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RESEARCH PAPER

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

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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 among 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.*

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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 nonsteroidal 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 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 autoimmune 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 the 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 postapproval 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 Sicifarma 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 behavior 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 Phillips 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 disks 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 disk 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 disks 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 disk 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):

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

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 more than a 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 therefore are 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).

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. 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.

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

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%.

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 disks (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 behavior 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).

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

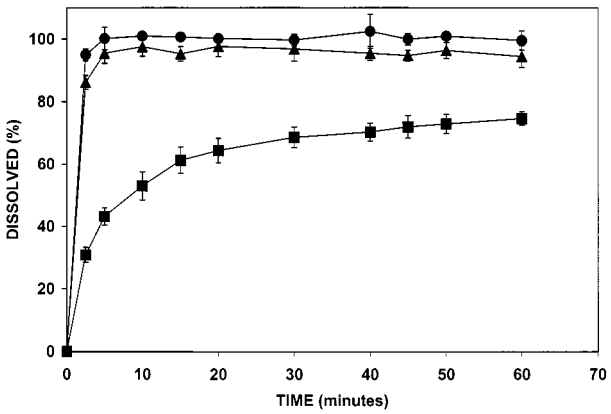

Figure 1. Powder dissolution profiles for powder 1 with and without surfactants. ●, Simulated gastric fluid without pepsin; ■, simulated gastric fluid without pepsin plus 0.05% polysorbate 80; ■, simulated gastric fluid without pepsin plus 1% SLS.

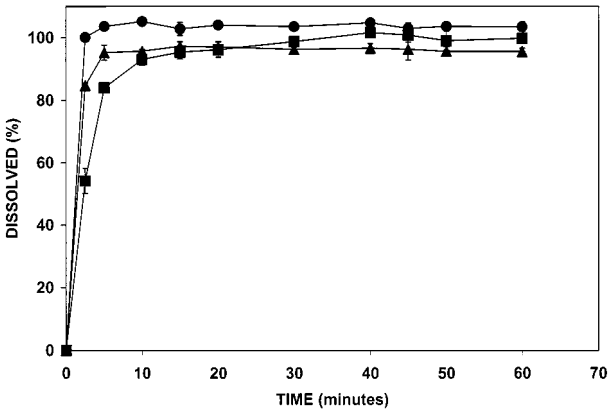

Figure 2. Powder dissolution profiles for powder 2 with and without surfactants. ●, Simulated gastric fluid without pepsin; ▲, simulated gastric fluid without pepsin plus 0.05% polysorbate 80; ■, simulated gastric fluid without pepsin plus 1% SLS (n).

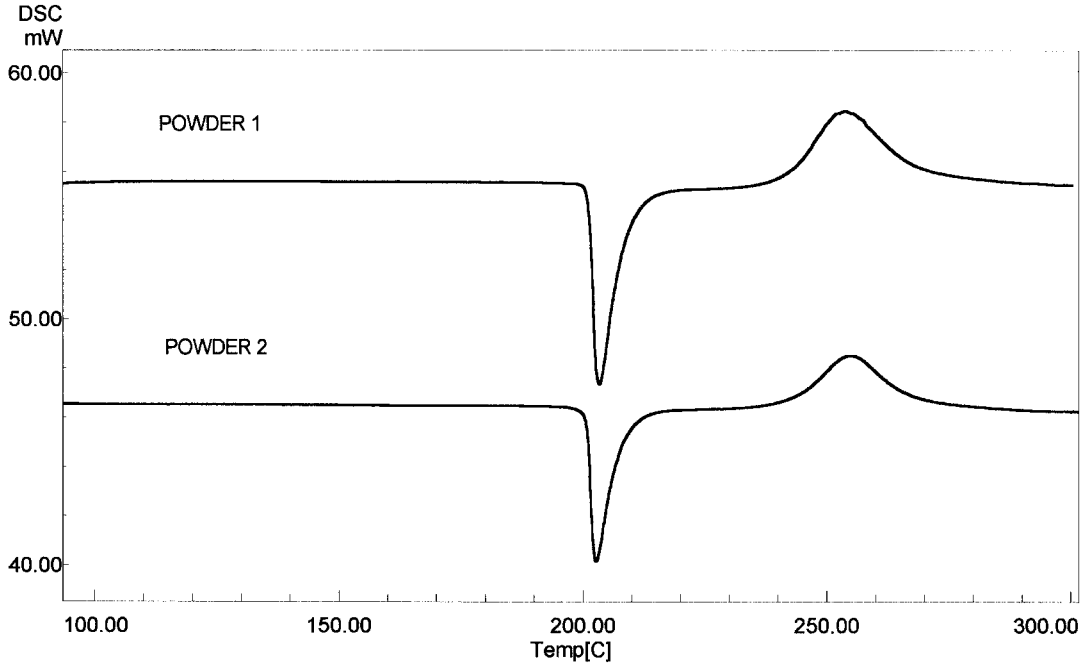

Figure 3. DSC curves of the piroxicam powders.

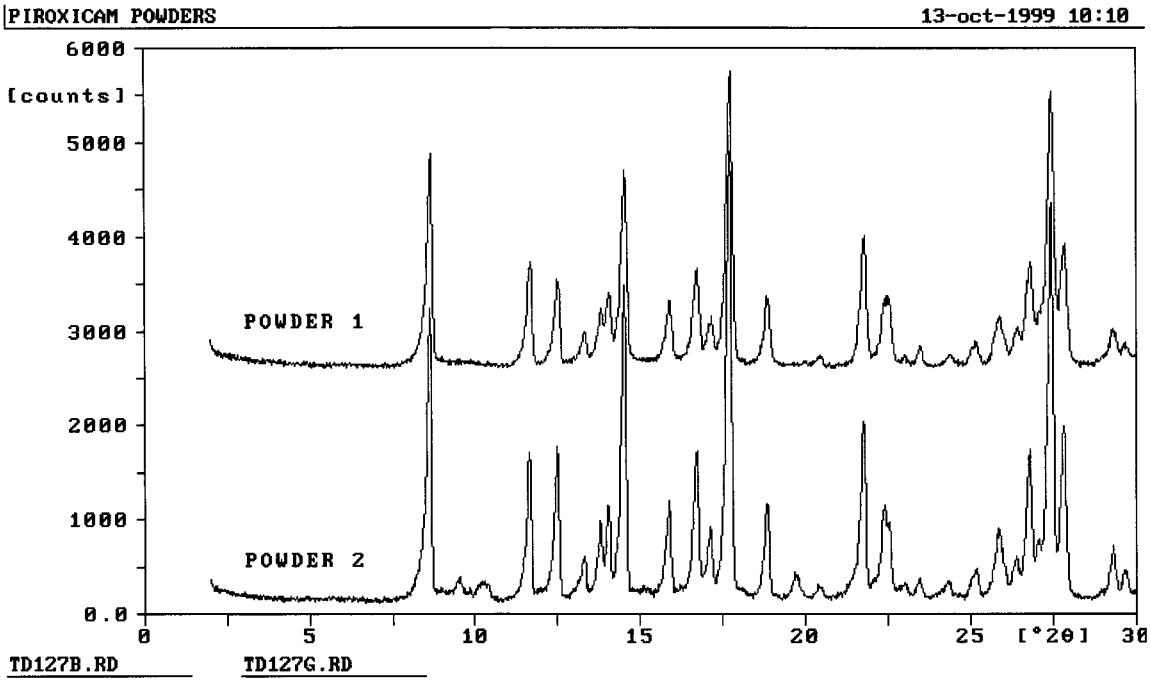

Figure 4. XRPD patterns of the piroxicam powders.

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.

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 for that influence piroxicam dissolution is the effect of piroxicam particle size and aggregation on its

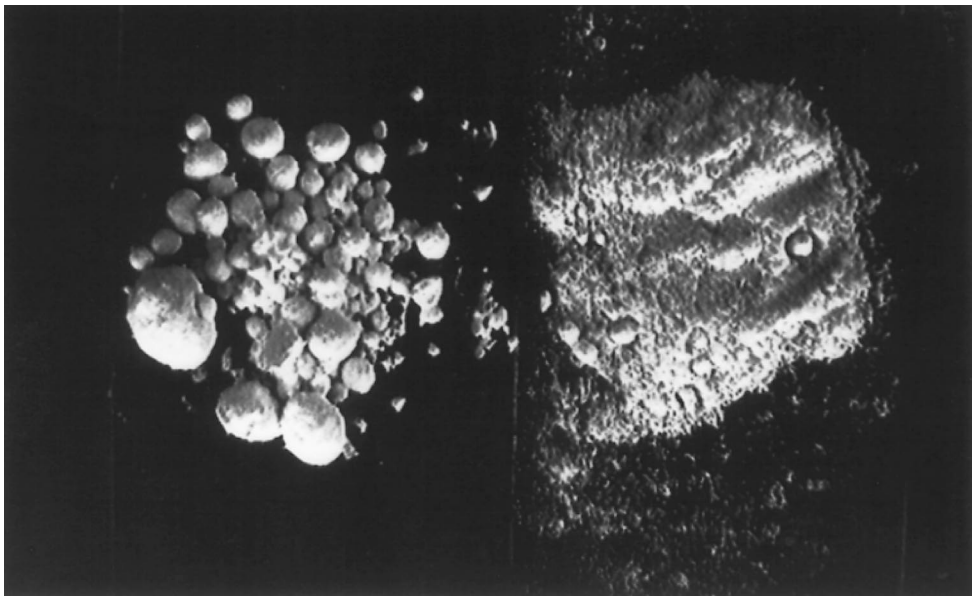

Figure 5. Photograph of the powders showing the aggregation of powder 1 on the left.

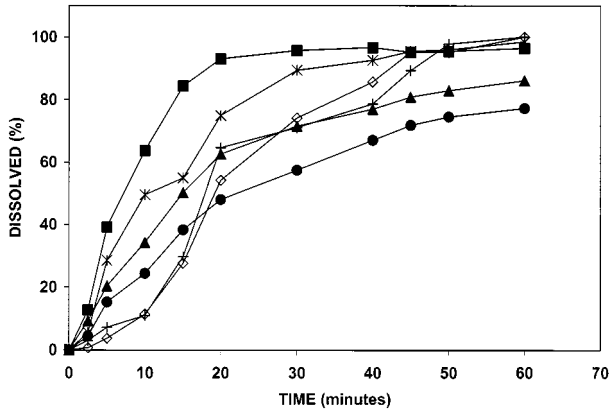

Figure 6. Dissolution profiles of piroxicam capsules in simulated gastric fluid without pepsin. ■, A; ▲, B; ●, C; ◆, D; ◊, E; +, F.

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 five 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 gelatin 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 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.

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.

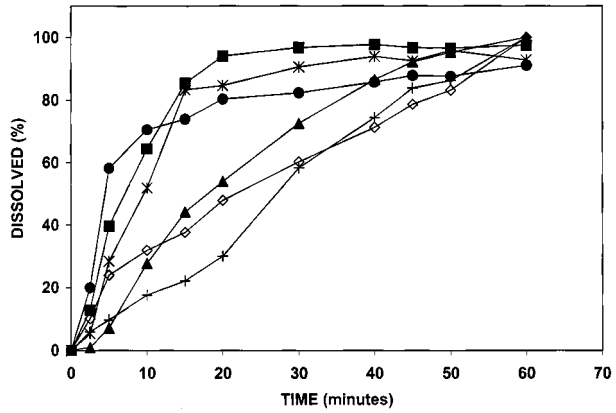

Figure 7. Dissolution profiles of piroxicam capsules in simulated gastric fluid without pepsin plus 1% SLS. ■, A; ▲, B; ●, C; ◆, D; ◊, E; +, F.

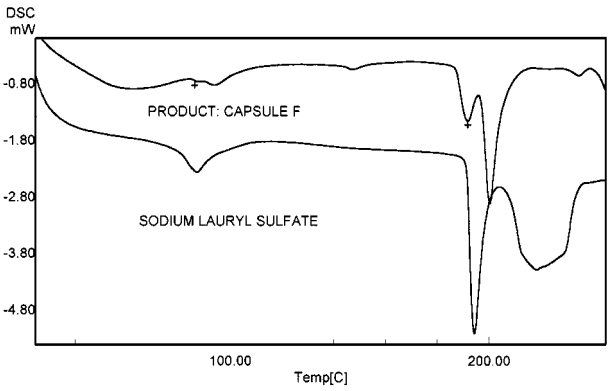

Figure 8. DSC thermograms of SLS and the capsule content of product F.

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.

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).

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

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