

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL
REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN
USE

ICH HARMONISED TRIPARTITE GUIDELINE

**SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA
FOR NEW DRUG SUBSTANCES AND NEW DRUG PRODUCTS:
CHEMICAL SUBSTANCES
Q6A**

Current *Step 4* version
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This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

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SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR NEW DRUG SUBSTANCES AND NEW DRUG PRODUCTS: CHEMICAL SUBSTANCES

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 6 October 1999, this guideline is recommended for adoption to the three regulatory parties to ICH

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SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR NEW DRUG SUBSTANCES AND NEW DRUG PRODUCTS: CHEMICAL SUBSTANCES

1. INTRODUCTION

1.1 Objective of the Guideline

This guideline is intended to assist to the extent possible, in the establishment of a single set of global specifications for new drug substances and new drug products. It provides guidance on the setting and justification of acceptance criteria and the selection of test procedures for new drug substances of synthetic chemical origin, and new drug products produced from them, which have not been registered previously in the United States, the European Union, or Japan.

1.2 Background

A specification is defined 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. "Conformance to specifications" means that the drug substance and / or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

Specifications are one part of a total control strategy for the drug substance and drug product designed to ensure product quality and consistency. Other parts of this strategy include thorough product characterization during development, upon which specifications are based, and adherence to Good Manufacturing Practices; e.g., suitable facilities, a validated manufacturing process, validated test procedure, raw material testing, in-process testing, stability testing, etc.

Specifications are chosen to confirm the quality of the drug substance and drug product rather than to establish full characterization, and should focus on those characteristics found to be useful in ensuring the safety and efficacy of the drug substance and drug product.

1.3 Scope of the Guideline

The quality of drug substances and drug products is determined by their design, development, in-process controls, GMP controls, and process validation, and by specifications applied to them throughout development and manufacture. This guideline addresses specifications, i.e., those tests, procedures, and acceptance criteria which play a major role in assuring the quality of the new drug substance and new drug product at release and during shelf life. Specifications are an important component of quality assurance, but are not its only component. All of the considerations listed above are necessary to ensure consistent production of drug substances and drug products of high quality.

This guideline addresses only the marketing approval of new drug products (including combination products) and, where applicable, new drug substances; it does not address drug substances or drug products during the clinical research stages of drug development. This guideline may be applicable to synthetic and semi-synthetic antibiotics and synthetic peptides of low molecular weight; however, it is not sufficient

to adequately describe specifications of higher molecular weight peptides and polypeptides, and biotechnological/biological products. The ICH Guideline Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products addresses guideline specifications, tests and procedures for biotechnological/biological products. Radiopharmaceuticals, products of fermentation, oligonucleotides, herbal products and crude products of animal or plant origin are similarly not covered.

Guidance is provided with regard to acceptance criteria which should be established for all new drug substances and new drug products, i.e. universal acceptance criteria, and those that are considered specific to individual drug substances and / or dosage forms. This guideline should not be considered all encompassing. New analytical technologies, and modifications to existing technology, are continually being developed. Such technologies should be used when justified.

Dosage forms addressed in this guideline include solid oral dosage forms, liquid oral dosage forms, and parenterals (small and large volume). This is not meant to be an all-inclusive list, or to limit the number of dosage forms to which this guideline applies. The dosage forms presented serve as models, which may be applicable to other dosage forms which have not been discussed. The extended application of the concepts in this guideline to other dosage forms, e.g., to inhalation dosage forms (powders, solutions, etc.), to topical formulations (creams, ointments, gels), and to transdermal systems, is encouraged.

2. GENERAL CONCEPTS

The following concepts are important in the development and setting of harmonized specifications. They are not universally applicable, but each should be considered in particular circumstances. This guideline presents a brief definition of each concept and an indication of the circumstances under which it may be applicable. Generally, proposals to implement these concepts should be justified by the applicant and approved by the appropriate regulatory authority before being put into effect.

2.1 Periodic or Skip Testing

Periodic or skip testing is the performance of specified tests at release on pre-selected batches and / or at predetermined intervals, rather than on a batch-to-batch basis with the understanding that those batches not being tested still must meet all acceptance criteria established for that product. This represents a less than full schedule of testing and should therefore be justified and presented to and approved by the regulatory authority prior to implementation. This concept may be applicable to, for example, residual solvents and microbiological testing, for solid oral dosage forms. It is recognized that only limited data may be available at the time of submission of an application (see section 2.5). This concept should therefore generally be implemented post-approval. When tested, any failure to meet acceptance criteria established for the periodic test should be handled by proper notification of the appropriate regulatory authority(ies). If these data demonstrate a need to restore routine testing, then batch by batch release testing should be reinstated.

2.2 Release vs. Shelf-life Acceptance Criteria

The concept of different acceptance criteria for release vs. shelf-life specifications applies to drug products only; it pertains to the establishment of more restrictive criteria for the release of a drug product than are applied to the shelf-life. Examples where this may be applicable include assay and impurity (degradation product) levels. In Japan and the United States, this concept may only be applicable to in-house criteria, and not to the regulatory release criteria. Thus, in these regions, the

regulatory acceptance criteria are the same from release throughout shelf-life; however, an applicant may choose to have tighter in-house limits at the time of release to provide increased assurance to the applicant that the product will remain within the regulatory acceptance criterion throughout its shelf-life. In the European Union there is a regulatory requirement for distinct specifications for release and for shelf-life where different.

2.3 In-process Tests

In-process tests, as presented in this guideline, are tests which may be performed during the manufacture of either the drug substance or drug product, rather than as part of the formal battery of tests which are conducted prior to release.

In-process tests which are only used for the purpose of adjusting process parameters within an operating range, e.g., hardness and friability of tablet cores which will be coated and individual tablet weights, are not included in the specification.

Certain tests conducted during the manufacturing process, where the acceptance criterion is identical to or tighter than the release requirement, (e.g., pH of a solution) may be sufficient to satisfy specification requirements when the test is included in the specification. However, this approach should be validated to show that test results or product performance characteristics do not change from the in-process stage to finished product.

2.4 Design and Development Considerations

The experience and data accumulated during the development of a new drug substance or product should form the basis for the setting of specifications. It may be possible to propose excluding or replacing certain tests on this basis. Some examples are:

- microbiological testing for drug substances and solid dosage forms which have been shown during development not to support microbial viability or growth (see Decision Trees #6 and #8);
- extractables from product containers where it has been reproducibly shown that either no extractables are found in the drug product or the levels meet accepted standards for safety;
- particle size testing may fall into this category, may be performed as an in-process test, or may be performed as a release test, depending on its relevance to product performance;
- dissolution testing for immediate release solid oral drug products made from highly water soluble drug substances may be replaced by disintegration testing, if these products have been demonstrated during development to have consistently rapid drug release characteristics (see Decision Trees #7(1) through #7(2)).

2.5 Limited Data Available at Filing

It is recognized that only a limited amount of data may be available at the time of filing, which can influence the process of setting acceptance criteria. As a result it may be necessary to propose revised acceptance criteria as additional experience is gained with the manufacture of a particular drug substance or drug product (example: acceptance limits for a specific impurity). The basis for the acceptance criteria at the time of filing should necessarily focus on safety and efficacy.

When only limited data are available, the initially approved tests and acceptance criteria should be reviewed as more information is collected, with a view towards

possible modification. This could involve loosening, as well as tightening, acceptance criteria as appropriate.

2.6 Parametric Release

Parametric release can be used as an operational alternative to routine release testing for the drug product in certain cases when approved by the regulatory authority. Sterility testing for terminally sterilized drug products is one example. In this case, the release of each batch is based on satisfactory results from monitoring specific parameters, e.g., temperature, pressure, and time during the terminal sterilization phase(s) of drug product manufacturing. These parameters can generally be more accurately controlled and measured, so that they are more reliable in predicting sterility assurance than is end-product sterility testing. Appropriate laboratory tests (e.g., chemical or physical indicator) may be included in the parametric release program. It is important to note that the sterilization process should be adequately validated before parametric release is proposed and maintenance of a validated state should be demonstrated by revalidation at established intervals. When parametric release is performed, the attribute which is indirectly controlled (e.g., sterility), together with a reference to the associated test procedure, still should be included in the specifications.

2.7 Alternative Procedures

Alternative procedures are those which may be used to measure an attribute when such procedures control the quality of the drug substance or drug product to an extent that is comparable or superior to the official procedure. Example: for tablets that have been shown not to degrade during manufacture, it may be permissible to use a spectrophotometric procedure for release as opposed to the official procedure, which is chromatographic. However, the chromatographic procedure should still be used to demonstrate compliance with the acceptance criteria during the shelf-life of the product.

2.8 Pharmacopoeial Tests and Acceptance Criteria

References to certain procedures are found in pharmacopoeias in each region. Wherever they are appropriate, pharmacopoeial procedures should be utilized. Whereas differences in pharmacopoeial procedures and/or acceptance criteria have existed among the regions, a harmonized specification is possible only if the procedures and acceptance criteria defined are acceptable to regulatory authorities in all regions.

The full utility of this Guideline is dependent on the successful completion of harmonization of pharmacopoeial procedures for several attributes commonly considered in the specification for new drug substances or new drug products. The Pharmacopoeial Discussion Group (PDG) of the European Pharmacopoeia, the Japanese Pharmacopoeia, and the United States Pharmacopoeia has expressed a commitment to achieving harmonization of the procedures in a timely fashion.

Where harmonization has been achieved, an appropriate reference to the harmonized procedure and acceptance criteria is considered acceptable for a specification in all three regions. For example, after harmonization sterility data generated using the JP procedure, as well as the JP procedure itself and its acceptance criteria, are considered acceptable for registration in all three regions. To signify the harmonized status of these procedures, the pharmacopoeias have agreed to include a statement in their respective texts which indicates that the procedures and acceptance criteria from all three pharmacopoeias are considered equivalent and are, therefore, interchangeable.

Since the overall value of this Guideline is linked to the extent of harmonization of the analytical procedures and acceptance criteria of the pharmacopoeias, it is agreed by the members of the Q6A expert working group that none of the three pharmacopoeias should change a harmonized monograph unilaterally. According to the PDG procedure for the revision of harmonized monographs and chapters, "no pharmacopoeia shall revise unilaterally any monograph or chapter after sign-off or after publication."

2.9 Evolving Technologies

New analytical technologies, and modifications to existing technology, are continually being developed. Such technologies should be used when they are considered to offer additional assurance of quality, or are otherwise justified.

2.10 Impact of Drug Substance on Drug Product Specifications

In general, it should not be necessary to test the drug product for quality attributes uniquely associated with the drug substance. Example: it is normally not considered necessary to test the drug product for synthesis impurities which are controlled in the drug substance and are not degradation products. Refer to the ICH Guideline Impurities in New Drug Products for detailed information.

2.11 Reference Standard

A reference standard, or reference material, is a substance prepared for use as the standard in an assay, identification, or purity test. It should have a quality appropriate to its use. It is often characterized and evaluated for its intended purpose by additional procedures other than those used in routine testing. For new drug substance reference standards intended for use in assays, the impurities should be adequately identified and / or controlled, and purity should be measured by a quantitative procedure.

3. GUIDELINES

3.1 Specifications: Definition and Justification

3.1.1 Definition of Specifications

A specification is defined 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 new drug substance or new drug product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the drug substance and / or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

It is possible that, in addition to release tests, a specification may list in-process tests as defined in 2.3, periodic (skip) tests, and other tests which are not always conducted on a batch-by-batch basis. In such cases the applicant should specify which tests are routinely conducted batch-by-batch, and which tests are not, with an indication and justification of the actual testing frequency. In this situation, the drug substance and / or drug product should meet the acceptance criteria if tested.

It should be noted that changes in the specification after approval of the application may need prior approval by the regulatory authority.

3.1.2 Justification of Specifications

When a specification is first proposed, justification should be presented for each procedure and each acceptance criterion included. The justification should refer to relevant development data, pharmacopoeial standards, test data for drug substances and drug products used in toxicology and clinical studies, and results from accelerated and long term stability studies, as appropriate. Additionally, a reasonable range of expected analytical and manufacturing variability should be considered. It is important to consider all of this information.

Approaches other than those set forth in this guideline may be applicable and acceptable. The applicant should justify alternative approaches. Such justification should be based on data derived from the new drug substance synthesis and/or the new drug product manufacturing process. This justification may consider theoretical tolerances for a given procedure or acceptance criterion, but the actual results obtained should form the primary basis for whatever approach is taken.

Test results from stability and scale-up / validation batches, with emphasis on the primary stability batches, should be considered in setting and justifying specifications. If multiple manufacturing sites are planned, it may be valuable to consider data from these sites in establishing the initial tests and acceptance criteria. This is particularly true when there is limited initial experience with the manufacture of the drug substance or drug product at any particular site. If data from a single representative manufacturing site are used in setting tests and acceptance criteria, product manufactured at all sites should still comply with these criteria.

Presentation of test results in graphic format may be helpful in justifying individual acceptance criteria, particularly for assay values and impurity levels. Data from development work should be included in such a presentation, along with stability data available for new drug substance or new drug product batches manufactured by the proposed commercial processes. Justification for proposing exclusion of a test from the specification should be based on development data and on process validation data (where appropriate).

3.2 Universal Tests / Criteria

Implementation of the recommendations in the following section should take into account the ICH Guidelines "Text on Validation of Analytical Procedures" and "Validation of Analytical Procedures: Methodology".

3.2.1 New Drug Substances

The following tests and acceptance criteria are considered generally applicable to all new drug substances.

a) Description: a qualitative statement about the state (e.g. solid, liquid) and color of the new drug substance. If any of these characteristics change during storage, this change should be investigated and appropriate action taken.

b) Identification: identification testing should optimally be able to discriminate between compounds of closely related structure which are likely to be present. Identification tests should be specific for the new drug substance, e.g., infrared spectroscopy. Identification solely by a single chromatographic retention time, for example, is not regarded as being specific. However, the use of two chromatographic procedures, where the separation is based on different principles or a combination of tests into a single procedure, such as HPLC/UV diode array, HPLC/MS, or GC/MS is generally acceptable. If the new drug substance is a salt, identification testing should be specific for the individual ions. An identification test that is specific for the salt itself should suffice.

New drug substances which are optically active may also need specific identification testing or performance of a chiral assay. Please refer to 3.3.1.d) in this Guideline for further discussion of this topic.

c) *Assay*: A specific, stability-indicating procedure should be included to determine the content of the new drug substance. In many cases it is possible to employ the same procedure (e.g., HPLC) for both assay of the new drug substance and quantitation of impurities.

In cases where use of a non-specific assay is justified, other supporting analytical procedures should be used to achieve overall specificity. For example, where titration is adopted to assay the drug substance, the combination of the assay and a suitable test for impurities should be used.

d) *Impurities*: Organic and inorganic impurities and residual solvents are included in this category. Refer to the ICH Guidelines Impurities in New Drug Substances and Residual Solvents in Pharmaceuticals for detailed information.

Decision tree #1 addresses the extrapolation of meaningful limits on impurities from the body of data generated during development. At the time of filing it is unlikely that sufficient data will be available to assess process consistency. Therefore it is considered inappropriate to establish acceptance criteria which tightly encompass the batch data at the time of filing. (see section 2.5)

3.2.2 New Drug Products

The following tests and acceptance criteria are considered generally applicable to all new drug products:

a) *Description*: A qualitative description of the dosage form should be provided (e.g., size, shape, and color). If any of these characteristics change during manufacture or storage, this change should be investigated and appropriate action taken. The acceptance criteria should include the final acceptable appearance. If color changes during storage, a quantitative procedure may be appropriate.

b) *Identification*: Identification testing should establish the identity of the new drug substance(s) in the new drug product and should be able to discriminate between compounds of closely related structure which are likely to be present. Identity tests should be specific for the new drug substance, e.g., infrared spectroscopy. Identification solely by a single chromatographic retention time, for example, is not regarded as being specific. However, the use of two chromatographic procedures, where the separation is based on different principles, or combination of tests into a single procedure, such as HPLC/UV diode array, HPLC/MS, or GC/MS, is generally acceptable.

c) *Assay*: A specific, stability-indicating assay to determine strength (content) should be included for all new drug products. In many cases it is possible to employ the same procedure (e.g., HPLC) for both assay of the new drug substance and quantitation of impurities. Results of content uniformity testing for new drug products can be used for quantitation of drug product strength, if the methods used for content uniformity are also appropriate as assays.

In cases where use of a non-specific assay is justified, other supporting analytical procedures should be used to achieve overall specificity. For example, where titration is adopted to assay the drug substance for release, the combination of the assay and a suitable test for impurities can be used. A specific procedure should be used when there is evidence of excipient interference with the non-specific assay.

d) Impurities: Organic and inorganic impurities (degradation products) and residual solvents are included in this category. Refer to the ICH Guidelines Impurities in New Drug Products and Residual Solvents for detailed information.

Organic impurities arising from degradation of the new drug substance and impurities that arise during the manufacturing process for the drug product should be monitored in the new drug product. Acceptance limits should be stated for individual specified degradation products, which may include both identified and unidentified degradation products as appropriate, and total degradation products. Process impurities from the new drug substance synthesis are normally controlled during drug substance testing, and therefore are not included in the total impurities limit. However, when a synthesis impurity is also a degradation product, its level should be monitored and included in the total degradation product limit. When it has been conclusively demonstrated via appropriate analytical methodology, that the drug substance does not degrade in the specific formulation, and under the specific storage conditions proposed in the new drug application, degradation product testing may be reduced or eliminated upon approval by the regulatory authorities.

Decision tree #2 addresses the extrapolation of meaningful limits on degradation products from the body of data generated during development. At the time of filing it is unlikely that sufficient data will be available to assess process consistency. Therefore it is considered inappropriate to establish acceptance criteria which tightly encompass the batch data at the time of filing. (see section 2.5)

3.3 Specific Tests / Criteria

In addition to the universal tests listed above, the following tests may be considered on a case by case basis for drug substances and/or drug products. Individual tests/criteria should be included in the specification when the tests have an impact on the quality of the drug substance and drug product for batch control. Tests other than those listed below may be needed in particular situations or as new information becomes available.

3.3.1 New Drug Substances

a) Physicochemical properties: These are properties such as pH of an aqueous solution, melting point / range, and refractive index. The procedures used for the measurement of these properties are usually unique and do not need much elaboration, e.g., capillary melting point, Abbé refractometry. The tests performed in this category should be determined by the physical nature of the new drug substance and by its intended use.

b) Particle size: For some new drug substances intended for use in solid or suspension drug products, particle size can have a significant effect on dissolution rates, bioavailability, and / or stability. In such instances, testing for particle size distribution should be carried out using an appropriate procedure, and acceptance criteria should be provided.

Decision tree #3 provides additional guidance on when particle size testing should be considered.

c) Polymorphic forms: Some new drug substances exist in different crystalline forms which differ in their physical properties. Polymorphism may also include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms. Differences in these forms could, in some cases, affect the quality or performance of the new drug products. In cases where differences exist which have been shown to affect drug product performance, bioavailability or stability, then the appropriate solid state should be specified.

Physicochemical measurements and techniques are commonly used to determine whether multiple forms exist. Examples of these procedures are: melting point (including hot-stage microscopy), solid state IR, X-ray powder diffraction, thermal analysis procedures (like DSC, TGA and DTA), Raman spectroscopy, optical microscopy, and solid state NMR.

Decision trees #4(1) through 4(3) provide additional guidance on when, and how, polymorphic forms should be monitored and controlled.

Note: These decision trees should be followed sequentially. Trees 1 and 2 consider whether polymorphism is exhibited by the drug substance, and whether the different polymorphic forms can affect performance of the drug product. Tree 3 should only be applied when polymorphism has been demonstrated for the drug substance, and shown to affect these properties. Tree 3 considers the potential for change in polymorphic forms in the drug product, and whether such a change has any effect on product performance.

It is generally technically very difficult to measure polymorphic changes in drug products. A surrogate test (e.g., dissolution) (see Decision tree 4(3)) can generally be used to monitor product performance, and polymorph content should only be used as a test and acceptance criterion of last resort.

d) *Tests for chiral new drug substances:* Where a new drug substance is predominantly one enantiomer, the opposite enantiomer is excluded from the qualification and identification thresholds given in the ICH Guidelines on Impurities in New Drug Substances and Impurities in New Drug Products because of practical difficulties in quantifying it at those levels. However, that impurity in the chiral new drug substance and the resulting new drug product(s) should otherwise be treated according to the principles established in those Guidelines.

Decision tree #5 summarizes when and if chiral identity tests, impurity tests, and assays may be needed for both new drug substances and new drug products, according to the following concepts:

Drug Substance: Impurities. For chiral drug substances which are developed as a single enantiomer, control of the other enantiomer should be considered in the same manner as for other impurities. However, technical limitations may preclude the same limits of quantification or qualification from being applied. Assurance of control also could be given by appropriate testing of a starting material or intermediate, with suitable justification.

Assay. An enantioselective determination of the drug substance should be part of the specification. It is considered acceptable for this to be achieved either through use of a chiral assay procedure or by the combination of an achiral assay together with appropriate methods of controlling the enantiomeric impurity.

Identity. For a drug substance developed as a single enantiomer, the identity test(s) should be capable of distinguishing both enantiomers and the racemic mixture. For a racemic drug substance, there are generally two situations where a stereospecific identity test is appropriate for release/acceptance testing: 1) where there is a significant possibility that the enantiomer might be substituted for the racemate, or 2) when there is evidence that preferential crystallization may lead to unintentional production of a non-racemic mixture.

Drug Product: Degradation products. Control of the other enantiomer in a drug product is considered necessary unless racemization has been shown to be insignificant during manufacture of the dosage form, and on storage.

Assay: An achiral assay may be sufficient where racemization has been shown to be insignificant during manufacture of the dosage form, and on storage. Otherwise a chiral assay should be used, or alternatively, the combination of an achiral assay plus a validated procedure to control the presence of the opposite enantiomer may be used.

Identity: A stereospecific identity test is not generally needed in the drug product release specification. When racemization is insignificant during manufacture of the dosage form, and on storage, stereospecific identity testing is more appropriately addressed as part of the drug substance specification. When racemization in the dosage form is a concern, chiral assay or enantiomeric impurity testing of the drug product will serve to verify identity.

e) *Water content:* This test is important in cases where the new drug substance is known to be hygroscopic or degraded by moisture or when the drug substance is known to be a stoichiometric hydrate. The acceptance criteria may be justified with data on the effects of hydration or moisture absorption. In some cases, a Loss on Drying procedure may be considered adequate; however, a detection procedure that is specific for water (e.g., Karl Fischer titration) is preferred.

f) *Inorganic impurities:* The need for inclusion of tests and acceptance criteria for inorganic impurities (e.g., catalysts) should be studied during development and based on knowledge of the manufacturing process. Procedures and acceptance criteria for sulfated ash / residue on ignition should follow pharmacopoeial precedents; other inorganic impurities may be determined by other appropriate procedures, e.g., atomic absorption spectroscopy.

g) *Microbial limits:* There may be a need to specify the total count of aerobic microorganisms, the total count of yeasts and molds, and the absence of specific objectionable bacteria (e.g., *Staphylococcus aureus*, *Escherichia coli*, *Salmonella*, *Pseudomonas aeruginosa*). These should be suitably determined using pharmacopoeial procedures. The type of microbial test(s) and acceptance criteria should be based on the nature of the drug substance, method of manufacture, and the intended use of the drug product. For example, sterility testing may be appropriate for drug substances manufactured as sterile and endotoxin testing may be appropriate for drug substances used to formulate an injectable drug product.

Decision tree #6 provides additional guidance on when microbial limits should be included.

3.3.2 New Drug Products

Additional tests and acceptance criteria generally should be included for particular new drug products. The following selection presents a representative sample of both the drug products and the types of tests and acceptance criteria which may be appropriate. The specific dosage forms addressed include solid oral drug products, liquid oral drug products, and parenterals (small and large volume). Application of the concepts in this guideline to other dosage forms is encouraged. Note that issues related to optically active drug substances and to solid state considerations for drug products are discussed in part 3.3.1. of this guideline.

3.3.2.1 The following tests are applicable to tablets (coated and uncoated) and hard capsules. One or more of these tests may also be applicable to soft capsules and granules.

a) *Dissolution:* The specification for solid oral dosage forms normally includes a test to measure release of drug substance from the drug product. Single-point measurements are normally considered to be suitable for immediate-release dosage

forms. For modified-release dosage forms, appropriate test conditions and sampling procedures should be established. For example, multiple time point sampling should be performed for extended-release dosage forms, and two-stage testing (using different media in succession or in parallel, as appropriate) may be appropriate for delayed-release dosage forms. In these cases it is important to consider the populations of individuals who will be taking the drug product (e.g., achlorhydric elderly) when designing the tests and acceptance criteria. In some cases (see 3.3.2.1 b) Disintegration) dissolution testing may be replaced by disintegration testing (see Decision Tree #7 (1)).

For immediate-release drug products where changes in dissolution rate have been demonstrated to significantly affect bioavailability, it is desirable to develop test conditions which can distinguish batches with unacceptable bioavailability. If changes in formulation or process variables significantly affect dissolution and such changes are not controlled by another aspect of the specification, it may also be appropriate to adopt dissolution test conditions which can distinguish these changes (see Decision Tree #7(2)).

Where dissolution significantly affects bioavailability, the acceptance criteria should be set to reject batches with unacceptable bioavailability. Otherwise, test conditions and acceptance criteria should be established which pass clinically acceptable batches (see Decision Tree #7(2)).

For extended-release drug products, in vitro / in vivo correlation may be used to establish acceptance criteria when human bioavailability data are available for formulations exhibiting different release rates. Where such data are not available, and drug release cannot be shown to be independent of in vitro test conditions, then acceptance criteria should be established on the basis of available batch data. Normally, the permitted variability in mean release rate at any given time point should not exceed a total numerical difference of $\pm 10\%$ of the labeled content of drug substance (i.e., a total variability of 20%: a requirement of 50 $\pm 10\%$ thus means an acceptable range from 40% to 60%), unless a wider range is supported by a bioequivalency study (see Decision Tree #7(3)).

b) Disintegration: For rapidly dissolving (dissolution $>80\%$ in 15 minutes at pH 1.2, 4.0 and 6.8) products containing drugs which are highly soluble throughout the physiological range (dose/solubility volume < 250 mL from pH 1.2 to 6.8), disintegration may be substituted for dissolution. Disintegration testing is most appropriate when a relationship to dissolution has been established or when disintegration is shown to be more discriminating than dissolution. In such cases dissolution testing may not be necessary. It is expected that development information will be provided to support the robustness of the formulation and manufacturing process with respect to the selection of dissolution vs. disintegration testing (see Decision Tree #7(1)).

c) Hardness/friability: It is normally appropriate to perform hardness and/or friability testing as an in-process control (see section 2.3). Under these circumstances, it is normally not necessary to include these attributes in the specification. If the characteristics of hardness and friability have a critical impact on drug product quality (e.g., chewable tablets), acceptance criteria should be included in the specification.

d) Uniformity of dosage units: This term includes both the mass of the dosage form and the content of the active substance in the dosage form; a pharmacopoeial procedure should be used. In general, the specification should include one or the other but not both. If appropriate, these tests may be performed in-process; the acceptance criteria should be included in the specification. When weight variation is applied for

new drug products exceeding the threshold value to allow testing uniformity by weight variation, applicants should verify during drug development that the homogeneity of the product is adequate.

e) Water content: A test for water content should be included when appropriate. The acceptance criteria may be justified with data on the effects of hydration or water absorption on the drug product. In some cases, a Loss on Drying procedure may be considered adequate; however, a detection procedure which is specific for water (e.g., Karl Fischer titration) is preferred.

f) Microbial limits: Microbial limit testing is seen as an attribute of Good Manufacturing Practice, as well as of quality assurance. In general, it is advisable to test the drug product unless its components are tested before manufacture and the manufacturing process is known, through validation studies, not to carry a significant risk of microbial contamination or proliferation. It should be noted that, whereas this guideline does not directly address excipients, the principles discussed here may be applicable to excipients as well as to new drug products. Skip testing may be an appropriate approach in both cases where permissible. (See Decision Tree #6 for microbial testing of excipients.)

Acceptance criteria should be set for the total count of aerobic microorganisms, the total count of yeasts and molds, and the absence of specific objectionable bacteria (e.g., *Staphylococcus aureus*, *Escherichia coli*, *Salmonella*, *Pseudomonas aeruginosa*). These should be determined by suitable procedures, using pharmacopoeial procedures, and at a sampling frequency or time point in manufacture which is justified by data and experience. The type of microbial test(s) and acceptance criteria should be based on the nature of the drug substance, method of manufacture, and the intended use of the drug product. With acceptable scientific justification, it should be possible to propose no microbial limit testing for solid oral dosage forms.

Decision tree #8 provides additional guidance on the use of microbial limits testing.

3.3.2.2 Oral liquids: One or more of the following specific tests will normally be applicable to oral liquids and to powders intended for reconstitution as oral liquids.

a) Uniformity of dosage units: This term includes both the mass of the dosage form and the content of the active substance in the dosage form; a pharmacopoeial procedure should be used. In general, the specification should include one or the other but not both. When weight variation is applied for new drug products exceeding the threshold value to allow testing uniformity by weight variation, applicants should verify during drug development that the homogeneity of the product is adequate.

If appropriate, tests may be performed in-process; however, the acceptance criteria should be included in the specification. This concept may be applied to both single-dose and multiple-dose packages.

The dosage unit is considered to be the typical dose taken by the patient. If the actual unit dose, as taken by the patient, is controlled, it may either be measured directly or calculated, based on the total measured weight or volume of drug divided by the total number of doses expected. If dispensing equipment (such as medicine droppers or dropper tips for bottles) is an integral part of the packaging, this equipment should be used to measure the dose. Otherwise, a standard volume measure should be used. The dispensing equipment to be used is normally determined during development.

For powders for reconstitution, uniformity of mass testing is generally considered acceptable.

b) pH: Acceptance criteria for pH should be provided where applicable and the proposed range justified.

c) *Microbial limits:* Microbial limit testing is seen as an attribute of Good Manufacturing Practice, as well as of quality assurance. In general, it is advisable to test the drug product unless its components are tested before manufacture and the manufacturing process is known, through validation studies, not to carry a significant risk of microbial contamination or proliferation. It should be noted that, whereas this Guideline does not directly address excipients, the principles discussed here may be applicable to excipients as well as to new drug products. Skip testing may be an appropriate approach in both cases where permissible. With acceptable scientific justification, it may be possible to propose no microbial limit testing for powders intended for reconstitution as oral liquids.

Acceptance criteria should be set for the total count of aerobic microorganisms, total count of yeasts and molds, and the absence of specific objectionable bacteria (e.g., *Staphylococcus aureus*, *Escherichia coli*, *Salmonella*, *Pseudomonas aeruginosa*). These should be determined by suitable procedures, using pharmacopoeial procedures, and at a sampling frequency or time point in manufacture which is justified by data and experience.

Decision tree #8 provides additional guidance on the use of microbial limits testing.

d) *Antimicrobial preservative content:* For oral liquids needing an antimicrobial preservative, acceptance criteria for preservative content should be established. Acceptance criteria for preservative content should be based upon the levels of antimicrobial preservative necessary to maintain microbiological quality of the product at all stages throughout its proposed usage and shelf-life. The lowest specified concentration of antimicrobial preservative should be demonstrated to be effective in controlling microorganisms by using a pharmacopoeial antimicrobial preservative effectiveness test.

Testing for antimicrobial preservative content should normally be performed at release. Under certain circumstances, in-process testing may suffice in lieu of release testing. When antimicrobial preservative content testing is performed as an in-process test, the acceptance criteria should remain part of the specification.

Antimicrobial preservative effectiveness should be demonstrated during development, during scaleup, and throughout the shelf-life (e.g., in stability testing: see the ICH Guideline, "Stability Testing of New Drug Substances and Products"), although chemical testing for preservative content is the attribute normally included in the specification.

e) *Antioxidant preservative content:* Release testing for antioxidant content should normally be performed. Under certain circumstances, where justified by developmental and stability data, shelf-life testing may be unnecessary, and in-process testing may suffice in lieu of release testing where permitted. When antioxidant content testing is performed as an in-process test, the acceptance criteria should remain part of the specification. If only release testing is performed, this decision should be reinvestigated whenever either the manufacturing procedure or the container/closure system changes.

f) *Extractables:* Generally, where development and stability data show evidence that extractables from the container/closure systems are consistently below levels that are demonstrated to be acceptable and safe, elimination of this test can normally be accepted. This should be reinvestigated if the container/closure system or formulation changes.

Where data demonstrate the need, tests and acceptance criteria for extractables from the container/closure system components (e.g., rubber stopper, cap liner, plastic bottle, etc.) are considered appropriate for oral solutions packaged in non-glass

systems, or in glass containers with non-glass closures. The container/closure components should be listed, and data collected for these components as early in the development process as possible.

g) Alcohol content: Where it is declared quantitatively on the label in accordance with pertinent regulations, the alcohol content should be specified. It may be assayed or calculated.

h) Dissolution: In addition to the attributes recommended immediately above, it may be appropriate (e.g., insoluble drug substance) to include dissolution testing and acceptance criteria for oral suspensions and dry powder products for resuspension. Dissolution testing should be performed at release. This test may be performed as an in-process test when justified by product development data. The testing apparatus, media, and conditions should be pharmacopoeial, if possible, or otherwise justified. Dissolution procedures using either pharmacopoeial or non-pharmacopoeial apparatus and conditions should be validated.

Single-point measurements are normally considered suitable for immediate-release dosage forms. Multiple-point sampling, at appropriate intervals, should be performed for modified-release dosage forms. Acceptance criteria should be set based on the observed range of variation, and should take into account the dissolution profiles of the batches that showed acceptable performance in vivo. Developmental data should be considered when determining the need for either a dissolution procedure or a particle size distribution procedure.

i) Particle size distribution: Quantitative acceptance criteria and a procedure for determination of particle size distribution may be appropriate for oral suspensions. Developmental data should be considered when determining the need for either a dissolution procedure or a particle size distribution procedure for these formulations.

Particle size distribution testing should be performed at release. It may be performed as an in-process test when justified by product development data. If these products have been demonstrated during development to have consistently rapid drug release characteristics, exclusion of a particle size distribution test from the specification may be proposed.

Particle size distribution testing may also be proposed in place of dissolution testing; justification should be provided. The acceptance criteria should include acceptable particle size distribution in terms of the percent of total particles in given size ranges. The mean, upper, and / or lower particle size limits should be well defined.

Acceptance criteria should be set based on the observed range of variation, and should take into account the dissolution profiles of the batches that showed acceptable performance in vivo, as well as the intended use of the product. The potential for particle growth should be investigated during product development; the acceptance criteria should take the results of these studies into account.

j) Redispersibility: For oral suspensions which settle on storage (produce sediment), acceptance criteria for redispersibility may be appropriate. Shaking may be an appropriate procedure.

The procedure (mechanical or manual) should be indicated. Time required to achieve resuspension by the indicated procedure should be clearly defined. Data generated during product development may be sufficient to justify skip lot testing, or elimination of this attribute from the specification may be proposed.

k) Rheological properties: For relatively viscous solutions or suspensions, it may be appropriate to include rheological properties (viscosity/specific gravity) in the specification. The test and acceptance criteria should be stated. Data generated

during product development may be sufficient to justify skip lot testing, or elimination of this attribute from the specification may be proposed.

l) Reconstitution time: Acceptance criteria for reconstitution time should be provided for dry powder products which require reconstitution. The choice of diluent should be justified. Data generated during product development may be sufficient to justify skip lot testing or elimination of this attribute from the specification may be proposed.

m) Water content: For oral products requiring reconstitution, a test and acceptance criterion for water content should be proposed when appropriate. Loss on drying is generally considered sufficient if the effect of absorbed moisture vs. water of hydration has been adequately characterized during the development of the product. In certain cases a more specific procedure (e.g., Karl Fischer titration) may be preferable.

3.3.2.3 Parenteral Drug Products: The following tests may be applicable to parenteral drug products.

a) Uniformity of dosage units: This term includes both the mass of the dosage form and the content of the active substance in the dosage form; a pharmacopoeial procedure should be used. In general, the specification should one or the other but not both and is applicable to powders for reconstitution. When weight variation is applied for new drug products exceeding the threshold value to allow testing uniformity by weight variation, applicants should verify during drug development that the homogeneity of the product is adequate.

If appropriate (see section 2.3), these tests may be performed in-process; the acceptance criteria should be included in the specification. This test may be applied to both single-dose and multiple-dose packages.

For powders for reconstitution, uniformity of mass testing is generally considered acceptable.

b) pH: Acceptance criteria for pH should be provided where applicable and the proposed range justified.

c) Sterility: All parenteral products should have a test procedure and acceptance criterion for evaluation of sterility. Where data generated during development and validation justify parametric release, this approach may be proposed for terminally sterilized drug products (see section 2.6).

d) Endotoxins/Pyrogens: A test procedure and acceptance criterion for endotoxins, using a procedure such as the limulus amoebocyte lysate test, should be included in the specification. Pyrogenicity testing may be proposed as an alternative to endotoxin testing where justified.

e) Particulate matter: Parenteral products should have appropriate acceptance criteria for particulate matter. This will normally include acceptance criteria for visible particulates and / or clarity of solution, as well as for sub-visible particulates as appropriate.

f) Water content: For non-aqueous parenterals, and for parenteral products for reconstitution, a test procedure and acceptance criterion for water content should be proposed when appropriate. Loss on drying is generally considered sufficient for parenteral products, if the effect of absorbed moisture vs. water of hydration has been adequately characterized during development. In certain cases a more specific procedure (e.g., Karl Fischer titration) may be preferred.

g) Antimicrobial preservative content: For parenteral products needing an antimicrobial preservative, acceptance criteria for preservative content should be established. Acceptance criteria for preservative content should be based upon the

levels of antimicrobial preservative necessary to maintain microbiological quality of the product at all stages throughout its proposed usage and shelf life. The lowest specified concentration of antimicrobial preservative should be demonstrated to be effective in controlling microorganisms by using a pharmacopoeial antimicrobial preservative effectiveness test.

Testing for antimicrobial preservative content should normally be performed at release. Under certain circumstances, in-process testing may suffice in lieu of release testing where permitted. When antimicrobial preservative content testing is performed as an in-process test, the acceptance criteria should remain part of the specification.

Antimicrobial preservative effectiveness should be demonstrated during development, during scaleup, and throughout the shelf-life (e.g., in stability testing: see the ICH Guideline, "Stability Testing of New Drug Substances and Products"), although chemical testing for preservative content is the attribute normally included in the specification.

h) Antioxidant preservative content: Release testing for antioxidant content should normally be performed. Under certain circumstances, where justified by developmental and stability data, shelf-life testing may be unnecessary and in-process testing may suffice in lieu of release testing. When antioxidant content testing is performed as an in-process test, the acceptance criteria should remain part of the specification. If only release testing is performed, this decision should be reinvestigated whenever either the manufacturing procedure or the container/closure system changes.

i) Extractables: Control of extractables from container/closure systems is considered significantly more important for parenteral products than for oral liquids. However, where development and stability data show evidence that extractables are consistently below the levels that are demonstrated to be acceptable and safe, elimination of this test can normally be accepted. This should be reinvestigated if the container/closure system or formulation changes.

Where data demonstrate the need, acceptance criteria for extractables from the container/closure components are considered appropriate for parenteral products packaged in non-glass systems or in glass containers with elastomeric closures. This testing may be performed at release only, where justified by data obtained during development. The container/closure system components (e.g., rubber stopper, etc.) should be listed, and data collected for these components as early in the development process as possible.

j) Functionality testing of delivery systems: Parenteral formulations packaged in pre-filled syringes, autoinjector cartridges, or the equivalent should have test procedures and acceptance criteria related to the functionality of the delivery system. These may include control of syringeability, pressure, and seal integrity (leakage), and/or parameters such as tip cap removal force, piston release force, piston travel force, and power injector function force. Under certain circumstances these tests may be performed in-process. Data generated during product development may be sufficient to justify skip lot testing or elimination of some or all attributes from the specification.

k) Osmolarity: When the tonicity of a product is declared in its labeling, appropriate control of its osmolarity should be performed. Data generated during development and validation may be sufficient to justify performance of this procedure as an in-process control, skip lot testing, or direct calculation of this attribute.

l) Particle size distribution: Quantitative acceptance criteria and a procedure for determination of particle size distribution may be appropriate for injectable suspensions. Developmental data should be considered when determining the need for either a dissolution procedure or a particle size distribution procedure.

Particle size distribution testing should be performed at release. It may be performed as an in-process test when justified by product development data. If the product has been demonstrated during development to have consistently rapid drug release characteristics, exclusion of particle size controls from the specification may be proposed.

Particle size distribution testing may also be proposed in place of dissolution testing, when development studies demonstrate that particle size is the primary factor influencing dissolution; justification should be provided. The acceptance criteria should include acceptable particle size distribution in terms of the percent of total particles in given size ranges. The mean, upper, and / or lower particle size limits should be well defined.

Acceptance criteria should be set based on the observed range of variation, and should take into account the dissolution profiles of the batches that showed acceptable performance in vivo and the intended use of the product. The potential for particle growth should be investigated during product development; the acceptance criteria should take the results of these studies into account.

m) Redispersibility: For injectable suspensions which settle on storage (produce sediment), acceptance criteria for redispersibility may be appropriate. Shaking may be an appropriate procedure. The procedure (mechanical or manual) should be indicated. Time required to achieve resuspension by the indicated procedure should be clearly defined. Data generated during product development may be sufficient to justify skip lot testing, or elimination of this attribute from the specification may be proposed.

n) Reconstitution time: Acceptance criteria for reconstitution time should be provided for all parenteral products which require reconstitution. The choice of diluent should be justified. Data generated during product development and process validation may be sufficient to justify skip lot testing or elimination of this attribute from the specification for rapidly dissolving products.

4. GLOSSARY

(The following definitions are presented for the purpose of this Guideline)

Acceptance criteria:

Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures.

Chiral:

Not superimposable with its mirror image, as applied to molecules, conformations, and macroscopic objects, such as crystals. The term has been extended to samples of substances whose molecules are chiral, even if the macroscopic assembly of such molecules is racemic.

Combination product:

A drug product which contains more than one drug substance.

Degradation product:

A molecule resulting from a chemical change in the drug molecule brought about over time and/or by the action of e.g., light, temperature, pH, water, or by reaction with an excipient and/or the immediate container/closure system. Also called decomposition product.

Delayed Release:

Release of a drug (or drugs) at a time other than immediately following oral administration.

Enantiomers:

Compounds with the same molecular formula as the drug substance, which differ in the spatial arrangement of atoms within the molecule and are nonsuperimposable mirror images.

Extended Release:

Products which are formulated to make the drug available over an extended period after administration.

Highly Water Soluble Drugs:

Drugs with a dose/solubility volume of less than or equal to 250 mL over a pH range of 1.2 to 6.8. (Example: Compound A has as its lowest solubility at $37 \pm 0.5^\circ\text{C}$, 1.0 mg/mL at pH 6.8, and is available in 100 mg, 200 mg, and 400 mg strengths. This drug would be considered a low solubility drug as its dose/solubility volume is greater than 250 mL ($400 \text{ mg}/1.0 \text{ mg/mL} = 400 \text{ mL}$).

Immediate Release:

Allows the drug to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption of the drug.

Impurity:

(1) Any component of the new drug substance which is not the chemical entity defined as the new drug substance. (2) Any component of the drug product which is not the chemical entity defined as the drug substance or an excipient in the drug product.

Identified impurity:

An impurity for which a structural characterization has been achieved.

In-process tests:

Tests which may be performed during the manufacture of either the drug substance or drug product, rather than as part of the formal battery of tests which are conducted prior to release.

Modified Release:

Dosage forms whose drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as a solution or an immediate release dosage form. Modified release solid oral dosage forms include both delayed and extended release drug products.

New drug product:

A pharmaceutical product type, for example, tablet, capsule, solution, cream, etc., which has not previously been registered in a region or Member State, and which contains a drug ingredient generally, but not necessarily, in association with excipients.

New drug substance:

The designated therapeutic moiety, which has not previously been registered in a region or Member State (also referred to as a new molecular entity or new chemical entity). It may be a complex, simple ester, or salt of a previously approved drug substance.

Polymorphism:

The occurrence of different crystalline forms of the same drug substance. This may include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms.

Quality:

The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity.

Racemate:

A composite (solid, liquid, gaseous, or in solution) of equimolar quantities of two enantiomeric species. It is devoid of optical activity.

Rapidly Dissolving Products:

An immediate release solid oral drug product is considered rapidly dissolving when not less than 80% of the label amount of the drug substance dissolves within 15 minutes in each of the following media: (1) pH 1.2, (2) pH 4.0, and (3) pH 6.8.

Reagent:

A substance, other than a starting material or solvent, which is used in the manufacture of a new drug substance.

Solvent:

An inorganic or an organic liquid used as a vehicle for the preparation of solutions or suspensions in the synthesis of a new drug substance or the manufacture of a new drug product.

Specification:

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. "Conformance to specifications" means that the drug substance and / or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities.

Specific test:

A test which is considered to be applicable to particular new drug substances or particular new drug products depending on their specific properties and/or intended use.

Specified impurity:

An identified or unidentified impurity that is selected for inclusion in the new drug substance or new drug product specification and is individually listed and limited in order to assure the quality of the new drug substance or new drug product.

Unidentified impurity:

An impurity which is defined solely by qualitative analytical properties, (e.g., chromatographic retention time).

Universal test:

A test which is considered to be potentially applicable to all new drug substances, or all new drug products; e.g., appearance, identification, assay, and impurity tests.

5. REFERENCES

International Conference on Harmonisation; *"Impurities in New Drug Substances"*, 1995.

International Conference on Harmonisation; *"Impurities in New Drug Products"*, 1996.

International Conference on Harmonisation; *"Stability Testing of New Drug Substances and Products"*, 1994.

International Conference on Harmonisation; *"Text on Validation of Analytical Procedures"*, 1994.

International Conference on Harmonisation; *"Validation of Analytical Procedures: Methodology"*, 1996.

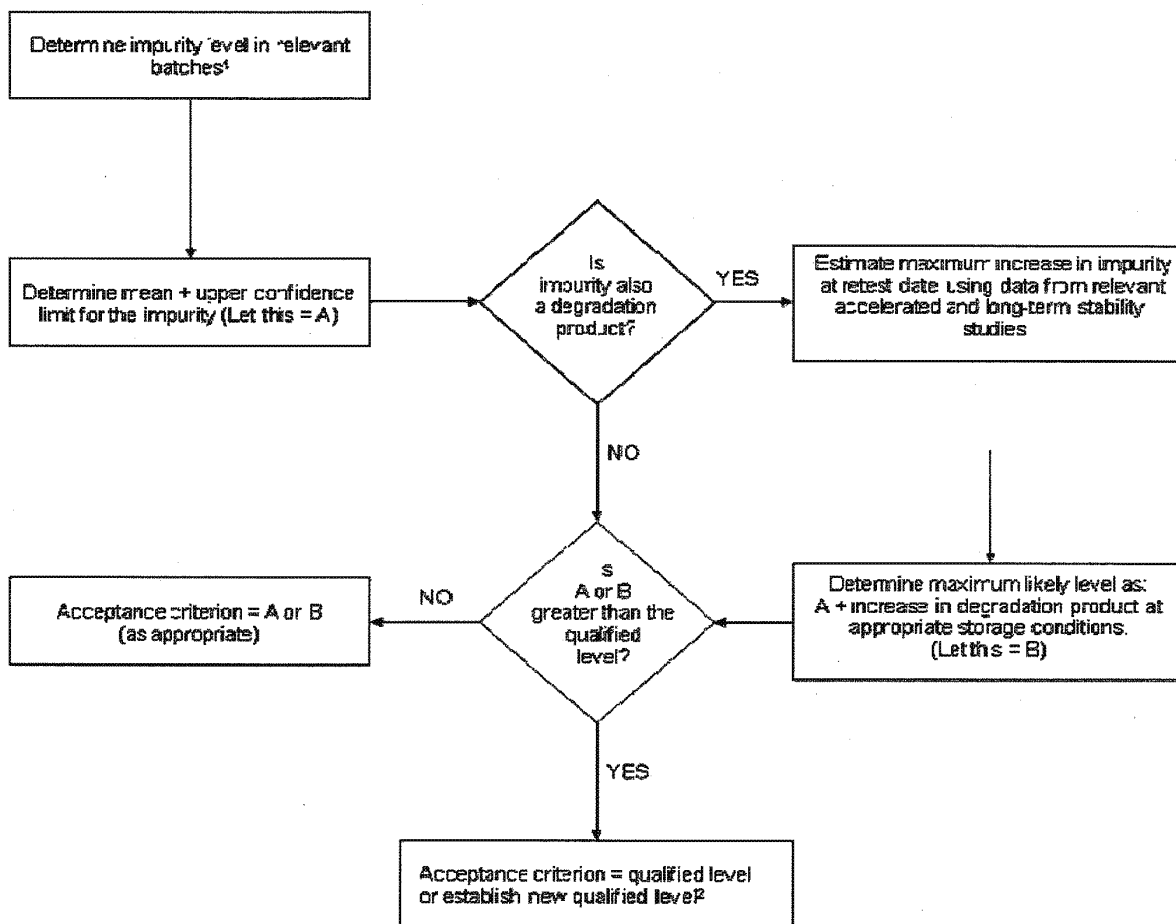
International Conference on Harmonisation, *"Residual Solvents in Pharmaceuticals"*, 1996.

International Conference on Harmonisation, *"Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products"*, 1999

6. ATTACHMENTS

Decision Trees #1 through #8

DECISION TREE #1: ESTABLISHING ACCEPTANCE CRITERION
FOR A SPECIFIED IMPURITY IN A NEW DRUG SUBSTANCE

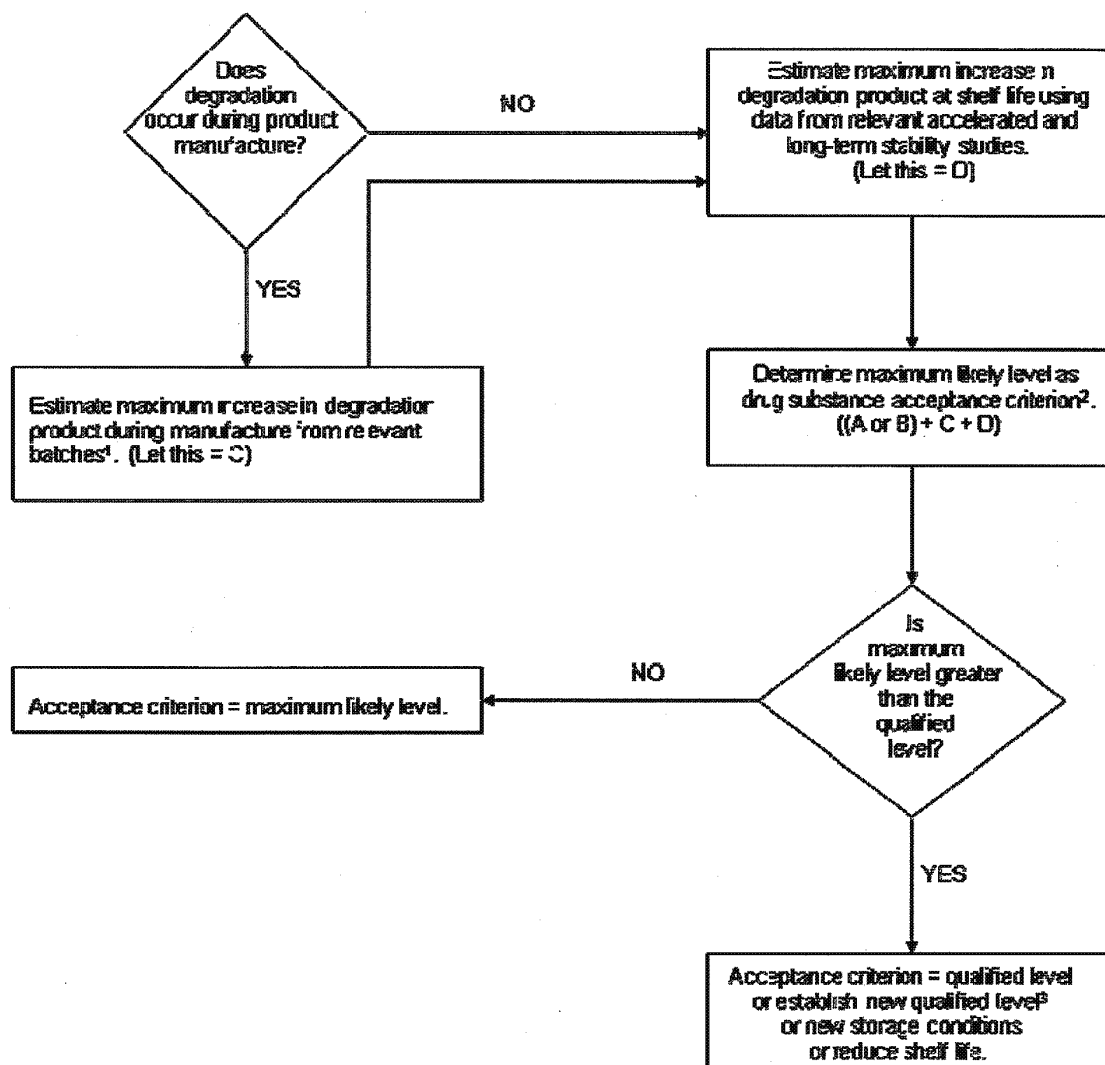


¹ Relevant batches are those from development, pilot and scale-up studies.

² Refer to ICH Guideline on Impurities in New Drug Substances

Definition: upper confidence limit = three times the standard deviation of batch analysis data

DECISION TREE #2: ESTABLISHING ACCEPTANCE CRITERION FOR A DEGRADATION PRODUCT IN A NEW DRUG PRODUCT

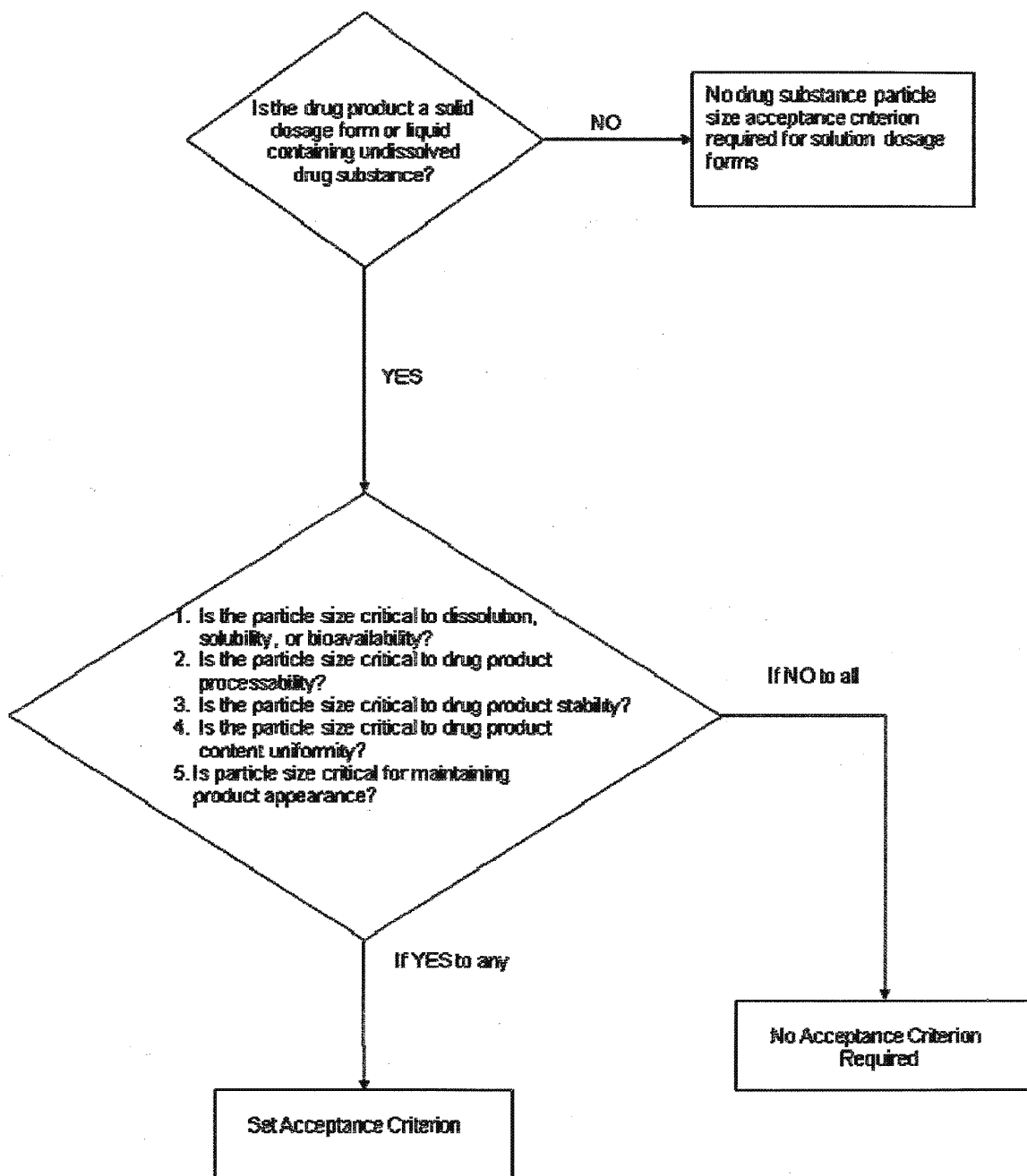


¹ Relevant batches are those from development, pilot and scale-up studies.

² Refer to Decision Tree 1 for information regarding A and B.

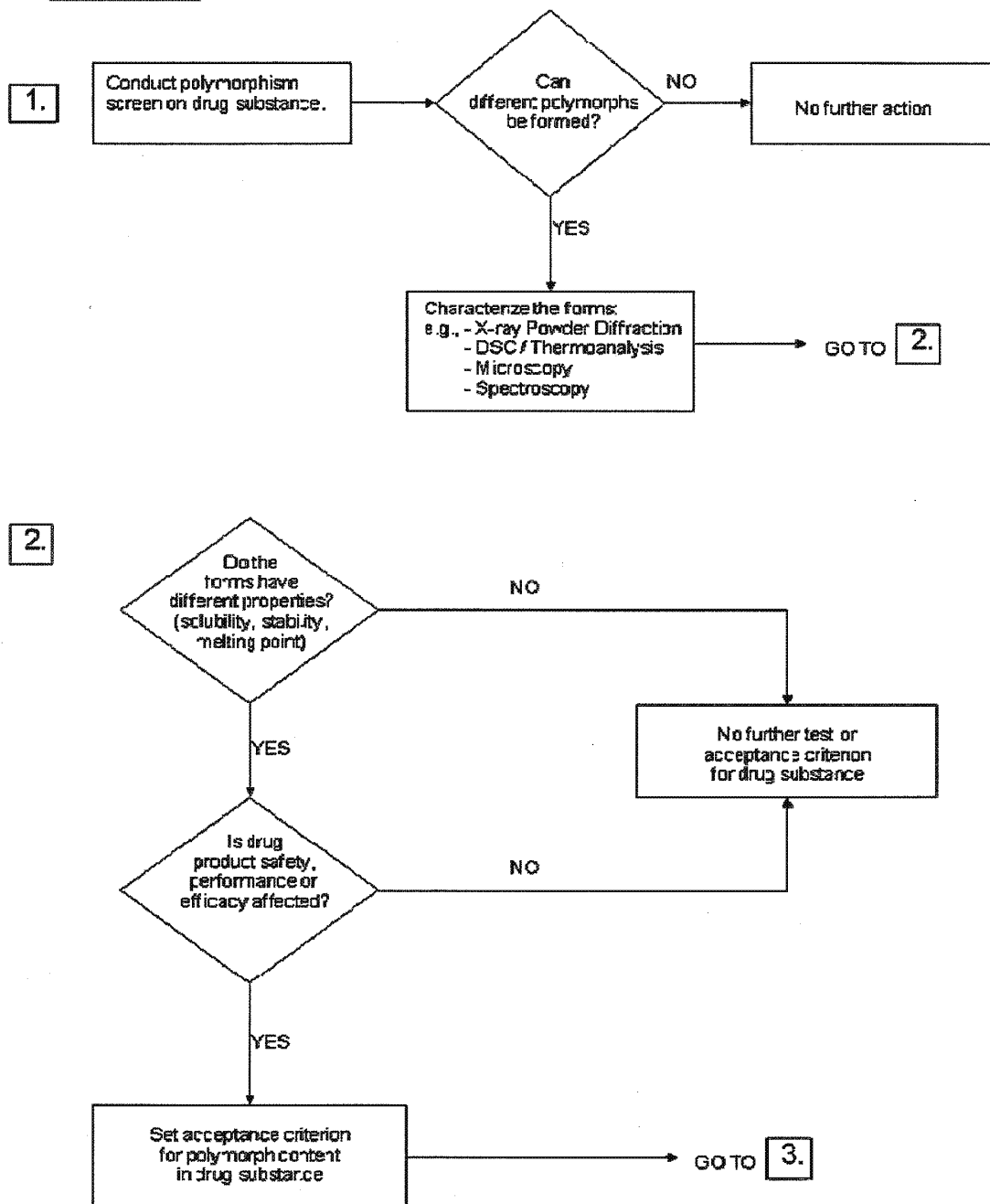
³ Refer to ICH Guideline on Impurities in New Drug Products.

**DECISION TREE #3: SETTING ACCEPTANCE CRITERIA FOR
DRUG SUBSTANCE PARTICLE SIZE DISTRIBUTION**



**DECISION TREE #4: INVESTIGATING THE NEED TO SET
ACCEPTANCE CRITERIA FOR POLYMORPHISM
IN DRUG SUBSTANCES AND DRUG PRODUCTS**

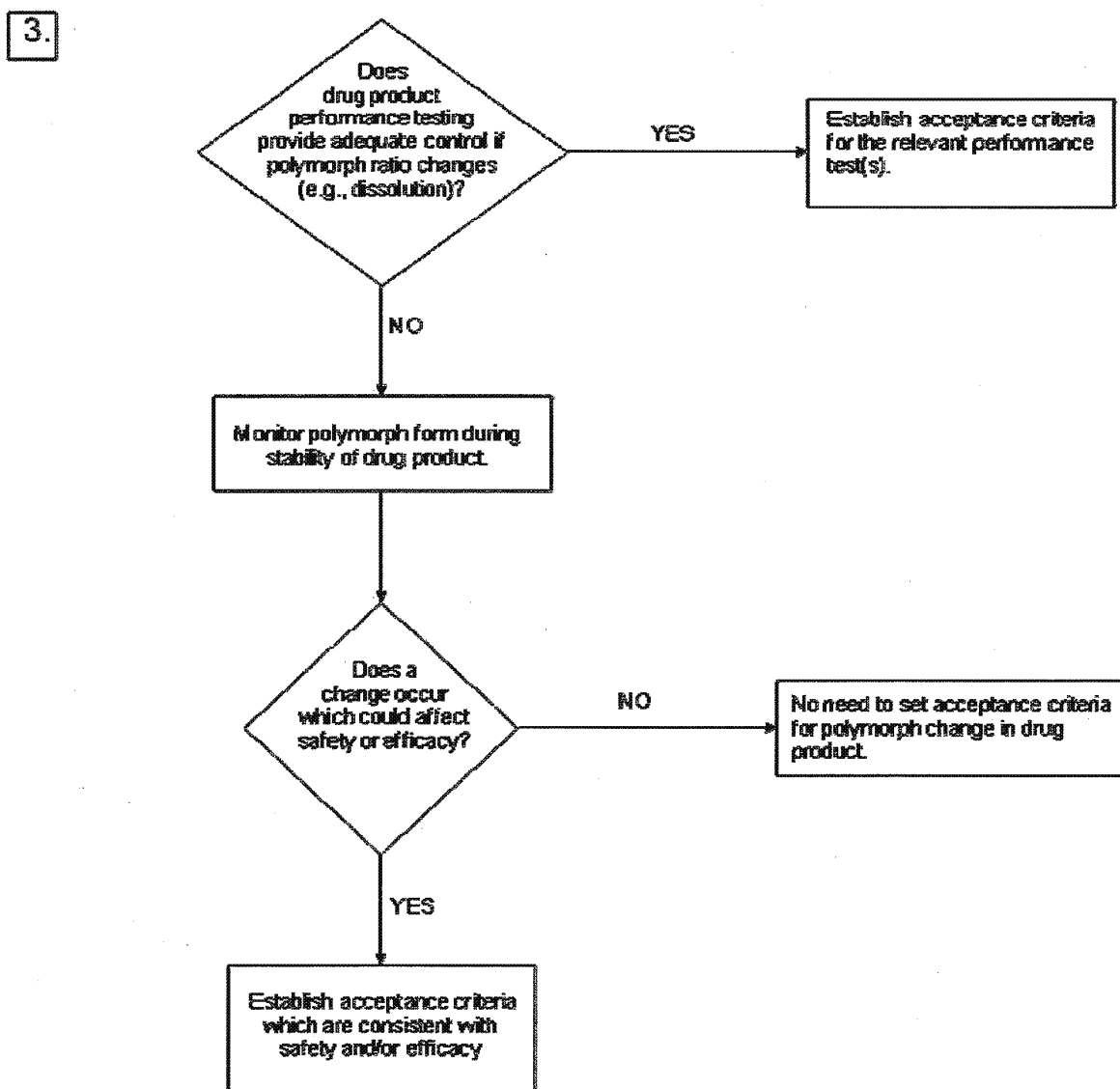
Drug Substance



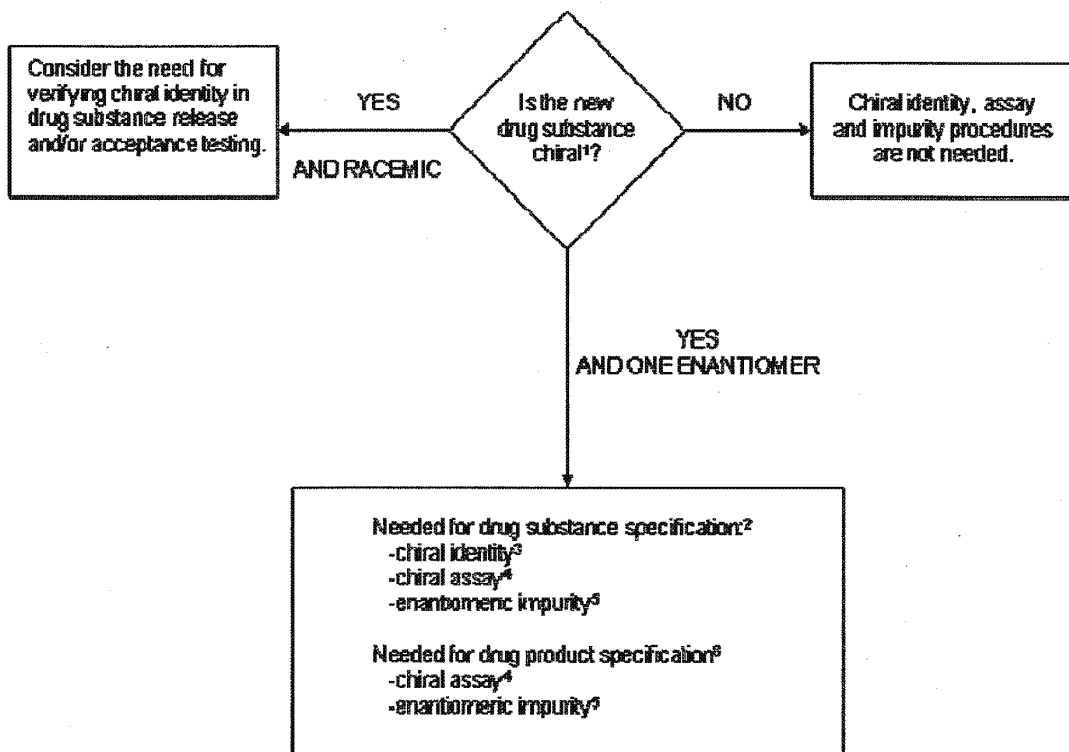
**DECISION TREE #4: INVESTIGATING THE NEED TO SET
ACCEPTANCE CRITERIA FOR POLYMORPHISM
IN DRUG SUBSTANCES AND DRUG PRODUCTS**

Drug Product - Solid Dosage Form or Liquid Containing Undissolved Drug Substance

N.B.: Undertake the following processes only if technically possible
to measure polymorph content in the drug product.



**DECISION TREE#5: ESTABLISHING IDENTITY, ASSAY
AND ENANTIOMERIC IMPURITY PROCEDURES FOR CHIRAL
NEW DRUG SUBSTANCES AND NEW DRUG PRODUCTS
CONTAINING CHIRAL DRUG SUBSTANCES**



¹ Chiral substances of natural origin are not addressed in this Guideline.

² As with other impurities arising in and from raw materials used in drug substance synthesis, control of chiral quality could be established alternatively by applying limits to appropriate starting materials or intermediates when justified from developmental studies. This essentially will be the case when there are multiple chiral centers (e.g., three or more), or when control at a step prior to production of the final drug substance is desirable.

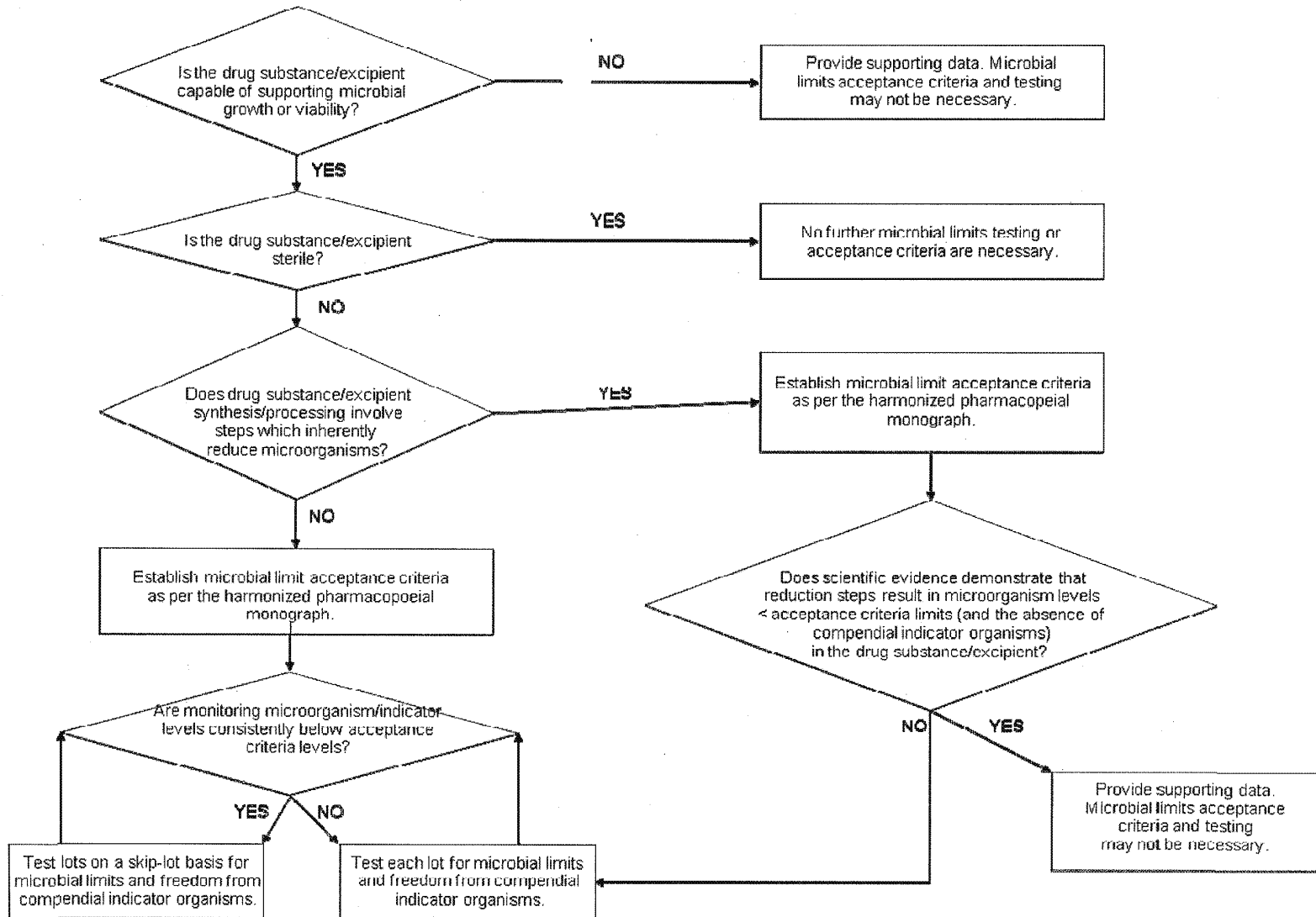
³ A chiral assay or an enantiomeric impurity procedure may be acceptable in lieu of a chiral identity procedure.

⁴ An achiral assay combined with a method for controlling the opposite enantiomer is acceptable in lieu of a chiral assay.

⁵ The level of the opposite enantiomer of the drug substance may be derived from chiral assay data or from a separate procedure.

⁶ Stereospecific testing of drug product may not be necessary if racemization has been demonstrated to be insignificant during drug product manufacture and during storage of the finished dosage form.

DECISION TREE #6: MICROBIOLOGICAL QUALITY ATTRIBUTES OF DRUG SUBSTANCE AND EXCIPIENTS



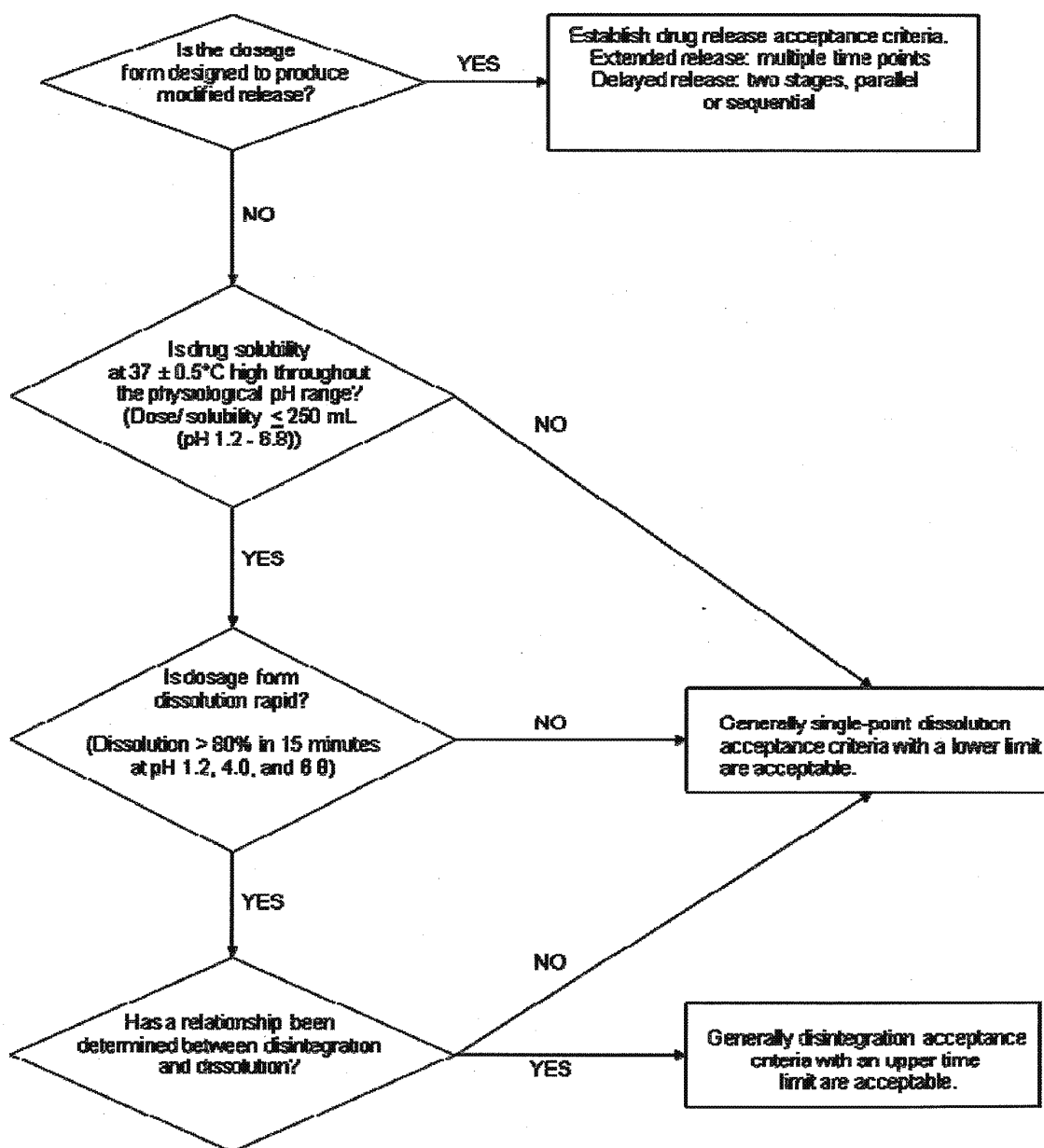
Specifications: New Chemical Drug Substances and Products

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DECISION TREES #7: SETTING ACCEPTANCE CRITERIA FOR DRUG PRODUCT DISSOLUTION

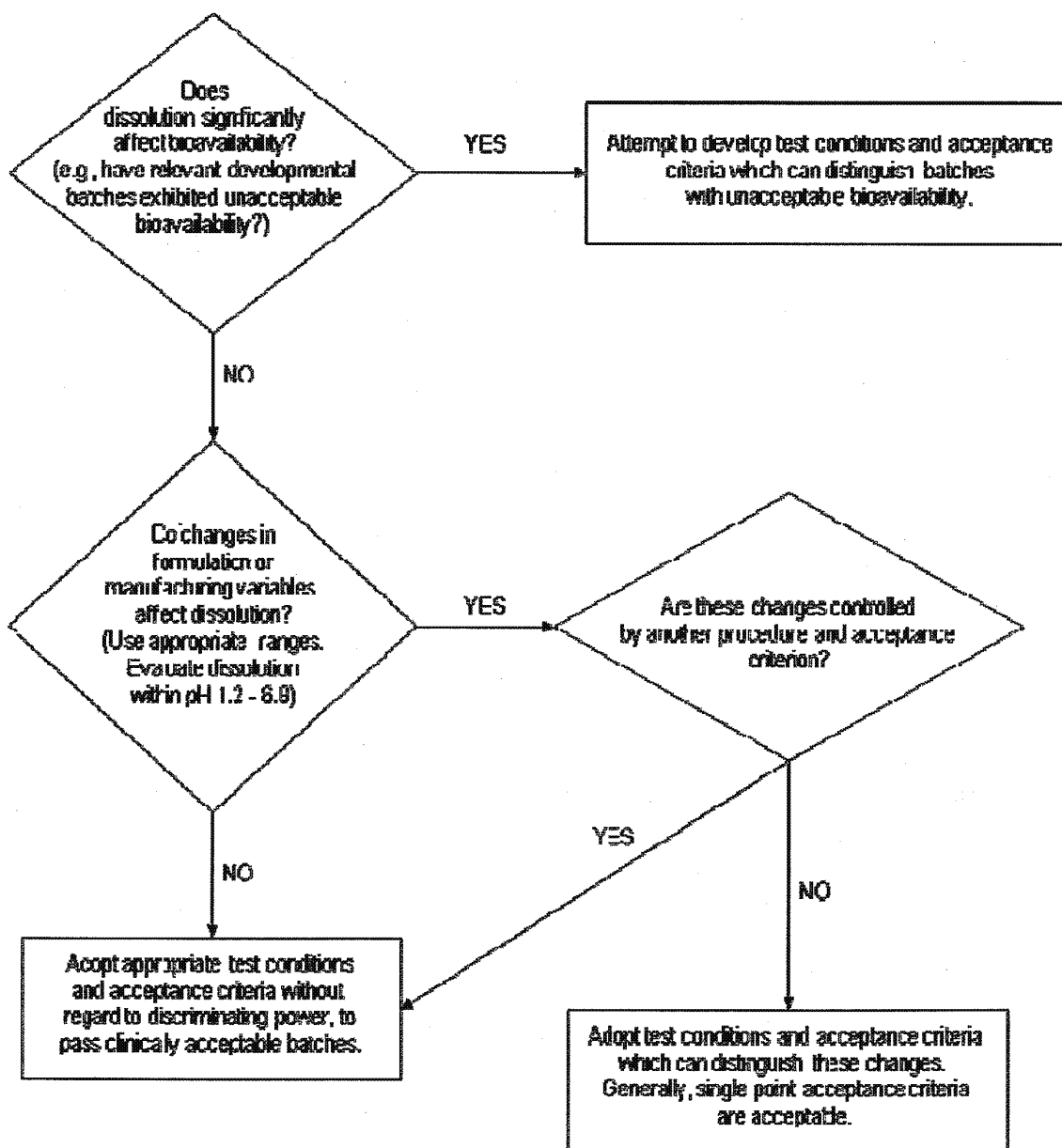
1. What type of drug release acceptance criteria are appropriate?



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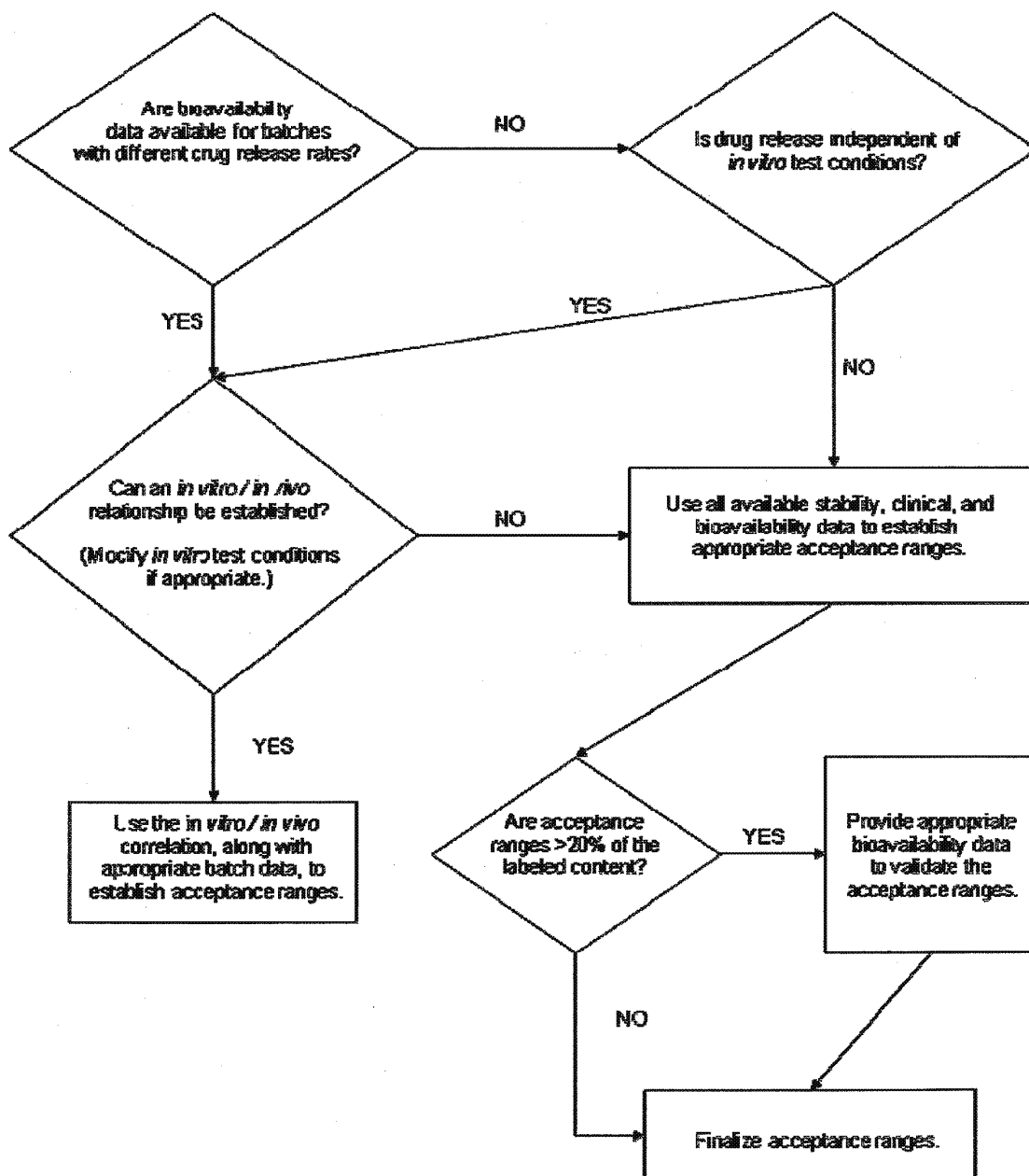
DECISION TREES #7: SETTING ACCEPTANCE CRITERIA FOR DRUG PRODUCT DISSOLUTION

2. What specific test conditions and acceptance criteria are appropriate? [immediate release]

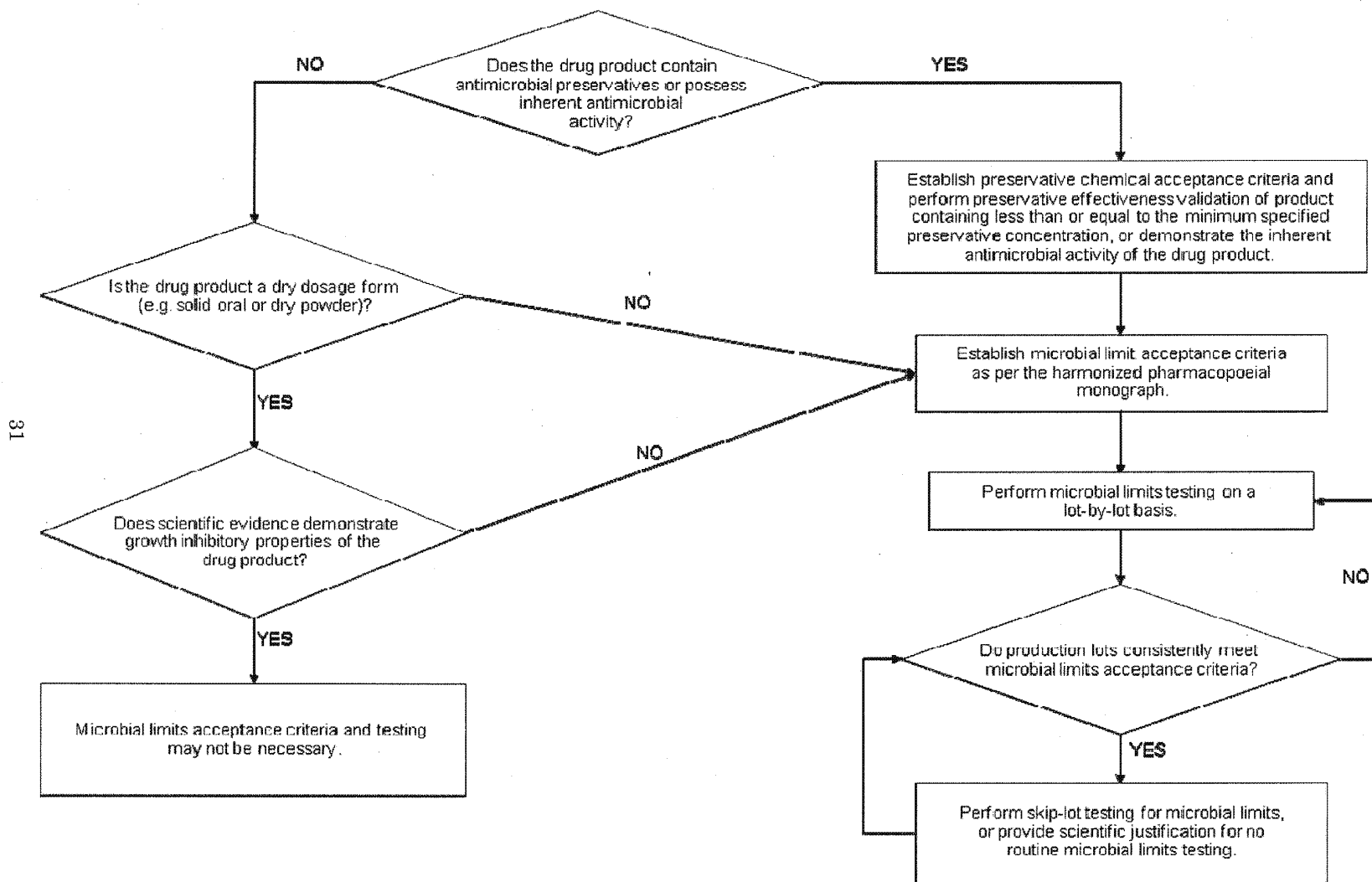


DECISION TREES #7: SETTING
ACCEPTANCE CRITERIA
FOR DRUG PRODUCT DISSOLUTION

3. What are appropriate acceptance ranges? [extended release]



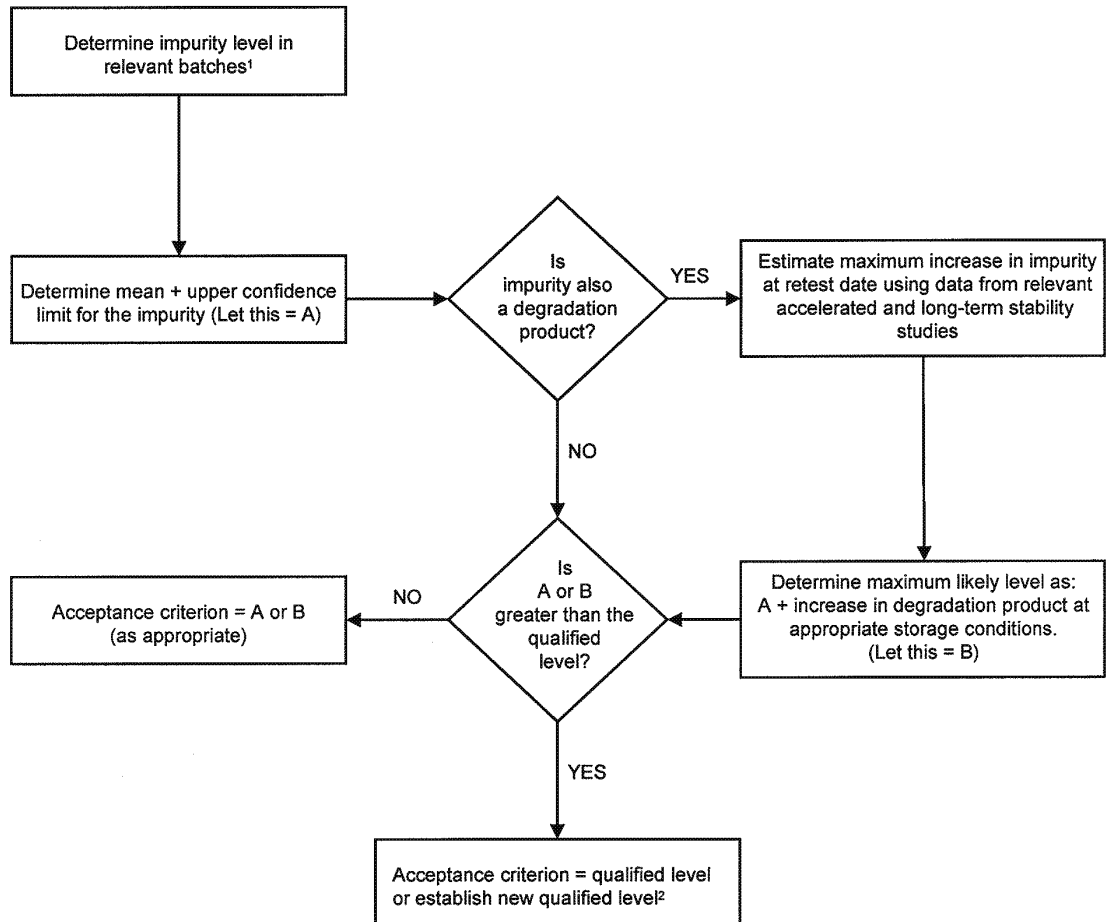
DECISION TREE #8: MICROBIOLOGICAL ATTRIBUTES OF NON-STERILE DRUG PRODUCTS



Specifications: New Chemical Drug Substances and Products

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DECISION TREE #1: ESTABLISHING ACCEPTANCE CRITERION
FOR A SPECIFIED IMPURITY IN A NEW DRUG SUBSTANCE

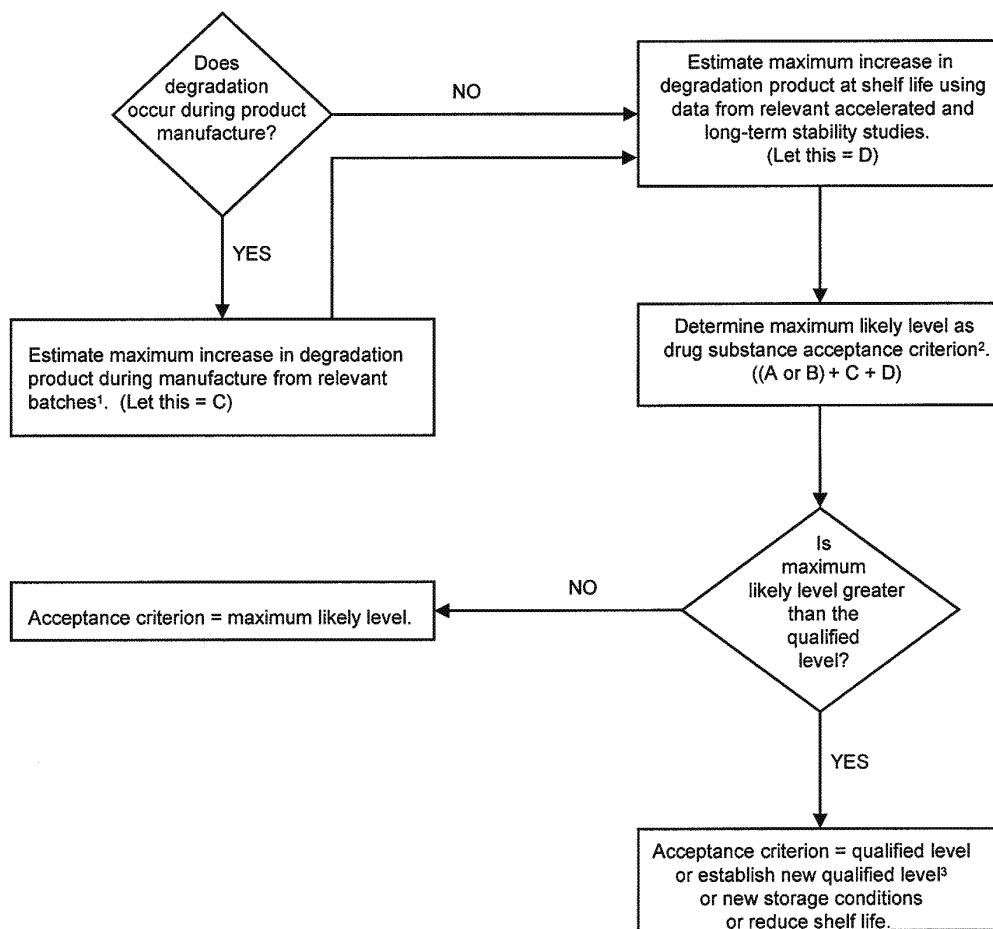


¹ Relevant batches are those from development, pilot and scale-up studies.

² Refer to ICH Guideline on Impurities in New Drug Substances

Definition: upper confidence limit = three times the standard deviation of batch analysis data

DECISION TREE #2: ESTABLISHING ACCEPTANCE CRITERION
FOR A DEGRADATION PRODUCT IN A NEW DRUG PRODUCT

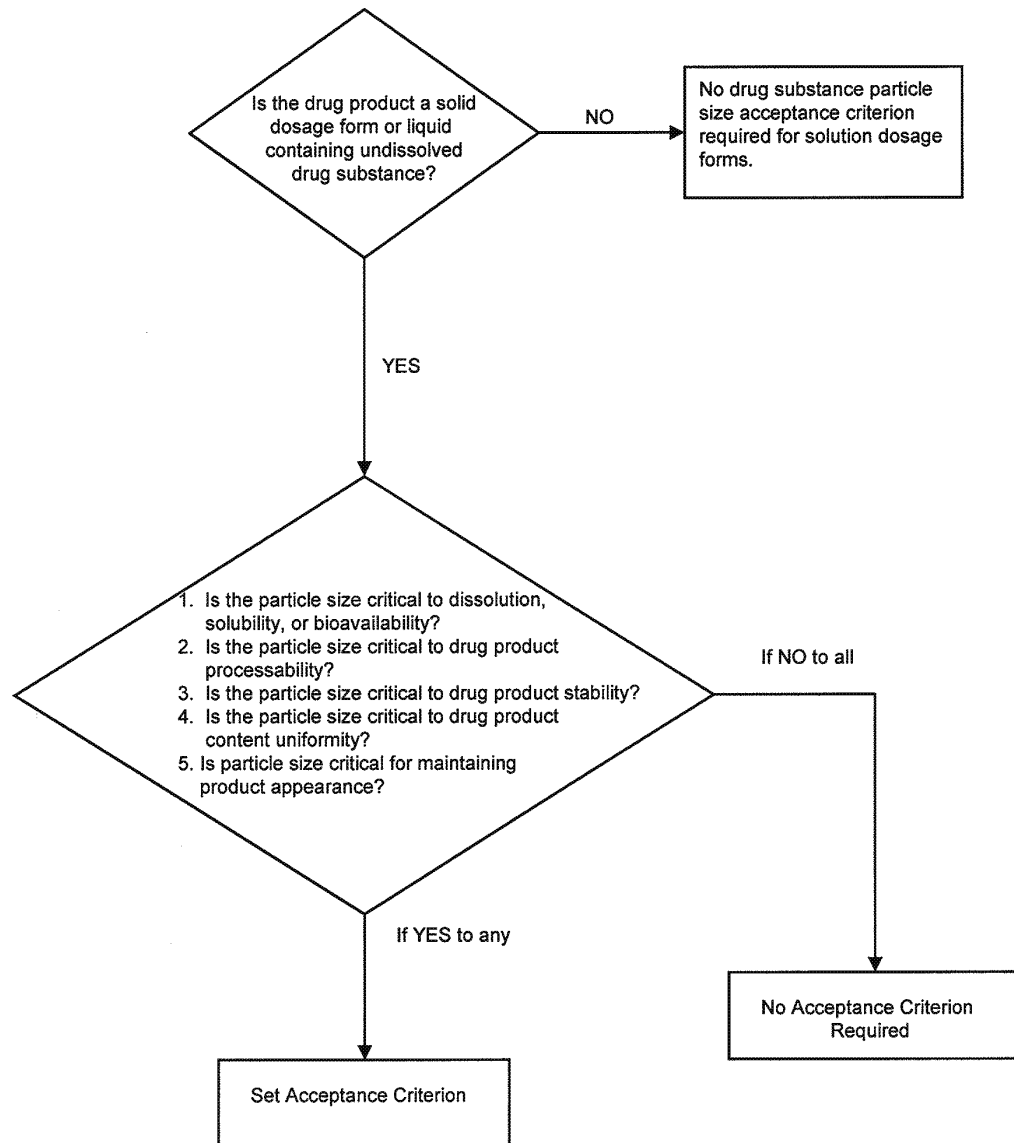


¹ Relevant batches are those from development, pilot and scale-up studies.

² Refer to Decision Tree 1 for information regarding A and B.

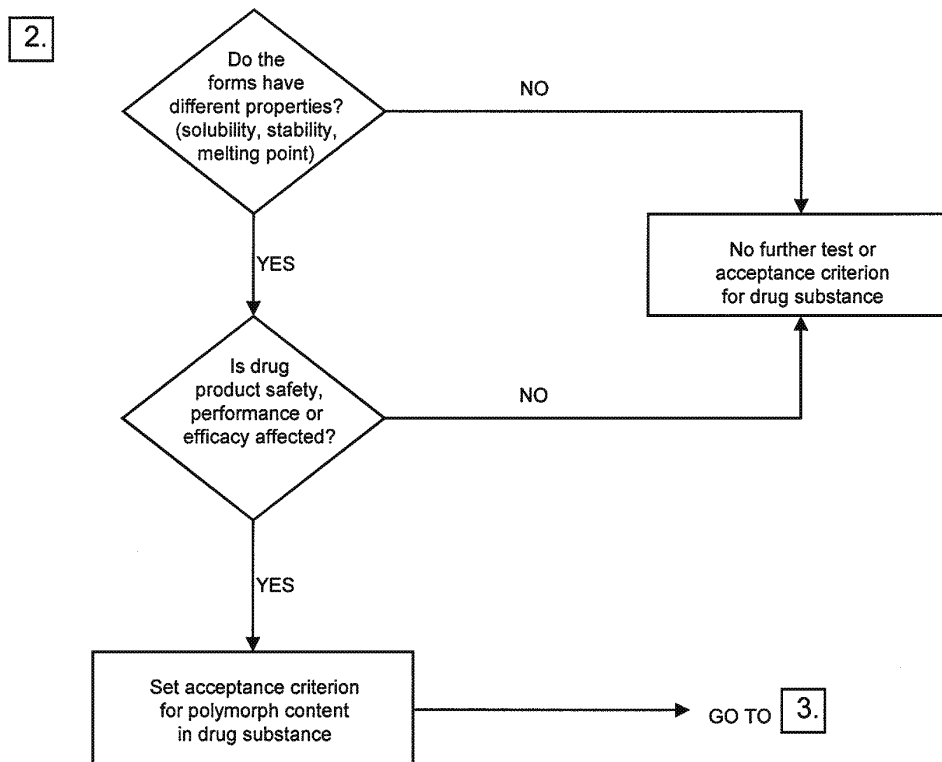
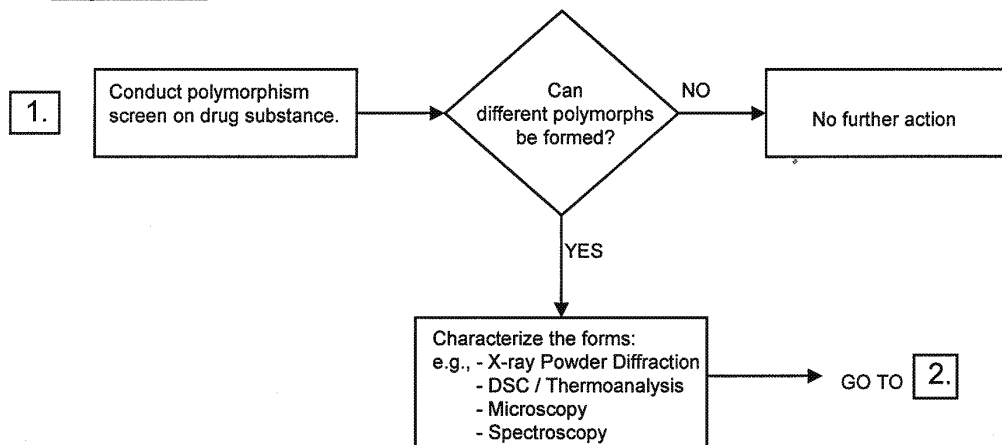
³ Refer to ICH Guideline on Impurities in New Drug Products.

DECISION TREE #3: SETTING ACCEPTANCE CRITERIA FOR
DRUG SUBSTANCE PARTICLE SIZE DISTRIBUTION



DECISION TREE #4: INVESTIGATING THE NEED TO SET
ACCEPTANCE CRITERIA FOR POLYMORPHISM
IN DRUG SUBSTANCES AND DRUG PRODUCTS

Drug Substance

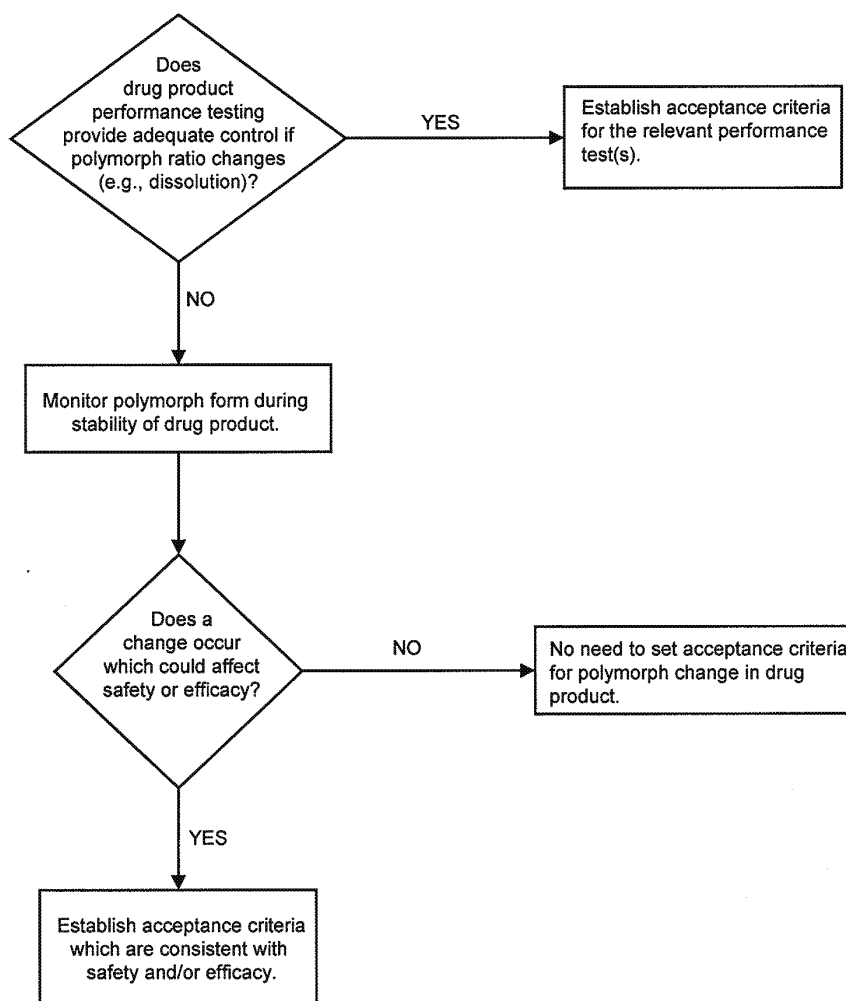


DECISION TREE #4: INVESTIGATING THE NEED TO SET
ACCEPTANCE CRITERIA FOR POLYMORPHISM
IN DRUG SUBSTANCES AND DRUG PRODUCTS

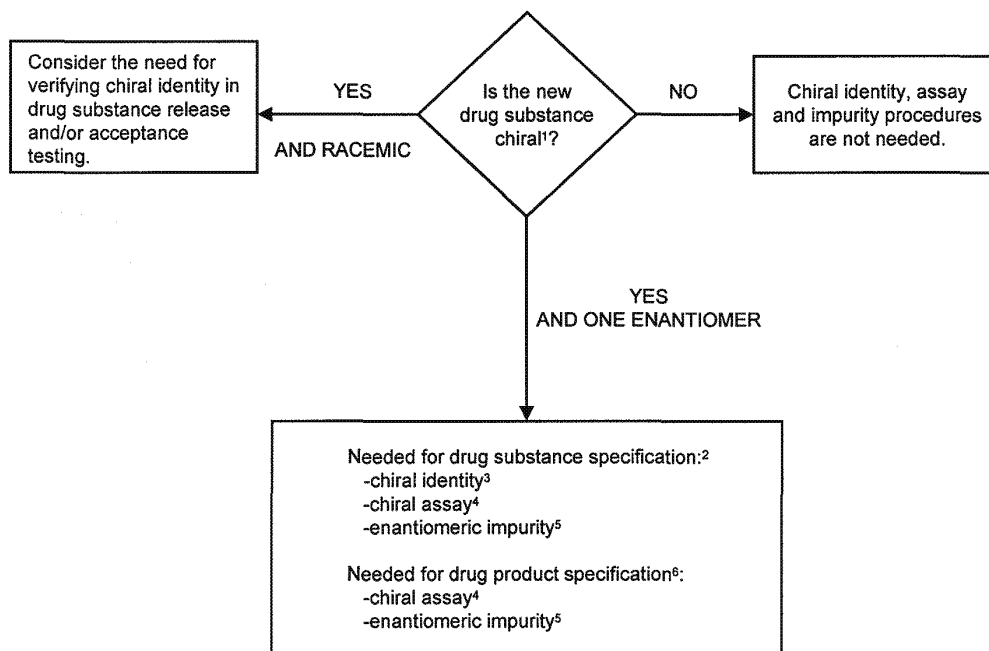
Drug Product - Solid Dosage Form or Liquid Containing Undissolved Drug Substance

N.B.: Undertake the following processes only if technically possible
to measure polymorph content in the drug product.

3.



**DECISION TREE #5: ESTABLISHING IDENTITY, ASSAY
AND ENANTIOMERIC IMPURITY PROCEDURES FOR CHIRAL
NEW DRUG SUBSTANCES AND NEW DRUG PRODUCTS
CONTAINING CHIRAL DRUG SUBSTANCES**



¹ Chiral substances of natural origin are not addressed in this Guideline.

² As with other impurities arising in and from raw materials used in drug substance synthesis, control of chiral quality could be established alternatively by applying limits to appropriate starting materials or intermediates when justified from developmental studies. This essentially will be the case when there are multiple chiral centers (e.g., three or more), or when control at a step prior to production of the final drug substance is desirable.

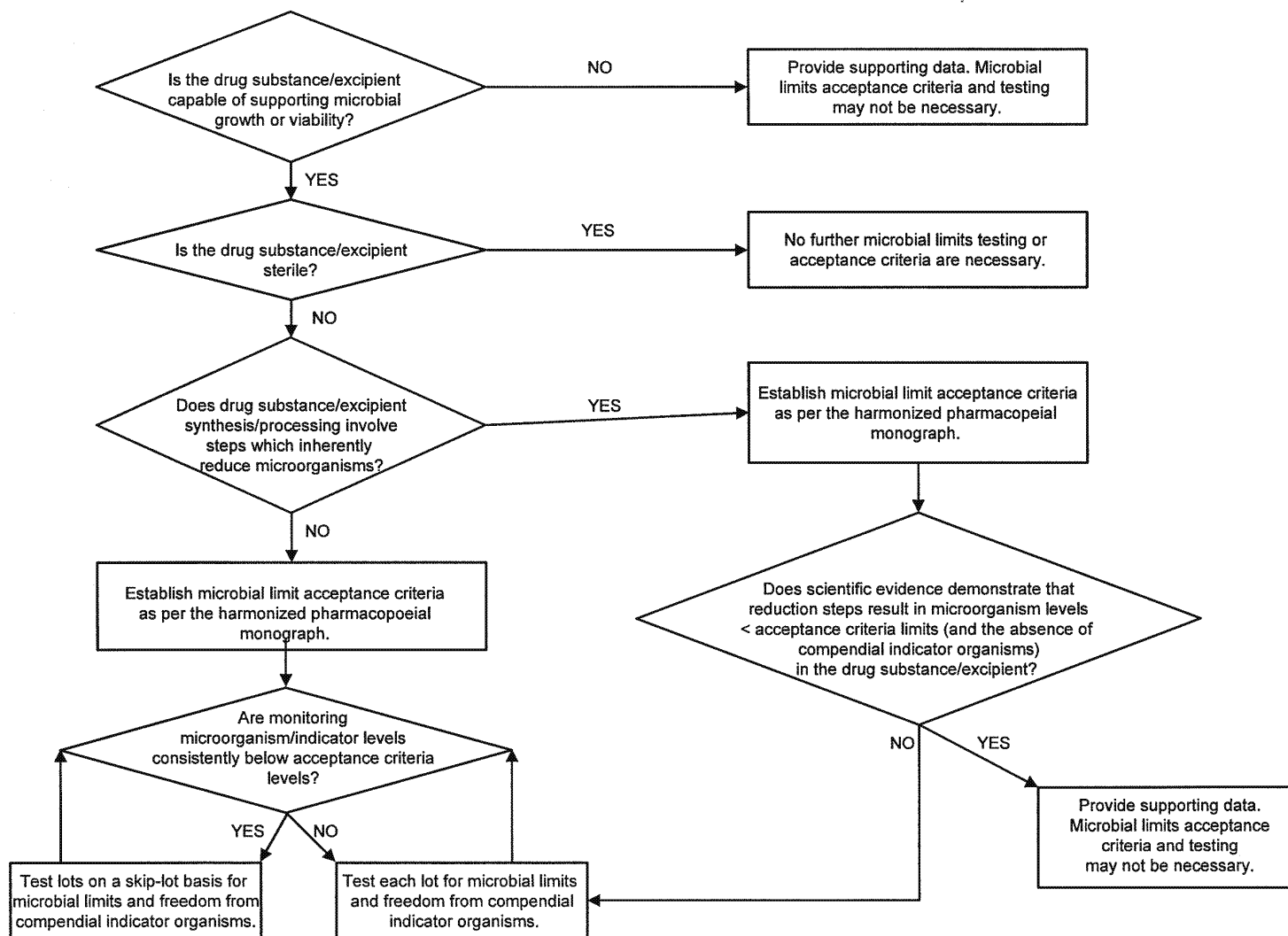
³ A chiral assay or an enantiomeric impurity procedure may be acceptable in lieu of a chiral identity procedure.

⁴ An achiral assay combined with a method for controlling the opposite enantiomer is acceptable in lieu of a chiral assay.

⁵ The level of the opposite enantiomer of the drug substance may be derived from chiral assay data or from a separate procedure.

⁶ Stereospecific testing of drug product may not be necessary if racemization has been demonstrated to be insignificant during drug product manufacture and during storage of the finished dosage form.

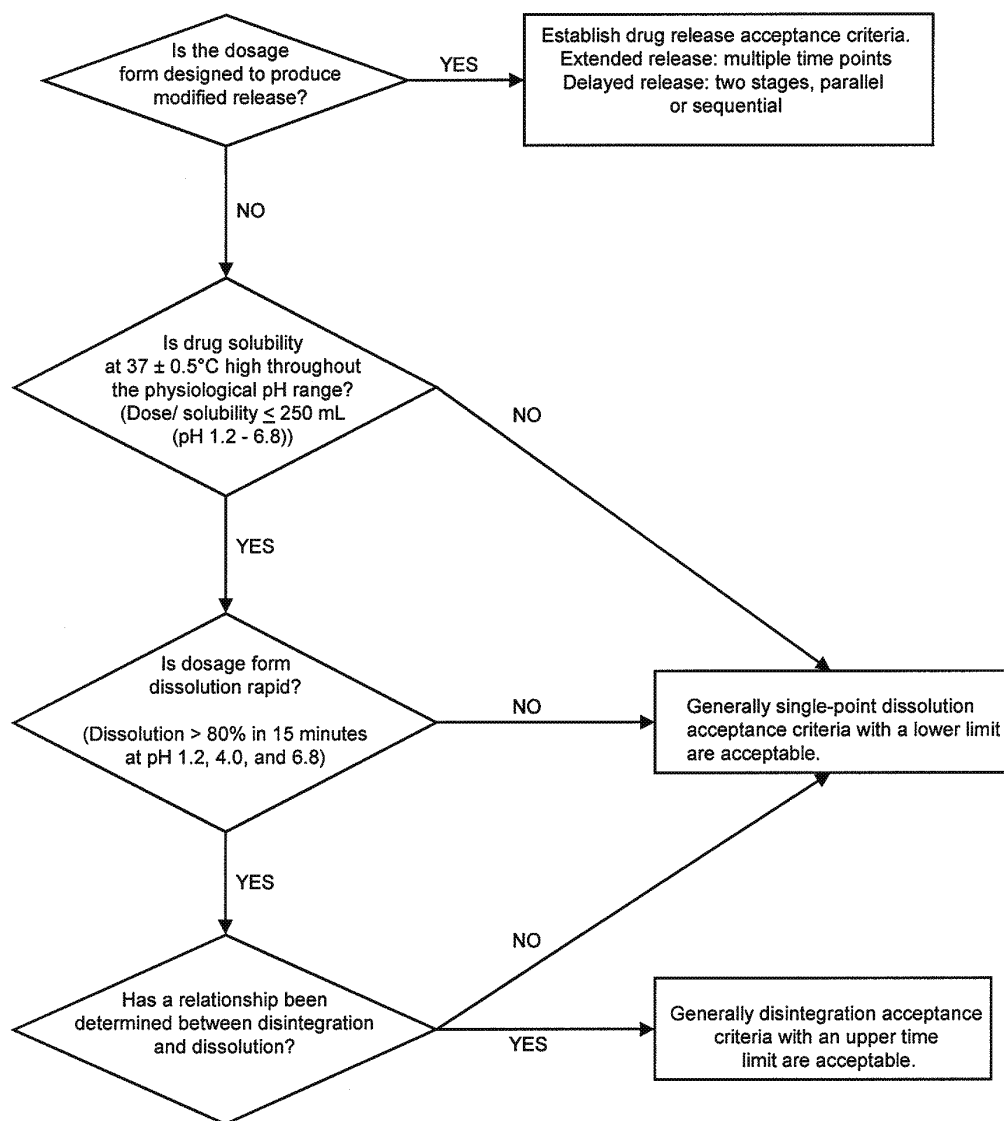
DECISION TREE #6: MICROBIOLOGICAL QUALITY ATTRIBUTES OF DRUG SUBSTANCE AND EXCIPIENTS



UM00017455

DECISION TREES #7: SETTING ACCEPTANCE CRITERIA FOR DRUG PRODUCT DISSOLUTION

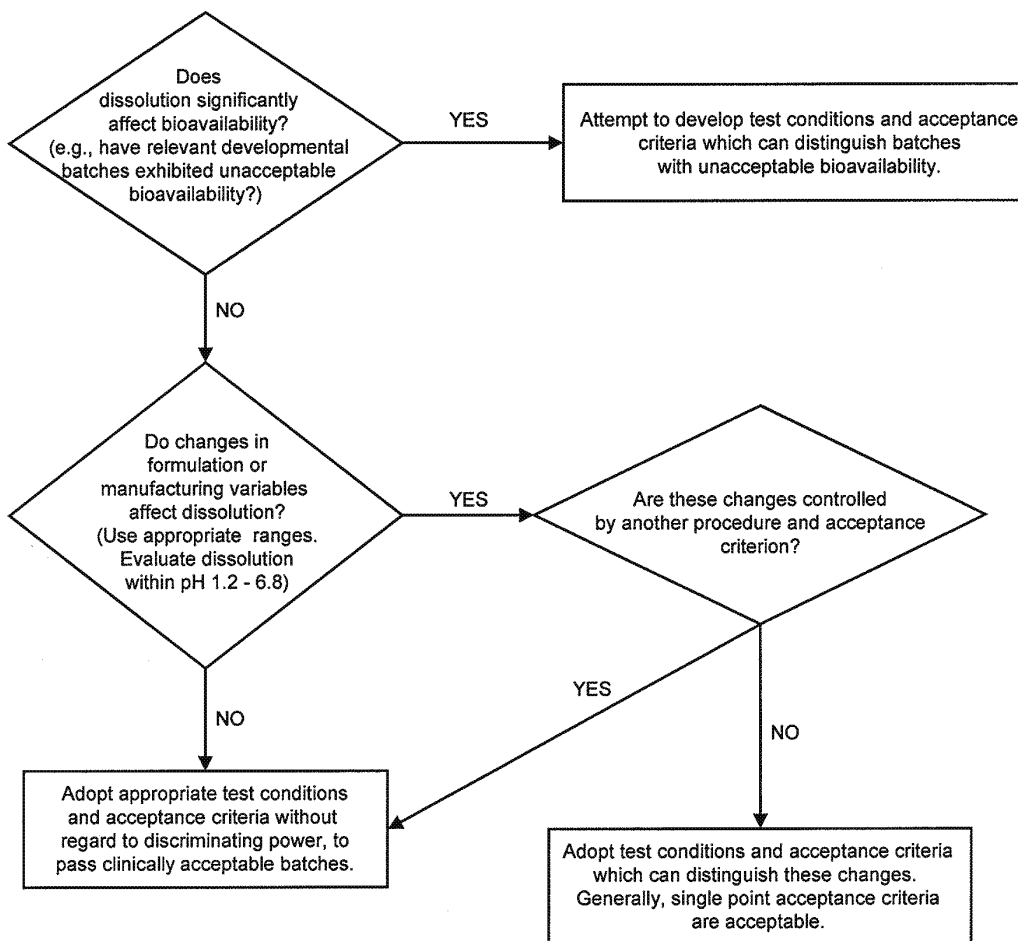
1. What type of drug release acceptance criteria are appropriate?



Continued on next page.

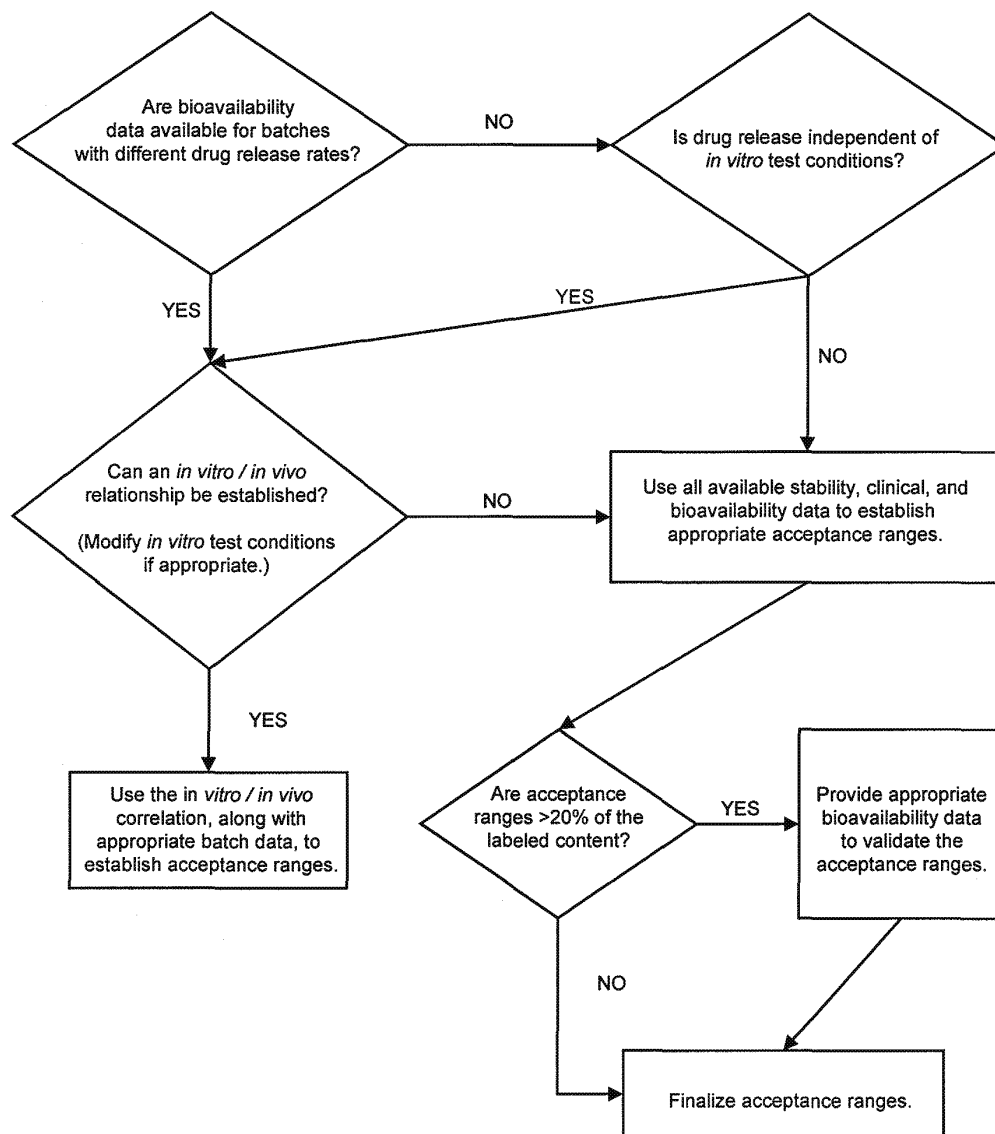
DECISION TREES #7: SETTING ACCEPTANCE CRITERIA
FOR DRUG PRODUCT DISSOLUTION

2. What specific test conditions and acceptance criteria are appropriate? [immediate release]

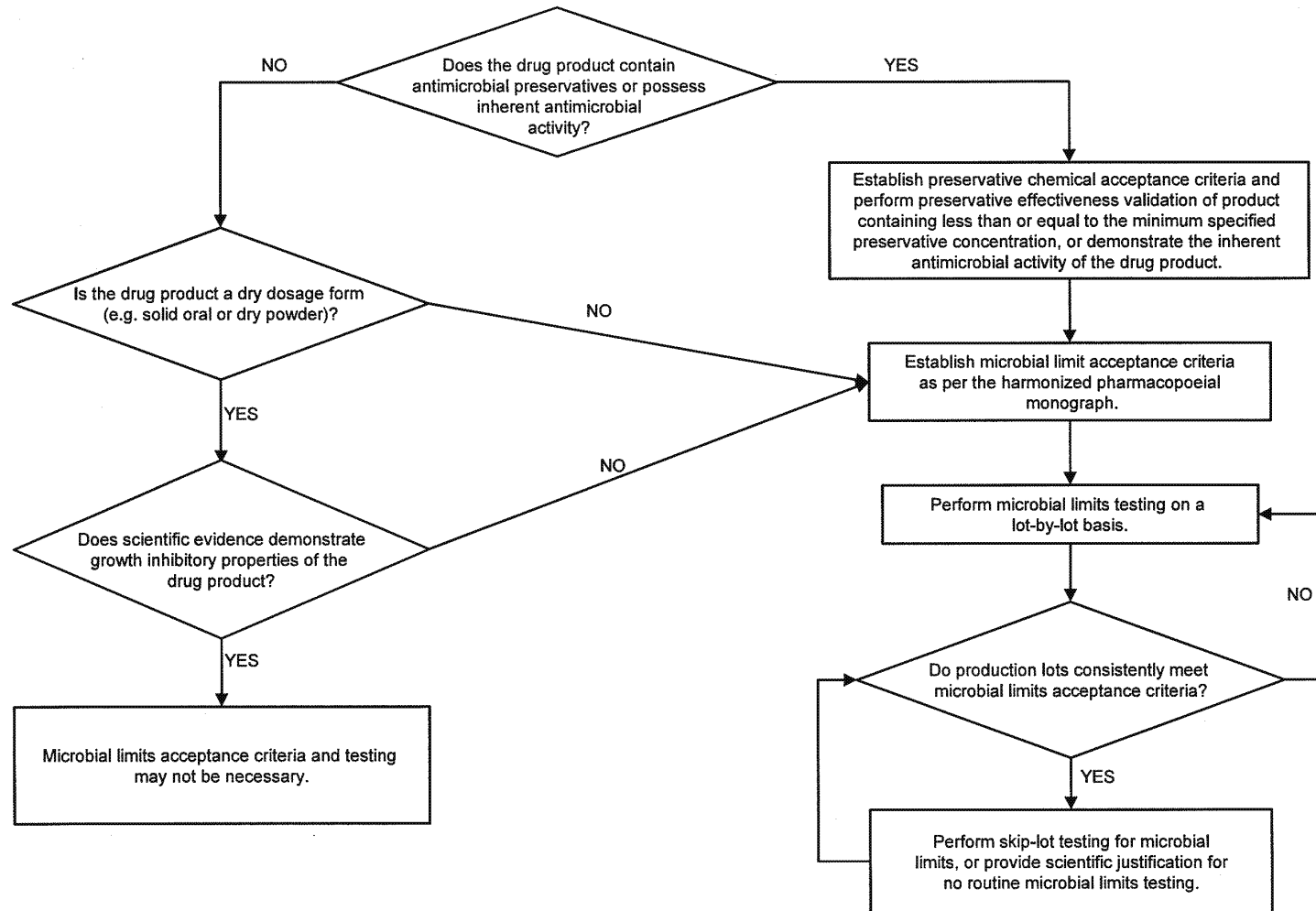


DECISION TREES #7: SETTING
ACCEPTANCE CRITERIA
FOR DRUG PRODUCT DISSOLUTION

3. What are appropriate acceptance ranges? [extended release]



DECISION TREE #8: MICROBIOLOGICAL ATTRIBUTES OF NON-STERILE DRUG PRODUCTS



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2000

USP 24

THE UNITED STATES PHARMACOPEIA

NF 19

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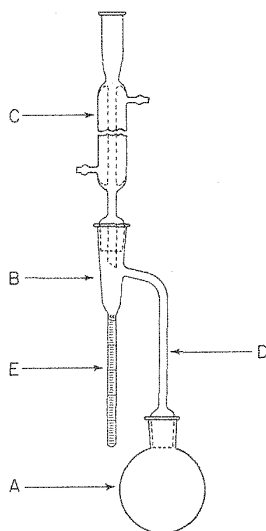
or as accurately prepared solutions in appropriate anhydrous solvents.

Where the specimen is an insoluble solid, the water may be extracted using a suitable anhydrous solvent from which an appropriate quantity, accurately weighed, may be injected into the anolyte solution. Alternatively an evaporation technique may be used in which water is released and evaporated by heating the specimen in a tube in a stream of dry inert gas, this gas being then passed into the cell.

Procedure—Using a dry syringe, quickly inject the *Test Preparation*, accurately measured and estimated to contain 0.5 to 5 mg of water, into the anolyte, mix, and perform the coulometric titration to the electrometric endpoint. Read the water content of the *Test Preparation* directly from the instrument's display, and calculate the percentage that is present in the substance. Perform a blank determination, and make any necessary corrections.

METHOD II (AZEOTROPIC—TOLUENE DISTILLATION)

Apparatus—Use a 500-mL glass flask *A* connected by means of a trap *B* to a reflux condenser *C* by ground glass joints (see figure).



Toluene Moisture Apparatus

The critical dimensions of the parts of the apparatus are as follows. The connecting tube *D* is 9 to 11 mm in internal diameter. The trap is 235 to 240 mm in length. The condenser, if of the straight-tube type, is approximately 400 mm in length and not less than 8 mm in bore diameter. The receiving tube *E* has a 5-mL capacity, and its cylindrical portion, 146 to 156 mm in length, is graduated in 0.1-mL subdivisions, so that the error of reading is not greater than 0.05 mL for any indicated volume. The source of heat is preferably an electric heater with rheostat control or an oil bath. The upper portion of the flask and the connecting tube may be insulated.

Clean the receiving tube and the condenser with chromic acid cleansing mixture, thoroughly rinse with water, and dry in an oven. Prepare the toluene to be used by first shaking with a small quantity of water, separating the excess water, and distilling the toluene.

Procedure—Place in the dry flask a quantity of the substance, weighed accurately to the nearest centigram, which is expected to yield 2 to 4 mL of water. If the substance is of a pasty character,

weigh it in a boat of metal foil of a size that will just pass through the neck of the flask. If the substance is likely to cause bumping, add enough dry, washed sand to cover the bottom of the flask, or a number of capillary melting-point tubes, about 100 mm in length, sealed at the upper end. Place about 200 mL of toluene in the flask, connect the apparatus, and fill the receiving tube *E* with toluene poured through the top of the condenser. Heat the flask gently for 15 minutes and, when the toluene begins to boil, distil at the rate of about 2 drops per second until most of the water has passed over, then increase the rate of distillation to about 4 drops per second. When the water has apparently all distilled over, rinse the inside of the condenser tube with toluene while brushing down the tube with a tube brush attached to a copper wire and saturated with toluene. Continue the distillation for 5 minutes, then remove the heat, and allow the receiving tube to cool to room temperature. If any droplets of water adhere to the walls of the receiving tube, scrub them down with a brush consisting of a rubber band wrapped around a copper wire and wetted with toluene. When the water and toluene have separated completely, read the volume of water, and calculate the percentage that was present in the substance.

METHOD III (GRAVIMETRIC)

Procedure for Chemicals—Proceed as directed in the individual monograph preparing the chemical as directed under *Loss on Drying* (731).

Procedure for Biologics—Proceed as directed in the individual monograph.

Procedure for Vegetable Drugs—Place about 10 g of the drug, prepared as directed (see *Vegetable Drugs—Methods of Analysis* (561)) and accurately weighed, in a tared evaporating dish. Dry at 105° for 5 hours, and weigh. Continue the drying and weighing at 1-hour intervals until the difference between two successive weighings corresponds to not more than 0.25%.

(941) X-RAY DIFFRACTION

Every crystal form of a compound produces its own characteristic X-ray diffraction pattern. These diffraction patterns can be derived either from a single crystal or from a powdered specimen (containing numerous crystals) of the material. The spacings between and the relative intensities of the diffracted maxima can be used for qualitative and quantitative analysis of crystalline materials. Powder diffraction techniques are most commonly employed for routine identification and the determination of relative purity of crystalline materials. Small amounts of impurity, however, are not normally detectable by the X-ray diffraction method, and for quantitative measurements it is necessary to prepare the sample carefully to avoid preferred orientation effects.

The powder methods provide an advantage over other means of analysis in that they are usually nondestructive in nature (specimen preparation is usually limited to grinding to ensure a randomly oriented sample, and deleterious effects of X-rays on solid pharmaceutical compounds are not commonly encountered). The principal use of single-crystal diffraction data is for the determination of molecular weights and analysis of crystal structures at the atomic level. However, diffraction established for a single crystal can be used to support a specific powder pattern as being truly representative of a single phase.

Solids—A solid substance can be classified as being crystalline, noncrystalline, or a mixture of the two forms. In crystalline materials, the molecular or atomic species are ordered in a three-dimensional array, called a lattice, within the solid particles. This ordering of molecular components is lacking in noncrystalline material. Noncrystalline solids sometimes are referred to as glasses or amorphous solids when repetitive order is nonexistent in all three dimensions. It is also possible for order to exist in only one or two dimensions, resulting in mesomorphic phases (liquid crystals). Although crystalline materials are usually considered to have well-defined visible external morphologies (their habits), this is not a necessity for X-ray diffraction analysis.

The relatively random arrangement of molecules in noncrystalline substances makes them poor coherent scatterers of X-rays, resulting in broad, diffuse maxima in diffraction patterns. Their X-

ray patterns are quite distinguishable from crystalline specimens, which give sharply defined diffraction patterns.

Many compounds are capable of crystallizing in more than one type of crystal lattice. At any particular temperature and pressure, only one crystalline form (polymorph) is thermodynamically stable. Since the rate of phase transformation of a metastable polymorph to the stable one can be quite slow, it is not uncommon to find several polymorphs of crystalline pharmaceutical compounds existing under normal handling conditions.

In addition to exhibiting polymorphism, many compounds form crystalline solvates in which the solvent molecule is an integral part of the crystal structure. Just as every polymorph has its own characteristic X-ray patterns, so does every solvate. Sometimes the differences in the diffraction patterns of different polymorphs are relatively minor, and must be very carefully evaluated before a definitive conclusion is reached. In some instances, these polymorphs and/or solvates show varying dissolution rates. Therefore, on the time scale of pharmaceutical bioavailability, different total amounts of drug are dissolved, resulting in potential bioinequivalence of the several forms of the drug.

Fundamental Principles—A collimated beam of monochromatic X-rays is diffracted in various directions when it impinges upon a rotating crystal or randomly oriented powdered crystal. The crystal acts as a three-dimensional diffraction grating to this radiation. This phenomenon is described by Bragg's law, which states that diffraction (constructive interference) can occur only when waves that are scattered from different regions of the crystal, in a specific direction, travel distances differing by integral numbers (n) of the wavelength (λ). Under such circumstances, the waves are in phase. This condition is described by the Bragg equation:

$$\frac{n\lambda}{2 \sin \theta} = d_{hkl}$$

in which d_{hkl} denotes the interplanar spacings and θ is the angle of diffraction.

A family of planes in space can be indexed by three whole numbers, usually referred to as Miller indices. These indices are the reciprocals, reduced to smallest integers, of the intercepts that a plane makes along the axes corresponding to three nonparallel edges of the unit cell (basic crystallographic unit). The unit cell dimensions are given by the lengths of the spacings along the three axes, a , b , c , and the angles between them, α , β , and γ . The interplanar spacing for a specific set of parallel planes hkl is denoted by d_{hkl} . Each such family of planes may show higher orders of diffraction where the d values for the related families of planes nh , nk , nl are diminished by the factor $1/n$ (n being an integer: 2, 3, 4, etc.). Every set of planes throughout a crystal has a corresponding Bragg diffraction angle associated with it (for a specific λ).

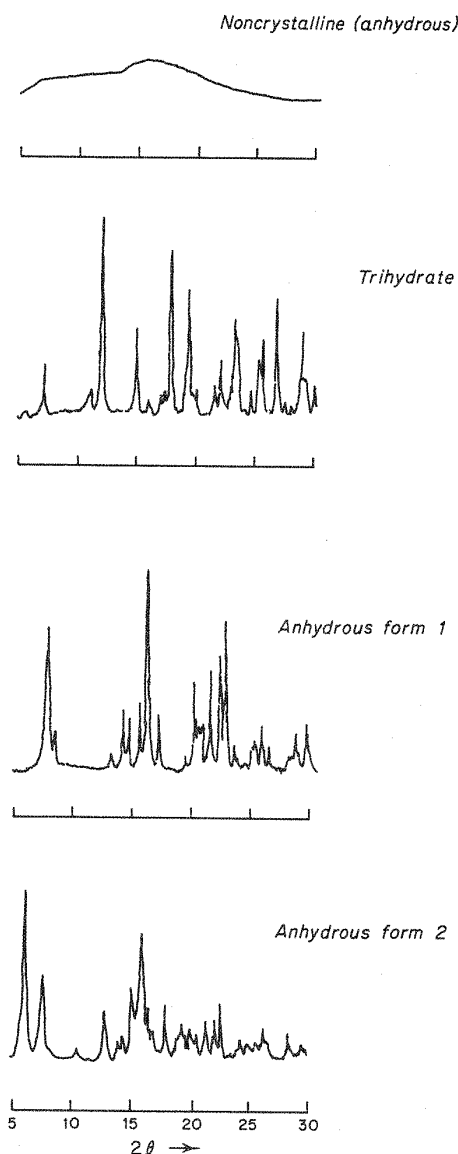
The amplitude of a diffracted X-ray beam from any set of planes is dependent upon the following atomic properties of the crystal: (1) position of each atom in the unit cell; (2) the respective atomic scattering factors; and (3) the individual thermal motions. Other factors that directly influence the intensities of the diffracted beam are: (1) the intensity and wavelength of the incident radiation; (2) the volume of crystalline specimen; (3) the absorption of the X-radiation by the specimen; and (4) the experimental arrangement utilized to record the intensity data. Thus, the experimental conditions are especially important for measurement of diffraction intensities.

Only a limited number of Bragg planes are in a position to diffract when monochromatized X-rays pass through a single crystal. Techniques of recording the intensities of all of the possible diffracting hkl planes involve motion of the single crystal and the recording media. Recording of these data is accomplished by photographic techniques (film) or with radiation detectors.

A beam passing through a very large number of small, randomly oriented crystals produces continuous cones of diffracted rays from each set of lattice planes. Each cone corresponds to the diffraction from various planes having a similar interplanar spacing. The intensities of these Bragg reflections are recorded by either film or radiation detectors. The Bragg angle can be measured easily from a film, but the advent of radiation detectors has made possible the construction of diffractometers that read this angle directly. The intensities and d spacings are more conveniently determined with powder diffractometers employing radiation detectors than by film

methods. Microphotometers are frequently used for precise intensity measurements of films.

An example of the type of powder patterns obtained for four different solid phases of ampicillin are shown in the accompanying figure. These diffraction patterns were derived from a powder diffractometer equipped with a Geiger-Müller detector; nickel-filtered Cu K α radiation was used.



Typical Powder Patterns Obtained for Four Solid Phases of Ampicillin

Radiation—The principal radiation sources utilized for X-ray diffraction are vacuum tubes utilizing copper, molybdenum, iron, and chromium as anodes; copper X-rays are employed most commonly for organic substances. For each of these radiations there is an element that will filter off the K β radiation and permit the K α radiation to pass (nickel is used, in the case of copper radiation). In this manner the radiation is practically monochromatized. The choice of radiation to be used depends upon the absorption characteristics of the material and possible fluorescence by atoms present in the specimen.

Caution—Care must be taken in the use of such radiation. Those not familiar with the use of X-ray equipment should seek expert advice. Improper use can result in harmful effects to the operator.

Test Preparation—In an attempt to improve randomness in the orientation of crystallites (and, for film techniques, to avoid a grainy pattern), the specimen may be ground in a mortar to a fine powder. Grinding pressure has been known to induce phase transformations; therefore, it is advisable to check the diffraction pattern of the unground sample.

In general, the shapes of many crystalline particles tend to give a specimen that exhibits some degree of preferred orientation in the specimen holder. This is especially evident for needle-like or plate-like crystals where size reduction yields finer needles or platelets. Preferred orientation in the specimen influences the relative intensities of various reflections.

Several specialized handling techniques may be employed to minimize preferred orientation, but further reduction of particle size is often the best approach.

Where very accurate measurement of the Bragg angles is necessary, a small amount of an internal standard can be mixed into the specimen. This enables the film or recorder tracing to be calibrated. If comparisons to literature values (including compendial limits) of d are being made, calibrate the diffractometer. NIST standards are available covering to a d -value of 0.998 nm. Tetradecanol¹ may be used (d is 3.963 nm) for larger spacing.

The absorption of the radiation by any specimen is determined by the number and kinds of atoms through which the X-ray beam passes. An organic matrix usually absorbs less of the diffracted radiation than does an inorganic matrix. Therefore, it is important in quantitative studies that standard curves relating amount of material to the intensity of certain d spacings for that substance be

determined in a matrix similar to that in which the substance will be analyzed.

In quantitative analyses of materials, a known amount of standard usually is added to a weighed amount of specimen to be analyzed. This enables the amount of the substance to be determined relative to the amount of standard added. The standard used should have approximately the same density as the specimen and similar absorption characteristics. More important, its diffraction pattern should not overlap to any extent with that of the material to be analyzed. Under these conditions a linear relationship between line intensity and concentration exists. In favorable cases, amounts of crystalline materials as small as 10% may be determined in solid matrices.

Identification of crystalline materials can be accomplished by comparison of X-ray powder diffraction patterns obtained for known² materials with those of the unknown. The intensity ratio (ratio of the peak intensity of a particular d spacing to the intensity of the strongest maxima in the diffraction pattern) and the d spacing are used in the comparison. If a reference material (e.g., USP Reference Standard) is available, it is preferable to generate a primary reference pattern on the same equipment used for running the unknown sample, and under the same conditions. For most organic crystals, it is appropriate to record the diffraction pattern to include values for 2θ that range from as near zero degrees as possible to 40 degrees. Agreement between sample and reference should be within the calibrated precision of the diffractometer for diffraction angle (2θ values should typically be reproducible to ± 0.10 or 0.20 degrees), while relative intensities between sample and reference may vary considerably. For other types of samples (e.g., inorganic salts), it may be necessary to extend the 2θ region scanned to well beyond 40 degrees. It is generally sufficient to scan past the ten strongest reflections identified in the Powder Diffraction File.²

¹ Brindley, GW and Brown, G, eds., *Crystal Structures of Clay Minerals and their X-ray Identification*, Mineralogical Society Monograph No. 5, London, 1980, pp. 318 ff.

² The International Centre for Diffraction Data, Newtown Square Corporate Campus, 12 Campus Boulevard, Newtown Square, PA 19073, maintains a file on more than 60,000 crystalline materials, both organic and inorganic, suitable for such comparisons.

Network hydrogen bonding in two new cocrystals sustained by $[\text{Mn}(\text{CO})_3(\mu_3\text{-OH})]_4$, a tetrahedral hydrogen bond donor

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We report details of the synthesis and X-ray crystal structures of two new cocrystals that are sustained by the tetrahedral hydrogen bond donor $[\text{Mn}(\text{CO})_3(\mu_3\text{-OH})]_4$. $[\text{Mn}(\text{CO})_3(\mu_3\text{-OH})]_4 \cdot 2(2,3,5,6\text{-tetramethylpyrazine}) \cdot 2\text{H}_2\text{O} \cdot 2\text{MeCN}$, $a = 21.503(3)$, $b = 12.674(1)$, $c = 17.318(2)$, $\beta = 102.15(2)$, $C 2/c$, $D_{\text{calc}} = 1.46 \text{ mg/m}^3$, $Z = 4$, 4188 observed refls, $R_f = 0.047$, $R_w = 0.040$; **1**. $[\text{Mn}(\text{CO})_3(\mu_3\text{-OH})]_4 \cdot 4,4'\text{-dipyridyl} \cdot 2\text{MeCN}$, $a = 16.942(6)$, $b = 12.395(2)$, $c = 18.790(6)$, $\beta = 114.88(3)$, $C 2/c$, $D_{\text{calc}} = 1.60 \text{ mg/m}^3$, $Z = 4$, 2430 observed refls, $R_f = 0.043$, $R_w = 0.051$; **2**. **1** crystallizes as a 2-D grid, whereas **2** forms 1-D strands. The hydrogen bond patterns exhibited by **1** and **2** are analyzed in the context of our earlier studies involving $[\text{Mn}(\text{CO})_3(\mu_3\text{-OH})]_4$ and other relevant literature.

KEY WORDS: Crystal engineering; hydrogen bonding; acetonitrile.

Introduction

Crystal engineering,¹ an emerging area of supramolecular chemistry, challenges our ability to manipulate and control the self-assembly of molecules and/or ions in the solid state. Molecules that possess supramolecular functionalities such as multiple hydrogen bond donor or acceptor sites are of particular interest since their ability to direct self-assembly of complementary components or pleromers² into polymeric motifs is already well documented.³ The cubane molecule $[\text{Mn}(\text{CO})_3(\mu_3\text{-OH})]_4$,⁴ Mn_4 , has been of particular interest to us since it has four hydroxyl groups rigidly directed toward the vertices of a tetrahedron (Fig. 1) and no strong hydrogen bond acceptor sites. It is therefore predisposed to form adducts and cocrystals with molecules which have strong hydrogen bond acceptor functionalities.

Such a molecule is key to our general strategy for crystal engineering, which involves designing multiple component systems of complementary molecules that cocrystallize with predictable architecture via hydrogen bonding.⁵ Mn_4 is obviously a prototypal building block in designing solid state architecture and we have

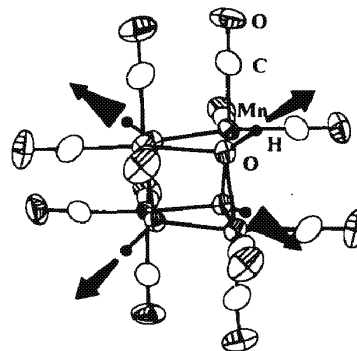


Fig. 1. ORTEP perspective view of Mn_4 in **1**. The O-H moieties point towards the vertices of a tetrahedron, since Mn_4 has T_d point group symmetry. Average bond distances ($\text{\AA}$): Mn-C 1.792(3), Mn-O 2.039(6) and C-O 1.152(7).

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previously exploited its symmetry and functionality to prepare multiple component 3-D diamondoid networks,⁶ 2-D square grid networks,⁷ and 4:1 discrete adducts.⁸

In this contribution, we report on two networks sustained by Mn₄ that are influenced by the ability of acetonitrile to act as a hydrogen bond acceptor. Crystallographic parameters for **1** and **2** are presented in Table 1. Fractional atomic coordinates are presented in Tables 2 and 3.

Results and discussion

We have already reported a series of crystal structures based upon cocrystals containing Mn₄ in which infinite 2-D or 3-D networks are sustained by either conventional O–H···N, O–H···O or OH···π hydrogen bonding.^{6,7} 2,3,5,6-tetramethylpyrazine, 2,3,5,6-Me₄pz, and 4,4'-dipyridyl, 4,4'-dipy, have the ability to act as linear “spacers” and the appropriate stoichiometry, 1:2 of Mn₄:“spacer,” would be expected to

Table 1. Summary of data collection and structure refinement parameters.

	1	2
Formula	Mn ₄ O ₁₈ N ₆ C ₃₂ H ₃₈	Mn ₄ O ₁₆ N ₄ C ₂₆ H ₁₈
Formula weight	1014.15	862.19
Crystal dimensions (mm)	0.8 × 0.5 × 0.5	0.4 × 0.5 × 0.5
Crystal color	Dark yellow	Dark orange
Crystal system	Monoclinic	Monoclinic
Space group	C 2/c	C 2/c
a, Å	21.503(3)	16.942(6)
b, Å	12.6743(10)	12.3951(16)
c, Å	17.3184(23)	18.790(6)
β, °	102.157(16)	114.88(3)
V, Å ³	4614.1(10)	3579.6(18)
Z	4	4
D _{calc} , mg/m ³	1.46	1.60
F(000)	2064	1720
μ, cm ⁻¹	11.0	13.9
Transmission range	0.890–0.999	0.709–0.982
2θ (max)	49.9	44.9
Data collected	4188	2430
Independent data	4051	2336
Observed data	2595	1779
Parameters refined	271	226
R ^a	0.047	0.043
R _w ^a	0.04	0.051
Goodness of fit ^b	3.34	3.10
Final shift/error residual	0.0	0.0

^a $R = \|F_o\| - \|F_c\|/\|F_o\|$. $R_w = [w(\|F_o\| - \|F_c\|)^2/w\|F_o\|^2]^{1/2}$.

^b $GOF = [w(\|F_o\| - \|F_c\|)^2/(N_{\text{observations}} - N_{\text{variables}})]^{1/2}$.

Table 2. Fractional atomic coordinates x,y,z and B_{iso} for **1**.

	x	y	z	B _{iso} ^a
Mn1	0.48064(4)	0.39875(6)	0.15740(5)	3.94(4)
Mn2	0.42710(4)	0.22039(6)	0.25522(5)	4.08(4)
O1	0.44178(14)	0.37864(24)	0.25409(17)	3.62(16)
O2	0.48366(14)	0.23848(24)	0.17571(18)	3.83(16)
O3	0.35031(18)	0.5164(3)	0.2559(3)	7.3(3)
O11	0.54990(24)	0.4004(4)	0.0280(3)	8.7(3)
O12	0.48300(22)	0.6310(3)	0.1554(3)	7.2(3)
O13	0.35754(22)	0.4198(4)	0.0449(3)	7.9(3)
O21	0.30510(21)	0.2112(4)	0.1391(3)	8.6(3)
O22	0.42415(20)	−0.0112(3)	0.2572(3)	7.2(3)
O23	0.35478(22)	0.2114(4)	0.3812(3)	8.1(3)
N30	0.22772(23)	0.4275(4)	0.2536(4)	5.9(3)
N31	0.16467(22)	0.2399(4)	0.2516(4)	5.6(3)
N40	0.4539(4)	1.0708(6)	0.0618(4)	11.4(5)
C11	0.5225(3)	0.3992(5)	0.0782(3)	5.5(3)
C12	0.4823(3)	0.5406(5)	0.1570(3)	4.8(3)
C13	0.4061(3)	0.4085(5)	0.0877(3)	5.4(3)
C21	0.3527(3)	0.2168(5)	0.1842(4)	5.6(4)
C22	0.4262(3)	0.0804(5)	0.2555(4)	5.0(3)
C23	0.3837(3)	0.2177(5)	0.3330(4)	5.4(3)
C32	0.2238(3)	0.3789(5)	0.3216(4)	5.8(4)
C33	0.1924(3)	0.2843(5)	0.3207(4)	5.5(4)
C34	0.1673(3)	0.2884(5)	0.1843(4)	5.2(3)
C35	0.1998(3)	0.3835(5)	0.1852(4)	5.6(3)
C36	0.2554(3)	0.4345(5)	0.3967(4)	8.4(4)
C37	0.1884(3)	0.2241(6)	0.3949(4)	7.3(4)
C38	0.1380(3)	0.2330(6)	0.1076(4)	8.0(4)
C39	0.2063(3)	0.4396(5)	0.1119(4)	8.0(4)
C41	0.4576(4)	0.9773(8)	0.0725(5)	9.4(6)
C42	0.4652(4)	0.8657(6)	0.0848(6)	11.6(7)

^a B_{iso} is the mean of the principal axes of the thermal ellipsoid.

generate 3-D diamondoid networks. However, in the presence of competing hydrogen bond acceptors such as acetonitrile, MeCN, and water, other networks may result. Indeed, such is the case for Mn₄ and 4,4'-dipy, which form a fourfold diamondoid network when crystallized from MeCN^{6b} but a three component 2-D grid, Mn₄·2(4,4'-dipy)·2MeOH, when crystallized from MeOH.⁷ The compounds reported in this study both involve competing hydrogen bond acceptors: [Mn(CO)₃(μ₃-OH)]₄·2(2,3,5,6-tetramethylpyrazine)·2H₂O·2MeCN, **1** and [Mn(CO)₃(μ₃-OH)]₄·4,4'-dipyridyl·2MeCN, **2**.

1 contains three residues that have the potential to act as hydrogen bond acceptors: H₂O, MeCN, and 2,3,5,6-Me₄pz. One might therefore consider the architecture of **1** to be anything but predictable, even given the stoichiometry, since there are several possible permutations for self-assembly. However, Etter has established that organic solids follow relatively simple and

Table 3. Fractional atomic coordinates x, y, z and B_{iso} for 2.

	x	y	z	B_{iso}^a
Mn1	0.90706(5)	0.31729(6)	0.17773(4)	4.30(5)
Mn2	1.04621(5)	0.13578(6)	0.19244(5)	4.53(5)
O1	0.92637(21)	0.15489(24)	0.19097(18)	4.18(19)
O2	1.03585(20)	0.29755(24)	0.20379(18)	4.05(17)
O11	0.9010(3)	0.5554(3)	0.1748(3)	7.8(3)
O12	0.7260(3)	0.3327(4)	0.1578(3)	8.8(3)
O13	0.8414(3)	0.3182(5)	0.0059(3)	8.9(3)
O21	0.9971(4)	0.1333(4)	0.0227(3)	8.9(3)
O22	1.2281(3)	0.1198(4)	0.2162(3)	8.1(3)
O23	1.0394(4)	-0.1018(4)	0.1815(3)	9.3(4)
N30	0.8181(4)	0.0010(4)	0.0970(3)	6.6(3)
N40	0.9227(5)	0.4566(6)	0.3830(4)	9.9(5)
C11	0.9050(4)	0.4626(5)	0.1764(3)	5.6(3)
C12	0.7975(4)	0.3228(5)	0.1653(3)	5.8(4)
C13	0.8679(4)	0.3168(5)	0.0730(4)	5.8(3)
C21	1.0147(4)	0.1360(5)	0.0894(4)	6.0(4)
C22	1.1561(4)	0.1291(5)	0.2082(3)	5.4(3)
C23	1.0421(4)	-0.0096(5)	0.1883(4)	6.4(4)
C32	0.8166(5)	-0.0179(5)	0.0296(4)	7.8(5)
C33	0.7915(5)	-0.1148(5)	-0.0119(4)	6.8(4)
C34	0.7643(4)	-0.1967(4)	0.0193(3)	5.1(3)
C35	0.7625(6)	-0.1765(6)	0.0908(5)	10.4(6)
C36	0.7881(6)	-0.0738(7)	0.1255(5)	10.3(6)
C41	0.9364(5)	0.5444(8)	0.3873(5)	8.2(5)
C42	0.9555(8)	0.6579(7)	0.3987(8)	14.7(11)

^a B_{iso} is the mean of the principal axes of the thermal ellipsoid.

predictable rules by which hydrogen bond donors and acceptors self-assemble: the strongest donor and the strongest acceptor *always* match up first.⁹ Of the three potential hydrogen bond acceptors in 1, one is of intermediate strength (H_2O)⁸ and two are weak (MeCN , 2,3,5,6- Me_4pz). It is therefore unsurprising that the two H_2O molecules accept hydrogen bonds from two of the four hydroxyl groups of Mn_4 . The $\text{O}\cdots\text{O}$ distances of 2.635(5) Å are short when compared to $\text{Mn}_4\cdot 2\text{H}_2\text{O}$, $d(\text{O}\cdots\text{O}) = 2.911(7)$ Å,⁸ and ice.¹⁰ The other two hydroxyl groups of Mn_4 form $\text{O}-\text{H}\cdots\text{N}$ hydrogen bonds to the two MeCN residues with $\text{O}\cdots\text{N}$ distances of 2.879(5) Å. This is difficult to compare to other structures because few examples of MeCN acting as a hydrogen bond acceptor have been previously reported.¹¹ All four $\mu_3\text{-OH}$ moieties of Mn_4 are utilized as hydrogen bond donors, while the other nitrogen atoms of the 2,3,5,6- Me_4pz residues and the hydrogen atoms of the H_2O residues remain unused. Therefore, the completion of the hydrogen bond network by $\text{O}-\text{H}\cdots\text{N}$ hydrogen bonds between H_2O and 2,3,5,6- Me_4pz is also unsurprising. These $\text{O}\cdots\text{N}$ distances of 2.859(5) Å are well within expected ranges.¹⁰

An ORTEP^{12c} diagram of the network that exists in 1 is presented in Fig. 2.

The IR spectrum of 1 is consistent with the presence of hydrogen bonding. In pure Mn_4 there is a strong sharp $\text{O}-\text{H}$ peak at 3565 cm^{-1} ,¹³ while in 1 this peak is split and shifted to lower frequencies, 3482 cm^{-1} and 3148 cm^{-1} , the latter being considerably broadened. The remainder of the spectrum is consistent with the individual residues.

2 crystallizes in the same space group as 1, $C2/c$ with $Z = 4$, but possesses only two residues that have the potential to act as hydrogen bond acceptors: 4,4'-dipy and MeCN . As previously noted, $\text{Mn}_4\cdot 2(4,4'\text{-dipy})$ forms a 4-fold diamondoid network with separation between Mn_4 molecules of 15.22 Å ,^{6b} and $\text{Mn}_4\cdot 2(4,4'\text{-dipy})\cdot\text{MeOH}$ forms a 2-D infinite grid with large intercube separation of 15.75 Å , when recrystallized from methanol.⁷ However, a 1:1 ratio of 4,4'-dipy to Mn_4 , generates a 1-D strand (Fig. 3).

The $\text{O}\cdots\text{N}$ distance to the 4,4'-dipy is $2.719(6)\text{ Å}$, which is consistent with the values in the 3-D

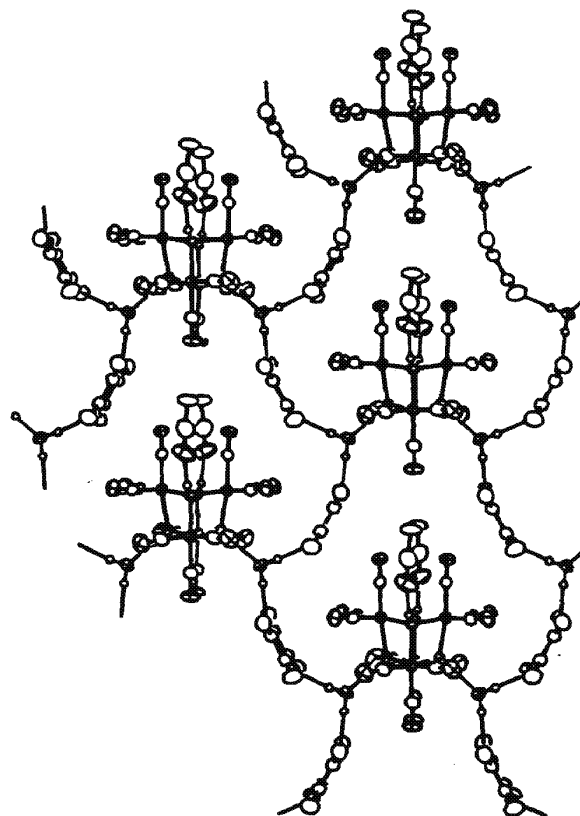


Fig. 2. ORTEP perspective view of the hydrogen bonding motif in the ac plane of 1.

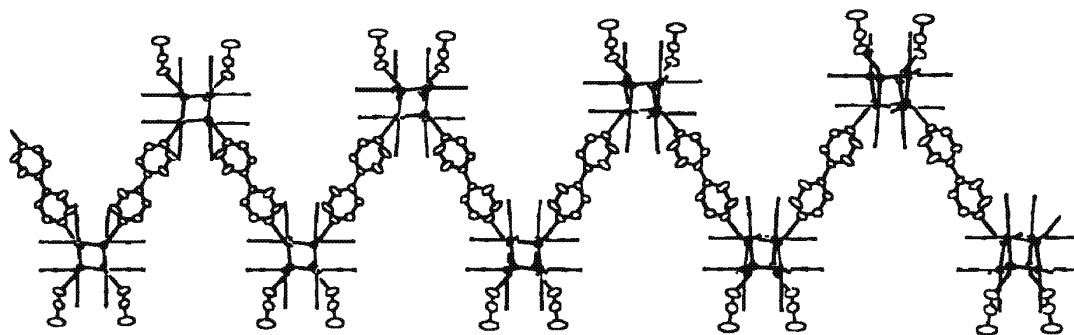


Fig. 3. ORTEP perspective view of the 1-D strand formed by 2.

network, 2.744(9) Å,^{6b} but longer than the 2.606(11) Å separations encountered in the 2-D network.⁷ The MeCN molecules form terminal hydrogen bonds to Mn₄ with O...N distances of 2.829(8) Å, consistent with the distances in **1** and those reported elsewhere.¹¹ Once again all four μ₃-OH moieties of Mn₄ are utilized as hydrogen bond donors and there are no strong hydrogen bond donors that remain unbonded.

Hydrogen bonding is evident from the IR spectrum: the O–H peak is split into two peaks at 3406 cm^{−1} and 2954 cm^{−1},¹³ the latter being significantly stronger and broader than that observed in pure Mn₄.

In both **1** and **2** the covalent bond distances and angles of the cubane Mn₄ are very similar to those observed in other crystal structures that involve Mn₄ (Table 3 and Table 4).

Conclusions

In summary, the nature of the cocrystals formed using Mn₄ as a hydrogen bond donor template is dependent on the complementarity of the other components (i.e. hydrogen bond acceptor functionalities). If the stoichiometries of **1** and **2** are known their complex hydrogen bond patterns can be readily rationalized based upon the known hierarchy of hydrogen bond strengths.

Experimental

The following materials were purchased from Aldrich Chemical Company Inc.: calcium hydride, 2,3,5,6-tetramethylpyrazine and benzophenone. Mn₂(CO)₁₀ was purchased from Strem Chemical Co. Toluene, tetrahydrofuran and acetonitrile were pur-

chased from BDH Inc. All solvents, with the exception of THF, were distilled over calcium hydride and stored over molecular sieves prior to use. THF was distilled in the presence of benzophenone and sodium metal. Melting points were determined on a Fisher-Johns melting point apparatus. The IR spectrum was recorded on a Perkin Elmer FT 1600 Spectrophotometer by diffuse reflectance in potassium bromide. [Mn(CO)₃(μ₃-OH)]₄·2toluene was synthesized according to the method reported by Clerk and Zaworotko.^{4b}

Preparation of 1

0.17g (1.2 mmol) of 2,3,5,6-Me₄pz was added to 0.50g (0.62 mmol) of [Mn(CO)₃(μ₃-OH)]₄·2toluene dissolved in 20.0 ml of distilled MeCN under ambient conditions. Crystallization of **1** was achieved by cooling the resulting solution for two days at −5°C. m.p. = decomposed at 146°C.

IR (KBr), cm^{−1}: O–H 3482.1(m), O–H 3148.2 (H-bonding, m, b), C≡O 2020.8 (s) and 1927.0 (s).

Preparation of 2

0.50g (0.80 mmol) of [Mn(CO)₃(μ₃-OH)]₄·2toluene dissolved in 2.5 mL of MeCN were added to 0.28g (1.9 mmol) of α-naphthol dissolved in 3 mL of MeCN. 0.20g (1.3 mmol) of 4,4'-dipy were dissolved in 2.5 mL of MeCN and upon addition to the reaction mixture the solution turned cloudy. The reaction was heated until the solution became clear, then cooled to room temperature. X-ray quality crystals were obtained within an hour. m.p. = decomposed at 163–164°C.

IR (KBr), cm^{−1}: O–H 2954 (H-bonding, m, b), C≡O 2018 (s) and 1916 (s).

Table 4. Interatomic distances (Å) and angles (°) for 1.

Distances	
Mn1–O1 2.039(3)	O13–C13 1.156(8)
Mn1–O1a 2.030(3)	O21–C21 1.151(8)
Mn1–O2 2.055(3)	O22–C22 1.162(7)
Mn1–C11 1.791(6)	O23–C23 1.144(8)
Mn1–C12 1.798(6)	N30–C32 1.347(10)
Mn1–C13 1.796(6)	N30–C35 1.332(9)
Mn2–O1 2.031(3)	N31–C33 1.343(9)
Mn2–O2 2.033(3)	N31–C34 1.330(9)
Mn2–O2a 2.049(3)	N40–C41 1.199(13)
Mn2–C21 1.801(7)	C32–C33 1.376(9)
Mn2–C22 1.774(6)	C32–C36 1.509(9)
Mn2–C23 1.793(7)	C33–C37 1.511(10)
O1–Mn1a 2.030(3)	C34–C35 1.392(9)
O2–Mn2a 2.049(3)	C34–C38 1.518(9)
O11–C11 1.149(7)	C35–C39 1.488(9)
O12–C12 1.147(7)	C41–C42 1.435(12)
Angles	
O1–Mn1–O1a 77.16(12)	C22–Mn2–C23 88.3(3)
O1–Mn1–O2 75.80(12)	Mn1–O1–Mn1a 101.00(13)
O1–Mn1–C11 171.04(21)	Mn1–O1–Mn2 102.87(14)
O1–Mn1–C12 98.09(20)	Mn1a–O1–Mn2 102.79(13)
O1–Mn1–C13 95.65(21)	Mn1–O2–Mn2 102.24(13)
O1a–Mn1–O2 76.41(12)	Mn1–O2–Mn2a 101.30(13)
O1a–Mn1–C11 96.48(20)	Mn2–O2–Mn2a 102.25(14)
O1a–Mn1–C12 96.57(20)	C32–N30–C35 119.1(5)
O1a–Mn1–C13 172.40(21)	C33–N31–C34 119.7(5)
O2–Mn1–C11 96.68(21)	Mn1–C11–O11 179.1(6)
O2–Mn1–C12 171.48(20)	Mn1–C12–O12 178.9(5)
O2–Mn1–C13 99.58(21)	Mn1–C13–O13 176.2(5)
C11–Mn1–C12 88.8(3)	Mn2–C21–O21 177.8(5)
C11–Mn1–C13 90.4(3)	Mn2–C22–O22 177.8(5)
C12–Mn1–C13 86.8(3)	Mn2–C23–O23 176.7(5)
O1–Mn2–O2 76.46(12)	N30–C32–C33 120.7(6)
O1–Mn2–O2a 76.52(12)	N30–C32–C36 116.2(6)
O1–Mn2–C21 97.79(21)	C33–C32–C36 123.2(7)
O1–Mn2–C22 171.62(20)	N31–C33–C32 120.0(6)
O1–Mn2–C23 97.62(21)	N31–C33–C37 116.9(6)
O2–Mn2–O2a 76.27(12)	C32–C33–C37 123.1(6)
O2–Mn2–C21 96.45(22)	N31–C34–C35 120.3(6)
O2–Mn2–C22 97.09(21)	N31–C34–C38 117.8(6)
O2–Mn2–C23 172.35(21)	C35–C34–C38 121.7(6)
O2a–Mn2–C21 171.56(22)	N30–C35–C34 120.2(6)
O2a–Mn2–C22 96.89(20)	N30–C35–C39 117.0(6)
O2a–Mn2–C23 97.78(22)	C34–C35–C39 122.8(6)
C21–Mn2–C22 88.2(3)	N40–C41–C42 177.2(9)
C21–Mn2–C23 89.1(3)	

^a 1.000 – x, y, 0.500 – z.

X-ray crystallography

Single crystals were mounted in thin-walled glass capillaries and optically centered in the x-ray beam of an Enraf-Nonius CAD-4 diffractometer. Unit cell dimensions were determined *via* least squares refine-

Table 5. Interatomic distances (Å) and angles (°) for 2.

Distances (Å)	
Mn1–O1 2.038(3)	O12–C12 1.166(8)
Mn1–O2 2.040(3)	O13–C13 1.147(8)
Mn1–O2a 2.035(3)	O21–C21 1.159(8)
Mn1–C11 1.802(7)	O22–C22 1.171(8)
Mn1–C12 1.772(7)	O23–C23 1.149(8)
Mn1–C13 1.793(7)	N30–C32 1.278(10)
Mn2–O1 2.033(3)	N30–C36 1.278(11)
Mn2–O1a 2.053(3)	N40–C41 1.109(12)
Mn2–O2 2.032(3)	C32–C33 1.397(9)
Mn2–C21 1.779(7)	C33–C34 1.348(8)
Mn2–C22 1.759(7)	C34–C34B 1.487(10)
Mn2–C23 1.803(7)	C34–C35 1.379(9)
O1–Mn2a 2.053(3)	C35–C36 1.413(10)
O2–Mn1a 2.035(3)	C41–C42 1.441(13)
O11–C11 1.152(8)	
Angles (°)	
O1–Mn1–O2 75.62(12)	O2–Mn2–C23 170.72(22)
O1–Mn1–O2a 76.68(12)	C21–Mn2–C22 89.7(3)
O1–Mn1–C11 172.09(20)	C21–Mn2–C23 88.0(3)
O1–Mn1–C12 99.17(22)	C22–Mn2–C23 88.8(3)
O1–Mn1–C13 95.54(21)	Mn1–O1–Mn2 103.00(14)
O2–Mn1–O2a 75.81(13)	Mn1–O1–Mn2a 101.35(13)
O2–Mn1–C11 97.78(20)	Mn2–O1–Mn2a 101.29(14)
O2–Mn1–C12 172.54(21)	Mn1–O2–Mn1a 102.49(14)
O2–Mn1–C13 97.33(21)	Mn1–O2–Mn2 102.95(14)
O2a–Mn1–C11 97.64(21)	Mn1a–O2–Mn2 102.20(13)
O2a–Mn1–C12 97.93(21)	C32–N30–C36 115.8(5)
O2a–Mn1–C13 170.61(21)	Mn1–C11–O11 177.9(5)
C11–Mn1–C12 87.0(3)	Mn1–C12–O12 176.1(5)
C11–Mn1–C13 89.6(3)	Mn1–C13–O13 178.4(5)
C12–Mn1–C13 88.4(3)	Mn2–C21–O21 177.1(5)
O1–Mn2–O1a 77.14(13)	Mn2–C22–O22 176.3(5)
O1–Mn2–O2 75.91(12)	Mn2–C23–O23 176.1(6)
O1–Mn2–C21 98.32(22)	N30–C32–C33 125.9(6)
O1–Mn2–C22 170.99(21)	C32–C33–C34 118.9(6)
O1–Mn2–C23 95.47(22)	C33–C34–C34b 123.9(5)
O1a–Mn2–O2 76.40(12)	C33–C34–C35 116.0(5)
O1a–Mn2–C21 172.27(21)	C34b–C34–C35 120.1(5)
O1a–Mn2–C22 94.42(20)	C34–C35–C36 119.0(7)
O1a–Mn2–C23 98.56(22)	N30–C36–C35 124.0(7)
O2–Mn2–C21 96.51(21)	N40–C41–C42 175.9(9)
O2–Mn2–C22 99.24(21)	

^a 2.000 – x, y, 0.500 – z.

ment of the setting angles of 24 high-angle reflections and intensity data were collected using the ω -2 θ scan mode. Data were corrected for Lorentz, polarization, and absorption effects, but not for extinction. Pertinent data collection and structure refinement parameters are presented in Table 1. The structures were solved using direct methods and all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were either located *via* difference Fourier map

inspection (OH, CH₃) or placed in calculated positions (CH: sp², D_{C-H} = 1.00 Å). Hydrogen atoms were given isotropic thermal parameters based upon the atom to which they are bonded and fixed during least squares refinement. Weights based upon counting statistics were used with the weight modifier, *k*, in *k*Fo² being determined via evaluation of variation in the standard reflections that were collected during the course of data collection. Values of *R* and *R_w* were given by $R = \sum(|F_o| - |F_c|) / \sum |F_o|$ and $R_w = [\sum(w|F_o| - |F_c|)^2 / \sum(wF_o^2)]^{1/2}$. All crystallographic calculations were effected using the PC version of the NRCVAX¹² system implemented on 80486 based IBM compatible computers. Crystallographic figures were generated using ORTEP.^{12c}

Acknowledgments

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Pharmaceutical Patent Analyst

The A to Z of pharmaceutical cocrystals: a decade of fast-moving new science and patents

Örn Almarsson^{*1}, Matthew L. Peterson² & Michael Zaworotko³

From aspirin to zoledronic acid, pharmaceutical cocrystals emerged in the past decade as a promising new weapon in the arsenal of drug development. Resurgence of interest in multicomponent crystal compositions has led to significant advances in the science of cocrystal design and discovery. These advances have built upon crystal engineering, which provides a deep understanding of supramolecular interactions between molecules that govern crystal packing and physicochemical properties of crystalline materials. Concomitantly, the patent landscape of pharmaceutical cocrystals developed rapidly in the last decade. This review presents a broad survey of patents issued in the area of pharmaceutical cocrystals. In addition, the review contains analyses of key patents in the area involving compositions and methodologies. Along the way, the main events of the past decade representing a renaissance of cocrystals of pharmaceutical materials are chronicled. Future directions in the area are discussed in light of key pending patent applications and recent publications of seminal interest.

Solid forms of active pharmaceutical ingredients

The solid form of an active pharmaceutical ingredient (API), in particular its physicochemical properties relevant to clinical performance and long-term stability, represents an important aspect of modern drug discovery, development and pharmaceutical science [1,2]. Over the course of the past century of modern drug development and manufacture, drugs such as aspirin and many antibiotics have owed their purity and storage stability to their existence as crystalline solids. Crystalline solids are solids in which the atoms, molecules or ions pack together to form a regular repeating array that extends in three dimensions. Crystalline solids are formed when a solution becomes supersaturated with crystallizing solute(s), and the vast majority of substances, if not all of them, will crystallize to form one or more crystalline phases under the right conditions. Cocrystals are a class of crystalline solids that occur when complementary molecules of different structures are crystallized to form single crystalline phases that contain stoichiometric ratios of the components. A prototypical example is a 1:1 composition cocrystal as illustrated in Figure 1. The crystalline form of a given API confers important properties to the material, such as thermodynamic solubility, melting point, shape, mechanical properties and thermal stability. Aqueous solubility and dissolution rate are particularly important in the context of drug performance since orally delivered drugs must dissolve from their dosage form within the gastrointestinal tract in order to be absorbed, first by the tissue of the intestines and ultimately into circulation. Aqueous solubility is also important for injectable drug formulations, in particular when intravenous injection is required. Because of the tight regulation of drug review and approvals across the world, detailed information on the crystalline form of an API, its synthesis, purity profile and properties are required as part of regulatory filings. Finally, and most relevant to this review, the IP associated



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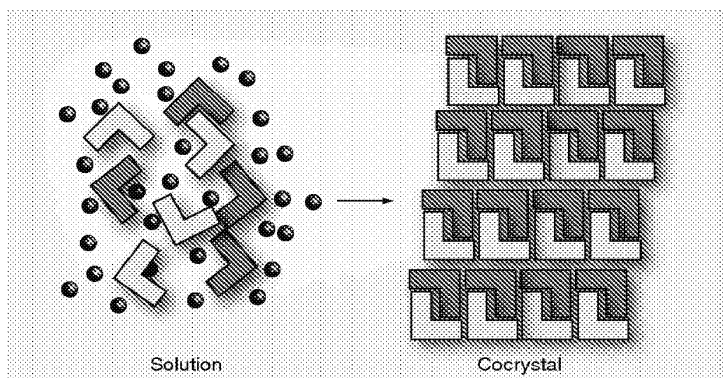


Figure 1. Stoichiometric cocrystals are formed when two complementary molecules are crystallized from solution.

with the crystalline form of an API came to the fore in the 1990s, thanks initially to high-profile patent litigation on what was at the time the best-selling drug in the world, ranitidine hydrochloride (Zantac®) [3]. Today, the characteristics and preparation of an API solid form can be of significant importance when seeking to register a new drug product using a crystalline API, and crystal forms continue to be the subject of litigations related to patent validity and infringement.

The motivation for studying cocrystals of pharmaceutical compounds

Solid-form screening in drug development has traditionally focused upon the need to find a solid form with optimal physicochemical properties, but has until recently focused almost exclusively on the generation of polymorphs, solvates, hydrates or salts of an API [4]. Pharmaceutical cocrystals [5] emerged in the last decade as an alternative class of crystal form available to pharmaceutical scientists. Despite recent emergence, pharmaceutical cocrystals are already established as an integral part of solid-form screening because they provide an opportunity to modify, sometimes with dramatic results, the physicochemical properties of an API without the need for applying medicinal chemistry, which involves covalent modification of the API. Rather, pharmaceutical cocrystals exploit the supramolecular chemistry of the API to create a new crystal form through formation of a multiple-component crystal that comprises of the API and a second compound or 'cocrystal former' (also known by various alternative names, such as 'coformer' or cocrystallizing agent). It has already been demonstrated that the aqueous solubility [6,7], physical stability [8] and mechanical properties [9] of an API can be affected by cocrystallization. Furthermore, pharmaceutical cocrystals represent an opportunity to patent new solid forms of APIs (or avoid infringement of existing patent claims

on solid forms of an API). That a high proportion of new chemical entities are classified as having low solubility has, if anything, provided added impetus for solid-form screening and the study of pharmaceutical cocrystals. Pharmaceutical cocrystals can offer advantages over other solid forms as follows: salts only form for APIs that ionize (protonate or deprotonate with acid or base, respectively) in water, whereas cocrystals can be made for essentially all APIs; amorphous forms; and solvates and hydrates tend to be physically unstable during processing and on the shelf. Finally, medicinal chemistry involves chemical modification of the molecular structure of the API, requiring extensive and time-consuming toxicology and clinical testing of the resulting new molecule(s). In short, pharmaceutical cocrystals offer an opportunity to address challenges of low solubility and other physicochemical properties of APIs with relatively low cost and limited incremental risk.

History & nomenclature of cocrystals

As mentioned, cocrystals can be broadly defined as supramolecular assemblies that contain more than one type of molecule in the crystalline lattice. For the purposes of this review we more specifically define a cocrystal as follows: a multiple component crystalline solid formed in a stoichiometric ratio between two compounds that are crystalline solids under ambient conditions. At least one of these compounds is molecular (the cocrystal former) and forms supramolecular synthons(s) with the remaining component(s). If one uses this definition then cocrystals were reported as far back as the 1840s [10] and they have had various terms coined for them: addition compounds, organic molecular compounds, complexes and heteromolecular crystals [11–14]. Cocrystals are thereby distinct from solvates and hydrates if one adopts this definition. It should be noted that APIs are a natural target for cocrystal formation since the nature of APIs means that they contain exterior functional group(s) that can engage in molecular recognition events, especially hydrogen-bond formation, with biological targets. These same functional group(s) are often responsible for different crystal packing arrangements (i.e., polymorphism) and can interact with water molecules to form hydrates. However, the term cocrystal as used today did not come into widespread usage until it was popularized by MC Etter in the 1980s [15], and a pharmaceutical cocrystal, that is, a cocrystal between an API and a pharmaceutically acceptable cocrystal former, was not widely used until the 2000s. Interestingly, pharmaceutical cocrystals also have a long history in that they have been known since at least the 1930s [101]. Even earlier, glucose:sodium chloride monohydrate was described, a possible early

example of an ionic cocrystal of a salt with a sugar [16]. In terms of nomenclature, it should be noted that there are some ambiguities; for example, there are other proposed definitions of cocrystal [17–25] and the work of Leiserowitz in the 1970s [24], as well as the compositions studied by Caira in the 1980s and 1990s [25], were referred to as complexes. Additionally, the term cocrystal is also occasionally applied to crystals of proteins with small molecules bound, for instance, within the active site of the protein. Leaving aside such issues, which are not relevant to this review, until the 2000s the motivation for the study of cocrystals of small organic molecules was oriented towards creating materials for purification or for optical, electronic and other material applications. In summary, both cocrystals and pharmaceutical cocrystals have a long history, but it is fair to assert that they had not been systematically and widely studied in the context of pharmaceutical science until the last decade.

Other solid forms of APIs

At the end of the 20th century, prior to the advent of pharmaceutical cocrystals, crystal polymorphism became a topic of major concern and highlighted the need for systematic solid-form screening of APIs, which also included the study of amorphous solid forms of APIs, with the aid of automation approaches [26]. Polymorphism in crystals is the ability of a particular chemical composition to adopt more than one type of crystal packing. Each different crystalline polymorph has its own set of properties, such as a melting point, heat of fusion and dissolution profile. Awareness of polymorphism in pharmaceutical compounds increased dramatically during the 1990s because of the aforementioned litigation on Zantac (ranitidine HCl). The need for regulatory bodies to address polymorphism was then highlighted by Norvir® (ritonavir) – an API in which catastrophic loss of drug product performance occurred due to sudden and unexpected appearance of a more stable polymorph of the drug with lower solubility than the form originally in use [27]. In addition to issues of polymorphs, crystalline hydrates created a level of concern for the same reasons. Hydrates of pharmaceutical compounds, which are special cases of solvates wherein a water molecule is included in the crystalline lattice along with the compound of interest, tend to display dynamics of water inclusion/exclusion dependent on temperature and relative humidity. Some hydrate-forming drugs have multiple hydrate forms, either as polymorphs or different levels of hydrate (e.g., mono, di- and tri-hydrate). Use of hydrates and solvates in products, while acceptable (and sometimes common, as in the case of β -lactam antibiotics [28]), is generally not preferred by innovators. From a regulatory standpoint,

in the USA at least, hydrates are considered similar to polymorphs in terms of how they are treated. The US FDA guidance published in 2007 [29] states that a particular hydrate of a compound is not a different API from a non-hydrate (or alternative hydrate state). Accordingly, there exist regulatory definitions of crystal forms that do not necessarily match scientific differentiation. A similar situation has recently arisen with respect to the comparison of cocrystals with non-ionic complexes with excipients, generally regarded as safe additives or other suitable coformers, and distinction of pharmaceutical cocrystals from salts.

Design of cocrystals

Rapid advances in crystal engineering [30–32] in the 1990s facilitated a better understanding of crystal-form diversity as represented by polymorphs, salts, solvates and hydrates, and enabled the design (as distinct from high-throughput screening) of new multiple-component pharmaceutical compositions. Practitioners of methodology increasingly directed testing to targeting the functional groups in drugs. The understanding developed that an API molecules' chemical functionality can be addressed by selection of complementary functional groups from another molecule, the coformer, led to a rational approach to the development of two-component crystals. This is conceptually similar to the manner in which salt-screening targets the ionizable groups in an API and means that there is a degree of control over cocrystal composition that is not likely to be present in hydrates and solvates. This design philosophy led to the adoption of the 'synthon' approach of cocrystal discovery. The synthon as it applies to cocrystals is analogous to the term as used in the retrosynthetic approach of organic synthesis. In a sense, making cocrystals this way is a supramolecular synthetic strategy. The key to understanding and designing cocrystals of an API lies with our capability to predictably form supramolecular synthons with the API. Supramolecular synthons exist in two distinct categories: supramolecular homosynthons that are composed of identical complementary functional groups such as carboxylic acid dimers (e.g., aspirin) (Figure 2A); and supramolecular heterosynthons composed of different but complementary functional groups such as acid–weakly basic nitrogen (e.g., aspirin–meloxicam) (Figure 2B) and acid–amide (e.g., aspirin–carbamazepine) (Figure 2C). Whereas it is quite well documented that some of these supramolecular heterosynthons are reliable for the preparation of cocrystals (i.e., they form preferentially over supramolecular homosynthons), studies related to the occurrence of a particular supramolecular heterosynthon in the presence of several competing supramolecular synthons are limited in quantity and scope. Therefore,

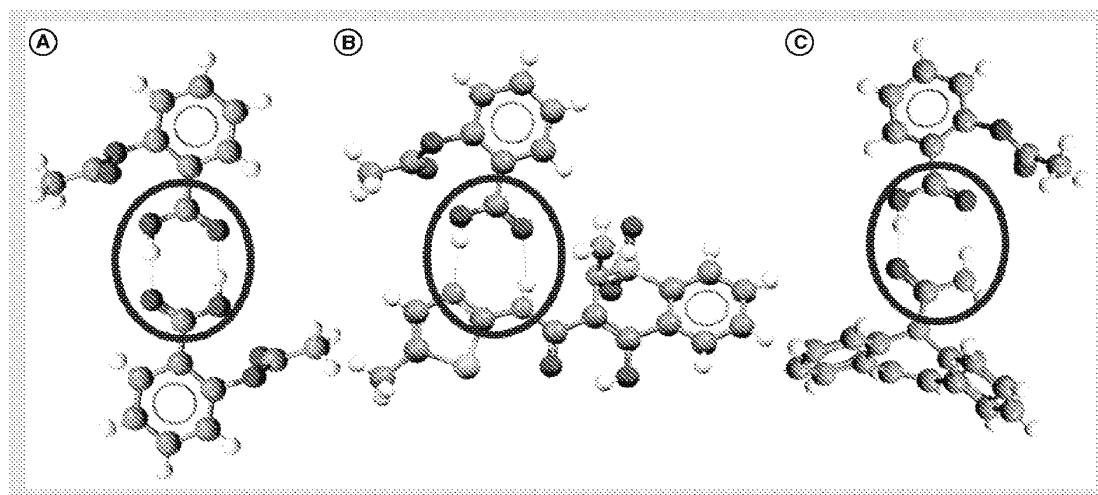


Figure 2. Synthon examples in pharmaceutical cocrystals involving carboxylic acids and amides. (A) The carboxylic acid-carboxylic acid supramolecular homosynthon as seen in aspirin. (B) The carboxylic acid-weakly basic nitrogen atom supramolecular heterosynthon as exemplified by the aspirin: meloxicam cocrystal. (C) The carboxylic acid-amide supramolecular heterosynthon observed in the cocrystals of aspirin and carbamazepine. The blue ovals highlight each supramolecular synthon.

APIs with multiple functional groups, although still amenable to cocrystal formation, tend to be less predictable in terms of structure and composition. To summarize the background to this article, the motivation to systematically study solid forms of APIs lies with the need to fine-tune physicochemical properties (especially modulate drug solubility, increase dissolution rate and to enhance stability), and satisfy regulatory bodies with respect to drug stability and reproducibility. This need had become apparent by the late 1990s and arose partly based on the types of compounds in development (e.g., compounds with poor aqueous solubility and other inadequate physical properties), and in part because a new level of innovation was needed at a time of productivity crisis in the pharmaceutical industry. In essence, pharmaceutical cocrystals joined the arsenal of pharmaceutical R&D as a useful new design tool – with patent prospects – to augment product design and elucidate new pharmaceutical product opportunities. Today, the fruits of almost 10 years of screening for pharmaceutical cocrystals is evidenced by the number of patent applications and issued patents for pharmaceutical cocrystals.

Pharmaceutical cocrystals: recent literature & definition

■ Primary literature

Before reviewing patents on pharmaceutical cocrystals, it is useful to survey the published literature. The first publications signaling the initiation of the pharmaceutical cocrystal era resulted from

collaboration between researchers at the University of South Florida, USA, and the University of Michigan, USA. The work was also associated with patent filings, and ultimately resulted in issued claims on the compositions in this paper. A key theme in the papers was the demonstration of design and detailed structural analysis to extend considerably the crystal form diversity of aspirin and carbamazepine, an important antiepileptic drug having low aqueous solubility. These papers were quickly followed by a paper on cocrystals of itraconazole, a highly water-insoluble and poorly bioavailable (as crystalline base) antifungal agent, published by a pharmaceutical technology company, which described the utility of the cocrystal approach for dissolution enhancement. In particular, the cocrystal construct with 1,4-diacids such as succinic, fumaric and tartaric acid involved in a pair of heterosynthons with the 1,2,4-triazole group of two itraconazole molecules showed significant improvement in dissolution rate in aqueous medium compared with the crystalline free base. Additionally, the best of the cocrystals in the series matched the dissolution rate of a solid dispersion, which is an amorphous form with optimized dissolution (used in the capsule product Sporano[®]). A fourth example of a publication marking the area is on cocrystals of fluoxetine HCl, an antidepressant and the active agent in Prozac[®]. This article, contributed by another technology company, highlighted the option of making pharmaceutical cocrystals of a salt, such that the cocrystal has three components. Modulation of solubility was observed by the inclusion of a carboxylic acid such

as benzoic and fumaric acid to the HCl salt. The four primary literature references cited above were arguably the highest profile publications on pharmaceutical cocrystals in the first half of the decade. The subject matter reported in these publications is summarized in Table 1.

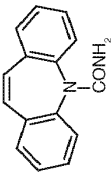
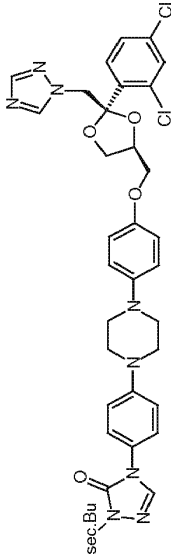
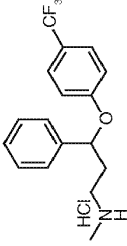
An early and key review in 2004 captured the definition of pharmaceutical cocrystals [33]. The review, now cited over 280 times, suggested that pharmaceutical cocrystals are amenable to design, and that they allow a selection of motifs that can then affect pharmaceutical properties. Pharmaceutical cocrystals were also regarded as more similar to salts than hydrates/polymorphs, given the composition types, variety and some aspects of crystal packing were seen to offer a measure of control. In contrast, polymorphs and hydrates were seen as being less amenable to design and prediction. A number of other review articles were published in the period after 2004, and these concepts have continued to be discussed and refined.

■ US patents on pharmaceutical cocrystals

A significant number of patent applications have been filed on pharmaceutical cocrystals, with many filed in the last decade. The US and EP patent authorities have granted patents in the area in recent years, starting with one patent from 1999 and ending (at the time of writing) with eight patents issued in 2012. With initial focus on the US-granted patents, we observe that the issued patents fall into two main categories: methodologies and compositions.

■ Methodology patents

The first claims to issue on pharmaceutical cocrystal methods were those in [102]. The title of the patent is 'Cocrystallization Process', and claims cover purification of chiral compounds by way of formation of cocrystals. In several cases the results are likely to be salt forms, though this has not been verified. In any event, this patent covers methodologies related to pharmaceutical cocrystals. Another cocrystallization methodology patent was filed in January 2004 and issued on November 18, 2008 [103]. The independent claim reads partially "*a method of screening for a cocrystal of a hydrochloric acid salt of an active agent.*" This patent is related to the publication on fluoxetine HCl cocrystals referred to in the previous section [7]. While claim 1 of [103] has several limitations, it allows for a range of carboxylic acids (at least four carbons) with the HCl salt of an active agent (e.g., an antidepressant drug). The inventor and assignee, SSCI, exemplified the approach with a set of carboxylic acid cocrystals of fluoxetine HCl (Table 1). The acidic -COOH function coordinates the chloride ion of an HCl salt of a basic drug. As a component of a supramolecular synthon, Cl⁻ appears to be a

Table 1. Chemical formulas of carbamazepine, itraconazole and fluoxetine HCl along with lists of synthon targets in the cocrystal material and examples of cofomers.			
	Carbamazepine [6]	Itraconazole [6]	Fluoxetine HCl [7]
Structure			
Synthons	Amide–amide homodimer periphery (C=O acceptor and N–H donor)	1,2,4-triazole (2:1 itraconazole to diacid units)	Chloride ion (coformer hydrogen-bond donor)
Cofomers	Hydrogen-bond acceptors (e.g., saccharin, nicotinamide and others)	1,4-dicarboxylic acids as hydrogen-bond donors (e.g., succinic, fumaric, tartaric and malic acids); requirement for extended conformation of the diacid (Z-trans configuration)	Carboxylic acids (≥4 carbon) as hydrogen-bond donors (e.g., benzoic and fumaric acid)

ready acceptor of -OH hydrogen bond donors, affording aforementioned carboxylic acid cocrystals, alcohol solvates and hydrates. Examples were provided on solubility and dissolution effects of the cocrystals. A process patent from Cilag (part of J&J), [104], involves the use of a cocrystal for purification of the opioid tramadol. Tramadol HCl cocrystallized with topiramate, an antiepileptic, to produce enantiomerically enriched 1S,2S-tramadol HCl, illustrating the utility of a chiral auxiliary (which is incidentally also a drug) to form a specific pharmaceutical cocrystal.

Two additional cocrystal methodology patents are illustrative of the interest in processes to make pharmaceutical cocrystals. The former, [105] issued on July 27 2010 to TransForm Pharmaceuticals (at this point part of J&J) claimed “a method of producing cocrystals, comprising” steps of processing with grinding materials in small capsules within an array created by two plates and containing a ball that effected the mechanical grinding once the competed array was placed on a shaker apparatus. Mechanical grinding of powder blends with and without solvent drops, a powerful technique championed by the Jones’ group at Cambridge University [34,35] had become popular within the community of cocrystal hunters by the middle of the decade. The latter patent [106] issued on 3 August 2010 to Avantium in The Netherlands claimed “a process for inducing and/or accelerating at least one phase transformation in solid organic molecules, wherein the solid organic molecules are subjected to a tribochemical treatment.” Cocrystals are not the sole subject of this patent, but are nonetheless explicitly named in dependent claims. The examples of innovation in methodologies relevant to cocrystal formation indicate a level of interest in protecting platform technologies to discover and make these new solid phases. The key challenge with these patents is the degree to which enforcement is practical: once a cocrystallization technology is enabled and patented, it will be difficult to prove that a specific cocrystal composition described was discovered or made using

a patented process. It is therefore not surprising that composition patents and applications involving pharmaceutical cocrystals are more numerous than the methodology patents.

The landscape of issued pharmaceutical cocrystallization methodology and process patents in the USA is summarized in Table 2 [102–106]. Three of the five patents originated in companies whose business at the time was crystal form screening and characterization for pharmaceutical materials.

■ Composition patents

The first US patent located on the subject issued in 1999 and originated from Eli Lilly & Co. It describes compositions that can clearly be classified as pharmaceutical cocrystals: cephalosporin antibiotic complexes with parabens. The latter are excipients generally used as preservatives. The complexes were intended for purification and isolation of the hydrolytically labile β -lactam antibiotics, and thus, evidently, the concept was conceived and applied for scale-up of purification and isolation. The first composition claimed this past decade for a pharmaceutical cocrystal was issued in 2006, claiming an itraconazole form with tartaric acid and HCl. This patent has one independent claim, which in addition to naming the components comprising the cocrystal further includes a specific melting point, such that the composition in the claim is a unique species. Species claims are narrow and specific and, therefore, ostensibly easier to support and grant relative to broad composition claims. The broadest extreme of composition claim is a genus. Since cocrystals have been observed across a range of molecules for decades, a genus of pharmaceutical cocrystals is likely not a supportable patent claim at this point. The broad option of sub-genus claims, meaning the inclusion of a drug molecule or a related group of molecules plus a cocrystal former (or a group of cocrystal formers) is an alternative that has been issued in select cases. The sub-genus claim is exemplified by the itraconazole carboxylic acid cocrystals, which was issued in a later

Table 2. Methodology patents issued in the USA involving cocrystallization 2000–2010

US patent	Date of issue	Assignee	Nonprovisional priority date	Claims	Cocrystals in claim 1	Ref.
US6570036	27 May 2003	Reuter Chemische Apparatebau KG	3 March 2000	17	Yes	[102]
US7378519	27 May 2008	Cilag GmbH Intl	16 May 2003	1	Yes	[104]
US7452555	18 November 2008	S.S.C.I., Inc.	21 January 2004	11	Yes	[103]
US7763112	27 July 2010	TransForm Pharmaceuticals, Inc.	28 April 2006	12	Yes	[105]
US7766979	3 August 2010	Avantium International B.V.	26 January 2005	20	No	[106]

patent [107]. In essence, the independent claim allows the license holder to exclude any composition that contains the drug itraconazole and a carboxylic acid.

Table 3 [107–124] summarizes the compositions with granted claims. There are also a number of pending applications, such that the list of issued patents is likely to grow at an increasing pace over the next decade.

Two patents in Table 3, [113] and [119], contemplate compositions with variable stoichiometric ratios – in addition to the standard use of open-ended language in the claims construction. The former patent is an example of continuous variation of the coformer ratio: one coformer can be substituted in portions by an isomorphically substitutable coformer, for example uracil for 5-fluorouracil. Modafinil, a narcolepsy drug, was cocrystallized in this manner with fumaric acid and succinic acid in a system that created isomorphous cocrystals of the composition (Modafinil)₂[fumaric acid]_x[succinic acid]_(1-x), where x ranges from 0 to 1. The net result, regardless of the value of x , is a 2:1 cocrystal of modafinil and a dicarboxylic acid. An alternative label for these varying compositions is to call them solid solutions. Nomenclature aside, the approach is intriguing, because it invites tailoring of a physical property in a pharmaceutical crystal form (e.g., the melting point), by the choice of ratio of the coformer. Ordinarily, a crystal form is thought of as a discrete entity with fixed properties. The possibility of blending and selection of properties with cocrystal composition vastly increases the power of the approach.

The patent matter in [110] highlights the challenge of applying definitions of pharmaceutical cocrystals. There is occasional confusion as to whether a composition is a cocrystal or a solvate – the resolution mainly depends on how the coformer is regarded. The patent claims the acetic acid form of (-)-gossypol, a natural product with potential as an anticancer agent. The independent composition claim 1 specifies, “A composition consisting essentially of cocrystals of (-)-gossypol with acetic acid in a molar ratio of about 1:1.” Glacial acetic acid crystallizes below room temperature at 16.6°C. Additionally, the presence of minute amounts of water in acetic acid lowers the solvents’ melting point further [36]. Since glacial acetic acid is a liquid at room temperature, assuming the convention of 20°C as a lower end cut-off for the value of room temperature, the common conclusion would be that the gossypol acetic acid compound is in fact a solvate. The pharmaceutical cocrystal definition advanced in [34] excludes solvates. The exclusion was based largely on the observation that solvates are regarded as by-products of crystallization from or adventitious exposure to a solvent, and that design of solvates is less fruitful than that involving cocrystals.

The Novelix patent, covering an anticancer drug candidate rendered as a cocrystal with oxalic acid [120], provides a contrast with salt forms. Oxalate is infrequently used as a counterion in salt-form drug compounds (e.g., escitalopram oxalate, the active ingredient in the antidepressant drug Lexapro®), while oxalic acid cocrystals are well exemplified in the pharmaceutical cocrystal literature. The inventors of [120] cite as art a caffeine cocrystal with oxalic acid, reported by the Jones group in Cambridge [35]. The NVX-412 oxalic cocrystal in the patent has superior physical properties over the NVX-144 free base form of the drug candidate. Two patents from two different pharmaceutical companies involve compositions of sodium–glucose transporter type 2 (SGLT-2) inhibitors, a new drug class targeted to treat diabetes by facilitating excretion of glucose in the urine. The sugar-like drug candidate by Pfizer in [121] is PF-04971729, a drug candidate that is not described in a crystalline form by itself, this was cocrystallized with pyroglutamic acid and L-proline. The Astellas SGLT-2 compound claimed in [122] is a cocrystal of a C-glycoside with L-proline. That these two patents were issued in the same timeframe and on a similar subject matter is interesting, and speaks to the potential importance of the therapeutic class (glucose control and diabetes) as well as the utility of cocrystals in preparing crystalline, pharmaceutically acceptable forms of the drug candidates. At the time of writing, the most recent pharmaceutical cocrystal patent involves cocrystals of the anti-infective drug metronidazole and an example of an imipramine HCl cocrystal – in both cases the drug is cocrystallized with a carboxylic acid. All species claimed are defined by at least one characteristic x-ray diffraction peak. This most recent case highlights that cocrystal composition claims are being granted without the limitation of any bioperformance data (or suitable surrogate such as dissolution, or solubility), but evidently the claims in these cases are narrow species claims rather than sub-genus or genus-type claims.

Based on a brief survey of the pending applications for pharmaceutical cocrystal compositions in the USA, one should expect continued activity in 2012 and beyond. Several applications detail significant improvements in both physicochemical and bioperformance properties of the drug candidates under consideration.

■ Patents in countries outside the USA

Given that standards used to evaluate proposed patent claims differ between countries, it is perhaps not surprising that the area of pharmaceutical cocrystals has seen a slightly slower pace of patent activity outside the USA. Another reason for the lesser activity

Table 3. Composition patents issued in the USA for pharmaceutical cocrystals 1999–2012^{*}

US patent	Date of issue	Assignee	Compound(s)	Claims	Ref.
US6001996	14 December 1999	Eli Lilly & Co., Inc.	Complexes of (carba)-cephalosporins with parabens	2	[108]
US7078526	18 July 2006	TransForm Pharmaceuticals, Inc.	Itraconazole; tartaric cocrystal of the HCl salt having melting point of 161°C	16	[109]
US7342046	11 March 2008	The Regents of the University Of Michigan	(-)-Gossypol, acetic acid co-crystal (1:1 ratio)	13	[110]
US7446107	4 November 2008	TransForm Pharmaceuticals, Inc.	Itraconazole; cocrystals with a carboxylic acid	3	[107]
US7625910	1 December 2009	Astra Zeneca AB	AZD1152; a phosphate prodrug and maleic acid cocrystal	6	[111]
US7566805	28 July 2009	TransForm Pharmaceuticals, Inc. (Cephalon, Inc.)	Modafinil; carboxylic acid cocrystals (e.g., malonic and glycolic)	53	[112]
US7671093	2 March 2010	TransForm Pharmaceuticals, Inc.	Mixed cocrystals, 'isomorphically substitutable'	2	[113]
US7691827	6 April 2010	Eli Lilly & Co.	Gemcitabine: a prodrug cocrystallized with aromatic sulfonic acid, hydrate	6	[114]
US7803786	28 September 2010	TransForm Pharmaceuticals, Inc. and University of South Florida	Stavudine; aromatic amines such as melamine and 2-aminopyridines	15	[115]
US7927613	19 April 2011	University of South Florida/University of Michigan/ TransForm Pharmaceuticals, Inc.	Carbamazepine, celecoxib, 5-fluoro-uracil, acetaminophen, phenytoin, ibuprofen, flurbiprofen; multitude of coformers	36	[116]
US7935817	3 May 2011	Apotex Pharmachem Inc.	Adefovir dipivoxil; nicotinamide and salicylamide conformers	22	[117]
US8003700	23 August 2011	Mutual Pharmaceutical Co., Inc.	Cochicine; solid complexes, malic acid cocrystal	7	[118]
US8039475	18 October 2011	Vertex Pharmaceuticals, Inc.	Telaprevir; salicylic acid, variable stoichiometry	8	[119]
US8058437	15 November 2011	Novelix Pharmaceuticals, Inc.	(Pyrroloquinoxaliny)pyrazinecarbo-hydrazide, oxalic acid co-crystal	12	[120]
US8080580	20 December 2011	Pfizer Inc.	SGLT-2 inhibitors, L-proline and pyroglutamic acid cocrystals	20	[121]
US8097592	17 January 2012	Astellas Pharma Inc., Kotobuki Pharmaceutical Co. Ltd.	SGLT-2 Inhibitor, L-proline cocrystal	6	[122]
US8124603	28 February 2012	Thar Pharmaceuticals	Meloxicam with various carboxylic acids, aliphatic and aromatic, and maltol and ethyl maltol	25	[123]
US8163790	24 April 2012	New Form Pharmaceuticals, Inc.	Metronidazole cocrystals with gentisic acid and gallic acid (specific x-ray reflections in each case) and a cocrystal of imipramine HCl and (+)-camphoric acid	15	[124]

^{*}Through to April 2012.

SGLT-2: Sodium-glucose cotransporter subtype 2.

Table 4. Method and compositions patents issued on pharmaceutical cocrystals in Europe, 2003–2012.

EP patent	Date of issue	Assignee	Main content of claims	US counter-part(s)
EP1156864B1 [125]	14 May 2003	Reuter Chemische Apparatebau KG	Process for isolating enantiomer components from mixtures	US6570036 [102]
EP1011838B1 [126]	24 May 2006	Reuter Chemische Apparatebau KG	Crystallization process for separating a desired substance from mixture	
EP1831237B1 [127]	20 August 2008	Eli Lilly & Co., Inc.	Amide prodrug of gemcitabine, cocrystal of the prodrug	US7691827 [114]
EP1755388B1 [128]	6 October 2010	TransForm Pharmaceuticals, Inc.	Mixed cocrystals of modafinil	US7671093 [113]
EP2139885B1 [129]	8 December 2010	Syngenta Ltd.	Cocrystals of propiconazole (an agro-chemical fungicide)	
EP2170284B1 [130]	24 August 2011	Feyecon B.V.	A method of preparing a pharmaceutical cocrystal composition	
EP2185546B1 [131]	26 October 2011	Vertex Pharmaceuticals, Inc.	Cocrystals and pharmaceutical compositions, telaprevir (VX-950)	
EP2334687B1 [132]	4 January 2012	Pfizer Inc.	SGLT-2 inhibitors, L-proline and pyroglutamic acid cocrystals	US8080580 [121]
EP2300472B1 [133]	18 January 2012	Boehringer Ingelheim Intl. GmbH	Glucocorticoid analogs, phosphoric acid and acetic acid cocrystals	
EP2114924B1 [134]	25 January 2012	Vertex Pharmaceuticals Inc.	Cocrystals of telaprevir with 4-hydroxybenzoic acid; solvates	
EP2288606B1 [135]	15 February 2012	Bayer Pharma AG	Rivaroxaban cocrystal with malonic acid	
EP1608339B1 [136]	21 March 2012	McNeil PPC	Celecoxib cocrystal with nicotinamide	US7927613 [116]

may be strategic decisions on the part of innovators to pursue US patents in preference to prosecuting claims in other countries. However, an increasing role of pharmaceutical cocrystals in drug development may lead to an increase in foreign patent filings. Beyond the USA and Europe, the pharmaceutical industry often pursues patent protection in countries such as Japan, Canada and Australia.

European patents in the area of pharmaceutical cocrystals

In Europe, there has so far been limited issuance of patents as yet. Patents issued in Europe on pharmaceutical cocrystals, methods as well as composition claims, are listed in Table 4 [125–136].

Five of the composition patents in Table 4 have an accompanying issued US patent counterpart.

The EPO has long taken a utilitarian (problem-solving) approach to review and allowance of patents, including crystal form patents. In contrast, the USPTO has determined the patentability of crystals on a case-by-case basis, considering the differences in physical and chemical properties of the new form relative to any previously known form. Observing recent patent case law and implementation of the Leahy–Smith America Invents Act of 2011, it is possible that a philosophical approach akin to that taken

in Europe to examine crystal form patent applications will become prevalent in the USA in the near future.

Summary of the last decade of pharmaceutical cocrystals

Some points can be made in summary about the science and patent activity in pharmaceutical cocrystals. The science has advanced, the patents are arriving, but do we have product candidates arising from the technology at this point?

Scientific & patent literature on pharmaceutical cocrystals

Approximately a decade of extensive activity in the area of pharmaceutical cocrystals has been summarized in this review. The scientific literature on the topic is vast, and a number of the key papers and reviews have been included to illustrate the breadth of coverage of the topic. The patent literature on pharmaceutical cocrystals is commensurately sizable. At the time of writing, there are a number of pending applications on compositions in the category of pharmaceutical cocrystals making their way through patent prosecution. A selection of these pending cases will be discussed in the next section as examples of patents that might emerge in the next few years.

■ Language of crystal forms in patents

An early (and apparently lasting) impact of the advent of pharmaceutical cocrystals is a change in the way in which crystal form types are generically named in patents and pending applications. Writers of patents have required a veritable catch basin of terms to comprehensively describe crystal forms and provide scope in their applications. The evolution of the language of crystal forms can be illustrated using a few examples of the numerous patents that have these general phrases to encompass crystal-form types. The language in pharmaceutical composition patents historically included, “the drug and any pharmaceutically acceptable salt” (e.g., [137,138]). When polymorphs became an issue in the 1990s, the general language was extended to include polymorphs, solvates and hydrates (e.g., [139,140]). Most recently, some have added the cocrystal term as part of the general description of material forms (e.g., published patent applications [141,142]). Evidently, awareness of the cocrystal possibility in these pharmaceutical form cases is prompting the addition of the cocrystal term to the generic language capturing the crystal form types that a pharmaceutical compound might adopt.

■ Pharmaceutical products containing cocrystals

Drug development is a painstaking, highly regulated and long process. While several options appear on the horizon, a clear-cut pharmaceutical product example involving a cocrystal is currently lacking. This situation is likely to change within the next 5–10 years as more pharmaceutical cocrystal patents issue and drugs based on pharmaceutical cocrystals as APIs make their way through clinical trials and registration. The pharmaceutical cocrystal technology has seen many applications in patents and the scientific literature, and a handful of the specific cocrystals of drug candidates are observed to be in clinical development based on data from public sources. Based on the small number of drugs approved in a given year, the approval of a cocrystal-based drug product may occur in the next few years. In general, the overall palette of drugs in regulatory review will likely continue to use a mix of technologies, cocrystals being one representative technology. Some of the candidate pharmaceutical cocrystals with a probability of becoming drugs of the future are discussed in the next section.

Current perspective on pharmaceutical cocrystals

■ Pharmaceutical cocrystals at the beginning of 2012

This review covers over 30 issued patents. Many applications, perhaps numbering in the hundreds, are pending in various countries and are beyond the scope of this review. So what does the future hold for pharmaceutical cocrystals and indeed for the cocrystal field in general? The chemical enterprise, including pharma-

ceutical drug-substance design and manufacture, faces a range of challenges over the next few decades. Cocrystals have a role to play in resolving some of these challenges, and provide an overall technological advance for the chemistry of materials. A future perspective must be comprehensive, if a bit aspirational in certain areas. The subsections below represent the areas of opportunity perceived for the coming decades of cocrystal research and development.

■ Cocrystals as alternative materials for pharmaceutical products of established drug molecules

There exists a range of products whose properties make them amenable for cocrystal design in order to preserve, ensure or enhance drug performance; examples include: replacing amorphous drug material with a cocrystal (to avoid perceived risk associated with non-crystalline drug in the product), substituting crystalline low-soluble drug form with cocrystal for enhanced solubility, dissolution and bio-performance, and designing bio-equivalent cocrystal forms of known products to create generic equivalents or products for alternative uses to those already approved. The itraconazole cocrystals in [107] and [109] were proposed as a substitution approach to the use of an amorphous drug coated on a bead. The concept was not to improve bioavailability, which had been optimized with considerable effort through the use of a bead-coating approach. Instead, cocrystals would simplify processing by changing to a conventional dosage form design and, thus, facilitate removal of a methylene chloride solvent system required in the coating process. The Sporanox[®] product enjoyed significant patent protection based on the coating process, but has now become generic and, hence, it is doubtful that the cocrystal product will compete and recover the investment needed to develop the new product. Nevertheless, this general concept of replacing amorphous with crystalline material has merit. An example from recent patents is found in [119,131] by Vertex Pharmaceuticals on telaprevir, a newly approved hepatitis C viral protease inhibitor. This orally active antiviral compound has exceedingly poor bioavailability as a crystalline base compound, and is therefore presented as an amorphous dispersion prepared by spray-drying and incorporation of stabilizing polymers. The resulting amorphous drug is reportedly chemically and physically stable in the product at room temperature for years. The recently issued Incivo[®] (telaprevir) cocrystal patents may indicate an interest in contrasting a crystalline composition, not of the base molecule but of a well-performing pharmaceutical cocrystal. If developed, the approach may become a case of life cycle management for telaprevir and possible combinations of the drug with other antiviral agents as the therapeutic algorithm for hepatitis C infection evolves.

■ Life cycle management with cocrystals

Proprietary pharmaceutical companies and generic drug manufacturers alike will undoubtedly study the recent FDA guidance on pharmaceutical cocrystals, which issued in draft form in December 2011 [37]. The guidance proposes regulatory classification of pharmaceutical cocrystals, with a main recommendation that cocrystals can be regarded as process intermediates en route to a drug product (e.g., tablet and capsule), while the labelling of the final product can remain confined to the original API. For example, if a known API is processed in a pharmaceutical operation to form a cocrystal by inclusion of an excipient (coformer), then the requirement to relabel the drug as a new API can be avoided. There are nevertheless requirements for characterization of the process and cocrystal material. In particular, two constraints are placed on sponsors who wish to employ a cocrystal in their drug product: they must define the difference in pK_a between the drug and coformer to be within range of three units, so as to rationalize the lack of proton transfer and resulting ionization; the developer must show that the cocrystal dissociates to release the free API before reaching the target site. These requirements may prove to be non-trivial in some cases.

■ Product enhancement, enabling bioperformance

Arguably the most technically challenging applications of cocrystals could prove to be the act of improving bioperformance for difficult-to-formulate drug candidates. Occasionally, a compound with excellent pharmacological activity and safety can pose a major formulation challenge from the perspective of bioperformance. For example, attaining sufficient overall exposure of an oral dose may require extraordinary formulation efforts, such as those described for itraconazole and telaprevir in previous sections. A patented example of a development compound benefiting dramatically from a cocrystal form is AMG-517, a TrpV1 antagonist that was in development by Amgen, Inc. as a putative pain drug. Published patent application [143] describes the enhancement of oral exposure to this water-insoluble compound by a sorbic acid cocrystal. The effect of the cocrystal on bioavailability was particularly striking in preclinical studies (oral pharmacokinetics in rat) [38]. The boosting effect observed on bioavailability has significant practical impact, since the doses required for qualification and definition of a margin of safety for the drug candidate far exceed those envisioned in clinical use. In the absence of the cocrystal, the super-exposures may never be attained, and hence the true *in vivo* toxicology profile of a compound may be obscured. In summary, a cocrystal can benefit a clinical product and, perhaps even more strikingly, a toxicology formulation.

The use of a cocrystal form to bring about an intravenous-to-oral switch is exemplified in a recently published patent application [144]. The compound in question, zoledronic acid, a bone-resorption inhibitor, is water-soluble but not optimally permeable for absorption from the gut. In addition, compounds in this class are irritating to the esophagus and stomach lining. A cocrystal approach was employed to increase oral bioavailability and a coating was also applied to allow the compound to be absorbed only once the drug form is past the stomach.

■ Scale-up & manufacture of cocrystals in batch mode

As useful cocrystal materials are discovered, aspects of their development into useful products will gain importance. Of primary importance will be the ability to reproducibly manufacture the materials in large quantities. Some progress in this area has already been demonstrated. For example, in some cases traditional solvent-based crystallization can be used to prepare large batches of cocrystals. Detailed knowledge of the phase diagram involving the drug, coformer(s) and solvent is essential in these cases. Though not yet exemplified, the grinding method used for screening may well be a candidate for scale-up in batch mode, either as a unit operation to create a new API form or in order to generate an *in situ* cocrystal en route to a drug product. In addition, by reducing solvent use, a practitioner is fulfilling one of the goals of green chemistry.

■ Cocrystals in the context of continuous processing

The modern pharmaceutical enterprise has depended on batch manufacturing through the 20th century, and manufacturing groups have been surprisingly slow to adopt concepts from continuous process engineering. In contrast to pharma, chemical companies employ continuous processing extensively in high-volume chemical manufacture. As part of a push to improve manufacture in the pharmaceutical industry, the FDA and other regulatory bodies have been pursuing the Critical Path Initiative and Quality-by-Design in the last decade. The push is starting to generate activity and funding in continuous processing. As an example, Novartis Pharmaceuticals has sponsored a large continuous processing initiative, the main contributors to which are at the Massachusetts Institute of Technology. Cocrystals have been shown in recent publications to be good candidate compositions for certain unit operations that fit with continuous processing.

While there is limited patent activity, a few publications in the literature have introduced continuous processing examples with cocrystals. For example, large amounts of cocrystals were prepared solvent-free

(or essentially without use of solvent) using twin screw extrusion [39]. This type of processing has been common in polymer production, but is less extensively applied in pharmaceutical manufacture. Spray-drying, a technique often used to prepare amorphous materials, was used in the preparation of several cocrystals [40]. In another example, demonstrating the utility of cocrystals in modern chemical transformations, a cocrystal with lower solubility than either of the parent compounds was used to precipitate the product in a fermentation reaction [41]. Each of the techniques described above can be utilized as batch operations or as continuous (or semicontinuous) manufacturing operations.

✱ Synthesis with cocrystals green chemistry opportunities

Cocrystals offer the potential to eliminate the need for use of solvent in a chemical reaction and thereby reduce the cost of materials used in processing and all of the costs of dealing with solvent waste. Such 'cocrystal controlled solvent-free synthesis' [42] approaches have already demonstrated that high yield solvent-free synthesis can be accomplished in several classes or reaction through two strategies: the use of cofomers to serve the role of a template for aligning reactive groups (e.g., photodimerization of olefins [32]), and the formation of cocrystals from two reactive cofomers followed by application of stress (e.g., condensation [43]).

Future perspective

The future outlook for pharmaceutical cocrystals indicates promise in the following areas:

- ✱ Reformulation of existing drugs for improved performance;
- ✱ Life cycle management with recently approved drugs;
- ✱ Enabling novel development compounds: bio-performance and purification;
- ✱ Scale-up: both batch mode and continuous;
- ✱ Green chemistry and synthesis with cocrystals as intermediates.

The regulatory arena is beginning to deal with the appearance of pharmaceutical cocrystals as a class of materials. Examples are the FDA guidance published in December 2011 [37], as well as a recent literature report from the FDA on carbamazepine saccharin [44], one of the prototypes of the class as it emerged in a systematic way in the past decade. In regard to the patent landscape for pharmaceutical cocrystals, we should expect to see continued and likely accelerating activity in various regions, as is likely to continue to be the case for solid forms in general [45]. The target compounds and uses will likely reflect some or all of the areas in the above future outlook. And perhaps further opportunities will be identified in the current decade.

Disclaimer

This review describes the opinions and observations of the authors as scientists in the field of pharmaceutical crystal engineering, and does not necessarily represent the viewpoints of the authors' employers. No legal opinions or advice are provided herein.

Executive summary

Background

- ✱ Solid forms of active pharmaceutical ingredients (APIs) are important to the function of products. Physicochemical properties of compounds are determined by the crystal structure.
- ✱ The motivation for studying cocrystals of pharmaceutical compounds comes from the need to optimize properties, such as solubility, dissolution rate and bioavailability. There are also patenting motivations for studying cocrystals in the context of drugs and drug candidates. For regulatory review, the solid form of a drug candidate must be well characterized and described.

History & nomenclature of cocrystals

- ✱ Cocrystals have been long known, but not until recently have they been studied systematically for pharmaceutical compounds. Alternative names include complexes and multicomponent crystals. This review excludes cocrystals of drugs with proteins; the focus is on the drug compound and its compositions with cocrystal formers (abbreviated as 'coformers').
- ✱ Other solid forms of APIs include the pure form, solvates and salt forms. A salt comes from proton transfer to or from a drug substance with an oppositely charged counterion to balance charge of the ionized drug. Cocrystals do not have this requirement, and cocrystals of salts exist. Any of the possible crystal form types are subject to potential polymorphism – the appearance of multiple crystal forms of the same chemical composition having different properties from one another.
- ✱ Design of cocrystals is a great opportunity for pharmaceutical compounds. Rapid advances in crystal engineering and characterization capabilities have given the field of pharmaceutical cocrystals a big boost in the last decade. Making cocrystals represents a supramolecular synthetic strategy: synthesis of new compounds with the desired pharmacological agent as part of distinct non-covalent crystal compositions.

Executive summary (cont.)*Pharmaceutical cocrystals: recent literature & definition*

- The primary literature surveyed includes multiple citations from the 20th century. The beginning of the 21st century saw a section of key papers highlighting the potential of pharmaceutical cocrystals to tailor and improve performance of compounds like carbamazepine, fluoxetine HCl and itraconazole.

US patents on pharmaceutical cocrystals

- Methodology patents – five US patents and two EP – patents are discussed. The key challenge with methodology and process patents on pharmaceutical cocrystals (and crystal forms in general) is the degree to which enforcement is practical. Composition patents are more prevalent in the field of pharmaceutical cocrystals.
- Composition patents: 18 US patents have been issued in the past decade (based on our survey through to April 2012). A large number of pending applications are in process, and only a few of these are mentioned in this review. Composition claims range from very specific (a particular form of a specific cocrystal composition characterized by a physical property) to sub-genus claims (any cocrystal of a particular drug with a class of coformers).

Patents in countries outside the USA

- European patents in the area of pharmaceutical cocrystals are not yet as numerous as patents in the USA, but there remains significant ongoing activity. Ten European patents have been issued to date, and most EP patents have pending or issued US counterparts.

Summary of the last decade of pharmaceutical cocrystals

- The language in pharmaceutical composition patents historically included 'the drug and any pharmaceutically acceptable salt'. In the 1990s, the general language was extended to include polymorphs, solvates and hydrates. Most recently, some have added the cocrystal term as part of the general description of material forms.
- While several options appear on the horizon, a clear-cut pharmaceutical product example involving a cocrystal is currently lacking. The signs are that this will change within the next decade.

Current perspective on pharmaceutical cocrystals

- Cocrystals as alternative materials for pharmaceutical products of established drug molecules. A range of products exist for which structure and properties make them amenable for cocrystal design in order to preserve, ensure or enhance drug performance. Examples include:
Replacing amorphous drug material with a cocrystal to avoid perceived risk associated with non-crystalline drug in the product;
Substituting crystalline low-soluble drug form with cocrystal for enhanced solubility, dissolution and bioperformance;
Designing bioequivalent cocrystal forms of known products.
- Life cycle management with cocrystals: proprietary pharmaceutical companies and generic drug manufacturers alike will undoubtedly study (and perhaps also comment on) the recent US FDA guidance on pharmaceutical cocrystals, which was issued in draft form in December 2011.
- Product enhancement, enabling bio-performance: a key use of pharmaceutical cocrystals is to improve bioperformance (e.g., bioavailability, rate of absorption) for difficult-to-formulate drug candidates. The use of a cocrystal form to bring about an intravenous-to-oral reformulation is also exemplified.
- Scale-up and manufacture of cocrystals in batch mode relies on engineering capability and physical understanding of the cocrystal at hand. In principle (and in practice) traditional solvent-based crystallization can be developed to prepare large batches of cocrystals. A successful crystallization process must be based on detailed knowledge of the phase diagram (solubility and temperature dependence of solubility) involving the drug, coformer(s) and solvent.
- Cocrystals in the context of continuous processing; the modern pharmaceutical enterprise has depended on batch manufacturing through the 20th century, with slow adoption of concepts from continuous process engineering. As part of a push to improve manufacture in the pharmaceutical industry, the FDA and other regulatory bodies have been pursuing the Critical Path Initiative and Quality-by-Design in the last decade. Recent activity and funding in continuous processing is exemplified by the Novartis/MIT continuous processing initiative.

Synthesis with cocrystals & green chemistry opportunities

- Cocrystals offer the potential to eliminate the need for use of solvent in a chemical reaction and, thereby, reduce the cost of materials used in processing and all costs associated with dealing with solvent waste. Such 'cocrystal-controlled solvent-free synthesis' approaches have been demonstrated in literature recently.

Future perspective

- The future outlook for pharmaceutical cocrystals indicates promise in the following areas:
Reformulation of existing drugs for improved performance;
Life cycle management with recently approved drugs;
Enabling novel development compounds: bioperformance and purification;
Scale-up: batch mode and continuous;
Green chemistry and synthesis with cocrystals as intermediates.

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Understanding Lyophilization Formulation Development

Frank Kofi Bedu-Addo

The author covers the fundamentals of lyophilization and provides case studies about the development of lyophilized biopharmaceutical products and the importance of biophysical characterization in formulation and the lyophilization process.

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Lyophilization or freeze-drying is often used to stabilize various pharmaceutical products, including virus vaccines, protein and peptide formulations, liposome, and small-chemical drug formulations (1–4).

Often a pharmaceutical product may be susceptible to physical and chemical degradation when stored as a ready-to-use solution. The goal of the formulations scientist is to identify the right formulation conditions, the right excipients in optimal quantities, and the right dosage form to maximize stability, biological activity, safety, and marketability of a particular product.

Desired characteristics of a lyophilized product

A lyophilized product should possess certain desirable characteristics, including

- long-term stability
- short reconstitution time
- elegant cake appearance
- maintenance of the characteristics of the original dosage form upon reconstitution, including so-

lution properties; structure or conformation of proteins; and particle-size distribution of suspensions

- isotonicity upon reconstitution (in some cases, also for bulk solution).

The lyophilization process

The lyophilization process consists of three stages: freezing, primary drying, and secondary drying.

Freezing. During this stage the formulation is cooled. Pure crystalline ice forms from the liquid, thereby resulting in a freeze concentration of the remainder of the liquid to a more viscous state that inhibits further crystallization. Ultimately, this highly concentrated and viscous solution solidifies, yielding an amorphous, crystalline, or combined amorphous–crystalline phase.

Primary drying. The ice formed during freezing is removed by sublimation at subambient temperatures under vacuum. This step traditionally is carried out at chamber pressures of 40–400 Torr and shelf temperatures ranging from -30°C to $+10^{\circ}\text{C}$. Throughout this stage, the product is maintained in the solid state below the collapse temperature of the product in order to dry the product with retention of the structure established in the freezing step. The collapse temperature is the glass transition temperature (T_g) in the case of amorphous products or the eutectic temperature (T_e) for crystalline products.

Secondary drying. The relatively small amount of bound water remaining in the matrix is removed

by desorption. During this stage, the temperature of the shelf and product are increased to promote adequate desorption rates and achieve the desired residual moisture.

Possible destabilizing effects of the lyophilization process

Freezing. Freezing damage can occur with labile products such as liposomes, proteins, and viruses (5,6). Initial ice-crystal size depends on the relative contributions of nucleation and crystal growth of ice. A rapid nucleation and growth rate resulting from a large degree of supercooling leads to a larger number of small ice crystals, which in turn presents a large ice–water interface (7). Exposure of proteins to this ice–water interface can lead to denaturation. Freezing stresses also can disrupt the liposome bilayer and emulsion structure.

The freezing step will determine the structure of the final dried cake as well as the drying rate. Small ice crystals produce pores with lower volume–surface area, thus resulting in lower diffusive flux and slower sublimation rates (7).

Drying. Removal of the hydration shell from proteins and products such as liposomes during drying in the absence of the appropriate stabilizers can cause destabilization of the protein structure and fusion of liposomes (8,9). Extremely low water content in the final product can result in destabilization, and optimal water content should be determined (10). The desired residual moisture must be correlated to stability during long-term storage as

part of development studies.

Excipients in a lyophilized formulation

The design of a lyophilized formulation is dependent on the requirements of the active pharmaceutical ingredient (API) and intended route of administration. A formulation may consist of one or more excipients that perform one or more functions. Excipients may be characterized as buffers and pH adjusters, bulking agents, stabilizers, and tonicity modifiers.

Buffers. Buffers are required in pharmaceutical formulations to stabilize pH. In the development of lyophilized formulations, the choice of buffer can be critical. Phosphate buffers, especially sodium phosphate, undergo drastic pH changes during freezing (6,11,12). A good approach is to use low concentrations of a buffer that undergoes minimal pH change during freezing such as Tris, citrate, and histidine buffers (13).

Bulking agents. The purpose of the bulking agent is to provide bulk to the formulation. This is important in cases in which very low concentrations of the active ingredient are used. Crystalline bulking agents produce an elegant cake structure with good mechanical properties. However, these materials often are ineffective in stabilizing products such as emulsions, proteins, and liposomes but may be suitable for small-chemical drugs and some peptides (14,15). If a crystalline phase is suitable, mannitol can be used. Sucrose or one of the other

disaccharides can be used in a protein or liposome product.

Stabilizers. In addition to being bulking agents, disaccharides form an amorphous sugar glass and have proven to be most effective in stabilizing products such as liposomes and proteins during lyophilization (1,8,9,16). Sucrose and trehalose are inert and have been used in stabilizing liposome, protein, and virus formulations. Glucose, lactose, and maltose are reducing sugars and can reduce proteins by means of the mailard reaction (17–19).

Two hypothesis have been postulated to explain the stabilizing effects of the disaccharides.

- ◆ The water replacement hypothesis: Disaccharides have been found to interact with these products by hydrogen bonding similarly to the replaced water.
- ◆ The vitrification hypothesis: Disaccharides form sugar glasses of extremely high viscosity. The drug and water molecules are immobilized in the viscous glass, leading to extremely high activation energies required for any reactions to occur (8,9,16,20,21).

Tonicity adjusters. In several cases, an isotonic formulation might be required. The need for such a formulation may be dictated by either the stability requirements of the bulk solution or those for the route of administration. Excipients such as mannitol, sucrose, glycine, glycerol, and sodium chloride are good tonicity adjusters. Glycine can lower the glass-transition temperature if it is maintained in the amorphous phase. Tonicity modifiers also can

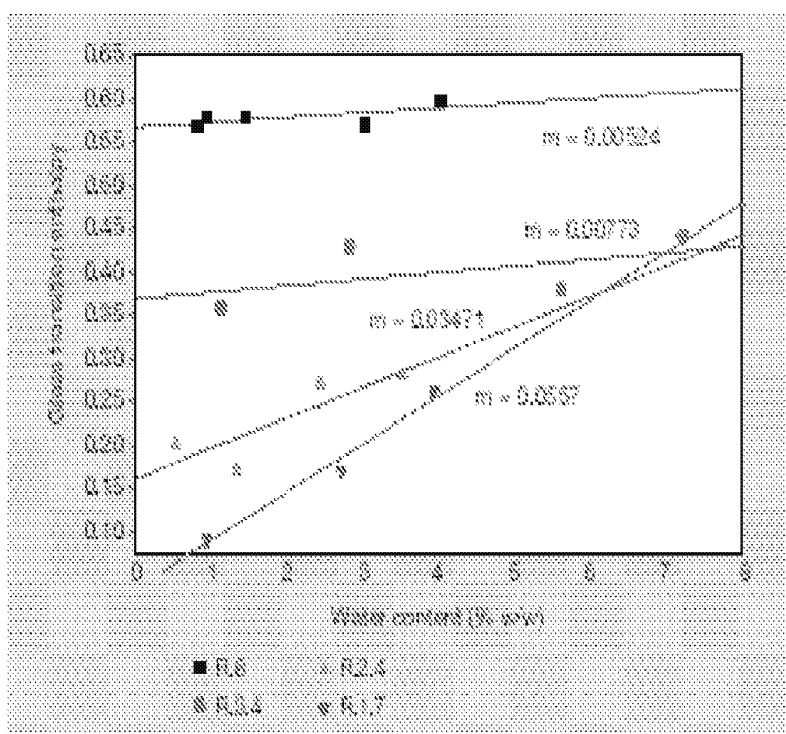


Figure 1: Effect of water content on glass-transition enthalpy. Plot of enthalpy versus water content for four formulations having various sugar/lipid ratios (R).

be included in the diluent rather than the formulation.

Glass-transition temperature and its significance

When heated, sugar glasses undergo a second-order transition from a rigid state to a viscoelastic rubbery state. The temperature at which the vitreous transformation occurs is the glass-transition temperature (T_g). When a product exceeds the T_g value, the rigid glass softens to become a highly viscous rubbery material and collapses. The T_g value of a formulation can be determined by differential scanning calorimetry (DSC), and the collapse temperature is measured by freeze-drying microscopy (22–24). Primary drying is always performed at the highest possible temperature while

maintaining the product below the collapse temperature. A 5 °C increase in product temperature can lead to a decrease in drying time by a factor of two (13).

The dried amorphous product material also has a T_g value. As water is removed during secondary drying, T_g increases. Storage below T_g is important for several products to maintain the rigid-glass structure and hence stability of the product (25,26).

Formulation example 1: development of a lyophilized liposome formulation

Preformulation studies were performed to select optimal pH, ionic strength, and excipients to optimize stability of the drug and lipids (F.K. Bedu-Addo, R. Coe, S. Bhamadi-

Table I. Effect of water content and sugar:lipid ratio on liposome stability

Residual water content (%)	Average liposome size (nm)		
	Sugar:lipid ratio 3.4	Sugar:lipid ratio 2.1	Sugar:lipid ratio 1.7
7.2	108	-	-
4.8	111	132	-
3.9	-	-	151
3.5	-	138	-
3.0	104	145	-
2.7	105	-	177
1.0	124	-	177

patti, and J. Pawelchak, The Liposome Co., 1997). A diacyl phosphatidylcholine was used as the matrix lipid, cholesterol was included in the formulation to improve rigidity of the bilayer, and a negatively charged lipid was included to improve blood circulation time. Mannitol was selected as the bulking agent, and maltose was a stabilizer. Dynamic light scattering and microscopy were used to monitor liposome fusion and disintegration. Lipid and drug stability were monitored by reverse-phase high-performance liquid chromatography (RP-HPLC). Water content was evaluated by Karl Fisher titration.

Lipid and drug concentrations were determined on the basis of the required dosage, therefore optimal sugar:lipid ratios were investigated by altering maltose concentrations. Maltose concentrations of 200, 125, and 100 mg/mL were investigated, thus resulting in sugar:lipid weight ratios of 3.4, 2.1, and 1.7, respectively. The effect of water content between 1 and 9% also was investigated.

Glass-transition enthalpy was evaluated using DSC to obtain a quantitative estimate of glass structure existing in the formulation. As shown in Figure 1, the effect of water content on glass content was dependent on the maltose:lipid ratio. Glassy structure content decreased with a decrease in water content. This effect diminished as the sugar:lipid ratio was increased. The T_g value, as measured by DSC, increases linearly with water content. T_g , which is an indicator of the rigidity of the sugar glass, also increased with an increase in the sugar:lipid ratio. Liposome stability increased linearly with an increase in the amount of glassy structure existing in the formulation. Fusion leading to increase in particle size was observed at lower maltose:lipid ratios as water content was decreased. At a 1.7 ratio, liposome disintegration was observed below 2.7% water (see Table I).

Fusion leading to an increase in liposome size and potential drug leakage was observed at the lower maltose:lipid ratios and water con-

tent. A maltose: lipid ratio of 3.4 provided good stability during lyophilization. The T_g value and glass-transition enthalpy were good indicators of liposome stability.

Formulation example 2: development of a lyophilized protein formulation

A study was conducted to develop a lyophilized protein formulation (E.K. Bedu-Addo, R. Moreadith, and S. Advant, Diosynth-RTP/Thrombogenics Ltd, 2000). The first step in developing any formulation is determining the solubility and liquid stability at various pH, ionic strength, and excipient conditions conducted as part of the preformulation study. At this stage, it is necessary to have the right analytical tools to fully characterize the product. In the case of proteins, one must also understand the effects of various potential formulation conditions and excipients on conformation and conformational stability. This is typically achieved using biophysical techniques such as circular dichroism (CD), fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry, and fluorescence spectroscopy (27–32). FTIR can also be used to evaluate protein structure in the dried cake (27).

On the basis of the results of a preformulation study, five formulations were developed and evaluated using a conservative lyophilization cycle:

- Formulation 1 contained a disaccharide and no crystalline bulking agent.

- Formulation 2 contained a low ratio of disaccharide to bulking agent.
 - Formulation 3 contained a high ratio of disaccharide to bulking agent with 0.005% of a nonionic surfactant.
 - Formulation 4 contained a high ratio of disaccharide to bulking agent with 0.01% of a nonionic surfactant
 - Formulation 5 contained a high ratio of disaccharide to bulking agent with no nonionic surfactant
- A nonionic surfactant was included in two of the formulations because in some cases, even in the presence of the appropriate stabilizers, a surfactant is required to inhibit aggregation upon reconstitution (33,34). Studies also have shown that the long-term stability of a lyophilized protein formulation and also the tendency to form aggregates upon reconstitution correlates with the extent of deviation from the protein's native conformation.

Deamidation and oxidation were evaluated by RP-HPLC, formation of insoluble aggregates by UV400, soluble aggregate formation by size exclusion chromatography (SEC), protein concentration by UV280 and conformational change by CD.

Formulation 2 underwent significant conformational change during freezing and resulted in 2% aggregates by SEC. All formulations except Formulation 1 exhibited some conformational change during the freezing step. No further conformational changes were observed during drying, no chemical changes were observed in any formulation. No in-

soluble aggregates were observed during reconstitution.

Formulation 1 exhibited the longest drying and reconstitution times and also had the least elegant-looking cake structure. Formulations 3 and 4 containing surfactant did not provide any advantages over Formulation 5 and were eliminated. Formulations containing a crystalline bulking agent provided an elegant cake. Formulation 5 was selected. The very minor differences between the formulations were expected because preformulation studies had been performed to identify optimal conditions and the formulations optimized with respect to pH, buffer, stabilizer and bulking agent before lyophilization.

Effects of the formulation on the lyophilization process

One must understand that the process will be determined by the formulation. For example, the use of disaccharides will result in a low collapse temperature, which causes primary drying to be performed at low temperatures and implying a long process. A large volume fill or high solids content in the formulation will provide increased resistance to mass transfer, hence a longer process (35).

The process also can determine the properties of the formulation. The freezing process can influence crystallization of excipients such as mannitol and glycine (36–39). Incomplete crystallization will depress the collapse temperature.

Significant crystallization of the bulking agent will reduce drying

time. However, large amounts of crystalline bulking agent can reduce stabilizing effects of the amorphous stabilizer especially with proteins.

Summary

Always optimize the formulation (pH, buffer, ionic strength, stabilizers) to provide maximum stability of the bulk solution before lyophilization as well as dried product upon long term storage.

Select the right excipients (amount and type) to provide product stability and efficient drying. For example, a dried small-chemical drug might be stable in only a crystalline bulking agent, whereas a dried protein product may require an amorphous stabilizer.

Select the lyophilization process to allow maximum drying efficiency while maintaining product integrity.

Understand the effect of each step of the process on the formulation to design the right process for the product.

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Review

Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations

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Purpose. This review describes a conceptual approach to the characterization of pharmaceutical solids. **Methods.** Four flow charts are presented: (1) polymorphs, (2) hydrates, (3) desolvated solvates, and (4) amorphous forms. **Results.** These flow charts (decision trees) are suggested as tools to develop information on pharmaceutical solids for both scientific and regulatory purposes. **Conclusions.** It is hoped that this review will lead to a more direct approach to the characterization of pharmaceutical solids and ultimately to faster approval of regulatory documents containing information on pharmaceutical solids.

KEY WORDS: polymorph; hydrate; amorphous form; desolvated solvate.

Interest in the subject of pharmaceutical solids stems in part from the Food and Drug Administration's (FDA's) drug substance guideline that states "appropriate" analytical procedures should be used to detect polymorphic, hydrated, or amorphous forms of the drug substance. These guidelines suggest the importance of controlling the crystal form of the drug substance. The guideline also states that it is the applicant's responsibility to control the crystal form of the drug substance and, if bioavailability is affected, to demonstrate the suitability of the control methods.

Thus, while it is clear that the New Drug Application (NDA) should contain information on solid state properties, particularly when bioavailability is an issue, the applicant may be unsure about how to scientifically approach the gathering of information and perhaps what kind of information is needed. This review is intended to provide a strategic approach to remove much of this uncertainty by presenting concepts and ideas in the form of flow charts rather than a set of guidelines or regulations. This is especially important because each individual compound has its own peculiarities which require flexibility in approach. The studies proposed herein are part of the Investigational New Drug (IND) process.

Solid drug substances display a wide and largely unpredictable variety of solid state properties. Nevertheless, application of basic physicochemical principles combined with appropriate analytical methodology can provide a strategy

for scientific and regulatory decisions related to solid state behavior in the majority of cases. By addressing *fundamental* questions about solid state behavior at an early stage of drug development, both the applicant and the FDA are in a better position to assess the possible effects of any variations in the solid state properties of the drug substance. The resulting early interaction of the parties with regard to this area would not only tend to ensure uniformity of the materials used throughout the clinical trials but also fully resolve solid state issues before the critical stages of drug development. A further benefit of these scientific studies is the development of a meaningful set of solid state specifications which critically describe the solid form of the drug substance. These specifications would thus also facilitate the approval of a change in supplier or chemical process.

Our approach in this review is to suggest a sequence for collecting data on a drug substance that will efficiently answer specific questions about solid state behavior in a logical order. In "difficult" cases, perhaps where mixtures of forms must be dealt with, or other unusual properties are encountered, the suggested sequences would still have to be followed as a first stage in this investigation.

We have chosen to present this approach in the form of a series of decision trees, or flow charts (algorithms), one for each of the most common solid state forms. The charts are accompanied by examples from the literature representing the kind of data that would be useful in supporting the various decisions.

Decision trees provide conceptual frameworks for understanding how the justification for different crystal forms might be presented in the drug application. Industry may wish to use these decision trees as a strategic tool to organize the gathering of information early in the drug development process. Put another way, these decision trees provide a thought process that will lead to development of the most

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appropriate analytical controls. One should also note that it is the responsibility of the industry to select the appropriate test or tests to identify the phase of the solid and determine its relevant pharmaceutical properties. This approach is superior to simply performing a broad range of tests without regard to their relevance.

We should point out that, from a regulatory standpoint, if a company can establish a specification/test to ensure production of a well defined solid form of the drug substance, then it is not necessary to do all of the physical/chemical testing outlined in the decision trees. From a scientific standpoint, however, such an approach is risky since new forms may appear unpredictably during various stages of the development process. The appearance of these new forms usually slows the drug approval process and makes planning difficult.

Four decision trees are described in the sections that follow: Polymorphs; Hydrates (Solvates); Desolvated Solvates; and Amorphous Forms. Polymorphs exist when the drug substance crystallizes in different crystal packing arrangements all of which have the same elemental composition (Note that hydrates can exist in polymorphs). Hydrates exist when the drug substance incorporates water in the crystal lattice in either stoichiometric or non-stoichiometric amounts. Desolvated solvates are produced when a solvate is desolvated (either knowingly or unknowingly) and the crystal retains the structure of the solvate. Amorphous forms exist when a solid with no long range order and thus no crystallinity is produced. It is apparent that the appropriate flow chart can only be determined after the solid has been characterized using some of the tests described in the first decision point of the decision trees/flow charts (i.e. X-ray powder diffraction, elemental analysis, etc.). If there is no interest in marketing or producing an amorphous form or desolvated solvate at any stage in the process, then the corresponding flow charts do not need to be addressed. As already mentioned, it is advisable to investigate the drug substance for the existence of polymorphs and hydrates since these may be encountered at any stage of the drug manufacturing process or upon storage of the drug substance or dosage form.

All of the flow charts end (see for example Figure 1) with an indication of the types of controls which will be required based on whether a single morphic form or a mixture will be produced as the drug substance. Although this ending provides a simplistic view of a very complicated process of selecting appropriate controls, it is included to illustrate the consequence of the decisions made with regard to the drug substance. The reader should realize that the actual selection of the appropriate control could be the subject of another review which might contain another set of flow charts or decision trees.

POLYMORPHS

The flow chart/decision tree for polymorphs is shown in Figure 1. It outlines investigations of the formation of polymorphs, the analytical tests available for identifying polymorphs, studies of the physical properties of polymorphs and the controls needed to ensure the integrity of drug substance containing either a single morphic form or a mixture.

A. Formation of Polymorphs—Have Polymorphs Been Discovered?

The first step in the polymorphs decision tree is to crystallize the substance from a number of different solvents in order to attempt to answer the question: Are polymorphs possible? Solvents should include those used in the final crystallization steps and those used during formulation and processing and may also include water, methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, ethyl acetate, hexane and mixtures if appropriate. New crystal forms can often be obtained by cooling hot saturated solutions or partly evaporating clear saturated solutions. The solids produced are analyzed using X-ray diffraction and at least one of the other methods. In these analyses, care must be taken to show that the method of sample preparation (i.e. drying, grinding) has not affected the solid form. If the analyses show that the solids obtained are identical (e.g. have the same X-ray diffraction patterns and IR spectra) then the answer to the question "Are polymorphs possible?" is "No",

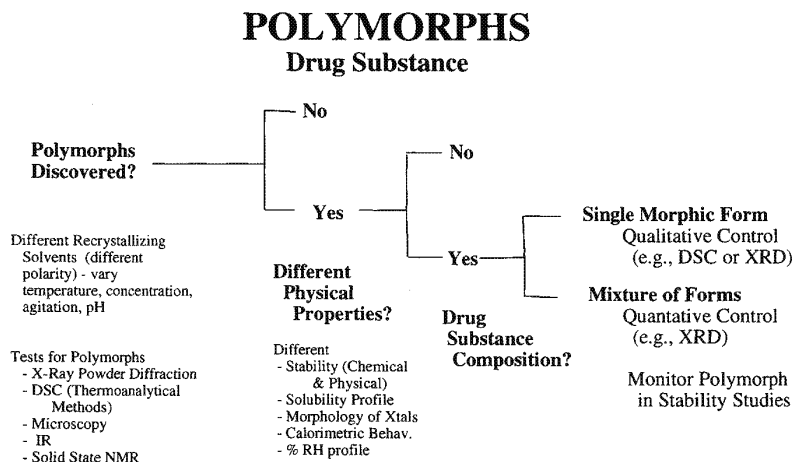


Figure 1. Flow chart/decision tree for polymorphs.

and further research is not needed. The work of Miyamae *et al.* serves as a good example of solid state studies of a drug substance which exists as polymorphs (1). Powder diffraction showed that there were two crystal forms (see Figure 2).

These workers also carried out single crystal analysis of the two crystal forms of the compound. The structures are shown in Figure 3. While such studies are not required, and indeed sometimes not possible, they provide an unequivocal confirmation of the existence of polymorphs. Moreover, once the single crystal structure of a phase has been determined, it is possible to calculate the corresponding X-ray powder pattern. This provides an irrefutable standard for identifying the phase by that method.

The DSC thermal curves of the two forms are slightly different, as shown in Figure 4 and thus may not be the preferred way of differentiating these polymorphs.

The IR spectra of the two polymorphs are quite similar(1), and IR does not appear to be a powerful method for differentiating the crystal forms in this case. Thus, for 8-(2-methoxycarbonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)-imidazo[1,2-a]pyridine, powder diffraction appears to be the best method for differentiating the two forms.

Solid-state NMR is another powerful technique for analyzing different crystal forms (2,3). Figure 5 shows the solid-state C-13 NMR spectra of Forms I and II of prednisolone. Differences in the positions of the two resonances in the 120 ppm range clearly differentiate the two forms. In principle, solid state NMR is an absolute technique in which the signal intensity is proportional to the number of nuclei provided appropriate conditions are met. In addition, solid state NMR is a bulk technique which is not very sensitive to surface changes. This method appears to be very sensitive and will undoubtedly be used more often in the future as a tool to detect different crystal forms. However, with present technology, errors in solid-state quantitative studies may be rather large.

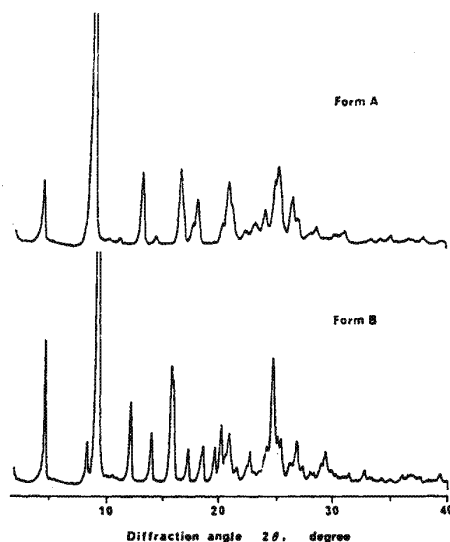


Figure 2. Powder X-ray diffraction patterns of the polymorphs of 8-(2-methoxycarbonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)-imidazo[1,2-a]pyridine (1).

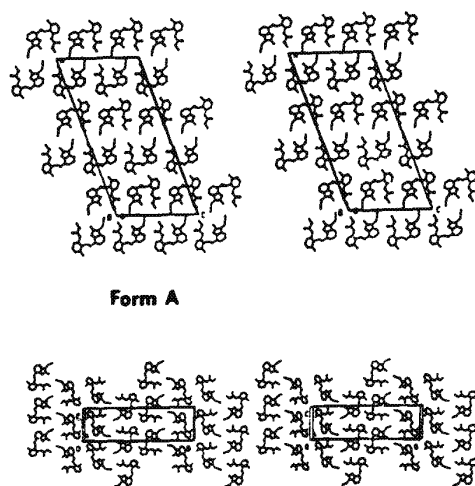


Figure 3. Stereoscopic drawings of the crystal packing of both polymorphs of 8-(2-methoxycarbonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)-imidazo[1,2-a]pyridine viewed along the shortest axis (Form A, b-axis; Form B, a-axis) (1).

B. Do the Polymorphs Have Different Physical Properties?

If polymorphs exist then it is necessary to examine the physical properties of the different polymorphs that can affect dosage form performance (bioavailability and stability) or manufacturing reproducibility. The properties of interest are solubility profile (intrinsic dissolution rate, equilibrium solubility), stability (chemical and physical), and crystal morphology (including both shape and particle size), calorimetric behavior, and %RH profile. If there are no discernible differences between these physico-chemical properties, then the answer to the second question in the decision tree, "Different physical properties?" is "No."

The variable physical properties of several drugs with different polymorphs are reported in the literature. For example, the dissolution profiles of the polymorphs of chloramphenicol are significantly different (4). In addition, van't Hoff solubility analysis has been used to elucidate the dif-

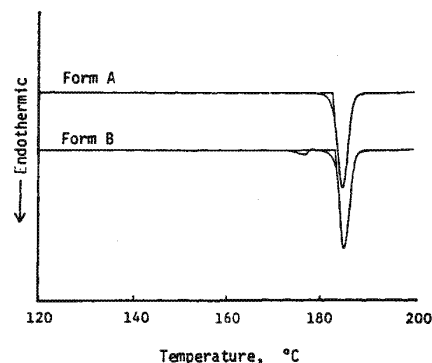


Figure 4. DSC thermal curves of the polymorphs of 8-(2-methoxycarbonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)-imidazo[1,2-a]pyridine (1). These curves show that Form A melts whereas Form B undergoes a small endothermic transition and then melts at the same temperature as Form A.

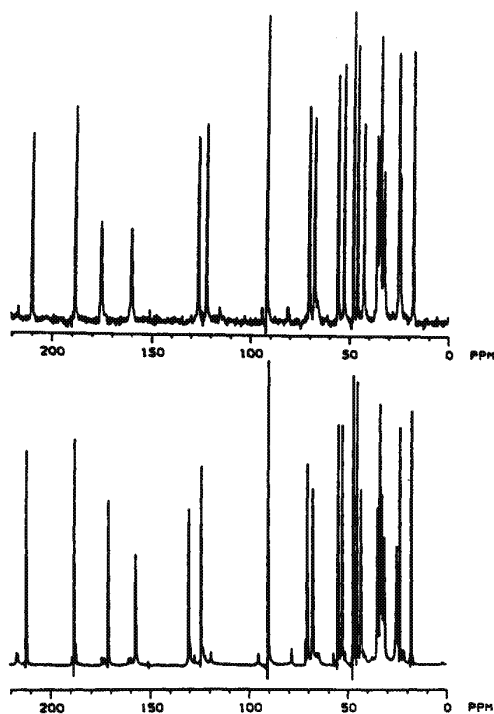


Figure 5. Solid state NMR of the two Crystal Forms of Prednisolone (2).

ferent solubilities of two polymorphs of methyl prednisolone(5). This method involves determining the equilibrium solubility of each polymorph at various temperatures. The log of the equilibrium solubility is then plotted vs $1/T$. This should give straight lines for each polymorph and the temperature at which the curves intersect is the transition temperature. This technique does not work if the polymorphs interconvert.

For balance, it is important to point out that there are also cases where polymorphs exist but they have virtually identical dissolution properties(6).

C. Drug Substance Control

The important question lies in the properties that differ among polymorphs and whether those properties affect the dosage form performance (i.e., quality or bioavailability). If they do then from a regulatory standpoint it is appropriate to establish a specification/test (e.g. powder X-ray diffraction or IR) to ensure the proper form is produced. From a production standpoint, it is important to develop a process that reproducibly produces the desired polymorph.

If mixtures of forms cannot be avoided, then quantitative control is needed to ensure that a fixed proportion of forms is obtained. Furthermore, the method of analyzing for the proportion of forms would have to be validated. Also, the proportion of forms would have to remain within stated limits through the retest date of the drug substance and potentially throughout the shelf life of the product; a difficult requirement if the forms interconvert. Thus, the way to avoid a substantial amount of work in this area is to select a single

solid form for production. Usually, this would be the most physically stable form when their bioavailabilities are not significantly different. Selection of the most stable form would, of course, insure that it there would be no conversion into other forms.

Powder diffraction is often a useful method to determine the percentages of polymorphs in a mixture; however, the detection limit is variable from case to case and can be as high as 15%. Matsuda (7) carried out a mixture analysis of phenylbutazone polymorphs. Diffraction lines disappear and appear as the ratio of the crystal forms change. Some of these calibration curves developed from this analysis are almost horizontal, meaning that any given mixture gives the same line intensity in this mixture range. However, other calibration curves are sloped and would appear to allow a reasonable analysis. It is fair (although Matsuda did not carry out an estimate) to estimate the errors in this analysis as $\pm 15\%$.

Tanninen and Ylirussi (8) used computer curve fitting to carry out a mixture analysis of prazosin. In this particular case, they reported a highly accurate analysis, and, in fact, showed a calibration curve that could detect 0.5% of one form in another. This is obviously a highly accurate mixture analysis by powder diffraction and shows the power of this method for some applications. However, this analysis required extreme care in sample preparation and may be more difficult to carry out in a production setting where particle size may not be controlled. Similar comments apply to the analysis of mixtures by IR, where the accuracy and precision may also vary considerably from case to case. Given the analytical problems in dealing with mixtures of forms, it may generally be simpler to develop a method to prepare only one crystal form.

In summary, it is important to determine whether polymorphs are present and to solve any problems before pivotal clinical studies are initiated.

D. Determination of the Polymorph Present in the Drug Product

In cases where stability or bioavailability issues exist, the solid form present in the drug product should be investigated, if possible.

For bulk drug substances, X-ray powder diffraction and other techniques can identify the polymorph; however, solid state NMR appears to be the best method for the study of the drug substance in the dosage form (2, 3). Solid-state NMR study of three commercial products containing prednisolone showed that the products A and B contain Form I, whereas product C contains Form II. This analysis was possible even though these tablets contain approximately 95 mg of excipients and 5 mg of drug. There are numerous cases, often involving complex mixtures or low dose products, where solid state NMR (and, in fact, any technique) will not be sensitive enough to identify the polymorph present in the drug product. However, the safety and efficacy is, of course, controlled by the potency assays and by the physical tests (e.g., dissolution).

HYDRATES (SOLVATES)

The flow chart/decision tree for hydrates (solvates) is shown in Figure 6. It outlines investigations of the formation

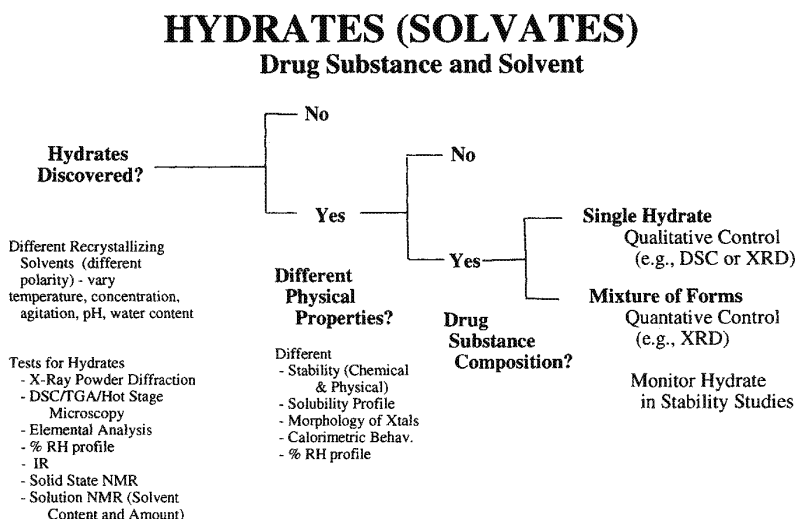


Figure 6. Flow chart for solvates or hydrates.

of hydrates (solvates), the analytical tests available for hydrates (solvates), studies of the physical properties of hydrates (solvates) and the controls needed to ensure the integrity of drug substance containing either a single morphic form or a mixture.

A. Have Hydrates (Solvates) Been Discovered?

The flow chart for hydrates (solvates) (Figure 7) is applied after the preliminary crystallizations have been completed. These are essentially the same as in the polymorph decision tree but, in addition, should include solvent-water mixtures in order to maximize the chance for hydrate formation. These experiments can be guided by the moisture uptake (% RH) studies. Any solids that indicate a significant change in water content as indicated by the % RH-moisture profile should also be examined. The resulting solid phases are preferably characterized by a combination of methods—two for phase identity and two to reveal composition and stoichiometry.

With a very few exceptions, the structural solvent contained in marketed crystalline drug products is water. It is nevertheless often desirable to characterize other solvated crystalline forms of a drug for several reasons: they may be the penultimate form used to crystallize the final product and thus require controlled characterization; they may form if the final crystallization from solvents, especially mixed solvents, is not well controlled; they may be the actual crystallized form of a final product that is desolvated during a final drying step; they may be the form used in recovery for subsequent rework. The relevance of these points will vary from case to case, but for the present discussion we shall treat the subject of solvates in its broadest form.

Examples taken from the literature serve to illustrate the kind of data that proves useful in characterizing solvated crystal forms. For example, a recent report from our laboratory showed that IR and solid state NMR was useful for the identification of the different crystal forms of dirithromycin(9). TGA is another powerful method for the analysis

of solvates. For example, one early study showed that TGA could differentiate three different hydrated salts of fenoprofen(10). Combined with IR or other methods, TGA is an unequivocal method for the verification of the existence of solvates. In addition, TGA is a good method for looking at mixtures of solvated and unsolvated crystal forms, and probably can be developed into an analytical method for determining the ratios of solvated and unsolvated forms.

DSC is also a good method for detecting solvates since there is usually heat change involved in desolvation, especially for hydrates(11). Specifically, DSC by itself does not prove the existence of a solvate, but once other analytical

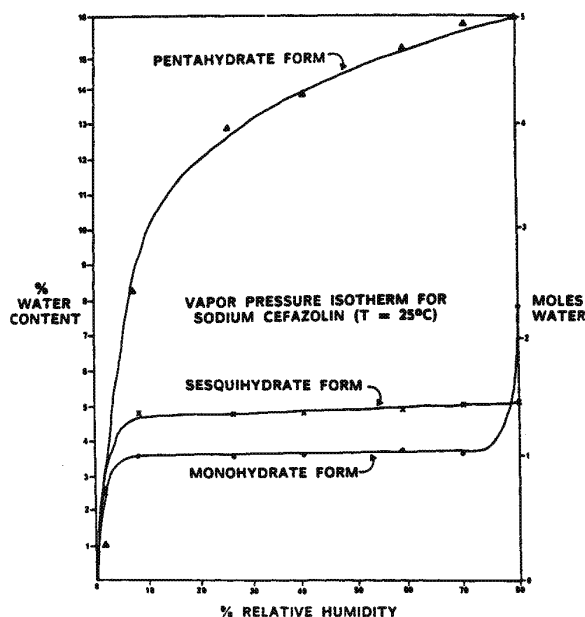


Figure 7. Water uptake vs percent relative humidity for sodium cefazolin.

data from TGA, NMR, etc. are available, DSC becomes a good method for analyzing solvates and determining a percentage of solvates present.

The three solvates of ethynylestradiol (0.5 acetonitrile, 1.0 methanol, 0.5 water) provides another interesting example (12). These solvates have different cell parameters and are crystallographically completely distinct materials. The hemihydrate was obtained from an organic solvent which is not completely miscible with water but was saturated with water. In fact, it is known that crystallization from water-immiscible solvents containing small but slightly different proportions of water can produce different hydrates of a substance.

The DSC/TGA of the three ethynylestradiol solvates(12) are unique and in this case it may be possible to develop DSC/TGA into an analytical procedure for determining the proportions of each solvate. The DSC in some of these traces appears to show a melt and recrystallization corresponding to the loss of solvent of crystallization. However, the exact interpretation of this is not possible without either a DSC microscope or interrupting the tracing to analyze the sample at various temperatures. The methanolate appears to lose solvent in two equal steps, indicating that there may also be a hemimethanolate of this compound. Again, confirmation of this would require interrupting the heating and analyzing the substance after the first solvent loss has occurred. In addition, the DSC/TGA traces suggest that all of the forms are converted to an anhydrous form which then melts at a higher temperature. Thus, interrupting any one of these thermal curves just prior to the final melt could reveal a new form that gives the powder pattern for the anhydrate. Unfortunately, no data of this type is provided in the case cited.

DSC analysis of solvates should be carried out using either an open pan or a pan with a pin-prick; otherwise, unusual and variable results will be obtained because the solvent is not provided a way of escape from the pan. One advantage of using an open pan for DSC is that it reproduces the conditions under which the TGA is performed.

Comparison of the ethynylestradiol powder diffraction patterns clearly establishes that these solvates are different crystal forms as would be expected from the single crystal data(12). In summary, DSC, TGA, and powder diffraction are all good methods for analysis of the different crystal forms of ethynylestradiol.

Figure 7 shows a percent relative humidity versus water uptake study of the type recommended by the USP committee on water(13) In this case, there are two hydrates which are relatively well behaved insofar as they are completely hydrated at about 10% relative humidity and remain uniformly hydrated throughout a wide humidity range. On the other hand, the so-called pentahydrate, which really is only a pentahydrate at very high humidity, changes water content considerably as the relative humidity is changed. The USP committee on moisture specifications recommended that moisture uptake vs relative humidity studies should be routinely performed on all drug substances and excipients (13).

B. Do the Hydrates (Solvates) Have Different Physical Properties?

The physical properties of hydrates are often quite different from the anhydrate form. Figure 8 shows the dissolu-

tion profile of theophylline hydrate and anhydrate. This figure shows that the anhydrate reaches a much higher solubility in water, and on extended exposure recrystallizes to the less soluble hydrate. Such differences must be further examined for possible effects on bioavailability.

In our laboratory we have described the different crystal forms of hydrocortisone-21-tertiary butylacetate(14). Our studies showed that the nonstoichiometric ethanolate is oxygen-sensitive and, of course, would show different physical properties from the stoichiometric ethanolate and the other solvates. Prednisolone tertiary-butylacetate also exists as a nonstoichiometric hydrate which is oxygen sensitive(15). Thus, these are cases where different crystal forms have different chemical stability, although there may be no significant differences in solubility.

C. Mixtures of Polymorphs and Hydrates

Other drug substances exist as both polymorphs and solvates. For example, furosemide exists in two polymorphs, two solvates, and an amorphous form (16, 17). The polymorphs are enantiotropically related, which means that at one temperature one polymorph is more stable, but at a different temperature the other polymorph is physically more stable. That is, plots of solubility versus temperature cross for the two polymorphs. In addition, the different crystal forms have different photostability (chemical stability in light) and moreover have different dissolution rates. Thus, there are significant differences in both chemical and physical properties.

The five different forms, or modifications of furosemide, give clearly different powder patterns. Thus, powder diffraction is a good method for analysis of these different forms. There are similarities between the IR spectra of the five different forms but there are also some significant differences, and expansion and careful analysis could lead to an FT/IR method for analysis of these different forms. IR would probably be a useful method for analysis at least for pairs of these compounds. However, it is not clear whether IR could be used to determine the percentages of several different forms in a more complex mixture. The DSC and TGA of the different forms are significantly different. As expected, the solvates show weight loss in the TGA.

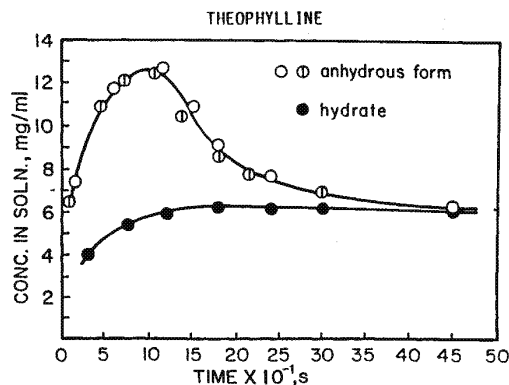


Figure 8. The dissolution-time curves for anhydrous and hydrated theophylline in water at 25°. The two types of open circles represent successive experiments (18).

The interconversion of the different forms of furosemide have been analyzed and a diagram constructed. Such a diagram can be experimentally difficult when so many pairs of crystal forms must be studied for possible interconversions and under different conditions. It is clear from this diagram that many of the forms of furosemide can be converted to form I. This study is one of the most complete reports of solvates and polymorphs available in the literature and serves as a model for studies of such systems for regulatory submissions.

D. Determination of the Hydrate Present in the Drug Product

Another important area is the analysis of the material which is produced after wet granulation of a substance which can form hydrates. We are aware of cases where the bulk drug substance is manufactured and stored as the anhydrate. However, upon wet granulation, there is a conversion (either partial or complete) to a hydrate. Subsequent drying is sometimes not adequate to convert the substance back to the anhydrate, and a hydrate or a mixture of hydrate and anhydrate remain. The formation of a hydrate and its subsequent drying can result in a change in particle size of the drug substance (19). It may also be possible to cause transformations during other processing steps. It is thus recommended that if wet granulation or processing that subjects the drug to even brief changes in temperature or pressure (e.g. milling or compression) is contemplated, then extensive studies of the ability to convert the drug substance to a new crystal form be carried out by mimicking the processing step in the laboratory.

DESOLVATED SOLVATES

The term "desolvated solvates" refers to compounds that are crystallized as solvates but undergo desolvation prior to analysis. Often these "desolvated solvates" retain

the structure of the solvate with relatively small changes in the lattice parameters and atomic coordinates, but no longer contain the solvent. In addition, desolvated solvates are apt to be less ordered than their crystalline counterparts. These forms are particularly difficult to characterize properly since analytical studies indicate that they are unsolvated materials (anhydrous crystal forms) when, in fact, they have the structure of the solvated crystal form from which they were derived. Several observations may give clues that one is dealing with a desolvated form: (1) The form can be obtained from only one solvent; (2) On heating, the form converts to a structure known to be unsolvated; and (3) The form has a particularly low density compared to other forms of the same substance. Experiments that help to clarify whether an apparently solvent free modification is a desolvated form or a true anhydrate include: (1) Single crystal X-ray structure determination in the presence of mother liquor from the crystallization; (2) comparison of the X-ray powder diffraction patterns and solid state NMR spectra of the solvated and desolvated crystal forms; and (3) determination of the vapor pressure isotherm by varying the vapor pressure of the specific solvent involved. A desolvated form will often take up stoichiometric amounts of the relevant solvent. In addition, crystals of the form directly isolated from the crystallizing medium will show a plateau in their isotherm as the vapor pressure of the solvent is reduced.

Figure 9 shows the flow chart used to address regulatory issues involving desolvated solvates. It is similar to the polymorphs flow chart except that the first question involves determining whether a solvate was formed initially and then desolvated, perhaps by "air drying." The remaining questions are identical to the polymorphs flow chart.

Figure 10 shows the behavior of three different crystal forms of the same antibiotic. One crystal form takes up about two waters of hydration and further analysis indicated that it was the dimethanolate which had been desolvated by drying. The second crystal form takes up approximately one water and was originally the monomethanolate which had been desolvated by drying. The third crystal form also takes up

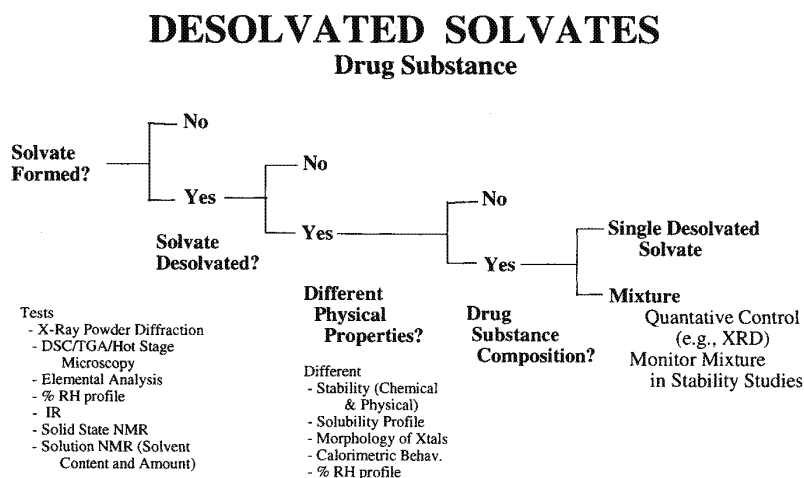


Figure 9. Flow chart for desolvated solvates.

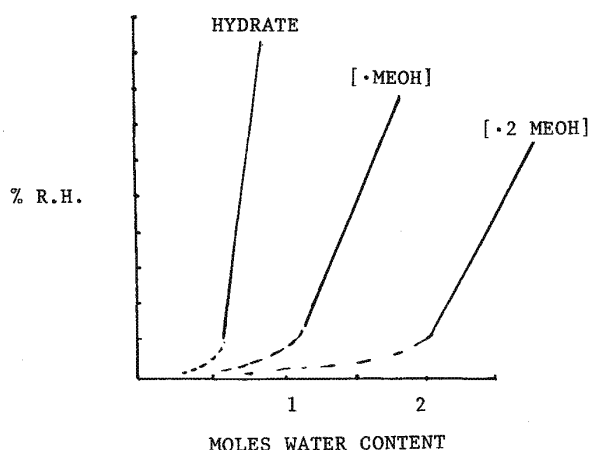


Figure 10. Water sorption by three crystal forms of cephaloridine. The brackets indicate the crystal form produced by desolvating the designated methanolate.

about one molecule of water and is the 0.75 hydrate typically obtained from water solution.

AMORPHOUS FORMS

Amorphous forms are of substantial interest because they usually are much more soluble than their crystalline counterparts. Indeed, there are cases where the amorphous form is the only solid form that has adequate bioavailability. The initial question with this flow chart (Figure 11) is similar to the previous ones: "Are amorphous forms possible?" Amorphous forms can be prepared in different ways, for example, by spray drying or by freeze drying. One can test whether an amorphous form has been produced by using one of the methods listed. X-ray powder diffraction and microscopy are the two primary methods for determining whether an amorphous form has been produced. Powder diffraction is an

excellent method for determining the existence of an amorphous form since they usually exhibit a broad hump between 2 and 20° 2θ. An amorphous form is expected to have no peaks in the powder diffraction pattern. The USP test for the presence of an amorphous form involves determining, by microscopy, whether the material lacks birefringence. IR and solid-state NMR may be useful for detecting amorphous forms since the amorphous nature of the solid sometimes results in broad lines, or in NMR, altered relaxation times. The next question on the flow chart is: "Do the amorphous forms have different physical properties?" The answer to this question will almost certainly be "Yes." Three differences from crystalline forms may generally be expected: 1) Amorphous forms would have greater solubility, 2) Amorphous forms take up water more extensively, and 3) Amorphous forms are sometimes less chemically stable. Another key question for an amorphous form is: "Does it crystallize, and how and when?" This question is very important since inadvertent crystallization can greatly affect the solubility and dissolution rate, and lead to other failures in formulation. Attempts to purposely cause amorphous forms to crystallize can provide information on the parameters involved in crystallization of amorphous forms. Specific questions include: (1) "Does the amorphous form crystallize upon exposure to heat and/or humidity?" and (2) "What other factors (e.g. mechanical pressure and seeding) can lead to the crystallization of the amorphous forms?"

The amorphous form of any substance can be partly characterized by the glass transition temperature, T_g (11). When heated to a temperature above T_g , the solid transforms from a glassy state to a more fluid-like rubbery state. The corresponding increased molecular mobility greatly raises the likelihood of two adverse events: (1) Crystallization and subsequent decreased solubility; and (2) Reduced chemical stability in the more reactive amorphous solid. Amorphous solids are also often prone to absorb moisture and this water sorption reduces the glass transition temperature further. The weight of water required to reduce the glass transition

AMORPHOUS FORMS

Drug Substance

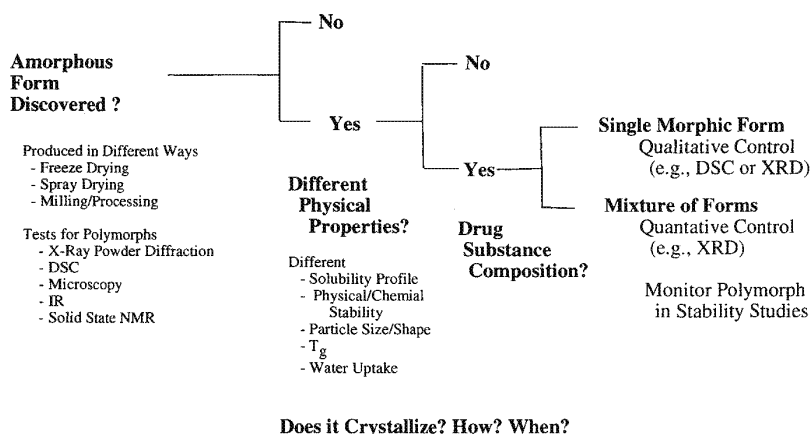


Figure 11. Flow chart for amorphous solids.

temperature to room temperature is of obvious interest and is termed W_g . Table I shows a series of interesting studies on amorphous forms of some common pharmaceuticals.

The table compares the glass transition temperatures (T_g) of a number of pharmaceutical solids with the melting temperatures (T_m). It is interesting that the average ratio of the glass transition temperature to the melting temperature is about 0.70. This table provides a simple rule of thumb which allows the prediction of the glass transition temperature of pharmaceuticals from the known melting point. Crystallization and other solid-state phenomena, such as degradation reactions, as we have said, would be more likely to occur at temperatures above the glass transition temperature. For stability, one might, therefore, wish to prepare amorphous forms only for drugs which have a T_g well above room temperature.

Amorphous indomethacin crystallizes upon standing at room temperature (Figure 12). Obviously, formulations containing amorphous indomethacin are at significant risk to crystallize and thus become less soluble. This has to some extent hampered preparing more bioavailable indomethacin dosage forms.

Quantitative analysis of mixtures of amorphous and crystalline forms provides some challenges. Cefixamine trihydrate is the subject of some early research in this area. This antibiotic, upon grinding, became a mixture of crystalline and amorphous forms. A calibration curve based upon analyzing the height of a selected powder X-ray peak was constructed and used to determine the crystallinity versus grinding time for this system. It is clear that powder diffraction provides a way to estimate the amount of amorphous cefiximine. These studies show that milling and other similar processing steps can create amorphous material and that this process may be detectable. As with wet granulation where transitions to hydrated forms can occur, processing of the drug substance can promote the formation of amorphous drug.

Pikal has compared the analysis of mixtures of crystalline and amorphous forms of several antibiotics by powder diffraction and calorimetry (20). His studies indicate that calorimetry can be a more accurate method for analysis of percent crystallinity but are complicated by water sorption. Zografis and co-workers (unpublished results) have developed a powerful method for the determination of low per-

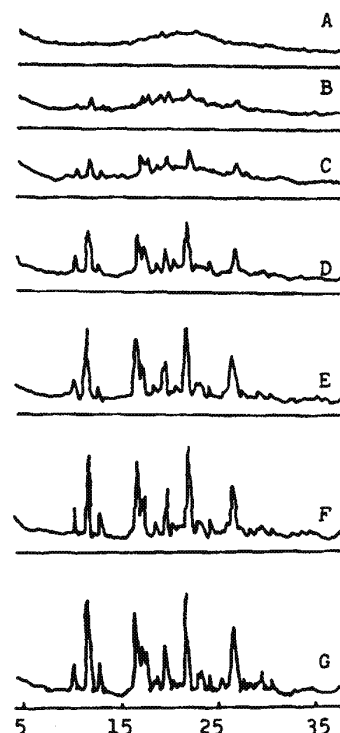


Figure 12. Behavior of amorphous indomethacin upon standing: A, at start; B 24 h; C, 48 h; D, 7d; E, 14d; F, 30d; G, 67d (22).

centages of amorphous material based on the general propensity of amorphous materials to sorb moisture.

SUMMARY

Four flow charts which describe approaches to regulatory issues involving pharmaceutical solids have been developed. These flow charts are for the different types of solids generally encountered (polymorphs, solvates, desolvated solvates, and amorphous forms). It is hoped that these flow charts will guide the solid-state research needed to prepare a comprehensive regulatory submission on the physicochemical properties of a pharmaceutical. It is also hoped that this review has provided enough information to allow the generation of results and information necessary to prepare a drug substance submission that will be quickly approved.

ACKNOWLEDGMENTS

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Table I. Pharmaceuticals Forming Glasses Above Room Temperature (21)

Pharmaceutical	T_g (K)	T_m (K)	T_g/T_m
Cholecalciferol	296	352	0.84
Sulfisoxazole	306	460	0.67
Stilbestrol	308	439	0.70
Phenobarbital	321	443	0.72
Quinidine	326	445	0.73
Salicin	333	466	0.71
Sulfathiazole	334	471	0.71
Sulfadimethoxine	339	465	0.73
Dehydrocholic acid	348	502	0.69
17 β -Estradiol	351	445	0.80

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REVIEW ARTICLE

Pharmaceutical Salts

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Keyphrases □ Pharmaceutical salts—general pharmacy, physicochemical properties, bioavailability, pharmaceutical properties, toxicology, review □ Salts, pharmaceutical—general pharmacy, physicochemical properties, bioavailability, pharmaceutical properties, toxicology, review □ Physicochemical properties—dissolution, solubility, stability, and organoleptic properties of pharmaceutical salts, review □ Bioavailability—formulation effects, absorption alteration and pharmacokinetics of pharmaceutical salts, review □ Toxicology—pharmaceutical salts, review

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The chemical, biological, physical, and economic characteristics of medicinal agents can be manipulated and, hence, often optimized by conversion to a salt form. Choosing the appropriate salt, however, can be a very difficult task, since each salt imparts unique properties to the parent compound.

Salt-forming agents are often chosen empirically. Of the many salts synthesized, the preferred form is selected by pharmaceutical chemists primarily on a practical basis: cost of raw materials, ease of crystallization, and percent yield. Other basic considerations include stability, hygroscopicity, and flowability of the resulting bulk drug. Unfortunately, there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound. Furthermore, even after many salts of the same basic agent have been prepared, no efficient screening techniques exist to facilitate selection of the salt most likely to exhibit the desired pharmacokinetic, solubility, and formulation profiles.

Some decision-making models have, however, been developed to help predict salt performance. For example, Walkling and Appino (1) described two techniques, "decision analysis" and "potential problem analysis," and applied them to the selection of the most suitable derivative of an organic acid for development as a tablet. The derivatives considered were the free acid and the potassium, sodium, and calcium salts. Both techniques are based on the chemical, physical, and biological properties of these specific derivatives and offer a promising avenue for developing optimal salt forms.

Information on salts is widely dispersed throughout the pharmaceutical literature, much of which addresses the use of salt formation to prolong the release of the active component, thereby eliminating various undesirable drug properties (2-6). This review surveys literature of the last 25 years, emphasizing comparisons between the properties of different salt forms of the same compound. Included also is a discussion of potentially useful salt forms. Our purpose is twofold: to present an overview of the many different salts from which new drug candidates can be chosen and

Table I—FDA-Approved Commercially Marketed Salts

Anion	Percent ^a	Anion	Percent ^a
Acetate	1.26	Iodide	2.02
Benzenesulfonate	0.25	Isethionate ⁱ	0.88
Benzoate	0.51	Lactate	0.76
Bicarbonate	0.13	Lactobionate	0.13
Bitartrate	0.63	Malate	0.13
Bromide	4.68	Maleate	3.03
Calcium edetate	0.25	Mandelate	0.38
Camsylate ^b	0.25	Mesylate	2.02
Carbonate	0.38	Methylbromide	0.76
Chloride	4.17	Methylnitrate	0.38
Citrate	3.03	Methylsulfate	0.88
Dihydrochloride	0.51	Mucate	0.13
Edetate	0.25	Napsylate	0.25
Edisylate ^c	0.38	Nitrate	0.64
Estolate ^d	0.13	Pamoate (Embonate)	1.01
Esylate ^e	0.13	Pantothenate	0.25
Fumarate	0.25	Phosphate/diphosphate	3.16
Gluceptate ^f	0.18	Polygalacturonate	0.13
Gluconate	0.51	Salicylate	0.88
Glutamate	0.25	Stearate	0.25
Glycolylarsanilate ^g	0.13	Subacetate	0.38
Hexylresorcinolate	0.13	Succinate	0.38
Hydrabamine ^h	0.25	Sulfate	7.46
Hydrobromide	1.90	Tannate	0.88
Hydrochloride	42.98	Tartrate	3.54
Hydroxynaphthoate	0.25	Teoclate ^j	0.13
		Triethiodide	0.13
Cation	Percent ^a	Cation	Percent ^a
Organic:		Metallic:	
Benzathine ^k	0.66	Aluminum	0.66
Chloroprocaine	0.33	Calcium	10.49
Choline	0.33	Lithium	1.64
Diethanolamine	0.98	Magnesium	1.31
Ethylenediamine	0.66	Potassium	10.82
Meglumine ^l	2.29	Sodium	61.97
Procaine	0.66	Zinc	2.95

^a Percent is based on total number of anionic or cationic salts in use through 1974. ^b Camphorsulfonate. ^c 1,2-Ethanedisulfonate. ^d Lauryl sulfate. ^e Ethanesulfonate. ^f Glucoheptonate. ^g *p*-Glycollamidophenylarsonate. ^h *N,N'*-Di(dehydroabietyl)ethylenediamine. ⁱ 2-Hydroxyethanesulfonate. ^j 8-Chlorotheophyllinate. ^k *N,N'*-Dibenzylethylenediamine. ^l *N*-Methylglucamine.

to assemble data that will provide, for the student and practitioner alike, a rational basis for selecting a suitable salt form.

POTENTIALLY USEFUL SALTS

Salt formation is an acid-base reaction involving either a proton-transfer or neutralization reaction and is therefore controlled by factors influencing such reactions. Theoretically, every compound that exhibits acid or base characteristics can participate in salt formation. Particularly important is the relative strength of the acid or base—the acidity and basicity constants of the chemical species involved. These factors determine whether or not formation occurs and are a measure of the stability of the resulting salt.

The number of salt forms available to a chemist is large; surveys of patent literature show numerous new salts being synthesized annually. Various salts of the same compound often behave quite differently because of the physical, chemical, and thermodynamic properties they impart to the parent compound. For example, a salt's hydrophobicity and high crystal lattice energy can affect dissolution rate and, hence, bioavailability. Ideally, it would be desirable if one could predict how a pharmaceutical agent's properties would be affected by salt formation.

Tables I and II list all salts that were commercially marketed through 1974. The list was compiled from all agents listed in "Martindale The Extra Pharmacopoeia,"

26th ed. (7). Table I categorizes all salt forms approved by the Food and Drug Administration (FDA), while Table II lists those not approved by the FDA but in use in other countries. (Only salts of organic compounds are considered because most drugs are organic substances.) The relative frequency with which each salt type has been used is calculated as a percentage, based on the total number of anionic or cationic salts in use through 1974. Because of simple availability and physiological reasons, the monoprotic hydrochlorides have been by far the most frequent choice of the available anionic salt-forming radicals, outnumbering the sulfates nearly six to one. For similar reasons, sodium has been the most predominant cation.

Knowledge that one salt form imparts greater water solubility, is less toxic, or slows dissolution rate would greatly benefit chemists and formulators. In some cases, such generalizations can be made. Miller and Heller (8) discussed some properties associated with specific classes of salt forms. They stated that, in general, salt combinations with monocarboxylic acids are insoluble in water and lend themselves to repository preparations, while those of dicarboxylic acids confer water solubility if one carboxylic group is left free. Pamoic acid, an aromatic dicarboxylic acid, is an exception since it is used as a means of obtaining prolonged action by forming slightly soluble salts with certain basic drugs. Saia *et al.* (9) reviewed the use of this salt form in preparing sustained-release preparations. More recently, latentiation of dihydrostreptomycin (10)

Table II—Non-FDA-Approved Commercially Marketed Salts

Anion	Percent ^a
Adipate	0.13
Alginate	0.13
Aminosalicylate	0.25
Anhydromethylenecitrate	0.13
Arecoline	0.13
Aspartate	0.25
Bisulfate	0.25
Butylbromide	0.13
Camphorate	0.13
Digluconate	0.13
Dihydrobromide	0.13
Disuccinate	0.13
Glycerophosphate	0.88
Hemisulfate	0.13
Hydrofluoride	0.13
Hydroiodide	0.25
Methylenebis(salicylate)	0.13
Napadisylate ^b	0.13
Oxalate	0.25
Pectinate	0.13
Persulfate	0.13
Phenylethylbarbiturate	0.13
Picrate	0.13
Propionate	0.13
Thiocyanate	0.13
Tosylate	0.13
Undecanoate	0.13
Cation	Percent ^a
Organic:	
Benethamine ^c	0.33
Clemizole ^d	0.33
Diethylamine	0.33
Piperazine	0.98
Tromethamine ^e	0.33
Metallic:	
Barium	0.33
Bismuth	0.98

^a Percent is based on total number of anionic and cationic salts in use through 1974. ^b 1,5-Naphthalenedisulfonate. ^c *N*-Benzylphenethylamine. ^d 1-*p*-Chlorobenzyl-2-pyrrolidin-1'-ylmethylbenzimidazole. ^e Tris(hydroxymethyl)aminomethane.

using pamoic acid resulted in the formation of a delayed-action preparation. Numerous studies using pamoate salts are dispersed throughout the literature (11–15).

Alginic acid also has been used to prepare long-acting pharmaceuticals. Streptomycin alginate was prepared (16) and shown to be effective in sustained-release preparations. A striking example of a long-acting alginate salt is that of pilocarpine. When dispersed in sterile water and dried to a solid gel, this compound was found useful in the preparation of long-acting ophthalmic dosage forms (17). While liquid preparations of the alginate and hydrochloride salts possess similar miotic activity, studies showed that solid pilocarpine alginate flakes constricted pupil size more effectively and increased the duration of miosis significantly when compared with the liquid preparations. Solid dose pilocarpine may be more uniformly available, because it diffuses more slowly through the gel matrix which holds the drug in reserve. In contrast, drops of the commonly employed solution dosage form release the dose immediately to the conjunctival fluid.

Málek *et al.* (18) devised a unique way of prolonging action through salt formation; they showed that the distribution of several antibiotics could be markedly altered by merely preparing macromolecular salts. Since macromolecules and colloidal particles have an affinity for the lymphatic system, streptomycin, neomycin, viomycin, and

streptothrycin were combined with high molecular weight compounds such as polyacrylic acids, sulfonic or phosphorylated polysaccharides, and polyuronic derivatives. Parenteral administration of these compounds produced low blood levels of the antibiotic for long periods, while lymph levels were high. (In comparison, streptomycin sulfate gave high blood levels but low lymph levels.) This alteration in distribution caused the streptomycin to prolong its passage through the body, since lymphatic circulation is quite slow.

The appropriate choice of a salt form has been found to reduce toxicity. It can be rationalized that any compound associated with the normal metabolism of food and drink must be essentially nontoxic. The approach of choosing organic radicals that are readily excreted or metabolized opened up a new class of substances from which to select a salt form. For example, certain salts of the strong base choline have proven to be considerably less toxic than their parent compound. The preparation and properties of choline salts of a series of theophylline derivatives were reported (19), and it was shown that choline theophyllinate possessed a greater LD₅₀ than theophylline or its other salts (20). It was postulated that this agent would be less irritating to the GI tract than aminophylline, because "its basic constituent, choline, is an almost completely nontoxic substance of actual importance to the physiologic economy." This evidence led to the preparation of choline salicylate (21) as an attempt to reduce the GI disturbances associated with salicylate administration. Clinical studies indicated that choline salicylate elicited a lower incidence of GI distress, was tolerated in higher doses, and was of greater benefit to the patient than was acetylsalicylic acid (aspirin).

Amino acids and acid vitamins also have been used as salt-forming agents. Based on the evidence that coadministration of amino acids with aminoglycoside antibiotics reduced their toxicity, a series of amino acid salts of dihydrostreptomycin was prepared (22). In all but one case, the acute toxicities of these salts were lower than the toxicity of the sulfate. The ascorbate and pantothenate also were synthesized and shown to be less toxic than the sulfate. Of the salts prepared, the ascorbate had the highest LD₅₀.

The vitamins most commonly used for forming salts exhibiting reduced toxicity are ascorbic and pantothenic acids. Keller *et al.* (23) were the first to use pantothenic acid as a means of "detoxifying" the basic streptomycetes antibiotics. Parenteral administration of the pantothenates of streptomycin and dihydrostreptomycin had a significantly reduced incidence of acute neurotoxicity in cats as compared with the sulfates. Subsequent studies (24–28) supported this finding and showed that the pantothenates of neomycin and viomycin also are less toxic. The ascorbate of oleandomycin was synthesized and its pharmacological properties were reported (29). Upon intramuscular injection in rats, it produced less irritation than the phosphate.

p-Acetamidobenzoic acid, an innocuous metabolite of folic acid present in normal blood and urine, has been used in preparing salts. In particular, it yields stable salts with amines that otherwise tend to form hygroscopic products with conventional acid components (30).

Often the salt form is chosen by determining a salt

component that will pharmacologically antagonize an unfavorable property or properties exhibited by the basic agent. Salts of *N*-cyclohexylsulfamic acid are an example of the practical application of this approach. *N*-Cyclohexylsulfamic acid salts, better known as cyclamates, have a characteristic sweet, pleasing taste. Although presently under investigation by the FDA for potentially carcinogenic properties, salts incorporating this compound can render unpleasant or bitter-tasting drugs acceptable. For example, the cyclamates of dextromethorphan and chlorpheniramine exhibit greatly improved bitterness thresholds compared to commonly occurring salts (31). Furthermore, their stability in aqueous solution was described as good when maintained at a pH not greater than 4.

N-Cyclohexylsulfamic acid salts of thiamine hydrochloride and lincomycin also have been synthesized. Thiamine *N*-cyclohexylsulfamate hydrochloride was reported to have a more pleasant taste than other thiamine salts while having an equal or greater stability (32). Lincomycin cyclamate, shown to possess an enhanced thermal stability over its hydrochloride, was prepared (33) to test the hypothesis that reduced lincomycin absorption in the presence of small quantities of cyclamates was due to a simple metathetic reaction. However, this assumption was found not to be true. An extensive study of the preparation and characterization of cyclamic acid salts of several widely used classes of drugs including antihistamines, antibiotics, antitussives, myospasmolytics, and local anesthetics was reported (34, 35).

Various salts of penicillin and basic amine compounds have been formulated in an effort to produce a long-acting, nonallergenic form of penicillin. Since antihistamines appear to mitigate the symptomatology of penicillin reactions in some patients, coadministration of the two has been advocated. The preparation of the benzhydrallamine salt of penicillin was an attempt to produce a repository form of penicillin with antiallergic properties (36). Blood levels achieved with this salt were comparable to those of penicillin G potassium; however, its antiallergic properties were not evaluated. In fact, the investigators noted that antihistamines can actually cause sensitization at times and stated that "despite their occasionally favorable influence on the symptoms of penicillin sensitivity, they contribute directly to the potential of drug sensitivity when co-administered with penicillin."

Silver salts of sulfanilamide, penicillin, and other antibiotics have been prepared and represent cases where the species (ions) are complementary. When aqueous solutions of the salts were applied topically to burned tissue, they yielded the combined benefits of the oligodynamic action of silver and the advantages of the antibacterial agents (37).

The use of 8-substituted xanthines, particularly the 8-substituted theophyllines, as salt-forming agents was first reported in the preparation of a series of antihistamine salts (38–41). Synthesis of these xanthine salts was an attempt to find a drug to counteract the drowsiness caused by the antihistamines with the stimulant properties of the xanthines. When an electronegative group is introduced into the xanthine molecule at the 8-position, the electron-drawing capacity of the substituent results in the creation of an acidic hydrogen at position 7. Thus, these

moderately strong acidic compounds can undergo salt formation with various organic bases.

The 8-halotheophyllines were the first group of xanthines studied as potential salt-forming agents. Since the report on the preparation of the 8-chlorotheophylline salt of diphenhydramine (42), synthesis of the 8-halotheophyllinates of a number of organic bases has been attempted. The 8-chlorotheophylline salts of quinine, ephedrine, and strychnine were prepared and characterized (43). These salts were less water soluble than the corresponding free alkaloidal bases. In a similar report, the 8-chlorotheophyllinates of three synthetic narcotics, meperidine, levorphanol, and metopon, were prepared (44).

Pharmacological and clinical studies involving the 8-bromotheophylline pyrilamine salt revealed the unusual diuretic properties associated with the 8-halotheophylline portion of the compound (45, 46). This finding initiated an investigation into the preparation of a soluble 8-bromotheophylline salt of high diuretic activity. With readily available amines, over 30 salts were synthesized and screened for diuretic activity (47). When tested against theophylline salts of the same amines, the 8-bromotheophyllinates showed greater activity in every case.

With the successful formation of 8-halotheophyllinates of organic bases, Morozowich and Bope (48) proposed that, if the halogen moiety was replaced with a more electronegative substituent such as a nitro group, a more acidic compound would be formed. Presumably, more stable salts would result and precipitation of the free xanthine derivative in the stomach would be less likely to occur. On this premise, they successfully prepared pharmacologically effective 8-nitrotheophyllinates of several pharmaceutically useful bases.

Duesel *et al.* (19), in their study of choline theophyllinate, prepared the 8-chloro-, 8-bromo-, and 8-nitrotheophylline salts of choline. Oral toxicity studies in mice showed that the LD₅₀ of the 8-nitrotheophyllinate was much greater than that of either 8-halotheophylline. In fact, it remained nonlethal at doses as high as 5 g.

Polygalacturonic acid, a derivative of pectin, has been used to prepare quinidine salts exhibiting reduced toxicity (49, 50). The compound possesses special demulcent properties and inhibits mucosal irritation. The rationale for use of this agent is to reduce the ionic shock to the GI mucosa resulting from the flood of irritating ions liberated by rapid dissociation of the conventional inorganic quinidine salts. Studies have shown that it is four times less toxic orally than the sulfate. This difference was attributed to the slower release of quinidine from the polygalacturonate.

Other compounds reported to be potentially useful as pharmaceutical salt forms are listed in Table III.

PHYSICOCHEMICAL STUDIES

Biological activity of a drug molecule is influenced by two factors: its chemical structure and effect at a specific site and its ability to reach—and then be removed from—the site of action. Thus, a knowledge of the physicochemical properties of a compound that influence its absorption, distribution, metabolism, and excretion is essential for a complete understanding of the onset and duration of ac-

Table III—Potentially Useful Salt Forms of Pharmaceutical Agents

Salt-Forming Agent	Compound Modified	Modification	Reference
Acetylaminoacetic acid	Doxycycline	Solubility	51
<i>N</i> -Acetyl-L-asparagine	Erythromycin	Solubility, activity, stability	52
<i>N</i> -Acetylcystine	Doxycycline	Combined effect useful in pneumonia	53
Adamantoic acid	Alkylbiguanides	Prolonged action	54
Adipic acid	Piperazine	Stability, toxicity, organoleptic properties	55
<i>N</i> -Alkylsulfamates	Ampicillin	Absorption (oral)	56
	Lincomycin	Solubility	57
Anthraquinone-1,5-disulfonic acid	Cephalexin	Stability, absorption	58
Arabogalactan sulfate (arabino)	Various alkaloids	Prolonged action	59, 60
Arginine	Cephalosporins	Toxicity	61
	α -Sulfobenzylpenicillin	Stability, hygroscopicity, toxicity	62
Aspartate	Erythromycin	Solubility	63
Betaine	Tetracycline	Gastric absorption	64
Bis(2-carboxychromon-5-yloxy)alkanes	7-(Aminoalkyl)theophyllines	Activity, prolonged prophylactic effect	65
Carnitine	Metformin	Toxicity	66
4-Chloro- <i>m</i> -toluenesulfonic acid	Propoxyphene	Organoleptic properties	67
Decanoate	Heptaminol	Prolonged action	68
Diacetyl sulfate	Thiamine	Stability, hygroscopicity	69
Dibenzylethylenediamine	Ampicillin	Prolonged action	70, 71
Diethylamine	Cephalosporins	Reduced pain on injection	72
Diguaiacyl phosphate	Tetracycline	Activity	73
Dioctyl sulfosuccinate	Vincamine	Organoleptic properties	74
Embonic (pamoic) acid	Kanamycin	Toxicity	75
	2-Phenyl-3-methylmorpholine	Toxicity	76
Fructose 1,6-diphosphoric acid	Tetracycline	Solubility	77
	Erythromycin	Solubility	
Glucose 1-phosphoric acid, glucose	Tetracycline	Solubility	77
6-phosphoric acid	Erythromycin	Solubility	
1-Glutamine	Erythromycin	Solubility, activity, stability	52
Hydroxynaphthoate	Bephenium	Toxicity	78
2-(4-Imidazolyl)ethylamine	Prostaglandin	Prolonged action	79
Isobutanolamine	Theophylline	Stability	80
Lauryl sulfate	Vincamine	Organoleptic properties	81
Lysine	α -Sulfobenzylpenicillin	Toxicity, stability, hygroscopicity	62
	Cephalosporins		61
Methanesulfonic acid	Pralidoxime (2-PAM)	Solubility	82
<i>N</i> -Methylglucamine	α -Sulfobenzylpenicillin	Toxicity, stability, hygroscopicity	62
	Cephalosporins	Reduced pain on injection	72
<i>N</i> -Methylpiperazine	Phenylbutazone	Toxicity, faster onset of action	83
Morpholine	Cephalosporins	Reduced pain on injection	72
2-Naphthalenesulfonic acid	Propoxyphene	Organoleptic properties	84
Octanoate	Heptaminol	Prolonged action	68
Probenecid	Pivampicillin	Organoleptic properties	85
Tannic acid	Various amines	Prolonged action	86, 87
Theobromine acetic acid	Propoxyphene	Activity	88
3,4,5-Trimethoxybenzoate	Tetracycline	Organoleptic properties	89
	Heptaminol	Prolonged action	68
Tromethamine	Aspirin	Absorption (oral)	90
	Dinoprost (prostaglandin F _{2α})	Physical state	91

tion, the relative toxicity, and the possible routes of administration (2).

In a review in 1960, Miller and Holland (92) stated that "different salts of the same drug rarely differ pharmacologically; the differences are usually based on the physical properties." In a subsequent review (93), Wagner expanded upon this statement, asserting that, although the nature of the biological responses elicited by a series of salts of the same parent compound may not differ appreciably, the intensities of response may differ markedly.

The salt form is known to influence a number of physicochemical properties of the parent compound including dissolution rate, solubility, stability, and hygroscopicity. These properties, in turn, affect the availability and formulation characteristics of the drug. Consequently, the pharmaceutical industry has systematically engaged in extensive preformulation studies of the physicochemical properties of each new drug entity to determine the most suitable form for drug formulation. Published information concerning such studies, however, is sparse. Preformulation studies have been outlined, and the influence of the salt form on the volatility and hygroscopicity of an agent under investigation was discussed (94).

In one such study, methylpyridinium-2-aldoxime (pralidoxime) salts were investigated (95). This study set out to prepare a salt with water solubility adequate to allow intramuscular injection of a low volume (2–3 ml) therapeutic dose. The original compound, the methiodide, had the disadvantages of limited aqueous solubility and high potential toxicity, since its high iodide content could result in iodism. On the basis of physiological compatibility, better water solubility, favorable stability, and relatively high percentage of oxime, the chloride salt of pralidoxime was selected for therapeutic administration; it was claimed that "the anion used to form the salt can confer physical properties of importance and significance for the formulation and administration of the compound" (95).

Some physicochemical properties of a series of mineral acid salts of lidocaine also were determined (96). While the hydrochloride and hydrobromide were more hygroscopic, they were more soluble in a number of solvents than the nitrate, perchlorate, phosphate, or sulfate salts.

Dissolution Rate—The dissolution rate of a pharmaceutical agent is of major importance to the formulator. In many cases, particularly with poorly soluble drugs, this characteristic best reflects the bioavailability of the com-

pound. As a rule, a pharmaceutical salt exhibits a higher dissolution rate than the corresponding conjugate acid or base at an equal pH, even though they may have the same equilibrium solubility. The explanation for this result lies in the processes that control dissolution.

Dissolution can be described by a diffusion layer model¹ in terms of an equation developed by Nernst and Brunner (97):

$$\frac{dW}{dt} = \frac{DS}{h} (C_s - C) \quad (\text{Eq. 1})$$

where W is the mass of the solute dissolved at time t , dW/dt is the rate of mass transfer per unit time, D is the solute molecule diffusion coefficient, S is the surface area of the dissolving solid, h is the diffusion layer thickness, C is the concentration of the drug in the bulk solution at time t , and C_s is the saturation solubility of the solute in the diffusion layer.

The driving force for dissolution in Eq. 1 is the difference between the saturation solubility of the drug and the concentration of the drug in the bulk fluid. If the drug is not rapidly absorbed after it dissolves, then C , the concentration in the bulk solution, approaches C_s and the dissolution rate is retarded. When this occurs, absorption is "absorption rate" limited (or "membrane transport" limited). If the absorption rate is rapid (or if the absorption mass transfer coefficient is much larger than DS/h of Eq. 1), however, C becomes negligible compared to C_s and dissolution occurs under "sink" conditions. Absorption is then said to be dissolution rate limited, which is what occurs with most poorly soluble drugs. In either case, an increase in C_s , as in salt formation, increases dissolution.

Salts often speed dissolution by effectively acting as their own buffers to alter the pH of the diffusion layer, thus increasing the solubility of the parent compound, C_s , in that layer over its inherent solubility at the pH of the dissolution medium. Hence, dissolution is controlled by solubility in the diffusion layer which, in turn, is determined by the pH of that layer. The influence of K_{sp} on the solubility term, C_s , and dissolution rate, should an accumulation of ions be allowed to occur, will be treated later.

Nelson (98), in a study of theophylline salts, was the first to show the correlation between diffusion layer pH and dissolution rate. The major impact that this study had on the pharmaceutical sciences was its conclusion that, if other factors remained constant, the dissolution rate of a compound determined the rate of buildup of blood levels with time and the maximum levels obtained. Those salts of the acidic theophylline with high diffusion layer pH's had greater *in vitro* dissolution rates than those exhibiting a lower diffusion layer pH. And, indeed, the rank order of dissolution rates correlated well with clinically determined blood levels. Presumably, the higher pH in the diffusion layer retards hydrolysis of the salt, thereby maintaining the anionic charge of the theophyllinate ion. This report led to many additional studies which illustrate the influence of the salt form on dissolution and the beneficial effects of changing nonionized drugs into salts.

Juncher and Raaschou (99) demonstrated that the rank order of peak blood levels of penicillin V, obtained upon

administration of three different salts and the free acid, was the same as the rank order of their rates of dissolution *in vitro*. While the investigators ascribed these differences to the solubility properties of the salts, their experiments actually compared dissolution rates, not solubilities. The relative order of dissolution rates and mean maximal blood levels was: potassium salt > calcium salt > free acid > benzathine salt.

Nelson (100) determined dissolution rates for several weak acids and their sodium salts in media whose pH's represented GI fluids. In all cases, the sodium salt dissolved more rapidly than the free acid. This finding resolved the misconception that absorption of drugs is related only to solubility in the appropriate medium; rather, solubility affects absorption only to the extent that it affects dissolution rate. Absorption of drugs is a dynamic process, and the ultimate solubility of a drug in fluid at absorption sites is of limited consequence since absorption prevents the attainment of saturated solutions. Therefore, dissolution rate, more than solubility, influences absorption since it is a preceding process.

In two subsequent studies, Nelson and coworkers further illustrated the effects of changing nonionized drugs into salts. A report concerning tolbutamide (101), a weak acid, showed that the initial dissolution rate of tolbutamide sodium was approximately 5000 times more rapid than the free acid in acidic media and 300 times more rapid in neutral media. This difference, measured *in vitro*, reflected the differences observed between the free acid and the salt when administered to human subjects. Oral administration of tolbutamide sodium produced an immediate drop in blood sugar comparable to that produced by intravenous injection of the salt, while the slowly dissolving tolbutamide produced a smooth, sustained fall in blood sugar (102).

Correlation of urinary excretion rates and dissolution rates of tetracycline and some of its acid salts also was demonstrated by Nelson (103). The salts that exhibited greater *in vitro* dissolution rates showed greater urinary excretion rates, indicating more rapid absorption.

Benet (104), in a discussion of the biopharmaceutical basis for drug design, referred to the influence of the salt form on dissolution. He compared the dissolution rates of tetracycline and tolbutamide and their salts, as reported in the studies previously cited, and explained why the rates differ at the pH's exhibited by physiological fluids.

Although salt formation usually increases the dissolution rate of a drug, studies with aluminum acetylsalicylate (105, 106), warfarin sodium (107), and benzphetamine pamoate (108) showed that administration of the salt *slowed* dissolution of the drug and subsequent absorption compared to the nonionized form. This decrease appeared to result from precipitation of an insoluble particle or film on the surface of the tablet. Such a phenomenon decreases the effective surface area and prevents deaggregation of the particles. Theoretical considerations of the processes controlling dissolution of an acid salt of a base (108) and the sodium salt of a weak acid (109, 110) in reactive media have been discussed.

Tablet processing and various formulation factors can decrease the dissolution rate of a salt in human gastric juice over its nonionized form (111). Granulation and tableting caused the dissolution rate of phenobarbital sodium to

¹ The authors recognize the existence of other models; this one was chosen simply for illustrative purposes.

decrease but had the opposite effect on phenobarbital. Therefore, as a tablet dosage form, the dissolution rate of the sodium salt was slower than that of the free acid. These results were attributed to differences in the disintegrating properties of the tablets; in some instances, rapid dissolution may in fact be a problem for very soluble drugs.

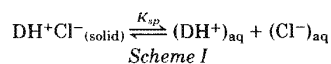
Others have illustrated a phenomenon that decreases the dissolution rate of a salt below that of its nonionized form. Lin *et al.* (112) studied the relationship between salts and biological activity by dissolving three salts and the free base of an experimental antihypertensive in water, 0.1 N HCl, and pH 7.2 phosphate buffer. The dissolution rate of the monohydrochloride salt was lower than that of the free base in 0.1 N HCl and higher than the free base in both water and phosphate buffer. These authors ascribed this variation to the common ion effect and substantiated it experimentally. Although the biological activity of the monohydrochloride was greater than that of the free base, the implications of altered absorption characteristics on the activity of any other hydrochloride salt in GI fluids must be considered. Similar results also were reported for hydrochloride salts of some tetracyclines (113).

Some consideration must be given to the influence of salt formation on oral toxicity, which often reflects the relationship between the *in vivo* dissolution rate and the appearance of drug in the circulation (114, 115). Morozowich *et al.* (114) showed that the relative toxicities of a series of salts of a drug reflect the rate of absorption, providing the salt-forming agents themselves are relatively nontoxic. They stated that "when absorption is rate-limited by dissolution of the salt in the gastrointestinal tract, as will be the case with slowly soluble salts, the toxicity of a slowly dissolving salt will most probably be lower than that of a more rapidly dissolving salt." The implications of salt formation on toxicology will be discussed under *Toxicological Considerations*.

Several reviews dealt with the influence of the dissolution rate on drug availability and, in particular, salt effects (116, 117). Other reports illustrating the influence of salts and salt form on dissolution rate are listed in Table IV.

Solubility—Knowledge of the solubility characteristics of a pharmaceutical agent is essential, because solubility is usually an important factor in the pharmacokinetic profile, the chemical stability, and, ultimately, the formulation of the drug. As discussed previously, it is certainly a primary factor in controlling dissolution rates. The solubility of a compound depends basically upon the physical and chemical properties of the solute; *e.g.*, a lower melting point for a compound within a series reflects a decreased lattice energy, which would suggest a higher solubility. Solubility depends as well upon such elements as temperature, pressure, solvent properties (such as resulting pH), and, to a lesser extent, the state of subdivision of the solute.

An important solvent property which is often overlooked involves the common ion effect; in particular, hydrochloride salts of drugs often exhibit less than desirable solubility in gastric juice because of the abundance of chloride ions. The equilibrium involved is shown in Scheme I.



Salt formation is perhaps one of the first approaches

Table IV—Additional References on Salt Form and Dissolution Rate

Topic	Reference
Dissolution rate of mixtures of weak acids and tribasic sodium phosphate	118
Physiological availability and <i>in vitro</i> dissolution characteristics of some solid dosage formulations of aminosalicic acid and its salts	119
Biopharmaceutics, rate of dissolution: chronological bibliography	120
Biopharmaceutics: rate of dissolution <i>in vitro</i> and <i>in vivo</i>	121
Dissolution tests and interpretation of anomalies observed in the dissolution process of sulfaquinolone based on salt formation	122
Influence of the dissolution rate of lithium tablets on side effects	123
Dissolution kinetics of drugs in human gastric juice	124
Comparison of dissolution and absorption rates of different commercial aspirin tablets	125
<i>In vitro</i> dissolution rates of aminorex dosage forms and their correlation with <i>in vitro</i> availability	126

considered as a means of increasing a compound's water solubility. As with dissolution rates, however, salt formation does not always confer greater solubility. Liberally dispersed throughout the pharmaceutical literature are studies that compare the solubilities of different salt forms of the same compound with those of its free acid or base (Table IV). Selection of the salt form exhibiting the desired solubility properties is critical, since these properties often dictate the formulation characteristics of the drug.

Phase solubility techniques were used to study the formation of complex salts of triamterene (127). The results indicated that the organic acid salts of basic drugs, such as amines, were more soluble in water than the corresponding inorganic (halide) salts. This consideration is important in the synthesis and selection of a salt form that will exhibit enhanced bioavailability and desirable formulation characteristics.

The hydrogen-ion concentration can significantly affect the solubility of a salt. Anderson (128) discussed the influence of pH on the solubility of pharmaceuticals. Mathematical relationships between pH and solubility of therapeutically useful weak acids and bases and their salts were given along with some considerations in the formulation of solutions of these particular agents.

An extensive study on the solubility interrelationships of the hydrochloride and free base of two pharmaceutically useful amines was reported (129). Mathematical equations describing the total solubility at an arbitrary pH in terms of the independent solubilities of the hydrochloride and free base species and the dissociation constant of the salt were derived and fitted to experimental data with good results. This report elucidated the point that, while the solubility of the amine hydrochloride generally sets the maximum obtainable concentration for a given amine, the solubility of the free base and the pKa determine the maximum pH at which formulation as a solution is possible (assuming that the desired concentration exceeds the free base solubility). Shifting the pH-solubility profile to higher pH values for formulation purposes may require increasing the solubility of the free base. This increase might be accomplished by using an appropriate cosolvent. Since the dissociation characteristics of carboxylic acids and other acidic organic species are similar to those of organic hydrochlorides, it is expected that the pH-solubility profiles

of these organic acids, although reversed, can be characterized theoretically using the same treatment.

Several reports showed that the structure of an organic salt-forming radical influences the solubility of the resulting salt. The water solubilities of 16 salts (carboxylates, sulfates, sulfamates, and phosphates) of the weak base erythromycin were dependent on the size of the alkyl group of the acid (130). In a study with *N*-alkylsulfamates of lincomycin (66), a similar phenomenon was observed: solubility of these salts decreased as the size of the alkyl group attached to the acidic function increased.

Senior (131), in a study on the formulation and properties of the antibacterial chlorhexidine, determined the water solubilities of 35 salts and the free base. He found that inorganic salts had remarkably low solubilities while those of the lower aliphatic acids proved to be somewhat more soluble. Hydroxylation of the acid increased solubility, since salt formation with polyhydroxy acids, particularly the sugar acids, conferred extensive water solubility to the molecule.

Several investigators reported the influence of the solubility of a drug on its formulation and subsequent availability from the dosage form. In a discussion of the preparation and formulation of epinephrine salts in an aerosol system using liquefied gas propellants, Sciarra *et al.* (132) pointed out that the solubility characteristics of the agent are important in two respects. First, the solubility of the therapeutically active ingredient in the various propellants is an important consideration if the product is to be used for either local action in the lungs or systemic therapy. Second, the solubility of the drug in extracellular fluids plays an important role in selection of the compound. The bitartrate, malate, maleate, and fumarate salts of epinephrine were prepared and subjected to solubility and stability studies. While all salts had similar partition coefficients, the solubility of the maleate in several propellants and its stability in formulated aerosols made it the drug form of choice.

Ephedrine hydrochloride was more rapidly released than the free base from theobroma oil suppositories containing different surfactants (133). This enhanced rate of release (dialysis) was ascribed primarily to the greater aqueous solubility of the hydrochloride, which solubilized faster from the oil-in-water emulsion, whereas the ephedrine alkaloid base tended to remain behind in the oil phase.

The solubility of the active ingredient in ointment bases can dramatically influence its diffusion properties. A study of salicylic acid and its sodium salt showed that the diffusion of both was very low from hydrophobic bases, whereas the solubility of the drug significantly affected the diffusion from hydrophilic bases. The more soluble sodium salicylate diffused much faster from these latter bases than did salicylic acid (134).

Additional references on the relationship of salt form and solubility are listed in Table V.

Organoleptic Properties—Modern medicine requires that a pharmaceutical formulation be efficacious, safe, stable, and acceptable to the patient. Of primary importance in the development of oral dosage forms is taste acceptability. This factor presents no major problems when the drug is to be administered as a tablet or a capsule and swallowed as a unit but is clearly a prominent factor in

Table V—Additional References on Salt Form and Solubility

Topic	Reference
Influence of solubility on the rate of GI absorption of aspirin	135
Effect of dosage form upon the GI absorption rate of salicylates	136
Physical-chemical properties of polyene macrolide esters and their water-soluble salts	137
Isolation and reaction products of otrotic acid and amines and their solubility in water	138
Solubility and stability of erythromycin salts	139
Studies on pharmaceutical preparations of otrotic acid: water-soluble properties of otrotic acid salts	140
Solubility of antibiotics in 24 solvents	141, 142
Solubility of antibiotics in 26 solvents	143

patient acceptability when it is to be administered as a liquid, chewable tablet, or lozenge.

Since taste is a chemical sense, a substance must be dissolved if it is to elicit a taste sensation—either by taking it as a solution or by its dissolving in the saliva. Therefore, one method used to minimize undesirable organoleptic properties of pharmaceuticals involves the preparation of a poorly soluble salt form of the drug such that the saturation concentration is less than the taste threshold.

Erythromycin estolate (lauryl sulfate) has approximately one-twelfth the solubility of the free base, is tasteless, and is useful in the formulation of oral suspensions (144). A study on erythromycin salts showed that the bitterness level was dependent on two properties: (a) the water solubility of the salt, which is dependent on the size of the alkyl group attached to the acid function; and (b) the strength of the acid used to form the salt, *i.e.*, the stability of the salt (130). The stearyl sulfamate salt possessed the most desirable organoleptic properties.

Many problems concerned with formulation and stability of topical and oral pharmaceuticals containing bacitracin have been overcome by incorporating bacitracin into the formulation as its zinc salt. One distinct advantage over the parent compound is its lack of taste, caused by its relative insolubility. Thus, it is the preferred drug form for preparations where taste is a factor (145). Taste panel evaluations of the comparative bitterness of bacitracin zinc and bacitracin indicate that the taste of the zinc salt is more easily masked and that the presence of a bitterness-masking adjuvant, such as sucrose, increases the bitterness threshold ratio differences between the two compounds even further (146).

Propoxyphene napsylate, nearly water insoluble, is only slightly bitter to the taste as compared to the highly water-soluble hydrochloride (147) and can be readily formulated into a flavored aqueous suspension. The taste of these suspensions can be improved significantly by the addition of a common ion (sodium or calcium napsylate) to depress solubility further.

A newer approach to the improvement of drug palatability has been to form insoluble salts with ion-exchange resins. Several investigators described and tested the practical application of this method (148–150). Spross *et al.* (149) outlined the conditions necessary for improving the palatability of a drug by adsorbing it onto an ion-exchange resin without appreciably modifying its pharmacological effects. They found that: (a) the degree of drug release from the ion-exchange adsorbate depends on the

equivalent quotient between the electrolytes in the surrounding fluid and the ionic drugs, (b) the amount of ions is far less in the saliva than in the gastric juice (the temporary electrolyte contents can be estimated at 0.05 mEq in the saliva and at 10 mEq in the gastric juice), and (c) the exchange rates should allow the equilibria to be attained within a fairly short period. Insoluble drug resins formed between dextran gel² cation exchangers and several basic drugs were in many cases much more pleasant tasting than their parent compounds. Furthermore, release of the drug from the ion-exchange adsorbate was quite rapid and complete under conditions prevailing in the GI tract.

Similar findings were reported using a polymethacrylic acid ion-exchange resin (150). In addition, coating the adsorbate particles with a 4:1 ethylcellulose-hydroxypropyl methylcellulose mixture further reduced bitterness. While *in vitro* release from the uncoated resinate was rapid and complete, release from coated adsorbates varied with the extent of coating.

Another approach to improving the taste properties of pharmaceutical agents is to prepare a pleasant-tasting soluble salt of a poor-tasting parent drug. This approach often can be very difficult, however, since solubilization of the parent compound usually imparts its unpleasant taste to the preparation. Nevertheless, some success has been reported using the artificial sweeteners cyclamate sodium and saccharin.

As described earlier, formation of *N*-cyclohexylsulfamate salts of several drug substances has produced better tasting derivatives with enhanced solubility properties (31, 32). The physicochemical and toxicological properties of benzalkonium saccharinate and a series of saccharinates of other quaternary ammonium compounds were reported (151). While conventional quaternary ammonium compounds have a very bitter taste, their saccharin analogs are sweet.

Potassium salts frequently possess an unpleasant taste and a metallic aftertaste. The palatability of some potassium salts in flavored vehicles was reported (152); while the salts had similar taste thresholds at effective therapeutic levels, all potassium salts exhibited inferior palatability.

Table III includes several samples of other salts that exhibit an improved taste relative to their free acid or base forms.

Stability—The chemical and physical stability of a pharmaceutical must be known, because it can influence the choice of dosage form, the manufacturing and packaging, and the therapeutic efficacy of the final preparation. Systematic determination of the thermal stability, solution stability (at various pH's), and light sensitivity of a drug and its derivatives, both alone and in the presence of common additives, provides essential input toward selecting the most suitable derivative and dosage form.

Depending on the route of degradation, different salt forms impart different stability characteristics to the parent drug by various mechanisms. Most commonly used are sparingly soluble salts which, when used in the formulation of suspensions, reduce the amount of drug in solution and, hence, its degradation. Differences in hygroscopicity of several salts influence the stability of the

drug in the dry state. In some cases, the salt-forming radical itself enhances the stability of the parent agent.

The stability of penicillin G and its salts has been widely studied due to the drug's therapeutic importance and its characteristic instability. Schwartz and Buckwalter (153) described some of the stability characteristics of this antibiotic, stating that, with present techniques, a solution of penicillin cannot be made stable for more than 2 weeks, even at refrigerator temperatures. They also discussed the use of suspensions of sparingly soluble amine salts in aqueous vehicles as a means of "allowing marketing of a 'ready-made' penicillin product." Procaine, benzathine, and hydrabamine salts are marketed, and their acceptable stability as aqueous suspensions is based mainly on their insolubility and the minimization of degradation in solution.

A theoretical treatment of the solubility of these salts was presented in which equations were derived for calculating the solubility as a function of pH and the pH of minimum solubility (154, 155). These equations are based on the mass action law and its relationship to the ionization constants of the amine and the penicillin and the solubility of the salt in water. Since the salt in solution is partially dissociated, further suppression of the solubility may be achieved by the common ion effect. Swintosky *et al.* (156) demonstrated this effect with penicillin G procaine by adding procaine hydrochloride to the preparation and further enhancing its stability. The 8-chlorotheophylline salt (or complex) of penicillin G was reported to be water soluble, yet stable in solution (157). Since 8-chlorotheophylline is acidic, it has been postulated that a buffer effect could account for the stabilization of this "salt."

While penicillin G procaine is more stable in aqueous vehicles, it is less thermally stable than the sodium or potassium salts, decomposing if heated much above 60°. The sodium and potassium salts are known to withstand heating up to 100° for 4 days with little loss in potency (158). This behavior might well be due to differences in melting points—*viz.*, 106° for penicillin G procaine and ~215° dec. for the potassium salt.

Since hydrolysis of penicillin is dependent on moisture content, preparations in which moisture is rigorously excluded are quite stable in the dry state. A study on the effect of moisture on penicillin salts found the calcium salt to be less hygroscopic than the sodium salt and, hence, more stable in moist atmospheres (159). Similarly, penicillin G potassium is also much less hygroscopic than penicillin G sodium and has become the preferred form for marketing in the dry state (160).

Several studies reported the relative stabilities of thiamine salts, particularly the hydrochloride and the mononitrate (161–163). The mononitrate is observed to be less hygroscopic and is accordingly much less water soluble than the hydrochloride. Investigations of various preparations including compressed tablets, multivitamin capsules, and dry-filled vitamin B complex capsules at various temperatures showed that the mononitrate was more stable than the hydrochloride (164, 165). The stabilities of numerous thiamine salts were studied in aqueous solution and in dry powder preparations with various excipients (166, 167). In aqueous solution, the resulting pH was the chief factor controlling hydrolysis and oxidative decomposition of thiamine salts; their stability as powder

² Sephadex.

preparations was related to their aqueous solubility, with the sparingly soluble salts being more stable (and presumably less hygroscopic).

An orally administered drug must be stable in acidic solution because it generally must pass intact through the acidic environment of the stomach if it is to exhibit therapeutic blood levels. The advantage of erythromycin estolate over the free base lies in its low solubility in gastric juice, which enables it to be administered with food without any decrease in attained blood levels. The salt is more stable in the stomach because it remains undissolved. Therefore, it retains its potency even when exposed to acidic environments for extended periods (144).

In a study on the preparation and characterization of lincomycin cyclamate (33), it was noted that the cyclamate salt had an enhanced thermal stability over the hydrochloride. In a subsequent report (168), differential thermal analysis and thermogravimetric analysis showed that while the hydrochloride easily undergoes thermal degradation, the cyclamate anion confers a considerably greater thermal stability on the lincomycin moiety.

Mullins and Macek (169) showed that the physical and chemical stability of the calcium salt of novobiocin makes it the form of choice for the formulation of a liquid preparation of the antibiotic. The amorphous calcium novobiocin salt proved to be tasteless, yet fully biologically active and perfectly stable in aqueous suspension. Neither the sodium salt nor the free acid is suitable; the sodium salt cannot be formulated in a liquid due to its chemical instability, while the crystalline free acid is not absorbed from the GI tract. Amorphous novobiocin is absorbed but is metastable in solution and slowly converts to the unabsorbed crystalline form.

Other reports of alterations in stability characteristics due to salt formation are listed in Table VI.

Miscellaneous Properties—The salt form has been reported to influence other physicochemical properties of a drug substance. Studies illustrating the effect of the salt-forming radical on surface tension, deaggregation behavior, and ion-pair extraction have appeared.

The influence of the anion on the absorption processes of two charged species, dextromethorphan and tetracycline, was studied in the rat stomach (186, 187). A linear relationship existed between the rate of absorption from buffer solutions of the anions under investigation and their surface tensions. Thus, the absorption process was related to the surface activity of the various salts and not to their lipid solubilities. This change of surface activity with the buffer (or salt) species is similar to the results reported in a study of the surface activity of various phenothiazine salts (188).

The antibacterial chlorhexidine possesses surface activity. A study of the colloidal properties of some chlorhexidine salts showed that the counterion can affect the critical micelle concentration of a surface-active agent, and this effect was usually associated with a change in micellar size (189).

The deaggregation behavior of a relatively insoluble acid and its sodium salt was studied, and deaggregation was postulated to be a possible rate-limiting step in the absorption of a drug from a dosage form (190). While no direct comparisons of the two forms were made, inspection of the data shows that the deaggregation rate of the salt

Table VI—Additional References on Salt Form and Stability

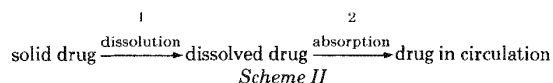
Topic	Reference
Stability of chlorhexidine solutions	170
Stability of chlorhexidine when autoclaved	171
Anhydrotetracycline and 4-epianhydrotetracycline in marketed tetracycline and aged tetracycline products	172
Solid-state stability of some crystalline vitamin A compounds	173
Physicochemical studies on the stability of penicillin salts	174
Light sensitivity of tetracyclines	175
Hygroscopic properties, thermostability, and solubility of oleandomycin salts	176
Stability of orotic acid and its amine salts in aqueous solution	177
Some factors influencing the stability of tablets (aspirin)	178
Stability of aqueous solutions of sodium aminosalicylate	179
Hygroscopic properties of various preparations of erythromycin	180
Physicochemical studies on the decomposition of aminosalicylic acid and its salts	181
Stabilities of aqueous solutions of 2-diethylaminoethyl-3-methyl-2-phenylvalerate hydrochloride and its methobromide	182
Investigation of some properties of penicillin G salts	183
Stability of ferrous iron tablets on storage	184
Stability of aspirin aluminum compounded with antacids	185

was considerably more rapid than that of the free acid in equivalent dosage forms. Therefore, if absorption is dependent on the dissolution rate, which in turn is dependent on the deaggregation rate, the salt should produce the highest and earliest blood levels. On the other hand, it is possible that hygroscopic (and deliquescent) salts can absorb atmospheric moisture, cause a sticky surface, and inhibit deaggregation.

Higuchi and coworkers presented an extensive study on the physicochemical basis of the ion-pair extraction of pharmaceutical amines. Distribution ratios of dextromethorphan (191) and chlorpheniramine (192) between an organic layer and water were highly dependent on the concentration and nature of the anion present. Less hydrophilic anions yielded more readily extractable ion-pairs. A study of the thermodynamic properties, enthalpy, free energy, and entropy, involved in the extraction equilibria of dextromethorphan ion-pairs indicated that the entropy change associated with transfer of the different anions between phases is the main controlling factor in the extraction process (193).

BIOAVAILABILITY

Most drugs prescribed in the United States are administered in solid and polyphasic dosage forms. Consequently, dissolution of the drug must precede the absorption process. The simplest model that adequately describes this process is shown in Scheme II.



Since the dissolution rate is generally slow for drugs with poor solubility, Step 1 is frequently rate limiting in the overall absorption process. As a result, the onset, intensity, duration of pharmacological activity, and, hence, bioavailability are affected by changes in dissolution rate. As discussed previously, administering a salt of the parent drug often proves to be an effective means of altering dissolution rate and absorption.

Table VII—Additional References on Bioavailability and Formulation Effects

Topic	Reference
Effects of various substances on the absorption of tetracycline in rats	197
Effects of dosage form upon the GI absorption rate of salicylates	136
Determination of <i>in vivo</i> and <i>in vitro</i> release of theophylline aminoisobutanol in a prolonged-action system	198
Ion-exchange resin salts for oral therapy: carbinoxamine	199
Latentiation of dihydrostreptomycin by pamoate formation	10
Solid-state ophthalmic dosage systems in effecting prolonged release of pilocarpine in the cul-de-sac	17
Absorption of erythromycin: various pharmaceutical forms	200
Comparative study of the absorption of drugs from old and new rectal preparations	201

Formulation Effects—Choice of the salt form of a drug may have a pronounced effect on the formulation of the parent compound. For example, Fenton and Warren (194) found there was no release of medicament from proflavine cream BPC, a water-in-oil emulsion containing 0.1% proflavine as the hemisulfate salt. They also investigated the release of various salts of proflavine with aliphatic carboxylic acids from water-in-oil cream emulsions. Salts formed with the water-soluble, oil-insoluble “lower” acids, such as formic and acetic acids, showed very poor release from a water-in-oil cream. The “higher” acid salts (e.g., *n*-valeric, caproic, cyclohexanecarboxylic, and caprylic) all showed increased diffusion from similar emulsions since these salts are soluble in both water and oil. Their release was even greater from oil-in-water emulsions, however, in agreement with their preferential oil solubility. The *n*-valerate salt provided the most effective water-in-oil cream. The primary factor responsible for diffusion of proflavine from a water-in-oil cream is the low hydrophilic-lipophilic balance conveyed to the salt by the acid. This finding illustrates the desirability of carefully selecting the salt anion of a cationic drug in lieu of the nature of the dosage form.

Studies of the effect of formulation on the bioavailability of warfarin sodium relative to warfarin yielded interesting results (107, 195). Absorption of warfarin upon administration of the sodium salt as a lactose-base tablet was no better than that from a similar formulation of the free acid. In fact, absorption was further depressed when the salt was formulated with starch instead of lactose. Later results indicated that the *in vitro* water dissolution rate of a warfarin sodium tablet was 350 times that of a slowly dissolving warfarin tablet formulation, yet the latter exhibited rapid and complete absorption *in vivo*. The virtual insolubility of warfarin in acidic gastric fluids precluded its absorption from the stomach. However, the strongly acidic medium was necessary for tablet disintegration, which, in turn, was critical for absorption. Following initial exposure to 0.1 *N* HCl, *in vitro* dissolution of the warfarin tablet in pH 7.4 buffer was 14 times faster than that of the sodium salt, a result that explained the otherwise contradictory *in vivo* blood level data. Therefore, absorption was ultimately dependent upon gastric emptying rate and gastric pH, as long as the formulation disintegrated properly in the stomach.

The rectal absorption of aspirin, aspirin aluminum, and

calcium carbaspirin from several suppository bases was studied in dogs (196). The absorption of aspirin aluminum from either cocoa butter or a polyethylene glycol base was poor. While the maximum salicylate levels produced by aspirin and calcium carbaspirin from the cocoa butter base occurred at a later time than from the other bases studied, minimal plasma levels were exhibited by a polysorbate 61 base formulation. The highest peak and largest area under the blood level curve were seen with calcium carbaspirin in a vegetable fatty acid glyceride base. The poor absorption of aspirin aluminum from suppositories was not unexpected since it is poorly soluble. Furthermore, as pointed out for aspirin aluminum tablets (105, 106), an insoluble aluminum compound may form on the surface of the dissolving drug, further impeding its dissolution rate and bioavailability.

Additional references on bioavailability and formulation effects are given in Table VII.

Absorption Alteration—Several years ago, clinicians claimed that certain salts of theophylline were therapeutically preferable to other salts or to the free acid (202–204). For example, Schluger *et al.* (204) found higher blood theophylline levels after administering uncoated tablets of theophylline ethylenediamine than were observed with enteric-coated tablets of choline theophyllinate. These results were at variance with the *in vivo* work of Gagliani *et al.* (202), who found that the oral ingestion of choline theophyllinate produced significantly higher blood levels than the ethylenediamine salt. This apparent discrepancy could be explained by the formulation effects of tablet coating, *etc.*, which was not discussed in the work of Gagliani *et al.* In another study, a slightly more rapid rise in blood concentration and a greater area under the curve were observed with theophylline isopropanolamine than with theophylline ethylenediamine (203). It was suggested that the difference was a result of the greater water solubility of the isopropanolamine salt.

The *in vitro* dissolution rates of the choline and isopropanolamine salts of theophylline have been observed to be three to five times greater than the ethylenediamine salt, depending on the dissolution medium (98). It has been suggested that these differences in dissolution rate are consistent with, and offer an explanation for, the clinical results.

In a comparative study of the absorption of ampicillin trihydrate and ampicillin potassium following oral administration (205), the potassium salt yielded 37% higher peak levels and a larger area under the curve. Only 36% of the administered ampicillin trihydrate was absorbed while 53% of the potassium salt was absorbed. Determining the percentage of each drug eliminated in the urine showed that 39% was eliminated following administration of the trihydrate and 52% from the potassium salt. The entire difference between the two drug forms was accounted for in the initial 4 hr postadministration.

Several studies compared blood levels obtained with erythromycin and its salts and esters. Erythromycin estolate produced blood levels that were severalfold higher than those obtained with erythromycin base or erythromycin stearate (206–208). These differences were found to persist in the fasting as well as nonfasting subjects (207), indicating that food did not appreciably alter the absorption of erythromycin estolate when given under single or

multiple dosing (207). This finding is explained by the fact that this salt is acid stable and alkaline dissociable, permitting its passage through the acid of the stomach both in fasting and nonfasting subjects (209). Accordingly, the antibacterial activity remained essentially the same when this form of erythromycin was given, regardless of the state of fasting of the subject (209).

On first inspection, the higher serum levels attained with erythromycin estolate suggest that the salt form is more readily absorbed. Also critical to efficacy, however, is the volume of distribution of the drug, since extensive binding to plasma proteins can render a drug unavailable for activity at the biophase. Therefore, the significance of blood level data greatly depends on the measure of the free or unbound fraction of total antibiotics in the blood, which more directly indicates probable therapeutic benefit.

Wiegand and Chun (210) showed that, despite the higher blood levels attained with erythromycin estolate (after correction for half-life differences), the stearate salt produced seven times more free drug in serum than did the estolate salt. This finding explained the higher total tissue levels observed on administration of the stearate. They attributed the difference to a greater serum protein binding of the intact erythromycin estolate, proving that its higher serum levels did not necessarily reflect more efficient absorption.

Marked differences have been observed following oral administration of various salts of penicillin. Penicillin G potassium has been compared with penicillin G benzathine (benzethacil) (211, 212), penicillin G hydrabamine (213), penicillin V (214), penicillin G procaine (212), and penicillin G ammonium (215). As anticipated, penicillin G potassium produced higher and earlier blood levels than penicillin G benzathine (211, 212). Furthermore, tablets of penicillin G potassium buffered with sodium citrate yielded higher peak levels than unbuffered penicillin G potassium. While the absorption of buffered tablets was apparently not significantly affected by food intake, the unbuffered tablets yielded lower average levels and irregular absorption under similar conditions.

When penicillin G potassium was compared with penicillin G hydrabamine (213), a less soluble salt, blood levels similar to those produced by penicillin G benzathine were observed. When equivalent doses were administered, the penicillemia that occurred with penicillin G hydrabamine was only one-third or one-fourth as great and was of shorter duration than that produced by penicillin G potassium.

Budolfson *et al.* (212) found that peak concentrations of penicillin G potassium were three to four times those obtained with penicillin G procaine and five to six times those of penicillin G benzathine, indicating a more rapid rate of absorption. The therapeutic action was related to the maximum concentration attained, but it also depended on the persistence of penicillemia, which was greater with penicillin G potassium than with the other two compounds. The authors suggested that the lower blood levels attained with the relatively insoluble penicillin G benzathine were caused by its destruction in the GI tract prior to absorption. This suggestion seems unlikely, however, since the drug should not degrade very rapidly as an undissolved suspension.

Because of its superior stability in gastric juice, penicillin

V produces higher blood penicillin levels than corresponding doses of penicillin G. As a result, extensive investigations have been conducted with various salts of penicillin V (99, 214–220). For instance, tablets, capsules, and oral suspensions of penicillin V acid produced significantly higher blood concentrations than comparable penicillin G preparations (214). In the same study, the average serum levels produced by the benzathine salt of penicillin V were significantly higher than comparable doses of penicillin G benzathine for the first 4 hr but lower thereafter, again illustrating the value of using an insoluble salt to prolong blood levels of an acid-unstable compound. In another study (215), penicillin V acid was shown to produce higher and more prolonged plasma concentrations than either penicillin G potassium or ammonium, whose properties were comparable.

Plasma levels were correlated with dissolution rates of various forms of penicillin V (99). As solid dosage forms, the readily soluble potassium and calcium salts produced earlier and higher blood levels in fasting subjects than either the free acid or its benzathine salt. On the other hand, when the potassium and benzathine salts were administered orally as solutions, absorption was the same, implying that the poor solubility of the benzathine salt was responsible for the inferior blood levels obtained from its solid dosage forms. Other studies found that, while the potassium salt is 40% better absorbed than the free acid in fasting subjects, both forms produce therapeutic levels when administered with food (218).

Experiments with fistulated dogs indicated that penicillin V is absorbed primarily from the stomach. Therefore, it is not surprising that the potassium salt should show higher blood levels on oral administration since it is the most soluble salt in gastric pH (216). In accordance with this observation, it was also reported that the benzathine salt exhibited higher serum levels in patients with gastric achlorhydria (pernicious anemia) than in patients with normal gastric function (219). Differences in gastric emptying time may also explain this result.

Several studies compared the absorption of tetracycline and its salts (103, 221, 222). For example, serum concentrations in dogs and humans showed that a phosphate complex salt of tetracycline was absorbed more rapidly and gave higher blood levels during the first 6–8 hr than did tetracycline hydrochloride (221). The total amount of drug absorbed was about twice as great with the former compound.

Another study (222) suggested that tetracycline base produced higher blood levels than tetracycline hydrochloride. However, a subsequent investigation (223) showed that, in the absence of adjuvants or fillers, tetracycline hydrochloride and tetracycline base were absorbed equally well. Results obtained in this same study indicated that tetracycline hydrochloride encapsulated with citric acid produced higher serum concentrations than tetracycline hydrochloride mixed with hexametaphosphate or the phosphate complex salt of tetracycline.

In a study comparing urinary excretion rates and *in vitro* dissolution, the absorption of tetracycline and tetracycline phenolsulfonaphthaleinate was rate limited by their dissolution rates, whereas tetracycline hydrochloride absorption was rate limited by the absorption process itself (103).

Several lincomycin salts were studied for their comparative availability (224). In particular, the blood levels obtained with the relatively water-insoluble hexadecylsulfamate salt were compared to those of the hydrochloride following oral administration. Higher and extended whole blood and serum concentrations were obtained in mice, rats, and dogs with the hexadecylsulfamate. However, subcutaneously administered lincomycin did not produce significantly different fractions absorbed, regardless of which salt was administered. It is not known whether the greater area under the curve with oral administration of lincomycin hexadecylsulfamate is due to greater absorption from the GI tract, slower renal clearance, or greater enterohepatic circulations.

Salts of streptomycin, neomycin, viomycin, and streptothricin have been formed with: (a) polyacrylic acids, (b) sulfonic or phosphorylated polysaccharides, and (c) natural polycarboxyl acids from a series of polyuronic substances and polysaccharide derivatives containing carboxyl groups (18). The report indicated that these salts were absorbed from the injection locus primarily by the lymph system. Blood levels from the salts were generally lower but were maintained for a longer time than the equivalent amount of antibiotic alone, and higher concentrations of longer duration may actually be produced in the lymphatic drainage.

The influence of salt formation on the onset and duration of pharmacological activity also was illustrated with tolbutamide and several of its salts (101). Following oral administration, the sodium salt produced a rapid decrease in blood sugar level followed by a rapid recovery. By contrast, the free acid of tolbutamide caused a slow and prolonged drop in blood sugar level, a preferred effect since the chance of hypoglycemic shock would be lessened. This finding also illustrates the often overriding influence of the actual disease state on the choice of drug form.

Additional references on the implications of salt formation on absorption are listed in Table VIII.

Pharmacokinetics—Because of the various new properties that are usually imposed on a compound by salt formation, the pharmacokinetics of the drug necessarily change as a function of these properties.

For example, a pharmacokinetic evaluation comparing ampicillin sodium and potassium with ampicillin trihydrate was performed after oral administration to beagle dogs (243). The absorption rate constants of the sodium and potassium salts, which were similar, proved significantly greater than the rate constant of ampicillin trihydrate, resulting in earlier, higher peak concentrations with two to three times higher serum concentrations during the 1st hr. Yet, any differences between the fraction absorbed for the three products were not statistically significant. Apparently, although dissolution of the ampicillin trihydrate was the rate-limiting step in its absorption, the overall extent of bioavailability remained unaffected.

An interesting study of the biliary excretion of erythromycin base and erythromycin estolate was reported (244). The biliary excretion of erythromycin base was high, while that of erythromycin estolate was much lower; preferential secretion of erythromycin in the bile could partially account for the lower serum levels exhibited by the base. However, the proportion of the ingested dose secreted in the bile was small, and the total amounts in-

Table VIII—Additional References on Bioavailability and Absorption Alteration

Topic	Reference
Blood levels produced by three theophylline-containing elixirs	225
Naproxen oral absorption characteristics	226
Effect of food on absorption of a new form of erythromycin propionate	227
Effect of the anion on the absorption of tetracycline from the rat stomach	186
Blood levels following oral administration of different preparations of novobiocin	228
Absorption of iopanoic acid and its sodium salt	229
Oral absorption of secobarbital (quinalbarbitone) and its sodium salt	230
Absorption rate of barbiturates in humans	231
Morphine and atropine mucate	232
Excretion of buphenium salts in urine of human volunteers	233
Polymethylene bis(isothiuronium) salts: antituberculosis activity	234
Prolonged antitussive action of a resin-bound noscapine preparation	235
Pharmacology of sulfapyridine and sulfathiazole	236
Evaluation of plasma concentrations of propoxyphene utilizing a hybrid principal component analysis of variance technique: equimolar doses	237
Antrycide, a new trypanocidal drug	238
Pralidoxime methanesulfonate: plasma levels and pharmacokinetics after oral administration to humans	239
Intestinal absorption of pralidoxime and other aldoximes	240
Blood plasma levels and elimination of salts of pralidoxime (2-PAM) in humans after oral administration	241
Enhancement of GI absorption of a quaternary ammonium compound by trichloroacetate	242

involved were not sufficient to account entirely for the differences in serum concentrations attained. Undoubtedly, the protein binding studies of Wiegand and Chun (210) (discussed under *Absorption Alteration*) more satisfactorily explain the difference in serum concentrations.

Often, salt formation can be used to modify drug absorption and dose tolerance favorably. For example, aminosalicic acid exhibits a short half-life and, therefore, requires large and frequent doses which may cause gastric irritation. Consequently, different chemical forms such as salts have been prepared (119, 245–247) to reduce the incidence of gastric irritation, increase absorption, and prolong blood levels.

Aminosalicic acid is an interesting example in other ways; considerable confusion about this drug exists because many fail to recognize its nonlinear pharmacokinetics. Several definitive studies were reported regarding the absorption of the acid and its sodium, potassium, and calcium salts from solution, suspension, and tablet formulations (245, 246). Comparison of the relative bioavailabilities of aminosalicic acid suspended in water and its salts dissolved in water showed that, while differences in rate of absorption were found to exist, absorption of both the acid and its salts was essentially complete. Absorption of the free acid from tablets reached only 77% of the dose, whereas that of the tableted salts was rapid and complete.

Regardless of formulation, the area under the plasma concentration–time curve of unmetabolized drug from free acid administration was less than that for the salts. This result was attributed to concentration-dependent metabolism during absorption: when the rate of absorption is high, the metabolic processes become saturated and more unmetabolized drug remains in the blood; conversely,

Table IX—Additional References on Bioavailability and Pharmacokinetics

Topic	Reference
Pharmacodynamics of fosfomycin (phosphonomycin) after intravenous administration to humans	248
Pharmacodynamics of phosphonomycin after oral administration to humans	249
Comparative studies on distribution, excretion, and metabolism of ³ H-hydroxyzine and its ¹⁴ C-methiodide in rats	250
Pharmacokinetics of ampicillin trihydrate, ampicillin sodium, and dicloxacillin sodium following intramuscular injection	251
Physiological disposition of fenoprofen in humans: pharmacokinetic comparison of calcium and sodium salts administered orally	252

when the absorption rate is low, as for the free acid, a higher percentage of drug is metabolized.

Additional references regarding bioavailability and pharmacokinetics are presented in Table IX.

GENERAL PHARMACY

Pharmacological Effect—Chlorpromazine hydrochloride and quaternary chlorpromazine chloride were investigated with respect to their effects on the central nervous system (CNS) (253). The quaternized compound was less potent and more toxic in rodents than the parent tertiary compound.

Naloxone, an effective opiate antagonist, is generally used as the hydrochloride salt; however, the drug has a very short duration of action. The mucate salt was prepared to extend its duration of action, since mucic acid is only slightly soluble in water (254). In a test on the blocking of morphine activity in mice, however, the mucate salt did not differ in duration from the hydrochloride. These investigators assumed the same receptor site for naloxone as for morphine and, since Heron's (232) work suggested that the receptor had a greater affinity for morphine mucate than for the free base, it also should have a greater affinity for naloxone mucate. The results disproved this hypothesis. Furthermore, this theory implies that intact salt reaches the receptor, which is highly unlikely, regardless of whether the drug is administered as a solution or as a suspension.

A series of salts of 9-aminoacridine and its derivatives was prepared and screened for antifungal and antibacterial activity (255–257). By using salts of fatty acids, the antifungal action was found to parallel the length of the carbon chain of the anion, with maximal activity occurring with acridine caproate, undecylate, and undecylenate (where undecylenic acid also exhibits some intrinsic antifungal activity) (255). This result appears reasonable, because these salts would be more lipid soluble and could be expected to pass through the cell wall of the infecting organism more readily, probably as an ion-pair.

The efficacy of bases or salts as topical anesthetics for relieving cutaneous itch, burning, and pain in unbroken skin has also been examined (258). In these experiments, itching and pricking were induced by an alternating current of low amperage and voltage applied to the skin or by exposure of the skin to UV light. Interestingly, aqueous solutions of salts of the local anesthetics did not alleviate itching or burning in any of the subjects, although saturated solutions of their bases in a mixture of water, 40%

Table X—Additional References on General Pharmacy and Pharmacological Effect

Topic	Reference
Differential excretion of bromide and chloride ions and its role in bromide retention	259
Pharmacological study of calcium methionate	260
Synthesis and <i>in vitro</i> fungistatic evaluation of some <i>N</i> -substituted amides and amine salts of sorbic acid	261
Antiamoebic studies on clomoxiquin [5-chloro-7-[[[(3-diethylaminopropyl)amino]methyl]-8-quinolinol] <i>in vitro</i> and in experimentally infected animals	262
Adjunctive value of oral prophylaxis with the oximes pralidoxime (2-PAM) lactate and pralidoxime methanesulfonate to therapeutic administration of atropine in dogs poisoned by inhaled sarin vapor	263
Pralidoxime (2-hydroxyiminomethyl- <i>N</i> -methylpyridinium) methanesulfonate and atropine in the treatment of severe organophosphate poisoning	264
Efficacy and limitations of oxime-atropine treatment of organophosphorus anticholinesterase poisoning	265
Antitussive activity of enoxolone (glycyrrhetic acid) and its derivatives	266
Pharmacological properties of glycyrrhetic acid hydrogen succinate (disodium salt)	267
Ganglionic blocking activity of diastereomeric dimethylaminobornyl acetates and their methiodides	268
A new potent nonnarcotic antitussive, 1-methyl-3-[bis(2-thienyl)methylene]piperidine: pharmacology and clinical efficacy	269

alcohol, and 10% glycerol were claimed to be effective. Such transport phenomena across the stratum corneum are often dependent on the polarity of the drug and vehicle and on the binding of the drug to keratin.

Additional references on pharmacological effects can be found in Table X.

Dialysis—Dialysis through a cellophane membrane of the hydrochloride or sodium salts has been studied with several drugs (270). In many cases, it appeared that the ionic form of the drug was bound to the membrane whereas the nonionized form was not. Ephedrine hydrochloride presented an interesting example, however, since it dialyzed considerably faster than its corresponding base. It was theorized that the chloride ion dialyzed rapidly, enhancing the rate of dialysis of the ephedrine ion. Accordingly, when chloride ion was present on both sides of the membrane, the observed rate of dialysis for the ephedrine ion was comparable to the ephedrine base.

The diffusion of sodium chloride through a lipoprotein interface was very slow, especially if calcium chloride was present on both sides of the interface (271). In the presence of low concentrations of choline chloride or carbamylcholine chloride, the diffusion of sodium chloride is more rapid. Apparently, choline salts are able to increase the permeability of the lipoprotein to salts, which may relate to the physiological action of choline salts.

Miscellaneous—Release rates were determined for aminophylline, ephedrine alkaloid, and ephedrine hydrochloride from theobroma oil suppositories containing nonionic surfactants (133). While surfactants with hydrophilic-lipophilic balance (HLB) values less than 11 only minimally affected release rate, rates increased with surfactants of HLB values greater than 11. Under optimal conditions, aminophylline was faster than ephedrine hydrochloride which, in turn, was superior to the ephedrine base.

Willis and Banker (272) reported on the formation of polymer-drug salts as an approach to the physicochemical design of dosage forms. Poly(methyl vinyl ether/maleic

anhydride) salts of methapyrilene were prepared and tested with the free base for *in vitro* dissolution and dialysis. Their dissolution and dialysis rates were not appreciably different from the free drug or its hydrochloride salt. Various poly(methyl vinyl ether/maleic anhydride) hemi-ester salts of methapyrilene exhibited substantially slower release than the polymer ether salts, hydrochloride salt, or free base forms. Polymer-drug salts thus appear to have promise.

A series of metallic salts of edetic (ethylenediaminetetraacetic) acid were tested *in vitro* to determine their effect on blood coagulation (273). The results showed that only the dipotassium and disodium salts had any effect on coagulation. It was theorized that the lack of anticoagulant activity resulted from an almost complete suppression of ionization of the heavy metal salts.

Interesting research regarding the angina-preventive effect of some chromone-2-carboxylate salts showed a direct correlation between biological activity and pKa of the salt-forming amines (274).

Lin *et al.* (112) investigated the relationship between salt form and biological activity of a given antihypertensive. While the intrinsic dissolution rates of the dihydrochloride and disulfate salts were many fold greater than the monohydrochloride, the hypotensive potencies of the salts did not differ significantly from one another in an anesthetized dog study. Yet, when administered to renal hypertensive dogs, the dihydrochloride and disulfate salts produced greater hypotensive effects than did the monohydrochloride.

TOXICOLOGICAL CONSIDERATIONS

Toxicity of Salt Ion—Any discussion regarding the toxicity of salts of a drug must consider the pharmacological properties of the cation or anion used to form the salt as well as those of the free drug, since any of these may produce toxic effects. The toxicology of several ions that are commonly used to form salts and that are relevant to this review were discussed in depth (275).

Toxicity from ingestion of calcium salts of drugs is rare. If hypercalcemia occurs, however, calcium deposits in the kidney can bring on a reduction of renal function. The principal toxic effects of lithium also involve the kidneys. When small amounts of lithium are taken, no apparent damage occurs; yet large amounts of the metal can lead to irreversible damage. An apparent correlation was observed between lithium dosage and sodium intake (276). When lithium dosage was low or sodium intake was high, rats were able to excrete all lithium given and sustained a reversible polyuria. Conversely, if large amounts of lithium were administered to the rats or if their sodium intake was lowered, they incurred irreversible kidney damage. Ammonium ion, although it serves a major role in maintenance of the acid-base balance of the body, can be toxic in high concentrations and initiate CNS derangements.

Sulfate ions given orally tend to be minimally absorbed and may act as a laxative. The nitrate ion is irritating to the GI tract, causing nausea and gastric distress. Also, intestinal bacteria may convert the nitrate ion to nitrite which oxidizes hemoglobin to methemoglobin. The citrate ion, an intermediary in carbohydrate metabolism, can form a soluble complex with calcium which is poorly dissociable

and rarely causes any toxic reactions. While tartrate ions are usually absorbed minimally from the GI tract, high concentrations reaching the circulation can cause renal damage.

Acetate and lactate ions are normal metabolites and appear to be well tolerated in relatively large amounts. Iodide and bromide ions can produce conditions known as iodism and bromidism, respectively. Bromide intoxication occurs quite frequently, since bromides are used as ingredients in some nonprescription preparations (277–280). Bromide is slowly excreted by the kidney (its half-life is 12 days) and tends to accumulate when taken for prolonged periods or when used by patients with decreased renal function (277).

Toxicity of Salt Form—Provided the salt-forming agents are nontoxic, the relative toxicities of a series of salts of a compound are often observed to reflect directly their absorption rates. For example, the toxicities of dibromide, dichloride, diiodide, and dimethylsulfate salts of quinapyramine³, a trypanocidal drug, were determined (238). The sparingly soluble halogen salts were much less toxic subcutaneously or intramuscularly than the freely soluble dimethylsulfate, yet all salts showed about equal toxicity upon intravenous administration. The difference in toxicities obviously resulted from rapid absorption of the methylsulfate compared to the slowly absorbed, poorly soluble halogen salts. Similar reasoning has been used to explain the acute oral toxicity of propoxyphene hydrochloride in rodents, which is twice that of equimolar doses of the napsylate salt (281).

Several salts of benzphetamine and etryptamine were prepared as potential sustained-release formulations (114). The water solubility, *in vitro* dissolution rates at pH 1.0 and 7.2, and the median lethal times (LT₅₀) were determined for each salt. Both the LT₅₀ and LD₅₀ (determined on only a few salts) increased as the *in vitro* dissolution rate at pH 7.2 decreased. While dissolution at pH 1.0 did not correlate well with toxicity, the LT₅₀'s were inversely related to the square root of the dissolution rates at pH 7.2.

Toxicity studies comparing iopanoic acid, a cholecystographic contrast medium, with its sodium salt (115) showed that the salt form has 10-fold greater toxicity. The LD₅₀'s of the free acid and the salt were 22 and 2.32 g/kg, respectively. It was postulated that the free acid precipitated from the sodium salt upon its reaction with gastric hydrochloric acid. The fine, amorphous particles of precipitated acid had a greatly increased surface area and, therefore, dissolved more rapidly than even fine crystals of the free acid. The faster and more complete drug absorption then resulted in increased toxicity.

Salts exhibiting greater water solubility than their parent compounds or less soluble salts are not always more toxic. For example, various inorganic and organic ions were used to prepare salts of methyl pyridinium-2-aldoxime that would have greater water solubility and would eliminate undesirable side effects due to the iodide ion (95). Even though the aqueous solubility of the majority of these salts was many times greater than the iodide, their toxicity on a molar basis was not significantly different, with the exception of the dihydrogen phosphate salt which was 15%

³ Arityride.

Table XI—Additional References on Toxicological Considerations

Topic	Reference
Toxicity and absorption of 2-sulfanilimidopyridine and its soluble sodium salt	285
Sorbic acid as a fungistatic agent for foods: harmlessness of sorbic acid as a dietary component	286
Toxicity and distribution of erythromycin	287
Further toxicological studies with erythromycin	288
Pharmacology and toxicology of erythromycin estolate	289
Erythromycin propionate (propionylethromycin): a review of 20,525 case reports for side-effect data	290
New class of antibiotic salts of reduced toxicity	22
GI intolerance to oral iron preparations	291
Comparative toxicology of iron compounds	292
Influence of the dissolution rate of lithium tablets on side effect	123
Toxicity and tissue distribution studies on the hydrochloride, bismuth iodide complex, and a resinate of emetine	293
Bacitracin zinc in pharmaceutical preparations	145
New approach to quaternary ammonium compounds	151
Pharmacology of choline theophyllinate	294

more toxic. Further research with oximes revealed that other salts are also toxic (282).

GI bleeding is a common toxic effect of aspirin for a large percentage of the population. Consequently, a search was initiated for an aspirin derivative that would not induce GI blood loss (283). All compounds prepared, however, including the sodium and calcium salts, caused GI hemorrhage with a severity similar to aspirin.

Polyene antibiotics are potent antifungal agents but bear considerable toxicity. Even though the methyl ester hydrochlorides of these compounds are more soluble, they retain almost all of their antifungal activity and, more significantly, show a uniform decrease in toxicity compared to their parent compounds (284).

Additional references on toxicological considerations of salt formation are given in Table XI.

CONCLUSIONS

Salt formation is a means of altering the physical, chemical, and biological characteristics of a drug without modifying its chemical structure. Clearly, the salt form can have a dramatic influence on the overall properties of the parent compound. At present, selecting a salt form that exhibits the desired combination of properties is a difficult semiempirical choice. Pharmaceutical scientists now recognize these facts and are beginning to study the effects of different salt forms on the physicochemical properties, bioavailability, and toxicity of drug substances.

Although now only a few generalizations are available to predict the effect of particular salt forms on the characteristics of a drug, perhaps in time it will be possible to evolve increasingly more powerful generalizations regarding the effect of a salt on the properties of its parent compound. In addition, we predict that polymer-drug salts will have a revolutionary effect on future trends in drug therapy, particularly in the areas of reducing drug toxicity and in controlling the release profile of novel drug delivery systems.

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Electronic Patent Application Fee Transmittal				
Application Number:		10378956		
Filing Date:		03-Mar-2003		
Title of Invention:		Multiple-component solid phases containing at least one active pharmaceutical ingredient		
First Named Inventor/Applicant Name:		Michael J. Zaworotko		
Filer:		Jessica Russell Colantonio/Holly Johnson		
Attorney Docket Number:		U0157.70023US01		
Filed as Small Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
Submission- Information Disclosure Stmt	2806	1	90	90
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Electronic Acknowledgement Receipt	
EFS ID:	23839307
Application Number:	10378956
International Application Number:	
Confirmation Number:	4742
Title of Invention:	Multiple-component solid phases containing at least one active pharmaceutical ingredient
First Named Inventor/Applicant Name:	Michael J. Zaworotko
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Deposit Account	232825
Authorized User	COLANTONIO, JESSICA R.
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	
Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	U015770023US01-TRN-JRC.pdf	24717 0a1e222caf0bcc925ee7b60fc2d706cf7092f71	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	U015770023US01-FEE-JRC.pdf	31561 3d8f9706424052e8d569393b40524868e66510df	no	1
Warnings:					
Information:					
3		U015770023US01-IDS-JRC.pdf	37061 0337dee935f348a120ae5e94b0fefaed147260e2	yes	4
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Transmittal Letter		1	3	
	Information Disclosure Statement (IDS) Form (SB08)		4	4	
Warnings:					
Information:					
4	Non Patent Literature	No_author_listed_ICH_Harmonised_triparite_Guideline_1999_v4_QC.pdf	2442781 747835b8e0b15956ab114a3cc6d145103da923a4	no	46
Warnings:					
Information:					
5	Non Patent Literature	No_author_listed_The_United_States_Pharmacopeia_2000_c941_p2005_QC.pdf	497148 7976f7928a1e19a239b25608277a92295959180a	no	5
Warnings:					
Information:					
6	Non Patent Literature	Abourahma_et_al_J_Chem_Crystallogr_1995_v25_p731_QC.pdf	440712 87887d79f79167c5745ee6be4805e13ff9e14434	no	6
Warnings:					
Information:					

7	Non Patent Literature	Almarsson_et_al_Pharm_Pat_Analyst_2012_v1_p313_QC.pdf	1362507 9194f56d9be310e03b80304c8515c4f611ce05a	no	15
Warnings:					
Information:					
8	Non Patent Literature	Bedu-Addo_Pharmaceutical_Technology_2004_p10_QC.pdf	93037 a0e5062a8456c8cb023b8a7e5227fe0a8eb76275	no	9
Warnings:					
Information:					
9	Non Patent Literature	Byrn_et_al_Pharm_Res_1995_v12_p945_QC_QC.pdf	1718212 3d6ae40a9d1212bd1ae60108dce3b134565837f1	no	10
Warnings:					
Information:					
10	Non Patent Literature	Berge_et_al_J_Pharm_Sci_1977_v66_p1_QC.pdf	5706721 c4acd836130f7ca6fe348120d8354a20a3c40901	no	19
Warnings:					
Information:					
11	Fee Worksheet (SB06)	fee-info.pdf	30437 ff4575d6ce1373d374f8c75b2006474d069166d9	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			12384894		
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. <u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.					

TRANSMITTAL FORM <i>(to be used for all correspondence after initial filing)</i>	Application Number	10/378,956-Conf. #4742
	Filing Date	March 3, 2003
	First Named Inventor	Michael J. Zaworotko
	Art Unit	1627
	Examiner Name	S. Javanmard
Total Number of Pages in This Submission	Attorney Docket Number	U0157.70023US01

ENCLOSURES (Check all that apply)		
☒ Fee Transmittal Form ☐ Fee Attached ☐ Amendment/Reply ☐ After Final ☐ Affidavits/declaration(s) ☐ Extension of Time Request ☐ Express Abandonment Request ☒ Information Disclosure Statement ☐ Certified Copy of Priority Document(s) ☐ Reply to Missing Parts/ Incomplete Application ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53	☐ Drawing(s) ☐ Licensing-related Papers ☐ Petition ☐ Petition to Convert to a Provisional Application ☐ Power of Attorney, Revocation Change of Correspondence Address ☐ Terminal Disclaimer ☐ Request for Refund ☐ CD, Number of CD(s) _____ ☐ Landscape Table on CD	☐ After Allowance Communication to TC ☐ Appeal Communication to Board of Appeals and Interferences ☐ Appeal Communication to TC (Appeal Notice, Brief, Reply Brief) ☐ Proprietary Information ☐ Status Letter ☒ Other Enclosure(s) (please Identify below): Form PTO-1449 Copies of Cited References
Remarks		

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT			
Firm Name	WOLF, GREENFIELD & SACKS, P.C.		
Signature	/Jessica R. Colantonio/		
Printed name	Jessica R. Colantonio, Ph.D.		
Date	October 20, 2015	Reg. No.	66,132

Certificate of Electronic Filing Under 37 CFR 1.8 I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4). Dated: <u>October 20, 2015</u> Electronic Signature for Holly E. Johnson: /Holly E. Johnson/	
--	--

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor: Michael J. Zaworotko
Application No.: 10/378,956
Confirmation No.: 4742
Filed: March 3, 2003
For: MULTIPLE-COMPONENT SOLID PHASES
CONTAINING AT LEAST ONE ACTIVE
PHARMACEUTICAL INGREDIENT
Examiner: Sahar Javanmard
Art Unit: 1627

CERTIFICATE OF ELECTRONIC FILING UNDER 37 C.F.R. § 1.8

The undersigned hereby certifies that this paper, along with any paper referred to as being attached or enclosed, is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4), on the 20th day of October, 2015.

/Holly E. Johnson/
Holly E. Johnson

MAIL STOP AMENDMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

STATEMENT FILED PURSUANT TO THE DUTY OF
DISCLOSURE UNDER 37 C.F.R. §§ 1.56, 1.97 AND 1.98

Madam:

Pursuant to the duty of disclosure under 37 C.F.R. §§ 1.56, 1.97 and 1.98, the undersigned requests consideration of this Information Disclosure Statement.

PART I: Compliance with 37 C.F.R. § 1.97

This Information Disclosure Statement has been filed more than three months after the filing date of this application and after the mailing date of a first Office Action, but before the mailing date of any of a Final Action under 37 C.F.R. § 1.113, a Notice of Allowance under 37 C.F.R. § 1.311, or an action that otherwise closes prosecution in this application.

Please charge our Credit Card in the amount of \$90.00 covering the fee set forth in 37 C.F.R. § 1.17(p).

PART II: Information Cited

The undersigned hereby makes of record in the above-identified application the information listed on the attached form PTO-1449 (modified PTO/SB/08). The order of presentation of the references should not be construed as an indication of the importance of the references.

PART III: Remarks

Documents cited anywhere in the Information Disclosure Statement are enclosed unless otherwise indicated. It is respectfully requested that:

1. The Examiner consider completely the cited information, along with any other information, in reaching a determination concerning the patentability of the present claims;
2. The enclosed form PTO-1449 (modified PTO/SB/08) be signed by the Examiner to evidence that the cited information has been fully considered by the United States Patent and Trademark Office during the examination of this application;
3. The citations for the information be printed on any patent which issues from this application.

By submitting this Information Disclosure Statement, the undersigned makes no representation that a search has been performed, of the extent of any search performed, or that more relevant information does not exist.

By submitting this Information Disclosure Statement, the undersigned makes no representation that the information cited in the Statement is, or is considered to be, material to patentability as defined in 37 C.F.R. § 1.56(b).

By submitting this Information Disclosure Statement, the undersigned makes no representation that the information cited in the Statement is, or is considered to be, in fact, prior art as defined by 35 U.S.C. § 102.

Notwithstanding any statements by the undersigned, the Examiner is urged to form his or her own conclusion regarding the relevance of the cited information.

Application No.: 10/378,956
Conf. No.: 4742

- 3 -

Art Unit: 1627

An early and favorable action is hereby requested.

The Director is hereby authorized to charge any deficiency or credit any overpayment in the fees occasioned by the filing of this Information Disclosure Statement to our Deposit Account No. 23/2825 under Docket No. U0157.70023US01 from which the undersigned is authorized to draw.

Respectfully submitted,

By: _____/Jessica R. Colantonio/_____
Jessica R. Colantonio, Ph.D.,
Reg. No. 66,132
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
Telephone: (617) 646-8000

Docket No.: U0157.70023US01
Date: October 20, 2015

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875				Application or Docket Number 10/378,956		Filing Date 03/03/2003		☐ To be Mailed	
ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO									
APPLICATION AS FILED – PART I									
(Column 1)		(Column 2)							
FOR		NUMBER FILED		NUMBER EXTRA		RATE (\$)		FEE (\$)	
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))		N/A		N/A		N/A			
☐ SEARCH FEE (37 CFR 1.16(k), (l), or (m))		N/A		N/A		N/A			
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))		N/A		N/A		N/A			
TOTAL CLAIMS (37 CFR 1.16(j))		minus 20 =		*		X \$ =			
INDEPENDENT CLAIMS (37 CFR 1.16(h))		minus 3 =		*		X \$ =			
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))		If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).							
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))									
						TOTAL			
* If the difference in column 1 is less than zero, enter "0" in column 2.									
APPLICATION AS AMENDED – PART II									
(Column 1)		(Column 2)		(Column 3)					
AMENDMENT	10/20/2015	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))	* 29	Minus	** 26	= 3	X \$40 =		120	
	Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X \$210 =		0	
	☐ Application Size Fee (37 CFR 1.16(s))								
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))								
						TOTAL ADD'L FEE		120	
(Column 1)		(Column 2)		(Column 3)					
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))	*	Minus	**	=	X \$ =			
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X \$ =			
	☐ Application Size Fee (37 CFR 1.16(s))								
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))								
						TOTAL ADD'L FEE			
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3. ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20". *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3". The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.									

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

LIE
/LAMONT MCLAUCHLIN/



UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/378,956	03/03/2003	Michael J. Zaworotko	U0157.70023US01	4742
23628	7590	02/25/2016	EXAMINER	
WOLF GREENFIELD & SACKS, P.C.			JAVANMARD, SAHAR	
600 ATLANTIC AVENUE			ART UNIT	PAPER NUMBER
BOSTON, MA 02210-2206			1627	
			NOTIFICATION DATE	DELIVERY MODE
			02/25/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents_eOfficeAction@WolfGreenfield.com
WGS_eOfficeAction@WolfGreenfield.com

Office Action Summary	Application No. 10/378,956	Applicant(s) ZAWOROTKO ET AL.	
	Examiner SAHAR JAVANMARD	Art Unit 1627	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10/20/15.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

- 5) ☒ Claim(s) 25,28,37,39-51,53-60 and 62-66 is/are pending in the application.
5a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 6) ☐ Claim(s) ____ is/are allowed.
- 7) ☒ Claim(s) 25,28,37,39-51,53-60 and 62-66 is/are rejected.
- 8) ☐ Claim(s) ____ is/are objected to.
- 9) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

- a) ☐ All b) ☐ Some** c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) ☒ Notice of References Cited (PTO-892) | 3) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)
Paper No(s)/Mail Date ____. | 4) ☐ Other: ____. |

DETAILED ACTION

Status of the Application

The present application is being examined under the pre-AIA first to invent provisions.

This Office Action is in response to applicant's arguments filed on October 20, 2015. Claim(s) 25, 28, 37, 39-51, 53-60, and 62-66 are pending and examined herein.

Response to Arguments

The outstanding nonstatutory double patenting rejection is hereby maintained as a result of Applicant's decision to hold said rejection in abeyance.

Applicant's arguments with respect to the 102(b) rejection of claims 25, 28, 39-42, 48-49, and 58 as being anticipated by McCoy (CA 1148020A1) have been fully considered. Applicant argues:

"The equal amounts of cocrystallizer disclosed by McCoy are equal amount by weight, not equal amount by moles. In contrast to the McCoy, the present claims require preparation of a co-crystal having stoichiometric proportions of the active pharmaceutical ingredient (API) and the selected co-crystal former."

Further, Applicant argues:

"McCoy discloses freeze drying of the mixture of amino acid material and soluble edible cocrystallizer material. (McCoy, page 7, lines 17-19). One of ordinary skill in the art would understand freeze drying to produce an amorphous solid or a mix of crystalline and amorphous phase..."

In view of the arguments above, Examiner is persuaded and said 102(b) is hereby withdrawn.

Examiner respectfully notes, however, that while the McCoy reference may not disclose each and every element of the claimed invention in an anticipatory manner, said reference would still render the instant invention obvious (not including claim 28). Specifically, as set forth on record previously and as discussed below, McCoy teaches "an effective amount of cocrystallizer material will be such that the ratio by weight of the amount of cocrystallizer to the amount of edible amino acid salt is from about 0.9:1 to about 6:1". As pointed out by Applicant, McCoy teaches "by weight" and not in "stoichiometric proportions" as instantly claimed. Nonetheless, the range disclosed for the ratio between cocrystallizer and edible amino acid salt would encompass a cocrystal that is also stoichiometrically proportional. Therefore, it is the opinion of the Examiner that although McCoy does not teach specific examples of an API and co-crystal former in stoichiometric proportions, the range of 0.9:1 to about 6:1 embraces such proportions to be possible.

Applicant's arguments with respect to the 103(a) rejection of claims 25, 28, 37, 39-43, 46-51, 53-60, and 62-66 as being unpatentable over Huffman (US Patent No. 3,664,858) of record have been fully considered and are not fully persuasive.

Applicant argues:

"Huffman is not analogous art as required by MPEP §2141.01(a) as described above because it is not from the same field of endeavor as the claimed subject matter and the reference is not reasonably pertinent to the problem faced by the inventors. With respect to the field of endeavor, the present claims are directed to methods relating to co-crystal formation with an active pharmaceutical ingredient (API) and therefore relate to the field of pharmaceutical arts. Huffman is related to improved projection transparencies, which is not the same field of endeavor as the pharmaceutical arts."

With respect to this argument, Examiner respectfully notes that the instant claims are drawn to a method for designing and preparing a cocrystal, wherein the first chemical functionality is an API, with certain requirements as set forth in claim 25 and a cocrystal former. Although the claim 25 requires an API, it does not mandate that the endeavor relate to the pharmaceutical arts. The reason or motivation to modify a reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. While there must be motivation to make the claimed invention, there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention. MPEP 2144. Moreover, it is respectfully noted that many of the acids taught in Huffman are in fact commonly employed in the pharmaceutical art, namely acids of ascorbic, succinic, malonic, oxalic, glyoxylic, and glycolic (references can be provided if requested). Therefore, based on the foregoing reasons, said rejection is hereby maintained/modified for claim 25 and dependent claims thereon. The rejection is withdrawn for claim 58 and dependent claims thereon

The new rejections of record are set forth in the Non-Final Office action below as necessitated by amendment.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent

and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit <http://www.uspto.gov/forms/>. The filing date of the application will determine what form should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to <http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp>.

Claims 25, 28, 37, 39-51, 53-60, and 62-66 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 37-50 and 52-58 of copending Application No. 14/179,862. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending claims are drawn to a pharmaceutical composition comprising a co-crystal comprising an API and a co-former (see claims for details), whereas the instant claims are drawn to the method of designing said co-crystals. The two inventions overlap greatly in scope and the utilities are the same.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 25, 39-42, 46-51, 53-60, and 62-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCoy (CA 1148020A1) of record.

McCoy teaches improved amino acid food additive comprising a uniform cocrystalline matrix of (1) an amino acid material, and (2) an "effective amount of a soluble edible cocrystallizer material, wherein said improved amino acid food additive is better-tasting, more stable and less hygroscopic than the amino acid material alone.

McCoy teaches the amino acid material is preferably selected from the group consisting of: lysine, tryptophan, methionine, threonine, phenylalanine, leucine, valine, isoleucine, histidine, cystine, cysteine, their derivatives, their salts and mixtures thereof. All nutritionally useful amino acids, their derivatives, particularly their salts and mixtures thereof are contemplated. The other essential component of the improved amino acid food additive is a soluble, edible, cocrystallizer material preferably selected from the group consisting of: alkali and alkaline earth metal salts of halides, phosphates and nitrates, polyhydric alcohols, crystalline cellulose, crystalline starches, crystalline organic acids and their salts, and mixtures thereof (page 6-7; page 15, Table II).

McCoy teaches the method comprises dissolving at least one amino acid material in water along with an effective amount of at least one edible cocrystallizer

material. The term "an effective amount" means "enough" to enable successful dehydration of the amino acid cocrystallizer solution. Then the solution is preferably neutralized to form a salt of the amino acid. Generally, an effective amount of cocrystallizer material will be such that the ratio by weight of the amount of cocrystallizer to the amount of edible amino acid salt is from about 0.9:1 to about 6:1. Preferably, equal amounts of amino acid and cocrystallizer are used. The final pH range of the solution should be from about 2 to 7 and more preferably 4 to 7.

McCoy teaches the amount of cocrystallizer to the amount of edible amino acid salt by weight and not in stoichiometric proportions.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have envisioned cocrystals comprising a first chemical functionality and a cocrystal former by weight as taught by McCoy as well as in stoichiometric amounts to arrive at the instant invention. McCoy teaches the amount of cocrystallizer to the amount of edible amino acid salt is from about 0.9:1 to about 6:1, the range disclosed for the ratio between cocrystallizer and edible amino acid salt would encompass a cocrystal that is also stoichiometrically proportional. Therefore, the skilled artisan would have appreciated that although McCoy does not teach specific examples of an API and co-crystal former in stoichiometric proportions, the range of 0.9:1 to about 6:1 embraces the possibility of such proportions.

McCoy identifies the amino acid food additive comprising a uniform cocrystalline matrix of (1) an amino acid material, and (2) an "effective amount of a soluble edible cocrystallizer material, however, specific examples wherein the homo- and

heterosynthons as required by claims 50, 51, 53-57, 59, 60, and 62-66 are not explicitly exemplified.

Moreover, McCoy does not specifically teach the identification of the synthon from the crystal structure.

As discussed above, McCoy teaches specific amount of amino acid to co-crystallizer.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have envisioned the co-crystals as taught by McCoy to have also envisioned that the potential choices of amino acid material and cocrystallizer as taught could be formed in combinations with the same functionalities, giving rise to a homosynthon, or two different functionalities, giving rise to heterosynthons. Therefore, preparing and identifying the cocrystals, as required by the limitations of the instant claims, are well within the scope of the teachings of McCoy.

Therefore, based on the foregoing reasons, the instant claims are deemed unpatentable over the cited art.

Claims 25, 28, 37, 39-43, 46-51, and 53-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huffman (US Patent No. 3,664,858) of record.

Examiner respectfully notes at the outset that the instant invention is drawn to method of designing and preparing a co-crystal, wherein said method comprises a first chemical functionality and a co-crystal former. Applicant is labeling the first chemical functionality as an "API", however, it is respectfully pointed out that a recitation of an

intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Thus in the instant case, if the first chemical functionality is capable of forming a co-crystal with a co-crystal former, then the limitations of the claims are met.

Huffman teaches co-crystal complexes or adducts of amines with aromatic hydroxy compounds.

Examples of organic acidic materials which have been found useful are carboxylic acid, sulfonic acid, phenolic, and fluorosulfone compounds. Typical examples include the following, the name of the acid being followed by its pKa value where known: benzoic 4.17, o-chlorobenzoic 2.92, o-bromobenzoic 2.84, p-chlorobenzoic 3.98, o-hydroxybenzoic 2.97, 2,5-dihydroxybenzoic 2.94, 3,4-dihydroxybenzoic 4.48, o-nitrobenzoic 2.16, trihydroxybenzoic 1.68, o-iodobenzoic 2.85, 2,4-dinitrophenol 3.96, 3,6-dinitrophenol 5.15, gallic 4.41, trichlorophenol 6.00, trinitrophenol 0.80, o-chlorophenylacetic 4.07, o-chlorophenoxyacetic 3.05, o-bromophenoxyacetic 2.60, benzosulfonic 0.70, terephthalic 3.82, alpha naphthol 3.70, o-phthalic 2.89, naphthalenesulfonic 0.57, quinolinic 2.52, thiophencarboxylic 3.48, mandelic 3.85, maleic 1.83, furancarboxylic 3.15, dihydroxymalic 1.92, ascorbic 4.10, succinic 4.17,

malonic 2.80, oxalic 1.46, glyoxylic 4.88, glycolic 3.83, trichloroacetic 4.08, fluoroacetic 2.66, citric, bis(trifluoromethylsulfanyl)methane, xanthanoic, thiophendicarboxylic, cyclohexanecarboxylic, norcamphoric, naphthalenedicarboxylic, naphthalenetetracarboxylic, mellitic, trimesic, biphenyldicarboxylic, resorcinol-o-acetic, anthracenecarboxylic, o-bromotoluic, p-bromomandelic, salicylacetic, dinitrophenylacetic, 2-furanacetate, 4-sulfobenzoic, 3-formylbenzoic, 5-formylsalicylic, lactic, phenanthrenecarboxylic, isophthalic, 2-cyclopentenecarboxylic, naphthylaminetrisulfonic, 5-chlorosalicylic, 3,5-dinitrotoluic, benzohydroxamic, indolecarboxylic, xanthenecarboxylic, 2,3 pyridinecarboxylic, pentanetricarboxylic, cyanoacetic (column 1-2, bridging paragraph).

Huffman teaches substantially stoichiometric proportions of amine and acid are normally preferred but other ratios are not precluded, provided that the adduct composition contains no free amine, since it is the liberation of the basic organic nitrogen compound by heat-promoted dissociation of the adduct which initiates the color change.

Huffman teaches piperidine and morpholine are presently preferred examples of basic organic amino nitrogen compounds useful in the practice of the invention. Primary, secondary and tertiary amines, and hydrazines, are useful. Typical examples include the following: triethanolamine, ethanolamine, cyclohexylamine, tributylamine, di-n-propylamine, isopropylamine, 2-amino-1-butanol, monoisopropanolamine, propylenediamine, isobutylamine, di-n-hexylamine, di-n-butylamine, hydrazine, di-isopropylamine, diamylamine, methylhydrazine, phenyl hydrazine, hexanediamine,

methylaniline, aniline, guanidine, propylenediamine, polyglycolamine, ethylenediamine, diethylamine, diethanolamine, hydroxyethyl diethylenetriamine, isooctylamine, n-decylamine, methylethanolamine, tetramethylguanidine, methyl diethanolamine, 2-amino--propanediol, diethylaminopropylamine, amino-bispropylamine, benzylamine, morpholine, piperidine, dimethylformamide (column 2, lines 44-68).

In a typical preparation, salicylic acid (1.39 gm., 0.1 mol) and piperidine (0.85 gm., 0.1 mol) are mixed together in 20 grams of benzene, the mixture is evaporated to dryness, and the cocrystal adduct is washed with hexane and dried (column 2, lines 30-35).

Huffman does not teach the first chemical functionality as an API.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have envisioned that the adducts taught by Huffman, while not employed in the pharmaceutical art, can be formed regardless of the utility of the adduct. See *In re Dillon* 16 U.S.Q.P.2d 1897, 1900 (CAFC 1990) (en banc) ("it is not necessary in order to establish a prima facie case of obviousness that both a structural similarity between a claimed and prior art compound (or a key component of a composition) be shown and that there be a suggestion in or expectation from the prior art that the claimed compound or composition will have the same or a similar utility as one newly discovered by applicant. To the extent that Wright suggests or holds to the contrary, it is hereby overruled. In particular, the statement that a prima facie obviousness rejection is not supported if no reference shows or suggests the newly-discovered properties and results of a claimed structure is not the law. ").

Moreover, it is respectfully noted that many of the acids taught in Huffman are in fact commonly employed in the pharmaceutical art, namely acids of ascorbic, succinic, malonic, oxalic, glyoxylic, and glycolic.

Therefore, it would have been obvious to one skilled in the art to envision the adducts disclosed by Huffman for pharmaceutical compositions.

Based on the foregoing arguments, the instant claims are deemed unpatentable over the cited art.

Claims 25, 28, 39-41, 46-51, 53-56, 58-60, and 62-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (Journal of Chemical Crystallography, 1997) in view of Evgen'ev (Journal of Analytical Chemistry, 2000) as evidenced by Duke (Handbook of Phytochemical Constituents of GRAS Herbs and Other Economic Plants, 2001).

Smith teaches a number of molecular adducts of 4-aminobenzoic acid (4-ABA) with 4-nitroaniline [(4-ABA) (C₆H₆N₂O₂)], 4-(4-nitrobenzyl) pyridine, [(4-ABA)₂(C₁₂H₁₀N₂O₂)₄], and (4-nitrophenyl)acetic acid, [(4-ABA) (C₈H₇NO₄)]. The cocrystals were prepared, isolated by total evaporation of the solvent and characterized using infrared spectroscopy and in three cases by X-ray diffraction methods (Experimental section, bridging paragraph pages 309-310). Other compounds described are with 4-chlorobenzoic acid, [(4-ABA) (C₇H₅ClO₂)], 4-bromobenzoic acid, [(4-ABA) (C₇H₅BrO₂)], 4-cyanobenzoic acid, [(4-ABA) (C₇H₆N₂)], 2-nitrobenzoic acid, [(4-ABA)

(C₇H₅NO₄)], and 3-nitrobenzoic acid, [(4-ABA) (C₇H₅NO₄)]. All compounds have 1:1 stoichiometry except that with 4-(4-nitrobenzyl)pyridine (1:2) which is unique in being retro-stoichiometric (abstract; page 309, column 1-2, bridging paragraph).

Smith does not teach 4-ABA as an API as required by claim 25 (and dependent claims thereon) or teach the method for the preparation of a pharmaceutical product.

Evgen'ev teaches 4-ABA is widely employed in medicine as local anesthetics, antiarrhythmic agents, and antitubercular drugs.

As evidenced by Duke, 4-ABA is considered a GRAS compound (page 419, column 2, line 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have envisioned that the cocrystals taught by Smith to be employed in the pharmaceutical art. The motivation provided by Evgen'ev teaches 4-ABA is employed frequently in medicine in a variety of areas as discussed above. Therefore, one skilled in the art would have found it obvious to have employed the cocrystals taught by Smith for pharmaceutical purposes.

Therefore, based on the foregoing reasons, the instant claims are deemed unpatentable over the cited art.

Conclusion

Claims 25, 28, 37, 39-51, 53-60, and 62-66 are not allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAHAR JAVANMARD whose telephone number is (571) 270-3280. The examiner can normally be reached on 8 AM-5 PM MON-FRI (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/SAHAR JAVANMARD/

Examiner, Art Unit 1627

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	Examiner SAHAR JAVANMARD	Art Unit 1627	Page 1 of 1

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	B	US-				
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	P					
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	S					
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NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Smith, "The utility of 4-aminobenzoic acid in promotion of hydrogenbonding in crystallization processes: the structures of the cocrystals with halo and nitro substituted aromatic compounds, and the crystal structures of the adducts with 4-nitroaniline (1:1), 4-(4-nitrobenzyl)pyridine (1:2), and (4-nitrophenyl)acetic acid (1:1)",...
	V	Smith (cont'd above) ... Journal of Chemical Crystallography, Vol. 27. No. 5, 1997, pp. 307-317.
	W	Evgen'ev, "Selective Determination of 4-Aminobenzoic and 4-Aminosalicylic Acid Derivatives in Mixtures by Flow-Injection Analysis", Journal of Analytical Chemistry, Vol. 55, No. 7, 2000, pp. 696-702.
	X	Duke, Handbook of Phytochemical Constituents of GRAS Herbs and Other Economic Plants, 2001, CRC Press LLC, page 419.

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

U.S. Patent and Trademark Office
PTO-892 (Rev. 01-2001)
20160221

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Part of Paper No.

The utility of 4-aminobenzoic acid in promotion of hydrogen bonding in crystallization processes: the structures of the cocrystals with halo and nitro substituted aromatic compounds, and the crystal structures of the adducts with 4-nitroaniline (1:1), 4-(4-nitrobenzyl)pyridine (1:2), and (4-nitrophenyl)acetic acid (1:1)

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Received May 23, 1996

A number of molecular adducts of 4-aminobenzoic acid (4-ABA) have been prepared and characterized using infrared spectroscopy and in three cases by X-ray diffraction methods. These three compounds are with 4-nitroaniline [(4-ABA) (C₆H₅N₂O₂)], 4-(4-nitrobenzyl) pyridine, [(4-ABA)₂ (C₁₂H₁₀N₂O₂)₄], and (4-nitrophenyl)acetic acid, [(4-ABA) (C₈H₇NO₄)]. Other compounds described are with 4-chlorobenzoic acid, [(4-ABA) (C₇H₅ClO₂)], 4-bromobenzoic acid, [(4-ABA) (C₇H₅BrO₂)], 4-cyanobenzoic acid, [(4-ABA) (C₇H₄N₂)], 2-nitrobenzoic acid, [(4-ABA) (C₇H₅NO₄)], and 3-nitrobenzoic acid, [(4-ABA) (C₇H₅NO₄)]. All compounds have 1:1 stoichiometry except that with 4-(4-nitrobenzyl)pyridine (1:2) which is unique in being retro-stoichiometric. A review of the systematics of the 4-aminobenzoic acid adducts is also made, particularly with respect to the infrared characterization of the cocrystalline materials and prediction of their NLO potential.

KEY WORDS: Cocrystals; molecular adducts; carboxylic acids; 4-aminobenzoic acid.

Introduction

4-Aminobenzoic acid (4-ABA) is one of the most versatile of the carboxylic acids for cocrystal formation, promoting molecular self-assembly via hydrogen bonding through both the carboxylic acid group and the ring-substituted amino group. Since the first crystallographic characterization in 1984 of a 1:1 adduct with 4-nitropyridine-N-oxide,¹ only three other complexes had been described until the work completed

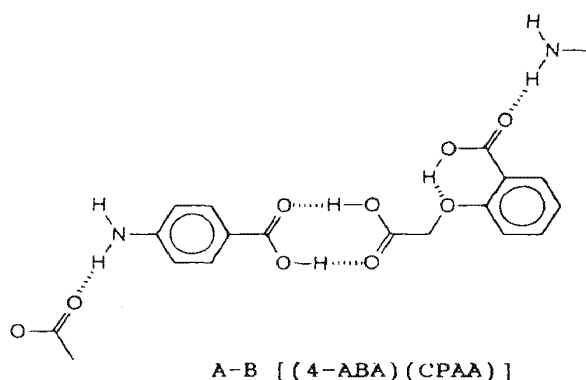
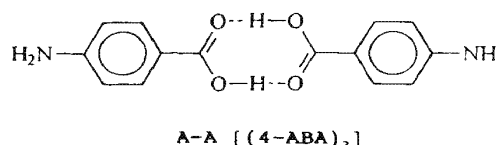
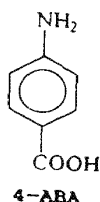
by our group. These were with 1,3-dimethyl-1-imidazolidinone [(4-ABA) (DMI)]² and 3,5-dinitrobenzoic acid [(4-ABA) (DNBA)]³ (both 1:1), while the third, a 2:1 inclusion adduct with 18-crown-6 had been partially characterized.⁴ The current list includes eight additional adducts, four with carboxylic acids, two with Lewis bases, one with a neutral organic species and one with both an acid and a neutral species. The organic acids involved are (2,4-dichlorophenoxy)acetic acid, [(4-ABA) (2,4-D)]⁵ (2-carboxyphenoxy)acetic acid, [(4-ABA) (CPAA)]⁶ pyrazine-2,3-dicarboxylic acid, [(4-ABA)⁺ (PDCA)⁻],⁷ 2,4,6-trinitrobenzoic acid, [(4-ABA)⁺ (TNBA)⁻ (H₂O)]⁸ and the only reported 2:1 adduct with 3,5-dinitrosalicylic acid, [(4-ABA) (4-ABA)⁺ (DNSA)⁻],⁹ the third example in which proton transfer occurs. In all of these, the acid is sufficiently strong to protonate the amino group of

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4-ABA, this group subsequently being involved in hydrogen bonding interactions with up to five acceptor centers, promoting stability in the resulting cocrystal system. With the 2:1 adduct, the primary association is between two 4-ABA molecules giving a cyclic hydrogen bonded **A–A** homodimer [graph set $R_2^2(8)^{10}$], similar to that found not only in the solid-state structure of the parent acid (4-ABA)¹¹ but in the majority of the carboxylic acids. In contrast, the complex [(4-ABA) (CPAA)] has a primary **A–B** $R_2^2(8)$ interaction between the heteromolecular pair (4-ABA and the phenoxyacetic acid group of CPAA), with secondary carboxylic acid (the benzoic acid) to amine group hydrogen bonding giving a chain structure.



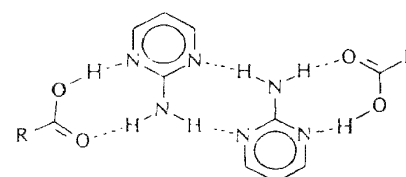
The adduct with the heterocyclic base 2-aminopyrimidine, [(4-ABA) (2-AP)], has the primary **A–P–P–A** hydrogen bonding association, characteristic of this molecule with carboxylic acids.¹² Each **A–P–P–A** unit is also linked laterally to the amino group of a symmetry-related 4-ABA molecule by hydrogen bonding associations through both amine protons, giving a 2-dimensional layer structure.¹³

Another analogous but simpler **A–P** system involving 4-ABA and the substituted pyrimidine, 4-amino-*N*-(4,6-dimethyl-2-pyrimidinyl)benzenesulfonamide, [(4-ABA) (4-APBS)] has also been characterized.¹⁴ The historically significant red complex

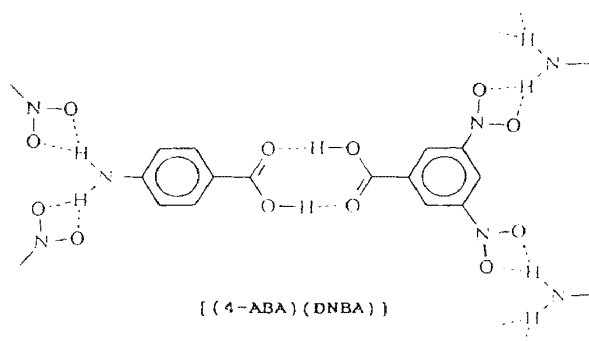
formed between 4-ABA and 1,3,5-trinitrobenzene (TNB),¹⁵ has also been determined as a 1:1 adduct [(4-ABA) (TNB)] with a primary **A–A** association between two 4-ABA molecules while the TNB molecules are held in essentially π bonding interactions.¹⁶ The 4-ABA-2,4,6-trinitrobenzoic acid system (obtained from the solid-state interaction of the two components), when recrystallized from water, yielded not only this same compound [(4-ABA) (TNB)] as a minor product but also yellow [(4-ABA)⁺(TNBA)[–](H₂O)]⁸ as a major product and the unusual (3:1:1) triheteromolecular cocrystal, [(4-ABA)₂(4-ABA)⁺(TNBA)[–](TNB)],¹⁷ the TNB being derived from the partial decarboxylation of the TNBA.¹⁸ Other chemically characterized cocrystals of

4-ABA for which X-ray data are not available are the adducts with 4-methyl-3,5-dinitrobenzoic acid,¹⁹ 4-nitrobenzoic acid,²⁰ and 3,5-dinitrobenzamide.¹⁹ Two (1:1) adducts of the substituted 4-ABA compound 4-(*N,N'*-dimethylamino) benzoic acid, the first with 3,5-dinitrocinnamic acid, [(DMABA) (DNCA)], the second with 3,5-dinitrobenzoic acid, [(DMABA)₂(DNBA)₂],²¹ are worthy of note. Although the first involves conventional **A–B** heterodimers, the second has two unique **A–A** homodimers.

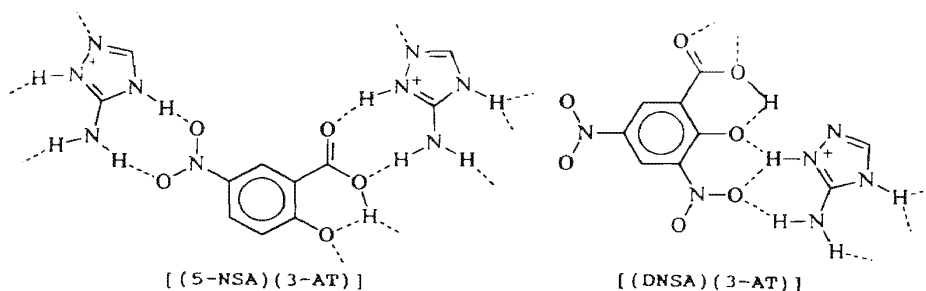
The structures reported here, the cocrystalline products from the interaction of a series of halo and nitro substituted aromatic compounds with 4-amino-benzoic acid represent a series with the properties necessary for extended hydrogen bonding structure formation via secondary group interactions, hence possessing asymmetry potential, an important criterion for



nonlinear optical applications.^{22,23} With nitro substituted compounds, participation of this group in hydrogen bonding associations with cocrystal formation has been found in a number of structures, including [(4-ABA) (DNBA)]³ and [(4-ABA)(4-ABA)⁺(DNSA)⁻].⁹ In the DNBA structure, in which no proton transfer occurs, both nitro oxygens in the first order network **A-B** structural unit form three-center associations with two amine protons of adjacent units in the layer structure.

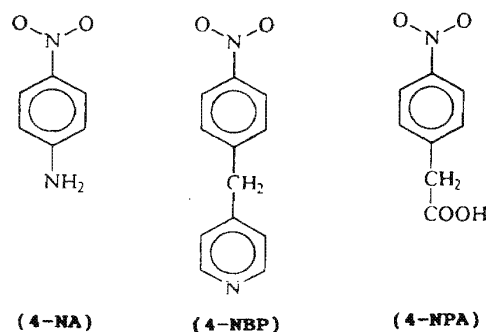


Although this behavior would suggest (at least in this cocrystal) that nitro group participation is part of the secondary structure, examples are known, particularly with those involving proton transfer, in which nitro groups appear to be involved in the primary interaction.²⁴ However, such interactions may be aided by proximal group participation, as is found in the 1:1 complexes of 3-amino-1,2,4-triazole with 5-nitrosalicylic acid [(3-AT)⁺(5-NSA)⁻] and 3,5-dinitrosalicylic acid [(3-AT)⁺(DNSA)⁻].²⁴



The adducts of 4-ABA are with 4-nitroaniline (4-NA), [(4-ABA) (4-NA)], **1**; 4-(4-nitrobenzyl)pyridine (4-NBP) [(4-ABA)₂(4-NBP)₄], **2**; 4-nitrophenylacetic acid (4-NPA), [(4-ABA) (4-NPA)], **3**; 4-chlorobenzoic acid (4-CBA), [(4-ABA) (4-CBA)], **4**; 4-bromobenzoic acid (4-BBA), [(4-ABA) (4-BBA)], **5**; 4-cyano-

benzoic acid (4-CNBA), [(4-ABA) (4-CNBA)], **6**; 2-nitrobenzoic acid (2-NBA), [(4-ABA) (2-NBA)], **7** and 3-nitrobenzoic acid (3-NBA), [(4-ABA) (3-NBA)], **8**. The crystal structures of compounds **1-3** have been determined by single crystal X-ray diffraction. Compound **2** is unusual in that it represents not only a rare example of a combination giving other than a 1:1 cocrystal but is also the first example in which 4-ABA forms a retro-stoichiometric complex, with a 1:2 rather than a 2:1 stoichiometry.



Experimental

Preparations

Complexes **1-8** were prepared using equimolar amounts (2.2mmol) of 4-aminobenzoic acid (4-ABA) and respectively 4-nitroaniline (4-NA), (**1**); 4-(4-nitrobenzyl)pyridine (4-NBP), (**2**); 4-nitrophenylacetic acid

(4-NPA), (**3**); 4-chlorobenzoic acid (4-CBA), (**4**), 4-bromobenzoic acid (4-BBA), (**5**); 4-cyanobenzoic acid (4-CNBA), (**6**); 2-nitrobenzoic acid (2-NBA), (**7**) and 3-nitrobenzoic acid (3-NBA), (**8**). All preparations involved refluxing for 20 mins. at ca. 110°C in 40cm³ of 95% ethanol, the product being subsequently

obtained by the total evaporation of the solvent at room temperature: for **1**, yellow plates (mp 151–153°C); for **2**, pale brown needles (mp 139–141°C); for **3**, yellow prisms (mp 136–138°C); for **4**, **5**, and **6**, pale brown powders (mp 188–190, 204–205.5 and 204–206°C respectively); for **7** and **8**, yellow powders (mp 131.5–133.5 and 170–173°C respectively). Analyses indicated 1:1 stoichiometries for all compounds except **2** which was 1:2. [Found for **1**: C, 56.5; H, 4.7; N, 15.6%. $C_{13}H_{13}N_3O_4$ requires C, 56.7; H, 4.8; N, 15.3%. Found for **2**: C, 65.6; H, 4.8; N, 12.3%. $C_{31}H_{27}N_5O_6$ requires C, 65.8; H, 4.8; N, 12.4%. Found for **3**: C, 57.3; H, 4.5; N, 8.7%. $C_{15}H_{14}N_2O_6$ requires C, 56.6; H, 4.4; N, 8.8%. Found for **4**: C, 60.5; H, 4.4; N, 4.9%. $C_{14}H_{12}ClNO_4$ requires C, 57.3; H, 4.1; N, 4.8%. Found for **5**: C, 52.0; H, 3.6; N, 4.3%. $C_{14}H_{12}BrNO_4$ requires C, 49.7; H, 3.6; N, 4.1%. Found for **6**: C, 62.9; H, 4.2; N, 9.6%. $C_{15}H_{12}N_2O_4$ requires C, 63.4; H, 4.3; N, 9.9%. Found for **7**: C, 55.3; H, 3.9; N, 9.4%. Found for **8**: C, 56.0; H, 3.8; N, 9.8%. $C_{14}H_{12}N_2O_6$ requires C, 55.3; H, 4.0; N, 9.2%]. Infrared spectra were recorded for all samples as pressed KBr disks on a Perkin-Elmer 1600 Fourier-transform infrared spectrometer. The use of other than 1:1 stoichiometric ratios of reactants in the preparations invariably resulted in the formation of the same products **1–8**. In those examples where suitable crystals for single crystal X-ray analysis could not be obtained, cocrystal formation was also identified by powder diffraction, the *d*-spacings (Å) and the normalized intensities (*I*/*I*₀) for the three strongest lines for **4–8** being as follows: for **4**, 3.22(100), 4.82(90), 3.63(70); for **5**, 3.27(100), 3.70(90), 4.69(70); for **6**, 4.70(100), 3.60(70), 3.90(70); for **7**, 5.71(100), 7.14 (80), 3.74 (70); for **8**, 5.64 (100), 3.22 (100), 3.41 (60). For 4-aminobenzoic acid, comparative *d*(*I*/*I*₀) values are 5.76(100), 3.62(93), 6.39(73). Qualitative second harmonic generation (SHG) measurements on powdered samples were carried out by using a Quantel 470 Q-switched Nd:YAG laser with 20mJ pulses at 1Hz.

Crystal data, data collection, structure solution and refinement

Details of cell data, X-ray data collection, structure solution and refinement are given in Table 1. Structures were solved by direct methods (*SHELXS*-86)²⁵. Full-matrix least-squares refinement (on *F*²) (*SHELXL*-93)²⁶ with anisotropic thermal parameters for all non-hydrogen atoms was used. Hydrogens

involved in the hydrogen bonding interactions were located by difference methods and both positional and thermal parameters were refined while others were either located or included at calculated positions in the refinements as riding models. It is of note that for **2**, intensity statistics and general systematic absences indicated the centrosymmetric space group *P*2₁/*n*, in which a structure solution was obtained but a refinement residual of no better than 9% could be obtained. However, a close examination of the data revealed a significant number of extinction violations for *P*2₁/*n* (for *h*0*l*, *h*+*l* = odd, expected absent) so that the subsequent successful solution and refinement in the non-centrosymmetric space group *P*2₁ indicates the presence of subtle pseudo *n*-glide symmetry in the crystals.

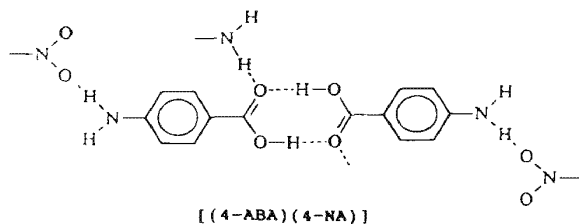
Results and discussion

Final atomic coordinates are listed in Table 1. Bond distances and angles, anisotropic thermal parameters, hydrogen atom coordinates and observed and calculated structure factors for adducts **1–3** have been deposited and are available on request. In the structures of **1** and **3**, molecule A refers to 4-aminobenzoic acid while molecule B refers to the second adduct molecule. With **2**, molecules A and B are 4-aminobenzoic acid while molecules C–F are 4-(4-nitrobenzyl)pyridine. Atom numbering schemes for the two associated molecule types and the hydrogen bonding schemes are shown in Figs. 1–3.

The structures of complexes **1–3**

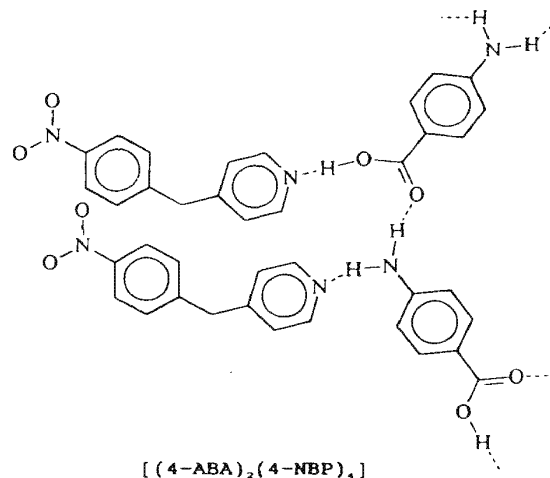
In the structure of the 1:1 complex of 4-aminobenzoic acid with 4-nitroaniline (4-NA), [(4-ABA) (4-NA)] **1**, a relatively simple association is found (Fig. 1). The primary interaction is between the carboxylic acid groups of two inversion-related 4-ABA pairs giving a cyclic hydrogen bonded A–A dimer [graph set *R*₂² (8)] [O(11A)–H(11A)---O(10A), 2.659(7)Å; O–H---O, 172(6)°]. This dimer is similar to that found in the parent acid¹¹ as well as to that in some of the adduct structures of 4-ABA, including those in which proton transfer occurs, e.g., in [(4-ABA) (4-ABA)⁺ (DNSA)[−]].⁹ In addition to this primary association, a secondary lateral interaction occurs between one of the carboxylic acid oxygens of 4-ABA and one of the amine protons of 4-NA [O(10A)---H(11B)–N(11B),

3.049(7) Å, O---H-N, 166(6)°], while this nitrogen gives a further lateral link to a symmetry related 4-ABA amine proton [N(11B)---H(42A)---N(41A), 3.245(7) Å, N---H-N, 137(6)°]. One more association between the second 4-ABA amine proton and a 4-NA nitro oxygen [N(41A)---H(41A)---O(40B), 3.250(7) Å, N-H---O, 160(6)°], completes the two-dimensional hydrogen bonding pattern, giving a layer structure which lies parallel to the *bc* plane.

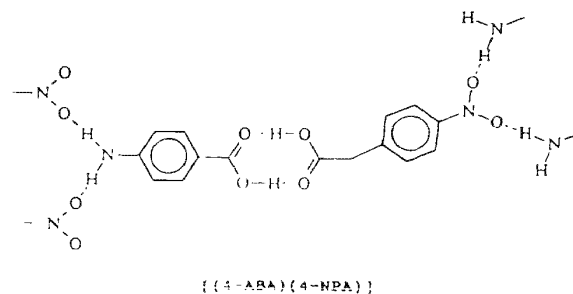


Compound **2** is an unusual pseudo-centrosymmetric 2:4 adduct of 4-ABA with 4-(4-nitrobenzyl)pyridine, [(4-ABA)₂(4-NBP)₄], in which the primary interaction between the two independent 4-ABA molecules (A and B) is head to tail *via* single weak hydrogen bonds between the carbonyl oxygen and the amine group of the adjacent molecule [O(10A)---H(41B)---N(41B), 3.326(5) Å, O---H-N, 175(4)°; O(10B)---H(41A)---N(41A), 3.356(5) Å, O---H-N, 175(4)°]. This gives a zig-zag ribbon structure extending along the *c* direction of the cell (Fig. 2). A parallel stack of alternating 4-NBP molecules (molecules C-F) tie into this basic chain *via* single hydrogen bonds between their pyridine nitrogens and the second amine nitrogen of the 4-ABA molecules [N(41B)---H(42B)---N(1C), 3.039(5) Å, N-H---N, 157(4)°; N(41A)---H(42A)---N(1D), 2.990(5) Å, N-H---N, 160(4)°] and the second carboxylic oxygen [O(11A)---H(11A)---N(41E), 2.654(5) Å, O-H---O, 159(4)°; O(11B)---H(11B)---N(1F), 2.663(5) Å, O-H---N, 152(4)°]. All carboxyl protons were located and satisfactorily refined, and support the spectroscopic evidence indicating no proton transfer from 4-ABA to the pyridine nitrogen. The value of Δ*pK*_a, the difference between the *pK*_a values for similar substituted pyridines and 4-ABA, is estimated to be >3.75, which is considered the minimum for proton transfer to occur at least with pyridine complexes.²⁷ This suggests that compound **2** could involve proton transfer, which might justify the unusual and unique occurrence of the 1:2 retro-stoichiometry, just as the 2:1, 4-ABA to strong acid ratio [such as found in the complex [(4-ABA)(4-ABA)⁺(DNSA)⁻]⁹] only occurs after proton transfer to 4-ABA. However, this is not the case. In

addition, the nitro oxygens are not involved in the stabilization of the herringbone structural motif except for possible C-H---O interactions²⁸ [C(6B)---H(6B)---O(40C), 3.373(5) Å, C-H---O, 147(4)°].



Structure **3**, the 1:1 adduct of 4-ABA with (4-nitrophenyl) acetic acid, [(4-ABA)(4-NPA)], is based on a primary cyclic hydrogen bonded **A-B** heterodimer pair similar to **1** [O(11A)---H(11A)---O(20B), 2.740(9) Å; O-H---O, 161(7)°; O(12A)---H(21B)---O(21B), 2.592(9) Å; O---H-O, 161(7)°]. The two nitro oxygens are then weakly associated with the amine protons of adjacent translated 4-ABA molecules [N(41A)---H(41A)---O(41B), 3.161(9) Å; N-H---O, 158(8)°] [N(41A)---H(42A)---O(40B), 3.134(8) Å; N-H---O, 141(8)°], giving a two-dimensional sheet structure which stacks down the *a* cell direction (Fig. 3).



Spectroscopy

As previously described,¹² heteromolecular dimer formation between carboxylic acid groups can also be

Table 1. Crystal data for [(4-ABA) (4-NA)], (1), [(4-ABA)₂(4-NBP)₄], (2), and [(4-ABA) (4-NPA)], (3)

Compound	(1)	(2)	(3)
Formula	C ₁₃ H ₁₃ N ₃ O ₄	C ₆₂ H ₅₄ N ₁₀ O ₁₂	C ₁₅ H ₁₄ N ₂ O ₆
<i>M_r</i>	275.3	1131.2	318.3
Color, shape	yellow plates	brown needles	yellow prisms
Space group	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁	<i>P</i> 2 ₁ / <i>a</i>
<i>a</i> (Å)	4.869 (3)	10.052 (2)	15.272 (2)
<i>b</i> (Å)	31.25 (1)	17.973 (3)	5.910 (2)
<i>c</i> (Å)	8.637 (6)	15.883 (3)	17.194 (2)
β(°)	93.69 (4)	103.173 (8)	108.80 (2)
<i>V</i> (Å ³)	1311 (1)	2794.0 (9)	1469.1 (6)
<i>D_c</i> (g cm ⁻³)	1.394	1.345	1.439
<i>Z</i>	4	2	4
μ (cm ⁻¹)	1.06	0.95	1.13
<i>F</i> (000)	576	1184	664
Temperature (°C)	25 (2)	25 (2)	25 (2)
<i>Data collection</i>			
a. Crystal size (mm)	0.30×0.25×0.12	0.50×0.30×0.25	0.40×0.30×0.12
b. 2θ _{max} (°)	50	50	50
c. Unique data	2299	10410	2570
d. Collection range (<i>h,k,l</i>)	5, 37, ±10	11, ±21, ±18	18, 7, -20 to 19
e. Data used	1006	5911	840
f. Discrimination	<i>I</i> > 2σ(<i>I</i>)	<i>I</i> > 2σ(<i>I</i>)	<i>I</i> > 2σ(<i>I</i>)
g. <i>R</i> 1 ^a	0.051	0.042	0.058
h. <i>wR</i> 2 ^b	0.151	0.113	0.180
i. GOF	0.82	0.94	0.90
j. <i>w</i> ^c <i>A</i>	0.176	0.093	0.206
<i>B</i>	0.93	0.03	0.00
k. Max. Residual peak (e Å ⁻³)	0.14	0.11	0.15

^a *R*1 [= Σ{| *F_o* | - | *F_c* | } / Σ | *F_o* |]^b *wR*2 [= {Σ*w*(*F_o*² - *F_c*²)²/Σ*w*(*F_o*²)}^{1/2}], with^c *w*=[σ²*F_o*² + (*AP*)² + *BP*], where *P* = [max (*F_o*², 0) + 2*F_c*²]/3.

detected using infrared spectroscopy. By comparing characteristic absorptions in the IR spectra, Etter was able to confirm that the (1:1) 4-ABA adduct with 4-chloro-3,5-dinitrobenzoic acid complex was structurally similar to the known 1:1 complex of 4-ABA with DNBA [(4-ABA) (DNBA)]. Characteristic IR absorptions for the two complexes include a N-H peak at 3488cm⁻¹, and a C=O stretch at 1687cm⁻¹. Further evidence indicating the formation of a carboxylic acid dimer, of any type, may be found in the presence of a broad asymmetric peak at *ca.* 3300–2300cm⁻¹ due to O-H stretching and a broad medium-intensity band in the 960–875cm⁻¹ region, characteristic of O-H...O out-of-plane hydrogen bond deformation.²⁹ Complex 1, comprising two neutral molecules, displays this in the IR region. Carboxylic acid dimer formation is evident from a broad asymmetric peak at *ca.* 3300–2300cm⁻¹ as well as a broad medium-intensity band at 926cm⁻¹. Interestingly, the C=O stretch is observed

at a lower frequency than usually expected (1663cm⁻¹). This could be due to the additional hydrogen bonding interaction involving the amino group on 4-NA. A third, lower frequency N-H stretch is also observed at 3226cm⁻¹ *cf.* the usual two stretching frequencies at 3430 and 3348cm⁻¹. Complexes 3–8 all involve hetero-dimer formation, as confirmed in the crystal structure of 3 and from the spectroscopic evidence. Characteristics N-H peaks ranging from 3498–3459 and 3396–3392cm⁻¹ together with sharp carbonyl stretches ranging from 1686–1678cm⁻¹ are evident in each spectrum. Furthermore, broad O-H stretching peaks (*ca.* 3000cm⁻¹) as well as O-H...O out-of-plane deformation peaks occur from 930–920cm⁻¹. In comparison, proton transfer complex formation is identified in the infrared region by the presence of N⁺-H and CO₂⁻ frequencies. Protonated tertiary amines absorb in the infrared in the 2500–1800cm⁻¹ region with medium to broad bands, due to

overtones and combinations, as well as a medium to weak peak between 1670 and 1610 cm⁻¹. Carboxylate ions have strong antisymmetric and symmetric stretching frequencies between 1610–1550 and 1420–1300 cm⁻¹ respectively. However, infrared data for 2 support the crystallographic evidence which confirms that 4-(4-nitrobenzyl)acetic acid is not sufficiently strong to protonate 4-aminobenzoic acid.

In addition, unpublished infrared spectroscopic data on 1:1 cocrystals of 2-aminobenzoic acid (2-ABA) with 2-nitrobenzoic acid (2-NBA) and 3-nitrobenzoic acid (3-NBA),⁽⁴⁾ and 3-aminobenzoic acid (3-ABA) with 2-NBA, and 3-NBA⁽⁵⁾ confirm that the two 2-ABA compounds are hetero-dimers while the two 3-ABA compounds exhibit proton transfer complex characteristics.

Effect of *pKa*

It has been shown from both the X-ray structures and IR spectroscopy, that 4-aminobenzoic acid

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic thermal parameters ($\text{\AA}^2, \times 10^3$) U_{eq} is defined as one third of the orthogonalized U_{ij} tensor (1)

	x	y	z	U(eq)
C (1A)	4659 (10)	4510 (2)	2833 (6)	48 (1)
C (2A)	5035 (12)	4071 (2)	2962 (6)	52 (1)
C (3A)	6791 (12)	3856 (2)	2073 (7)	55 (2)
C (4A)	8252 (10)	4071 (2)	981 (6)	49 (1)
C (5A)	7871 (11)	4509 (2)	833 (6)	52 (1)
C (6A)	6123 (11)	4723 (2)	1739 (6)	51 (1)
C (11A)	2707 (10)	4726 (2)	3783 (6)	47 (1)
O (10A)	1493 (8)	4541 (1)	4802 (4)	60 (1)
O (11A)	2353 (8)	5136 (1)	3486 (5)	61 (1)
N (41A)	9883 (11)	3849 (2)	16 (6)	60 (1)
C (1B)	3348 (11)	3565 (2)	7059 (6)	53 (1)
C (2B)	1160 (12)	3479 (2)	5990 (6)	57 (2)
C (3B)	278 (14)	3073 (2)	5746 (7)	68 (2)
C (4B)	1566 (13)	2739 (2)	6542 (7)	59 (2)
C (5B)	3678 (13)	2815 (2)	7603 (8)	63 (2)
C (6B)	4594 (14)	3224 (2)	7869 (8)	62 (2)
N (11B)	4210 (14)	3980 (2)	7351 (7)	68 (2)
N (40B)	647 (15)	2300 (2)	6265 (8)	87 (2)
O (40B)	1866 (14)	2005 (2)	6921 (7)	115 (2)
O (41B)	-1343 (15)	2246 (2)	5340 (8)	129 (2)

(2)

	x	y	z	U(eq)
C (1A)	2349 (4)	2381 (2)	4809 (3)	55 (1)
C (2A)	1516 (4)	2562 (2)	4006 (3)	60 (1)
C (3A)	907 (4)	2025 (3)	3435 (3)	60 (1)
C (4A)	1110 (4)	1269 (2)	3645 (3)	54 (1)
N (41A)	509 (5)	729 (3)	3073 (3)	78 (1)
C (5A)	1941 (4)	1087 (2)	4447 (3)	58 (1)
C (6A)	2540 (4)	1631 (3)	5013 (3)	59 (1)
O (10A)	3685 (4)	2826 (2)	6148 (2)	80 (1)
O (11A)	2752 (4)	3642 (2)	5122 (2)	86 (1)
C (11A)	2995 (5)	2958 (3)	5434 (4)	64 (1)
C (1B)	2793 (4)	6649 (2)	172 (3)	52 (1)
C (11B)	2253 (5)	6072 (3)	-459 (3)	62 (1)
O (10B)	1535 (4)	6190 (2)	-1174 (2)	77 (1)
O (11B)	2629 (3)	5388 (2)	-199 (2)	85 (1)
C (2B)	2431 (4)	7392 (3)	4 (3)	58 (1)
C (3B)	2878 (4)	7939 (2)	600 (3)	58 (1)
C (4B)	3760 (4)	7774 (2)	1398 (3)	57 (1)
N (41B)	4191 (5)	8320 (3)	1994 (3)	73 (1)
C (5B)	4136 (4)	7037 (3)	1562 (3)	60 (1)
C (6B)	3673 (4)	6495 (2)	964 (3)	60 (1)
N (1C)	3398 (5)	-131 (2)	1300 (3)	83 (1)
C (11C)	2570 (4)	2540 (2)	297 (3)	60 (1)
C (2C)	2368 (6)	249 (3)	1447 (4)	86 (2)
C (21C)	3842 (5)	2776 (2)	190 (3)	65 (1)
C (3C)	1837 (5)	878 (3)	999 (3)	76 (1)
C (31C)	4417 (5)	3416 (2)	562 (3)	64 (1)
C (4C)	2434 (4)	1145 (2)	355 (3)	60 (1)
C (41C)	3732 (4)	3828 (2)	1060 (3)	50 (1)
N (41C)	4334 (4)	4514 (2)	1463 (2)	64 (1)

⁽⁴⁾ For 2-aminobenzoic acid with 2-nitrobenzoic acid [(2-ABA) (2-NBA)], and 3-nitrobenzoic acid [(2-ABA) (3-NBA)], the total evaporation of ethanol at room temperature yielded: light brown needle crystals (mp 112–114°C), and a brown powder (mp 153–155°C) respectively. {Found for [(2-ABA) (2-NBA)]: C, 56.3; H, 4.1; N, 9.6%. Found for [(2-ABA) (3-NBA)]: C, 57.0; H, 4.0; N, 9.5%. $C_{14}H_{12}N_2O_6$ requires C, 55.3; H, 4.0; N, 9.2%. [(2-ABA) (2-NBA)]: $d(Ill)$ 3.75(100), 6.68(50), 6.28Å(20). [(2-ABA) (3-NBA)]: $d(Ill)$ 6.09(100), 5.08(80), 6.53Å(60). For 2-Aminobenzoic acid (2-ABA): α -form, $d(Ill)$ 3.66(100), 4.76(95), 6.44Å(60); β -form, $d(Ill)$ 5.84(100), 8.04(75), 4.03Å(70); γ -form, $d(Ill)$ 6.04(100), 7.66(50), 3.79Å(50). Attempts to prepare the 1:1 adducts of 2-ABA with 4-nitrobenzoic acid, and DNBA yielded powders consisting of both starting materials, which were identified using X-ray powder diffraction techniques.

⁽⁵⁾ For 3-aminobenzoic acid with 2-nitrobenzoic acid [(3-ABA) (2-NBA)], and 3-nitrobenzoic acid [(3-ABA) (3-NBA)], the total evaporation of ethanol at room temperature yielded: yellow-brown plate-like needles (mp 143–145°C), and a light brown powder (mp 163–165°C) respectively. {Found for [(3-ABA) (2-NBA)]: C, 56.3; H, 4.0; N, 9.6%. Found for [(3-ABA) (3-NBA)]: C, 57.0; H, 4.1; N, 9.5%. $C_{14}H_{12}N_2O_6$ requires C, 55.3; H, 4.0; N, 9.3%. [(3-ABA) (2-NBA)]: $d(Ill)$ 4.49(100), 5.31(98), 3.73Å(85). [(3-ABA) (3-NBA)]: $d(Ill)$ 3.66(100), 3.41(98), 3.22Å(95). 3-Aminobenzoic acid (3-ABA): $d(Ill)$ 5.20(100), 3.41(70), 3.31Å(60). Weissenberg photographs for [(3-ABA) (2-NBA)] indicated crystal twinning. However, the space group was determined as $P2_12_12_1$, with approximate cell dimensions $a = 7.0$, $b = 12.4$, $c = 17.1$ Å V 1484 Å³, $D_c(Z = 4)$ 1.36 g cm⁻³ ($M_r = 304.1$), $D_m < 1.50$ g cm⁻³ (CHCl₃). Attempts to prepare the 1:1 adduct of 3-ABA with 4-nitrobenzoic acid, yielded a powder consisting of both starting materials, which were identified using X-ray powder diffraction techniques.

Table 2. Continued.

O (40C)	3804 (4)	4828 (2)	1972 (2)	86 (1)
O (41C)	5369 (3)	4743 (2)	1272 (2)	87 (1)
C (5C)	3506 (5)	745 (3)	196 (3)	71 (1)
C (51C)	2503 (4)	3601 (2)	1200 (3)	61 (1)
C (6C)	3955 (5)	122 (3)	674 (4)	82 (1)
C (61C)	1929 (4)	2957 (3)	816 (3)	68 (1)
C (7C)	1907 (5)	1841 (2)	-130 (3)	80 (2)
N (1D)	1164 (5)	9196 (3)	3820 (3)	90 (1)
C (11D)	2559 (4)	6546 (2)	4682 (3)	58 (1)
C (2D)	708 (6)	8834 (3)	4417 (4)	86 (2)
C (21D)	1383 (5)	6247 (3)	4848 (3)	70 (1)
C (3D)	1292 (5)	8231 (2)	4853 (3)	66 (1)
C (31D)	826 (5)	5587 (2)	4455 (3)	67 (1)
C (4D)	2489 (4)	7951 (2)	4675 (3)	56 (1)
C (41D)	1484 (4)	5246 (2)	3899 (2)	51 (1)
N (41D)	922 (4)	4544 (2)	3492 (2)	62 (1)
O (40D)	1493 (4)	4258 (2)	2967 (2)	80 (1)
O (41D)	-74 (3)	4277 (2)	3695 (2)	83 (1)
C (5D)	2996 (5)	8308 (3)	4055 (3)	77 (1)
C (51D)	2637 (4)	5531 (2)	3705 (3)	61 (1)
C (6D)	2301 (6)	8926 (3)	3656 (3)	91 (2)
C (61D)	3173 (4)	6195 (3)	4105 (3)	64 (1)
C (7D)	3158 (5)	7260 (2)	5127 (3)	73 (1)
N (1E)	3614 (5)	4806 (2)	6146 (2)	74 (1)
C (11E)	4548 (4)	7413 (3)	7433 (2)	52 (1)
C (2E)	4728 (5)	5203 (3)	6138 (3)	72 (1)
C (21E)	3388 (4)	7821 (2)	7450 (3)	58 (1)
C (3E)	5135 (5)	5810 (3)	6669 (3)	68 (1)
C (31E)	3145 (4)	8507 (2)	7056 (3)	59 (1)
C (4E)	4359 (4)	6026 (2)	7230 (3)	54 (1)
C (41E)	4083 (4)	8784 (2)	6635 (3)	52 (1)
N (41E)	3822 (4)	9506 (2)	6198 (2)	69 (1)
O (40E)	4498 (4)	9677 (2)	5687 (2)	105 (1)
O (41E)	2931 (5)	9904 (2)	6359 (3)	112 (1)
C (5E)	3215 (5)	5626 (3)	7227 (3)	77 (1)
C (51E)	5251 (4)	8408 (3)	6604 (3)	62 (1)
C (6E)	2877 (5)	5031 (3)	6674 (3)	90 (2)
C (61E)	5484 (4)	7728 (3)	7009 (3)	62 (1)
C (7E)	4783 (5)	6657 (3)	7856 (3)	64 (1)
N (1F)	1752 (4)	14220 (2)	8799 (3)	73 (1)
C (11F)	337 (4)	11605 (3)	7605 (3)	57 (1)
C (2F)	2456 (5)	13863 (3)	8319 (3)	83 (1)
C (21F)	1426 (4)	11162 (2)	7535 (3)	61 (1)
C (3F)	1998 (5)	13264 (3)	7812 (3)	74 (1)
C (31F)	1634 (4)	10480 (3)	7944 (3)	60 (1)
C (4F)	706 (5)	12998 (2)	7762 (3)	58 (1)
C (41F)	741 (4)	10253 (2)	8425 (3)	54 (1)
N (41F)	979 (4)	9521 (2)	8862 (2)	71 (1)
O (40F)	1731 (5)	9082 (2)	8635 (3)	111 (1)
O (41F)	407 (4)	9403 (2)	9443 (2)	101 (1)
C (5F)	-15 (5)	13349 (3)	8281 (3)	71 (1)
C (51F)	-371 (4)	10674 (3)	8505 (3)	63 (1)
C (6F)	524 (6)	13946 (3)	8769 (3)	81 (2)
C (61F)	-554 (4)	11356 (3)	8082 (3)	66 (1)
C (7F)	144 (5)	12353 (3)	7169 (3)	75 (1)

Table 2. Continued.

(3)			
	x	y	z
C(1A)	6211(5)	1254(13)	7169(5)
C(2A)	6621(6)	2212(16)	7943(5)
C(3A)	6619(6)	1121(16)	8640(5)
C(4A)	6211(5)	-985(15)	8609(5)
C(5A)	5801(6)	-1973(15)	7839(6)
C(6A)	5807(5)	-883(14)	7140(5)
C(11A)	6213(5)	2510(15)	6441(4)
O(10A)	6624(4)	4292(10)	6469(3)
O(11A)	5738(4)	1513(11)	5739(4)
N(41A)	6209(8)	-2038(19)	9309(7)
C(1B)	6301(5)	5965(14)	13069(4)
C(2B)	5868(6)	6903(15)	12298(5)
C(3B)	5864(5)	5849(14)	11584(5)
C(4B)	6307(5)	3774(13)	11652(4)
C(5B)	6746(5)	2780(16)	12392(5)
C(6B)	6750(5)	3918(15)	13097(5)
C(11B)	6357(7)	7231(16)	13835(5)
C(21B)	6254(6)	5832(15)	14518(5)
O(20B)	5834(4)	4052(11)	14436(3)
O(21B)	6651(5)	6754(11)	15229(3)
N(40B)	6307(5)	2618(14)	10899(4)
O(40B)	5975(5)	3562(11)	10239(3)
O(41B)	6650(5)	757(12)	10958(4)

(together with its 2- and 3-substituted isomers) form hetero-dimers both with Lewis bases and benzoic acids having acceptor substituent groups, although if proton transfer occurs, the resulting association involving the carboxylic acid group is via only one hydrogen bond. With complexes 3–8, for which the evidence indicates the formation of hetero-dimers, the pK_a of the carboxylic acid group of the acceptor-substituted benzoic acid is either approximately equal to or greater than the pK_a of the carboxylic acid group of the corresponding amino-substituted benzoic acid. For examples known to form proton transfer complexes, the pK_a of the acceptor-benzoic acid is either approximately equal to or less than the pK_a of the corresponding amino-benzoic acid. Comparative pK_a values for each species in both heterodimer and proton transfer complexes are given in Table 3. In complexes of acids with approximately equal pK_a values, steric factors and competing hydrogen bonding systems may also be important in controlling the process of structure making.

Of the ten adducts of 4-ABA which are known or probable heterodimers, the crystallographic space groups for only three are known, $\{[(4\text{-ABA})(4\text{-NPA})] (P2_1/a), [(4\text{-ABA})(2\text{-CPAA})] (P2_1/c) \text{ (both centrosymmetric) and } [(4\text{-ABA})(\text{DNBA})] (Fdd2) \text{ (non-}$

Table 3. Comparative pKa values, space groups and observed SHG for the donor and acceptor species in both heterodimer and proton transfer complexes in aminobenzoic acid cocrystals

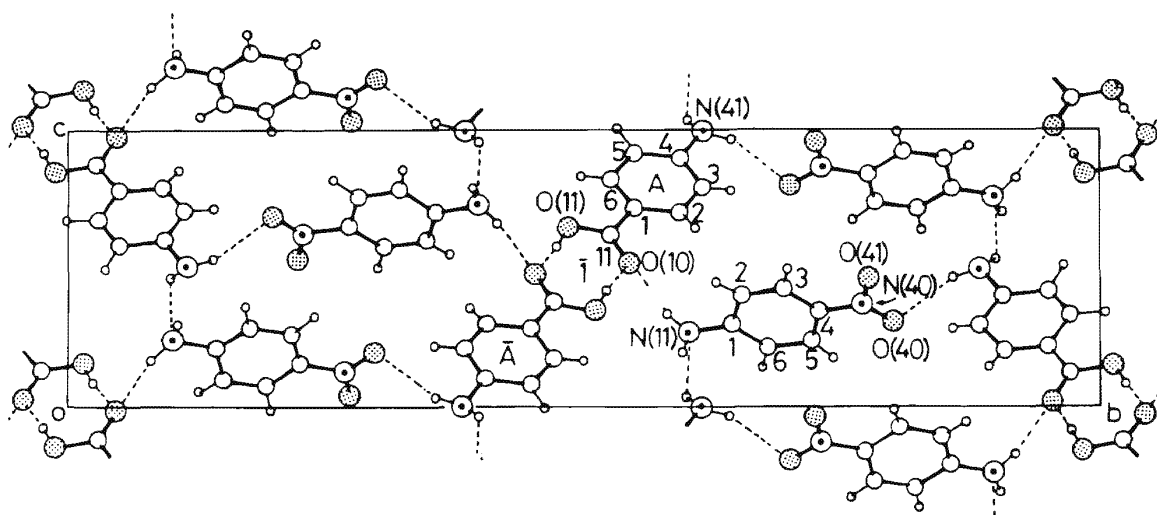
	pKa	Space group	SHG	Reference
Heterodimer Complex				
[(4-ABA) (DNBA)]	2.38, 2.82	<i>Fdd2</i>	+	3
[(4-ABA) (2-CPA)]	2.38, 2.50	<i>P2₁/c</i>	—	6
[(4-ABA) (4-NPA)]	2.38, 3.85	<i>P2₁/a</i>	—	This work 3
[(4-ABA) (4-CBA)]	2.38, 3.98	*	—	This work 4
[(4-ABA) (4-BBA)]	2.38, 3.97	*	—	This work 5
[(4-ABA) (4-CNBA)]	2.38, 3.55	*	—	This work 6
[(4-ABA) (2-NBA)]	2.38, 2.22	*	—	This work 7
[(4-ABA) (3-NBA)]	2.38, 3.44	*	—	This work 8
[(2-ABA) (2-NBA)]	2.05, 2.22	*	—	This work
[(2-ABA) (3-NBA)]	2.05, 3.44	*	—	This work
Proton Transfer Complex				
[(4-ABA) ⁺ (PDCA) [−]]	2.38, 2.27 ³	<i>P2₁/c</i>	—	7
[(4-ABA) ⁺ (TNBA) [−] (H ₂ O)]	2.38, 0.65	<i>Pbcn</i>	—	8
[(4-ABA) (4-ABA) ⁺ (DNSA) [−]]	2.38, 2.14	<i>P1̄</i>	—	9
[(3-ABA) ⁺ (2-NBA) [−]]	3.07, 2.22	<i>P2₁2₁2₁</i>	—	This work
[(3-ABA) ⁺ (3-NBA) [−]]	3.07, 3.44	*	—	
[(3-ABA) ⁺ (DNBA) [−]]	3.07, 2.82	<i>P1̄</i>	—	30
[(3-ABA) (DNBA) (3-ABA) ⁺ (DNBA) [−] (H ₂ O)]	3.07, 2.82	<i>P2₁2₁2₁</i>	+	30

* not known

³ pKa₁ for pyrazine-2, 3-dicarboxylic acid. pKa₂ = 4.63.

centrosymmetric)). The available structural information on the remaining seven gives no indication of the nature of the packing arrays expected or the possibility of molecular asymmetry existing. However, preliminary qualitative second harmonic generation tests were

carried out on powdered samples of all listed compounds (except [(4-ABA) (DNBA)]) as a check for possible noncentrosymmetric packing. Although no quantitative optical measurements were possible a strong SHG signal, evident as a visible green glow

**Fig. 1.** Packing of **1** in the unit cell showing atom numbering scheme. Unless otherwise indicated, atoms are carbon. In all figures, for clarity, only those molecules involved in hydrogen bonding interactions (broken lines) are shown.

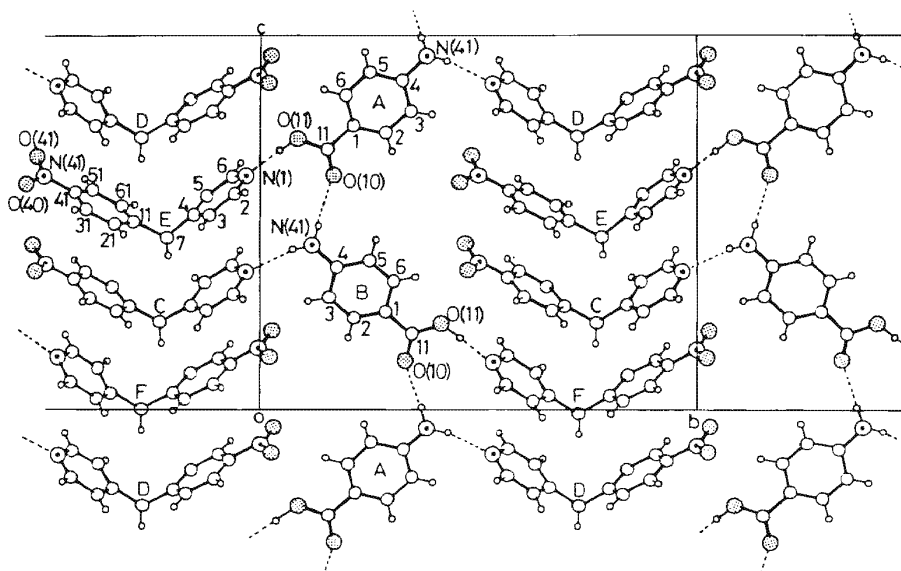


Fig. 2. Packing of 2 in the unit cell.

(532nm) from the sample upon irradiation with the Nd:YAG laser source (1064nm) indicates an active compound. These tests confirm that of the heterodimer complexes listed, only [(4-ABA) (DNBA)] is optically active. Of the seven compounds known to be proton transfer complexes, four [(4-ABA)⁺ (PDCA)⁻], [(4-ABA)⁺ (TNBA)⁻ (H₂O)], [(4-ABA) (4-ABA)⁺

(DNSA)⁻], and [(3-ABA)⁺ (DNBA)⁻]] are centrosymmetric, two are noncentrosymmetric [(3-ABA)⁺ (2-NBA)⁻] and [(3-ABA) (DNBA) (3-ABA)⁺ (DNBA)⁻ (H₂O)]], while for (3-ABA)⁺ (3-NBA)⁻], the space group is unknown. However, of these only [(3-ABA) (DNBA) (3-ABA)⁺ (DNBA)⁻ (H₂O)] displayed any visible SHG signal.

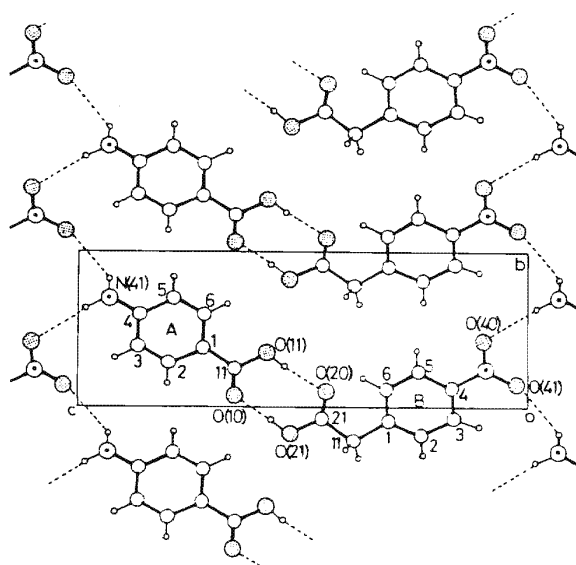


Fig. 3. Packing of 3 in the unit cell.

Conclusions

The structures of a relatively large set of 4-amino-benzoic acid adducts with nitro-substituted aromatic compounds have provided a set of data which enables the more accurate description of the characteristics of the possible interactions. Two basic interactions are possible, the first and most common involving no proton transfer, the second, occurring with the stronger carboxylic acids results in proton transfer to the amino group of 4-ABA. Such proton transfer interactions result in the disruption of the process proposed by Etter^{22,23} which leads to possible formation of the linear arrays required for acentric packing. However, such interactions do aid in adduct formation, as well as generally increasing the thermal stability of the subsequent crystals, and as has been observed in the series reported here, still allows formation of optically active noncentrosymmetric crystal lattices. With those processes involving no proton transfer, the primary molec-

ular association results, in the majority of cases in a cyclic hydrogen bonded A-A dimer with the A-B heterodimer associations less prevalent or predictable. Also, in most examples, the natural packing of either homo- or heterodimers of 4-ABA (or carboxylic acids generally) is centric, with rare acentric examples, these being potentially useful optically. In all cases, infrared spectroscopy may be used to recognize the nature of the association. However, prediction of the general outcome of the crystallisation process is not as yet a reality in the design of organic compounds with NLO properties.

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Supplementary material. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1003/5157 (for 1), CCDC-1003/5158 (for 2), and CCDC-1003/5159 (for 3). Copies of available material can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: teched@chemcrs.cam.ac.uk).

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				FILING DATE: March 3, 2003		CONFIRMATION NO.: 4742	
				FIRST NAMED INVENTOR: Michael J. Zaworotko			
				GROUP ART UNIT: 1627		EXAMINER: Sahar Javanmard	
Sheet	1	of	1				

U.S. PATENT DOCUMENTS

Examiner's Initials [#]	Cite No.	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication or Issue of Cited Document MM-DD-YYYY
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Examiner's Initials [#]	Cite No.	Foreign Patent Document			Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Translation (Y/N)
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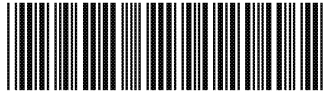
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		[NO AUTHOR LISTED], Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances Q6A. ICH Harmonised Tripartite Guideline. 1999 Oct 6; 4:46.	
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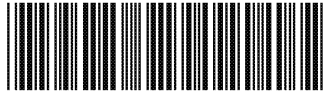
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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.J./

<i>Index of Claims</i> 	Application/Control No. 10378956	Applicant(s)/Patent Under Reexamination ZAWOROTKO ET AL.
	Examiner SAHAR JAVANMARD	Art Unit 1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant											☐ CPA											☐ T.D.											☐ R.1.47										
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ARTICLES

Selective Determination of 4-Aminobenzoic and 4-Aminosalicylic Acid Derivatives in Mixtures by Flow-Injection Analysis

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Abstract—The working conditions were found for the determination of medicinal substances anesthesin (benzocaine, I), novocaine (II), novocainamide (procainamide, III), and sodium 4-aminosalicylate (IV) as their 4,6-dinitrobenzofuroxan derivatives by flow-injection analysis with spectrophotometric detection (λ 510 nm). The best conditions were attained using a mixture of ethanol (methanol) and a buffer solution of pH 6.68 (30 : 70 vol %). The analytical range for the analytes was 0.08–5.0 $\mu\text{g/mL}$. The detection limits (3σ , $n = 4$) were 0.04 (I), 0.05 (II), 0.07 (III), and 0.03 (IV) $\mu\text{g/mL}$. Procedures for determining 4-aminobenzoic and 4-aminosalicylic acid derivatives in pharmaceuticals containing ephedrine, atropine, dimedrol, and inorganic salts and in biological fluids (protein hydrolyzate, blood plasma, and whole blood) were developed.

4-Aminobenzoic and 4-aminosalicylic acid derivatives are widely used in medicine as local anesthetics (anesthesin and novocaine), antiarrhythmic agents (novocainamide), and antitubercular drugs (4-aminosalicylate, sodium salt) [1]. However, possibilities of rapidly and efficiently determining these substances by flow-injection analysis in both technological mixtures and multicomponent drugs are essentially restricted, because of an insufficient selectivity of the spectrophotometric detection of their derivatives forming in the flow. The reaction of the formation of diazo derivatives of *o*-phthalic aldehyde is not selective to phenols and other compounds containing labile hydrogen atoms bound to carbon atoms [2, 3]. The spectrophotometric determination of primary arylamines as their derivatives with carbonyl compounds also does not solve the selectivity and sensitivity problems [4]. It was found previously [5–7] that reactions with chlorodinitro-substituted benzo-2,1,3-oxadiazoles provide the most selective determination of these compounds by flow-injection (FI) spectrophotometric analysis.

The aim of this work was to find the conditions for the selective determination of 4-aminobenzoic acid (PABA) and 4-aminosalicylic acid (PASA) as their 4,6-dinitrobenzofuroxan and 5,7-dinitrobenzofurazan derivatives in complex medicinal substances and biological fluids using flow-injection analysis.

EXPERIMENTAL

An SF-26 spectrophotometer was used for recording absorption spectra. An MV-87S potentiometer (Germany) with an ESL-43-07 glass electrode and a SE-20 silver–silver chloride reference electrode was used for pH measurements. The experiments were performed using a reverse-mode single-channel flow-

injection system [5–7] equipped with a D1 plunger pump (Mikrotechna, Czech Republic) and a photometric flow cell (6 μL , $l = 0.5$ cm). A Spekol-210 spectrophotometer (Carl Zeiss, Germany) was used as a detector. A TZ-4100 recorder (Laboratorni Pristroje, Czech Republic) was used for recording flowgrams. A six-way injection valve (Mikrotechna, Czech Republic) with a calibrated loop (110 μL) was used throughout. Communication tubes (inside diameter 0.6 mm) were made of Teflon. The reaction coil (coil diameter 20 cm) was 2.0 m in length. The intensity of the analytical signal was calculated by subtraction of the blank signal.

Chromatographic analyses were performed on an HP-1100 chromatograph (Germany). Anesthesin (ethyl 4-aminobenzoate), novocaine (diethylamino 4-aminobenzoate hydrochloride), novocainamide (4-aminobenzoic acid β -diaminoethylamide hydrochloride), and sodium 2-aminosalicylate as well as drugs containing these substances were of pharmaceutical grade. If required, organic solvents were purified using the procedure described in [8, 9]. 4-Chloro-5,7-dinitrobenzofurazan (BFZ) and 7-chloro-4,6-dinitrobenzofuroxan (BFO) were synthesized by the procedures described in [10, 11]. A protein hydrolyzate reference solution and serum albumin were obtained from Reanal (Hungary). Whole blood was sampled from patients in the course of clinical examinations. The deproteinization of biological fluids was performed using the procedure described in [5]. 5,7-Dinitrobenzofurazan derivatives of medicinal substances were synthesized by adding a methanol solution of BFZ (0.6 mmol) to a solution of the equivalent amount of anesthesin or PASA in methanol. Yellow or orange crystalline precipitates were washed with a methanol–water mixture and recrystallized from methanol.

Chemical analysis data. For the anesthesin derivative anal. calcd. (wt %): H, 3.08; C, 50.42; N, 19.61; found (wt %): H, 3.16; C, 50.31; N 19.55. For the PASA derivative, calcd. (wt %): H, 2.03; C, 45.22; N, 32.46; found (wt %): H, 1.92; C, 45.01; N, 32.23.

Determination Procedures

Pharmaceuticals. Liquid pharmaceuticals (injection solutions and drops) were diluted with water to the analyte concentrations from 0.5 to 3.0 µg/mL. An aliquot portion of the solution was then placed in a 25-mL volumetric flask, to which a mixture of ethanol and a phosphate buffer solution (pH 6.86–7.1, 0.06 M, obtained from Radelkis, Hungary) 30 : 70 (vol %) was added. The resulting solution was used as a carrier stream (flow rate 1.3 mL/min). After injecting a 110-µL portion of a solution of BFO in acetonitrile (0.01 M), flowgrams were recorded at $\lambda = 510$ nm. The concentrations of medicinal substances were determined using calibration plots or by a standard addition method.

In the analysis of suppositories, a 0.5-g weighed portion of the test substance was mixed with ethanol (10 mL), and the mixture was heated on a water bath until the matrix melted. Next, the solution was stirred up and filtered. Treatment with 10-mL ethanol portions was repeated three times. The extracts were collected into a 50-mL volumetric flask. The subsequent procedure was similar to the procedure described above.

Tablets to be analyzed were crushed to powder. Next, 0.5-g portions were mixed with ethanol (20 mL), and the mixtures were shaken for 10 min. Extraction was repeated. The solution was placed in a 50-mL volumetric flask, diluted with ethanol to the mark, and analyzed by the procedure described above.

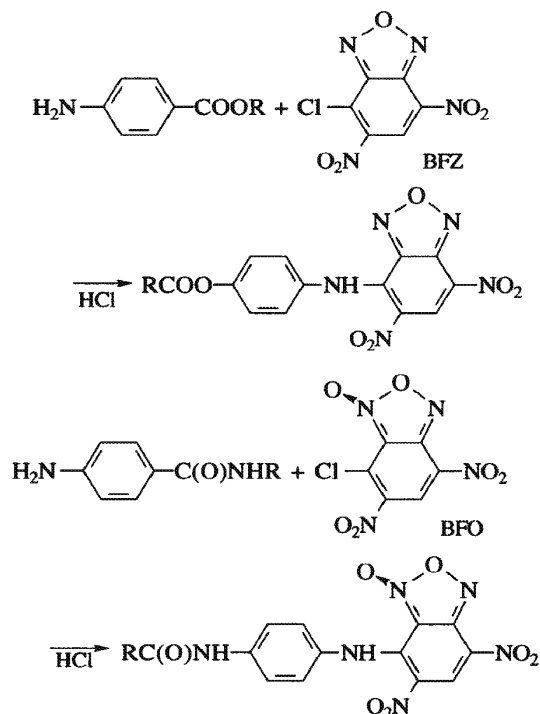
In the analysis of anesthesin- and novocaine- containing pharmaceuticals, a 0.5 mL-portion of the drug was mixed with water (5 mL). Anesthesin was extracted with 5-mL portions of ether under shaking for 1 min (four times). The ether layers were separated, and the solvent was removed by distillation. The residue was dissolved in ethanol. Anesthesin and novocaine in the residue after their dissolution in ethanol and in the aqueous phase were determined by the procedure described above.

Determination of novocainamide and PASA in the biological fluids. Blood serum samples were prepared after removing the blood clot from blood samples. Next, proteins were precipitated by adding trichloroacetic acid (1 mL of a 30% solution) followed by doubly repeated centrifugation (5000 rpm). The final centrifugate was analyzed.

RESULTS AND DISCUSSION

Conditions for the spectrophotometric detection of the derivatives of medicinal substances The reactions of BFO and BFZ with the derivatives of PABA

and PASA in polar nonaqueous or mixed solvents give rise to intensely colored compounds. Absorption spectra of these compounds are shown in Fig. 1. The composition of the reaction products according to the data of chemical analysis and results of potentiometric titration of NH-acids with lithium methylate in methanol suggest the following reaction mechanism:



As a whole, the benzofuroxan derivatives of the compounds under study are characterized by stronger long-wave shifts of absorption maxima than the benzofurazan derivatives. Flow-injection determinations of primary arylamines using BFZ as a reagent are hampered by the partial overlapping of the absorption bands of the derivatives (the products of the analytical reaction) and of the hydrolyzed reagent. For the dinitrobenzofuroxan derivatives of arylamines, the overlapping of the bands of the products of concurrent reactions is negligible. Therefore, we used BFO for the FI determination of PABA and PASA derivatives. Moreover, compared to BFZ, this reagent possesses higher reactivity to primary amines [7]. The analytical wavelengths were selected taking into account the spectral properties of the derivatives (Fig. 1).

Selection of the composition of the carrier stream. The rate and degree of completion of the analytical reaction between amino compounds and BFZ or BFO in nonequilibrium conditions are affected by the solvent and the composition of the reaction solution [12, 13]. Thus, to optimize the conditions for the flow-injection determinations of PABA and PASA deriva-

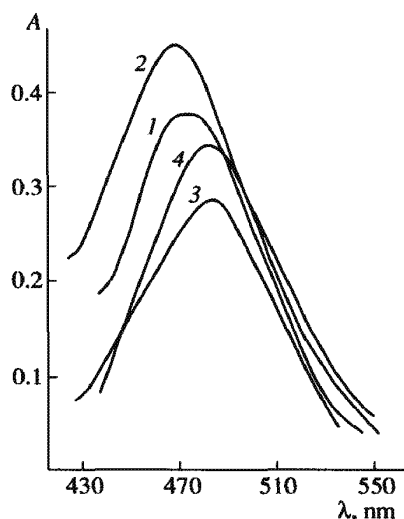


Fig. 1. Absorption spectra of the 4,6-dinitrobenzofuroxan derivatives (10^{-5} M) of (1) anesthesin, (2) novocaine, (3) novocainamide, and (4) sodium 4-aminosalicylate; solvents: (1-3) methanol-water (30 : 70 vol %) and (4) phosphate buffer solution (pH 6.68).

tives, we examined the effect of the carrier stream composition on the analytical signal.

The use of low-polarity solvents as carriers in the FIA of PABA and PASA derivatives is limited because of the existence of spectral equilibria between different

forms of dinitrobenzoxadiazole derivatives of the substances under study. Thus, the addition of a nonpolar solvent (chloroform or tetrachloromethane) to a solution of derivatives in a polar nonaqueous solvent (dimethylsulfoxide or alcohols) resulted in the appearance of a new absorption band ($\lambda_{\text{max}} = 430$ nm) in the electronic spectra. The intensity of this band increased with an increase in the concentration of the nonpolar component (Fig. 2). The equilibrium is reversible and can be shifted to the initial substances as the concentration of the nonpolar component in the mixed solution containing the polar solvent decreases.

Table 1 presents peak heights for anesthesin and novocainamide obtained for organic and water-organic solutions. The data of Table 1 demonstrate that the signal intensity increases with an increase in the concentration of water in the binary mixture. However, the signal intensities for aqueous solutions are lower than for organoaqueous mixtures. Studying the effect of solvents on the recorded signal reveals an important role of the basic properties of the solution. This effect becomes evident if we compare signals obtained for water-alcohol mixtures. For these mixtures, the peak heights differ for ethanol, propanol, and methanol, provided that the water concentration is equal. The experimental data testify that the solvent acts as a basic catalyst in the reaction of the substances under study with BFO. This effect was noticed in the previous studies on the flow-injection determination of hydrazine and a number of aromatic and heteroaromatic amines [5-7]. It should be pointed out that the PABA and PASA

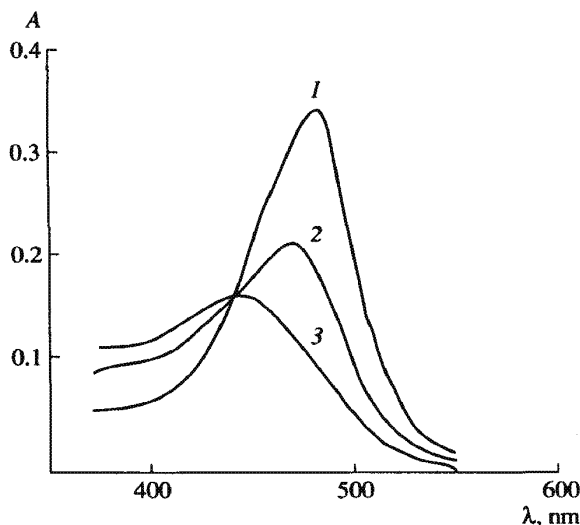


Fig. 2. Absorption spectra of the 5,7-dinitrobenzofurazan derivative of anesthesin (10^{-5} M) in dimethylsulfoxide recorded at various concentrations of chloroform (vol %): (1) 0, (2) 30, and (3) 60.

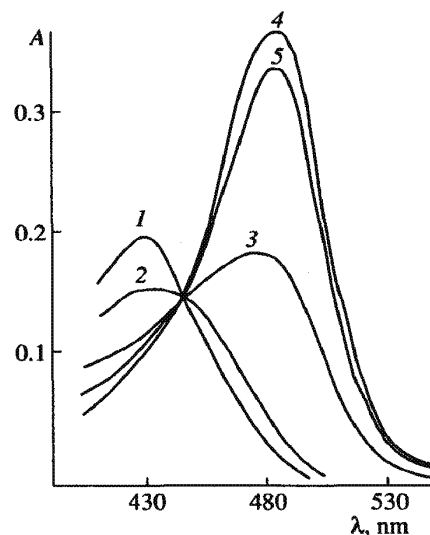


Fig. 3. Effect of pH on the absorption spectra of the 5,7-dinitrobenzofurazan derivative of anesthesin (10^{-5} M) in a dimethylsulfoxide-water solution (2 : 98, vol %): (1) 1.1, (2) 3.3, (3) 5.1, (4) 6.7, and (5) 9.18.

derivatives under study and their dinitrobenzofuroxan derivatives are poorly soluble in water and water–propanol solutions. Sedimentation processes that occur in aqueous solutions in a flow-injection system make the analysis difficult (almost impossible for anesthesin). At the same time, the solutions in ethanol (methanol)–water mixtures remain homogeneous. Therefore, the optimum ratio between the acidic and basic properties of the solvent and a sufficient solubility of both the source substances and the reaction products are achieved in ethanol (methanol)–water mixtures.

Optimization of pH. Because dinitrobenzoxazole derivatives exhibit acid properties (NH-acidity), the spectral properties (the positions of the absorption band and their intensities) are affected by the acidity of the solution. The intensity of the long-wave absorption bands decreases with an increase in the acidity of the solution (Fig. 3). Moreover, the rate of the formation of dinitrobenzofuroxan derivatives of the analytes in the flow system and, consequently, the magnitude of the analytical signals depends on the pH of the solution. For this reason, we examined the optimum conditions for the FIA determination of medicinal substances. Figure 4 shows a typical pH dependence of the peak height in determining novocainamide. As illustrated, the maximum intensities of the signals and, thus, the maximum sensitivity of determination are attained using a neutral solution. In an acid solution, the analytical reaction is suppressed. However, the high reactivity of BFO provides the detection of the reaction products even in acid solutions, although signal intensities in these solutions decrease significantly.

A decrease in the signal intensities in basic solutions is apparently due to the effect of the competing reaction of BFO with hydroxyl ions, which results in the formation of the hydroxyl derivative and in a decrease in the effective reagent concentration in the flow. Thus, we selected a phosphate buffer (pH 6.86) for the subsequent experiments.

Effect of the hydrodynamic parameters and the reagent concentration on the signal intensity. To select the working conditions for the determination of PABA and PASA derivatives in a flow-injection system, we studied the effect of the reagent concentration, flow rate of the carrier stream, and the length of the reaction coil on the intensity of the analytical signal. The height and shape of the peaks depended on the flow rate, the coil length (volume), and the injected sample volume. Moreover, the coil length and the flow rate affected the residence time of reaction zones in the system and, hence, the completeness of the chemical reaction. As an example, the data in Table 2 illustrate a typical dependence for anesthesin. As a whole, the dependence of the signal intensity for the substances under study on the flow rate of the carrier stream are flattened in the range 1–1.6 mL/min. We performed our experi-

Table 1. Effect of components on the signal intensity of dinitrobenzofuroxan derivatives. Concentration of the reagent 10^{-3} M; novocainamide (I), 4.5×10^{-6} M; and anesthesin (II), 7×10^{-6} M; flow rate 1.15 mL/min, λ 510 nm ($n = 4$)

Carrier-stream composition (vol %)	Analyte	Peak height (mean), mm
Methanol (100)	II	58
Methanol–water (85 : 15)	II	84
Methanol–water (70 : 30)	II	93
Methanol–water (50 : 50)	II	96
Methanol–water (30 : 70)	II	98
Methanol–water (15 : 85)	II	82
Methanol (100)	I	39
Methanol–water (30 : 70)	I	44
Ethanol (100)	I	45
Ethanol–water (70 : 30)	I	50
Ethanol–water (50 : 50)	I	53
Ethanol–water (30 : 70)	I	62
Ethanol–water (10 : 90)	I	51
Acetonitrile (100)	I	25
Acetonitrile–water (30 : 70)	I	43
DMSO (100)	I	20
DMSO–water (30 : 70)	I	36
Propanol-2 (100)	I	43
Propanol-2–water (30 : 70)	I	63
Water (100)	I	32

Table 2. Effect of the flow rate on the signal intensity. Concentration of BFO and anesthesin are 10^{-2} and 5.36×10^{-6} M, respectively; methanol–water (30 : 70 vol %); λ 510 nm ($n = 4$)

Flow rate, mL/min	Peak height (mean), mm
0.66	23
0.80	49
1.00	75
1.34	75
1.43	75
1.53	76
1.75	60
2.07	47
2.50	38

ments within this range. At low flow rates, a decrease in the signal intensity is due to diffusion processes. An increase in the coil length over 90 cm (inside diameter 0.6 mm) did not affect the signal intensity. In this case, the optimum injected volume was 110 μ L.

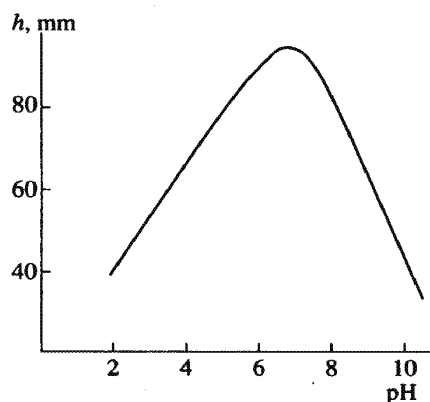


Fig. 4. pH dependence of the peak height of novocainamide (7.2×10^{-5} M); ethanol-phosphate buffer solution of pH 6.86 (0.06 M) (30 : 70, vol %); flow rate 1.3 mL/min.

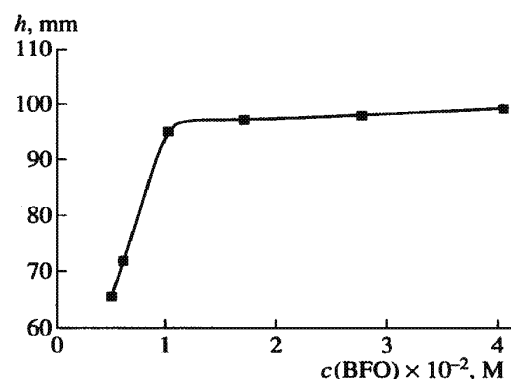


Fig. 5. Effect of the reagent concentration on the signal intensity in determining novocaine (5.6×10^{-6} M); methanol-water mixture (30 : 70, vol %); pH 7.12; flow rate 1.2 mL/min.

The selection of a solvent for the FIA determination of drugs is governed by the possible effect of the hydrolytic transformations of the reagents with the formation of inactive hydroxy derivatives [14]. We selected acetonitrile as a solvent, because it provided high hydrolytic stability of the reagent solutions [7]. The reagent concentrations in the injected solution in determining the drugs were $(1-2) \times 10^{-2}$ M. A decrease in the signal intensity was observed for the reagent concentrations lower than 8×10^{-3} M. Meanwhile, an increase in the BFO concentration to 4×10^{-2} M and higher made the flow inhomogeneous, which led to a baseline drift and hampered the analysis (Fig. 5).

Selectivity of the determination of PABA and PASA derivatives. The characteristics of the determinations of PABA and PASA derivatives under the optimized conditions are listed in Table 3. The data of Table 3 demonstrate that the calibration graphs for the analytes are linear within the range from 0.08 to 5.0 $\mu\text{g/mL}$. The detection limits (3σ , $n = 4$) are 0.04, 0.05, 0.07, and 0.03 $\mu\text{g/mL}$ for anesthesin, novocaine, novocainamide, and sodium 4-aminosalicylate, respectively.

The capabilities of the FIA spectrophotometric procedure in determining PABA and PASA derivatives in the matrices under study were tested using anesthesin, novocaine, and novocainamide in various model mixtures; pharmaceuticals; and biological liquids as examples (Tables 4, 5). It was preliminary found that tablet excipients did not affect the results of analysis. The results of analyses indicate that various components of biological fluids bearing functional amino groups (amino acids and biogenic amines) do not influence the results of FIA determination of the PABA and PASA derivatives. The experimental data also demonstrate that, in the analyses of protein hydrolyzate, serum albumin, blood plasma, and whole blood, the recorded signals insignificantly differ from the background signals. This fact allows the determination of PABA and PASA derivatives in these biological matrices. An insignificant decrease in the PASA concentration in blood samples (Table 4) is, probably, due to secondary reactions between the medicinal substance and the components of biological matrices of individual patients. Moreover, these substances can be selectively determined even in

Table 3. Analytical characteristics of flow-injection determinations of 4-aminobenzoic and 4-aminosalicylic acid derivatives

Analyte	Stream components (30 : 70, vol %)	Calibration function	<i>r</i>	Concentration range ($\mu\text{g/mL}$)	Throughput (samples/hour)
Anesthesin	Methanol-water	$h(\text{mm}) = 83.84c_X$ ($\mu\text{g/mL}$) - 0.4	0.9998	0.1-2.5	25
Novocaine	Methanol-phosphate buffer (pH 6.68)	$h(\text{mm}) = 63.73c_X$ ($\mu\text{g/mL}$) + 0.2	0.9998	0.12-3.5	24
Novocainamide	Ethanol-phosphate buffer (pH 6.68)	$h(\text{mm}) = 48.2c_X$ ($\mu\text{g/mL}$) - 0.8	0.9999	0.16-5.0	26
Sodium 4-aminosalicylate	Ethanol-phosphate buffer (pH 6.68)	$h(\text{mm}) = 95.1c_X$ ($\mu\text{g/mL}$) + 0.5	0.9999	0.08-2.5	28

Table 4. Determination of novocainamide and sodium 4-aminosalicylate in biological fluids using the standard addition method; ethanol-phosphate buffer solution of pH 6.86 (0.06 M) (30 : 70, vol %); carrier flow rate 1.3 mL/min

Biological fluid	Analyte	Added, µg/mL	Found ($\bar{c} \pm \delta$), µg/mL	RSD, % ($n = 4$, $P = 0.95$)
Protein hydrolyzate	PASA	0.55	0.60 ± 0.06	6
	Novocainamide	1.3	1.4 ± 0.1	6
Serum albumin	Novocainamide	0.85	0.90 ± 0.08	6
	PASA	1.8	1.8 ± 0.1	5
Blood plasma	Novocainamide	5.12	4.8 ± 0.4	5
	PASA	16.5	16 ± 1	5
Blood	PASA	4.30	3.9 ± 0.3	5
	Novocainamide	2.8	2.9 ± 0.2	5
	Novocainamide	10.25	10 ± 1	5
	PASA	28.1	28 ± 2	4

Table 5. Determination of 4-aminobenzoic and 4-aminosalicylic acid derivatives in pharmaceutical preparations; methanol-phosphate buffer solution of pH 6.86 (0.06 M) (30 : 70, vol %); carrier flow rate 1.3 mL/min ($n = 4$, $P = 0.95$)

Mixture composition	Analyte	Found according to the RF Pharmacopoeia, g	Found, g
Novocaine hydrochloride, 0.25 g HCl 0.1 M, 0.3 mL NaCl, 0.85 g Water to 100 mL	Novocaine	0.24 ± 0.01	0.25 ± 0.01
CaCl ₂ (6.0 g) solution, 200.0 mL NaBr, 4.0 g	Novocaine	0.98 ± 0.03	1.01 ± 0.03
Novocaine hydrochloride, 1.0 g Ephedrine hydrochloride, 6.0 g Novocaine hydrochloride 1%, 200 mL	Novocaine	1.98 ± 0.06	1.99 ± 0.06
Dimedrol, 2.0 g Atropine sulfate, 0.02 g Ephedrine hydrochloride, 0.05 g Novocaine hydrochloride, 0.04 g Water to 10.0 mL	Novocaine	0.043 ± 0.002	0.042 ± 0.002
Dimedrol, 0.025 g Ephedrine, 0.025 g Novocaine hydrochloride, 0.2 g NaCl, 0.06 g	Novocaine	0.18 ± 0.01	0.19 ± 0.01
Novocaine suppositories Novocaine, 0.1 g	Novocaine	0.11 ± 0.01	0.10 ± 0.01
Anesthesol suppositories Anesthesin, 0.1 g Dermatol, 0.04 g Zinc oxide, 0.02 g Menthol, 0.004 g Polyethylene-oxide matrix, to 2.73 mg	Anesthesin	0.095 ± 0.03	0.096 ± 0.02
Novocaine, 0.5 g Anesthesin, 0.5 g Menthol, 1.25 g Ethanol 70%, 50.0 g	Novocaine	0.49 ± 0.02	0.50 ± 0.02
	Anesthesin	0.48 ± 0.02	0.49 ± 0.01
Novocainamide tablets, 0.25 g	Novocainamide	0.23 ± 0.01	0.22 ± 0.01
Sodium 4-aminosalicylate, 3% solution for injections	Sodium 4-aminosalicylate	0.028 ± 0.002 g/mL	0.029 ± 0.003 g/mL

the presence of other drug constituents, such as inorganic salts, ephedrine, dimedrol, and others. Because of the selectivity of the analytical signal, 7-chloro-4,6-dinitrobenzofuroxan is superior to other reagents for derivatization in FIA.

Thus, spectral properties of 4,6-dinitrobenzofuroxan derivatives of medicinal substances provide their flow-injection determination in pharmaceuticals and biological fluids. Simple and rapid analytical procedures can be used in therapeutic monitoring in clinics.

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RETUSIN
 ROSMARINIC-ACID 790 LF NAP
 ROSMARINIC-ACID 4,000-16,600 PL ABS
 HHB NAP
 ROSMARINIC-ACID 55,000 PL FT62:166
 RUTIN PL PAS
 SABINENE 50-2,096 PL BML
 CIS-SABINENE-HYDRATE 1-46 PL BML
 SELINENE PL HHB
 SODIUM 109-205 PL USA
 SPATHULENOL 10-50 PL BML
 STACHYOSE PL HHB
 STEARIC-ACID 5,800-6,247 PL USA
 SYRINGIC-ACID PL NAP
 TANNINS 80,000 PL HHB
 TERPINEN-4-OL 17-390 PL BML
 ALPHA-TERPINENE 9-178 PL BML
 GAMMA-TERPINENE 1-1,476 PL BML
 JAD NAP
 TERPINOLENE 2-16 PL BML
 TERPINYL-ACETATE 54-216 PL BML
 THIAMIN 3-4 PL USA
 ALPHA-THUJENE 6-32 PL BML
 ALPHA-THUJONE PL BML
 THYMOL 2-5,000 PL BML HHB
 THYMYL-METHYL-ETHER 12-60 PL
 BML
 2-UNDECANONE 6-30 PL BML
 URSOLIC-ACID 3,100 PL HHB
 VANILLIC-ACID PL NAP
 VITEXIN PL PAS
 WATER 68,380-74,820 PL USA
 ZINC 39-49 PL USA

ORNITHOGALUM UMBELLATUM
L.

"STAR OF BETHLEHEM"

CONVALLOSIDE BU HHB
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 MUCILAGE BU HHB
 RHODEXIN-A BU HHB
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"RICE"

ACETALDEHYDE PL HHB
 ACETONE PL HHB
 TRANS-ACONITIC-ACID SH NAP
 ADENINE SD WOI
 D-ALANYL-D-ALANINE LF NAP
 D-ALANYL-GLYCINE LF NAP
 ALLANTOIN SD WOI

P-AMINOBENZOIC-ACID PL HHB
 AMYLOSE 0-131,075 SD WOI
 ANTHRAXANTHIN PL HHB
 D-ARABINO-1,4-LACTONE PL NAP
 ARABINOSE SD WOI
 ARACHIDIC-ACID SD HHB
 ARSENIC 0.211 SD HAM33(4):42
 ARUNDIN SH NAP
 ASCORBIC-ACID 0 SD CRC
 ASH 75,000-185,800 PL CRC WOI
 ASH 7,000-57,000 SD CRC
 ASPARAGINE 2.8-10.5 g/gL JU NAP
 ASPARTIC-ACID HA NAP
 BEHENIC-ACID SD HHB
 BUTANAL PL HHB
 CADMIUM 0.18 SD HAM33(4):42
 CALCIUM 1,900-3,300 PL CRC WOI
 CALCIUM 71-364 SD CRC
 CAMPESTEROL PL HHB
 CARBOHYDRATES 430,000-478,000 PL
 CRC WOI
 CARBOHYDRATES 734,000-892,000 SD
 CRC
 CARLINSIDE LF NAP
 BETA-CAROTENE 0 SD CRC
 CASTASTERONE 13.6 PPT SH NAP
 CELLOPENTAOSYLSITOSTEROL PL
 JSG
 CELLOTETRAOSYLSITOSTEROL PL
 JSG
 CELLULOSE 190,000-210,000 FR HU
 WOI
 CELLULOSE 340,000-534,600 PL ABS 1/
 WOI
 CERAMIDE 15 SH NAP
 CERYL-CEROTATE FR WOI
 CHOLINE 880 SD WOI
 CHRYSANTHEMIN PL HHB
 COPROSTAN PL HHB
 CORONARIC-ACID 0.1 SH NAP
 P-COUMARIC-ACID 0.9 PE NAP
 CYANIDIN-DIGLYCOSIDE LF NAP
 CYANIDIN-5-GLYCOSIDE LF NAP
 CYANIDIN-MONOGLYCOSIDE LF
 NAP
 CYANIN PL HHB
 CYCLOARTANOL PL HHB
 CYCLOARTENOL PL HHB
 CYCLOBRANOL PL HHB
 CYCLOEUCALENOL SD NAP
 CYLINDRIN SH NAP
 CYSTEINE PL PAS
 BETA-CYCLOORYSTENOL SD HHB
 (+)-DEHYDROVOMIPOLIOL 1 PE NAP

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Search Notes 	Application/Control No. 10378956	Applicant(s)/Patent Under Reexamination ZAWOROTKO ET AL.
	Examiner SAHAR JAVANMARD	Art Unit 1627

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
424	400 (update 5/19/14)	9/30/2008	

SEARCH NOTES		
Search Notes	Date	Examiner
EAST (searched each inventor name)(update 6/17/10)	8/31/2009	SJ
EAST (keyword search)(update 6/17/10)	8/31/2009	SJ
Pubmed	8/31/2009	SJ
Google	8/31/2009	SJ
(update 6/11/15)		SJ
Google Patents (search amine acid cocrystal; aspirin cocrystal; bipyridine cocrystal)	6/11/2015	SJ
updated 2/21/16		SJ

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

/SAHAR JAVANMARD/ Examiner.Art Unit 1627	
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To: Patents_eOfficeAction@WolfGreenfield.com,WGS_eOfficeAction@WolfGreenfield.com,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 23628

Feb 25, 2016 05:33:02 AM

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UNITED STATES

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Application	Document	Mailroom Date	Attorney Docket No.
10378956	CTNF	02/25/2016	U0157.70023US01
	892	02/25/2016	U0157.70023US01
	1449	02/25/2016	U0157.70023US01

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UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

Docket No.: U0157.70023US01
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor: Michael J. Zaworotko
Application No.: 10/378,956
Confirmation No.: 4742
Filed: March 3, 2003
For: MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT
LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT
Examiner: S. Javanmard
Art Unit: 1627

Certificate of Electronic Filing Under 37 CFR 1.8

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: July 25, 2016

Electronic Signature for Allison E. Parker: /Allison E. Parker/

**AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION UNDER 37 C.F.R. §
1.111**

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

INTRODUCTORY COMMENTS

In response to the Office Action dated February 25, 2016 please amend the above-identified U.S. patent application as follows. This paper is filed along with a petition for a two month extension of time, thereby extending the period of response to July 25, 2016.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 6 of this paper.

4612870.1

Claims

Please replace all prior versions, and listings, of claims in the application with the following list of claims:

1-27. (Canceled)

28. (Currently Amended) The method of claim [[25]]58, wherein said preparing comprises crystallization from solution, crystallization from a melt, sublimation, or grinding.

29-36. (Canceled)

37. (Currently Amended) The method according to claim [[25]]58, wherein said API is selected from aspirin, ibuprofen, flurbiprofen, carbamazepine, phenytoin or acetaminophen.

38. (Canceled)

39. (Currently Amended) The method of claim [[25]]58, wherein the co-crystal former is a GRAS compound.

40. (Currently Amended) The method of claim [[25]]58, wherein the co-crystal former is a food additive.

41. (Currently Amended) The method of claim [[25]]58, wherein the co-crystal former is a low toxicity organic.

42. (Currently Amended) The method of claim [[25]]58, wherein the co-crystal former is a metal organic complex.

43. (Currently Amended) The method of claim ~~[[25]]~~58, wherein the co-crystal former comprises at least two heterocyclic groups.

44. (Currently Amended) The method of claim ~~[[25]]~~58, wherein the co-crystal former is bipyridine.

45. (Currently Amended) The method of claim ~~[[25]]~~58, wherein the co-crystal former is bis(pyridyl)ethene.

46. (Currently Amended) The method of claim ~~[[25]]~~58, wherein said homosynthon is identified from the crystal structure of said API.

47. (Currently Amended) The method of claim ~~[[25]]~~58, wherein said homosynthon is identified by determining the structure of at least one pure solid phase of said API.

48. (Currently Amended) The method of claim ~~[[25]]~~58, wherein the complementary second chemical functionality is an unsaturated N-heterocycle, saturated N-heterocycle, aldehyde, amide, carboxylic acid, nitro, ketone, or sulfoxide.

49. (Currently Amended) The method of claim ~~[[25]]~~58, wherein the complementary second chemical functionality is a carboxylic acid.

50-57. (Canceled)

58. (Currently Amended) A method for the preparation of a pharmaceutical product containing a co-crystal, said method comprising:

(a) providing an active pharmaceutical ingredient (API) comprising a first chemical functionality, wherein said first chemical functionality forms a first crystal of API homosynthons that is non-covalent hydrogen bonding;

(b) selecting a co-crystal former having a second chemical functionality complementary to the first chemical functionality via non-covalent bonding, wherein said co-crystal former forms a supramolecular synthon by non-covalent hydrogen bonding between the first chemical functionality of the API and the complementary second chemical functionality of said co-crystal former, wherein said selected co-crystal former in its pure form is a solid at room temperature and atmospheric pressure, and wherein the co-crystal former is not an active pharmaceutical ingredient;

(c) preparing a co-crystal ~~of~~ using stoichiometric proportions of said API and said co-crystal former, said co-crystal consisting of said supramolecular synthon, and

(d) combining said co-crystal with a pharmaceutically acceptable carrier to form the pharmaceutical product, and wherein the first chemical functionality is a carboxylic acid, a carboxamide, a carbonyl or an amine.

59. (Previously Presented) The method of claim 58, wherein said co-crystal comprises heterosynthons of said co-crystal former and said API.

60. (Previously Presented) The method of claim 58, wherein said co-crystal comprises homosynthons of said API.

61. (Canceled)

62. (Previously Presented) The method of claim 58, wherein said complementary second chemical functionality is an amine, amide, or unsaturated aromatic nitrogen base.

63. (Previously Presented) The method of claim 58, wherein the non-covalent bonding between said co-crystal former and complementary second chemical functionality and said first chemical functionality of said API to form said supramolecular synthon comprises carbonyl:amine hydrogen bonding.

64. (Previously Presented) The method of claim 58, wherein the non-covalent bonding between said co-crystal former and complementary second chemical functionality and said first chemical

functionality of said API to form said supramolecular synthon comprises carboxylic acid:pyridine hydrogen bonding.

65. (Previously Presented) The method of claim 60, wherein the non-covalent bonding of said homosynthons of said API is carboxylic acid:carboxylic acid hydrogen bonding.

66. (Previously Presented) The method of claim 60, wherein the non-covalent bonding of said homosynthons of said API is carboxamide:carboxamide hydrogen bonding.

REMARKS

Applicant respectfully requests reconsideration. Claims 25, 28, 37, 39-51, 53-60 and 62-66 were previously pending in this application. Claims 25, 50, 51, and 53-57 have been canceled without prejudice or disclaimer. Claims 28, 37, 39-49, and 58 have been amended. As a result, claims 28, 37, 39, 39-49, 58-60, and 62-66 are pending for examination with claim 58 being an independent claim. No new matter has been added.

Interview Summary

Applicant thanks Examiner Javanmard and Examiner Padmanabhan for the courtesy of a telephone interview on February 24, 2016 with Applicant's representatives Edward Gates and Jessica Colantonio. During the interview, the obviousness rejection over McCoy was discussed.

Double Patenting Rejection

The Examiner provisionally rejected claims 25, 28, 37, 39-51, 53-60 and 62-66 as allegedly being unpatentable over claims 37-50 and 52-58 of co-pending application 14/179,862.

Respectfully, Applicant does not concede to the rejection. Applicant also respectfully requests that this rejection be held in abeyance until the Examiner has agreed to otherwise allowable subject matter in the instant case. Only then can Applicant fashion an appropriate strategy and response.

Rejections under 35 U.S.C. §103

McCoy

The Examiner rejected claims 25, 39-42, 46-51, 53-60 and 62-66 under 35 U.S.C. §103(a) as being unpatentable over McCoy (CA 1148020A1). Reconsideration is respectfully requested in light of the amendments and arguments presented herein.

The instant claims relate to preparation of a pharmaceutical product containing a co-crystal, and have been amended to further clarify that the methods require preparation of a co-crystal *using stoichiometric proportions* of the active pharmaceutical ingredient (API) and the selected co-crystal former.

In contrast to the instantly claimed methods, McCoy discloses physical mixtures of multiple components in a range of *non-stoichiometric* ratios. Indeed, McCoy discloses that “[g]enerally, an effective amount of cocrystallizer material will be such that the *ratio by weight* of the amount of cocrystallizer to the amount of edible amino acid salt is from about 0.9:1 to about 6:1. Preferably, equal amounts of cocrystallizer are used.” (McCoy, page 7, lines 10-15, emphasis added). The equal amounts of cocrystallizer disclosed by McCoy are equal amount by *weight*, not equal amount by *moles*.

The Examiner appreciates that “McCoy teaches the amount of cocrystallizer to the amount of edible amino acid salt by weight and not in stoichiometric proportions” as recited in the instant claims (Office Action, page 8). However, the Examiner contends that “the range disclosed for the ratio between cocrystallizer and edible amino acid salt would encompass a cocrystal that is also stoichiometrically proportional”, and therefore, the skilled artisan would appreciate that “the range of 0.9:1 to about 6:1 embraces the possibility of such proportions” (Office Action, page 8). Applicant respectfully submits that the Examiner has not established a *prima facie* case of obviousness.

“‘[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.’” (KSR, 550 U.S. at 418, 82 USPQ2d at 1396). Here, the Examiner contends that the range of 0.9:1 to about 6:1 embraces the *possibility* of stoichiometric proportions. The mere *possibility* of embracing a stoichiometric proportion of co-crystal components does not make the selection of the stoichiometric proportion obvious. The Examiner does not articulate any reasoning (nor does the art provide any such reasoning) that one of skill in the art would have been motivated to select a stoichiometrically proportional amount of co-crystal components in view of the disclosure of the range of *non-stoichiometric* ratios disclosed by McCoy. The obviousness rejection levied by the Examiner is supported only by conclusory statements and is therefore improper.

Furthermore, the disclosure in McCoy provides no motivation to select stoichiometric amounts of co-crystal components. In making a determination of such a motivation, “where there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of

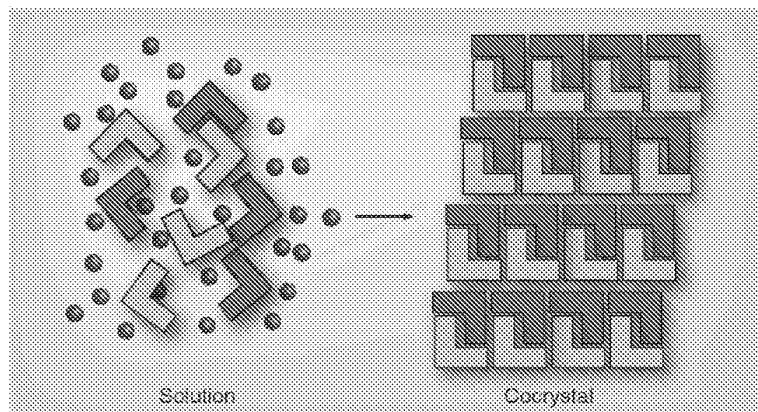
production falls upon the patentee to come forward with evidence that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations. (citation omitted)” Galderma Laboratories, L.P. v. Tolmar, Inc., 737 F.3d 731 (Fed.Cir.2013) at 738. Unexpected results that are probative of nonobviousness are those that are “different in kind and not merely in degree from the results of the prior art. (citation omitted)” Id. at 739. In Galderma, the prior art disclosed 0.01%–1% adapalene, which encompassed the claimed composition comprising 0.3% adapalene. The expected result was an increase by some percentage in the prevalence of certain side effects, which increase did not materialize. This unexpected tolerability of the 0.3% adapalene was a difference merely in *degree* (of side effects), and not in kind. See Id.

In contrast, the instantly claimed methods provide unexpected results which are different in *kind* from the prior art, not merely in degree. The unexpected difference between the instant claims and the cited art is the difference between a pure co-crystal, e.g., as obtained using the claimed methods, and a non-crystalline structure, such as an amorphous solid or a mix of crystalline and amorphous phase.

Stoichiometric proportions, as recited in the instant claims, are important for intermolecular interactions between two or more independent molecular entities in a co-crystal. Indeed, as provided in the review article by Almarsson, “[c]ocrystals are a class of crystalline solids that occur when complementary molecules of different structures are crystallized to form single crystalline phases that contain stoichiometric ratios of the components” (Almarsson et al.; Pharm. Pat. Analyst 1(3):313-327 (2012); of record).

Co-crystal formers encompassed by the presently claimed methods also contribute to the co-crystal structure in that they are complementary in supramolecular chemistry, i.e., they form supramolecular synthons with the API molecules” (see, e.g., paragraph [0009] of the instant application). These multiple-component solids “exhibit physical properties different from the parent pharmaceutical ingredient as a direct result of hydrogen bonding interaction”, which “can afford improved drug solubility, dissolution rate, stability and bioavailability, for example” (see, e.g., paragraph [0039] of the instant application). Figure 1 of Almarsson et al., reproduced below for the Examiner’s convenience, provides a prototypical example of a 1:1 composition co-crystal,

and demonstrates that stoichiometric ratios of the complementary components permit formation of the co-crystal structure, e.g., a repeating array of molecules or ions in three dimensions.



Almarsson et al.; Pharm. Pat. Analyst 1(3):313-327 (2012) (page 314)

The instant application provides many examples of multiple-component phase preparations which “confirm the ability to persistently and rationally disrupt the homosynthon by judicious choice of a second molecular component that is predisposed to form a supramolecular heterosynthon.” (paragraph [0057] of the instant application). Cocrystals were prepared using stoichiometric proportions of the API and the co-crystal former.

In contrast to the instantly claimed methods, McCoy discloses physical mixtures of multiple components where the *ratio by weight* of the amount of cocrystallizer to the amount of edible amino acid salt ranges from about 0.9:1 to about 6:1. McCoy discloses examples of such physical mixtures, none of which specifically read on *stoichiometric* ratios. Example 5 in McCoy is the closest example Applicant identified, which uses a 3:1 weight ratio of components, corresponding to a 1.05:1 molar ratio, which is not a stoichiometric ratio.

There is no evidence in McCoy that the mixture of the amino acid material and soluble edible cocrystallizer material in non-stoichiometric amounts leads to the formation of a crystalline structure, e.g., a repeating array of molecules or ions in three dimensions, for example, as opposed to an amorphous solid or some other structure. McCoy discloses freeze drying of the mixture of amino acid material and soluble edible cocrystallizer material. (McCoy, page 7, lines 17-19). One of ordinary skill in the art would understand freeze drying to produce an amorphous solid or a mix

of crystalline and amorphous phase (e.g., Bedu-Addo, *Pharmaceutical Technology Lyophilization* 10-18 2004; of record). However, one skilled in the art would also understand you would not use freeze drying in order to get an ordered supramolecular synthon as presently claimed. Instead, at the time of the invention, one of skill in the art would have understood that co-crystals can be prepared by melt-crystallization, grinding, or recrystallization from solvents. (see Almarsson et al., *Chem Comm* 1889-1896 (2004) at page 1892, left column; of record).

As further support of the non-obviousness of the claimed invention, there was a long-felt but unsolved need for predictable crystal engineering technology at the time of the present invention. Indeed, as disclosed at paragraph [0003] of the instant application:

“Physical properties of crystalline solids are critically dependent on the internal arrangement of molecules or ions, making prediction of composition, crystal structure and morphology from knowledge of molecular structure a scientific challenge of the highest order. However, crystal structure prediction and even prediction of composition remains a largely unmet goal.” (WO2003/074474, paragraph [0003]).

Prior to the present invention, cocrystal engineering relied heavily on *empirical* determination of structures. The instant application teaches an expectation that pharmaceutical compounds will form pharmaceutical co-crystals if (a) the pharmaceutical will form a homosynthon and (b) one selects a co-crystal co-former that will form a supramolecular synthon with the pharmaceutical via non-covalent hydrogen bonding. In addition, Dr. Zoworotko co-authored an early and key review in 2004 summarizing pharmaceutical cocrystal technology. The review suggested that pharmaceutical cocrystals are amenable to design and allow a selection of motifs that can effect pharmaceutical properties. (Almarsson et al., *Chem Comm* 1889-1896 (2004); of record). To-date, this review article has been cited 393 times¹. Thus, the instant application provided a transformative technology which allowed predictable crystal engineering, which was previously lacking in the art.

For at least these reasons, McCoy does not teach or suggest the methods for preparing pharmaceutical products containing co-crystals as recited by the present claims.

¹ According to Google Scholar Citations accessed on July 25, 2016

Huffman

The Examiner rejected claims 25, 28, 37, 39-43, 46-51 and 53-57 under 35 U.S.C. §103(a) as being unpatentable over Huffman (US Patent No.: 3,664,858).

Without conceding to the correctness of the rejection, and solely to advance prosecution, claims 25, 50, 51, and 53-57 have been canceled. Claims 28, 37, 39-43, and 46-49 have been amended to depend from claim 58, which was not rejected as being unpatentable over Huffman. Thus, the rejection is moot and should be withdrawn.

Smith, Evgen'ev, and Duke

The Examiner rejected claims 25, 28, 39-41, 46-51, 53-56 and 58-60 under 35 U.S.C. §103(a) as being unpatentable over Smith (Journal of Chemical Crystallography, 1997) in view of Evgen'ev (Journal of Analytical Chemistry, 2000) as evidenced by Duke (Handbook of Phytochemical Constituents of GRAS Herbs and Other Economic Plants, 2001). Reconsideration is respectfully requested in light of the amendments and arguments presented herein.

The combination of cited references does not provide all of the elements of the claimed invention, and thus cannot render the claimed invention obvious. In particular, the combination of cited references does not teach or suggest methods for preparation of a pharmaceutical product containing a co-crystal, including selecting co-crystal formers and predicting co-crystal structure.

Smith discloses *empirical* determination of 4-amino-benzoic acid adducts with nitro-substituted aromatic compounds. Smith does not disclose crystal structure prediction. Indeed, Smith discloses that “prediction of the general outcome of the crystallization process is not as yet a reality in the design of organic compounds with NLO properties.” (Smith, page 317, left column).

As discussed above, prior to the present invention, there were challenges to crystal engineering, as disclosed at paragraph [0003] of the instant application:

“Physical properties of crystalline solids are critically dependent on the internal arrangement of molecules or ions, making prediction of composition, crystal structure and morphology from knowledge of molecular structure a scientific challenge of the highest order. However, crystal structure prediction and even

prediction of composition remains a largely unmet goal.” (WO2003/074474, paragraph [0003]).

The instant application teaches an expectation that pharmaceutical compounds will form pharmaceutical co-crystals if (a) the pharmaceutical will form a homosynthon and (b) one selects a co-crystal co-former that will form a supramolecular synthon with the pharmaceutical via non-covalent hydrogen bonding. Indeed, the instant application provides many examples of multiple-component phase preparations which “confirm the ability to persistently and rationally disrupt the homosynthon by judicious choice of a second molecular component that is predisposed to form a supramolecular heterosynthon.” (paragraph [0057] of the instant application). The instantly claimed methods facilitated prediction and preparation of 19 co-crystals, as exemplified in the instant application - an unprecedented feat at the time of the invention.

Furthermore, APIs could not only be used to make co-crystals using the instantly claimed methods, but the application demonstrates that such co-crystals exhibit improved characteristics as compared to the API alone. Indeed, these multiple-component solids “exhibit physical properties different from the parent pharmaceutical ingredient as a direct result of hydrogen bonding interaction”, which “can afford improved drug solubility, dissolution rate, stability and bioavailability, for example” (see, e.g., paragraph [0039] of the instant application).

Smith does not disclose the instantly claimed methods, including (a) providing an API that will form a homosynthon, and (b) selecting a co-crystal co-former that will form a supramolecular synthon with the API via non-covalent hydrogen bonding. The Examiner cited Evgen’ev for its alleged disclosure that 4-ABA is employed in medicine, and Duke for its alleged disclosure that 4-ABA is a GRAS compound (Office Action, page 14). The disclosures of Evgen’ev and Duke do not cure the deficiencies in the disclosure of Smith to render the instant claims obvious.

Accordingly, withdrawal of this rejection is respectfully requested.

CONCLUSION

In view of the foregoing, the present application is believed to be in condition for allowance. A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. U0157.70023US01.

Dated: July 25 , 2016

Respectfully submitted,

By /Jessica R. Colantonio/ _____
Edward R. Gates
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Electronic Patent Application Fee Transmittal				
Application Number:		10378956		
Filing Date:		03-Mar-2003		
Title of Invention:		Multiple-component solid phases containing at least one active pharmaceutical ingredient		
First Named Inventor/Applicant Name:		Michael J. Zaworotko		
Filer:		Jessica Russell Colantonio/Allison Parker		
Attorney Docket Number:		U0157.70023US01		
Filed as Small Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension - 2 months with \$0 paid	2252	1	300	300
Miscellaneous:				
Total in USD (\$)				300

Electronic Acknowledgement Receipt	
EFS ID:	26445739
Application Number:	10378956
International Application Number:	
Confirmation Number:	4742
Title of Invention:	Multiple-component solid phases containing at least one active pharmaceutical ingredient
First Named Inventor/Applicant Name:	Michael J. Zaworotko
Customer Number:	23628
Filer:	Jessica Russell Colantonio/Allison Parker
Filer Authorized By:	Jessica Russell Colantonio
Attorney Docket Number:	U0157.70023US01
Receipt Date:	25-JUL-2016
Filing Date:	03-MAR-2003
Time Stamp:	15:50:31
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	\$ 300
RAM confirmation Number	072616INTEFSW15521200
Deposit Account	8543
Authorized User	Wolf Greenfield
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	U015770023US01-TRN-JQC.pdf	24367	no	1
			5811737112f220f2cd9beb71a30bcb04e9a ecba6		

Warnings:

Information:

2	Examination support document	U015770023US01-EXT-JQC.pdf	23392	no	1
			23a62d08593c972df99fb3f202781f56b88c f64		

Warnings:

Information:

3	Fee Worksheet (SB06)	U015770023US01-FEE-JQC.pdf	31560	no	1
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Warnings:

Information:

4		U015770023US01-AMN-JQC. pdf	160049	yes	13
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Multipart Description/PDF files in .zip description

	Document Description	Start	End
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	5
	Applicant Arguments/Remarks Made in an Amendment	6	13

Warnings:

Information:

5	Fee Worksheet (SB06)	fee-info.pdf	30419	no	2
			d62a39a2a974fe26912181f7f33713de74fd b06f		

UM00017595

NOVARTIS EXHIBIT 1017

Novartis v. Regents, IPR2023-01346

Page 4423 of 4460

Warnings:	
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Total Files Size (in bytes):	269787
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TRANSMITTAL FORM <i>(to be used for all correspondence after initial filing)</i>	Application Number	10/378,956-Conf. #4742
	Filing Date	March 3, 2003
	First Named Inventor	Michael J. Zaworotko
	Art Unit	1627
	Examiner Name	S. Javanmard
Total Number of Pages in This Submission	Attorney Docket Number	U0157.70023US01

ENCLOSURES (Check all that apply)			
☒ Fee Transmittal Form ☐ Fee Attached ☒ Amendment/Reply ☐ After Final ☐ Affidavits/declaration(s) ☒ Extension of Time Request ☐ Express Abandonment Request ☐ Information Disclosure Statement ☐ Certified Copy of Priority Document(s) ☐ Reply to Missing Parts/ Incomplete Application ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53	☐ Drawing(s) ☐ Licensing-related Papers ☐ Petition ☐ Petition to Convert to a Provisional Application ☐ Power of Attorney, Revocation Change of Correspondence Address ☐ Terminal Disclaimer ☐ Request for Refund ☐ CD, Number of CD(s) _____ ☐ Landscape Table on CD	☐ After Allowance Communication to TC ☐ Appeal Communication to Board of Appeals and Interferences ☐ Appeal Communication to TC (Appeal Notice, Brief, Reply Brief) ☐ Proprietary Information ☐ Status Letter ☐ Other Enclosure(s) (please Identify below):	
<table border="1"><tr><td>Remarks</td></tr></table>			Remarks
Remarks			

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT			
Firm Name	WOLF, GREENFIELD & SACKS, P.C.		
Signature	/Jessica R. Colantonio/		
Printed name	Jessica R. Colantonio, Ph.D.		
Date	July 25, 2016	Reg. No.	66,132

Certificate of Electronic Filing Under 37 CFR 1.8 I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4). Dated: July 25, 2016 Electronic Signature for Allison E. Parker: /Allison E. Parker/	
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4884984.1

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)		Docket Number (Optional) U0157.70023US01																																			
Application Number 10/378,956-Conf. #4742		Filed March 3, 2003																																			
For MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT																																					
Art Unit 1627		Examiner S. Javanmard																																			
This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application. The requested extension and fee are as follows (check time period desired and enter the appropriate fee below): <table border="0" style="width: 100%;"><thead><tr><th></th><th style="text-align: center;">Fee</th><th style="text-align: center;">Small Entity Fee</th><th style="text-align: center;">Micro Entity Fee</th><th></th></tr></thead><tbody><tr><td>☐ One month (37 CFR 1.17(a)(1))</td><td style="text-align: center;">\$200</td><td style="text-align: center;">\$100</td><td style="text-align: center;">\$50</td><td>\$ _____</td></tr><tr><td>☒ Two months (37 CFR 1.17(a)(2))</td><td style="text-align: center;">\$600</td><td style="text-align: center;">\$300</td><td style="text-align: center;">\$150</td><td>\$ 300.00</td></tr><tr><td>☐ Three months (37 CFR 1.17(a)(3))</td><td style="text-align: center;">\$1,400</td><td style="text-align: center;">\$700</td><td style="text-align: center;">\$350</td><td>\$ _____</td></tr><tr><td>☐ Four months (37 CFR 1.17(a)(4))</td><td style="text-align: center;">\$2,200</td><td style="text-align: center;">\$1,100</td><td style="text-align: center;">\$550</td><td>\$ _____</td></tr><tr><td>☐ Five months (37 CFR 1.17(a)(5))</td><td style="text-align: center;">\$3,000</td><td style="text-align: center;">\$1,500</td><td style="text-align: center;">\$750</td><td>\$ _____</td></tr></tbody></table> ☒ Applicant asserts small entity status. See 37 CFR 1.27. ☐ Applicant certifies micro entity status. See 37 CFR 1.29. Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously. ☐ A check in the amount of the fee is enclosed. ☒ Payment by credit card. ~~Form PTO-2038 is attached.~~ ☐ The Director has already been authorized to charge fees in this application to a Deposit Account. ☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 23/2825 . ☒ Payment made via EFS-Web. WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038. I am the ☐ applicant/inventor. ☐ assignee of record of the entire interest. See 37 CFR 3.71. 37 CFR 3.73(b) statement is enclosed (Form PTO/SB/96). ☒ attorney or agent of record. Registration number 66,132 . ☐ attorney or agent acting under 37 CFR 1.34. Registration number _____ . <table border="0" style="width: 100%;"><tr><td style="width: 50%; text-align: center;">_____ /Jessica R. Colantonio/ Signature</td><td style="width: 50%; text-align: center;">_____ July 25, 2016 Date</td></tr><tr><td style="text-align: center;">_____ Jessica R. Colantonio, Ph.D. Typed or printed name</td><td style="text-align: center;">_____ 617.646.8000 Telephone Number</td></tr></table> NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*. ☐ * Total of 1 forms are submitted.					Fee	Small Entity Fee	Micro Entity Fee		☐ One month (37 CFR 1.17(a)(1))	\$200	\$100	\$50	\$ _____	☒ Two months (37 CFR 1.17(a)(2))	\$600	\$300	\$150	\$ 300.00	☐ Three months (37 CFR 1.17(a)(3))	\$1,400	\$700	\$350	\$ _____	☐ Four months (37 CFR 1.17(a)(4))	\$2,200	\$1,100	\$550	\$ _____	☐ Five months (37 CFR 1.17(a)(5))	\$3,000	\$1,500	\$750	\$ _____	_____ /Jessica R. Colantonio/ Signature	_____ July 25, 2016 Date	_____ Jessica R. Colantonio, Ph.D. Typed or printed name	_____ 617.646.8000 Telephone Number
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I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).	
Dated: July 25, 2016	Electronic Signature for Allison E. Parker: /Allison E. Parker/

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FEE TRANSMITTAL		Complete if known																																																																																				
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		First Named Inventor	Michael J. Zaworotko																																																																																			
		Examiner Name	S. Javanmard																																																																																			
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TOTAL AMOUNT OF PAYMENT	(\$) 300.00	Practitioner Docket No.	U0157.70023US01																																																																																			
METHOD OF PAYMENT (check all that apply) ☐ Check ☒ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____ ☐ Deposit Account Deposit Account Number: <u>23/2825</u> Deposit Account Name: <u>Wolf, Greenfield & Sacks, P.C.</u> For the above-identified deposit account, the Director is hereby authorized to (check all that apply): ☐ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, except for the filing fee ☒ Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17 ☒ Credit any overpayment of fee(s) WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.																																																																																						
FEE CALCULATION 1. BASIC FILING, SEARCH, AND EXAMINATION FEES (U = undiscounted fee; S = small entity fee; M = micro entity fee)																																																																																						
<table border="0" style="width: 100%;"><tr><td></td><td colspan="3" style="text-align: center;">FILING FEES</td><td colspan="3" style="text-align: center;">SEARCH FEES</td><td colspan="3" style="text-align: center;">EXAMINATION FEES</td><td></td></tr><tr><td style="text-align: left;"><u>Application Type</u></td><td><u>U (\$)</u></td><td><u>S (\$)</u></td><td><u>M (\$)</u></td><td><u>U (\$)</u></td><td><u>S (\$)</u></td><td><u>M (\$)</u></td><td><u>U (\$)</u></td><td><u>S (\$)</u></td><td><u>M (\$)</u></td><td style="text-align: right;"><u>Fees Paid (\$)</u></td></tr><tr><td>Utility</td><td>280</td><td>140*</td><td>70</td><td>600</td><td>300</td><td>150</td><td>720</td><td>360</td><td>180</td><td></td></tr><tr><td>Design</td><td>180</td><td>90</td><td>45</td><td>120</td><td>60</td><td>30</td><td>460</td><td>230</td><td>115</td><td></td></tr><tr><td>Plant</td><td>180</td><td>90</td><td>45</td><td>380</td><td>190</td><td>95</td><td>580</td><td>290</td><td>145</td><td></td></tr><tr><td>Reissue</td><td>280</td><td>140</td><td>70</td><td>600</td><td>300</td><td>150</td><td>2,160</td><td>1,080</td><td>540</td><td></td></tr><tr><td>Provisional</td><td>260</td><td>130</td><td>65</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td></td></tr></table>											FILING FEES			SEARCH FEES			EXAMINATION FEES				<u>Application Type</u>	<u>U (\$)</u>	<u>S (\$)</u>	<u>M (\$)</u>	<u>U (\$)</u>	<u>S (\$)</u>	<u>M (\$)</u>	<u>U (\$)</u>	<u>S (\$)</u>	<u>M (\$)</u>	<u>Fees Paid (\$)</u>	Utility	280	140*	70	600	300	150	720	360	180		Design	180	90	45	120	60	30	460	230	115		Plant	180	90	45	380	190	95	580	290	145		Reissue	280	140	70	600	300	150	2,160	1,080	540		Provisional	260	130	65	0	0	0	0	0	0	
	FILING FEES			SEARCH FEES			EXAMINATION FEES																																																																															
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* The \$140 small entity status filing fee for a utility application is further reduced to \$70 for a small entity applicant who files the application via EFS-Web.																																																																																						
2. EXCESS CLAIM FEES																																																																																						
Fee Description				<u>Undiscounted Fee (\$)</u>		<u>Small Entity Fee (\$)</u>		<u>Micro Entity Fee (\$)</u>																																																																														
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Each independent claim over 3 (including Reissues)				420		210		105																																																																														
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3. APPLICATION SIZE FEE																																																																																						
If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is \$400 (\$200 for small entity) (\$100 for micro entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).																																																																																						
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4. OTHER FEE(S)																																																																																						
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Non-English specification, \$130 fee (no small or micro entity discount)																																																																																						
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SUBMITTED BY																																																																																						
Signature	/Jessica R. Colantonio/				Registration No. (Attorney/Agent)	66,132	Telephone	617.646.8000																																																																														
Name (Print/Type)	Jessica R. Colantonio, Ph.D.				Date	July 25, 2016																																																																																

Certificate of Electronic Filing Under 37 CFR 1.8	
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Dated: July 25, 2016	Electronic Signature for Allison E. Parker: /Allison E. Parker/

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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875					Application or Docket Number 10/378,956		Filing Date 03/03/2003		☐ To be Mailed				
ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO													
APPLICATION AS FILED – PART I													
(Column 1)		(Column 2)											
FOR		NUMBER FILED		NUMBER EXTRA		RATE (\$)		FEE (\$)					
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))		N/A		N/A		N/A							
☐ SEARCH FEE (37 CFR 1.16(k), (l), or (m))		N/A		N/A		N/A							
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))		N/A		N/A		N/A							
TOTAL CLAIMS (37 CFR 1.16(j))		minus 20 =		*		X \$		=					
INDEPENDENT CLAIMS (37 CFR 1.16(h))		minus 3 =		*		X \$		=					
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))		If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).											
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))													
						TOTAL							
* If the difference in column 1 is less than zero, enter "0" in column 2.													
APPLICATION AS AMENDED – PART II													
(Column 1)		(Column 2)		(Column 3)									
AMENDMENT	07/25/2016	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR		PRESENT EXTRA		RATE (\$)		ADDITIONAL FEE (\$)			
	Total (37 CFR 1.16(i))	* 21	Minus	** 29	= 0		X \$40 =		0				
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0		X \$210 =		0				
	☐ Application Size Fee (37 CFR 1.16(s))												
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))												
						TOTAL ADD'L FEE		0					
(Column 1)		(Column 2)		(Column 3)									
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR		PRESENT EXTRA		RATE (\$)		ADDITIONAL FEE (\$)			
	Total (37 CFR 1.16(i))	*	Minus	**	=		X \$		=				
	Independent (37 CFR 1.16(h))	*	Minus	***	=		X \$		=				
	☐ Application Size Fee (37 CFR 1.16(s))												
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))												
						TOTAL ADD'L FEE							
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3. ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20". *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3". The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.										LIE CHARLENE / HERBERT			

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/378,956	03/03/2003	Michael J. Zaworotko	U0157.70023US01	4742
23628 7590 01/05/2017 WOLF GREENFIELD & SACKS, P.C. 600 ATLANTIC AVENUE BOSTON, MA 02210-2206			EXAMINER JAVANMARD, SAHAR	
			ART UNIT 1627	PAPER NUMBER
			NOTIFICATION DATE 01/05/2017	DELIVERY MODE ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents_eOfficeAction@WolfGreenfield.com
WGS_eOfficeAction@WolfGreenfield.com

Office Action Summary	Application No. 10/378,956	Applicant(s) ZAWOROTKO ET AL.	
	Examiner SAHAR JAVANMARD	Art Unit 1627	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 7/25/16.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

- 5) ☒ Claim(s) 28,37,39-49,58-60 and 62-66 is/are pending in the application.
5a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 6) ☐ Claim(s) ____ is/are allowed.
- 7) ☒ Claim(s) 28, 39-49, 58-60, and 62-66 is/are rejected.
- 8) ☒ Claim(s) 37 is/are objected to.
- 9) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

- a) ☐ All b) ☐ Some** c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) ☐ Notice of References Cited (PTO-892) | 3) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)
Paper No(s)/Mail Date ____. | 4) ☐ Other: ____. |

DETAILED ACTION

Status of the Application

The present application is being examined under the pre-AIA first to invent provisions.

This Office Action is in response to Applicant's arguments filed on July 25, 2016.

Claim(s) 28, 37, 39-49, 58-60, and 62-66 are pending and examined herein.

Response to Arguments

The outstanding nonstatutory double patenting rejection is hereby maintained as a result of Applicant's decision to hold said rejection in abeyance.

Applicant's arguments with respect to the 103(a) rejection of claims 25, 28, 39-42, 48-49, and 58 as being anticipated by McCoy (CA 1148020A1) have been fully considered. Applicant argues:

"The equal amounts of cocrystallizer disclosed by McCoy are equal amount by weight, not equal amount by moles. In contrast to the McCoy, the present claims require preparation of a co-crystal having stoichiometric proportions of the active pharmaceutical ingredient (API) and the selected co-crystal former."

Further, Applicant argues:

"McCoy discloses freeze drying of the mixture of amino acid material and soluble edible cocrystallizer material. (McCoy, page 7, lines 17-19). One of ordinary skill in the art would understand freeze drying to produce an amorphous solid or a mix of crystalline and amorphous phase..."

Additionally, it is argued:

"In contrast to the instantly claimed methods, McCoy discloses physical mixtures of multiple components where the *ratio by weight* of the amount of cocrystallizer to the amount of edible amino acid salt ranges from about 0.9:1 to about 6:1. McCoy discloses examples of such physical mixtures, none of which specifically read on *stoichiometric* ratios. Example 5 in McCoy is the closest example Applicant identified, which uses a 3:1 weight ratio of components, corresponding to a 1.05:1 molar ratio, which is not a stoichiometric ratio."

In view of the arguments above, Examiner maintains the opinion that the McCoy reference renders the instant invention obvious (not including claim 28). Specifically, as set forth on record previously and as discussed below, McCoy teaches "an effective amount of cocrystallizer material will be such that the ratio by weight of the amount of cocrystallizer to the amount of edible amino acid salt is from about 0.9:1 to about 6:1". As pointed out by Applicant, McCoy teaches "by weight" and not in "stoichiometric proportions" as instantly claimed. Nonetheless, the range disclosed for the ratio between cocrystallizer and edible amino acid salt would encompass a cocrystal that is also stoichiometrically proportional. Therefore, it is the opinion of the Examiner that although McCoy does not teach specific examples of an API and co-crystal former in stoichiometric proportions, the range of 0.9:1 to about 6:1 embraces such proportions to be possible. As disclosed above, Applicant provides a teaching from example 5 taught by McCoy wherein a 3:1 weight ratio of components, corresponding to a molar ratio of 1.05:1. While not 1:1 in a molar ratio, the skilled artisan would have had enough teaching from McCoy to also arrive at a 1:1 molar ratio. As set forth on record previously, McCoy teaches the amount of cocrystallizer to the amount of edible amino acid salt is from about 0.9:1 to about 6:1, the range disclosed for the ratio between

cocrystallizer and edible amino acid salt would encompass a cocrystal that is also stoichiometrically proportional.

Therefore, the arguments above with respect to the instant rejection are not persuasive and said rejection is hereby maintained.

Applicant's arguments with respect to the 103(a) rejection of claims 28, 37, 39-43, 46-51, and 53-57 as being unpatentable over Huffman (US Patent No. 3,664,858) of record have been fully considered and are not fully persuasive. Applicant is arguing based on amended claims, therefore said rejection is hereby withdrawn.

Applicant's arguments with respect to the 103(a) rejection of claims 28, 39-41, 46-51, 53-56, 58-60, and 62-65 as being unpatentable over Smith (Journal of Chemical Crystallography, 1997) in view of Evgen'ev (Journal of Analytical Chemistry, 2000) as evidenced by Duke (Handbook of Phytochemical Constituents of GRAS Herbs and Other Economic Plants, 2001) have been fully considered but are not persuasive.

Applicant argues:

"Smith discloses *empirical* determination of 4-amino-benzoic acid adducts with nitro-substituted aromatic compounds. Smith does not disclose crystal structure prediction. Indeed, Smith discloses that "prediction of the general outcome of the crystallization process is not as yet a reality in the design of organic compounds with NLO properties." (Smith, page 317, left column)."

With respect to this argument, Examiner respectfully notes that the instant claims are drawn to a method for preparing a pharmaceutical product, the claims are not to

“predicting” as argued above by Applicant. Therefore, the arguments are not commensurate in scope of the claimed invention. Therefore, based on the foregoing reasons, said rejection is hereby maintained/modified.

Any rejection from the previous Office action not made of record below is hereby withdrawn.

The rejections of record are set forth in the Final Office action below as necessitated by amendment.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory

double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit <http://www.uspto.gov/forms/>. The filing date of the application will determine what form should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to <http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp>.

Claims 28, 37, 39-49, 58-60, and 62-66 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 37-50 and 52-58 of copending Application No. 14/179,862. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending claims are drawn to a pharmaceutical composition comprising a co-crystal comprising an API and a co-former (see claims for details), whereas the instant claims are drawn to the method of designing said co-crystals. The two inventions overlap greatly in scope and the utilities are the same.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 39-42, 46-51, 58-60, and 62-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCoy (CA 1148020A1) of record.

McCoy teaches improved amino acid food additive comprising a uniform cocrystalline matrix of (1) an amino acid material, and (2) an "effective amount of a soluble edible cocrystallizer material, wherein said improved amino acid food additive is better-tasting, more stable and less hygroscopic than the amino acid material alone.

McCoy teaches the amino acid material is preferably selected from the group consisting of: lysine, tryptophan, methionine, threonine, phenylalanine, leucine, valine, isoleucine, histidine, cystine, cysteine, their derivatives, their salts and mixtures thereof. All nutritionally useful amino acids, their derivatives, particularly their salts and mixtures thereof are contemplated. The other essential component of the improved amino acid food additive is a soluble, edible, cocrystallizer material preferably selected from the group consisting of: alkali and alkaline earth metal salts of halides, phosphates and nitrates, polyhydric alcohols, crystalline cellulose, crystalline starches, crystalline organic acids and their salts, and mixtures thereof (page 6-7; page 15, Table II).

McCoy teaches the method comprises dissolving at least one amino acid material in water along with an effective amount of at least one edible cocrystallizer material. The term "an effective amount" means "enough" to enable successful dehydration of the amino acid cocrystallizer solution. Then the solution is preferably neutralized to form a salt of the amino acid. Generally, an effective amount of cocrystallizer material will be such that the ratio by weight of the amount of cocrystallizer to the amount of edible amino acid salt is from about 0.9:1 to about 6:1. Preferably, equal amounts of amino acid and cocrystallizer are used. The final pH range of the solution should be from about 2 to 7 and more preferably 4 to 7.

McCoy teaches the amount of cocrystallizer to the amount of edible amino acid salt by weight and not in stoichiometric proportions.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have envisioned cocrystals comprising a first chemical functionality and a

cocrystal former by weight as taught by McCoy as well as in stoichiometric amounts to arrive at the instant invention. McCoy teaches the amount of cocrystallizer to the amount of edible amino acid salt is from about 0.9:1 to about 6:1, the range disclosed for the ratio between cocrystallizer and edible amino acid salt would encompass a cocrystal that is also stoichiometrically proportional. Therefore, the skilled artisan would have appreciated that although McCoy does not teach specific examples of an API and co-crystal former in stoichiometric proportions, the range of 0.9:1 to about 6:1 embraces the possibility of such proportions.

McCoy identifies the amino acid food additive comprising a uniform cocrystalline matrix of (1) an amino acid material, and (2) an "effective amount of a soluble edible cocrystallizer material, however, specific examples wherein the homo- and heterosynthons as required by claims 50, 51, 53-57, 59, 60, and 62-66 are not explicitly exemplified.

Moreover, McCoy does not specifically teach the identification of the synthon from the crystal structure.

As discussed above, McCoy teaches specific amount of amino acid to co-crystallizer.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have envisioned the co-crystals as taught by McCoy to have also envisioned that the potential choices of amino acid material and cocrystallizer as taught could be formed in combinations with the same functionalities, giving rise to a homosynthon, or two different functionalities, giving rise to heterosynthons. Therefore,

preparing and identifying the cocrystals, as required by the limitations of the instant claims, are well within the scope of the teachings of McCoy.

Therefore, based on the foregoing reasons, the instant claims are deemed unpatentable over the cited art.

Claims 28, 39-41, 46-49, 58-60, and 62-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (Journal of Chemical Crystallography, 1997) in view of Evgen'ev (Journal of Analytical Chemistry, 2000) as evidenced by Duke (Handbook of Phytochemical Constituents of GRAS Herbs and Other Economic Plants, 2001).

Smith teaches a number of molecular adducts of 4-aminobenzoic acid (4-ABA) with 4-nitroaniline [(4-ABA) (C₆H₆N₂O₂)], 4-(4-nitrobenzyl) pyridine, [(4-ABA)₂(C₁₂H₁₀N₂O₂)₄], and (4-nitrophenyl)acetic acid, [(4-ABA) (C₈H₇NO₄)]. The cocrystals were prepared, isolated by total evaporation of the solvent and characterized using infrared spectroscopy and in three cases by X-ray diffraction methods (Experimental section, bridging paragraph pages 309-310). Other compounds described are with 4-chlorobenzoic acid, [(4-ABA) (C₇H₅ClO₂)], 4-bromobenzoic acid, [(4-ABA) (C₇H₅BrO₂)], 4-cyanobenzoic acid, [(4-ABA) (C₇H₆N₂)], 2-nitrobenzoic acid, [(4-ABA) (C₇H₅NO₄)], and 3-nitrobenzoic acid, [(4-ABA) (C₇H₅NO₄)]. All compounds have 1:1 stoichiometry except that with 4-(4-nitrobenzyl)pyridine (1:2) which is unique in being retro-stoichiometric (abstract; page 309, column 1-2, bridging paragraph).

Smith does not teach 4-ABA as an API as required by claim 25 (and dependent claims thereon) or teach the method for the preparation of a pharmaceutical product.

Evgen'ev teaches 4-ABA is widely employed in medicine as local anesthetics, antiarrhythmic agents, and antitubercular drugs.

As evidenced by Duke, 4-ABA is considered a GRAS compound (page 419, column 2, line 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have envisioned that the cocrystals taught by Smith to be employed in the pharmaceutical art. The motivation provided by Evgen'ev teaches 4-ABA is employed frequently in medicine in a variety of areas as discussed above. Therefore, one skilled in the art would have found it obvious to have employed the cocrystals taught by Smith for pharmaceutical purposes.

Therefore, based on the foregoing reasons, the instant claims are deemed unpatentable over the cited art.

Conclusion

Claims 28, 39-49, 58-60, and 62-66 are not allowed.

Claims 37 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

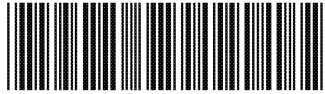
Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAHAR JAVANMARD whose telephone number is (571) 270-3280. The examiner can normally be reached on 8 AM-5 PM MON-FRI (EST).

Art Unit: 1627

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

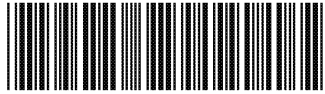
/SAHAR JAVANMARD/

Primary Examiner, Art Unit 1627

<i>Index of Claims</i> 	Application/Control No. 10378956	Applicant(s)/Patent Under Reexamination ZAWOROTKO ET AL.
	Examiner SAHAR JAVANMARD	Art Unit 1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant											☐ CPA	☐ T.D.	☐ R.1.47
CLAIM		DATE											
Final	Original	09/30/2008	09/28/2009	06/18/2010	07/01/2013	05/19/2014	06/11/2015	02/21/2016	10/31/2016				
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<i>Index of Claims</i> 	Application/Control No. 10378956	Applicant(s)/Patent Under Reexamination ZAWOROTKO ET AL.
	Examiner SAHAR JAVANMARD	Art Unit 1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47										
CLAIM		DATE								
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	40			✓	✓	✓	✓	✓	✓	
	41			✓	✓	✓	✓	✓	✓	
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Search Notes 	Application/Control No. 10378956	Applicant(s)/Patent Under Reexamination ZAWOROTKO ET AL.
	Examiner SAHAR JAVANMARD	Art Unit 1627

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
424	400 (update 5/19/14)	9/30/2008	

SEARCH NOTES		
Search Notes	Date	Examiner
EAST (searched each inventor name)(update 6/17/10)	8/31/2009	SJ
EAST (keyword search)(update 6/17/10)	8/31/2009	SJ
Pubmed	8/31/2009	SJ
Google	8/31/2009	SJ
(update 6/11/15)		SJ
Google Patents (search amine acid cocrystal; aspirin cocrystal; bipyridine cocrystal)	6/11/2015	SJ
updated	10/31/2016	SJ

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

	/SAHAR JAVANMARD/ Primary Examiner.Art Unit 1627
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10378956	CTFR	01/05/2017	U0157.70023US01

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Electronic Acknowledgement Receipt	
EFS ID:	26445739
Application Number:	10378956
International Application Number:	
Confirmation Number:	4742
Title of Invention:	Multiple-component solid phases containing at least one active pharmaceutical ingredient
First Named Inventor/Applicant Name:	Michael J. Zaworotko
Customer Number:	23628
Filer:	Jessica Russell Colantonio/Allison Parker
Filer Authorized By:	Jessica Russell Colantonio
Attorney Docket Number:	U0157.70023US01
Receipt Date:	25-JUL-2016
Filing Date:	03-MAR-2003
Time Stamp:	15:50:31
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	\$ 300
RAM confirmation Number	072616INTEFSW15521200
Deposit Account	232825
Authorized User	Wolf Greenfield
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37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	U015770023US01-TRN-JQC.pdf	24367 5811737112f220f2cd9beeb71a30bcb04e9a ecba6	no	1

Warnings:

Information:

2	Examination support document	U015770023US01-EXT-JQC.pdf	23392 23a62d08593c972df99fb3f202781f56b88c f64	no	1
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Warnings:

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Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Claims	2	5
Applicant Arguments/Remarks Made in an Amendment	6	13

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Information:

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UM00017620

NOVARTIS EXHIBIT 1017

Novartis v. Regents, IPR2023-01346

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Warnings:	
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TRANSMITTAL FORM <i>(to be used for all correspondence after initial filing)</i>	Application Number	10/378,956-Conf. #4742
	Filing Date	March 3, 2003
	First Named Inventor	Michael J. Zaworotko
	Art Unit	1627
	Examiner Name	S. Javanmard
Total Number of Pages in This Submission	Attorney Docket Number	U0157.70023US01

ENCLOSURES (Check all that apply)		
☒ Fee Transmittal Form ☐ Fee Attached ☐ Amendment/Reply ☐ After Final ☐ Affidavits/declaration(s) ☒ Extension of Time Request ☐ Express Abandonment Request ☐ Information Disclosure Statement ☐ Certified Copy of Priority Document(s) ☐ Reply to Missing Parts/ Incomplete Application ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53	☐ Drawing(s) ☐ Licensing-related Papers ☐ Petition ☐ Petition to Convert to a Provisional Application ☐ Power of Attorney, Revocation Change of Correspondence Address ☐ Terminal Disclaimer ☐ Request for Refund ☐ CD, Number of CD(s) _____ ☐ Landscape Table on CD	☐ After Allowance Communication to TC ☐ Appeal Communication to Board of Appeals and Interferences ☐ Appeal Communication to TC (Appeal Notice, Brief, Reply Brief) ☐ Proprietary Information ☐ Status Letter ☐ Other Enclosure(s) (please Identify below):
Remarks		

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT			
Firm Name	WOLF, GREENFIELD & SACKS, P.C.		
Signature	/Edward R. Gates/		
Printed name	Edward R. Gates		
Date	6/30/2017	Reg. No.	31,616

Certificate of Electronic Filing under 37 CFR §1.8 I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 CFR § 1.6(a)(4).	
Dated: June 30, 2017	Electronic Signature for Nicole M. Forgrave: /Nicole M. Forgrave/

5565659.1

FEE TRANSMITTAL		Complete if known	
☒ Applicant asserts small entity status. See 37 CFR 1.27.		Application Number	10/378,956-Conf. #4742
☐ Applicant certifies micro entity status. See 37 CFR 1.29. Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.		Filing Date	March 3, 2003
		First Named Inventor	Michael J. Zaworotko
		Examiner Name	S. Javanmard
		Art Unit	1627
TOTAL AMOUNT OF PAYMENT	(\$) 700.00	Practitioner Docket No.	U0157.70023US01

METHOD OF PAYMENT (check all that apply)

☐ Check
 ☒ Credit Card
 ☐ Money Order
 ☐ None
 ☐ Other (please identify): _____

☐ Deposit Account
 Deposit Account Number: 23/2825
 Deposit Account Name: Wolf, Greenfield & Sacks, P.C.

For the above-identified deposit account, the Director is hereby authorized to (check all that apply):

☐ Charge fee(s) indicated below
 ☐ Charge fee(s) indicated below, **except for the filing fee**

☒ Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17
 ☒ Credit any overpayment of fee(s)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES (U = undiscounted fee; S = small entity fee; M = micro entity fee)

Application Type	FILING FEES			SEARCH FEES			EXAMINATION FEES			Fees Paid (\$)
	U (\$)	S (\$)	M (\$)	U (\$)	S (\$)	M (\$)	U (\$)	S (\$)	M (\$)	
Utility	280	140*	70	600	300	150	720	360	180	
Design	180	90	45	120	60	30	460	230	115	
Plant	180	90	45	380	190	95	580	290	145	
Reissue	280	140	70	600	300	150	2,160	1,080	540	
Provisional	260	130	65	0	0	0	0	0	0	

* The \$140 small entity status filing fee for a utility application is further reduced to \$70 for a small entity status applicant who files the application via EFS-Web.

2. EXCESS CLAIM FEES

Fee Description	Undiscounted Fee (\$)	Small Entity Fee (\$)	Micro Entity Fee (\$)
Each claim over 20 (including Reissues)	80	40	20
Each independent claim over 3 (including Reissues)	420	210	105
Multiple dependent claims	780	390	195

Total Claims Extra Claims Fee (\$) Fee Paid (\$) Multiple Dependent Claims

- or HP = _____ x _____ = _____ Fee (\$) Fee Paid (\$)

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims Extra Claims Fee (\$) Fee Paid (\$)

- or HP = _____ x _____ = _____

HP = highest number of independent claims paid for, if greater than 3.

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is \$400 (\$200 for small entity) (\$100 for micro entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee (\$)	Fee Paid (\$)
_____	_____	_____	_____	_____

_____ - 100 = _____ / 50 = _____ (round up to a whole number) x _____ = _____

4. OTHER FEE(S)

Non-English specification, \$130 fee (no small or micro entity discount)	<u>Fees Paid (\$)</u>
Non-electronic filing fee under 37 CFR 1.16(t) for a utility application, \$400 fee (\$200 small or micro entity)	
Other (e.g., late filing surcharge): <u>2253 Extension for response within third month</u>	<u>700.00</u>

SUBMITTED BY			
Signature	/Edward R. Gates/	Registration No. (Attorney/Agent)	31,616
Telephone	617.646.8000		
Name (Print/Type)	Edward R. Gates		Date
		6/30/2017	

Certificate of Electronic Filing under 37 CFR §1.8	
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 CFR § 1.6(a)(4).	
Dated: June 30, 2017	Electronic Signature for Nicole M. Forgrave: /Nicole M. Forgrave/

5565657.1

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)		Docket Number (Optional) U0157.70023US01																																			
Application Number 10/378,956-Conf. #4742		Filed March 3, 2003																																			
For MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT																																					
Art Unit 1627		Examiner S. Javanmard																																			
This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application. The requested extension and fee are as follows (check time period desired and enter the appropriate fee below): <table style="width: 100%; border-collapse: collapse;"><thead><tr><th></th><th style="text-align: center;">Fee</th><th style="text-align: center;">Small Entity Fee</th><th style="text-align: center;">Micro Entity Fee</th><th></th></tr></thead><tbody><tr><td>☐ One month (37 CFR 1.17(a)(1))</td><td style="text-align: center;">\$200</td><td style="text-align: center;">\$100</td><td style="text-align: center;">\$50</td><td>\$ _____</td></tr><tr><td>☐ Two months (37 CFR 1.17(a)(2))</td><td style="text-align: center;">\$600</td><td style="text-align: center;">\$300</td><td style="text-align: center;">\$150</td><td>\$ _____</td></tr><tr><td>☒ Three months (37 CFR 1.17(a)(3))</td><td style="text-align: center;">\$1,400</td><td style="text-align: center;">\$700</td><td style="text-align: center;">\$350</td><td>\$ 700.00</td></tr><tr><td>☐ Four months (37 CFR 1.17(a)(4))</td><td style="text-align: center;">\$2,200</td><td style="text-align: center;">\$1,100</td><td style="text-align: center;">\$550</td><td>\$ _____</td></tr><tr><td>☐ Five months (37 CFR 1.17(a)(5))</td><td style="text-align: center;">\$3,000</td><td style="text-align: center;">\$1,500</td><td style="text-align: center;">\$750</td><td>\$ _____</td></tr></tbody></table> ☒ Applicant asserts small entity status. See 37 CFR 1.27. ☐ Applicant certifies micro entity status. See 37 CFR 1.29. Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously. ☐ A check in the amount of the fee is enclosed. ☒ Payment by credit card. ~~Form PTO-2038 is attached.~~ ☐ The Director has already been authorized to charge fees in this application to a Deposit Account. ☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number <u>23/2825</u>. ☒ Payment made via EFS-Web. WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038. I am the ☐ applicant/inventor. ☐ assignee of record of the entire interest. See 37 CFR 3.71. 37 CFR 3.73(b) statement is enclosed (Form PTO/SB/96). ☒ attorney or agent of record. Registration number <u>31,616</u>. ☐ attorney or agent acting under 37 CFR 1.34. Registration number _____. <table style="width: 100%; border-collapse: collapse;"><tr><td style="width: 60%; text-align: center;"><u>/Edward R. Gates/</u> Signature</td><td style="width: 40%; text-align: center;"><u>6/30/2017</u> Date</td></tr><tr><td style="text-align: center;"><u>Edward R. Gates</u> Typed or printed name</td><td style="text-align: center;"><u>617.646.8000</u> Telephone Number</td></tr></table> NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*. ☐ * Total of <u>1</u> forms are submitted.					Fee	Small Entity Fee	Micro Entity Fee		☐ One month (37 CFR 1.17(a)(1))	\$200	\$100	\$50	\$ _____	☐ Two months (37 CFR 1.17(a)(2))	\$600	\$300	\$150	\$ _____	☒ Three months (37 CFR 1.17(a)(3))	\$1,400	\$700	\$350	\$ 700.00	☐ Four months (37 CFR 1.17(a)(4))	\$2,200	\$1,100	\$550	\$ _____	☐ Five months (37 CFR 1.17(a)(5))	\$3,000	\$1,500	\$750	\$ _____	<u>/Edward R. Gates/</u> Signature	<u>6/30/2017</u> Date	<u>Edward R. Gates</u> Typed or printed name	<u>617.646.8000</u> Telephone Number
	Fee	Small Entity Fee	Micro Entity Fee																																		
☐ One month (37 CFR 1.17(a)(1))	\$200	\$100	\$50	\$ _____																																	
☐ Two months (37 CFR 1.17(a)(2))	\$600	\$300	\$150	\$ _____																																	
☒ Three months (37 CFR 1.17(a)(3))	\$1,400	\$700	\$350	\$ 700.00																																	
☐ Four months (37 CFR 1.17(a)(4))	\$2,200	\$1,100	\$550	\$ _____																																	
☐ Five months (37 CFR 1.17(a)(5))	\$3,000	\$1,500	\$750	\$ _____																																	
<u>/Edward R. Gates/</u> Signature	<u>6/30/2017</u> Date																																				
<u>Edward R. Gates</u> Typed or printed name	<u>617.646.8000</u> Telephone Number																																				

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I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 CFR § 1.6(a)(4).	
Dated: June 30, 2017	Electronic Signature for Nicole M. Forgrave: /Nicole M. Forgrave/

5565660.1

Electronic Patent Application Fee Transmittal				
Application Number:		10378956		
Filing Date:		03-Mar-2003		
Title of Invention:		Multiple-component solid phases containing at least one active pharmaceutical ingredient		
First Named Inventor/Applicant Name:		Michael J. Zaworotko		
Filer:		Edward R. Gates/Nicole Forgrave		
Attorney Docket Number:		U0157.70023US01		
Filed as Small Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension - 3 months with \$0 paid	2253	1	700	700
Miscellaneous:				
Total in USD (\$)				700

Electronic Acknowledgement Receipt	
EFS ID:	29666030
Application Number:	10378956
International Application Number:	
Confirmation Number:	4742
Title of Invention:	Multiple-component solid phases containing at least one active pharmaceutical ingredient
First Named Inventor/Applicant Name:	Michael J. Zaworotko
Customer Number:	23628
Filer:	Edward R. Gates/Nicole Forgrave
Filer Authorized By:	Edward R. Gates
Attorney Docket Number:	U0157.70023US01
Receipt Date:	30-JUN-2017
Filing Date:	03-MAR-2003
Time Stamp:	14:21:28
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	\$ 700
RAM confirmation Number	070317INTEFSW14271400
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	U015770023US01-TRN-ERG.pdf	24933	no	1
			411b53d0b2c49155c85d1cfc8ecaae358992bef4		
Warnings:					
Information:					
2	Fee Worksheet (SB06)	U015770023US01-FEE-ERG.pdf	31130	no	1
			ba64f13262ab3287e8c6f96ccb7f3a73c77c3cba		
Warnings:					
Information:					
3	Extension of Time	U015770023US01-EXT-ERG.pdf	23602	no	1
			653556d23a37b36a1600ea93f3857723038c599d		
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30390	no	2
			493e2dc453c6c5451315f32f0b9198f84ad6acd3		
Warnings:					
Information:					
Total Files Size (in bytes):			110055		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



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United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/378,956	03/03/2003	Michael J. Zaworotko	U0157.70023US01	4742
23628	7590	07/14/2017	EXAMINER	
WOLF GREENFIELD & SACKS, P.C.			JAVANMARD, SAHAR	
600 ATLANTIC AVENUE			ART UNIT	PAPER NUMBER
BOSTON, MA 02210-2206			1627	
			NOTIFICATION DATE	DELIVERY MODE
			07/14/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents_eOfficeAction@WolfGreenfield.com
WGS_eOfficeAction@WolfGreenfield.com

Notice of Abandonment	Application No.	Applicant(s)
	10/378,956	ZAWOROTKO ET AL.
	Examiner	Art Unit
	SAHAR JAVANMARD	1627

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

This application is abandoned in view of:

1. ☒ Applicant's failure to timely file a proper reply to the Office letter mailed on 05 January 2017.
 - (a) ☐ A reply was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply (including a total extension of time of _____ month(s)) which expired on _____.
 - (b) ☐ A proposed reply was received on _____, but it does not constitute a proper reply under 37 CFR 1.113 to the final rejection. (A proper reply under 37 CFR 1.113 to a final rejection consists only of: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) if this is utility or plant application, a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. Note that RCEs are not permitted in design applications.)
 - (c) ☐ A reply was received on _____ but it does not constitute a proper reply, or a bona fide attempt at a proper reply, to the non-final rejection. See 37 CFR 1.85(a) and 1.111. (See explanation in box 7 below).
 - (d) ☒ No reply has been received.
2. ☐ Applicant's failure to timely pay the required issue fee and publication fee, if applicable, within the statutory period of three months from the mailing date of the Notice of Allowance (PTOL-85).
 - (a) ☐ The issue fee and publication fee, if applicable, was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the statutory period for payment of the issue fee (and publication fee) set in the Notice of Allowance (PTOL-85).
 - (b) ☐ The submitted fee of \$_____ is insufficient. A balance of \$_____ is due.
The issue fee required by 37 CFR 1.18 is \$_____. The publication fee, if required by 37 CFR 1.18(d), is \$_____.
 - (c) ☐ The issue fee and publication fee, if applicable, has not been received.
3. ☐ Applicant's failure to timely file corrected drawings as required by, and within the three-month period set in, the Notice of Allowability (PTO-37).
 - (a) ☐ Proposed corrected drawings were received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply.
 - (b) ☐ No corrected drawings have been received.
4. ☐ The letter of express abandonment which is signed by the attorney or agent of record or other party authorized under 37 CFR 1.33(b). See 37 CFR 1.138(b).
5. ☐ The letter of express abandonment which is signed by an attorney or agent (acting in a representative capacity under 37 CFR 1.34) upon the filing of a continuing application.
6. ☐ The decision by the Board of Patent Appeals and Interference rendered on _____ and because the period for seeking court review of the decision has expired and there are no allowed claims.
7. ☒ The reason(s) below:

CALLLED TO CONFIRM ABANDONMENT OF THE APPLICATION WITH ATTORNEY EDWARD GATES. CALL WAS NOT RETURNED.

	/SAHAR JAVANMARD/ Primary Examiner, Art Unit 1627
--	--

Petitions to revive under 37 CFR 1.137, or requests to withdraw the holding of abandonment under 37 CFR 1.181, should be promptly filed to minimize any negative effects on patent term.

To: Patents_eOfficeAction@WolfGreenfield.com,WGS_eOfficeAction@WolfGreenfield.com,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 23628

Jul 14, 2017 04:28:50 AM

Dear PAIR Customer:

WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 23628 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

Disclaimer:

The list of documents shown below is provided as a courtesy and is not part of the official file wrapper. The content of the images shown in PAIR is the official record.

Application	Document	Mailroom Date	Attorney Docket No.
10378956	ABN	07/14/2017	U0157.70023US01

To view your correspondence online or update your email addresses, please visit us anytime at <https://sportal.uspto.gov/secure/myportal/privatepair>.

If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM