Relation between solid-state properties and pharmaceutical quality of generic drug raw materials available in South Africa

Erna Swanepoel

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Erna Swanepoel, B. Pharm., M. Sc. (Pharmaceutics)

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Promoter : Prof. Melgardt M. de Villiers

Co-Promoter: Dr Wilna Liebenberg

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GENERAL INTRODUCTION AND AIM OF THE THESIS

Effective health care requires a judicious balance of preventive and curative services. A crucial and often deficient element in curative services is an adequate supply of appropriate medicines. The essential drug was defined by the WHO in the 1960s in answer to the uncertainty of supplies to developing countries: "Essential drugs are those that meet the needs of the majority of the health need of a population; they should be available at all times in sufficient quantity and in an appropriate pharmaceutical form".

The term "generic drug" has been legally defined as a copy of an original medicinal drug whereby production and marketing are made possible by the expiration of the patent covering the innovator product. Almost 90% of essential drugs contained in the WHO Model List are off-patent and available in generic form. Although generics are currently the only way of making essential drugs financially accessible to most of the world's population, in no case should their quality, effectiveness and safety be sacrificed. These three criteria are the cornerstone for health products, and they have to be demonstrated and verified. In fact, for generic drugs, these three descriptions of quality, safety and efficacy are based on the concept of quality of raw materials, stability studies and bioequivalence.

The quality of the active ingredient is the focal point of a drug. For generic drugs, it takes on even greater importance. When the licence of a drug expires, the active substance may be manufactured anywhere, and the process of synthesis, purification and crystallization may vary from place to place. Also, their cost can vary considerably depending on labour costs, quality of the facilities, reputation of the supplier, and quality and purity testing applied to the material. Professional judgement must be exercised in the purchase of such materials because compliance with pharmacopoeial specifications may not necessarily indicate good quality. The price of the raw material often represents more than 50% of the industrial cost price of a generic, which may lead manufacturers to target a lower quality raw material in their efforts to offer competitively attractive prices.

Apart from full information on the origin and the specific characteristics of the raw materials, the registration file for a generic has to provide proof of bioequivalence and the results of tests demonstrating its stability in the climatic conditions where it will be used. A generic drug must be interchangeable, thus clinically equivalent to a reference drug. *In vitro* dissolution tests are one method to prove that generic drugs are equivalent from a therapeutic point of view. For solid oral forms, national regulations advocate the use of *in vitro* dissolution tests for development and quality control. It can help to synthesize information about the raw material, but also about the formulation and the pharmacotechnical features of the form. The stability of a drug is evaluated through its ability to maintain chemical, physical, microbiological and biopharmaceutical properties within specified limits during the entire extent of its validity. Since the active principles of generic drugs are known molecules, in most cases it is possible to limit stability studies of the finished product.

The raw material market is extensive and a great choice of products is available worldwide. The aim of this study was to investigate the pharmaceutical quality of generic raw materials available to manufacturers in South Africa, as well as the influence of solid-state properties of these raw materials on dissolution. Part I focuses on the quality of raw materials. A short introduction to and the pharmaceutical importance of drug crystal polymorphism is given in chapter 1, whereas chapter 2 summarizes inconsistent and questionable results obtained for pharmaceutical quality of specific raw materials tested. In Part II dissolution requirements, as an important indicator of bioequivalence, are discussed. Chapter 3 focuses on international dissolution standards and harmonization of dissolution testing and standards, while chapters 4, 5, 6 and 7 deal with the dissolution problems experienced with oxytetracycline, piroxicam and mebendazole products and raw materials. In Part III stability issues are discussed where the difference in the dissolution properties of oxytetracycline capsules after accelerated stability testing is focused on in chapter 8. In chapter 9 the results of this study are summarized and recommendations for generic manufacturers are given.

PART I – Solid-state Requirements for Drug Powders

CHAPTER 1

Introduction to and importance of drug crystal polymorphism

1.1 Polymorphism

Many pharmaceutical solids exhibit polymorphism, which is frequently defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice (Haleblian & McCrone, 1969:911; Haleblian, 1975:1270; Threlfall, 1995:2435). Thus, in the strictest sense, polymorphs are different crystalline forms of the same pure substance in which the molecules have different arrangements and/or different conformations of the molecules (Grant, 1999:2).

Solvates are molecular complexes that have incorporated the crystallizing solvent molecule into their crystal lattice, hydrates being formed when the solvent is water. To distinguish solvates/hydrates from polymorphs, the term pseudopolymorph has been used and indeed polymorphism can be exhibited by solvates/hydrates (York, 1983:16), as for example in the ethanolic solvates of fluocortolone (Kuhnert-Brandstätter & Gasser, 1971:419), and the hydrates of nitrofurantoin (Caira *et al.*, 1996:241).

Pseudopolymorphism is a term also used to describe a variety of other phenomena sometimes confused with polymorphism. They include desolvation, second-order transitions (some of which are polymorphism), dynamic isomerism, mesomorphism, grain growth, boundary migration, recrystallization in the solid state, and lattice strain effects (Haleblian & McCrone, 1969:927).

Many pharmaceutical solids can exist in an amorphous form, which, because of its distinctive properties, is sometimes regarded as a polymorph. However, unlike true polymorphs, amorphous forms are not crystalline (Haleblian & McCrone, 1969:914; Haleblian, 1975:1272; Hancock & Zografi, 1997:1). In fact, amorphous solids consist of disordered arrangements of molecules and therefore possess no distinguishable crystal lattice nor unit cell and consequently have zero crystallinity. In amorphous forms, the

molecules display no long-range order, which causes the molar entropy of the amorphous form to exceed that of the crystalline state (Grant, 1999:8).

Table 1 List of physical properties that differ among various polymorphs (Grant 1999:7)

1. Packing properties
   a. Molar volume and density
   b. Refractive index
   c. Conductivity, electrical and thermal
   d. Hygroscopicity

2. Thermodynamic properties
   a. Melting and sublimation temperatures
   b. Internal energy (i.e., structural energy)
   c. Enthalpy (i.e., heat content)
   d. Heat capacity
   e. Entropy
   f. Free energy and chemical potential
   g. Thermodynamic activity
   h. Vapor pressure
   i. Solubility

3. Spectroscopic properties
   a. Electronic transitions (i.e., ultraviolet-visible absorption spectra)
   b. Vibrational transitions (i.e., infrared absorption spectra and Raman spectra)
   c. Rotational transitions (i.e., far infrared or microwave absorption spectra)
   d. Nuclear spin transitions (i.e., nuclear magnetic resonance spectra)

4. Kinetic properties
   a. Dissolution rate
   b. Rates of solid-state reactions
   c. Stability

5. Surface properties
   a. Surface free energy
   b. Interfacial tensions
   c. Habit (i.e., shape)

6. Mechanical properties
   a. Hardness
   b. Tensile strength
   c. Compactibility, tableting
   d. Handling, flow, and blending

Polymorphs can exist either as enantiotrophs or monotrophs (Haleblian & McCrone, 1969:920). Two forms are said to be enantiotropic when each of the polymorphs is thermodynamically stable within a definite range of temperature and pressure. Each form is able to transform reversibly into the other. However, if one of the two forms is thermodynamically unstable at all temperatures below the melting point and the other form is thermodynamically stable, these two polymorphs are said to be monotropic. In other words, monotrophs exist as one stable form and one or more metastable ones (Frederick, 1961:535).

Since polymorphism involves differences in crystal structure, different polymorphs will have different energy contents, the energy difference being associated with their molecular binding energies. For a given set of physical conditions the polymorph with the lowest free energy is the most stable and other polymorphic forms, termed metastable, will tend to transform to the most stable form. As a result, polymorphs may differ substantially with respect to certain physicochemical properties (York, 1983:14). Table 1 lists some of the many properties that differ among different polymorphs (Haleblian & McCrone, 1969:911; Haleblian, 1975:1275; Threlfall, 1995:2436; Giron, 1995:2; York, 1983:14).

The naming of polymorphs may follow either of two contemporary conventions. They may be designated by roman numerals whereby the form I is the most stable, form II the next stable, etc. No rigid convention can be laid down for use of the higher numerals, since further work is always attended by the possibility of discovering an intermediate form difficult to designate by roman numerals and to insert without disrupting the previous assignments of numerals. Alternatively, they may be named in order of their discovery, i.e., A, B or C (Haleblian & McCrone, 1969:920).

1.2 Methods available for the characterization of polymorphs

Certainly the most important aspect relating to an understanding of polymorphic solid and solvate species is the range of analytical methodology used to perform the characterization studies (Threlfall, 1995:2438; Brittain *et al.*, 1991:963; Brittain, 1995:3). A variety of experimental techniques are available for the characterization of polymorphic solids. Table 2 summarizes the information provided by each technique for different types of

Table 2 Information obtained from different physical techniques for each type of polymorph (Yu *et al.*, 1998:124)

Types of polymorphs	Single crystal x-ray crystallography	X-ray powder diffraction	IR/Raman spectroscopy	Solid-state NMR spectroscopy	Thermal methods	Microscopy
True polymorphs	Same chemical composition. Unique unit cell parameters, molecular conformation and packing	Unique diffraction peaks. Useful for determination of phase purity and % crystallinity	Characteristic spectra. Sensitive to H bonding	Unique chemical shifts. Useful for determining phase purity, molecular mobility	Unique melting point, heat capacity, heats of fusion/transition, solubility. Useful for determining relative stability of forms	Characteristic indices of refraction, birefringence, dispersion colour and crystal habit
Solvates	Same as true polymorphs	Same as true polymorphs	Unique solvent bands. Shifted drug bands. Sensitive to H	Unique solvent resonances. Shifted drug resonances. Solvent mobility can be determined	Low-temperature transitions due to desolvation (thermal gravimetric analysis loss)	Same as true polymorphs. Desolvation observable by hot-stage microscopy

Isomorphic desolvates	Not applicable	Diffraction pattern only slightly changed from parents solvates	Solvent bands disappear. Drug bands shifted	Solvent resonances disappear. Drug resonances shift	Low-temperature desolvation absent. Events due to crystallization or lattice relaxation	Birefringent microcrystalline domains, with cracks and fissures
Amorphous solids	Not applicable	No diffraction peaks	Broadened spectra	Broadened spectra	Glass transition seen. Often followed by crystallization and melting. "Fragility" related to width of T_g (glass transition temperature)	No birefringence, irregular particle shape
Polymorphic mixtures	Not applicable	Composite pattern of crystalline components	Composite spectrum of all components	Nuclei-specific composite spectrum of all components	Thermal behaviour indicative of phase diagram (e.g. melting point depression, eutectic melting, dissolution)	Composite of distinct crystalline and amorphous particles

polymorphs. From this summary, the inter-disciplinary nature of polymorph characterization is clearly indicated (Yu *et al.*, 1998:121). The most important of these techniques is X-ray powder diffraction. All other methods reflect the crystal structure of the material in some manner that must be interpreted, but only the direct crystallographic technique yields unequivocal information. In the event that fully solved crystal structures cannot be obtained for each polymorphic phase, the relative identity of each suspected phase is deduced through the use of powder X-ray powder diffraction. The nature of conclusions deduced from all other techniques must always take a secondary, supporting role to genuine structural studies (Brittain, 1994:51).

1.3 Pharmaceutical importance of polymorphism

Differences in physical properties of various solid forms have an important effect on the processing of drug substances into drug products (Haleblian & McCrone, 1969:912), while differences in solubility may have implications on the absorption of the active drug from its dosage form (Higuchi *et al.*, 1963:153), by affecting the dissolution rate and possibly the mass transport of the molecules. These concerns have led to an increased regulatory interest in understanding the solid-state properties and behaviour of drug substances. For approval of a new drug, the drug substance guideline of the US Food and Drug Administration (FDA) states that "appropriate" analytical procedures need to be used to detect polymorphs, hydrates and amorphous forms of the drug substance and also stresses the importance of controlling the crystal form of the drug substance during the various stages of drug development (Byrn *et al.*, 1995:945). The latter because any phase change due to polymorph interconversions, desolvation of solvates, formation of hydrates and change in the degree of crystallinity can alter the bioavailability of the drug. When going through a phase transition, a solid drug may undergo a change in its thermodynamic properties, with consequent changes in its dissolution and transport characteristics (Nerurkar *et al.*, 2000:575).

Various pharmaceutical processes during drug development significantly influence the final crystalline form of the drug in the dosage form. Processes such as lyophilization and spray drying may lead to the formation of the amorphous form of drug, which tends to be less stable and more hygroscopic than the crystalline product. Also, processing stresses,

such as drying, grinding, milling, wet granulation, oven drying and compaction, are reported to accelerate the phase transitions in pharmaceutical solids. The degree of polymorphic conversion will depend on the relative stability of the phases in question, and on the type and degree of mechanical processing applied (Brittain & Fiese, 1999:357). It is therefore desirable and usual to choose the most stable polymorphic form of the drug in the beginning and to control the crystal form and the distributions in size and shape of the drug crystals during the entire process of development. The presence of a metastable form during processing or in the final dosage form often leads to instability of drug release as a result of phase transformation (Rodríguez-Hornedo *et al.*, 1992:149).

Summary and conclusions

The polymorphic behaviour of organic solids can be of crucial importance in the pharmaceutical industry and investigating the polymorphic behaviour of drugs and excipients is an important part of preformulation work. In order to save time and cost it is very important to choose the most suitable form of the crystalline drug in the initial stages of drug development. With all the information available from these initial studies, it should be possible to design and to select processing conditions which would give a desired polymorph and maintain the desired form throughout the various stages of drug processing and manufacture (Vippagunta *et al.*, 2001:24). Manipulation and control of crystal form can also be exploited for commercial advantage by marketing a drug in a crystal form with maximum bioavailability and longest shelflife (Madan & Kakkar, 1994:1571).

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CHAPTER 2

Inconsistent and questionable pharmaceutical quality of generic raw materials available in South Africa

SWANEPOEL, E., DE VILLIERS, M.M., LIEBENBERG, W. & DEKKER, T.G. 1999. Inconsistent and questionable pharmaceutical quality of generic raw materials available in South Africa. (*In* Drug Information Association. Drug safety: a shared responsibility. Poster presented at the DIA Symposium held at the Eskom Conference Centre, Gauteng, on 31 August and 1 September 1999.)

DE VILLIERS, M.M., SWANEPOEL, E. & LIEBENBERG, W. 2000. Pharmaceutical quality of generic drug raw materials classified as essential drugs by the WHO. (*In* Proceedings of the Materials Science Conference, University of New Orleans, New Orleans.) [CD-ROM.]

ABSTRACT

Problem: *The quality of pharmaceuticals has been a concern of the World Health Organization (WHO) since its inception. This includes the quality of starting materials, active substances and excipients, for the production of medicinal products. In the USA the Food and Drug Administration's (FDA) drug substance guideline requires that appropriate analytical procedures be used to detect polymorphic, hydrated or amorphous forms of new drug substances. However, very few studies report comprehensive reviews of the quality of generic raw materials, although generic substitution is a worldwide phenomenon.* ***Objective:*** *This study dealt with the identification and characterization of generic raw materials. Determining the frequency at which crystal polymorphism and/or other physicochemical differences occur amongst 830 powders from different manufacturers, representing 135 drugs, available to generic manufacturers in South Africa.* ***Methods:*** *Powders were characterized by X-ray powder diffractometry; thermal analysis (differential scanning calorimetry, thermogravimetric analysis and hot stage microscopy); Fourier transform infrared analysis; mass spectroscopy; and particle size analysis. Solubility measurements and powder and dosage form dissolution testing were also performed.* ***Results:*** *Crystal polymorphism was found for 15 of the 135 drugs studied (± 10%). In 7 instances the different polymorphs decreased the powder*

dissolution rates (± 5%). Polymorphs were detected among the powders of 9 drugs known to exhibit polymorphism (± 7%). New polymorphs were detected for 6 drugs (± 4%). For 5 drug powders known for polymorphism dissolution problems were detected not related to polymorphism (± 3%). New polymorphs of 2 drugs known to exhibit polymorphism were detected (± 1.5%). ***Conclusions:*** *From these results the following drugs with potential problems were found. Known polymorphs detected: amiloride HCl (5); carbamazepine (6); mebendazole (7); nystatin (8); oxytetracycline HCl (9); ranitidine HCl (10); rifampicin (11); terbutaline SO_4 (12); chlorpropamide (3) and acyclovir (13). New polymorphs: phenylephrine HCl (4); potassium citrate (5); niclosamide (6); ivermectin (3) and tetracaine HCl (3). Dissolution problems: chlorthalidone (14); glibenclamide (15); phenylbutazone (16); furosemide (6) and piroxicam (17). The number in brackets represents the number of samples tested. All these differences in the solid-state properties can lead to bioavailability problems. It will also affect the pharmaceutical performance and quality of products produced using these raw materials.*

INTRODUCTION

The safety of pharmaceutical dosage forms is highly dependent upon the quality of the raw materials from which they are fabricated and the integrity of their supplier. Therefore, the quality of pharmaceuticals has been a concern of the World Health Organization (WHO) since its inception. This includes the quality of starting materials, active substances and excipients, for the production of medicinal products.

In the USA the Food and Drug Administration's (FDA) drug substance guideline, requires that appropriate analytical procedures be used to detect polymorphic, hydrated or amorphous forms of new drug substances (1). However, very few studies report comprehensive reviews of the quality of generic raw materials, although generic substitution is a worldwide phenomenon. Furthermore, relying on tests in official compendia does not always guarantee physicochemical equivalence.

This study dealt with the identification and characterization of generic raw materials. Determining the frequency at which crystal polymorphism and/or other physicochemical

differences occur amongst 830 powders from different manufacturers, representing 135 drugs, available to generic manufacturers in South Africa.

MATERIALS AND METHODS

Materials

All raw materials were used as received from the suppliers. The drugs complied with official monograph tests regarding purity and degradation products. Assay results were between 98-101%.

Physicochemical Characterization

The powders were characterised according to their XRD patterns, IR spectra, DSC thermograms, TGA and particle size analysis.

XRD powder diffraction patterns were obtained at room temperature with a Philips PM9901/00 diffractometer. IR spectra were recorded on a Shimadzu FTIR-4200 spectrometer over a range of 4000-400 cm^{-1} using the KBr disc technique.

DSC thermograms and TGA curves were recorded with a Shimadzu DSC-50/TGA-50 instrument (Shimadzu, Kyoto, Japan). The heating rate was 10°C/minute under nitrogen gas flow of 20 ml/minute.

Particle size distributions in suspension were measured with a Galai-Cis-1 particle size analyzer. Suitable dispersing solutions were selected based on the solubility properties of the drug.

Powder Dissolution

Powder dissolution was performed according to the described method (2) using apparatus 2, paddle, of the USP 23 (3). Where available the dissolution conditions as described in the USP or BP (4) were followed. This included paddle speed, the composition of the dissolution medium and the assay method. Samples were drawn from the dissolution medium at predetermined times and percentage of drug dissolved plotted as a function of time.

In cases where no official dissolution methods were available, the dissolution medium was chosen based on reports in the literature, suggestions from the manufacturer or the solubility of the drug.

RESULTS

Polymorphism was found for thirteen of the 135 drugs studied. In seven instances, the different polymorphs decreased the powder dissolution rates.

From the known cases described in literature, polymorphism were detected for the following substances:

Amiloride HCl (5); carbamazepine (6); mebendazole (7); nystatin (8); oxytetracycline HCl (9); ranitidine HCl (10); rifampicin (11); terbutaline SO_4 (12) and acyclovir (13).

New cases where polymorphism occurred without any reference in the literature were:

Phenylephrine HCl; potassium citrate; niclosamide; zopiclone; ivermectin and tetracaine HCl.

Drug powders, which are known for polymorphism where only dissolution problems were detected, were:

Chlorthalidone (14); glibenclamide (15); phenylbutazone (16) and piroxicam (17).

Those cases where differences in the physicochemical properties might lead to bioavailability problems are discussed.

AMILORIDE HYDROCHLORIDE

Amiloride HCl is an oral diuretic, which acts by enhancing sodium ion excretion. It is a yellow to greenish yellow crystalline powder, which is odourless and slightly soluble in water. Two polymorphs, form A and B, are reported for this drug (5). Either polymorphic form may be received when purchasing USP grade material, and this can vary by both

vendor and lot number (18). It was found that a slight variation in the temperature, rate, or solvent mixture used during the recrystallization of this drug profoundly affects the reproducibility of the polymorphic form.

In this study, five batches of amiloride HCl powder from four manufacturers were tested. The powders were identical with respect to IR spectra, required for identity by the USP, and melting points. However, XRD analysis identified three of the powders as form A and two as form B (Fig. 1).

There was no difference in the dissolution properties of these powders and all complied with the specification set in the USP (80% dissolved within 30 minutes). The samples may therefore be regarded as substitutable, though not strictly speaking equivalent. In the case of amiloride HCl, polymorphism does not affect the solubility of the drug and is therefore not pharmacologically important for bioavailability. It could however, affect the stability and processing of dosage forms.

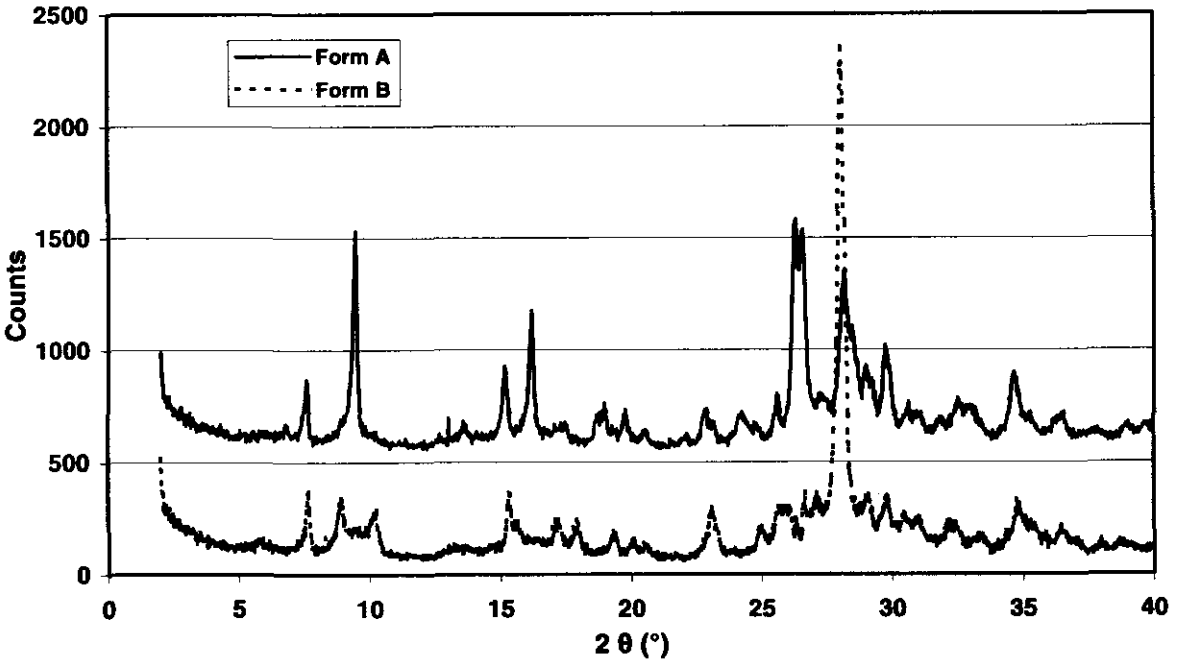

Figure 1: XRD patterns of amiloride HCl powders representing form A and form B.

GLIBENCLAMIDE

Glibenclamide is a sulfonylurea derivative that is orally active as a hypoglycemic drug. It is a white, crystalline, odourless and tasteless powder, which is virtually insoluble in water. Systematic investigations on rate and extent of bioavailability of products exhibiting different dissolution properties have shown that bioavailability clearly depends on dissolution behaviour of glibenclamide formulations (19). This applies primarily to the rate of absorption, which is strongly associated with the rate of dissolution during the first 10-15 minutes.

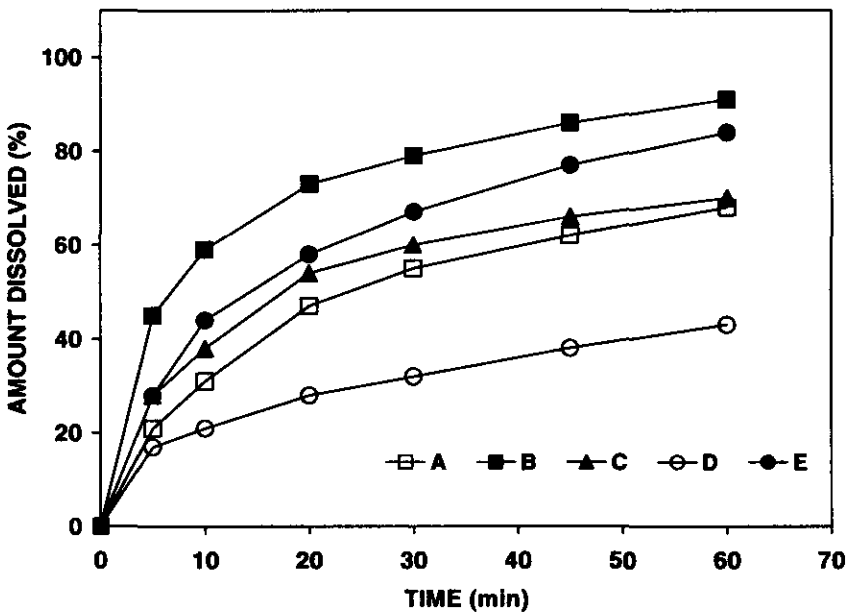

Figure 2: Powder dissolution profiles of glibenclamide in buffer pH 7.5.

Of the five batches of glibenclamide powder from five manufacturers tested, the particle size of one sample was significantly larger, mean volume size 135 μm, than that of the other four samples, mean volume size ± 30 μm. The larger particles were rod-like in shape, while the smaller ones were shapeless. The dissolution rate of larger particles was significantly slower in buffer pH 7.5 (only 43% dissolved after 60 minutes) (Fig. 2). XRD analysis, Fig. 3, showed that the fast dissolving powders contained a large percentage of an X-ray amorphous material. When these powders were sieved to remove the fines, the

X-ray counts increased from about 600 to almost 5500. Poor dissolution results could be ascribed to differences in both particle size and crystal structure. In this case, inconsistency in physicochemical properties will lead to bioavailability problems as described by Blume *et al.* (19).

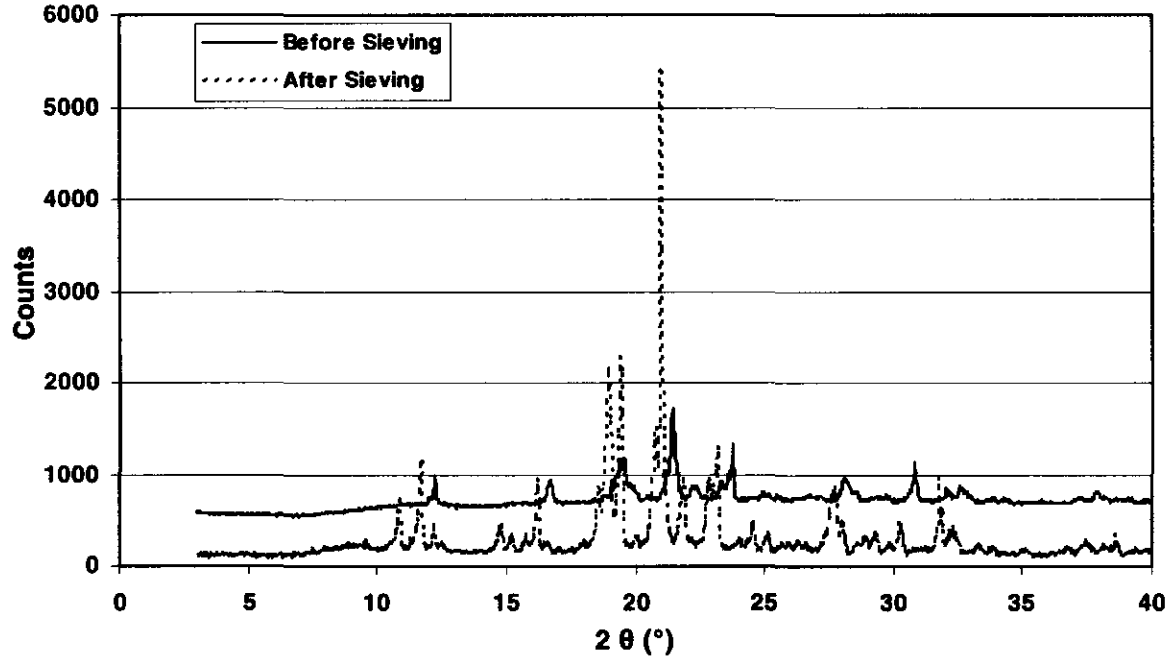

Figure 3: XRD patterns of fast dissolving glibenclamide powder before and after sieving.

CARBAMAZEPINE

Carbamazepine is an anti-epileptic drug that is commonly used for the control of different seizures. It is a relatively stable drug with poor water solubility and no acidic or basic properties (20). Carbamazepine is reported to have at least four polymorphic modifications in the anhydrous state and one dihydrate (6). The β-polymorph, also known as modification III, is the USP reference standard.

The transition between the anhydrous form and the dihydrate is highly dependent on the temperature and the relative humidity (21). Due to its poor water solubility, the drug also

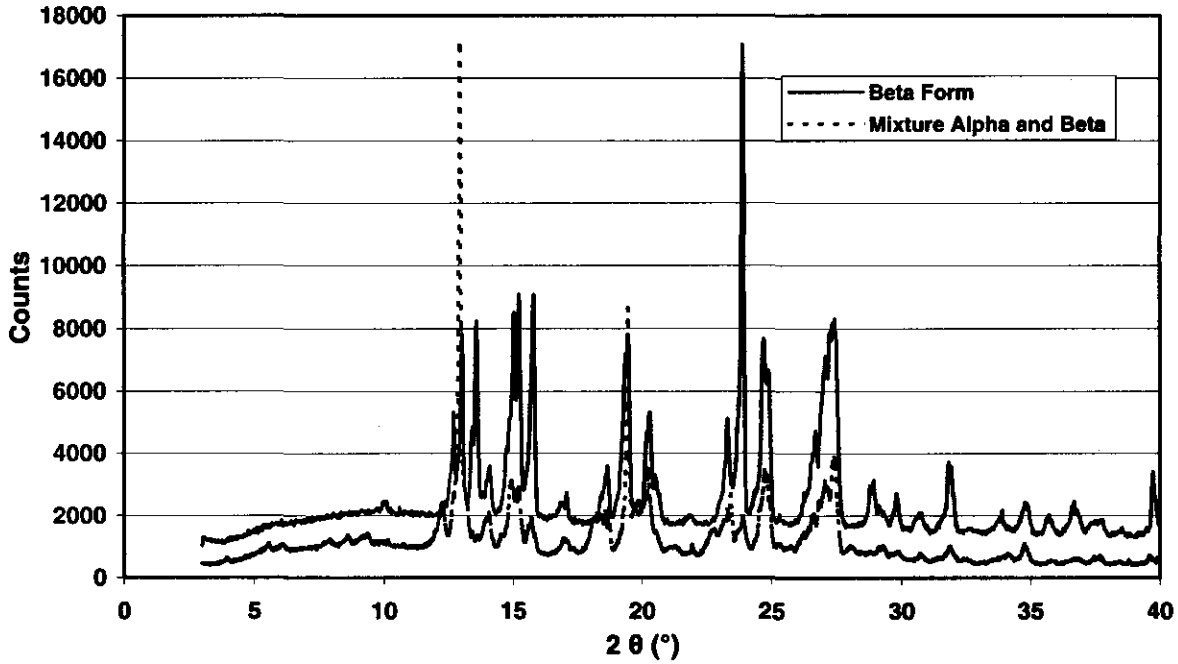

Figure 4: XRD patterns of carbamazepine powders.

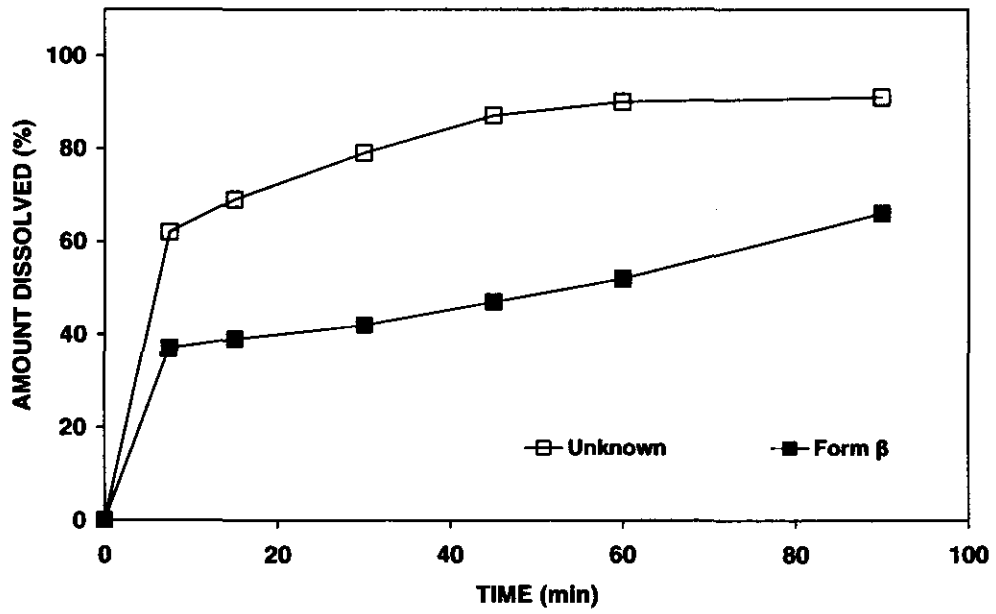

Figure 5: Powder dissolution profiles of carbamazepine in water containing 1% sodium lauryl sulphate.

exhibits variable absorption rates from the gastrointestinal tract (22). Dissolution studies indicated a decrease in dissolution rate as humidity and temperature increase. Thus, the hardening effect and poor dissolution properties could be attributed to the formation of dihydrate crystals (23).

In this study, eight powders from eight different manufacturers were tested. Seven powders had the β-modification (Fig. 4) while one sample consisted of a mixture of two crystal forms, one rod-like and the other shapeless. This powder dissolved much faster (Fig. 5) than the other powders. In this case, the differences in the dissolution rate will lead to problems with the bioavailability of carbamazepine.

MEBENDAZOLE

Mebendazole is a broad spectrum anthelmintic. It is an off-white to slightly yellow amorphous powder, almost insoluble in water. Three polymorphic forms of mebendazole identified as A, B and C can be formed through controlled crystallization (7). Because mebendazole is poorly water-soluble, it has a slow dissolution rate.

Significant therapeutic differences have been observed between the different polymorphic forms, which supports the fact that the low solubility and poor rate of dissolution of the drug are important factors limiting its use in the treatment of several diseases (7). The solubility of the three polymorphs in both water and 0.03 M HCl is in the order: B > C > A. The polymorphs differ with respect to their IR spectra, X-ray powder diffractograms and DSC thermograms. Polymorph C is pharmaceutically favoured.

Of thirteen powders from ten different manufacturers tested, eleven were identified as polymorph C, while one sample was form A and the other form B (Fig. 6). Although literature suggests that one should use polymorph C, there are still other polymorphic forms available on the generic market. IR spectroscopy was ideally suited to distinguish between the different mebendazole polymorphs in both powders and tablets (Fig. 6) (24).

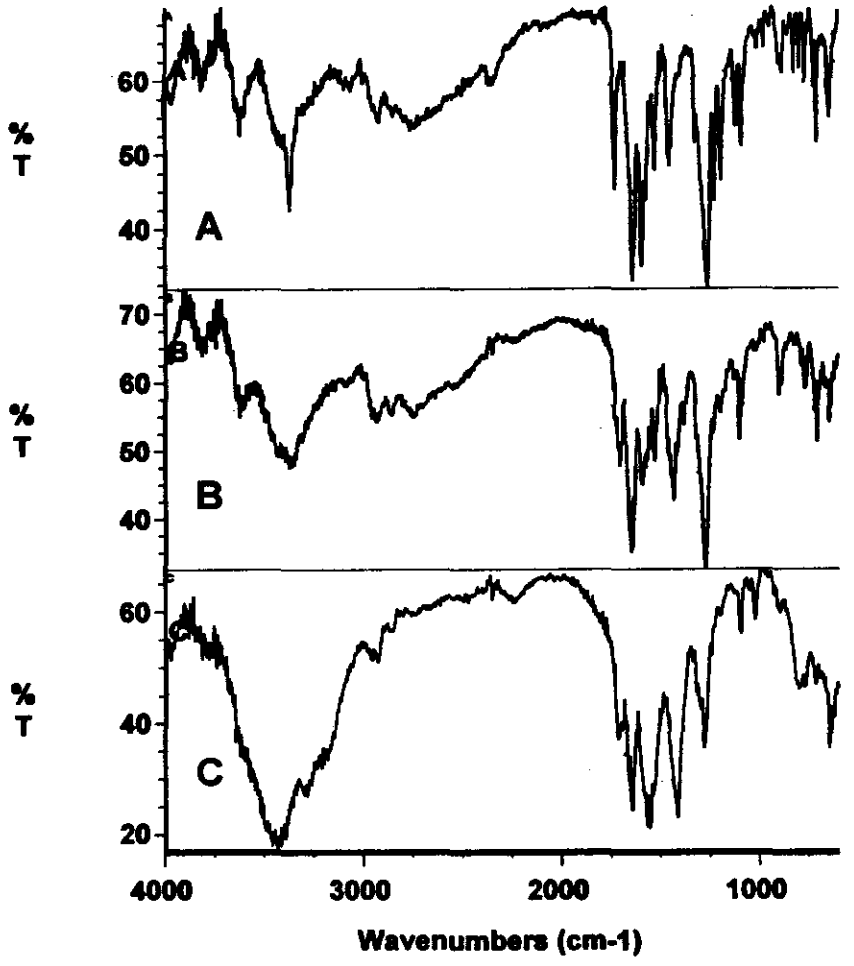

Figure 6: IR spectra of mebendazole form A , B and C.

RIFAMPICIN

Rifampicin is an essential component of the currently recommended regimen for treating tuberculosis. It is a red-orange, odourless, crystalline powder that is poorly soluble in water. Two crystalline forms, an amorphous form and four solvates; two from water, one from tetrahydrofuran and one from carbon tetrachloride, have been isolated and characterized by thermal analysis, IR spectroscopy and XRD (11). Differences in the solubility of rifampicin powders can lead to bio-inequivalence (25).

In order to evaluate substitutability fourteen batches of rifampicin powder from ten manufacturers were studied for polymorphism. Although most of the powders contained

the same crystal structure, form II identified by Pelizza *et al.* (11), differences in the dissolution behaviour of some powders prompted closer inspection of these powders (Fig. 7).

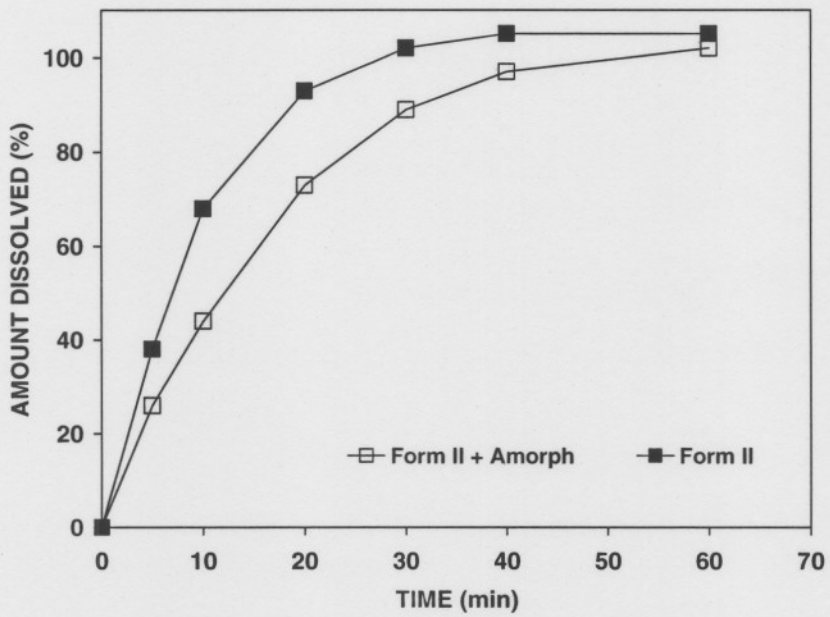

Figure 7: Powder dissolution profiles of rifampicin powders in water.

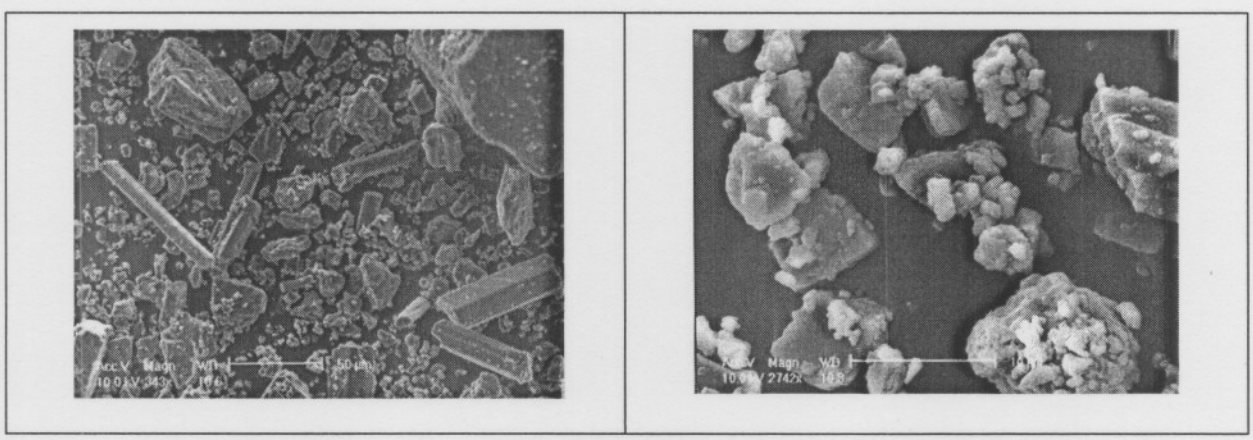

Figure 8: SEM micrographs of rifampicin powder containing fine non-crystalline particles.

Particle size analysis showed that slow dissolving powders contained a significant amount of extremely fine powders, mean volume size < 1μm. This was confirmed by scanning electron microscopy evaluation of the powder (Fig. 8). XRD analysis showed that these fine powders were non-crystalline. However, contradictory to expectation the amorphous content was poorly water-soluble, 0.89 mg/ml compared to 1.47 mg/ml for form II.

CHLORTHALIDONE

Chlorthalidone is an antihypertensive diuretic used in the treatment of oedema associated with congestive heart failure. It is a white to yellowish-white crystalline powder that is poorly soluble in water, < 0.2 mg/ml (14). No polymorphs or pseudopolymorphs are reported for this drug.

Table 1: Particle size results for chlorthalidone powders.

Powder	Mean Volume Size (μm)	Mean Number Size (μm)
A	143.5	69.4
B	10.6	9.8
C	180.5	51.2
D	4.6	2.8
E	25.1	3.4
F	10.7	3.3
G	6.8	3.5
H	6.5	3.6
I	8.6	4.6
J	7.5	4.4

In this study, ten batches of bulk drug powder from four manufacturers were studied and no differences were detected in the XRD, IR and thermal properties of the powders. Analysis results corresponded to that reported by Singer *et al.* (14).

Narurkar *et al.* (26) studied the effect of particle size on the dissolution characteristics of chlorthalidone and found that the minimum specific surface area needed for maximum dissolution rate of the drug was about 3.5 m^2/g. This represents a mean volume particle size of about 3-5 μm. The mean volume particle size of the powders studied were significantly different, Table 1.

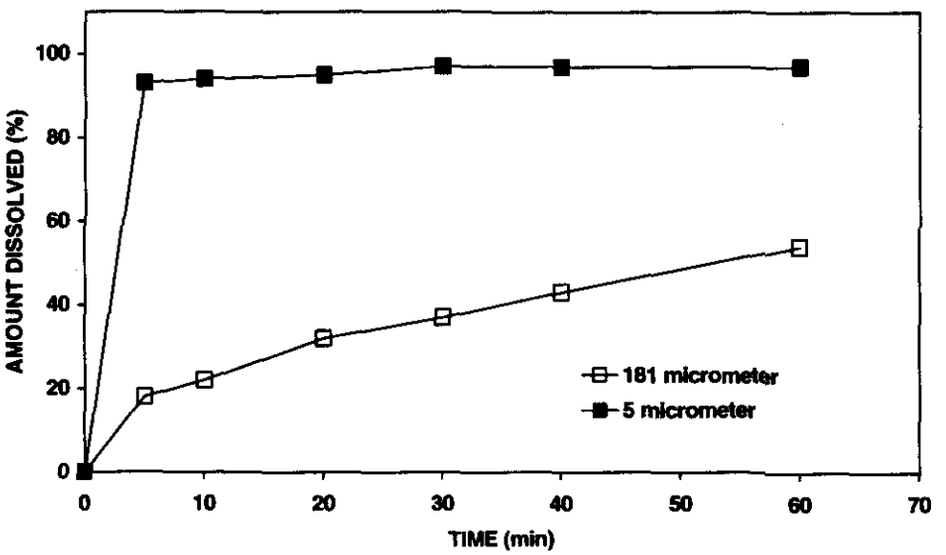

Figure 9: Powder dissolution profiles of chlorthalidone powders with different mean volume particle sizes.

The two powders with mean sizes above 50 μm failed the USP specification for tablet dissolution (3). The powder with a mean size of 25 μm also failed dissolution but in this instance the powder contained about 20 percentage of very fine particles (< 5 μm) which decreased the mean measured size. However, the dissolution rate was determined by the large particles (> 50 μm) present in this powder. Differences in particle size analysis results were confirmed by scanning electron microscopic analysis.

These results suggest that, when manufacturers set the bulk drug specifications for chlorthalidone, particle size should be included as a release criteria to satisfy the expectations that the producers of solid dosage forms might have in terms of USP regulations.

CONCLUSION

Generic drugs and the manufacturing thereof are very important in a developing country such as South Africa. This implies that generic raw materials are sought after at reasonable prices. The physicochemical properties of these drug powders might not be conducive to reliable product manufacturing due to the occurrence of crystal polymorphism. This study showed that the incidence of polymorphism is quite high, about 10%, amongst raw materials obtained from a large number of suppliers.

Of the 135 drugs studied, ten raw material batches failed dissolution specifications as set in the USP/BP or dissolved significantly slower than the powder to which it was compared. These powders included drugs such as carbamazepine, niclosamide, rifampicin, chlorthalidone, mebendazole, glibenclamide, piroxicam and phenylbutazone, which all are known to have bioavailability problems.

In many instances the effect of polymorphism and particle size on the solubility and dissolution rate of these drugs are known, but apparently, many manufacturers of bulk materials don't consider this when setting raw material specifications for their products. Perhaps this problem can be solved if specifications regarding polymorphism and particle size are set by official bodies and compendia.

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PART II – Dissolution Requirements

CHAPTER 3

International dissolution standards and harmonization of dissolution testing and standards

Melgardt M. de Villiers[1], Erna Swanepoel[2], Antonie P. Lötter[2] and Wilna Liebenberg[2]

[1]College of Pharmacy, University of Louisiana Monroe, Monroe LA 71201, USA, [2] Institute for Industrial Pharmacy, Potchefstroom University for CHE, Potchefstroom 2520, South Africa.

In Palmieri A., *ed.* Dissolution theory, methodology and testing. (In press.)

Introduction

During the last twenty years dissolution test methodology has been introduced to many pharmacopoeias and a number of regulations and guidelines on bioavailability, bioequivalence and *in vitro* dissolution have been issued at national and international levels (1). This means that although requirements for dissolution testing have been described and reviewed in the scientific literature, the development of dissolution tests for drugs or drug products is predominantly influenced by pharmacopoeial and regulatory requirements. Normally the steps involved in selecting an appropriate dissolution procedure consist of the selection of a dissolution apparatus, dissolution media, decision on deaeration, time points to collect samples, specification to set and development of a procedure to measure drug in dissolution fluid. The relative importance of these steps differs worldwide. This is demonstrated by differences in dissolution testing conditions, acceptance criteria and specifications found in the major pharmacopoeias.

In this chapter information on dissolution test procedures, method development, validation, regulatory guidance and dissolution specifications for specific drugs required in the major pharmacopoeias is provided. Efforts to harmonize dissolution requirements are

also described. The discussion will focus mainly on developments in the United States of America, the European Union and Japan.

Pharmacopoeial requirements for dissolution testing

Large numbers of different dissolution apparatuses are described in the literature, but only a few have withstand critical methodological examination (2, 3). These apparatuses have proved their effectiveness and are described in major pharmacopoeias such as:

- United States Pharmacopeia - USP (4)
- The British Pharmacopoeia – BP (5)
- The European Pharmacopoeia – EP (6)
- The Japanese Pharmacopoeia – JP (7)

Specific monographs that refer to dissolution testing in these pharmacopoeias are listed in Table 1.

Table 1 Pharmacopoeial monographs that describe dissolution testing.

USP	BP	EP	JP
<711> Dissolution	Appendix XII D – Dissolution test for tablets and capsules	2.9.3. Dissolution test for solid dosage forms	Dissolution centre
<724> Drug release	Appendix XII E – Dissolution test for transdermal patches	2.9.4. Dissolution test for transdermal patches	
<1088> *In vitro* and *in vivo* evaluation of dosage forms			

Types of dissolution apparatuses and mechanical allowances for testing

Several different dissolution test apparatuses are described in the various pharmacopoeias. These apparatuses are listed in Table 2. The most commonly used apparatuses are the rotating basket and the paddle method. Both these devices are simple, robust and adequately standardized apparatuses that are used all over the world and thus are supported by the widest experience of experimental use (3).

Table 2 The different dissolution apparatuses described in pharmacopoeia.

Test	USP	EP/BP	JP
Paddle apparatus	x- 2[1]	X	x
Basket apparatus	x-1	X	x
Flow-through apparatus	x- 3	X	x
Reciprocating cylinder	x- 4	X	
Reciprocating disk (also used for transdermal)	x-7		
Adaptations for transdermal patch (temperature= 32 °C):			
Disk assembly method	x-5	x	
Cell method		x	
Rotating cylinder method	x-6	x	
Special apparatus for medicated chewing gum EP 2.9.25.		x	

[1]Refers to the number of the apparatus as described in the pharmacopoeia, 1 refers to basket, 2 paddle, etc.

Table 3 Comparison of dimensions in millimeters of the paddle and basket apparatus described in different pharmacopoeia (1).

Apparatus	EP/BP	USP	JP	Harmonized Proposal[1]
Vessel				
Height	168±8	160-175	160-175	160-210
Internal Diameter	102±4	98-106	98-106	102±4
Paddle				
Shaft Diameter Before coating	9.75±0.35	9.4-10.1	9.75±0.35	9.75±0.35
Blade				
Upper chord	74.5±0.5	74.0-75.0	74.5±0.5	74.5±0.5
Lower chord	42.0±1	42.0±1.0	42±1	42.0±1.0
Height	19.0	19.0±0.5	19.0±0.5	19.0±0.5
Radius of disk	41.5	42.0±1.0	41.5	41.5±0.5
Radius upper corners	1.2	1.2	1.2	1.2
Thickness	4.0±1	4.0±1.0	3-5	4.0±1.0
Basket				
Shaft diameter	9.75±0.35 or 6.4±0.1	9.4-10.1 or 6.3-6.5	9.75±0.35 or 6.4±0.1	9.4-10.1

Screen				
Wire diameter	0.254	0.254[2]	No. 36 wire gauze	0.254
Openings	0.381	0.381[2]	0.425	0.381
Height of screen	27.1±1	27.0±1.0	27±1	27.0±1.0
Height basket	36.8±3.0	36.8±3	36.8±3	36.8±3
Internal diameter	20.2±1	20.2±1.0	20.2±1	20.2±1.0
External diameter	22.2±1	22.2±1.0	22.2±1	22.2±1.0
External diameter ring	25.4±3	25.4±3.0	25.4±3	25.4±3.0
Vent hole diameter	2	2.0	2	2.0±0.5
Height coupling disk	5.1±0.5	5.1±0.5	5.1±0.5	5.1±0.5
Position stirring device				
Distance between bottom flask and the blade/basket	25±2	25±2	25±2	25±2
Distance between shaft axis and vertical axis of vessel	≤ 2	≤ 2	≤ 2	≤ 2
Stirring	Smoothly without wobble (≤ 0.5 mm)	Smoothly without wobble		Smoothly without wobble (≤ 0.5 mm)

[1]Proposed by ICH
[2]Basket and wire size is indicated in individual monographs

Some minor discrepancies, Table 3, are still found in the detailed description of these apparatuses in the different pharmacopoeia (8). Currently the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is addressing this issue. Proposed ICH dimensions are also listed in Table 3. The description of only the flow-through apparatus is concurrent worldwide.

Selecting dissolution media

Consensus among the pharmacopoeia is that dissolution testing should be carried out under physiological conditions, if possible (8). This allows interpretation of dissolution data with regard to *in vivo* performance of the product. However, strict adherence to the gastrointestinal environment need not be used in routine dissolution testing. The testing conditions should be based on physicochemical characteristics of the drug substance and the environmental conditions the dosage form might be exposed to after oral administration. The volume of the dissolution medium is generally 500, 900, or 1000 ml. An aqueous medium with pH range 1.2 to 6.8 (ionic strength of buffers the same as in USP) should be used. To simulate intestinal fluid (SIF), a dissolution medium of pH 6.8 should be employed. A higher pH should be justified on a case-by-case basis and, in general, should not exceed pH 8.0. To simulate gastric fluid (SGF), a dissolution medium of pH 1.2 should be employed without enzymes. The need for enzymes in SGF and SIF should be evaluated on a case-by-case basis and should be justified. For gelatin capsules the possible need for enzymes (pepsin with SGF and pancreatin with SIF) to dissolve pellicles is permitted to ensure the dissolution of the drug (9).

Use of water as a dissolution medium is discouraged because test conditions such as pH and surface tension can vary depending on the source of water and may change during the dissolution test itself, due to the influence of the active and inactive ingredients (10, 11). For water insoluble or sparingly water soluble drug products, use of a surfactant such as sodium lauryl sulphate is recommended (3, 12). The need for and the amount of the surfactant should be justified. The use of hydro alcoholic mediums is discouraged.

All dissolution tests for immediate release dosage forms should be conducted at 37±0.5°C. The basket and paddle method can be used for performing dissolution tests under

multimedia conditions (e.g., the initial dissolution test can be carried out at pH 1.2, and, after a suitable time interval, a small amount of buffer can be added to raise pH to 6.8). Alternatively, if addition of an enzyme is desired, it can be added after initial studies (without enzymes). Use of Apparatus 3 allows easy change of the medium. Apparatus 4 can also be adopted for a change in dissolution medium during the dissolution run.

The equipment and dissolution methodology should include the product related operating instructions such as deaeration of the dissolution medium and use of a wire helix for capsules. Certain drug products and formulations are sensitive to dissolved air in the dissolution medium and will need deaeration. The method of deaeration described in the USP is to heat the medium, while stirring gently, to about 41°C (4). The heated solution is immediately filtered under vacuum using a filter having a porosity of 0.45 µm or less. The filtered solution is then vigorously stirred under vacuum for about 5 minutes. The deaeration procedure must be validated (not necessarily specifically for the media you are using but in general). Capsule dosage forms tend to float during dissolution testing with the paddle method. In such cases, it is recommended that capsule sinkers be used as described in each of the pharmacopoeias.

Only the USP chapter suggests that "sink" conditions are necessary with the other guidances suggesting that test conditions should be validated relative to *in-vitro-in-vivo* associations (correlations). Sink is defined as 33% of solubility necessary for dissolution (1). Furthermore, the USP allows pooling and default low pH media has been changed from 0.1 N HCl to 0.01 N HCl. It is also allowed to change the dissolution tests of hard or soft gelatin capsules and gelatin-coated tablets that do not conform to the dissolution specification due to cross-linking, by repeating the test with the addition of enzymes. For dissolution media with pH of less than 6.8 pepsin, and for pH of 6.8 or greater, pancreatin should be used. These options do not exist in EP/BP or JP.

Calibration and suitability testing

All pharmacopoeias require apparatus suitability tests to be carried out with a performance standard (i.e., dissolution calibrators). This must be done upon installation of a new dissolution apparatus and on a regular basis thereafter, at least twice a year and after any

significant change or movement. A change from basket to paddle or vice versa may also need recalibration.

The USP describes specific calibrator tablets, but recently there has been considerable discussion and literature published on the effectiveness of calibrator tablets for suitability testing. As a result of these efforts the number of tests required using the calibrator tablets has been reduced (13). Special concern has been expressed with the batch to batch reproducibility of calibrators and the insensitivity of calibrators to perturbations of the system (14). Efforts are currently on-going in the evaluation of alternatives to USP calibrator tablets, such as mechanical calibration (14, 15).

Only validated analytical procedures must be used to measure drug content. This includes validation of the dissolution test conditions such as sampling and filtration. Validation is required for both manual and automated methods and apparatuses.

Dissolution acceptance criteria

Dissolution test specifications described in pharmacopoeias include the definition of limits, the number of units to be examined, and the respective acceptance criteria (8). Significant differences are seen in the acceptance criteria set in different pharmacopoeias. A comparison of the dissolution acceptance criteria is shown in Table 4. Acceptance criteria are based on the Q-values (percentage dissolved within a specified time) and different stages (S). Additional acceptance criteria for enteric coated tablets, extended release dosage forms and delayed release dosage forms are given in the USP.

Dissolution specifications

The purpose of establishing dissolution specifications is to ensure batch-to-batch consistency within a range which guarantees acceptable biopharmaceutical performance (8). In the different pharmacopoeias dissolution specifications for individual products are given. These specifications usually states a percentage of the drug (Q) that must dissolve in a specified time when dissolution is measured using the pharmacopoeial method.

Table 4 Comparison of dissolution acceptance criteria for immediate release products.

	USP		JP		BP/EP	
Stage	Number Tested	Acceptance Criteria	Number Tested	Acceptance Criteria	Number Tested	Acceptance Criteria
S_1	6	Each unit is NLT Q+5%	6	Each unit meets specification	6	All must release 70% or Q in required time
S_2	6	Average of 12 units ($S_1 + S_2$) is equal to or greater than Q, and no unit is less than Q - 15%.	6	Ten of 12 tablets meet specification	6 (if 1 fails S1)	All 6 must comply
S_3	12	Average of 24 units ($S_1 + S_2 + S_3$) is equal to or greater than Q, not more than 2 units are less than Q - 15%, and no unit is less than Q - 25%				

Appendix 1 summarizes the dissolution specifications for products with monographs in the USP and BP/EP. It is clear from the information listed in Appendix 1 that there are significant differences in the number of products that require dissolution testing, the dissolution tests and the dissolution specifications. There are many more products that require dissolution tests in the USP.

Regulatory requirements for dissolution testing

Unlike many other pharmaceutical tests and procedures, there are well defined guidelines that dictate much of the experimental detail surrounding dissolution testing. The predominant dissolution guidances used by pharmaceutical manufacturers and regulatory agencies worldwide are those published in the USA, Europe and Japan.

United States of America – Food and Drug Administration (FDA)

Several guidance documents that address dissolution testing are published by the FDA.

1. Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), August 1997, BP 1.

2. Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of *In Vitro/In Vivo* Correlations. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), September 1997, BP 2.

3. Guidance for Industry: Waiver of *In Vivo* Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), August 2000, BP.

4. Guidance for Industry: Immediate Release Solid Oral Dosage Forms. Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, *In Vitro*

Dissolution Testing, and *In Vivo* Bioequivalence Documentation. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), November 1995, CMC.

5. Guidance for Industry: SUPAC-IR/MR: Immediate Release and Modified Release Solid Oral Dosage Forms, Manufacturing Equipment Addendum. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), January 1999, CMC 9 (revision 1).

6. Guidance for Industry: SUPAC-MR: Modified Release Solid Oral Dosage Forms. Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; *In Vitro* Dissolution Testing and *In Vivo* Bioequivalence Documentation. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), September 1997, CMC 8.

7. Guidance for Industry: SUPAC-SS: Nonsterile Semisolid Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; *In Vitro* Release Testing and *In Vivo* Bioequivalence Documentation. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), May 1997, CMC 7.

8. Guidance for Industry: SUPAC-SS: Nonsterile Semisolid Dosage Forms. Manufacturing Equipment Addendum. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), December 1998, CMC 3 (Draft guidance).

Copies of these documents are available from the Office of Training and Communications, Division of Communications Management, the Drug Information Branch, HFD-210, 5600 Fishers Lane, Rockville, MD 20857.

Europe – The European Agency for the Evaluation of Medicinal Products (EMEA)

The following guidances regulate dissolution testing in Europe:

1. CPMP/EWP/QWP/1401/98. Note For Guidance on the Investigation of Bioavailability and Bioequivalence (Re-released for Consultation, December 2000).

2. CPMP/QWP/604/96. Note For Guidance on Quality of Modified Release Products: A. Oral Dosage Forms; B. Transdermal Dosage Forms; Section I (Quality) (CPMP adopted 1996).

3. CPMP/QWP/486/95. Note for Guidance on Manufacture of the Finished Dosage Form (CPMP adopted Sept. 95).

Copies of these documents are available from the European Agency for the Evaluation of Medicinal Products, 7 Westferry Circus, Canary Wharf, London, E1 14HD, United Kingdom.

Japan – National Institute for Health Services (NIHS)

The following drug registration guidances from Japan address dissolution testing:

1. Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms, February 14, 2000.

2. Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms, February 14, 2000.

3. Guideline for Bioequivalence Studies of Generic Products, February 14, 2000.

Copies of these documents are available from National Institute of Health and Science, Organization of Pharmaceuticals and Medical Devices Evaluation Center, Division of Drugs.

International Pharmaceutical Federation - FIP

As far back as 1981 FIP published a joint report of the section of official laboratories and medicinal control services and the section of industrial pharmacists which developed in the following document (8):

> FIP Guidelines for Dissolution Testing of Solid Oral Products (final draft, 1995). Joint report of the section of official laboratories and medicines control services and the section of industrial pharmacists, Federation International Pharmaceutique, The Hague, Netherlands. Published in Drug Information Journal, Vol. 30, pp. 1071–1084, 1996 0092-8615/96.

This guideline was intended as suggestions primarily directed to compendial committees, working on the introduction of dissolution and release tests for the respective pharmacopoeias (8). This whole process combined with initiatives made by the FDA eventually led to dissolution being addressed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

International Conference on Harmonization

ICH is an unique project that brings together, since 1990, the drug regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration (16).

The purpose is to make recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration in order to reduce or eliminate the need to duplicate the testing carried out during the research and development of new and generic pharmaceutical products. To achieve this ICH has five specific goals:

1. To maintain a forum for a constructive dialogue between regulatory authorities and the pharmaceutical industry on the real and perceived differences in the technical requirements for product registration in the EU, USA and Japan in order to ensure

a more timely introduction of new medicinal products, and their availability to patients.

2. To monitor and update harmonized technical requirements leading to a greater mutual acceptance of research and development data.

3. To avoid divergent future requirements through harmonization of selected topics needed as a result of therapeutic advances and the development of new technologies for the production of medicinal products.

4. To facilitate the adoption of new or improved technical research and development approaches which update or replace current practices, where these permit a more economical use of human, animal and material resources, without compromising safety.

5. To facilitate the dissemination and communication of information on harmonized guidelines and their use to encourage the implementation and integration of common standards.

Participants in ICH

Since the focus of ICH has been on the technical requirements for medicinal products containing new drugs and due to the fact that the vast majority of those new drugs and medicines were developed in Western Europe, Japan and the United States of America when ICH was established, it was agreed that its scope would be confined to drug registration in those three regions. From the beginning there were six parties directly involved, as well as observers and the International Federation of Pharmaceutical Manufacturers Association (IFPMA).

The six founder members of ICH represent the regulatory bodies and the research-based industry in the European Union, Japan and the USA (16). The six parties are:

1. European Commission - European Union (EU)

   The European Commission represents the fifteen members of the EU. The Commission is working, through harmonization of technical requirements and procedures, to achieve a single market in pharmaceuticals which would allow free movement of products throughout the EU. The European Agency for the Evaluation of Medicinal Products (EMEA) has been established by the Commission and is situated in London. Technical and scientific support for ICH activities are provided by the Committee for Proprietary Medicinal Products (CPMP) of the EMEA.

2. European Federation of Pharmaceutical Industries and Associations (EFPIA)

   EFPIA is situated in Brussels and has, as its members, Member Associations in sixteen countries in Western Europe. Much of the Federation's work is concerned with the activities of the European Commission and the new EMEA.

3. Ministry of Health, Labor and Welfare, Japan (MHLW)

   MHLW is responsible for the improvement and promotion of social welfare, social security and public health. One of its nine bureaus is the Pharmaceutical Affairs Bureau within which is the Pharmaceuticals and Cosmetics Division. This Division is responsible for review and licensing of all medicinal products and cosmetics.

4. Japan Pharmaceutical Manufacturers Association (JPMA)

   JPMA represents ninety member companies. Membership includes all the major research-based pharmaceutical manufacturers in Japan. ICH work is coordinated through specialized committees of industry experts who also participate in expert working groups.

5. US Food and Drug Administration (FDA)

   The US Food and Drug Administration has a wide range of responsibilities for drugs, biological products, medical devices, cosmetics and radiological products.

The largest of the world's drug regulatory agencies, FDA is responsible for the approval of all drug products used in the USA. Technical advice and experts for ICH work are drawn from the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research within the FDA.

6. Pharmaceutical Research and Manufacturers of America (PhRMA)

   The Pharmaceutical Research and Manufacturers of America - PhRMA - represents the research-based industry in the USA. The Association has close to seventy companies in membership which are involved in the discovery, development and manufacture of prescription medicines. There are also research affiliates which conduct biological research related to the development of drugs and vaccines.

Since ICH was initiated there have been observers associated with the process, to act as a link with non-ICH countries and regions. Some of the observers to ICH are:

- The World Health Organization (WHO)
- The European Free Trade Area (EFTA), represented at ICH by Switzerland
- Canada, represented at ICH by the Drugs Directorate, Health Canada

The activities of ICH are controlled by a secretariat which operates from the IFPMA offices, in Geneva. It is primarily concerned with preparations for, and documentation of, meetings of the Steering Committee as well as coordination of preparations for Expert Working Group meetings and six-party drafting groups. At the time of ICH Conferences, the secretariat is responsible for the technical documentation and for liaison with the speakers for the Conference. Organizational aspects of the Conferences are handled by the industry and regulatory parties in the country where the Conference takes place. The first ICH Conference was held in Brussels, 1991, followed by ICH 2, Orlando, Florida, 1993, ICH 3, Yokohama, Japan 1995, ICH 4, 1997, Brussels, and ICH 5, 2000, San Diego. The next ICH Conference will be held in Osaka, Japan, in 2003.

ICH topics and guidelines

The ICH Topics are divided into four major categories and ICH Topic Codes are assigned according to these categories. The Guidelines deriving from the Topics are frequently referred to using the ICH Codes (16).

Q **"Quality"** Topics, i.e., those relating to chemical and pharmaceutical Quality Assurance.

S **"Safety"** Topics, i.e., those relating to *in vitro* and *in vivo* pre-clinical studies.

E **"Efficacy"** Topics, i.e., those relating to clinical studies in human subjects.

M **"Multidisciplinary"** Topics, i.e., cross-cutting topics which do not fit uniquely into one of the above categories.

Status of harmonization initiatives

To date ICH has developed over 40 harmonized guidelines to regulatory authorities and the research-based industry in the member countries aimed at removing redundancy and duplication in the development and review process. The member countries are finally supposed to sign off the guidelines to produce regulations. Successfully initiated and completed harmonization efforts include: Stability testing of new drugs substances and products, validation of analytical procedures, impurity testing, quality of biotechnological products, specifications for new drug substances and products, GMP for pharmaceutical ingredients, carcinogenicity testing, genotoxicity testing, toxicokinetics and pharmacokinetics, toxicity, reproductive toxicity, safety studies and clinical trials.

An ongoing effort that has not been successful yet is pharmacopoeial harmonization. However, pharmacopoeial authorities have been closely involved with the work of ICH since the onset and harmonization between the major pharmacopoeias, which started before ICH, has proceeded in parallel (17). The ICH Steering Committee receives regular reports on pharmacopoeial harmonization at its meetings. Pharmacopoeial harmonization is not impossible; the harmonization of the BP and EP has proved this.

Harmonization of the dissolution test and standards

Harmonization of dissolution tests for individual drugs and drug products, such as those listed in Appendix 1, has not yet been addressed by ICH. However, harmonization of the dissolution test is currently under development. The USP general chapter on dissolution is currently at the official inquiry stage, Step 4, of the harmonization process (17). The proposed chapter is consistent with the current version of Dissolution <711> with the exception of a few minor changes (4).

In more general terms dissolution tests for drugs and drug products have been addressed in several of the ICH guidance documents. Details of these recommendations are given in the following discussion, listing specific dissolution references in each of the guidances.

Q1A and Q1A(R): STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS (18, 19)

ICH Harmonized Tripartite Guideline, endorsed by the ICH Steering Committee at Step 4 of the ICH Process, 27 October 1993 then revised under Step 2 of the ICH Process on 7 October 1999, and recommended for adoption under Step 4 of the ICH Process on 8 November 2000 by the ICH Steering Committee.

The purpose of the stability study as described in this guidance is to establish, based on testing a minimum of three batches of the drug product, a shelf life and label storage instructions applicable to all future batches of the drug product manufactured and packaged under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout its shelf life. This guidance spells out a systematic approach that should be adopted in the presentation and evaluation of the stability information, which should include, as appropriate, results from the physical, chemical, biological, and microbiological tests, including particular attributes of the dosage form (for example, dissolution rate for solid oral dosage forms). A significant change in the dissolution properties during stability testing is defined as failure to meet the acceptance criteria for dissolution for 12 dosage units.

Q1B: STABILITY TESTING: PHOTOSTABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS (20)

Recommended for adoption at Step 4 of the ICH Process on 6 November 1996 by the ICH Steering Committee.

This guidance states that for each drug product, samples should be analyzed at the end of the exposure to conditions conducive to possible photochemical degradation of the drug. These samples should be examined for any changes in physical properties (e.g., appearance, clarity or color of solution, dissolution/disintegration for dosage forms such as capsules, etc.) and for assay and degradation products by a method suitably validated for products likely to arise from photochemical degradation processes.

Q1E: DRAFT CONSENSUS GUIDELINE EVALUATION OF STABILITY DATA (21)

Released for consultation at Step 2 of the ICH Process on 7 February 2002 by the ICH Steering Committee.

This guidance asks that a systematic approach should be adopted in the presentation and evaluation of the stability information, which should include, results from the physical, chemical, biological, and microbiological tests, including those related to particular attributes of the dosage form (for example, dissolution rate for solid oral dosage forms).

The recommendations in this guideline on some practical statistical approaches are not intended to imply that use of statistical evaluation is preferred when it can be justified to be unnecessary. For example, qualitative attributes are not amenable to statistical analysis, and microbiological attributes and certain quantitative attributes (e.g., pH, dissolution) are generally not amenable to the type of statistical analysis described in this guidance. Furthermore, the following physical changes can be expected to occur at the accelerated condition at high temperature and would not be considered significant change that calls for testing at an intermediate temperature if there is no other significant change (potential interaction effects should also be considered in establishing that there is no other significant change): (1) softening of a suppository that is designed to melt at 37°C, if the melting point is clearly demonstrated; and (2) failure to meet acceptance criteria for

dissolution for 12 units of a gelatin capsule or gel-coated tablet if it can be unequivocally attributed to cross-linking. However, phase separation of semisolid dosage forms at the accelerated condition could call for testing at the intermediate condition.

Q2A: TEXT ON VALIDATION OF ANALYTICAL PROCEDURES (22)

Recommended for adoption at Step 4 of the ICH Process on 27 October 1994 by the ICH Steering Committee.

The discussion of the validation of analytical procedures in this guidance document is directed to the four most common types of analytical procedures:

1. Identification tests.
2. Quantitative tests for impurities' content.
3. Limit tests for the control of impurities.
4. Quantitative tests of the active moiety in samples of drug substance or drug product or other selected component(s) in the drug product.

Although there are many other analytical procedures, such as dissolution testing for drug products or particle size determination for drug substance, these have not been addressed in the initial text on validation of analytical procedures. Validation of these additional analytical procedures is equally important to those listed herein and may be addressed in subsequent documents.

Q2B: VALIDATION OF ANALYTICAL PROCEDURES: METHODOLOGY (23)

Recommended for adoption at Step 4 of the ICH Process on 6 November 1996 by the ICH Steering Committee.

This guidance document makes particular note of procedures to validate the range acceptable for a specific analytical procedure. For dissolution testing, variation of +/-20% over the specified range is recommended. For example, if the specifications for a

controlled released product cover a region from 20%, after 1 hour, up to 90%, after 24 hours, the validated range would be 0-110% of the label claim.

Q5C: QUALITY OF BIOTECHNOLOGICAL PRODUCTS: STABILITY TESTING OF BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS (24)

Recommended for Adoption at Step 4 of the ICH Process on 30 November 1995 by the ICH Steering Committee.

For biotechnological and biological products the dissolution time for powders, though not specifically relating to quality of the compound, should be monitored and reported for the drug product in its final container.

Q6A: SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR NEW DRUG SUBSTANCES AND NEW DRUG PRODUCTS: CHEMICAL SUBSTANCES (25)

Recommended for adoption at Step 4 of the ICH Process on 6 October 1999 by the ICH Steering Committee.

This guidance requires that data collected during the design and development stage 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. For example, 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.

For new drug substances dissolution testing is also recommended as a surrogate test for determining crystal polymorphic changes in the drug substance and/or product. However, the use of dissolution testing in this instance is to monitor product performance. The use of this test to estimate the actual polymorph content should only be used as a last resort to set test and acceptance criteria.

Dissolution testing is also recommended as a test to measure release of drug substance from drug products. 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, sampling at multiple time points should be performed for extended-release dosage forms, and two-stage testing using different media in succession or in parallel 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., children or the elderly) when designing the tests and acceptance criteria.

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.

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. When 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 +/-10% of the labeled content of drug substance, unless a wider range is supported by a bioequivalence study.

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.

Interestingly the guidance also recommends that 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. It should be performed at release and it may be performed as an in-process test when justified by product development data. 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 and the mean, upper, and/or lower particle size limits should be well defined. The potential for particle growth should also be investigated during product development and the acceptance criteria should take the results of these studies into account.

The testing apparatus, media, and conditions recommended in this guidance should be pharmacopoeial, if possible, or otherwise justified. Dissolution procedures using either pharmacopoeial or non-pharmacopoeial apparatus or conditions should be validated. 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.

M4Q: THE CTD – QUALITY (26)

Released for consultation at Step 2 of the ICH Process on 20 July 2000 by the ICH Steering Committee.

This is one in a series of guidances that provide recommendations for applicants preparing the Common Technical Document for the Registration of Pharmaceuticals for Human Use (CTD) for submission to the U.S. Food and Drug Administration (FDA). It presents the agreed upon common format for the preparation of a well-structured Quality section of the CTD for applications that will be submitted to regulatory authorities.

In the CTD a tabulated summary of the composition of the formulations used in clinical trials and a presentation of dissolution profiles for these products should be imported directly, where relevant. Dissolution differences between clinical formulations and the formulation (i.e., composition) should be discussed and results from comparative *in vitro* studies (e.g., dissolution) or comparative *in vivo* studies (e.g., bioequivalence) should be

discussed when appropriate. Furthermore, parameters relevant to the performance of the drug product, such as dissolution, should be addressed.

Conclusion and future directions

Dissolution testing is continuing to grow as a critical technique applied for formulation selection, assessment of product quality and evaluation of product and process changes. Worldwide regulatory agencies and national and international pharmacopoeias are relying on this test more and more not only for assessment of drug products but for relevance to *in vivo* performance. It is uncertain if the drive to establish *in vitro in vivo* correlations will attempt ultimately to encompass all dissolution tests listed in official monographs intended for product release.

Regardless of the outcome, there is still much to be done to establish dissolution testing as a harmonized regulatory quality control procedure. Harmonization must continue to address differences in pharmacopoeial monograph tests, apparatus dimensions, acceptance criteria, and regulatory guidelines. Pharmacopoeial harmonization of the USP, EP and JP, similar to the combination of the BP and EP, would go a long way in addressing these differences. The ICH initiative has moved significantly towards resolution of regulatory harmonization. Not withstanding these differences it is anticipated that dissolution testing will continue to grow as a meaningful and cost-effective indicator of the physical consistency of pharmaceutical products.

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Appendix 1

Comparison of dissolution test conditions and specifications for products listed in the USP and EP/BP.

Product	USP			EP/BP		
	Method	Medium	Tolerance[1]	Method	Medium	Tolerance
Acetaminophen capsules	2[2] (50 rpm)	Water	75% (45 min)			
Acetaminophen tablets	2[3] (50 rpm)	Phosphate buffer pH 5.8	80% (30 min)	2 (50 rpm)	Phosphate buffer pH 5.8	70% (45 min)
Acetaminophen and aspirin tablets	2 (50 rpm)	Water	75% (45 min)			
Acetaminophen, aspirin and caffeine tablets	2 (100 rpm)	Water	75% (60 min)			
Acetaminophen and caffeine tablets	2 (100 rpm)	Water	75% (60 min)			
Capsules containing three of the following: Acetaminophen, salts of chlorpheniramine, dextromethorphan, phenylpropanolamine	1 (50 rpm)	Water	75% (45 min)			

Tablets containing three of the following: Acetaminophen, salts of chlorpheniramine, dextromethorphan, phenylpropanolamine	2 (50 rpm)	Water	75% (45 min)			
Capsules containing three of the following: Acetaminophen, salts of chlorpheniramine, dextromethorphan, pseudoephedrine	1 (100 rpm)	Water	75% (45 min)			
Tablets containing three of the following: Acetaminophen, salts of chlorpheniramine, dextromethorphan, pseudoephedrine	2 (50 rpm)	Water	75% (45 min)			
Acetaminophen and codeine phosphate capsules	2 (50 rpm)	0.1 N HCl	75% (30 min)			
Acetaminophen and codeine phosphate tablets	2 (50 rpm)	0.1 N HCl	75% (30 min)	2 (50 rpm)	Phosphate buffer pH 5.8	70% (45 min)

Acetaminophen and dihydrocodeine phosphate tablets				2 (50 rpm)	Phosphate buffer pH 5.8	70% (45 min)
Acetaminophen and diphenhydramine citrate tablets	2 (50 rpm)	Water	75% (45 min)			
Acetaminophen, diphenhydramine HCl and pseudoephedrine HCl tablets	2 (50 rpm)	Phosphate buffer pH 5.8	75% (30 min)			
Acetaminophen and pseudoephedrine HCl tablets	2 (50 rpm)	Phosphate buffer pH 5.8	75% (45 min)			
Acetazolamid tablets	1 (100 rpm)	0.1 N HCl	75 % (60 min)			
Acetohexamide tablets	1 (100 rpm)	Phosphate buffer pH 7.6	75% (60 min)			
Acyclovir capsules	1 (100 rpm)	0.1 N HCl	75% (45 min)			
Acyclovir tablets	2 (50 rpm)	0.1 N HCl	80% (45 min)	2 (50 rpm)	0.1 M HCl	70% (45 min)
Albendazole tablets	2 (50 rpm)	0.1 N HCl	80% (30 min)			
Albuterol tablets	2 (50 rpm)	Water	80% (30 min)			
Allopurinol tablets	2 (50 rpm)	0.1 N HCl	75% (45 min)			

Alprazolam tablets	1 (100 rpm)	Phosphate buffer pH 6.0	80 % (30 min)			
Altretamine capsules	1 (100 rpm)	0.1 N HCl	75% (30 min)			
Amantadine HCl capsules	1 (100 rpm)	Water	75% (45 min)			
Amiloride HCl tablets	2 (50 rpm)	0.1 N HCl	80 % (30 min)			
Amiloride HCl and hydrochlorothiazide tablets	2 (50 rpm)	0.1 N HCl	80 % (30 min)			
Aminocaproic acid tablets	1 (100 rpm)	Water	75% (45 min)			
Aminoglutethimide tablets	1 (100 rpm)	Dilute	75% 30 min)			
Aminophylline tablets	2 (50 rpm)	Water	75% (45 min)	2 (50 rpm)	Phosphate buffer 7.0	70 % (45 min)
Aminosalicylate sodium tablets	1 (100 rpm)	Water	75% (45 min)			
Aminosalicylic acid tablets	1 (100 rpm)	Phosphate buffer pH 7.5	75% (45 min)			
Amitriptyline HCl tablets	1 (100 rpm)	0.1 N HCl	75% (45 min)			

Amodiaquine HCl tablets	2 (50 rpm)	Water	75% (30 min)			
Amoxapine tablets	2 (50 rpm)	Simulated gastric fluid without enzyme	80% (30 min)			
Amoxycillin 250 mg capsules	1 (100 rpm)	Water	80% (60 min)			
Amoxycillin 500 mg capsules	2 (75 rpm)	Water	80% (60 min)			
Amoxycillin tablets	2 (75 rpm)	Water	80% (90 min)			
Amoxycillin and clavulanate potassium tablets	2 (75 rpm)	Water	85% Amoxycillin and 80 % Clavulanate K (30 min)	2 (75 rpm)	Water	70 % (45 min)
Amphetamine sulfate tablets	1 (100 rpm)	Water	75% (45 min)			
Ampicillin capsules	1 (100 rpm)	Water	75% (45 min)			
Anileridine HCl tablets	1 (100 rpm)	0.1 N HCl	65% (45 min)			
Ascorbic acid tablets	2 (50 rpm)	Water	75% (45 min)			
Aspirin capsules	1 (100 rpm)	0.05 M Acetate buffer pH 4.5	80% (30 min)			

Aspirin tablets	1 (50 rpm)	0.05 M Acetate buffer pH 4.5	80% (30 min)	1 (50 rpm)	pH 4.5 buffer (500 ml)	70% (45 min)
Buffered aspirin capsules	2 (75 rpm)	0.05 M Acetate buffer pH 4.5	80% (30 min)			
Aspirin and caffeine tablets				2 (50 rpm)	pH 4.5 buffer (500 ml)	70% (45 min)
Aspirin, alumina and magnesia tablets	2 (75 rpm)	0.05 M Acetate buffer pH 4.5	75% (45 min)			
Aspirin, alumina and magnesium oxide tablets	1 (100 rpm)	0.05 M Acetate buffer pH 4.5	75% (45 min)			
Aspirin, caffeine and dihydrocodeine bitartrate capsules	1 (50 rpm)	0.05 M Acetate buffer pH 4.5	75% (45 min)			
Aspirin and codeine phosphate capsules	2 (75 rpm)	0.05 M Acetate buffer pH 4.5	75% (30 min)	2 (50 rpm)	pH 4.5 buffer (500 ml)	70% (45 min)
Aspirin, codeine phosphate, alumina and magnesia tablets	2 (75 rpm)	0.05 M Acetate buffer pH 4.5	75% (30 min)			
Astemizole tablets	2 (100 rpm)	Simulated gastric fluid TS without enzymes (800 ml)	80% (45 min)			

Atenolol tablets	2 (50 rpm)	Water	80% (30 min)			
Atenolol, chlorthalidone tablets	2 (150 rpm)	Water	80% (45 min)			
Azatidine maleate tablets	2 (50 rpm)	0.1 N HCl	80% (30 min)			
Azathioprine tablets	2 (50 rpm)	Water	75% (30 min)			
Azithromycin capsules	2 (100 rpm)	Phosphate buffer pH 6.0	75% (45 min)			
Bacampicillin HCl tablets	2 (75 rpm)	Water	85% (30 min)			
Baclofen tablets	2 (50 rpm)	0.1 N HCl	75% (30 min)	2 (50 rpm)	0.1 M HCl	70% (45 min)
Bendroflumethiazide tablets	2 (50 rpm)	0.1 N HCl	75% (45 min)			
Benztropine mesylate tablets	2 (50 rpm)	0.1 N HCl	80% (30 min)			
Betamethasone tablets	2 (50 rpm)	Water	75% (45 min)			
Betaxolol tablets	2 (50 rpm)	Water	80% (30 min)			
Bethanechol chloride tablets	2 (50 rpm)	0.1 N HCl	80% (30 min)			
Biperiden HCl tablets	2 (50 rpm)	0.1 N HCl	75% (45 min)			

Brompheniramine maleate tablets	1 (100 rpm)	Water, 500 ml	75% (45 min)			
Bumetamide tablets	2 (50 rpm)	Water	85% (30 min)			
Bumetanide and slow potassium tablets				2 (100 rpm)	Water	**Bumetanide**: 70% (45 min) **KCl**: not more than 50% in 1 hour; after 2 hours not less than 25% and not more than 75%; after 6 hours not less than 75%
Buspirone HCl tablets	2 (50 rpm)	0.1 N HCl	80% (30 min)			
Butabarbital sodium tablets	1 (100 rpm)	Water	75% (45 min)			
Butalbital, acetaminophen and caffeine capsules	1 (100 rpm)	Water	80% (60 min)			

Butalbital, acetaminophen and caffeine capsules	1 (100 rpm)	Water	80% (30 min)			
Butalbital and aspirin tablets	1 (100 rpm)	Water	75% (60 min)			
Butalbital, aspirin and caffeine capsules	2 (50 rpm)	Water	80% (30 min) butalbital and caffeine; 80% (60 min) aspirin			
Butalbital, aspirin and caffeine tablets	2 (50 rpm)	Water	80% (30 min) butalbital and caffeine; 80% (60 min) aspirin			
Butalbital, aspirin, caffeine and codeine phosphate capsules	2 (50 rpm)	Water	75% (60 min)			
Calcifediol capsules	2 (50 rpm)	Water, 500 ml	Capsules rapture < 15 min			
Calcium acetate tablets	2 (50 rpm)	Water	80% (30 min)			
Calcium carbonate tablets	2 (75 rpm)	Water	75% (30 min)			
Calcium gluconate tablets	2 (50 rpm)	Water	75% (45 min)	2 (50 rpm)	Water	70% (45 min)

Calcium lactate tablets	1 (100 rpm)	Water, 500 ml	75% (45 min)			
Calcium pantothenate tablets	2 (50 rpm)	Water	75% (45 min)			
Dibasic calcium phosphate tablets	2 (75 rpm)	0.1 N HCl	75% (45 min)			
Captopril tablets	1 (50 rpm)	0.1 N HCl	80% (20 min)			
Captopril and hydrochlorothiazide tablets	1 (50 rpm)	0.1 N HCl	80% (20 min) captopril; 60% (30 min) hydrochlorothiazide			
Carbamazepine tablets	2 (75 rpm)	Water with 1 % sodium lauryl sulfate	75% (60 min)			
Carbenicillin indanyl sodium tablets	1 (100 rpm)	Water	75% (45 min)			
Carbidopa and levodopa tablets	1 (50 rpm)	0.1 N HCl	80% (30 min)	1 (50 rpm)	0.1 M HCl (750 ml)	70% (45 min)
Carbinoxamine maleate tablets	2 (50 rpm)	Water	75% (45 min)			
Carisoprodol tablets	2 (75 rpm)	0.05 M Phosphate buffer pH 6.9	80% (60 min)			

Carisoprodol and aspirin tablets	2 (75 rpm)	Water	75% (45 min)			
Carisoprodol, aspirin and codeine phosphate tablets	2 (75 rpm)	Water	75% (45 min)			
Cortcolol HCl tablets	2 (50 rpm)	Water	80% (30 min)			
Cefaclor capsules	2 (50 rpm)	Water	80% (30 min)	2 (50 rpm)	Water	70% (45 min)
Cefadroxil capsules	1 (100 rpm)	Water	80% (30 min)	1 (100 rpm)	Water	70% (45 min)
Cefradine capsules				1 (100)	0.12 M HCl	70% (45 min)
Cefadroxil tablets	2 (50 rpm)	Water	75% (30 min)			
Cefixime tablets	1 (100 rpm)	0.05 M Potassium phosphate buffer pH 7.2	75% (45 min)			
Cefprozil tablets	1 (100 rpm)	Water	75% (45 min)			
Cefuroxime and axetil tablets	2 (55 rpm)	0.07 N HCl	60% (15 min) cefuroxime; 75% (45 min) axetil	2 (50 rpm)	0.1 M HCl	70% (45 min)
Cephalexin capsules	1 (100 rpm)	Water	80% (30 min)			
Cephalexin tablets	1 (100 rpm; 40 mesh)	Water	80% (30 min)			

Cephalexin HCl tablets	1 (150 rpm; 10 mesh)	Water	75% (45 min)			
Cephadrine capsules	1 (100 rpm)	0.12 N HCl	75% (45 min)			
Cephadrine tablets	1 (100 rpm)	0.12 N HCl	85% (60 min)			
Chloral hydrate capsules	2 (50 rpm)	Water	Rapture within 15 min			
Chloramphenicol capsules	1 (100 rpm)	0.1 N HCl	85% (30 min)	1 (100 rpm)	0.1 M HCl	70% (45 min)
Chlordiazepoxide tablets	1 (100 rpm)	Simulated gastric fluid TS without pepsin	85% (30 min)			
Chlordiazepoxide and amitriptylin HCl tablets	1 (100 rpm)	Simulated gastric fluid TS without pepsin	85% (30 min)			
Chlordiazepoxide HCl capsules	1 (100 rpm)	Water	85% (30 min)	1 (100 rpm)	0.1 M HCl	70% (45 min)
Chlordiazepoxide and didinium bromide capsules	1 (100 rpm)	Water	75% (30 min)			
Chloroquine phosphate tablets	2 (100 rpm)	Water	75% (45 min)	1 (100 rpm)	0.1 M HCl	70% (45 min)

Chloroquine sulfate tablets				1 (100 rpm)	0.1 M HCl	70% (45 min)
Chlorothiazide	2 (75 rpm)	0.05 M phosphate buffer pH 8	75% (60 min)			
Chlorpheniramine maleate tablets	2 (50 rpm)	Water, 500 ml	75% (45 min)			
Chlorpromazine HCl tablets	1 (50 rpm)	0.1 N HCl	80% (30 min)	2 (50 rpm)	0.1 M HCl`	70% (45 min)
Chlorpropamide tablets	2 (50 rpm)	Water	75% (60 min)	1 (100 rpm)	Phosphate buffer pH 6.8	70% (45 min)
Chlorthalidone tablets	2 (75 rpm)	Water	70% (60 min)			
Chlorzoxazine tablets	2 (75 rpm)	Phosphate buffer pH 8 (1800 ml)	75% (60 min)			
Cimetidine HCl tablets	1 (100 rpm)	Water	75% (15 min)			
Cinoxacin capsules < 250 mg	1 (100 rpm)	Phosphate buffer pH 6.5 (500 ml)	60% (30 min)			
Cinoxacin capsules > 250 mg	1 (100 rpm)	Phosphate buffer pH 6.5 (1000 ml)	60% (30 min)			

Ciprofloxacin tablets	2 (50 rpm)	Water	80% (30 min)	2 (50 rpm)	Water	70% (45 min)
Clarithromycin tablets	2 (50 rpm)	0.1 M acetate buffer pH 5	80% (30 min)			
Clemastine fumarate tablets	2 (50 rpm)	Citrate buffer pH 4 (500 ml)	75% (30 min)			
Clindamycin HCl capsules	1 (100 rpm)	Water	80% (30 min)			
Clobazam capsules				2 (75 rpm)	0.1 M HCl (500 ml)	70% (45 min)
Clofazimine capsules	2 (50 rpm)	Water, 500 ml	Rapture within 15 min			
Clofibrate capsules	2 (75 rpm)	Sodium lauryl sulfate solution (5:100) 1000 ml	75% (180 min)			
Clomiphene citrate tablets	1 (100 rpm)	Water	75% (30 min)	1 (100 rpm)	Water	70% (45 min)
Clonazepam tablets	2 (100 rpm)	Water, degassed	80% (60 min)			
Clonidine HCl tablets	2 (50 rpm)	Water, 500 ml	75% (30 min)			

Clonidine HCl and chlorthalidone tablets	2 (100 rpm)	Water	50% (60 min) clonidine HCl; 80% (60 min) chlorthalidone			
Clorazepate dipotassium tablets	2 (50 rpm)	Water	80% (30 min)			
Cloxacillin sodium capsules	1 (100 rpm)	Water	75% (45 min)			
Codeine phosphate tablets	2 (50 rpm)	Water	75% (45 min)			
Codeine sulfate tablets	1 (100 rpm)	Water, 500 ml	75% (45 min)			
Colchicine tablets	1 (100 rpm)	Water, 500 ml	75% (30 min)			
Cortisone acetate tablets	1 (100 rpm)	Isopropyl alcohol and dilute HCl (3:7)	60% (30 min)	2 (50 rpm)	0.3 % w/v sodium dodecyl sulphate	70 % (45 min)
Cyclizine HCl tablets	2 (50 rpm)	Water	75% (45 min)			
Cyclobenzaprine HCl tablets	1 (50 rpm)	0.1 N HCl	75% (30 min)			
Cyclosporine capsules	2 (50 rpm)	Water, 500 ml	Rapture in 15 min			
Cyproheptadine HCl tablets	2 (50 rpm)	0.1 N HCl	80% (30 min)			

Danazol capsules	2 (75 rpm)	Sodium lauryl sulfate 0.75%	75% (30 min)			
Dapsone tablets	1 (100 rpm)	HCl (2:100)	75% (60 min)	1 (100 rpm)	0.1 M HCl	70% (45 min)
Democlocycline HCl capsules (Demo of deme?	2 (75 rpm)	Water	75% (45 min)	2 (50 rpm)	0.1 M HCl	70% (45 min)
Democlocycline HCl tablets	2 (75 rpm)	Water	75% (45 min)			
Dergocrine mesylate tablets				1 (120 rpm)	0.1 M HCl, 500 ml	70% (45 min)
Desipramine HCl tablets	2 (50 rpm)	0.1 N HCl	75% (60 min)			
Dexamethasone tablets	1 (100 rpm)	HCl (1:100)	70% (45 min)			
Dexchlorpheniramine maleate tablets	2 (50 rpm)	Water, 500 ml	75% (45 min)			
Dextroamphetamine sulfate capsules	1 (100 rpm)	Water, 500 ml	75% (45 min)			
Dextroamphetamine sulfate tablets	1 (100 rpm)	Water, 500 ml	75% (45 min)			
Diazepam capsules	1 (100 rpm)	0.1 N HCl	85% (45 min)			
Diazepam tablets	1 (100 rpm)	0.1 N HCl	85% (30 min)	1 (100 rpm)	0.1 M HCl	70% (45 min)

Diazoxide capsules	1 (100 rpm)	Phosphate buffer pH 6.8	75% (45 min)			
Dichlorophenamide tablets	2 (75 rpm)	0.1 M phosphate buffer pH 8	80% (60 min)			
Diclofenac sodium						
Dicloxacillin sodium capsules	1 (100 rpm)	Water	75% (30 min)			
Dicyclomine HCl capsules	2 (50 rpm)	0.01 N HCl	75% (45 min)			
Dicyclomine HCl tablets	2 (50 rpm)	0.01 N HCl	75% (45 min)			
Diethylpropion HCl tablets	2 (50 rpm0	Water	75% (45 min)			
Diflunisal tablets	2 (50 rpm)	0.1 M tris buffer pH 7.2	80% (30 min)	2 (50 rpm)	pH 7.2 buffer	70% (45 min)
Digitoxin capsules	1 (120 rpm)	HCl (3:500), 500 ml	60% (30 min) and 85% (60 min)			
Digoxin capsules	1 (120 rpm)	0.1 N HCl, 500 ml	80% (60 min)			
Digoxin tablets				1 (120 rpm)	Water (600 ml)	75% (45 min)

Diltiazin HCl tablets	2 (75 rpm)	Water	< 60% (30 min) and > 75% (180 min)			
Dimenhydrinate tablets	2 (50 rpm)	Water	75% (45 min)			
Diphenhydramine HCl capsules	1 (100 rpm)	Water, 500 ml	80% (30 min)			
Diphenhydramine and pseudoephedrine capsules	1 (100 rpm)	Water	75% (30 min)			
Diphenoxylate HCl and atropine sulfate tablets	1 (50 rpm)	0.2 M acetic acid	75% (45 min)			
Dipyridamol tablets	2 (50 rpm)	0.1 N HCl	70% (30 min)			
Disopyramide phosphate capsules	2 (50 rpm)	Water, 1000 ml	80% (30 min)	2 (50 rpm)	Water	70% (45 min)
Domperidone tablets				2 (50 rpm)	0.1 M HCl	70% (45 min)
Doxepin HCl capsules	1 (50 rpm)	Water	80% (30 min)			
Doxycycline dispersible tablets				2 (75 rpm)	2 g of sodium chloride in 7 ml of HCl and water to 1000 ml	70% (45 min)
Doxycycline capsules	2 (75 rpm)	0.1 N HCl	85% (60 min)			

Doxycycline hyclate capsules	2 (75 rpm)	Water	80% (30 min)			
Doxycycline hyclate tablets	2 (75 rpm)	Water	80% (90 min)			
Doxylamine succinate tablets	2 (50 rpm)	0.1 N HCl	80% (30 min)			
Dronabinol capsules	2 (50 rpm)	Water, 500 ml	Rapture in 15 min			
Droperidol tablets				2 (75 rpm)	0.1 M HCl	70% (45 min)
Dydrogesterone tablets	2 (100 rpm)	0.3 % sodium lauryl sulfate, 500 ml	75% (60 min)			
Dyphylline tablets	1 (100 rpm)	Water	75% (45 min)			
Enalapril maleate tablets	2 (50 rpm)	Water	80% (30 min)			
Enalapril maleate and hydrochlorothiazide tablets	2 (50 rpm)	Water	80% (30 min) enalapril maleate; 65% (30 min) hydrochlorothiazide			
Ephedrine sulfate capsules	1 (100 rpm)	Water, 500 ml	80% (30 min)			
Ergoloid mesylate capsules	1 (50 rpm)	Water, 500 ml	Rapture in 15 min			

Ergoloid mesylate tablets	1 (50 rpm)	Water, 500 ml	75% (30 min)			
Ergonovine maleate tablets	1 (100 rpm)	Water	75% (45 min)			
Ergotamine tartrate tablets	2 (75 rpm)	Tartaric acid solution (1:100)	75% (30 min)			
Ergotamine and caffeine tablets	2 (75 rpm)	Tartaric acid solution (1:100)	70% (30 min) ergotamine; 750% (30 min) caffeine			
Erythromycin tablets	2 (50 rpm)	0.05 M phosphate buffer pH 6.8	70% (60 min)			
Erythromycin ethylsuccinate tablets	2 (50 rpm)	0.1 N HCl	75% (45 min)			
Erythromycin stearate tablets	2 (100 rpm)	0.05 M phosphate buffer pH 6.8	75% (120 min)	2 (50 rpm)	Acetate buffer, pH 5.0	70% (45 min)
Estradiol tablets	2 (100 rpm)	0.3 % sodium lauryl sulfate, 500 ml	75% (60 min)			
Estropipate tablets	2 (75 rpm)	Water	75% (60 min)			

Ethacrynic acid tablets	2 (50 rpm)	0.1 M phosphate buffer pH 8	75% (45 min)	2 (50 rpm)	Phosphate buffer, pH 8.0	70% (45 min)
Ethambutol HCl tablets	1 (100 rpm)	Water	75% (45 min)			
Ethchlorvynol capsules	2 (50 rpm)	Water, 500 ml	Rapture in 15 min			
Ethosuximide capsules	1 (100 rpm)	Water	75% (45 min)			
Ethotoin tablets	2 (100 rpm)	0.1 N HCl	80% (60 min)			
Etidronate disodium tablets	1 (100 rpm)	Water	70% (30 min)			
Etodolac capsules				1 (100 rpm)	Phosphate buffer pH 7.5	70% (45 min)
Etodolac tablets	1 (100 rpm)	Phosphate buffer pH 6.8	80% (30 min)	1 (100 rpm)	Phosphate buffer pH 7.5	70% (45 min)
Etoposide capsules	2 (50 rpm)	Acetate buffer pH 4.5	80% (30 min)			
Famotidine capsules	2 (50 rpm)	0.1 M phosphate buffer pH 4.5	75% (30 min)			
Famotidine tablets				2 (50 rpm)	Phosphate buffer pH 4.5	70% (45 min)

Fenbufen capsules				2 (100 rpm)	Phosphate buffer pH 7.5	70% (45 min)
Fenbufen tablets				2 (100 rpm)	Phosphate buffer pH 7.5	70% (45 min)
Fenoprofen calcium capsules	1 (100 rpm)	Phosphate buffer pH 7	75% (60 min)			
Ferrous fumarate capsules				2 (50 rpm)	0.1 M HCl	70% (45 min)
Ferrous fumarate tablets	2 (75 rpm)	0.1 N HCl with 0.5 % sodium lauryl sulfate	75% (45 min)	2 (75 rpm)	0.1 M HCl	70% (45 min)
Ferrous gluconate capsules	1 (100 rpm)	0.1 N HCl	75% (45 min)			
Ferrous gluconate capsules	1 (150 rpm)	Simulated gastric fluid TS	80% (80 min)			
Ferrous sulfate tablets	2 (50 rpm)	0.1 N HCl	75% (45 min)			
Flecainide acetate tablets < 50 mg	2 (50 rpm)	0.075 N HCl	70% (30 min)			
Flecainide acetate tablets > 50 mg	2 (50 rpm)	0.075 N HCl	70% (60 min)			
Flucytosine capsules	2 (100 rpm)	Water	75% (45 min)			

Fludrocortisone acetate tablets	2 (75 rpm)	0.01 N HCl	80% (30 min)			
Fluoxetine HCl capsules				2 (50 rpm)	0.1 M HCl	70% (45 min)
Fluoxymestrone tablets	2 (75 rpm)	0.1 N HCl	70% (60 min)			
Fluphenazine HCl tablets	1 (100 rpm)	0.1 N HCl	75% (45 min)			
Flurazepam HCl capsules	1 (100 rpm)	0.1 N HCl	75 % (20 min)			
Flurbiprofen tablets	2 (50 rpm)	Phosphate buffer pH 7.5	75% (45 min)			
Flutamide capsules	2 (75 rpm)	2 % sodium lauryl sulfate, 100o ml	75% (60 min)			
Fluvoxamine tablets				2 (50 rpm)	Water	70% (45 min)
Folic acid tablets	2 (50 rpm)	Water, 500 ml	75% (45 min)			
Furosemide tablets	2 (50 rpm)	Phosphate buffer pH 5.8	80% (60 min)	2 (50 rpm)	Phosphate buffer pH 5.8	70% (45 min)
Gemfibrozil capsules				2 (50 rpm)	Phosphate buffer pH 7.5	70% (45 min)
Gemfibrozil tablets	2 (50 rpm)	Phosphate buffer pH 7.5	80% (30 min)	2 (50 rpm)	0.2 M phosphate buffer pH 7.5	70% (45 min)

Gliclazide tablets				2(100 rpm)	Phosphate buffer 7.4	70% (45 min)
Glipizide tablets	2 (50 rpm)	Simulated gastric fluid TS without pancreatin	80% (45 min)			
Gliquidone tablets				2 (75 rpm)	Citro-phosphate buffer, pH 8.5	70% (45 min)
Glycopyrrolate tablets	1 (100 rpm)	Water, 500 ml	75% (45 min)			
Griseofulvin capsules	2 (50 rpm)	Water with 5.4 mg/ ml sodium lauryl sulfate	80% (30 min)			
Griseofulvin tablets	2 (750 rpm)	Water with 40 mg/ ml sodium lauryl sulfate	75% (90 min)	2 (100 rpm)	1.5% sodium dodecyl sulphate (1000 ml)	70% (45 min)
Ultramicronized griseofulvin tablets	2 (75 rpm)	Water with 5.4 mg/ ml sodium lauryl sulfate	80% (45 min)			
Guaifenesin capsules	1 (100 rpm)	Water	75% (45 min)			
Guaifenesin capsules	2 (50 rpm)	Water	75% (45 min)			
Guanabenz acetate tablets	2 (50 rpm)	Water, 1000 ml	75% (60 min)			

Guamadrel sulfate tablets	2 (50 rpm)	Phosphate buffer pH 6.8	70% (20 min)
Guanethidine monosulfate tablets	1 (100 rpm)	Water, 500 ml	75% (45 min)
Guanfacine tablets	2 (50 rpm)	Water, 500 ml	75% (45 min)
Haloperidol tablets	1 (100 rpm)	Simulated gastric fluid TS without enzymes	80% (60 min)
Homatropine methylbromide tablets	2 (50 rpm)	Water	75% (45 min)
Hydralazine HCl tablets	1 (100 rpm)	0.1 N HCl	75% (45 min)
Hydrochlorothiazide tablets	1 (100 rpm)	0.1 N HCl	60% (60 min)
Hydrocodone bitartrate tablets	2 (50 rpm)	Water, 500 ml	75% (45 min)
Hydrocodone and acetaminophen tablets	2 (50 rpm)	Phosphate buffer pH 5.8	80% (30 min)
Hydrocortisone tablets	2 (50 rpm)	Water	70% (30 min)
Hydroflumethiazide tablets	2 (50 rpm)	HCl (1:100)	80% (60 min)

Hydromorphone HCl tablets	2 (50 rpm)	Water	75% (45 min)			
Hydrochloroquine sulfate tablets	2 (50 rpm)	Water	70% (60 min)			
Hydroxyurea tablets	2 (50 rpm)	Water, 500 ml	80% (30 min)			
Hydroxyzine HCl tablets	Disintegration apparatus	Water, 800 ml	75% (45 min)			
Hydroxyzine pamoate capsules	2 (50 rpm)	0.1 N HCl	75% (60 min)			
Ibuprofen tablets	2 (50 rpm)	Phosphate buffer pH 7.2	80% (60 min)			
Ibuprofen tablets and pseudoephedrine HCl tablets	2 (50 rpm)	Phosphate buffer pH 7.2	75% (30 min) ibuprofen; 75% (45 min) pseudoephedrine			
Imipramine HCl tablets	1 (100 rpm)	0.1 N HCl	75% (45 min)			
Indapamide tablets	1 (100 rpm)	0.05 M phosphate buffer pH 6.8	75% (45 min)			
Indomethacin capsules	1 (100 rpm)	1:4 phosphate buffer pH 7.2 and water	80% (20 min)	2 (50 rpm)	Phosphate buffer pH 7.2	70% (45 min)

Indoramine tablets				2 (50 rpm)	0.1 M HCl	70% (45 min)
Inositol nicotinate tablets				2 (50 rpm)	0.1 M HCl	70% (45 min)
Isometheptene mucate, dichloral phenazone and acetaminophen capsules	1 (100 rpm)	Water	65% (60 min)			
Isoniazid tablets	1 (100 rpm)	0.1 N HCl	80% (45 min)	1 (100 rpm)	Water	70% (45 min)
Isopropamide iodide tablets	2 (100 rpm)	Water, 500 ml	70% (60 min)			
Isoproterenol HCl tablets	2 (50 rpm)	Water	75% (45 min)			
Isosorbide dinitrate tablets	2 (75 rpm)	Water	70% (45 min)	2 (50 rpm)	0.1 M HCl	70% (45 min)
Isosorbide dinitrate sublingual tablets	2 (50 rpm)	Water	80% (20 min)			
Isoxsuprine HCl tablets	1 (100 rpm)	Water	75% (45 min)			
Kanamycin sulfate capsules	1 (100 rpm)	0.1 N HCl	75% (45 min)			
Ketoprofen capsules				2 (50 rpm)	Phosphate buffer pH 7.5 (900 ml)	70% (45 min)

Ketorolac tromethamine tablets	2 (50 rpm)	Water, 600 ml	75% (45 min)			
Labetalol HCl tablets	2 (50 rpm)	Water	75% (30 min)			
Leucovarin calcium tablets	2 (50 rpm)	Water	75% (30 min)			
Levamisole HCl tablets	2 (50 rpm)	0.1 M HCl	80% (45 min)			
Levocarnitine tablets	2 (75 rpm)	Water	75% (30 min)			
Levodopa capsules	1 (100 rpm)	0.1 N HCl	75% (30 min)	2 (50 rpm)	0.1 M HCl	70% (45 min)
Levodopa tablets	1 (100 rpm)	0.1 N HCl	75% (30 min)			
Levonorgesterol and ethinyl estradiol tablets	2 (75 rpm)	Polysorbate 80 5 ppm, 500 ml	Uncoated 80% levonorgeterol and 75% estradiol (60 min); coated 60% (60 min)			
Levorphanol tartrate tablets	2 (50 rpm)	Water, 500 ml	75% (30 min)			
Levothyroxine sodium tablets	2 (100 rpm)	0.05 M phosphate buffer pH 7.4	55% (30 min)			
Liothyronine sodium tablets	Apparatus 3	0.05 M borate buffer pH 10	70% (45 min)			

Lisinopril tablets	2 (50 rpm)	0.1 N HCl	80% (30 min)			
Lithium carbonate capsules	1 (100 rpm)	Water	80% (30 min)			
Lithium carbonate tablets	1 (100 rpm)	Water	80% (30 min)			
Loperamide HCl capsules	1 (100 rpm)	Acetate buffer pH 4.7	80% (30 min)	2 (50 rpm)	Buffer pH 4.7 (acetic acid and water)	70% (45 min)
Loperamide HCl tablets	1 (50 rpm)	0.1 N HCl	80% (30 min)			
Loracorbef capsules	2 (50 rpm)	Water	75% (30 min)			
Lorazepam tablets	1 (100 rpm)	Water, 500 ml	60% (30 min) and 80% (60 min)			
Lovastatin tablets	2 (50 rpm)	Phosphate buffer pH 7 with dodecyl sodium sulfate	80% (30 min)			
Loxapine capsules	1 (100 rpm)	Water	75% (45 min)			
Magnesium gluconate tablets	2 (50 rpm)	Water	80% (30 min)			
Magnesium oxide capsules	1 (100 rpm)	0.1 N HCl	75% (45 min)			

Magnesium oxide tablets	2 (75 rpm)	0.1 N HCl	75% (45 min)			
Magnesium salicylate tablets	2 (50 rpm)	Water	80% (120 min)			
Maprotiline HCl tablets	HCl (7:1000)	75% (60 min)				
Mazindol tablets	2 (50 rpm)	0.1 N HCl	80% (120 min)			
Mebendazole tablets	2 (75 rpm)	0.1 N HCl with 1 % sodium lauryl sulfate	75% (120 min)			
Mecamylamine HCl tablets	2 (50 rpm)	Water, 750 ml	75% (30 min)			
Meclizine HCl tablets	1 (100 rpm)	0.1 N HCl	75% (45 min)			
Meclofenamate sodium capsules	2 (50 rpm)	0.05 M phosphate buffer pH 7.5	75% (45 min)			
Medroxyprogesterone acetate tablets	2 (50 rpm)	0.5 % sodium lauryl sulfate	50% (45 min)			
Megesterol acetate tablets	2 (75 rpm)	1 % sodium lauryl sulfate	75% (60 min)			
Melphalen tablets	2 (50 rpm)	Water, 500 ml	80% (45 min)	1 (100 rpm)	0.1 M HCl	70% (45 min)
Menadiol sodium diphosphate tablets	1 (100 rpm)	0.1 N HCl	75% (30 min)			

Mependine HCl tablets	1 (100 rpm)	Water, 500 ml	75% (45 min)			
Meprobamate tablets	1 (100 rpm)	Water, dearated	75% (30 min)			
Mesoridazine besylate tablets	2 (100 rpm)	0.1 N HCl, 1000 ml	80% (60 min)			
Metaproterenol sulfate tablets	2 (50 rpm)	Water, 500 ml	70% (30 min)			
Metformin tablets				1 (100 rpm)	0.68% w/v solution of potassium dihydrogen orthophosphate, pH 6.8	70% (45 min)
Methacydine HCl capsules	1 (100 rpm)	Water	75% (60 min)			
Methadone HCl tablets	1 (100 rpm)	Water, 500 ml	75% (45 min)			
Methamphetamine HCl tablets	2 (50 rpm)	Water	75% (45 min)			
Methazolamid tablets	2 (75 rpm)	Acetate buffer pH 4.5	75% (45 min)			
Methdilazine HCl tablets	1 (100 rpm)	Water	75% (45 min)			

Methenamine mandelate tablets	1 (100 rpm)	Water	75% (45 min)			
Methimazole tablets	1 (100 rpm)	Water, 500 ml	80% (30 min)			
Methocarbamol tablets	2 (50 rpm)	Water	75% (45 min)			
Methotrextrate tablets	2 (50 rpm)	0.1 N HCl	75% (45 min)	2 (50 rpm)	0.1 M HCl	70% (45 min)
Methoxsalen capsules	2 (50 rpm)	Water	75% (45 min)			
Methsuximide capsules	1 (100 rpm)	Water	75% (120 min)			
Methylclothiazide tablets	2 (50 rpm)	0.1 N HCl	70% (60 min)			
Methyldopa tablets	2 (50 rpm)	0.1 N HCl	80% (20 min)			
Methyldopa and hydrochlorothiazide tablets	2 (50 rpm)	0.1 N HCl	80% (30 min) methyldopa; 80% (60 min) hydrochlorothiazide			
Methylergonovine maleate tablets	2 (75 rpm)	Tartaric acid (1:200)	70% (30 min)			
Methylphenidate HCl tablets	1 (100 rpm)	Water	75% (45 min)			
Methylphenobarbital tablets				2 (75 rpm)	Borate buffer pH 10.0	70% (45 min)

Methylprednisolone tablets	2 (50 rpm)	Water	70% (30 min)			
Methyltestosterone capsules	1 (100 rpm)	Water	70% (45 min)			
Methysergide maleate tablets	2 (100 rpm)	Tartaric acid (1:200)	70% (30 min)	1(120 rpm)	0.1 M HCl (500 ml)	70% (45 min)
Metoclopramide tablets	1 (50 rpm)	Water	75% (30 min)			
Metoprolol tartrate tablets	1 (100 rpm)	Simulated gastric fluid TS without enzyme	75% (30 min)			
Metoprolol tartrate and hydrochlorothiazide tablets	1 (100 rpm)	Simulated gastric fluid TS without enzyme	80% (30 min)			
Metronidazole tablets	1 (100 rpm)	0.1 N HCl	85 (60 min)			
Metyrupine tablets	1 (100 rpm)	0.1 N HCl	60% (45 min)			
Metyrosine capsules	1 (100 rpm)	0.1 N HCl, 750 ml	75% (60 rpm)			
Minocycline HCl capsules	2 (50 rpm)	Water	75% (45 min)			
Minocycline HCl tablets	2 (50 rpm)	Water	75% (45 min)	2 (50 rpm)	0.1 M HCl	70% (45 min)

Minoxidil HCl tablets	1 (100 rpm)	Phosphate buffer pH 7.2	75% (15 min)			
Molindone HCl tablets	1 (100 rpm)	0.1 N HCl	80% (30 min)			
Morphine tablets				2 (50 rpm)	Phosphate buffer pH 6.5	70% (45 min)
Nadolol tablets	1 (100 rpm)	0.01 N HCl	80% (50 min)			
Nadolol and Bendroflumethiazide tablets	2 (50 rpm)	0.1 N HCl	80% (30 min)			
Nafcillin sodium capsules	2 (50 rpm)	Citrate buffer pH 4	75% (45 min)			
Nalidixic acid capsules	2 (60 rpm)	Water	80% (30 min)			
Nalidixic tablets				2 (60 rpm)	Methanolic phosphate buffer	70% (45 min)
Naltrexane HCl tablets	2 (50 rpm)	Water	80% (45 min)			
Naproxen tablets	2 (50 rpm)	0.1 M phosphate buffer pH 7.4	80% (45 min)			
Naproxen sodium tablets	2 (50 rpm)	0.1 M phosphate buffer pH 7.4	80% (45 min)			

Neostigmine bromide tablets	2 (50 rpm)	Water, 500 ml	75% (45 min)			
Niacin tablets	1 (100 rpm)	0.1 N HCl	65% (60 min)			
Niacinamide tablets	2 (50 rpm)	Water	75% (45 min)			
Nifedipine capsules	2 (50 rpm)	Simulated gastric fluid TS without pepsin	80% (20 min)	2 (50 rpm)	0.1 M HCl	70% (45 min)
Nimodipine tablets				2 (75 rpm)	Acetate buffer pH 4.5	70% (45 min)
Nitrazepam tablets				2 (50 rpm)	0.1 M HCl	70% (45 min)
Nitrofurantoin capsules	1 (100 rpm)	Phosphate buffer pH 7.2	20-60% (60 min); >45% (180min); >60% (480 min)			
Nitrofurantoin tablets	1 (100 rpm)	Phosphate buffer pH 7.2	25% (60 min); 85% (120 min)			
Nizatidine capsules	2 (50 rpm)	Water	75% (30 min)			
Norethindone and ethinyl estradiol tablets	2 (75 rpm)	0.09 % sodium lauryl sulfate in 0.1 N HCl	75% (60 min)			
Norethindone and mestronol tablets	2 (75 rpm)	0.09 % sodium lauryl sulfate in 0.1 N HCl	75% (60 min)			

Norethindone acetate tablets	1 (100 rpm)	0.02 % sodium lauryl sulfate in HCl (1:100)	70% (60 min)			
Norethindrone acetate and ethinyl estradiol tablets	2 (75 rpm)	0.025 M acetate buffer pH 5 in 0.15 % sodium lauryl sulfate	80% (60 min)			
Norflaxin tablets	2 (50 rpm)	Acetate buffer pH 4	80% (30 min)	2 (50 rpm)	Acetate buffer pH 4 (750 ml)	85% (45 min)
Nortriptyline HCl capsules	1 (100 rpm)	Water, 500 ml	80% (30 min)			
Oxacillin sodium capsules	1 (100 rpm)	Water	75% (45 min)			
Oxazepam capsules	2 (75 rpm)	0.1 N HCl	75% (60 min); 80% (60 min)			
Oxazepam tablets				2 (50 rpm)	0.1 M HCl	70% (45 min)
Oxprenolol HCl tablets	1 (100 rpm)	0.1 N HCl	80% (30 min)			
Oxtriphylline chloride tablets	2 (50 rpm)	Water	80% (30 min)			
Oxybutynin HCl tablets	2 (50 rpm)	Water	80% (30 min)			
Oxycodone HCl tablets	2 (50 rpm)	Water, 500 ml	70% (45 min)			

Oxycodone and acetaminophen capsules	2 (50 rpm)	0.1 N HCl	75% (45 min)			
Oxycodone and aspirin tablets	1 (50 rpm)	0.05 M acetate buffer pH 4.5	80% (30 min)			
Oxymetholone tablets	1 (100 rpm)	0.05 M borate buffer pH 8.5	75% (45 min)			
Oxytetracycline tablets	1 (100 rpm)	0.1 N HCl	75% (45 min)	1 (100 rpm)	0.1 M HCl	70% (45 min)
Oxytetracycline and nystatin capsules	1 (100 rpm)	0.1 N HCl	75% (45 min)			
Oxytetracycline HCl capsules	2 (75 min)	Water	80% (60 min)	1 (100 rpm)	0.1 M HCl	70% (45 min)
Papaverine HCl tablets	1 (100 rpm)	Water	80 (30 min)			
Penbutolol sulfate tablets	2 (50 rpm)	Water	75% (30 min)			
Penicillamine capsules	1 (100 rpm)	0.1 N HCl	80% (30 min)			
Penicillamine tablets	1 (100 rpm)	0.5 % edesate disodium in 0.05 % sodium lauryl sulfate	80% (60 min)			
Penicillin G potassium tablets	2 (75 rpm)	Phosphate buffer pH 6	70% (60 rpm)			

Penicillin V tablets	2 (50 rpm)	Water	75% (45 rpm)	1 (100 rpm)	0.68% w/v solution of potassium dihydrogen orthophosphate, pH 6.8	70% (45 min)
Penicillin V potassium tablets	2 (50 rpm)	Phosphate buffer pH 6	75% (45 rpm)			
Pentazocine capsules				1 (100 rpm)	Water	70% (45 min)
Pentazocine HCl and aspirin tablets	1 (80 rpm)	Water	80% (30 min) pentazocine; 70% (30 min) aspirin			
Pentazocine and naloxone HCl tablets	2 (50 rpm)	Water	75% (45 min)			
Pentobarbital sodium capsules	1 (100 rpm)	Water	75% (45 min)			
Perphenazine tablets	2 (50 rpm)	0.1 N HCl	75% (45 rpm)			
Phendimetrazine tartrate capsules	1 (100 rpm)	Water	70% (60 min)			
Phendimetrazine tartrate capsules	1 (100 rpm)	Water	70% (60 min)			

Phendimetrazine tartrate tablets	1 (100 rpm)	Water	70% (60 min)
Phenmetrazine HCl tablets	2 (50 rpm)	Water	75% (45 min)
Phenobarbital tablets	2 (50 rpm)	Water	75% (45 min)
Phenoxybenzamine HCl capsules	1 (100 rpm)	0.1 N HCl	75% (45 min)
Phensuximide capsules	1 (100 rpm)	Water	75% (120 min)
Phentermine HCl capsules	2 (50 rpm)	Water, 500 ml for < 15 mg	75% (45 min)
Phentermine HCl capsules	2 (50 rpm)	Water, 500 ml for < 15 mg	75% (45 min)
Phenylbutazone tablets	1 (100 rpm)	Simulated gastric fluid TS without enzyme	70% (30 min)
Phenylpropanolamine HCl capsules	1 (100 rpm)	Water	75% (45 min)
Phenylpropanolamine HCl tablets	2 (50 rpm)	Water	75% (45 min)
Phenytoin tablets	2 (100 rpm)	0.05 M tris buffer	70% (120 min)

Phenytoin sodium capsules	1 (50 rpm)	Water	70% (120 min)			
Pimozide tablets	2 (50 rpm)	0.1 N HCl	80% (30 min)			
Pindolol tablets	2 (50 rpm)	0.1 N HCl	80% (15 min)			
Piperazine citrate tablets	2 (50 rpm)	Water	75% (45 min)			
Piroxicam capsules	1 (50 rpm)	Simulated gastric fluid TS without pepsin	75% (45 min)	1 (100 rpm)	0.1 M HCl	70% (45 min)
Potassium gluconate tablets	2 (100 rpm)	Water	75% (45 min)			
Potassium chloride slow tablets				2 (50 rpm)	Water	< 50% (60 min); 25-75% (120 min); > 75% (360 min)
Potassium iodide tablets	2 (50 rpm)	Water	75% (15 min)	1 (100 rpm)	Water	70% (45 min)
Praziquantel tablets	2 (50 rpm)	0.1 N HCl with 2 mg/ml sodium lauryl sulfate	75% (60 min)			

Prazosin HCl capsules	1 (100 rpm)	0.1 N HCl with 3 % sodium lauryl sulfate	75% (60 min)			
Prednisolone tablets	2 (50 rpm)	Water	70% (30 min)	1 (100 rpm)	Water	70% (45 min)
Prednisolone enteric coated tablets				Use the apparatus described in the disintegration test for enteric-coated tablets, one tablet into each of 6 tubes for 60 minutes in 0.1 M HCl; Remove the tablets and use these tablets to carry out the dissolution test. 1 (100 rpm)	Phosphate buffer pH 6.8	70% (45 min)

Prednisone tablets	2 (50 rpm)	Degassed water, 500 ml < 10 mg, 900 ml > 10 mg	80% (30 min)	1 (100 rpm)	Water	70% (45 min)
Primaquine phosphate tablets	2 (50 rpm)	0.1 N HCl	80% (60 min)			
Primidone tablets	2 (50 rpm)	Water	75% (60 min)			
Probenecid tablets	2 (50 rpm)	Simulated gastric fluid TS without pancreatin	80% (30 min)	2 (50 rpm)	Phosphate buffer pH 7.5	70% (45 min)
Probenecid and colchicine tablets	2 (50 rpm)	Phosphate buffer pH 6.8	80% (30 min)			
Procainamide HCl capsules	2 (50 rpm)	0.1 N HCl	75% (90 min)			
Procainamide HCl tablets	1 (100 rpm)	0.1 N HCl	80% (75 min)			
Procarbazine HCl capsules	2 (50 rpm)	Water	75% (45 min)			
Prochlorperazine maleate tablets	2 (75 rpm)	0.1 N HCl	75% (60 min)			
Procyclidine HCl tablets	2 (50 rpm)	Water	75% (45 min)			

Proguanil tablets				2 (50 rpm)	0.2 M HCl containing 0.2 % w/v sodium chloride	70% (45 min)
Promethazine HCl tablets	1 (100 rpm)	0.1 N HCl	75% (45 min)			
Propantheline bromide tablets	2 (50 rpm)	Acetate buffer pH 4.5	75% (45 min)			
Propoxyphene HCl capsules	1 (100 rpm)	Acetate buffer pH 4.5, 500 ml	85% (60 min)			
Propoxyphene HCl and acetaminophen tablets	2 (50 rpm)	Acetate buffer pH 4.5	80% (30 min)			
Propoxyphene HCl, aspirin and caffeine tablets	1 (100 rpm)	Acetate buffer pH 4.5, 500 ml	75% (60 min)			
Propoxyphene napsylate tablets	1 (100 rpm)	Acetate buffer pH 4.5, 500 ml	75% (60 min)			
Propoxyphene napsylate and acetaminophen tablets	1 (100 rpm)	Acetate buffer pH 4.5, 500 ml	75% (60 min)	2 (50 rpm)	Phosphate buffer pH 5.8	70% (45 min)
Propoxyphene napsylate and aspirin tablets	1 (100 rpm)	Acetate buffer pH 4.5, 500 ml	75% (60 min)			

Propranolol HCl tablets	1 (100 rpm)	HCl (1:100)	75% (30 min)
Propranolol HCl and hydrochlorothiazide tablets	1 (100 rpm)	0.1 N HCl	80% (30 min)
Propyl thiouracil tablets	1 (100 rpm)	Water	85% (30 min)
Protriptyline HCl tablets	1 (100 rpm)	Water	75% (45 min)
Pseudoephedrine HCl tablets	2 (50 rpm)	Water	75% (45 min)
Pyrazinamide tablets	2 (50 rpm)	Water	75% (45 min)
Pyridoxine HCl tablets	2 (50 rpm)	Water	75% (45 min)
Pyrilamine maleate tablets	2 (50 rpm)	Water	75% (45 min)
Pyrimethamine tablets	2 (50 rpm)	0.1 N HCl	75% (45 min)
Quazepam tablets	2 (50 rpm)	1% sodium lauryl sulfate	80% (30 min)
Quinidine sulfate capsules	1 (100 rpm)	0.1 N HCl	85% (30 min)
Quinidine sulfate tablets	1 (100 rpm)	0.1 N HCl	85% (30 min)
Quinine sulfate capsules	1 (100 rpm)	0.1 N HCl	75% (45 min)

Quinine sulfate tablets	1 (100 rpm)	0.1 N HCl	75% (45 min)	1 (100 rpm)	0.1 M HCl	70% (45 min)
Quinine bisulfate tablets				1 (100 rpm)	0.1 M HCl	70% (45 min)
Ranitidine tablets	2 (50 rpm)	Water	80% (45 min)			
Reserpine tablets	1 (100 rpm)	0.1 N acetic acid	75% (45 min)			
Reserpine and Chlorothiazide tablets	1 (100 rpm)	Phosphate buffer pH 8 and n-propyl alcohol (3:2)	75% (60 min)			
Reserpine and hydrochlorothiazide tablets	2 (50 rpm)	0.1 N HCl and n-propyl alcohol (3:2)	80% (45 min) Reserpine; 80% (60 min) hydrochlorothiazide			
Riboflavin tablets	2 (50 rpm)	Water	75% (45 min)			
Rifabutin capsules	1 (100 rpm)	0.01 N HCl	75% (45 min)			
Rifampin capsules	1 (100 rpm)	0.1 N HCl	75% (45 min)	1 (100 rpm)	0.1 M HCl	70% (45 min)
Rifampin and isoniazid capsules	1 (100 rpm)	0.1 N HCl	75% (45 min) Rifampin; 80% (45 min) Isoniazid			
Ritodrine HCl tablets	2 (50 rpm)	0.1 N HCl	80% (30 min)			

Salsalate tablets	2 (50 rpm)	0.25 M phosphate buffer pH 7.4	70% (60 min)			
Secobarbital sodium capsules	1 (100 rpm)	Water, 500 ml	75% (60 min)			
Secobarbital sodium and amobarbital sodium capsules	1 (100 rpm)	Water, 500 ml	60% (60 min)			
Selegiline HCl tablets	1 (50 rpm)	Water, 500 ml	80% (20 min)			
Sennosides tablets	1 (100 rpm)	Water	75% (120 min)			
Simvastatin tablets	2 (50 rpm)	Phosphate buffer pH 7 with 0.5 % sodium lauryl sulfate	75% (45 min)			
Sodium salicylate tablets	1 (100 rpm)	Water	75% (45 min)			
Sodium valproate tablets				2 (50 rpm)	Phosphate buffer pH 6.8	70% (45 min)
Spironolactone tablets	2 (75 min)	0.1 N HCl with 0.1 % sodium lauryl sulfate	75% (60 min)	2 (75 rpm)	0.1 M HCl with sodium dodecyl sulphate, 1000 ml	70% (45 min)

Spironolactone and hydrochlorothiazide tablets	2 (75 rpm)	0.1 N HCl with 0.1 % sodium lauryl sulfate	75% (60 min)			
Stanozolol tablets	2 (50 rpm)	0.1 N HCl, 500 ml	75% (45 min)			
Sulfadiazine tablets	2 (75 rpm)	0.1 N HCl	70% (90 min)			
Sulfadoxin and pyrimethamine tablets	2 (75 rpm)	Phosphate buffer pH 6.8	60% (30 min)			
Sulfamethizole tablets	2 (50 rpm)	0.1 N HCl	75% (30 min)			
Sulfamethoxazole tablets	1 (100 rpm)	HCl (7:100)	80% (30 min)			
Sulfamethoxazole and trimethroprim tablets	2 (75 rpm)	0.1 N HCl	70% (60 min)			
Sulfapyridine tablets	2 (50 rpm)	0.1 N HCl	70% (60 min)			
Sulfasalazine tablets	1 (100 rpm)	Phosphate buffer pH 7.5	85% (60 min)	2 (50 rpm)	Phosphate buffer pH 6.8	70% (45 min)
Sulfinpyrazone capsules	1 (100 rpm)	Phosphate buffer pH 6.8	75% (45 min)			
Sulfinpyrazone tablets	1 (100 rpm)	Phosphate buffer pH 6.8	75% (45 min)			
Sulfisoxazole tablets	1 (100 rpm)	HCl (1:12.5)	70% (30 min)			

Sulindac tablets	2 (50 rpm)	0.1 M phosphate buffer pH 7.2	80% (45 min)	2 (50 rpm)	Phosphate buffer pH 7.2	70% (45 min)
Tamoxifen citrate tablets	1 (100 rpm)	0.02 N HCl	75% (30 min)			
Temazepam capsules	2 (75 rpm)	Acetate buffer pH 4 with 0.05 % polysorbate 80	80% (30 min)			
Temazepam tablets				2 (50 rpm)	0.1 M HCl	70% (45 min)
Terbutaline sulfate tablets	1 (100 rpm)	Water	75% (45 min)			
Terfenadine tablets						
Testolactone tablets	2 (75 rpm)	0.1 N HCl	80% (120 min)			
Tetracycline HCl capsules	2 (75 rpm)	Water	80% (60 min); 80% (90 min) for > 500 mg	1 (100 rpm)	0.1 M HCl	70% (45 min)
Tetracycline HCl tablets	2 (75 rpm)	Water	80% (60 min)	1 (100 rpm)	0.1 M HCl	70% (45 min)
Tetracycline HCl and nystatin capsules	2 (75 rpm)	Water	70% (60 min)			
Theophylline capsules	2 (50 rpm)	Water	80% (60 min)			
Theophylline tablets	2 (50 rpm)	Water	80% (45 min)			

Theophylline, ephedrine HCl and phenobarbitol tablets	1 (100 rpm)	Water	75% (30 min)
Theophylline and guaifenesin capsules	1 (100 rpm)	Simulated gastric fluid	75% (45 min)
Theophylline sodium glycinate tablets	1 (100 rpm)	Water	75% (45 min)
Thiamine HCl tablets	2 (50 rpm)	Water	75% (45 min)
Thiethylperazine maleate tablets	1 (120 rpm)	0.1 N HCl	75% (30 min)
Thioquanine tablets	2 (50 rpm)	Water	75% (45 min)
Thioridazine HCl tablets	2 (75 rpm)	0.1 N HCl, 1000 ml	75% (60 min)
Thiothixene capsules	1 (100 rpm)	Diluted HCl with sodium chloride	80% (20 min)
Timolol maleate tablets	1 (100 rpm)	0.1 N HCl, 500 ml	80% (20 min)
Timolol maleate and hydrochlorothiazide tablets	2 (50 rpm)	0.1 N HCl	80% (30 min)
Tocainide HCl tablets	2 (50 rpm)	Water, 750 ml	80% (20 min)

Tolazamide tablets	2 (75 rpm)	0.05 M tris buffer pH 7.6	70% (30 min)			
Tolbutamide tablets	2 (75 rpm)	Phosphate buffer pH 7.4	70% (30 min)	1 (100 rpm)	2.04% w/v disodium hydrogen orthophosphate and 0.135% w/v of potassium dihydrogen orthophosphate	70% (45 min)
Tolmetrin sodium capsules	2 (50 rpm)	Phosphate buffer pH 4.5 containing sodium chloride	85% (30 min)			
Trazodane HCl tablets	2 (50 rpm)	0.01 N HCl	80% (60 min)			
Triamcinolone tablets	1 (100 rpm)	0.1 N HCl	75% (45 min)			
Triamterene capsules	1 (100 rpm)	0.1 N HCl	75% (45 min)			
Triamterene and hydrochlorothiazide capsules	2 (100 rpm)	0.1 M acetic acid with 1 % polysorbate 80	80% (120 min)			
Triamterene and hydrochlorothiazide tablets	2 (75 rpm)	0.1 N HCl	80% (30 min)			

Triazolam tablets	2 (50 rpm)	Water, 500 ml	70% (30 min)
Trichlormethiazide tablets	2 (50 rpm)	Water	65% (60 min)
Trientine HCl capsules	2 (50 rpm)	Water, 500 ml	80% (30 min)
Trifluoperazine HCl tablets	1 (50 rpm)	0.1 N HCl	75% (30 min)
Triflupromazine HCl tablets	1 (100 rpm)	0.1 N HCl	75% (45 min)
Trihexyphenidyl HCl tablets	1 (100 rpm)	Acetate buffer pH 4.5	75% (45 min)
Trimeprazine tartrate tablets	1 (100 rpm)	0.1 N HCl	75% (45 min)
Trimethobenzamide HCl capsules	1 (100 rpm)	Water	75% (45 min)
Trimethroprim tablets	2 (50 rpm)	0.01 N HCl	75% (45 min)
Trioxsalen tablets	2 (100 rpm)	Simulated gastric fluid TS (1:12)	75% (60 min)
Tripelennamine HCl tablets	1 (100 rpm)	Water	75% (45 min)

Triprolidine HCl tablets	1 (50 rpm)	Acetate buffer pH 4	80% (30 min)			
Triprolidine and pseudoephedrine tablets	2 (50 rpm)	Water	75% (45 min)			
Trisulfapyrimidines tablets	2 (50 rpm)	0.1 N HCl	70% (60 min)			
Ursodiol capsules	2 (75 rpm)	0.2 M phosphate buffer pH 8.4	80% (30 min)			
Valproic acid capsules	2 (50 rpm)	Simulated gastric fluid without enzyme with 5 mg/ml sodium lauryl sulfate	85% (60 min)			
Vancomycin HCl capsules	1 (100 rpm)	Water	85% (45 min)			
Verapamil HCl tablets	2 (50 rpm)	0.1 N HCl	75% (30 min)			
Warfarin sodium tablets	2 (50 rpm)	Water	80% (30 min)	1 (100 rpm)	0.68% w/v potassium dihydrogen orthophosphate adjusted to pH 6.8	70% (45 min)

Zalatabine tablets	2 (50 rpm)	Water	80% (20 min)
Zisovudine capsules	2 (50 rpm)	Water	75% (45 min)

CHAPTER 4

Dissolution Properties of Piroxicam Powders and Capsules as a Function of Particle Size and the Agglomeration of Powders

Erna Swanepoel, Wilna Liebenberg, Melgardt M. De Villiers, and Theo G. Dekker

Research Institute for Industrial Pharmacy, Potchefstroom University for CHE, Potchefstroom, 2520, South Africa

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ABSTRACT

The poor dissolution characteristics of relatively insoluble drugs have long been a problem to the pharmaceutical industry. An example is piroxicam, a highly potent anti-inflammatory agent. In many countries, a large number of generic piroxicam products are available to the prescriber. The aim of this study was to investigate the cause of the dissolution problems experienced by manufacturers of generic piroxicam capsules. Two raw material batches and the dissolution properties of several piroxicam capsules were studied. Differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD) results showed that the two raw material samples were identical with respect to polymorphic modification. The particles of powder 1 were smaller than those of powder 2, but the dissolution of powder 1 was much slower than that of powder 2. The dissolution results for the capsules showed a marked difference between different brands, with capsule C not meeting the USP tolerance. Adding surfactant to the dissolution medium increased the dissolution of both powder 1 and capsule C. Failure of powder 1 or capsule C to meet USP dissolution criteria could result in differences in product efficacy, as well as in potential side effects. Such observations should be taken into account along with other relevant considerations when decisions regarding the generic substitution of oral piroxicam products are made.

Key words: *Agglomeration; Dissolution; Particle size; Piroxicam; Powder.*

INTRODUCTION

The poor dissolution characteristics of relatively insoluble drugs have long been a problem to the pharmaceutical industry. An example is piroxicam, a highly potent, acidic, nonsteroidal anti-inflammatory agent used in the treatment of rheumatoid arthritis (RA), ankylosing spondylitis, acute gout, acute musculoskeletal disorders, primary dysmenorrhea, and postoperative and post-traumatic pain (1,2). Pfizer and Company first developed piroxicam about 25 years ago; in the 1970s, it entered into medical practice. Worldwide, numerous generic piroxicam products are also marketed. As with most non-steroidal anti-inflammatory drugs, the main side effects that are observed with the administration of oral piroxicam products are gastrointestinal in nature, including rare gastrointestinal bleeding (2).

In particular, piroxicam is used extensively for the initial and long-term treatment of RA to reduce the pain and swelling and improve function. The advantage is that a single 20-mg dose daily is recommended for these conditions. This improves patient compliance. RA is an auto-immune disease that affects about 1% of the U.S. adult population. It is characterized by inflammation of the synovial tissue that lines the joints, causing pain, swelling, and stiffness. Women are three times more likely than men to develop the disease. There is no cure. If left untreated, RA results in progressive joint destruction, deformation, disability, and premature death.

Piroxicam is known for its low solubility and dissolution rate under acidic conditions in which its absorption takes place (3). Dissolution testing has become accepted widely as a method of controlling the quality of drug products. For post-approval changes such as (*a*) scaleup, (*b*) manufacturing site, (*c*) component and composition, and (*d*) equipment and process changes, a comparison of dissolution profiles between prechange and postchange products is recommended in SUPAC-IR guidance as it produces a more precise measurement of product similarity using dissolution characteristics. Dissolution profiles may be considered similar by virtue of (*a*) overall profile similarity and (*b*) similarity at every dissolution time point.

It has been found that a number of internationally available piroxicam capsules and tablets do not meet the USP 23 (4) dissolution requirement for capsules (5). Although it cannot be assumed that there will be correlation between performance in a dissolution test and bioavailability, it is nonetheless also widely accepted that dissolution performance may be an indicator of potential bioavailability or bioequivalency problems. If such differences in bioavailability were to exist, they could result in differences in product efficacy as well in potential side effects (5).

To complicate things further, piroxicam exists in four polymorphic forms and at least one pseudopolymorphic modification (6,7). Crystal form differences between raw material batches therefore may also be the cause of dissolution problems. Particle size differences might also explain dissolution differences. The effect of the particle size of drugs on their dissolution rates and bioavailability was reviewed comprehensively by Fincher (8). For drugs with gastrointestinal absorption that is rate limited by dissolution, reduction of the particle size generally increases the rate of absorption and/or total bioavailability. This commonly occurs for drugs with poor water solubility, like piroxicam.

However, reduction in particle size may not produce the expected faster dissolution and absorption. This results from the possible aggregation and agglomeration of the fine particles due to their increased surface energy and the subsequent stronger van der Waal attraction between nonpolar molecules (9). Another inherent disadvantage of these fine powders is their poor wettability in water (10).

Several techniques have been employed to increase the solubility of poorly water soluble drugs. These include solid dispersions (10), the use of surface-active agents and hydrophilic polymers (11), molecular dispersions (12), solid-state manipulations such as polymorphic transformation (13), and glass formation (14). In the case of surfactants, the increase in solubility, and therefore dissolution, may be due to the surface activity of these materials resulting in better wetting of the drug, which in turn increases the dissolution of the drug (15).

The aim of this study was to correlate the performance of piroxicam solid dosage forms with the physicochemical properties of the drug and formulation powders. To do this, the dissolution properties of several piroxicam powders and capsules on the South African market were studied to ascertain whether the dissolution of these capsules met the USP dissolution requirements. This is important since a large number of generic piroxicam products are available worldwide to the prescriber. These are pharmaceutically equivalent drug formulations with supposedly similar or identical labeling, but from different manufacturers. Pharmaceutical equivalence refers to drug products that contain the same active drug ingredient and are identical in strength, concentration, dosage form, and route of administration. However, generic piroxicam capsules from various manufacturers still experience many dissolution problems.

EXPERIMENTAL

Materials

Two raw material batches of piroxicam from Secifarma S.p.A. (Milan, Italy; batches 412216 and 403148) were studied after problems were experienced with the dissolution properties of capsules manufactured using these powders. The dissolution behaviour of the following piroxicam capsules, bought from a local pharmacy, was also studied: Feldene (Pfizer, batch 735370); Adco Piroxicam (Adcock Ingram, batch 203633); Xycam (Lennon, batch 73430); Pyrocaps (Be Tabs, batch 9505098); and two batches of Roxicam (Rolab, batches 94N32 and 97G51).

X-ray Powder Diffractometry

X-ray powder diffraction (XRPD) patterns were obtained at room temperature with a Philips PM9901/00 diffractometer. The measurement conditions were target, CoK_{α}; iron filter; 40 kV voltage; 20 mA current; 0.2-nm slit; scanning speed, 2° per minute. Samples of approximately 200 mg were loaded into an aluminum sample holder, taking care not to introduce a preferential orientation of crystals.

Thermal Analysis

Differential scanning calorimetry (DSC) thermograms were recorded with a Shimadzu DSC-50 instrument (Shimadzu, Kyoto, Japan). Samples weighing approximately 3-5 mg were heated in closed aluminum crimp cells at a rate of 10°C/min under nitrogen gas flow of 20 ml/min.

Particle Size Analysis

A Galai-Cis-1 particle size analyzer (Galai, Ltd., Migdal Ha'Emek, Israel) was used to measure particle size distributions in suspension. Particle sizing on this instrument is done by a dual-discipline analysis, integrating laser diffraction and image analysis. Samples suspended in liquid paraffin were placed in small cuvettes and fitted into the analyzer. A small magnetic stirrer inside the cuvette prevented sedimentation of the particles during the measurement. The acquired data were used to compute means, medians and standard deviations based on the total particle population. From particle size data, particle surface areas were also estimated.

Dissolution Studies

Powder and capsule dissolution studies were performed according to the USP using apparatus 2 (paddle) and simulated gastric fluid without pepsin at 37°C as the dissolution medium (4). The paddles were rotated at 50 rpm, and samples were drawn from the dissolution medium at 2.5, 5, 10, 15, 20, 30, 40, 45, 50, and 60 min. The amount of piroxicam dissolved at each time interval was measured spectrophotometrically at the wavelength of maximum absorption, 333 nm. To increase the wettability in the dissolution medium, either 0.05% polysorbate 80 or 1% SLS was added to the dissolution medium.

Powder Wettability Measurements

The contact angle of water on the powders was measured using discs compressed on a Carver press at a constant pressure of 5×10^5 N/m^2. The size of the drop of water placed on the disc was about 10 µl. Results are the mean of three measurements. However,

although powders are ubiquitous in the pharmaceutical industry and their processing often requires knowledge of their wettability, results on compressed discs are not always representative of powder wettability. Due to particle surface roughness and small size, no direct contact angle measurements are available for powder particles. To overcome this, an indirect method to assess and compare wettability must be used (16).

In this study, the flow rate of distilled water, which does not completely wet piroxicam, through a mildly compressed plug of the drug or formulation powder was measured under constant pressure. Faster flow rates were related to less resistance to flow and to more wettable powders, slower flow rates are related to less wettable powders. To make these measurements, a Bistadil® (Schott Glaswerke, Mainz, Germany) glass column was filled with powder to a height of 20 mm. The column had an internal diameter of 25 mm, a filling height of 500 mm, and a fused-in filter disc with porosity (PO) in the bottom. Enough powder was filled from the top, and the column was lightly tapped until the height of the powder plug stayed constant at 20 mm. Then, 50 ml of the solvent was poured on top, and the vacuum pump (Speedivac, model 2SC20, Edwards, Sussex, England) was switched on. From the moment the stopcock was opened, the time was measured until all the solvent was caught up at the bottom (mean recovery 48.6 ± 0.5 ml for powder samples).

The flow rate of water without powder was 96.9 ± 1.93 ml/min. Results are the mean of five determinations, and all flow rates were adjusted to compensate for the flow rate of water without powder.

Calculating the Similarity Between Dissolution Profiles

Throughout the study, similarity factors were used to compare dissolution results (profiles). The similarity factor f_2 and a similarity testing criteria based on f_2 are recommended for dissolution profile comparison in the FDA's guidelines for industry. According to the FDA profile, comparison in general refers to the comparison of two dissolution profiles between (*a*) a reference batch and a test batch, (*b*) a prechange batch and a postchange batch, and (*c*) different strengths of products for biowaivers.

Moore and Flanner (17) introduced the similarity factor as a simple model-independent approach using mathematical indices to define differences and similarities between dissolution profiles. These factors are divided from Minkowski differences (average absolute differences) and mean-square difference, respectively. In this study, a similarity factor was calculated using the following mathematical equation (17):

$$f_2 = 50 \cdot \log\left(\left[1 + \left(\frac{1}{n}\right)\sum_{t=1}^{n} w_t (R_t - T_t)^2\right]^{-0.5} \cdot 100\right) \qquad (1)$$

where n is the number of dissolution time points; R_t and T_t are the reference and test dissolution values at time t, respectively; and w_t is an optional weighting factor. The value of f_2 is 100 when the test and reference mean profiles are identical. The test and reference products are not equivalent when there is a more than 10% difference in dissolution profiles, indicated by a similarity factor less than 50 (17). Similarity factors were calculated for all dissolution results.

RESULTS AND DISCUSSION

Factors that might affect the dissolution rate of piroxicam from dosage forms can be classified under three main categories:

1. Factors relating to the physicochemical properties of the drug
2. Factors relating to the dissolution apparatus and test parameters
3. Factors relating to the dosage form

The results from this investigation into the dissolution properties of piroxicam powders and solid dosage forms containing this drug are therefore discussed in relation to these factors.

Effect of Physicochemical Properties on the Dissolution of Piroxicam Raw Materials

The physicochemical properties of piroxicam that might influence its dissolution rate include solubility, particle size, and crystalline state such as polymorphism, state of

hydration, solvation, and complexation. The reported solubility of piroxicam in water is approximately 0.015 mg/ml (3). However, most references describe the drug as being insoluble in water. The drug is therefore classified as a poorly water soluble compound. It is also a weak acid drug, pK_a = 5.3; therefore, the solubility increases with increasing pH from 0.023 mg/ml at pH 2.0 to 1.03 mg/ml at pH 7.5 (3).

Table 1

Similarity Factors for Comparison of Powder Dissolution Curves

Reference	Test	f_2[a]
Powder 2	Powder 1	**25**
Powder 2 + polysorbate 80	Powder 1 + polysorbate 80	90
Powder 2 + SLS	Powder 1 + SLS	72
Powder 2	Powder 2 + polysorbate 80	**48**
Powder 2	Powder 2 + SLS	**39**
Powder 2 + polysorbate 80	Powder 2 + SLS	53
Powder 1	Powder 1 + polysorbate 80	**22**
Powder 1	Powder 1 + SLS	**19**
Powder 1 + polysorbate 80	Powder 1 + SLS	64

[a]Bold f_2 values less than 50 indicate dissolution curves that differ more than 10%.

The dissolution rates of the piroxicam powders (powder 1 and powder 2) were first determined in gastric fluid without pepsin. The dissolution curves showed that powder 1 dissolved much slower than powder 2, and the dissolution profiles were not similar (Table 1). Powder 1 even failed the USP tolerance for capsules (75% in 45 min) because only 72% dissolved within 45 min, as shown in Figs. 1 and 2.

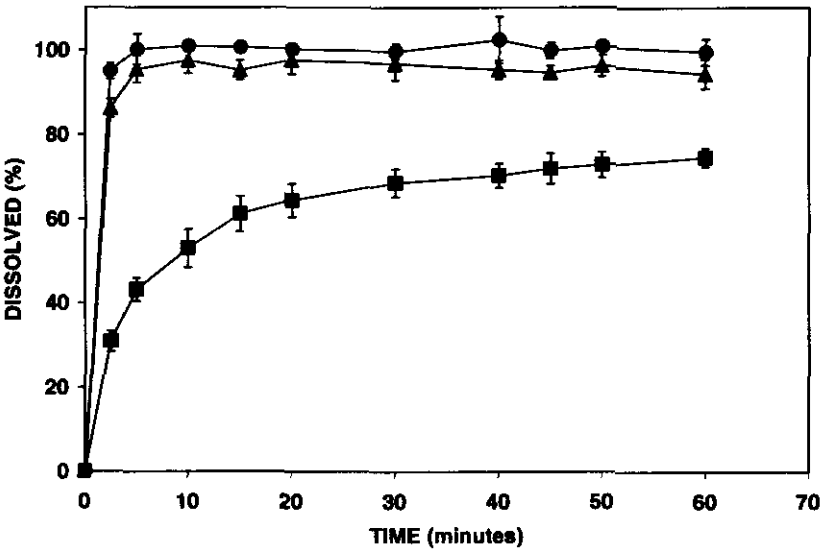

Figure 1. Powder dissolution profiles for powder 1 with and without surfactants. ●, Simulated gastric fluid without pepsin; ▲, simulated gastric fluid without pepsin plus 0.05% polysorbate 80; ■, simulated gastric fluid without pepsin plus 1% SLS.

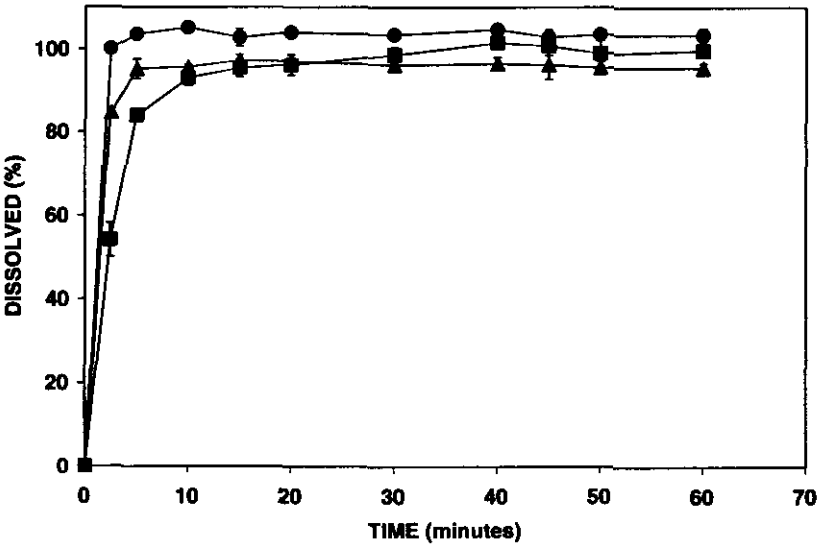

Figure 2. Powder dissolution profiles for powder 2 with and without surfactants. ●, Simulated gastric fluid without pepsin; ▲, simulated gastric fluid without pepsin plus 0.05% polysorbate 80; ■, simulated gastric fluid without pepsin plus 1% SLS.

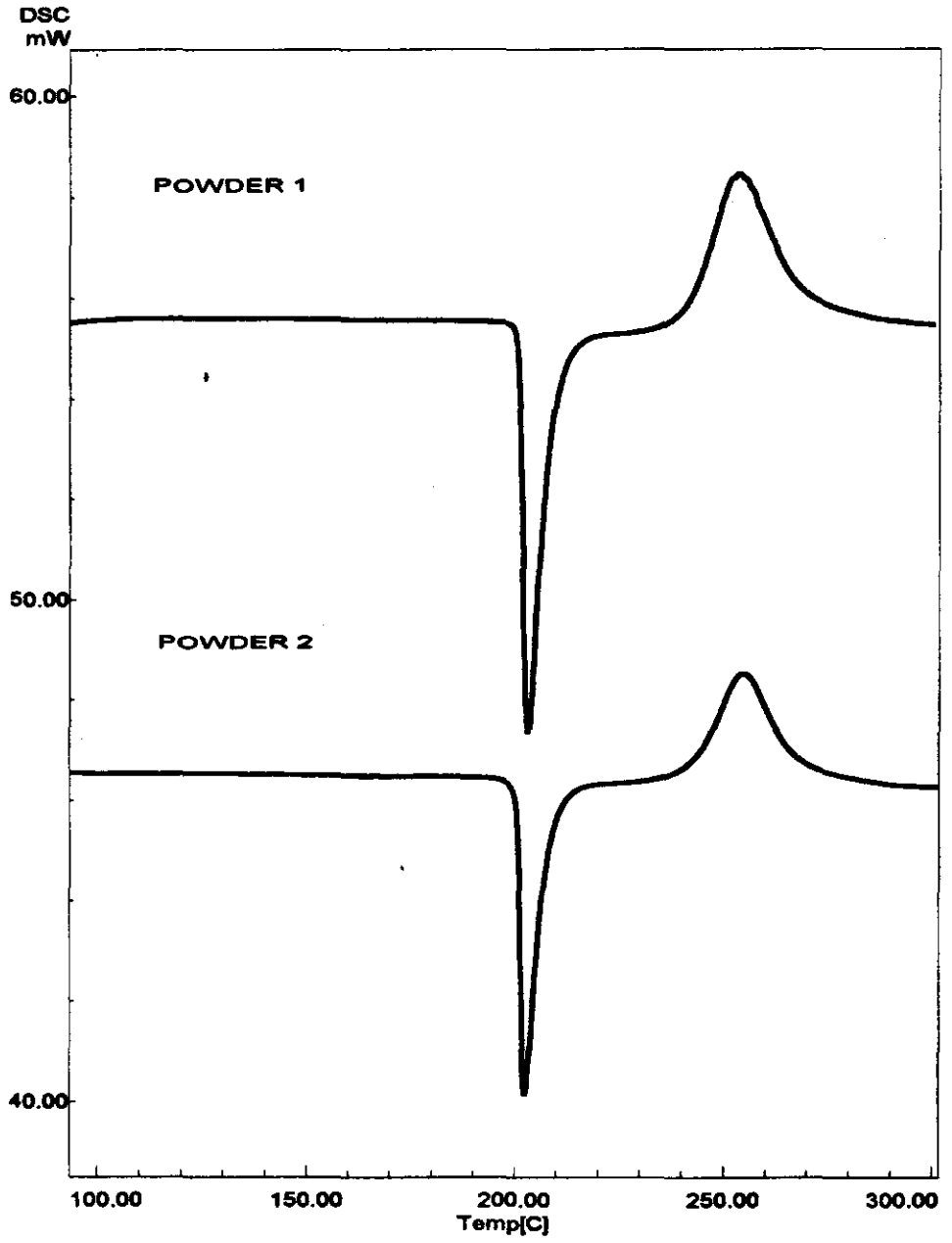

Figure 3. DSC curves of the piroxicam powders.

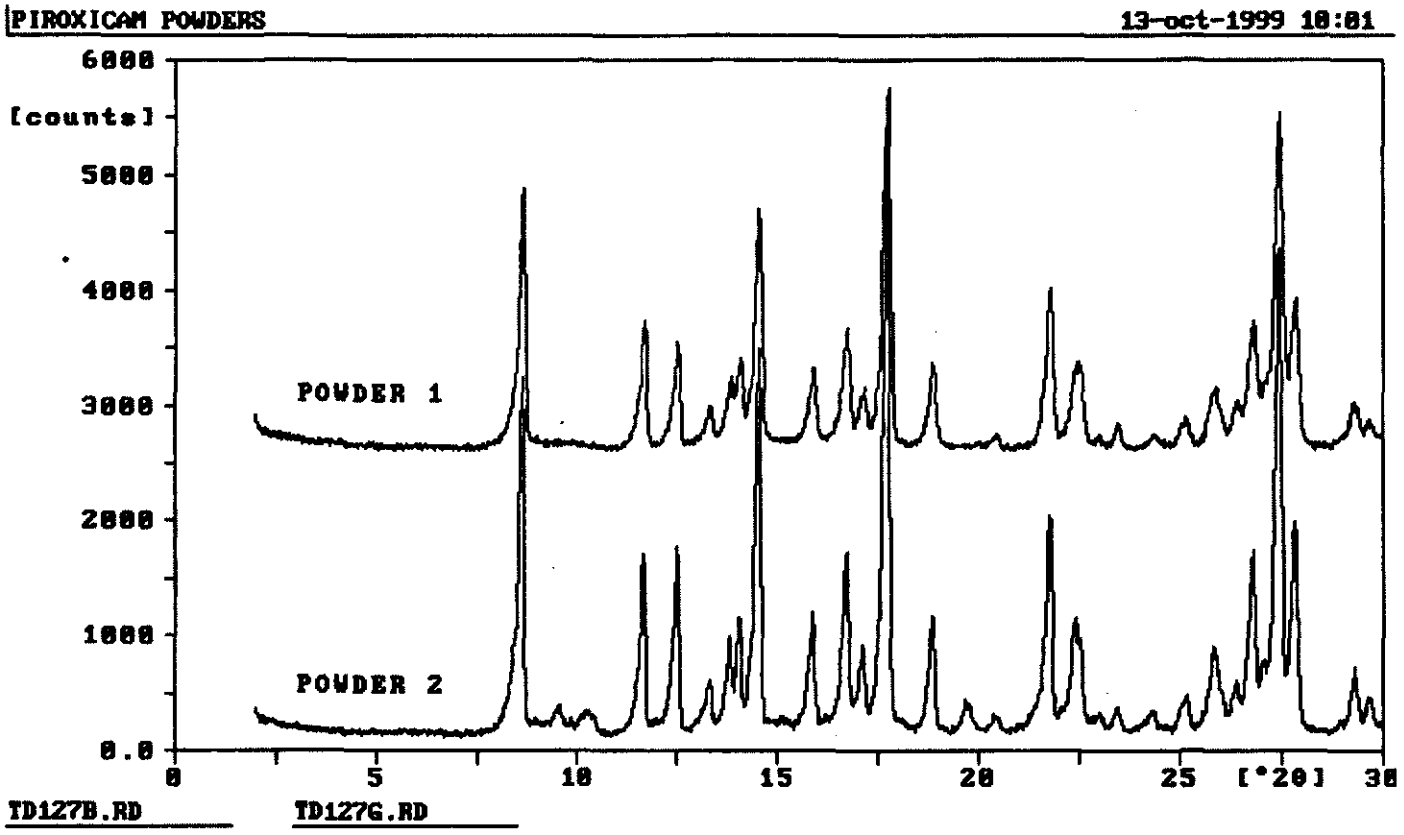

Figure 4. XRPD patterns of the piroxicam powders.

Differences in crystal properties might have caused this because Mihalić et al. (6) and Vrecer et al. (7) reported that piroxicam exhibits crystal polymorphism.

According to these studies, piroxicam predominantly exists in two different interchangeable crystal forms with melting points of 196°C-198°C for needles and 199°C-201°C for the cubic form. The drug also crystallizes as a monohydrate (18). All these forms were also characterized by distinct XRPD patterns. DSC and XRPD results (Figs. 3 and 4) clearly indicate that the piroxicam powders used in this study were identical with respect to crystal form and state of hydration and solvation. Crystal polymorphism was thus excluded as a reason for poor dissolution properties.

Table 2

Solid-State Properties of Piroxicam Powders

Powder	Mean Volume Diameter (μm)	Surface Area (m^2/g)	Contact Angle (°)	Flow Rate Water (ml/min)[a]
1	3.71	2.89	23 ± 2.2	59.2 ± 2.49
2	8.59	1.35	63 ± 1.6	249.1 ± 7.39

[a]Flow rate of water through a 20 mm high compacted powder bed under pressure less the flow rate in the absence of powder.

Particle size and calculated surface areas (Table 2) showed that the particles of powder 1 (mean volume size 3.71 μm) were smaller than those of the particles of powder 2 (mean volume size 8.59 μm). The large amount of small particles (65% < 10 μm based on the volume size and 97% < 5 μm based on the number of particles) present in powder 1 caused aggregation, resulting in larger lumps (Fig. 5), which were also observed during the powder dissolution measurements of sample 1. Powder 2 contained only 25% particles less than 10 μm based on the volume size and 57% less than 5 μm based on the number of particles. Subsequently, the surface area of powder 1 was almost twice that of powder 2.

Contact angle measurements on compressed discs (Table 2) did not indicate any significant difference in the wettability of the powders. However, resistance to water flow through small powder beds did indicate (Table 2) that the smaller particles were less wettable. Under the same pressure, the flow rates through powder 2 were four times faster than through powder 1. Based on these results, it was concluded that piroxicam is hydrophobic in nature, and because of this, the drug had a definite tendency to form large particle aggregates in the dissolution medium, therefore diminishing the effective surface area.

Spontaneous aggregation could only be explained by the electrostatic behaviour of the finer particles. This was observed when powder 1 was handled (i.e., weighed, transferred to the dissolution medium, or the lumps shown in Fig. 5 were dispersed mechanically).

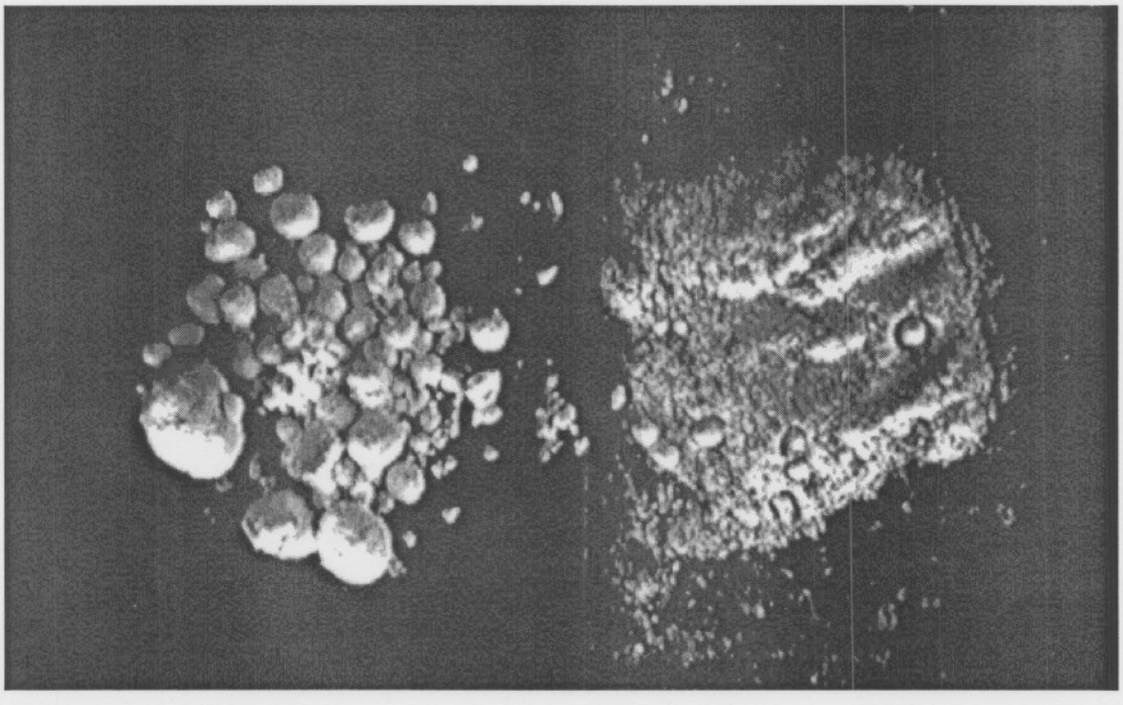

Figure 5. Photograph of the powders showing the aggregation of powder 1 on the left.

Effect of Dissolution Apparatus and Test Parameters on the Dissolution of Piroxicam Powders

The dissolution rate is directly proportional to the effective surface area of the drug. This is the surface area available to the dissolution medium. Since piroxicam is hydrophobic and the simulated gastric fluid dissolution medium has poor wetting properties, reduction in particle size led to aggregation, a smaller effective surface area, and a slower dissolution rate. If surfactants such as polysorbate 80 or SLS are added to the dissolution medium, most hydrophobic powders dissolve much faster, and the dissolution rate increases with decreasing particle size. After addition of these surfactants, the dissolution medium is capable of wetting the entire surface of the drug powder, and the dissolution rate will increase with the degree of dispersion.

This was also true for piroxicam powders 1 and 2 because the dissolution rate of powder 1 was increased drastically by the presence of a wetting agent (0.05% polysorbate 80 or 1% SLS) in the dissolution medium (Figs. 1 and 2). Similarity factors listed in Table 1 showed that the dissolution of powders 1 and 2 were similar (within 10%) when either polysorbate 80 or SLS was added to the dissolution medium. These dissolution media now did not differentiate between the two powders. For example, the $T_{75\%}$ values for powders 1 and 2 were obtained in less than 5 min in simulated gastric fluid containing SLS or polysorbate 80. It appeared that the magnitude of this effect increased as a function of surfactant concentration and approached a maximum at concentrations in the range of the critical micelle concentration (CMC).

Factors Relating to the Dosage Form That Influence Piroxicam Dissolution

Most important, of course, of the factors relating to the dosage form that influence piroxicam dissolution is the effect of piroxicam particle size and aggregation on its dissolution rate from tablets and capsules. Bioavailability studies performed on piroxicam capsules by Patel et al. (19) showed that maximum piroxicam plasma concentrations were significantly less with capsules having less than 75% dissolution within 45 min. To determine if poor dissolution of commercial products might be the result of wettability problems, the dissolution properties of 5 different brands (six batches) of capsules (20 mg)

available to prescribers in South Africa were studied (Figs. 6 and 7). The capsules were randomly denoted A-F.

In addition to the effect of particle size, the rate of dissolution of piroxicam from capsules is, of course, a complex function of many variables. These include the rate of different processes, such as the solution of the gelatine shell, the penetration of water into the powder mass, the deaggregation of the powder mass, and the dissolution of the powder particles. The results obtained (Table 3) showed that the products differed markedly with respect to dissolution rate. One product, capsule C, did not meet the USP tolerance (75% in 45 min). The dissolutions of capsules A, E, and F were the fastest, followed closely by B and D. Except for product C, the dissolution from capsules was reasonable and in some cases even better than that of powder 1. First, the reason for this is that the procedures employed in capsule production (i.e., mixing the drugs with usually hydrophilic diluents and perhaps a subsequent granulation) will make the hydrophobic drug particles more hydrophilic. Second, in the case of hydrophobic piroxicam, a hydrophilic filler will tend

Table 3

USP Dissolution Results for Piroxicam Capsules

Product	Gastric Fluid (Gf)	Gf + SLS
A	95.1 ± 1.30	96.7 ± 0.85
B	80.7 ± 14.36	92.2 ± 4.30
C	71.8 ± 1.42[a]	87.8 ± 11.32
D	89.3 ± 1.07	83.9 ± 8.80
E	95.2 ± 1.92	78.6 ± 0.83
F	95.4 ± 8.23	92.5 ± 7.30

[a]Less than USP tolerance of 75% within 45 min.

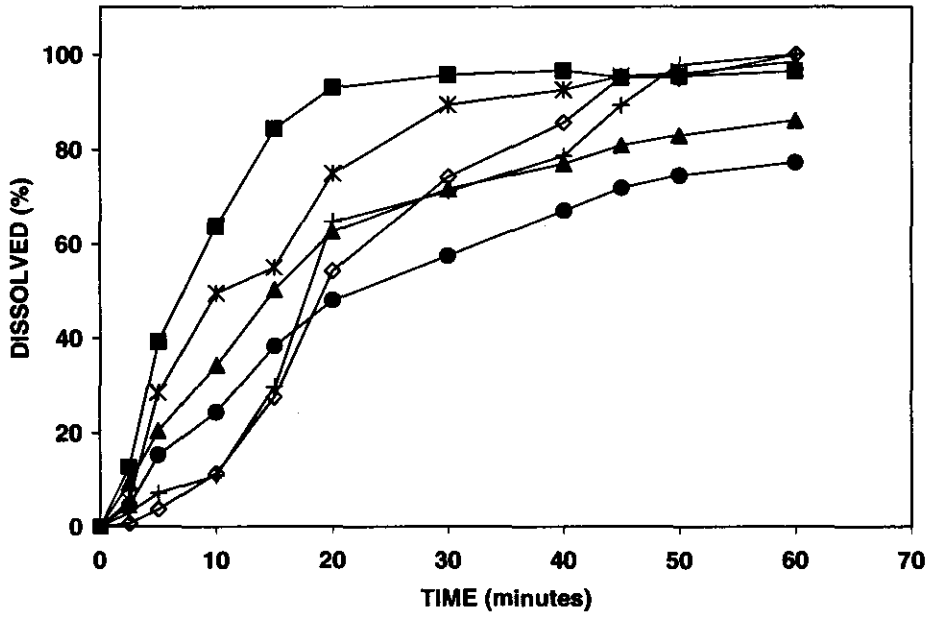

Figure 6. Dissolution profiles of piroxicam capsules in simulated gastric fluid without pepsin. ■, A; ▲, B; ●, C; +, D; ◊, E; ∗, F.

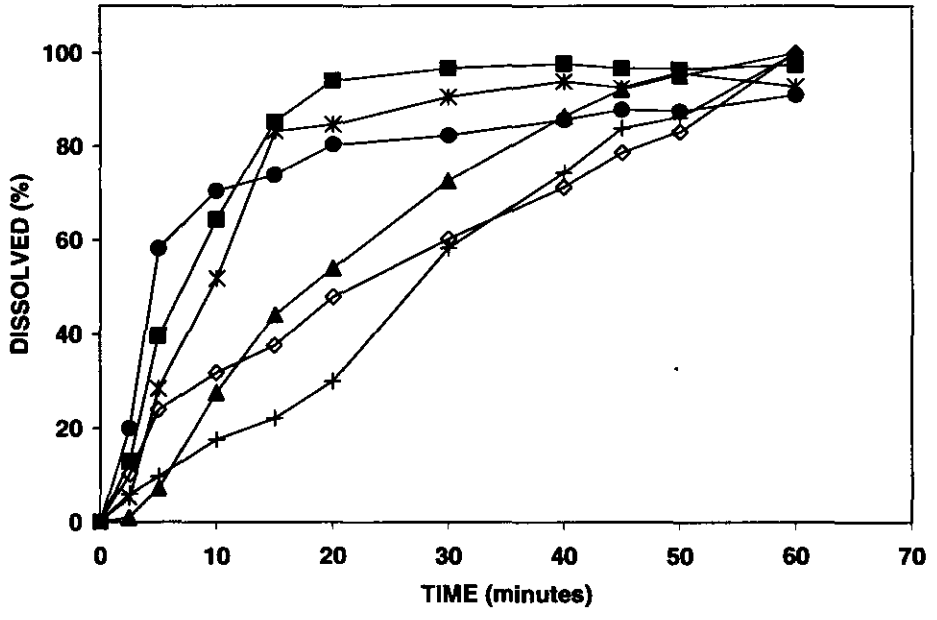

Figure 7. Dissolution profiles of piroxicam capsules in simulated gastric fluid without pepsin plus 1% SLS. ■, A; ▲, B; ●, C; +, D; ◊, E; ∗, F.

to enhance dissolution, especially if this filler acts at the same time as a wetting agent. DSC studies (Fig. 8) showed that at least one product contained SLS as an excipient.

Similarity factors for comparison of the dissolution profiles of the different capsules with and without SLS added to the dissolution medium are given in Table 4. The dissolution of capsules B and C was improved significantly by the addition of SLS (Table 3). For capsule C, the improvement was enough to ensure that it complied with the USP tolerance of 75% dissolved within 45 min (4).

Table 4

Influence of Sodium Lauryl Sulfate on the Wettability and Dissolution of Piroxicam Capsules

Product	f_2[a]	Contact angle (°)	Flow rate of water (ml/min)[b]
A	92.76	75 ± 1.9	55.1 ± 4.57
B	50.33	52 ± 1.8	35.9 ± 2.97
C	**26.94**	70 ± 2.7	28.9 ± 1.25
D	**44.41**	52 ± 3.2	43.5 ± 1.76
E	**43.08**	46 ± 2.1	45.2 ± 3.80
F	60.53	Completely wetted	79.8 ± 6.91

[a]Bold f_2 values less than 50 indicate dissolution curves with and without SLS that differ more than 10%.
[b]Flow rate of water through a 20 mm high compacted powder bed under pressure less the flow rate in the absence of powder.

Again, no correlation was found between the contact angle of the powders and the poor dissolution behaviour, but flow rate measurements did indicate that there were

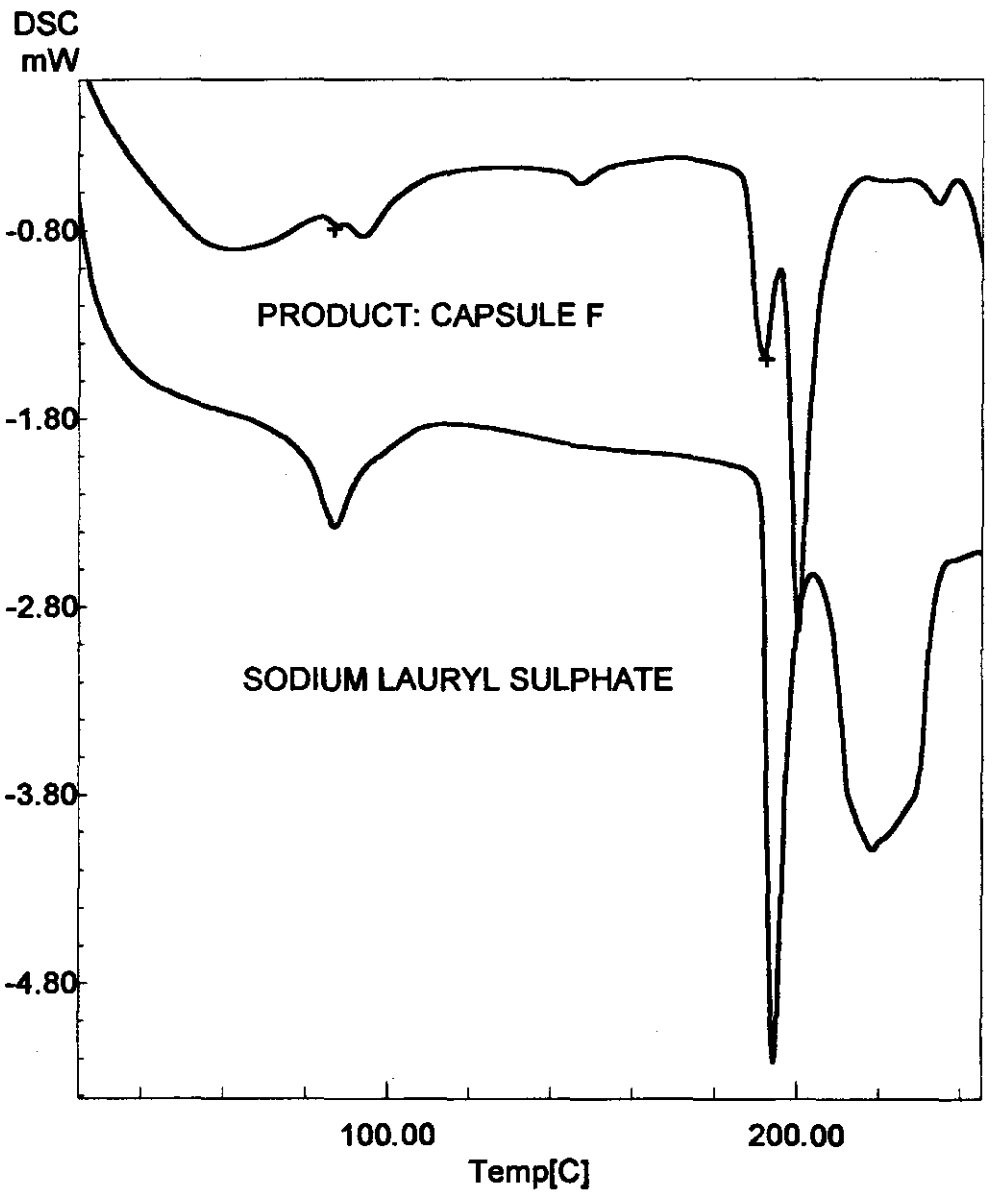

Figure 8. DSC thermograms of SLS and the capsule content of product F.

differences in the wetting of the capsule contents (Table 3). Powders with slow flow rates had poorer dissolution properties. However, the dissolution rate of piroxicam from these products was not always increased when the dissolution was tested in simulated gastric fluid containing 1% SLS (Table 4). Products D and E dissolved slower in this medium, and it was observed that the capsule contents of these products formed a plug that did not readily disintegrate. Capsules D and E were different batches of the same product. This phenomenon could only be explained if an interaction occurred between one or more of the excipients and the dissolution medium, and that this prevented deaggregation of the powder mass.

It is of course not possible to give a definite answer to explain the differences in capsule dissolution observed in this study. However, the results indicated that the wettability of the powder mass in combination with the effect of particle size and wettability of the drug powder definitely influenced the dissolution performance of the capsules.

CONCLUSION

It was concluded from this study that piroxicam is hydrophobic and poorly wettable, and when the drug particles are very small, they tend to aggregate. Contact angle measurements performed on compressed powders and capsule contents did not really help in establishing wettability differences between the powders and capsules. However, a simple resistance to flow measurement that determined differences in the rate that water flowed through similar powder beds under equal pressure did indicate marked differences in the wettability of the drug powder and capsule contents. Poor wettability was most probably the result of electrostatic behaviour of very fine piroxicam particles.

Due to this phenomenon, some piroxicam powders and capsules failed to meet USP dissolution criteria. This could result in differences in product efficacy, as well as in potential side effects. The main side effect observed after continuous use of oral piroxicam products is gastrointestinal damage. Differences in dissolution rate in the gastrointestinal tract and absorption rate profiles could alter the incidence of such side effects in certain patient populations. Such observations should be taken into account

along with other relevant considerations when physicians and pharmacists make decisions regarding generic substitution of oral piroxicam products.

Under the conditions of the experiments, the rate of dissolution of hydrophobic piroxicam increased with decreasing particle size when the dissolution medium had a low surface tension and decreased when the surface tension was high. The surface tension of the dissolution medium could be controlled by the addition of surfactants near the CMC. With the addition of polysorbate 80 or SLS to the dissolution medium, the aggregation and poor wettability of piroxicam powders were almost completely eliminated. This result, however, does indicate that simulated gastric fluid without pepsin, and not surfactant media, is a suitable medium for discriminating among the dissolution properties of generic piroxicam solid dosage forms.

The results of this study make it apparent that the properties of the interface of drug/ dissolution medium were a deciding factor as far as the dissolution rate of piroxicam was concerned. This is due to a wetting and/or deaggregation effect, both of which would result in an increased effective surface area available to the dissolution medium.

ACKNOWLEDGEMENT

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CHAPTER 5

The Effect of Polymorphism on Powder Compaction and Dissolution Properties of Chemically Equivalent Oxytetracycline Hydrochloride Powders

Wilna Liebenberg,[1] Melgardt M. de Villiers,[1] Dale Eric Wurster,[2] Erna Swanepoel,[1] Theo G. Dekker,[1] and Antonie P. Lötter[1]

[1]Research Institute for Industrial Pharmacy, Potchefstroom University for CHE, Potchefstroom, 2520, South Africa
[2]College of Pharmacy, University of Iowa, Iowa City, IA 52242

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ABSTRACT

In South Africa, oxytetracycline is identified as an essential drug; many generic products are on the market, and many more are being developed. In this study, six oxytetracycline hydrochloride powders were obtained randomly from manufacturers, and suppliers were compared. It was found that compliance to a pharmacopoeial monograph was insufficient to ensure the optimum dissolution performance of a simple tablet formulation. Comparative physicochemical raw material analysis showed no major differences with regard to differential scanning calorimetry (DSC), infrared (IR) spectroscopy, powder dissolution, and particle size. However, the samples could be divided into two distinct types with respect to X-ray powder diffraction (XRD) and thus polymorphism. The two polymorphic forms had different dissolution properties in water or 0.1 N hydrochloride acid. This difference became substantial when the dissolution from tablets was compared. The powders containing form A were less soluble than that containing form B.

Key Words: *Compaction; Dissociation; Oxytetracycline; Polymorphism; Powder.*

INTRODUCTION

Oxytetracycline hydrochloride absorption varies according to the oral pharmaceutical form (1). Serum levels reached with the formulation in capsules were superior to those observed with coated tablets, and the simultaneous administration of two 250-mg capsules led to higher serum levels compared to that reached with one 500-mg capsule. Brice and Hammer (2) performed disintegration and dissolution tests on oxytetracycline tablets and found that batches that gave poor serum levels had slower in vitro dissolution rates. Other investigations (3,4) reported that the dissolution rate profiles also varied among generic brands from different manufacturers and between and within batches of one source.

The occurrence of crystal polymorphism could be one factor that negatively influences absorption and especially in vitro dissolution rates. Oxytetracycline hydrochloride appears in at least three crystal forms, two polymorphs (A and B) and a stable adduct compound with either ethanol or methanol (C) (5). Their physical and physicochemical properties differ in a decisive way. The solubility of form B at ambient temperature in water is 28 times higher than that of form A. In contrast to forms B and C, form A is not hygroscopic. Esezebo and Pilpel (6) studied the effect of various formulations and processing factors on the dissolution of uncoated oxytetracycline tablets. It was found that the dissolution rate constants depended on the gelatin content and packing fraction of the tablets. Oxytetracycline hydrochloride was also examined for possible incompatibility with a variety of excipients in tablet formulations and was found to be incompatible with magnesium stearate, sodium alginate, mannitol, and anhydrous dextrose (7,8). Polymorphism, formulation differences, processing factors, and incompatibilities all can adversely affect the dissolution properties of oxytetracycline tablets and subsequently the in vivo absorption.

In South Africa, raw materials from different sources and at substantially different prices are available for the generic manufacturer. The scope of this study was to ascertain whether six randomly chosen samples of oxytetracycline hydrochloride were within acceptable limits of performance and thereby equivalent for substitution in pharmaceutical manufacturing. To ascertain substitutability, both compliance to compendial tests and a

general preformulation assessment of the powder samples were determined. These tests included differential scanning calorimetry (DSC), X-ray powder diffraction (XRD), infrared (IR) spectroscopy, particle size analysis, and powder dissolution studies. Preformulation assessment included measurement of the disintegration, hardness, and dissolution properties of tablets containing the powders.

MATERIALS AND METHODS

Chemicals

The oxytetracycline hydrochloride powder samples (Table 1) were supplied with certificates of analysis, and all of them complied with the monograph of the BP 1988 (9) and USP 23 of 1995 (10). Solvents used were analytical grade and were supplied by Saarchem (Krugersdorp, South Africa). All materials were used as supplied.

Table 1

Description and Assay Values of the Oxytetracycline Hydrochloride Powders

Code	Color of the Samples	Assay Result Certificate of Analysis Dried (μg base/mg)	Assay Result SABS[a] (μg base/mg)
GA	Yellow	890.0	885.5
JB	Yellow	892.0	925.7
MC	Yellow/brown	900.5	934.6
RD	Yellow	895.9	935.6
TE	Yellow/brown	894.1	940.3
WF	Yellow	893.0	932.8

[a]South African Bureau of Standards, Pretoria.

Characterization of Powders

The IR spectra of the samples (Fig. 1) were recorded on a Shimadzu FTIR 4200 spectrometer (Shimadzu, Kyoto, Japan) over a range of 600-4000 cm^{-1}. The KBr disk technique was used. XRD profiles (Fig. 2) were obtained at room temperature with a Philips PM9901/00 diffractometer. The measurement conditions were target, CoK_{α}; iron filter; 40 kV voltage; 20 mA current; 0.2-nm slit; and 2°/min scanning speed. Approximately 200 mg of sample was loaded into an aluminum sample holder, taking care not to introduce a preferential orientation of the crystals. DSC thermograms were recorded with a Shimadzu DSC-50 instrument using the following measurement conditions: sample weight, approximately 2 mg; sample holder, aluminum crimp cell; gas flow, nitrogen at 20 ml/min; heating rate, 10°C per minute.

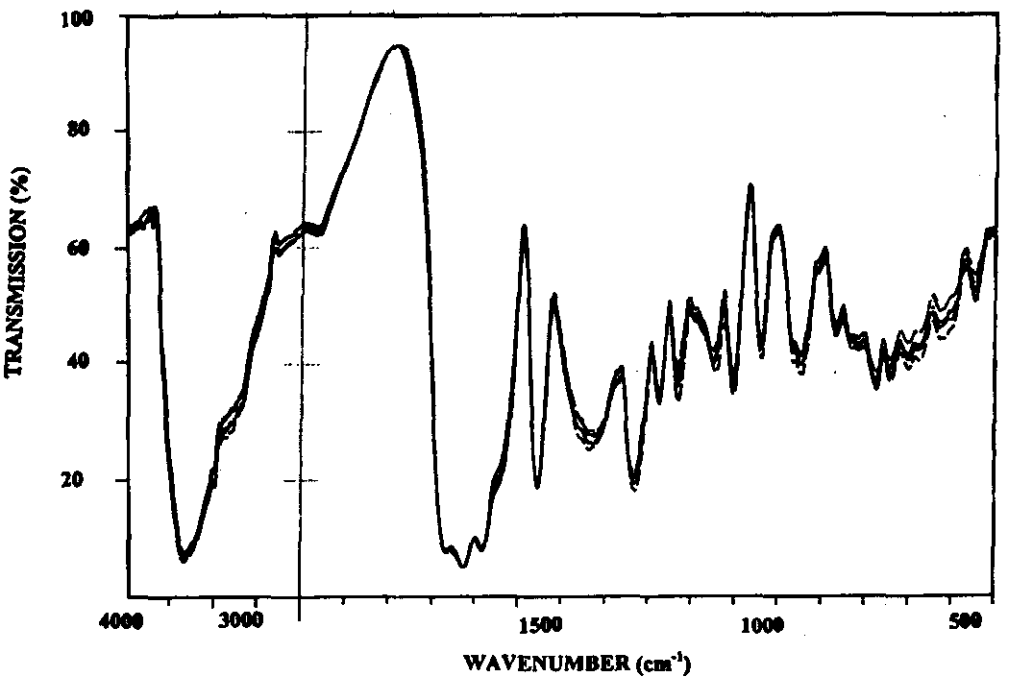

Figure 1. IR spectra of the six different oxytetracycline hydrochloride samples.

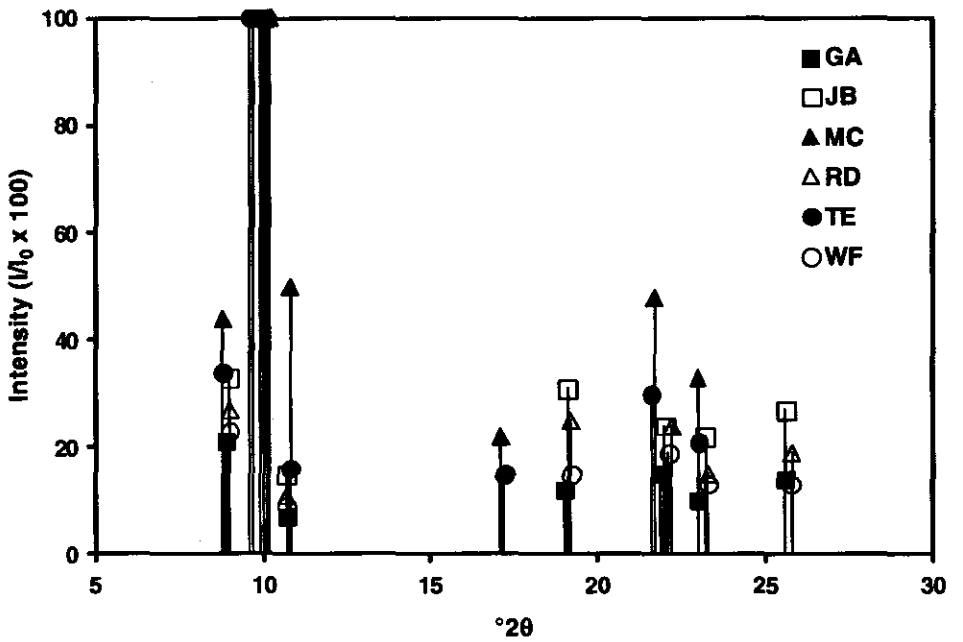

Figure 2. XRD patterns of the six different oxytetracycline hydrochloride samples.

Dissolution Studies

Powder dissolution rate profiles were measured using method II, paddle, of the USP 23 (10) or BP (9) as described for oxytetracycline hydrochloride capsules. A VanKel six-station dissolution apparatus was used (VanKel, Edison, NJ). The paddles rotated at 75 rpm or 100 rpm, and samples were taken from the dissolution medium, either water or 0.1 N hydrochloride acid, at 7.5, 15, 30, 45, and 60 min. To comply with the USP specification, not less than 80% (Q) of the oxytetracycline hydrochloride must be dissolved in water in 60 min, and 70% (Q) in 0.1 N hydrochloride acid in 45 min is required by the BP.

The powder sample (250 mg) was rinsed from the glass weighing boat into a 10-ml test tube with exactly 2 ml of the dissolution solution. Glass beads (125 mg) with a mean size of 0.1 mm were added to the suspension, and the mixture was agitated for 60 sec using a vortex mixer. The contents of the test tubes were transferred immediately to 900 ml of dissolution medium kept at 37°C. The concentration of dissolved drug was determined from the ultraviolet (UV) absorbance at 273 nm for the USP method and 353

nm for the BP method (Beckman DU 650I spectrophotometer, Beckman, Puerto Rico).

Particle Size Measurements

Particle size distributions in suspension were measured with a Galai-Cis-1 particle size analyzer (Galai, Jerusalem, Israel). This analyzer uses dual-discipline analysis, integrating laser diffraction and image analysis for particle sizing. Samples of the powder suspended in a suitable dispersing solution were each placed in a small cuvette, and the cuvette was fitted into the analyzer. A small magnetic stirrer inside the cuvette prevented sedimentation of the particles during the measurement. The acquired data were used to compute means, medians, and standard deviations based on the total particle population. Allen (11) gives a detailed discussion of these calculations.

Preparation of Tablets

The oxytetracycline hydrochloride powders were mixed in a ratio of 5 : 1 with directly compressible microcrystalline cellulose powder (Avicel PH200, FMC, Cork, Ireland). The tablets weighed 300 mg and contained 250 mg oxytetracycline hydrochloride. Each had a diameter of 13 mm and were compressed at a constant pressure of 1500 kPa using a 25-ton ring press (RIIC, London, England) used to compress KBr tablets for infrared spectroscopic analysis.

Characterization of Tablets

The dissolution of oxytetracycline hydrochloride from tablets was measured using the dissolution apparatus and conditions described for powder dissolution measurements. Results are the mean for 6 tablet samples. The time it took for individual tablets to disintegrate was measured with a Manesty tablet disintegration tester (Liverpool, England). Results are the mean for 10 tablet samples, and measurements were obtained in water at 37°C. Tablet hardness was measured using a Pharmatest PTB 311, tablet hardness meter (Pharmatest, Hamburg, Germany). Tablet hardness and dimensions were used to calculate the tensile strength for 10 tablets. The Student-Newman-Keuls test was used to determine any statistically significant differences in disintegration times and tensile strength measurements.

RESULTS AND DISCUSSION

The overlaid IR spectra of the six samples (Fig. 1) were virtually identical and therefore indicated that the six samples were identical with respect to chemical structure. All of the powders complied to the USP (10) and BP (9) potency specifications (Table 1) of 835 or 860 μg base/milligram, respectively. The samples also passed the test for light absorption impurities (i.e., the test for breakdown products). Based on these results, the six oxytetracycline hydrochloride powders complied with all official quality control tests and could be used in the formulation of dosage forms.

Powder dissolution rate profiles (Figs. 3 and 4) showed that all six raw materials dissolve practically immediately in water or 0.1 N HCl. This is to be expected since oxytetracycline hydrochloride is very soluble in water (12). The dissolution rates of the oxytetracycline hydrochloride powders from tablets compressed at the same pressure and composition (Figs. 5 and 6) were not the same, and were slower in both water and 0.1 N HCl. Compared to the powder dissolution results, tablets prepared with powders GA and RD were almost equivalent, WF and JB were slightly slower, and TE and MC were slowest. Both the powder and tablet dissolution rates complied with the USP (10) specification for capsules (Table 2) that not less than 80 % of the labeled oxytetracycline hydrochloride amount should be dissolved in 60 min. Dissolution tests performed according to the BP (9) test in 0.1 N hydrochloride acid (Table 2) showed that dissolution from tablets prepared with powders TE and MC did not comply with the specification that 70 % must be dissolved in 45 min.

To determine if particle size difference might explain the differences in dissolution rates, the median particle diameters (volume) and particle size distributions (Table 3) were measured. It was concluded that the samples are fairly comparable with respect to particle size, although sample JB had a slightly smaller mean (volume) particle size. Measured disintegration times (Table 2) showed that tablets with slow dissolution rates had significantly slower disintegration times ($p < .05$). The mean tablet tensile strength (Table 2) of the slow-dissolving tablets was significantly higher ($p < .05$) than that of fast-dissolving tablets.

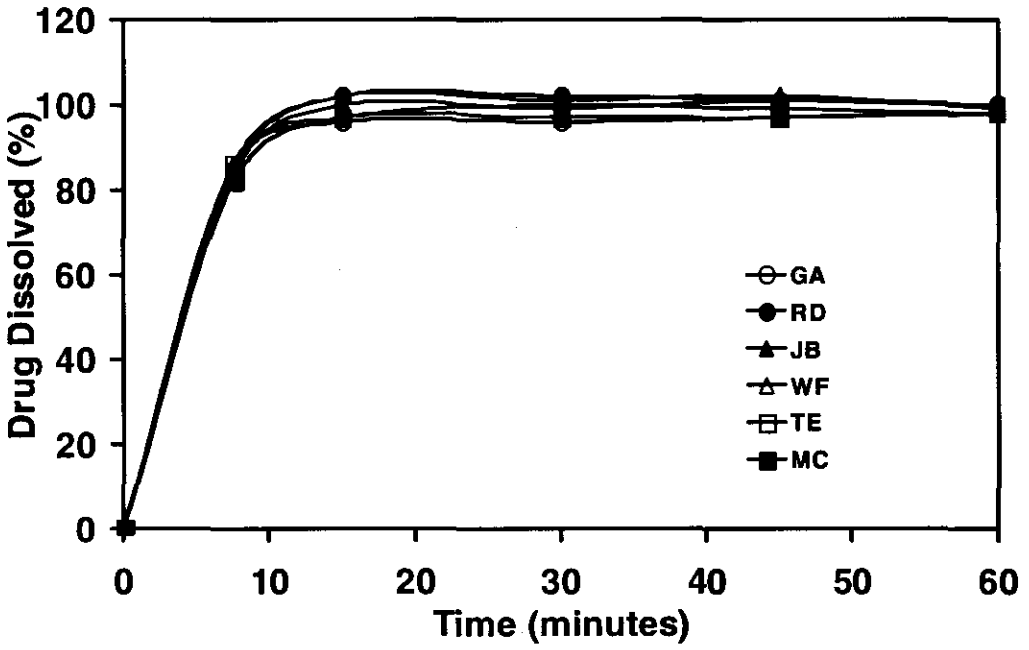

Figure 3. Dissolution of the powder in water (mean of six determinations) measured according to the USP (1995) test for oxytetracycline hydrochloride capsules.

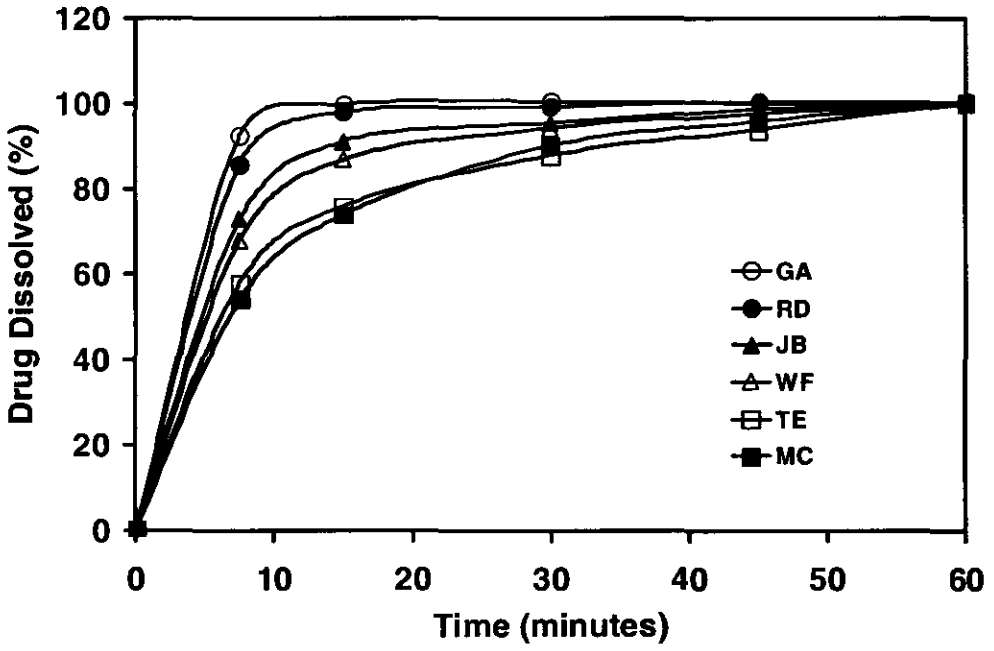

Figure 4. Dissolution of the powder in 0.1 N HCl (mean of six determinations) measured according to the BP (1988) test for oxytetracycline hydrochloride capsules.

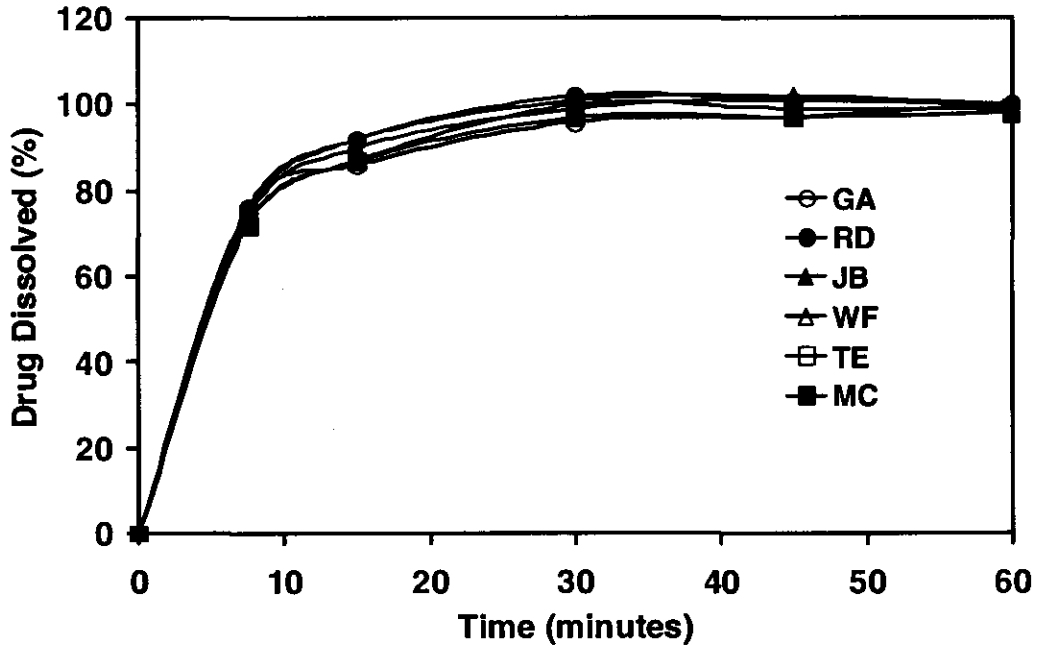

Figure 5. Dissolution of the tablets in water (mean of six determinations) measured according to the USP (1995) test for oxytetracycline hydrochloride capsules.

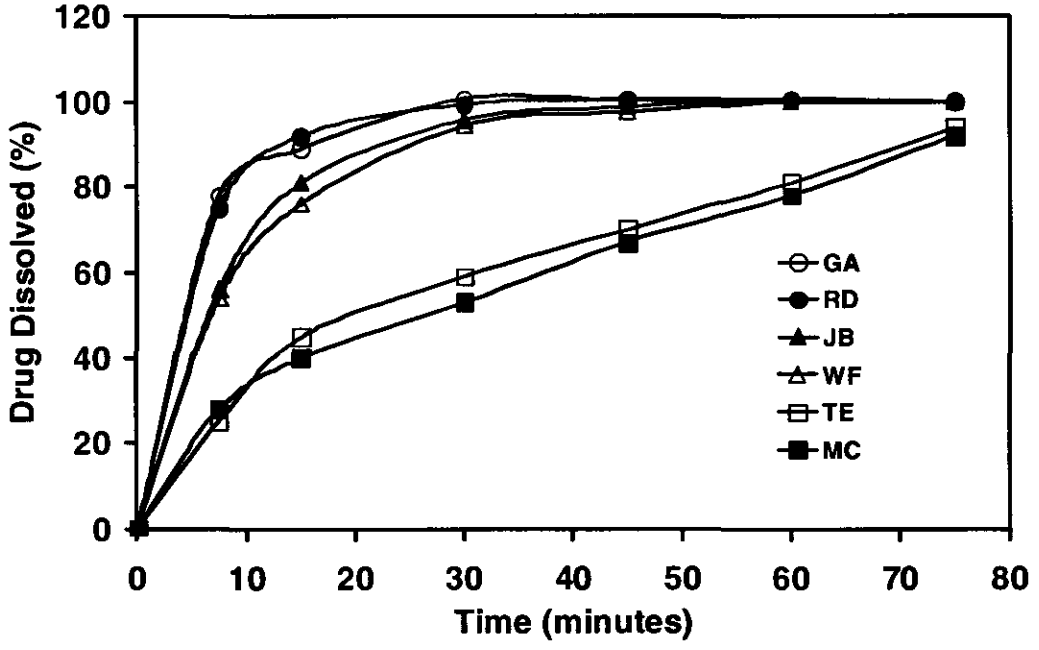

Figure 6. Dissolution of the tablets in 0.1 N HCl (mean of six determinations) measured according to the BP (1988) test for oxytetracycline hydrochloride capsules.

Table 2

Mean Tablet Dissolution Values (Q) According to the USP (1995) and BP (1988) Tests for Oxytetracycline Hydrochloride Capsules and Disintegration and Tablet Tensile Strength Results

Powder	Dissolved in 60 min (USP) (% *Q*)	Dissolved in 45 min (BP) (% *Q*)	Disintegration Time (sec)	Tablet Tensile Strength (x 10^5 Nm^{-2})
GA	100 ± 1.5	98 ± 3.1	83 ± 10	8.3 ± 0.5
JB	99 ± 2.7	99 ± 2.6	148 ± 15	18.1 ± 1.1
MC	100 ± 2.3	67 ± 3.4	169 ± 12	11.7 ± 0.6
RD	100 ± 2.6	100 ± 2.3	84 ± 16	9.3 ± 0.8
TE	100 ± 4.9	69 ± 2.5	170 ± 10	12.9 ± 1.0
WF	99 ± 1.9	97 ± 3.6	145 ± 15	20.4 ± 1.1

Table 3

Median Particle Diameter by Volume and Particle Size Distribution of the Oxytetracycline Hydrochloride Samples

Sample	Median Diameter by Volume (μm)	Particle Size Distribution by Volume (μm ± SD)
GA	45	10.42 ± 8.52
JB	24	10.18 ± 7.27
MC	36	12.59 ± 9.41
RD	37	11.61 ± 9.56
TE	41	14.95 ± 12.41
WF	46	10.45 ± 8.19

Table 4

Intensity Values (I/I_o) at the Main X-ray Diffraction Peak Angles (°2θ)

Main X-ray	°2θ (I/I_o x 100)					
Peaks	GA	JB	MC	RD	TE	WF
1	8.9 (21)	9.0 (33)	8.8 (44)	9.0 (27)	8.8 (34)	9.0 (23)
2	9.9 (100)	10.0 (100)	9.7 (100)	10.2 (100)	9.6 (100)	10.1 (100)
3	10.7 (7)	10.7 (15)	10.8 (50)	10.7 (11)	10.8 (16)	10.7 (9)
4			17.1 (22)		17.2 (15)	
5	19.0 (12)	19.1 (31)		19.2 (25)		19.2 (15)
6	21.9 (15)	22.0 (24)	21.7 (48)	22.2 (24)	21.6 (30)	22.1 (19)
7	23.0 (10)	23.2 (22)	23.0 (33)	23.3 (15)	23.0 (21)	23.3 (13)
8	25.6 (14)	25.6 (27)		25.8 (19)		25.8 (13)

Although these results might explain the huge differences in dissolution, the tablet hardnesseses all were below 80 N, and the tablets disintegrated within 5 min.

The low intrinsic solubilities of the oxytetracycline powders TE and MC were the biggest contributors to poor dissolution. XRD (Fig. 2) intensity values at the main diffraction peak angles (Table 4) showed there were two polymorphic modifications present among the samples. Samples GA, JB, RD, and WF fell into one group and had a yellow color. Samples MC and TE belonged to the second group and had a much darker color, which could be described as yellow/brown. This color difference was confirmed by microscopic evaluation, and although it could be coincidental, it was nevertheless striking that a correlation between color and polymorphic form was observed. Burger, Ratz, and Brox (5) prepared and identified two oxytetracycline hydrochloride polymorph forms. Form A was 28 times less soluble than form B. XRD results (Table 4) confirmed that samples MC and TE were similar to form A. The poor dissolutions obtained from tablets containing samples MC and TE were largely due to the poor solubility of this crystal form present in these powders.

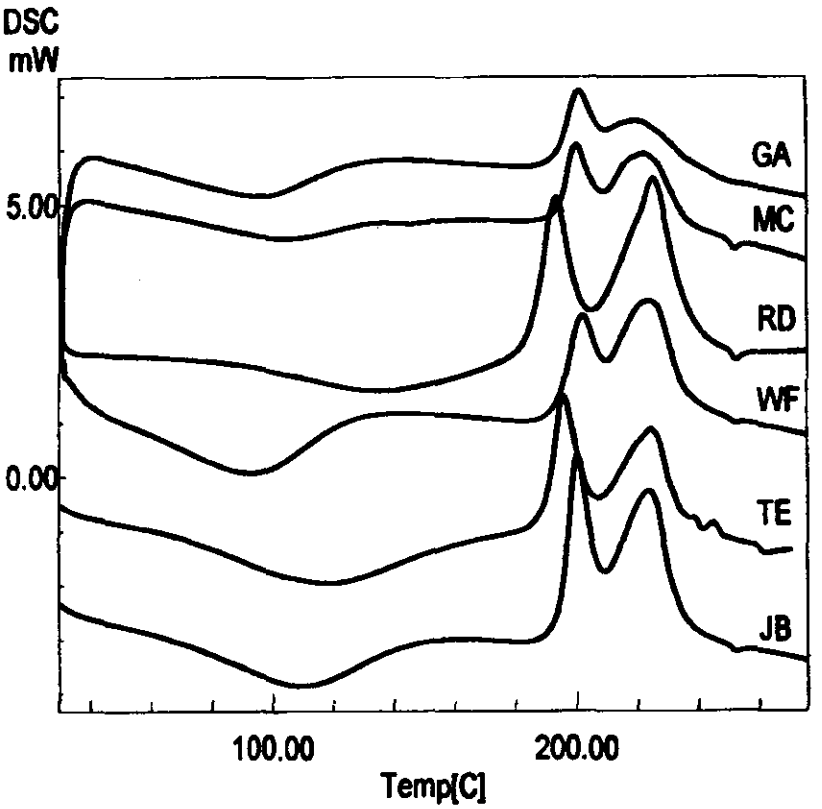

Figure 7. DSC thermograms of the oxytetracycline hydrochloride samples.

The oxytetracycline hydrochloride DSC thermograms had no sharp melting endotherms (Fig. 7). A broad endotherm seen between 70°C and 130°C was probably due to the absorption of moisture (5). Burger et al. (5) demonstrated that form B was hygroscopic, and form A was not. The differences in endotherm size and range provide further proof for the conclusion made from the X-ray study, namely, that samples MC and TE were form A and not the commonly used, and more hygroscopic, form B. The broad endotherm is followed by two exotherms, the first of which appears at 180°C-200°C. It can be concluded that the DSC thermograms of the samples were comparable, and although not suited for detailed characterization of forms A and B, the size of the broad endotherm indicated that the extent of water adsorption on form A powders was less.

CONCLUSION

In South Africa, oxytetracycline is identified as an essential drug; many generic products are on the market, and many more are being developed. In this study, in which six oxytetracycline hydrochloride powders obtained randomly from manufacturers and suppliers were compared, it was found that compliance to a pharmacopoeial monograph was insufficient to ensure the optimum dissolution performance of a simple tablet formulation. A preformulation solid-state characterization of the drug powders combined with the evaluation of simple tablet formulations pointed out significant differences in the solubility of the powder samples.

The solubility difference was because the samples contained different polymorphic forms. The question whether this difference is important from a manufacturer's point of view and/or in terms of bioavailability was demonstrated by the fact that the dissolution rate from tablets prepared with the poorly soluble powders were significantly slower. On the basis of the variability reported for the fast-disintegration tablets, it might be expected that a similar variability would be seen with capsules.

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CHAPTER 6

Developing a discriminating dissolution test for three mebendazole polymorphs based on solubility differences

E. SWANEPOEL[1], W. LIEBENBERG[1], B. DEVARAKONDA[2], M.M. DE VILLIERS[2]

Research Institute for Industrial Pharmacy[1], School of Pharmacy, Potchefstroom University for CHE, Potchefstroom 2520, South Africa, and Department of Basic Pharmaceutical Sciences[2], School of Pharmacy, University of Louisiana at Monroe, USA

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Mebendazole, a broad spectrum anthelmintic drug, is practically insoluble in water and exists in three polymorphic forms, A, B, and C, of which C is pharmaceutically favoured. Since the dissolution of drugs from solid oral dosage forms can depend on the crystal form of the drug an attempt should be made while developing dissolution tests to set test parameters that are sensitive to changes in the crystal form. USP 24 describes 0.1 M hydrochloric acid containing 1.0% sodium lauryl sulphate (SLS) as the dissolution medium for mebendazole tablets. Results showed that the high concentration of sodium lauryl sulphate in the USP dissolution medium does not allow the use of this test to distinguish between the solubility differences of the three mebendazole polymorphs. By decreasing the amount of sodium lauryl sulphate in the dissolution medium clear differences in the dissolution rates of the three forms were observed. The most discriminating medium was 0.1 M HCl, containing no sodium lauryl sulphate.

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1. Introduction

Mebendazole is a broad spectrum anthelmintic drug producing high cure rates in infestations by *Ascaris*, threadworms, hookworms and whipworms [1]. Mebendazole is practically insoluble in water and a study of its polymorphism has led to the identification and characterisation of three polymorphic forms (A, B, C) displaying significantly different solubilities and therapeutic differences [2, 3]. The polymorphs differ with

respect to their IR spectra, x-ray powder diffractograms (XRPD), and differential scanning calorimetry (DSC) thermograms [2, 4]. The solubility of the three polymorphs in 0.03 M hydrochloric acid is in the order B > C > A [4]. Solubility studies and clinical trials have shown that polymorph C is pharmaceutically favoured [5, 6].

Dissolution of drugs from solid oral dosage forms is a necessary criterion for drug bioavailability. Therefore, the dissolution test for solid oral drug products has emerged as the single most important control test for assuring batch-to-batch bioequivalence once its bioavailability has been defined [7]. In developing dissolution tests, attempts are made to design test parameters that are sensitive to manufacturing/process/formulation changes. The determination of dissolution profiles of water-insoluble drug products, like mebendazole, requires dissolution media different from those normally used for water-soluble drug products [8]. Selecting a dissolution medium of acceptable volume and composition as well as having a good discriminating power is difficult for these drugs [9]. Approaches used in the design of dissolution media for poorly soluble drugs include: (a) bringing about drug solubility by increasing the volume of the aqueous sink or removing the dissolved drug [10, 12]; (b) solubilization of the drug by co-solvents, up to 40% [13, 14] and by anionic [8] or non-ionic [8, 15] surfactants added to the dissolution medium in postmicellar concentrations; (c) alteration of pH to enhance the solubility of ionizable drug molecules [8]. The last two approaches seem less cumbersome and have been more widely employed in pharmacopeial dissolution tests. USP 24 [16] prescribes 0.1 M hydrochloric acid containing 1% sodium lauryl sulphate as the dissolution medium for mebendazole tablets.

Surfactants like sodium lauryl sulphate enhance the dissolution rate of poorly water-soluble drug products due to wetting, micellar solubilization, and/or deflocculation [8]. However, the sodium lauryl sulphate present in the dissolution medium may reduce the discriminative power between the three polymorphic forms of mebendazole, in the USP dissolution test. The aim of this study was to investigate the dissolution properties of mebendazole polymorphs. Changes in the USP dissolution medium, involving varying concentrations of sodium lauryl sulphate, were also investigated to determine the medium that would be the most discriminative between the solubility of polymorphs A, B and C.

This is important, since products that contain all three polymorphic forms of mebendazole are found on the market in developing countries [17]. For example, in South Africa there is a number of generic mebendazole products from different manufacturers available and these products are widely used because mebendazole forms an integral part of the essential drug list in South Africa.

2. Investigations, results and discussion

2.1. Characterization of mebendazole polymorphs

It is known that mebendazole can exist in three crystal polymorphic forms with different solubilities. The three polymorphic forms of mebendazole, form A, B and C, were identified amongst raw materials available to generic manufacturers or prepared as described by Himmelreich et al. [2] and Costa et al. [4].

Table 1: Main absorbencies in the Fourier transform IR spectra of the mebendazole polymorphs

Crystal form	-NH (cm^{-1})	-C=O (cm^{-1})
Form A	3370	1730
Form B	3340	1700
Form C	3410	1720

In Fig. 1 the DSC thermograms, Fig. 2 the XRPD patterns and in Table 1 the main FTIR signals of the three forms are given. The thermogram of form A was characterised by two melting endotherms at 264 and 331 °C. Form B displayed three melting endotherms at 243, 254 and 327 °C. The second endotherm at 243 °C was an endo-exothermic recrystallization with the exotherm following at 254 °C. Form C has a small endotherm at 195 °C followed by two endotherms corresponding to that of form A. This suggests that form C might be a non-crystalline form that is converted to the more crystalline form at

255-260 °C. XRPD patterns were similar to those reported by Costa et al. [4]. Characteristic IR-signals, Table 1, were also an easy way to identify the three forms [17].

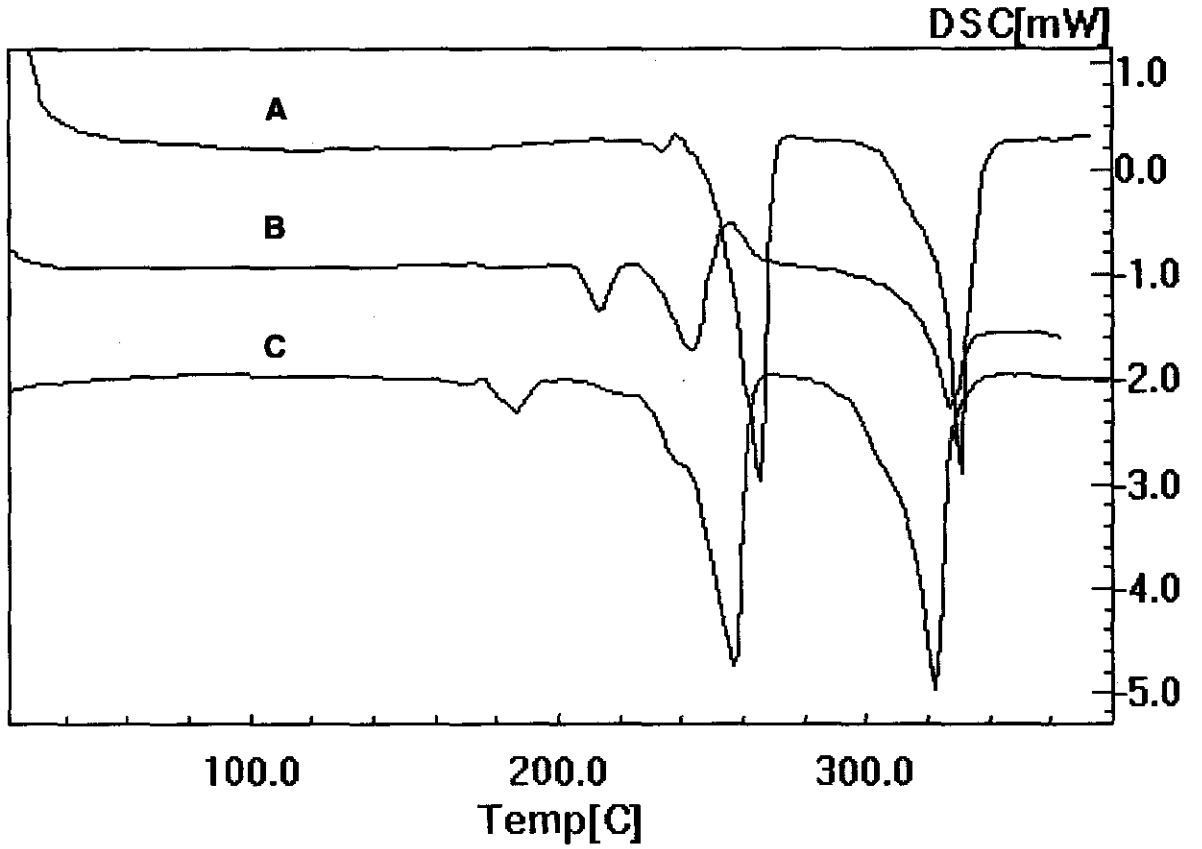

Fig. 1: DSC thermograms of the three mebendazole polymorphs

The solubilities of the polymorphs in 0.1 M HCl were in the order B (0.07 mg/ml) > C (0.04 mg/ml) > A (0.02 mg/ml). However, the solubility in water after 24 h at 30 °C was extremely low, less than 0.2 x 10^{-4} mg/ml for form C. In some samples no discernible concentration of mebendazole could be detected by UV-analysis.

2.2. Powder properties and particle morphology

The importance of geometrical form (i.e., size and shape) of the particles in the dissolution rate of fine particulate sparingly soluble drugs should be emphasized. It was observed that the dissolution rates of sparingly soluble drugs, like mebendazole, are related to particle

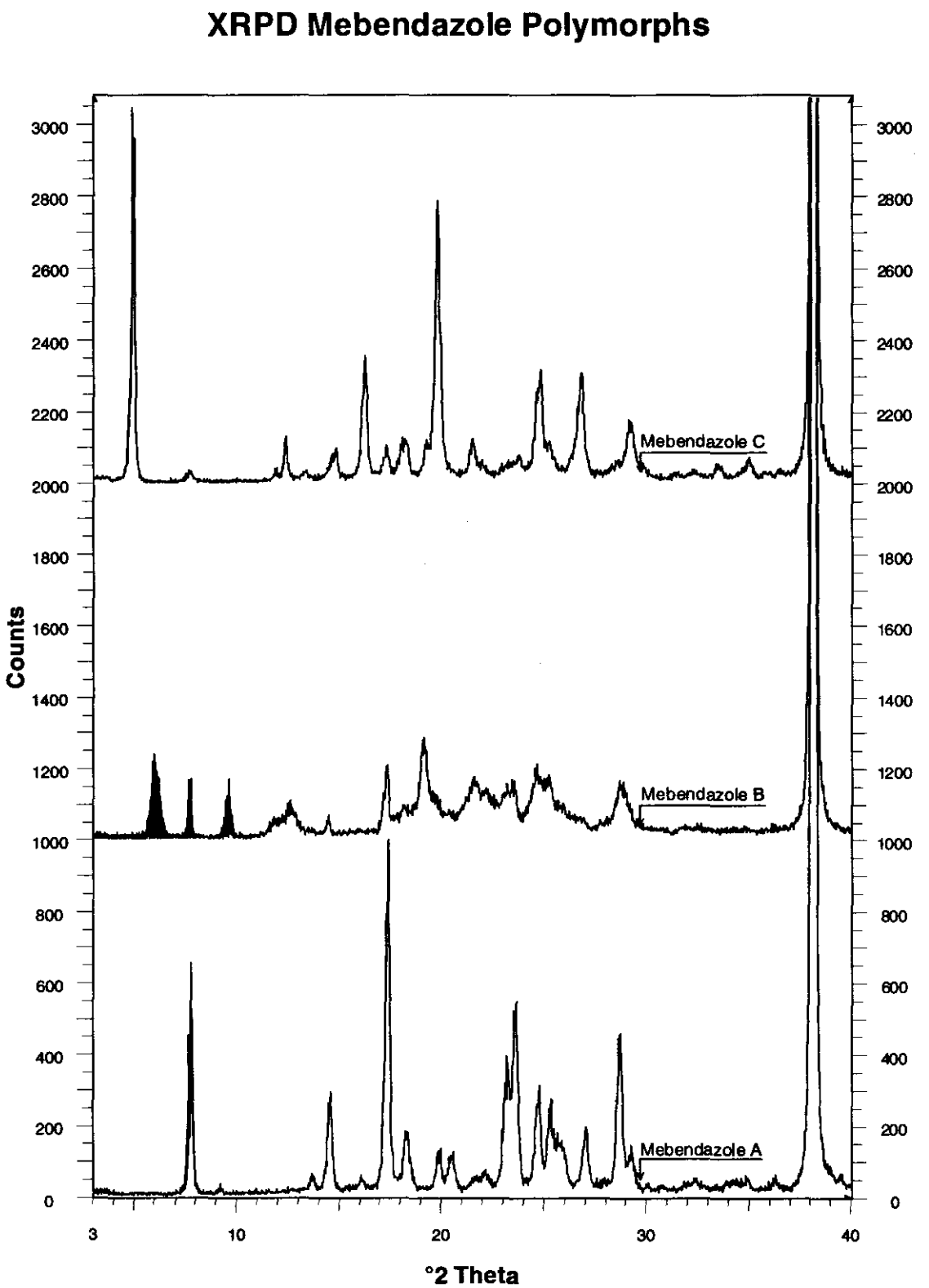

Fig. 2: XRPD patterns of the three mebendazole polymorphs

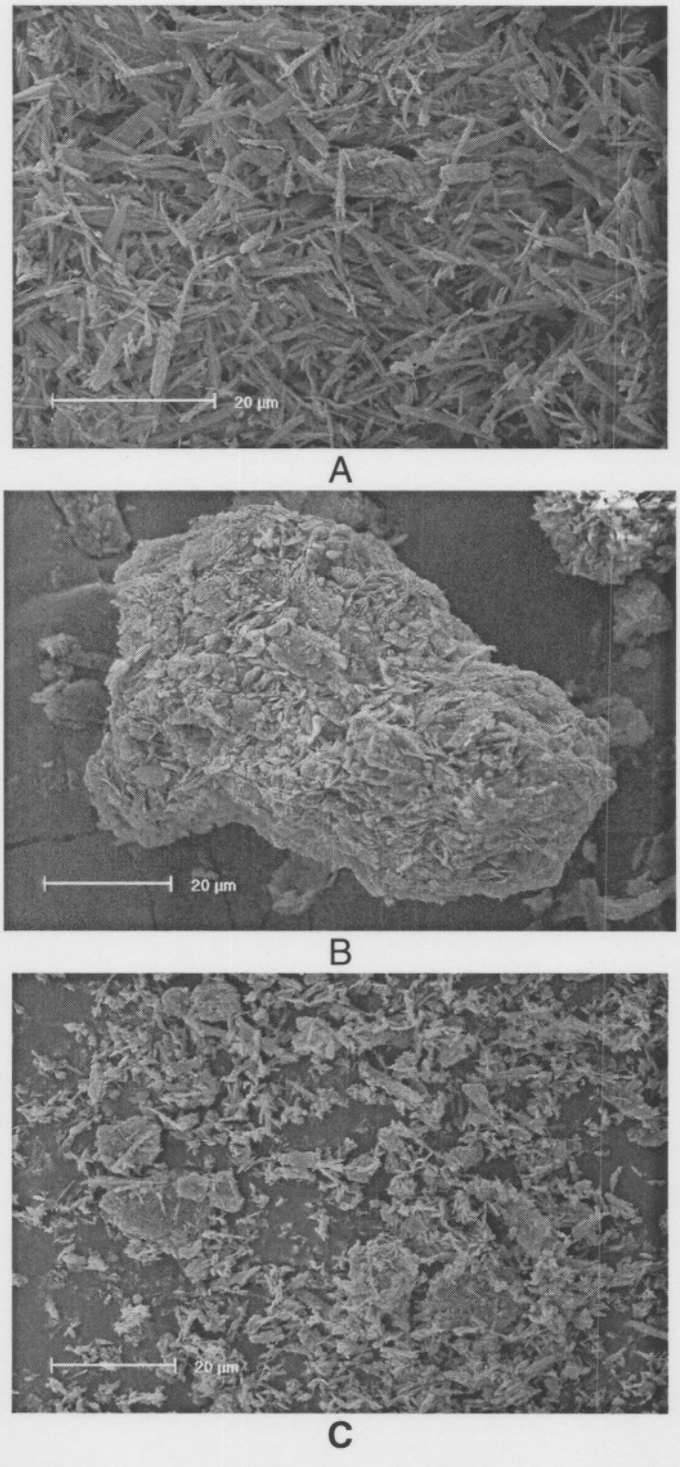

Fig. 3: SEM photomicrographs of (A) form A, (B) form B and (C) form C

shape and size [18]. Form A and B were free-flowing powders while form C was strongly aggregated. The mean volume particle sizes of the powders were: A = 3.56 ± 1.54 μm; B = 6.18 ± 1.72 μm; C = 3.35 ± 1.02 μm. For particles of the same size, the dissolution rate decreased as the level of flakiness and irregularity increased. This phenomenon can be explained by an increase in the average hydrodynamic boundary layer thickness as the particles become more irregular [18]. The differences in aggregation behaviour of the three forms were inspected closer with a SEM. In Fig. 3 these photomicrographs are shown. From these results it was clear that form A, was the least aggregated. Form B contained a large number of agglomerates with a mean size around 20-50 μm. Form C was also agglomerated but these were not as big or tightly packed.

2.3. Powder dissolution behavior

The dissolution rates of the three forms, as dispersed powders with particle sizes below 10 μm, were measured according to the method of the USP. The dissolution medium was 0.1 M HCl containing 1 % sodium lauryl sulphate and the dissolution profiles obtained therein are shown in Figs. 4-6.

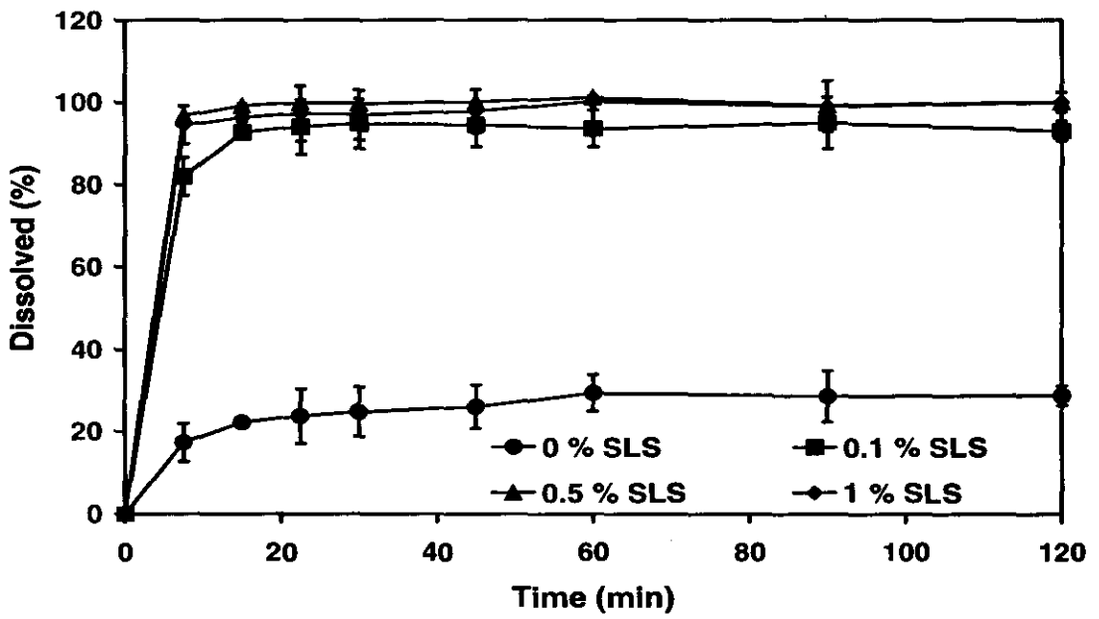

Fig. 4: Powder dissolution profiles of form A

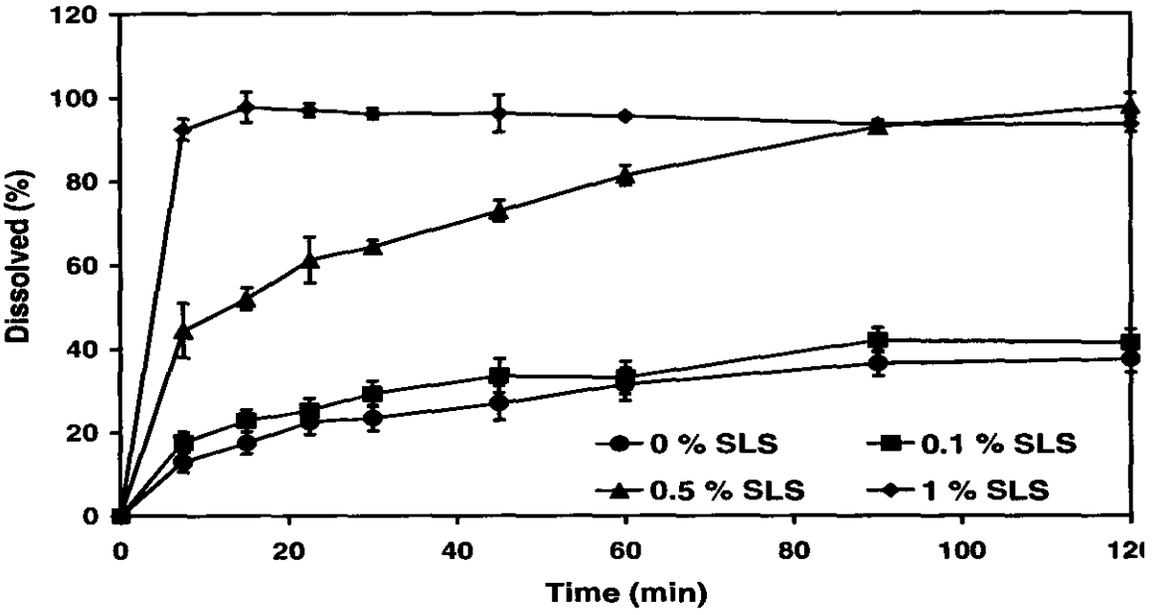

Fig. 5: Powder dissolution profiles of form B

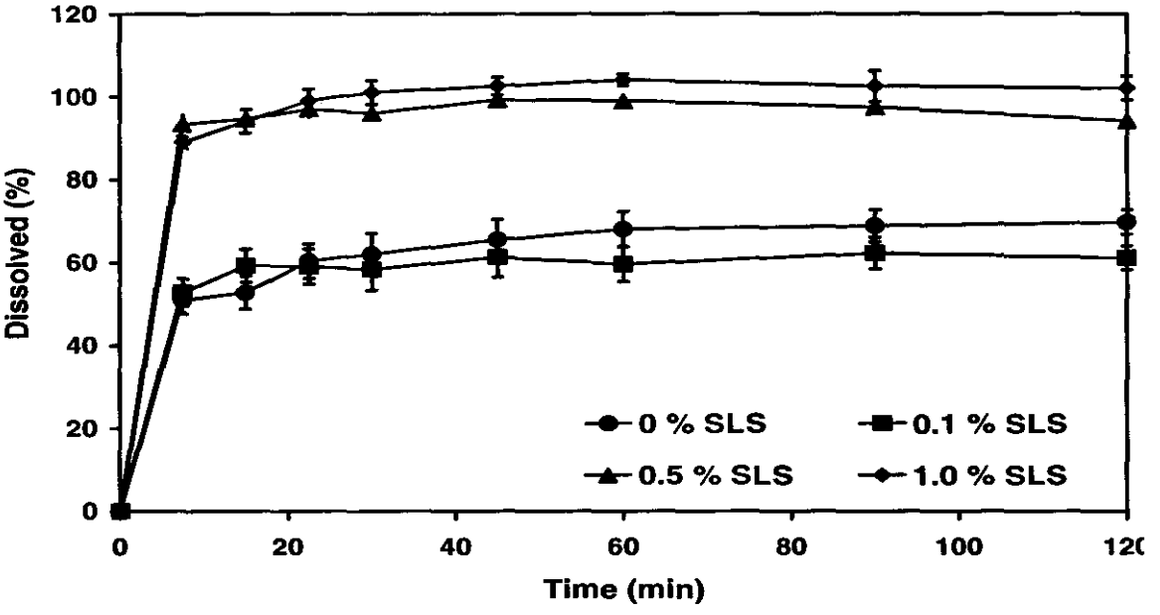

Fig. 6: Powder dissolution profiles of form C

These figures also show the dissolution in 0.1 M HCl without surfactant and the effect of surfactant concentration on dissolution when the concentration of sodium lauryl sulphate was varied from 0.1 – 1%.

According to the USP not less than 75% (Q) of the drug must be dissolved within 120 min (Fig. 7). In the USP medium all three polymorphs dissolved more than 75% within 120 min. Form C = 102% > Form A = 95% > Form B = 94%. In 0.1 M HCl the dissolution rates were significantly lower but this medium distinguished between the differences in the solubility of the three forms. Form C = 72% > Form B = 45% > Form A = 20%. By increasing the concentration of sodium lauryl sulphate in the dissolution medium the discriminating power of the medium was diminished.

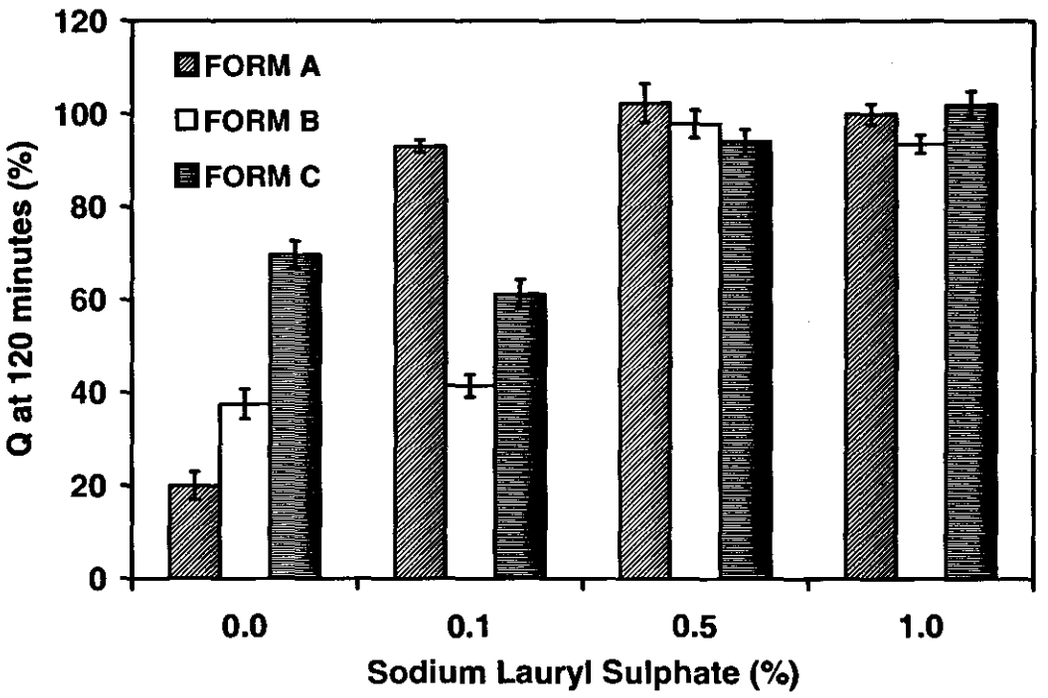

Fig. 7: Effect of sodium lauryl sulphate concentration on Q at 120 min

These results suggest that the solubility of the mebendazole polymorphs depended on how the powdered drug is wetted by the medium in which it is dissolving. As shown in Fig. 3, the mebendazole polymorphs spontaneously aggregate to form large poorly wettable aggregates.

Table 2: Solubility of mebendazole polymorphs at increasing pH with and without the addition of 1 % sodium lauryl sulphate (SLS)

pH	Form A		Form B		Form C	
	0 %	1 %	0 %	1 %	0 %	1 %
1.2	0.011±0.0010	0.101±0.0080	0.077±0.0050	0.107±0.0080	0.039±0.0040	0.096±0.0020
3.6	0.008±0.0009	0.070±0.0060	0.032±0.0030	0.074±0.0030	0.025±0.0030	0.073±0.0030
4.6	0.005±0.0006	0.058±0.0030	0.015±0.0010	0.061±0.0020	0.010±0.0010	0.058±0.0030
6.0	0.003±0.0004	0.017±0.0008	0.004±0.0003	0.011±0.0001	0.003±0.0001	0.011±0.0005
7.4	0.001±0.0003	0.007±0.0001	0.003±0.0002	0.008±0.0003	0.002±0.0001	0.008±0.0030

2.4. Effect of pH and surfactant concentration on solubility

The effect of pH and SLS concentration on the solubility of three polymorphs of mebendazole was studied individually (Table 2). The results indicate that both SLS concentration and pH significantly influence the solubility of form A and C. At 1% SLS concentration, the solubility of all the polymorphs is more or less the same at any given pH (Fig. 8, 9). Significant differences in solubility began to appear when the amount of SLS in the dissolution was reduced. In the absence of SLS and at pH 1.2, pH 3.6, and pH 4.6 all the polymorphs showed significant differences in the solubility with maximum differences at pH 1.2 (Fig. 9). This shows that in the USP dissolution medium, the surface properties of the powders are sufficiently changed by sodium lauryl sulphate so that aggregates are dispersed, improving the dissolution rate and eliminating any differences in dissolution due to changes in the crystal form.

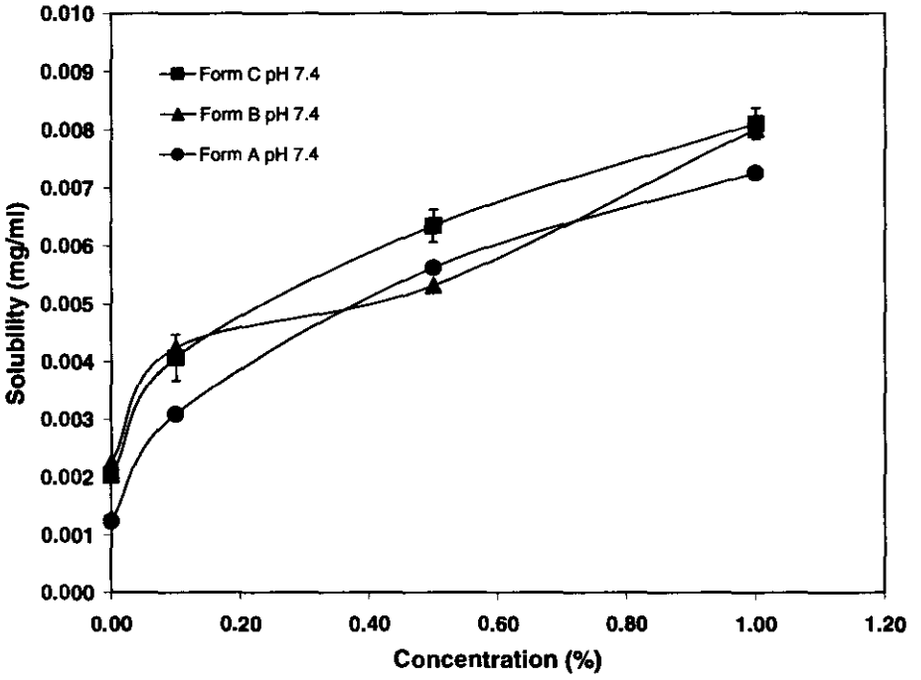

Fig. 8: Change in solubility of mebendazole polymorphs at pH 7.4 with an increase in SLS concentration

2.5. Conclusion

Drug solubility studies and clinical trials have shown that form C of mebendazole is preferred. However, the high concentration of sodium lauryl sulphate in the USP dissolution medium does not allow the use of this test to determine if form C is used or not. By decreasing the amount of sodium lauryl sulphate in the dissolution medium clear differences in the dissolution rates of the three forms were observed. The most discriminating medium was 0.1 M HCl, containing no sodium lauryl sulphate.

Manufacturers and regulatory agencies should take note of this effect. When buying or sourcing raw material, tablets or suspensions, dissolution results obtained using the USP conditions would not ensure that the products contain polymorph C. Consideration should therefore be given to changing the dissolution medium to improve its discriminating power. Simply eliminating sodium lauryl sulphate from the USP dissolution medium would give manufacturers and regulatory agencies a simple method to ensure that

mebendazole tablets and suspensions contain the right crystal polymorph.

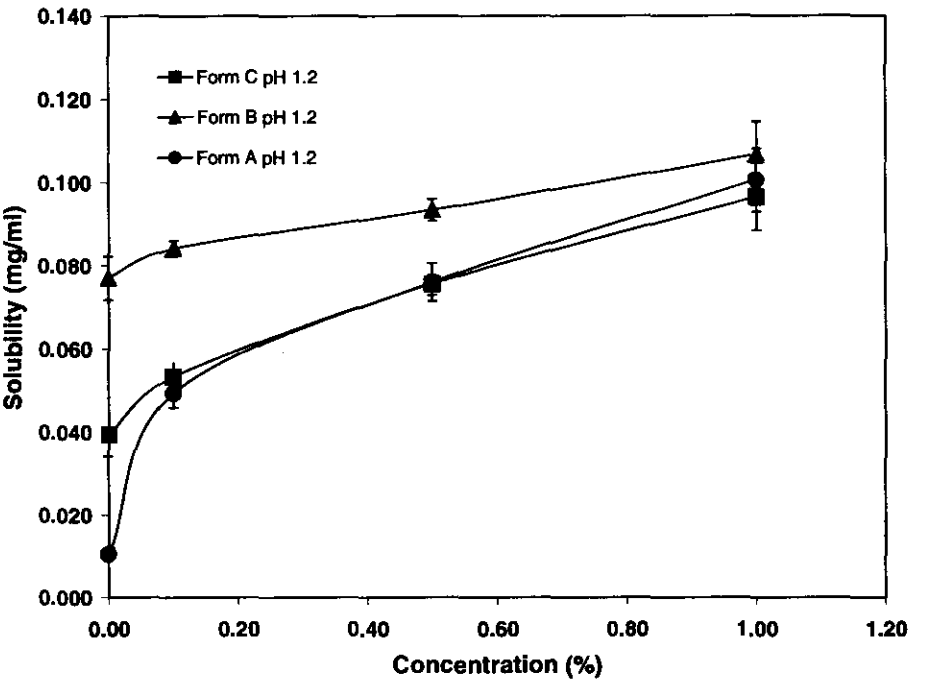

Fig. 9: Change in solutility of mebendazole polymorphs at pH 1.2 with an increase in SLS concentration

3. Experimental

3.1. Materials

Three mebendazole polymorphs were identified among raw material samples obtained from a number of manufacturers or prepared by recrystallization [11, 12]. The purity of the powders was between 99-101%.

3.2. Identification and characterization of crystal forms

IR spectra were recorded on a Nicolet Nexus 470-FT-IR spectrometer (Nicolet Instrument Corporation, Madison WI 53711) over a range of 600-4000 cm^{-1}. The diffuse reflectance method was used. Powders of the samples were mixed with KBr prior to measurement. Main differences in IR-peaks are listed in Table 1. The aggregation properties of the three polymorphic powders were studied with a scanning electron microscope (Fig. 3). A

Philips XL 30 scanning electron microscope (Philips, Netherlands) was used to obtain photomicrographs of the different mebendazole crystal forms. Samples were adhered to a small piece of carbon tape mounted on a metal stub and coated under a vacuum with carbon (Emscope TB500 sputter-coater) before being coated with a thin gold-palladium film (Eiko Engineering ion Coater IB-2). The thermal properties of the crystal forms were measured by differential scanning calorimetry. DSC thermograms were recorded with a Shimadzu DSC-50 instrument (Shimadzu, Kyoto, Japan). The measurement conditions were sample weight, approximately 2 mg; sample holder, aluminium crimp cell; gas flow, nitrogen at 20 ml/min.; heating rate, 10 °C/min. All ambient X-ray powder diffraction patterns (XRPD) of the crystal forms were obtained at room temperature (unless otherwise indicated) using a Bruker D8 Advance diffractometer (Bruker, Germany). The measurement conditions were: target, Cu; voltage, 40 kV; current, 30 mA; divergence slit, 2 mm; anti-scatter slit, 0.6 mm; receiving slit, 0.2 mm; monochromator; detector slit, 0.1 mm; scanning speed, 2°/min (step size 0.025°, step time, 1.0 s). Approximately 300 mg samples were weighed into aluminium sample holders, taking care not to introduce a preferential orientation of crystals.

3.3. Powder dissolution studies

Powder dissolution studies of forms A, B and C were performed using Method 2, paddle, of the USP 24 [16]. The paddles were rotated at 75 rpm and samples were withdrawn from the dissolution medium at 7.5, 15, 22.5, 30, 45, 60, 90 and 120 min. The powder sample, 50 mg, was rinsed from the glass weighing boat into a 10 ml test tube with exactly 2 ml of dissolution medium. Glass beads, 50 mg, with a mean size of 0.1 mm, were added to the suspension and the mixture was agitated for 120 s using a vortex mixer. The contents of the test tube were then transferred into the dissolution medium. The dissolution media used were 0.1 M hydrochloric acid and 0.1 M hydrochloric acid containing sodium lauryl sulphate in concentrations of 0.1%, 0.5% and 1%, which is the medium prescribed by the USP 24. The concentration of dissolved powder was calculated from the UV absorbancy values obtained at 254 nm. Results are the mean of three determinations.

3.4. Solubility determination

To determine the solubility in water, 12 ml vials containing distilled, deionised water with increasing concentrations of sodium lauryl sulphate, and excess amounts of each crystal form were rotated (100 rpm) in a water bath kept at 30 ± 0.1 °C. After 48 h, equilibrium was reached and aliquots of the solution were withdrawn from the vials and filtered through a 0.25 µm filter. The solutions were suitably diluted with methanol and assayed with a spectrophotometer at 254 nm. Results are the mean of five determinations.

3.5. Statistical evaluation of data

An experiment was set up to compare the effect of different pHs and SLS additives on the increase in solubility for 3 mebendazole polymorphs. Experiments were conducted at pH value levels of 1.2, 3.6, 4.6, 6.0, and 7.4. Four levels of SLS (0.00%, 0.10%, 0.50%, and 1.00%) were also applied. All factor-level combinations of these two variables were used in the experiment. At the end of 48 h, five solubility readings were taken at each factor-level combination.

Statistical Model: $Y_{ijk} = \mu + \alpha_i + \beta_j + \alpha\beta_{ij} + \varepsilon_{ijk}$

Where i = 1, 2, 3, 4, and 5; j = 1, 2, 3, and 4; k = 1, 2, 3, 4, and 5.
Since pH and % SLS interaction is significant (P is 0.0001) for all the 3 polymorphs, we could not test for the main effects. So the effect of pH on the solubility was analyzed at a fixed level of SLS and vice versa.

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CHAPTER 7

Quality evaluation of generic drugs by dissolution test: changing the USP dissolution medium to distinguish between active and non-active mebendazole polymorphs

Erna Swanepoel[a], Wilna Liebenberg[a], Melgardt M. de Villiers[b]

[a] Research Institute for Industrial Pharmacy, Potchefstroom University for CHE, Potchefstroom, South Africa
[b] School of Pharmacy, University of Louisiana at Monroe, Monroe, LA, USA

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Abstract

Mebendazole is practically insoluble in water and studies of its polymorphism has led to the identification and characterization of three polymorphic forms (A, B, C) displaying solubility and therapeutic differences that show that polymorph C is therapeutically favored. The objective of this study was to adjust the USP dissolution test for mebendazole so that it was able to distinguish between the dissolution properties of three mebendazole polymorphs. This would provide generic manufacturers with one more test to ensure that the therapeutically active polymorph C is used. The results obtained in this study show that the USP dissolution test conditions were not able to distinguish between the dissolution properties of completely dispersed mebendazole polymorphs with comparable particle sizes. When sodium lauryl sulfate was removed from the dissolution medium, the percentage dissolved versus time profiles changed so that polymorph C dissolved faster (70% within 120 min) compared to polymorph B (37% within 120 min) and polymorph A (20% within 120 min).

Keywords: *Mebendazole; Dissolution; Polymorph; Pharmacopeial; Surfactant*

1. Introduction

In a recent letter published in the *South African Medical Journal*, Evans et al. [1] asked for the establishment of a procedure to ensure that all batches of imported mebendazole raw material and tablets contain the molecular, or rather, crystal polymorph C which has been demonstrated to be, the most efficacious form [2 - 4]. Mebendazole is a broad-spectrum anthelmintic drug producing high cure rates in infestations by *Ascaris*, threadworms, hookworms and whipworms [5]. The drug is practically insoluble in water and studies of its polymorphism has led to the identification and characterization of three polymorphic forms (A, B, C) displaying solubility and therapeutic differences [2,3,6]. The polymorphs differ with respect to their spectral and thermal properties [2,5]. In the DSC thermograms of the three polymorphs, a common endotherm at 235 °C is observed which represents the thermal decomposition of the drug. The thermograms of forms B and C show additional endotherms at 210 and 170 °C, respectively. The solubility of the three polymorphs in 0.03 M hydrochloric acid is in the order A < C < B [4]. Solubility studies and clinical trials have shown that polymorph C is therapeutically favored [3,4,7].

In one therapeutic trial the use of mebendazole, 300 mg polymorph A, 300 mg polymorph C and 500 mg polymorph C, in the treatment of hookworm and Trichuris infections was carried out at primary schools in Southern Thailand [7]. A total of 958 children were randomly allocated in seven treatment groups including the placebo control and the standard dose control (100 mg polymorph C b.i.d. for 3 days). The egg reduction rates and the cure rates of 300 and 500 mg polymorph C were similar, while the efficacy of single dose 300 mg polymorph A was not different from that of the placebo control in both infections. In a further attempt to test the biological activity of three polymorphic forms of mebendazole, forms A, B and C, both the LD_{50} in mice after oral and intraperitoneal administration and the anthelmintic effect of these forms on the enteral and parenteral phases of the nematode *Trichinella spiralis* were studied. They observed that the polymorphic form A was the least toxic and effective against *T. spiralis*.

In developing countries, pharmaceutical manufacturers and regulatory agencies usually rely on pharmacopeial tests to ensure the quality of pharmaceuticals. In the USP [8], BP [9] and EP [10] there are monographs describing several chemical tests for

mebendazole raw material, tablets, and suspensions. However, none of these tests, except perhaps the IR identification test and possibly the dissolution test described in the USP, can be used to distinguish between crystal polymorphs [4,6]. The objective of this study was to adjust the USP dissolution test for mebendazole so that it was able to distinguish between the dissolution properties of mebendazole polymorphs. This would provide generic manufacturers with one more test to ensure that the therapeutically active polymorph C is used.

2. Materials and methods

The mebendazole polymorphs were identified amongst raw material samples obtained from a number of manufacturers and were prepared by recrystallization [2,4]. Form A was recrystallized from glacial acetic acid, form B from chloroform and form C from ethanol. The purity of the powders was between 99 and 101% as determined using the methods described in the USP [8]. Both infrared (IR) spectra and X-ray powder diffraction (XRPD) were used to characterize the three mebendazole polymorphs. IR spectra were recorded on a Nexus 470 spectrophotometer (Nicolet Instrument Corp., Madison, WI, USA) over a range of 4000-400 cm^{-1} with the Avatar Diffuse Reflectance smart accessory. Samples weighing approximately 2 mg were mixed with 200 mg of KBr (Merck, Darmstadt, Germany) by means of an agate mortar and pestle, and placed in sample cups for convenient, fast sampling. The XRPD profiles were obtained at room temperature with a Philips PM9901/0 diffractometer (Philips, Netherlands). The measurement conditions were target, Cu; filter, Fe; voltage, 40 kV; current, 20 mA; slit, 0.2 nm; scanning speed, 2°/min. Approximately 200 mg of sample was loaded into an aluminum sample holder and care taken not to introduce a preferential orientation of the crystals. Particle size distributions in suspension of all samples were measured with a Galai-Cis-1 particle size analyzer (Galai, Israel). This instrument used dual discipline analysis integrating laser diffraction and image analysis for particle sizing. Samples, 10 mg, suspended in a suitable dispersing solution (water) were placed in small cuvettes and fitted into the analyzer. A small magnetic stirrer inside the cuvette prevented sedimentation of the particles during the measurement. The acquired data were used to compute means, medians and standard deviations based on the total particle population.

Powder dissolution studies of forms A, B and C were performed using Method 2, paddle, of the USP 25 [8]. The paddles were rotated at 75 rpm and samples were withdrawn from the dissolution medium at 7.5, 15, 22.5, 30, 45, 60, 90 and 120 min. The powder sample, 50 mg, was rinsed from the glass weighing boat into a 10 ml test tube with exactly 2 ml of dissolution medium. Glass beads, 50 mg, with a mean size of 0.1 mm, were added to the suspension and the mixture was agitated for 20 s using a vortex mixer. The contents of the test tube were then transferred into the dissolution medium. The dissolution media used were 900 ml 0.1 M hydrochloric acid and 900 ml 0.1 M hydrochloric acid containing 1 % sodium lauryl sulfate, this is the medium prescribed by the USP. The concentration of dissolved powder was calculated from the UV absorbance obtained at 254 nm. Results are the mean of 12 individual dissolution tests. When a powder did not comply with the USP criteria the dissolution test was repeated in accordance to USP specifications.

To determine the solubility in water, 12-ml vials containing 0.1 M HCl and excess amounts of each crystal form were rotated (100 rpm) in a water bath kept at 30 ± 0.1 °C. After 48 h, equilibrium was reached and aliquots of the solution were withdrawn from the vials and filtered through a 0.25-μm filter. The solutions were suitably diluted with methanol and assayed with a spectrophotometer at 254 nm. Results are the mean of five determinations.

3. Results

Infrared spectroscopy (Fig. 1) has emerged as the preferred method to identify the polymorphic forms of mebendazole [5,6]. In Table 1 some physicochemical properties and the main IR signals and XRPD intensities for the powders used in this study are listed. XRPD patterns were similar to those reported by Costa et al. [4]. Together with the characteristic IR-signals and data as provided in Table 1, confirmed that the three powders tested were the three polymorphs of mebendazole. The solubility of the powders in 0.03 M HCl are reported to be in the order B > C > A [4]. Similar results listed in Table 1 were obtained in this study when the solubility was measured in 0.1 M HCl at 30 °C. The mean volume particle sizes of the powders (Table 1) were approximately the same.

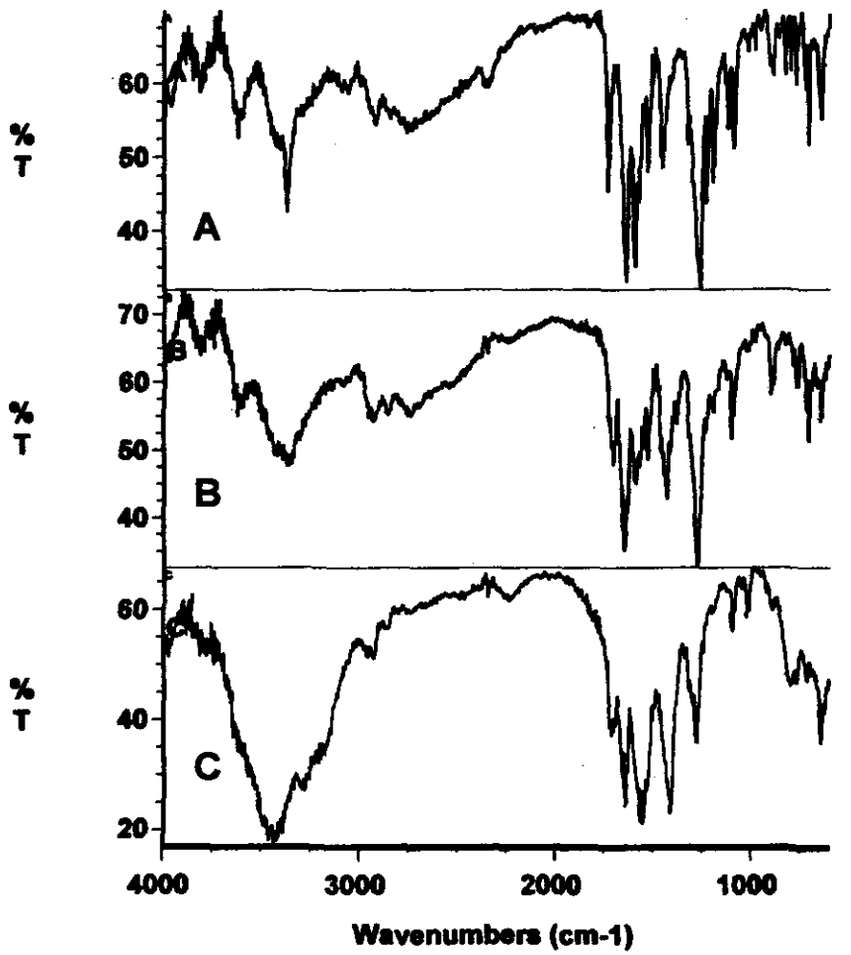

Fig. 1. FTIR spectra of the three mebendazole polymorphs.

Differences in dissolution should therefore not be due to differences in particle size. All three powders were cohesive and did not flow easily. Light microscopy (Fig. 2) revealed differences in the powder properties of the three polymorphs. Form B was a looser, freer flowing powder while the particles of form A and C were more aggregated. To eliminate the effect of particle aggregation on dissolution rate the powders were dispersed with the aid of small glass beads before it was added to the dissolution medium.

The percentage dissolved versus time for the three polymorphs, as dispersed powders with particle sizes below 10 μm, are shown in Fig. 3. According to the USP not less than 75% (Q) of mebendazole must be dissolved within 120 min. The results in Figs.

3 and 4 show that these test conditions were not able to distinguish between the solubility properties of mebendazole polymorphs. More than 75% of the polymorphs dissolved in 120 min in the USP medium, all within the USP tolerance. Form C = 100% > Form A = 98% > Form B = 94%. In 0.1 M HCl the dissolution rates were significantly lower and there were clear differences in the dissolution properties of the three polymorphs. The percentage dissolved in 120 min (Q) were in the order Form C = 70% > Form B = 37% > Form A = 20%. Compared to the USP dissolution medium in 0.1 M HCl none of the powders passed the requirement of 75% dissolved in 120 min.

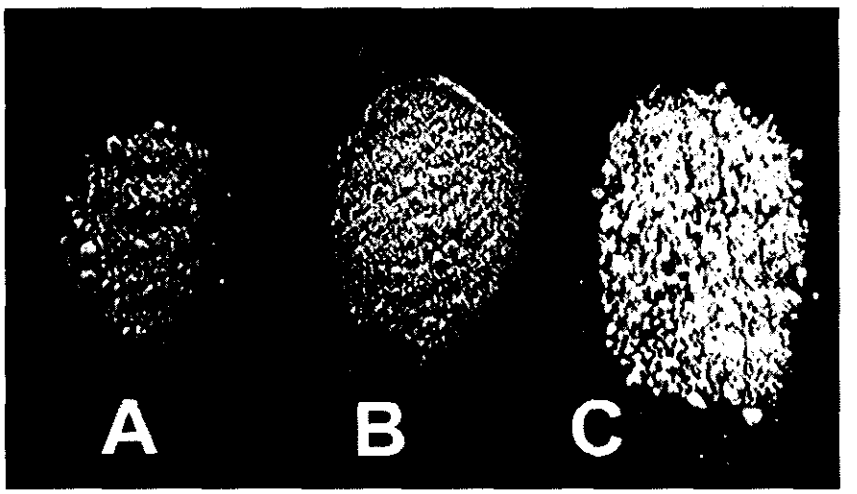

Fig. 2. Light microscope photo of the three mebendazole polymorphs.

4. Discussion

According to the USP dissolution test for mebendazole, not less than 75% (Q) of the labeled amount of the drug must dissolve in 120 min from six individual tablets, in 900 ml of a 0.1 M hydrochloric acid solution containing 1% sodium lauryl sulfate, a surface active agent. The results obtained in this study show that these test conditions were not able to distinguish between the differences in the dissolution properties of completely dispersed mebendazole polymorphs with comparable particle sizes. Solubility studies in 0.1 M HCl have shown the solubility of mebendazole to be very low (Table 1) and in the order A < C < B [4]. Since more than 75% of the polymorphs dissolved in 120 min, all within the USP

Table 1

Characteristic spectral and physicochemical properties of mebendazole polymorphs used in this study

Form	IR (cm^{-1})		XRPD		Particle size (μm)	Solubility in 0.1 M HCl (mg ml^{-1})[a]
	-NH	-C=O	d (Å)	I/I_1 (%)		
A	3370	1730	11.52	100	5.36 ± 1.54	0.02 ± 0.005
			5.13	70		
			3.84	47		
			3.11	43		
B	3340	1700	4.65	100	6.18 ± 1.72	0.07 ± 0.004
			9.36	83		
			3.62	67		
			4.11	63		
C	3410	1720	4.48	100	5.35 ± 1.02	0.04 ± 0.003
			3.32	73		
			17.91	72		
			3.59	54		

[a] Costa et al. [4].

tolerance, the dissolution properties of the powders are equal in the USP medium. Under these conditions, increased solubility, due to the presence of sodium lauryl sulfate, dominates dissolution and differences in the dissolution rate are eliminated because sodium lauryl sulfate enhanced the solubility of this poorly water-soluble drug due to wetting, micellar solubilization, and/or deflocculation. However, for mebendazole the

sodium lauryl sulfate present in the dissolution medium reduced the ability of the test to distinguish between the three polymorphic forms of mebendazole.

When sodium lauryl sulfate was removed from the dissolution medium, the percentage dissolved versus time profiles changed dramatically. Now it was clear that polymorph C went into solution faster (70% in 120 min) compared to polymorph B (37% in 120 min) and polymorph A (20% in 120 min). This order in the dissolution rate (A < B < C) does not correlate with the reported differences in solubility but does correlate with the reported in vivo effectiveness of the polymorphs [3,4,7]. This suggests that the dissolution rate of the polymorphs depended on more than just the inherent solubility of each polymorph and the degree of dispersion of the drug in the medium in which it is dissolving.

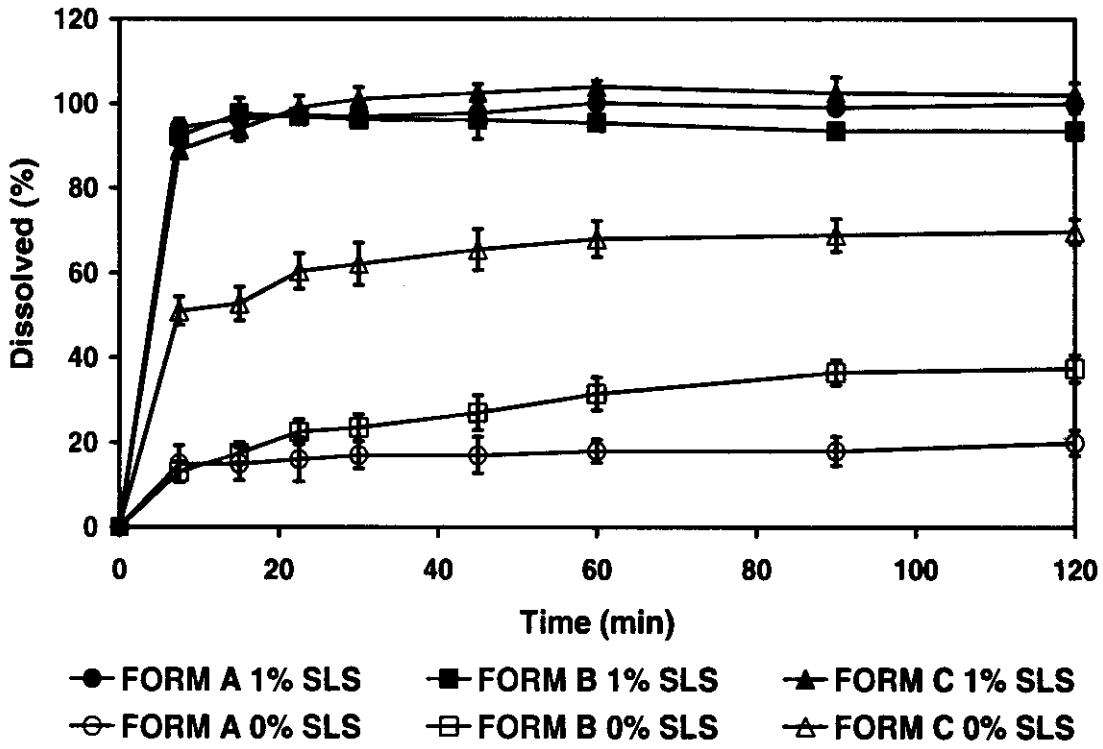

Fig. 3. Powder dissolution profiles of mebendazole polymorphs in 0.1 M HCl (open symbols) and 0.1 M HCl containing 1 % sodium lauryl sulfate (closed symbols).

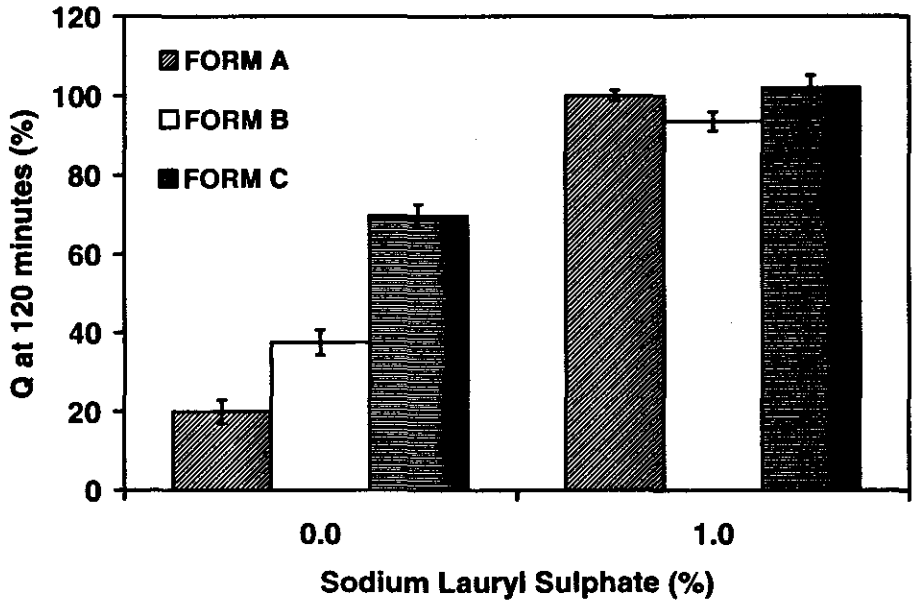

Fig. 4. Effect of 1 % sodium lauryl sulfate in the dissolution medium on Q at 120 min for mebendazole polymorphs.

5. Summary and conclusions

Manufacturers and regulatory agencies should take care when buying or sourcing mebendazole raw material, tablets or suspensions because dissolution results obtained using the USP conditions would not ensure that the products contain the preferred polymorph C. This is important, since all three polymorphic forms of mebendazole are found in the market [10]. In developing countries such as South Africa, there are numerous generic mebendazole products available and these products are widely used because the drug forms an integral part of the essential drug list in this country. Consideration should therefore be given to eliminating sodium lauryl sulfate from the dissolution medium for mebendazole because it will increase the ability of the dissolution test to discriminate between mebendazole polymorphs. Furthermore, other tests including IR analysis and X-ray powder diffractometry should also be used to ensure that the therapeutically preferred polymorph of mebendazole is present in drug products.

Acknowledgements

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PART III – Stability Requirements

CHAPTER 8

Differences between USP and BP dissolution results for oxytetracycline capsules after accelerated stability testing

E. SWANEPOEL[1], W. LIEBENBERG[1], M.M. DE VILLIERS[2]

Research Institute for Industrial Pharmacy[1], School of Pharmacy, Potchefstroom University for CHE, Potchefstroom 2520, South Africa, and Department of Basic Pharmaceutical Sciences[2], School of Pharmacy, University of Louisiana at Monroe, Monroe LA71209, USA

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The aim of this investigation was to determine whether there was any difference in the dissolution profiles of generic oxytetracycline hydrochloride capsules after storage at accelerated conditions as required in the ICH guidelines on stability testing [1]. In particular, dissolution results measured using the methods described in the USP and BP were analyzed and compared. In South Africa, oxytetracycline is identified as an essential drug with many generic equivalents available. Stability testing is performed on these products to assure their quality [2]. According to the ICH guidelines on stability testing, products must be exposed to accelerated testing at 40°C + 75% relative humidity for three months [1]. During this time dissolution testing is performed to help control the quality of drug products. There is a dissolution test for oxytetracycline in both the USP [3] and the BP [4]. These tests help to assure the consistency of the preparations with respect to its drug release properties because dissolution performance may be an indicator of potential bioavailability or bioequivalency problems [5, 6]. Various investigators have reported that commercial oxytetracycline hydrochloride capsules produced by different manufacturers, are not biologically equivalent [7, 8]. Brice and Hammer [7] performed disintegration and dissolution tests and found that, in general, batches that gave poor serum levels also had

slower in vitro dissolution rates. Further investigations [8, 9] on several samples of commercial 250 mg oxytetracycline dihydrate tablets showed that the dissolution rate varied between generic brands obtained from different manufacturers and also between and within batches from one source.

For this study six generic oxytetracycline hydrochloride capsules available on the South African market we purchased from a local pharmacy and subjected to accelerated stability conditions (40°C + 75% RH) for a period of three months. The capsules were numbered from A-F and dissolution results are the mean of three dissolution tests. Dissolution profiles were compared using a mathematical method described by Moore and Flanner [10]. The equation used to calculate the similarity factor, f_2, is

$$f_2 = 50 \cdot \log\left(\left[1 + \left(\frac{1}{n}\right)\sum_{t=1}^{n} w_t (R_t - T_t)^2\right]^{-0.5} \cdot 100\right)$$

where n is the number of dissolution time points, R_t and T_t are the reference and test dissolution values at time t, respectively, and w_t is an optional weighting factor. The value of f_2 is 100 when the test and reference mean profiles are identical. Values greater than 50 indicate that dissolution profiles are similar. There is no similarity between profiles for values less than 50. For the dissolution of oxytetracycline hydrochloride capsules the USP 24 [3] prescribes water as the dissolution medium utilizing the paddle method at a stirring speed of 75 rpm and the release requirement is that not less than 80% of the labeled amount of oxytetracycline hydrochloride should be dissolved in 60 minutes. The concentration in solution is calculated from the UV absorbance at 273 nm. The BP 2000 [4] prescribes a tolerance of not less than 70% of oxytetracycline hydrochloride dissolved in 45 minutes in 0.1 M HCl using the basket method at 100 rpm. The percentage in solution is determined from the UV absorbance at 353 nm.

After 3 months' stability testing at 40°C + 75% RH two changes were observed in the appearance of the oxytetracycline capsules. First, a change in the colour of the capsule content from yellow to brownish-yellow was seen and secondly the shells of all capsules, except product B, became sticky. However, the mean initial assay for all capsules was 104.31 ± 3.20% and after three months 102.46 ± 2.82%, all within the USP and BP specifications. The dissolution results, summarized in the Table, for all the capsules

complied with either the USP and BP dissolution specifications at time 0. At time 0 the mean dissolution profiles of capsules B and C obtained with the USP method were significantly different from that obtained using the BP method ($f_2 < 50$).

Table: Initial dissolution results compared to dissolution results obtained after 3 months at 40°C + 75% RH. Tolerance for USP is 80% dissolved within 60 minutes and BP 70% dissolved within 45 minutes

Product	USP (% dissolved within 60 min)		BP (% dissolved within 45 min)	
	Initial	3 months	Initial	3 months
A	99±5.4	88±1.2	100±1.0	104±1.4
B	96±1.7	96±2.3	105±3.7	95±4.2
C	93±0.1	67±8.5*	106±6.0	90±4.3
D	100±1.8	54±3.0*	102±2.8	102±9.8
E	100±0.8	93±3.0	105±0.5	101±3.1
F	100±0.6	99±0.8	104±1.4	102±0.6

*Products did not comply with USP tolerance

After 3 months at 40°C + 75% RH two products, C and D, failed the USP dissolution test because less than 80% of the drug dissolved within 60 minutes (Figure). In contrast after 3 months, the dissolution results for all the capsules complied with the BP specification requiring 70% of the drug to be dissolved within 45 minutes. Using the test described by Moore and Flanner [10] there was also no similarity found between the mean dissolution profiles of the capsules measured with the USP and BP methods after 3 months' accelerated storage. For the USP test, the mean dissolution profile after 3 months' accelerated storage of only capsule B was comparable to that at time 0. However, for the BP test the mean dissolutions profiles for all the products after 3 months' accelerated storage were not significantly different from that at time 0. These results show that accelerated stability testing leads to physicochemical changes in oxytetracycline capsules

and that the BP dissolution method for oxytetracycline hydrochloride capsules was not able to measure the effect of these changes on the dissolution properties of the capsules. Based on previous reports [7, 8] describing bioavailability problems with oxytetracycline capsules, relying on the BP dissolution test might lead to the acceptance of clinically unacceptable and bio-inequivalent products.

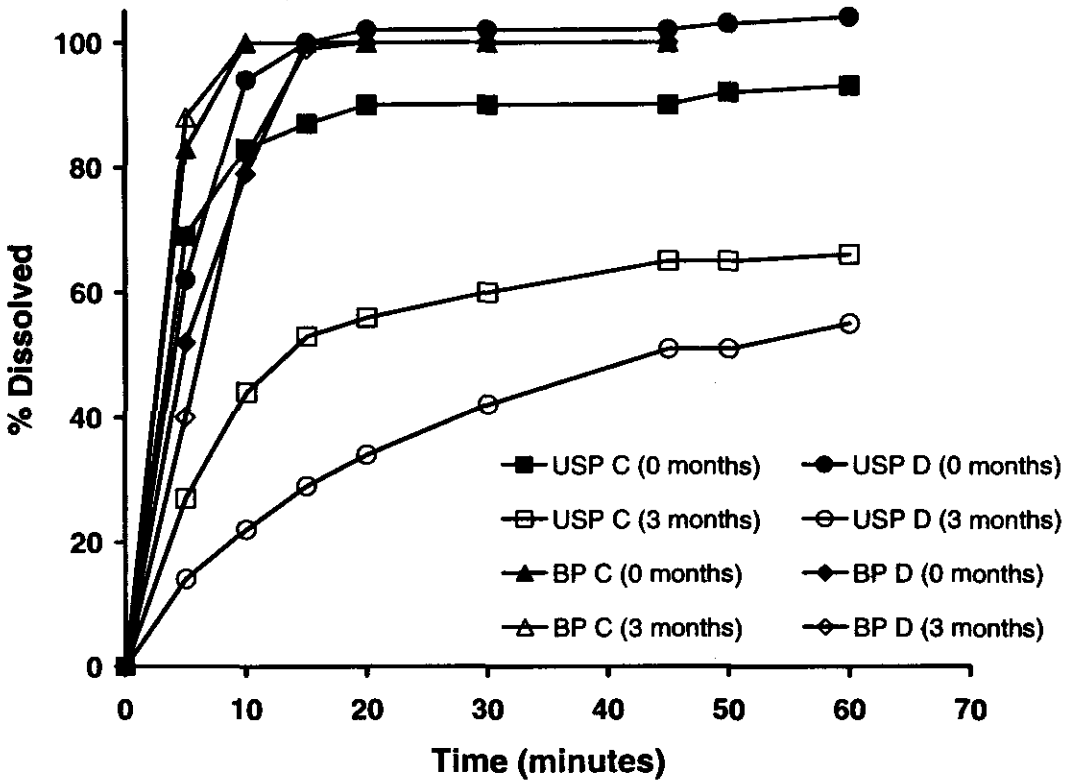

Fig.: Dissolution profiles for oxytetracycline products C and D showing the inability of the BP test to detect the decrease in dissolution after 3 months' storage at 40°C + 75% RH

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PART IV – Summary and Final Conclusions

CHAPTER 9

Summary and recommendations

Although improving the quality of drugs is a responsibility to be shared, the generic sector of the pharmaceutical industry, as the source of the majority of essential drugs, must play a critical role in improving drug quality. To ensure that this happen, awareness of quality issues should be increased among manufacturers, patients, and all cadres of health care providers. One sector often overlooked is raw material manufacturers and suppliers. The raw material market is extensive and a great choice of products is available worldwide. The quality of these materials is essential for the safety, efficacy and quality of drug products. The aim of this study was to investigate the pharmaceutical quality of generic raw materials available to manufacturers in South Africa, as well as the influence that variations in the solid-state properties of these raw materials have on the *in vitro* availability (dissolution) of these drugs.

Part I – Solid-state requirements for drug powders

The importance of drug crystal polymorphism in the pharmaceutical industry was highlighted and it is clear that in order to save time and cost it is very important to choose the most suitable form of the crystalline drug in the initial stages of drug development. Differences in physical properties of various solid forms have an important effect on the processing of drug substances into drug products. Of the variety of experimental techniques available for the characterization of polymorphic solids, X-ray powder diffraction is the most important.

Generic drugs and the manufacturing thereof are very important in a developing country such as South Africa. This implies that generic raw materials are sought after at reasonable prices. The results of 135 drug substances studied, showed inconsistent and questionable pharmaceutical quality. Crystal polymorphism was found for 15 drugs, and in 7 of these cases the powder dissolution rate was decreased due to different polymorphs. Polymorphism was also detected among the powders of 9 drugs known to exhibit polymorphism, whereas new polymorphs were detected for 6 drugs. Dissolution

problems, not related to polymorphism, were reported for 5 drug powders. New polymorphic forms for 2 drugs known to exhibit polymorphism were detected.

Part II – Dissolution requirements

Dissolution testing is continuing to grow as a critical technique applied for formulation selection, assessment of product quality and evaluation of product and process changes. Worldwide regulatory agencies and national and international pharmacopoeias are relying on this test, not only for assessment of drug products, but for relevance to *in vivo* performance. There is still much to be done to establish dissolution testing as a harmonized regulatory quality control procedure. The ICH initiative has moved significantly towards resolution of regulatory harmonization.

Dissolution problems experienced with specific generic raw materials and drug products were discussed in detail for piroxicam, oxytetracycline and mebendazole. In the case of piroxicam, poor wettability due to electrostatic behaviour of very fine piroxicam particles caused some piroxicam powders and capsules to fail the USP dissolution requirements. The could result in differences in product efficacy, as well as in potential negative side effects. A preformulation solid-state characterization of six oxytetracycline HCl drug powders combined with the evaluation of simple tablet formulations pointed out significant differences in the solubility of the powder samples. The solubility difference was attributed to different polymorphic forms among the oxytetracycline raw materials. The dissolution rate from tablets prepared with the poorly soluble powders were significantly slower. Polymorph C of mebendazole is pharmaceutically favoured, but the high concentration of sodium lauryl sulphate in the USP dissolution medium does not allow the use of this test to determine if form C is used or not. By decreasing the amount of sodium lauryl sulphate in the dissolution medium, clear differences in the dissolution rates of the three forms were observed, with 0.1 M HCl, containing no sodium lauryl sulphate, the most discriminating dissolution medium. Simply eliminating sodium lauryl sulphate from the dissolution medium would give manufacturers and regulatory agencies a simple method to ensure that mebendazole tablets and suspensions contain polymorph C.

PART III – Stability requirements

Stability testing is performed on drug products to assure their quality. According to ICH guidelines on stability testing, products must be exposed to accelerated testing at 40°C + 75% relative humidity for three months. During this time dissolution testing is performed to help control the quality of drug products. A dissolution test for oxytetracycline is included in both the USP and BP. The results obtained in this study showed that accelerated stability testing leads to physicochemical changes in oxytetracycline capsules and that the BP dissolution method was not able to measure the effect of these changes on the dissolution properties of the capsules.

Recommendations

The work done in this study only scratched the surface of the many problems with which manufacturers of generic drug products are faced. Professional judgement must be exercised in the purchase of generic drug raw materials by manufacturers, because the quality of these products tends to be jeopardized by overriding considerations of cost. To avoid these difficulties, a manufacturer of medicines must possess all the details of the origin of the starting materials and a clear audit trail for them. Therefore every plant manufacturing such products intended for pharmaceutical use, as well as the active substances, excipients and packaging involved, should employ a suitable quality management system such as GMP or the ISO 9000 series, and be regularly audited and authorized. Documentation supporting a generic pharmaceutical product should meet the following criteria: (1) manufacture (GMP) and quality control; (2) product characteristics and labeling; and (3) therapeutic equivalence. In-house manufacturers can use existing techniques such as X-ray analysis, melting point measurements and especially dissolution testing to monitor and detect variations in product quality due to changes in the solid-state properties of drugs.

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Soli Deo Gloria

ABSTRACT

Relation between solid-state properties and pharmaceutical quality of generic drug raw materials available in South Africa

Although improving the quality of drugs is a responsibility to be shared, the generic sector of the pharmaceutical industry, as the source of the majority of essential drugs, must play a critical role in improving drug quality. One sector often overlooked is raw material manufacturers and suppliers. The quality of these materials is essential for the safety, efficacy and quality of drug products. The aim of this study was to investigate the pharmaceutical quality of generic raw materials available to manufacturers in South Africa, as well as the influence that variations in the solid-state properties of these raw materials have on the *in vitro* availability (dissolution) of these drugs.

In order to save time and cost it is very important to choose the most suitable form of the crystalline drug substance in the initial stages of drug development. Differences in physical properties of various solid forms have an important effect on the processing of drug substances into drug products. Substantial inconsistent and questionable pharmaceutical quality were found among 135 drugs available on the South African market. In particular differences in crystal form, solubility and dissolution were seen.

Worldwide regulatory agencies and national and international pharmacopoeias are relying on the dissolution test, not only for assessment of drug products, but for relevance to *in vivo* performance. There is still much to be done to establish dissolution testing as a harmonized regulatory quality control procedure, although the ICH initiative has moved significantly towards resolution of regulatory harmonization. Dissolution problems experienced in this study with specific generic raw materials and drug products, namely piroxicam, oxytetracycline and mebendazole, showed that harmonization is urgently needed. Harmonization of dissolution should however not be done in isolation from other regulatory requirements, because it was found that accelerated stability testing at 40°C + 75% relative humidity for three months leads to physicochemical changes in oxytetracycline capsules and that the BP dissolution method was not able to measure the effect of these changes on the dissolution properties of the capsules.

This study shows that professional judgement must be exercised in the purchase of generic drug raw materials by manufacturers. Existing techniques such as X-ray analysis, melting point measurements and especially dissolution testing can be used by manufacturers to monitor and detect variations in product quality due to changes in the solid-state properties of drugs.

UITTREKSEL

Verband tussen die vastetoestandeienskappe en die farmaseutiese kwaliteit van grondstowwe gebruik in die vervaardiging van geneesmiddels vir die generiese mark in Suid-Afrika

Die verbetering van die kwaliteit van geneesmiddels is 'n verantwoordelikheid wat gedeel moet word. Die generiese sektor van die farmaseutiese nywerheid, as die grootste verskaffer van essensiële medisyne, kan hier 'n kritiese rol speel. 'n Sektor wat dikwels oor die hoof gesien word is die vervaardigers en verskaffers van farmaseutiese grondstowwe. Die kwaliteit van hierdie grondstowwe is essensieel vir die veiligheid, effektiwiteit en kwaliteit van farmaseutiese produkte. Die doel van hierdie studie was om die farmaseutiese kwaliteit van grondstowwe vir generiese vervaardiging in Suid-Afrika te ondersoek. Dit sluit in die invloed van variasie in die eienskappe van die vaste toestand op die *in vitro* beskikbaarheid (dissolusie) van hierdie grondstowwe, asook dié van produkte bevattende die grondstowwe.

Om tyd en koste te bespaar, is dit belangrik om op die mees geskikte kristalvorm van die geneesmiddel te besluit tydens die inisiële fases van produkontwikkeling. Die verwerking van grondstowwe in farmaseutiese produkte word beïnvloed deur verskille in die fisiese eienskappe wat deur verskille in die vaste toestand teweeg gebring word. Nie-vergelykbare en twyfelagtige farmaseutiese kwaliteit is gevind vir die grondstowwe van 135 geneesmiddels wat beskikbaar in die Suid-Afrikaanse mark is. Verskille in kristalvorm, oplosbaarheid en dissolusie was veral opmerklik.

Wêreldwyd maak beheerrade en nasionale en internasionale farmakopees staat op die dissolusietoets, nie net vir gehaltebeheer van geneesmiddelprodukte nie, maar ook vir verwysing na *in vitro/in vivo* korrelasie. Baie moet nog gedoen word om dissolusietoetsing te vestig as 'n geharmoniseerde gehaltebeheer metode, alhoewel die ICH-inisiatief reeds 'n betekenisvolle bydrae daartoe gelewer het. Probleme wat tydens hierdie studie met die dissolusie van spesifieke geneesmiddelprodukte en grondstowwe, naamlik piroksikam, oksitetrasiklien en mebendasool, ondervind is, beklemtoon opnuut dat harmonisering dringend nodig is. Laasgenoemde moet egter in samehang met ander

regulatoriese vereistes geskied, want daar is ook gevind dat versnelde stabiliteitstoetsing by 40°C + 75% relatiewe voggehalte vir drie maande, fisies-chemiese verandering in oksitetrasiklienkapsules tot gevolg gehad het. Die effek van hierdie fisies-chemiese veranderinge op die dissolusie van oksitetrasiklienkapsules kon egter nie deur die dissolusietoets van die BP uitgewys word nie.

Hierdie studie bewys dat professionele oordeel aan die dag gelê moet word by die aankoop van grondstowwe by verskaffers. Gevestigde tegnieke soos X-straalanalise, smeltpuntbepalings en veral dissolusietoetsing kan deur vervaardigers gebruik word om verandering in produkkwaliteit, wat deur veranderinge in die eienskappe van die vaste toestand veroorsaak word, te bespeur en te monitor.