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Microencapsulation of ibuprofen and Eudragit® RS 100 by the emulsion solvent diffusion technique

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Abstract

The emulsion solvent diffusion was employed to prepare modified release microspheres of ibuprofen. The technique was optimised for the following processing variables: the absence/presence of baffles in the reaction vessel, agitation rate and drying time. Thereafter, the influence of various formulation factors on the microencapsulation efficiency, in vitro drug release and micromeritic properties was examined. The variables included the methacrylic polymer, Eudragit® RS 100, ibuprofen content and the volume of ethanol used during microencapsulation. The results obtained were then interpreted on a triangular phase diagram to map the region of microencapsulation, as well as those formulations that yielded suitable modified release ibuprofen microspheres. © 2001 Published by Elsevier Science B.V.

Keywords: Microencapsulation; Ibuprofen; Emulsion solvent diffusion technique; Eudragit®; Triangular phase diagram

1. Introduction

Microencapsulation is a well-known method that is used to modify and retard drug release from pharmaceutical dosage forms (Kristl et al., 1991). Various microencapsulation techniques and coating materials may be employed to prepare the formed units.

In this study, the preparation of ibuprofen microspheres was accomplished using the emulsion solvent diffusion method, which is a simultaneous process that combines spherical agglomeration and microencapsulation of the drug (Kawashima et al., 1988). The technique was selected to prepare modified release ibuprofen microspheres due to its simplicity, low cost, success with poor aqueous solubility drugs and the production of microspheres of relatively high drug loading. Eudragit® RS 100, a methacrylate resin, was favoured as the retarding polymer in view of the many advantages that they possess (Watts et al., 1991).

The non-steroidal anti-inflammatory drug, ibuprofen, was selected as the model drug in this study. The short plasma half-life of 1–3 h following oral dosing (Kantor, 1979) makes it an ideal candidate for a modified release multiple-unit ibuprofen preparation.

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The present study undertook to optimise the emulsion solvent diffusion technique for the absence/presence of baffles in the reaction vessel, agitation rate and drying time. The influence of various formulation variables on microsphere formation, micromeritic properties (such as particle size, size distribution, surface morphology) and in vitro drug release characteristics was examined and interpreted using a triangular phase diagram.

2. Materials and methods

2.1. Materials

The following materials were used in the study: ibuprofen (Lennon, South Africa); Eudragit® RS 100 (Röhm Pharma, Darmstadt, Germany); sucrose fatty acid ester F-70 (Croda Chemicals, South Africa); ethanol (Protea, South Africa); potassium dihydrogen orthophosphate and sodium hydroxide (SAAR Chem., South Africa). All other chemicals and solvents were of analytical grade and used as received.

2.2. Preparation of microspheres

The emulsion solvent diffusion technique (Kawashima et al., 1988) was used to produce ibuprofen microspheres, according to the procedure outlined in Perumal et al. (1999). All microspheres in this study were prepared in a 1-l tall-form beaker fitted with a lid having ports for a thermometer and a propeller rod, as well as a port for drug–polymer solvent addition (Fig. 1).

Microencapsulation of ibuprofen was achieved using the following procedure: ibuprofen and Eudragit® RS 100 polymer were dissolved in ethanol. An emulsifying agent, sucrose fatty acid ester F-70 (0.025% m/v), was triturated with water ($\pm$ 5 ml) to form a paste. This was quantitatively transferred by washing with the balance of 800 ml of water into a cylindrical tall-form beaker. The drug–polymer solution was then quickly poured into the aqueous phase. Mixing of the two liquid phases was effected with the use of a Heidolph three-blade propeller-type modified agitator at various speeds. The ethanolic solution immediately dispersed into fine droplets that subsequently solidified into rigid microspheres. The system was performed in a thermally controlled room at 20 ± 2°C. Following 30 min of agitation, the solidified microspheres were recovered by decantation and washed several times with deionised water. Drying of microspheres was achieved by heating in an air-heated Heraeus oven for 24 h at 40 ± 0.5°C. The above procedure was also used to prepare a batch of microspheres with 0% polymer.

2.3. Optimisation of the emulsion solvent diffusion technique

2.3.1. Effect of side baffles

Two batches of microspheres of the same fo-

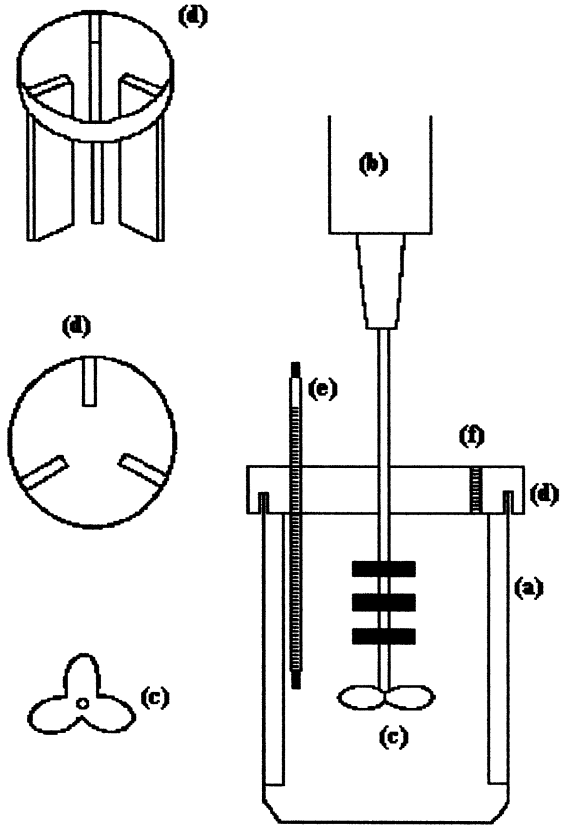

Fig. 1. Schematic representation of the apparatus used in the microencapsulation of ibuprofen by the emulsion solvent diffusion technique. (a) 1-l cylindrical vessel; (b) motor; (c) 3-blade propeller-type agitator; (d) baffle support/cover; (e) thermometer; (f) sample port.

rmulation (one Eudragit® RS 100: three ibuprofen) were prepared. One was prepared without the use of side baffles and the other with side baffles. Three removable Teflon side baffles were fitted beneath the covering lid so that when the lid was placed over the beaker, the baffles were suspended at regular intervals along the inner circumference of the beaker (Fig. 1d). The agitation rate for this experiment was set at 300 rpm. The obtained microspheres of each batch were characterised and evaluated for particle size attributes, yield and drug content.

2.3.2. Effect of agitation rate

Various batches of the same formulation were made, but the agitation rate was the only parameter that was varied between 200 and 700 rpm. After drying, the weighed batch of microspheres was subjected to particle size and drug content analyses. The microsphere size and size distribution of each batch of microspheres were determined using the usual statistical formulae (for normal distribution) and the Quatro Pro version 3.01 programme.

2.3.3. Effect of drying time for the microspheres

In order to determine the optimum drying time for ibuprofen–Eudragit® RS 100 microspheres, the moisture content was determined before and after drying at 40 ± 0.5°C for various periods of time in an air-heated Heraeus oven. An automated Mettler DL 18 Karl Fischer titrator was used for triplicate analysis of samples for moisture content.

2.4. Influence of formulation variables

The influence of formulation variables on microsphere formation, micromeritic and drug release characteristics was investigated. These variables included the methacrylic polymer, Eudragit® RS 100, ibuprofen content and the volume of the solvent, ethanol. The data obtained were then interpreted on a triangular phase diagram.

2.5. Microsphere characterisation and evaluation

Drug content of the microspheres was determined by ultra-violet spectrophotometry, according to the procedure outlined in Perumal et al. (1999).

In all experiments, the drug release profiles of the prepared microspheres were evaluated using Apparatus 1 method of the USP XXII (1990). A volume of 900 ml of phosphate buffer (pH 6.8) at 37 ± 0.5°C was employed as the dissolution medium at 100 rpm agitation. The addition of 0.02% v/v Polysorbate 80 to the medium improved the dispersion and wettability of the microspheres. The in vitro dissolution of ibuprofen from the microspheres is reported as a mean of four determinations.

Standard sieves, as stipulated in the USP XXII (1990), were used to determine the particle size attributes of the microsphere batches. The average diameter and the S.D. of the batch were calculated using the usual statistical formulae for normal distribution on the Quatro Pro version 3.01 programme. The S.D. was used as an indication of the size distribution of microspheres about the mean.

The percentage yield is defined as the quantity of microspheres produced as a function of loaded drug and polymer. The recovery is the percentage of microspheres of size 125–2000 μm to loaded drug and polymer.

3. Results and discussion

3.1. Microsphere formation using the emulsion solvent diffusion technique

The emulsion solvent diffusion technique was successfully employed for the microencapsulation of ibuprofen with Eudragit® RS 100 polymer. The addition of the drug–polymer–ethanol phase to the aqueous medium resulted in the immediate formation of discrete coacervate-like oil droplets of the ethanol solution (Fig. 2). The droplets solidified to form well-shaped, rigid microspheres (Fig. 3) on diffusion of the ethanol from the droplets. A model for the process and mechanism

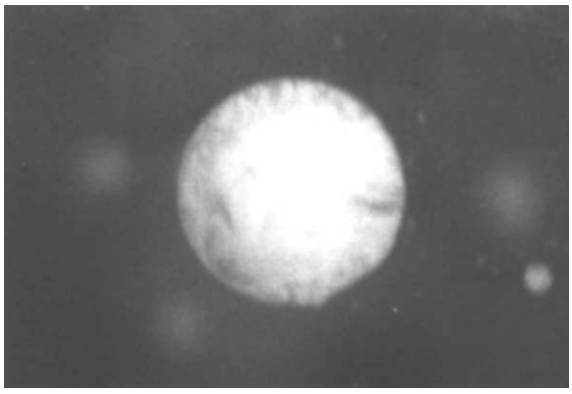

Fig. 2. Formed oil droplet on addition of the drug–polymer–ethanol phase to the aqueous medium (15 × magnification) (10 mm = 652 μm).

of microsphere formation has been suggested by Kawashima et al. (1989). Ethanol and water counter-diffuse out of and into the oil droplets, respectively. The diffused water within the droplets may decrease the drug and polymer solubilities. Both components co-precipitate and continued ethanol diffusion results in further solidification, producing matrix-type microspheres, as shown in Fig. 3.

3.2. Optimisation of the emulsion solvent diffusion technique

3.2.1. Effect of side baffles

Results of the influence of side baffles on the particle size characteristics of the formed ibuprofen microspheres are presented in Fig. 4. The effect of the side baffles on the microsphere yield and characteristics is shown in Table 1. Fig. 4

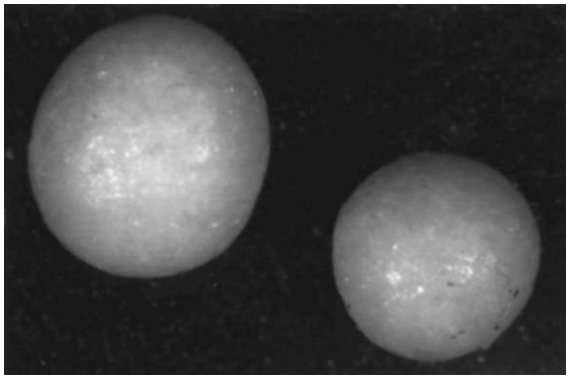

Fig. 3. Formed ibuprofen microspheres on diffusion of the ethanol from the oil droplets (40 × magnification) (10 mm = 244 μm).

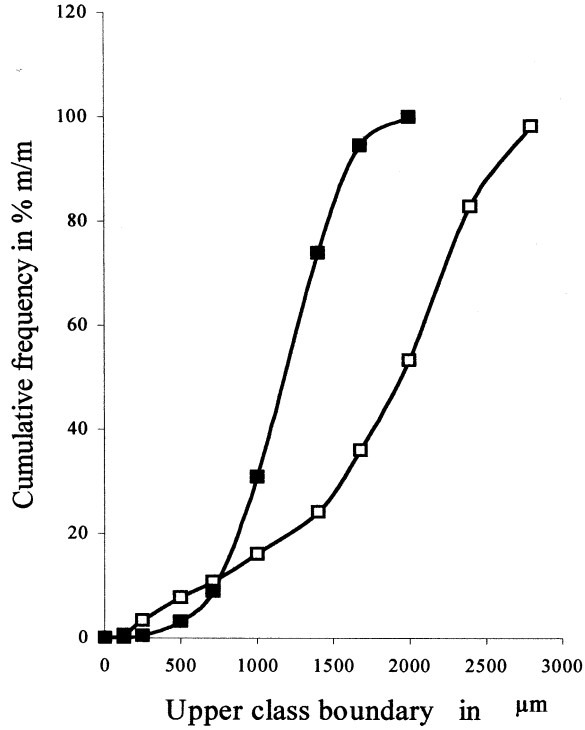

Fig. 4. Effect of side baffles on the cumulative undersize frequency polygon of ibuprofen microspheres.

Table 1
Characteristics of microsphere batches made with and without side baffles

Characteristics	Batch 1: without side baffles	Batch 2: with side baffles
Yield (%)	81.67	94.16
Recovery (%)	43.49	94.02
Irregular non-sphere (%)	8.55	0.26
Mean particle size (μm)	1925 ± 695	1232 ± 498
Assayed drug content (%)	71.89 ± 0.70	73.09 ± 0.52
Theoretical drug content of microspheres (%)	75.02	75.00

clearly demonstrates that the inclusion of side baffles to the apparatus improved the particle size attributes of the microspheres. Both the size distribution of the microspheres (also denoted by the S.D. in Table 1) and the median particle size, indicated by the 50% undersize frequency mark in Fig. 4, were significantly smaller when side baffles were present in the apparatus.

The results in Table 1 indicate a lower yield, a severely compromised recovery, a greater quantity of irregularly formed particles, a larger mean microsphere diameter and a wider size distribution for the batch of microspheres that was prepared without side baffles in the apparatus. By comparison, the inclusion of side baffles in the cylindrical reactor vessel resulted in a significant improvement in the efficiency of microsphere formation and in particle size characteristics. The drug content of microspheres in both batches was similar and comparable to the theoretical drug quantity. The side baffles, suspended from the underside of the lid to the inner circumference of the vessel (Fig. 1d) may have decreased the extent of the vortex or turbulence, hence uniformly distributing the mixing force throughout the emulsion mixture. This is likely to have promoted droplet stability and uniformity. The droplets, formed on addition of the drug–polymer–ethanol phase to the aqueous medium, are likely to have collided with one another and the side baffles, coalesced and re-divided until a steady-state droplet size distribution was approached. The net result was a narrower size distribution, a smaller average particle size, a lower percentage of irregularly shaped microspheres and a higher microsphere yield and recovery (Table 1).

Burger et al. (1985), using the suspension–crosslinking microencapsulation technique, showed a similar advantage in the particle size distribution of albumin microspheres with the use of side baffles in the reactor vessel. The same provision in the mixing vessel of an emulsion solvent evaporation apparatus was reported to significantly increase the yield of the product from 50 to 90% (Watts et al., 1991).

Due to the enhanced microsphere yield and microsphere attributes, all subsequent batches of ibuprofen microspheres were prepared in the reactor vessel fitted with side baffles, as illustrated in Fig. 1(d).

3.2.2. Effect of agitation rate during microencapsulation

Drug release from microspheres is dependent on its particle size (Beck et al., 1979). The stirring rate of the emulsion mixture at the time of manufacture influences the particle size (Barkai et al., 1990) and, in some cases, the size distribution of the prepared microspheres (Nixon and Hassan, 1980). Hence, a suitable agitation rate to optimise particle size, size distribution and consequent drug release from the microspheres was investigated.

The effect of agitation rate on the particle size distribution and on the mean particle size of the microspheres, prepared with 0.025% (w/v) sucrose fatty acid ester F-70 (emulsifier), is presented in Figs. 5 and 6.

Fig. 5 illustrates the cumulative undersize percentage of microspheres plotted on a log–normal scale against the upper class boundaries of sieve diameters for each of the batches made at the various agitation rates. The plotted results indicate that, as the agitation rate was decreased, the microsphere size and size distribution increased. The plot of the mean microsphere diameter and agitation rate employed, presented in Fig. 6, demonstrates that the average microsphere diameter and the width of the size distribution (denoted by 1, 2 or 3 S.D. for 66, 95 and 99.7% of the population, respectively) decreased with increasing agitation rate.

At an agitation rate of < 350 rpm, the mean particle diameter and the size distribution of the microspheres, increased significantly. The tendency of the droplets to coalesce and aggregate at the slower agitation rates (i.e. < 350 rpm), may have been correspondingly high, resulting in larger mean microsphere diameters. These low agitation rates may have decreased the uniformity of the mixing force throughout the emulsion mixture, hence resulting in a wider size distribution of the final microspheres.

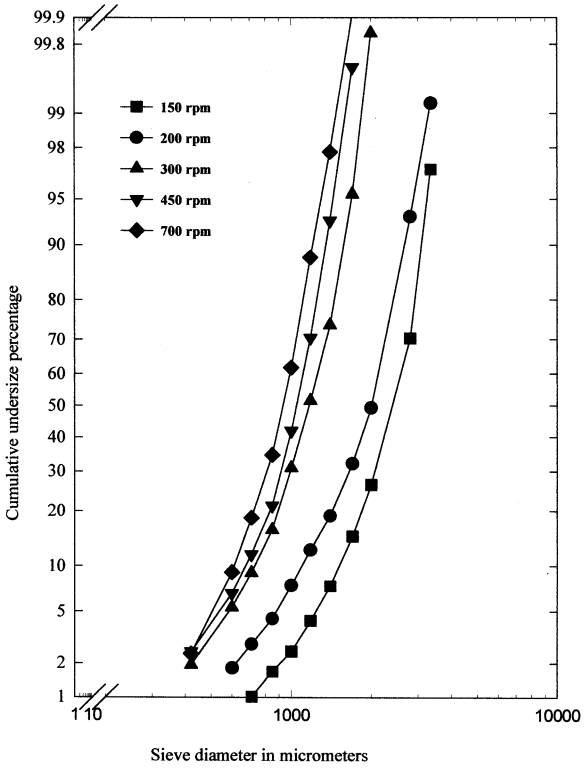

Fig. 5. Particle size distribution of ibuprofen microspheres as a function of agitation rate during microencapsulation.

At agitation rates of >350 rpm, the particle size attributes changed to a lesser extent. At these higher agitation rates, a vigorous, uniform, increased mechanical shear may have resulted. The addition of the ethanol phase to the aqueous medium therefore resulted in rapid division of the formed droplets that may have had lesser chance of coalescing into bigger droplets. This suggests that the size of the droplets formed during microencapsulation may therefore be closely related to the size of the final microspheres, which increased significantly with decreasing agitation rate (Fig. 6).

Other authors have also reported a similar inverse relationship between the agitation rate and the mean microsphere size (Praveen Reddy et al., 1990; Al-Kassas et al., 1993). However, Barkai et al. (1990) reported that, while increasing the agitation rate decreased the mean particle diameter, no change was observed in the width of the size distribution in their study. Moreover, it was revealed in the above study that drug loss may have been an inverse function of agitation rate. This finding, regarding the drug content–agitation rate, was not observed in the present study.

The agitation rate of 350 rpm yielded a mean particle diameter of 1172 ± 343 mm with a satisfactory size distribution of microspheres. More than 95% of the microsphere population of this batch, as well as the mean microsphere diameter, were <2000 μm particle size. These units would therefore not be dependent on gastric emptying, as they would be sufficiently small to pass the pylorus even when the sphincter is closed. In view of these particle size attributes, the agitation speed of 350 rpm was selected for all subsequent manufacturing of ibuprofen microspheres by the emulsion solvent diffusion technique.

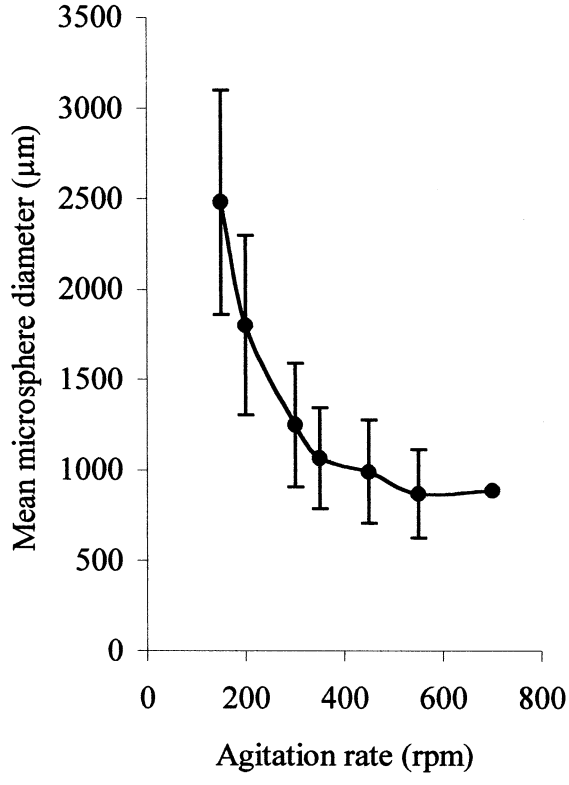

Fig. 6. Mean microsphere diameter and size distribution as a function of the agitation rate used during microencapsulation.

Table 2
Moisture content of ibuprofen microspheres during the drying at 40 ± 0.5°C

Drying time (h)	Moisture content (%)			Mean ± S.D.
	S1	S2	S3	
0*	26.19	23.86	25.91	25.32 ± 1.27
1	22.37	23.79	21.89	22.68 ± 0.99
3	8.15	9.72	8.01	8.94 ± 1.11
4	6.66	5.98	6.72	6.45 ± 0.41
24	0.49	0.65	0.84	0.66 ± 0.18
48	0.55	0.79	0.61	0.65 ± 0.12

* Microspheres prior to any drying.

3.2.3. Effect of drying time for ibuprofen microspheres

Storage of microspheres at 40 ± 0.5°C yielded dry, free-flowing single units with no evidence of aggregation after 24 h storage in an air-heated oven. The process of water removal from the microspheres was monitored over 48 h. The moisture content during the drying process and of the final microspheres of the same batch is presented in Table 2. The results indicate that the moisture content decreased as a function of drying time. After 24 h, the moisture content of the ibuprofen microspheres decreased to a mean value of 0.66% indicating that the drying method was effective in removing moisture from the microspheres. This moisture level is well below the stipulated limit of 5% for ibuprofen tablets (USP XXII, 1990).

The mean moisture content after a further 24 h storage (i.e. 48 h) did not indicate any significant change. Hence, all subsequent batches prepared in this study were oven-dried at 40 ± 0.5°C for 24 h prior to further testing.

3.3. Effect of formulation variables

3.3.1. Effect of Eudragit® RS 100

The ability of Eudragit® RS 100 to alter the drug release characteristics of the prepared ibuprofen microspheres is demonstrated in Fig. 7.

Comparison of the batches made with Eudragit® RS 100 and the batch made without polymer shows that microencapsulation of ibuprofen with Eudragit® RS 100 resulted in a marked decrease in the drug release rate of the microspheres. Further, Fig. 7 clearly illustrates that the rate of drug release from the microspheres depended on the polymer concentration of the prepared devices. An inverse relationship was observed between polymer content and drug release rate from the prepared microspheres. Microspheres containing 9.1% Eudragit® RS 100 released the drug more rapidly, while those with 33.3% Eudragit® RS 100 exhibited a relatively slower drug release profile.

A similar trend was observed for diethylpropion hydrochloride pellets prepared in a fluid bed apparatus and coated with various percentages or thicknesses of Eudragit® RS 100 polymer (Chetty and Dangor, 1994). However, Becirevic and Begic (1994) demonstrated that the release of potassium chloride from spray-dried coated crystals did not significantly depend on the quantity of Eudragit® RS 100 used and that no relationship was seen between polymer content and particle size. This study also found that polymer content did not influence the microsphere size (Table 3).

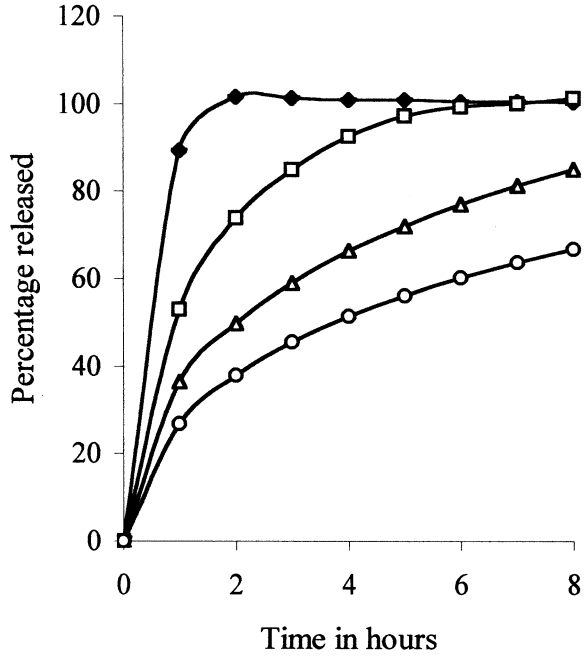

Fig. 7. Effect of Eudragit® RS 100 on the drug release profiles of ibuprofen microspheres.

Table 3
Effect of Eudragit® RS 100 on ibuprofen microsphere properties

Characteristics	Percentage Eudragit® RS 100				
	0	9.1	25.0	33.3	50.0*
Yield (%)	92.79	96.82	94.19	90.45	0
Recovery (%)	92.15	96.45	94.10	90.01	–
Mean diameter ± S.D. (μm)	1211 ± 326	840 ± 241	1172 ± 343	912 ± 337	–
Drug content (%)	101.07 ± 1.89	89.36 ± 1.09	73.07 ± 0.73	65.68 ± 0.57	–
Theoretical drug content (%)	100.00	90.90	75.00	66.07	50.00

* No microspheres formed.

The batch containing 25% Eudragit® RS 100 demonstrated a satisfactory drug release from the microspheres. The profile was characterised by 36 and 85% ibuprofen release at the end of 1st and 8th hour of dissolution, respectively.

3.4. Effect of ethanol volume

The effect of ethanol volume on drug release from microspheres is presented in Fig. 8. Varying volumes of ethanol were used in the preparation of the dispersed phase. The quantity of ibuprofen and Eudragit® RS 100 (30 and 10 g, respectively) added was constant for all batches, therefore varying the ethanol volumes affected drug and polymer concentration in ethanol (Table 4). Since ethanol diffuses out and is not part of the final product, the composition of the dried microspheres was the same for each batch, i.e. 25% Eudragit® RS 100 and 75% ibuprofen.

Fig. 8 illustrates that the drug release profiles differed according to the volume of ethanol used during microencapsulation. The use of increasing volumes of ethanol produced microspheres with increasing drug release, despite the final composition of the batches being the same.

The ethanol volume of the dispersed phase also influenced the microencapsulation efficiency and microsphere properties of the various batches. The microsphere yield declined sharply as larger volumes of ethanol or less viscous dispersed phase solutions were used. When a solvent volume of 150 ml was used, the resulting ethanol phase was very dilute, with a reduced viscosity of 2.02 ± 0.25 mPa/s (Table 4). The addition of the two phases together produced rapid intermixing of the phases, resulting in immediate precipitation of drug and polymer before droplets could form. Hence, no microspheres were produced. When more viscous dispersed phases (75–100 ml ethanol) were used, some intermixing of the phases, as

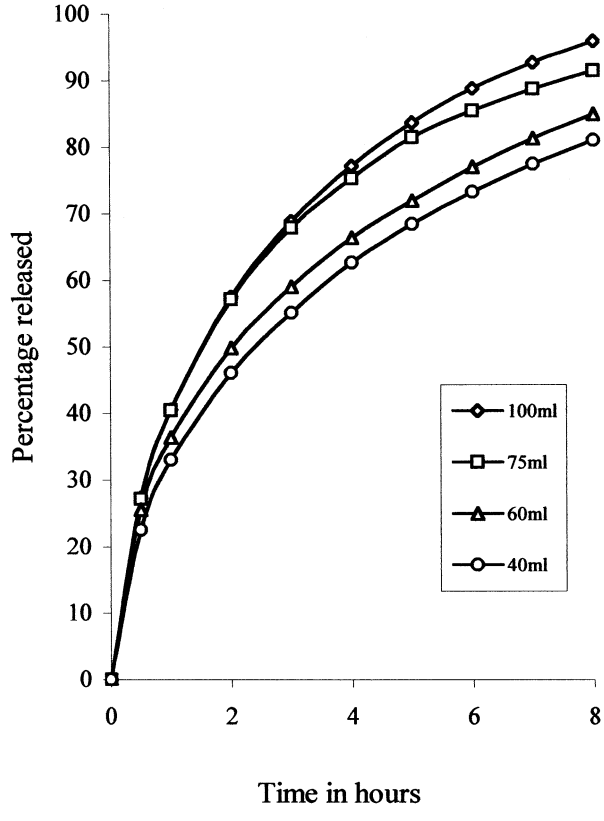

Fig. 8. Effect of ethanol volume on the drug release profiles of ibuprofen microspheres.

Table 4
Characteristics of microspheres prepared with different ethanol volumes

Characteristics	Ethanol volume (ml)				
	40	60	75	100	150*
Ibuprofen concentration in ethanol (g/ml)	0.75	0.50	0.40	0.30	0.20
Polymer concentration in ethanol (g/ml)	0.25	0.17	0.13	0.10	0.07
Viscosity of dispersed phase at 20 ± 2°C (mPa/s)	8.84 ± 0.11	5.14 ± 0.05	3.82 ± 0.08	2.78 ± 0.04	2.02 ± 0.25
Yield (%)	86.93	94.19	84.89	67.04	0
Recovery (%)	85.68	94.10	83.50	66.02	–
Mean diameter $\pm$ S.D. (μm)	1363 ± 303	1172 ± 343	1149 ± 260	1047 ± 363	–
Drug content (%)	75.64 ± 0.00	73.07 ± 0.73	74.58 ± 0.72	70.46 ± 0.73	–
Theoretical drug content (%)	75.00	75.00	75.01	75.00	75.0

* No microspheres formed.

well as droplet formation, occurred to yield both a precipitated drug/polymer mass as well as microspheres, hence the improved yields and recoveries. With the use of 60 ml of ethanol, the dispersed phase viscosity increased to 5.14 ± 0.05 mPa/s (Table 3). Almost all of the viscous dispersed phase divided into droplets that solidified to form microspheres when the ethanol diffused out. The use of an even more viscous ethanol solution (40 ml ethanol) resulted in the formation of concentrated droplets, which yielded well-formed microspheres of a larger particle size. The lower yield observed with this batch was expected because some of the highly viscous ethanol phase adhered to the beaker, thereby hindering complete transfer into the reactor vessel.

Particle size analysis of these batches revealed an increase in the particle size with a decrease in ethanol volume (Table 4). Hence, it is likely that particle size changes as a result of changes in the volume of ethanol or drug/polymer concentration may account for the drug release profiles seen in Fig. 8. Pongpaibul et al. (1984) and Barkai et al. (1990), using the emulsion solvent evaporation technique, demonstrated a similar particle size relationship with solvent volume or drug/polymer concentration. Barkai et al. (1990) attributed this finding to the viscosity of the dispersed phase. On the other hand, Arshady (1990) reported that the dependence of particle size on polymer concentration was more significant than on drug concentration in solvent. The previous experiment in this study (Section 3.3.1) demonstrated that polymer concentration alone did not influence the particle size of the microspheres.

The drug content of the microspheres in the various batches showed good correlation with the theoretical drug loadings, although the batch made with 100 ml ethanol showed a drug content on the lower side. This could be due to drug loss during intermixing of the phases. The results of this study highlighted the importance of selecting the correct solvent volume in the preparation of ibuprofen microspheres with the desired attributes.

3.5. Triangular phase diagram

The phase diagram (Fig. 9), constructed using the Sigma Plot Version 5.00 programme, was based on the percentage (m/m) concentration of the components, ibuprofen, Eudragit® RS 100 and ethanol in the dispersed phase for 0.025% (m/v) of sucrose fatty acid ester F-70. In the case of ethanol, the labelled specific gravity was used to calculate the percentage concentration.

Attempts to microencapsulate some formulations yielded no microspheres, agglomerates, stringy drug–polymer masses, large drug–polymer marbles or even viscous milky solutions. These formulations plotted as Points 7, 8 and 13–17, respectively, on the triangular phase diagram of Fig. 9 (open circles), were found to enclose an approximate region of microencapsulation (denoted by A).

Within region A, the hatched circles, plotted as Points 1–6, represent formulations of increasing Eudragit® RS 100, decreasing drug and ethanol levels. These formulations produced microspheres. The highest Eudragit® RS 100 concentration incorporated into the microspheres was 15.5% (Point 6). The diagram indicates that Eudragit® RS 100 at a level of $\approx 20\%$ (Point 7) and above, did not microencapsulate ibuprofen; instead, numerous long, stringy, firm masses were recovered. This may be as a result of the solubility characteristics of Eudragit® RS 100 either alone or together with ibuprofen in decreasing amounts of ethanol. In addition, the viscosity of the ethanol phase was likely to increase as more Eudragit® RS 100 was added, hence making division into droplets increasingly difficult.

The black circles, plotted as Points 9–12, represent formulations of decreasing ethanol percentages and increasing drug/polymer concentrations. As with the formulations represented by the hatched circles, these batches yielded clearly defined spherical microspheres. The highest drug percentage (drug concentration in ethanol 0.88 g/ml) that yielded microspheres was 42.7 (Point 12). However, at drug percentages of 44.5 (Point 13) (drug concentration 1.05 g/ml) and above, ibuprofen did not dissolve completely in the ethanol and was present in suspension. Microencapsulation of these suspensions yielded agglomerates with numerous distinctly evident ibuprofen crystals on the surface. Ibuprofen has a solubility of 1 in 1.5 ethanol and therefore, microencapsulation of drug levels $> 40\%$ of ethanol may be limited by the solubility of ibuprofen in ethanol. On addition of the ethanol phase, the suspended ibuprofen drug may have served as nuclei for continued irregular crystal growth that formed agglomerates with Eudragit® RS 100 rather than microspheres.

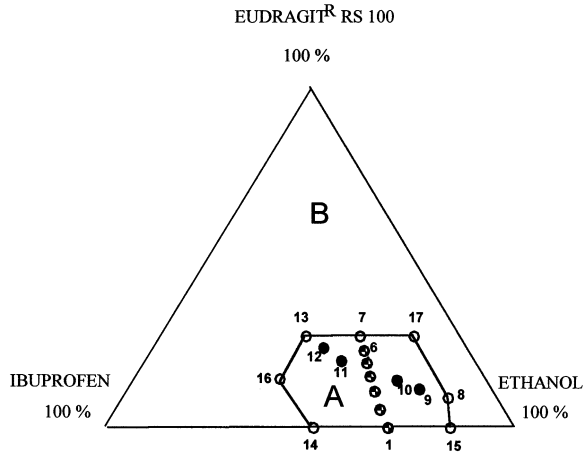

Fig. 9. Triangular phase diagram of formulations containing various levels of dispersed phase components.

Furthermore, formulations containing large volumes of ethanol, for example (Point 15) which contained 79.9% ethanol, resulted in milky viscous solutions when poured into the aqueous phase. The dilute solutions that had low viscosities may have influenced microencapsulation, as was the case in (Point 8) which contained 76.3% ethanol. Formulations of Points 9 and 10 prepared with 68.3 and 61.7% ethanol, respectively, did produce microspheres but with compromised yields.

From the above results, it was deduced that the region of successful microencapsulation of ibuprofen and Eudragit® RS 100 was limited to region A on the triangular phase diagram. Additional batches with formulations that fit the inner border of the 'proposed' microencapsulation region should be investigated in order to exactly define the actual microencapsulation area.

The study also undertook to identify a region of microsphere formulations which exhibited suitable drug release profiles. Drug release from the microspheres prepared with formulations proceeding from Points 1–6 in the triangular phase diagram (Fig. 9) demonstrated a trend of decreasing ibuprofen release rate. A similar pattern was obtained as one proceeded from Points 9 to 12 that decreased in solvent volume. An interesting feature was that the formulation, which had displayed the more suitable sustained drug release, was found at the intersection of these two lines.

The phase diagram constructed proved very useful in approximating the region of microencapsulation of ibuprofen and Eudragit® RS 100 by the emulsion solvent diffusion technique. Furthermore, the phase diagram of this study estimated a formulation area, Points 4–6, of suitable drug release within the microencapsulation region A.

4. Conclusions

The emulsion solvent diffusion technique was successful in producing ibuprofen microspheres. The formulation variables, ibuprofen percentage, Eudragit® RS 100 content and the volume of ethanol used influenced the microencapsulation efficiency, micromeritic and in vitro drug release characteristics of the prepared microspheres. The triangular phase diagram was successful in mapping the region of microencapsulation of ibuprofen and Eudragit® RS 100 for the selected emulsifier and the technique used. The application of the triangular phase diagram would be useful in future studies requiring microsphere formulation and manufacture via the emulsion solvent diffusion technique.

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