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RESEARCH PAPER

Modification of Crystal Habit of Ibuprofen Using the Phase Partition Technique: Effect of Aerosil and Tween 80 in Binding Solvent

Kaisri Umprayn,* Angkana Luengtummuen, Chutiporn Kitiyadisai, and Tussaporn Pornpiputsakul

Department of Manufacturing Pharmacy, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok 10330, Thailand

ABSTRACT

A ternary diagram, representing the solubility of binding solvent (chloroform) in a mixture of ethanol and water, was constructed. For this study, the solvent mixture that gave the best ibuprofen pellets (IPs) was composed of chloroform:ethanol:water at a ratio of 1.5%:8%:90.5%. The suitable agitator speed, temperature, and mixing time were found to be 1500 rpm, 25°C ± 2°C, and 20 min, respectively. In addition, suitable stirring time when the phase partition process of IPs began was 15 min. IPs obtained from these conditions were small and round, approximately 1 mm; surface determination by scanning electron microscopy (SEM) indicated that the IPs were composed of drug microcrystals rearranged on the surface. For the dissolution, IPs showed lower drug release when compared with pure ibuprofen crystal (IC) (f_2 analysis). An attempt to modify the dissolution property of IP by incorporating various concentrations of Aerosil and Tween 80 in the binding solvent was made. Microscopic appearance showed that both Aerosil and Tween 80 gave less spherical pellets when compared with the use of binding solvent alone. For both the Aerosil and Tween 80 employed, the results indicated a change in rearrangement of drug microcrystals and a change in crystal habit. However, Tween 80 gave more change of the

*Corresponding author.

crystallographic direction of drug microcrystals than Aerosil. In term of dissolution, the results showed that employing Tween 80 at 1.2% gave the highest drug release compared to the use of Aerosil and IC alone (f_2 analysis). These pellets had a good flow property, as indicated by Carr's compressibility, flow rate, and angle of repose, and they can be compressed into a tablet, encapsulated by suitable polymer, or pulverized to obtain micronized crystals. In the case of compression into tablets, the dissolution profiles of these tablets compared with those of commercial product meet the USP 24 requirement ($Q \geq 80\%$ at 60 min).

Key Words: *Effect of Aerosil; Effect of Tween 80; Ibuprofen; Spherical crystallization*

INTRODUCTION

The wet granulation process is one of the most widely used in the preparation of the tablet dosage form. However, this process involves many steps, such as pulverization, kneading, drying, granulating, and mixing. In addition, each step of the operation requires very expensive equipment, is time consuming, and is costly in terms of labor. On the other hand, the concept of the ''powder engineering technique'' may be used by various high-technology equipment (e.g., spray-drying or fluid bed granulators) with a small amount of binder for direct tableting (1); however, the equipment is very expensive. Recently, many researchers also developed a novel particulate design technique called spherical crystallization, which can design simultaneously the primary and secondary particulate properties of crystals during the crystallization process (2). Veillard and Deleuil (3) summarized the technique of spherical crystallization of various active ingredients (such as salicylic acid, aminophylline, calcium carbonate, lactose, and sulfamethoxazole) that had done before by many scientists. The concept of the powder engineering technique using the phase partition method to obtain spherical pellets will have an impact in the field of pharmaceutical technology. This technique can cut down the cost of expensive equipment and labor and is capable of minimizing the complications of the manufacturing process of various solid dosage forms.

The objective of this study was to prepare ibuprofen pellets (IPs) using the phase partition technique. We studied the effect of the amount of binding solvent, optimum dispersion time, and optimum phase partition time. In addition, the effects of Aerosil and Tween 80 in binding solvent were also investigated. The various pellets obtained were directly compressed, and dissolution profiles were examined in comparison with product on the market.

EXPERIMENTAL

Materials

Materials used were 2-(4-isobutylphenyl) propionic acid (Ibuprofen, Acdon Co., Ltd., Thailand); colloidal silicon dioxide (Aerosil, Degussa, Germany); polysorbate 80 (Tween 80, Srichand Sahaosoth Co., Ltd., Thailand); sodium starch glycolate (Explotab®, Edward Mendell, USA); talc USP (Srichan Sahaosoth Co., Ltd., Thailand); magnesium stearate USP (Bhajsudpanich Co., Ltd., Thailand); lactose monohydrate USP (Lactose Company of New Zealand); chloroform and ethanol (Mallinckrodt, USA). All other reagents used were analytical grade.

Equipment

Equipment used were a cylindrical reactor (Chulalongkorn Equipment and Research Centre, Thailand); laboratory test sieve (ASTM11, Endecotts, Ltd., England); sieve shaker (Josef Deckelmann, type EMK4, Western Germany); cube mixer (Erweka, Heusenstamm, Germany); scanning electron microscope (Jeol, JSM T220, Japan); dissolution apparatus (Hanson model SR2, Hanson Research Corp., USA); ultraviolet/visible (UV/Vis) recording spectrophotometer (Shimadzu UV 160A, Shimadzu Co., Ltd., Japan); single-punch tableting machine (Viuhang Engineering, Thailand).

Preparation of Ibuprofen Pellets

Phase Diagram for Chloroform, Water, and Ethanol

A ternary phase diagram for chloroform in a mixture of ethanol and water was constructed to select a suitable zone with the appropriate ratio of the three solvent systems for further study. It was noticed that chloroform behaves as a binding solvent; ethanol is a dissolving solvent for drug; and water is a dispersion solvent.

Phase Partition Technique to Obtain Ibuprofen Pellets

Approximately 11 g ibuprofen were weighed accurately on a tared and then transferred into a 50-ml volumetric flask. We added 16 ml ethanol and then warmed the mix at 40°C ± 2°C until a clear solution was obtained. Chloroform at a concentration indicated in Table 1 was dispersed in approximately 180 ml of water (which was contained in the reactor). The agitator was turned on and adjusted to 1500 rpm at 25°C ± 2°C for 20 min to disperse binding solvent into small droplets. Then, a clear saturated solution of drug in ethanol was added to the reactor, and the phase partition of drug in ethanol to binding solvent started to occur. The appropriate time for stirring after phase partition started was 15 min (4).

After that, the pellets were separated and dried in a tray dryer at 60°C for 6 h; then, their physical characteristics were determined.

Effect of Aerosil and Tween 80 on Physical Properties of Pellets

From the preliminary study, when pellets were prepared without Aerosil and Tween 80 in the binding solvent, it was clearly observed that microcrystals of ibuprofen appeared to be strongly packed, and the porosity of the pellets was minimized. The previous results could reduce dissolution of the pellets. In this experiment, Aerosil and Tween 80 were incorporated in the binding solvent; the physical properties of the pellets obtained were determined; and the dissolution profiles were constructed. The concentrations of Aerosil used were 0.025%, 0.05%, 0.1%, 0.3%, and 0.5%. In the case of Tween 80, concentrations used were 0.4%, 0.8%, 1.0%, and 1.2%. It was noticed that reverse partition of Tween 80 from binding solvent to the mixture of ethanol and water might not occur according to results from our previous studies (4).

Table 1

Amount of Solvents Selected from Phase Diagram Used to Prepare Pellets

Chloroform (%)	Chloroform Amount (ml)	Ethanol Am ount (ml)	Water Amount (ml)
1.5	3	16	181
2.0	4	16	180
2.5	5	16	179
3.0	6	16	178

Evaluation of Ibuprofen Pellets

Physical properties of IPs, such as examination of pellet appearance by scanning electron microscopy (SEM), particle size distribution, bulk density, tapped density, Carr's compressibility, flow rate, angle of repose, and percentage friability, were determined according to the manner of our previous studies (5,6).

Dissolution Profiles of Ibuprofen Pellets and Tablets

For preformulation studies, the dissolution testing was performed using dissolution apparatus I (basket) at 150 rpm with 900 ml of dissolution medium equilibrated to 37°C ± 0.5°C. The dissolu-

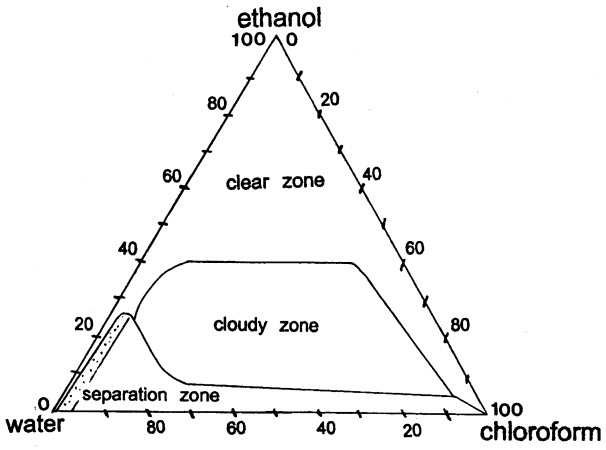

Figure 1. A ternary diagram of chloroform (binding solvent), ethanol, and water (dotted area indicates suitable mixture zone for phase partition of ibuprofen in this study).

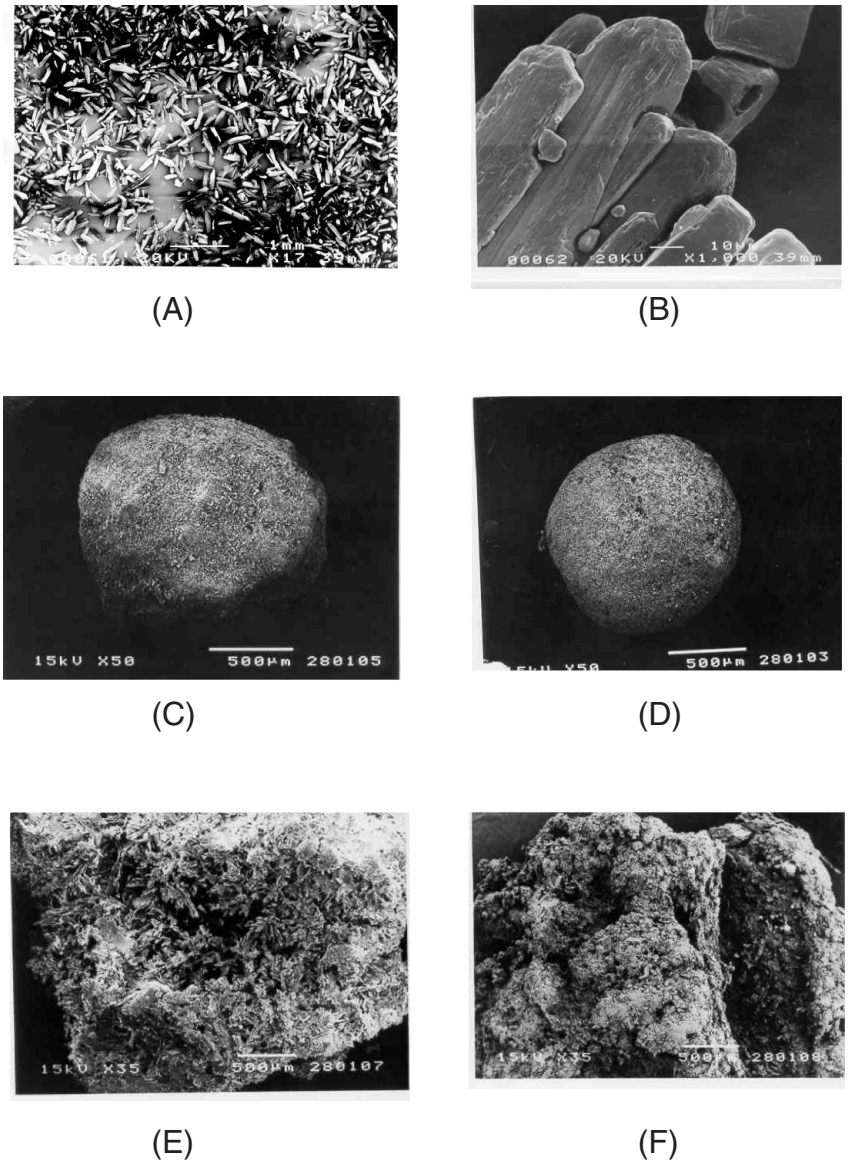

Figure 2. Photomicrographs of ibuprofen crystal (2A, ×17; 2B, ×1000) and pellets obtained using 3 ml and 4 ml binding solvent (2D, ×50; 2C, ×50; respectively); at 5 and 6 ml binding solvent, ibuprofen pellets did not occur (2E and 2F, ×35, respectively).

tion medium was 0.05 M potassium dihydrogen orthophosphate adjusted to pH 7.2 with 1.0 N sodium hydroxide. An accurately weighed portion of pellets equivalent to about 400 mg of ibuprofen was added to the basket of each dissolution vessel. Samples were taken at predetermined times of 5, 10, 15, 20, 30, 45, 60, 75, and 90 min. These samples were assayed by UV spectrophotometer at 265 nm. In the case of IPs compressed into tablets, the dissolution test was determined using dissolution apparatus II (paddle) according to USP 24. The similarity factor f_2 was used to determine the difference between dissolution profiles, as suggested by Shah et al. (7), to specify the immediate-release dosage form.

Preparation of Ibuprofen Pellet Tablets

IPs from the phase partition method retained on 14–20 mesh cut and Explotab® (at 3% and 4%,

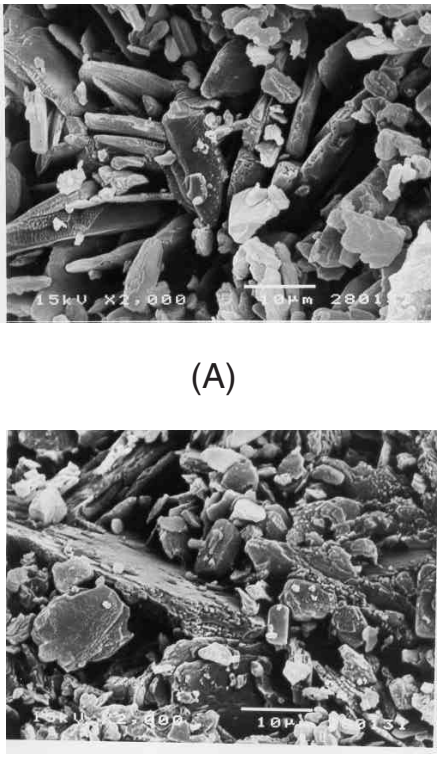

Figure 3. Photomicrographs illustrating the surface phenomenon of ibuprofen pellets prepared from 3 ml binding solvent (3A, ×2000), which clearly show more porosity compared with ibuprofen pellets prepared from 4 ml binding solvent (3B, ×2000).

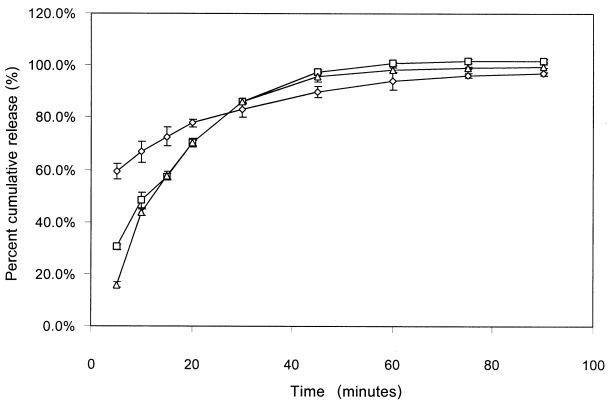

Figure 4. Dissolution profiles of ibuprofen crystal and pellets obtained from phase partition using chloroform as a binding solvent ($n = 6$) (◇, ibuprofen crystal; □, 3 ml binding solvent; Δ, 4 ml binding solvent 4 ml).

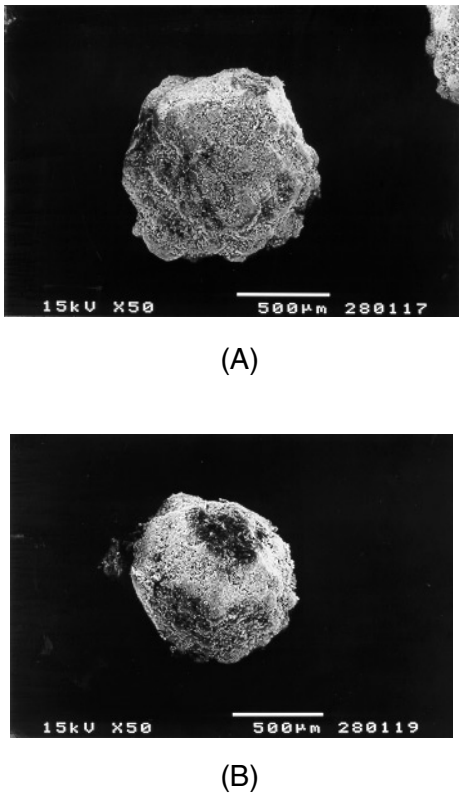

Figure 5. Photomicrographs of ibuprofen pellets prepared from 3 ml binding solvent containing Aerosil (5A, ×50) and Tween 80 (5B, ×50).

respectively) were blended for 10 min in a cube mixer. Then, the pellets and disintegrant were mixed with lubricant (magnesium stearate 3% and talc USP 1%) for another 5 min. The resulting mixtures were directly compressed into tablets using a single-punch tablet machine with a round 0.5-inch diameter, flat-faced tooling. The press was operated to produce tablets with an average weight of 550 ± 12 mg and a tablet hardness of 8 ± 2 Kp. The results of the dissolution test were compared with those for a commercial product (Brufen® 400, Boot, Thailand).

RESULTS AND DISCUSSION

A ternary phase diagram, representing the solubility of binding solvent (chloroform) in mixtures of ethanol and water, was constructed (Fig. 1). There

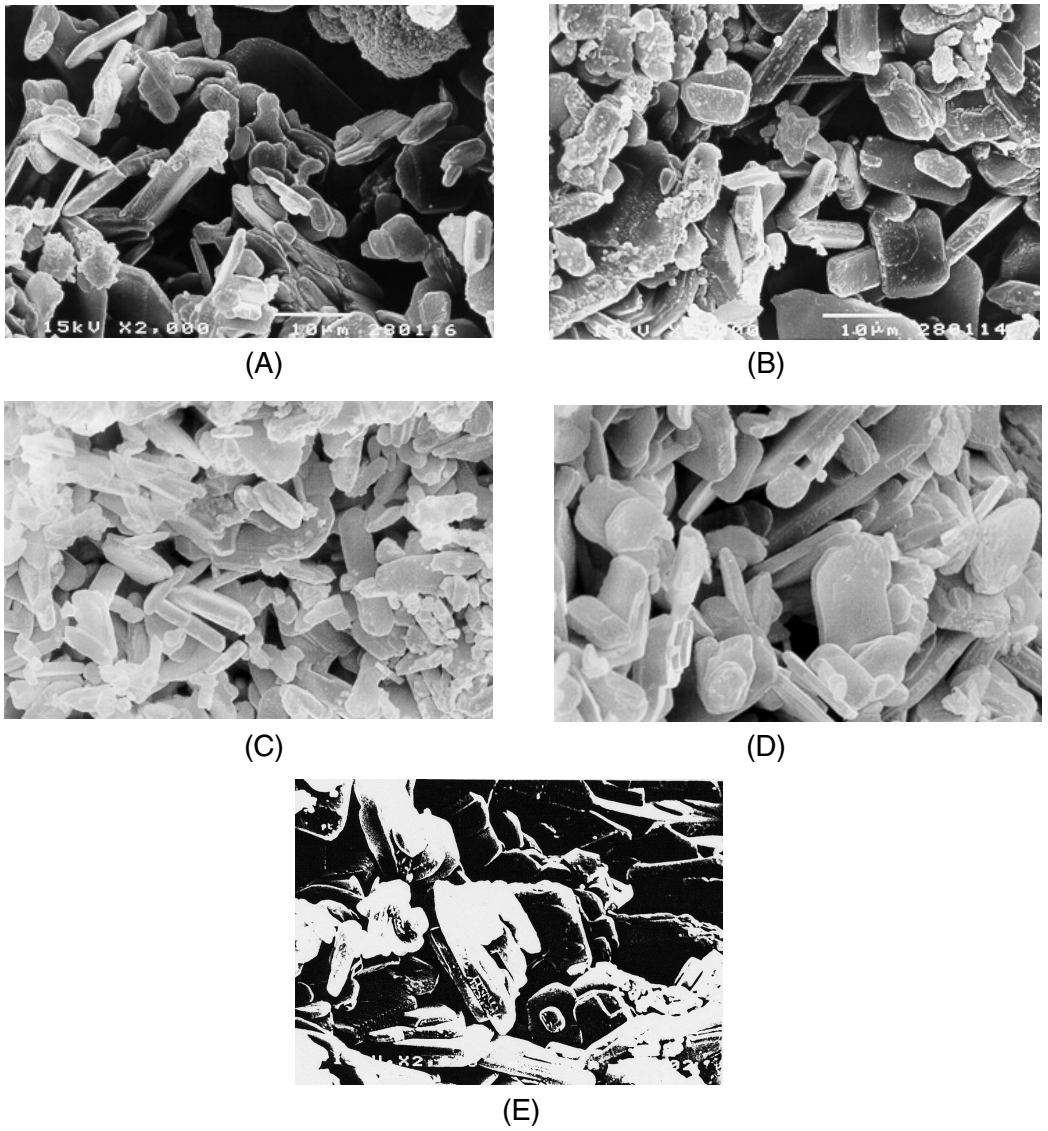

Figure 6. Photomicrographs illustrating surface phenomena of ibuprofen pellets prepared from 3 ml binding solvent containing Aerosil at various concentrations (×2000): (A) Aerosil 0.025%; (B) Aerosil 0.05%; (C) Aerosil 0.1%; (D) Aerosil 0.3%; (E) Aerosil 0.5%.

are three zones presented: clear, cloudy, and separation. The clear and cloudy zones are unsuitable for the phase partition of ibuprofen. Spherical crystallization of ibuprofen appeared to take place in the separation zone, which consisted of a large amount of water with approximately not more than 30% ethanol and 2% to 6% chloroform (see dotted line in the ternary diagram). The results are in agreement with a previous studied by Kawashima (2).

The amounts of solvents selected from a ternary diagram for further study of spherical crystallization are given in Table 1. Photomicrographs of the pellets and original ibuprofen crystal are provided in Fig. 2. The microscopic appearance of the original ibuprofen crystal (IC) showed many short rods and some needle-shape crystals (Figs. 2A, 2B). Figures 2C–2F show IPs using 4, 3, 5, and 6 ml binding solvent, respectively. At 3 ml of binding solvent, small round IPs (~1 mm) were obtained, as well as for pel-

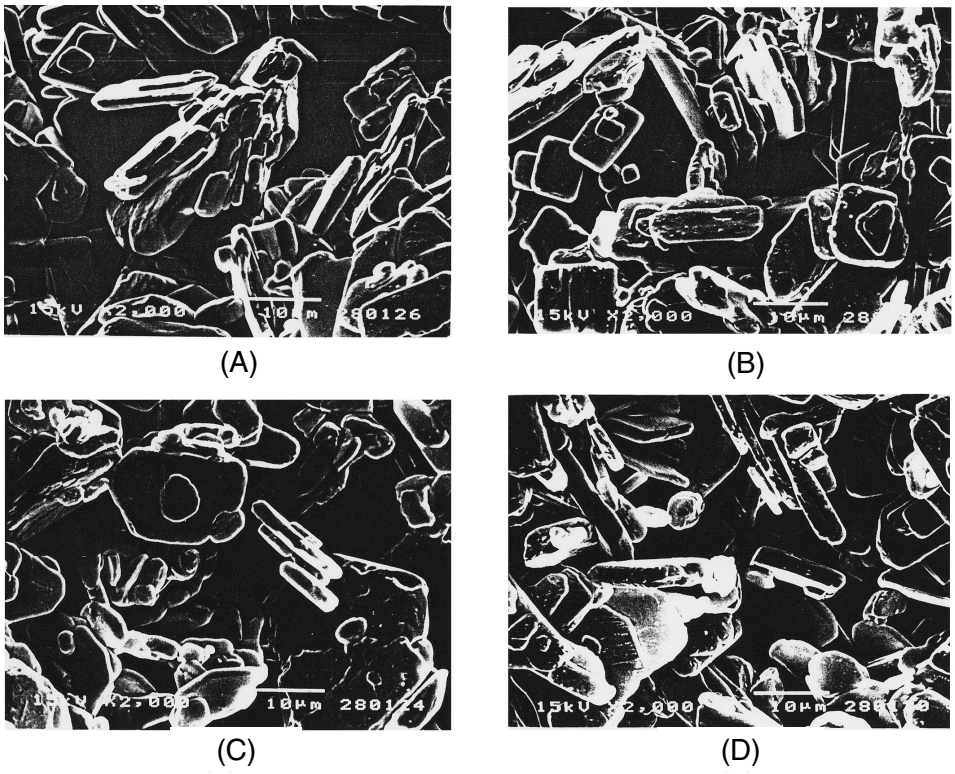

Figure 7. Photomicrographs illustrating surface phenomena of ibuprofen pellets prepared from 3 ml binding solvent containing Tween 80 at various concentrations (×2000): (A) 0.4% Tween 80; (B) 0.8% Tween 80; (C) 1.0% Tween 80; (D) 1.2% Tween 80.

lets prepared with 4 ml binding solvent; however, at 3 ml binding solvent, the IPs seemed to be rounder. The result could be because the phase partition of drug from ethanol:water to smaller droplets when using 3 ml chloroform gave smaller, round pellets compared with 4 ml chloroform. In the case of 5 and 6 ml binding solvent, very large granules ($\geq$ 6 mm) resulted, and suitable IPs could not be produced (Figs. 2E, 2F).

Surface investigation of the IPs prepared from 3 and 4 ml binding solvent indicated that, at 3 ml binding solvent (Fig. 3A), the surface of the pellets was composed of small ibuprofen crystals (~10–30 μm) rather loosely packed on the surface. The same phenomenon was observed at 4 ml binding solvent; however, rather tight packing was obtained (Fig. 3B).

Dissolution profiles of IPs from Figs. 3A and 3B were determined along with those for IC. It was found that IPs prepared from 3 ml binding solvent showed similar a percentage drug release when compared with pellets prepared from 4 ml (f_2 analysis). In the case of IC alone, fast initial release was observed and was found to be better than both dissolution profiles, as previously mentioned. However, it was noticed that the IC was not completely released up to 90 min (Fig. 4).

Based on the results from photomicrographs and dissolution profiles, pellets prepared from 3 ml binding solvent were selected for further study. As mentioned, IPs prepared from 3 ml binding solvent gave lower drug release when compared with IC.

An attempt to modify the physical properties of IPs by incorporating Aerosil (a viscosity-increasing agent) and Tween 80 (surfactant) in binding solvent was examined. Microscopic appearance showed that both Aerosil and Tween 80 gave less-spherical pellets compared with using binding solvent alone, and Aerosil appeared to give larger size pellets than Tween 80 (Figs. 5A and 5B). The concentration of both materials used did not affect the size of the IPs.

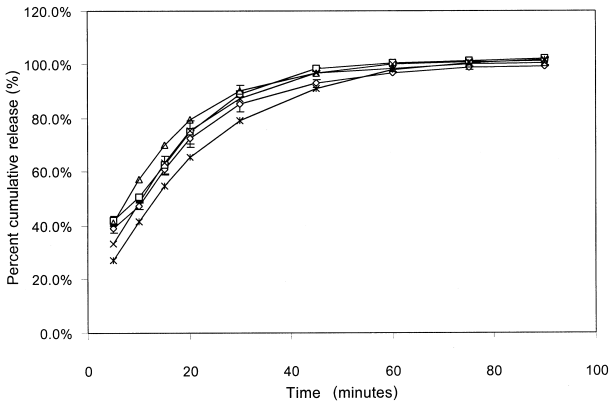

Figure 8. Dissolution profiles of ibuprofen pellets obtained from phase partition using 3 ml chloroform containing Aerosil at various concentrations as a binding solvent ($n = 6$): □, Aerosil 0.025%; ◇, Aerosil 0.05%; Δ, Aerosil 0.1%; ×, Aerosil 0.3%; *, Aerosil 0.5%.

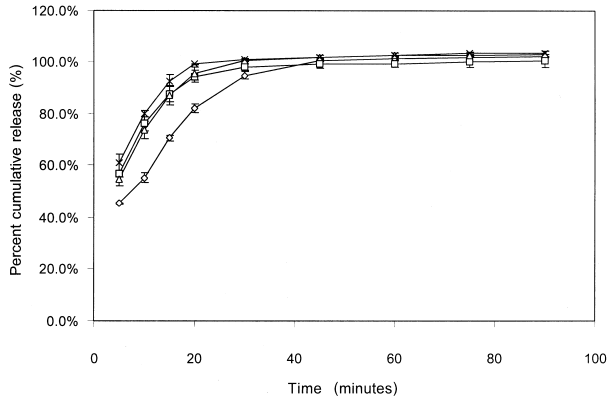

Figure 9. Dissolution profiles of ibuprofen pellets obtained from phase partition using 3 ml chloroform containing Tween 80 at various concentrations as a binding solvent ($n = 6$): ◇, 0.4% Tween 80; Δ, 0.8% Tween 80; □, 1.0% Tween 80; ×, 1.2% Tween 80.

The surface of the pellets when employing Aerosil at various concentrations (i.e., 0.025%, 0.05%, 0.1%, 0.3%, 0.5%) incorporated in the binding solvent was determined (Figs. 6A–6E). According to the viscosity-increasing property of Aerosil in binding solvent, when Aerosil concentrations varied, the results from microscopic examination indicated that rearrangement of ibuprofen microcrystals and a change of crystal habit occurred. At 0.025%, 0.05%, and 0.1% Aerosil, a combination of rod, plated

Table 2

Physical Properties of Ibuprofen Pellets Prepared by the Phase Partition Technique Using 1.2% Tween 80 in Binding Solvent

Physical Properties	
Sieve analysis[a]	
Percentage weight retained on	
Sieve 12	0
Sieve 14	21.50
Sieve 16	28.03
Sieve 18	16.22
Sieve 20	6.10
Sieve 40	19.43
Sieve 60	2.32
Sieve 80	2.77
Sieve pan	3.63
Percentage sieve fraction on 14/20 mesh cut pellets	71.85
Granule size by sieve analysis (mm)[a]	1.11 (0.27)
Bulk density (g/ml, ± SD)[b]	0.36 (0.02)
Tapped density (g/ml, ± SD)[b]	0.38 (0.02)
Carr's compressibility (%)[b]	5.28 (0.28)
Flow rate (g/min, ± SD)[b]	223.74 (3.96)
Angle of repose (°, ± SD)[b]	21.4 (2.42)
Friability (%)[a]	3.8 (0.58)

[a]Averaged from two determinations.
[b]Averaged from three determinations.

shapes, and some Aerosil on the crystal surface was observed. In the case of porosity, the less Aerosil in the binding solvent, the greater the porosity of the pellet obtained. At 0.3% and 0.5% Aerosil, most of the microcrystals on the surface of the pellets appeared to be in the plate form; these microcrystals were packed tightly and seemed to be larger in size than 0.025%, 0.05%, and 0.1%, respectively. This might be explained because, at a high concentration of Aerosil, a strong structural network probably occurred in the binding solvent, thus leading to a strong barrier for phase partition of drug in ethanol:water to binding solvent. The slower the partition of drug into the binding solvent, the better the seeding of ibuprofen microcrystals might presented according to the ibuprofen concentration in binding solvent at supersaturation was increased. In this case, a change in crystallographic direction could appear. Particle size, shape, strong packing, and probably smaller surface area of drug crystals could be observed (Figs. 6D and 6E). There are

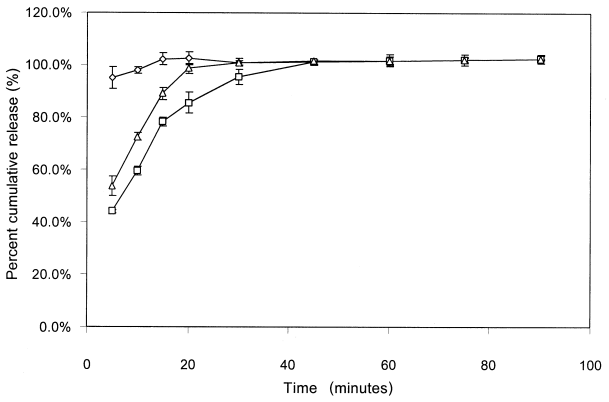

Figure 10. Dissolution profiles of Brufen tablets (◇), compressed pellets from the phase partition technique (using 3 ml chloroform containing 1.2% Tween 80) plus Explotab 3% (□), compressed pellets the same as above plus Explotab 4% (Δ) ($n = 6$).

two steps that should be involved: (1) transport of ibuprofen molecule to the surface of binding solvent and (2) arrangement of the molecule in an orderly fashion in the lattice within the binding solvent.

A modification of the Noyes and Whitney equation could be applied to determine the rate of crystal growth as follows (8):

$$dc/dt = Ak_g(C_{ss} - C_s)^n \quad (1)$$

where A is the surface area of the crystal nucleus, k_g is the overall crystal growth coefficient that is proportional to D/δ (D is the diffusion coefficient of solute, and δ is the thickness of the diffusion layer), n is the order of the crystal growth process, C_{ss} is the concentration at supersaturation, and C_s is the concentration at saturation.

On the other hand, when concentrations of Aerosil were small, a weak structural network was probably presented, thus leading to less seeding of ibuprofen microcrystals and little change in size, shape, and loose packing, and probably a large surface area could result (Figs. 6A–6C).

In the case of the effect of Tween 80 in the binding solvent, it was clearly seen from photomicrographs that the concentration of Tween used had little effect on size, shape, and porosity of the microcrystals on the surface of the pellets. At all concentrations of Tween 80 used in this study, microcrystals on the surface of the pellets seemed to be composed of some aggregates of rod shape and plate form. In addition, Tween 80 was found to be adsorbed onto the hydrophobic surface of drug microcrystals.

In the case of Tween 80, it was noticed that more than almost half of the microcrystals transformed from the rod shape to the plate form compared with the initial drug crystal (Fig. 7). The change in the crystal structure and the crystal habit might occur in the present of surfactant (9,10).

In terms of dissolution, Aerosil 0.025% gave similar drug release profiles when compared with the other concentrations (Fig. 8) (f_2 analysis). As indicated above from microscopic examination of the surface of pellets containing Aerosil, influx of medium into the network of the pellets seemed to be faster according to the increased porosity and large surface area of drug microcrystals (Figs. 6A–6E).

For the effect of Tween 80 on the dissolution profiles, the results showed that concentrations of 0.8%, 1.0%, and 1.2% gave similar drug release; however, release was higher than for the 0.4% concentration (Fig. 9) (f_2 analysis). The 1.2% Tween 80 concentration was selected for further study according to its better solubilizing property when compressed into a tablet. Furthermore, when comparing the release profiles of Aerosil 0.025% and 1.2% Tween 80 using f_2 analysis, Tween 80 indicated better drug release than Aerosil.

In summary, IPs prepared by phase partition using chloroform containing 1.2% Tween 80 as binding solvent at a solvent:ethanol:water ratio of 1.5%:8%:90.5% gave the best result in this study. The physical properties of IPs are given in Table 2. The results indicate that the sieve fraction on the 14/20-mesh cut was about 71.85%, and the mean particle size was approximately 1.11 ± 0.27 mm. The IPs had a good flow rate, as indicated by Carr's compressibility and angle of repose (11). In the case of friability, even if it was rather high, no problem was found when making the tablet; also, this value was obtained from a rather drastic condition (5,6).

Ibuprofen pellets were compressed into tablets using a single-punch tablet machine tooled with a 0.5-inch, round, flat-face punch. The tablet weight was 550 ± 12 mg and used 453 mg IPs, which was equivalent to 400 mg ibuprofen.

The dissolution profiles of these tablets were compared with that of a commercial tablet (Brufen

400). The results showed that the initial release of both compressed pellets (Explotab 3, 4%) was lower than for the commercial product. This can be because both compressed pellets require some time for initial drug release due to influx of medium into the compressed core. However, compressed pellets of both formulas meet the USP 24 requirement ($Q \geq 80\%$ at 60 min). The amount of drug released for both formulas was found to be 97% and 100%, respectively (Fig. 10).

These results showed that the use of the powder engineering technique by the phase partition method could produce round pellets that can be directly compressed into tablets. In addition, this technique should have an advantage and an impact in the new millennium.

CONCLUSION

This research demonstrated that ibuprofen, a poorly water soluble drug, could be prepared by the phase partition technique to obtain rather round pellets. The suitable system used in this study consisted of 1.2% Tween 80 in binding solvent chloroform:ethanol:water at 1.5%:8%:90.5%. However, the influence of such process variables as the speed of propeller, mixing time, suitable mixing time after phase partition of drug from start to end, temperature, and the like should be taken into consideration. Adding Aerosil and Tween 80 can change the porosity and microcrystalline habit of IPs. This concept can be applied to the other water-insoluble drugs, as well by varying the solvent system or other variables as described above. The resulting pellets could probably be ground to micronized crystals, encapsulation or direct compression into tablets. This technique may be useful in the pharmaceutical field in the next decade.

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