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The influence of excipient particle size, solubility and acid strength on the dissolution of an acidic drug from two-component compacts

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Abstract

The dissolution properties of mixed compressed discs containing ibuprofen and one of three different acid excipients were investigated and the effect of various processing variables examined. Ibuprofen dissolution rate was shown to change depending on the acid excipient particle size used, the solubility of the excipient and its acid strength. Decreasing the excipient particle size resulted in a lowering of the ibuprofen dissolution rate. A decrease of an order of magnitude up to 20-fold could be achieved when smaller sized excipient particles were used. The observed dissolution phenomena associated with changing excipient particle size were explained in terms of percolation theory and dissolution from pores of a dimension similar to or larger than that of the aqueous boundary layer. It was also observed that the stronger the acid used as the excipient and the greater its solubility, the greater was its suppressing effect on the dissolution rate of the drug.

Keywords: Acid excipients; Dissolution; Ibuprofen; Particle size; Percolation theory; Pores

1. Introduction

In classical theory (Higuchi et al., 1965), the dissolution behaviour of nondisintegrating compacts of polyphase mixtures is taken to be independent of particle size. Previously we have applied this theory (with modification) to the dissolution behaviour of ibuprofen from compressed discs containing various acid excipients in different weight fraction ratios (Healy and Corrigan, 1992).

The porous layer, which develops at the surface of a two-component ibuprofen-acid excipient compressed disc as dissolution proceeds, plays an important role in determining dissolution behaviour. The structure of this porous layer will be

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Table 1
Particle size analysis of L-(+)-tartaric acid used to make 50:50 L-(+)-tartaric acid/ibuprofen compressed discs for dissolution studies

Fraction	Processing	D[v,0.5] (μm)	D[v,0.9] (μm)	D[v,0.1] (μm)
1	Sieved, <600 μm and >300 μm	a	a	a
2	Ground in an agate mortar and pestle for 10 min and then sieved <180 μm	123.39	227.76	11.94
3	Ground in MM2 mill for 30 min at 85% maximum vibrations and then sieved <40 μm	9.45	31.81	3.16
4	Ground in MM2 mill for 40 min at 90% maximum vibrations and then sieved <32 μm	7.88	29.29	2.36
5	Ground in MM2 mill for 50 min at 90% and 10 min at 95% maximum vibrations and then sieved <20 μm	b	b	b

[a]The distribution of this fraction extended out of the range of the particle sizer, which has a limit at the high end of 564 μm.
[b]The weight of fraction recovered after processing was too small for dry powder particle sizing to be performed.

affected by the properties of the two components of the compact, including their solubility, particle size and packing arrangement.

Changes in the nature of the porous layer may alter the dissolution behaviour of the components of the disc.

In the present study the effect of acid excipient particle size, acid strength (as reflected by the pKa) and solubility on the dissolution of ibuprofen from two-component discs is examined.

2. Materials and methods

2.1. Materials

B.P. grade Ibuprofen was used. All excipients and other chemicals used were of analytical grade.

2.2. Dissolution studies

2.2.1. Preparation of compressed discs

Discs were prepared by compressing 250 mg of powder in a Perkin-Elmer hydraulic press, for 10 min under 7000 kg of pressure, using a 13 mm punch and die set. Powders were mixed in an agate mortar before compression. Composition was on a weight for weight basis. Discs were coated with paraffin wax as previously described so that dissolution was from one surface only (Corrigan and Timoney, 1975) and were affixed to the base of the dissolution vessel using molten paraffin wax.

2.2.2. Dissolution medium

The dissolution medium used was phosphate buffer pH 7.35 prepared using freshly distilled water.

2.2.3. Dissolution procedure

Dissolution studies were performed using the United States Pharmacopeia (U.S.P. XXII) paddle apparatus (Vankel dissolution apparatus VK6000). The stirring speed of the paddles was set to 60 rpm and 500 ml of dissolution medium at 37 ± 0.1°C was used.

Samples (3 ml) were withdrawn at intervals and filtered through a 0.45 μm membrane filter. The volume removed was replaced with 3 ml fresh medium at 37°C.

Samples were analysed by HPLC and UV spectroscopy as previously described (Healy and Corrigan, 1992).

Results of the dissolution runs are the mean of at least two determinations.

2.3. Grinding

Particle size reduction was performed using a Retsch MM2 Mixer Mill. Stainless steel grinding jars having a volume of 25 ml were used with two stainless steel grinding balls (12 mm diameter) in the Mixer Mill.

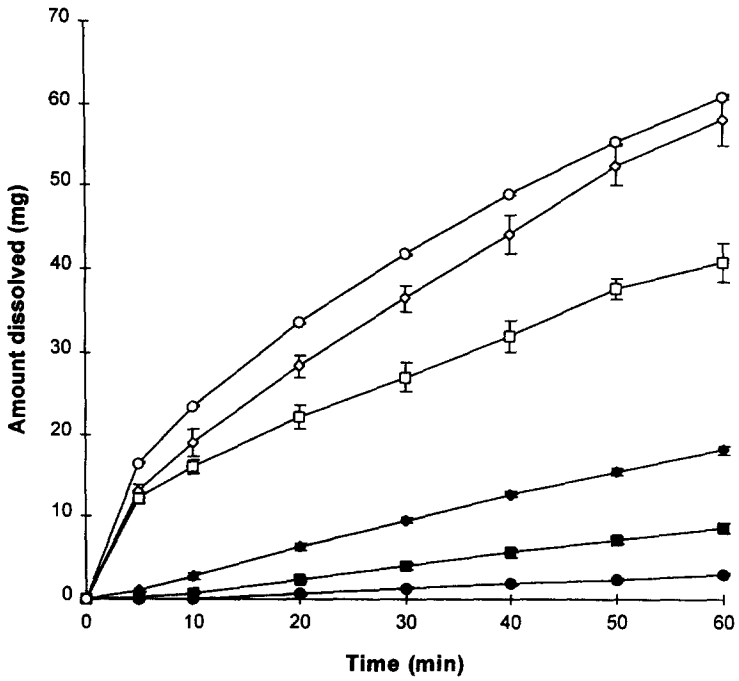

Fig. 1. The dissolution profiles of ibuprofen and L-(+)-tartaric acid from 50:50 compressed discs containing L-(+)-tartaric acid of varying particle size: Ibuprofen release from discs containing L-(+)-tartaric acid sieved between 300 and 600 μm (—◆—), ground and sieved <180 μm (—■—) and ground and sieved <40 μm (—●—); L-(+)-tartaric acid release from discs containing L-(+)-tartaric acid sieved between 300 and 600 μm (—◇—), ground and sieved <180 μm (—□—) and ground and sieved <40 μm (—○—).

2.4. Sieving

Sieving was performed using Endecotts (BS 410) hand held sieves (aperture sizes 600, 300 and 180 μm) or using an Alpine Air Jet sieve with fines collecting filter (with Haver and Boecker sieves of aperture sizes 20, 32 and 40 μm).

2.5. Particle sizing

Dry powder particle sizing of all powders was performed using a Malvern 2600c laser diffraction particle size analyser with a dry powder feeder attachment. A 300 and/or a 100 mm lens was used. Results quoted (percent undersize) are the average of at least three determinations.

The D[v,0.5] is the median diameter of the volume distribution of particles, the D[v,0.1] is the diameter at the 10% point in the distribution and the D[v,0.9] is the diameter at the 90% point in the distribution.

2.6. X ray diffraction

X-ray diffraction (XRD) patterns were obtained using a Siemens D500 x-ray powder diffractometer. Powdered samples were studied by placing a thin packed layer of a finely ground powder on a glass slide.

2.7. Differential scanning calorimetry

Differential scanning calorimetry (DSC) was performed using a Mettler DSC 20 standard cell, TC10A TA processor and associated software. The sample weight used was between approximately 3 and 7 mg. The heating rate was 10°C/min over a range which included the melting point of the drug. Nitrogen gas flowed over the aluminium crucible containing the sample.

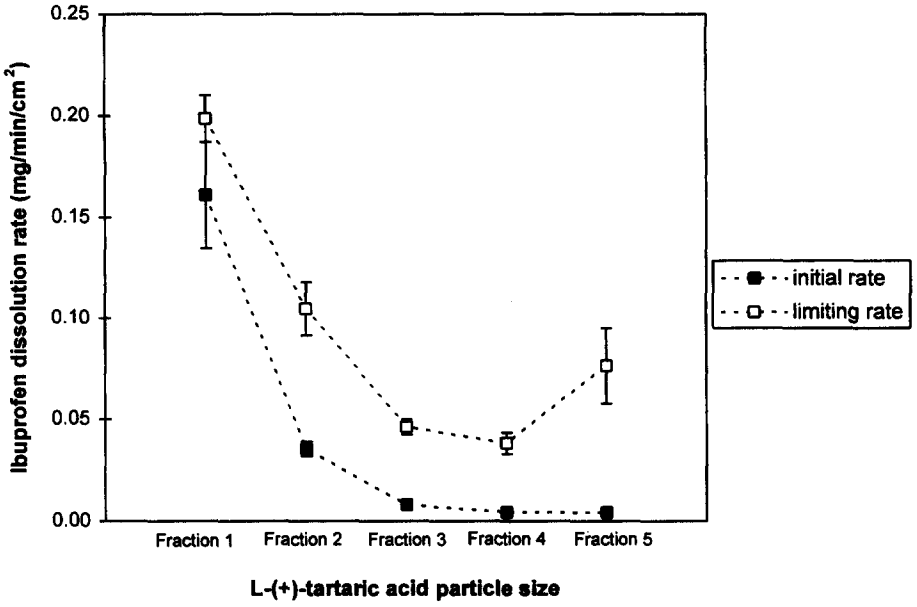

Fig. 2. Initial and limiting dissolution rates of ibuprofen from 50:50 L-(+)-tartaric acid/ibuprofen compressed discs containing L-(+)-tartaric acid of varying particle size (as listed in Table 1).

2.8. Melt formation

Adipic acid and ibuprofen were melted in a 10 ml beaker and subsequently cooled by lowering the beaker into liquid nitrogen. Adipic acid (the component with the higher melting point) was melted first and ibuprofen was then added to the beaker. The mixed melt solidifies on cooling.

2.9. Statistical techniques

Statistical analysis of results was performed using Microsoft Excel 4.0 for Windows. Statistical significance was tested using t-tests. A significant difference was assumed when $p < 0.05$.

3. Results

3.1. The effect of changing excipient particle size on ibuprofen dissolution from two-component compacts

Profilometry studies previously performed on 50:50 L-(+)-tartaric acid-ibuprofen discs clearly illustrated the development of pores at the disc surface as dissolution proceeded (Healy et al., 1995). The size of the pores formed may influence the dissolution properties of the second component of the disc and is likely to depend on the particle size of the excipient used.

Particle sizing of the powders used to make the discs showed that there was a large difference in the size of the two powders. The D[v,0.5] for ibuprofen was 11 μm, while that for L-(+)-tartaric acid was 123 μm.

The effect of reducing the particle size of L-(+)-tartaric acid was investigated to see if a change in L-(+)-tartaric acid particle size would result in altering the dissolution properties of the second component of a mixed disc, i.e. ibuprofen.

All discs examined were made from 50:50 mixtures of ibuprofen and L-(+)-tartaric acid and were subject to a single compression period. In contrast to earlier work where a double compression process was used, in the present study a single compression process was used for all discs since the double compression process could in itself alter particle size.

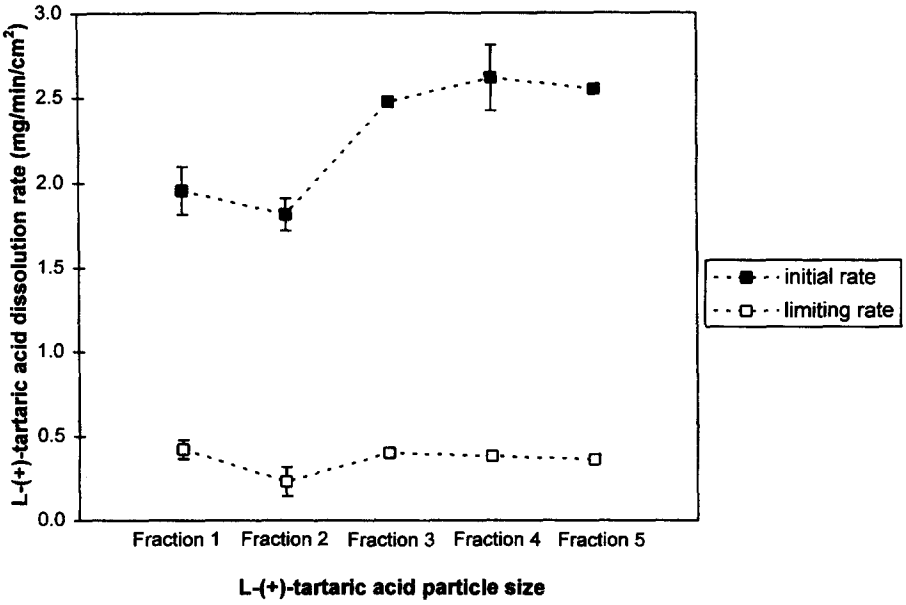

Fig. 3. Initial and limiting dissolution rates of L-(+)-tartaric acid from 50:50 L-(+)-tartaric acid/ibuprofen compressed discs containing L-(+)-tartaric acid of varying particle size (as listed in Table 1).

L-(+)-tartaric acid fractions of varying particle size were obtained by sieving or by grinding and sieving. Results of the particle size analysis of the powder fractions obtained are given in Table 1.

Fig. 1 shows the average dissolution profiles of ibuprofen and L-(+)-tartaric acid from discs made using L-(+)-tartaric sieved between 600 and 300 μm, sieved <180 μm or sieved <40 μm.

The initial (calculated at the 5 min sampling time point) and limiting (60 min) dissolution rates for ibuprofen dissolving from each of the 50:50 compressed discs studied are shown in Fig. 2. Fig. 3 shows the corresponding dissolution rates for L-(+)-tartaric acid.

A systematic decrease in ibuprofen dissolution rate was seen with a decrease in the particle size of the acid excipient.

There was approximately a 20-fold difference between the initial dissolution rates of ibuprofen dissolving from discs containing the largest L-(+)-tartaric acid particle size and those containing acid excipient sieved <40 μm. There was a 4-fold difference in limiting dissolution rates.

In our previous study (Healy and Corrigan, 1992) of mixed ibuprofen-acid excipient discs it was noted that the ibuprofen dissolution rate was decreased in the presence of acid excipients and that suppression of dissolution increased with increasing concentration of acid excipient in the disc. The dissolution profiles obtained showed that the greater the weight fraction of acid excipient in the disc, the greater was the amount of excipient dissolved at a particular time. Also, the greater the extent of excipient dissolution, the lower was the amount of ibuprofen in solution at a given time.

It was expected therefore that acid excipient dissolution would be highest from the discs from which ibuprofen dissolution was lowest and vice versa. However as shown in Fig. 1 no obvious trend was seen. Although L-(+)-tartaric acid dissolution was highest from the discs containing acid excipient of the smallest particle size fraction (<40 μm), it was lowest from the discs containing the middle size fraction of excipient (<180 μm). There was no significant difference at any time point between L-(+)-tartaric acid dissolution from discs containing either L-(+)-tartaric

Table 2
Particle size analysis of succinic acid used to make 50:50 succinic acid/ibuprofen compressed discs for dissolution studies

Fraction	Processing	D[v,0.5] (μm)	D[v,0.9] (μm)	D[v,0.1] (μm)
1	Sieved, <600 μm and >300 μm	a	a	a
2	Ground in an agate mortar and pestle for 10 min and then sieved <180 μm	59.13	194.51	7.24
3	Ground in MM2 mill for 30 min at 85% maximum vibrations and then sieved <40 μm	13.58	39.68	3.54
4	Ground in MM2 mill for 15 min at 90% maximum vibrations	16.93	146.51	2.86

[a]The distribution of this fraction extended out of the range of the particle sizer, which has a limit at the high end of 564 μm.

sieved between 300 and 600 μm or sieved <40 μm (Fig. 1).

When the acid excipient particle size was decreased further (i.e. <32 and <20 μm) there was no significant further reduction in ibuprofen dissolution rate. Similarly, there was no significant difference in the acid excipient profiles from discs containing excipient <40, <32 and <20 μm.

With a view to ascertaining if the effect of particle size of excipient on dissolution is common to other acid excipients used previously (Healy and Corrigan, 1992), the dissolution properties of mixed discs of ibuprofen-succinic acid and ibuprofen-adipic acid were investigated. The particle sizing details of the various acid excipient fractions used are shown in Tables 2 and 3.

Again, it was observed that the smaller the particle size of the acid excipient, the lower was the dissolution rate of ibuprofen from the disc.

It is interesting to note that, in the case of the ibuprofen-succinic acid system, dissolution was lowest from the discs containing succinic acid which was simply ground and not sieved. Although this fraction had a higher D[v,0.9] and D[v,0.5] than the fraction which was ground and sieved <40 μm, its D[v,0.1] was lower. Thus, there was a greater volume of smaller particles in this fraction than in the sieved fraction.

There was approximately a 9-fold difference between the initial dissolution rates of ibuprofen from discs containing the largest succinic acid particle size and those containing the smallest acid excipient particle size (as reflected by the D[v,0.1]). There was a 3-fold difference between the limiting rates.

As was the case with the L-(+)-tartaric acid/ibuprofen discs, dissolution profiles of the acid excipient showed the greatest amount of succinic acid to be dissolved at any time when either the largest or smallest succinic acid particle size was used. Dissolution of the excipient was greater in the case of discs made using fraction 1, 3 or 4, than when succinic acid <180 μm was used (fraction 2).

In the case of the ibuprofen-adipic acid systems there was an approximate 4-fold difference between the initial dissolution rates for ibuprofen dissolving from discs made using the largest and smallest particle size fractions of excipient. There was no real difference seen between the limiting rates however.

As was the case with the L-(+)-tartaric acid/ibuprofen and succinic acid/ibuprofen discs, acid excipient dissolution was greatest from discs containing the smallest excipient particle size.

3.1.1. Dissolution from adipic acid/ibuprofen melt

With a view to forming a more intimate mix of the two-component system, a melt was prepared.

XRD and DSC showed the form of adipic acid to remain unchanged on melting and resolidification. Ibuprofen also remains unchanged on melting and cooling. The similarity of the X-ray diffraction pattern and DSC trace for the 50:50 adipic acid/ibuprofen melt and a mechanical mix of similar composition showed that no change appears to have occurred on melting.

Unlike adipic acid, differences were seen in the X-ray diffraction patterns and DSC traces of both L-(+)-tartaric acid and succinic acid melts com-

Table 3
Particle size analysis of adipic acid used to make 50:50 adipic acid/ibuprofen compressed discs for dissolution studies

Fraction	Processing	D[v,0.5] (μm)	D[v,0.9] (μm)	D[v,0.1] (μm)
1	None, i.e. used as supplied by manufacturer	180.98[a]	380.12[a]	43.86[a]
2	Ground in an agate mortar and pestle for 10 min and then sieved <180 μm	135.50	206.10	63.50
3	Ground in MM2 millfor 30 min at 85% maximum vibrations and then sieved <40 μm	11.27	35.33	2.13

[a]The distribution of this fraction extended slightly out of the range of the particle sizer, which has a limit at the high end of 564 μm. The diameter values obtained are therefore underestimates (as the distribution is expressed as % undersize).

pared to the original powders. Hence dissolution from mixed melts of these acids with ibuprofen was not examined.

A 50:50 adipic acid/ibuprofen melt was prepared, ground, and sieved through a 40 μm sieve. The fraction <40 μm was used to prepare compressed discs. The dissolution profiles of ibuprofen and the acid excipient were compared to the profiles obtained from discs prepared from a 50:50 mechanical mix of the two components. The adipic acid used in the mechanical mix was ground and sieved <40 μm.

Ibuprofen dissolution profiles were similar. This indicates, as was seen with the L-(+)-tartaric acid/ibuprofen systems, that there is a particle size of excipient below which further particle size reduction does not lead to changes in drug dissolution rate. The adipic acid profiles were found to be significantly different at all except the 5 min time point.

3.2. The effect of excipient solubility and acid strength on ibuprofen dissolution from two-component compacts

The dissolution rates of ibuprofen from discs containing different acid excipients which were similarly sized (i.e. ground and sieved <180 or <40 μm) are compared in Figs. 4 and 5. The pKas and solubility of each of the acid excipients is shown in Table 4. The dissolution rate is seen to decrease in general with increasing acid excipient solubility and acid strength (reflected by a low pKa value). For example, there is approximately a 6-fold difference in the initial ibuprofen dissolution rates between discs containing adipic acid <40 μm and L-(+)-tartaric acid <40 μm. When the excipient used is sieved <180 μm the difference is 4-fold.

4. Discussion

It was seen from the dissolution studies described above that dissolution of ibuprofen from mixed acid excipient/ibuprofen compressed discs was lowered when the particle size of the acid excipient was reduced. Dissolution of the acid excipient was increased when either very small (<40 μm) or very large (300–600 μm) particles were used as compared to discs which contained acid excipient <180 μm.

The behaviour of these binary systems may be qualitatively explained on the basis of percolation theory.

The surface area of excipient exposed to the medium at each moment can be considered to be the sum of all the sections corresponding to the pores where the excipient is being dissolved.

The acid excipient surface exposed initially to the medium will be similar regardless of particle size.

The use of smaller particle sizes however, will result in the easier formation of an infinite cluster of the substance (Caraballo et al., 1993). Thus, the compacts prepared with acid excipient <40 μm will contain a more consistent infinite cluster with fewer isolated pockets of these particles. As the excipient dissolves from one surface, uninterrupted connecting porous pathways will extend inwards towards the other surface. Hence, all of the acid excipient present in the disc will be made available for dissolution.

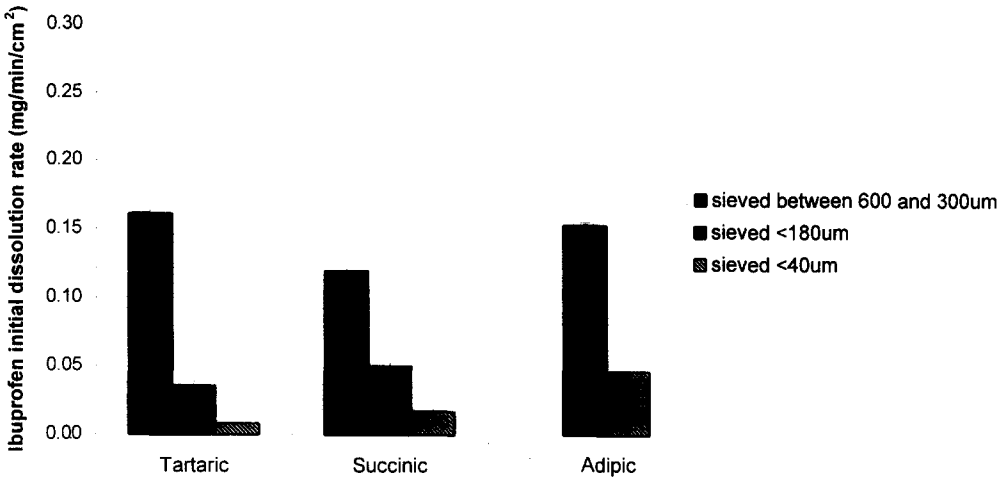

Fig. 4. Changing initial dissolution rates of ibuprofen with changing acid excipient and excipient particle size.

In the case of larger particle size excipient (e.g. < 180 μm), this component of the system may be below its percolation threshold, i.e. it ceases to have an infinite cluster. Where a component is below its percolation threshold, it ceases to span the whole system and isolated clusters will exist which will not be available for dissolution. Thus dissolution may be incomplete. In a binary mixture such as this, the substance which has the greater particle size needs a higher volume fraction to percolate the compact (Caraballo et al., 1994).

If the acid excipient is of a very large particle size however (e.g. 300–600 μm), as it dissolves, pores with a large cross-sectional area should be produced. Consequently, solvent access and the diffusion process are facilitated. In this manner, solvent inside the pores is far from the saturated state and dissolution is also facilitated (Caraballo et al., 1993). In the case of smaller excipient particle size in contrast, pores will have a smaller cross-sectional area and saturation conditions will be achieved more readily.

Thus, systems containing the largest and smallest particle size excipient appear to show the greatest dissolution for this component. This may be due either to the formation of percolating infinite porous pathways (in the case of smallest excipient particles) or because of undersaturation of the pores and facilitated solvent penetration (in the case of largest excipient particles).

What must now be considered is how the dissolution of the acid excipients influence the dissolution profile obtained for ibuprofen.

Although there was no significant difference in excipient dissolution profiles between discs containing a very large (300–600 μm) and a very small (< 40 μm) particle size of excipient, the corresponding ibuprofen profiles were significantly different.

If the particle size of the acid excipient is much larger than that of the drug, there will be fewer particles per unit volume acid excipient in the mix with the result that large areas of ibuprofen particles may be non-adjacent to dissolving acid excipient and be less affected by the retarding influence of the excipient on solubility and dissolution. On the basis of percolation theory, as the acid excipient (receding component) dissolves and this front moves inwards, the composition of the surface exposed to the dissolution medium may be significantly different from that found initially. In the case of mixtures containing large acid excipient particle size, because there is a smaller number of spanning porous networks formed by the dissolution of the excipient, large areas of ibuprofen surface may be non-adjacent to a porous pathway opening and so remain less exposed to the dissolv-

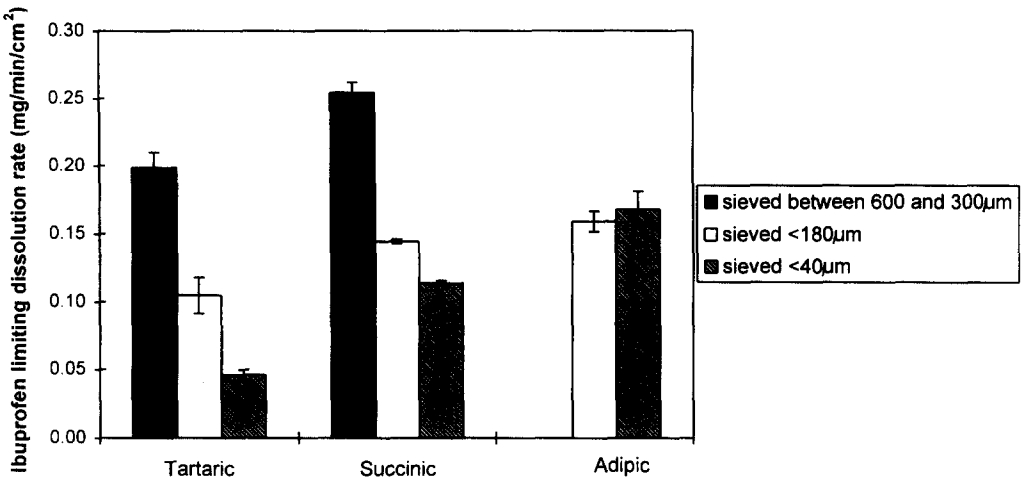

Fig. 5. Changing limiting dissolution rates of ibuprofen with changing acid excipient and excipient particle size.

ing acid. When acid excipient with a smaller particle size is used, since there are a greater number of interconnecting porous pathways, the chances of ibuprofen being exposed to the full retarding effects of the dissolving acid is increased.

Thus, the smaller the acid excipient particle size, the more uniform is the suppressing effect of the acid excipient on ibuprofen dissolution at the disc surface. The likelihood of there being areas of ibuprofen at the surface which will remain unexposed to the suppressing effect on dissolution of the acid excipient is decreased and the ibuprofen dissolution rate is reduced.

A second factor which may influence ibuprofen dissolution is that the presence of non-percolating clusters in the disc will result in the porous layer being thicker at any particular time than if all the excipient was present as an interconnecting network.

If the porous layer thickness in the case of discs containing the smaller acid excipient particle size is smaller at any particular time than those containing larger particles, the result will be that the acid excipient concentration at the disc surface will be greater and ibuprofen dissolution will be lowered relative to dissolution from discs containing bigger excipient particles. Differences in porous layer thickness depending on excipient particle size have previously been demonstrated using non-contact laser profilometry (Healy et al., 1995). Various roughness parameters, which reflect the surface microstructure, can be calculated using this technique. The roughness parameter, R_{tm}, which may be related to the thickness of the surface porous layer suggested a thicker porous layer at a particular time in the case of discs containing the larger excipient particles.

It was noted that there appeared to be a lower limit of acid excipient particle size, below which further reduction in size did not produce any significant change in ibuprofen dissolution. For example, in the case of L-(+)-tartaric acid/ibuprofen 50/50 discs, the dissolution of ibuprofen from discs containing L-(+)-tartaric acid sieved < 180 μm was significantly different to that from discs containing L-(+)-tartaric acid sieved < 40 μm, however, no further significant suppression of ibuprofen dissolution was achieved by using excipient which was sieved < 20 μm. In the case of adipic acid-ibuprofen systems, the dissolution properties of discs prepared from the melt were similar to those prepared from a mechanical mix where the excipient particle size was < 40 μm.

On the basis of classical theory (Higuchi et al., 1965) it is assumed that ibuprofen will only dissolve from the surface of the disc. As dissolution proceeds however, and acid excipient recedes from the surface, porous channels extend from the surface towards the disc centre. It has been suggested (van der Graaff et al., 1979) that if the

Table 4
The dissolution rate of ibuprofen form 50:50 discs in relation to acid excipient solubility, acid strength and particle size

Acid excipient	Solubility(mg/ml)[a]	pK_{a1}^{b}	pK_{a2}^{b}	Particle size	Ibuprofen dissolution rate (mg/min/cm^2)	
					5 min	60 min
Adipic acid	49.4	4.418	5.412	<40 μm	0.0462	0.1677
				<180 μm	0.1530	0.1590
Succinic acid	134.6	4.207	5.635	<40 μm	0.0170	0.1138
				<180 μm	0.0499	0.1444
L-(+)-tartaric acid	875.3	2.930	4.230	<40 μm	0.0080	0.0461
				<180 μm	0.0354	0.1047

[a]Measured in phosphate buffer pH 7.35 at 37°C in the presence of excess ibuprofen (Healy and Corrigan, 1992).
[b]In water at 25°C (Dean, 1992; Merck, 1989).

diffusional pathlength within a pore becomes comparable or larger than the pathlength in the diffusion layer, the diffusion layer can be visualised as being curved within the pore, leading to an increased area for dissolution and thus an increased dissolution rate. de Blaey and van der Graaff (1977) found that, in the case of sodium chloride discs, with increasing porosity, the dissolution process proceeded faster than predicted on the basis of the diffusion-convection model. This was explained by assuming an increased effective dissolution surface.

Thus, if pores develop in the disc surface, due to acid excipient dissolution, which are of a width comparable or larger than the diffusion layer, ibuprofen may dissolve from the pore walls and the dissolution rate will be greater than expected. If only pores which are smaller than the diffusion layer are present, they will be filled rapidly with a saturated solution of ibuprofen and the effective dissolution surface then equals the outside dimension of the disc (exposed to the dissolution medium).

Therefore, the number of pores of a dimension equivalent to, or greater than, the diffusion layer will play an important role in determining the dissolution of the surface component of the disc. The dissolution from pure ibuprofen discs (dissolving from one surface only) was used to determine the thickness of the diffusion layer. A value of 59×10^{-4} cm was calculated.

Thus, particles of excipient greater than or equal to 59 μm in diameter can, on dissolving, leave behind pores of a similar dimension and dissolution of ibuprofen from the pore walls may lead to an increased dissolution rate for this component.

5. Conclusions

The dissolution properties of an acidic drug in a two-component compact containing an acidic excipient can be altered, dramatically in some cases, by changing the excipient particle size or the nature of the excipient.

Dissolution results from discs where the size of the acid excipient particle was altered showed that the smaller the excipient particle size used, the lower was the dissolution rate of ibuprofen. Suppression of ibuprofen dissolution increased with increasing acid excipient solubility and acid strength. The use of an excipient of high solubility, high acid strength and low particle size maximises the suppression of dissolution of the acidic drug.

It has been shown that the excipient particle size used is a critical determining factor in the dissolution rate of the ibuprofen and that by decreasing this particle size the ibuprofen dissolution rate can be lowered.

Possible explanations for the effect of reducing the acid excipient particle size on ibuprofen dissolution may be summarised as follows:

(1) The larger the excipient particle size, the less uniform will be the suppressing effect of the excipient on ibuprofen dissolution from the disc surface. Areas of ibuprofen which are not adjacent to dissolving excipient particles may be less affected by the pH lowering effect of the excipient.
(2) When larger excipient particles are used, more isolated clusters of excipient will tend to exist within the compact. The presence of non-percolating clusters in the disc will result in the porous layer being greater at any particular time than if all the excipient was present as an interconnecting network. Thus the concentration of acid excipient at the surface will be lower and suppression of drug dissolution will not be as pronounced.
(3) The larger the excipient particles, the more pores will develop at the surface of a dimension equal to or larger than the diffusion layer thickness. Ibuprofen dissolution from the surface of these pores may lead to an increased dissolution rate.

The effect of changing excipient particle size is one which should be considered in the manufacture of solid dosage forms. The particle size of the active ingredient is commonly subject to tight control. The results reported here however suggest that it may be necessary to impose similar controls, in certain instances, on the particle size of the excipient(s) used. Differences in excipient particle size may be responsible for observed but unexplained batch to batch variability in, for example, the dissolution behaviour of tablets.

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