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The preparation and characterization of solid dispersions on pellets using a fluidized-bed system

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Abstract

In this study, solid dispersions of a poorly water-soluble drug, nifedipine, were prepared in hydroxypropylmethylcellulose (HPMC) on sugar spheres using a fluidized-bed coating system and characterized by differential scanning calorimetry (DSC) and dissolution measurements. A mixture of acetone and water (7:3) was found to be suitable as a spraying solution for simultaneous application of nifedipine and HPMC. DSC studies showed that the peak corresponding to the melting point of nifedipine became broadened when nifedipine was incorporated in a solid dispersion with HPMC at both ratios of 1:1 and 1:3. The results demonstrated that dissolution rates were fastest at the lowest nifedipine loading. Furthermore, the dissolution rate of nifedipine increased as more HPMC was added to the solid dispersions. The enhancement in the dissolution rate of nifedipine upon addition of Tween 80 in simulated gastric acid was attributed to the solubilizing effect of Tween 80 on nifedipine. Tween 80 had less influence when nifedipine was incorporated in solid dispersions containing higher fractions of HPMC.

Keywords: Solid dispersions; Nifedipine; Hydroxypropylmethylcellulose (HPMC); Fluidized-bed system

1. Introduction

Faster release rates of sparingly soluble drugs can be achieved by dispersion of drugs in water-soluble carriers as a solid dispersion, a concept introduced by Sekiguchi and Obi (1961). The use of solid dispersions in this context has been thoroughly reviewed (Chiou and Riegelman, 1970, 1971a,b; Chiou, 1977; Ford, 1986). A solid dispersion is defined as a dispersion of one or more active ingredients in an inert carrier or matrix in the solid state prepared by the melting (fusion), solvent, or melting-solvent methods (Chiou and Riegelman, 1971a). The formation of amorphous forms to increase drug solubility, reduction of

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particle size to expand the surface area for dissolution, and decrease in interfacial tension with the aid of water-soluble carriers are among the possible mechanisms for increasing dissolution rate, and improving the bioavailability of poor water-solubility drugs (Abdou, 1989).

Traditionally, solid dispersions were prepared by coprecipitation, coevaporation or cogrinding methods (Nakagawa, 1989; Otsuka et al., 1993). Several steps are usually involved in the preparation. Drugs with one or more suitable water-soluble carriers are dissolved in an appropriate solvent or mixture, or are melted together by heating at a temperature several degrees above the melting point of the carriers. After evaporation of the dissolving solvent or solidification by lowering the temperature, the solid dispersion of drug and water-soluble carrier is collected for further processing to produce the desired dosage forms. Freeze drying and spray drying have been employed to solidify the melt or to remove the dissolving solvent, respectively (Otsuka et al., 1993).

A method that could produce solid dispersions of drugs in a dosage form in one step would be valuable for making solid dispersions. Fluidized-beds are capable of spraying solutions onto the granular surface of excipients or sugar spheres to produce granules ready for tableting or drug-coated pellets for encapsulation in one step (Ghebre-Sellasie et al., 1985; Mahta et al., 1986). In this study, nifedipine was selected as a model drug with poor water-solubility to examine the possibility of employing fluidized-bed systems to prepare solid dispersions in a pellet form.

2. Materials and methods

Hydroxypropylmethylcellulose (HPMC, 5 cps) was supplied by Dow Chemical Co. (USA). Nifedipine was obtained from Sunlite Chemical Ind. Co., Ltd. (Japan). Sugar spheres (0.71–0.85 mm) were from Wei-Ming Pharm., MFG. Co., Ltd. (Taipei, Taiwan). Tween 80 and Acetone were from E. Merck Co., Ltd. (Germany)

2.1. Preparation of spraying solution

After several trials, it was found that acetone and water at a volume ratio of 7:3 were able to adequately dissolve both nifedipine and HPMC. To prepare a spraying solution, HPMC was first dispersed in a portion of acetone. Water was then added and HPMC was rapidly and completely dissolved. Nifedipine was added and was completely dissolved by adding the remaining acetone.

2.2. Production of solid dispersions on sugar spheres

Five hundred grams of sugar spheres were charged into the chamber of a fluidized-bed granulator and coater (Glatt Air Techniques Inc., model GPCG-1) and fluidized by opening the inlet air flap. When the outlet temperature reached 35°C, acetone/water solution containing nifedipine was bottom-sprayed onto the fluidized sugar spheres from an atomizing nozzle (10 mm) attached to a peristaltic pump. During processing, the spraying rate and inlet air temperature were adjusted to maintain the outlet temperature between 28 and 31°C. When the spraying was finished, the pellets were dried at 40°C for another 5 min. The pellets were discharged and further dried in a hot air oven to a water content of less than 1% measured by a moisture balance (Ohaus, model MB200). All operations were protected from light exposure. Different amounts of nifedipine were loaded on the sugar spheres by the same process as described above. Solid dispersions of nifedipine in HPMC at ratios of 1:1 and 1:3 (nifedipine:HPMC) were manufactured as well by the same method.

2.3. Differential scanning calorimetry (DSC) characterization

Pellet samples containing approximately equal amounts of drug were examined using a differential scanning calorimeter (Dupont, DSC-10). A heating rate of 10°C/min was employed from 30 to 200°C in an atmosphere of nitrogen with the samples placed in aluminum pans. Indium was used as the calibration standard.

Table 1
Formulations and drug recovery (%) of nifedipine pellets

Formulation	N-1	N-2	N-3	N-4	N-5
Components (g)					
Nifedipine	25	50	72	72	72
HPMC	—	—	—	72	216
Nu-pareil seed	500	500	500	500	500
Batch					
I	93.7	90.7	92.9	92.2	95.6
	(2.3)[a]	(0.7)	(2.0)	(2.6)	(2.4)
II	97.0	94.7	93.5	93.9	94.3
	(0.6)	(0.8)	(1.2)	(2.9)	(1.1)

[a] Standard deviation ($n = 6$).

2.4. Solubility measurement

The solubility of nifedipine in simulated gastric acid with varying amounts of Tween 80 (0–2% w/v) was determined by adding an excess amount of drug to the solution. Suspensions were equilibrated by stirring for at least 24 h at 37°C in a thermostatically controlled water bath. Suspensions were then filtered and the supernatant was analyzed spectrophotometrically at a wavelength of 350 nm after appropriate dilution. The average of triplicate determinations were reported.

2.5. Dissolution studies

The dissolution profiles of nifedipine from pellet samples (an amount equivalent to 10 mg of nifedipine was used) were determined at a temperature of 37°C and a stirring rate of 50 rpm using the paddle method (USP XXIII) in 900 ml of simulated gastric acid containing varying amounts of Tween 80. Samples were automatically circulated to the UV spectrophotometer (Jasco Type-7800, Japan) at appropriate intervals to measure the UV absorbance at a wavelength of 350 nm. Exposure to light was minimized during operations.

Polyvinyl pyrrolidone (PVP) is the most common used water-soluble carrier for the preparation of solid dispersion. However, the hygroscopic properties of PVP can cause poorly water-soluble drugs, such as nifedipine, to recrystallize from a solid dispersion by uptake of moisture by PVP (Sugimoto et al., 1980). Since HPMC is less hygroscopic than PVP and can be dissolved in several organic solvents as well, it was selected as the water-soluble carrier for nifedipine in the present study (Morimoto et al., 1987).

To prepare a solid dispersion by the solvent evaporation method in a fluidized-bed system, a solvent mixture must be formulated to simultaneously dissolve both the drug and the water-soluble carrier. Ethanol is probably the first choice for this purpose due to its low toxicity. However, the solubility of nifedipine in ethanol is inadequate for this purpose. After several trials, a solvent mixture of acetone and water in a volume ratio of 7:3 was found to be appropriate. Preparation of the spraying solution containing both nifedipine and HPMC in a completely dissolved state could be accomplished easily and rapidly. Also, the viscosity of the resulting solution did not impair the normal operation of the fluidized-bed system. Therefore, this spraying solution was employed in the fluidized-bed to prepare nifedipine solid dispersions with HPMC on the surface of sugar spheres.

Table 1 shows the components of five different formulations and the results of drug recovery after spraying these five different formulations onto sugar spheres. Two batches were manufactured for each formulation. All recoveries were greater than 90% and batch differences were small. This result demonstrates that the process is

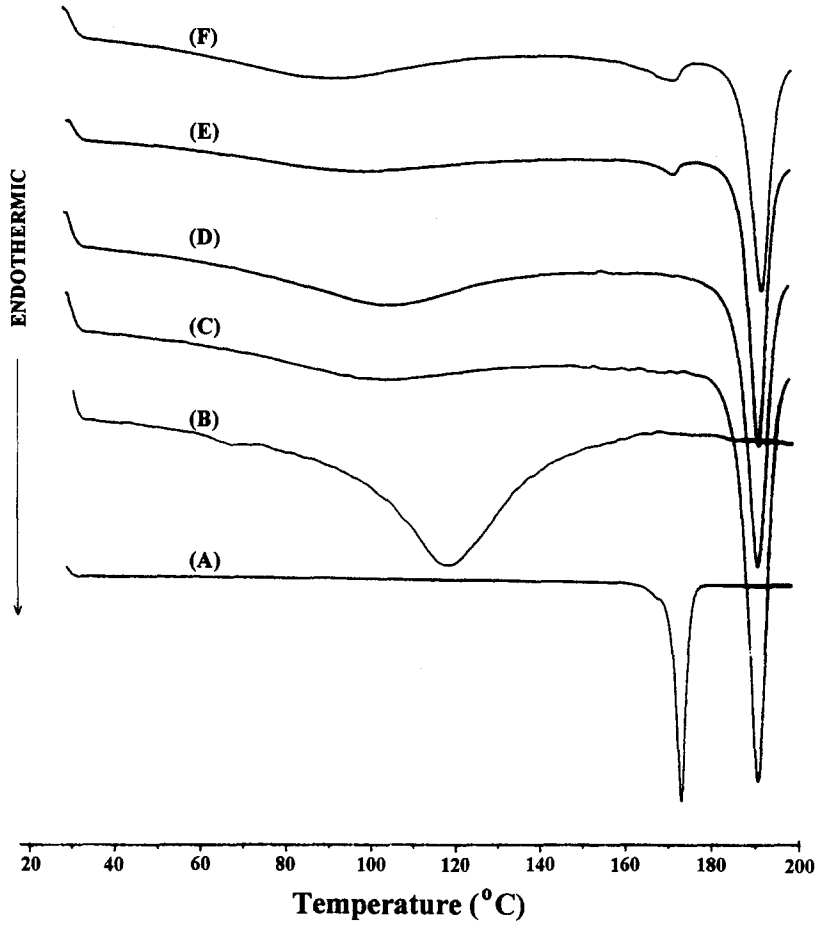

Fig. 1. DSC thermograms of nifedipine pellets, (A) nifedipine alone; (B) HPMC alone; (C) sugar sphere alone; (D) HPMC + sugar sphere (1:7); (E) nifedipine-HPMC (1:1) on sugar sphere; (F) nifedipine-HPMC (1:3) on sugar sphere.

reproducible with an acceptable recovery for practical applications, therefore confirming that employing the fluidized-bed system to prepare solid dispersion is possible. Solid dispersions in such a pellet form can be filled into capsules to finish the product preparation.

Fig. 1 compares the DSC thermograms of solid dispersions with nifedipine, HPMC, and sugar spheres alone. A large and sharp endothermic peak at a temperature around 190°C is due to the phase transition of excipients used for preparing sugar spheres. A broadened peak was observed for HPMC alone at a temperature between 100 and 150°C, as well as in the mixture of HPMC with sugar spheres at a ratio of 1:7. This peak might be attributed to the residual water in the HPMC sample. Without HPMC, a typical melting peak for nifedipine was noticed at approximately 172°C. With HPMC at both ratios of 1:1 and 1:3, the melting peak for nifedipine broadened, and another shallow and broadened peak appeared at a temperature of approximately 100°C. This shallow and broad peak might come from the evaporation of reserved water in the sugar spheres or HPMC. Besides that, there are no additional peaks to demonstrate the formation of different crystalline or amorphous forms of nifedipine. This result is only able to indicate that

nifedipine is dissolvable in the melt of sugar sphere or HPMC during DSC measurement. It is concluded that the formation of solid dispersions by solvent evaporation in the fluidized-bed system is workable.

As expressed in Fig. 2, the gastric solubility of nifedipine is approximately 20.82 ± 4.56 μg/ml. The total soluble amount of nifedipine in 900 ml of gastric acid would be equivalent to 18 mg, exceeding the amount added for dissolution of 10 mg. Fig. 2 further shows the effect of Tween 80 on the solubility of nifedipine in the gastric acid. There was a linear increase in nifedipine solubility with increasing Tween 80, showing that Tween 80 was able to solubilize nifedipine in the gastric acid solution to an extent suitable for maintaining sink conditions. By definition, a sink condition means that the final concentration of drug in the solution should be below 10–15% of its maximum solubility. Therefore, to maintain 10 mg of nifedipine in 900 ml of gastric acid in a sink condition, it is necessary to increase drug solubility to 70–120 μg/ml. Tween 80 at 0.5–1.0% appeared to be adequate in this case.

Fig. 3 compares the dissolution profiles of two batches of three formulations containing different ratios of nifedipine to HPMC in the gastric acid with the addition of 1% Tween 80 to maintain sink condition. The dissolution profiles for the two batches were greatly reproducible, further supporting that it is highly practical to employ the fluidized-bed system to prepare solid dispersions.

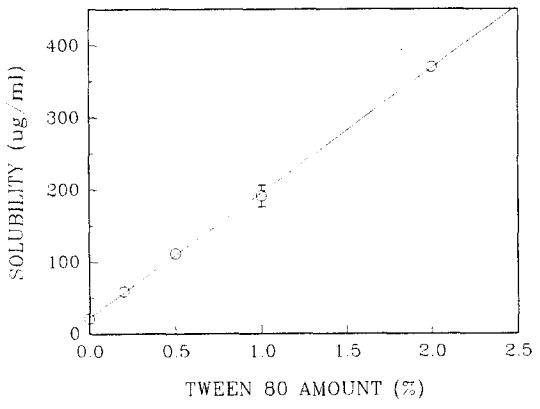

Fig. 2. The solubility profile of nifedipine in gastric acid containing various amounts of Tween 80.

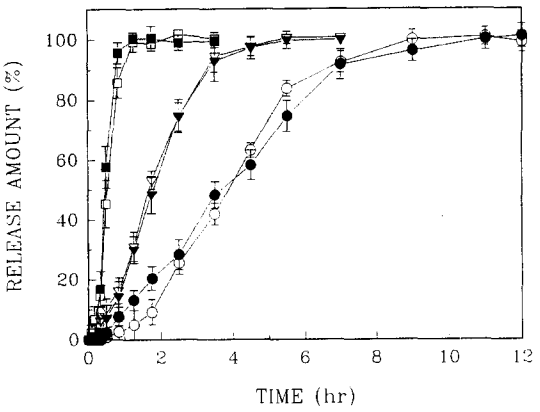

Fig. 3. The dissolution of two nifedipine pellet batches in the gastric acid containing 1% w/v Tween 80; hollow symbols, batch I; filled symbols, batch II; (○) N-3; (▽) N-4; (□)N-5.

The dissolution of nifedipine from preparations containing different amounts of nifedipine with no addition of HPMC was also examined in the same medium. Fig. 4 shows that the dissolution rate, expressed by the time to reach 80% of the amount released, was in the order of N1 (ca. 2.5 h) > N2 (4.2 h) > N3 (5.5 h), due to the larger surface area for dissolution when less of the drug is loaded on the same amount of sugar spheres. It is obvious that the increase of exposed surface for dissolution promotes the dissolution rate for water-insoluble drugs at a sink condition.

A lag time was noted in the dissolution profiles, and it was increased with increasing the loading

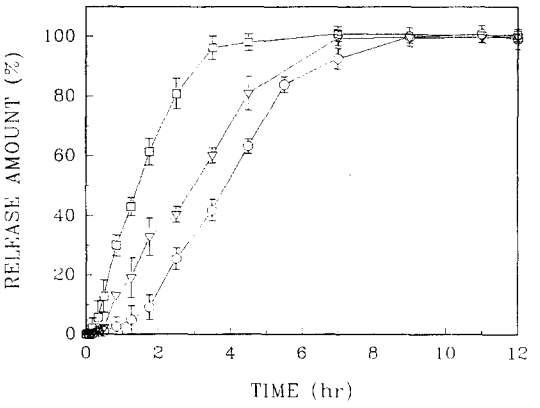

Fig. 4. The dissolution profiles of pellets containing different amounts of nifedipine in gastric acid containing 1% w/v Tween 80, (□) N-1; (▽) N-2; (○) N-3.

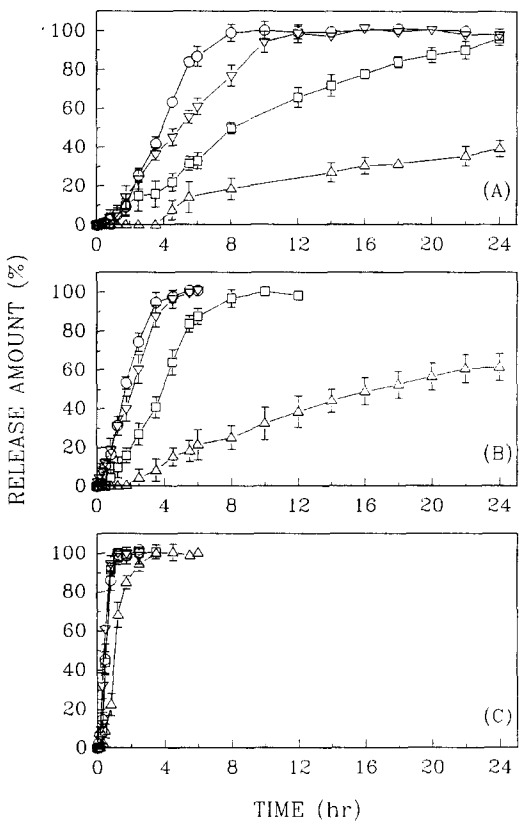

Fig. 5. The dissolution profiles of nifedipine pellet formulations in gastric acid containing various amounts of Tween 80, (A) N-3; (B) N-4; (C) N-5; (○) 1%; (▽) 0.5%; (□) 0.2%; (△) 0%.

amount. The lag time is needed for the dissolution medium to wet or hydrate the surface of drug crystals on sugar spheres before constructing the concentration gradient for drug dissolution. It would take a longer period of time for a more hydrophobic surface to reach full extent of hydration or wetting. The larger the drug load of a poorly water-soluble drug on the surface of sugar spheres, the more hydrophobic the surface would become, thus the fastest dissolution rate for N1 formulation is expected.

The dissolution of nifedipine from solid dispersions in gastric acid solution using varying amounts of Tween 80 as a solubilizing agent were compared. Increasing amounts of Tween 80 in the gastric acid solution enabled faster dissolution of nifedipine (Fig. 5). The improvement in the dissolution rate was more significant for preparations with a higher nifedipine:HPMC ratio. Tween 80 affected the dissolution of nifedipine to a lesser extent when increasing amounts of HPMC were added as a water-soluble carrier. Without HPMC, the dissolution of nifedipine primarily depends on the solubility of nifedipine in the dissolution medium. Nifedipine dissolution would therefore increase as more Tween 80, which increases the nifedipine solubility, was added.

In the presence of HPMC as a water-soluble carrier, however, several mechanisms are possibly responsible for increasing the dissolution rate: the formation of amorphous nifedipine to increase drug solubility; the reduction of particle size to expand the surface area for dissolution; and the decrease of interfacial tension with the aid of HPMC. The formation of amorphous nifedipine is inconclusive by DSC measurement. It has been reported that a five-fold increase in the solubility of nifedipine in water was observed at a HPMC concentration of 150 mg/500 ml. However, the highest concentration of HPMC achievable in our study with formulation N5 is only 30 mg/900 ml, which is too poor to play the same role being a solubilizing agent as Tween 80 in the dissolution medium. On the other hand, 900 ml of gastric acid has the ability to dissolve 10 mg of nifedipine without any solubilizing agent as explained in the solubility study. Therefore, the local concentration of HPMC in the inner surface of diffusion layer might be high enough to increase the solubility of nifedipine at the interface. This would set up a higher concentration gradient promoting the drug diffusion. This indicates that solid dispersions of nifedipine with an HPMC ratio of 1:3 possibly gives an adequate drug solubility at the inner surface. The addition of Tween 80 thus has little effect. The dissolution of such a solid dispersion would be expected to be unhindered in vivo and result in fewer absorption problems.

According to the Noyes-Whitney equation, the higher the surface area, the faster the dissolution rate. However, too low a concentration gradient across the diffusion layer could not significantly promote the dissolution rate even if the surface area of particles available for dissolution are in-

creased to a larger extent. On the other hand, the decrease of the interfacial tension due to the hydrophilic nature of HPMC is expected. Nevertheless, its effect on the hydration rate of the medium on the particle surface causing the dissolution of drug particles seems to be more profound than on the dissolution rate. Therefore, the effect of HPMC on the solubility of nifedipine is more likely a dominant factor influencing the dissolution rate of nifedipine from these preparations.

3. Conclusions

In conclusion, the employment of a fluidized-bed to evaporate solvent to prepare solid dispersions is possible. A solvent mixture of acetone and water (7:3) to solubilize nifedipine and the water-soluble carrier HPMC was used to demonstrate the feasibility. The dissolution rate of nifedipine from solid dispersions can be significantly improved without addition of Tween 80 as a solubilizing agent in the medium.

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