PHARMACEUTICAL MANUFACTURING HANDBOOK

Production and Processes

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Drug substances are most frequently administered as solid dosage formulations, mainly by the oral route. The drug substance's physicochemical characteristics, as well the excipients added to the formulations, all contribute to ensuring the desired therapeutic activity. Tablets and capsules are the most frequently used solid dosage forms, have been in existence since the nineteenth century, and are unit dosage forms, comprising a mixture of ingredients presented in a single rigid entity, usually containing an accurate dose of a drug. There are other types of solid dosage forms designed to fulfill specific delivery requirements, but they are generally intended for oral administration and for systemic delivery. The major solid oral dosage form is the tablet, and these can range from relatively simple, single, immediate-release dosage forms to complex modified-release systems. Tablets offer advantages for both patients and manufacturers (Table 1). Most tablets are intended to be swallowed whole and to rapidly disintegrate and release drug in the gastrointestinal tract. Tablets are classified by their route of administration or their function, form, or manufacturing process. For example, some tablets are designed to be placed in the oral cavity and to dissolve there or to be chewed before swallowing, and there are many kinds of formulation designed for sustained or controlled release (Table 2).

Solid dose formulations, including tablets, must have the desired release properties coupled with manufacturability and aesthetics and must involve rational formulation design. The dose of the drug and its solubility are important considerations

TABLE 1 Advantages of Tablets as a Dosage Form

Easy to handle
Variety of manufacturing methods
Can be mass produced at low cost
Consistent quality and dosing precision
Can be self-administered
Enhanced mechanical, chemical, and microbiological stability compared to liquid dosage forms
Tamperproof
Lend themselves to adaptation for other profiles, e.g., coating for sustained release

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TABLE 2 Types of Solid Dosage Form

Formulation type	Description
Immediate-release tablet/capsule	Intended to release the drug immediately after administration
Delayed-release tablet/capsule	Drug is not released until a physical event has occurred, e.g., change in pH
Sustained-release tablet/capsule	Drug is released slowly over extended time
Soluble tablets	Tablet is dissolved in water prior to administration
Dispersible tablet	Tablet is added to water to form a suspension prior to administration
Effervescent tablet	Tablet is added to water, releasing carbon dioxide to form a effervescent solution
Chewable tablet	Tablet is chewed and swallowed
Chewable gum	Formulation is chewed and removed from the mouth after a directed time
Buccal and sublingual tablets	Tablet is placed in the oral cavity for local or systemic action
Orally disintegrating tablet	Tablet dissolves or disintegrates in the mouth without the need for water
Lozenge	Slowly dissolving tablet designed to be sucked
Pastille	Tablet comprising gelatin and glycerine designed to dissolve slowly in the mouth
Hard gelatin capsule	Two-piece capsule shell that can be filled with powder, granulate, semisolid or liquid
Soft gelatin capsule (softgel)	One-piece capsule containing a liquid or semisolid fill

in the design of the formulation as are the type of dosage form and its method of preparation.

4.1.1 BIOPHARMACEUTICS CLASSIFICATION SYSTEM

Dissolution of the drug must occur before or on reaching the absorption site before absorption can occur, and generally water-soluble drugs do not exhibit formulation difficulties. For poorly water-soluble drugs, the absorption rate may be dictated by the dissolution rate, and, if dissolution is slow, bioavailability may be compromised. The solubility of a drug should, therefore, be considered along with its dose when designing formulations, and unsuitable biopharmaceutical properties is the major reason for the failure of new drugs.

In 1995, the Biopharmaceutics Classification System (BCS) was devised to classify drugs based on their aqueous solubility and intestinal permeability [1]. According to the BCS, drug substances are classified as follows [2]:

Class I: high permeability, high solubility
Class II: high permeability, low solubility
Class III: low permeability, high solubility
Class IV: low permeability, low solubility

A dose solubility volume can be defined for all drugs (i.e., the volume required to dissolve the dose). A drug substance is considered highly soluble when the highest dose strength is soluble in ≤250 mL water over a pH range of 1–7.5. A drug substance is considered highly permeable when the extent of absorption in humans is determined to be ≥90% of an administered dose, based on mass balance or in comparison to an intravenous reference dose. A drug product is considered to be rapidly dissolving when ≥85% of the labeled amount of drug substance dissolves within 30 min using U.S. Pharmacopeia (USP) apparatus I or II in a volume of ≤900 mL buffer solutions.

It was recognized that dissolution rate has a negligible impact on bioavailability of highly soluble and highly permeable (BCS class I) drugs when dissolution of their formulation is sufficiently rapid. As a result, various regulatory agencies including the U.S. Food and Drug Administration (FDA) now allow bioequivalence of formulations of BCS class I drugs to be demonstrated by in vitro dissolution (often called a biowaiver) [3]. Therefore, one of the goals of the BCS is to recommend a class of immediate-release (IR) solid oral dosage forms for which bioequivalence may be assessed based on in vitro dissolution tests.

4.1.2 SYSTEMATIC FORMULATION DEVELOPMENT

Systematic development approaches are needed to gather a full and detailed understanding of marketable formulations in order to satisfy the requirements of regulatory bodies and to provide a research database. Efficient experimental design using in-house or commercial software packages can ensure quality while avoiding expensive mistakes and lost time. Information from various categories such as the properties of the drug substance and excipients, interactions between materials, unit operations, and equipment are required [4]. Design of experiments (DOE) and statistical analysis have been applied widely to formulation development. Using DOE facilitates evaluation of all formulation factors in a systematic and timely manner to optimize the formulation and manufacturing process. Abbreviated excipient evaluation techniques such as Plackett–Burman design can be applied to minimize the number of experiments and identify critical components or processes. Optimization processes can then be applied. When the formulation and manufacturing processes of a pharmaceutical product are optimized by a systematic approach, the scale-up and processes validation can be very efficient because of the robustness of the formulation and manufacturing process.

Innovations in statistical tools such as multivariate analysis, artificial intelligence, and response surface methodology have enabled rational development of formulations, and such methods allow formulators to identify critical variables without having to test each combination.

4.1.3 STANDARD AND COMPRESSED TABLETS

The simplest tablet formulations are uncoated products that are made by direct compression or compression following wet or dry granulation. They are a versatile drug delivery system and can be intended for local action in the gastrointestinal

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(GI) tract or for systemic effects. General design criteria for tablets are accuracy and uniformity of drug content, stability of the drug candidate and the formulation, optimal dissolution and availability for absorption (whether immediate or extended release), and patient acceptability in terms of organoleptic properties and appearance. Flocculant, low-density drugs can be difficult to compress and formulate into tablets. This is a particular issue with drugs of low potency. Also some poorly water-soluble, poorly permeable drugs or highly metabolized drugs cannot be given this way. Additionally, local irritant effects can be harmful to the mucosa of the GI tract.

Tablets are a popular dosage form due to their simplicity and economy of manufacture, relative stability, and convenience in packaging, shipping, and storage. For the patient, uniformity of dose, blandness of taste, and ease of administration ensure their popularity. Thus, the purpose of the formulation and the identification of suitable excipients are of primary importance in the development of a successful formulation. A well-designed formulation should contain, within limits, the stated quantity of active ingredient, and it should be capable of releasing that amount of drug at the intended rate and site. Tablets need to be strong enough to withstand the rigors of manufacture, transport, and handling, and they need to be of acceptable size, taste, and appearance. A typical manufacturing process for a tablet product includes weighing, milling, granulation and drying, blending and lubrication, compression, and coating. Each processing step involves several process parameters. For a given formulation, all processing steps should be thoroughly evaluated so that a robust manufacturing process can be defined, and DOE can be applied effectively to optimize this process.

Direct compression is a simple process being more economical and less stressful to ingredients in terms of heat and moisture, However, there are limitations governed by the physical properties of the ingredients, and raw materials must be carefully controlled. It is difficult to form directly compressed tablets containing high-dose and poorly compactible drugs. Granulation can be employed to improve the compaction characteristics of the powder. Granulation can also improve flow properties and reduce the tendency for segregation of the mix due to a more even particle size and bulk density. Granules can be produced by either wet or dry methods based on the stability of the drug and excipients.

Although the basic mechanical process of producing tablets by compression has not changed, there has been much work on improving tableting technology [5]. Understanding of the physical and mechanical properties of powders and the compaction process has improved and will continue to improve product design while increases in the speed and uniformity of action of tableting presses improve the process.

4.1.4 EXCIPIENTS IN SOLID DOSE FORMULATIONS

In addition to the active ingredients, solid oral dosage forms will also contain a range of substances called excipients. The role of excipients is essential in ensuring that the manufacturing process is successful and that the quality of the resultant formulation can be guaranteed. The appropriate selection of excipients and their relative concentrations in the formulation is critical in development of a successful product.

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TABLE 3 Excipients Used in Solid Dose Formulations

Excipient Category	Examples
Fillers/diluents	Lactose, sucrose, glucose, microcrystalline cellulose
Binders	Polyvinyl pyrrolidone, starch, gelatin, cellulose derivatives
Lubricants	Magnesium stearate, stearic acid, polyethylene glycol, sodium chloride
Glidants	Fine silica, talc, magnesium stearate
Antiadherents	Talc, cornstarch, sodium dodecylsulfate
Disintegrants and superdisintegrants	Starch, sodium starch glycollate, cross-linked polyvinyl pyrrolidone
Colorants	Iron oxide, natural pigments
Flavor modifiers	Mannitol, aspartame

Although they are often categorized as inert, preformulation studies can determine the influence of excipients on stability, bioavailability, and processability. Excipients are categorized into groups according to their main function, although some may be multifunctional, and examples of common excipients used in the manufacture of tablets and capsule are detailed in Table 3.

4.1.4.1 Diluents

An inert substance is frequently added to increase the bulk of a tablet for processing and handling. The lower weight limit for formulation of a tablet is usually 50 mg. Ideally, diluents should be chemically inert, nonhygroscopic, and hydrophilic. Having an acceptable taste is important for oral formulations, and cost is always a significant factor in excipient selection.

Lactose is a common diluent in both tablets and capsules, and it fulfils most of these criteria but is unsuitable for those who are lactose intolerant. Various lactose grades are commercially available which have different physical properties such as particle size distribution and flow characteristics. This permits the selection of the most suitable material for a particular application. Usually, fine grades of lactose are used for preparation of tablets by wet granulation or when milling during processing is carried out, since the fine size permits better mixing with other formulation ingredients and facilitates more effective action of the binder [6].

Diluents for direct compression formulations are often subject to prior processing to improve flowability and compression, for example, amorphous lactose, but this can contribute to reduced stability especially under high-humidity conditions when reversion to the crystalline form is more likely [6].

Microcrystalline cellulose (Avicel) is purified partially depolymerized cellulose, prepared by treating α-cellulose with mineral acids. In addition to being used as a filler, it is also used as dry binder and disintegrant in tablet formulations. Depending on the preparation conditions, it can be produced with a variety of technical specifications depending on particle size and crystallinity. It is often used as an excipient in direct compression formulations but can also be incorporated as a diluent for tablets prepared by wet granulation, as a filler for capsules and for the production of spheres.

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Diluents, although commonly presumed inert, do have the ability to influence the stability or bioavailability of the dosage form. For example, dibasic calcium phosphate (both anhydrous and dihydrate forms) is the most common inorganic salt used as a filler–binder for direct compression. It is particularly useful in vitamin products as a source of both calcium and phosphorous. Milled material is typically used in wet-granulated or roller-compacted formulations. The coarse-grade material is typically used in direct compression formulations. It is insoluble in water, but its surface is alkaline and it is therefore incompatible with drugs sensitive to alkaline pH. Additionally, it may interfere with the absorption of tetracyclines [7].

4.1.4.2 Binders

Binders (or adhesives) are added to formulations to promote cohesiveness within powders, thereby ensuring that the tablet remains intact after compression as well as improving the flow by forming granules. A binder should impart adequate cohesion without retarding disintegration or dissolution. Binders can be added either as a solution or as a dry powder. Binders added as dry powders are mixed with other powders prior to agglomeration, dissolving in water or solvent added during granulation, or added prior to compaction. Solution binders can be sprayed, poured, or mixed with the powder blend for agglomeration and are generally more effective, but further dry binder can be added prior to tableting. Starch, gelatin, and sugars are used along with gums, such as acacia and sodium alginate, and are used at concentrations between 2 and 10% w/w. Celluloses and polyvinyl pyrrolidone (PVP) are also utilized, often as dry binders.

4.1.4.3 Lubricants

Lubricants can reduce friction between the tablet and the die wall during compression and ejection by interposing an intermediate film of low shear strength at the interface between the tablet and the die wall. The best lubricants are those with low shear strength but strong cohesive tendencies perpendicular to the line of shear [8]. The hydrophobic stearic acid and stearic acid salts, primarily magnesium stearate, are the most widely used and are included at concentrations less than 1% w/w in order to minimize any deleterious effects on disintegration or dissolution. They should be added after the disintegrant to avoid coating it and preferably at the final stage prior to compression to ensure mixing time is kept to a minimum. Hydrophilic lubricants such as polyethylene glycols (PEGs) and lauryl sulfates can be used to redress the issues with dissolution but may not be as efficient as their hydrophobic counterparts.

4.1.4.4 Glidants and Antiadherents

Like lubricants, glidants are fine powders and may be required for tablet compression at high production speeds to improve the flow properties of the material into the die or during initial compression stages. They are added in the dry state immediately prior to compression and, by virtue of their low adhesive potential, reduce the friction between particles. Colloidal silica is popular, as are starches and talc.

Antiadherents can also be added to a formulation that is especially prone to sticking to the die surface (or picking). Water-insoluble lubricants such as magnesium stearate can be used as antiadherents, as can talc and starch.

4.1.4.5 Disintegrants

Disintegrants are added to a formulation to overcome the cohesive strength imparted during compression, thus facilitating break up of the formulation in the body and increasing the surface area for dissolution. They can be either intragranular, extragranular, or both, and there is still a lack of understanding concerning their precise mechanism of action. On contact, disintegrants can draw water into the tablet, swelling and forcing the tablet apart. Starch, a traditional and still widely used disintegrant, will swell when wet, although it has been reported that its disintegrant action could be due to capillary action [6]. Levels can be increased beyond the normal 5% w/w to 15–20% w/w if a rapid disintegration is required. Surfactants can also act as disintegrants promoting wetting of the formulation, and sodium lauryl sulfate can be combined with starch to increase effectiveness.

Tablet disruption following production of carbon dioxide is another mechanism used to enhance disintegration. This uses a mixture of sodium bicarbonate and a weak acid such as citric acid or tartaric acid and is exploited for effervescent formulations.

4.1.4.6 Superdisintegrants

Compared to the more traditional starch, newer disintegrants are effective at much lower levels and comprise three groups: modified starches, modified cellulose, and cross-linked povidone. Their likely mechanism of action is a combination of proposed theories including water wicking, swelling, deformation recovery, repulsion, and heat of wetting [9]. Superdisintegrants are so called because of the relatively low levels required (2–4% w/w). Sodium starch glycollate (Primojel, Explotab) is made by cross-linking potato starch and can swell up to 12-fold in less than 30 s. Crospovidone is completely insoluble in water, although it rapidly disperses and swells in water, but does not gel even after prolonged exposure. It rapidly exhibits high capillary activity and pronounced hydration capacity with little tendency to form gels and has a greater surface area–volume ratio compared to other disintegrants. Micronized versions are available to improve uniformity of mix. Croscarmellose sodium, a cross-linked polymer of carboxymethyl cellulose sodium is also insoluble in water, although it rapidly swells to 4–8 times its original volume on contact with water [6].

4.1.4.7 Added Functionality Excipients

Adverse physiochemical and mechanical properties of new chemical entities prove challenging for formulation development. There is an increasing demand for faster and more efficient production processes. Also, biotechnological developments and various emerging protein-based therapies are broadening the definition for excipient products. Although the description of excipients from inactive ingredients is shifting toward functionally active materials and will continue to grow in this area, the intro-

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duction of improved versions of long-existing excipients is probably the more successful development. New single-component and coprocessed products have been introduced, for example, filler–binders. In addition, there have been advances in the understanding of how such substances act and hence how they can be optimally designed. Excipients for use in direct compression product forms or physically or chemically modified excipients used in relatively new drug delivery systems, such as patches or inhalation systems, are examples of these developments.

4.1.4.8 Colorants

Colorants are frequently used in uncoated tablets, coated tablets, and hard and soft gelatin capsules. They can mask color changes in the formulation and are used to provide uniqueness and identity to a commercial product. Concerns over the safety of coloring agents in formulations generally arise from adverse effects in food substances. Colorants are therefore subject to regulations not associated with other pharmaceutical excipients. Legislation specifies which colorants may be used in medicinal products and also provides for purity specifications. The number of permitted colors has decreased in recent years, and a list of approved colorants allowed by regulatory bodies can vary from country to country.

Colorants can be divided into water-soluble dyes and water-insoluble pigments. Some of the insoluble colors or pigments can also provide opacity to tablet coatings or gelatin shells, which can promote stability of light-sensitive active materials. Pigments such as the iron oxides, titanium dioxide, and some of the aluminum lakes are especially useful for this purpose.

Water-soluble dyes are usually incorporated within the granulation process to ensure even distribution throughout the formulation, but there can be an uneven distribution due to migration of the dye during drying processes. Therefore, water-soluble dyes can also be adsorbed into a carrier such as starch or lactose and dry blended prior to the final mix. Water-insoluble pigments are more popular in direct compression and are dry blended with the other ingredients.

Lakes are largely water-insoluble forms of common synthetic water-soluble dyes and are prepared by adsorbing the sodium or potassium salt of a dye onto a very fine substrate of hydrated alumina, followed by treatment with a further soluble aluminum salt. The lake is then purified and dried. Lakes are frequently used in coloring tablet coatings since they are more stable and have greater opacity than a water-soluble dye [6].

4.1.4.9 Interactions and Safety of Excipients

Because there is such a wide selection available, rational choice of the necessary excipients and their concentration is required. Consideration must also be given to cost, reliability, availability, and international acceptability. Although generally considered inert, formulation incompatibility of excipients is also necessary. Lactose, for example, can react with primary and secondary amines via its aldehyde group by Maillaird condensation reaction [6], and calcium carbonate is incompatible with acids due to acid–base chemical reaction and with tetracyclines due to complexation. Additionally, excipients can contribute to the instability of the active substance through moisture distribution.

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Despite the importance of drug–excipient compatibility testing, there is no generally accepted method available for this purpose. After identification of any major known incompatibilities, a compatibility screen needs to be proposed. Issues such as sample preparation, storage conditions, and methods of analysis should be addressed and factorial design applied to reduce the number if tests required. Drug–excipient compatibility studies can be performed with minimal amounts of materials. Usually, small amounts of each material are weighed into a glass vial, in a ratio representative of the expected ratio in the formulation. The vials can be sealed as is or with additional water, either in an air environment or oxygen-free (nitrogen head space) environment, and stored in the presence or absence of ambient light, at various temperatures. Factorial or partial factorial design experiments can be set up to determine important binary and multiple component interaction factors. This information helps determine which excipients should be avoided and whether oxidation or light instability in the formulation is a consideration. Controls consisting of the active pharmaceutical ingredient (API) alone in the various conditions also should be run to determine whether the API is susceptible alone or must have the mediating excipient or water additives for instability.

4.1.5 COATED TABLETS

Tablets are often coated to protect the drug from the external environment, to mask bitter tastes, add mechanical strength, or to enhance ease of swallowing. A coating can also be used for aesthetic or commercial purposes, improving product appearance and identity.

4.1.5.1 Sugar-Coated Tablets

Sugar coating can be beneficial in masking taste, odors, and colors. It is useful in protecting against oxidation, and sugar coating was once very common due to its aesthetic results and cheapness of materials. Use has declined in recent years due to the complexity of the process and skills required, but advances in technology have led to a resurgence in popularity. Typical excipients used are sucrose (although this can be substituted with low-calorie alternatives), fillers, flavors, film formers, colorants, and surfactants. It is usually carried out in tumbling coating pans and comprises several stages.

The first sealing stage uses shellac or cellulose acetate phthalate, for example, to prevent moisture from reaching the tablet core. This has to be kept to a minimum to prevent impairment of drug release. The subcoating is an adhesive coat of gum (such as acacia or gelatin) and sucrose used to round off the edges, and the tablets can be dusted with substances such as kaolin or calcium carbonate to harden the coating. A smoothing coat is built up in layers using 70% v/v sucrose syrup and often opacifiers such as titanium dioxide, and the tablets are dried between each application. A colorant is added to the final few layers and followed with a final polishing step which can make further embossing difficult. The coating is relatively brittle, prone to chipping or cracking, and there is a substantial increase in weight, up to 50%, and size of the product.

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4.1.5.2 Compression Coating and Layered Tablets

A coating can be applied by compression using specially designed tablet presses. The same process can be used to produce layered tablets which can comprise two or even three layers if complete separation of the ingredients is required. This process is used when physical separation of ingredients is desired due to incompatibility or to produce a repeat-action product. The formulation can also be designed to provide an immediate and a slow-release component. Release rates can be controlled by modification of the geometry, the composition of the core, and the inclusion of a membrane layer.

The technique involves using a preliminary compression step to produce a relatively soft tablet core which is then placed in a large die containing coating material. Further coating material is added and the content compressed. A similar light compression is used for the production of layers and a final main compression step used to bind the layers together.

4.1.5.3 Film-Coated Tablets

Film coating, although most often applied to tablets, can also be used to coat other formulations including capsules. Film coating imparts the same general characteristics as sugar coating but weight gain is significantly less (typically up to 5%), it is easier to automate, and it has capacity to include organic solvents if required. The main methods involved are modified conventional coating pans, side-vented pans, and fluid-bed coating. Celluloses are often used as film-forming polymers, as detailed in Table 4, and usually require addition of a compatible plasticizer as glass transition temperatures are higher than the temperatures used in the process. Polyethylene glycol, propylene glycol, and glycerol are commonly used, and colorants and opacifiers can also be added to the coating solution. Specialist coatings such as Opadry fx and Opaglos 2 can be used to give a high gloss finish to improve brand identity and consumer recognition.

4.1.5.4 Tablet Wrapping or Enrobing[1]

Recent innovations in tablet coating include the use of gelatin and non-animal-derived coatings for tablets that require formulation of a pre-formed film that is then used to encapsulate the product (e.g., Banner's Soflet Gelcaps or Bioprogress' Nrobe technology). The coated formulations are tamper evident and can be designed with different colors for branding purposes. They are reported to be preferred by patients due to their ease of swallowing and superior taste- and odor-masking properties. An alternative is the Press-fit Geltabs system, which uses a high-gloss gelatin capsule shell to encapsulate a denser caplet formulation.

4.1.6 HARD AND SOFT GELATIN CAPSULES

Capsules are solid oral dosage forms in which the drug is enclosed within a hard or soft shell. The shell is normally made from gelatin and results in a simple, easy-to-swallow formulation with no requirement for a further coating step. They can be

[1]See http://www.banpharm.com/technologiesSofletGelcap.cfm and http://www.fmcmagenta.com/NRobe/tabid/145/Default.aspx.

TABLE 4 Polymers Commonly Used in Film Coating of Tablets

Polymer	Soluble in	Description
Methylcellulose (MC)	Cold water, GI fluids, and organic solvents	Low-viscosity grades best for aqueous films
Ethylcellulose (EC)	Organic solvents and GI fluids (insoluble in water)	Used in combination with water-soluble agents for immediate release
Hydroxyethyl cellulose (HEC)	Water and GI fluids	Similar to MC with clear solutions
Hydroxypropyl cellulose (HPC)	Cold water, GI fluids, and polar solvents	Results in a tacky coat and used in combination to promote adhesion
Hydroxypropylmethyl cellulose (HPMC)	Cold water, GI fluids, and alcohols	Excellent film former, low-viscosity grades best
Sodium carboxymethyl cellulose	Water and polar solvents	Cannot be used if presence of moisture is a problem
Methylhydroxyethyl cellulose (MHEC)	Water and GI fluids	Similar to HPMC but less soluble in organic solvents
Povidone (PVP)	Water, GI fluids, alcohol, and isoproplyl alcohol (IPA)	Can lead to tackiness during drying, often brittle and hygroscopic
PEGs	Water, GI fluids, some organic solvents	High molecular weights best for film forming and low molecular weights used as plasticizer; can be waxy
Enteric coatings such as poly(methacrylates) or cellulose acetate phthalate	Soluble at elevated pHs	Used for delayed-release formulations

Source: Adapted from refs. 5 and 10.

either hard or soft depending on the nature of the capsule shell, with soft capsules possessing a flexible, plasticized gelatin film. Hard gelatin capsules are usually rigid two-piece capsules that are manufactured in one procedure and packed in another totally separate operation, whereas the formulation of soft gelatin capsules is more complex but all steps are integrated.

There is a growing interest in using non-animal-derived products for formulation of the capsule shells to address cultural, religious, and dietary requirements. HPMC (e.g., V-caps, Quali-VC, Vegicaps) and pullulan shells (NPCaps) and starch are alternatives.

4.1.6.1 Hard-Shell Gelatin Capsules

Although the challenges of powder blending, homogeneity, and lubcricity exist for capsules as for tablets, they are generally perceived to be a more flexible formulation as there is no requirement for the powders to form a robust compact. This means that they may also be more suitable for delivery of granular and beadlike formulations, fragile formulations that could be crushed by the normal compaction step. They are commonly employed in clinical trials due to the relative ease of blinding and are useful for taste masking.

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Capsules are usually more expensive dosage forms than an equivalent tablet formulation due to the increased cost of the shells and the slower production rates. Even with modern filling equipment, the filling speeds of capsule machines are much slower than tablet presses. However, increased costs can be offset by avoiding a granulation step. Capsules, although smoother and easy to swallow, also tend to be larger than corresponding tablet formulations, potentially leading to retention in the esophagus. Humidity needs to be considered during manufacture and storage, with moisture leading to stickiness and desiccation causing brittleness. Cross-linking of gelatin in the formulation can also lead to dissolution and bioavailability concerns.

Capsule excipients are similar to those required for formulation of tablets and include diluents, binders, disintegrants, surfactants, glidants, lubricants, and dyes or colorants. The development of a capsule formulation follows the same principles as tablet development, and consideration should be given to the same BCS issues. The powder for encapsulation can comprise simple blends of excipients or granules prepared by dry granulation or wet granulation. There is a reduced requirement for compressibility, and often the flow properties are not as critical as in an equivalent tablet formulation. The degree of compressibility required is the major difference, and capsules can therefore be employed when the active ingredient does not possess suitable compression characteristics.

4.1.6.2 Manufacture of Hard Gelatin Shells

Gelatin is a generic term for a mixture of purified protein fractions obtained either by partial acid hydrolysis (type A gelatin) or by partial alkaline hydrolysis (type B gelatin) of animal collagen. Type A normally originates from porcine skin while B is usually derived from animal bones, and they have different isoelectric points (7.0–9.0 and 4.8–5.0, respectively) [6]. The protein fractions consist almost entirely of amino acids joined together by amide linkages to form linear polymers, varying in molecular weight from 15,000 to 250,000. Gelatin can comprise a mixture of both types in order to optimize desired characteristics, with bone gelatin imparting firmness while porcine skin gelatin provides plasticity. Gelatin Bloom strength is measured in a Bloom gelometer, which determines the weight in grams required to depress a standard plunger in a 6.67% w/w gel under standard conditions. Bloom strength and viscosity are the major properties of interest for formulation of capsules, and Bloom strength of 215–280 is used in capsule manufacture.

Gelatin is commonly used in foods and has global regulatory acceptability, is a good film former, is water soluble, and generally dissolves rapidly within the body without imparting any lag effect on dissolution. Gelatin capsules are strong and robust enough to withstand the mechanical stresses involved in the automated filling and packaging procedures.

In addition to gelatin, the shells may contain colorants, opacifiers, and preservatives (often parabens esters). There are eight standard capsule sizes, and the largest capsule size considered suitable for oral use is size 0 (Table 5).

To manufacture the shells, pairs of molds, for the body and the cap, are dipped into an aqueous gelatin solution (25–30% w/w), which is maintained at about 50 °C in a jacketed heating pan. As the pins are withdrawn, they are rotated to distribute the gelatin evenly and blasted with cool air to set the film. Drying is carried out by

TABLE 5 Capsule Size and Corresponding Volume or Weight of Fill

Size	Volume (mL)	Fill weight[a] (g)
000	1.37	1.096
00	0.95	0.760
0	0.68	0.544
1	0.50	0.400
2	0.37	0.296
3	0.30	0.240
4	0.21	0.168
5	0.13	0.104

Source: Adapted from http://capsugel.onlinemore.info/download/BAS192-2002.pdf.

[a]Assumes a powder density of 0.8 g/cm^3.

passing dry air over the shell as heating temperatures are limited due to the low melting point of gelatin. The two parts are removed from the pins, trimmed, and joined using a prelock mechanism. The external diameter of the body is usually wider at the open end than the internal diameter of the cap to ensure a tight fit. They can be made self-locking by forming indentations or grooves on the inside of both parts so that when they are engaged, a positive interlock is formed (e.g., Posilok, Conicap, Loxit).

Alternatively, they may be hermetically sealed using a band of gelatin around the seam between the body and the cap (Qualicaps). This can be applied without the application of heat and provide a tamper-evident seal. LEMS (liquid encapsulation microspray sealing) used in Licaps is a more elegant seal in which sealing fluid (water and ethanol) is sprayed onto the joint between the cap and body of the capsule. This lowers the melting point of gelatin in the wetted area. Gentle heat is then applied which fuses the cap to the body of the Licaps capsule. The moisture content of manufactured shells is 15–18% w/w and levels below 13% will result in problems with the capsule filling machinery. Therefore, capsules are stored and filled in areas where relative humidity is controlled to between 30 and 50%.

4.1.6.3 Hard-Gelatin Capsule Filling

The filling material must be compatible with the gelatin shell and, therefore, deliquescent or hygroscopic materials cannot be used. Conversely, due the moisture content in the capsule shells, they cannot be used for moisture-sensitive drugs. All ingredients need to be free of even trace amounts of formaldehyde to minimize cross-linking of gelatin.

Powders and granules are the most common filling materials for hard-shell gelatin capsules, although pellets, tablets, pastes, oily liquids, and nonaqueous solutions and suspensions have been used. Filling machines are differentiated by the way they measure the dose of material and range in capacity from bench-top to high-output, industrial, fully automated machines. Those that rely on the volume of the shell are known as capsule dependent, whereas capsule-independent forms measure the quantity to be filled in a separate operation. The simplest dependent method of filling is leveling where powder is transferred directly from a hopper to the capsule

TABLE 6 Liquid Excipients Compatible with Hard Gelatin Capsules

Peanut oil	Paraffin oil
Hydrogenated peanut oil	Cetyl alchohol
Castor oil	Cetostearyl alcohol
Hydrogenated castor oil	Stearyl alcohol
Fractionated coconut oil	Stearic acid
Corn oil	Beeswax
Olive oil	Silica dioxide
Hydrogenated vegetable oil	Polyethylene glycols
Silicone oil	Macrogol glycerides
Soya oil	Poloxamers

Source: Adapted from http://www.capsugel.com/products/licaps_oil_chart.php.

body, aided by a revolving auger or vibration. Additional powder can be added to fill the space arising, and the fill weight depends on the bulk density of the powder and the degree of tamping applied.

Most automated machinery is of the independent type and compresses a controlled amount of powder using a low compression force (typically 50–200 *N*) to form a plug. Most are piston-tamp fillers and are dosator or dosing disk machines. The powder is passed over a dosing plate containing cavities slightly smaller than the capsule diameter, and powder that falls into the holes is tamped by a pin to form a plug. This can be repeated until the cavity is full and the plugs (or slugs) are ejected into the capsule shells. The minimum force required to form a plug should be used to reduce slowing of subsequent dissolution.

In the dosator method, the plug is formed within a tube with a movable piston that controls the dosing volume and applies the force to form the plug. The dose is controlled by the dimensions of the dosator, the position of the dosator in the powder bed, and the height of the powder bed. Fundamental powder properties to ensure even filling are good powder flow, lubricity, and compressibility. The auger or screw method, now largely surpassed, uses a revolving archimedian screw to feed powder into the capsule shell.

A liquid fill can be useful when manufacturing small batches if limited quantities of API are available. Liquid fills also offer improved content uniformity for potent, low-dose compounds and can reduce dust-related problems arising with toxic compounds. Two types of liquid can be filled into hard gelatin capsules: nonaqueous solutions and suspensions or formulations that become liquid on application of heat or shear stress. These require hoppers with heating or stirring systems. For those formulations that are liquid at room temperature, the capsule shells need to be sealed after filling to prevent leakage of the contents and sticking of the shells. It is essential to ensure the liquid is compatible with the shell (Table 6).

4.1.6.4 Soft-Gelatin Capsules

Soft gelatin capsules are hermetically sealed one-piece capsules containing a liquid or a semisolid fill. Like liquid-filled hard capsules, although the drug is presented in a liquid formulation, it is enclosed within a solid, thus combining the attributes

of both. Soft gelatin capsules (softgels) offer a number of advantages including improved bioavailability, as the drug is presented in a solubilized form, and enhanced drug stability. Consumer preference regarding ease of swallowing, convenience, and taste can improve compliance, and they offer opportunities for product differentiation via color, shape, and size and product line extension. The softgels can be enteric coated for delayed release. They are popular for pharmaceuticals, cosmetics, and nutritional products, but highly water-soluble drugs and aldehydes are not suitable for encapsulation in softgels. Formulations are tamper evident and can be used for highly potent or toxic drugs. However, they do require specialist manufacture and incur high production costs.

4.1.6.5 Manufacture of Soft Gelatin Capsules

The shell is primarily composed of gelatin, plasticizer, and water (30–40% wet gel), and the fill can be a solution or suspension, liquid, or semisolid. The size of a softgel represents its nominal capacity in minims, for example, a 30 oval softgel can accommodate 30 minims (or 1.848 cm^3). Glycerol is the major plasticizer used, although sorbitol and propylene glycol can also be used. Other excipients are dyes, pigments, preservatives, and flavors. Up to 5% sugar can be added to give a chewable quality. Most softgels are manufactured by the process developed by Scherer [11]. The glycerol–gelatin solution is heated and pumped onto two chilled drums to form two separate ribbons (usually 0.02–0.04 in. thick) which form each half of the softgel. The ribbons are lubricated and fed into the filling machine, forcing the gelatin to adopt the contours of the die. The fill is manufactured in a separate process and pumped in, and the softgels are sealed by the application of heat and pressure. Once cut from the ribbon, they are tumble-dried and conditioned at 20% relative humidity.

Fill solvents are selected based on a balance between adequate solubility of the drug and physical stability. Water-miscible solvents such as low-molecular-weight PEGs, polysorbates, and small amounts of propylene glycol, ethanol, and glycerin can be used. Water-immiscible solvents include vegetable and aromatic oils, aliphatic, aromatic, and chlorinated hydrocarbons, ethers, esters, and some alcohols. Emulsions, liquids with extremes of pH (<2.5 and >7.5), and volatile components can cause problems with stability, and drugs that do not have adequate stability in the solvents can be formulated as suspensions. In these instances, the particle size needs to be carefully controlled and surfactants can be added to promote wetting.

Vegicaps soft capsules from Cardinal Health are an alternative to traditional softgels, containing carageenan and hydroxyproyl starch. As with traditional soft gelatin capsules, the most important packaging and storage criterion is for adequate protection against extremes of relative humidity. The extent of protection required also depends on the fill formulation and on the anticipated storage conditions.

4.1.6.6 Dissolution Testing of Capsules

In general, capsule dosage forms tend to float during dissolution testing with the paddle method. In such cases, it is recommended that a few turns of a wire helix around the capsule be used [12]. Inclusion of enzymes in the dissolution media must be considered on case-by-case basis. A Gelatin Capsule Working Group (including

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participants from the FDA, industry, and the USP) was formed to assess the noncompliance of certain gelatin capsule products with the required dissolution specifications and the potential implications on bioavailability [13]. The working group recommended the addition of a second tier to the standard USP and new drug and abbreviated new drug applications (NDA/ANDA) dissolution tests: the incorporation of enzyme (pepsin with simulated gastric fluid and pancreatin with simulated intestinal fluid) into the dissolution medium. If the drug product fails the first tier but passes the second tier, the product's performance is acceptable. The two-tier dissolution test is appropriate for all gelatin capsule and gelatin-coated tablets and the phenomenon may have little significance in vivo.

4.1.7 EFFERVESCENT TABLETS

Effervescence is the reaction in water of acids and bases to produce carbon dioxide, and effervescent tablets are dissolved or dispersed in water before administration. Advantages of effervescent formulations over conventional formulations are that the drug is usually already in solution prior to ingestion and can therefore have a faster onset of action. Although the solution may become diluted in the GI tract, any precipitation should be as fine particles that can be readily redissolved. Variability in absorption can also be reduced. Formulations can be made more palatable and there can be improved tolerance after ingestion. Thus, the types of drugs suited to this formulation method are those that are difficult to digest or are irritant to mucosa. Analgesics such as paracetamol and aspirin and vitamins are common effervescent formulations. The inclusion of buffering agents can aid stability of pH-sensitive drugs. There is also the opportunity to extend market share and to deliver large doses of medication.

Effervescents comprise a soluble organic acid and an alkali metal carbonate salt. Citric acid is most commonly used for its flavor-enhancing properties. Malic acid imparts a smoother after taste and fumaric, ascorbic, adipic, and tartaric acids are less commonly used [14]. Sodium bicarbonate is the most common alkali, but potassium bicarbonate can be used if sodium levels are a potential issue with the formulation. Both sodium and potassium carbonate can also be employed. Other excipients include water-soluble binders such as dextrose or lactose, and binder levels are kept to a minimum to avoid retardation of disintegration. All ingredients must be anhydrous to prevent the components within the formulation reacting with each other during storage.

Lubricants such as magnesium stearate are not used as their aqueous insolubility leads to cloudy solutions and extended disintegration times. Spray-dried leucine and PEG are water-soluble alternatives [15, 16]. Both artificial and natural sweeteners are used and an additional water-soluble flavoring agent may also be required. If a surfactant is added to enhance wetting and dissolution, the addition of an antifoaming agent may also be considered [17].

4.1.7.1 Manufacture of Effervescent Tablets

Essentially, effervescent formulations are produced in the same way as conventional tablets, although due to the hygroscopicity and potential onset of the effervescence

reaction in the presence of water, environmental control of relative humidity and water levels is of major importance during manufacture. A maximum of 25% relative humidity (RH) at 25°C is required. Closed material-handling systems can be used or open systems with minimum moisture content in the ventilating air.

A dry method of granulation is preferred as no liquid is involved but may not always be possible. Wet granulation can be carried out under carefully controlled conditions using two separate granulators for the alkaline and acid components. Water can be added at 0.1–1.0% w/w, and it initiates a preeffervescent reaction. The cycle is stopped by drying, usually by transfer into a preheated fluidized-bed dryer. Fluid-bed spray granulation is a process wherein granulation and drying are simultaneous and can be useful for effervescent formulations. Water (or a binder solution) is sprayed onto the mixture, which is suspended in a stream of hot, dry air. Organic solvents can also be employed for granulation avoiding the need for water and are useful for heat-labile formulations, although complex handling equipment is required.

Effervescent formulations must contain less than 0.3% w/w water and are often quite large. Sticking due to insufficient lubrication can be overcome by adaptation of punches for external lubrication or using flat-faced punches with disks of poly (tetrafluoroethylene) (PTFE). Poor lubrication can also be the cause of poor flow characteristics, and this can be addressed by using a constant level powder feed system. The tablets should be stored in tightly closed containers or moisture-proof packs. In tube arrangements, dry air is added prior to sealing and desiccants to reduce enclosed moisture levels once the pack has been opened. Foil packaging should be heavy gauge to minimize risk of holes, and the surrounding pocket should be large enough to hold the tablets but minimize inclusion of air.

In-process quality control is of major importance for these formulations as are stability testing and stress testing of packaging. Tablet disintegration and dissolution are of prime importance, and disintegration should be carried out using representative conditions. Hardness and friability are also important as these large tablets tend to chip easily. Common areas for problems are that the packaging permits entry of water, the seal is compromised or that the excipients can react with each other.

4.1.8 LOZENGES

Lozenges are tablets that dissolve or disintegrate slowly in the mouth to release drug into the saliva. They are easy to administer to pediatric and geriatric patients and are useful for extending drug form retention within the oral cavity. They usually contain one or more ingredient in a sweetened flavored base. Drug delivery can be either for local administration in the mouth, such as anaesthetics, antiseptics, and antimicrobials or for systemic effects if the drug is well absorbed through the buccal lining or is swallowed. More traditional drugs used in this dosage form include phenol, sodium phenolate, benzocaine, and cetylpyridinium chloride. Decongestants and antitussives are in many over-the-counter (OTC) lozenge formulations, and there are also lozenges that contain nicotine (as bitartrate salt or as nicotine polacrilex resin), flurbiprofen (Strefen), or mucin for treatment of dry mouth (A.S Saliva Orthana).

Lozenges can be made by molding or by compression at high pressures, often following wet granulation, resulting in a mechanically strong tablet that can dissolve

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in the mouth. Compressed lozenges (or troches) differ from conventional tablets in that they are nonporous and do not contain disintegrant. As the formulation is designed to release drug slowly in the mouth, it must have a pleasant taste, smoothness, and mouth feel. The choice of binder, filler, color, and flavor is therefore most important. The binder is particularly important in ensuring retardation of dissolution and pleasant mouth feel. Suitable binders include gelatin, guar gum, and acacia gum. Sugars such as sucrose, dextrose, and mannitol are preferred to lactose, and xylitol is often included in sugar-free formulations. In order to ensure adequate sweetness and taste masking, artificial sweeteners including aspartame, saccharin, and sucralose are also included subject to regulatory guidelines.

Other variations include hard-candy-type and soft or chewable lozenges. Most hard-candy-type lozenges contain sugar, corn syrup, acidulant, colorant, and flavors. They are made by heating sugars and other ingredients together and then pouring the mixture into a mold. Corn syrup combined with sucrose and dextrose can form an amorphous glass suitable for such formulations [18]. Colorants can be added to enhance product appearance or to mask products of degradation. Stability and compatibility with the drug must be established along with the other excipients. Flavors tend to be complex entities, and stability or compatibility can pose major formulation challenges. Acidulants such as citric and tartaric acids are often added to enhance flavors, thus lowering pH of the formulation as low as 2.5–3.0. Addition of bases such as calcium carbonate, sodium bicarbonate, and magnesium trisilicate is common to increase pH and enhance drug stability. For example, in vivo and in vitro studies confirmed that the pH of the dissolved lozenge solution was the single most influential, readily adjustable formulation parameter influencing the activity of cetylpyridinium chloride activity in candy-based lozenges [19]. The dosage form needs a low moisture content (0.5–1.5% w/w), so water is evaporated off by boiling the sugar mixture during the compounding process, thus limiting the process to nonlabile drugs, and the manufacture requires specialized candy processing facilities. Packaging also needs to protect the formulated product from moisture and ranges from individual bunch wrapping to foil wraps.

4.1.8.1 Chewable Lozenges

Chewable lozenges are popular with the pediatric population since they are "gummy-type" lozenges. Most formulations are based on a modified suppository formula consisting of glycerin, gelatin, and water. These lozenges are often highly fruit-flavored and may have a slightly acidic taste to cover the acrid taste associated with glycerin. Soft lozenges typically comprise ingredients such as PEG 1000 or 1450, or a sugar–acacia base. Silica gel can be added to prevent sedimentation, and again this dosage form requires flavors and sweeteners to aid compliance. Soft lozenges tend to dissolve faster than gelatin bases and can be used if taste masking is not effective.

4.1.9 CHEWABLE TABLETS

Chewable tablets are designed to be mechanically disintegrated in the mouth. Potential advantages of chewable tablets are mainly concerning patient convenience and acceptance, although enhanced bioavailability is also claimed. This can be due

to a rapid onset of action as disintegrate is more rapid and complete compared to standard formulations that must disintegrate in the GI tract. The dosage form is an appealing alternative for pediatric and geriatric consumers. Chewable tablets also offer convenience for consumers, avoiding the necessity of coadministration with water, and creation of palatable formulations can increase compliance. Antacids and pediatric vitamins are often formulated as chewable tablets, but other formulations include antihistamines (Zyrtec), antimotility agents (Imodium Plus) and antiepileptic agents (Epanutin Infatabs), antibiotics (Augmentin Chewable), asthma treatments (Singulair), and analgesics (Motrin).

Constraints with these systems are that many pharmaceutical actives have an unpleasant bitter taste that can actually reduce compliance among patients. Iron salts, for example, can impart a rusty taste, and some antihistamines such as promethazine HCl can have a bitter aftertaste. As such, active formulations require very effective taste-masking strategies to provide acceptable patient tolerance and to ensure patient adherence to their pharmaceutical regimen.

Formulation factors governing design are similar to standard formulations (e.g., compactability, flow, etc.), but disintegrants are not included. Organoleptic properties are a major concern, especially in the design of products for children, and usage has been limited as formulators have encountered difficulties in achieving satisfactory sensory characteristics.

Certain diluents are beneficial in the formulation of chewable tablets by compression such as mannitol, lactose, sucrose, and sorbitol. They can aid disintegration upon chewing and can help with acceptable taste and mouth feel. Mannitol, for example, can impart a cooling or soothing sensation. Specialist excipients with improved sensory components such as mouth feel and lack of grittiness have been developed for formulation of chewable tablets. For example, Avicel CE-15 [a combination of microcrystalline cellulose (MCC) and guar gum] can reduce grittiness, leading to a creamier mouth feel and improved overall compatibility.

Citric acid, grape, raspberry, lemon, and cherry flavors are often used in chewable tablets and lozenges (Table 7). Flavoring agents are commonly volatile oils, and they can be dissolved in alcohol and then sprayed onto another excipient or granules. They are usually added immediately prior to compression to avoid loss due to their volatile nature. Dry flavors have advantages in terms of stability and ease of handling and are formed by emulsification of the flavor into an aqueous solution of a carrier followed by drying, encapsulating the flavor within the carrier. This is useful if the agent is prone to oxidation. Common carrier substances are acacia gum, starch, and maltodextrin. Sweeteners such as aspartame can also be added. Low-calorie and non-sugar-based excipients may present a marketing advantage.

Issues of taste masking for chewable formulations may be addressed by coating in wet granulation. The granulating/coating agent should form a flexible rather than

TABLE 7 Flavor Groups for Taste Types

Sweet	Vanilla, grape, maple, honey
Sour	Citrus, raspberry, anise
Salty	Mixed fruit, mixed citrus, butterscotch, maple
Bitter	Licorice, coffee, mint, cherry, grapefruit
Metallic	Grape, lemon, lime

Source: From ref. 18.

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brittle film, have no unpleasant taste of its own, not interfere with dissolution, and be insoluble in saliva. Microencapsulation for taste masking can be achieved by phase separation or coacervation and may also impart stability. The same taste-masking technologies may be used to encapsulate drugs for formulation into chewable, softchew, and fast dissolving dosage forms. Coating materials include carboxymethylcellulose, polyvinyl alcohol (PVA), and ethylcellulose. Xylitol is the sweetest sugar alcohol, and it has a high negative heat of solution, making it a good candidate as an excipient for chewable tablets. There are many types of compressible sugars today, and most of them are composed of sucrose granulated with small amounts of modified dextrins in order to make the sucrose more compressible [20]. Modifications to sugar-based excipients such as spray-dried crystalline maltose and directly compressible sucrose (95% sucrose and 5% sorbitol) to facilitate direct compression are also aiding development in this area [21].

4.1.9.1 Testing of Chewable Tablets

Dissolution testing for chewable tablets should be the same as that used for regular tablets [22]. This is because patients could swallow the dosage form without adequate chewing, in which case the drug would still need to be released to ensure the desired pharmacological action. However, as outlined, chewable tablets will typically have different excipients than standard formulations, including agents to either mask or add flavor, and may undergo a different manufacturing process. Where applicable, test conditions would preferably be the same as used for non-chewable tablets of the same active pharmaceutical ingredient, but because of the nondisintegrating nature of the dosage form, it may be necessary to alter test conditions (e.g., increase the agitation rate) and specifications (e.g., increase the test duration). The reciprocating cylinder (USP apparatus 3) with the addition of glass beads may also provide more intensive agitation for in vitro dissolution testing of chewable tablets. As another option, mechanical breaking of chewable tablets prior to exposing the specimen to dissolution testing could be considered. Chewable tablets should also be evaluated for in vivo bioavailability and/or bioequivalence.

Additional concerns in the testing of chewable tablets are organoleptic, chemical, and physical stability. As it is a critical factor in the design of such formulations, taste masking should be incorporated into excipient testing during preformulation studies. Technologies like the "electronic tongue" can be used to match desirable taste characteristics [23, 24].

4.1.10 CHEWING GUMS

4.1.10.1 Composition of Chewing Gum

Medicated chewing gums are gums made with a tasteless masticatory gum base that consists of natural or synthetic elastomers [25]. They include excipients such as fillers, softeners, and sweetening and flavoring agents. Natural gum bases include chicle and smoked natural rubber and are permitted in formulations by the FDA, but modern gum bases are mostly synthetic in origin and approved bases include

TABLE 8 Typical Formulation of Gum Base

Ingredient	Weight (%)	Example
Elastomer	10	Styrene–butadiene rubber
Plasticizer	30	Rosin esters
Texture agent/filler	35	Calcium carbonate
Wax	15	Paraffin wax
Lipid	7	Soya oil
Emulsifier	3	Lecithin
Miscellaneous	1	Colorant, antioxidant

Source: From ref. 26.

TABLE 9 Example Chewing Gum Formulations

Ingredient (%)	Sugar Gum	Sugar-Free Gum
Gum base	19.4	25.0
Corn syrup	19.8	—
Sorbitol, 70%	—	15.0
Sugar	59.7	—
Glycerin	0.5	6.5
Sorbitol	—	52.3
Flavor	0.6	1.2

Source: From ref. 26.

styrene–butadiene rubber, polyethylene, and polyvinylacetate. Gum base usually forms about 40% of the gum, but can comprise up to 65%, and is a complex mixture, insoluble in saliva, comprising mainly of elastomer, plasticizers, waxes, lipids, and emulsifiers (see Table 8). It will also contain an adjuvant such as talc to modify the texture of the gum and low quantities of additional excipients including colorants and antioxidants such as butylated hydroxyanisole. Elastomers control the gummy texture while the plasticizers and texture agents regulate the cohesiveness of the product. The lipid and waxes melt in the mouth to provide a cooling, lubricating feeling while the juicy feel of the gum texture is from the emulsifiers. The choice and formulation of gum base will affect the release of active ingredient, and the texture, stability, and method of manufacture of the product.

The remaining ingredients in the chewing gum itself include drug, sweeteners, softeners, and flavoring and coloring agents. A typical chewing gum formulation is shown in Table 9. The sugar is for sweetening the product while the corn syrup keeps the gum fresh and flexible. Softeners or fillers are included to help blend the ingredients and retain moisture. Sugar-free gum has sorbitol, mannitol, aspartame, or saccharin instead of sugar. Optimized chewing gum formulations will require tailoring for each individual product. For example, nicotine-containing gums are formulated with the nicotine within an ion exchange resin and pH-modifying carbonates and/or bicarbonates to increase the percentage of the drug in its free base form in saliva.

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4.1.10.2 Manufacture of Chewing Gum

The majority of chewing gum delivery systems today are manufactured using conventional gum processes. The gum base is softened or melted and placed in a kettle mixer where sweeteners, syrups, active ingredients, and other excipients are added at a defined time. The gum is then sent to a series of rollers that form it into a thin, wide ribbon. During this process, a light coating of an antisticking agent can be added (e.g., magnesium stearate, calcium carbonate, or finely powdered sugar or sugar substitute). Finally, the gum is cut to the desired size and cooled at a carefully controlled temperature and humidity.

As the heating process involved in conventional methods may limit the applicability of the process for formulation of thermally labile drugs, directly compressible, free-flowing powdered gums such as Pharmagum (SPI Pharma) and MedGumBase (Gumbase Co) have been proposed to simplify the process. These formulations can be compacted into a gum tablet using a conventional tablet press and have the potential to simplify the manufacture, facilitating inclusion of a wider range of drugs.

4.1.10.3 Drug Release from Chewing Gums

Until recently, the release of substances from chewing gums during mastication was studied using a panel of tasters and chew-out studies. During the mastication process, the medication contained within the gum product should be released into the saliva and is either absorbed through the buccal mucosa or swallowed and absorbed via the GI tract. The need for, and value of, in vitro drug release testing is well established for a range of dosage forms, however, standard dissolution apparatus is not suitable for monitoring release of drug from chewing gums as mastication is essential in order to provide a renewable surface for drug release after chew action. A number of devices to mimic the chewing action have been reported [26–28]. In 2000, the European Pharmacopoeia produced a monograph describing a suitable apparatus for studying the in vitro release of drug substances from chewing gums [25]. The chewing machine consists of a temperature-controlled chewing chamber in which the gum piece is chewed by two electronically controlled horizontal pistons driven by compressed air. The two pistons transmit twisting and pressing forces to the gum while a third vertical piston operates alternately to the two horizontal pistons to ensure that the gum stays in the right place (see Figure 1). The temperature of the chamber can be maintained at 37°C ± 0.5°C and the chew rate varied. Other adjustable settings include the volume of the medium, distance between the jaws and the twisting movement. The European Pharmacopoeia recommends using 20 mL of unspecified buffer in a chewing chamber of 40 mL and a chew rate of 60 strokes per minute. This apparatus has been used to study release of nicotine from commercial gums and directly compressible gums [26].

Factors affecting the release of medicament from chewing gum can be divided into three groups: the physicochemical properties of the drug, the gum properties, and chew-related factors, including rate and frequency. Drugs can be incorporated into gums as solids or liquids. For most pharmaceuticals, aqueous solubility of the drug will be a major factor affecting the release rate. In order for drugs to be

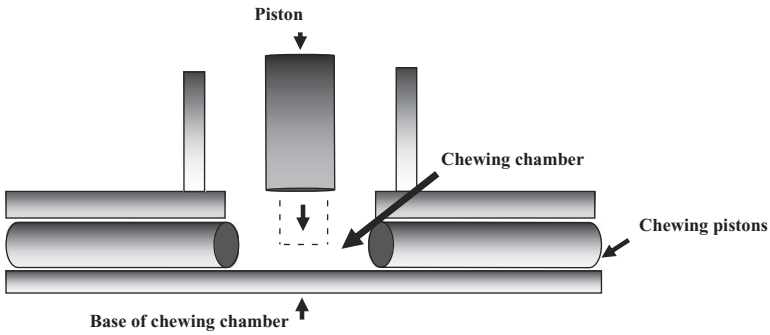

FIGURE 1 Schematic of chewing chamber of in vitro chewing apparatus [26].

released, the gum would need to become hydrated; the drugs can then dissolve and diffuse through the gum base under the action of chewing.

For treatment of local conditions, a release period less than 1 h may be desirable, but a faster release may be required if a rapid onset of action is required for a systemically absorbed formulation. There are a number of strategies that can be undertaken in order to achieve the desired release rate. Decreasing the amount of the gum base will enhance the release of lipophilic drugs and addition of excipients designed to promote release can also be considered. Release can be sustained using, for example, ion exchange resins as described for nicotine-containing gums. Changes in gum texture as a consequence of changes in excipient levels provide a further challenge to controlling the release of drugs. A quantitative measure of gum texture during the process is possible using texture analysis techniques [26].

4.1.10.4 Applications for Chewing Gums

The promotion of sugar-free gums to counteract dental caries by stimulation of saliva secretion has led to a more widespread use and acceptance of gums. Medicated gums for delivery of dental products to the oral cavity are marketed in a number of countries, for example, fluoride-containing gums as an alternative to mouthwashes and tablets or chlorhexidine gum for treatment of gingivitis. The potential use of medicated chewing gums in the treatment of oral infections has also been reported. Gums have been prepared containing antifungal agents such as nystatin [29] and miconazole [30] or antibiotics, such as penicillin and metronidazole for the treatment of oral gingivitis [31].

Chewing gum is also useful as a delivery system for agents intended for systemic delivery. Drug that is released from the gum within the oral cavity can act locally, be absorbed via the buccal mucosa, or swallowed with the saliva. The buccal mucosa is well vascularized, and if a drug is absorbed by this route, then first-pass metabolism could be avoided. Associated increases in bioavailability can permit the use of lower dosages. Like orally disintegrating tablets, chewing gum is a convenient dosage form; it can be administered without water and to those who have difficulty swallowing. Although medicated gums are generally intended to be chewed for 10–30 min and can therefore be designed for sustained release, a fast onset of action can result either from buccal absorption or as a consequence of the active being

already dissolved in the saliva prior to swallowing. Guidance can be given regarding chewing conditions (e.g., time, frequency), but factors such as the force of chewing and salivary flow will impact on drug release and the fraction of drug absorbed via the oral mucosa. Released drug can be swallowed with the saliva, therefore leading to multiple absorption sites, which can result in variable pharmacokinetics.

Along with nicotine replacement patches, nicotine chewing gum for smoking cessation therapy has met with major sales success. The principal active ingredient of currently marketed nicotine chewing gums is nicotine polacrilex USP. The nicotine is loaded at approximately 18% w/w on an ion exchange resin (Amberlite IRP64). Recent product variations have been launched with improved flavors such as mint and fruit, rather than the original peppery flavoring, designed to reduce the unpleasant taste and burning sensation arising from nicotine itself and flavored coated gums that are sweeter and easier to chew.

Other applications for chewing gum formulations include delivery of antacids such as calcium carbonate, antiemetics for travel sickness, and vitamins and minerals. However, the potential for a buccal delivery, a fast onset of action, and the opportunity for product line extension makes it an attractive alternative delivery form for other applications.

4.1.11 ORALLY DISINTEGRATING TABLETS

The demand for fast-dissolving/disintegrating tablets or fast-melting tablets that can dissolve or disintegrate in the mouth has been growing particularly for those with difficulty swallowing tablets such as the elderly and children. They are referred to using a range of terminologies: fast dissolving, orodispersible, and fast melting and the FDA has adopted the term orally disintegrating tablets (ODTs). Patients with persistent nausea or those who have little or no access to water could also benefit from ODTs. Other advantages include product differentiation and market expansion, and applications exist in the veterinary market for oral administration to animals.

Orally disintegrating tablets disintegrate and/or dissolve rapidly in the saliva without the need for water, within seconds to minutes. Some tablets are designed to dissolve rapidly in saliva, within a few seconds, and are true fast-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity and are more appropriately termed fast-disintegrating tablets, as they may take up to a minute to completely disintegrate. Increased bioavailability using such formulations is sometimes possible if there is sufficient absorption via the oral cavity prior to swallowing [32]. However, if the amount of swallowed drug varies, there is the potential for inconsistent bioavailability. Patented orally disintegrating tablet technologies include OraSolv, DuraSolv, Zydis, FlashTab, WOWTAB, and others. They are generally prepared using freeze drying, compaction, or molding. Examples of marketed products, excipients, and technologies used are given in Table 10.

Platform technologies based on freeze drying include Zydis (Cardinal Health) and Quicksolv (Janssen Pharmaceutica). Zydis was the first ODT to be successfully launched, and it is ideal for poorly soluble drugs. It can incorporate doses up to 400 mg, but high loadings can extend disintegration time. The porous matrix consists of a network of water-soluble carriers and active ingredient. The maximum dose for

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TABLE 10 Examples of Marketed ODT Products and Technologies

Name (Company)	Examples	Ingredients[a]	Technology
Zydis (Cardinal Health)	Claritin Reditab	*Micronized loratadine (10 mg)*, citric acid, gelatin, mannitol, mint flavor	Freeze drying
Zydis (Cardinal Health)	Zofran ODT	*Ondansetron (4 or 8 mg)*, aspartame, gelatin, mannitol, methylparaben sodium, propylparaben sodium, strawberry flavor	Freeze drying
Zydis (Cardinal Health)	Zyprexa Zydis	*Olanzapine (5, 10, 15, or 20 mg)*, gelatin, mannitol, aspartame, methylparaben sodium, propylparaben sodium	Freeze drying
Oralsolv (CIMA Labs Inc.)	Remeron Soltab	*Mirtazepine (15, 30, or 45 mg)*, aspartame, citric acid, crospovidone, hydroxypropyl methylcellulose, magnesium stearate, mannitol, microcrystalline cellulose, polymethacrylate, povidone, sodium bicarbonate, starch, sucrose, orange flavor	Compression
Durasolv (CIMA Labs Inc.)	Zomig ZMT	*Zolmitriptan (2.5 mg)*, mannitol, microcrystalline cellulose, crospovidone, aspartame, sodium bicarbonate, citric acid, anhydrous, colloidal silicon dioxide, magnesium stearate, orange flavor	Compression
WOWTAB (Yamanouchi Pharma Technologies, Inc.)	Benadryl Allergy & Sinus Fastmelt	*Diphenhydramine citrate (19 mg), pseudoephedrine HCl (30 mg),* aspartame, citric acid, D&C red no. 7 calcium lake, ethylcellulose, flavor, lactitol, magnesium stearate, mannitol, and stearic acid	Compression molded tablet
Flashtab (Prographarm/ Ethypharm)	Excedrin Quicktabs	*Acetaminophen (500 mg), caffeine (65 mg)*, aminoalkyl methacrylate copolymers, citric acid, colloidal silicon dioxide, crospovidone, distilled acetylated monoglycerides, ethylcellulose, flavors, magnesium stearate, mannitol, methacrylester copolymer, polyvinyl acetate, povidone, propylene glycol, propyl gallate, silica gel, sodium lauryl sulfate, sucralose, talc	Compression

[a]Active ingredients appear in italics.

water-soluble drugs is 60 mg, and particle sizes of drug and excipients should be below 50 μm.

Excipients used in the formulation usually include a mixture of a water-soluble polymer and a crystalline sugar. Mannitol and natural polysaccharides such as gelatin and alginates are used. Microencapsulation and complexation with ion exchange resins can be combined with additional flavors and sweeteners for taste masking of bitter drugs. The fairly complex nature of manufacture and scale-up contributes to

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a relatively high manufacturing cost. Manufacture comprises three stages. The production sequence begins with the bulk preparation of an aqueous drug solution or suspension and subsequent precise dosing into preformed blisters. It is the blister that actually forms the tablet shape and is, therefore, an integral component of the total product package. The second phase of manufacturing entails passing the filled blisters through a cryogenic freezing process to control the ultimate size of the ice crystals. This aids in ensuring porosity and the product is freeze dried. The final phase of production involves sealing the open blisters via a heat-seal process to ensure stability and protect the fragile tablet during removal by the patient.

The manufacture of Flashdose (Fuisz Technologies/Biovail) is patented as Shearform process and utilizes a unique spinning mechanism to produce a flosslike or shear-form crystalline structure, much like cotton candy. The matrix comprises saccharides or polysaccharides which are subjected to simultaneous melting and centrifugal force and then partially recrystallized [33]. High temperatures are involved so the technology is only suitable for thermostable agents. Drug can then be incorporated, either as coated or uncoated microspheres, into the sugar and the formulation is compressed into a tablet. Manufacture of the microspheres is patented as Ceform and will help with taste masking. The final product has a very high surface area for dissolution and it disperses and dissolves quickly once placed onto the tongue. Like freeze-drying processes, the manufacture is expensive and resultant formulations are friable and moisture sensitive, therefore requiring specialized packaging.

Most commercial ODTs have been developed using mannitol as the bulk excipient of choice because of its extremely low hygroscopicity, excellent compatibility, good compressibility, better sweetness, and relatively slower dissolution kinetics. Although lactose also has a relatively low aqueous solubility compared with other excipients that have acceptable palatabilities, the dispersibility of a bulk excipient is more important than its aqueous solubility for a successful ODT formulation. Many of the initially marketed ODTs were prepared by the wet granulation of mannitol followed by direct compression. However, added functionality mannitols are now available to simplify the process of ODT manufacturing by direct compression.

Direct compression is, as for normal tablets, the most straightforward process for manufacturing ODTs. Conventional equipment can be used and high doses can be incorporated. The excipients play a major role in the successful formulation and superdisintegrants, hydrophilic polymers, and effervescent compounds are included. Patented technologies include Orasolv and Durasolv (Cima Labs) and Ziplets (Eurand). The OraSolv technology is best described as a fast disintegrating, slightly effervescing tablet; the tablet matrix dissolves in less than one minute, leaving coated drug powder. Both the coating and the effervescence contribute to taste masking in OraSolv. The tablet is prepared by direct compression but at a low pressure, yielding a weaker and more brittle tablet in comparison with conventional tablets. For that reason, Cima developed a special handling and packaging system for OraSolv called Packsolv. Acidic compounds such as citric or fumaric acid are included in the formulation together with a carbonate or bicarbonate. An advantage that goes along with the low degree of compaction of OraSolv is that the particle coating used for taste masking is not compromised by fracture during processing.

DuraSolv is Cima's second-generation fast-dissolving/disintegrating tablet formulation and is also produced using direct compression but using higher compaction

pressures during tableting, resulting in a stronger product. It is thus produced in a faster and more cost-effective manner and may not require specialized packaging. Large amounts of finely milled conventional fillers are used (mannitol, lactose) while the effervescing agents are reduced. It is best suited to potent drugs, requiring only low doses, and the taste-masking coating can be disturbed following compaction. DuraSolv is currently available in two products: NuLev and Zomig ZMT.

Compression following wet or dry granulation is also employed in the manufacture of ODTs. Patented formulations include WOWTAB and Flashtab. WOWTAB relies on a combination of low moldable sahharides (mannitol, glucose, sucrose) with a highly moldable saccharide (malitol, sorbitol, maltose) using conventional granulation and tableting techniques to form a tablet of suitable mechanical properties with desired disintegration. It is manufactured by compression of molded granules, can accommodate a high level of drug loading (up to 50% in some cases), and can be packed using conventional methodology.

Flashtab (Ethypharm) is the technology behind Exedrin QuickTabs and uses swellable agents and disintegrants along with sugars and polyalcohols to achieve a fast dispersible formulation. The manufacture involves either wet or dry granulation of the excipients, blending with the active followed by direct compression.

4.1.11.1 Dissolution Testing of ODTs

Taste masking (drug coating) is very often an essential feature of ODTs and thus can also be the rate-determining mechanism for dissolution/release. If taste masking is not an issue, then the development of dissolution methods is comparable to the approach taken for conventional tablets and pharmacopeial conditions should be used [34]. Due to the nature of the product, the dissolution of orally disintegrating tablets is very fast when using USP monograph conditions, and slower paddle speeds can be used to obtain a profile. Other media such as 0.1 N HCl can also be used. USP 2 paddle apparatus is the most suitable and common choice for orally disintegrating tablets, with a paddle speed of 50 rpm commonly used [34]. Faster agitation rates may be necessary in the case of sample mounding. The method can be applied to the ODTs (finished product) as well as to the bulk intermediate (in the case of coated drug powder/granulate). A potential difficulty for in vitro dissolution testing may arise from floating particles [35]. Similarly, difficulties can arise using USP I due to trapping of disintegrated fragments.

A single-point specification is considered appropriate for ODTs with fast dissolution properties. For ODTs that dissolve very quickly, a disintegration test may be used in lieu of a dissolution test if it is shown to be a good discriminating method. If taste masking (using a polymer coating) is a key aspect of the dosage form, a multipoint profile in a neutral pH medium with early points of analysis (e.g., ≤5 min) may be recommended [34].

4.1.12 SOLID DOSAGE FORMS FOR NONORAL ROUTES

Although the majority of tablets and capsules are intended for oral delivery, there are a number of other delivery routes suitable for drug delivery by these formula-

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tions. Some buccal formulations have been discussed above, and tablets can also be administered via the rectal and vaginal routes for local and systemic treatment.

Many types of product have been designed for vaginal administration with creams, gels, and pessaries being most popular, although powders and tablets have also been used. Despite the effectiveness of systemic vaginal absorption, the majority of products administered by this route are for the treatment of localized infections, especially *Candida albicans*, (e.g., Canestan vaginal tablets). Estradiol tablets (Vagifem) were also designed for delivery via vaginal route to address patient preference issues with vaginal creams. The formulations are administered with an applicator and are designed to dissolve or erode slowly in the vaginal secretions [36]. Bioadhesion as a means of retaining the formulation at the site of delivery is widely accepted to retain formulations in the buccal cavity [37] and has also been reported for the vaginal route [38]. An increased residence time may improve drug absorption by these routes.

REFERENCES

1. Amidon, G. L., Lennernas, H., Shah, V. P., and Crison, J. R. (1995), A theoretical basis for a biopharmaceutic drug classification: The correlation of *in vitro* drug product dissolution and *in vivo* bioavailability, *Pharm. Res.*, 12, 413–420.
2. Waiver of *in-vivo* bioavailability and bioequivalence studies for immediate release solid oral dosage forms based on a biopharmaceutics classification system, available: http://www.fda.gov/cder/OPS/BCS_guidance.html.
3. Waiver of in vivo bioequivalence studies for immediate release solid oral dosage forms based on a biopharmaceutics classification system, available: http://www.fda.gov/cder/guidance/index.html.
4. Zhao, C., Jain, A., Hailemariam, L., Suresh, P., Akkisetty, P., Joglekar, G., Venkatasubramanian, V., Reklaitis, G.V., Morris, K., and Basu, P. (2006), Toward intelligent decision support for pharmaceutical product development, *J. Pharm. Innovation*, 1, 23–35.
5. Banker, G. S., and Rhodes, C. T. (2002), *Modern Pharmaceutics*, 4th ed., Drugs and the Pharmaceutical Sciences 121, Marcel Dekker, New York.
6. Rowe, R. C., Sheskey, P. J., and Weller, P. J. (2001), *Handbook of Pharmaceutical Excipients*, 4th ed., Pharmaceutical Press, London.
7. Weiner, M., and Bernstein I. L. (1989), *Adverse Reactions to Drug Formulation Agents: A Handbook of Excipients*, Marcel Dekker, New York, pp. 93–94.
8. Lachman, L., Lieberman, H. A., and Kanig, J. L. (1986), *The Theory and Practice of Industrial Pharmacy*, 3rd ed., Lea & Febiger, Philadelphia.
9. Augsburger, L. L., Hahm, H. A., Brzeczko, A. W., and Shah, U. (2002), Superdisintegrants: Characterization and function, in Swarbrick, J., and Boylan, J. V., Eds., *Encyclopedia of Pharmaceutical Technology*, Vol. 3, 2nd ed., Marcel Dekker, New York.
10. Gibson, M. (2001), Pharmaceutical preformulation and formulation; a practical guide from candidate drug selection to commercial dosage form, IHS Health Group, Englewood, Colorado.
11. Stanley, J. P. (1986), Soft gelatin capsules, in Lachman, L., Lieberman, H. A., and Kanig, J. L., Eds., *The Theory and Practice of Industrial Pharmacy*, 3rd ed., Lea & Febiger, Philadelphia.

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12. *The United States Pharmacopeia*, 26th revision, United States Pharmacopeial Convention, Rockville, MD, 2003.
13. Gelatin Capsule Working Group, Collaborative development of two-tier dissolution testing for gelatin capsules and gelatin-coated tablets using enzyme-containing media, *Pharmacop. Forum*, 24(5), Sept./Oct. 1998.
14. Lee, R. E., Effervescent tablets. Key facts about a unique effective dosage form, *Tablets Capsules*, available: http://www.amerilabtech.com/EffervescentTablets&KeyFacts.pdf, accessed Aug. 6, 2004.
15. Rotthauser, B., Kraus, G., and Schmidt, P. C. (1998), Optimization of an effervescent tablet formulations containing spray-dried L-leucine and polyethylene glycol 6000 as lubricants using a central composite design, *Eur. J. Pharm. Biopharm.*, 46, 85–94.
16. Stahl, H. (2003), Effervescent dosage manufacturing, *Pharm. Technol. Eur.*, 4, 25–28.
17. Lindberg, N.-O., and Hansson, H. (2002), Effervescent pharmaceuticals, in Swarbrick, J., and Boylan, J. V., Eds., *Encyclopedia of Pharmaceutical Technology*, Vol. 2, 2nd ed., Marcel Dekker, New York.
18. Mendes, R. W., and Bhargava, H. (2002), Lozenges, in Swarbrick J., and Boylan, J. V., Eds., *Encyclopedia of Pharmaceutical Technology*, Vol. 2, 2nd ed., Marcel Dekker, New York.
19. Richards, R. M. E., Xing, J. Z., and Weir, L. F. C. (1996), The effect of formulation on the antimicrobial activity of cetylpyridinium chloride in candy based lozenges, *Pharm. Res.*, 13, 583–587.
20. Bolhuis, G., and Armstrong, A. N. (2006), Excipients for direct compaction—An update, *Pharm. Dev. Technol.*, 11, 111–124.
21. Bowe, K. E. (1998), Recent advances in sugar-based excipients, *Pharm. Sci. Technol. Today*, 1(4), 166–173.
22. FDA guidance for industry: Bioavailability and bioequivalence studies for orally administered drug products—General considerations, Oct. 2000.
23. Murray, O. J., Dang, W., and Bergstrom, D. (2004), Using an electronic tongue to optimize taste-masking in a lyophilized orally disintegrating tablet formulation, *Pharm. Technol. Outsourcing Res.*, 42–52.
24. Zheng, J. Y., and Keeney, M. P. (2004), Taste masking analysis in pharmaceutical formulation development using an electronic tongue, *Int. J. Pharm.*, 310, 118–124.
25. *European Pharmacopoeia*, 4th ed., European Directorate for the Quality of Medicines, Strasbourg, 2001.
26. Morjaria, Y., Irwin, W. J., Barnett, P. X., Chan, R. S., and Conway, B. R. (2004), *In vitro* release of nicotine from chewing gum formulations, *Dissolution Technol.*, 11, 12–15.
27. Rider, J. N., Brunson, E. L., Chambliss, W. G., Cleary, R. W., Hikal, A. H., Rider, P. H., Walker, L. A., Wyandt, C. M., and Jones, A. B. (1992), Development and evaluation of a novel dissolution apparatus for medicated chewing gum products, *Pharm. Res.*, 9, 255–260.
28. Kvist, C., Andersson, S.-B., Fors, S., Wennergren, B., and Berglund, J. (1999), Apparatus for studying *in vitro* release from medicated chewing gums, *Int. J. Pharm.*, 89, 57–65.
29. Andersen, T., Gram-Hansen, M., Pedersen, M., and Rassing, M. R. (1990), Chewing gum as a drug delivery system for nystatin. Influence of solubilising agents on the release of water-soluble drugs, *Drug Dev. Ind. Pharm.*, 16, 1985–1994.
30. Pedersen, M., and Rassing, M. R. (1991), Miconazole chewing gum as a drug delivery system test of release promoting additives, *Drug Dev. Ind. Pharm.*, 17, 411–420.
31. Emslie, R. D. (1967), Treatment of acute ulcerative gingivitis. A clinical trial using chewing gums containing metronidazole or penicillin, *Br. Dent. J.*, 122, 307–308.

Dr. Falk Pharma Ex. 1041
IPR Petition - USP 11,260,061

32. Habib, W., Khankari, R., and Hontz, J. (2002), Fast-dissolve drug delivery system, *Crit. Rev. Therap. Drug Carrier Syst.*, 17, 61–72.
33. Dobetti, L. (2001), Fast-melting tablets: Developments and technologies, *Pharm. Technol. Drug Deliv. Suppl.*, 44–50.
34. Klanke, J. (2003), Dissolution testing of orally disintegrating tablets, *Dissolution Technol.*, 10(2), 6–8.
35. Siewert, M., Dressman, J., Brown, C., and Shah, V. P. (2003), FIP/AAPS. Guidelines for dissolution/*in vitro* release testing of novel/special dosage forms, *Dissolution Technol.*, 10(1), 6–15.
36. Conine, J. W., and Pikal, M. J. (1989), Special tablets, in Lieberman, H. A., Lachman, L., and Schwartz, J. B. Eds., *Pharmaeutical Dosage Forms: Tablets*, Vol. 1, 2nd ed., Marcel Dekker, New York.
37. Sudhakar, Y., Kuotsu, K., and Bandyopadhyay, A. K. (2006), Buccal bioadhesive drug delivery—A promising option for orally less efficient drugs, *J. Controlled Release*, 114, 15–40.
38. Hussain, A., and Ahsan, F. (2005), The vagina as a route for systemic drug delivery, *J. Controlled Release*, 103, 301–313.

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