International Journal of Pharmaceutics, 69 (1991) 175–180

ADONIS 0378517391001273

IJP 02336

Characterization of calcium fenoprofen 2. Dissolution from formulated tablets and compressed rotating discs

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(Received 11 July 1990)
(Modified version received 1 November 1990)
(Accepted 10 November 1990)

Key words: Intrinsic dissolution rate; Rotating disc; Calcium fenoprofen; Characterization; Tablet dissolution; Crystal engineering

Summary

Calcium fenoprofen samples previously studied in powder form have been made into formulated tablets and into pure compressed discs. The wide variation in dissolution rate noted for powders is not noted in the early stages of tablet dissolution, all samples giving about the same rate in spite of variation in the disintegration rate. It is possible that smaller particles have been compressed or agglommerated to larger ones, or have been rendered hydrophobic by magnesium stearate. In later stages there is some intersample variation, apparently linked to larger particles in the parent active ingredient. Intrinsic dissolution rates from compressed discs cannot be influenced by any excipients as these are not present, or by particle size considerations as the area of the discs is constant. Rates differ only slightly after compression, and this is thought to be due to only partial retention of energetic differences following compression.

Introduction

In part 1 (Hendriksen, 1990), it was shown that crystalline fenoprofen calcium could be engineered by incorporating dopants or modifying the crystallization process, and that these modified samples exhibited dissolution rates which correlated approximately with the degree of crystallinity as determined from the heats of solution. Other workers have similarly investigated crystals of pharmaceutical (Chow et al., 1985; Chow and Grant, 1988) and other substances (Liu and Nancollas, 1976; Burt and Mitchell, 1980), but few have sought correlation between powder properties, compressed disc dissolution rates, and formulated tablet dissolution rates. Recently, Chan and Grant (1989) compared engineered crystals of acetaminophen and adipic acid in the form of powders and as compressed discs, and found that differences between acetaminophen samples almost disappeared, while differences between adipic

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acid samples persisted, though somewhat reduced. They consider that in the acetaminophen system, differences between powders were due to habit modification, which is lost in compression, but in the adipic acid system differences were due to variable crystal energetics, retained but reduced in compression. Stoltz et al. (1988) investigated solvates of oxyphenbutazone and found a similar ranking order for powders and compressed discs. In this case differences were due to different types and degrees of solvation, and one would not anticipate that compression would change the chemistry of the system.

In the present work the previously studied powders are formulated into tablets and their dissolution properties examined. However, making formulated tablets involves granulation and compression steps, as well as mixing with several formulation excipients, one or more of which could contribute to observed changes. Accordingly compressed discs were also studied, as their preparation required no granulation or mixing with excipients.

Materials and Methods

Materials

Tablets. Preparation of the batches of fenoprofen used here has been described previously (part 1), and included production materials (P8, P9), scaled-up batched modified with 0.67% ethyl acetate (S2), 1.349 M sodium chloride (S3), or slowly crystallized at high dilution (S4). Batches of fenoprofen calcium were formulated to give oval biconvex tablets, nominally 472 mg and containing 346 mg active, but weights and assays were individually determined and used. The formulation process involved aqueous granulation; two levels of water addition were employed, qualitatively referred to here as dry and wet. After drying, granules were compressed at varying pressures to give tablets of two thicknesses, thin ($\approx$ 5.22 mm) or thick ($\approx$ 5.62 mm).

Compressed discs. Active ingredient was sieved on an Alpine air-jet sieve, and the fraction below 75 μm ($\approx$ 0.24 g) was compressed on an Apex laboratory hydraulic press to a pressure of 40 bar, except batch S4 which required 85 bar to make a usable disc. No excipients were present and no lubricants were used. Each face of the disc had an area of 1.19 cm^2.

Methods

Tablet dissolution. The dissolution rates of formulated tablets were studied in a Hansen Research Corp. dissolution bath in rotating baskets (100 rpm, 37 °C). Tablets were dissolved into 900 ml of pH 7.4 buffer and the concentration with time was followed by UV absorption at 284 nm. Two measures of dissolution rate were noted. Firstly, the initial rate over the first 10 min, expressed as percent per minute. This basis was chosen rather than mg/min because of minor weight and assay variations between tablets. Typically, about half the active ingredient dissolved in the first 10 min. Secondly, to study the much slower subsequent release, the percent dissolved after 1 h was noted. Generally this was about 90–98% of the total, and thus gave a reasonable measure of the slowly-dissolving portion of the tablet.

Compressed disc dissolution. Compressed discs were fitted into purpose-made stainless-steel holders similar to those described by Nicklasson and Magnusson (1985). The holder had a centric cavity in which the disc fitted, being held in place with a small quantity of vaseline. Dissolution rates were studied in the Hansen dissolution bath (150 rpm, 25 °C) using 100 ml distilled water. Concentration with time was followed by UV absorbance at 220 nm.

Disintegration. Ten tablets of each batch were tested at 37 °C in a Manesty disintegration apparatus, and the mean result presented.

Results

Tablets

Dissolution rates of thin and thick tablets are listed in Table 1. Means of four tablets are given, with the corresponding standard deviations. Disintegration rates of the tablets and particle size distributions of the corresponding active ingredients are shown in Table 2.

TABLE 1

Dissolution rates of formulated tablets (and their standard deviations)

	Thin tablets		Thick tablets	
	Initial rate (% per min) (±SD)	% dissolved after 1 h (±SD)	Initial rate (% per min) (±SD)	% dissolved after 1 h (±SD)
S1, dry	5.6 ± 0.6	97.6 ± 2.1	6.6 ± 0.9	96.9 ± 4.2
S1, wet	6.0 ± 0.2	98.8 ± 1.7	5.8 ± 0.5	95.7 ± 2.9
S2, dry	5.6 ± 0.7	98.2 ± 2.8	6.1 ± 1.2	97.0 ± 0.8
S2, wet	5.9 ± 0.3	97.8 ± 1.8	6.0 ± 0.7	97.0 ± 1.5
S3, wet	5.9 ± 0.7	95.2 ± 2.7	5.3 ± 0.8	95.5 ± 1.9
S4, dry	5.4 ± 0.3	68.3 ± 2.9		66.1 ± 1.9
P8, dry	5.7 ± 0.9	92.8 ± 2.4	6.3 ± 1.2	90.4 ± 2.9
P8, wet	6.0 ± 0.3	96.1 ± 1.9	7.5 ± 2.9	90.6 ± 4.0
P9, dry	6.6 ± 0.5	94.2 ± 2.8	4.9 ± 0.7	91.3 ± 0.4
P9, wet	6.0 ± 0.4	93.9 ± 2.5	5.4 ± 1.0	92.5 ± 3.8

Tablet dissolution was fast during the first 10 min, commonly reaching 50% of the total. Surprisingly all tablets gave approximately equal rates during this period, regardless of the batch of active ingredient from which they had been made, and in contrast to the same batches examined as pure powders, in which substantial differences were noted. After 10 min the dissolution rates gradually declined, and after 1 h they were considerably slower, and showed some inter-sample variation.

TABLE 2

Disintegration times of formulated tablets, and particle size distributions of raw active ingredient batches from which they were made

	Disintegration (min)		Particle size distribution of active ingredient used (%)		
	Thin	Thick	> 420 μm	420–210 μm	< 210 μm
S1, dry	13.6	1.9	1	11	88
S1, wet	13.8	2.2			
S2, dry	15.3	1.5	5	34	61
S2, wet	15.8	1.9			
S3, wet	12.4	1.8	0	77	23
S4, dry	5.3	1.5	93	4	3
P8, dry	11.0	1.6	9	22	69
P8, wet	12.0	1.6			
P9, dry	10.9	1.5	10	27	63
P9, wet	9.5	1.4			

TABLE 3

Intrinsic dissolution rates from compressed discs (and their standard deviations)

Sample and brief description	Intrinsic dissolution rate (mg cm^{-2} s^{-1})($\times 10^3 \pm$ SD)
P6 (production batch)	4.96 ± 0.06
S1 (control)	5.02 ± 0.14
S2 (ethyl acetate)	5.20 ± 0.43
S3 (sodium chloride)	5.22 ± 0.22
S4 (high dilution)	3.98 ± 0.24

Centric discs

Intrinsic dissolution rates from centrically mounted rotating discs are shown in Table 3 for a selection of powdered active ingredient samples; the means and standard deviations of four results per disc are given. Intrinsic dissolution rates do not vary greatly between samples; one sample, S4, is 22% lower than the other four, which are all quite close.

Discussion

Tablet dissolution

When pure powdered fenoprofen is made into tablets it is subjected to a mixing process with several formulation excipients, a granulation with varying amounts of water (dry or wet), air-drying, and compression to various degrees (giving thin or

thick tablets). Any or all of these steps could potentially alter the original powder form. Compression force certainly influenced disintegration times; thick tablets disintegrated in about 2 min, thin tablets made with a higher compressional force understandably disintegrated over much longer periods, yet the initial dissolution rates, which must result at least in part from disintegrated particles, were not correlated with disintegration times.

The question of dissolution rates correlating with disintegration times has been commented upon by several investigators, and the overall conclusion is far from simple. Igwilo and Pilpel (1983) found correlation for lactose tablets, as did Carstensen et al. (1980) for prednisone. However, Selmeczi et al. (1981) found no correlation for acetylsalicyclic acid and neither did Chowhan (1979) for naproxen tablets. Chow and Parrott (1978) compared tablets of six actives with the same tablets pulverized and put into capsules. Some became slower, some the same, and one faster. Das and Jarowski (1979) compared granules of two actives with their corresponding tablets and found dexamethazone faster as tablets, but sulfadiazine faster as granules. Brossard et al. (1981) sought correlation with nitrofurantin tablets, and found it depended on the experimental method employed for the dissolution testing. Kitamori and Iga (1978) suggested that when powder dissolution rates are high, then disintegration directly influences tablet dissolution, but the correlation is slight if powders dissolve only slowly. Calcium fenoprofen may be considered in the latter category; even so the present absence of correlation is hard to explain.

Particle size has been shown to be a significant factor in powder dissolution studies (Kaneniwa and Watari, 1974; Hendriksen, 1990). The present initial dissolution rates of about 60 mg min^{-1} g^{-1} active ingredient, are much slower than were observed in part 1 for powdered samples at the much lower temperature of 4° C, even those of the largest sieve size tested (210–250 μm), and suggest that the moieties dissolving here are equivalent to particles considerably larger than this. The particle size distributions of the present raw active ingredient samples show considerable variation in the finest (–210 μm) fraction, from 3 to 88%, and one would have expected commensurate variation in dissolution rate unless the smallest particles were changed during one or more of the tabletting steps. As variation is not observed, small particles must have been changed, and this could be due to their having been granulated or compressed to larger entities or being rendered hydrophobic by magnesium stearate. The possible role of magnesium stearate in imparting hydrophobicity to particles is known (Dansereau and Peck, 1987; Billany, 1981), and this excipient was present at a constant level for all samples studied here.

In the later stages differences do become more apparent. The slowly crystallized sample (S4) only achieved about 67% dissolution after 1 h, in line with its slow dissolution in the form of a powder. The two production samples (P8 and P9) were somewhat slower than the pilot-scale samples (S1 and S2), also in line with their relative dissolution rates in the form of powders. However, the advantageous effects of incorporating sodium chloride (S3), or ethyl acetate (S2) are lost in the tabletting process, with S2 becoming no better than the control (S1), and S3 becoming slightly inferior to it. The particle size distributions offer a possible explanation. In the latter stages of dissolution, when less than 10% of the sample remains undissolved, it is presumably the most slowly dissolving (larger) particles which determine dissolution rate. Thus, sample S4 is by far the most coarse sample employed, and is slowest by a larger margin. A comparison of the group P8 and P9 with S1 and S2 indicate small but real differences in the levels above 420 μm, in line with the modest but real differences in their dissolution rates. This suggests that the changes upon compression influence the smaller particles much more than the larger ones.

Compressed disc dissolution

Formulated tablets introduce complicating process variables largely absent from compressed discs; in the latter case there are no excipients, no granulation or drying stages, and no disintegration. Compressed discs furthermore present a constant surface area during the timescale of the experiment. The differences observed in powder

dissolutions have largely disappeared following the compression step, as Chan and Grant (1989) found for acetaminophen and in part for adipic acid. It is worth noting that S4 had to be compressed at 85 bar rather than 40 bar in order to make usable discs. In the present work, varying the compaction pressure in the case of other batches was found not to influence the result, and others have concluded similarly for alaprociate (Nicklasson et al., 1981) and benzoic acid (Kanke and Sekiguchi, 1973).

Chan and Grant suggested habit changes between acetaminophen samples were lost upon compression. Among calcium fenoprofen samples there is no visible evidence of varying habit; all were made from aqueous environments and microscopically looked alike except for the much larger and more perfectly crystalline S4. Destruction of variable habit is probably not the cause of the present tendency to equalise intrinsic dissolution rates.

Chan and Grant further suggested that the nature, concentration and profile of the defects that determine crystal energetics, are altered but not eliminated among adipic acid samples. The energetics of most of the present samples have not been determined, but some of the closely similar laboratory samples were studied and their 'processing values', a measure of their relative crystal energetics, were reported in part 1. Thus the highly crystalline sample (S4) is expected to be the lowest in energy of the present samples, and gives the lowest intrinsic dissolution rate, while S2 and S3 are likely to be the most energetic and these give slightly higher rates. The errors involved are substantial, but there remains a possibility that the defects originally engineered into these samples as powders have persisted in small measure after compression.

The large and relatively well formed, low-energy crystals of S4 were the slowest to dissolve in powder form, as compressed discs, and in the later stages of tablet dissolution, and yet the initial stages were as rapid as other samples. The higher-energy engineered crystals (S2, S3) were particularly rapid in dissolution in powder form, yet as tablets or as discs showed little or no increase over controls. The uniformity of tablet dissolution rates in the early stages conflicts with expectations based on the particle size distributions of the parent batches, and suggests that the smaller particles have been changed by one or more of the processing steps perhaps into larger or more hydrophobic entities. Larger particles appear not to have been changed as the later stages of tablet dissolution are in line with the proportion of larger particles. The intrinsic dissolution rates, not influenced by particle size variations or by possible interaction with magnesium stearate, suggest that the influence of crystal energetics only partially survives the compression step.

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