (salbutamol) had the best chemical and physical stability for a pMDI formulation. Results showed that all of the sulfate formulations were chemically stable for up to 12 months, however, the base was less stable. In terms of physical stability, the base formulations showed crystal growth and agglomeration, illustrating the need for a salt selection process to be undertaken.

One significant challenge in the transition from the CFCs to HFAs is that the surfactants and polymers used as suspension stabilizers in CFC formulations are not soluble enough in the HFAs to be effective. For example, sorbitan monooleate (Span 85), commonly used in CFC formulations, is not soluble in HFA 134a or 227, however, other surfactants and polymers have been screened for their effectiveness in stabilizing propellant suspensions with some success. Some solubility of the surfactant in the propellant is a prerequisite, and while some suitable agents have been identified, they have not been progressed because of their potential toxicity in the lung. Some apparent solubilities of surfactants in HFAs 134a and 227 are shown in Table 13 (Vervaet and Byron, 1999).

It would of value to know if and how much surfactant or polymer was adsorbed by the particles. In an attempt to understand this process, Blackett and Buckton (1995) used

Table 13 Apparent Solubilities of Some Surfactants in HFA 134a and HFA 227

Surfactant	hydrophile-lipophile balance (HLB)	Apparent solubility (% w/w)	
		HFA 134a	HFA 227
Oleic acid	1.0	<0.02	<0.02
Sorbitan trioleate	1.8	<0.02	<0.01
Propoxylated PEG	4.0	≈3.6	1.5–15.3 32.0–60.3
Sorbitan monooleate	4.3	<0.01	<0.01
Lecithin	7.0	<0.01	<0.01
Brij 30	9.7	≈1.8	0.8–1.2
Tween 80	15.0	<0.03	0–10.0 25.0–89.8
Tween 20	16.7	≈0.1	1.4–3.5
PEG 300	20	≈4.0	1.5–4.3 16.1–100
Polyvinylpyrrolidone, PVA		>0.1	
Oligolactic acids		≈2.7	

Abbreviations: HFA, hydrofluoroalkane; PEG, polyethylene glycol.

Source: From Vervaet and Byron (1999), with permission from Elsevier.

isothermal microcalorimetry. The system investigated was the model CFC Arcton 113, salbutamol sulfate (crystalline and partially crystalline), and oleic acid or Span 85 as stabilizers. Using a perfusion-titration setup, they titrated suspensions of the drug with solutions of the surfactant and followed heat output as a function of time. It was shown that the heat output and adsorption were different depending on the crystallinity of the sample; that is, there was less heat output for the more energetic, partially crystalline sample. From these data, it was hypothesized that the orientation of the surfactant molecule during adsorption was different depending on the surface energy of the particles in suspension.

Drug substances for inhalation therapy via a pMDI (and DPIs) are reduced in size by micronization to particles of approximately 1 to 6 μm , which are capable of penetrating the deep airways and impact at the site of action. As noted earlier, micronization can cause problems because of the reduction in crystallinity and poor flow properties as a result of the milling process (Buckton, 1997). The effect of micronization on samples can be assessed by a variety of techniques, for example, DVS, microcalorimetry, and IGC. For example, IGC has been used to determine the surface properties of two batches of salbutamol sulfate (Ticehurst et al., 1994). This group also investigated the surface properties of α -lactose monohydrate (an excipient used in DPIs, see next section) using this technique to detect batch variation (Ticehurst et al., 1996). It was hypothesized that these differences in surface energetics between the nominally equivalent batches were due to small variations in surface crystallinity or purity. One common way of removing the high-energy portions from the surface is to condition the powder with moist air, which crystallizes the amorphous regions (Ahmed et al., 1996).

Williams et al. (1999) have reported the influence of ball milling and micronization on the formulation of triamcinolone acetonide (TAA) for MDIs. Both methods reduced the particle size of the powder, however, ball milling produced material with a greater amorphous content. This was shown by solution calorimetry measurements. Although the ball-milled material was less crystalline, it was found to have the smallest particles and the highest respirable fraction.

It is possible that a number of physical changes can occur because of suspension in the propellant. The first is due to Ostwald ripening, a phenomenon described earlier in this chapter. This arises when the compound shows some solubility in the propellant resulting in particle growth and caking. In this process, the smallest micronized particles dissolve and then recrystallize on the larger particles. As shown by Phillips et al. (1993), optical microscopy can be used to assess the crystal growth of micronized salicylic acid in CFC pMDIs. In this study, the increase in the axial ratio (length/breadth) of the crystals was measured as a function of time. Although the crystals continued to grow after an initial increase in the axial ratio, after some time, it did not change. It was therefore concluded that axial ratios of crystals should always be determined by microscopy to detect any physical instability in the early stages of MDI formulation development. In another paper by this group, Phillips et al. (1994) have investigated the surfactant-promoted crystal growth of micronized methylprednisolone in trichloromono-fluoromethane (CFC-11). The effect of drug concentration, surfactant type, and composition on the solubility of methylprednisolone was determined and related to the observed crystal growth in suspension. In particular, high concentrations of Span 85 (sorbitan trioleate) were found to increase the solubility of the compound, with the consequence of crystal growth. Oleic acid and lower concentrations of Span 85, on the other hand, showed little particle size change. In addition to an increase in particle size, the crystals may also solvate the propellants, and this may also lead to crystal growth. Apart from the obvious increase in particle size of the suspension, there are a number of techniques that can be used to confirm the existence of the solvate. These include DSC, TGA, hot-stage microscopy, XRPD, and infrared spectroscopy.

An example of this phenomenon is a development compound that was found to have changed from a micronized powder to much larger particles after storage in propellant. When the recovered crystals were analyzed using TGA, a mass loss of 25.5% was detected in the range of 40°C to 100°C. This thermal event was also evident in the DSC, which showed an endotherm corresponding to solvent loss followed by an exotherm probably due to crystallization. Hot-stage microscopy showed that, when heated in silicone oil, a gas was evolved as the temperature was raised. This is illustrated in Figure 19. Notice how the crystals broke apart as the gas was released as the temperature was raised.

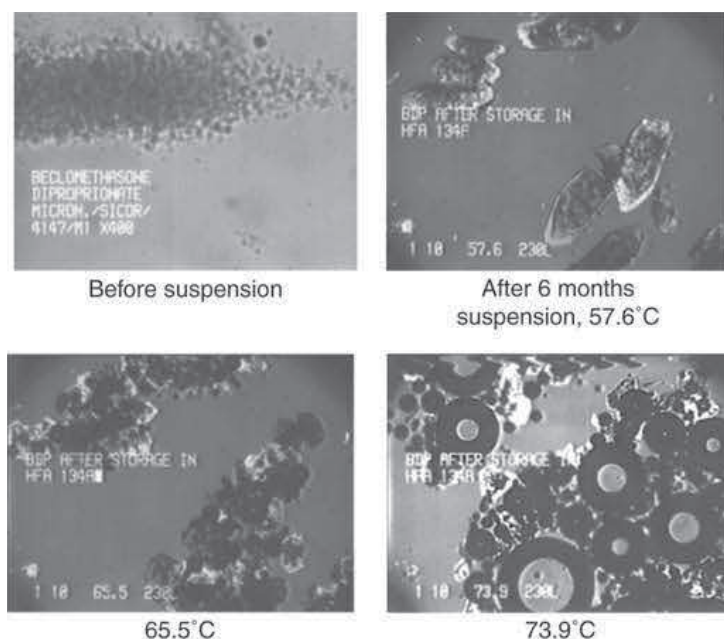


Figure 19 HSM photographs of an inhalation drug before and after suspension in gHFA 134a.

To confirm that the crystals had solvated the propellant, infrared spectroscopy provided a useful test, whereby the main difference was the appearance of a medium-strong peak at 1289/cm. By reference to standard tables of infrared stretching frequencies, this new peak was assigned as a C-F stretch that, with the other information, lead to the conclusion that the compound had solvated the propellant gas (134a).

For pMDIs, the compatibility of the propellants with the valve elastomers also needs to be evaluated. For example, Tiwari et al. (1998) investigated the effect of 134a on a number of valve elastomers and found that it adversely affected the performance of the valve. Inhalation dosage forms are discussed in more detail in chapter 10.

Dry-Powder Inhalers

DPIs do not rely on the CFC or HFA propellant gases and are hence more “environmentally friendly” than MDIs. There are a number of devices that can deliver drugs to the lung as dry powders, for example, Turbuhaler™ and Diskhaler™. DPIs rely on a larger carrier particle such as α -lactose monohydrate to which the drug is attached. (The lactose is usually fractionated such that it lies in the size range 63–90 μm .) On delivery, the drug detaches from the lactose, and because the drug is micronized, it is delivered to the lung, whereas the lactose is swallowed. The use of alternative carriers, such as erythritol, mannitol, and trehalose, has been investigated by Jones et al. (2008). As noted elsewhere, micronization is a somewhat aggressive method of particle size reduction commonly used for inhalation compounds. A common way of restoring the crystallinity after this process is to condition the surface of the micronized drug by exposing it to elevated relative humidities or organic vapors. The net effect of this procedure is to crystallize the amorphous regions, making the powder better suited for formulation in a DPI. Brodka-Pfeiffer et al. (2003) have described work on the conditioning of salbutamol sulfate. As noted elsewhere, crystallization from supercritical fluids has been investigated as a method for producing micronized particles for inhalation (Martin and Cocero, 2008). Young and Price (2004) have examined the effect of humidity on the aerosolization of micronized salbutamol sulfate. Using DVS, AFM, and twin-stage impinger data, they showed that at increased humidities, the fine-particle fraction for both samples decreased because of the amorphous character induced by the micronization process: the crystallization of the amorphous regions due to the elevated humidity causes the particles to fuse to the lactose carrier.

The performance of DPIs is governed by a number of factors such as van der Waals, electrostatic, and capillary forces (Young et al., 2003a, b; Jones and Price, 2006; Jones et al., 2008). When formulating a DPI, considerable attention needs to be paid to the physical form of

the drug substance. For example, it needs to have a reasonably high melting point ($>80^{\circ}\text{C}$), not show significant moisture uptake (probably less than 2% w/w), not taste significantly, and not be significantly colored. Of these, moisture sorption is arguably the most important since moisture can affect the deagglomeration of the compound from the lactose carrier (Maggi et al., 1999; Young et al., 2003). The use of hydrates in DPI formulations can be problematic, particularly those that sorb moisture to form non-stoichiometric hydrate (see chapter 10). It is recommended that these physical forms be avoided because of potential difficulties with deagglomeration. For example, Young et al. (2003, 2006) examined the effect of storing disodium cromoglycate (a channel hydrate that takes up moisture from the atmosphere nonstoichiometrically for 12 hours at 15%, 30%, 45%, 60%, and 75% RH). Not unsurprisingly, the delivered dose and the fine-particle dose were decreased with increasing RH. Clarke et al. (2000), on the other hand, found that the stoichiometric channel hydrate, nedocromil sodium trihydrate, when stored between 12% and 76% RH, did not have a perceptible effect on its performance. However, storage of the micronized powder above 86% RH, where the trihydrate converts to the heptahemihydrate, caused a significant reduction of the deaggregation performance. The effect of storing two DPI devices under hot and humid conditions showed that the performance of one DPI was affected *in vitro* (Borgström et al., 2005).

As noted by Jashnani and Byron (1996), in formulation terms, it is always worth optimizing the salt form of a compound. In this study, the performance of dry-powder aerosol generation in different environments for the sulfate, adipate (diethanolate), and stearate salts of albuterol were determined. Overall, the stearate emptied and aerosolized best from the inhaler and showed the least sensitivity to environmental factors such as temperature and humidity. Another use of low-solubility salts is to mask the taste of compounds that is unpleasant when delivered by DPI (or pMDI for that matter). By lowering the solubility and hence dissolution rate, the taste can often be effectively eliminated.

It has also shown that the polymorphic form of the lactose used can affect the aerosolization properties of the formulation. The results showed that, as function of flow rate, the β -form was easily entrained but held on to the drug particles most strongly. The anhydrous α -form showed the opposite behavior, and the α -form (the monohydrate) showed intermediate behavior. Processing of lactose was the subject of a paper by Young et al. (2007).

Micronized particles form strong agglomerates, and the size of these agglomerates, among other things, depends on the surface free energy of the powder. Since micronization can change the surface free energy of a material, the adherence properties of the compound will also be changed. For example, Podczek et al. (1994, 1995a,b) have performed adhesion and autoadhesion measurements of salmeterol xinafoate particles of various sizes to compacted lactose monohydrate surfaces using a centrifuge technique. This work was followed up by work investigating the adhesion force of micronized salmeterol xinafoate particles to pharmaceutically relevant surface materials (Podczek et al., 1996). Results showed that long contact times with PVC, polyethylene, or aluminum should be avoided because the adhesion force between the drug and these surfaces was much higher than that between it and the lactose carrier. Thus, detachment and loss of drug in the formulation could occur. In another study, Podczek et al. (1996a, b) investigated the adhesion strength of some salts of salmeterol to lactose and other substrates with varying surface roughness, surface free energy, and Young's modulus. It was concluded that many of these factors play a part, as well as chemical forces, and that only experimental assessment could indicate whether the material was suitable.

Using AFM, Bérard et al. (2002) showed that an increased RH increased the adhesion between their probe molecule, zanamivir, and lactose. As has been noted earlier, micronized particles can contain amorphous regions, which can be crystallized at elevated levels of RH. However, the recrystallization process can lead to particle growth, with bridges being formed between the micronized particles (Brodka-Pfeiffer et al., 2003).

Because lactose is the most commonly used carrier excipient in DPIs, its compatibility with the drug substance should be assessed, particularly if it is a primary amine (see the section on compatibility). The physicochemical characteristics of some alternative carrier particles have been described by Byron et al. (1996). The effect of the surface morphology of lactose carriers on the inhalation properties of pranlukast hydrate has been reported

Table 14 Solubility of an Sibenadit HCl in Water and Isotonic Saline as a Function of Temperature

Solvent	Solubility ($\mu\text{g/mL}$)		
	4°C	25°C	40°C
Water	1789	2397	6837
Saline	<30	61	157

(Kawashima et al., 1998). The lactose carriers investigated were pharmatose 325M, pharmatose 200M (sieved to $\sim 60\mu\text{m}$), and fluidized-bed granulated lactose. Results showed that with increasing specific surface area and roughness, the effective index of inhalation decreased because of the drug being held more tightly in the inhaled airstream. Therefore, characterization of the carrier particles by, for example, surface area measurements, SEM, as well as other solid-state techniques is recommended in preformulation activities for DPIs. Jones and Price (2006) have shown that inclusion of fine lactose particles improved the performance of a DPI formulation.

Nebulizer Solutions

Nebulizer formulations are normally solutions, however, suspensions are also used, for example, the insoluble steroid budesonide has been successfully formulated for delivery by nebulization (Dahlback, 1994). Some important preformulation considerations for nebulizers are stability, solubility, viscosity, and surface tension (McCallion et al., 1996; Nikander, 1997). In terms of solubility, the common ion effect may be important where, for example, a hydrochloride salt is to be dissolved in saline. In addition, the temperature dependence of the solubility of the drug may be important, for example, Taylor et al. (1992) found that the temperature of a solution of a pentamidine isethionate decreased by up to 13°C , causing the drug to crystallize from solution. The osmolality of solutions has been found to increase during nebulization, although the pH does not appear to do so (Schoeni and Kraemer, 1989).

Table 14 shows solubility data for the potential inhalation drug sebenadit hydrochloride, which was to have been delivered by a pMDI and as a nebulizer solution (Cosgrove et al., 2005).

These data show the increase in solubility of the compound with respect to temperature and how the presence of the chloride ion depressed its solubility. Wong-Beringer et al. (2008) have performed in more depth investigation into the optimal physicochemical properties for the delivery of the antibiotic caspofungin by nebulizer solution. They found that caspofungin required dilution with a 0.9% w/v sodium chloride adjusted to between pH 6.17 and 6.26 with sodium hydroxide to give a solution that had an osmolality that was optimal for delivery to the lung.

If the drug is insoluble, it is important that for a suspension formulation, the drug is micronized to a size of less than $2\mu\text{m}$ (Dahlback, 1994). The particle size distribution of nebulized droplets can be measured using, for example, laser diffraction (Clark et al., 1995). Validation experiments showed that laser diffraction was robust and reliable and that the diffraction data was a good measure of the particle size of the aerosolized droplets.

Nebulized inhalation drugs are often admixed with others, however, their physical and chemical compatibility should be assessed before proceeding. For a discussion of this aspect of nebulizer therapy, see Kamin et al. (2007).

COMPATIBILITY

Compatibility studies are conducted to accelerate the development of formulations by allowing formulators to eliminate those excipients that cause API degradation. Factors that affect the compatibility between drugs and potential formulation aids include local pH and water content, which affect the chemical stability of the API. Typically, incompatibilities can arise because of either intrinsic degradation of the API and is facilitated by the excipients or a

Table 15 Known Reactivities of Some Functional Groups

Functional group	Incompatibilities	Type of reaction
Primary amine	Mono- and disaccharides	Amine-aldehyde and amine-acetal
Ester, cyclic, lactone	Basic components	Ring-opening ester-base hydrolysis
Carbonyl, hydroxyl	Silanol	Hydrogen bonding
Aldehyde	Amine carbohydrates	Aldehyde-amine Schiff base or glycosylamine
Carboxyl	Bases	Salt formation
Alcohol	Oxygen	Oxidation to aldehydes and ketones
Sulfhydryl	Oxygen	Dimerization
Phenol	Metals	Complexation
Gelatin capsule shell	Cationic surfactant	Denaturation

Source: From Monkhouse (1993), reproduced with permission.

covalent chemical reaction between the API and the excipients (Damien, 2004). Of course, it is worth checking whether there are any known incompatibilities, as shown in Table 15 (Monkhouse, 1993). After checking for any known incompatibilities, experimental investigations of compatibility should be undertaken. Akers (2002) has reviewed drug-excipient interactions with respect to parenteral formulations.

While the Maillard reaction between lactose and primary amines is well known, the same reaction between the secondary amine fluoxetine hydrochloride (Prozac) and lactose has recently been reported (Wirth et al., 1998). In the solid-state water content, lubricant concentration and temperature were also found to influence the degradation. In addition to the chemical reactions noted above, the drug may interact to form a molecular compound. For example, solid-state interactions between trimethoprim and antimicrobial paraben esters to form a 1:1 molecular compound have been reported (Pedersen et al., 1994).

When conducting compatibility studies, there are four steps to be considered, which are as follows:

1. Sample preparation
2. Statistical design
3. Storage conditions
4. Method of analysis

Traditionally, a binary mixture of drug and the excipient being investigated is intimately mixed, the ratio of drug to excipient being often 1:1; however, other mixtures may also be investigated. These powder samples, one set of which is moistened, are then sealed into ampoules to prevent moisture loss. These are then stored at a suitable temperature and analyzed at various time points using HPLC, DSC, FTIR (Fourier transform infra-red), or TGA as appropriate (Stulzer et al., 2008). Using DSC alone is not recommended since it can throw up false negatives and positives and should be used as guide only. Indeed, Larkshama et al. (2008) have concluded that DSC experiments need to be supported by other techniques such as FTIR and HPLC. The use of microthermal analytical technologies such as localized thermomechanical analysis (L-TMA), localized differential thermal analysis (L-DTA), nanosampling, thermally assisted particle manipulation (TAPM), and photothermal microspectrometry (PTMS) has been described by Harding et al. (2008). It is fair to say, however, that these are quite specialized techniques not widely available in industry at this point in time. Alternatively, the drug in suspension with excipients may be investigated (Waltersson, 1986). Table 16 shows data for 250 mg of remacemide hydrochloride mixed with 250 mg of spray-dried lactose and dispensed into clear, neutral glass ampoules. Half of the ampoules were sealed without further treatment, and to the others, 25 μ l of distilled water was added prior to sealing. The ampoules were then stored at 25°C for 1, 4, and 12 weeks.

As expected, there is clear evidence of incompatibility between the amine hydrochloride and the spray-dried lactose. However, the results also showed that moisture was the catalyst for decomposition as no degradation was observed in the dry state even after 12 weeks' storage at 90°C.

Table 16 Compatibility Study Between Remacemide HCl and Spray-Dried Lactose

Water added (μ l)	Storage temperature ($^{\circ}$ C)	Storage time (wk)	Color	Moisture by TGA	% Drug recovered
0	25	1	White	2.6	101.2
		4	White	2.6	99.4
		12	White	2.6	102.8
	70	1	White	2.6	105.0
		4	White	2.6	101.8
		12	Off-white	2.5	100.3
	90	1	White	2.6	102.5
		4	White	2.6	98.5
		12	Off-white	2.2	100.2
25	25	1	White	2.6	93.6
		4	White	6.8	102.6
		12	White	5.0	88.4
	70	1	Brown	3.2	91.4
		4	Brown/black	N/I ^a	99.7
		12	Brown/black	N/I	74.4
	90	1	Brown	4.0	98.5
		4	Brown/black	N/I	90.0
		12	Black	N/I	51.4

^aThermogram not interpretable because of extensive sample degradation.

Ahlneck and Lundgren (1985) have described methods for the evaluation of solid-state stability and compatibility between drugs and excipients. Three methods were studied and compared isothermally and non-isothermally, viz. suspension, storage of powders, and compacts at specified humidities and elevated temperatures. It was concluded that the suspension technique was good for fast screening of chemical instability. The other solid-state procedures were found to be better predictors of the solid dosage form.

The storage conditions used to examine compatibility can vary widely in terms of temperature and humidity, but a temperature of 50 $^{\circ}$ C for storage of compatibility samples is considered appropriate. Some compounds may require higher temperatures to make reactions proceed at a rate that can be measured over a convenient time period. Methods of analysis also vary widely, ranging from thermal methods, for example, DSC, microcalorimetry or chromatographic techniques like TLC and HPLC.

DSC has been used extensively for compatibility studies (Holgado et al., 1995). Although only milligram quantities of drug are needed for a DSC experiment, the interpretation of the thermograms may be difficult and conclusions may be misleading on the basis of DSC experiments alone (van Dooren, 1983; Joshi et al., 2002b). Nonetheless, the technique remains in use, for example, Verma and Garg (2005) and Araujo et al. (2005). The original protocol for DSC compatibility testing was proposed by van Dooren (1983), who suggested the following scheme:

1. Run the drug candidate and excipients individually
2. Run mixtures of the drug candidate and excipients immediately after mixing
3. Run the drug candidate and excipients individually after three weeks at 55 $^{\circ}$ C
4. Run the drug candidate–excipient mix after three weeks at 55 $^{\circ}$ C
5. Run the single components and mixtures after three weeks at 55 $^{\circ}$ C only if the curves of the mixtures before and after storage at this temperature differ from each other

An excipient that is particularly desired may be investigated further by examining different weight ratios with the drug. This method of compatibility testing has been criticized by Chrzanowski et al. (1986), who found that the DSC compatibility method was an unreliable

compatibility predictor for fenretinide and three mefenidil salts with various direct compression excipients. They concluded that an isothermal stress (IS) method (which requires a specific, quantitative assay method, for example, HPLC, for either test substance or its degradation products) was preferred for its accuracy over DSC in compatibility testing. In addition, the IS method gave quantitative information. Disadvantages of the IS system compared with DSC are that the tests tend to consume more compound than the DSC test and are conducted over longer storage times, one to two months at 60°C to 80°C. However, the whole point of DSC is speed of prediction, so DSC may be of use if the amount of drug available is small and an idea of compatibility is required (Venkataram et al. 1995). On the other hand, although DSC may be used to predict that interactions may occur, it provides little insight into the nature of the interaction (Hartauer and Guillory, 1991). Although most investigators use only binary mixtures of drug and excipient, Damien (2004) notes that the interactions are often complex and active substance-excipient compatibility studies must not be limited to simple binary mixtures.

Microcalorimetry has also been used in excipient compatibility studies (Phipps et al., 1998). In this study, 1:1 mixtures were prepared using a ball mill and examined for incompatibility by sealing samples in glass crimped vials using a microcalorimeter at 50°C at a set RH. After an equilibration period of between one to four days, thermal data were collected over 15 hours. Generally, the data from the thermal activity monitor (TAM) was comparable to the corresponding HPLC analysis. However, it was less successful in prediction when mixtures containing a hygroscopic component was present. Another work by Selzer et al. (1998) has shown that microcalorimetry can be used to detect incompatibility. However, since microcalorimetry only detects heat flow, they made the point that physical events such as crystallinity changes would be superimposed on the heat output signal. They also found that experimental temperatures close to the ambient could not be employed because the enthalpy change was not large enough.

In solid dose form technology, Monkhouse (1993) has argued that it may be a better idea to make tablets with proven excipient blends in a compaction simulator using representative compression forces. This, it was claimed, would use a small amount of the candidate drug and also take into account factors such as mixing, granulation, and compression. Then only if the tablet is proven to be unstable, should retrospective examination of the incompatibility be undertaken to identify the excipients that are incompatible. Indeed, according to this author, any formulations that do not contain lactose and magnesium stearate should be successful! Other investigators may have different experiences and may not have access to a compaction simulator. It is also worth being aware of processing-induced incompatibilities such as that reported by Wardrop et al. (2006), who found that even after conventional compatibility testing, degradation of their compound in a trial formulation was observed. The incompatibility was traced to an unusual anhydrate-to-amorphous transition that occurred because of granulation. A new dry process was developed, and polarized light microscopy was used to confirm the presence of the crystalline anhydrate after formulation.

Like other aspects of the work in the modern pharmaceutical industry, automation and high-throughput techniques are being employed to speed up the process. For example, Wyttenbach et al. (2005) have described a miniaturized high-throughput compound-excipient compatibility protocol, which included statistical experimental design techniques. In essence, they used 96-well technology, whereby the compound was mixed with the excipients in a ~1:100 ratio and stored under accelerated conditions of elevated temperature and humidity. At various time points, the mixtures were analyzed using fast gradient HPLC. Combined with the statistical experimental design factor interaction plots can be generated, and all this can be achieved using 0.1 mg of compound per data point. Workers from Pfizer (Thomas and Naath, 2008) have also reported an automated 96-well plate compatibility system, which can weigh and blend mixtures, conduct accelerated stress stability, extract the sample, and perform HPLC analysis. They have termed this system as drug-excipient compatibility automated system (DECCAS). Wakasawa et al. (2008) have conducted drug-excipient compatibility studies using a robotic system, which automatically dispenses, weighs, and stores powder samples, and then analyzes the drug substance using ultra-performance liquid chromatography (UPLC). After storage at 70°C for nine days, the samples are examined for degradation.

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8 | Product Optimization

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PURPOSE AND SCOPE

The major objective of product optimization is to ensure that the product selected for further development (the intended commercial product) is fully optimized and complies with the design specification and critical quality attributes (CQAs) described in the Target Product Profile and Product Design Report (refer to chap. 5). The traditional approach to product development described in the original version of this book emphasized that the following key outputs should be obtained from this stage of development:

- A quantitative formula defining the grades and quantities of each excipient and the quantity of candidate drug
- Defined pack
- Defined drug, excipient, and component specifications
- Defined product specifications

Although these are all still important, a paradigm shift led by the regulators in how products should be developed has added another dimension to the key outputs from product optimization. A series of quality-by-design (QbD) regulatory initiatives, including process analytical technology (PAT) and the ICH guidances [ICH Q8, pharmaceutical development; ICH Q9, quality risk management (QRM); ICH Q10, pharmaceutical quality systems (PQSs)], have been introduced to change the outputs from product optimization. The emphasis has changed from the need to demonstrate that the product will consistently meet relatively tight specifications to a new situation of being able to demonstrate that the product is controlled within a broader “design space.” Product optimization studies are conducted to determine the critical formulation attributes and critical process parameters and to assess the extent of their variation on quality attributes of the drug product, and hence to define the design space. Once this is defined, then changes within that design space should not require further regulatory approval. This QbD approach encourages the need for a greater scientific understanding of the product/process and to firmly link product development with manufacturing design. As continuous quality verification is built-in with PAT-based manufacturing and process control strategies, traditional end-product testing and tight product specifications should become less significant and the desired state of “real-time release” should be possible.

The Food and Drug Administration (FDA) (Nasr et al., 2008; Wechsler, 2007) has led the way in encouraging drug developers to adopt this new quality-based approach to achieve a shared vision to reach the “desired state” of drug manufacturing in the 21st century, whereby

- product quality and performance should be achieved and assured by design of effective and efficient manufacturing processes and
- product specifications should be based on mechanistic understanding of how formulation and process factors impact on product performance.

Under the traditional manufacturing model, drug developers submitted extensive chemistry, manufacturing, and controls data (CMC) to the regulatory authorities that set tight product specifications. The aim being to develop commercial manufacturing processes to meet those specifications and to avoid changes later. However, this approach has resulted in frequent manufacturing failures and product recalls, leading to drug shortages and higher manufacturing costs due to low manufacturing efficiency, considerable waste, and low

Table 1 Traditional Product Development Compared with the QbD Approach

Aspects	Traditional	Quality by design
Product optimization	Empirical; mostly univariate experiments	Structured; multivariate experiments
Manufacturing process	Fixed	Adjustable within the design space
Process control	In-process testing and off-line analysis, with slow response for go/no-go response	Utilization of PAT for rapid feedback and real-time response
Product specification	Relatively tight limits and primary means of quality control based on batch data; difficult to justify decreased testing based on limited data	Part of overall quality control strategy
Control strategy	Reliance mainly on end-product testing; not appropriate for real-time release	Risk-based control strategy associated with better process and product performance understanding; real-time release possible
Life cycle management	Reactive to problems and out-of-specification changes; could lead to more postapproval changes needing regulatory approval	Continual improvement with changes enabled within the design space

Abbreviations: PAT, process analytical technology; QbD, Quality by Design.

Source: From Nasr (2006).

facility/equipment utilization rates. This in turn has resulted in a need for more regulatory oversight to deal with these issues. The new QbD approach encourages drug developers to use modern statistical and analytical procedures to define the critical sources of variability in the product/process and to establish appropriate quality controls. The intention is to demonstrate to regulatory authorities a sufficiently high level of understanding of the design space and quality control (QC). The expectation is that there will be significant benefits to drug developers of reduced costs, a smoother application approval process, and the potential to gain regulatory relief when making changes within the design space post registration and over-the-product life cycle. It is anticipated that the regulatory authorities will also benefit from a reduction in post-registration manufacturing supplements for modifications and changes to the production process. They should also see a reduction in the time spent on inspecting companies to review massive amounts of information because risk management is intended to identify areas that require closer monitoring and also those that require less attention. According to the shared vision, patients should also benefit because they are more likely to get improved access to high-quality affordable and innovative treatment options.

The situation prior to these ICH guidances was disparate regulatory requirements in the United States, Europe, and Japan for product development and registration. In the United States, pharmaceutical development information was submitted in Investigational New Drugs (INDs) and New Drug Applications (NDAs) at minimal levels mostly, and a Pharmaceutical Development Report was produced to summarize the development history to aid preapproval inspection (PAI). Whereas, in the European Union (EU) the development pharmaceuticals sections describe formulation development and critical attributes and provide some information on the manufacturing design. In Japan, there was very limited product development information unless it involved a complex dosage form. Through these ICH initiatives there is greater harmonization of international agreement on key quality and Good Manufacturing Practice (GMP) principles, so narrowing the gap between regional expectations. The key differences between the traditional approach to product development and the QbD approach is summarized in Table 1 (Nasr, 2006).

ICH Guideline Q8 “Pharmaceutical Development”

The purpose of the ICH Q8 guidance on pharmaceutical development is to provide harmonized guidance for the suggested contents of section 3.2 P.2 (pharmaceutical development) contained in Module III of the Common Technical Document (CTD) for new drugs and biologics (FDA, May 2006). It was adopted as an ICH topic in October 2003 (International

Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use), was finalized in November 2005, and came into effect in May 2006. ICH Q8 recommends that drug developers present the knowledge gained from pharmaceutical studies, which provide scientific understanding to support the establishment of the drug product and its specifications and manufacturing controls in the pharmaceutical development section of the drug marketing application. ICH Q8 adopts the FDA principles of QbD, also known as “building quality in” and “right first time.” This deeper understanding of process control allows for the development of an expanded design space, which is defined as: “... the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post-approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval” (FDA, 2006). Section 2 of the Q8 document states how the design space is established through product/process design. By making changes to formulations and manufacturing processes during development, drug developers should generate the scientific knowledge that supports “establishment of the design space.” The Q8 document implies that both positive results and negative results are important to understanding the design space.

ICH Q8 (R1), the first revision of Q8, provides an annex to the already approved Q8 guideline and shows how the concepts and tools outlined in the parent document can be put into practice (ICH, 2008). This annex describes the principles of QbD and elaborates on the concept of design space with guidance on the selection of variables, defining and describing a design space in a regulatory submission, unit operation design space, relationship of design space to scale of equipment, design space versus proven acceptable ranges, and design space and edge of failure. Appendix 1 of ICH Q8 (R1) contains a useful table that compares a “minimal” approach with pharmaceutical development with an “enhanced” QbD approach. At a minimum, the pharmaceutical development report for a submission should provide information to support the formulation and manufacturing process proposed. To achieve this, pharmaceutical studies should identify properties of the active ingredient(s), excipient(s), and manufacturing process “that are critical and that present significant risk to product quality, and therefore should be monitored or otherwise controlled.” However, although not mandatory, there is an opportunity for drug developers to perform additional pharmaceutical development studies that can enhance “knowledge of product performance over a wider range of material attributes, processing options and parameters” (Fig. 1). They can share this information with the regulatory bodies in the development report section of the marketing application to demonstrate a higher degree of understanding of the manufacturing process and process controls. By doing this, pharmaceutical companies can benefit from the possibility of risk-based review and inspection, being able to make manufacturing process changes within the approved design space without further regulatory oversight, and also, the potential for reduced end-product release testing through real-time QC.

Process Analytical Technology

The PAT guidance initiative was introduced by the FDA in 2004 to encourage the pharmaceutical and biotechnology industries to improve their production processes by implementing new monitoring and control technology (FDA, 2004), and the FDA definition of PAT has been broadly accepted by the industry and its regulatory partners. In the PAT guidance, FDA defines PAT as “a system for designing, analyzing and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality.” The PAT initiative and design space are intricately linked, and it is the PAT tools described in the guidance that the FDA proposes should be used for gaining process understanding and can also be used to meet the regulatory requirements for validating and controlling the manufacturing process. For example, in traditional manufacturing processes, fixed blending times are specified, whereas in a PAT system mixing would continue until the system indicates that the blend is homogenous. A range of blending times may be specified on the basis of the variability of the process. A higher level of assurance of

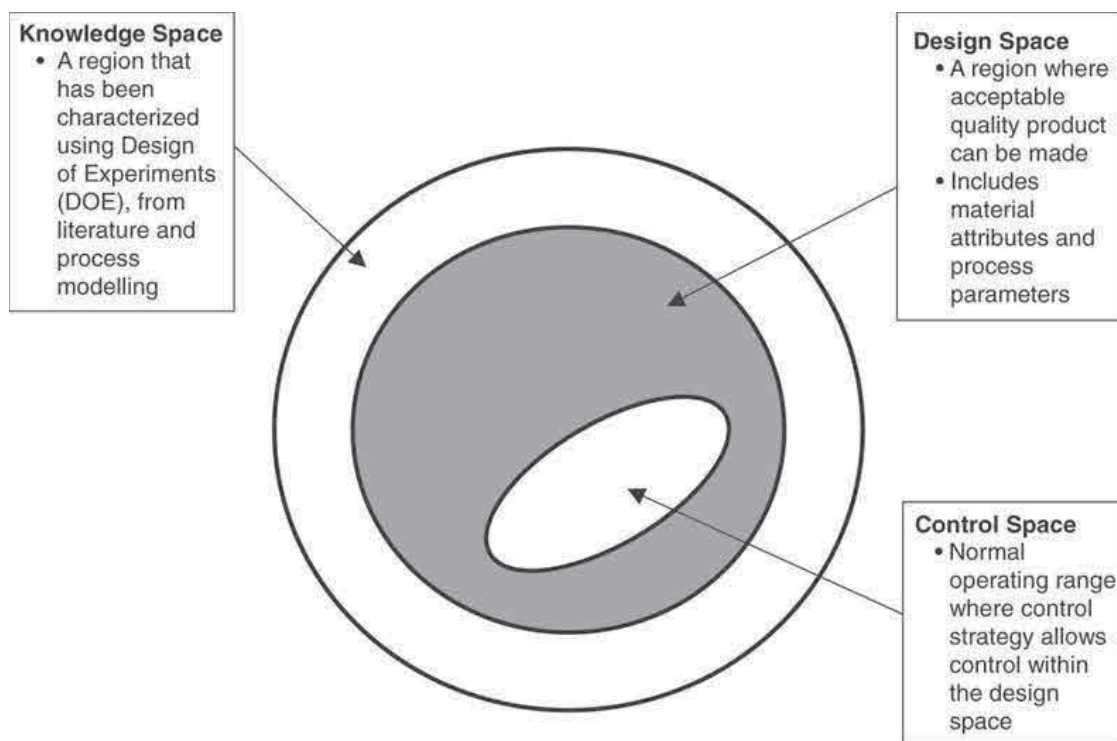


Figure 1 Representation of design space.

quality should be achieved by continuously monitoring, evaluating, and adjusting every batch, using validated in-process measurements, tests, controls, and process endpoints.

- *At line*: Measurements where the sample is removed, isolated from, and analyzed in close proximity to the process stream.
- *On-line*: Measurements where the sample is diverted from the manufacturing process and may be returned to the process stream.
- *In-line*: Measurements where the sample is not removed from the process stream and can be invasive or noninvasive.

The types of technologies that can be applied at-, in-, and on-line to measure, monitor, and control products and processes include near-infrared (NIR) spectroscopy, Raman spectroscopy, gas chromatography (GC)/liquid chromatography (LC) and acoustics, for example.

ICH Guideline Q9 “Quality Risk Management”

ICH Q9 was released as FDA guidance in 2006 (FDA, June 2006) and was later implemented in Japan and Europe. It outlines risk management principles and methods that can be applied to establish QRM systems, which can determine the appropriate level of control for a manufacturing process, from development to postmarketing manufacturing (the product life cycle). QRM involves identifying risks and then analyzing them, evaluating the consequences of a high-risk event, and establishing policies for risk reduction. The aim is not only to determine the most essential areas to monitor but also to evaluate where such efforts may not be necessary. The expectation is that drug developers will incorporate risk assessments during product development, utilizing any prior knowledge and experimental design data to determine the critical and noncritical parameters and attributes.

ICH Guideline Q10 “Pharmaceutical Quality Systems”

A third ICH guidance document (Q10) reached step-4 of the ICH process in June 2008. It is intended to harmonize the concept of quality systems for the pharmaceutical industry between

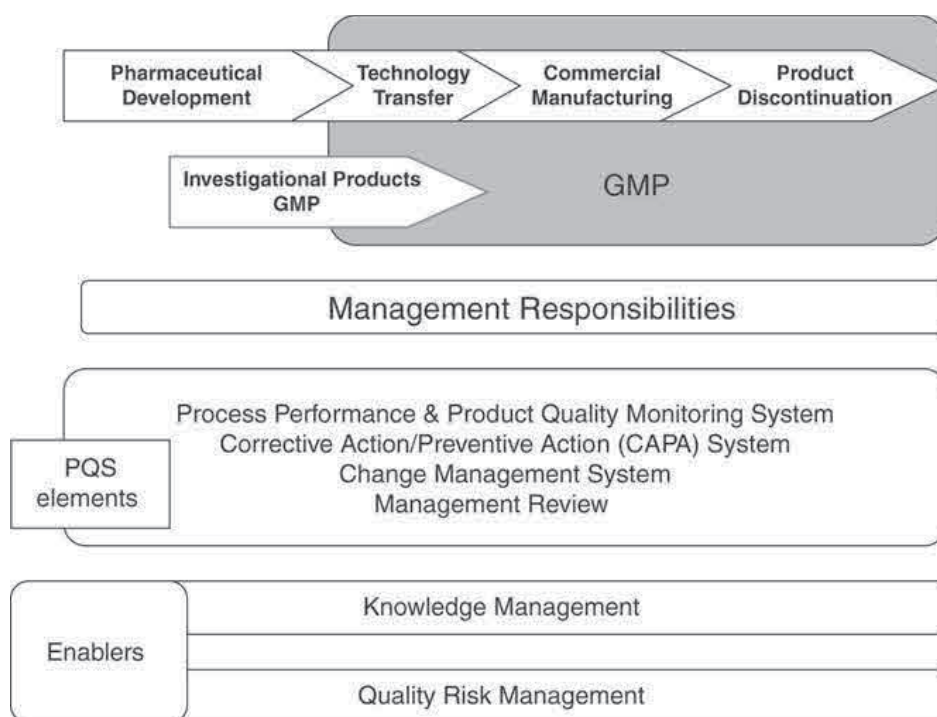


Figure 2 Diagram of the ICH Q10 pharmaceutical quality system model. *Abbreviation:* ICH, International Conference on Harmonisation.

the three regions: Europe, the United States, and Japan. This version contains a strong emphasis that one will only be able to achieve the aims of the new “quality paradigm” by implementing all three ICH guidelines Q8, Q9, and Q10. ICH Q10 enables the potential benefits from the other ICH guidance documents to be fully realized and links product development with risk management to assist drug developers in establishing PQSs. It encourages the industry to improve manufacturing processes, thus reducing undesired variability and leading to more consistent product quality, improved product robustness, and more efficient processes. Additionally, it recommends quality monitoring and review (e.g., data evaluation, statistical process control, and process capability measurements), which form the basis for continual improvement of processes. Figure 2 illustrates the major features of the ICH Q10 PQS model as defined in annex 2 of the ICH Q10 guidance.

The PQS covers the entire life cycle of the product, including pharmaceutical development, technology transfer, commercial manufacturing, and product discontinuation as shown in the upper part of the diagram. The PQS augments regional GMPs, including those applicable to the manufacture of investigational products. The next horizontal bar shows the importance of management responsibilities to all stages of the product life cycle as explained in section 2 of the ICH document. The following horizontal bar lists the PQS elements that support the PQS model. It is recommended that these elements be applied appropriately to each life cycle stage, recognizing opportunities to identify areas for continual improvement. The bottom set of horizontal bars shows the enablers the following: knowledge management and QRM that support the PQS objectives of achieving product realization, establishing and maintaining a state of control, and facilitating continual improvement.

ICH Q8 is a change from giving data to sharing knowledge with the regulatory authorities gained during product development, scale-up, and technology transfer from research and development (R&D) to Operations. Not every bit of information is mandatory, but it is understood that pharmaceutical development is a learning process, and it is acceptable to share information from both the successes and failures with the regulators. Discussions are ongoing between the regulators and the pharmaceutical industry using case studies and “mock” worked examples of regulatory submissions to illustrate the design space concept and to exemplify application of PAT, QbD, and QRM (ICH Q9) during the development process

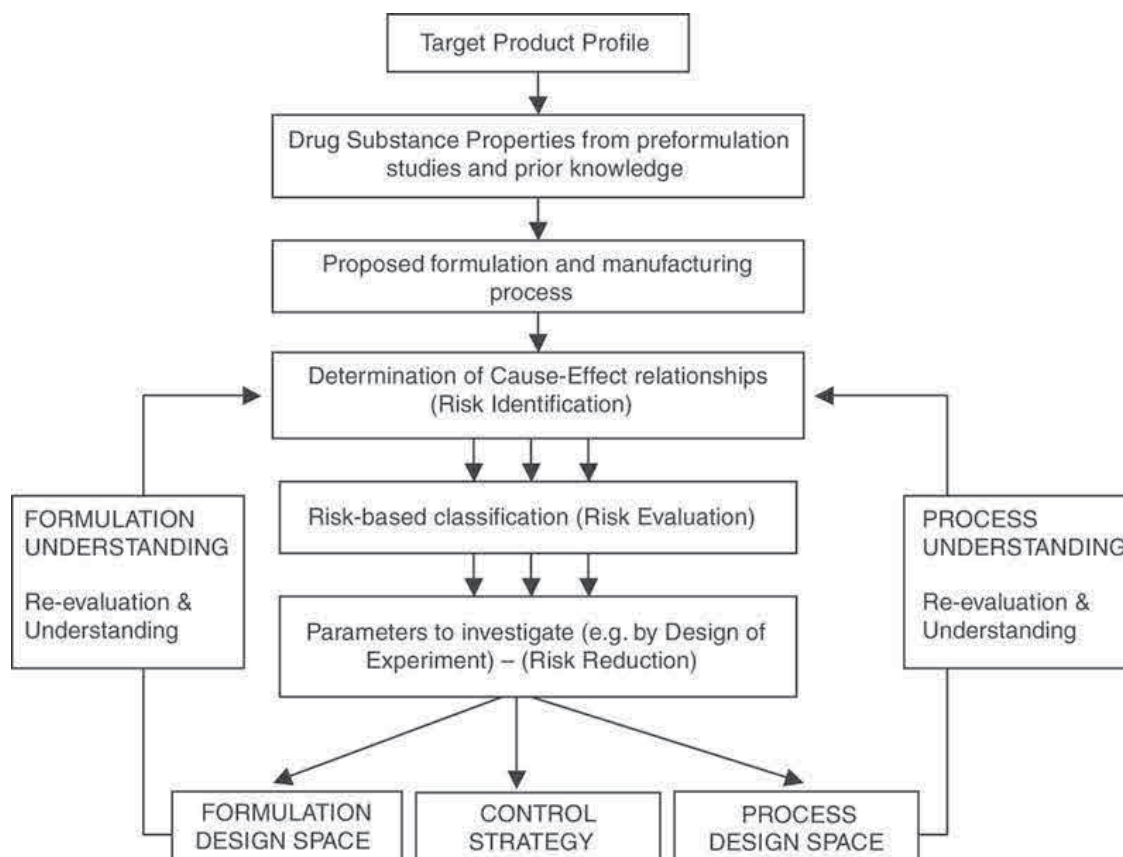


Figure 3 Iterative approach and application of ICH Q8 and Q9 to establish design space and control strategy. Abbreviation: ICH, International Conference on Harmonisation. Source: From Potter et al. (2006).

(Potter et al., 2006; Swanson, 2006). Figure 2 illustrates the iterative approach to formulation and process optimization of a pharmaceutical product using the scientific principles associated with the application of ICH Q8 and ICH Q9 to establish the design space and control strategy. Typically, the formulation and manufacturing process are developed first and then optimized by the iterative process described in Figure 3.

In July 2008, the FDA launched a QbD pilot program for biotechnology submissions to seek to define the clinically relevant attributes of biologics and link them to the manufacturing process. Many of the same fundamental QbD principles apply to both small molecules and biologics, but there is a greater challenge in characterizing complex proteins for routine QC. Through this program, the FDA will work with volunteer companies to gain the experience needed to implement a QbD, risk-based approach for complex biologics, and provide clear guidance to the industry. Additionally, ICH Q6B, Specifications: Test Procedures and Acceptance Criteria for Biotechnological and Biological Products, includes guidance for product characterization through the design of product specifications specifically aimed at controlling product heterogeneity. It allows for not testing certain impurities if supported by adequate process understanding and impurity clearance.

The approach to product optimization will depend on the nature of the product to be developed. It will always involve testing a range of options, for example, a variety of excipients from different sources, with different grades and concentrations, and in different combinations, or a range of pack sizes or different packaging materials. Additionally, it could involve testing a range of particle size distributions of the candidate drug or the excipients. Particle size may be critical for drug delivery or formulation processing. For example, material with a mean particle size distribution of 2 to 5 μm will be required for effective pulmonary delivery of aerosol suspensions and dry powders, whereas an even smaller particle size range (nanoparticles) may be required for the dissolution of poorly water-soluble drugs in parenteral formulations.

At the early stages of formulation optimization, preformulation studies are usually conducted to screen excipients or packaging materials and to select those compatible with the candidate drug, using accelerated stress-testing procedures. More details about the preformulation techniques, which can be employed for compatibility studies, are discussed in chapter 3. The importance of doing compatibility studies is for reducing the number of excipients and formulation options to test in further product optimization studies.

The final stage of formulation optimization will normally involve generating sufficient stability data on one or more variants to select the best variant. The optimal product will usually be selected on the basis of technical merit. However, there may be a need to consider other factors, such as the use of novel excipients and the associated safety/toxicological implications, supplier and sourcing issues, or the ability to patent the formulation or not. Some of these issues are discussed further below.

The manufacturing process used during product optimization should be designed with large-scale manufacture in mind. Ideally, the process should be as representative as possible to the eventual commercial-scale manufacture. This is because the manufacturing process may affect product performance characteristics and could influence the results of clinical studies. Although product and process design and optimization have been depicted as separate stages in the development framework, in practice they are often combined or closely linked. For example, it is important in pack optimization to select a pack that is suitable for use in production and will satisfy the demands of a high-speed automated filling line. Alternatively, the pack may have to be able to withstand stresses during processing, which could involve extremes of temperature or pressure, during autoclaving or freeze drying, for example. Process design and process optimization considerations are discussed later in this chapter.

At the completion of product optimization, when the best product variant has been selected, it is a good idea to summarize the work conducted in a Product Optimization Report. The report should reference the primary data from preformulation, product optimization, and stability studies, cross-referencing other investigational reports where necessary. It should clearly justify the recommendations for the quantitative formula, design space and the excipient, and component and product specifications. Such a document can be very useful to aid smooth technology transfer into production and for writing regulatory submissions.

EXCIPIENT AND PACK OPTIMIZATION CONSIDERATIONS

Excipient Selection

Historically, pharmaceutical excipients have been regarded as inert additives, but this is no longer the case. Each additive must have a clear justification for inclusion in the formulation and must perform a defined function in the presence of the active and any other excipients included in the formulation. Excipients are included for all sorts of reasons. They may function as an antimicrobial preservative, a solubility enhancer, a stability enhancer, or a taste masker, to name a few.

The International Pharmaceutical Excipients Council (IPEC) has defined a pharmaceutical excipient as any substance other than the active drug or prodrug that has been appropriately evaluated for safety and is included in a drug delivery system to

1. aid processing of the system during manufacture or
2. protect, support, or enhance stability, bioavailability, or patient acceptability or
3. assist in product identification or
4. enhance any other attribute of the overall safety and effectiveness of the drug product during storage or use.

In the 1960s, excipients were commodity items and tended to be of natural origin, but today many are synthetic or have been physically modified. Performance testing was done by the user, not the supplier. This has now changed with the introduction of recognized quality and performance standards for raw materials, which are defined in various pharmacopoeias (Moreton, 1999). The rationale for these changes is linked to the requirement to ensure that the

patient is provided with the correct dose as safely and consistently as possible. This can only be achieved if the raw materials are of a consistent standard, together with the active and consistent processing.

Unfortunately, the standards for the same raw material can vary in different pharmacopoeias, and so the choice of pharmacopoeia will depend on the intended market for the product (see later comments about harmonization of standards). Suppliers should provide materials that comply with the specified pharmacopoeial standards. Monographs for excipients provide minimum tests and specifications, which can save time and resource negotiating new specifications with the regulatory authorities. Even so, the user may have to do additional tests to show that the excipient is suitable for use in a particular product or drug delivery system.

The basic selection and acceptance criteria for excipients to be used in a product being developed should have been defined in the Product Design Report section on "Design Specifications and Critical Quality Parameters." In practice, each excipient must be shown to be compatible with the formulation and pack and effectively perform its desired function in the product. At the same time, the product design acceptance criteria should be complied with, such as the following: the excipient should be well established, and its intended route of administration should be safe and acceptable to the regulatory authorities, and the excipient should comply with pharmacopoeial requirements, be globally acceptable, and meet the proposed design specification.

The case for using well-established excipients (and packs) that have already been administered to humans by the intended route, and in similar dosage forms, has been emphasized previously in the section on "Safety Assessment Considerations" in chapter 5. New chemical excipients (i.e., those that have not been used in registered pharmaceutical products before) usually require a full development program, including comprehensive toxicological testing, to gain "approval" by the regulatory authorities.

There are clearly cost and time savings of using well-established excipients that have already been approved for use in other registered products and that have an established safety profile. The regulatory status of excipients can easily be checked by consulting the FDA's *Inactive Ingredient Guide*, the *Japanese Pharmaceutical Excipients Directory*, or other similar sources of information (Table 1). These sources should provide information about registered products already approved, which contain a particular excipient with quantities used or a list of all products by dosage form that have contained a particular excipient.

Excipients are normally considered to be acceptable if they are listed in the major pharmacopoeias from the United States, Europe, and Japan. There has been much progress in harmonizing the monographs for key excipients in these pharmacopoeias. For products being developed for Japan, excipients must comply with the Japanese pharmacopoeia. If other pharmacopoeial grades are used, a detailed explanation of how these are equivalent or of better quality is usually required. However, even if the excipient is listed in all the major pharmacopoeias, additional toxicological studies may still be required to qualify an excipient under certain circumstances, such as (i) excipients used previously in humans but not by the intended route or (ii) increased concentration of an excipient above that previously used by the intended route. In either case, more extensive testing will be required so that the tests and specifications applied are shown to be capable of controlling the identity, strength, quality, and purity of the excipient to commensurate with its intended use. In Japan, excipients that have not been used previously will be treated as new excipients, even if they have been used in other countries.

Some assurance can be gained about the quality and safety of an excipient if a Drug Master File (DMF) is available and the DMF holder provides permission to reference it. The DMF is a document submitted to the FDA by a vendor that provides detailed information, including toxicological data and specification tests. Type III DMF is for packaging materials and type IV for excipients. A DMF is never approved, but it will be reviewed by the FDA if it is associated with a product license application. For more information about DMFs, refer to the FDA Guideline for Drug Master Files (FDA, September 1989) and the FDA Web site at www.fda.gov/cder/dmf/.

Some food and color additives may have GRAS (generally recognized as safe) status, which also gives some assurance that they could be used in pharmaceutical products with minimal additional safety testing. This is especially the case if the excipient is not likely to be absorbed systemically from the formulation.

However, there will always be situations where the introduction of a new excipient is inevitable. The candidate drug, for instance, may be incompatible with the current range of excipients. Another reason might be the phasing out of existing excipients for safety or environmental concerns, such as chlorofluorocarbons (CFCs) in metered-dose aerosols. There may be a need to introduce a new excipient for a novel drug delivery system or to overcome disadvantages with the currently available materials.

A common factor that often influences the selection of excipients and excipient suppliers is a company's historical preference for certain excipients based on proven technical, commercial, and quality criteria. Many pharmaceutical companies have a list of preferred suppliers that have already been audited and approved. There are significant advantages of selecting excipients that the company already uses, in terms of time and costs. Limiting the range of standard excipients on a company's inventory should minimize overhead because of the reduced auditing, analytical testing, and development required. Also, a greater knowledge can be developed about the characteristics of excipients that have been extensively used. Technology transfer from R&D to the final manufacturing site should be easier and faster if the excipients are already in the inventory, and the release specifications and analytical methods are already known to the QC department. However, a downside to having a limited company inventory is the reduced options of excipient choice placed on the formulator when faced with a new formulation or drug delivery challenge.

For products intended for global marketing, selection of excipients that meet the regulatory requirements can often be more challenging than the technical issues. Obtaining marketing approval for a new product requires the regulatory acceptance of the new candidate drug and the excipients used in the formulation. The specifications for excipients must comply with the pharmacopoeial standard for the particular country. Unfortunately, there is a diversity of specification tests and limits for the same excipients in the different pharmacopoeias. This issue has long been recognized, and there is an ongoing program to harmonize or unify the different requirements for some excipients in the three major pharmacopoeias—Europe, Japan, and the United States—through the ICH program. However, the process of establishing agreed international excipient specifications has proved to be extremely slow. Inevitably, some excipients for which pharmacopoeial standards are in conflict may be discounted from consideration, even though they perform well in terms of functionality.

Another issue for global marketing is the differences of opinion about the safety of some excipients in different countries. For example, ethylenediaminetetraacetic acid (EDTA) is permitted in most countries for use in intravenous (IV) injections as a metal ion-sequestering agent, but not in Japan. Colors, artificial sweeteners, and bovine-derived products are other examples where safety concerns vary significantly from country to country (Tovey, 1995). All dyes available for food and drug use are banned in at least one country. However, it may be essential to add a coloring agent to a product to distinguish one product from another or to differentiate among a number of product strengths.

Coloring agents may also be required for developing placebos to match colored products for blinding in clinical trials. Nedocromil sodium nasal, ophthalmic, and respiratory products are all examples that require color matching because of the inherent yellow color of the drug substance. This can be especially challenging when a range of drug concentrations is required, with each concentration having a different color intensity. For the above reasons, it is not always possible to develop a single formulation for the worldwide market.

The sourcing of excipients can be another important selection and optimization criterion. It is generally desirable to have excipient sources available in the country where product manufacture is taking place, to avoid stockpiling material to compensate for possible transport and import delays. Even better is if there are multiple sources of the same type of excipient so that if one supplier fails to deliver or discontinues delivery, an alternative can be used. This might rule out the use of some suppliers or excipients. To cater to different manufacturing sites

in different countries, which might use slightly different equipment, it is important that the product and process developed are robust enough to cater to small differences in excipient characteristics and performance from different sources.

In conclusion, during product optimization, excipients will be selected on the basis of a variety of acceptance criteria. The quantities included in the formulation will be finalized on the performance characteristics of the excipient in the final product. At this stage it is important to fix the specifications of the excipients to ensure that the materials used, and hence the product, will be consistent throughout development. Setting product specifications is discussed in a following section.

Pack Selection and Optimization Considerations

A logical approach to packaging optimization is, first of all, to define the packaging function, followed by selection of the materials, and then testing the performance of the packaging to ensure that it will meet all the product design and functional requirements that were identified in the Product Design Report.

Product optimization of the pack should initially focus on defining the primary packaging (sometimes referred to as “primary container” or “immediate container”). This is most relevant to regulatory authorities because it is the primary packaging that is in direct contact with the drug product, including the closure, liner, and any other surface contacting the product.

The secondary packaging is the one outside the primary pack and, by definition, is not in direct contact with the drug product. Secondary packaging is often a carton or a blister, which may also function to protect the product from light or moisture. For example, it may be preferable to use a carton and a clear ampoule or vial, rather than an amber container for a photosensitive parenteral product, to allow users to inspect the contents of the primary package for contamination or signs of instability. There may be a requirement to have sterile secondary packaging, for example, for a sterile product likely to be used in an operating theater by a surgeon. The pharmaceutical company developing such a product should identify this requirement in the product design stage in the Target Product Profile to ensure that the pack and the sterilization process are considered during development. In the majority of cases, the purpose of the secondary packaging is simply to be elegant in its appearance, provide clear labeling instructions, and project a good marketing image.

Important selection and optimization criteria for the primary packaging may include the following:

- Satisfies environmental and legislative requirements for worldwide markets
- Availability of a DMF
- Ability to source from more than one supplier/country
- Acceptable cost of goods (particularly if a sophisticated device)
- Consistency of dimensions
- Consistency of pack performance
- Ability to meet function/user tests, customer requirements, and specifications

For some excipients, the global acceptability of some packaging materials varies from country to country. This can often stem from environmental concerns and the negative impact from the need to dispose of packaging waste. For example, polyvinyl chloride (PVC) is used widely to manufacture bottles and blisters for pharmaceutical products, but there is a growing concern about its safe use and disposal in some countries (Hansen, 1999). Incineration is the preferred method of disposal for PVC, with the downside that it emits toxic gases. Materials that are readily biodegradable, or that can be recycled, are preferred. This is not always possible with some types of synthetic materials.

Multiple sourcing of some synthetic polymeric materials may not always be possible, or desirable, because suppliers may have their own range of additives for the basic packaging material. It is therefore important that, once the packaging material has been established for a product, there is an understanding between the pharmaceutical company and the supplier not

to alter the polymer formula or processing conditions without consultation. Any changes should become apparent if the supplier has filed a DMF with the regulatory authorities. Some sophisticated drug delivery systems, such as valves for metering pumps used for nasal and pulmonary delivery, can contain a multitude of components made of different materials and grades. It is important that the pharmaceutical company is made aware of any changes during development so that the implications for product performance and stability can be considered.

The role of the pack will include the following:

- Containment and protection of the product: to ensure stability over shelf life, protection to withstand the influences of climate, distribution, warehousing and storage during use, and protection for child safety.
- Presentation to the user (e.g., doctors, patients, parents): provides relevant information, identification, visually attractive appearance, and assurance against tampering.
- Administration of the product: provides convenient and consistent dose delivery.

Protection of the Product

The formulation must be protected from the environmental elements of heat, light, moisture, gaseous and sometimes chemical or microbial attack, as well as physical protection during transport and handling. A product license will not be granted unless the quality, safety, and stability of the formulation in the commercial pack of choice over the declared shelf life have been demonstrated to the regulatory authorities. They will be looking for acceptable stability data when the product is stored under anticipated normal conditions, in addition to acceptable data from “accelerated” or stressed conditions. This might include, for example, storage of the product in different orientations or in adverse conditions of extremes of temperature and humidity. Even though products will have recommended storage conditions on the label, there will be times when they are challenged to extremes outside of this, for example, during transportation. In the United States, it is common to post medicines to patients, and the product may be retained in postboxes that are very hot or humid. Appropriate stressed stability studies should demonstrate the integrity of the container and closure and any possible interaction between product and container. However, there is a possibility that components may be leached from packaging under accelerated/stressed conditions, which may not occur under normal conditions of use. Accelerated studies can be very useful for compatibility testing and screening materials, but they should be accompanied by long-term stability studies under normal conditions of use to confirm the suitability.

Other stress tests worth considering to establish the robustness of the product and pack include vibration and impact testing. Successful testing should instill confidence that the product can be transported and, to some extent, be physically abused (dropped) in the hands of users.

Two specific instances where the regulatory authorities will usually request extensive information are sorption of active(s) or excipient(s) from liquid and semisolid formulations and leaching of pack components into liquid or finely divided solid preparations, over the proposed shelf life of the product.

Plastics and rubber materials used in containers and closure systems can contain certain additives, for example, plasticizers, stabilizers, lubricants, and mold-release agents. It is worth asking the material suppliers what polymer additives are involved so that these can be analyzed when conducting compatibility studies. The regulatory authorities require that these additives should not be capable of extraction into the formulation or leach from the container/closure to contaminate the product. Mercaptobenzothiazole (MCBT) is a common additive to rubber compositions used in closures for multidose parenteral containers, which is extremely toxic. For synthetic polymeric materials, the leaching of additives can result in morphological changes to the packaging materials. These changes may in turn affect physical properties such as hardness, stiffness, tensile strength, or viscoelasticity, which can be vital for pack performance. Leaking can be a problem because of the viscoelastic nature of some injection closure compositions. Other less obvious properties may also be affected, such as gas permeability and absorption. Permeation of gases or water vapor through the container

material can affect formulation stability if the candidate drug is susceptible to hydrolysis or oxidation.

Drug and excipient interactions with the container may involve leaching, permeation, sorption, chemical reaction, or modification of the physical characteristics of the polymer or the product. During product optimization, formulation factors, such as the pH, concentration of ingredients, composition of the vehicle (solvents and surface active agents), area of contact, and contact time, will need to be evaluated. Also, processing variables such as temperature might be important. There are cases where the drug may absorb into components of the pack. This can be a particular problem with protein/polypeptide drugs onto glass and plastic packaging components. The best-known example of excipient adsorption or absorption is the loss of antimicrobial preservative from solutions to container/closure systems, most notably the rubber bungs of multidose injection containers, or the rubber gaskets used in metered-dose nasal pumps. The effective concentration in solution can be reduced to such an extent that the product is no longer protected from microbial growth.

There is also the possibility of constituents from label adhesives migrating through polyethylene or polypropylene containers. This is something to be aware of when carrying out stressed compatibility testing and long-term stability testing.

Packaging for sterile products must be effectively contained and sealed to prevent microbial contamination, and must be robust enough to withstand any sterilization process required. The sterilization process can affect the leaching of components from the container into the product or affect the physical properties of the container. For example, autoclaving can soften plastic containers, and γ -irradiation can cause certain polymers to cross-link.

Other protective elements have also become important in recent years, namely, those of child resistance and tamper evidence. Child-resistant packaging originated in the United States in the 1970s and was then introduced into Europe, where it was adopted mainly in the United Kingdom and Germany. There has been an ongoing debate between pharmaceutical manufacturers, container suppliers, and regulatory authorities on how to ensure that there is a practical balance between child safety and the pack being sufficiently user-friendly so that the elderly and arthritic can obtain their medication. Tamper-evident containers are closed containers fitted with a device that shows irreversibly whether the container has been opened. Tamper evidence is particularly important for sterile products and has become increasingly desirable for other products to demonstrate that the product has not been interfered with.

The FDA has published comprehensive information on container closure systems in a guidance for industry document, "Container Closure Systems for the Packaging of Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Documentation" (FDA, May 1999).

Presentation to the User/Administration of the Product

For traditional dosage forms, such as tablets and capsules, the role of the pack is mainly for protection of the product during storage and presentation to the user. The design is not so critical for administration of the dose or performance of the product in the hands of the administrator (doctor or patient). For other dosage forms, such as inhalers for respiratory drugs and self-injection devices for parenteral products (e.g., insulin), the pack is an integral part of the drug product. These are often referred to as "drug delivery systems" because the packaging system or device in the hands of the administrator provides a means of ensuring that the correct amount of active drug product is delivered to the site of action as easily, reliably, and conveniently as possible.

With metered-dose inhalers (MDIs), for example, the FDA considers the drug product to be the canister, the valve, the actuator, the formulation, any associated accessories (e.g., spacers), and any protective secondary packaging. This is because the clinical efficacy of MDIs may be directly dependent on the design, reproducibility, and performance characteristics of the packaging and closure system. For these types of products, and other more sophisticated drug delivery systems, it is important that these product performance aspects are addressed during the product optimization stage. During development and before initiating critical clinical studies, the performance characteristics of the MDI (e.g., dosing and particle size distribution of the spray), in addition to the compatibility with the formulation, need to be thoroughly investigated.

When developing a product for Europe, which uses both device and medicinal product components (such as MDIs or powder-filled inhalers or prefilled syringes), the pharmaceutical company must establish whether the product will have to conform to the Essential Requirements of European legislation applied to medical devices (Medical Device Directive 93/42/EEC). If the medicinal product has a separate device element that could be refilled/reused, or the device and medicinal substance are presented separately, the device component will be subject to medical device controls, in addition to an application being made to the medicines authority (Tarabiah and Taxacher, 1999). The letters “CE” are the abbreviations of the French phrase “Conformité Européenne” which literally means “European Conformity” and is a declaration from the manufacturer that the product complies with the essential requirements of European health, safety and environment legislation. To obtain a CE mark for a medical device registered in Europe, there will be implications for the pharmaceutical company (and its suppliers) to have suitable quality systems in place (e.g., EN46001). Obviously, this should be established early on in product design to enable the appropriate routes for authorization to be obtained. Similar regulations apply for medicinal devices that will be marketed in the United States (cGMP, 21 CFR Part 820).

The packaging must also be convenient to use to promote good patient compliance, which is to encourage patients to take their medication at the correct times. User acceptance of the pack and/or delivery device can lead to that product being preferred in the market place. Product optimization studies may involve testing a range of pack options using a volunteer panel to establish the most user-friendly or patient-compliant packs that can be easily opened and closed. If a novel pack has been designed in-house by the pharmaceutical company, there is the possibility of filing a patent to gain market exclusivity for a number of years. Some examples of new innovations in pharmaceutical packaging development to improve drug delivery systems are described by Williams (1997).

SOURCES OF INFORMATION

Knowing where to find information about excipients and packaging materials as well as development and regulatory guidelines is critical to the preformulation and formulation scientist during the product design and optimization stages of development. Typical information that is often required for excipients and packaging materials include the chemical composition, function, chemical and physical properties, regulatory and safety status, manufacturers and suppliers, qualitative and quantitative composition of marketed products, stability data, known incompatibilities, and so on. Having this information can save much valuable time in the laboratory, generating the data from scratch.

There are also a lot of guidelines and regulations from various regulatory authorities and standard organizations to be aware of that affect product development. Some of the regulatory documents are legal requirements (regulations) such as the Code of Federal Regulations by the FDA, and some are regulatory requirements, which are stipulated within license applications, such as pharmacopoeial monographs. Others are guidelines, which must be followed or, if not, a very strong scientific argument must be provided for justification. For example, many of the documents published by the FDA as guidance are being held up by the assessors as a regulatory requirement. Companies have ignored these to their peril!

There is a host of reference sources available from literature, reference books, Web sites, and publications from various regulatory authorities and standard organizations. This section is not meant to be exhaustive, but should provide some general guidance to those developing new formulations.

If the excipient or packaging material has been used previously in marketed products by one's own pharmaceutical company, and the supplier has been audited, most of the information about these materials should already be available within the company. More often than not, excipients not listed in the company inventory will have to be considered. Some useful reference sources that may provide details of specific excipients and packaging materials are given in Table 2. These sources can be used to gain information about the choice and status of materials available. It should be possible to easily check whether the material of interest is well established, safe, and meets regulatory authorities' requirements or not. Some

Table 2 Sources of Information for Excipients and Packaging Materials

Source	Information	Comments
Various pharmacopoeias, e.g., United States/National Formulary; British, European, Japanese pharmacopoeias; Martindale, The Extra Pharmacopoeia; The Merck Index; The British Pharmaceutical Codex	Include standards and monographs for drugs, excipients, containers/closures, and medical devices	Updated regularly; many available in book format or CD-ROM; can be obtained through various publishers including Informa Healthcare
FDA Inactive Ingredient Guide	Lists excipients used in FDA-approved drug products marketed for human use by route administration and dosage form	Published by FDA, DDIR; available through FDA Web site; updated regularly
<i>Handbook of Pharmaceutical Excipients</i>	Excipient monographs containing data on uses, properties, safety, excipient interactions, standards; also a supplier's directory	A joint publication of the American Pharmaceutical Society and the Royal Pharmaceutical Society of Great Britain
<i>Handbook of Pharmaceutical Additives</i>	Excipients used in prescription and OTC products approved by the FDA or recommended by USP/NF, BP, and Ph. Eur., details manufacturers, composition, properties, function, and applications, toxicology and regulatory status of additives	Compiled by M. and I. Ash; Published by Gower, Aldershot, U.K. and Vermont, U.S.A.
Japanese Pharmaceutical Excipients Directory	Monographs on excipients used in pharmaceutical and cosmetic products	Edited by the Japan Pharmaceutical Excipients Council
Le Dictionnaire VIDAL	A codex of French-approved medicines includes quantitative composition of many products	
ABPI Compendium of Data Sheets and Summaries of Product Characteristics	Data sheets prepared by pharmaceutical companies on prescription and OTC products, including quantitative details of formulation ingredients and packaging used	Published annually by Datapharm Publications Ltd., London. Available electronically
<i>Physicians' Desk Reference</i>	Compendium of FDA approved pharmaceutical products; details formulation, pack, administration and use; identification guide	Published by Medical Economics Co., N.J., U.S.A., in participation with individual manufacturers; also PDRs for ophthalmology and nonprescription drugs; CD-ROM or hard copy or available electronically

Abbreviations: FDA, Food and Drug Administration; DDIR, Division of Drug Resources.

of the reference sources reveal quantitative compositions of products, giving an indication of acceptable levels that have been used previously in approved products.

Other leads can be found by browsing pharmaceutical and packaging technology journals or visiting trade shows and exhibitions.

Once a lead has been found on an excipient or packaging material of interest, the next useful step often is to contact the supplier for further information. It is usually in their interest to persuade pharmaceutical companies to use their materials because of the potential commercial return if the product is successful. Often, suppliers will assist customers with any enquiries and provide any missing information. They may provide small amounts of samples to try in attempts to satisfy the customers that their materials should be used. However, if a new supplier or material is seriously anticipated, it is wise to arrange for an audit of the supplier to ensure that it meets your company's appropriate quality standards, before becoming too committed. Also, it is advisable that more than one batch be evaluated to ensure

Table 3 IT Sources of Information and Development Guidelines

Source	Information	Comments
Food and Drug Administration (FDA)	Guidance for industry notes on various aspects of pharmaceutical product development, registration in the U.S.A., and inspections	Web site: http://www.fda.gov/
Committee for Proprietary Medicinal Products (CPMP) and European Medicines Evaluation Agency (EMA)	Guidance for industry notes on various aspects of product development and registration in Europe, e.g., "Excipients in the dossier for application for marketing authorization of a medicinal product (III/3196/91)"	Web sites: http://www.eudra.org/ emea/cmp and http://www.eudra.org/w3/emea.html
National Institute of Health Sciences, Japan	Guidance notes on registration of pharmaceutical products in Japan	Web site: http://www.nihs.go.jp/
International Conference on Harmonisation (ICH)	Guidelines and information on harmonized requirements for product development and registration	Web sites: http://www.ifpma.org and http://www.chugai.co.uk
Web site for other regulatory authorities	Local regulatory guidance	Web site: http://www.pharmweb.net/
UK Medical Devices Agency (MDA)	Medical device regulations and guidance notes for industry on European Directives for medical devices	Web site: http://www.medical-devices.gov.uk/
<i>International Medical Device Registration</i>	A compilation of all the regulations affecting medical device registration worldwide	Book edited by M. E. Donawa Published by Interpharm
Parenteral Drug Association (PDA) and Pharmaceutical and Healthcare Sciences Society (PHSS)	Technical reports and guidelines prepared by industry on various parenteral topics, e.g., Sterile Pharmaceutical Packaging, compatibility and stability (PDA)	PDA Archive containing research papers, technical reports and conference proceedings available on CD-ROM; updated annually
International Federation of Pharmaceutical Manufacturers (IFPMA)	Information on pharmaceutical manufacturers	Web site: http://www.mcc.ac.uk/pharmweb/ifpma.html

Abbreviation: IT, information technology.

that the material is consistent. Be aware that sample materials are not always representative of purchased materials. They may have a different impurity profile, for example, or might have slightly different physicochemical properties that might give misleading performance results.

The rapid development in information technology (IT) in recent years has revolutionized the availability and speed of retrieval of information. Many reference sources are now available on CD-ROM, which are generally much easier to store, access, and search than books and journals. The introduction of the World Wide Web (WWW), with a user-friendly graphical interface based on hypertext links, provides easy access via the Internet to a wealth of information and databases, which are kept continually updated (D'Emanuele, 1996). Some of the useful Web sites for sources of information about pharmaceutical development and regulatory guidelines are listed in Table 3. The Web site addresses are correct at the time of this writing.

ARTIFICIAL INTELLIGENCE

Artificial intelligence (AI) technologies have been applied in the pharmaceutical field since the early 1990s. AI is defined as the ability of a machine to learn and "think" for itself from experience and perform tasks normally attributed to human intelligence, for example, problem solving, reasoning, and process understanding. Expert systems, neural networks, genetic

algorithms (GAs), and neurofuzzy logic have been used to assist with formulation design and to obtain improved understanding of formulation and process optimization. They are widely used in situations where tasks are multidimensional and where relationships are nonlinear and extremely complex, for example, the underlying relationships between formulation components, manufacturing process conditions, and drug product quality. AI has become important in helping to make better use of information, increasing efficiency, and enhancing productivity. Many AI technologies are available as commercial software applications or computer-based programs for applications that include predictive models for various formulation types, and also, to model manufacturing processes and predict relationships between formulation properties and various process parameters (de Matas et al., 2007; Rowe and Roberts, 1998).

The development of a new medicinal product from a new molecular entity is a very time consuming and costly process. The formulator will usually start with a design specification. This could be very general, or it could be quite specific, perhaps expressed in terms of performance levels to be met in a number of predefined tests. To develop the formulation that will meet the product specification, the formulator will have to take into account several different technical issues such as the physicochemical properties of the candidate drug, the compatibility of the drug with pharmaceutical excipients, and packaging and the manufacturing process to be used. The formulator might have to go through several iterative formulation optimization steps before the ideal product is achieved.

Pharmaceutical formulation development is thus a highly specialized and complex task that requires specific knowledge and often years of experience. This type of knowledge is very difficult to document and is therefore often passed on by word of mouth from experienced senior formulators to new personnel. The loss of senior formulators from a company through retirement or transfers to other companies can lead to the loss of irreplaceable knowledge. Formulation "expert systems" have been developed to provide a mechanism of capturing and utilizing this knowledge and expertise.

Several different definitions for an expert system have been used (Partridge and Hussain, 1994; Turban, 1995). They all state that an expert system is an advanced computer program that mimics the knowledge and reasoning capabilities of an expert in a particular discipline.

In essence, the programmer will build a system based on the expertise of one or more experts so that it can be used by the layperson to solve difficult or ambiguous problems. The intent of an expert system is not to replace the human expert but to aid or assist that person.

An expert system consists of three main components:

1. *The user interface*, which is necessary for the expert system to interact with the user and vice versa.
2. *The inference engine*, the procedure, which generates the consequences, conclusions, or decisions from the existing knowledge extracted from the knowledge base.
3. *The knowledge base*, the set of production rules that is supplied by the human expert and encoded into rules so that the system can understand the information.

Expert systems can be developed using various techniques, including conventional computer languages (PASCAL and C), artificial intelligence languages (PROLOG, LISP, and SMALLTALK), and specialized tools known as shells or toolkits.

Expert systems shells are computer programs written in both conventional and specialized languages, which are capable of forming an expert system when loaded with the relevant knowledge. The development time of an expert system using a shell is much faster than using conventional languages and has therefore proved to be the method of choice. Shells used in product formulation vary from the relatively small and simple systems, such as Insight 2+ and Knowledge Pro, to the large and flexible Product Formulation Expert System (PFES) from Logica (UK). PFES was developed from research work conducted by a consortium of Shell Research, Logica (UK) and Schering Agrochemicals under the UK Alvey Programme, 1985 to 1987 (Turner, 1991).

To build a pharmaceutical formulation expert system, the formulation process has to be broken down into a number of discrete elements to provide distinct problem-solving tasks, each of which can be reasoned about and manipulated. However, as the formulation process is

so complex, none of these tasks can be treated independently. A means of representing interactions and communicating information between tasks is therefore required. For example, one task may result in certain preferences that must be taken into account by subsequent tasks. To achieve this level of communication between tasks, the information in an expert system has to be highly structured and is therefore often represented as a series of production rules. An example of a production rule is as follows:

- IF (condition)
- THEN (action)
- UNLESS (exception)
- BECAUSE (reason)

Using a pharmaceutical example, this production rule would read:

- IF the drug is insoluble
- THEN use a soluble filler
- UNLESS the drug is incompatible with the filler
- BECAUSE instability will occur

The knowledge used in the production rules can come from many sources, including human experts, textbooks, past formulations, company standard operating procedures (SOPs), and development reports. The knowledge contained within these can be broken down into different types: facts, which are the objects and concepts about which an expert reasons, and rules and heuristics, which are often referred to as the expert's rules of thumb. The difference between rules and heuristics is that rules are always true and valid, whereas heuristics are the expert's best judgment in a particular situation and therefore may not always be true (Rowe, 1997). The knowledge will be put into the expert system shell by a knowledge engineer. The knowledge engineer is an IT expert who, through a series of interviews with the formulation experts, will capture all the steps involved in the formulation process. The knowledge engineer will then encode these tasks into a series of production rules, which he or she will build into the expert system. This process of knowledge acquisition can be very time consuming and therefore very expensive.

Reference to the use of expert systems in pharmaceutical product formulation first appeared on April 27, 1989, in the London's *Financial Times* (Bradshaw, 1989). This article was closely followed by one in the same year by Walko (1989). Both these authors described the work being undertaken by ICI (now Zeneca) Pharmaceuticals and Logica UK Ltd. to develop an expert system for formulating pharmaceuticals using PFES. Since these first publications, many companies and academic institutions have published on work being conducted in this area, as shown in Table 4.

A flow diagram of the AstraZeneca tablet formulation expert system is shown in Figure 4. The formulator enters the physicochemical information known about the drug, the

Table 4 Published Work on Pharmaceutical Formulation Expert Systems

Formulation	Company	System	Reference
Tablets	ICI (now AstraZeneca) Cadila Laboratories University of Heidelberg (GSH)	PFES PROLOG C/SMALLTALK	Rowe (1993a,b) Ramani et al. (1992)
Tablet film coating	GlaxoSmithKline (GSK) & AstraZeneca (AZ)		
Capsules	Sanofi Research Division Capsugel/University of London University of Heidelberg (GSH)	PFES C C/SMALLTALK	Bateman et al. (1996) Lai et al. (1995,1996)
Parenterals	ICI (now AstraZeneca) University of Heidelberg (GSH)	PFES C/SMALLTALK	Rowe et al. (1995)
Aerosols	University of Heidelberg (GSH)	C/SMALLTALK	

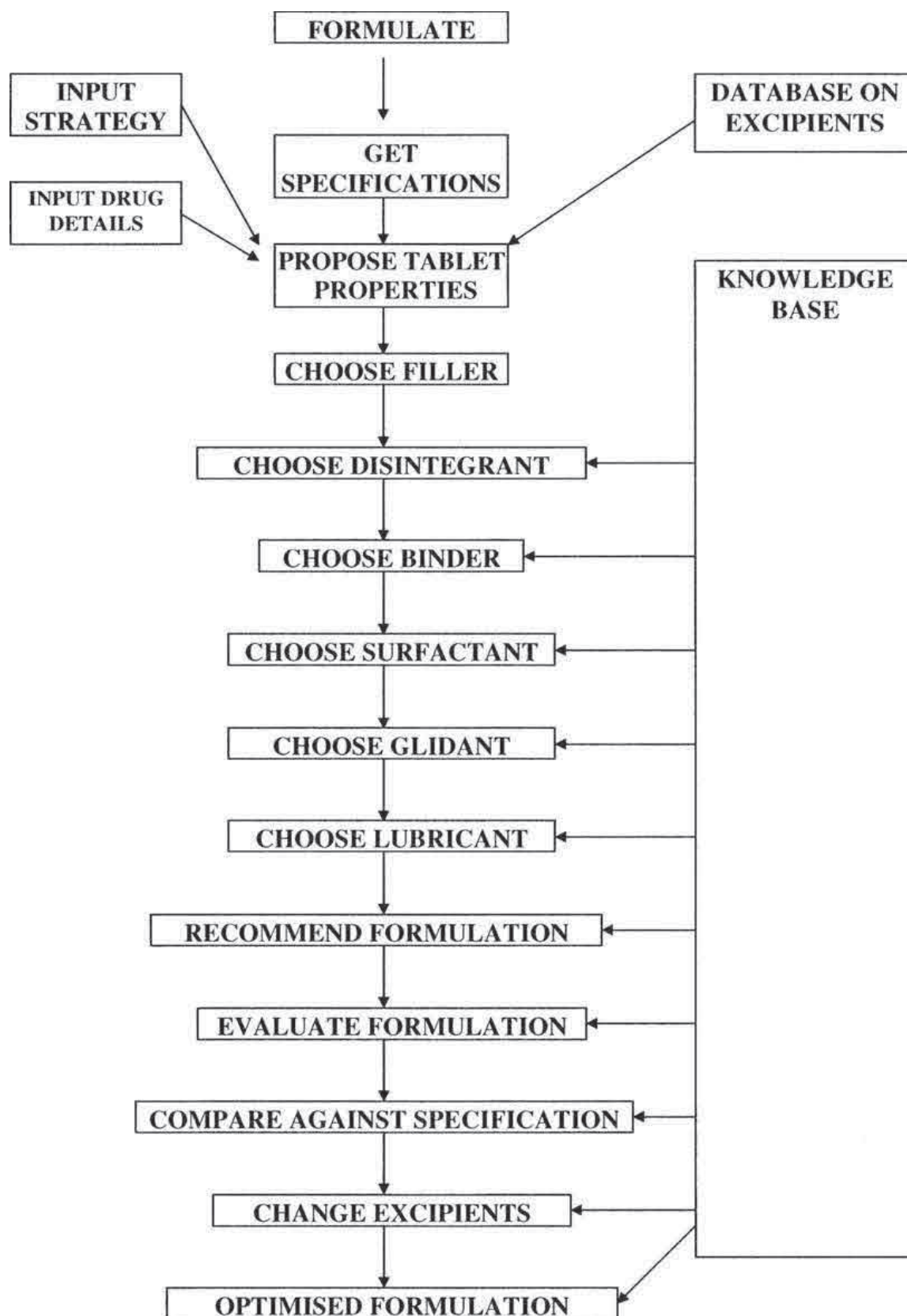


Figure 4 Flow diagram of the Zeneca tablet formulation.

specification for the formulation, and the formulation strategy (e.g., whether to use 1 or 2 fillers in the product). The system then goes through a series of steps from which the filler, the binder, the lubricant, the disintegrant, the glidant, and the surfactant and their relative proportions will be chosen. A formulation will then be recommended to the formulator. A series of defined tests can be carried out on the formulation to ensure that it meets the original specification. If it fails to satisfy the necessary requirements, the formulation can be optimized by feeding back the results into the system. The system has been designed to give a report on the decision processes used, which is the production rules that fired during the development of the formulation.

The following benefits have been seen from the development and use of formulation expert systems (Rowe and Upjohn, 1993):

- Protection of commercial knowledge. The expert system acts as a knowledge archive for formulation information, thereby overcoming the problems of staff turnover.
- Harmonization of formulation processes and excipient usage, giving a guarantee of a consistent approach to formulation within the same company.
- Training aid for novice formulators. Inexperienced formulators can quickly learn about a product or formulation area using an expert system. A spin-off from this is to release the time of more experienced formulators currently involved in the training process.
- Cost reduction. On the basis of the reduced time required for formulating and speed of development, Boots claim that they have saved 30 formulator days per year since the introduction of their sunscreen formulation expert system (Wood, 1991).
- Improved communication. The formulator and decision-making process is transparent to everyone in the company.

In spite of the many perceived benefits, the development of expert systems per se over recent years has been surprisingly slower than one would expect. One possible explanation for this is that when the systems were first introduced, their capabilities were overestimated, and they were seen as the panacea to all formulation problems. This was obviously not the case, but as a result, the systems are viewed with some degree of skepticism. Several reviews on the issues and limitations with the development of an expert system have been published (Dewar, 1989; Tinsley, 1992; Rees, 1996).

Other AI technologies that have been developed include neural networks, neurofuzzy logic, and GAs (Rowe and Roberts, 1998). Artificial neural networks are computer-based programs designed to mimic the process of the human brain's cognitive learning and work by building up a network of interconnecting processing units or nodes, which are the artificial equivalent of biological neurons. They can be used to find cause-effect relationships that may be hidden in experimental data and to generate predictive models, for example, to link important factors to measurable outputs such as the effect of drug particle size on tablet dissolution. Fuzzy logic is a powerful problem-solving technique based on mathematical theory that can be applied to control and decision making. It derives its power from being able to draw conclusions and to generate responses from vague, ambiguous, incomplete, and imprecise information. GAs are adaptive search algorithms, which are loosely derived from the principles of genetic variation and the Darwinian concept of natural selection. They provide another means of optimizing multivariate systems by identifying and evolving solutions until the desired combination of properties (e.g., formulation components or process parameters) giving optimum product performance is found. With the new regulatory paradigm where drug developers are expected to generate greater understanding of their products, the use of experimental design (see sect. "Experimental Design") coupled with AI technologies present a good opportunity to generate sufficient formulation and process understanding and build reliable predictive models. AI systems cannot be a substitute to an expert formulator, but can act as excellent decision-making tools.

EXPERIMENTAL DESIGN

The concept of experimental design originated in the agricultural industry and was developed by Sir Ronald Fisher. His first article appeared in the *Journal of the Ministry of Agriculture* in 1926, followed by a book *The Design of Experiments* in 1935. The concept of experimental design gradually spread to other industries, with the first publication of pharmaceutical relevance appearing in 1952 (Hwang, 1998). More recently, design of experiments (DOEs) techniques are being applied to formulation and process optimization because this is the most efficient means for identifying and studying the effect and interaction of product and process variables.

Pharmaceutical scientists are now almost universally aware of the disadvantages of traditional “one factor at a time” experimentation and recognize the advantages of a structured statistical approach to product development, as described below. Despite this, the routine use of experimental design in pharmaceutical development has only recently become widespread. The slow uptake of DOE techniques may have been a consequence of the lack of suitable user-friendly software packages. Until recently, scientists were forced to rely on SAS-literate statisticians, with the mechanics of data analysis being something of a “black box.” This situation is changing with a number of easy-to-use software packages, such as Modde and Design Expert, being available. The impact of this development cannot be overstated; with relatively little statistical training, scientists are able to build their own experimental designs and analyze their data. Good statistical support remains of paramount importance, however, for all but the simplest of experimental designs, so that potential pitfalls are not overlooked. The key message from experience of using experimental design in pharmaceutical development is the importance of the pharmaceutical scientist and the statistician working side by side.

Benefits of Experimental Design

The potential benefits of using a structured statistically valid experimental design rather than using traditional one factor at a time experimentation are summarized below and are illustrated by the examples given later in this section.

- *Savings in time, money, and drug substance.* This is particularly important in early formulation development when both time and drug substance are usually at a premium. The use of a suitable screening design, such as a fractional factorial, can allow the main effects of a number of variables to be evaluated in a minimal number of experiments.
- *Identification of interaction effects.* One of the most important benefits of experimental design is that interaction effects between variables as well as the main effects of the individual variables can be identified and quantified. This is vitally important in instances where the effect of one variable is dependent on the level of another.
- *Characterization of response surface.* By defining how a response variable responds to changes in process variables, a process that is in a plateau region can be selected, thus avoiding carrying out a process close to an optimization precipice. In addition, knowledge of how a process responds to changes in one or more operating variables is invaluable in defining the design space and normal operating range.

The Practical Use of DOE Techniques

A detailed discussion of the statistical principles underlying DOE techniques is beyond the scope of this book. Rather, some literature examples are presented that serve to illustrate the potential utility of DOE in all stages of pharmaceutical development.

Screening Studies

Partial factorial designs are widely used in early preformulation and formulation development, since they allow a large number of variables to be evaluated using a relatively small number of experiments. Variables may be either quantitative or qualitative; for example, the presence or absence of a particular component at a fixed level could be an experimental

variable. In full factorial experimental designs, every combination of variables is evaluated. This can lead to a large number of experiments, for example, a design that included four variables each at two levels would require 16 experiments. In a half factorial design this number would be reduced to eight. Clearly, there is a price to pay for this resource saving; some information on interaction effects will be lost by the process of confounding interaction effect terms with main effect terms. Nevertheless, the experiment can be structured such that those two-way interaction effects, which are suspected to be most significant, can be included in the model. Furthermore, fractional factorial experiments can be easily expanded by addition of the missing experimental runs. Hwang et al. (1998) described a tablet formulation optimization study in which a fractional factorial design was used to identify the formulation factors that were critical to achieving a high-quality product. Nine experimental factors were evaluated with only 16 experiments. Only main effects could be detected using such a small number of experimental runs, but statistical analysis of the data showed that only one factor required further optimization. This factor was then studied in detail in a subsequent optimization study. Plackett–Burnham designs, which are based on the two-level factorial approach, are widely used for screening studies where the main effects of a larger number of variables require evaluation in a limited number of experiments.

Optimization Studies

The use of a full factorial experimental design can provide a detailed understanding of the experimental response surface or design space. This type of design can be used when the number of variables to be investigated is small. Fransson and Hagman (1996) describe the use of a three-factor, two-level full factorial experimental design to evaluate the effects of light intensity, oxygen level, and phosphate content on methionine oxidation of human insulin-like growth factor. Although the basic design required eight experiments, a further four were carried out to provide an estimate of the inherent experimental variability. An interaction term was identified between the phosphate concentration and light intensity, with the effect of light being much greater when the phosphate concentration was high. The same technique was used by Bodea and Leucuta (1997) in the optimization of a sustained-release pellet formulation. Again, significant interaction effects were detected.

One of the limitations of two-level factorial designs is the assumption of linearity of the effects. In reality, it is rather unlikely that the factor/response relationship will be linear. This relationship can be characterized more fully by the use of three-level factorial experiments, but this adds considerably to the number of experimental runs required. Various other experimental designs can be used to obtain a detailed knowledge of the response surface. For example, Vojnovic et al. (1996) describe the use of a Doehlert experimental design in the optimization of a high shear granulation process. In this case, the authors were using experimental design to identify an experimental region in which the quality of the product was relatively insensitive to small changes in processing variables, thus verifying the robustness of the process.

An alternative method of optimization is the simplex search method. This is a model-independent procedure in which the results of earlier experiments are used to define subsequent experiments. This type of optimization is based on a systematic “trial and error” search for the optimum rather than statistical principles but can nevertheless be a useful method for defining the experimental region of interest.

Mixture Designs

Mixture designs are used in situations where the levels of individual components in a formulation require optimization, but where the system is constrained by a maximum value for the overall formulation. This is most easily illustrated by considering the optimization of a solution formulation containing a number of components each at a given percentage w/w. Clearly, the sum of all the components of the formulation, including water, must equal 100%. The experimental runs to be carried out depend on the model to be fitted. Marti-Mestres et al. (1997) describe the use of a simplex centroid design to optimize the relative proportions of three surfactants in a shampoo formulation. In this case, the total surfactant concentration was fixed at 18%, with the remainder being water and a number of minor components whose

concentrations were also fixed and therefore not considered as experimental variables. Seven experimental runs were used to generate a quadratic model; a further three runs were carried out using other combinations of variables within the experimental region to check the fit of the model. Three response factors were used to evaluate the quality of the formulations, and contour plots were developed illustrating acceptable formulations in terms of the individual responses. These contour plots were superimposed to yield a relatively small area of the experimental region in which all three response factors were satisfactory. Vojnovic and Chicco (1997) used a similar approach but employed an axial design to evaluate the solubility of theophylline in a four-component solvent system.

It is evident that the use of suitably designed experiments can be an invaluable aid to the optimum use of resource at all stages of product development. In early development, screening studies enable the rapid assessment of the effect of several variables on the key characteristics of the product. More elaborate experimental designs can be used at the formulation, pack, and process optimization stages to ensure that the effect of all components and process variables are fully understood. Finally, prior to process validation, the use of experimental design techniques is invaluable in ensuring that the process is robust and that the operating region is not close to an "optimization precipice." The software tools are now available to enable the pharmaceutical scientist to exploit the potential benefits of DOE, and the regulatory authorities are now expecting DOE to be used in support of QbD.

STABILITY TESTING

The purpose of stability testing is to provide evidence of how the quality of a drug substance or formulated product varies with time under the influence of a variety of environmental factors such as temperature, light, and humidity. The ultimate goal of stability testing is the application of appropriate testing to allow the establishment of recommended storage conditions, retest periods, and shelf lives.

It is necessary to establish the "fitness for purpose" of the product throughout a proposed shelf life, which is to establish that all those attributes affecting product performance in use are not unacceptably changed during the period of storage up to the proposed expiry date. Testing must include factors affecting drug potency, formation of degradation products, and the microbiological and physical integrity of the product. It may also be required to measure other quality parameters considered important, such as the organoleptic and aesthetic properties of the product.

Stability studies are carried out during all stages of development of new drug substances, formulated products, and where appropriate, novel formulation excipients. However, the stability design and type of testing will depend on the stage of the development process and the nature of the drug and product under test. The types of stability studies carried out during development will typically include the following:

- Accelerated stress stability testing
- Stability to support safety and clinical studies
- Stability to support product license applications

Accelerated Stress Stability Testing

These are studies in which samples are stored under conditions designed to stress the drug substance or product. Techniques and test conditions that can be used are further discussed in chapter 6, "Preformulation Studies as an Aid to Product Design in Early Drug Development." Generally, samples are exposed to extremes of temperature or humidity. Also, exposure to intense light, metal ions, and oxygen may be investigated. The aim of these studies is to provide information about the possible routes of degradation of the drug substance and what chemical and physical factors will affect degradation. For the drug product, the compatibility of the candidate drug with potential formulation excipients and packaging, routes of

degradation in potential formulations, and the identity of the major degradation products can be established. This information will provide important guidance to the formulator on the formulation factors that will affect product stability. Stability data from accelerated studies can also be used to predict shelf lives at ambient conditions as discussed below.

Stability to Support Safety and Clinical Studies

Although real-time data provide the ultimate test of the defined shelf life, the prediction of stability by the use of accelerated stress stability studies is vital in reducing the time to establish shelf lives for products used in safety and clinical studies. By applying the principles of chemical kinetics to data from accelerated storage tests, predictions can be made of the rate of decomposition at ambient temperatures. The Arrhenius relationship is often assumed for this modeling. However, this approach can sometimes fail to give good predictions when applied, because more complex decomposition is occurring, involving both chemical and physical factors. In these cases, more complex predictive models can be applied, but it may be that only real-time data can be used.

The regulatory authorities recognize that modifications are likely to be made to the method of preparation of the new drug substance and formulation and to the formulation itself during the early stages of development (phases I and II). The emphasis should generally be placed on providing information to develop a stable formulation and to support a shelf life suitable for the duration of the initial clinical studies.

During phases I and II, stability testing is required to evaluate the stability of formulations used in these clinical studies. The duration of the stability study will depend on the length of the clinical studies, usually one to two years. Data generated should be of the appropriate quality for submission to regulatory authorities, to support a Clinical Trials Application (CTA) or IND submission, for example. The information may also be used to provide supporting data for a product license application. These stability studies will monitor changes in product performance characteristics and identify formulation degradants produced under actual conditions of storage. Stability data should be sufficient to obtain the additional information needed to develop the final formulation and to select the most appropriate primary container and closure.

Stability to Support Product License Applications

In stability testing to support a product license application (usually conducted during phase III), the emphasis should be on testing the proposed commercial formulation stored in the proposed market packaging and using the final manufacturing process at the proposed commercial production site. Alternatively, the process must be representative of the final manufacturing process at a scale that should be at least 10% of that proposed for full commercial scale manufacture. Ideally, drug substance used should be synthesized using the final process. Stability data will be required on at least three batches of drug substance and for product batches made from three different batches of drug substance and different batches of excipients and packaging materials. If packaging components in contact with the product are obtained from more than one supplier and they are not considered to be equivalent, then product packed in components from both suppliers should be tested.

Detailed regulatory guidelines are available to provide assistance to companies making regulatory submissions, including recommendations regarding the design, conduct, and use of stability studies. Information is readily available from the Internet Web sites of various national and international regulatory authorities and manufacturers' associations:

- FDA (<http://www.fda.gov/cder/guidance/index.html>)
- CPMP (<http://www.fda.gov/cder/guidance/index.html>)
- ICH (<http://www.ifpma.org>)

Much progress has been achieved by ICH in harmonizing the requirements for stability testing in the three areas, namely, Europe, Japan, and the United States. Thus, information generated in any one of these three areas should be mutually acceptable in both of the other

two areas, thereby avoiding unnecessary duplication of effort. ICH Q1 “Stability Testing of Drug Substances and Drug Products” was initially published in 1994, but has been revised in 2001 and 2003. This guidance defines what stability data package is required for a new drug substance or drug product registration application in the three regions. Additional published guidance on “Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products” (2003) is intended to address recommendations on the application of bracketing and matrixing to stability studies conducted in accordance with principles outlined in the ICH parent guidance Q1A. The parent guidance notes that the use of matrixing and bracketing can be applied, if justified, to the testing of new drug substances and products, but provides no further guidance on the subject. In the Q1D guidance specific principles are defined for situations in which bracketing or matrixing can be applied. Examples are included where bracketing or matrixing could be acceptable for different strengths of the same product, different pack sizes, and different batch sizes, for example. A bracketing design can be usefully adopted to reduce the number of product strengths to be tested, but still cover the range of commercial product strengths. Similarly, a carefully designed matrix of testing can be used to reduce the number of product variants and time points tested, saving a lot of time and resource.

DEVELOPING SPECIFICATIONS

A specification is defined by ICH as a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use.

Specifications will be required for the pharmaceutical active ingredient, any excipients used in the formulation, the packaging components, and the finished product (at the time of manufacture and over the shelf life). In all cases, the specifications tests and limits will evolve during development, as illustrated in Table 5. It is clearly beneficial to have full specifications in place for the start of the phase III pivotal clinical studies, when the product and process should have been optimized to ensure that there is equivalence between the product used in phase III and the commercial product.

Raw Material Specifications

The requirements for developing, testing, and setting of specifications for raw materials, whether they are new chemical entities (NCEs), pharmacopoeial active materials, excipients, or packaging materials, are essentially the same. Most emphasis is placed on establishing

Table 5 Development of Specifications

	Phase I	Phase II	Phase III	Commercial product
Active	Batch analysis; CofA; test methods developing	Draft specification; test methods developed and validated	Full specification; test methods developed and validated	Full specification; test methods developed and validated
Excipient	CofA and test methods developing on functional properties	Draft specification; test methods developed and being validated	Full specification; test methods developed and validated	Full specification; test methods developed and validated
Packaging	CofA and limited testing depending on functional properties	Draft specification; test methods developing and being validated	Full specification; test methods developed and validated	Full specification; test methods developed and validated
Finished product	Batch analysis; draft specification; test methods being developed	Refined draft specification; test methods developed (provisional) and partially validated	Full specification; test methods developed and validated	Full specification; test methods developed and validated

Abbreviation: CofA, certificate of analysis.

excipient and packaging specifications here because this usually involves an external supplier and the pharmaceutical company working together.

The initial concept and basic requirements for both excipient and packaging specifications should have been identified at the product design stage. For example, the design requirements for an antioxidant to be used in an IV injection may be of parenteral grade, GRAS status, or previously approved for use by regulatory authorities but must be compatible with the active pharmaceutical ingredient under development. Similarly, the primary pack should meet the basic product design requirements and be acceptable to regulatory authorities, should be available from multiple sources and reputable suppliers, should have a suitable volume for use, and should be sealed to maintain sterility; the container closure system should be compatible with the formulation.

If compatibility testing of the pharmaceutically active ingredient, excipients, and primary packaging components are satisfactory, development specifications are prepared for excipients and packaging materials to be used. These will contain essential information about the materials to be used, including the grade, proposed use, specific physical properties, and any testing required for investigational purposes. The quality of the raw materials used is vital to the effectiveness and quality of the finished product.

At the early stages of development, for example, to support phase I studies, pharmaceutical companies often accept excipient and packaging raw materials on the basis of a certificate of analysis (CofA) or certificate of conformance provided by the supplier. This is especially the case if it is a reputable supplier of an established material used by the industry. This reduces the pressure on the pharmaceutical company's analytical department to develop methods to test the materials at this early stage. The supplier may also provide useful information such as details of the critical dimensions and drawings for packaging materials.

With a new supply source or a new material, a pharmaceutical company will usually want to audit the supplier prior to accepting the material on a CofA. They may even want to repeat some of the tests on the CofA until there is confidence on compliance with the specification. The pharmaceutical company will want to seek assurance from the supplier that they are quality conscious at every stage of their process and have the facilities and internal systems and procedures in place to support this.

As product development progresses, the critical qualities of the raw materials will be identified, which affect final product quality, and results of investigational studies will be obtained to enable the specifications to be developed and refined.

Typical tests performed on raw materials, including the active pharmaceutical ingredient, excipients, and packaging components, are as follows:

- Appearance, for example, visual inspection, free from visible contamination.
- Identity tests, for example, comparison with a standard or by direct analysis, conformance with supplier's drawing.
- Chemical tests where appropriate, for example, for active, related substances, impurities.
- Microbiological tests where appropriate, for example, bioburden, absence of specific microorganisms.
- Relevant physical properties, for example, leak test, tensile strength, moisture vapor transmission, closure removal torque.
- Dimensional analysis, for example, for filling tolerances.
- Investigational tests, for example, reproducibility of dosing devices, particle size distribution of excipients.

Official compendia may provide tests and standards for listed excipients and for glass and plastic containers.

Packaging and excipient specification functional tests are developed on the basis of the functional requirements of these in the product. For example, the pack may have to prevent liquid loss and moisture ingress and maintain sterility or deliver a defined dose. An excipient such as an antimicrobial preservative must be able to preserve the formulation in the presence of the active and other formulation ingredients and in the intended pack. Excipient and

packaging optimization must satisfy performance criteria, ensuring that packaging dimensional specifications and performance specifications can be consistently met at the extremes of the limits and during processing, handling, and transport. The evaluation of the sterilization process is particularly important for sterile products. Robustness to the sterilization process should be assessed, because it is possible that the thermal, electromagnetic, or chemical energy could adversely affect the properties of the materials in question. For example, there may be an irreversible loss in product viscosity, the embrittlement of polypropylene, or the loss in thermoplastic quality of polyethylene.

Once several batches of raw materials have been reviewed and tested to demonstrate that they will conform to the functional and quality requirements, the full excipient and packaging specifications can be finalized. Excipient and pack performance should be evaluated from a stability evaluation of the product and feedback from experience in clinical trials. Ideally, the specifications should be finalized for the start of phase III clinical trials. If for some reason, the excipient or packaging material has to be changed for phase III supplies, then some or all of the steps involved in the selection of materials, compatibility, and stability studies may have to be repeated.

Product Specifications

Product specifications will also evolve during development (Table 5). In the early stages, testing is typically performed on only a small number of samples due to the small scale of manufacture available. There may only be one or two product batches made to support phase I and early phase II studies. The specification limits also tend to be wide because of the limited data available. The specification limits are tightened as more information is gained from testing more batches, and the scale of manufacture is increased.

The product release specification contains tests and limits that apply after manufacture to release the product for use, whereas the product specification contains tests and limits with which the product must comply throughout its shelf life. The limits may differ from the product release limits to allow for changes during storage, for example, to allow for some drug degradation. Both product release and shelf life specifications are required for European regulatory submissions, but in Japan and the United States they are currently only interested in shelf life specifications. Some companies have internal or in-house specifications, which are different (usually tighter) from regulatory specifications. However, this can lead to confusion about which specification the product must comply with. Since the FDA only accepts the existence of the regulatory specifications, it is better to have "action limits" corresponding to the internal specification, rather than two sets of specifications.

When developing product specifications, test methods, and limits, the critical parameters must be identified and controlled, which affect the quality, safety, performance, and stability of the drug product. Several issues have to be considered, such as appropriate regulatory requirements and guidelines, for example, ICH, relevant compendial monographs and standards, and the capability of the manufacturing process and analytical methods used. Appropriate limits will also be influenced by safety/toxicology considerations. For example, impurities, degradation products, extractables and leachables, and preservatives should be qualified in safety studies.

Regulatory authorities such as the FDA publish specification guidelines with the expectation that pharmaceutical companies will comply with them. If there are difficulties in achieving the guideline requirements, or in the interpretation of them, it is advisable to discuss those points with the FDA. The internal regulatory group is usually the point of contact with external regulatory bodies. There are helpful ICH guidelines available on specifications, test procedures, and acceptance criteria, which describe the attributes that should usually be included for a variety of dosage forms. In particular, ICH Q6A and ICH Q6B provide guidance on specifications for new drug substances and new drug products, chemical substances, and biotechnological/biological substances, respectively. Other ICH guidelines are available, which describe impurities and residual solvents.

There are various general compendial monographs available on dosage forms, such as tablets and inhalation dosage forms, as well as compendial test methods and limits listed in the various pharmacopoeias. In spite of the progress made with harmonization, there are still

some significant differences in the test procedures and limits recommended in the major pharmacopoeias. Often, the testing applied is aimed to cover the most stringent requirements.

During process optimization, the capability and robustness of the manufacturing process is assessed (as described later in this chapter on process robustness) to confirm that the specifications can be met at the extremes of the limits to define the design space. The capability of the test method, accuracy, precision, and reproducibility will also affect the limits that can be achieved.

With all test methods and limits there must be a sound technical justification to support them based on data generated for product and process optimization, clinical batches, and stability studies. A specification set too wide is more likely to be challenged by regulatory authorities. However, if the specification is too tight, it may result in some batches failing. It is considered best to freeze the specifications as late as possible so that considerable confirmatory data are available from all batches made to justify the limits. It is also very important to document the justifications for the specifications, and any changes during development, so that the complete specification development can be accounted for. This information will be required for the development report to support FDA PAI and regulatory submissions.

PROCESS DESIGN, PROCESS OPTIMIZATION, AND SCALE-UP

The primary objective of the process design and optimization stages of product development is to ensure that manufacturing operations supporting phase III studies and ultimately commercial manufacture are carried out under optimal conditions. The product should consistently comply with specifications.

Process design is the initial stage of process development where an outline of the clinical trial and commercial manufacturing processes are identified on paper, including the intended scale(s) of manufacture. This should be documented in a process design report.

The process design report should include all the factors that need to be considered for the design of the process, including the facilities and environment, equipment, manufacturing variables, and any material handling requirements. A list of typical factors to consider is given in Table 6.

Table 6 Process Design Considerations

Factor	Requirement	Purpose
Facility	Organization and layout	GMP
	Space	Health and safety
	Environmental control	Product sensitivity to:
	Temperature	Temperature
	Humidity	Moisture
	Air quality	Particulates/microorganisms
	Electrical zoned (flameproof)	Allow solvents for cleaning
Equipment	Barrier protection	Operator protection
	Type and design, e.g., bottom- or top-mounted mixing elements, baffles, heating/cooling jacket, etc.	Suitability for process mixing efficiency
	Materials of construction	Compatibility, extractives
	Range of sizes	Ease of scale-up
	Access to internal parts	Ability to clean/maintain
Material transfer	Product protection	Clean/sterile products
	Operator protection	Hazardous materials
Manufacturing variables	Order of addition of active and excipients	Mixing effectiveness
	Temperature	Stability/dissolution
	Speed	Mixing effectiveness
	Time	Mixing effectiveness
	Differences in excipient batches	Robustness of process

It is important to involve Production during the product design stage in the selection of equipment and the process. The eventual technology transfer is likely to be smoother if the same type of equipment employed by R&D is also available in Production on a larger scale. If a completely novel approach to manufacture is being considered, it is important that Production is made aware of this and can plan ahead to deal with the new process. This might involve the purchase of new equipment, which will have to be validated and which are needed to allow the technology transfer plans.

Other process design factors to consider are the need for any in-process controls during manufacture, with details of the tests and proposed limits. For example, the thickness, hardness, friability, and weight of tablets might be measured during the filling of a tablet product. The tests and limits applied will be based on experience gained from product development, optimization, and stability studies. Depending on the product being developed and type of process, it may be necessary to conduct preliminary feasibility studies before the process design report can be written.

Process Optimization

Process optimization will define and investigate critical process parameters, varying these within practical constraints to establish limits for the process parameters, within which acceptable product can be manufactured. Depending on the product being developed and type of process, it may be necessary to conduct preliminary feasibility studies before proceeding to process optimization. In a traditional approach to process understanding, every process parameter could potentially receive the same degree of scrutiny. However, this is not a very efficient way to evaluate all the possible permutations of process steps, process parameters, and raw material components. Process optimization can be streamlined by using existing data and knowledge, incorporating risk assessment and risk management tools, and applying statistically designed experiments (DoE) to define the acceptable operating ranges for both critical and noncritical process parameters. The QbD concept refers to a product and process that consistently delivers a product with the desired product quality attributes and provides a more structured approach to the identification of critical product quality attributes and how the process parameters (both critical and noncritical), which define the design space, affect them.

A useful approach to process optimization is to identify all the critical process parameters (CPP) that could potentially affect product quality or performance and prepare a process optimization protocol. The definition and concept of “criticality” with respect to process variables, for example, parameters, material attributes, and conditions, is a current topic of debate. The criticality task team within the ISPE Product Quality Lifecycle Implementation (PQLI) initiative has provided a concise, coherent, and universal approach for determining criticality to facilitate the consistent implementation of QbD principles and ICH Q8, Q9, and Q10 guidelines in the development of pharmaceutical manufacturing processes. The work is illustrated by useful case studies to increase understanding (Nosal and Schultz, 2008; Garcia, et al., 2008). A regulatory definition for a “critical process parameter” is: “A process input that, when varied beyond a limited range, has a direct and significant influence on a CQA, where a CQA is a quantifiable property of an intermediate or final product that is considered critical for establishing the intended purity, efficacy, and safety of the product.” Risk is controlled for a CQA by establishing a product specification for the affected attribute.

From a business perspective, process parameters may have implications for optimizing yield, reducing costs, or improving process efficiency, but these should not be regarded as critical from a regulatory perspective. Typically, data used to identify CPPs will be derived from laboratory or pilot-scale batches and do not need to be confirmed on full-scale batches unless the control of the particular parameter can only be evaluated on a production scale (i.e., scale is a critical factor). There is good incentive to use the production facilities at the earliest opportunity, drug availability permitting, to iron out any transfer difficulties. Manufacture of the stability batches to support phase III studies, and also the phase III clinical batches, at the final commercial site should minimize any questions from the FDA during PAI about possible differences between R&D and Production process used.

The process optimization protocol should outline the program of work required to evaluate the effect of changes in the critical variables on product quality. This is to establish the working limits within which the process consistently produces product, which meets the CQAs. CPPs may include

- defining the order of addition of the active and excipients;
- defining the optimum equipment settings, for example, mixing speed;
- optimizing time-dependent process parameters, for example, mixing speed;
- defining the optimum temperature range;
- evaluating the effects of different excipient/active batches (within specification);
- setting in-process targets and controls; and
- developing cleaning procedures for the process.

Once the experiments have been completed, multiple regression analysis on the results can be performed using widely available statistical software to determine the effects of these process variables on the CQAs, their interactions, and their statistical significance. From this, a multidimensional picture of the design space can be produced. In the design space in which the process variables can consistently produce in-specification results, an area in the center can be selected as the operating space in which the process should be in control and should not drift into inoperable regions (Fig. 1).

On completion of the work program, a process optimization report should be written. This will summarize the results and evaluation of the activities specified in the protocol and also provide a rationale to define the operating limits for the process and the critical parameters affecting product quality or performance. The report should also conclude that the CQAs, including the specifications for the active excipients, components, in-process, and product can be met within the design space. The report and development data generated to establish process understanding provide the knowledge base to support and justify flexible regulatory relief for postapproval changes.

Process Capability and Robustness

Several pitfalls that are sometimes encountered with process development can hinder successful technology transfer to production, that is, if the process has not been designed or optimized with production in mind or a representative scale of production has not been used for the optimization studies. For example, the sterilization of a viscous ophthalmic gel by autoclaving at R&D on a 2-kg scale did not require any mixing of the bulk product for efficient heating and cooling. However, when transferred to production at a 100-kg scale, the heating and cooling times were found to be extensive, and the bulk contained hot spots because no stirring mechanism had been specified in the vessel.

Another pitfall is to design a process where the operating limits for one or more critical parameters are too narrow and cannot be consistently achieved. It is not acceptable if the process can be performed only by “experts” in R&D. Many pharmaceutical companies apply some measurement of process and equipment capability to demonstrate the reproducibility and consistency of the process in meeting specification limits. The process capability index (CpK) is often used to measure the reproducibility as a function of the specification limits. It is normally calculated from either of the two equations below, whichever gives the lowest number:

$$CpK = \frac{\text{upper limit of specification} - \text{mean}}{3 \times \text{standard deviation}}$$

or

$$CpK = \frac{\text{mean} - \text{lower limit of specification}}{3 \times \text{standard deviation}}$$

Some generally accepted rules, determined from experimental data, relate the CpK value with robustness. For example, a CpK of less than 0.8 is an indication that the process is not

capable, as the acceptance criteria cannot be met routinely. Further work will need to be done to develop a more robust process. CpK values between 0.9 and 1.0 indicate a marginal process, between 1.0 and 1.25 are satisfactory, between 1.25 and 1.5 are good, and greater than 1.5 are excellent. Using these measurements, it is possible to evaluate process variables and identify which variable has the least or most effect. However, a possible pitfall is to obtain excellent CpK values, but not to have an acceptable process because the mean value is not on target. The process developed needs to be reliable and consistently meet product specifications to demonstrate it is manufacturable. Another pitfall is to aim for a CpK value much higher than 1.5, which is probably a waste of effort. The process does not have to be “bombproof.”

Scale-Up

In reality, product and process development and scale-up will be progressing concurrently to meet the demands of phases I and II clinical and long-term safety supplies. The process used for initial clinical supply manufacture will probably be relatively small scale (laboratory scale). As more drug substance becomes available and the clinical requirements increase, the product batch size will increase to pilot scale, and the process may have to be modified during scale-up. If drug substance is available and very large phase III studies are anticipated, it may be essential to scale-up to production scale and transfer the process to the commercial production site at the earliest opportunity.

The objective of scale-up is to ensure that the process is scaled up to provide product, which will comply with specification and CQAs. Scale-up may encompass changes in process equipment and operation, with an associated increase in output, for example, in the following situations:

- An increase in batch size of 10-fold or greater on identical equipment
- Use of larger or high-speed versions of identical types of equipment
- Increase in output rate by more than 50% for identical equipment changes in equipment type for a given process step

Whenever scale-up is to be undertaken, it is strongly recommended that an experimental batch is manufactured to demonstrate that the process is still acceptable and the product is manufacturable on the increased scale. It must meet all the appropriate in-process and product specifications acceptance criteria.

Technology Transfer

The actual transfer of the manufacturing process from R&D to Production, along with the necessary knowledge and skills to be able to make the product, is referred to as “technology transfer.” The ultimate objective for successful technology transfer is to have documented proof that the process is robust and effective in producing product complying with the registered specifications and GMP requirements.

The approach taken by different pharmaceutical companies to technology transfer varies widely from a “hand over the wall” to a more structured team approach. Clearly, the latter approach is more likely to result in successful technology transfer. In some companies, a third party is involved in the process, a specialized technology transfer group, which liaises between R&D and Production to ensure a smooth transfer. Companies vary in the way they divide responsibilities for technology transfer and the point of handover of responsibility, but there do not appear to be any clear advantages, provided the guidelines below are followed:

- Responsibilities are clear and well defined.
- Representation from Production and the technology transfer group are involved early, for example, during product and process design/optimization.
- Good communications are maintained with good R&D/Production interface. Time is spent face to face in factory and laboratory.
- There is good scientific basis for product/process design.
- Equipment used at laboratory/pilot scale is similar to production equipment.
- There is good documentation of product/process development and technology transfer.

A more comprehensive overview and guide to the technology transfer process for drug substance and drug product and the corresponding analytical tests and methods from R&D to Production can be found elsewhere (Gibson, 2005).

VALIDATION AND LAUNCH

The impact of QbD on traditional process validation to establish improved process understanding and the design space is a current topic of discussion. So much has changed since the FDA issued its "Guideline on General Principles of Process Validation" in 1987 (FDA, updated in 1999 and new draft available 2008), describing the principles and practices that are acceptable to the FDA and containing a section that describes the types of activities that should be considered when conducting process validation. Likewise, in Europe in 1999, the European Agency for the Evaluation of Medicinal Products (EMA) and the Committee for Proprietary Medicinal Products (CPMP) issued a guidance on process validation with the aim of drawing together and presenting more clearly the requirements for effectively validating pharmaceutical manufacturing processes. With new levels of process understanding, and since the design space "assures quality" of the drug product, the value of conducting three arbitrary process validation batches to register a new product is being challenged (Bush, 2005). The design space limits should provide the basis of the validation acceptance criteria, and so once created, process validation becomes an exercise to demonstrate that the process will deliver a product of acceptable quality if operated within the design space and also that the smaller-scale systems used to establish the design space in R&D represent the performance of the commercial production scale process. It is anticipated that once the design space has been established and validated, the regulatory filing would include the acceptable ranges for all the CPPs within the design space and the control strategy. Although approaches to process validation may be changing, the principles of process validation have not changed:

- Identifying and controlling what is critical
- Using in-process measurements as part of evaluation
- Demonstrating a state of control
- Demonstrating reproducibility over time
- Identifying and documenting changes in controls

Clinical Trials Process Validation

At early clinical stages (phases I and II), where only limited GMP batches of product will have been produced and where product and process changes make batch replication difficult, only limited process validation may be possible. In such cases, the regulatory authorities will expect to see data from extensive in-process and end-product testing to demonstrate that the batch is adequately qualified, yielding a finished product that meets specification and quality characteristics.

For critical processes such as sterilization or aseptic manufacture, even for the earliest human studies, the regulatory authorities will expect the process to be qualified to attain a high degree of assurance that the end product will be sterile. If drug availability is an issue, the aseptic processing of sterile products may be validated using media fills to simulate the process (FDA 2004).

At later development stages, when process optimization has been completed and the design space and control strategy have been established, if clinical batches are being manufactured under replicated conditions, the regulatory authorities will expect process validation to be conducted. The actual process used and results obtained must be documented so that it can be duplicated. Normally, the product must meet predetermined product specifications and acceptance criteria on three occasions. The benefit of validating the process successfully is to reduce the amount of product testing.

Validation of Commercial Process

Process validation is currently still a requirement of the FDA Current Good Manufacturing Practices Regulations for Finished Pharmaceuticals, 21 CFR Parts 210 and 211, and of the Good Manufacturing Practice Regulations for Medical Devices, 21 CFR Part 820, and therefore is applicable to the manufacture of pharmaceuticals and medical devices intended for the United States.

The FDA's definition of process validation is to establish documented evidence, which provides a high degree of assurance that a specific process will consistently produce a product, meeting its predetermined specifications and quality characteristics.

As discussed earlier, the approaches to process validation are changing, but at the time of writing, the following still applies. Documented evidence must be achieved by preparing written validation protocols prior to doing the work and writing final reports at the completion of the work. The process equipment used should undergo installation qualification (IQ) and operational qualification (OQ) to establish confidence that the equipment was installed to specification and purpose and is capable of operating within established limits required by the process. Performance characteristics that may be measured include uniformity of speed for a mixer or the temperature and pressure of an autoclave, for example.

Performance qualification (PQ) is to provide rigorous testing to demonstrate the effectiveness and reproducibility of the process. PQ should not be initiated until the IQ/OQ has been completed and the process specifications have been essentially proven through laboratory, pilot, and scale-up batch manufacture. The PQ protocol should specify the approved procedures and tests to be conducted and the data to be collected. Acceptance criteria should be defined prior to starting the work. To gain a high degree of assurance that the process is reproducible, the traditional approach has been to manufacture at least three successive replicated process runs to ensure statistical significance. This approach may not be meaningful if it does not validate the design space, so it is recommended that the validation strategy is discussed with the regulatory authorities prior to commencing the work. According to QbD principles, validation consists of process development, process confirmation, and continual verification. The validation package of work will be flexible depending on the level of process knowledge and understanding and risk-based considerations. It is expected that the conditions for the different runs will encompass processing limits, widely known as "worst-case" conditions, but inside the design space limits. This will demonstrate whether the process limits are adequate to assure that the product specifications are met. PQ should ideally be undertaken at the scale at which commercial production will take place, although it may be acceptable to use different batch sizes if scale has been shown not to be a critical factor.

Preapproval Inspection

Once the clinical and safety evaluation studies for a new medicinal product have shown it to be safe, effective, and of acceptable quality, the pharmaceutical company will usually want to submit a marketing authorization application (MAA) or NDA to the regulatory authorities. Through the implementation of ICH Q8 guidance on pharmaceutical development the new regulatory submission will be defined according to section 3.2 P.2 (pharmaceutical development) contained in Module III of the CTD for new drugs and biologics (FDA, May 2006). ICH Q8 recommends that drug developers present the knowledge gained from pharmaceutical studies, which provide scientific understanding to support the establishment of the drug product and its specifications and manufacturing controls, in the pharmaceutical development section of the drug marketing application.

A current prerequisite to NDA approval in the United States is to have successfully passed an FDA PAI. The PAI will essentially be targeted at the commercial manufacturing facility to gain assurance that the facilities, equipment, procedures, and controls to manufacture the product are in place and conform with the NDA submission. The FDA will also want to check for compliance with current GMP (cGMP).

The FDA may also want to audit R&D to gain assurance that the product development has been done satisfactorily. In particular, the FDA may wish to see data that support the manufacturing process and controls from preformulation, product/process optimization, clinical trials process validation, and stability studies.

The FDA will check for equivalence, for both the drug substance and pharmaceutical product, between that used in the pivotal clinical studies, the pivotal stability studies, and commercial production. This is usually achieved by inspecting product and control data such as clinical trial batch records; in-process and end-product test results; and raw material, component, and product specifications. During an R&D PAI the FDA will also check for general compliance with cGMP, inspect the facilities and equipment used, and check the appropriateness of control systems and procedures.

It is in the interest of pharmaceutical companies to be in a state of readiness for a PAI. Staff should be aware of all procedures, policies, and regulations and have current training records. A good documentation storage and retrieval system is essential to be able to locate and retrieve records and reports efficiently. It is considered essential to have prepared a development report for the FDA to aid the PAI. The purpose of the report is to summarize all the product development and to demonstrate the equivalence of the manufacturing process and controls used for the pivotal clinical and stability batches and the commercial product. The typical contents of the development report requested by the FDA are as follows:

- Active and key excipients: physicochemical characteristics, particle size, purity, batch analysis.
- History of formulation and pack development: design rationale with critical characteristics affecting manufacture.
- History of process development: design rationale with CPPs.
- Specifications: rationale and supporting data for in-process and product.
- Product stability summary: equivalence of controls with commercial.
- Technology transfer batch history: list all batches made for development, safety, clinical, and transfer.
- Evaluate cause of failures and remedies.

The development report should be concise and structured. Clearly, it cannot be finalized until development is complete, but the preparation is much easier if summary reports have been compiled during development, such as the product and process optimization reports. The development report needs to be available to the FDA prior to the inspection, ideally, to give the FDA inspection team confidence that the product has been developed satisfactorily, perhaps resulting in a shorter inspection.

Consistent with the FDA's GMPs for the 21st century initiative, FDA is adopting a risk-based approach to prioritizing and conducting PAIs. They have reduced the number of PAIs on the basis of the current knowledge and cGMP status of companies. For a more comprehensive guide to successfully preparing for and passing PAIs, the book *Pharmaceutical Pre-Approval Inspections. A Guide to Regulatory Success* is recommended (Hynes III, 2008).

A successful PAI and regulatory approval of the NDA is usually followed by product launch. Launch activities need to be planned carefully and well in advance to ensure that no time is wasted after approval to sell the product on the market. The product insert and label claim will also have to be approved by the regulatory authorities. It may be better to wait for confirmation of approval before printing the labels and pack inserts; everything else can be prepared in advance. The launch stock is then packaged and labelled and QC released and then distributed for sale. Leading pharmaceutical companies can achieve this in one to two weeks postapproval, with good preparation and planning.

Postapproval Changes

Looking forward, submission of enhanced QbD information in a NDA or biologic license application toward the establishment of design space should enable the applicant to propose flexible regulatory approaches for postregulatory manufacturing changes. Therefore, changes within the approved design space should not require traditional postapproval regulatory submissions. However, the current status is that pharmaceutical companies and the regulators are still discussing how this will work in practice. Various workshops have been set up to discuss the types of information to be submitted and the type of regulatory flexibility as a

result of sharing more extensive pharmaceutical development information in a QbD-based application.

Historically, pharmaceutical companies have often acknowledged changes after regulatory submissions have been done. Requests for postapproval changes could be for reasons outside the company's control, for example, because the source of raw materials changed, compendial specifications were revised, or suppliers of processing equipment made modifications. Alternatively, the change could be because the company wants to transfer a product to another manufacturing site. Sometimes changes are forced because the manufacturing process has not been properly evaluated, and it is found not to be robust enough until a few production runs have been made. Such a situation may be a consequence of the company striving for the earliest submission date, with an attitude of "we'll fix it later"!

However, with the traditional product development approach, all these changes require regulatory approval, and this can take significant time and result in lost sales. There are guidelines on the process for making changes in an initiative known as SUPAC or "scale-up and postapproval changes". SUPAC is designed to enable changes to be made to manufacturing processes with reduced regulatory input by providing guidance on what additional testing is required for specific changes.

There are a number of SUPACs, some approved (e.g., Immediate-Release Dosage Forms, Modified-Release Dosage Forms, and Semisolid Dosage Forms) and some still being considered (e.g., Sterile Products). SUPAC establishes the regulatory requirements for making changes to the composition or components of the dosage form, the batch size, the manufacturing process or equipment, or the site of manufacture. Different levels of change are defined and require different actions, for example:

- Level I—unlikely to have a detectable impact on product quality, for example, a change in the mixing time within the validated range; action: notify FDA in the annual report.
- Level II—could have a significant impact, for example, a change of mixing time outside the validated limits; action: submit updated batch records, generate and submit long-term stability in annual report, generate dissolution profile data, and notify the FDA of changes for approval.
- Level III—likely to have a significant impact, for example, a change from direct compression to wet granulation; action: (i) submit updated batch records, three months' accelerated stability data, dissolution data, in vivo bioequivalence study (unless in vitro/in vivo correlation verified), and long-term stability data and (ii) notify the FDA of all changes for approval

In Europe, there are different arrangements from country to country when changes to MAAs are to be made. It is a legal requirement in the European Community (EC) that all marketed products comply with the details of the MAA. Changes may or may not require prior approval, depending on the type of change. For example, a type I variation or minor change, such as a change in batch size, may not require prior approval. Details are submitted to all member states where the product is sold and deemed approved if there are no objections within 30 days. Type II variations, or quite major changes, have to be submitted to all member states where the product is marketed, and the change must be approved or rejected within 90 days. A significant change such as a change of strength or indication would probably require a new application. Companies can make an early submission and avoid regulatory delays by knowing in advance what changes are allowed without preapproval.

In terms of the type of regulatory flexibility proposed or envisaged in a QbD application, it has been suggested that no postapproval filings should be required for the following changes (Nasr et al., 2008):

- Manufacturing site change, alternate packaging or packaging sites, alternate analytical methods, and testing sites, scale-up.
- Movement within the design space and/or proven acceptance ranges.
- Replacement of end-product testing with in-process testing.

It is clear that flexibility would be dependent on what information was submitted in the application, and although still early days, there is definitely opportunity for companies to benefit from the QbD approach.

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11 | Oral Solid Dosage Forms

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INTRODUCTION

In the last 25 to 30 years, a huge resource in both academia and industry has been devoted to the development of drug delivery systems that target drugs more effectively to their therapeutic site. Much of this work has been successful, and is reported in this text. In spite of this, oral solid dosage forms such as tablets and hard gelatin capsules, which have been in existence since the 19th century, remain the most frequently used dosage forms. This is not simply a reflection of the continued use of established products on the market; tablets and capsules still account for about half of all new medicines licensed (Table 1).

There are several reasons for the continued popularity of the oral solid dosage form. The oral route of delivery is perhaps the least invasive method of delivering drugs; it is a route that the patient understands and accepts. Patients are able to administer the medicine themselves. For the manufacturer, solid oral dosage forms offer many advantages: they utilize cheap technology, are generally the most stable forms of drugs, are compact, and their appearance can be modified to create brand identification.

Tablets and capsules are also very versatile. There are many different types of tablets, which can be designed to fulfill specific therapeutic needs (Table 2). It is beyond the scope of this chapter to cover all these dosage forms, instead it will review the common principles, with more specific detail being given for those most commonly used.

For drugs that demonstrate good oral bioavailability and do not have adverse effects on the gastrointestinal (GI) tract, there may be very little justification for attempting to design a specific drug delivery system. It is likely, therefore, that tablets and capsules will continue to remain one of the most used methods of delivering drugs to the patient in the future.

This chapter reviews the science behind the development of solid dosage forms, particularly tablets and hard gelatin capsules. Solid dosage forms are one of the most widely researched areas of pharmaceuticals and, given the space allowed, this chapter can only cover the science at a very basic level. It is an area that is served by a number of excellent texts, and these will be referenced at the appropriate points.

POWDER TECHNOLOGY

Virtually all solid dosage forms are manufactured from powders, and an understanding of the unique properties of powder systems is necessary for their rational formulation and manufacture. Powders consist of solid particles surrounded by spaces filled with fluid (typically air) and uniquely possess some properties of solids, liquids, and gases. Powders are not solids, even though they can resist some deformation, and they are not liquids, although they can be made to flow. Still further, they are not gases, even though they can be compressed. Powder technology is concerned with solid/fluid interactions, interparticle contact, and cohesion between particles. These are strongly influenced by particle size and shape and by adsorption of the fluid or other contaminants onto the surface of the particles.

While tablets and capsules, the two most common solid dosage forms, have their own unique requirements, there are similarities between them. They both require the flow of the correct weight of material into a specific volume, the behavior of the material under pressure is important; and the wetting of the powder is critical for both granulation and subsequent disintegration and dissolution of the dosage form.

While it is not possible to deal with all aspects of powder technology in a textbook covering such a diverse range of formulations, some basic principles of powder flow, mixing

Table 1 Number of FDA Drug Approvals for New Molecular Entities Presented as Tablet and Capsules Between 2003 and 2008

Year	No. of tablets approved	No. of capsules approved	No. of other dosage forms approved	Proportion of tablets and capsules (%)
2003	8	5	8	62
2004	11	3	16	49
2005	4	2	13	34
2006	9	4	6	68
2007	7	2	7	56
2008	7	2	6	60

Source: www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Reports.ReportsMenu.

Table 2 Types of Solid Dosage Forms

Formulation type	Description
Immediate release	The dosage form is designed to release the drug substance immediately after ingestion.
Delayed release	The drug substance is not released until a physical event has occurred, e.g., time elapsed, change in pH of intestinal fluids, change in gut flora.
Chewable tablets	Strong, hard tablets to give good mouth feel.
Lozenges	Strong, slowly dissolving tablets for local delivery to mouth or throat. Often prepared by a candy molding process.
Buccal tablets	Tablets designed to be placed in buccal cavity of mouth for rapid action.
Effervescent tablets	Taken in water, the tablet forms an effervescent, often pleasant-tasting drink.
Dispersible tablets	Tablets taken in water, the tablet forms a suspension for ease of swallowing.
Soluble tablets	Tablets taken in water, the tablet forms a solution for ease of swallowing.
Hard gelatin capsules	Two-piece capsule shells, which can be filled with powders, pellets, semisolids, or liquids.
Soft gelatin capsules	One-piece capsules containing a liquid or semisolid fill.
Pastilles	Intended to dissolve in mouth slowly for the treatment of local infections. Usually composed of a base containing gelatin and glycerin.

and compaction, and compression properties will be described. For those interested in a more in-depth treatment of the topic, there are a number of excellent texts available (Rhodes, 1990; Alderborn, 1995).

Particle Size and Shape

A knowledge of the particle shape and size distribution is essential to the understanding of the behavior of powders, as it will contribute to knowledge of the secondary properties of a powder, such as flow and deformation, which influence the processability. This topic is dealt with in detail in chapter 6.

Density

When a powder is poured into a container, the volume that it occupies depends on a number of factors, such as particle size, particle shape, and surface properties. In normal circumstances, it will consist of solid particles and interparticulate air spaces (voids or pores). The particles themselves may also contain enclosed or intraparticulate pores. If the powder bed is subjected to vibration or pressure, the particles move relative to one another to improve their packing arrangement. Ultimately, a condition is reached where further densification is not possible without particle deformation.

The density of a powder is, therefore, dependent on the handling conditions to which it has been subjected, and there are several definitions that can be applied either to the powder as a whole or to individual particles.

Particle Densities

British Standard 2955 (1958) defines three terms that apply to the particles themselves. Particle density is the mass of the particle divided by its volume. The different terms arise from the way in which the volume is defined.

1. True particle density is when the volume measured excludes both open and closed pores, and is a fundamental property of a material.
2. Apparent particle density is when the volume measured includes intraparticulate pores.
3. Effective particle density is the volume “seen” by a fluid moving past the particles. It is of importance in processes such as sedimentation or fluidization but is rarely used in solid dosage forms.

Powder Densities

The density of a powder sample is usually referred to as the bulk density, and the volume includes both the particulate volume and the pore volume. The bulk density will vary depending on the packing of the powder, and several values can be quoted.

- Minimum bulk density is when the volume of the powder is at a maximum, caused by aeration, just prior to complete breakup of the bulk.
- Poured bulk density is when the volume is measured after pouring powder into a cylinder, creating a relatively loose structure.
- Tapped bulk density is, in theory, the maximum bulk density that can be achieved without deformation of the particles. In practice, it is generally unrealistic to attain this theoretical tapped bulk density, and a lower value obtained after tapping the sample in a standard manner is used.

The porosity of a powder is defined as the proportion of a powder bed or compact that is occupied by pores, and is a measure of the packing efficiency of a powder.

$$\text{Porosity} = 1 - \left(\frac{\text{bulk density}}{\text{true density}} \right) \quad (1)$$

Relative density is the ratio of the measured bulk density divided by the true density.

$$\text{Relative density} = \frac{\text{bulk density}}{\text{true density}} \quad (2)$$

POWDER FLOW

Good flow properties are a prerequisite for the successful manufacture of both tablets and powder-filled hard gelatin capsules. It is a property of all powders to resist the differential movement between particles when subjected to external stresses. This resistance is due to the cohesive forces between particles. Three principal types of interparticle force have been identified (Harnby et al., 1985): forces due to electrostatic charging, van der Waals forces, and forces due to moisture.

Electrostatic forces are dependent on the nature of the particles, in particular, on their conductivity. For nonconducting particles, high cohesive stresses in the range of 10^4 to 10^7 N/m² have been reported.

Van der Waals forces are the most important forces for majority of pharmaceutical powders. The forces of attraction between two spherical particles is given by

$$F = Ad \left(\frac{A}{12x^2} \right) \quad (3)$$

where A is the Hamaker constant ($A = 10^{-19}$ J), x is the distance of separation of the particles, and d is the particle diameter. The forces are inversely proportional to the square of the distance

between the two particles, and hence diminish rapidly as particle size and separation increases. Powders with particles below $50\text{ }\mu\text{m}$ will generally exhibit irregular or no flow because of van der Waals forces. Particle shape is also important; for example, the force between a sphere and plane surface is about twice that between two equal-sized spheres.

At low relative humidity (RH), moisture produces a layer of adsorbed vapor on the surface of particles. Above a critical humidity, typically in the range 65% to 80%, it will form liquid bridges between particles. The attractive force due to the adsorbed layer may be about 50 times the van der Waals force for smooth surfaces, but surface roughness will reduce the effect. Where a liquid bridge forms, it will give rise to an attractive force between the particles due to surface tension or capillary forces.

The role of the formulator is to ensure that the flow properties of the powder are sufficient to enable its use on modern pharmaceutical equipment. Two types of flow present the formulator with particular challenges: flow from powder hoppers and flow through orifices.

Powder Flow in Hoppers

Tablet machines and capsule-filling machines store the powder to be processed in a hopper above the machine. It is important that the powder flows from the hopper to the filling station of the machine at an appropriate rate and without segregation occurring. There are two types of flow that can occur from a powder hopper: core flow and mass flow (Fig. 1).

The flow pattern of a core flow is shown in Figure 1A. When a small amount of powder is allowed to leave the hopper, there is a defined region in which downward movement takes place and the top surface begins to fall in the center. As more material leaves the hopper, the area that moves downward begins to widen, and the upper surface becomes conical. In the areas of the hopper outside the falling region, near the walls, the material has not moved. Even when the hopper has almost emptied, there will be regions where the powder is undisturbed. A core flow hopper is characterized by the existence of dead spaces during discharge. A mass

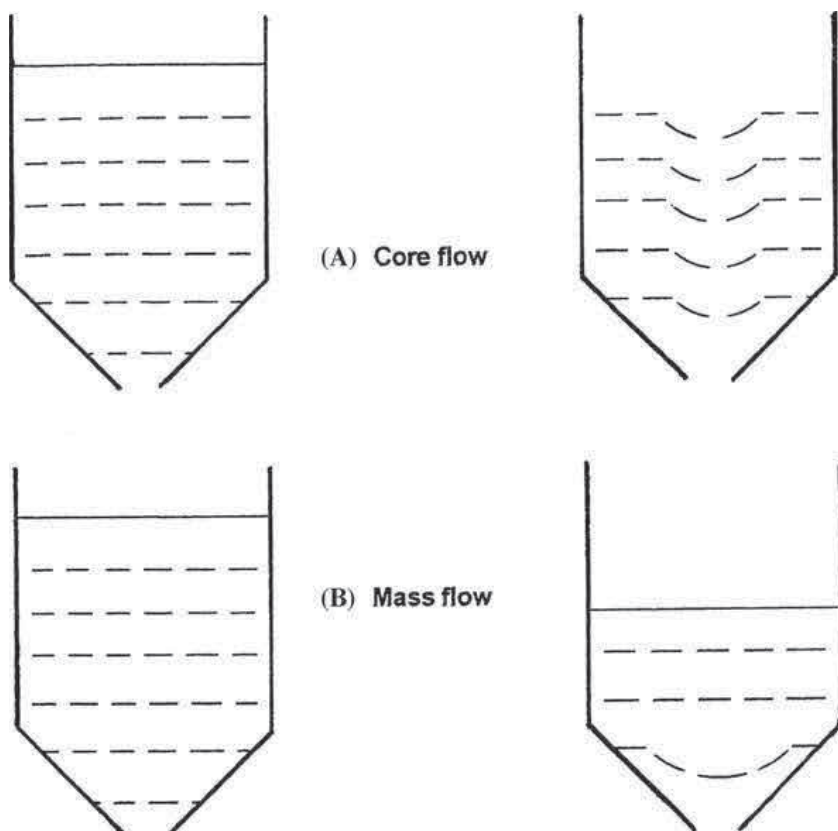


Figure 1 Powder flow patterns in hoppers.

flow hopper is one in which all the material is in motion during discharge, in particular the areas adjacent to the hopper wall (Fig. 1B). As a small amount of powder is discharged, the whole bulk of the powder moves downward.

Core flow hoppers have two significant disadvantages. First, flow from the hopper can stop for no apparent reason. The stoppage may be due to the formation of an arch between the walls of the hopper that is strong enough to support the weight of powder above it. Alternatively, it may be the result of piping or rat holing, in which the material directly above the outlet falls out, leaving an empty cylinder. The second disadvantage is that the flow pattern is likely to encourage segregation, and there may be a considerable loss of mixing quality.

Whether core flow or mass flow is achieved is dependent on the design of the hopper (geometry and wall material) and the flow properties of the powder. For most pharmaceutical applications, the hopper design for a particular machine will be fixed; thus, it is incumbent on the formulator to ensure that mass flow is achieved by modification of the powder properties.

Powder Flow into Orifices

Flow into orifices is important when filling dies in tablet machines and in certain types of capsule-filling machines. For a given material, the flow into or through an orifice is dependent on the particle size, and typically, a plot of flow rate versus particle size will display the trend shown in Figure 2. At the lower end of the particle size range, cohesive forces will result in poor flow. As the particle size increases, the flow rate increases until a maximum is achieved, at an orifice diameter/particle diameter ratio of 20 to 30. As the particle size continues to increase, the rate decreases because of mechanical blocking or obstruction of the orifice. Flow stops completely when the orifice/particle ratio falls below 6.

Measuring Powder Flow Properties

There are several different methods available for determining the flow properties of powders, and there are many literature examples demonstrating correlations between a test method and the manufacturing properties of a formulation. Listed below are some of the more commonly used tests, together with references, detailing their use in pharmaceutical applications.

Shear Cell Methods

Developed to aid silo and hopper design, shear cells provide an assessment of powder flow properties as a function of consolidation load and time. There are a number of types of shear cells available, the most common type being the Jenike shear cell (Fig. 3).

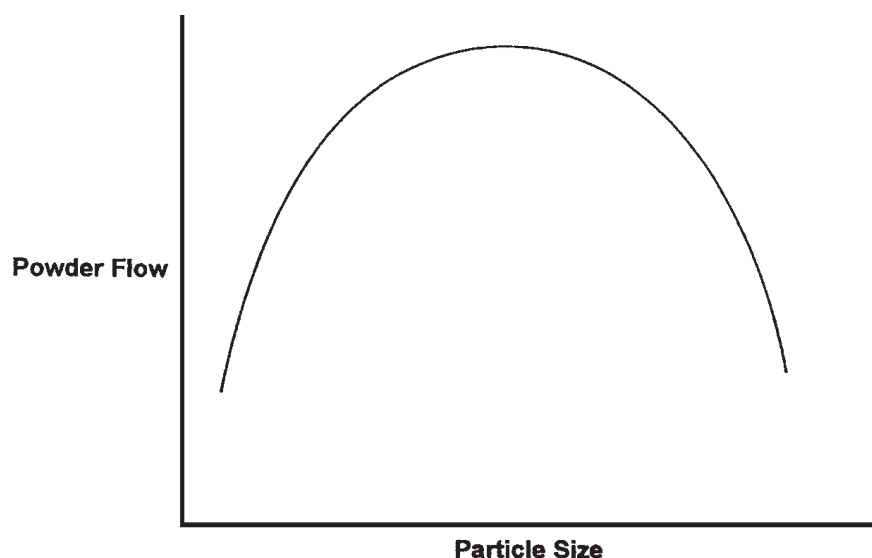


Figure 2 Effect of particle size on the rate of powder flow through an orifice.

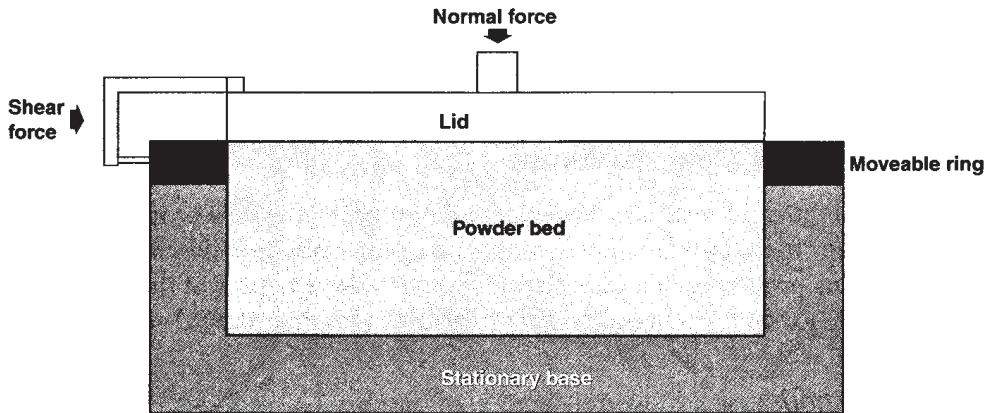


Figure 3 Jenike shear cell.

The shear cell is filled in a standard manner to produce a powder bed with a constant bulk density. A vertical (normal) force is applied to the powder bed and a horizontal force applied to the moveable ring. As the powder bed moves because of the horizontal shear stress, it will change volume, either expanding or contracting depending on the magnitude of the vertical force. A series of tests are performed to determine the vertical load under which the bed remains at constant volume when sheared, referred to as the critical state. Once the critical state has been determined, a series of identical specimens are prepared, and each is sheared under a different vertical load, with all loads being less than the critical state.

The test results are used to produce a graph referred to as a Jenike yield locus in which the shear stress required to initiate movement is plotted against the normal stress (Fig. 4). The line gives the stress conditions needed to produce flow for the powder when compacted to a fixed bulk density. If the material is cohesive, the yield locus does not produce a straight line, and it does not pass through the origin. The intercept OT is the tensile strength of the consolidated specimen, and OC is the cohesion of the specimen, that is, the shear stress needed

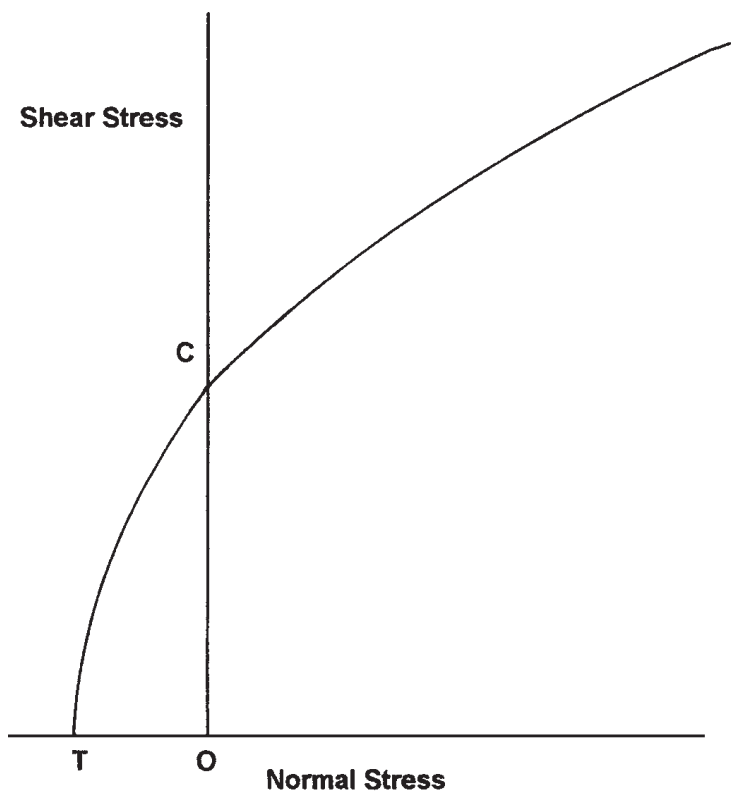


Figure 4 Jenike yield locus.

Table 3 Carr Indices

Carr index (%)	Flow
5–12	Free flowing
12–16	Good
18–21	Fair
23–35	Poor
33–38	Very poor
>40	Extremely poor

to initiate movement of the material when it is not subjected to normal force. The application of the yield loci to pharmaceuticals is well documented in the literature (Kocova and Pilpel, 1972, 1973; Williams and Birks, 1967).

The limitations of the Jenike shear cell are that it is not very useful for measuring bulk solids with large shear deformations, for example, plastic powders. The level of consolidation stresses required are inappropriate for pharmaceutical materials, and the quantity of material required is often beyond that available in the early stages of development. Alternative shear cells that have been used include annular shear cells (Nyquist and Brodin, 1982; Irono and Pilpel, 1982) and ring shear testers (Schulze, 1996).

Changes in Bulk Density

The increase in bulk density of a powder is related to its cohesiveness. Ratios of the poured to tapped bulk densities are expressed in two ways to give indices of flowability.

$$\text{Hausner ratio} = \frac{\text{tapped bulk density}}{\text{poured bulk density}} \quad (4)$$

$$\text{Compressibility (Carr index)} = \frac{100 \times (\text{tapped bulk density} - \text{poured bulk density})}{\text{tapped bulk density}} \quad (5)$$

The Hausner ratio varies from about 1.2 for a free-flowing powder to 1.6 for cohesive powders. The Carr index classifications are listed in Table 3.

Compressibility indices are a measure of the tendency for arch formation and the ease with which the arches will fail and, as such, is a useful measure of flow. A limitation of the bulk density indices is that they only measure the degree of consolidation; they do not describe how rapidly consolidation occurs.

Angle of Repose

If powder is poured from a funnel onto a horizontal surface, it forms a cone. The angle between the sides of the cone and the horizontal surface is referred to as the angle of repose. The angle is a measure of the cohesiveness of the powder, as it represents the point at which the interparticle attraction exceeds the gravitational pull on a particle. A free-flowing powder will form a cone with shallow sides, and hence a low angle of repose, while a cohesive powder will form a cone with steeper sides.

This method is simple in concept, but not particularly discerning. As a rough guide, angles less than 30° are usually indicative of good flow, while powders with angles greater than 40° are likely to be problematic.

Avalanching Behavior

If a powder is rotated in a vertical disc, the cohesion between the particles and the adhesion of the powder to the surface of the disc will lead to the powder following the direction of rotation until it reaches an unstable situation where an avalanche will occur. After the avalanche, the powder will again follow the disc prior to a further avalanche. Measurement of the time between avalanches and the variability in time is a measure of the flow properties of the powder.

MIXING

Mixing of powders is a key step in the manufacture of virtually all solid dosage forms. A perfect mixture of two particles is one in which any group of particles taken from any position within a mix contains the same proportions of each particle as the mixture as a whole (Fig. 5). With powders, unlike liquids, this is virtually unattainable. All that is possible to achieve is a maximum degree of randomness, that is, a mixture in which the probability of finding a particle of a given component is the same at all positions in the mixture (Fig. 6).

To determine the degree of mixing obtained in a pharmaceutical operation, it is necessary to sample the mixture and determine the variation within the mix statistically. In assessing the quality of a mixture, the method of sampling is more important than the statistical method used to describe it. Unless samples that accurately represent the system are taken, any statistical analysis is worthless. Furthermore, to provide meaningful information, the scale of scrutiny of the powder mix should be such that the weight of sample taken is similar to the weight that the powder mix contributes to the final dosage form.

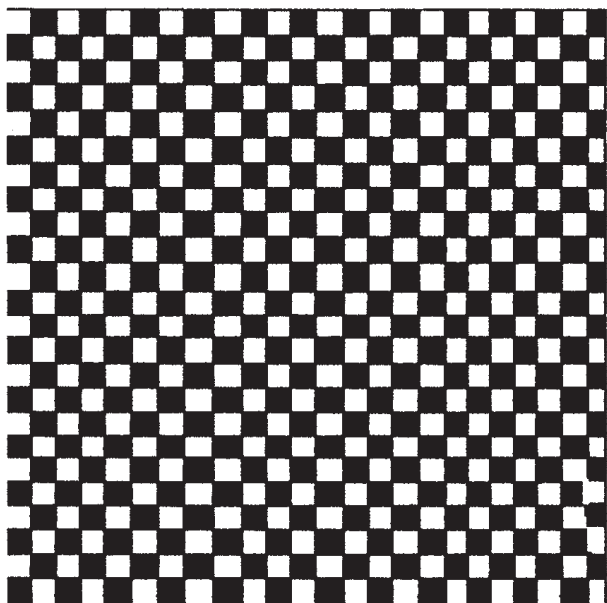


Figure 5 Perfect mix.

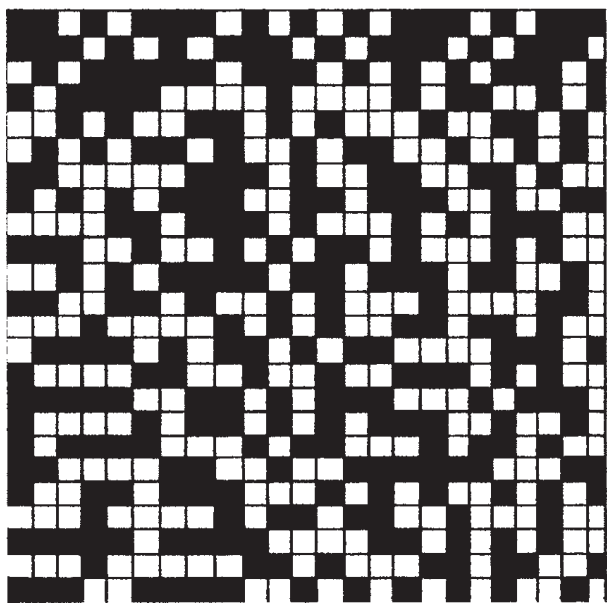


Figure 6 Random mix.

A large number of statistical analyses have been applied to the mixing of powders. These tend to be indices where the variance of the actual mix is compared to the theoretical random mix. The statistics are beyond the scope of this text and can be found in a number of standard texts on powder technology (Rhodes, 1990).

Segregation

If a powder consisting of two materials, both having identical physical properties, is mixed for sufficient time, random mixing will eventually be achieved. Unfortunately, most pharmaceutical powders consist of mixtures of materials with differing properties. This leads to segregation, where particles of similar properties tend to collect together in part of the powder. When segregating powders are mixed, as the mixing time is extended, the powders appear to unmix, and equilibrium is reached between the action of the mixer, introducing randomness and the resistance of the particles due to segregation.

While a number of factors can cause segregation, *differences in particle size* are by far the most important in pharmaceutical powders. There are a number of mechanisms by which segregation of different-sized particles can occur, and consideration should be given to these when designing pharmaceutical processes. *Trajectory segregation* occurs when a powder is projected horizontally in a fluid or gas; larger particles are able to travel greater horizontal distances than small particles before settling out. This could cause segregation at the end of conveyor belts or vacuum transfer lines. When a powder is discharged into a hopper or container, air is displaced upward. The upward velocity of this air may be sufficient to equal or exceed the terminal velocity of some of the smaller particles, and these will remain suspended as a cloud after the large particles have settled out. This process is known as *elutriation segregation*. The most common cause of segregation is due to *percolation* of fine particles. If a powder bed is handled in a manner that allows individual particles to move, a rearrangement in the packing of the particles occurs. As gaps between particles arise, particles from above are able to drop into them. If the powder contains particles of different sizes, there will be more opportunities for the smaller particles to drop, so there will be a tendency for these to move to the bottom of the powder, leading to segregation. This process can occur whenever movement of particles takes place, including when vibrating, shaking, and pouring.

Ordered Mixing

As stated above, differences in particle size are the most common cause of segregation in pharmaceutical powders. One exception to this is when one component of a powder mix has a very small particle size (< 5 mm) and the other is relatively large. In such circumstances, the fine powder may coat the surface of the larger particles, and the adhesive forces will prevent segregation. This is known as ordered mixing, and using this technique, it is possible to produce greater homogeneity than by random mixing.

COMPACTION

The manufacture of tablets, and to a lesser extent powder-filled hard gelatin capsules, involves the process of powder compaction, the purpose of which is to convert a loose incoherent mass of powder into a single solid object. Knowledge of the behavior of powders under pressure, and the way in which bonds are formed between particles, is essential for the rational design of formulations.

Powder in a container subjected to a low compressive force will undergo particle rearrangement until it attains its tapped bulk density. Ultimately, a condition is reached where further densification is not possible without particle deformation. If, at this point, the powder bed is subjected to further compression, the particles will deform elastically to accommodate induced stresses, and the density of the bed will increase with increasing pressure at a characteristic rate. When the elastic limit is exceeded, there is a change in the rate of reduction in the bed volume as plastic deformation or brittle fracture of particles begins (Fig. 7). Brittle materials will undergo fragmentation, and the fine particles formed will percolate through the bed to give secondary packing. Plastically deforming materials will distort to fill voids and

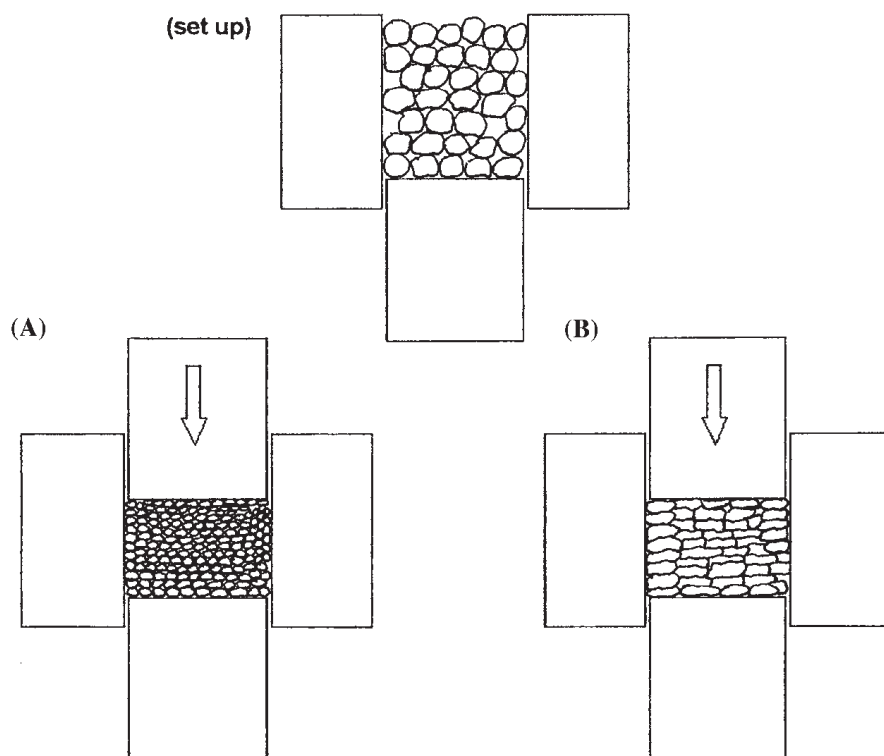


Figure 7 The behavior of powders subjected to a compaction force: (A) brittle fracture and (B) plastic deformation.

may also exhibit void filling by percolation when the limit of plastic deformation is reached and fracture occurs. Either mechanism, therefore, consists of at least two submechanisms, and the processes could be repeated on the secondary particles produced by the fracture until the porosity is at a minimum and the internal crystalline structure supports the compressional stress.

Both processes will aid bonding to form a single compact, as plastic flow increases contact areas between particles irreversibly and fragmentation produces clean surfaces that bond strongly. The successful production of compacts depends on achieving high contact areas between uncontaminated surfaces.

To fully understand the compaction behavior of a material, it is clear that it is necessary to be able to quantify its elasticity, plasticity, and brittleness.

Measurement of Compaction Properties

To characterize the compaction properties of a material or formulation, it must be possible to measure the relationship between the force applied to a powder bed and the volume of the powder bed. A typical instrumentation will consist of measurement of the forces on the upper and lower punches by means of strain gauges or load cells together with a measure of the punch movement, which is performed using displacement transducers, the most common type being linear variable-differential transducers (LVDTs). The positioning and installation of the load and displacement transducers are critical to obtain meaningful information. The topic of instrumentation is comprehensively covered by Ridgway and Watt (1988). There are three approaches that have been used to generate compaction information, as discussed below.

Conventional Testing Machines

Testing machines are widely used in materials science and engineering laboratories for the measurement of physical properties of various materials. Many of the basic principles of compaction and the test methodologies currently employed in pharmaceutical formulation have been developed on testing machines by the metallurgy and ceramic industries. The

drawback with testing machines is that the compression speeds that can be achieved are well below those encountered on tableting machines, so while they are of value in fundamental studies, they are not necessarily useful for predicting the behavior of a material or formulation in the factory.

Conventional Tablet Machines

The first tablet machines to be instrumented were single punch eccentric presses. While these provide useful information, the compression profiles differ from those of rotary tablet machines used for commercial production. The profile of a single punch involves the powder bed being compressed between a moving upper punch and a stationary lower punch, while on a rotary machine, both punches move together simultaneously. Consequently, rotary machines have been instrumented, even though this is technically more challenging than single punch machines. The instrumented rotary press provides information that is directly relevant to production conditions, although it should be borne in mind that profiles do vary between machines, and any results obtained may be peculiar to that machine. A major advantage of instrumented machines is that they provide information not only on the compaction properties but also on flow and lubrication. The disadvantage of using instrumented rotary machines is the quantity of material required to perform tests, making them unsuitable for preformulation activities, when material is in short supply.

Compaction Simulators

Compaction simulators are a development of testing machines. They consist of single punch machines in which the upper and lower punches are driven individually by hydraulic rams. The movement of the hydraulic rams is controlled by computer and can be programmed either to simulate the movement of any tablet machine or to follow a simple profile similar to a testing machine. The big advantage of the compaction simulator is that it can be used to prepare a single compact using a profile that might be encountered on a production machine, so only small quantities of material are required.

Quantitative Compaction Data

There are two principal types of compaction studies used to characterize material: pressure/volume relationships and pressure/strength relationships. While ultimately it is the strength of a tablet that is important, the pressure/volume relationships provide the information about the compaction properties of a material that allows an appropriate formulation to be developed.

Heckel Plots

A large number of equations have been proposed to describe the relationship between pressure and volume reduction during the compaction process. Many of these have an empirical basis and may relate to a particular material or range of pressures, while others attempt to define the complete process of densification. The equation that has been most widely used to describe the compaction of pharmaceutical powders is the Heckel equation (Heckel, 1961). This equation, originally used to describe the densification of ceramics, is essentially a curve-fitting equation that provides reasonable correlation with the observed facts over a wide range of pressures.

The equation is based on the premise that compaction is a first-order process where the rate at which pores within a powder can be eliminated is proportional to the number of pores present. As the compaction process continues, the number of pores continue to drop, and consequently, the rate of volume reduction per unit increase in pressure drops. This was expressed mathematically as

$$\ln\left(\frac{1}{1 - D_r}\right) = kP + A \quad (6)$$

In a system where there was no rearrangement of particles, and compaction was achieved solely by plastic deformation, a plot of $\ln(1/1 - D_r)$ versus P would yield a straight line (Fig. 8).

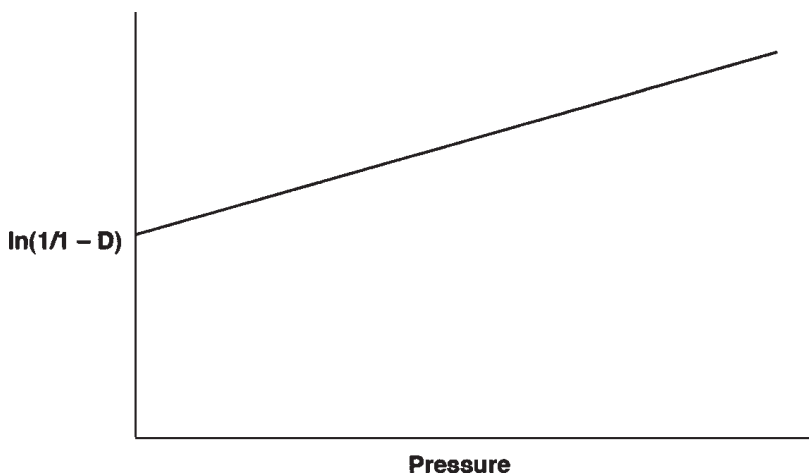


Figure 8 Theoretical Heckel plot.

Pharmaceutical powders do not produce perfect straight lines, and the type of deviation provides information about the compaction behavior of the material. A typical Heckel plot for a pharmaceutical powder is illustrated in Figure 9. A straight-line portion is obtained over a certain pressure range with a negative deviation at low pressures and a positive deviation at high pressures.

The curved portion at low pressures is due to particle rearrangement and possibly fragmentation, the deviation from a straight line (A–B) is a measure of its extent (Fig. 9).

The gradient of the straight-line portion of the plot is related to the reciprocal of the yield pressure of the material, and as such is a measure of the plasticity of the material. While the absolute values obtained for the yield pressure will be dependent on the equipment and test conditions employed, the relative values obtained under given test conditions will provide information about the compaction properties of materials. Table 4 displays the values for yield pressure obtained for excipients, known to have differing compaction properties, tested using a compaction simulator.

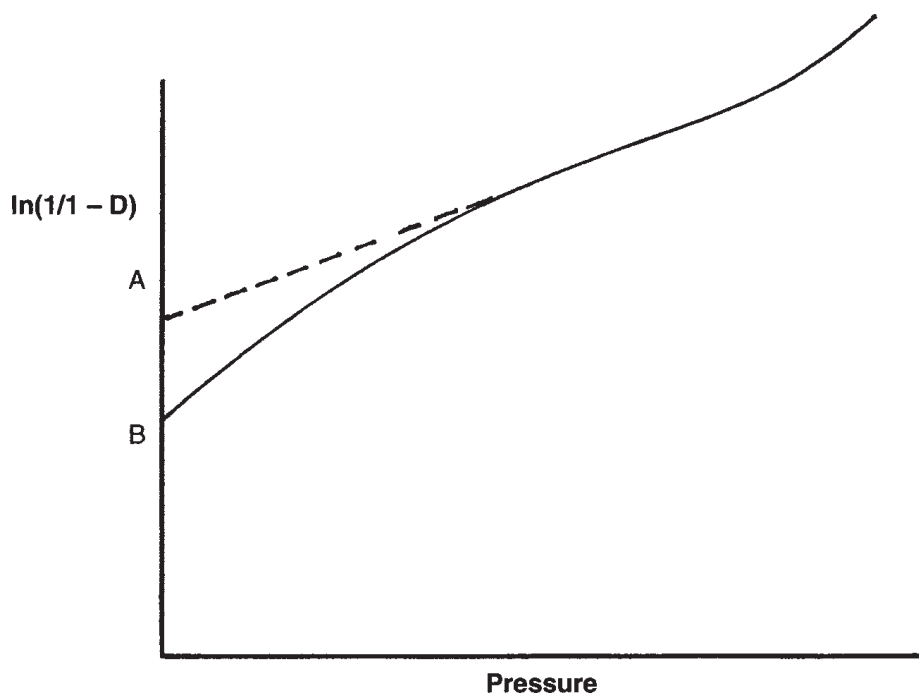


Figure 9 Heckel plots of pharmaceutical powders.

Table 4 Yield Pressure for Excipients

Excipient	Yield pressure (Mpa)	A-B	Deformation mechanism
Microcrystalline cellulose	54	0.15	Plastic/deforming
Anhydrous lactose	174	0.5	
Calcium phosphate dihydrate	396	0.95	Brittle/fragmenting
Starch 1500	53	0.1	

The densification behavior of powders has been categorized into types A, B, and C (York and Pilpel, 1973). Type A (plastic) exhibits parallel but distinct graphs for different size fractions, type B (fragmenting) exhibits particulate fragmentation at low pressures, with graphs becoming coincident at higher pressures, and type C (extremely plastic) is characterized by a small initial curved section, a low value of mean yield pressure, and a rapid approach to zero porosity at low pressure.

The effect of compression speed on the yield pressure of a material has been suggested as a method of determining the time-dependent nature of materials compression properties (Roberts and Rowe, 1985). Heckel plots are produced at two punch velocities, 0.03 and 300 mm/sec, and the yield pressures determined. The strain rate sensitivity (SRS) is calculated as

$$\text{SRS} = \frac{P_{Y2} - P_{Y1}}{P_{Y1}} \times 100 \quad (7)$$

where P_{Y1} = the yield pressure at 0.03 mm/sec and P_{Y2} = the yield pressure at 300 mm/sec. Materials that exhibit plastic deformation have larger SRS than values fragmenting materials.

Elasticity

While Heckel plots are able to distinguish between plastic and fragmenting mechanisms, they do not readily distinguish between plastic and elastic deformation. The data presented in Table 4 would suggest that microcrystalline cellulose and starch 1500 have very similar properties, yet the elastic nature of starch and its derivative products is well documented in the literature. Additional methods are, therefore, required to measure elasticity.

Elasticity can be determined either by monitoring the elastic energy during the decompression phase of a compact within the die or by comparing the dimensions of the ejected compact with the dimensions of the compact within the die at peak compaction pressure.

The elastic energy is determined by plotting a force-displacement curve. If punch force is plotted against punch tip displacement or punch tip separation, a curve with a progressively increasing slope is obtained, reaching a maximum force at the point of minimum separation. As the punch begins to retract, the compact will expand because of elastic recovery and will remain in contact with the punch. This recovery is apparent from the force-displacement curve. If the material being compressed is truly elastic, the curve for the decompression phase will overlay the compression phase. For a truly plastic material, the force will fall to zero immediately as the punch begins to retract. Pharmaceutical materials tend to show a combination of elastic and plastic deformation.

Integrating the force-displacement curves gives a measure of the energy involved in the compaction process (Fig. 10), it being possible to calculate both the elastic energy and the net energy of compaction.

An alternative measure of elasticity is the percentage elastic recovery ($ER\%$) (Armstrong and Haines-Nutt, 1972):

$$ER\% = \frac{H - H_c}{H_c} \times 100 \quad (8)$$

where H = thickness of compact after ejection and recovery and H_c = minimum thickness under load.

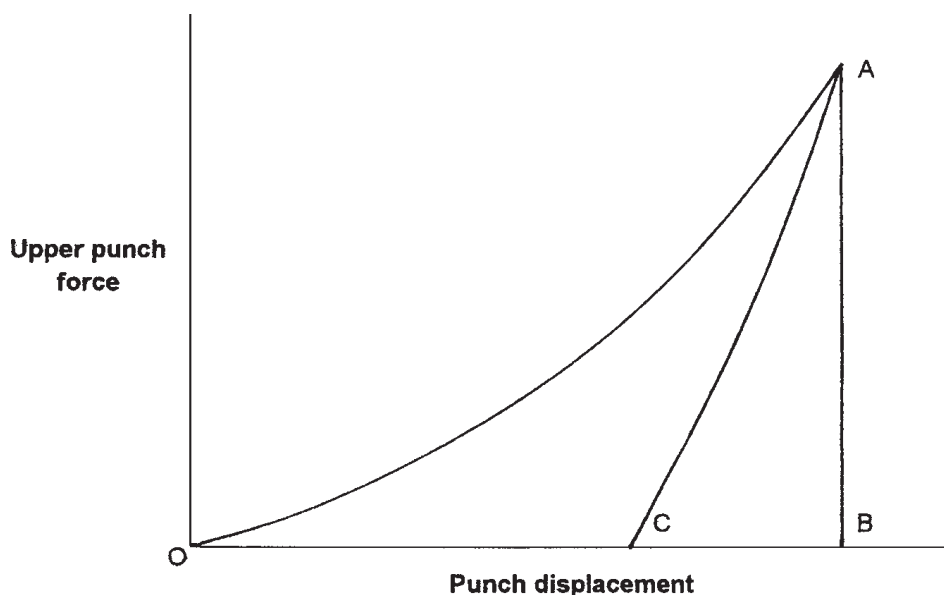


Figure 10 Force-displacement curve for a pharmaceutical powder. The total work of compaction is represented by the area defined by OAB; elasticwork by CAB. The network of compaction is the area defined by OAC.

This measure differs from the elastic energy in that it includes the viscous contribution to elastic recovery as well as the purely elastic behavior during the unloading period of compression. Whichever method is used to calculate the elasticity, it should be borne in mind that the punches will also display a degree of elasticity, and this must be allowed for when calculating punch separations at pressure.

Indentation Hardness

An alternative method of determining the plasticity and elasticity of a material is indentation hardness testing. The principle of indentation hardness testing is that a hard indenter of specified geometry, either a sphere or square-based pyramid, is pressed onto the surface of the test material with a measured load and the size of the indentation produced measured. The hardness of a material is the load divided by the area of the indentation to give a measure of the contact pressure.

There are two types of hardness tests: *static tests* that involve the formation of a permanent indentation on the surface of the test material and *dynamic tests* in which a pendulum is allowed to strike the test material from a known distance. Vickers and Brinell tests, two examples of static methods, are the most commonly used methods for determining the hardness of pharmaceutical materials. In the Brinell test, a steel ball of diameter D is pressed on to the surface of the material, and a load F is applied for 30 seconds and then removed. The diameter d_1 of the indentation produced is measured, and the Brinell Hardness Number (BHN) calculated by

$$\text{BHN} = \frac{2F}{\pi D_1 (D_1 - \sqrt{D_1^2 - d_1^2})} \quad (9)$$

The Vickers hardness test uses a square-based diamond pyramid as the indenter. The Vickers hardness, H_v is calculated by

$$H_v = \frac{2F \sin 68}{d^2} \quad (10)$$

where d is the length of the diagonals of the square impression.

Traditionally, it has been necessary to perform indentation testing on compacts because of the size of the indenters. The surfaces of compacts are not homogeneous, and this

introduced variability. Recently, nanoindentation testers have been developed, which are capable of performing indentation tests on single crystals. Such testers offer significant potential for characterizing the mechanical properties of materials at an early stage of development.

Pressure/Strength Relationships

The strength of tablets has traditionally been determined in terms of the force required to fracture a specimen across its diameter, the *diametral compression test*. The fracture load obtained is usually reported as a hardness value, an unfortunate use of a term that has a specific meaning in materials science, associated with indentation. The use of the fracture load does not allow for compacts of different shapes, diameters, or thicknesses to be directly compared. For flat-faced circular tablets, a complete analytical solution exists for the stress state induced during the test (Carneiro and Barcellos, 1953), allowing the tensile strength to be determined from the fracture load:

$$\sigma_x = \frac{2P}{\pi Dt} \quad (11)$$

where P is the fracture load, D the tablet diameter, and t the tablet thickness. The solution for tensile stresses can only be used for tablets that fail in tension, characterized by failure along the loaded diameter.

The stresses developed in the tested convex tablets undergoing the diametral compression test have been examined by Pitt et al. (1989), who proposed the following equation for the calculation of the tensile strength:

$$\sigma_f = \frac{10P}{\pi D^2} \times \left(\frac{2.84t}{D} - \frac{0.126t}{C_L} + \frac{3.15C_L}{D} + 0.01 \right) \quad (12)$$

where P is the fracture load of the convex tablet, D the diameter, C_L the cylinder length, and t the overall thickness of the tablet.

Typical plots of tensile strength versus compaction pressure are illustrated in Figure 11. Initially, most materials demonstrate an increase in tensile strength proportional to the compaction pressure applied. As the compaction pressure is increased, the tablet approaches zero porosity, and large increases in pressure are required to achieve small volume reductions, and consequently, small increases in bonding. Some materials will attain maximum strength, and subsequent increases in pressure will produce weaker tablets.

Other materials also display an initial increase in strength proportional to the applied pressure, but the strength reaches a maximum before falling off sharply. This is due to capping or lamination, which results in tablets failing in a characteristic manner (Fig. 12). Capping is the partial or complete removal of the crown of a tablet from the main body, while lamination

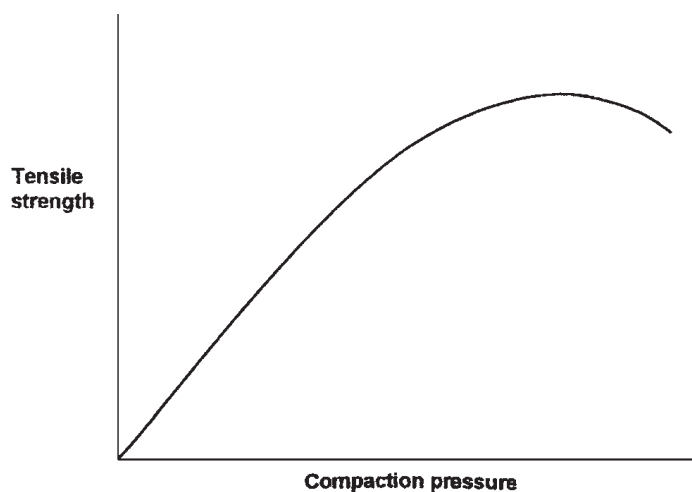


Figure 11 Compaction pressure/tensile strength profile. Typical plot for a pharmaceutical material.

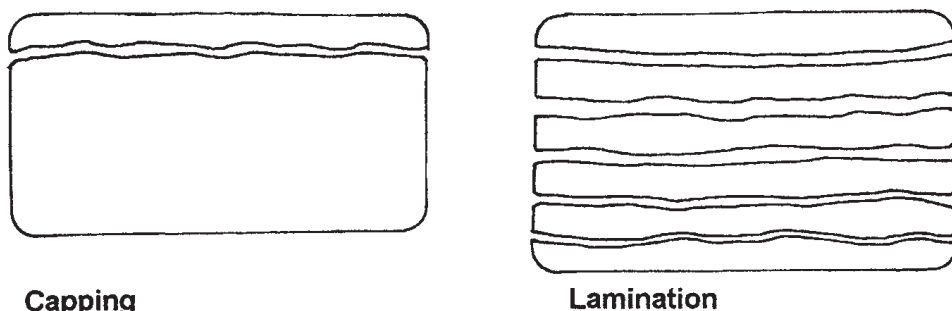


Figure 12 Tablet flaws: capping and lamination.

is the separation of a tablet into two or more distinct layers. The problem may be apparent on ejection of the tablet or may manifest itself when the tablet is subjected to further stress, for example, mechanical strength testing or film coating.

Capping

Capping and lamination can affect both individual substances and formulations and constitute one of the most common problems facing the formulator. It occurs when a material is unable to relieve stresses present within a compact following compression by plastic deformation (Hiestand and Smith, 1984). When a material is compressed within a die by means of two opposing punches, the axial load that is applied through the upper punch is transmitted to the die as a shearing force. In addition, force is transmitted radially to the die wall. The nature of this radial force is determined by the elastic or plastic behavior of the compact. When an axial force is applied to a column of powder in a die, the pressures developed within the powder vary with depth. This phenomenon is attributed to the development of friction between the powder and the die wall and leads to density variations within the final compact. The nature of such variations has been the subject of a number of investigations (Train, 1957; Kamm et al., 1949; Charlton and Newton, 1985). These studies have been performed on a number of materials that have been compressed in dies with one moving and one stationary flat-faced punch. The results obtained in each study indicated a similar density distribution within a compact, high-density region being present on the perimeter of the compact adjacent to the moving punch and low-density regions near the stationary punch. In addition, there was a second high-density region remote from the moving punch (Fig. 13). An explanation for the density distribution has been proposed on the basis of the development of high-density wedges of material at the die wall adjacent to the moving punch. Figure 14 represents the forces developed in the compact. At equilibrium, the axial force is supported by the punch in direction *a* and by the powder in direction *b*. The radial component is supported by the die wall in direction *c* and by the powder bed in direction *d*. The resultant force acting on the mass

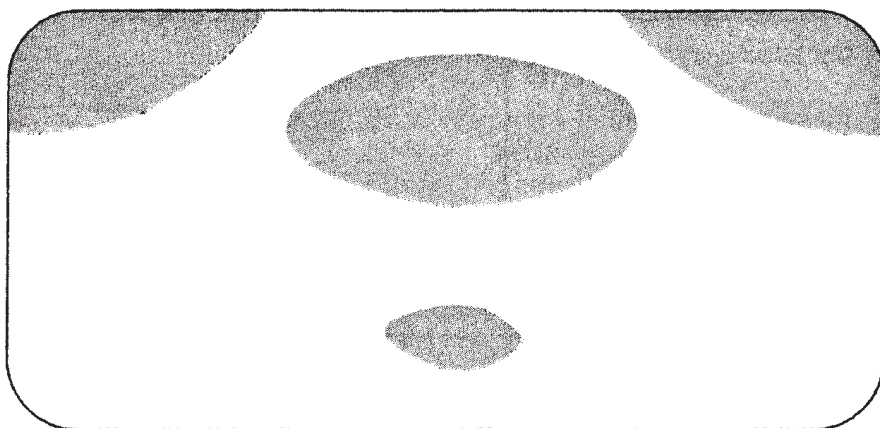


Figure 13 Regions of high density within a compact.

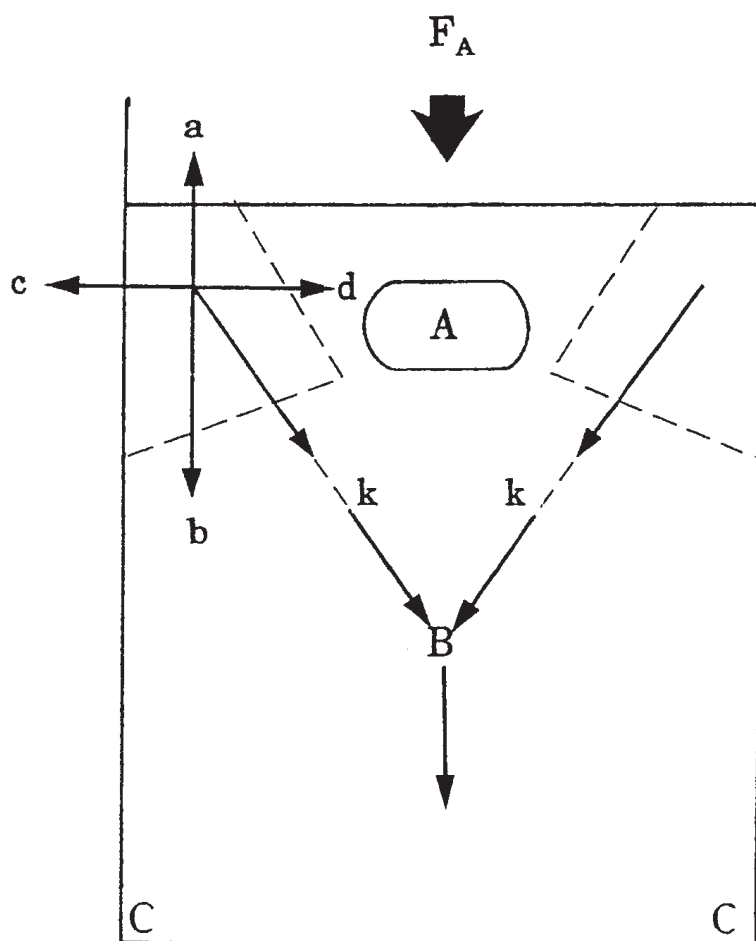


Figure 14 Development of the pressure pattern within a compact.
Source: From Train (1957).

is denoted by k . The pressure front can be considered as a conical surface with its focal point B . The region around point B will be exposed to the greatest pressure and will have a greater density than the surrounding areas. The wedge-shaped areas bounded by the dotted lines adjacent to the moving punch will be highly densified due to the high shearing forces that they are exposed to. The central area, A , will be subject to negligible shearing forces and will be protected from normal axial pressures by the vaulting effect of the high-density wedges resulting in an area of low density. The area C , adjacent to the stationary punch, will undergo no movement relative to the die wall, and thus will not be subject to shearing forces. Density in this region will be low, as consolidation will depend solely on transmitted axial forces.

On removal of the upper punch, there will be a degree of axial elastic recovery resulting in expansion of the compact within the die. Following ejection, expansion may also occur in the radial direction. This elastic recovery is considered to be the most likely cause of capping. Train (1956) attributed capping to the strain imposed by elastic recovery of the areas of high density within the compact on ejection (Fig. 15). The elastic recovery of the dense peripheral ring would be larger than that of the adjacent, less dense, part of the tablet. The differential stress in this region is exacerbated by both axial and radial relaxation of that part of the tablet extruded from the die during the early stages of ejection.

Attempts have been made to predict the capping tendencies of materials. Malamataris et al. (1984) examined the plastoelasticity of mixtures of paracetamol and microcrystalline cellulose and showed that the tensile strengths of compacts were inversely proportional to the ratios of the samples' elastic recovery: plastic compression (as defined in Fig. 10). Lamination and capping occurred when this ratio exceeded 9. Nyström et al. (1978) measured the tensile strength of compacts in both the radial and axial directions and found that the values were not equal, the axial strength often decreasing at high compaction pressures. It was proposed that

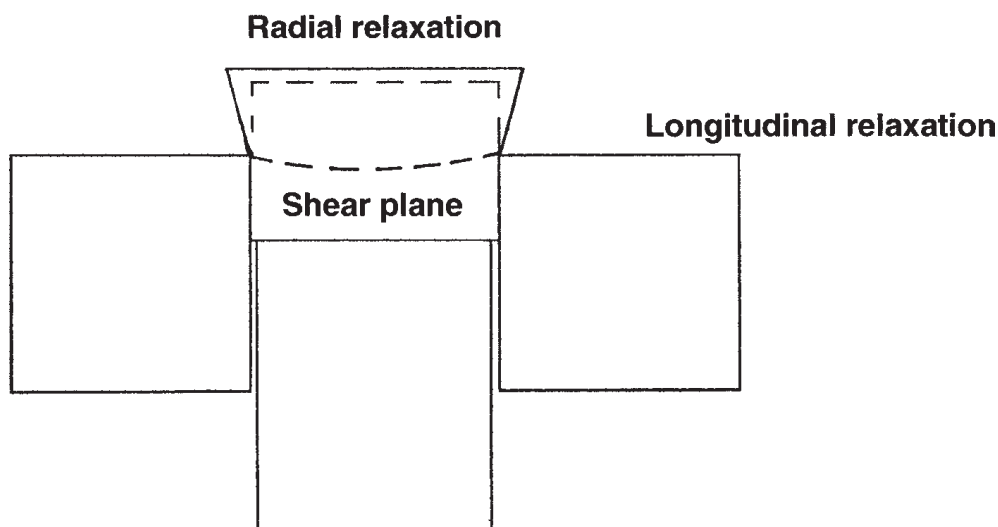


Figure 15 Elastic recovery of compact during ejection from die leading to capping. *Source:* From Train (1956).

the ratio of axial to radial tensile strength should be close to unity for a good formulation. Krycer et al. (1982) examined the capping tendencies of three grades of paracetamol and proposed a capping index defined as the slope of the $ER_{\%}$ versus residual die wall pressure (the pressure exerted on a die by a compact after removal of the upper punch). The higher the values of the capping index, the greater the tendency for capping. The residual die wall pressure relates to the irreversible deformation undergone during compaction. Low values for residual die wall pressure indicate that the compact had recovered axially and contracted radially, which would induce strain within the compact.

The methods of predicting capping discussed so far have been measures of the degree of elastic recovery occurring in the compact. For capping to occur, the stresses produced by the elastic recovery during decompression must be sufficient to disrupt the bonds that are formed during compression. Hiestand and Smith (1984) proposed a measure of the ability of a material to relieve localized stresses called the brittle fracture index (BFI). This test involves comparing the tensile strength value obtained using the diametral compression test of a compact that contains a central, axial hole with one that does not. Under the conditions of the test, the hole acts as a stress concentrator; elasticity theory predicts that the stress concentration factor is approximately 3.2 for a hole in an isotropic solid. However, for most pharmaceutical materials, the ratio of tensile strengths obtained is less than 3 due to the relief of the highly localized stresses by plastic deformation. The BFI is defined as

$$BFI = \frac{\sigma_s - \sigma_0}{2\sigma_0} \quad (13)$$

where σ_s is the tensile strength of the compact without the hole and σ_0 is the tensile strength of the tablet with the hole. A BFI of 1.0 would correspond to a purely brittle material; a value of zero would indicate that the stresses at the hole had been completely relieved by plastic deformation.

Hiestand and Smith (1984) proposed that a material with a high BFI would be less able to relieve the stresses occurring during decompression and ejection and would therefore be more susceptible to capping and lamination. Experiments showed that problems were likely to occur with materials having a BFI of 0.8 or more. The BFI will be dependent on the relative density of a material; at low densities, pores may act as stress concentrators in the same way as the central hole, so the measurements should be made at fixed, high relative densities. Roberts and Rowe (1986) determined the BFI of compacts produced at a range of relative densities using a range of compaction speeds. Magnesium carbonate, a brittle material, displayed increasing BFI values with increases in compaction speed and relative density, while microcrystalline cellulose showed little change.

Summary

It is clear from the preceding discussions that there is not one single technique that can be used to fully characterize the compaction properties of a powder. A number of tests have been widely applied to pharmaceutical materials, but used in isolation, they will not provide the formulator with all the data required to fully understand their behavior when tableted. Two sets of workers have tried to address this problem by suggesting a range of tests that, used in combination, will give a more complete picture of the materials properties.

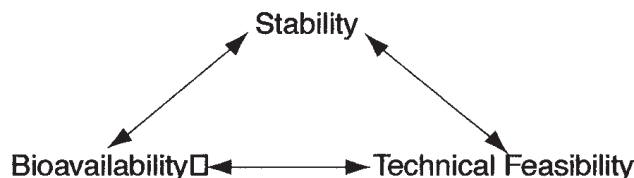
Hiestand and Smith (1984) proposed three indices referred to as Tableting Indices. The three indices are a strain index, bonding index, and the BFI, which was described in the section "Capping." The strain index is a measure of the strain present in a material following compaction and is a measure of elastic recovery calculated by a dynamic indentation hardness test. The bonding index is a measure of the material's ability to deform plastically and form bonds and is the ratio of a compact's tensile strength and indentation hardness.

Roberts and Rowe (1987) have proposed a material classification on the basis of the knowledge of Young's modulus of elasticity: yield stress, hardness, and SRS.

Rational formulation relies on a thorough understanding of the physicochemical properties of the material. Ideally, the mechanical properties should be determined at an early stage in the development process. It must, however, be borne in mind that the properties are sample dependent, and changes in particle size, morphology, and so on during development will affect the compaction properties.

SOLID DOSAGE FORMS

When formulating any pharmaceutical dosage form, it is important to remember that there is equilibrium between the bioavailability of the product, its chemical and physical stability and the technical feasibility of producing it.



Any changes made to a formulation in an attempt to optimize one of these properties is likely to have an effect on the other two parameters, which must be considered. This is especially true of immediate-release solid dosage forms. Many of the properties required to optimize the bioavailability through rapid disintegration and dissolution of the active constituent, for example, small particle size, must be balanced with the manufacturability, where the fluidity and compatibility of a powder will often be enhanced by an increase in particle size.

Tablets and hard gelatin capsules form the vast majority of solid dosage forms on the market. While the actual processes involved of filling capsules and compressing tablets differ, the preparations of the powders to be processed are, in many cases, very similar.

TABLETS

Tablet Machines

Tablets are produced using tablet presses. While these presses vary in their output, from approximately 3000 tablets per hour to more than 1 million per hour for the fastest machines, the principle of manufacture remains the same. Powder is filled to a specified depth in a die and compressed between two punches. The compression force is ended by removal of the upper punch, and the lower punch then moves upward in the die to eject the tablet. Presses can be divided into two types, single punch (or eccentric) presses and rotary presses.

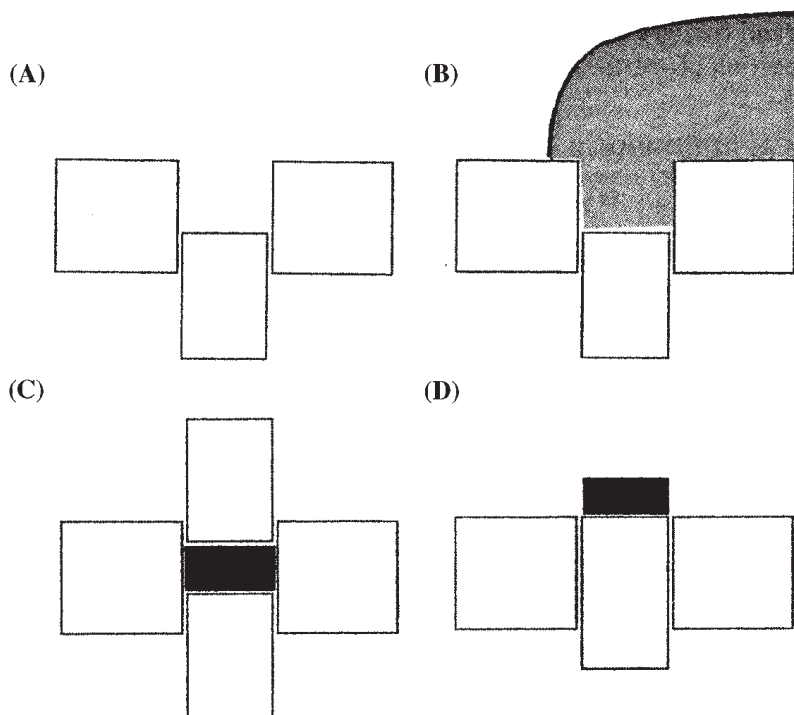


Figure 16 Schematic representation of a single punch tablet machine. (A) The upper punch is raised out of the die, and the lower punch drops to a set position. (B) The feed shoe oscillates above the die, filling it with powder. (C) The upper punch enters the die and compresses the powder. (D) The upper punch is removed, and the lower punch rises in the die to eject the tablet.

Single Punch Presses

Single punch presses are sometimes referred to as eccentric presses because the movement of the punches is controlled by an eccentric cam. The tabletting cycle of a single punch machine is represented schematically in Figure 16. The powder hopper is attached to a feed shoe, which oscillates horizontally.

The compression cycle starts with die filling. The lower punch descends in the die. The depth of the descent can be controlled, and this determines the tablet weight. The feed shoe then passes over the die a number of times, allowing the die to be filled with powder. As the die shoe moves away, it removes all excess powder away from the die table, leaving the die filled to an even level.

The upper punch then descends into the die, compressing the powder. The depth to which the punch descends into the die is adjustable, and this controls the compaction pressure applied. The lower punch remains stationary during the compression phase.

As the upper punch moves upward at the end of the compression phase, the lower punch rises in the die until it is level with the die table. The feed shoe then begins its oscillatory phase and knocks the tablet off the lower punch and down a collection chute. The lower punch then descends to its filling position as a second cycle commences.

Single punch presses are rarely seen in production environments because of their relatively slow production rates, although there are still a number of old products that can only be successfully produced on this type of machine. They are still used in development laboratories because they require only relatively small amounts of material to produce tablets compared with most rotary machines.

Rotary Tablet Machines

Commercial manufacture of tablets is performed almost exclusively on rotary tablet machines due to their higher output. On a rotary machine, the punch and dies are positioned on a rotating turret, and output depends on the number of stations positioned around the turret and the speed of rotation. Machines are available with anything from 4 stations for a development machine to 79 stations for the largest production machines. All such machines operate using virtually identical principles that are represented in Figure 17.

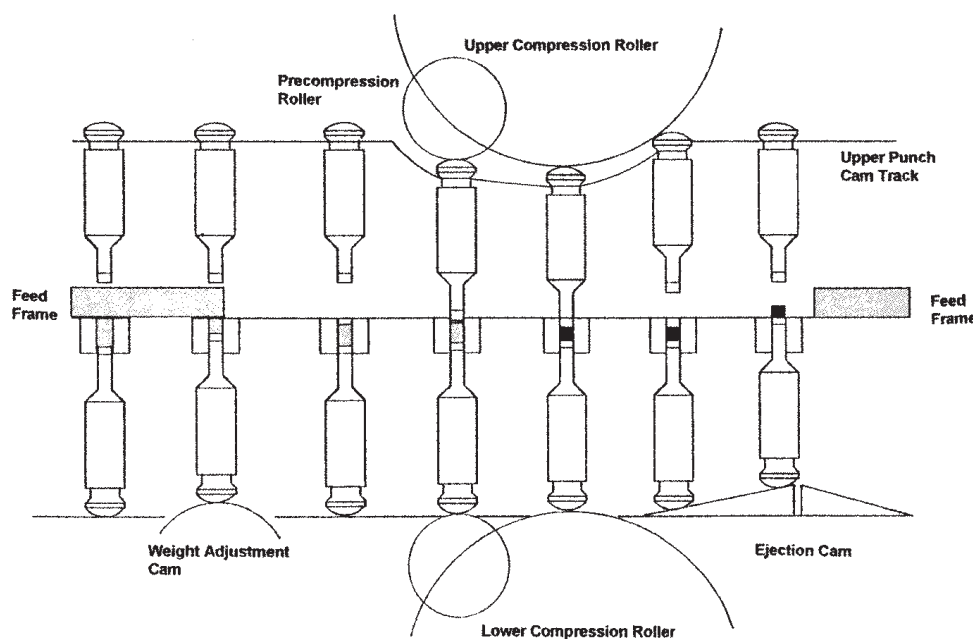


Figure 17 Schematic representation of a rotary tablet machine.

The powder hopper is positioned above a feed frame, a frame that retains a powder bed above the dies when the lower punch is in the filling position. As the lower punches pass below the feed frame, they descend within the die to their lowest possible position so the whole die cavity can be filled with powder. The powder is filled into the dies by the suction effect caused by their descent and gravity from the feed frame above. To optimize filling, the feed frame is designed so that the powder in contact with the die table and following the rotary action of the table is directed in a manner that makes it pass to and fro across the dies. Some machines also have mechanical paddles in the feed frame. As the lower punches approach the end of the feed frame, they pass over a weight-control cam; this causes the punch to rise, ejecting some of the powder that is scraped off by the edge of the feed frame. Adjusting the height of the cam controls the amount of material remaining in the die as the punch moves toward the compression stage.

Compression takes place when the upper and lower punches pass between compression rollers. During compression, the upper and lower punches move together, in contrast to the single punch machine, where only the upper punch moves. The compression force is controlled by moving the lower compression roller up or down, thus adjusting the distance between the punches at the point of maximum compaction. Some machines are fitted with two sets of rollers, a small roller being positioned between the feed frame and the main compression roller allowing a small degree of compression to take place. This is termed precompression, and was introduced to minimize capping and lamination by removing air from the powder bed and effectively increasing the dwell time of the compression phase.

Following compression, the upper punches are removed by the upper punch cam track, and the lower punches pass over an ejection cam, a gentle ramp that moves the lower punches vertically within the die until the tablet is fully ejected. The tablets are removed from the punch tip by a scraper blade positioned on the edge of the feed frame, and the punch then descends to allow die filling to occur for the next cycle.

When developing formulations, it is usual for the early batches to be manufactured on either single punch machines or small rotary machines due to the batch sizes being produced and the limited availability of new drug substances. It should be borne in mind that the formulations that are being developed may ultimately be required to run on larger rotary machines, and there are great differences in the rate of compression between the machines generally found in formulation laboratories and those found in production. These differences are summarized in Table 5.

The differences in punch speed at initial contact and dwell times, the period at which the compact is held at maximum compression, are likely to affect the nature of those tablets that

Table 5 Speed-Related Data for a Number of Commonly Used Tablet Presses Operating at Maximum Output

Tablet press	Production rate per die (tablets/min)	Time for punch to descend last 5 mm (msec)	Punch speed at first contact with powder (mm/sec)	Dwell time (msec)
Manesty				
F3 [Single punch]	85	68.6	139	0
B3B	44	61.4	163	10.84
Express	100	26.7	416	3.94
Unipress	121	19.1	485	3.16
Novapress	100	10.0	720	2.14
Kilian				
Tx	105	19.0	494	2.96
F1000	55	36.4	232	6.60
F1000	75	26.6	317	4.84
F2000	75	23.1	402	3.68
F2000	100	17.3	526	2.76
Korsch				
300	80	21.7	419	3.44
300	100	17.3	526	2.76

Source: Adapted from Armstrong, 1989.

have any viscoelastic components. Compaction simulators that are able to reproduce the punch speeds of production machines, yet only require small quantities of powder for testing, can have a valuable role to play in formulation development.

Tablet Formulation

A tablet formulation should possess the following properties to optimize the technical feasibility, stability, and bioavailability of the formulation:

- Compatibility of drug substance with excipients
- Flowability
- Compactibility
- Lubricity
- Appearance
- Disintegration
- Dissolution

Compatibility

Compatibility studies have been discussed in detail in chapter 6. The solid-state compatibility is of particular importance in tablets due to the compaction process increasing the contact area between particles, and hence the potential for reactivity.

Flowability

The importance of powder flow was emphasized in the section Powder Flow. The formulation should have sufficient flowability to ensure that the appropriate quantity of powder flows into the dies of the tablet machine on a consistent basis. While the tests described for powder flow are useful development tools, the ultimate test of a formulation is the uniformity of weight of tablets manufactured on a production tablet machine.

There is bound to be some variability in tablet weight during manufacture due to variation in the particle size of the material being compacted, flow property variation, and machine parameters (e.g., small differences in the lengths of the lower punches). To allow for such variability, pharmacopoeias set tolerances to ensure adequate control without providing a specification that is impossible to achieve in production. The European Pharmacopoeia (EP) test is to weigh 20 individual tablets and calculate the mean. The individual tablet weights are then compared to the mean. The sample is acceptable if no more than two tablets are outside

Table 6 European Pharmacopoeia Uniformity of Weight Limits

Average tablet weight (mg)	Percentage deviation
≤80 mg	10.0
>80 mg and <250 mg	7.5
≥250 mg	5.0

the stated percentage limit and no tablet is outside twice the stated limit (Table 6). The pharmacopoeial limits are generous, and typically much more stringent limits will be applied as in-process controls. The in-process controls will also apply strict limits for the value of the mean tablet weight.

Uniformity of weight does not guarantee that there is uniformity of active ingredient throughout a batch of tablets. If there is segregation of the active ingredient occurring, the weights may remain uniform, while the potency varies. For this reason, the U.S. Pharmacopeia (USP) only allows a uniformity of weight test for tablets containing 50 mg or more of an active ingredient comprising 50% or more, by weight, of the tablet. In all other instances, a content uniformity test must be performed.

Uniformity of weight is also important in achieving consistency of tablet strength, as there is a relationship between the quantity of powder in the die and the compaction pressure required to compress it to a given thickness, which is what the tablet machine is effectively doing. If the quantity of powder in the die is reduced to a lower compaction, pressure will be applied, producing a weaker tablet. Variation in tablet strength may in turn lead to variability in the disintegration and dissolution properties of the product.

With low-dose drugs, it may be possible to influence the flow properties by combining the drug substance with excipients possessing good flow properties. Where a formulation is prepared by simply dry mixing the drug with excipients prior to compaction, the process is referred to as direct compression. With high-dose drugs, the quantity of such excipients that would be needed to achieve suitable flow and compaction properties may result in the final weight of the dosage form being unrealistically high. In such cases, the usual formulation approach is to granulate, a process that imparts two primary requisites to formulations: compactibility and flowability. Granulation is a process of size enlargement, whereby small particles are gathered into larger, permanent aggregates in which the original particles can still be identified. The direct compression and granulation processes and their relative merits are discussed in greater detail in the section "Processing of Formulations."

The flow properties of a powder can be enhanced by the inclusion of a glidant. These are added to overcome powder cohesiveness by interposing between particles to reduce surface rugosity, thus preventing interlocking of particles and lowering the interparticulate friction. Commonly used glidants are listed in Table 7.

Talc is traditionally one of the most commonly used glidants, having the additional benefit of being an excellent anti-adherent. The level of talc that can be added to a formulation

Table 7 Commonly Used Glidants

Glidant	Typical percentage
Talc	1–5
Fumed silicon dioxide	0.1–0.5
Aerosil	–
Cab-O-Sil	–
Syloid	–
Starch	1–10
Calcium silicate	0.5–2.0
Magnesium carbonate (heavy)	1–3
Magnesium oxide (heavy)	1–3
Magnesium lauryl sulfate	0.2–2.0
Sodium lauryl sulfate	0.2–2.0

is restricted by its hydrophobic nature, too high levels resulting in decreased wetting of the tablet and a subsequent reduction in the rate of dissolution.

The *fumed silicon dioxides* are perhaps the most effective glidants. These are materials with very small (10 nm) spherical particles that may achieve their glidant properties by rolling over each other under shear stress. They are available in a number of grades with a range of hydrophobic and hydrophilic forms.

Starch has been used as a glidant, though relatively large amounts are required. The use of large amounts of starch has also aided the disintegration properties.

Compactibility

The aim of the formulator is to design a formulation that will reliably compact to form a strong tablet. The production manager wants a formulation that achieves the appropriate strength at a low compaction pressure, to reduce wear and tear on the tablet machine and increase the life of the punches.

The compaction properties of a formulation will largely be governed by its major components. For high-dose drugs, the active ingredient will strongly influence the compaction, while for low-dose drugs, it will be necessary for the tablet to be bulked out with an inactive material termed a diluent. High-dose formulations may also use a diluent to overcome compaction problems experienced with an active substance. The selection of the diluent will depend to an extent on the type of processing to be used. A direct compression formulation will require a diluent with good flow and compaction properties. While a granulated formulation can be more forgiving, some degree of compactibility is desirable.

There are a number of general rules for selecting a diluent. The compaction properties of the active ingredient should be considered. If the material is extremely plastic, it is appropriate to add a diluent that compacts by brittle fracture; similarly, a brittle drug substance should be combined with a plastic filler. The solubility of the drug substance should also be considered. A soluble drug is normally formulated with an insoluble filler to optimize the disintegration process.

Apart from their flow and compaction properties, all diluents, and indeed other tablet excipients, should have the following properties:

- They should be inert and physically and chemically compatible with the active substance and the other excipients being used in the formulation.
- They should be physiologically inert.
- They should not have an unacceptable microbiological burden.
- They should not have a deleterious effect on the bioavailability.
- They should have regulatory acceptability in all countries where the product is to be marketed.

There will also be commercial factors in the selection of the diluent. There are hundreds of different brands and grades of diluents available, but it would be unrealistic for the formulator to expect to have a totally free choice. Most manufacturing companies wish to limit the inventory that they carry, and will try to rationalize the excipients used in the factory. This inventory will have been selected on the basis of cost, availability, and performance and will provide the formulator with a starting point.

Table 8 lists the more commonly used diluents. These have been listed in terms of their chemical nature. For each of the substances listed, there will be several suppliers offering branded goods that may or may not be equivalent. Most products will be available with a range of particle sizes.

As can be seen from the table, the excipients all have pharmacopoeial monographs, but it is important to understand that compliance with a monograph does not indicate equivalence between different grades or suppliers. The monographs confirm the chemical identity and purity of the excipients but do not measure the performance of the materials as diluents. To establish the equivalency of excipients obtained from different sources, it is necessary to perform some kind of functionality testing. The *Handbook of Pharmaceutical Excipients*, a joint publication between the Pharmaceutical Press and the American Pharmaceutical

Table 8 Common Tablet Diluents

Diluent	Pharmacopoeia	Comments
Lactose	USP, Ph Eur, JP	Available as anhydrous and monohydrate. Anhydrous material used for direct compression due to superior compressibility.
Microcrystalline cellulose	USP, Ph Eur, JP	Originally a direct compression excipient, now often included in granulations due to its excellent compressibility.
Dextrose, glucose	USP, Ph Eur, JP	Direct compression diluent, often used in chewable tablets.
Sucrose	USP, Ph Eur, JP	Was widely used as a sweetener/filler in effervescent tablets and chewable tablets. Less popular nowadays due to cariogenicity.
Starch and derivatives	USP, Ph Eur, JP	Versatile material can be used as diluent binder and disintegrant.
Calcium carbonate	USP, Ph Eur, JP	Brittle material
Dicalcium phosphate	USP, Ph Eur, JP	Excellent flow properties. Brittle material.
Magnesium carbonate	USP, Ph Eur, JP	Direct compression diluent.

Association, contains some details of functional tests carried out on a wide range of excipients, but the onus on establishing equivalency of excipients still remains with the user (Kibbe, 2000).

Lubricity

The section “Flowability” discussed the role of glidants in tablet formulation. Glidants are one of the three interrelated types of lubricants employed in solid dosage form manufacture. The two other classes of lubricants are anti-adherent excipients, which reduce the friction between the tablet punch faces and tablet punches, and die-wall lubricant excipients, which reduce the friction between the tablet surface and the die wall during and after compaction to enable easy ejection of the tablet.

When two contacting solids are displaced relative to each other and parallel to the plane of contact, the resistance to the movement is termed friction. Contacting surfaces initially touch at points on the asperities of the two surfaces. If a force is applied, these asperities deform to form a contact area. For relative movement of the materials to occur parallel to the contact area, the materials must be sheared. The higher the shear strength of the materials in contact, the greater the force that will be required to produce movement. Die-wall lubricants work by reducing the shear force necessary to promote movement.

The level of a lubricant required in a tablet is formulation dependent and can be optimized using an instrumented tablet machine. On a single punch machine, strain gauges or load cells on the lower punch can directly measure the force required to eject the tablet. An alternative method of measuring lubrication is to measure the ratio of the maximum forces on the upper and lower punches during the compaction cycle (Hölzer and Sjögren, 1978). On a single punch machine, the lower punch remains stationary during the compaction phase, and the compaction pressure is exerted by the movement of the upper punch. If there were no resistance to the movement of particles in the die, the force transmitted through the powder bed to the lower punch would be the same as the force applied by the upper punch. In practice, the interparticle friction and friction between the particles and the die wall result in a lower force being transmitted to the lower punch. The ratio of the upper to lower punch forces, termed the *R*-value, has been used as a measure of the lubricant efficacy. The *R*-value cannot be used on a rotary machine because the compaction pressure is applied from both the upper and lower punches simultaneously. The ejection force can be measured either by instrumenting the punch tips or by positioning load cells or strain gauges below the ejection cam. If an instrumented machine is not available, the signs of inadequate lubricity are the presence of scoring around the tablet circumference and screeching during ejection. While these problems can be overcome by increasing the level of lubricant added, the aim should be to use the minimum level of lubricant required to produce an acceptable product, for reasons discussed later.

Die-wall lubricants can be divided into two classes, fluid and boundary lubricants. *Fluid lubricants* work by separating moving surfaces completely with a layer of lubricant. These are typically mineral oils or vegetable oils, and they may be either added to the mix or applied directly to the die wall by means of wicked punches. Tablets containing oily lubricants may have a mottled appearance due to uneven distribution. When added to the mix, they have an adverse effect on powder flow due to their tacky nature, and have been reported to reduce tablet strength (Asker et al., 1973). Low-melting-point lipophilic solids can also act as fluid lubricants because the heat generated at the die wall is sufficient to cause them to melt, forming a fluid layer, which solidifies on ejection. Fluid lubricants include stearic acid, mineral oils, hydrogenated vegetable oils, glyceryl behenate, paraffins, and waxes. Low-melting-point lubricants should be used with caution in tablets that are to be film coated. Lubricants can melt on the tablet surface during the film-coating process, resulting in tablets with a pitted appearance (Rowe and Forse, 1983). Their use tends to be restricted to applications where a suitable boundary lubricant cannot be identified.

Boundary lubricants work by forming a thin, solid film at the interface of the die and the tablet. Metallic stearates are the most widely used boundary lubricants, and their activity has been attributed to adherence of polar molecular portions on their surface to the surfaces of one particle species and of nonpolar surface components to the other species' surface. Such lubricants should have low shear strength of their own and form interparticulate films that resist wear and reduce surface wear. A list of lubricants with typical ranges for their usage is given in Table 9.

Magnesium stearate is the most widely used lubricant; it forms dense, high-melting-point films between the powder and the die wall to reduce friction and has low shear strength between its own surfaces. Despite its popularity, which is a reflection of its excellent lubricant properties, the material is far from ideal, and has had problems associated with product consistency, its effect on tablet strength, and its hydrophobicity.

The magnesium stearate used in the pharmaceutical industry is not a pure substance but a mixture of magnesium salts of fatty acids, though predominantly magnesium stearate and magnesium palmitate. The USP requires that the stearate content should account for not less than 40% of the fatty acid content of the material, and the stearate and palmitate combined should account for not less than 90%. Within this definition, there is clearly scope for a range of materials to be supplied as magnesium stearate. Furthermore, there is no pharmacopoeial particle size specification for the material. As the lubrication activity of the material is related to its surface area, substantial decreases in ejection force are noted when using sources of

Table 9 Lubricants and Their Usage

Lubricant	Level required (%)	Comments
Boundary lubricants		
Magnesium stearate	0.2–2.0	Hydrophobic, variable properties between suppliers.
Calcium stearate	0.5–4.0	Hydrophobic.
Sodium stearyl fumarate	0.5–2.0	Less hydrophobic than metallic stearates, partially soluble.
Polyethylene glycol 4000 and 6000	2–10	Soluble, poorer lubricant activity than fatty acid ester salts.
Sodium lauryl sulfate	1–3	Soluble, also acts as wetting agent.
Magnesium lauryl sulfate	1–3	Acts as wetting agent.
Sodium benzoate	2–5	Soluble.
Fluid lubricants		
Light mineral oil	1–3	Hydrophobic, can be applied to either formulation or tooling.
Hydrogenated vegetable oils	1–5	Hydrophobic, used at higher concentrations as controlled-release agents.
Stearic acid	0.25–2	Hydrophobic.
Glyceryl behenate	0.5–4.0	Hydrophobic also used as controlled-release agent.

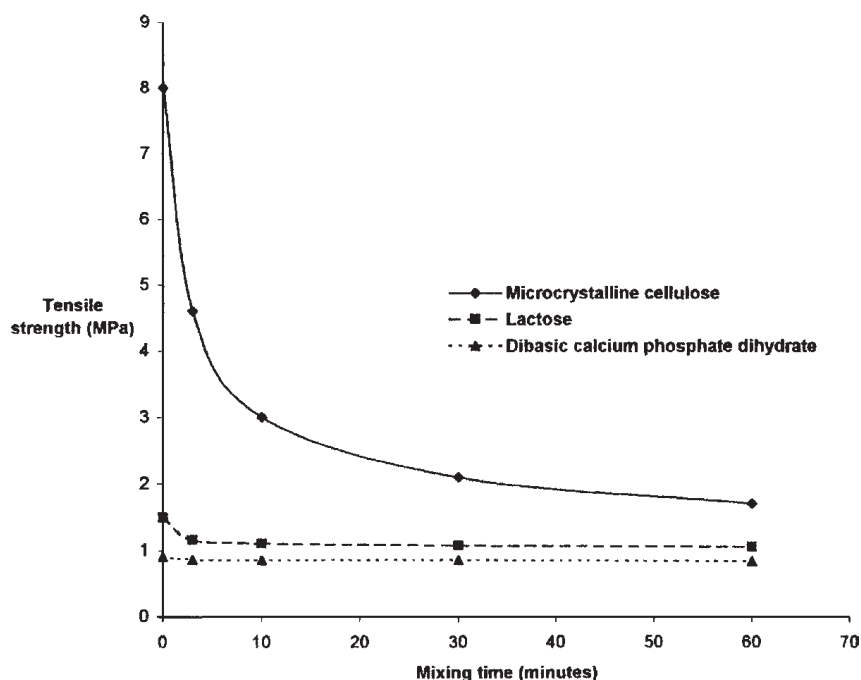


Figure 18 Effect of magnesium stearate mixing time on the strength of compacts.

magnesium stearate with larger surface areas. For a given formulation, it is important that a single source of magnesium stearate is used for all batches. A new supplier should not be used until the effect on the compaction properties and dissolution rates have been assessed.

The lubricant activity of magnesium stearate is related to its readiness to form films on the die wall surface. When it is mixed in a tablet formulation, it displays the same film-forming propensity on the surfaces of the drug and excipient particles, which can have two consequences: a reduction in the ability of the powder to form strong compacts and, due to its hydrophobicity, a deleterious effect on the dissolution rate of the tablets. Figure 18 illustrates the effect of mixing time on the mechanical strength of compacts produced using a range of excipients. While the strength decreases with increasing mixing time for all the materials tested, the effect is far more marked for materials that deform plastically. When plastic-deforming materials are compressed, the film of magnesium stearate around the particles remains relatively intact, so the interparticulate bonds are primarily between magnesium stearate particles, which, by virtue of its lubricant properties, are inherently weak. Materials that compact by fragmentation are less sensitive to the lubricant because the fragmentation process produces a number of clean, uncontaminated surfaces that are able to form strong bonds.

The hydrophobic surfaces created by magnesium stearate have been shown to reduce the rate of dissolution and bioavailability of several tablet formulations. To minimize this effect, the manufacturing process should be designed to ensure that the lubricant is the last excipient to be added. When both lubricant and disintegrant are being added to a granulated formulation, the disintegrant should be blended with the granules prior to the addition of the lubricant to minimize the risk of forming a hydrophobic film around the disintegrant. The mixing time for the lubricant should be set as the minimum time required to produce the desired effect.

The third class of lubricant activity is the anti-adherent. Some materials have adhesive properties and can adhere to the punch surfaces during compression. This will initially manifest itself as sticking, with a film forming on the surface of the tablets, leading to dull tablet surfaces. A more extreme version of sticking is picking, where solid particles from the tablet stick to the punch surface. This will often be evident in the intagliations on the tablet surface, resulting in poor definition of the surface markings.

Attempts have been made to assess picking tendencies using instrumented tablet machines. Load cells have been fitted to the edge of feed frames of rotary machines to monitor the force required to knock tablets off the lower punch following ejection. Shah et al. (1986) postulated that the magnitude of the residual force remaining on the lower punch of a single punch machine following removal of the upper punch was inversely related to the degree of adherence to the upper punch. In practice, sticking tends to be monitored during extended runs on tablet machines.

Most die-wall lubricants have anti-adherent actions, and in many formulations the addition of a specific anti-adherent is not required. Materials that can be added include talc, maize starch, and microcrystalline cellulose.

Appearance

The appearance of a tablet is of great importance to the way it is perceived by the patient. The macroscopic appearance of a tablet, its shape, size, color, and markings can all contribute to the patients' expectations of a medicine, while the microscopic appearance, such as surface roughness and color homogeneity, are easily perceived as measures of quality. It is now the norm to be able to identify new products because of their unique appearance achieved by a combination of shape, size, color, and surface markings.

The size of a tablet is very often governed by the dose being administered. The compression weight of a high-dose drug will usually be determined by the level of filler required to impart the appropriate compactibility on the formulation, the aim being to produce the smallest possible tablet for ease of swallowing. For low-dose drugs, the quantity of filler added is determined by the minimum acceptable size for a tablet. The actual minimum acceptable size for a tablet will vary between pharmaceutical companies but is generally in the region of 6 or 7 mm diameter for a circular tablet, which would equate with a compression weight of 80 to 100 mg. Tablets below this range tend to be difficult for the patients to handle.

Early tablets were produced in cylindrical dies with flat-faced, flat bevel-edged, or concave punches. While the majority of tablets are still circular, over the last 20 years, there has been an increasing shift away from circular to shaped tablets for new products. The tablet identification section of the *Chemist and Druggist Directory* (2000) describes 274 noncircular tablet products that are on the market in Britain, while the *Physicians' Desk Reference* (PDR) (1998) contains illustrations of 502 noncircular tablets that are available in the United States. After round tablets, the most common presentation is the capsule-shaped tablet, sometimes referred to as a caplet. This shape is particularly popular for high-dose products where the compression weight is necessarily high, as the elongated shape makes the tablet easier to swallow than round tablets of equal weight. A survey performed on the reaction of patients to the appearance of tablets has indicated that the tablet shape can influence patients' expectations of a medicine in terms of its potency, side effects, and suitability for a particular ailment (Anon, 1989). The studies found that tablets with highly angular appearances were universally disliked on the basis that they would be hard to swallow. Less predictable was the finding that other elements of tablet design, such as the number and depth of scorelines, the degree of rounding of corners, and the hardness of the finish indicated by surface shine, appeared to play a role in determining how easy or hard to swallow a tablet might be. When designing a tablet shape, consideration should also be given to the processes following compression, such as coating and packaging. These processes depend on tablets being able to move relative to each other, and if the tablet shape allows tablets to form "structures" (e.g., due to straight sides), it may be problematic.

The coloring of tablets can be achieved either by incorporating a dye or pigment into the powder prior to compression, or by applying a colored coat to the tablet following compression. Coating methods, which are dealt with in the section "Tablet Coating," tend to provide a more uniform color than inclusion of pigments in the compression mix but have the disadvantage of requiring an additional manufacturing process.

Colorants come in three forms: soluble dyes, insoluble pigments, and lakes. Lakes are formed by adsorbing dyes onto the surface of an inert substrate, usually aluminum hydroxide. If the colorant is being added to a granulate, soluble dyes can be dissolved in the granulating fluid to ensure a uniform mix. When adding colorants as solids, the mixing process needs to be

very efficient to achieve a uniform color with no mottling. The usual method of inclusion is to form a premix with a portion of the powder mix, and to mill this prior to incorporating the remaining ingredients. The problem can be reduced by the appropriate selection of colors, mottling being less evident with pastel shades. The insoluble pigments tend to be more light, stable, and less prone to fading than the soluble dyes.

The choice of color is severely restricted by the number of regulatory acceptable dyes and pigments available to the formulator. This is particularly true when trying to achieve a globally acceptable formulation, due to the lack of international harmonization of permitted colorants. Table 10 lists the commonly used pigments and dyes together with their international acceptability. It can be seen that for an international formulation, the choice of colorants is restricted to the iron oxide pigments and indigo carmine, and as a result, there are large

Table 10 Pharmaceutical Colorants and Their Regulatory Acceptability

Color	Other names	Regulatory acceptability				
		EU	USA	Japan	Canada	India
Azorubine	Carmoisine	+	—	—	+	+
Ponceau 4R	Cochineal Red A	+	—	+ ^a	+	+
	Brilliant Scarlet 4R					
Canthaxanthin	Food Orange 8	+	+	—	+	—
Sudan 3	Toney Red	—	+	—	—	+
FD&C Red 2	Amaranth	+	—	+ ^a	+	—
	Bordeaux S					
FD&C Red 3 lakes are prohibited	Erythrosine	+	+ ^b	+	+	+
FD&C Red 4	Ponceau SX	—	+	—	—	—
	Naphtalene Red B			ADI 0–0.75 mg		
FD&C Red 40	Allura Red	+	+ ^b	—	+	—
D&C Red 6	Lithol Rubin B	—	+	—	+	—
D&C Red 7	Lithol Rubin Ca	—	+	—	+	—
D&C Red 21	Tetrabromo Fluorescein	—	+	—	—	—
D&C Red 22	Eosin Y	—	+ ^b	—	+	+
D&C Red 28	Phloxine B	—	+ ^b	+	+	—
				AL-lake only		
D&C Red 30	Helindone Pink CN	—	+	—	+	—
D&C Red 31	Brilliant Lake Red R	—	+	—	—	—
D&C Red 33	Acid Fuchsin D	—	+	—	+	—
D&C Red 34	Lake Bordeaux B	—	+	—	—	—
D&C Red 36	Flaming Red	—	—	—	+	—
D&C Red 39	Alba Red	—	+	—	—	—
Cochineal Extract	Natural Red 4	+	+	+	+	+
	Carmine					
Iron Oxide–Red		+	+	+	+	+
				ADI 0–0.5 mg elemental iron		
Anthocyanin		+	—	—	+	—
Lutein		+	—	—	—	—
Lycopene		+	—	—	—	—
Paprika Extract		+	—	—	—	—
Beetroot Red	Betanin	+	—	—	—	—
FD&C Yellow 5	Tartrazine	+ ^c	+ ^{b,c}	+	+	+
FD&C Yellow 6	Sunset Yellow FCF	+	+	+	+	+
	Yellow Orange S					
D&C Yellow 7	Fluorescein	—	+	—	—	—
D&C Yellow 8	Uranine	—	+	—	—	—
D&C Yellow 10 ^d	Quinoline Yellow	—	+ ^b	—	+	+
	WS					

(Continued)

Table 10 Pharmaceutical Colorants and Their Regulatory Acceptability (*Continued*)

Color	Other names	Regulatory acceptability				
		EU	USA	Japan	Canada	India
Quinoline Yellow ^d	China Yellow	+	–	–	–	–
Fast Yellow	Acid Yellow G	–	–	–	–	–
Yellow 2G		–	–	–	–	–
D&C Orange 4	Orange II	–	+	–	–	–
D&C Orange 5	Dibromofluorescein	–	+	–	–	–
D&C Orange 10	Diiodofluorescein	–	+	–	–	–
D&C Orange 11	Erythrosine	–	+	–	–	–
	Yellowish Na					
β-Carotene		+	+	+	+	+
Turmeric	Curcumin	+	–	–	–	+
	Natural Yellow 3					
	Indian Saffron					
Annatto		–	–	–	–	+
Orange G		–	–	–	–	+
Iron Oxide–Yellow		+	+	+	+	+
				ADI 0–0.5 mg elemental iron		
Riboflavin	Lactoflavin	+	–	+	+	+
	Vitamin B ₂					
Gold		+	–	+	–	–
Patent Blue V		+	–	–	–	–
FD&C Blue 1	Brilliant Blue FCF	+	+ ^b	+	+	+
FD&C Blue 2	Indigotine	+	+	+	+	+
	Indigo Carmine					
Naphthol Blue		–	–	–	–	+
D&C Violet 2	Alizuril Purple SS	–	+	–	–	–
FD&C Green 3	Fast Green FCF	–	+ ^b	+	+	+
D&C Green 5	Alizarine Cyanine	–	+	–	–	+
	Acid Green					
D&C Green 6	Quinazarine Green	–	+	–	–	+
D&C Green 8	Pyranine Conc.	–	+	–	–	–
Acid Brilliant	Green S	+	–	–	–	–
Chlorophyllin		+	–	+	+	+
Powdered Green Tea		–	–	+	–	–
Rye Green Leaf Extract		–	–	+	–	–
Brilliant Black BN	Food Black 1	+	–	–	–	–
Carbon Black	Medicinal	+	–	+	+	–
	Vegetable Charcoal					
Iron Oxide–Black		+	+	–	+	+
				ADI 0–0.5 mg elemental iron		
Caramel	Burnt Sugar	+	+	+	+	+
Glycyrrhiza Extract		–	–	+	–	–
D&C Brown 1	Resorcin Brown	–	–	–	–	+
Brown HT		+	–	–	–	–
Titanium dioxide		+	+	+	+	+

Note: + Permitted; – Not permitted.

^aManufacturers have imposed a voluntary ban on this color.

^bRequires FDA certification on each lot of dye.

^cRequires label declaration.

^dThe quinoline yellow approved for use in the EU is not the same as D&C Yellow 10, the dyes differ in composition. Quinoline Yellow is primarily the disulfonated quinoline dye, whereas D&C Yellow 10 is the monosulfonated color.

numbers of tablets with varying shades of red, yellow, orange, and brown being introduced onto the market.

The easiest way to give a tablet a unique identity is to mark the surface with a code or unique identifier. This can be achieved by applying a printed logo to the surface of the tablet or by compressing the powder with punches that are embossed with the code, producing tablets with intagliations. Printing is performed with ink jet printers applying approved inks to the surface of tablets. The advantage of printing is that it is possible to fit more information on to the surface than is possible with embossed punches, but it is an additional process, and not all tablet surfaces are suitable for printing. The use of embossed punches does not increase the manufacturing time, but it does stress a formulation. The embossing of the punches will exacerbate any tendency for punch adherence, and this should be considered when selecting the levels of lubricant and anti-adherent in the tablet. The intagliations will also highlight the presence of any abrasion on the crown of the tablet, and care must be taken to ensure that the surfaces are sufficiently robust, particularly if they are to be subsequently film coated.

Disintegration

The chapter to date has concentrated on ensuring that it is possible to produce a tablet of sufficient strength that it can withstand the stresses of subsequent manufacturing operations, such as coating and packaging, and will reach the patient in an acceptable condition. However, once an immediate-release tablet is taken by the patient, it is important that it breaks up rapidly to ensure quick dissolution of the active ingredients.

To maximize the dissolution rate of a drug substance from a tablet, it is necessary to overcome the cohesive strength produced by the compression process and break the tablet into the primary particles as rapidly as possible (Fig. 19). This is achieved by adding disintegrants, which will induce this process.

Starch was the first disintegrant used in tablet manufacture and is still used, although it has largely been superseded by the so-called super disintegrants, croscarmellose sodium,

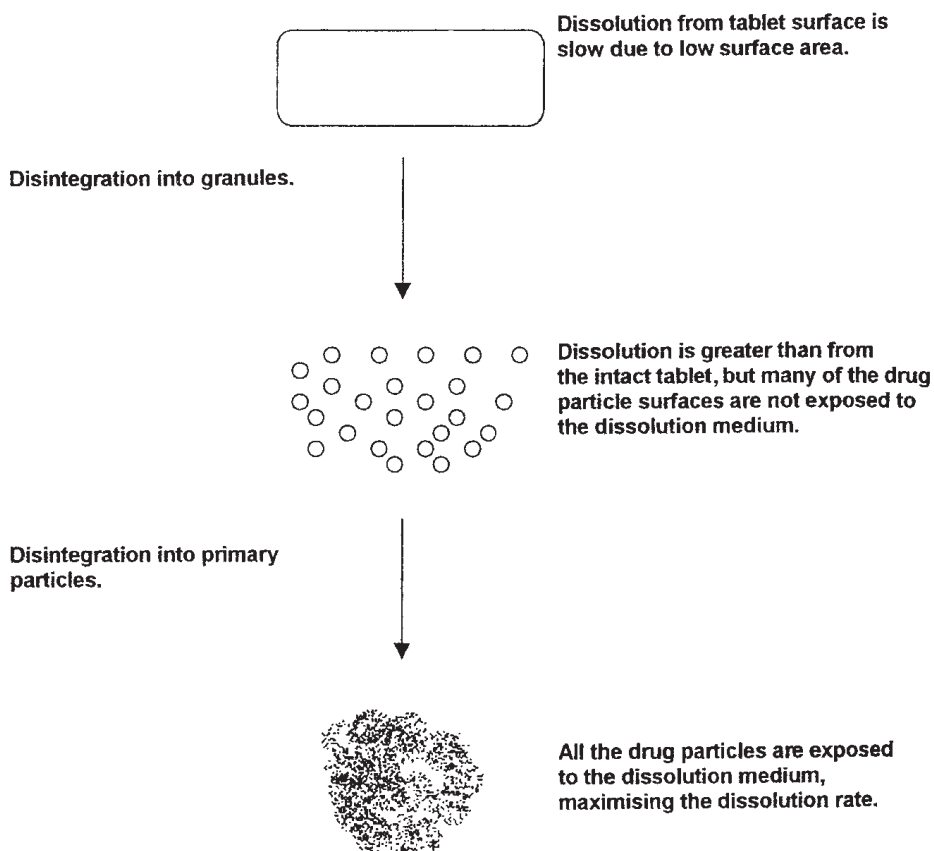


Figure 19 Dissolution of drugs from tablets.

sodium starch glycolate, and crospovidone, which display excellent disintegrant activity at low concentrations and possess better compression properties than starches.

Traditionally, swelling and rate of swelling have been regarded as the most important characteristics of disintegrants. Rudnic et al. (1982) quantified the rate of swelling and force generated by the swelling of disintegrants, and found no simple relationship between the maximum disintegrating force and disintegration time. It was the ability to develop a significant swelling force rapidly that appeared to be more important. The other important factor in a formulation is that as the swelling develops, it should not be accommodated within the tablet, which prevents a significant disruptive force from being generated. If the tablet displays elasticity to the swelling, the force will be expended on the system, and disintegration will not take place. Similarly, if the tablet is composed entirely of soluble components, their dissolution will deprive the disintegrant of a matrix to push against. As a general rule, soluble drugs are formulated with insoluble fillers to maximize the effect of disintegrants.

The positioning of disintegrants within the intragranular and extragranular portions of granulated formulations can affect their efficacy. Placing the disintegrant in the extragranular portion results in rapid disintegration to granular particles, while the disintegrant present in the granule will promote further disintegration to the primary particles, thus aiding dissolution. Studies performed to determine the optimum location of disintegrant (Shotton and Leonard, 1972; Rubenstein and Bodey, 1974) suggest that dividing it between the two portions, with between 20% and 50% being in the extragranular portion, produces the best results.

Optimizing the level of disintegrants in a formulation is a good example of a situation where there are a number of opposing factors to consider, and the final formulation needs to be a compromise. To optimize the biopharmaceutical properties of the formulation, the tablet should disintegrate rapidly, which can be achieved by increasing the level of disintegrants. The particle size of most disintegrants is too small to maximize the surface area, and thus increase the rate of water uptake. The addition of large quantities of such materials could have an adverse effect on the flow properties of the formulation. The compaction properties of many disintegrants, including starch, are less than ideal, and high concentrations could also reduce the strength of tablets produced. By their nature, disintegrants are hygroscopic materials and will absorb moisture from the atmosphere, which could negatively affect the stability of water-sensitive drugs. The super disintegrants, if used at excessive concentrations, can actually absorb sufficient moisture from the atmosphere to initiate disintegration on storage, if the packaging does not provide adequate protection from the environment. Disintegrant activity can be affected by mixing with hydrophobic lubricants, so care needs to be taken to optimize the manufacturing process as well as the formulation. The commonly used disintegrants are listed in Table 11.

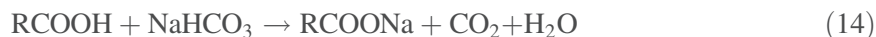
For a disintegrant to be able to function properly, the tablet surface must be amenable to wetting. If the tablet contains a high proportion of a hydrophobic drug that has a high contact

Table 11 Commonly Used Disintegrants

Disintegrant	Normal usage concentration (%)	Comments
Starch	5–10	Probably work by wicking; swelling is minimal at body temperature.
Microcrystalline cellulose		Strong wicking action. Loses disintegrant action when highly compressed.
Insoluble ion exchange resins		Strong wicking tendencies with some swelling action.
Sodium starch glycolate	2–8	Free-flowing powder that swells rapidly on contact with water.
Croscarmellose sodium	1–5	Swells on contact with water.
Gums—agar, guar, xanthan	<5	Swell on contact with water; form viscous gels that can retard dissolution, thus limiting concentration that can be used.
Alginic acid, sodium alginate	4–6	Swell like the gums but form less viscous gels.
Crospovidone	1–5	High wicking activity.

angle, it may be wise to include a wetting agent or surfactant in the formulation, which will aid not only the disintegration time of the tablet but also the subsequent dissolution of the drug substance. The most commonly used wetting agents are sodium lauryl sulfate and the polysorbates.

An alternative mechanism of disintegration is used in effervescent tablets, which utilizes a gas-liberating chemical reaction to effect rapid disintegration. These tablets contain an organic acid and an alkali metal carbonate, which, when added to water prior to administration, react to produce carbon dioxide, for example,



Most pharmacopoeias include a disintegration test, which can be applied to tablets and capsules. The USP test consists of six glass tubes, 3 in long and open at the top, with a 10-mesh screen at the bottom and immersed in a beaker of disintegration fluid that is maintained at 37°C. The tubes are raised and lowered 5 to 6 cm at 30 cycles per minute, such that the bottom of the tubes remain 2 to 5 cm below the liquid surface at the top of the stroke and are no closer than 2 to 5 cm from the base of the beaker at the lowest point. One tablet is placed in each tube, and the disintegration time is the time taken for all six tablets to break up sufficiently for all material to pass through the mesh at the bottom of the tube. If the dosage form floats, it is permitted to place perforated plastic discs in the tubes to ensure that they remain submerged during the test. Pharmacopoeial tests use water as the disintegration fluid for nonenteric-coated tablets, but during development, it is prudent to test the tablets over a range of pH values.

Disintegration testing is an important part of in-process control testing during production to ensure batch-to-batch uniformity, but its role in end-product testing has largely been superseded by dissolution testing.

Dissolution

Drug materials administered orally are required to dissolve in the GI fluids before absorption can take place. Dissolution occurs most rapidly from the primary particles of the drug substance, hence the importance of rapid disintegration to this state. However, disintegration studies only demonstrate that a tablet will break up when immersed in fluid; there are many other factors that can influence the dissolution of a material. A carefully designed dissolution test will, therefore, be a better indication of the performance of a dosage form. The design of dissolution tests and the correlation between in vitro dissolution and in vivo performance is discussed in chapter 7, "Biopharmaceutical Support in Formulation Development." The optimization of the dissolution of a substance is discussed in chapter 8.

Processing of Formulations

The performance requirements of a tablet were discussed in the previous section, and it is clear that most tablets contain several ingredients. The drug substance, probably a filler, a disintegrant, and a lubricant will be common to most formulations, while glidants, colorants, and wetting agents may also be included. The quality of the final product will be as dependent on the way in which the components are combined as it is on the components selected. Traditionally, tablet formulations have been prepared by one of two methods: direct compression or granulation.

Direct compression is the term used to define the process where powder blends of the drug substance and excipients are compressed on a tablet machine. There is no mechanical treatment of the powder apart from a mixing process. Granulation is a generic term for particle enlargement, whereby powders are formed into permanent aggregates. The purpose of granulating tablet formulations is to improve the flow and compaction properties prior to compression. There are a number of different methods that can be used to granulate a powder blend, but the most common one for pharmaceuticals is wet granulation, where a liquid is added to aid agglomeration and then removed by drying prior to compression. Even from this short description, it is obvious that direct compression is a much simpler process; yet it is not universally adopted. This section will review the advantages and disadvantages of the two

techniques in an attempt to explain why granulation still plays an important role in tablet manufacture.

Direct Compression

The term *direct compression* was initially applied to the formation of compacts from materials that required no pretreatment and the addition of no additives or excipients. As such, it was only used for inorganic materials such as potassium bromide. Today, within the pharmaceutical industry, the term is used for tablet manufacture that does not involve the pretreatment of the drug substance apart from blending with excipients.

Advantages of direct compression. The most obvious advantage of direct compression is its simplicity and subsequent economy. The manufacture requires fewer operations, and the omission of a drying step results in lower energy consumption. If a new production line is being built for a product, there will be considerable savings in the plant required, equipment such as granulators and driers being unnecessary. The reduced processing times will produce savings in labor costs, and the simplicity of the process should make process validation simpler. However, some of these savings will be offset by the need to use specialized, more expensive, excipients.

Direct compression can provide technical, as well as economic, benefits. Stability of certain drugs can be improved, and the elimination of a wetting and drying process can be beneficial when formulating drugs that are thermolabile or moisture sensitive.

For certain drugs, the dissolution rate can be improved by utilizing direct compression. In the section "Disintegration," it was stated that for optimal dissolution, the tablet must disintegrate into its primary particles as quickly as possible. With no agglomeration stage involved in direct compression, the tablets will disintegrate directly to the primary particles.

Disadvantages of direct compression. The main limitation of direct compression is that it cannot be used for all drug substances; the technique depends on the major components of the formulation having appropriate flow and compaction properties. While it is possible to modify the properties of drug substances by particle engineering, this is usually outside the scope of the formulator, and the formulation must be designed to accommodate the limitations imposed by the drug substance. For low-dose drugs, it is usually possible to overcome such limitations through careful selection of excipients, but there will be a dose level at which it becomes impractical to produce a tablet of acceptable size.

The challenges facing the formulator of low-dose drugs by direct compression are related to achieving and maintaining a homogeneous mix. Very low-dose drugs can be formulated to form ordered mixes that reduce the risk of segregation. Consideration must be given to the entire manufacturing process to minimize the possibility of segregation.

Direct compression places greater demands on the excipients, particularly the fillers. This has resulted in the introduction of a number of excipients that have been designed specifically for use in direct compression formulations, although they tend to be expensive.

Armstrong (1998) described the following requirements for direct compression fillers:

- Have good flow properties
- Possess good compaction properties
- Have high capacity (defined as the ability to retain their compaction properties when mixed with drugs substances)
- Have appropriate particle size distribution to minimize the segregation potential
- Have high bulk density
- Be capable of being manufactured reproducibly to minimize batch-to-batch variation

Jivraj et al. (2000) have classified the direct compression fillers in terms of their disintegration and flow properties (Table 12).

Table 12 Direct Compression Fillers

Classification	Examples	Comments
Materials that act as disintegration agents with poor flow characteristics	Microcrystalline cellulose	Probably the most widely used direct compression excipients. Excellent compactibility at low pressures, high-dilution capacity.
Free-flowing materials that do not disintegrate	Directly compressible starch Dibasic calcium phosphate dihydrate	Excellent flow properties. Very brittle material, and is best used in combination with microcrystalline cellulose or directly compressible starch.
Free-flowing powders that disintegrate by dissolution	Lactose	Anhydrous β -lactose possesses excellent compaction properties. Picks up moisture at elevated humidity and may be less compatible with moisture-sensitive compounds than the monohydrate form (Jain et al., 1998).
	Sorbitol	Good compactibility. Popular in chewable tablets due to its cool mouth feel.
	Mannitol	Hygroscopic.

In addition to these excipients, there are also a number of proprietary preparations that combine two or more materials to optimize the flow and compaction properties. Examples of such excipients include the following:

- Ludipress—a combination of α -lactose monohydrate, polyvinylpyrrolidone, and crospovidone
- Cellactose—microcrystalline cellulose and lactose
- Cel-O-Cal—coprocessed microcrystalline cellulose and calcium sulfate
- Silicified microcrystalline cellulose—coprocessed microcrystalline cellulose that has been silicified with colloidal silicon dioxide

A number of active drug substances are also available in coprocessed forms for use in direct compression formulations. While such materials might not be considered direct compression in its purest form, they do pass on the advantages of direct compression technology to the tablet manufacturers.

Granulation

Granulation is the most widely used technique to prepare powders for compaction. The term *granulation* is a generic description for a process of particle enlargement in which particles are agglomerated while retaining the integrity of the original particles. A number of methods can be used to achieve the agglomeration; these are normally classified as either wet granulation, where a liquid is used to aid the agglomeration process, or dry granulation, where no liquid is used.

The purpose of granulating is to transform the powdered starting materials, which would otherwise be unsuitable for tableting, into a form that will run smoothly on a tablet machine. This is achieved in a number of ways. The most obvious benefit of granulation is the improved flow properties resulting from the increase in particle size.

In forming granules, individual particles of the starting ingredients are agglomerated together. If a homogeneous powder mix is achieved before commencing agglomeration, the granules will consist of a homogeneous mix of those ingredients. More importantly, the particles of drug substance will be bound to the particles of the excipients, thus reducing the potential for segregation, and improving the chances of content uniformity.

The granulation process usually involves the addition of a polymeric binder that sticks the individual particles together. It has been demonstrated with paracetamol (Armstrong and

Morton, 1977) that this process can reduce the elasticity of starting materials, thus improving the compactibility.

The polymers used as binders are usually hydrophilic in nature. This can have a beneficial effect on the dissolution of hydrophobic drugs. During the granulation process, a film of hydrophilic polymer will form over the surface of hydrophobic drug particles, which will aid wetting.

One of the advantages of granulation is that it results in the densification and subsequent volume reduction of the starting material. This is particularly useful in the case of voluminous starting materials. A further benefit is that the densified, coarse material will reduce the amount of air entrapment.

A number of methods are routinely used within the pharmaceutical industry to produce granulations. These are traditionally classified as dry granulation and wet granulation, depending on whether a liquid is used to aid the agglomeration.

Wet granulation. Wet granulation methods are the most commonly used in tablet manufacture. These methods involve the addition of a liquid and, usually, a polymeric binder to the powdered starting materials, and a form of agitation to promote agglomeration followed by a drying process. In most cases, the liquid used is water, although in certain circumstances organic solvents such as ethanol or ethanol/water mixes are used. Nonaqueous granulation will be considered when the active substance is particularly unstable in the presence of water, when water will not wet the powder or, possibly, if the drug substance forms a significant portion of the granulate, and demonstrates extreme solubility in aqueous media, and control of the granulation process becomes difficult due to the occurrence of significant dissolution. While there are a number of approaches to wet granulation used in the pharmaceutical industry, they all share the following basic principles:

- Dry mixing: The starting materials are mixed together. Prior to mixing, the ingredients may be deagglomerated by a milling or sieving process. If the granulate has a low drug content, the active substance may be premixed with one of the ingredients prior to being added to the granulation vessel to ensure good content uniformity.
- Addition of granulating liquid: The granulating fluid is added to the dry ingredients and mixed to form a wet mass. The mixing of the fluid with the dry ingredients leads to agglomeration of the powder. This agglomeration can be controlled by altering the amount of fluid added, the intensity of the mixing, and the duration of the mixing. Depending on the state of agglomeration achieved, this stage may be followed by a wet sieving process to break up the larger agglomerates.
- Drying: The fluid is removed by a drying process.
- Milling: The dried granulate undergoes a sieving or milling operation to obtain the desired particle size distribution.

To understand the granulation process, it is necessary to consider what is occurring at the particulate level during the process. The aim of granulation is to increase the particle size of a powder mix, and this is achieved in wet granulation by the formation of liquid bridges between the powder particles. If a liquid that is able to wet the powder is added, the system will minimize its surface-free energy by forming liquid bridges between the particles. The nature and extent of these bridges will be dependent on the amount of liquid added.

At low liquid levels, it is assumed that the liquid will distribute itself evenly through the bed, forming discrete liquid bridges at points of contact between particles (Fig. 20). This is known as the pendular state. The strength of an individual pendular bond, σ , between two spherical particles can be calculated as

$$\sigma = \frac{2\pi rT}{1 + \tan \frac{1}{2}\phi} \quad (15)$$

where r is the radius of the spherical particle, T is the surface tension of the liquid, and ϕ is the angle formed between the line joining the center of the spheres and the edge of the pendular

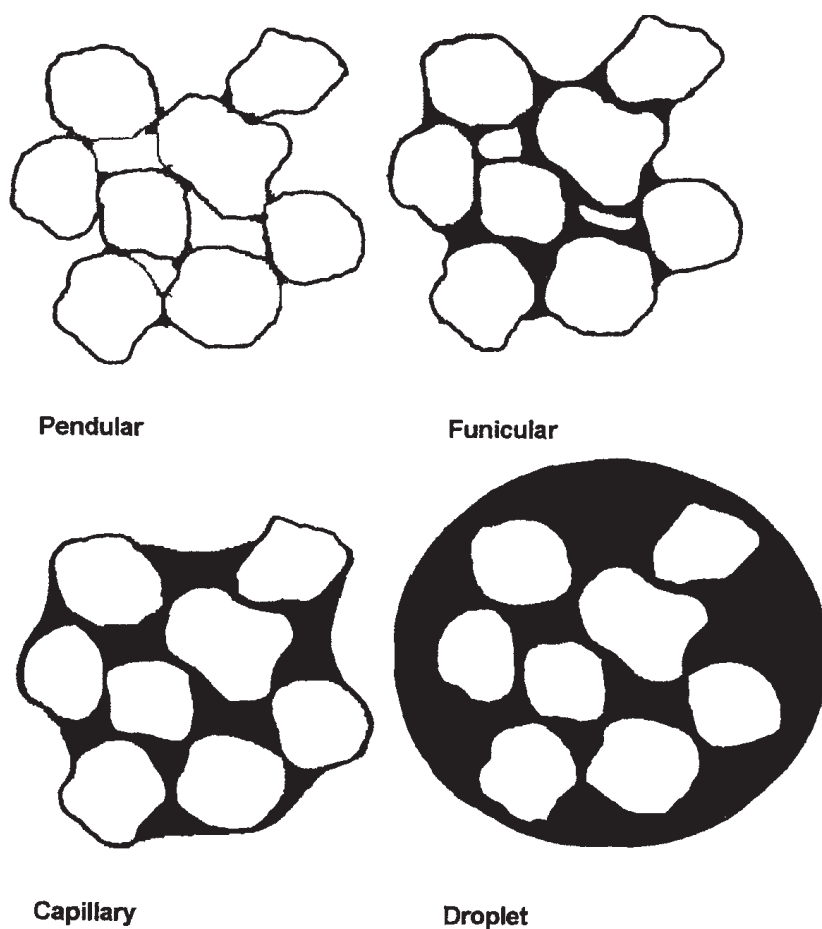


Figure 20 Stages involved in granulation.

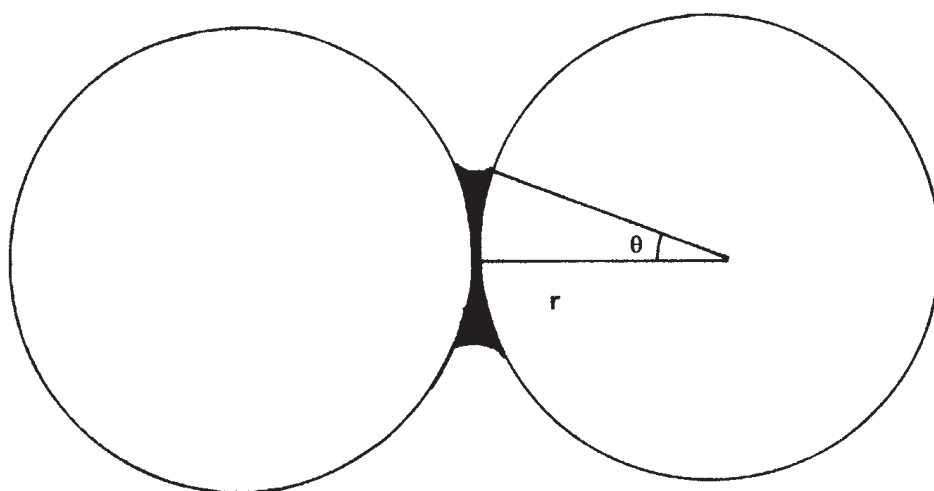


Figure 21 Calculation of the strength of a pendular liquid bridge.

bond (Fig. 21) (Eaves and Jones, 1972). This equation predicts that the bond strength will increase as the surface tension of the liquid increases and as the liquid content decreases. In practice, the strength of agglomerates tends to zero at very low liquid contents, and this has been attributed to the presence of dry joints occurring between particles, due to uneven distribution of the liquid throughout the powder bed.

As the liquid content is increased, the pendular state will remain until the pendular bonds start to coalesce and liquid bridges form between non-touching points. This is known as the funicular state (Fig. 20). The state depends on the degree of liquid saturation or voidage saturation, which is defined as the ratio of the liquid volume to the total volume of pores in the powder bed. Typically, a powder bed will remain in the pendular state until the liquid saturation reaches around 25%, and in the funicular state between 25% and 80%.

As the liquid saturation rises above 80%, the powder reaches the capillary state, and the granule is held together by capillary suction as the liquid air interfaces on the granule surface. While the tensile strength of the granule is greater in the capillary state, the granulate starts assuming a paste-like consistency, which is unsuitable for wet sieving.

The theoretical tensile strength of agglomerates in the funicular and capillary states has been derived by Rumpf et al. (1974)

$$\sigma = SC \left(\frac{1 - \varepsilon}{\varepsilon} \right) \left(\frac{\gamma}{d} \right) \cos \theta \quad (16)$$

This equation applies to the strength of agglomerates formed from monosize spheres with diameter d that are packed to porosity ε . The degree of liquid saturation is S , and the liquid has surface tension γ and a contact angle θ with the solid. C is a material constant. Note that in these states, the strength of agglomerates now increases with decreasing particle size. The porosity of the powder also affects the strength; if the material is densified, the agglomerate strength will increase. Addition of further liquid converts the capillary state into the droplet state, where the particles are enclosed in a water droplet and the mass takes on the properties of slurry.

The gradual transition from pendular through funicular to capillary bonding assumes that there is always a uniform distribution of liquid throughout a powder bed. In practice, this is obviously not always the case because the dispersion of liquid through the powder is achieved by mechanical agitation, which will take a finite time. What actually happens in a powder bed during a typical granulation process will be the creation of small areas of high saturation that will lead to the formation of agglomerates, which, through mechanical agitation, are dispersed throughout the powder bed. The fate of the agglomerates will change as the degree of liquid saturation increases.

Three phases of agglomeration are recognized, and these will to an extent be occurring simultaneously within a powder bed as the liquid becomes distributed by agitation. The first stage of particle growth is nucleation, which occurs whenever a powder is wetted, particles being held together by liquid bridges. In practice, the liquid addition will lead to overwet agglomerates being formed, to which further powder adheres until the number of liquid bridges is saturated. At low saturation levels, interactions such as friction will also contribute to the strength of the agglomerates. The theoretical strength of the agglomerates is proportional to the degree of liquid saturation, so the initial agglomerates will tend to be weak, and in an agitated environment, agglomerates will constantly be formed and destroyed. The survival of the agglomerates will increase during the granulation process as the liquid saturation increases and as densification occurs, reducing the porosity of the powder bed.

The powder then undergoes a transition state as it takes up sufficient liquid for the effects of particle interactions to diminish, and the strength becomes controlled by the liquid bridges. The agglomerates become less brittle and more plastic in nature. At this stage, coalescence between colliding particles occurs, and particle growth takes place.

The final stage of granulation is ball growth, a period characterized by rapid growth in particle size. Large granules are formed by the fracture of smaller granules, and the resulting fragments build up in layers on the surface of the larger agglomerates.

The above description of the granulation process illustrates that the formulator is dealing with a complex system, and the quality of the final product will be influenced by a large number of factors, from the selection of the raw materials to the processing conditions employed.

While one of the stated advantages of granulation over direct compression is that the technique is better able to cope with variations in raw material, the agglomeration process will

be affected by significant changes in the raw materials used. The particle size of the starting materials will affect the strength of granules produced, as predicted in equation 16. The quantity of granulating fluid required to achieve granulation is dependent on the particle size and shape. This additional requirement is partly related to the increase in surface area but also relates to the material-packing properties that affect the granule porosity and the degree of liquid saturation achieved. Granulation is essentially a wetting process and, as such, is dependent on the surface chemistry of the particles. It is well established that powder-handling processes such as milling and drying can significantly affect the surface properties of powders. Small areas of amorphous material on the particle surface produced by particle attrition, too small to be detected by techniques such as X-ray powder diffraction, can have dramatic effects on the wetting characteristics.

Granulating agents (binders). It is possible to granulate a powder simply by adding water or an organic solvent to a powder. Provided that the liquid is able to wet the powder surface, it will form liquid bridges. When the granulate dries, the crystallization of any solids that had dissolved in the liquid will form solid bonds between the particles. These bonds will usually be fairly weak, and friable granulates will be formed; often the granules will not be sufficiently robust to withstand the drying process. It is usual, therefore, to include granulating agents or binders to granulations to increase the granule strength. Granulating agents are usually hydrophilic polymers that have cohesive properties that both aid the granulation process and impart strength on the dried granulate.

For a granulating agent to be effective, it is vital that it is able to form a film on the particle surface. Rowe (1989) has suggested that binders should be selected on the basis of their spreading coefficients, where the spreading coefficient is defined as the difference between the “work of adhesion” of the binder and the substrate and the “work of cohesion” of the binder. The commonly used granulating agents are listed in Table 13.

The synthetic polymers such as polyvinyl pyrrolidone (PVP) and hydroxypropyl methylcellulose (HPMC) have almost totally superseded the use of natural products such as starch, acacia, and tragacanth in modern formulations. The most common method of adding binders is as a solution in the granulating fluid. It is possible to add some of the synthetic polymers such as PVP and HPMC as powders, and use water as the granulating agent. This approach, which has the advantage of not requiring a solution manufacturing step in production, is likely to result in incomplete hydration of the polymers during processing, which will affect the quality of the final granulate.

The level of binder used needs to be a balance between the level required to produce a robust, compressible granulate and the biopharmaceutical properties. As the granule strength increases, there is often an adverse effect on disintegration and dissolution. The binders form hydrophilic films on the surface of the granules, which can aid the wetting of hydrophobic

Table 13 Commonly Used Granulating Agents

Granulating agent	Normal usage concentration (%)	Comments
Starch	5–25	Was once the most commonly used binder. The starch has to be prepared as a paste, which is time consuming.
Pregelatinized starch	5–10	Cold water soluble, so easier to prepare than starch.
Acacia	1–5	Requires preparation of paste prior to use. Can lead to prolonged disintegration times if used at too high a concentration.
PVP	2–8	Available in range of molecular weights/viscosities. Can be added either dry or in solution. Soluble in water and ethanol.
HPMC	2–8	Available in range of molecular weight/viscosities. Soluble in water and ethanol.
MC	1–5	Low-viscosity grades most widely used.

Abbreviations: PVP, polyvinylpyrrolidone; HPMC, hydroxypropyl methylcellulose; MC, methylcellulose.

drugs; but if added in too great concentrations, the films can form viscous gels on the granule surface, which will retard dissolution. To optimize the dissolution of a drug from a granulated product, it is important that the granule should disintegrate into its primary particles as rapidly as possible, and it is usual to position at least a portion of any disintegrant inside the granules.

Wet granulation methods. A number of processing methods are commonly used within the pharmaceutical industry. Each method will impart particular characteristics and, as such, granulates produced by each method may not be equivalent in terms of either their physical properties (which will influence subsequent performance on tablet machines) or their biopharmaceutical properties. This latter point is well recognized by regulatory authorities that regard changes in the granulation method as potentially having a significant effect on the bioavailability of poorly soluble, poorly permeable compounds. The U.S. Food and Drug Administration (FDA) and industry representatives have outlined their expectations regarding the testing required when changing the method of granulation in *SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation*. This document concludes that changing the type of granulation process used can, for some drug substances, result in the need to perform a bioequivalence study prior to the change being granted regulatory approval.

The three main methods of producing pharmaceutical granulates are low-shear granulation, high-shear granulation, and fluid bed granulation. *Low-shear mixers* encompass machines such as Z-blade mixers and planetary mixers, which, as their names suggest, impart relatively low shear stresses onto the granulate. Widely used in the past, this approach has largely been superseded by high-shear mixers. The low level of shear applied is often insufficient to ensure good powder mixing, so a premix is often required. The process is forgiving in terms of the amount of liquid added, although it does result in long granulation times. The degree of ball growth tends to be uncontrolled because there is insufficient shear to break up the plastic agglomerates, so a wet screening stage is almost always necessary prior to drying to reduce the larger agglomerates.

High-shear granulators are closed vessels that normally have two agitators; an impeller, which normally covers the diameter of the mixing vessel, and a small chopper positioned perpendicular to the impeller. The powders are dry mixed using the impeller, and then the granulating fluid is added. Wet massing takes place using the impeller and the chopper, and granulation is usually completed in a number of minutes. The granulation process can be controlled using an appropriate combination of impeller and chopper speeds and time. The ability of the chopper to limit the size of the agglomerates can negate the need for a wet screening stage for many granulates. High-shear mixers provide a greater degree of densification than the low-shear mixers. This, combined with the relatively short processing times, can lead to the process being very sensitive to the amount of granulating liquid added.

In both high-shear and low-shear mixers, the mode of liquid addition can affect the quality of the final product. The liquid can either be added in one go or slowly sprayed onto the powders. Slow spraying leads to the most uniform distribution of liquid but can increase the overall processing time. Pouring the liquid onto the powder will result initially in large overwet granulates being formed. The mixer needs to impart sufficient energy to the system to break up the agglomerates to achieve uniform distribution of liquid.

Fluid bed granulation involves spraying the dry powder with a granulating fluid inside a fluid bed drier. The powder is fluidized in heated air and then sprayed with the granulating fluid. When all the granulating liquid has been added, the fluidization of the powder continues until the granules are dry. Advantages of this technique are that the granulation and drying are performed in a continuous manner in the same vessel, and there is no need for a wet screening operation. Nucleation occurs by random collisions between the droplets of granulating fluid and particles until all the individual particles have been incorporated into agglomerates. Densification of materials is limited due to the lack of shear forces.

Seager et al. (1985) produced a detailed analysis on the influence of manufacturing method on the tableting performance of paracetamol granulated with hydrolyzed gelatin.

The main difference in the granules produced by different methods was their final density, high-shear mixers producing denser granules than low-shear granulators, which in turn produced denser granules than fluid bed granulations. Disintegration times were greater for tablets produced from the denser granulates.

Extrusion/Spheronization

One specialized method of particle agglomeration is extrusion and spheronization, to produce spherical or near-spherical particles. Such particles are suitable for coating with release, modifying coats to produce controlled-release formulations. The particles are usually filled into hard gelatin capsules for administration to patients. The process of extrusion/spheronization is depicted in Figure 22.

The drug and filler are mixed with water to form a wet mass. This step is performed using equipment similar to that of conventional wet granulation, though the quantity of water added is greater, resulting in a plastic mass rather than granules. The mass is then extruded, that is, forced through a screen containing circular holes, to form a spaghetti-like extrudate. The extrudate is cut into lengths roughly twice the diameter of the holes and rolled by frictional and centrifugal forces on a rotating grooved plate known as a marumerizer or spheronizer. The rolling action compresses the cylinder along the length and rounds the ends, forming dumbbells, which become further compressed along their length to form spheres. The spheroids are discharged from the spheronizer and dried, usually by fluid bed drying.

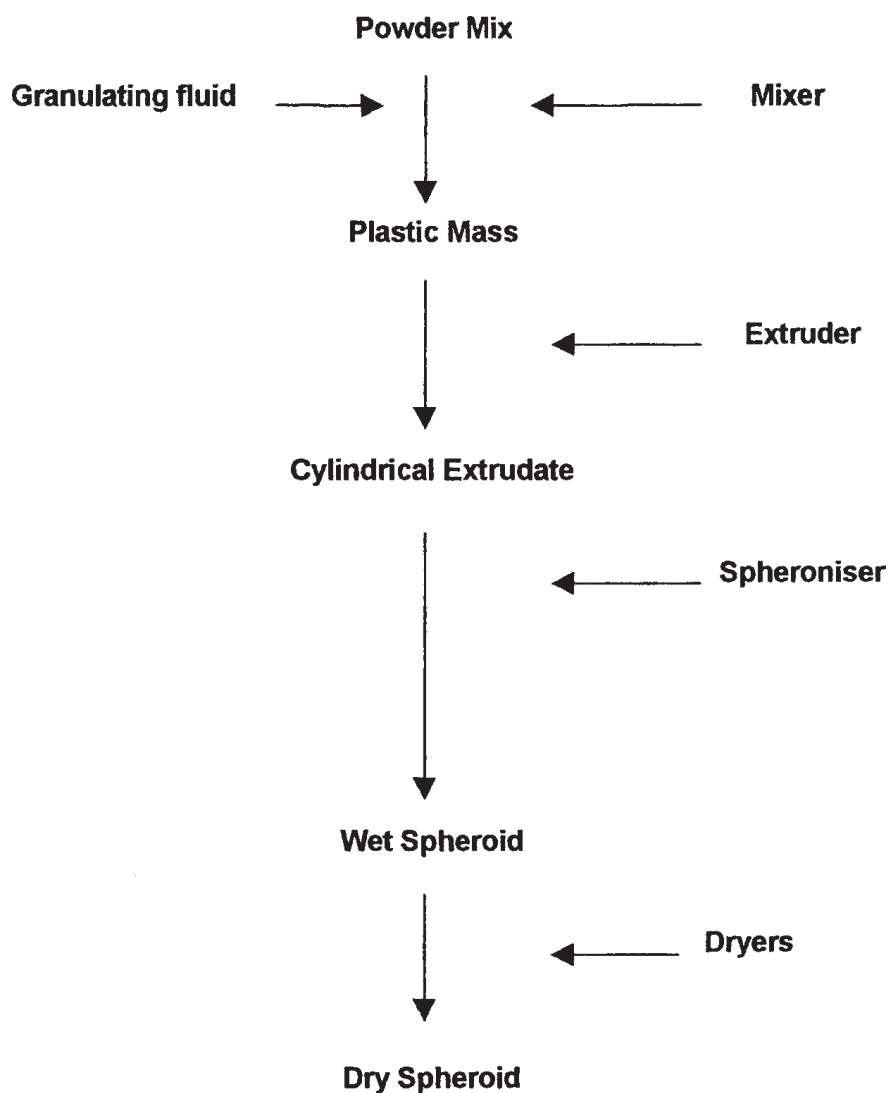


Figure 22 Schematic description of extrusion/spheronization.

The basic ingredients of most spheroids are the drug substance, microcrystalline cellulose, and water. Microcrystalline cellulose appears to be unique in its ability to form spheroids by this method due perhaps to its ability to hold onto the water during extrusion. The squeezing of the wet mass through a screen during extrusion forces most materials to lose water, and the resulting extrudates do not have the necessary plasticity to form spheroids.

The robustness of microcrystalline cellulose means that for most low-dose drugs, it is possible to make spheroids, certainly if the drug loading is below 10%. As the drug loading increases, the process becomes more difficult. Two factors appear to be required for success, the mass must retain the water during the extrusion process, and the extrudate must have the appropriate rheological properties.

There are many types of extruders available, with very different shear forces. The different shear forces will have an effect on the water distribution in the extrudates. As the water level is critical for optimizing the spheronization process, it is clear that the formulation development and process development need to be considered as one for this type of process.

Dry Granulation

It is possible to form granulates without the addition of a granulating fluid, by techniques generically referred to as dry granulation. These methods are useful for materials that are sensitive to heat and moisture, but which may not be suitable for direct compression.

Dry granulation involves the aggregation of particles by high pressure to form bonds between particles by virtue of their close proximity. Two approaches to dry granulation are used in the pharmaceutical industry: slugging and roller compaction. In either method, the material can be compacted with a binder to improve the bonding strength.

Slugging. Granulation by slugging is, in effect, the manufacture of large compacts by direct compression. The slugs produced are larger than tablets and are often poorly formed tablets exhibiting cracking and lamination. As with tablets, it may be necessary to add a lubricant to prevent the compacts sticking to the punches and dies. The compressed material is broken up and sieved to form granules of the appropriate size. The granules are then blended with disintegrant and lubricant, and compressed on a normal tablet machine.

Roller compaction. In roller compaction, the powder is compacted by means of pressure rollers (Fig. 23). It is fed between two cylindrical rollers, rotating in opposite directions. The rollers may be flat, which will produce sheets of compacted material, or they may be dimpled, in which case, briquettes in the shape of the dimples will be formed. If sheets are produced,

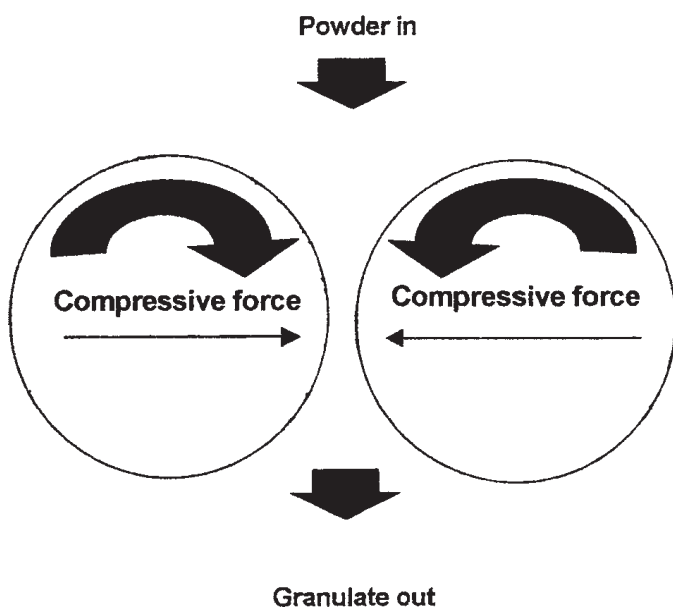


Figure 23 Principles of roller compaction.

they are milled and screened to the required size. Roller compaction requires less lubricant to be added than does slugging.

Selection of the Appropriate Process

The methods of formulating and manufacturing tablets have been described in the preceding sections. Each method has certain unique benefits and advantages as well as drawbacks, and these are summarized in Table 14.

For any given compound, there will normally be more than one approach that is technically feasible, so how does one choose which approach to take? For most formulators, the choice is strongly influenced by the philosophy of the production department of the company in which they work. Different companies can have very different philosophies; some believe that the cost savings of direct compression are such that attempts should be made to formulate all tablets by this route, other companies feel that wet granulation is a more robust process, and should be used even when a compound looks amenable to the direct compression route.

Tablet Coating

For some tablets, compression marks the final stage of the production process, but many formulations involve coating the compressed tablet. There are several reasons for applying a coat:

- Protecting the drug from the environment (moisture, air, light) for stability reasons
- Taste masking
- Minimizing patient/operator contact with drug substance, particularly for skin sensitizers
- Improving product identity and appearance
- Improving ease of swallowing
- Improving mechanical resistance; reducing abrasion and attrition during handling
- Modifying release properties

There are three main methods used to coat pharmaceutical tablets: sugar coating, film coating, and compression coating. Sugar coating was the most commonly used method until the 1970s, when it was largely superseded by film coating.

Sugar Coating

Sugar coating, as its name suggests, involves coating tablets with sucrose. This is a highly skilled, multistep process that is very labor intensive. The process involves applying a number of aqueous solutions of sucrose, together with additional components, which gradually build

Table 14 Manufacturing and Formulating Tablets—Advantages and Disadvantages

Method	Advantages	Disadvantages
Direct compression	Simple, cheap process. No heat or moisture, so good for unstable compounds. Prime particle dissolution.	Not suitable for all drugs, generally limited to low-dose compounds. Segregation potential. Expensive excipients.
Wet granulation (aqueous)	Robust process suitable for most compounds. Imparts flowability to a formulation. Can reduce elasticity problems. Coating surface with hydrophilic polymer can improve wettability. Binds drug with excipient, thus reducing segregation potential.	Expensive: time- and energy-consuming process. Specialized equipment required. Stability issues for moisture-sensitive and thermolabile drugs with aqueous granulation.
Wet granulation (nonaqueous)	Suitable for moisture-sensitive drugs. Vacuum-drying techniques can remove/reduce need for heat.	Expensive equipment; explosion proof; solvent recovery.
Dry granulation (slugging)	Eliminates exposure to moisture and drying.	Dusty procedure. Not suitable for all compounds. Slow process.
Dry granulation (roller compaction)	Eliminates exposure to moisture and drying.	Slow process.

up into a smooth, aesthetically pleasing coat. The final coat can account for up to 50% of the final tablet weight, and will result in a significant increase in the tablet size. Traditionally, sugar coating has been performed in coating pans in which the tablets are tumbled. With the appropriate tablet load and rotation speed, the tablets are tumbled in a three-dimensional direction. The pan is supplied with a source of warm air for drying and an extraction system to remove moist air and dust.

The coating solution is ladled onto the tablet bed and is distributed around the tablets by their tumbling action. The tablets are then tumbled for a period of time to allow the coating to dry before a further quantity of solution is added. A dusting powder may be sprinkled onto the surface of the tablets during the drying phase to prevent the tablets sticking together. One of the skills of sugar coating is adding an appropriate quantity of solution. If too little is added, then not all tablets will pick up some of the coating, and an uneven distribution will result. If too much solution is added, the tablets will stick together. The cycle of wetting and drying is continued until the desired amount of coating has been applied to the tablets. Typically, a sugar coating will consist of three types of coat: a sealing coat, a subcoat, and a smoothing coat (Fig. 24).

One of the reasons for coating tablets is to protect the drug substance from environmental factors such as moisture, so it is important that the coating solution does not penetrate into the core. This is achieved by applying a sealing coat. Traditionally, a coating of shellac dissolved in ethanol was applied, but this has largely been replaced by the use of synthetic water-resistant polymers such as cellulose acetate phthalate or polyvinylacetate phthalate. The challenge for the formulator is to optimize the quantity of subcoat applied to ensure the core is protected while minimizing the effect on drug release.

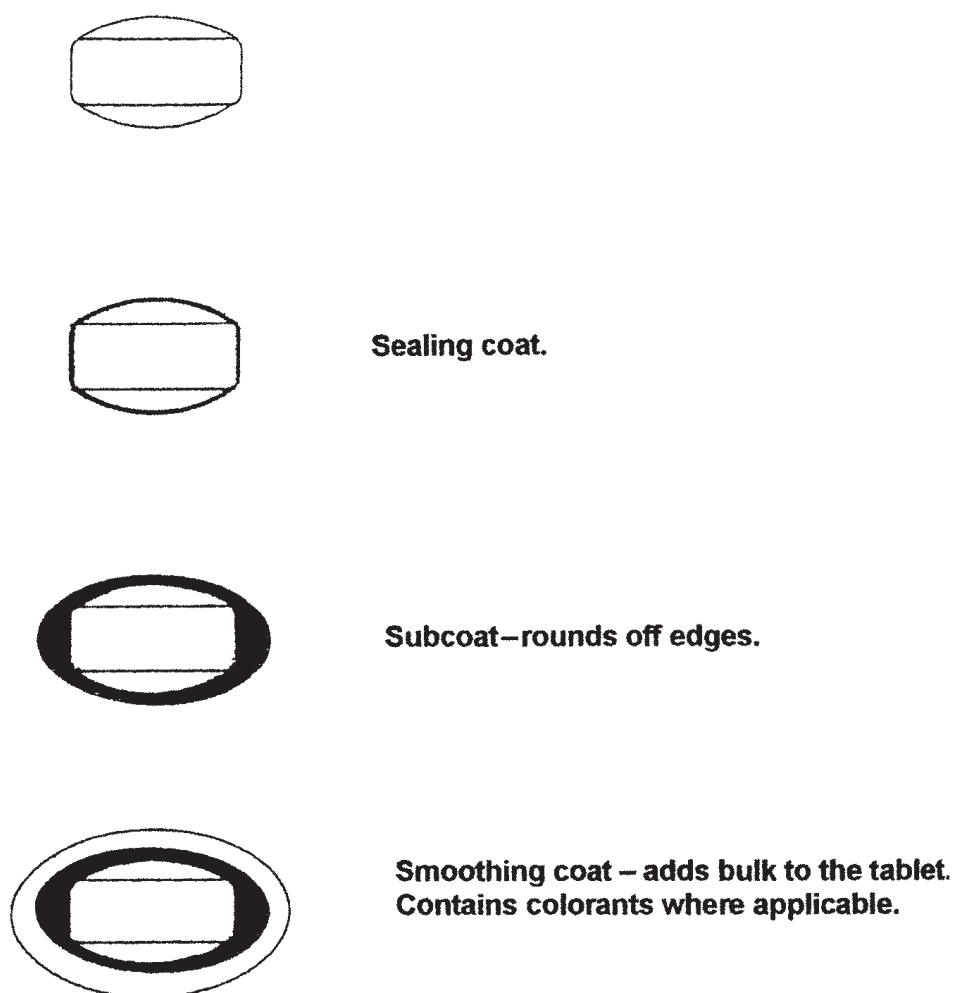


Figure 24 Stages of sugar coating.

The subcoat is an adhesive coat on which the smoothing coat can be built. A second purpose of the subcoat is to round off the sharp corners of the tablet to produce a smooth surface. The subcoat is a mixture of a sucrose solution and an adhesive gum, such as acacia or gelatin, which rapidly distributes over the tablet surface. A dusting follows each application of solution with a subcoat powder containing materials such as calcium carbonate, calcium sulfate, acacia, talc, and kaolin that help to produce a hard coat. The application of the subcoat continues until the tablets have a rounded appearance and the edges are well covered.

The smoothing coat consists of the majority of the tablet bulk, and provides the tablet with a smooth finish. The coat consists of sucrose syrup, which may contain starch or calcium carbonate. Each application is dried, and layers are added until the required bulk has been achieved. The last few coatings will consist of sucrose solution and colorants, where required. The colorants may be either soluble dyes or lakes, lakes often being preferred because a uniform color is easier to achieve with them.

The coated tablets are usually transferred to a polishing pan and coated with beeswax–carnauba wax mixture to provide a glossy finish to the surface.

Film Coating

Film coating involves the application of a polymer film to the surface of the tablet and, in contrast to sugar coating, only adds up to 5% weight to the final tablet, with a negligible increase in tablet size. It is a technique, which, while used mainly to coat tablets, can also be applied to hard gelatin capsules, soft gelatin capsules, and multiparticulate systems such as spheroids.

The method of application of the coat differs from sugar coating in that the coating suspension is sprayed directly onto the surface of the tablets, and drying occurs as soon as the coat hits the tablet surface. To achieve this, the tablet only receives a small quantity of coat at a time, and the coat is built up in an intermittent manner. While the coating can be applied using a number of methods, all share the following properties: a method of atomizing the coating suspension, the ability to heat large volumes of air (which heat the tablets and facilitate the rapid drying of the applied coat), and a method of moving the tablets that ensures all tablets are evenly sprayed. The main methods of coating are modified conventional coating pans, side-vented pans, and fluid bed coating.

When the technique of film coating was first applied to tablets, the coatings were suspended in organic solvents, and conventional coating pans were used. Additional air handling was required to provide the volume of air necessary to dry the tablets and to extract the vapors from drying. The nature of the pans was such that the drying air was only present on the surface of the tablet bed; there was no mechanism for it to percolate through it. Providing the volume of air required for such drying was difficult, and a number of modifications have been made to the pans. The limitation in drying efficiency, however, remains a constraint, particularly as most coating now uses aqueous suspensions, which impose even greater energy demands. A further limitation to the use of conventional coating pans is their poor mixing efficiency that results in dead spots in the tablet bed.

The side-vented pan, which is now the most commonly used equipment for film coating, was designed to maximize the interaction between the tablet bed and the drying air. In such apparatus, the coating pan is made of perforated metal. The drying air is introduced into the center of the pan but exhausted through the perforations in the pan beneath the tablet bed (Fig. 25). Mixing efficiency is achieved by the use of appropriately designed baffles on the pan surface.

Fluid bed coating offers an alternative to pan coating, and is particularly popular for coating multiparticulate systems. In fluid bed systems, the objects being coated are suspended in an upward stream of air, maximizing the surface available for coating. The coating is applied by an atomizer, and this is dried by the fluidizing air. There are three methods by which the coating can be applied (Fig. 26):

1. Top spraying involves the spray being applied from the top of the fluid bedchamber into the fluidizing air using equipment similar to that used for spray granulation.
2. Bottom spraying, sometimes referred to as the Wurster process, involves the spraying of the tablets at the bottom of the fluid bed. In this setup, there is a column

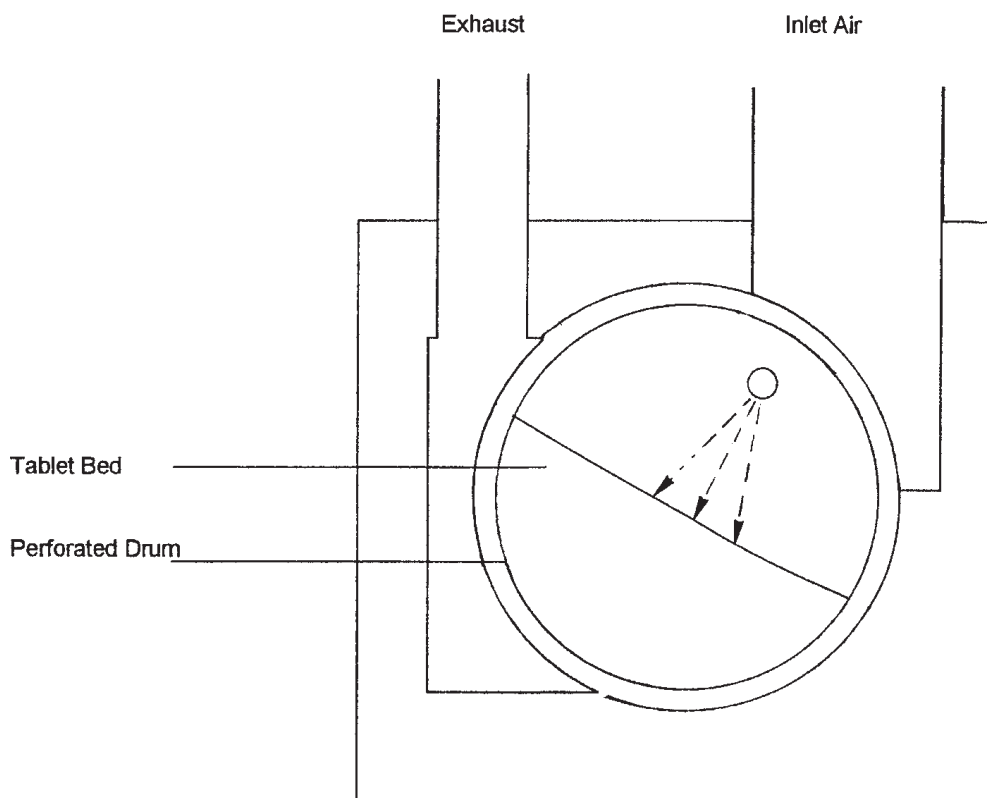


Figure 25 Schematic of the side-vented coating pan.

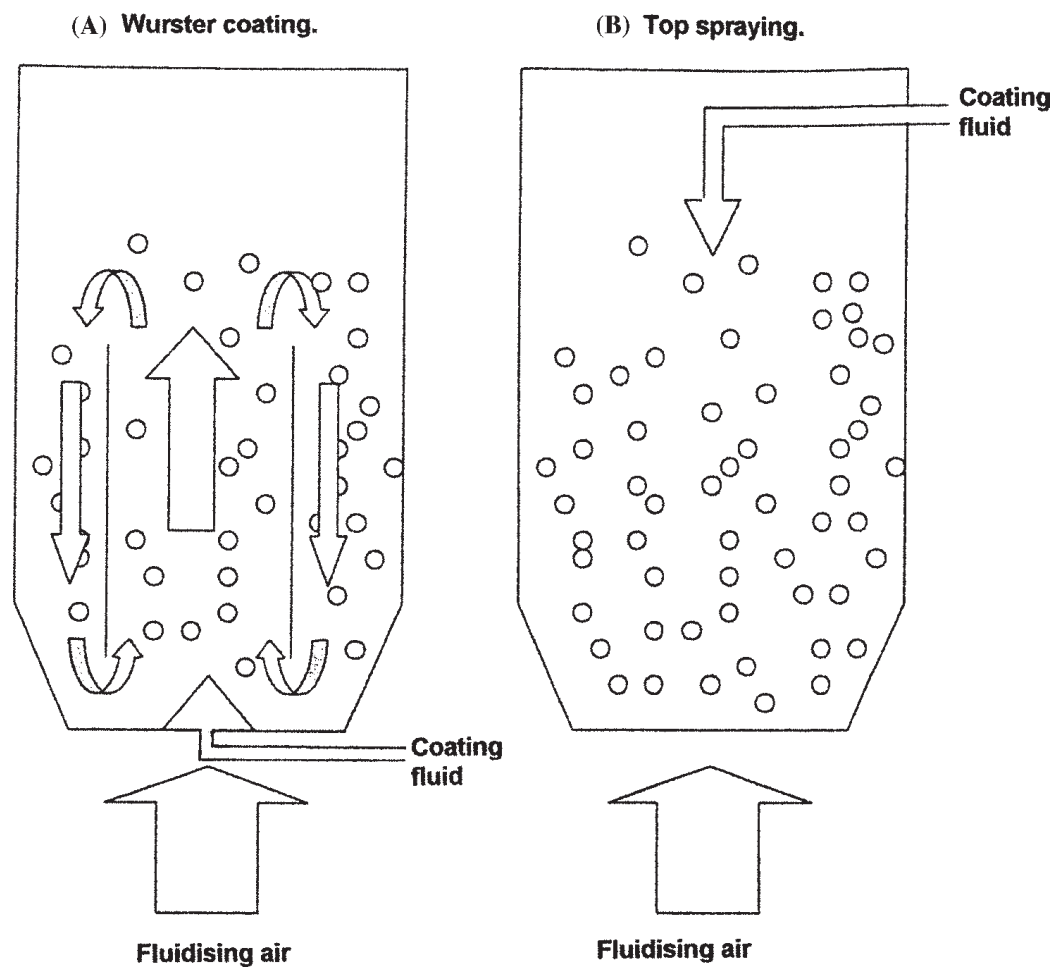


Figure 26 Fluid bed coating of tablets.

introduced into the fluid bedchamber, which ensures that tablets in the center of the chamber are directed upward. At the top of the column, the tablets descend the chamber at the edge of the chamber from where they will be redirected to the spraying region.

3. Tangential coating which is restricted to the coating of spheroids.

A polymer for film coating will ideally meet the following criteria:

- Solubility in the solvent selected for application. These days, the solvent will usually be water, although certain types of film coat may require organic solvents to be used. Commonly used solvents include alcohols (methanol, ethanol, and isopropanol), esters (ethyl acetate and ethyl lactate), ketones (acetone), and chlorinated hydrocarbons (dichloromethane and trichloroethane). The polymer should not only be soluble in the chosen solvent but should adopt a conformation in solution that yields the maximum polymer extension, which will result in films with the greatest cohesion strength. If mixed solvents are used, consideration should be given to the effect of the solvent ratios changing during the drying process. If the polymer is most soluble in the component with maximum volatility, it may precipitate out during the spraying before reaching the tablet surface.
- Solubility in GI fluids. Unless the coating is being applied for enteric coating or taste masking purposes, it should ideally be soluble across the range of pH values encountered in the GI tract.
- Capacity to produce an elegant film even in the presence of additives such as pigments and opacifiers
- Compatibility with film-coating additives and the tablet being coated
- Stability in the environment under normal storage conditions
- Free from undesirable taste or odor
- Lack of toxicity

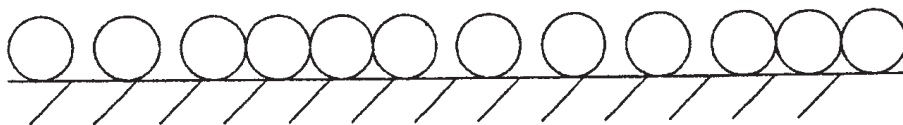
Table 15 lists the most commonly used polymers. With the exception of HPMC, the polymers are rarely used alone, but are combined with other polymers to optimize the film-forming properties.

The actual film-coating process is described schematically in Figure 27. There are two important stages: droplet formation and film formation. The film formation is itself a multistage process involving the wetting of the tablet surface followed by spreading of the

Table 15 Commonly Used Polymers

Polymer	Comments
MC	Soluble in cold water, GI fluids, and a range of organic solvents.
EC	Soluble in organic solvents, insoluble in water and GI fluids. Used alone in modified-release formulations and in combination with water-soluble celluloses for immediate-release formulations.
HEC	Soluble in water and GI fluids.
MHEC	Soluble in water and GI fluids. Has similar film-forming properties to HPMC, but is less soluble in organic solvents, which limited its popularity when solvent coating was the norm.
HPC	Soluble in cold water, GI fluids, and polar solvents. Becomes tacky when dried, so is unsuitable for use alone, often used in combination with other polymers to optimize adhesion of coat.
HPMC	Soluble in cold water, GI fluids, alcohols, and halogenated hydrocarbons. Excellent film former, and the most widely used polymer. Can be used with lactose to improve adhesiveness.
NaCMC	Soluble in water and polar solvents.

Abbreviations: MC, methylcellulose; EC, ethylcellulose; HEC, hydroxyethylcellulose; MHEC, methyl hydroxyethylcellulose; HPC, hydroxypropyl cellulose; HPMC, hydroxypropyl methylcellulose; NaCMC, sodium carboxymethylcellulose; GI, gastrointestinal.



Droplets of the coating suspension wet the surface of the tablet.



The droplets spread, forming a continuous film over the surface.



Eventually the droplets completely coalesce to form a smooth film.

Figure 27 Mechanism of film formation on the tablet surface.

film, and eventually coalescence of the individual film particles into a continuous film. For such coalescence to be able to occur, it is necessary for the polymer to be in a plasticized state, that is, above its glass transition temperature, the point at which a polymer goes from being a rigid, brittle material to a flexible material. Most film-forming polymers have glass transition temperatures in excess of the temperatures reached during the coating process (typically 40–50°C), so it is necessary to add plasticizers to the formulations, which act by reducing the glass transition temperature. The choice of plasticizer is dependent on the particular polymer (s) being used. The main factors to consider in selection are permanence and compatibility. Permanence is the duration of the plasticizer effect; the plasticizer should remain within the polymer film to retain its effect, so it should have a low vapor pressure and diffusion rate. Compatibility requires the plasticizer to be miscible with the polymer. Commonly used plasticizers include phthalate esters, citrate esters, triacetin, propylene glycol, polyethylene glycols, and glycerol.

Film coating provides an opportunity to color tablets, and most film coats will contain pigments or opacifiers. Insoluble pigments are normally preferred to soluble dyes for a number of reasons. Solid pigments produce a more opaque coat than dyes, protecting the tablet from light. The presence of insoluble particles in the suspension allows the rate of solid application to the tablet to be increased without having an adverse effect on the viscosity of the coating suspension, improving productivity. The pigments also tend to exhibit better color stability than dyes.

Film coating of tablets requires both the process and the formulation to be optimized if a uniform and intact coating is to be achieved. The most common flaws, their cause, and possible remedies are described in Table 16.

It has been emphasized to this point that the coat should not delay the release of the drug substance from the tablet. It is possible to design a coat that will modify the release of a drug substance for a beneficial effect.

Table 16 Film-Coating Defects

Flaw	Cause	Remedy
Wrinkling or blistering Film detaches from tablet surface, causing blister that can burst to form wrinkles.	Gases forming on tablet surface during coating; exacerbated by poor adhesion of film to tablet surface.	Reduce drying air temperature.
Picking Areas of tablet surface are not covered by film coat.	Overwet tablets stick together and pull film off surface as they move apart.	Decrease spraying rate. Increase drying temperature.
Pitting Holes appear on tablet surface.	Melting of lubricant on tablet surface. Most common with stearic acid.	Decrease coating temperature to below melting point of lubricant. Substitute lubricant.
Blooming Dulling of surface, normally after prolonged storage.	Migration of low-molecular-weight components of film to tablet surface.	Decrease temperature and length of drying process. Increase molecular weight of plasticizer.
Mottling Uneven color distribution in film.	Inadequate pigment dispersion. Color migration, a problem with dyes and lakes rather than pigments.	Alter suspension preparation to ensure pigment aggregates are dispersed. Replace dyes with pigments.
Orange peel Film surface has a rough finish resembling orange peel.	Film-coat droplets are too dry or too viscous to spread on tablet surface.	Reduce solids content of coating suspension. Reduce drying temperature. Reduce viscosity of polymer.
Bridging Film forms a bridge over intagliations, leaving them indistinct.	High internal stresses in film relieved by pulling the film off the Surface of the intagliation.	Increase adhesion of coat to tablet by changing core formulation. Add plasticizer or increase plasticizer concentration. Alter geometry of intagliations.
Cracking, splitting, peeling The film cracks on the crown of the surface or splits on the tablet edge. Can be differentiated from picking by presence of loose film around the flaw.	High stresses in the film that cannot be relieved due to the strong Adhesion of the film to the tablet surface.	Increase plasticizer concentration. Use stronger polymer.

The most common type of modified-release coating is the enteric coat, which is designed to prevent release of the drug substance in the stomach because the drug is either irritant to the gastric mucosa or it is unstable in gastric juice. The most common method of achieving an enteric coating is to apply a polymer that contains acidic substitutions, thus giving it a pH-dependent solubility profile. Examples of such polymers are listed in Table 17.

Film coating can also be used to delay the release of drugs. This is normally applied to multiparticulate systems where particles will be coated with differing thicknesses of water-insoluble polymers such as ethylcellulose.

Compression Coating

The third type of tablet coating used in pharmaceuticals is compression coating. This technique involves producing a relatively soft tablet core containing the drug substance and compressing

Table 17 Commonly Used Enteric-Coating Polymers

Polymer	Solubility profile	Comments
Shellac	Above pH 7	The original enteric-coating material, originally used in sugar-coated tablets. The high pH required for dissolution may delay drug release. Natural product that exhibits batch-to-batch variability.
CAP	Above pH 6	The high pH required for dissolution is a disadvantage. Forms brittle films, so must be combined with other polymers.
PVAP	Above pH 5	Optimal dissolution profile for enteric coating.
HPMCP	Above pH 4.5	
Polymers of methacrylic acid and its esters	Various grades available with dissolution occurring above pH 6	

Abbreviations: CAP, cellulose acetate phthalate; PVAP, polyvinylacetate phthalate; HPMCP, hydroxypropyl methylcellulose phthalate.

a coating around it (Fig. 28). This is achieved by placing the core in a large die that already contains some of the coating formulation. Further coating material is then added to the die and the contents compressed. The three types of coating have now been described, and the relative merits of each approach are summarized in Table 18.

HARD GELATIN CAPSULES

After tablets, hard gelatin capsules are the most common solid dosage form. Hard gelatin capsules are rigid two-piece capsules made from gelatin, water, and colorants. The capsules are produced as empty shells consisting of a cap and body, which during the manufacture of the finished product are separated, filled with the formulation, and then rejoined.

Hard gelatin capsules are generally considered to be more forgiving than tablets, from a formulator's perspective. While many of the challenges facing the formulator of tablets are still present, the need for a free-flowing material, powder homogeneity, lubricity, and optimizing the biopharmaceutical properties, the challenges of forming a robust compact have been removed. Capsules have traditionally been filled with solid formulations such as powder mixes and granulations, but increasingly, multiparticulate formulations, liquid, and semisolid fills are being developed.

Hard gelatin capsules have some disadvantages compared with tablets. The filling speeds of capsule machines are lower than the speeds of the fastest tablet presses, and the cost of the capsule shells makes them a more expensive dosage form. Certain materials are unsuitable for inclusion in capsule shells due to incompatibility with gelatin, or because of their affinity for water. One advantage sometimes claimed for capsules is ease of swallowing due to their elongated shape, but this may be countered by the fact that capsules are often larger than corresponding tablets due to the reduced compression of the powder and incomplete filling of the shells. Furthermore, there are concerns that capsules are more prone to sticking in the esophagus than tablets following swallowing.

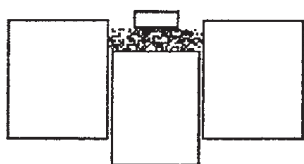
The manufacture and formulation of hard gelatin capsules has not been the subject of as much research as tableting, partly because encapsulation, unlike compression, is not a science shared by many other disciplines. Nevertheless, there has been important work performed on this dosage form, and much of it is captured in *Hard Capsules Development and Technology* (Ridgway, 1987).

Manufacture of Empty Capsule Shells

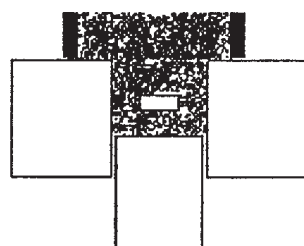
Gelatin is a heterogeneous product prepared by the hydrolysis of collagen, the principal constituent of connective tissue. The suitability of gelatin for capsule manufacture is due to the following properties:



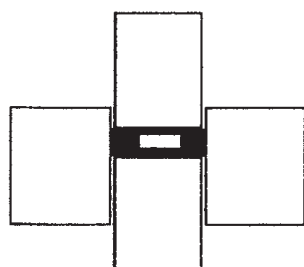
The die passes under the feed frame containing the compression coat material. A shallow fill takes place.



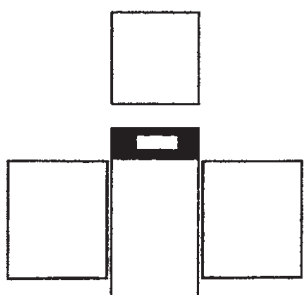
The tablet core that is to be coated is placed on the layer of coating material.



The lower punch moves down, and the die passes beneath a feed frame containing the coating material. The tablet core is now surrounded by the coating material.



The die contents are compressed between two punches to form a coherent compact.



The formed compression coated tablet is ejected from the die.

Figure 28 Schematic of the compression coating process.

- It is commonly used in foods and has global regulatory acceptability. However, because it can be derived from a number of animal sources, not all the gelatin is acceptable in all markets, and capsule manufacturers will produce capsules from different animal sources to allow for local religious restrictions. All pharmaceutical capsule manufacturers now use gelatin produced in accordance with current requirements relating to bovine spongiform encephalopathy.
- It is a good film former, producing a strong flexible film.

Table 18 Coating Methods

Coating method	Advantages	Disadvantages
Sugar coating	Elegant final product. Tablets can be printed for identification purposes. Cheap, readily available starting materials. Simple equipment requirements. Excellent protection from environment.	Long process time. Traditional manufacture more an art than a science; high operator dependency. Significantly increases tablet size.
Film coating	Quick process, easy to automate. Negligible increase in tablet size. Tablets can be identified either by printing or through intagliations. Minimal effect on drug release. Enteric coating feasible.	Finish not as elegant as sugar coating. Coating process stresses tablet formulation, cores must be robust to resist abrasion and edge chipping during coating.
Compression coating	It is a dry process; so suitable for moisture-sensitive compounds. Can be used for combination products where the active substances are incompatible.	Significant increase in tablet weight. Possible to produce tablets with no inner core.

- It is readily soluble in water and in GI fluids at body temperature, so will not retard the release of drugs.
- It changes state at low temperatures, enabling a homogeneous film to be formed at ambient temperature.

The properties of a given batch of gelatin are determined by a number of factors: the source of the parent collagen, method of extraction, the pH of the hydrolytic process, and its electrolyte content. The properties of most interest to capsule manufacturers are the bloom strength and the viscosity.

The bloom strength is a standard, but arbitrary, test of the rigidity of gel produced by a sample of gelatin. The test measures the force required to depress the surface of a 6.67% w/w gel, matured at 10°C for 16 to 18 hours, by a distance of 4 mm using a flat-bottomed plunger 12.7 mm in diameter. The force is applied in the form of a stream of lead shot, and the weight, in grams, is termed the bloom strength. Bloom strengths in the region of 230 to 275 are used for the manufacture of hard gelatin capsule shells. The standard viscosity is measured using a U-tube viscometer with a 6.67% w/w solution, and values in the range of 3.3 to 4.7 mPa sec being used for capsule shells.

Capsule shells are manufactured by dipping moulds into a gelatin solution, drying the gelatin to form a film, removing the dried film from the mould, and trimming the film to the right size. The moulds are made of stainless steel and are referred to as pins. The cap and body of the capsule shells are made on separate pins, with the body pins being longer than the cap. The external diameter of the body at its open end is slightly larger than the internal diameter of the cap at its closed end to ensure a snug fit when closed.

The empty capsule shells contain 13% to 15% water, a level that is important for optimum performance on capsule-filling machines. If the level falls below 13%, the capsules become brittle, while if they take up too much water, the gelatin becomes soft, and there are problems with capsule separation. The dimensions of the capsule shell will also change with variations in water content, typically increasing by 0.5% for every 1% increase in moisture content. It is important that capsule shells are both stored and filled in areas where the RH is controlled between 30% and 50%.

It is also important that the capsule fill not adversely affect the moisture content of the shell. This is not a suitable dosage form either for deliquescent materials, which will dry the capsules, making them brittle, causing cracking or splitting, or for efflorescent materials, which will soften the shells and may lead to capsules sticking together. Similarly, the presence of

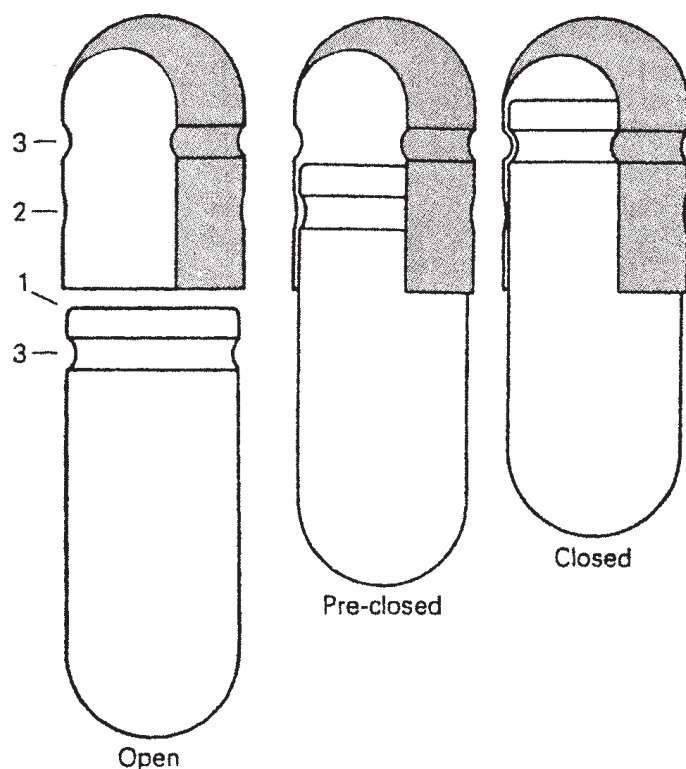


Figure 29 Locking mechanism of a hard gelatin capsule shell.

1. The tapered rim prevents faulty joins.
2. These indentations prevent the pre-closed capsules from opening too early.
3. These grooves lock the two halves together after filling.

moisture in the capsule shells makes them an unsuitable delivery form for drugs that are highly moisture sensitive.

Any fill materials must be chemically compatible with gelatin. Cross-linking of gelatin can be catalyzed by trace quantities of formaldehyde, rendering the gelatin insoluble in gastric fluids. Formaldehyde is sometimes present at trace levels in a number of excipients.

Capsules manufactured for use on automatic filling machines, which covers almost all pharmaceutical capsules, have locking devices molded into the side of the capsule (Fig. 29). There are two locking positions, a pre-lock to prevent premature opening prior to the filling process and a locked position, which forms an interference seal to prevent the capsule coming apart after filling.

There are a number of companies manufacturing capsule shells for use in the pharmaceutical industry, and all produce capsules to standard sizes, which enable them to be filled on standard filling machines. There are eight sizes of capsules commercially available, which are listed in Table 19. The largest capsule size normally considered for oral administration is size 0, with the 00 and 000 capsules being difficult to swallow due to their size.

Capsule Filling

Before considering how to formulate products for filling into hard gelatin capsules, it is necessary to understand the capsule-filling mechanisms available. All capsule-filling machines perform three basic operations: the orientation and separation of the empty capsule shell, the filling of the material into the shell, and finally rejoining the cap and the body. From the formulator's perspective, the important stage is the filling, as this will determine the properties required of the formulation. The requirements imposed by the filling mechanism will include

Table 19 Capsule Sizes

Capsule size	000	00	0	1	2	3	4	5
Fill volume (mL)	1.37	0.95	0.68	0.50	0.37	0.30	0.21	0.13

factors such as powder flow, lubricity, and compressibility, and as discussed in the section "Tablets," the optimization of these factors needs to take into consideration the effects on drug release from the formulation.

Drug release from capsules involves an additional step compared with tablets, the dissolution of the capsule shell. When placed in a dissolution medium at 37°C, the gelatin will begin to dissolve, initially retaining its integrity. Eventually, the capsule shell will rupture at its thinnest points, the shoulders of the cap and body, allowing the dissolution medium to penetrate into the capsule contents. The rate of penetration and, where appropriate, the disintegration of the capsule fill will be determined by a combination of the formulation and the processing method, including the filling mechanism.

Powder and Granulate Filling

The requirements of capsule formulations are very similar to those of tablets, and the general formulation principles described earlier apply equally to capsules. As with tablets, most capsules will contain a combination of ingredients including some or all of the following: the active drug substance, filler(s), disintegrant, binder, glidant, and lubricant. The main difference in the requirements is the demands placed on the compressibility of the formulation. With tablets, it is necessary to produce a compact capable of withstanding the rigors of subsequent handling. For capsules, it is often necessary to form a plug for ejection into the capsule body, but it is not necessary for the plug to retain its integrity beyond the filling stage. While good flow is necessary for the successful manufacture of both tablets and capsules, the filling mechanisms on certain capsule-production machines tend to be more forgiving than those on tablet-production machines.

Powder fills for capsules can be either simple blends of starting materials, analogous to direct compression formulations, or granulations. The reduced demands on compressibility and flow increase the options for powder mixes, making capsules a potential dosage form for active substances that do not possess the compression properties required for direct compression tablets, and are not amenable to granulation.

Powders account for the majority of capsule fills, and a number of quite disparate filling mechanisms have been developed unlike tableting, where the principle of manufacture, compression between two punches in a die, is the same for all machines. The mechanisms can be divided into two broad groups, those that rely on the volume of the capsule shell to control the dose, known as capsule dependent, and those methods where the quantity of powder to be filled is measured away from the capsule, known as capsule independent. The dependent mechanisms require the capsule shell to be well filled to achieve weight uniformity and are less flexible than the independent methods.

Dependent Methods

The simplest method of dependent capsule filling is leveling, in which the capsule bodies are held flush with a dosing table, and powder is filled into the bodies by gravity. The powder within the capsule bodies may be consolidated by vibration or tamping, and additional powder added to fill the space generated. The final fill weight will depend on the bulk density of the powder and the degree of tamping applied. This method is popular in hand-filling devices such as the Tevopharm, Feton, Bonaface, and Zuma, which are amenable to most powder mixes. Poor flowing powders will take longer to fill, but with skilled operators, should be feasible. The major formulation challenge is to prepare a blend that will provide an appropriate fill for a standard-sized capsule.

Osaka Automatic Machine Co. produces a fluidization machine, which is an automatic dependent filling machine. The capsule body in its holder passes below the powder hopper. The powder is fluidized by a vibrating plate to aid flow into the capsule body. The capsule body can be held below the hopper base so that it becomes overfilled, and the fill can be compressed into the capsule by raising the body against a flat surface prior to the capsule closing. This technique has not been the subject of published formulation studies, but appropriate flow properties and lubrication are likely to be required.

Independent Methods

Auger or screw method. This was the first mechanism used in industrial-scale machines, although the dosator and piston-tamp mechanisms have now largely superseded it. The capsule body in its holder passes beneath the powder hopper on a turntable. The powder is fed into the capsule body by a revolving Archimedean screw. The auger rotates at a constant rate so the fill weight is related to the duration of filling that is related to the speed of rotation of the turntable.

Formulation studies on auger machines have tended to concentrate on the optimization of fill weight uniformity. Reier et al. (1968) demonstrated that the variation in the capsule fill weight was influenced by the machine speed, capsule size, powder density, powder flow, and the presence of a glidant. Ito et al. (1969) determined that there was an optimum level of glidant for minimum weight variation. Powders still account for the majority of capsule fills, and a number of quite disparate filling mechanisms have been developed. Powders should be adequately lubricated to prevent build up of densified material on the auger.

Piston-tamp method. In piston-tamp machines, the powder passes over a dosing plate containing cavities slightly smaller than the internal diameter of the capsule. The powder falls into the holes by gravity, and is then tamped by a pin to form a soft plug. This procedure is repeated several times until the cavity is full. Excess powder is removed from above the cavity by a deflector plate. The cavity is then positioned over the capsule body and the plug ejected (Fig. 30). The dose is controlled by the thickness of the dosing plate, the degree of tamping applied, and the height of the powder bed above the dosing plate.

The uniformity of fill weight for the piston-tamp machines has been shown to correlate well with the angle of repose of the powders (Kurihara and Ichikawa, 1978) and the angle of internal flow (Podczech et al., 1999). Lubrication of formulations is important to prevent build up of material on the tamping pins, and to ensure smooth ejection of the plugs from the dosing plate. The ability of the material to compress into a plug is important; if a formulation does not form a plug, the ejection will not be as clean, and can lead to increased weight variation. Studies have shown that for certain formulations, the tamping pressure applied by the pins can affect the dissolution rate of the final product (Shah et al., 1983). The minimum tamping force necessary to obtain a plug that will fit inside the body of the capsule shell should be aimed for.

Dosator method. A dosator, consisting of a stainless steel cylinder containing a spring-loaded stainless steel piston, is lowered, open end first, into a flat powder bed. As the cylinder

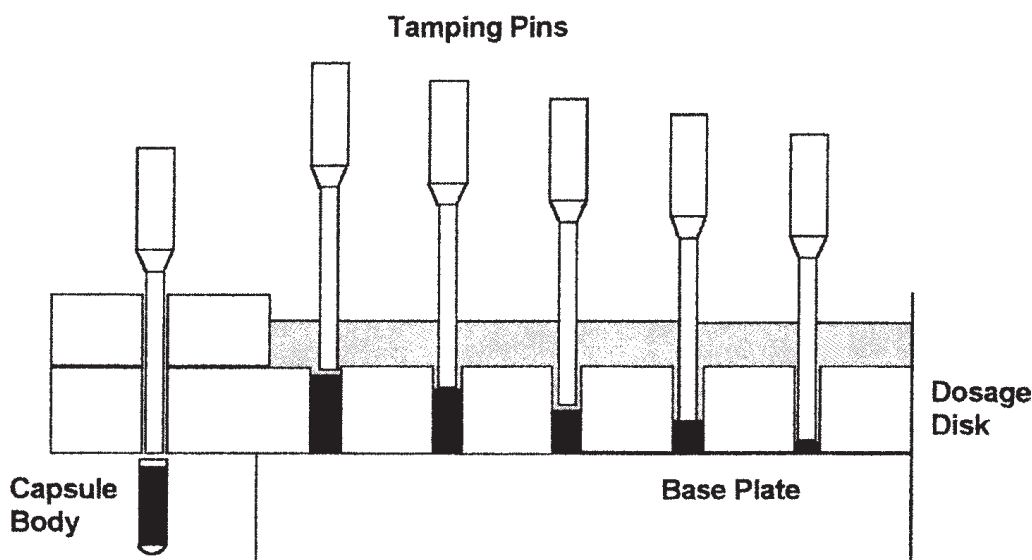


Figure 30 Schematic of a tamping pin-type capsule-filling machine.

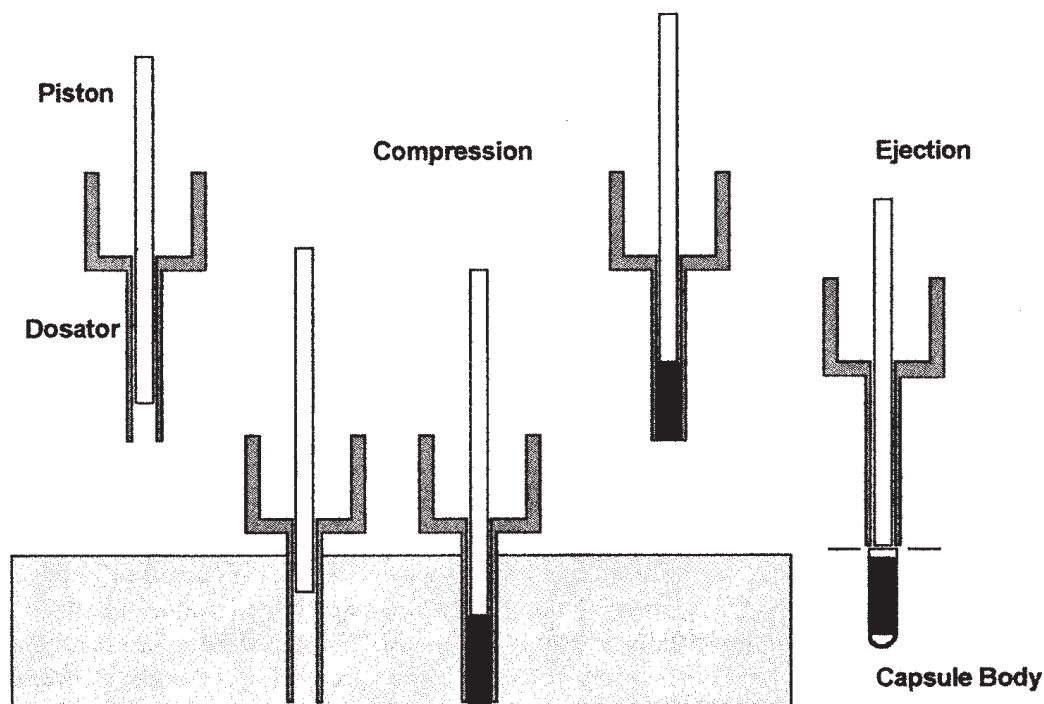


Figure 31 Schematic of a dosator-type capsule-filling machine.

passes into the bed, powder is forced up into the cylinder until it reaches the piston, forming a plug. Additional compression of the plug can be obtained by applying a downward pressure on the piston. The dosator is lifted from the powder bed and, if a suitable plug has formed, the powder will remain within. The dosator is positioned above a capsule body, and the plug ejected by lowering the piston. The dose is controlled by the dimensions of the dosator, the position of the piston within the dosator as it enters the powder bed, and the height of the powder bed (Fig. 31).

This mechanism is the most widely used one, and can be found on small pilot scale machines using an intermittent action similar to rotary machines, capable of production rates in excess of 120,000 capsules per hour. As a result of its popularity, there have been considerable studies into the formulation of powder for filling on these types of machines, and instrumentation of the dosators.

The fundamental requirements of a formulation to be filled on a dosator-type machine are good flow properties, compressibility, and lubricity. *Flow* is important in the powder bed: when the dosator dips into the powder, it leaves a void, which must be closed with material of the same bulk density prior to the next dosator entering that area of the hopper. Irwin et al. (1970) investigated the effect of powder flow on the uniformity of weight achieved on a Zanasi filling machine, and concluded that the better the rate of flow, the better the uniformity of fill.

Compressibility is necessary to form a plug of sufficient strength so that powder does not escape from the dosator as it leaves the powder hopper and position itself above the capsule body. Jolliffe and Newton (1982a,b) considered the theoretical aspects of powder retention using powder hopper design theory to calculate the forces required to hold a free powder surface in an open-end cylinder. The powder retention relies on the formation of a stable powder arch, which is dependent on the shear developed at the dosator walls and the unconfined yield strength. It was demonstrated that the angle of wall friction between the powder and dosator could have an important influence on powder retention. This was explored experimentally (Jolliffe and Newton, 1982a,b) by showing that the internal friction changed during manufacture as the powder fill coated the internal wall of the dosator. Furthermore, these authors proposed that the optimum design for a dosator would have two types of surface finish, a smooth finish with a low value of wall friction for the main body of

the cylinder together with a higher value of wall friction at the outlet to promote arch formation. The dosator mechanism does permit high compressive forces to be applied to powder beds. The objective of a capsule formulation is not to make a mini tablet that can be filled into a capsule; the compression force should be restricted to the minimum level necessary to form a coherent plug. Whenever powders are compressed, there is the possibility of elastic recovery when the compressive stress is removed. The tolerance between the internal diameter of the dosators and the internal diameter of capsule shells is fairly tight, and any elasticity in capsule formulations can lead to the plugs not sitting properly in the capsule shells, resulting in powder loss as the cap is reunited with the body. In such circumstances, the pragmatic approach is to use dosators designed for the next smallest capsule size.

The *lubricity* requirements of formulations being filled with dosators has been examined by Small and Augsburger (1978) using a Zanasi machine on which strain gauges had been attached to the dosator pistons. The magnitude of the force required to eject the powder plug from the piston was shown to be dependent on the identity and level of lubricant, the height of the initial powder bed, the piston height, and the compression force applied.

Filling Capsules with Pellets

The use of multiparticulate systems to provide modified-release formulations is ever increasing, and hard gelatin capsules provide an ideal way of delivering unit doses of such formulations. The two most common approaches to pellet formulation are extrusion/spheronization (discussed in an earlier section) and the coating of nonpareil seeds. Nonpareil seeds are sucrose beads, which can be film coated with a solution/suspension of the drug substance followed by layers of modified-release coatings to obtain the release profile required. The capsule-filling method has to be gentle enough on the pellets to retain the integrity of the coating.

As with powder filling, the filling of pellets into capsules can be dependent or independent. A dependent method often performed uses a modified augur-type machine, in which the pellets are simply poured by gravity into the capsule shells. The critical formulation aspect of this approach is ensuring that the required dosage of active substance is present in the volume of pellets taken to fill the capsule body.

An independent method uses a volumetric fill by a modified dosator method. The piston inside the dosator is narrower than that used for powder filling, and this allows air to flow between the piston and the dosator wall. The dosator is lowered into the pellet bed, but in this case, there is no compression applied. A vacuum source is applied from above the piston to retain the pellets as the dosator is moved above the capsule body. Once over the capsule body, the vacuum is removed and the ejection of the pellets is aided by an air jet.

Tablets

Capsules can also be filled with tablets, which can be of use when preparing blinded clinical trial materials. Tablets are fed from a hopper into a chamber that simply releases one or more tablets into the capsule body as it passes underneath. The optimum formulation for capsule filling is a biconvex film-coated tablet, the film coating reducing abrasion and material loss.

Capsugel produces a range of specially sized opaque capsules specifically for the encapsulation of tablets for double-blind clinical trial supplies. The capsules are wider than standard-sized capsules to allow larger diameter tablets to be filled but have shorter bodies to retain patient acceptability/tolerability.

Liquids and Semisolids

Two types of liquid formulations can be filled into hard gelatin capsules, those that are liquid at room temperature and those that are solid at room temperature. Such solid formulations can be liquefied either by heating to temperatures up to 70°C (the maximum temperature the gelatin shell can withstand) or by the application of shear stress. In the case of liquids that are mobile at room temperature, the capsules need to be sealed after filling to prevent leakage of the contents.

The filling of such formulations requires machines fitted with hoppers that can provide a heating and stirring system. For most formulations, the capsules are filled using a volumetric pump, although certain viscous preparations may require an extrusion pump. The pump must be designed to be non-drip, and the capsule handling needs to be modified to control product spillage. A sensing system is required to detect the presence or absence of caps or bodies so that the pump can be stopped and the bushes not contaminated with fill material. With powder fills, contamination of the exterior of capsules can be removed by vacuum dedusting. With liquids, if one capsule is covered with liquid, it can lead to major problems with capsules sticking together.

There are a number of applications for liquid/semisolid filled capsules:

- Improvement of bioavailability
- Safety—minimizing operator exposure to dusty processes
- Content uniformity—it is easier to achieve and maintain content uniformity in a solution system than a powder system
- Stability

These advantages are similar to those of soft gelatin capsules, and are dealt with in greater depth in a following section.

With soft gelatin capsule technology being so well established, what advantages does liquid filling of hard gelatin capsules provide the formulator? The major advantage is that it is a technology that can be installed in-house relatively simply, unlike soft gelatin capsule manufacture, which remains in the hands of a limited number of contract suppliers. This has been made possible by the development of techniques for sealing the capsules.

The approach taken to formulate a liquid-filled capsule will depend on the reason for selecting such a dosage form. The most important aspect of the formulation is to ensure that the fill is compatible with the gelatin shell. It is well known that the gelatin shell is sensitive to changes in moisture levels, and hence liquids that readily take up moisture such as the low-molecular-weight polyethylene glycols will be unsuitable. Capsugel, one of the main suppliers of capsule shells, performed extensive compatibility testing of liquid vehicles, and has published a list of those deemed to be compatible (Stegemann, 1999) (Table 20).

Table 20 Liquid Excipients Compatible with Hard Gelatin Capsule Shells

Lipophilic excipients	Hydrophilic excipients	Amphiphilic excipients
Vegetable oils	PEG 3000–6000 MW	Poloxamers
Peanut oil		Lecithin
Castor oil		PEG esters (e.g., Gelucir 44/14;
Olive oil		50/13; Labrafil)
Fractionated coconut oil		
Corn oil		
Sesame oil		
Hydrogenated vegetable oil		
Soybean oil		
Esters		
Glycerol stearate		
Glycol stearate		
Isopropyl myristate		
Ethyl oleate		
Fatty Acids		
Stearic acid		
Lauric acid		
Palmitic acid		
Oleic acid		
Oleic acid		
Fatty Alcohols		
Cetyl alcohol		
Stearyl alcohol		

Abbreviations: PEG, polyethylene glycol; MW, molecular weight.

Capsule Sealing

The filling of liquids into hard gelatin capsules has been thought about for many years, but was not commercially feasible until reliable methods for capsule sealing were available. The incidents involving the tampering of paracetamol capsules in the United States in the mid-1980s forced capsule manufacturers to develop a method of making capsules tamper evident. This, in turn, led to the development of the Quali-Seal capsule-banding machine. This machine applies a narrow band of gelatin around the joint of the cap and body of filled capsules, which can be dried without the application of heat. Heat would cause air expansion within the capsule, disrupting the seal.

A recent development in sealing technology has been liquid encapsulation microspray sealing (LEMS) in which a sealing fluid of approximately 50% water and 50% ethanol is sprayed onto the joint between the cap and body. This fluid penetrates the cap/body joint by capillary action and lowers the melting point of the gelatin; the capsule is then exposed to a short cycle of warm air, which melts and fuses the gelatin at the joint. This technique is an elegant method of sealing, as the seal is not visible to the user.

Alternatives to Gelatin Capsules

There have been a number of attempts to make capsules from materials other than gelatin. Initially, the attempts were aimed at overcoming the original patents filed by Mothe in the 19th century, and used materials such as starch, gluten, and animal membranes. However, the only material with the correct film-forming properties was gelatin.

More recently, the attention has moved to synthetic polymers, with the aim being to produce capsules that will overcome the shortcomings of gelatin, particularly its moisture content. Two alternative materials have been offered by capsule manufacturers, starch and HPMC.

The starch capsules are produced by an injection molding process using potato starch, and are produced in five sizes, all of the same diameter but with different lengths (Vilivalam et al., 2000). While the fill volumes are similar to gelatin capsules, the different dimensions necessitate specialized filling equipment. The capsule surface is less smooth than gelatin capsules, and the injection molding allows a smooth join between cap and body to be obtained. These properties make the capsules amenable to film-coating processes. The moisture content of the capsules is 14%.

HPMC capsules are made by the pin-dipping process used for gelatin capsules, and are made to the same size specifications, allowing them to be filled on conventional capsule-filling equipment. These capsules have a lower moisture content than gelatin capsules, and the moisture is tighter bound, making them more suitable for moisture-sensitive drugs and hygroscopic excipients. The capsule surfaces have rougher finishes than gelatin capsules, and coloring the capsules is more difficult. The rough coat leads to better adhesion with coating materials, so they could have applications for enteric coating.

SOFT GELATIN CAPSULES

Soft gelatin capsules are included in this chapter on oral solid dosage forms, although there is debate as to whether or not they are solid or liquid dosage forms. The drug is presented in a liquid encapsulated in a solid, thus combining advantages of liquid dosage forms with the unit dosage convenience of solid forms.

Manufacture

Unlike hard gelatin capsule shells, which are manufactured empty and subsequently filled in a separate operation, soft gelatin capsules are manufactured and filled in one operation. This is a specialized process, and tends to be performed by a limited number of companies. One consequence, therefore, of selecting a soft gelatin capsule formulation is that the product will probably be manufactured by a contract manufacturer. A desire to keep all manufacturing in-house is one of the reasons for companies considering the use of liquid-filled hard gelatin capsules as an alternative.

The shell ingredients of a soft gelatin capsule are gelatin, glycerol, which acts as a plasticizer, and potentially other ingredients, which could include additional plasticizers such as sorbitol or propylene glycol, dyes or pigments, preservatives, and flavors. The glycerol-gelatin mix is dissolved in water, then heated and pumped onto two cooling drums to form two gelatin ribbons, which are fed into the filling machine. The liquid fill is pumped between the gelatin ribbons as they pass between the two die rolls of the filling machine, forcing the gelatin to adopt the shape of the die. The two ribbons are sealed together by heat and pressure, and the capsules are cut from the ribbon (Fig. 32). They then pass through a tumble drier to remove the bulk of the water and are conditioned at 20% RH.

The fill can be either a solution or a suspension, liquid or semisolid. The main limitation is that the fill must be compatible with the shell. The main incompatibilities are high concentrations of water or other solvents, which will dissolve the shell, high pH (>7.5) solutions, which will cause cross-linking of the gelatin, which will retard dissolution of the shell, low pH solutions, which may hydrolyze the gelatin, and aldehydes, which promote cross-linking. The types of vehicles that can be used in soft gelatin capsules are similar to those used for liquid-filled hard gelatin capsule shells listed in Table 20.

Benefits of Soft Gelatin Capsule Formulations

Soft gelatin capsules are a more expensive dosage form than either tablets or capsules, so they tend to be considered when they can offer a major benefit to the formulator. Justifications for

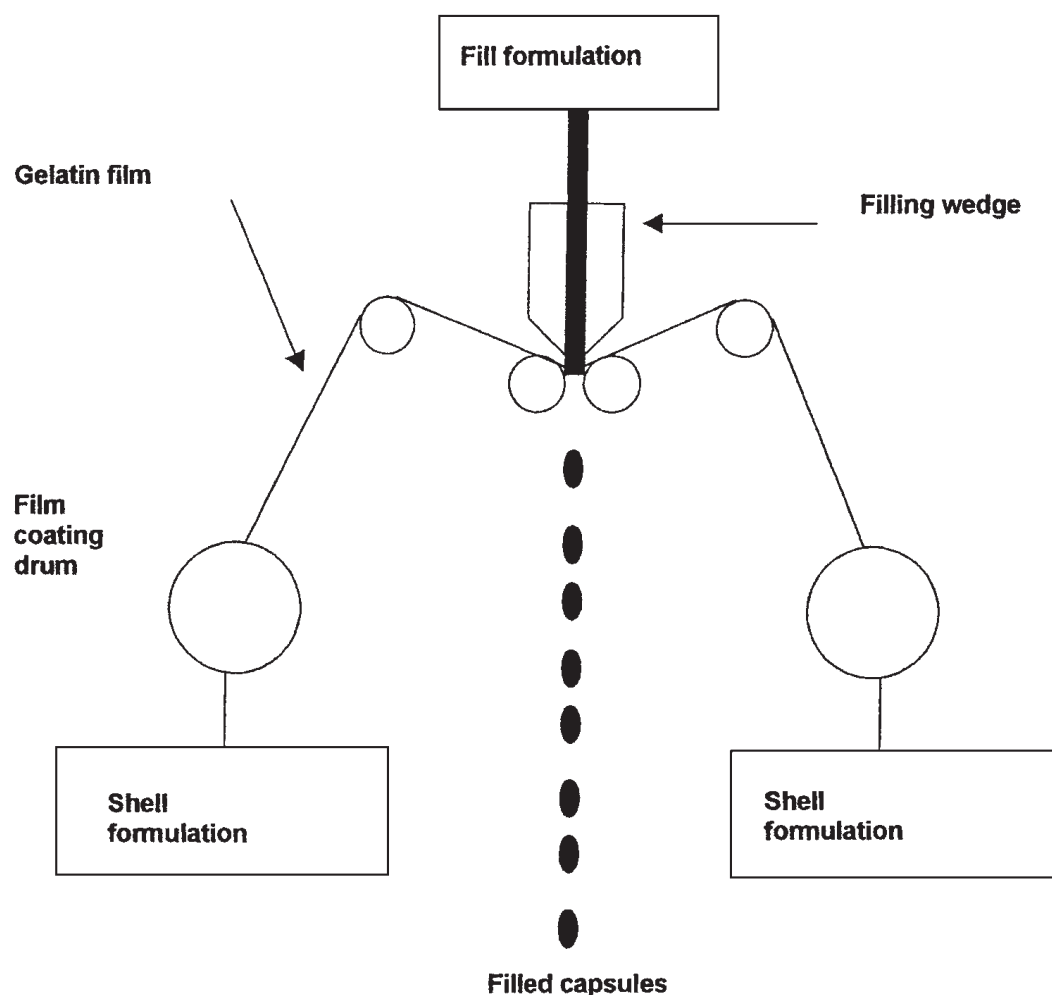


Figure 32 Schematic of the soft gelatin capsule manufacturing process.

their use include improved content uniformity, safety, improved stability, and improved bioavailability.

Improved Content Uniformity

Because soft gelatin capsules are filled with liquids or suspensions, excellent content uniformity can be achieved with even the most potent of drugs. The accuracy of the filling mechanism enables the dose to be filled to a tolerance of $\pm 1\%$ for solutions and $\pm 3\%$ for pastes.

Safety

Dissolving potent drugs in a liquid vehicle reduces the risk of operator exposure to dusts that is present with tablet and hard gelatin capsule-manufacturing operations.

Improved Stability

Varying the level of glycerol in the shell formulation will alter the permeability of the shell to oxygen. The filling process can be performed under nitrogen, so by appropriate selection of shell composition, this technology can provide excellent protection for oxygen-sensitive drugs.

Improved Bioavailability

Presenting the drug to the GI tract in a solubilized form overcomes the processes of disintegration and dissolution that are required from hard gelatin capsules and tablets before the drug substance is available for absorption. This has been utilized to improve the bioavailability of drugs with a range of solubilities.

Acid-soluble drugs can be dissolved or dispersed in water-miscible vehicles that rapidly distribute the drug throughout the stomach following administration. Acid-insoluble drugs can be dissolved in water-miscible vehicles, which results in the drug precipitating as a fine suspension in the stomach. The surface area of the solid in suspension is high, resulting in rapid dissolution.

Formulation of compounds that have very low aqueous solubility in lipid vehicles is an area that has seen the most growth in recent years. Two approaches can be used, depending on the solubility characteristics of the drug substance. For compounds with log *P* values in the region of 2 to 4, the preferred approach is to form self-emulsifying systems. These formulations comprise a lipid vehicle, typically a medium-chain triglyceride together with a surfactant, which, on contact with an aqueous environment, spontaneously form micelles. The drug remains solubilized in the micelles. Drugs with higher log *P* values can be dissolved in digestible oil such as medium-chain monoglycerides, which are immiscible with water. On release from the capsule, the drug remains solubilized in the immiscible oil. The precise mechanism by which the drug is absorbed from the oil is not fully understood, but there are a number of compounds on the market that have successfully demonstrated improved bioavailability by this route.

ORALLY DISINTEGRATING DOSAGE FORMS

One of the fastest growing categories of oral solid dosage forms is the orally disintegrating or rapidly dissolving dosage form. These dosage forms disintegrate in the mouth extremely rapidly and are thus swallowed without the need for water, making them extremely convenient to administer. The ideal properties for such formulations include

- Good stability—low sensitivity to temperature and humidity
- Robustness—requiring no special packaging
- Pleasant taste or, where the drug substance is unpalatable, delays dissolution of the drug until it reaches the stomach
- Ability to achieve a high drug loading

The first commercially available orally disintegrating dosage form was Zydis, a proprietary technology that involved filling solutions of the drug and excipients into blister packs and lyophilizing. This produced a porous wafer that rapidly dissolved when placed on the tongue. While this technology has been successfully applied to a number of products, there are limitations, particularly the amount of drug that can be incorporated into a formulation, which is typically less than 50 mg. The process also requires specialized equipment and protective packaging, as the wafers are very fragile.

The patient acceptability of the Zydis preparations prompted the development of a number of alternative technologies that have attempted to circumvent the intellectual property of Zydis or address one or more of its limitations.

The most productive approach to developing oral disintegrating tablets has been to utilize existing tableting technology. The two main approaches have been to produce softly compressed tablets that require protective packaging and to optimize the disintegration properties by careful selection of disintegrants. Novel approaches include the use of spinning sugars to produce a candy floss-type structure that can be compressed into tablets and the manufacture of porous structures using 3D printing techniques.

An alternative approach that is gaining acceptance in the over-the-counter (OTC) markets is the use of rapidly dissolving films. Initially used as a delivery device for breath fresheners, a number of drugs are now being formulated in films. The films can be prepared by one (or a combination) of the following processes; solvent casting, semisolid casting, hot melt extrusion, or rolling. The films possess certain advantages over orally disintegrating tablets including portability and cost effectiveness but do themselves have limitations, the principal one being the drug loading that can be achieved.

SUMMARY

This chapter has summarized some of the key aspects of powder technology that are important to the development of the principal solid dosage forms, tablets, and capsules. Space restrictions have prevented this from being a very detailed review, and there are many specific types of tablets that have not been discussed at all. The area of solid dosage forms is very well served by the literature, and those interested in studying the subject area further are encouraged to consult the texts listed in the reference section.

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