International Journal of Pharmaceutics, 94 (1993) 59–67

IJP 03064

Processing factors affecting particle size and in vitro drug release of sustained-release ibuprofen microspheres

R.S. Al-Kassas, C.A. Gilligan and A. Li Wan Po

Department of Pharmacy, Medical Biology Centre, The Queen's University of Belfast, 97 Lisburn Road, Belfast BT9 7BL (UK)

(Received 30 July 1992)
(Accepted 29 September 1992)

Key words: Sustained release; Microsphere; Matrix; Ibuprofen

Summary

Ibuprofen microspheres were prepared using an aqueous dispersion method. The method was adapted so that two processing factors, cooling time and stirring rate, could be altered. The subsequent effects of altering these parameters on the characterisation of the microspheres and the drug release kinetics were investigated. Particle size analysis showed that both stirring rate and cooling time significantly affected the mean particle size although the effects were independent of each other. In vitro release data were fitted to several models, the Higuchi square root of time model (with appropriate limits) giving the best fit for the release data. Increasing the cooling time or decreasing the stirring rate decreased the release of drug from the system. By using this method of manufacture, which allows alteration of processing parameters, it would be relatively straightforward to produce microspheres with tailored in vitro release characteristics.

Introduction

Relatively 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 the melt dispersion influenced the crystallinity of both drug and carrier. In a previous paper from this laboratory (Wong et al., 1992), sustained-release ibuprofen microspheres were produced using an aqueous dispersion method. This technique involved melting and suspension of drug-containing cetostearyl alcohol in an aqueous medium. The resulting emulsion was cooled under rapid stirring to produce the microspheres. This method proved to be reproducible but was limited in that it did not allow alteration of the cooling profile to enable the study of the effect of cooling time on the physico-chemical properties of the microspheres. In this study the method of cooling was adapted so that four cooling times were produced. It was thus possible to study the effect of this processing factor on the in vitro drug release and particle size of the resultant microspheres.

In addition the stirring rate of the emulsion was also altered. Changing this parameter has been shown in other studies to alter the particle size distribution (Benita et al., 1986; Torrado et al., 1989) and in vitro release characteristics

Correspondence to: A. Li Wan Po, Department of Pharmacy, Medical Biology Centre, The Queen's University of Belfast, 97 Lisburn Road, Belfast BT9 7BL, U.K.

(Wong et al., 1992). We wanted to confirm whether the results would be as expected at each of the four cooling times.

Materials and Methods

Ibuprofen, propylene glycol (Sigma Ltd, U.K.), cetostearyl alcohol (Thornton & Ross, Ltd, U.K.), disodium orthophosphate dodecahydrate, potassium chloride (BDH Ltd, U.K.) and citric acid (May & Baker, U.K.) were obtained from the indicated sources.

Preparation of ibuprofen-cetostearyl alcohol spheres

9 g of cetostearyl alcohol was melted on a water bath at 100°C; 1 g of ibuprofen was dispersed in the molten wax and stirred to obtain a homogeneous melt. This mixture was added to 200 ml of heated (65°C), acidified, deionised water contained within a 11.5 cm × 7.5 cm stainless-steel beaker. The mixture was agitated continuously at either 600 or 1300 rpm for 5 min using a Heidolph RZ50 stirrer with a stainless-steel rotor fitted with a four-blade impeller of approx. 45 mm diameter. After 5 min the beaker was cooled rapidly to 10°C. Four different cooling times were achieved by altering the cooling procedure:

(1) The hot water in the bath surrounding the beaker was drained out and replaced by a propylene glycol : water (25 : 75) mixture previously cooled to −3°C. By varying the outflow and the inflow to the water bath cooling times of 7 and 10 min were obtained.

(2) The hot water in the bath was drained out and replaced by a propylene glycol : water (45 : 55) mixture previously cooled to −15°C. A cooling time of 2 min was achieved with this protocol.

(3) The hot water was drained from the bath and the contents of the stainless-steel beaker allowed to cool at at room temperature. A cooling time of 100 min was achieved by this method.

In each instance, the temperature of the dispersion was monitored during the cooling stage by placing a temperature probe (Porter type K thermometer 8013) in the dispersion. The resultant spheres were filtered, washed with acidified deionised water, air dried and stored in an airtight desiccator. The pellets were fractionated by sieving or used as unfractionated samples.

Determination of drug loading of microspheres

In all instances, the cetostearyl alcohol microspheres were formulated to contain 10% w/w ibuprofen. The exact ibuprofen content was determined as follows. An amount of ibuprofen-cetostearyl alcohol spheres containing a theoretical weight of 6 mg of ibuprofen was accurately weighed. The pellets were crushed and placed in 100 ml of McIlvaine buffer pH 6.90, 1.0 M constant ionic strength, and shaken at 100 rpm for 48 h. The temperature was controlled to 37 ± 0.5°C. Before ultraviolet analysis at 230 nm the solutions were filtered through a 0.45 μm filter to obtain a clear solution. All samples which were used in dissolution studies were analysed for drug content.

Particle size analysis

Particle size determinations were performed using the Mastersizer IP Malvern particle sizer. Using a lens of 1000 μm the range of the Mastersizer was 4–2000 μm. The unfractionated pellets prepared at the two stirring speeds and four cooling temperatures were analysed, both before and after dissolution, to determine the effects of these parameters on the size distribution. The determinations were performed four times to establish the reproducibility of the results.

In vitro dissolution studies

Unfractionated microspheres and two sieve fractions, 180–250 and 710–1000 μm, prepared at two stirring speeds and four cooling times, were used in the dissolution studies. A mixture of the two sieve fractions with a ratio of 50 : 50 was also studied. Dissolution was performed using an automated assembly which consisted of an Apple IIe computer and TDS software, an Epson LX 86 printer, a peristaltic pump (Watson Marlow Ltd, U.K.), an LKB 4052 Ultrospec UV spectrophotometer, a Caleva model 7ST water bath fitted with a variable-speed stirring unit and a tempette junior JE-8J heater (Techne, U.K.) and water bath. Weighed quantities of microspheres equiva-

lent to 60 mg of ibuprofen were placed in baskets which were lowered into 1000 ml of McIlvaine's buffer pH 6.90, 1.0 M ionic strength. The buffer was previously warmed and maintained at 37 ± 0.5°C. The baskets were rotated at a speed of 100 rpm and the absorbance of the ibuprofen released recorded automatically at predetermined time intervals at a wavelength of 230 nm. All experiments were performed in quadruplicate for each sample.

Scanning electron microscopy

The shape and surface characteristics of the microspheres were examined and photographed using a scanning electron microscope (Jeol JSM-6400, Japan). The pellets were sputter coated with gold (Edwards s150 model, U.K.) with reduced coating time. The samples were examined at suitable magnifications using a voltage of 5 kV to minimise heat generation.

Density studies

Two sieve fractions, 180–250 and 710–1000 μm, prepared at the two stirring speeds and four cooling times, were employed for density measurements at room temperature. Initially, the density of 50 ml of 0.1 M hydrochloric acid was determined in a tared 50 ml density bottle. Approx. 1 g of ibuprofen-cetostearyl alcohol microspheres was weighed accurately and placed in a previously tared density bottle and filled with 0.1 M hydrochloric acid. The bottle was then stoppered taking care not to crush any of the microspheres and to exclude any air bubbles by gentle agitation. From the weight of the pellets and the weight of the displaced 0.1 M hydrochloric acid the density of the microsperes could be calculated. The determinations were performed four times to establish reproducibility of the results.

Water content of microspheres

The water content of two sieve fractions, 180–250 and 710–1000 μm, prepared at the two stirring speeds and four cooling times was determined. Approx. 1 g of ibuprofen-cetostearyl alcohol microspheres was accurately weighed and placed in a desiccator containing phosphorus pentoxide for 48 h. The water content was determined from the initial and the final weight of the microspheres.

Results and Discussion

The aqueous dispersion method was first patented in 1960 by Yamamato and Baba (cited in Draper and Becker, 1966). This method was used for preparation of the ibuprofen-cetostearyl alcohol microspheres as it is relatively straightforward and requires no investment in high cost equipment. In a previous paper from this laboratory (Wong et al., 1992) microspheres were produced by this method with a single cooling time. In this study the experimental conditions were altered so that four cooling times were produced. Cooling profiles which produced a drop in temperature from 65 to 10°C in 2, 7 and 10 min are shown in Fig. 1. The fourth cooling profile was produced by allowing the aqueous dispersion to cool at room temperature. The time taken in this instance for the temperature to drop from 65 to

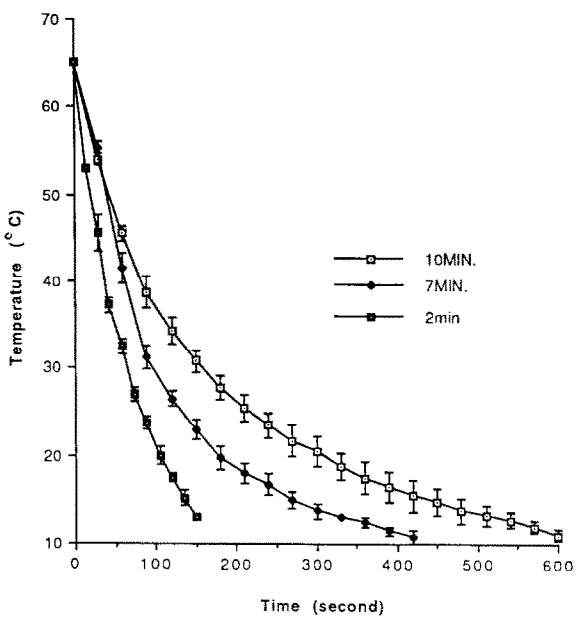

Fig. 1. Representative temperature-time profile of the aqueous phase during the cooling stage in the manufacture of cetostearyl alcohol pellets loaded with 10% w/w ibuprofen. Error bars are ± SD of mean values.

10°C was 100 min. The temperature-time profiles show non-linear cooling. The rate of cooling for each of the cooling profiles from 65 to 30°C, the temperature range in which all of the solid components would have precipitated out, is similar for all the samples and batches.

Test of drug content

Before discussing the factors which affect the in vitro release of drug from the microsphere system it is necessary to determine the actual drug loading of the pellets, as opposed to the theoretical drug loading, to enable the correct percentages of the drug released from the systems to be calculated. All of the fractions investigated in this study were examined for their drug content. It was found that the drug loading as a percentage of the theoretical amount was 96.84 ± 2.02%. In the following discussion the actual drug loading determined for each individual batch of matrix microspheres will be used as the value representing 100% of the drug released from the spheres.

Particle size study of the unfractionated microspheres

Major factors influencing the particle size distribution are the speed of mixing of the molten dispersed system before and during the cooling stage (Scott et al., 1964; Benita et al., 1986; Dhupar, 1987; Das and Gupta, 1988; Kawashima et al., 1989; Torrado et al., 1989; Biswanath et al., 1990), the ratio of drug to polymer (Kawashima et al., 1989; Torrado et al., 1989; Biswanath et al., 1990) and the viscosity of the dispersed phase (Scott et al., 1964; Das and Gupta, 1988).

One of the objectives of this investigation was to study the effect of the stirring rate and cooling time, during the preparation of the microspheres on the particle size and the size distribution of the resultant systems. The Malvern Mastersizer IP was used for all particle size determinations. The result of the measurement analysis, with this instrument, is a volume distribution. Two derived diameters will be used in the following discussion: the median diameter designated as $D[v,0.5]$ and the mean diameter designated as $D[4,3]$. Table 1 shows the effect of cooling time and stirring rate on the mean particle size and particle size distribution of the unfractionated pellets. The size distribution is represented by the standard deviation of the mean distribution. No values are given for the microspheres produced with a cooling time of 100 min as we were unable to obtain a full distribution of these due to the limitations of the Mastersizer. Analysis of the particle size distributions indicates that all of the profiles produced at the four cooling times and two stirring speeds are approximately normally distributed. Further comparison of the median values (Table 2) with the mean values (Table 1) indicates that this is in fact true as the two values are similar but not identical.

TABLE 1

Effect of cooling time and stirring speed on the particle size distribution of the unfractionated pellets

Cooling time (min)	Stirring speed: 600 rpm $D[4,3]$ [a] ± SD [b]	Stirring speed: 1300 rpm $D[4,3]$ [a] ± SD
Before dissolution		
10	905.38 ± 392.66	570.55 ± 259.05
7	670.72 ± 336.71	370.99 ± 164.29
2	666.29 ± 363.84	356.93 ± 227.94
After dissolution		
10	925.27 ± 401.4	635.29 ± 332.97
7	870.40 ± 455.59	571.95 ± 365.41
2	791.73 ± 452.94	431.45 ± 237.83

[a] Represents the mean diameter over the volume distribution.
[b] Represents the spread of the distribution.

TABLE 2

Effect of cooling time on the particle size of the unfractionated pellets

Cooling time (min)	Stirring rate: 600 rpm $D[v,0.5]$ [a] ± SD [b]	Stirring rate: 1300 rpm $D[v,0.5]$ ± SD
10	850.75 ± 47.13	506.26 ± 2.35
7	631.50 ± 19.91	327.50 ± 8.69
2	603.25 ± 47.15	305.25 ± 31.19

[a] Represents the median diameter.
[b] Represents the standard deviations of the repeat measurements.

Analysis of variance shows that both stirring rate and cooling time significantly affect the mean particle size although these effects are independent of each other (Table 3). Pairwise comparisons using Tukey's test has shown that there is no significant difference in the mean diameter of the particle size distribution produced with a cooling time of 2 and 7 min at either 600 and 1300 rpm although they were both significantly different from the values obtained with a cooling time of 10 min for both stirring rates. These results are evident from Table 1.

The fact that the cooling profiles of the 2 and 7 min cooling times (Fig. 1) exhibit similar slopes in the temperature range of 65–30°C, the range in which all the solid components would have precipitated out, could explain the insignificant difference in the mean diameters of the pellets produced at these two cooling times. Increasing the stirring speed from 600 to 1300 rpm produced a significant decrease in the mean diameters at the three cooling times (Table 1). These results confirm earlier findings, based on sieve analysis data, from this laboratory and reported in a previous paper (Wong et al., 1992).

The mean particle diameter was also examined after dissolution studies to investigate the effect, if any, the dissolution medium may have on this parameter. From Table 1 it can be seen that the microspheres remain intact after dissolution and indeed a slight increase in the mean diameter of all the microspheres examined was observed. The increase in diameter is probably due to hydration of the cetostearyl alcohol spheres.

In vitro release studies

The small intestine is the main site of ibuprofen absorption (Upjohn Co., 1974) and the peak serum concentration occurs about 1.5 h after ingestion (Adams et al., 1967; Kaiser and Vangiessen, al., 1974). The half-life of ibuprofen is about 2 h (Adams et al., 1969) and the drug is rapidly excreted in the urine. To prolong its duration of action and to minimise its direct irritant effect in the gastrointestinal tract it is sometimes formulated as sustained-release dosage forms. The in vitro release of the unfractionated microspheres, two sieve fractions, 180–250 and 710–1000 μm and a 50:50 mixture of the two fractions, was investigated to determine their release characteristics. The size fractions 180–250 and 710–1000 μm were prepared at 1300 and 600 rpm, respectively. The release data for the unfractionated and fractionated samples were fitted to several models as detailed in a previous paper (Wong et al., 1992). When the whole profile was examined none of the models studied gave adequate fits. The data were then refitted, with limits, and the mean slopes of the release profiles with the corresponding r^2 and mean square error values reported. Using the fractionated microspheres as an example the results of the modelling are given in Table 4. The best model for the majority of the systems was shown to be the

TABLE 3

Analysis of variance table for evaluating the effect of cooling time and stirring speed on mean particle size

Source	Degrees of freedom	Sum of squares	Mean square	F value	Pr > F
Cooling time (min)	2	281072.754	140536.377	111.68	0.0001
Stirring speed (rpm)	1	633727.2502	633727.2502	503.59	0.0001
Cooling time [a]	2	749.8909	374.9455	0.30	0.7459
Stirring speed					
Error	18	22651.6400	1258.4244		
Total	23	983201.5352			
R^2		0.975856			
Coefficient of variance		6.064372			
Root mean square		35.47428			
Mean diameter		584.962082			

TABLE 4

Kinetic assessment of the release of ibuprofen from fractionated cetostearyl alcohol pellets

Microsphere size fraction [cooling time (min)]	First-order equation [0–80]			Cube root equation [0–80]			Baker and Landsdale model [50–98]			Higuchi's $t^{0.5}$ model [20–80]		
	Slope $\times 10^{-1}$ (h^{-1}) $\pm$ SD ($\times 10^{-1}$)	% r^2	Mean square	Slope $\times 10^{-1}$ (h^{-1}) $\pm$ SD ($\times 10^{-1}$)	% r^2	Mean square	Slope $\times 10^{-1}$ (h^{-1}) $\pm$ SD ($\times 10^{-1}$)	% r^2	Mean square	Slope $\times 10^{-1}$ ($h^{-0.5}$) $\pm$ SD ($\times 10^{-1}$)	% r^2	Mean square
180–250 μm (2)	-6.99 ± 1.140	99.8	0.0085	-1.79 ± 0.210	99.4	0.00015	1.47 ± 0.076	98.6	0.00013	7.51 ± 0.439	99.9	0.00009
50:50 mixture (2)	-4.57 ± 0.334	98.2	0.0040	-1.26 ± 0.068	99.0	0.00018	1.07 ± 0.100	94.1	0.00049	6.92 ± 0.177	98.2	0.00015
710–1000 μm (2)	-2.99 ± 0.105	98.8	0.0017	-0.84 ± 0.019	99.6	0.00005	0.92 ± 0.031	97.1	0.00022	5.38 ± 4.360	99.5	0.00002
180–250 μm (7)	-5.49 ± 0.160	99.1	0.0034	-1.42 ± 0.037	98.4	0.00044	0.38 ± 0.032	90.2	0.00078	6.73 ± 0.290	98.7	0.00035
50:50 mixture (7)	-2.731 ± 0.125	99.9	0.0005	-0.71 ± 0.024	99.3	0.00014	0.54 ± 0.044	92.6	0.00068	4.22 ± 0.061	99.4	0.00023
710–1000 μm (7)	-2.39 ± 0.028	96.8	0.0092	-0.64 ± 0.005	98.3	0.00035	0.60 ± 0.015	98.0	0.00018	5.38 ± 0.051	99.3	0.00032
180–250 μm (10)	-3.75 ± 0.390	98.4	0.0058	-0.97 ± 0.080	97.4	0.00065	0.52 ± 0.018	98.4	0.00020	6.24 ± 0.074	98.3	0.00100
50:50 mixture (10)	-2.82 ± 0.087	99.9	0.0004	-0.73 ± 0.023	99.7	0.00007	0.46 ± 0.031	99.9	0.00001	4.08 ± 0.059	99.0	0.00042
710–1000 μm (10)	-2.33 ± 0.148	96.4	0.0105	-0.62 ± 0.031	98.5	0.00030	0.53 ± 0.019	99.7	0.00006	5.09 ± 0.120	99.8	0.00006
180–250 μm (100)	-1.92 ± 10.045	98.0	0.0047	-0.51 ± 0.009	99.3	0.00012	0.25 ± 0.025	94.1	0.00082	4.23 ± 0.015	99.8	0.00006
50:50 mixture (100)	-0.98 ± 0.048	99.8	0.0007	-0.25 ± 0.010	99.0	0.00020	0.14 ± 0.009	100.0	0.00000	2.48 ± 0.078	98.2	0.00070
710–1000 μm (100)	-0.59 ± 0.026	96.5	0.0073	-0.16 ± 0.006	98.3	0.00025	0.15 ± 0.003	98.0	0.00006	2.56 ± 0.083	98.9	0.00050

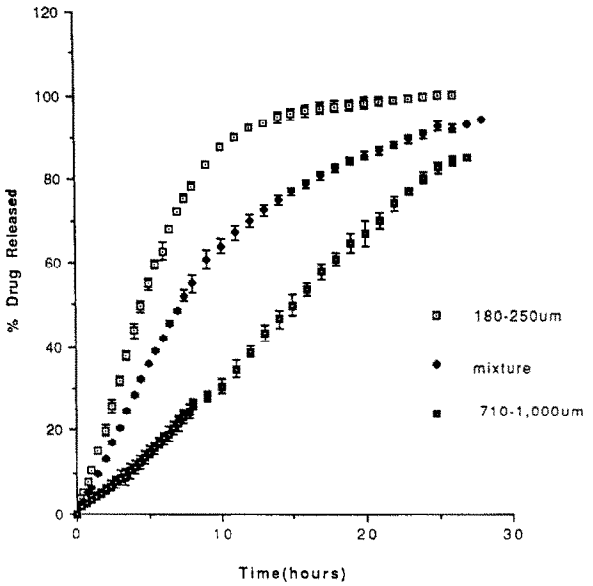

Fig. 2. Effect of pellet size on the release rate of ibuprofen from cetostearyl alcohol pellets containing 10% w/w ibuprofen and produced at a cooling time of 100 min. Error bars are ± SD of mean values.

square root of time model over the range 20–80% drug release.

Analysis of the slopes for the fractionated spheres shows that at each cooling time the smaller size fraction (180–250 μm) exhibited the quickest release while the largest size fraction (710–1000 μm) showed the slowest release, the mixture of the two fractions being intermediate between the two. These results can be explained in terms of the surface area, i.e., the smallest size fraction presents the greatest surface area for dissolution. The profiles of the fractionated pellets with a cooling time of 100 min are shown in Fig. 2.

Table 5 shows the results of the effect of the cooling time and stirring rate on the release kinetics of the unfractionated microspheres. The results are illustrated graphically in Figs 3 and 4. As expected, increasing the stirring rate produced an increase in vitro drug release. Figs 3 and 4 also show that increasing the cooling time decreased the release of drug from the system. It is thought that this effect is a function of two parameters: particle size and surface morphology. As the cooling time increases the mean particle diameter increases, thus decreasing the surface area available for dissolution. The resultant effect is a decrease in drug dissolution. Cooling time also affects the surface morphology of the microspheres, as was evident from electron microscopic analysis of the microspheres' surface. It can be

TABLE 5

Effect of cooling time and stirring speed on the release kinetics of the unfractionated pellets

Speed of rotation (rpm)	Cooling time (min)	Slope ± SD ($h^{-0.5}$)	r^2 (%)	mean square
600	100	0.246 ± 0.050	99.8	0.00019
600	10	0.463 ± 0.005	99.6	0.00020
600	7	0.468 ± 0.010	99.8	0.00017
600	2	0.621 ± 0.010	100.0	0.00001
1300	100	0.413 ± 0.022	99.4	0.00019
1300	10	0.506 ± 0.031	99.9	0.00003
1300	7	0.566 ± 0.025	99.8	0.00008
1300	2	0.665 ± 0.034	99.0	0.00093

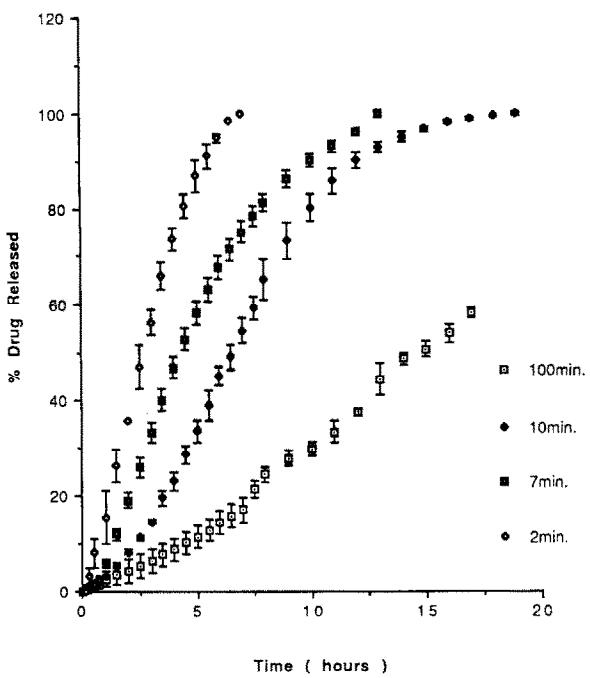

Fig. 3. Effect of cooling time on the release of ibuprofen from cetostearyl alcohol pellets prepared at a stirring rate of 600 rpm. Error bars are ± SD of mean values.

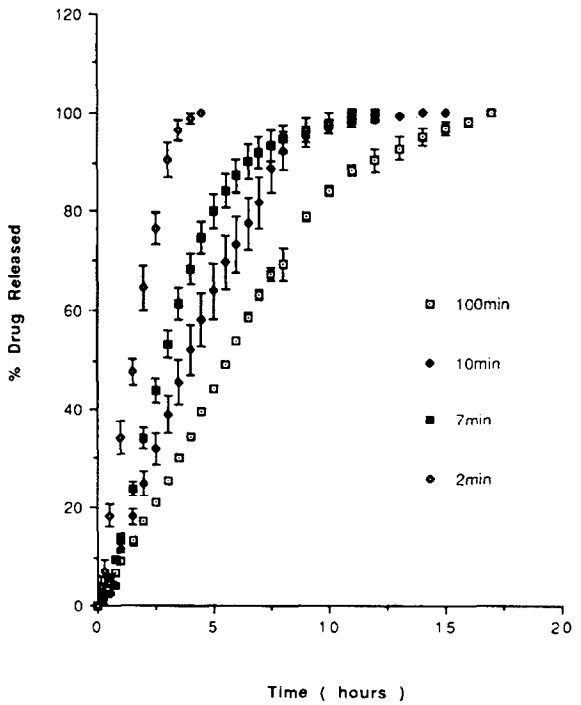

Fig. 4. Effect of cooling time on the release of ibuprofen from cetostearyl alcohol pellets prepared at a stirring rate of 1300 rpm. Error bars are ± SD of mean values.

seen from Figs 5 and 6 that the surface of the microspheres prepared at the fastest cooling time exhibit more cracks and channels than the surface of those formed at the slower cooling times. A similar observation was made by Bodmeier and

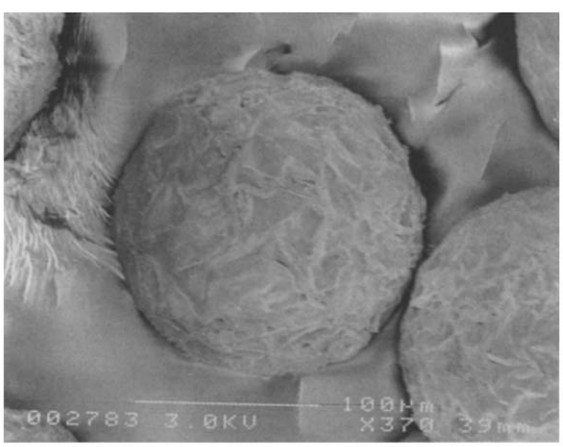

Fig. 5.

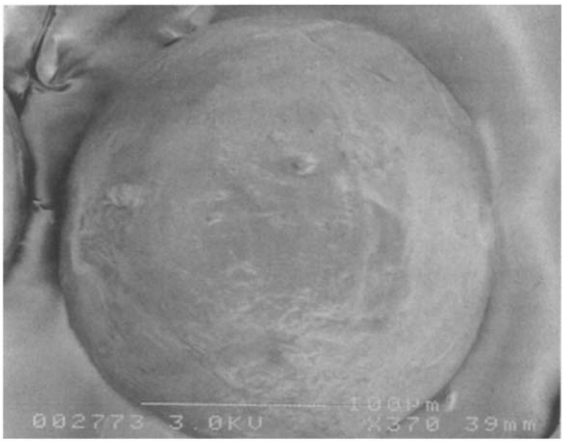

Fig. 6.

Paeratakal (1989); freeze-dried beads had a more porous internal structure than air-dried beads.

Table 6 shows that the density of the microspheres increases as the cooling time increases, suggesting that the microspheres formed at the slow cooling times are more compact and less porous than those prepared at the faster cooling times. Table 6 also shows that the microspheres from the 180–250 μm fraction at all four cooling times were denser than the 710–1000 μm fraction. After microsphere formation the amount of water contained in each microsphere system was investigated by measuring the water lost from the formed microspheres in a predetermined period of time. Table 7 lists the results of this study. The water lost from the microspheres increases as the

TABLE 6

Effect of the cooling time during formation of pellets, and particle size on the density of the resultant pellets

Cooling time (min)	Sieve fraction (μm)	Density ± SD (g cm^{-3})
100	710–1000	0.8956 ± 0.0063
10	710–1000	0.8938 ± 0.0045
7	710–1000	0.8874 ± 0.0074
2	710–1000	0.8384 ± 0.0016
100	180–250	0.9491 ± 0.0042
10	180–250	0.9376 ± 0.0083
7	180–250	0.9067 ± 0.0059
2	180–250	0.8406 ± 0.0062

TABLE 7

Effect of drying pellets under phosphorus pentoxide for 24 h

Cooling rate (min)	Sieve fraction (μm)	Water loss ± SD (g) ($\times 10^{-3}$)
100	710–1000	3.77 ± 0.21
10	710–1000	4.00 ± 0.25
7	710–1000	4.33 ± 0.49
2	710–1000	5.70 ± 0.15
100	180–250	2.75 ± 0.06
10	180–250	2.90 ± 0.32
7	180–250	3.30 ± 0.15
2	180–250	4.40 ± 0.40

cooling time decreases as is evident for both pellet fractions. The results show that at the same fraction size the microspheres prepared at slow cooling times contain less water and thus may be said to be less porous and more compact than those prepared at the fastest cooling times. The water lost from the 180–250 μm fraction is less than that of the 710–1000 μm fraction, confirming the results of the density experiments and suggesting that the smaller pellets are more compact and possibly less porous than the larger size fraction.

Conclusion

Preparation of matrix pellets by aqueous dispersion is relatively straightforward. By altering certain formulation parameters of this method pellets can be produced which exhibit different in vitro release profiles. The temperature range (65–30°C) in which all of the solid components of the pellets would have separated out was altered and subsequently shown to significantly affect mean particle diameter and morphology. Pellets could thus be formulated to give in vitro release profiles with good sustained-release properties.

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