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Preparation and characterisation of sustained-release ibuprofen-cetostearyl alcohol spheres

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Summary

Spherical ibuprofen-cetostearyl alcohol matrices were prepared using a technique involving melting and suspension of drug-containing cetostearyl alcohol in an aqueous medium. The resulting emulsion was cooled under rapid stirring to produce the spheres. Release of ibuprofen from the pellets was modelled using standard drug-release equations. Numerical fits indicate that the contracting sphere model (the cube root equation) was the most appropriate one for describing the complete release profiles. Within the range of drug release rates of 20–80% the model was indistinguishable from the Higuchi square root of time model. Using the slopes from the latter model, the effects of drug loading, particle size and stirring speed during the preparation of the pellets were investigated. Differential scanning calorimetry was used to explain some unusual observations and it was shown that eutectic formation between ibuprofen and cetostearyl alcohol may account for the unusually high ibuprofen release rates from pellets containing ibuprofen, at levels close to the eutectic composition.

Introduction

Non-steroidal anti-inflammatory agents are among the most widely used therapeutic drugs. However, their use has often been marred by a relatively high incidence of adverse drug reactions, notably, gastro-intestinal problems (Fowler, 1987; Cook, 1988). To minimise direct irritant effects, acidic non-steroidal anti-inflammatory drugs (NSAIDs) are often formulated as buffered systems (Li Wan Po, 1990) or as sustained-release dosage forms (Lanza et al., 1980; Ranlov et al., 1983). The work in this paper investigates the design of a sustained-release oral solid dosage formulation of ibuprofen. Matrix systems were chosen rather than reservoir systems because of the ease of manufacture and because of the relatively high loading doses required. For a poorly soluble drug this latter requirement usually leads to bulky dosage forms particularly with respect to reservoir systems.

In this report the preparation, characterisation and drug release kinetics of ibuprofen from cetostearyl alcohol-ibuprofen spheres are described.

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Materials and Methods

Ibuprofen was obtained from Ciba-Geigy (U.K.), cetostearyl alcohol from Thornton & Ross Ltd (U.K.), citric acid monohydrate GPR grade and hydrochloric acid (Convol®) from BDH (U.K.), and potassium chloride GPR grade and disodium hydrogen orthophosphate dodecahydrate GPR grade from May & Baker (U.K.).

Preparation of ibuprofen-cetostearyl alcohol spheres

The required amount of cetostearyl alcohol was melted in a water bath at 100 °C. On cetostearyl alcohol becoming molten, ibuprofen was stirred into it to obtain a homogeneous melt. This mixture was then added to 200 ml of heated (65 °C), acidified, deionised water agitated continuously at a predetermined speed of either 600, 800 or 1200 rpm. The whole mixture, contained in a 11.5 × 7.3 cm stainless-steel beaker, was agitated at the required speed for 5 min using a Heidolph RZR 50 stirrer with a stainless-steel rotor fitted with a four-bladed impeller of approx. 45 mm diameter. The height of the stirrer base was set at a distance of 3 cm from the base of the metal beaker. After 5 min, the beaker was cooled rapidly to below 5 °C by draining out of the hot water in the bath and replacing it with iced water. The temperature of the dispersion was monitored during this cooling stage by placing a temperature probe (Porter type K thermometer PE 8013) in the dispersion. With constant stirring the cooling stage normally took about 4 min. The resultant hardened spherical particles were filtered, washed, air dried and fractionated by sieving before storage in an air-tight desiccator. The formulations used are shown in Table 1.

TABLE 1

Formulations of ibuprofen pellets

Formulation No.	Ibuprofen loading (% w/w)	Weight of ibuprofen (g)	Weight of cetostearyl alcohol used (g)
1	10	1.0	9.0
2	20	2.0	8.0
3	30	3.0	7.0
4	40	4.0	6.0
5	50	5.0	5.0
6	60	6.0	4.0

Sieve analysis of ibuprofen-cetostearyl alcohol spheres

A sieve shaker (Pascal Engineering Co. Ltd, U.K.) and a set of BP test sieves of size range 45–1000 μm (Endecotts Ltd, U.K.) were used. Approx. 8–10 g of spheres were placed on top of a nest of sieves stacked from bottom to top in ascending order of aperture size and mounted on the mechanical shaker. The shaker was set to tap for 10 min as it rotated. The weight of spheres on each sieve was measured and the size distribution determined.

Particle density determination by liquid displacement

Initially, the weight of 50 ml of 0.1 M HCl was determined in a tared 50 ml density bottle. 0.1 M HCl was used to minimise any possible dissolution of ibuprofen. Approx. 1 g of unfractionated ibuprofen-containing cetostearyl alcohol spheres was accurately weighed (Sartorius 2006 MP four decimal place balance, Baird & Tatlock, U.K.) and placed in a previously tared density bottle via a glass weighing boat. The bottle was filled with 0.1 M HCl at room temperature and then stoppered, taking care not to crush any pellets and to exclude any air bubbles by gentle agitation. The exterior of the density bottle was dried carefully to remove excess liquid and then weighed. This determination was performed at least five times for each ibuprofen loading in the range 10–50% w/w. From the weight of the pellets used and the weight of 0.1 M HCl displaced, the density of the pellets at each ibuprofen loading could be calculated. The 50 ml density bottle was modified by glucing a nylon mesh of 125 μm mesh size to the surface of the stopper but ensuring that the capillary bore of the stopper was not sealed. Thus, excess liquid was allowed to flow out while the pellets were prevented from escaping.

Calculation of the specific surface area of spheres

For cetostearyl alcohol pellets produced at 600 rpm whose densities at various drug loadings were determined, the surface area per unit weight

can be calculated by assuming the mid-point of a size fraction to be the mean size:

$$\text{mean specific surface area} = 3/\rho r \quad (1)$$

All symbols are defined in the Glossary (see p. 113).

Scanning electron microscopy

The shape and surface characteristics of the pellets used were examined and photographed using a scanning electron microscope (Jeol JSM 35 CF, Japan). The pellets were held in place by tapping the particles lightly onto double-sided adhesive tape, mounted on aluminium stubs. These were then sputter coated with gold (Edwards S150 model, U.K.) with a reduced coating time. These samples were examined at suitable magnifications using a voltage of 7 kV to minimise heat generation.

Thermal analysis using differential scanning calorimetry

A differential scanning calorimeter (Perkin-Elmer model DSC4-TADS, U.K.) equipped with a computerised data station was used to examine the samples. The sample size varied between 3 and 8 mg and was accurately weighed to ± 0.2 mg on a micro-force balance (Mark 2B, CI Electronics, U.K.). All heating sequences were carried out at a rate of 5 °C/min, from 33 to 80 °C, purging continuously with nitrogen at 20 p.s.i. pressure. No thermal effects were observed after 80 °C and 33 °C was the lowest temperature attainable with water as the cooling medium for the sample holder. After heating, the sample was cooled at a rate of 320 °C/min. The endotherm was analysed to obtain enthalpy values and melting points. Triplicate runs were performed on each sample to check for reproducibility and consistency of the thermograms. Individual pure components of the matrix were investigated and various ibuprofen-cetostearyl alcohol mixtures were subjected to thermal changes for phase diagram construction.

Drug release studies

The dissolution apparatus used was a continuous automated system equipped with four 1-l perspex flat-bottomed flasks with clip-on baskets. The baskets were covered at the sides with nylon mesh, of 125 μm mesh size, held by silicone O-rings (Millipore Ltd, U.K.) and sealed at the bottom with parafilm to prevent the pellets from leaking out of the baskets and floating to the surface of the dissolution medium. The drive assembly consisted of four spoke wheels and a chain system driven by a variable-speed motor (Heidolph model RZR 50) mounted above a perspex water-bath equilibrated at 37 ± 0.5 °C by a Tempette Junior TE-8J (Techne, U.K.) thermostated water heater. The automated part was a Copley (U.K.) set-up consisting of an Apple IIe computer, TDS software, an Epson LX86 printer, a peristalic pump and a UV spectrophotometer.

Weighed quantities of pellets equivalent to 60 mg ibuprofen were placed in the baskets which were then lowered into 1000 ml of McIlvaine's citrate-phosphate buffer of ionic strength 1 M and pH 6.7. The buffer was previously warmed and maintained at 37 °C. The baskets were spun at a rate of 100 rpm and the absorbance of the ibuprofen released was recorded automatically at predetermined time intervals at a wavelength of 230 nm. All release experiments were carried out in quadruplicate for each sample.

Results and Discussion

Preparation of ibuprofen-cetostearyl alcohol spheres

The method used in this study, involving cooling-induced solidification of the oily phase of a two-phase system, was first patented by Yamamoto and Baba (1960) (cited in Draper and Becker, 1966). Despite its flexibility, this method has received relatively little attention in the literature. Kowarski et al. (1964) and later, Draper and Becker (1966), used this method for preparing sustained-release sulphonamide formulations. Modifications of the two phases have led to the production of micropellets of both water-soluble and insoluble drugs (Kawata et al., 1986; Das and Gupta, 1988). Kawashima et al. (1981) used a modified spherical agglomeration technique. In their method drug, pretreated to increase its affinity for the molten phase, was added during the heating process. In our study, with

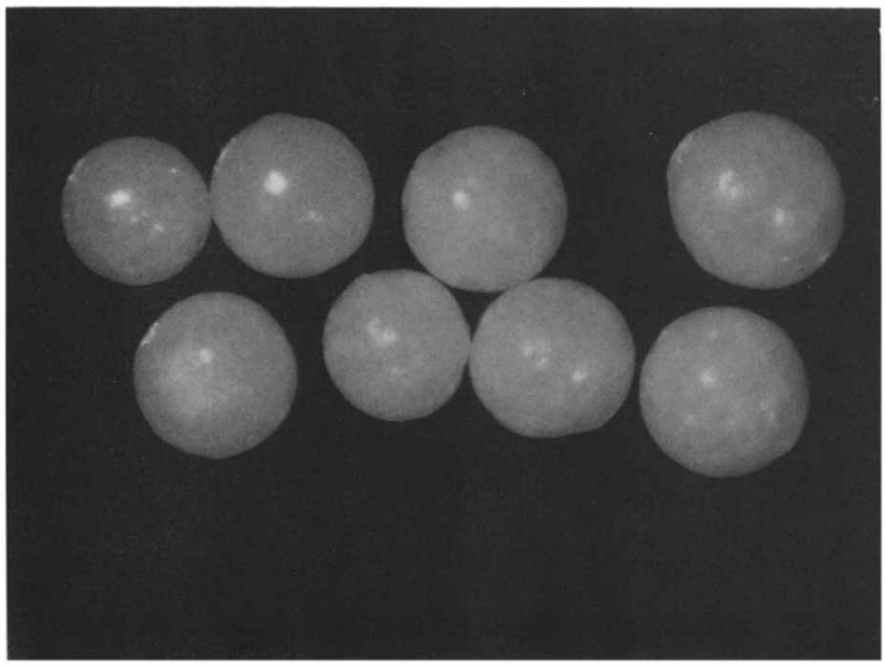

Fig. 1. Photomicrograph of ibuprofen-cetostearyl alcohol pellets.

ibuprofen-cetostearyl alcohol mixtures, it was found that the maximum ratio of drug to carrier was approx. 6:4. Higher proportions of ibuprofen led to the formation of droplets which aggregated during the cooling process. This in turn produced irregular matrices which were deemed unsuitable

TABLE 2

Size distribution of ibuprofen containing cetostearyl alcohol pellets by sieve analysis

Speed of stirring used (rpm)	Ibuprofen loading (% w/w)	Slopes from plots of Z score vs				Overall mean size (μm)	Overall standard deviation (μm)
		Log observed weight		Observed weight			
		Slope	$\%r^2$	Slope	$\%r^2$		
600	10	2.35	89.0	0.25	90.0	423.3	177.0
	20	1.70	95.3	0.57	91.7	406.9	119.9
	30	1.92	96.0	0.49	88.0	306.0	98.8
	40	2.27	97.1	0.59	90.8	308.5	106.8
	50	1.71	97.6	0.48	92.1	315.4	95.4
	60	1.52	96.2	0.45	87.4	309.7	89.6
1200	10	1.10	89.6	0.14	90.5	272.4	105.5
	20	2.70	98.2	0.68	90.5	310.9	114.1
	30	2.32	87.2	0.83	99.1	278.0	114.0
	40	1.73	81.6	0.62	96.9	241.0	75.6
	50	2.79	98.7	0.53	88.8	268.1	79.3

for our purposes. Within the range of stirring speeds and drug:carrier mixtures listed in Table 1, satisfactory spherical pellets were obtained (Fig. 1).

Very little importance has been given to the effect of the rate and method of cooling on the properties of drug matrices. McGinity et al. (1983) found that the rate of cooling of melt dispersions influenced the crystallinity of both drug and carrier. It is well known that with crystallisation the size of the crystals formed is a function of the rate of cooling. Generally, when cooling is slow, larger crystals are formed than with rapid cooling. Release rates are therefore usually faster with rapidly cooled particles because of the increased surface area. In the cooling stage, during the preparation of pellets, a drop in temperature from 65 °C to less than 5 °C was achieved within 4 min. The temperature-time profile shows non-linear cooling with an initial large temperature drop. The rate of cooling from 65 to 30 °C, the temperature range in which all the solid components would have separated out, is similar for all the samples and batches.

Characterisation of spheres

The spherical pellets (Fig. 1) produced were shiny and appeared glassy especially when hydrated.

The pellet sizes produced by this technique were up to 1000 μm. The normal scores of observed weight and log observed weight were plotted against the corresponding observed weight or log observed weight to ascertain the type of distribution. The size distribution of the pellets followed neither normal nor log normal distribution particularly well (Table 2). For the majority of the samples prepared at 600 rpm, the log normal probability fit appeared to give a better straight line, indicating that the pellets' size distribution more closely approximated the log normal than normal distribution. The mean size and standard deviation for each sample is calculated from the sieve analysis data and tabulated in Table 2. The standard deviations which define the spread of distribution are very large.

The most obvious factor influencing the size distribution is the stirring rate used during the manufacture of the pellets, although changes in rate cooling and geometry and dimensions of the production vessel could also result in a difference in size distribution. The effect of agitation speed on the mean size of the pellets is exemplified by the cetostearyl alcohol pellets containing 10% w/w ibuprofen. Increasing the stirring speed from 600 to 1200 rpm, as expected, decreased the average size of pellets from 423 to 272 μm. This effect can also be observed for all drug loadings by comparing the overall mean size of pellets produced at 600 and 1200 rpm in Table 2. Increasing the stirring rate also reduced the spread of the size distribution. The relationship between the mean size of the pellets and the speed of agitation is not linear. Kawashima et al. (1981), using a modified aqueous dispersion method, observed a sharp decrease in average particle size for a certain stirring speed range after which the size decreased only gradually and slowly. Babay

TABLE 3

Density of cetostearyl alcohol pellets at various ibuprofen loadings

Ibuprofen composition (%)	W_d/W_t [a]	Density of pellets (g/cm^3)	W_b/density (cm^3) [b]
10	0.1	0.8809 ± 0.0088	10.22
20	0.2	0.8952 ± 0.0053	8.94
30	0.3	0.9205 ± 0.0055	7.60
40	0.4	0.9441 ± 0.0044	6.36
50	0.5	0.9895 ± 0.0084	5.05

[a] W_d/W_t: fraction of drug in the pellets.
[b] W_b: weight of wax used.

et al. (1988) also observed a similar trend when the stirring speed was increased in the production of empty Eudragit RL® microspheres.

The size of the pellets is also dependent on the interfacial tension, the viscosity and density of the molten droplets dispersed in the aqueous phase. There is very little difference in the mean size of the pellets with drug loadings in the range 30–60% w/w made at 600 rpm (Table 2). At this speed the mean sizes of pellets containing 10 and 20% w/w ibuprofen are significantly greater than those containing 30–60% w/w ibuprofen. This trend, however, is not observed with pellets produced at 1200 rpm. Batches of pellets, prepared at the same ibuprofen loading and stirring speed, were reproducible in terms of mean pellet size.

Density and specific surface area of spheres

The densities of the pellets were determined and are presented in Table 3. The specific surface areas for these pellets were calculated from Eqn 1 and are tabulated in Table 4. It is observed from Table 3 that, as the composition of ibuprofen increases, the density of the pellets increases. The density of pellets with a 1:1 ratio of ibuprofen/cetostearyl alcohol is 0.9895 g/cm^3. The density (ρ) of pellets and (W_d/W_t), the ratio of weight of ibuprofen to the total weight, can be related according to the equation: $W_d/W_t = 1 - kW_b/\rho$. It is predicted from that derivation that a plot of the fraction of drug in the pellet (W_d/W_t) against weight of wax (W_b) used, divided by the density of pellets (ρ), should reflect a linear relationship with a slope equivalent to $-(3/(4n\pi r^3))$, the constant k. Fig. 2 shows that, using experimental data, a straight line is obtained for the pellets as predicted.

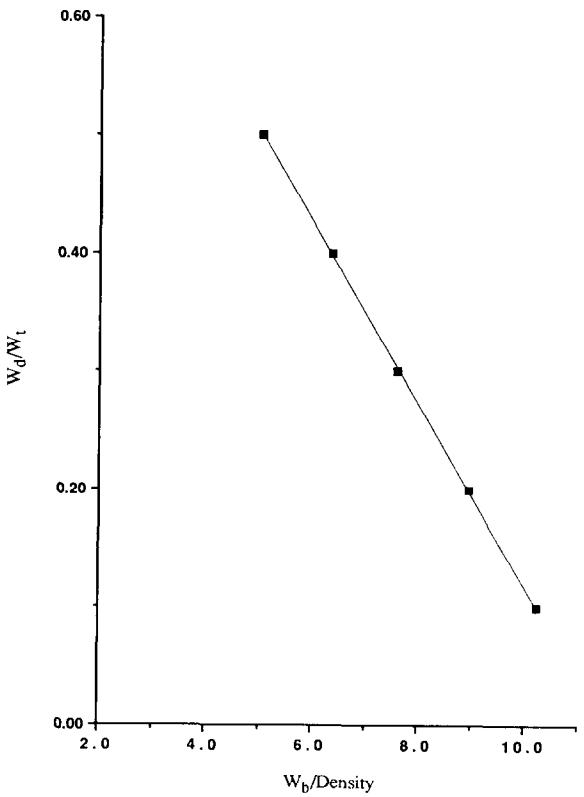

Fig. 2. Relationship between ibuprofen loading and density of cetostearyl alcohol pellets where W_d/W_t is the fraction of drug in the pellets and W_b is the weight of wax used.

Release characteristics of ibuprofen from the spheres

Using 30% w/w ibuprofen-loaded cetostearyl alcohol pellets of various sizes as an example (Fig. 3), it can be seen that the release of ibupro-

TABLE 4

Specific surface area of ibuprofen-loaded cetostearyl alcohol pellets made at 600 rpm

Ibuprofen composition (% w/w)	Density of pellets (g/cm^3)	Surface area per unit weight at various mean diameters of pellets (cm^2/g)						
		855 μm	605 μm	427.5 μm	302.5 μm	215 μm	135 μm	45 μm
10	0.8809	79.7	112.6	159.3	225.2	316.8	504.5	1513.6
20	0.8952	78.4	110.8	156.8	221.6	311.7	496.5	1489.4
30	0.9205	76.2	107.7	152.5	215.5	303.2	482.8	1448.5
40	0.9441	74.3	105.0	148.7	210.1	295.6	470.8	1412.3
50	0.9895	70.9	100.2	141.8	200.5	282.0	44.9	1347.5

fen is sustained. For sizes greater than 500 μm in diameter, complete release is in excess of 15 h. For sizes between 180 and 500 μm, complete release is achieved in 15 h. Even for pellets with a size range of 90–180 μm release occurred over a period of 7 h.

Kinetics and mechanism of ibuprofen release

Mathematical modelling of drug release is important for elucidating release mechanisms and for making predictions about the release behaviour of the system. For non-disintegrating non-porous uniform planar matrices, Higuchi

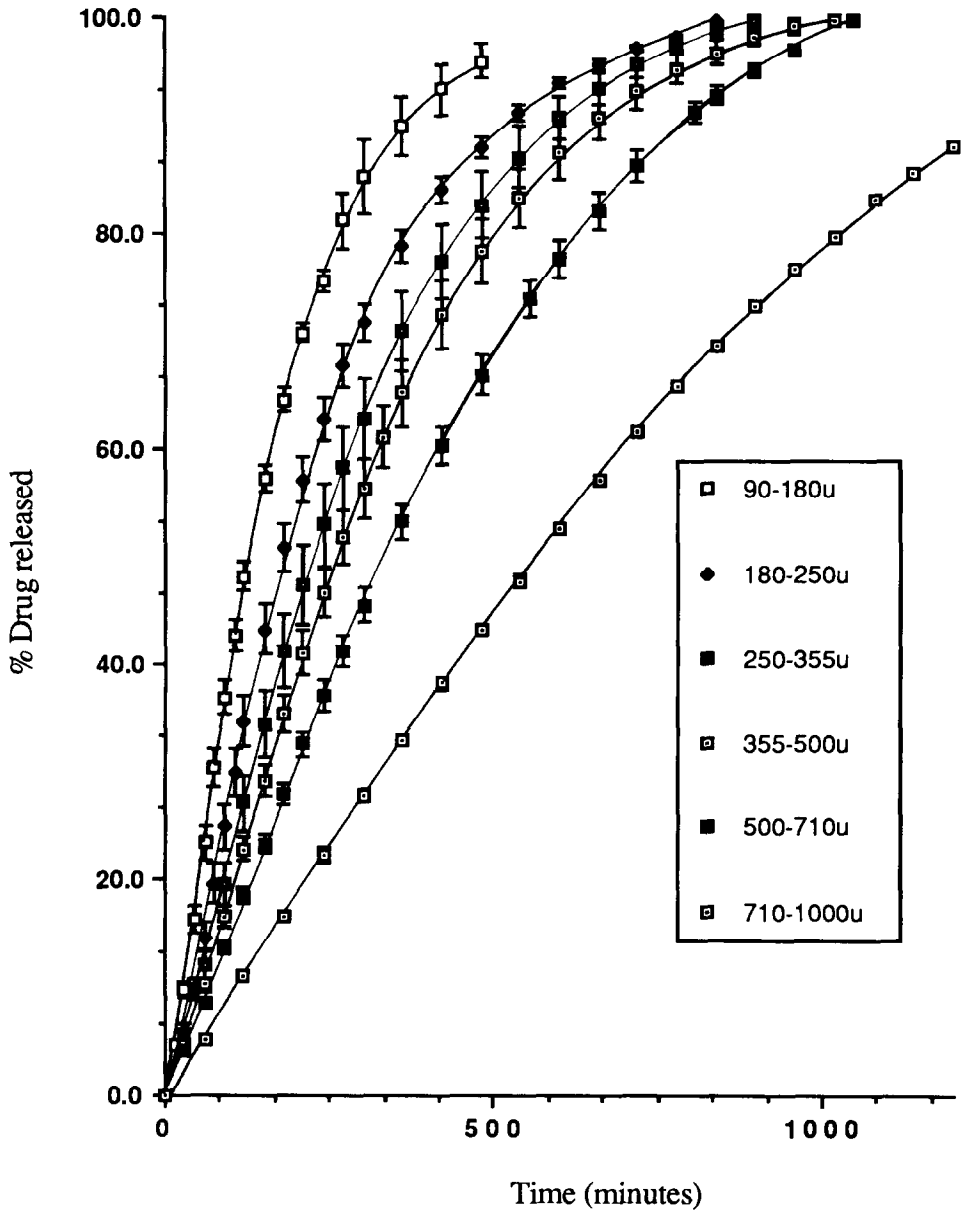

Fig. 3. Release of ibuprofen from 30% w/w ibuprofen-loaded cetostearyl alcohol pellets of various sizes and produced at 600 rpm.

(1963) presented a simple diffusional model for dispersed drug.

$$M_t = A[DtC_s(2C_0 - C_s)]^{1/2} \quad (2)$$

Although Higuchi's $t^{1/2}$ model relates to a planar system, it has been used frequently as a general empirical model for describing drug release from suspension matrix systems irrespective of their geometrical shapes. Higuchi (1963) has further proposed an equation for modelling drug release from homogeneous spherical suspension matrices and is expressed by Baker and Lonsdale (1974) as

$$\frac{3}{2}\left[1 - \left(1 - \frac{M_t}{M_\infty}\right)^{2/3}\right] - \frac{M_t}{M_\infty} = \frac{3DC_s t}{r^2 C_0} \quad (3)$$

Cobby et al. (1974) have also expressed drug release from homogeneous spherical suspension matrices in the form of a polynomial equation with $t^{1/2}$ as the predictor variable.

$$\frac{M_t}{M_\infty} = k_1 t^{1/2} - k_2 t + k_3 t^{3/2} \quad (4)$$

The experimental release data were fitted to the short and long time (Crank, 1975) approximation for drug dissolved in spherical matrices.

Long time:

$$\frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2}\exp\left(-\frac{D\pi^2 t}{r^2}\right) \quad (5)$$

which can be converted to

$$\ln\left(\frac{M_\infty - M_t}{M_\infty}\right) = \ln\left(\frac{6}{\pi^2}\right) - \frac{D\pi^2 t}{r^2} \quad (6)$$

Short time:

$$\frac{M_t}{M_\infty} = 6\left(\frac{Dt}{\pi r^2}\right)^{1/2} - \frac{3Dt}{r^2} \quad (7)$$

Two other equations that are frequently used to describe drug release from matrices are the first-order equation (Eqn 8) and the cube root equation (Eqn 9). The latter is used to check for dissolution rate limitation if the pellets are of a cubic shape and do not change in shape during drug release.

$$\ln\left(1 - \frac{M_t}{M_\infty}\right) = c - k_1 t \quad (8)$$

$$\left(1 - \frac{M_t}{M_\infty}\right)^{1/3} = -kt \quad (9)$$

The mean percentage of ibuprofen released for the quadruplicate runs was analysed for all data points using Eqns 1–9. Using size fraction 355–500 μm as an example, the mean slopes of release profiles fitted to a few models with their corresponding r^2 values and mean square error, at each drug loading, are tabulated in Table 5.

TABLE 5

Kinetic assessment of release of ibuprofen from cetostearyl alcohol pellets (355–500 μm) made at 600 rpm stirring speed

Drug loading (% w/w)	Higuchi's $t^{1/2}$ model			Baker and Lonsdale model			First-order model			Cube root equation		
	Slope ($\times 10^2$) (% $min^{-1/2}$)	$\%r^2$	Mean square error	Slope ($\times 10^2$) (% min^{-1})	$\%r^2$	Mean square error	Slope ($\times 10^2$) (% min^{-1})	$\%r^2$	Mean square error	Slope ($\times 10^2$) (% min^{-1})	$\%r^2$	Mean square error
10	3.13	98.7	0.0015	3.36	98.1	0.00042	−3.03	92.6	0.143	−5.71	99.5	0.0004
20	3.62	92.9	0.0103	4.45	96.3	0.00117	−4.74	96.7	0.117	−7.53	96.7	0.0029
30	3.83	97.4	0.0035	4.88	98.3	0.00047	−4.62	95.8	0.106	−8.28	99.9	0.0000
40	3.11	98.0	0.0022	2.56	95.1	0.00064	−2.09	97.2	0.024	−4.75	99.8	0.0001
50	3.28	98.6	0.0013	2.97	97.8	0.00024	−2.33	99.3	0.005	−5.36	99.9	0.0000
60	4.67	95.0	0.0055	8.68	98.5	0.00041	−8.35	99.5	0.013	−14.1	97.9	0.0015

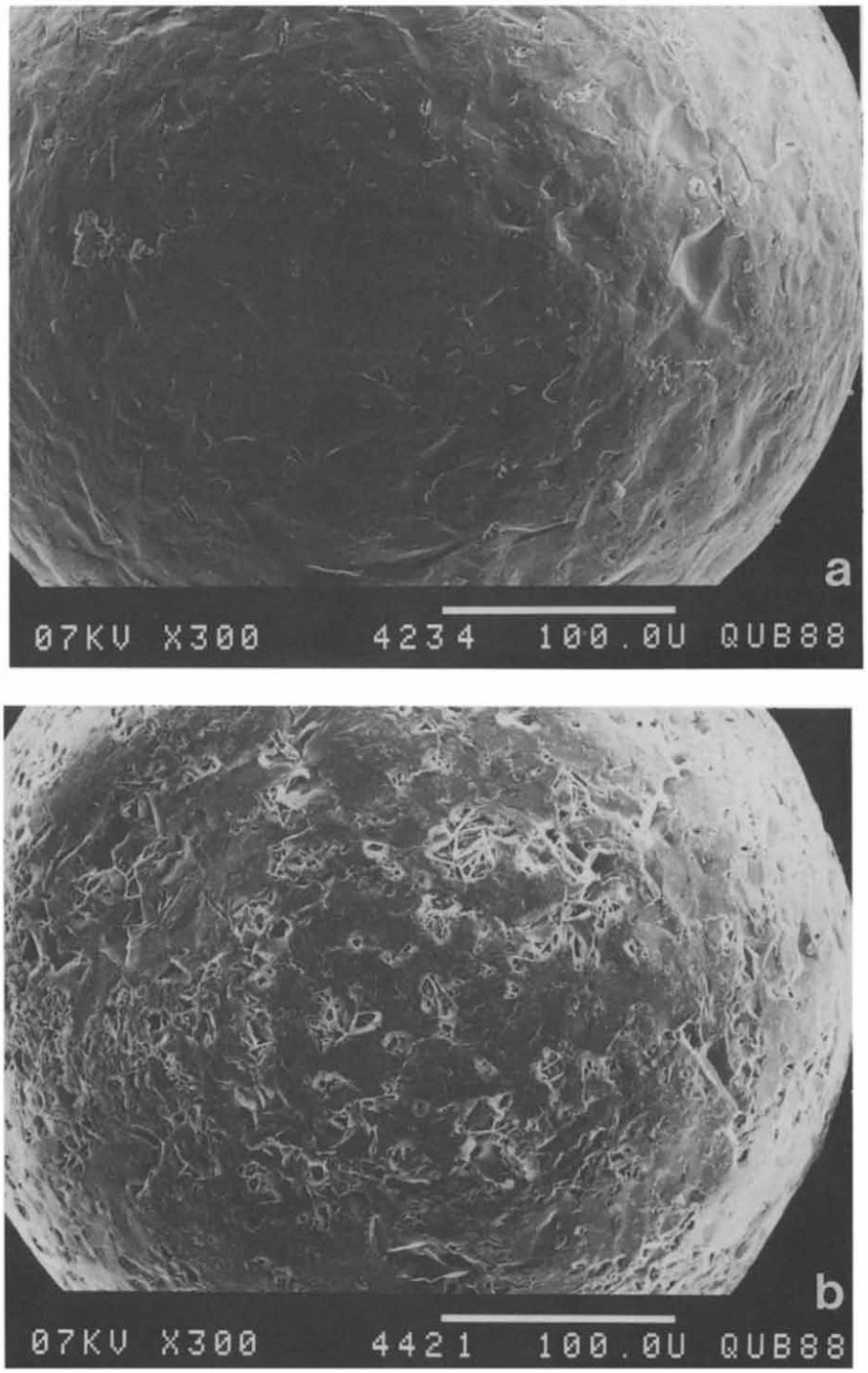

Fig. 4. Electron micrographs of ibuprofen-cetostearyl alcohol pellets (355–500 μm) before drug release. (a) 20% w/w ibuprofen loaded ($\times$300); (b) 60% w/w ibuprofen loaded ($\times$300).

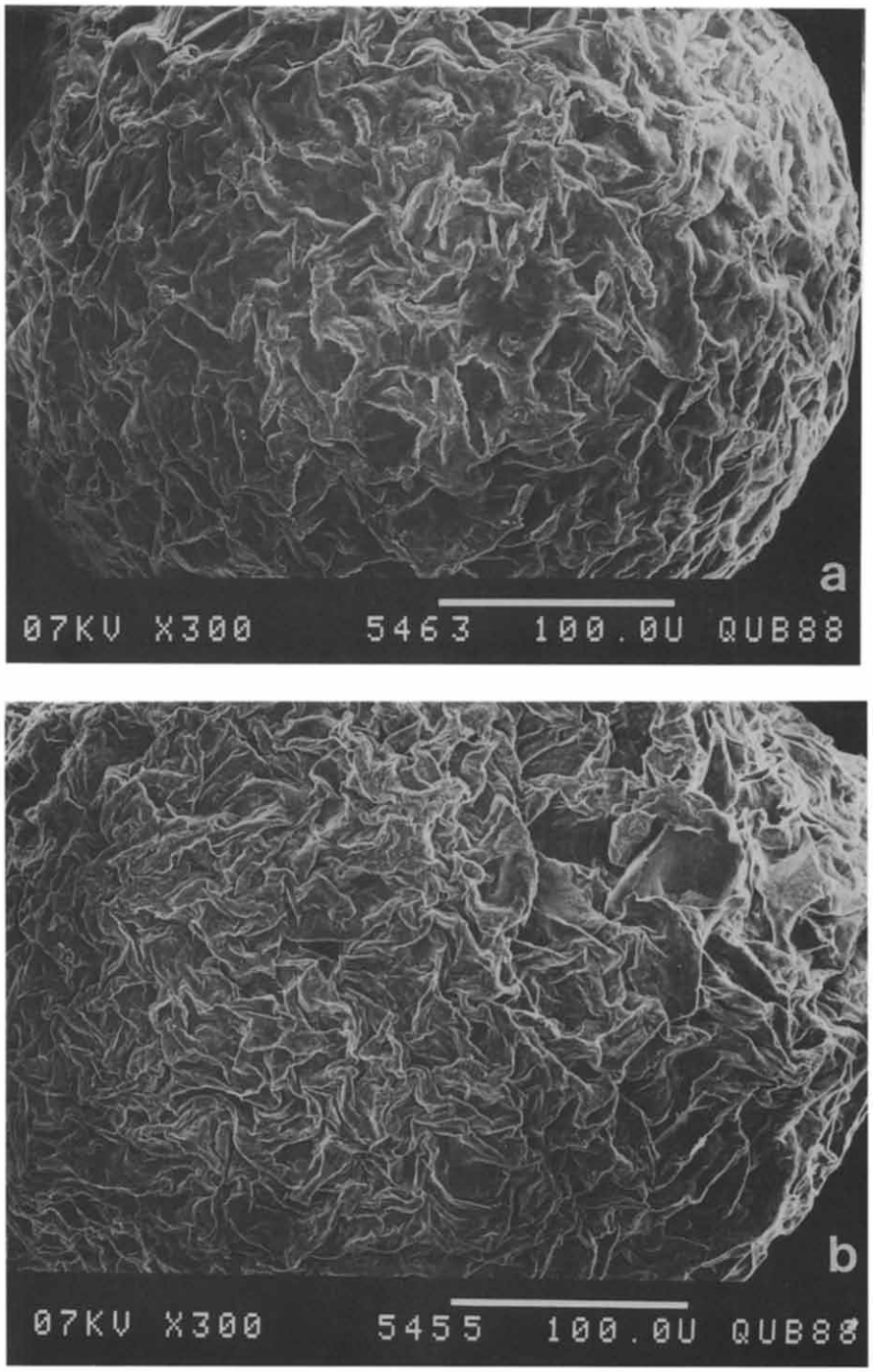

Fig. 5. Electron micrographs of ibuprofen-cetostearyl alcohol pellets (355–500 μm) after drug release. (a) 20% w/w ibuprofen loaded ($\times$300); (b) 60% w/w ibuprofen loaded ($\times$300).

A comparative evaluation of r^2 values and the residuals shows that the best model for the whole release profiles for all of the pellets, with the exception of those containing 60% w/w ibuprofen, appears to be the cube root equation. Good fits were also obtained for the square root of time model over the range of 20–80% drug released. It appears therefore that the pellets behave as contracting spheres during the drug release process with the drug-depleted zones providing little diffusive barrier. Studies conducted at 100 and 150 rpm showed that the release rates of ibuprofen, at those two speeds, from cetostearyl alcohol pellets were not different, indicating that boundary layer effects were negligible.

The mechanism of drug release from wax matrices has been a matter of controversy since wax systems tend to be crude and more heterogeneous than polymeric systems. Some have suggested that the mechanism of release from wax matrices involves the leaching of drug by the eluting medium. Fluid enters through the cracks and pores of the matrix with diffusion of drug through the matrix being insignificant (Dakkuri et al., 1978a,b). Others have reported that release from a typical wax matrix is diffusion-controlled and is best described by Higuchi's $t^{1/2}$ model (Schwartz et al., 1968a,b; Goodhart et al., 1974; Parab et al., 1986). However, it must be appreciated that the physical structure of a tabletted wax is very different from that of wax granules or spheres which are not subjected to compaction pressure as is the case in this study. Ritschel and Udeshi (1987), on analysing theophylline release from acrylic resin matrix tablets using zero-order kinetics, first-order kinetics and Higuchi's $t^{1/2}$ model, observed that linear plots and high correlation coefficients were obtained in each case. To further distinguish the mechanism of drug release they compared the goodness of fit by evaluating the residual sum of squares of the deviations as in this study. Babay et al. (1988), however, in evaluating the release of indomethacin from drug-loaded Eudragit RL® microspheres concluded that the true release mechanism can only be established by investigating drug release from single microspheres despite a satisfactory fit of the cumulative release profiles to the Higuchi equation for spherical suspension matrices.

The superiority of the cube root model, in the present study, over the other models, in describing the complete profile for ibuprofen release from the pellets is based purely on numerical fits. Since the other models also yield satisfactory fits, it is important to take account of the physicochemical properties of the pellets and other factors before making final conclusions. Indeed, over the 20–80% drug release interval, the non-specific square root of time plot is as good as any of the other models. Therefore, for simplicity in the subsequent studies evaluating the effect of variables such as drug loading, pellet size and agitation speed on drug release from the pellets, the slopes of the $t^{1/2}$ plots (equation) were used.

Scanning electron micrographs of cetostearyl alcohol pellets produced at 600 rpm, before release studies, are illustrated for two ibuprofen loadings in Fig. 4a and b. At low drug loadings (Fig. 4a), the pellets are spherical with a smooth, non-porous surface. As the concentration of ibuprofen in the pellets increases, more fissures are evident, particularly for 60% ibuprofen-loaded pellets (Fig. 4b). The brittle appearance is attributed to less wax being present to cover and bind all the available ibuprofen. There was no sign of surface drug at $\times 1000$ magnification.

After drug release, morphological changes were evident (Fig. 5a,b). Numerous folds and invaginations are observed. At 60% w/w drug loading (Fig. 5b), there is more structural breakdown compared to the lower drug loadings. The presence of a large number of invaginations even at 10% w/w ibuprofen loading may be due to a combination of the dissolution of ibuprofen and hydration of the cetostearyl alcohol pellets. However, the overall shape of the pellets is retained after drug release. At low magnification ($\times 300$) no pores could be observed in the pellets (Fig. 5a, b). However, at higher magnification ($\times 1000$), small worm-like indentations or pits, possibly due to the dissolution of ibuprofen, were observed. These indentations were larger and more continuous in 60% w/w ibuprofen loaded pellets than in pellets with lower ibuprofen content.

TABLE 6

Effect of speed during manufacture of ibuprofen-cetostearyl alcohol pellets on ibuprofen release from pellets of size fraction 355–500 μm

Ibuprofen loading (% w/w)	Slope from $\sqrt{t}$ plots ± S.D. ($\%/\sqrt{\text{min}}$) [a]		Test F value [b]
	600 rpm	1200 rpm	
10	3.76 ± 0.02	4.93 ± 0.03	$F_{1,6} = 4407$; significant
20	6.41 ± 0.08	5.26 ± 0.25	$F_{1,6} = 147.7$; significant
30	5.16 ± 0.18	4.54 ± 0.07	$F_{1,6} = 34.4$; significant
40	3.73 ± 0.04	4.72 ± 0.27	$F_{1,4} = 619.9$; significant
50	3.78 ± 0.02	4.38 ± 0.19	$F_{1,6} = 493.8$; significant

[a] Range of drug release covered, 20–80%; % r^2 of slopes, all greater than 99.0%.
[b] Critical $F_{1,6\alpha=0.05} = 5.99$; critical $F_{1,4,\alpha=0.05} = 7.71$.

Effect of speed of agitation during the manufacture of spheres

Ibuprofen release from pellets of similar size (355–500 μm) fraction and drug loading but produced at either 600 or 1200 rpm was investigated. The mean slopes from drug release runs for each sample are tabulated in Table 6. One-way analysis of variance shows that the stirring speed used in the production of pellets significantly altered the release rate of ibuprofen from pellets of the same sieve size fraction at each drug loading (Table 6).

Pellets of the same size fraction gave a higher drug release rate when prepared at the faster mixing speed of 1200 rpm for all ibuprofen loadings evaluated except for 20 and 30% w/w. In these two instances, the reverse trend was observed. Therefore, to explain this further, the effect of drug loadings was studied.

Effect of drug loading

Ibuprofen concentration in the pellets was varied in order to improve understanding of the system being investigated. Increasing drug con-

TABLE 7

Effect of particle size and drug loading on the rate of ibuprofen release from cetostearyl alcohol pellets

Agitation speed (rpm)	Size range (μm)	Mean slopes ± S.D. from Higuchi's $\sqrt{t}$ plots for each ibuprofen loading ($\%/\sqrt{\text{min}}$) [a]					
		10	20	30	40	50	60
600	90–180	–	7.82 ± 0.06	6.82 ± 0.11	5.67 ± 0.06	5.16 ± 0.13	8.08 ± 0.09
	180–250	3.27 ± 0.07 *	7.12 ± 0.10	5.81 ± 0.06	4.98 ± 0.05	4.55 ± 0.04	8.97 ± 0.17
	250–355	3.65 ± 0.05	6.96 ± 0.03	5.31 ± 0.13	4.17 ± 0.13	4.01 ± 0.16	7.76 ± 0.23
	355–500	3.76 ± 0.02	6.41 ± 0.08	5.16 ± 0.18	3.73 ± 0.04	3.78 ± 0.02	6.67 ± 0.07
	500–710	3.89 ± 0.02	5.74 ± 0.07	4.51 ± 0.08	3.42 ± 0.04	3.40 ± 0.01	–
	710–1000	–	4.66 ± 0.09	3.57 ± 0.05	2.99 ± 0.01	–	–
Significance of effect of pellet size at each speed using one-way analysis of variance	600	$F_{3,12} = 16.2$ [b] $F_{c,0.95} = 3.49$ [c]	$F_{3,18} = 671$ $F_{c,0.95} = 2.77$	$F_{5,17} = 264.5$ $F_{c,0.95} = 2.81$	$F_{5,18} = 699.5$ $F_{c,0.95} = 2.77$	$F_{4,19} = 158.4$ $F_{c,0.95} = 3.06$	$F_{3,12} = 131.7$ $F_{c,0.95} = 3.47$

[a] Range of drug release covered, 20–80%; % r^2 of slopes, all greater than 99.0% except for those with an asterisk where $98.0 < \% r^2 < 99.0$.
[b] F_{ν_1,ν_2}, test F values.
[c] $F_{c,0.95}$, critical F values.

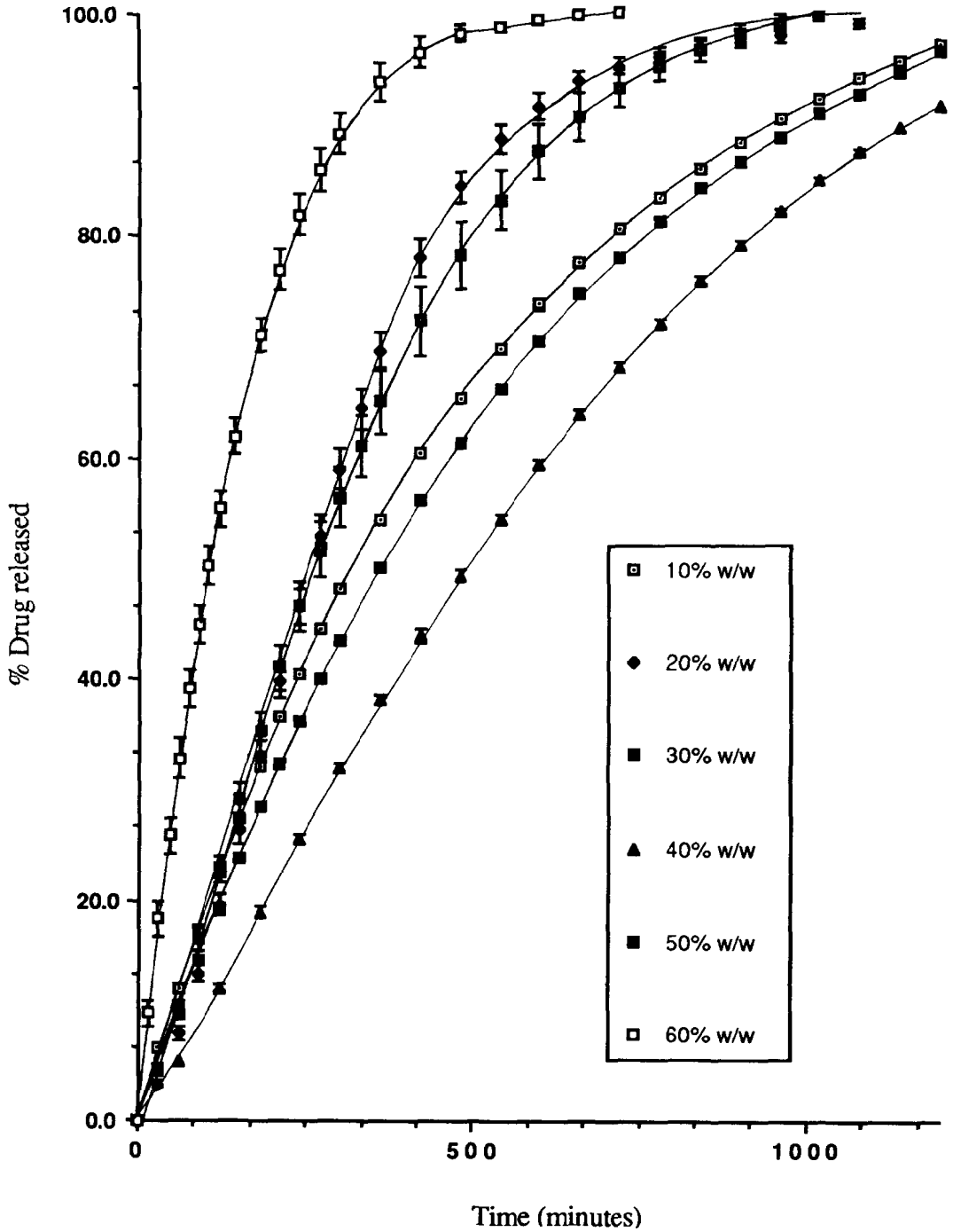

Fig. 6. Effect of ibuprofen loading on its release from cetostearyl alcohol pellets (355–500 μm) produced at 600 rpm.

TABLE 8

Effect of ibuprofen loading on its release from cetostearyl alcohol pellets: Slopes corrected for surface area

Stirring speed (rpm)	Size range (μm)	Normalised slopes of Higuchi's $\sqrt{t}$ plot for surface area difference at each ibuprofen loading (%/$\sqrt{\text{min}}$)					Significance of effect of drug loading using one-way analysis of variance		
		10%	20%	30%	40%	50%	Test F value	Critical $F_{c,0.95}$	Significance
600	90–180	–	15.89	21.38	24.31	28.98	$F_{3,12} = 470.2$	3.49	significant
	180–250	3.72	14.47	18.21	21.35	25.55	$F_{4,15} = 5326.3$	3.06	significant
	250–355	3.65	14.14	16.65	17.88	22.52	$F_{4,15} = 598.6$	3.06	significant
	355–500	3.76	13.03	16.18	15.99	21.23	$F_{4,15} = 166.8$	3.06	significant
	500–710	3.89	11.66	14.14	14.66	19.09	$F_{4,15} = 434.0$	3.06	significant
	710–1000	–	9.47	11.19	12.82	–	$F_{2,8} = 436.8$	4.46	significant

centration in a matrix will increase the release rate (Desai et al., 1965; Schwartz et al., 1968a, b) as predicted from Eqn 2. Fig. 6 shows representative release profiles determined with cetostearyl alcohol pellets (355–500 μm size range) produced using an agitation speed of 600 rpm, at different initial ibuprofen contents. The release profiles were linearised using Higuchi's $t^{1/2}$ plot

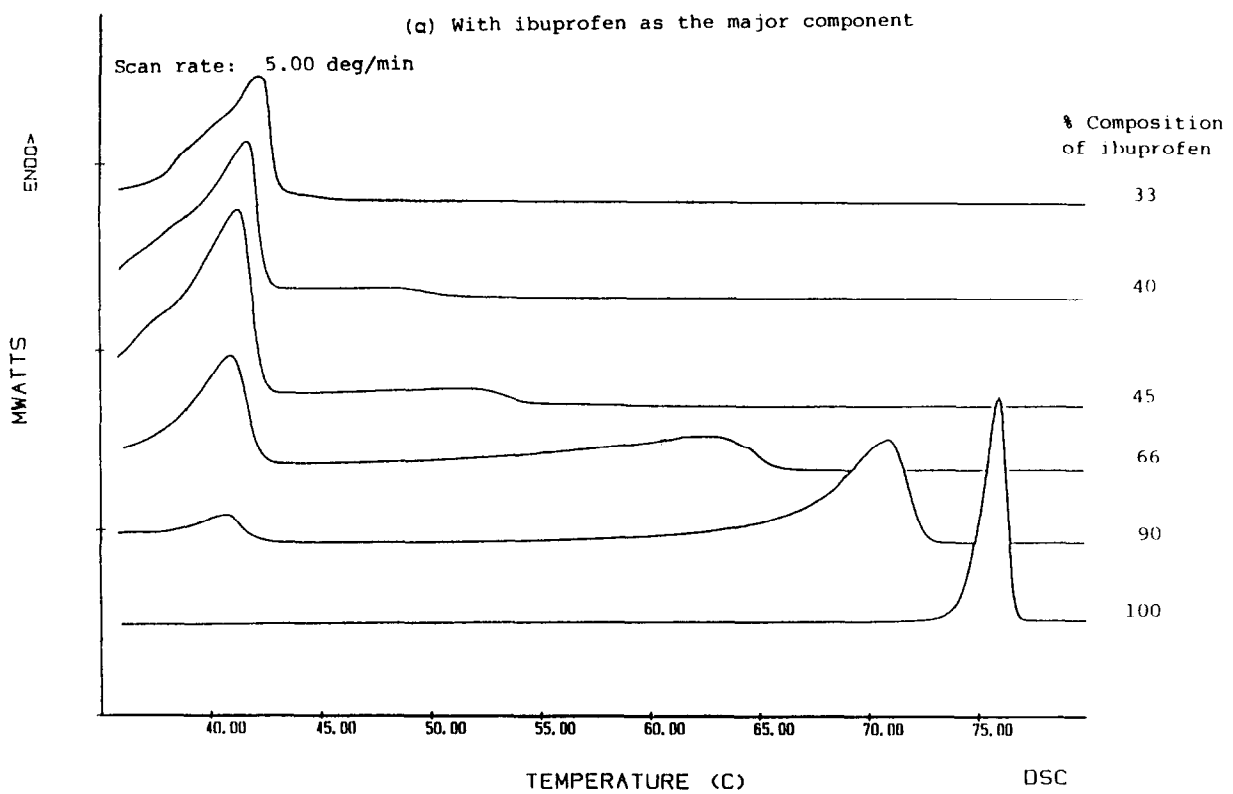

Fig. 7. DSC thermograms of ibuprofen-cetostearyl alcohol matrices.

and the mean slopes over the range of 20–80% drug release are tabulated in Table 7. Both Fig. 6 and Table 7 show that there is no obvious trend between release rates and ibuprofen content in the cetostearyl alcohol pellets at each size fraction. The release rates observed are a balance between two competing parameters, surface area and drug loading. Different quantities of pellets were used in the release studies in order to maintain the amount of ibuprofen constant at 60 mg. Therefore, when a constant amount of drug is employed in the study, drug loading has an unpredictable effect on release rates. Surface area was corrected for using the correction factor $W_1\rho_2/W_2\rho_1$ where W_1 and W_2 are the weights of pellets used for a 10% loading and any other drug loading, respectively, and ρ_2 and ρ_1 denote the corresponding densities.

These normalised $t^{1/2}$ slopes are listed in Table 8. The release rates reflected by the corrected slopes now show the expected (Eqn 2) increase with increasing drug loading.

Having therefore described the effect of drug loading, it is observed that pellets prepared with 20 and 30% w/w ibuprofen loadings have unusually high release rates. Ibuprofen is known to form eutectic mixtures with a wide range of additives including polyethylene glycol (Mura et al., 1987), stearates (Gordon et al., 1984) and polyvinylpyrrolidone (Najib et al., 1986). To determine whether eutectic formation with cetostearyl alcohol could account for the unusually high release rate of ibuprofen from the pellets containing 20 and 30% drug, differential calorimetric scans of ibuprofen-cetostearyl alcohol mixtures were recorded (Fig. 7) and a phase diagram drawn (Fig. 8). Indeed, addition of cetostearyl alcohol brought about a gradual depression in melting point of ibuprofen (Fig. 7) and eutectic formation was observed at about 26% w/w ibuprofen com-

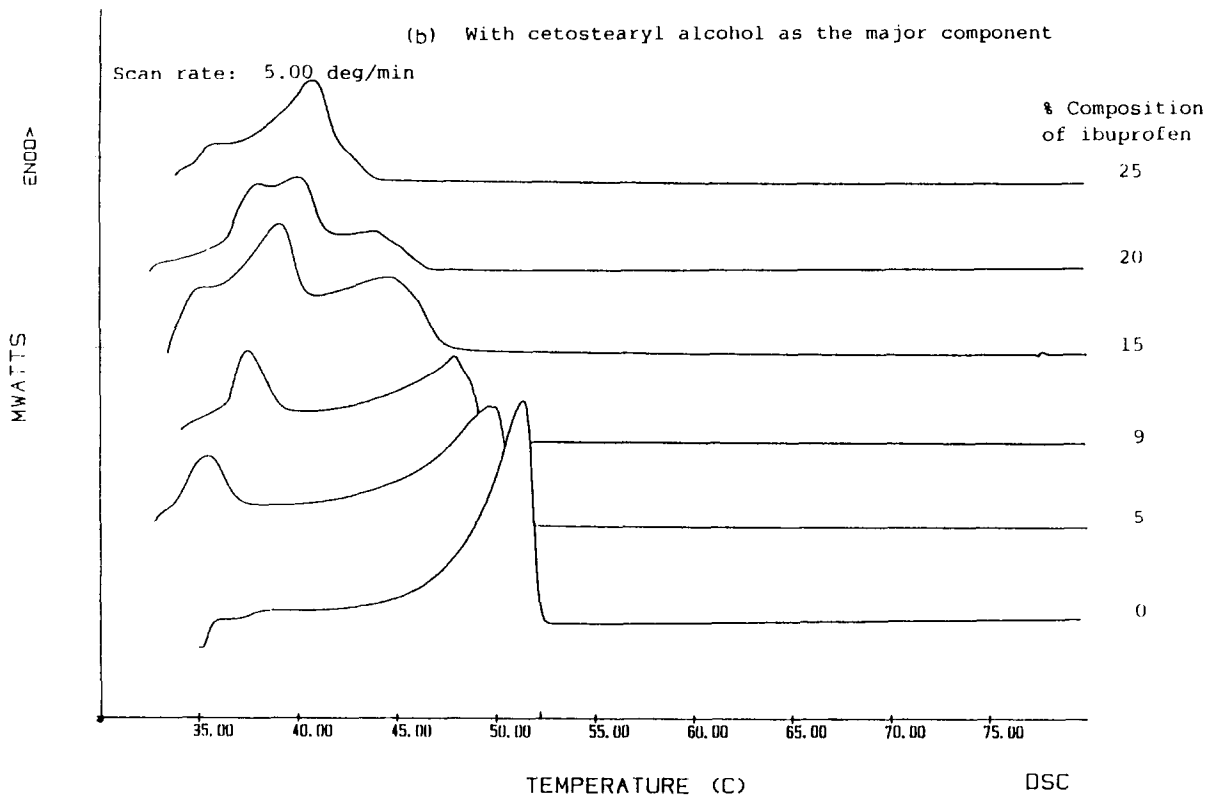

Fig. 7. (continued).

position (Fig. 8). Eutectic formation is therefore consistent with the pattern observed, for ibuprofen release rate, as ibuprofen content is altered in the pellets.

Effect of pellet size on ibuprofen release from cetostearyl alcohol spheres

The mean $t^{1/2}$ slopes, evaluated from four drug release runs over the range of 20–80%

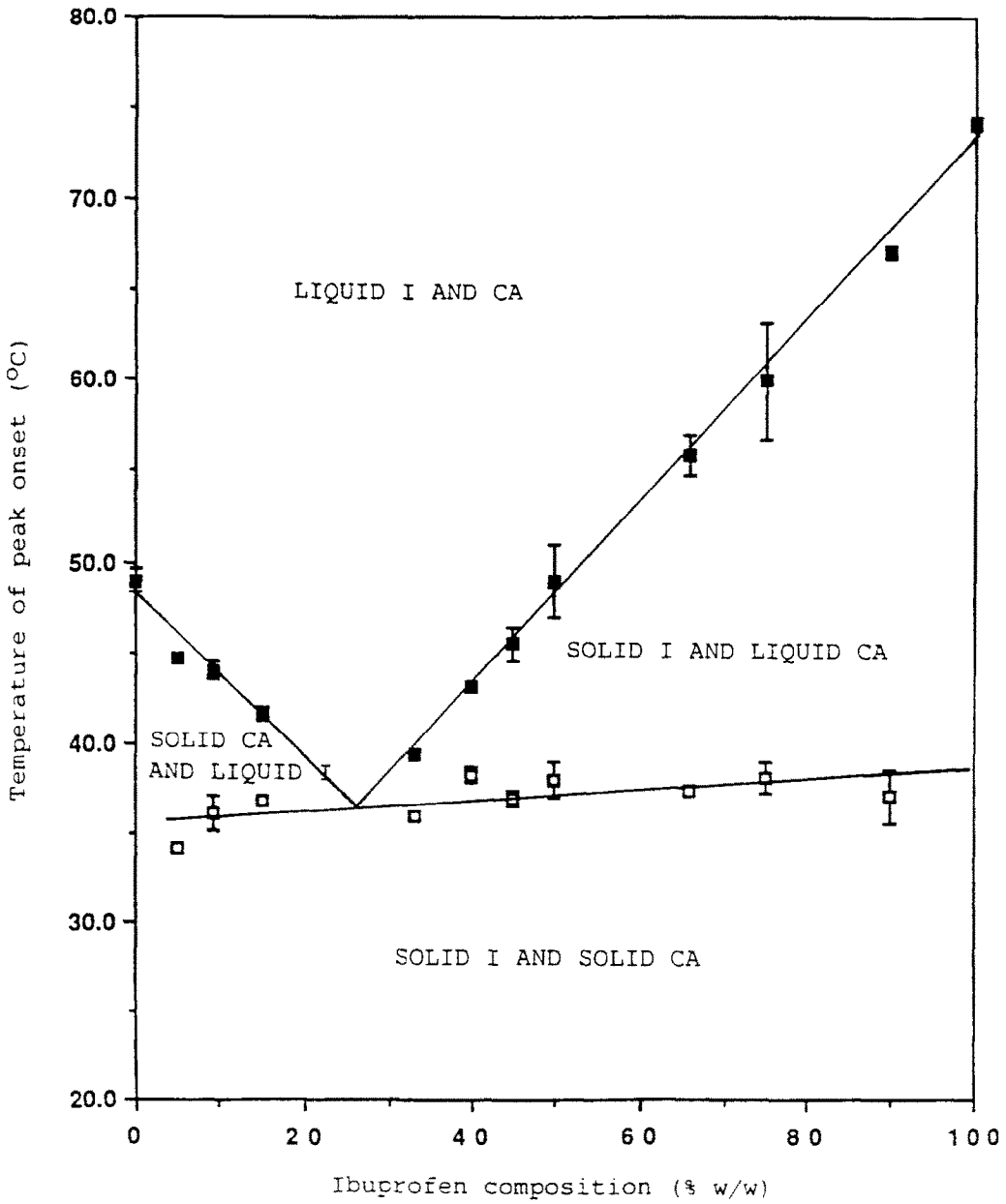

Fig. 8. Phase diagram of ibuprofen-cetostearyl alcohol binary system. I, ibuprofen; CA, cetostearyl alcohol.

release are presented in Table 7 for each drug loading. Analysis of variance shows that pellet size affected release rate at each drug loading. The influence of pellet size on the release rate is shown in Fig. 9 using a series of pellet size fractions containing 50% w/w ibuprofen produced at 600 rpm. As expected, smaller pellets yielded more rapid ibuprofen release for a given

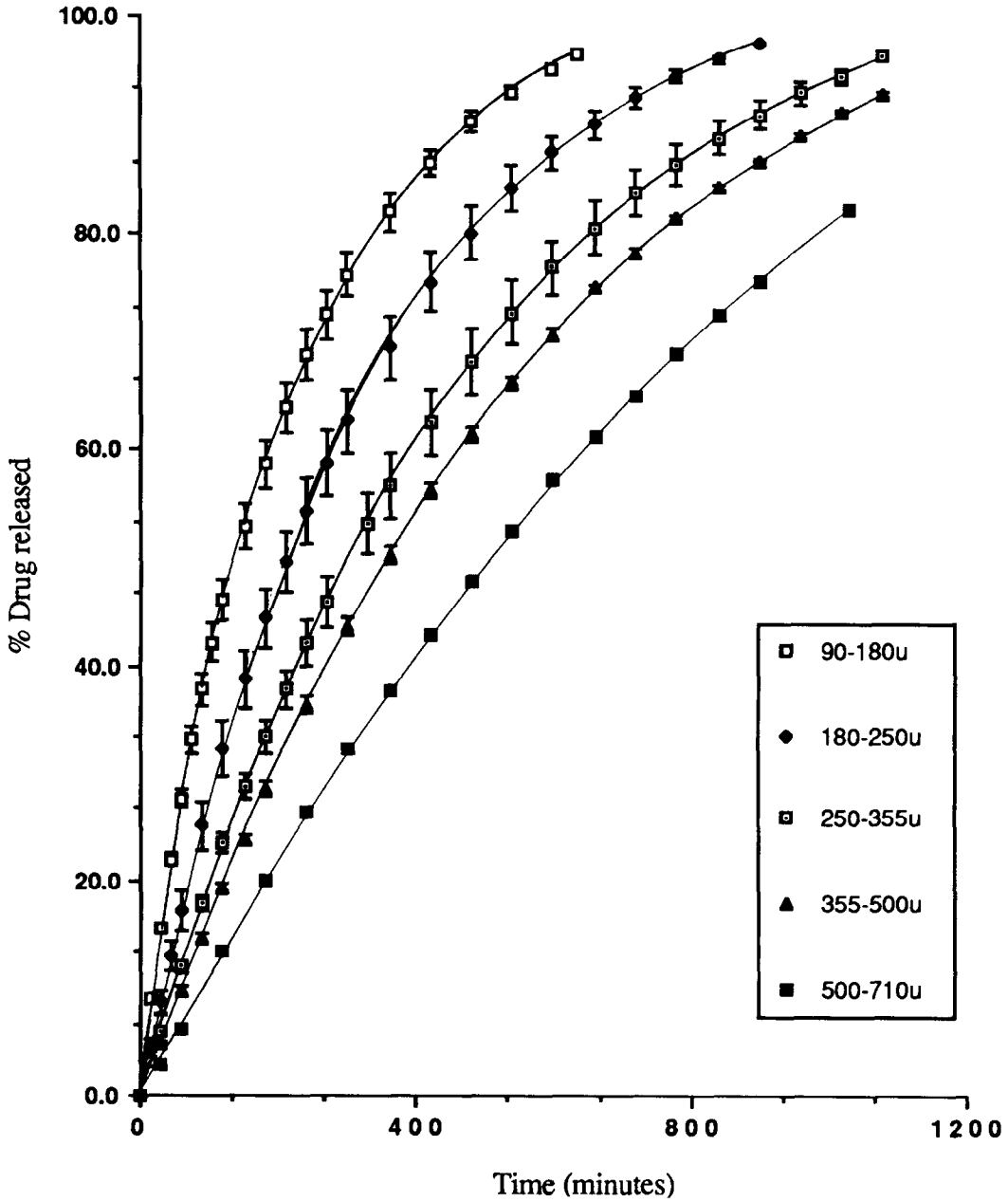

Fig. 9. Effect of pellet size on the release of ibuprofen from cetostearyl alcohol pellets containing 50% w/w ibuprofen and produced at 600 rpm.

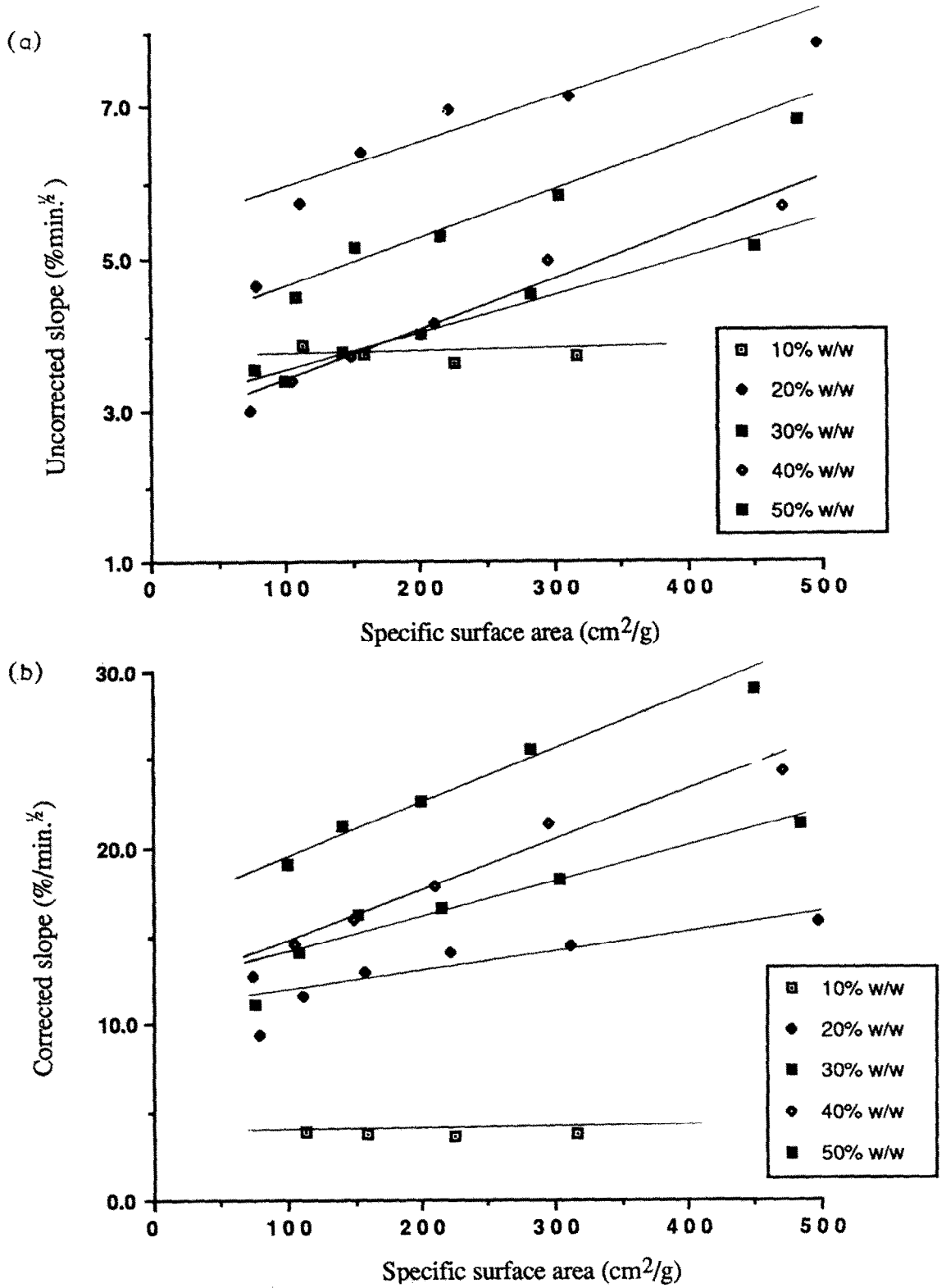

Fig. 10. Slopes from Higuchi's $t^{1/2}$ plots for different cetostearyl alcohol pellet sizes at each ibuprofen loading as a function of specific surface area at each size. (a) Uncorrected slopes; (b) corrected slopes.

amount of drug than larger pellets because the combined surface area of the smaller pellets is larger and the diffusional path is shorter.

The relationship between specific surface area and release rates is as indicated by the slopes from Higuchi's $t^{1/2}$ plots. Both uncorrected and corrected slopes for different pellets, at different drug loadings, are shown in Fig. 10a and b for pellets produced at 600 rpm. After correction for surface area, linearity is improved. Moreover, the release rate of ibuprofen from the 10% w/w ibuprofen loaded pellets appears to be independent of pellet size. This may be due to the 10% loading being insufficient to produce a suspension matrix.

In a recent study, Bodmeier and Chen (1989) investigated the formulation of non-steroidal anti-inflammatory agents including ibuprofen using a solvent evaporation method. It would appear that given the recent toxicological and environmental concerns about organic solvents, the aqueous system proposed in this study has major advantages.

Conclusion

The results reported in this study therefore show that reproducible sustained-release ibuprofen spheres could be prepared using the present emulsion melt-cool method. Analysis of the release data shows that drug release from the pellets adheres most closely to the contracting sphere model as defined by the cube root equation. However, highly satisfactory numerical fits were obtained with a number of the other mathematical models. Using the slope of the Higuchi square root of time-drug release plot, it has been shown that the effect of particle size, stirring speed and drug loading could be rationalised after adjustment for surface area. Within the range of 20–30% drug loading, unusually high ibuprofen release rates were observed and this was explained on the basis of eutectic formation at an ibuprofen drug loading of 26% w/w.

Glossary

Symbol	Meaning
ρ	density
r	radius
M_t	amount of drug released from time 0 to time t
M_∞	amount of drug released from time 0 to time ∞
D	diffusion coefficient
C_s	solubility of drug in matrix
C_0	initial drug concentration
A	surface area
t	time
k, k_1, k_2, k_3	constants depending on model

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