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COMMUNICATION

Investigation of Dissolution Enhancement of Nifedipine by Deposition on Superdisintegrants

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ABSTRACT

In this study we aimed to investigate the dissolution enhancement of nifedipine by the solvent deposition technique using superdisintegrants including Ac-Di-Sol, Kollidon CL, and Explotab as excipients. The relative significance of action of solvent deposition (deposition of small drug particles on the excipient after solvent is evaporated) and action of superdisintegrant was investigated. The effect of solvent on dissolution of nifedipine in the solvent deposition system was also investigated. Differential scanning calorimetry (DSC) was used to study the interaction between nifedipine and superdisintegrants. Capsules and tablets of a physical mixture and a solvent deposition system of nifedipine were prepared. The dissolution rate of nifedipine of these capsules and tablets was studied. The results of this study show that solvent deposition system with lactose and super disintegrants in capsule and tablet dosage forms can significantly enhance dissolution rate of nifedipine. Both the action of superdisintegrant and solvent deposition contribute to the enhancement of the dissolution, but the solvent deposition is mainly responsible for this enhancement. The solvent and disintegrants used can influence the dissolution rate also. The solvent deposition system using both Kollidon CL as excipient and dichloromethane as solvent has the highest dissolution rate. DSC study indicated Kollidon CL has the strongest interaction with nifedipine also.

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INTRODUCTION

Nifedipine is a calcium channel blocker which is widely used in the management of hypertension and of angina pectoris. However, its very low water solubility often give rise to concern on bioavailability.

Monkhouse and Lach developed the solvent deposition method to increase the dissolution rate of poorly water-soluble drugs by dissolving the poorly water-soluble drug in a solvent and then mixing it with a substance with extensive surface (1). When the solvent is evaporated, small drug particles are adsorbed on the surface of adsorbent and ready for dissolving into medium. Law and Chiang applied the same principle to increase the dissolution rate of griseofulvin but used disintegrants including unmodified wheat starch, Primojel, and Nymcel as excipients instead of those commonly used before (2). They prepared the solvent deposition system in the tablet dosage form, contrary to the common granule form. They attributed the dissolution increase to both the action of solvent deposition (deposition of small drug particles on the disintegrant when solvent is evaporated) and action of disintegrant. As the tablet is broken apart by the disintegrant, small drug particles are exposed and ready for dissolving. However, which action of the two is the important factor in causing the dissolution increase in not elucidated.

In this study we compared the dissolution of nifedipine from a physical mixture in capsule and tablet dosage forms with the solvent deposition system in capsule and tablet dosage forms to find out which is the important factor in causing dissolution increase when using the most effective and commonly used superdisintegrants, including Ac-Di-Sol, Kollidon CL, and Explotab. Although Explotab has the same chemical entity as Primojel, they might have quite different extents of action (3). So Explotab was used instead of Primojel. The effect of solvent on dissolution in the solvent deposition system was also investigated. Differential scanning calorimetry (DSC) was used to study the interaction between nifedipine and excipients.

MATERIALS AND METHODS

Materials

The lactose (DMV Corp.), sodium starch glycolate (Explotab, Edward Mendell Co., Inc.), crospovidone (Kollidon CL, BASF Wyandotte Corp.), croscarmellose sodium (Ac-Di-Sol, FMC Corp.), and nifedipine (Iek Co., Inc.) were all USP/NF grade. All reagents used were analytical grade.

Physical Mixture

Nifedipine and excipient (lactose, Explotab, Ac-Di-Sol, or Kollidon CL) were passed through a 60-mesh sieve first and then accurately weighed. They were mixed well in a mortar, by a pestle, and the content uniformity was confirmed.

Solvent Deposition Systems

The preparation was done as follows:

- Make 5% or 10% (w/v) nifedipine chloromethane solution depending on the buckiness of excipient.
- Pour the above solution into excipient and mix well.
- Dry the mixture at 105°C for 4 hr and divide into capsules after drying and sieving.

The content uniformity was confirmed. The nifedipine concentration is 10 mg per capsule containing 210 mg mixture (4.76% w/w).

Preparation of Capsules and Tablets

The powder blend from physical mixture or solvent deposition system was accurately weighed and divided into No. 3 capsules by hand for all excipients used except Kollidon CL. The powder blend containing Kollidon CL was divided into No. 2 capsules due to its buckiness. For making tablets, the powder blend, accurately weighed, was put between the lower punch and die of a rotary tableting machine (Chuan Yung Co., Model CY-RT-II) and compressed. The hardness of the tablets was measured by a hardness tester made by Imada Seisakusyo.

Dissolution Study

The dissolution of tablets and capsules was studied by the USP XXI basket method with 900 ml 0.1 N HCl solution as the medium. The rotating speed was 150 rpm and the temperature was 37°C. Solution, 5 ml was sampled at fixed intervals and replaced with an equivalent amount of fresh 0.1 N HCl solution.

The sample solutions were filtered through 0.45 nm Acrodisc filter and assayed by high-performance liquid chromatography (HPLC) at 235 nm. The LiChrospher

100 RP-18 end-capped (5 mm) column was used with the following conditions: mobile phase with flow rate 1 ml/min was 65% methanol in water. All the determinations were made in triplicate.

DSC Study

A Perkin–Elmer, Model DSC7, was used. Samples weighing 1 to 5 mg were placed in aluminum pans in an atmosphere of nitrogen using an empty aluminum pan as reference. A heating rate of 10.0°C/min. was employed over the range of 30° to 200°C.

RESULTS AND DISCUSSION

Nifedipine itself without any excipient dissolved very slowly, and in 1 hr nifedipine was only about 10% dissolved. When nifedipine was mixed with lactose or superdisintegrants in the capsule dosage form, its dissolution was increased as shown in Fig. 1. Because all these four excipients are hydrophilic, they readily draw water to the surroundings of nifedipine, thus, increasing its dissolution. The sequence for the excipients to enhance dissolution was Explotab > Ac-Di-Sol > lactose > Kollidon CL. Although a relatively large amount of superdisintegrants was used (the ratio of superdisintegrant to nifedipine was 20), they did not enhance the dissolution much more than that of lactose. Botzolakis et al. pointed out that the loose content, without compression, possesses large void space inside the capsule, and that the void space allows the swelling of superdisintegrants. This makes superdisintegrants relatively ineffective in enhancing disintegration and dissolution of the capsule dosage form (3).

When these above physical mixtures of superdisintegrants were compressed into tablets, the dissolution was further increased as shown in Table 1 (compare the amount of nifedipine dissolved at 30 and 60 min for formulations 1 and 2; 5 and 6; 9 and 10). It is in the tablet dosage form that the disintegrant produces both its swelling and capillary functions, so dissolution of nifedipine was increased.

Table 1 also shows that the solvent deposition system in the capsule dosage form largely increases dissolution, comparing the amount of nifedipine dissolved at 30 and 60 min for formulations 1 and 3, 5 and 7, and 9 and 11. This increase is much greater than that of the tableting physical mixture (compare the amount of nifedipine dissolved at 30 and 60 min for formulations 2 and 3, 6 and 7, 10 and 11). Monkhouse and Lach attributed this kind of increase to the micronization of particles adsorbed on the large surface of excipient, which is readily available for dissolving into medium, although these three superdisintegrants and lactose obviously do not have extensive surface as fumed silicon dioxide (1). Johansen and Møller stressed the importance of the ratio of the amount of adsorbate and adsorbent owing to the saturation of adsorbate on the adsorbent (4). In this study relatively large amount of excipient was used (the ratio of excipient to nifedipine was 20); the surface available for adsorption should not be a question of concern.

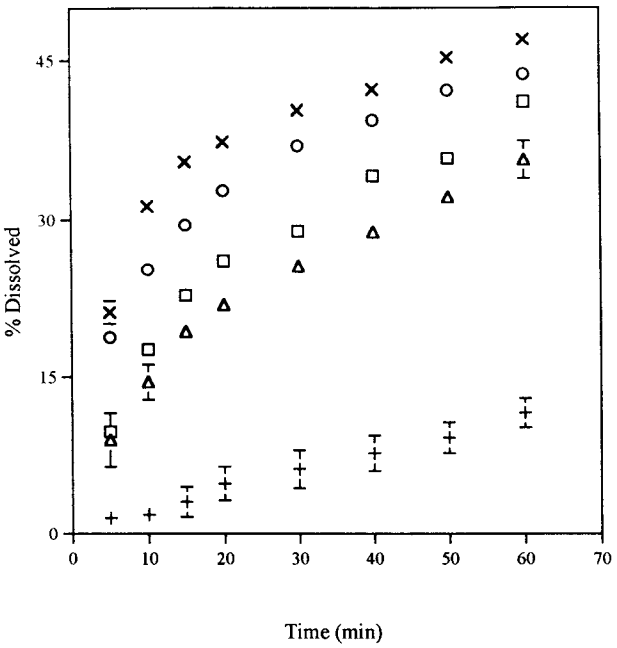

Figure 1. Effects of excipients on dissolution of nifedipine ×, Explotab; ○, Ac-Di-Sol; □, lactose; Δ, Kollidon CL; +, pure nifedipine.

When the mixture of solvent deposition system using Kollidon CL or Explotab as excipient was tableted, it increased the dissolution further (compare the amount of nifedipine dissolved at 30 and 60 min for formulations 3 and 4, and 7 and 8). The increase in dissolution by tableting the physical mixture or the solvent deposition system is much smaller than that achieved by solvent deposition method. Although tableting pressure can affect the dissolution, it is not an important factor here. As in formulations 10 and 12 of Table 1, the tablet from the physical mixture had the same hardness, 6 kg, as

Table 1

Percent of Nifedipine Dissolved at 30 min and 60 min[b]

Formulation	Excipient[a]	30 min (*SE*)	60 min (*SE*)
1	Explotab (PM, Cap)	40 (0.2)	47 (0.7)
2	Explotab (PM, Tab)	46 (0.6)	53 (0.4)
3	Explotab (SD, Cap)	62 (0.3)	71 (1.2)
4	Explotab (SD, Tab)	71 (1.1)	76 (0.6)
5	Kollidon CL (PM, Cap)	26 (0.4)	36 (1.8)
6	Kollidon CL (PM, Tab)	33 (0.9)	47 (1.2)
7	Kollidon CL (SD, Cap)	77 (1.2)	90 (0.6)
8	Kollidon CL (SD, Tab)	83 (1.3)	97 (0.8)
9	Ac-Di-Sol (PM, Cap)	37 (0.9)	44 (0.6)
10	Ac-Di-Sol (PM, Tab)	50 (1.1)	57 (0.6)
11	Ac-Di-Sol (SD, Cap)	77 (1.8)	83 (0.6)
12	Ac-Di-Sol (SD, Tab)	75 (1.0)	80 (1.2)
13	Lactose (methanol, Cap)	52 (0.5)	63 (0.9)
14	Lactose (dichloromethane, Cap)	64 (0.9)	70 (1.1)
15	Lactose (acetone, Cap)	69 (0.6)	77 (0.5)
16	Kollidon CL (methanol, Tab)	68 (2.8)	83 (3.5)
17	Kollidon CL (acetone, Tab)	78 (0.7)	93 (0.6)

[a]PM, physical mixture; SD, solvent deposition; Cap, capsule; Tab, tablet.
[b]SE, standard error.

that from the solvent deposition system, but its dissolution was much lower than that of the solvent deposition system. It was concluded that the action of disintegrant is not significant, but that the action of solvent deposition is the main factor in enhancing the dissolution of nifedipine.

The amount of nifedipine dissolved from formulations 13 to 15, Table 1, shows the effect of solvent on the dissolution of the solvent deposition system of lactose in capsule dosage form. Acetone resulted in the highest dissolution, with dichloromethane second, and methanol last. The recrystallization of nifedipine alone from these three organic solvents did not change the dissolution. McGinity and Harris reported that solvent has an effect on dissolution as it probably affects the crystalline form in the presence of excipient, or might influence the strength of the bonding between drug and excipient, or the orientation of drug on the surface of excipient (5).

When these three solvents were used on the solvent deposition system of Kollidon CL in capsule dosage form, dichloromethane resulted in the highest dissolution, with acetone second, and methanol still last. The sequence might be related to the solubilizing power of these solvents for the system, as dichloromethane and acetone have much stronger solubilizing power than methanol. When these solvent deposition systems of Kollidon CL were compressed into tablets, the sequence of solvent in enhancing dissolution of nifedipine remained the same, as shown in the amount of nifedipine dissolved in formulations 8, 16, and 17 of Table 1.

The DSC thermograms of nifedipine, Kollidon CL, solvent deposition system of nifedipine and Kollidon CL, solvent deposition system of nifedipine and Explotab, and physical mixture of nifedipine and Kollidon CL are shown in Fig. 2. Nifedipine has a sharp endothermic melting peak at 172.5°C. It is not affected by recrystallization from dichloromethane, acetone, or methanol. Kollidon CL shows broad peak, as do Explotab and Ac-Di-Sol. Lactose has a transition temperature at 147°C (not shown). Physical mixtures of nifedipine with Kollidon CL or the other three excipients show the nifedipine melting peak. This peak still exists in the solvent deposition system of nifedipine with Explotab, lactose, or Ac-Di-Sol. But it does not appear in the solvent deposition system of nifedipine with Kollidon CL, indicating a stronger interaction. No matter which solvent was used—acetone, methanol, or dichloromethane—the nifedipine peak was not observed. This phenomenon might be related with the fact that the sol-

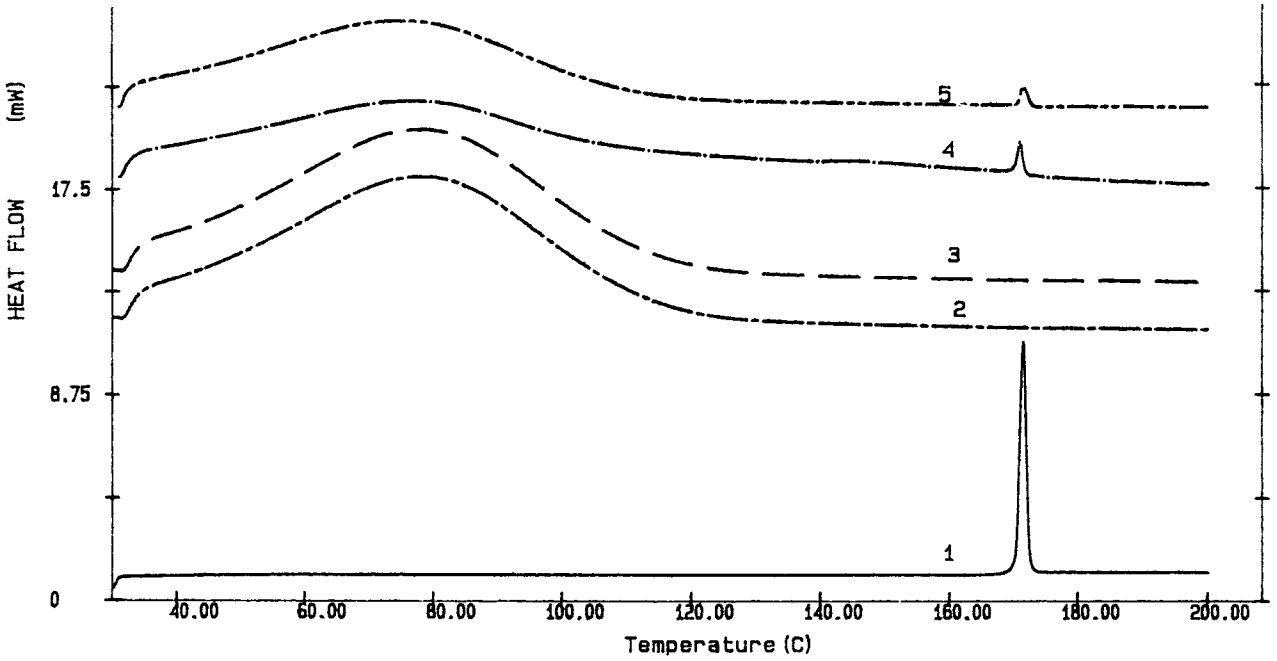

Figure 2. DSC thermograms of (1) nifedipine, (2) Kollidon CL, (3) the solvent deposition system of nifedipine and Kollidon CL, (4) the solvent deposition system of nifedipine and Explotab, and (5) the physical mixture of nifedipine and Kollidon CL.

vent deposition system using Kollidon CL as excipient has the highest dissolution.

CONCLUSIONS

A solvent deposition system in lactose and superdisintegrants in capsule and tablet dosage forms can significantly enhance dissolution of nifedipine. Both the action of superdisintegrant and solvent deposition contribute to the enhancement of the dissolution, but the solvent deposition is mainly responsible for this enhancement. The solvent and superdisintegrants used can influence the dissolution also. The solvent deposition system using Kollidon CL as excipient and dichloromethane as solvent has the highest dissolution. DSC study indicates that of the excipients, Kollidon CL has the strongest interaction with nifedipine in the solvent deposition system.

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REFERENCES

1. D. C. Monkhouse and J. L. Lach, J. Pharm. Sci., 61, 1430 (1972).
2. S. L. Law and C. H. Chaing, Drug Dev. Ind. Pharm., 16, 137 (1990).
3. J. E. Botzolakis, L. E. Small, and L. L. Augsburger, Int. J. Pharm., 12, 341 (1982).
4. H. Johansen and H. Møller, J. Pharm. Sci., 67, 134 (1978).
5. J. W. McGinity and M. R. Harris, Drug Dev. Ind. Pharm., 6, 35 (1980).