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Low substituted *N*-octenylsuccinate starch as a dissolution rate enhancer in solid dosage forms

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Summary

The dissolution rate enhancement properties of a low substituted *N*-octenylsuccinate starch was evaluated in a solid dosage form, containing nifedipine as a poorly soluble drug. The use of the modified starch improved dramatically the dissolution rate when prewetting was performed. The volume of wetting fluid had a critical influence on the dissolution rate and an optimum was reached when a 1% (w/w) dispersion was used. The binding efficacy of the starch was poor. Low substituted *N*-octenylsuccinate esters of waxy corn starch were shown to be a powerful dissolution enhancer of drugs in solid dosage forms.

Introduction

It is well known that the poor bioavailability of some drugs such as nifedipine is related to their low dissolution rate. Several techniques e.g., decreasing the particle size, the use of wetting agents, coprecipitation and solid solutions have been reported to increase the dissolution rate (Sugimoto et al., 1980; Summu, 1986; Meshal, 1990). We report on the use of a food accepted, low substituted, *N*-octenylsuccinate ester of waxy corn starch to increase the dissolution rate in solid dosage forms. Nifedipine is a poorly soluble drug and was chosen as a model substance during this investigation.

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Materials and Methods

Nifedipine was purchased from Sigma Chemical Co. (St. Louis, MO, U.S.A.). The *N*-octenylsuccinate esters of waxy corn starch were kindly provided by Cerestar (Vilvoorde, Belgium) and are indicated as CL487 and CL490, respectively. Tablets were prepared on an excentric compression machine (Korsch, type EKO, Germany), fitted with 8 mm flat punches. The following basic formula was used: nifedipine, 10 mg; microcrystalline cellulose (Avicel PH 102, FMC Int., Wallingstown, Ireland), 179 mg; Explotab (Edward Mendell, U.K.), 8 mg; magnesium stearate (< 90 μm, Flandria, Zwijnaarde, Belgium), 2 mg.

A mixture of nifedipine and microcrystalline cellulose was prewetted with an aqueous solution of sodium lauryl sulfate (1%, w/v) (Flandria, Zwijnaarde, Belgium) and polyvinylpyrrolidone (1%, w/v) (Kollidon 30, BASF, Ludwigshafen, Germany), Tween 20 (1%, w/v) (Frandria, Zwijnaarde, Belgium) and polyvinylpyrrolidone (Kollidon 30) (1%, w/v), polyvinylpyrrolidone (Kollidon 30) (1%, w/v), CL 487 (0.25, 0.5, 1, 2, 3 and 4%, w/v) or CL 490 (1, 2, 3 and 4%, w/v), respectively. After wetting of the nifedipine-microcrystalline cellulose powder blend, the mixture was sieved through a 1 mm screen and dried for 3 h at 50°C. After addition of Explotab and magnesium stearate and an additional blending step, tablets were compressed using the powder fraction below 90 μm. The volume of the wetting fluid was in all experiments 70% of dry weight calculated on the nifedipine-microcrystalline cellulose blend. In the case of the starch derivative, a fluid phase volume of 70, 80 and 95% of dry weight was used in order to study the influence of the fluid phase volume on the drug dissolution rate. The amount of modified starch added to the nifedipine-microcrystalline cellulose blend was kept constant. Tablets were also prepared by direct compression containing the same amount of starch ester, sodium lauryl sulfate-PVP, Tween 20-PVP or PVP, as in the tablets made with the prewetted mass. All tablets had an average hardness of 6 kg (Heberlein tester).

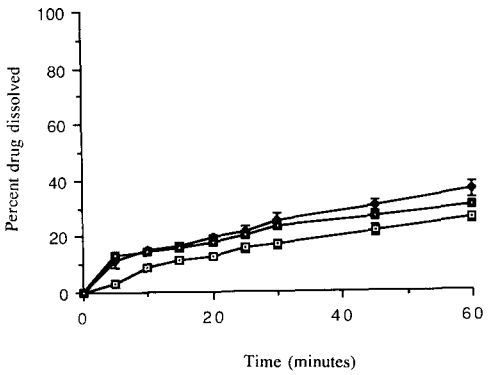

Fig. 1. Mean dissolution profiles ($n = 4$; $\pm$SD) of nifedipine from tablets containing a nifedipine-microcrystalline powder blend prewetted with PVP (1%) sodium lauryl sulphate (1%) (■——■), PVP (1%)-Tween 20 (1%) (♦——♦) and PVP (1%) (⊡——⊡).

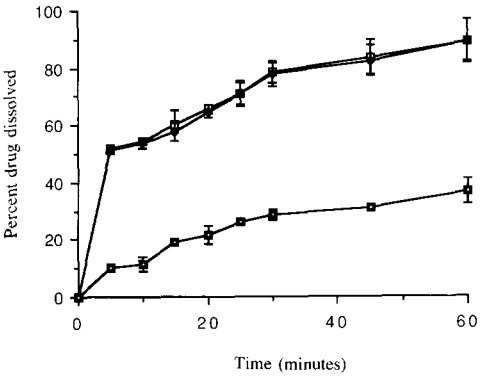

Fig. 2. Mean dissolution profiles ($n = 4$; $\pm$SD) of nifedipine from tablets containing a nifedipine-microcrystalline powder blend prewetted with *N*-octenylsuccinate esters CL487 (1%) (⊡——⊡) and CL490 (1%) (♦——♦) and of a physical blend with CL487 (1%) (■——■).

Tablet disintegration was performed according to the Ph. Eur., in water at 37°C without discs. Tablet dissolution was performed using the paddle method as described in the USP XXII. The dissolution medium was water and the temperature 37°C. The paddle was operated at 150 rpm. At intervals of 5 min, 5 ml were withdrawn from the medium, filtered through a 0.2 μm filter (Minisart, Sartorius GmbH, Heidelberg, Germany) and assayed spectrophotometrically at 340 nm (Shimadzu UV-140-02, Kyoto, Japan). All experiments were run four times. The calibration curve specifications were $y = 0.0109x$ (SD $\pm$ 0.00109) + 0.00325 (SD 0.002) ($n = 6$).

Binding capacity of the starch ester

Wet granulation of dicalcium phosphate dihydrate (Emcompress, Edward Mendell, NY, U.S.A.) was achieved by massing in a planetary mixer (Hobart K 45 SS, Troy, OH) using a K-shaped mixing arm and by the addition of the binding dispersion. The binding fluid was prepared by dispersing 5, 6 and 10% (w/v), respectively, of the starch esters in water. The freshly prepared dispersion was added to 300 g of dicalcium phosphate and granulated for 10 min at 80 rpm. The wet mass was than sieved through a 1.4 mm screen and oven dried at 50°C for 3 h.

Granule evaluation: granule size distribution for particles up to 250 μm was determined by sieving and by microscope for particles below 250

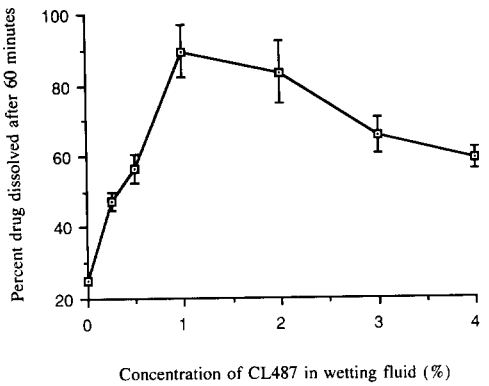

Fig. 3. Influence of the concentration of *N*-octenylsuccinate starch in the prewetting solution on the dissolution of nifedipine from tablets after 60 min ($n = 4$; $\pm$SD).

μm. The granule friability was determined as previously described (Visavarungroj et al., 1990).

Results and Discussion

Treatment of a waxy corn starch suspension with a cyclic dicarboxylic acid anhydride containing a hydrophobic substituent group yields products with tensioactive properties (BeMiller and Paschall, 1984). Such an anhydride is 1-octenylsuccinic anhydride. After chemical derivatisation the starch ester was pregelatinized in order to make it cold water dispersible. The products used have a degree of substitution (D.S.) bellow 0.03 and are to be considered as food approved products.

Fig. 1 shows the dissolution profile of nifedipine from tablets containing a nifedipine microcrystalline powder blend prewetted with PVP-sodium lauryl sulphate, PVP-Tween 20 or PVP. The dissolution rate was low in all cases and showed a maximal dissolution value of 35% after 1 h for the tablets made with a PVP-Tween 20 prewetted powder blend. Prewetting with a PVP solution or PVP-sodium lauryl sulfate solution showed an even lower dissolution profile. Fig. 2 shows the dissolution profiles of nifedipine from tablets made of a drug-microcrystalline mass prewetted with *N*-octenylsuccinate esters and of tablets compressed of a physical blend with the same amount of *N*-octenylsuccinate starch esters.

Two different batches of modified starches were used, CL 487 and CL 490, respectively. In those experiments prewetting was performed with 1% (w/v) dispersions. Dry blending of the starch ester showed a very low efficacy on drug dissolu-

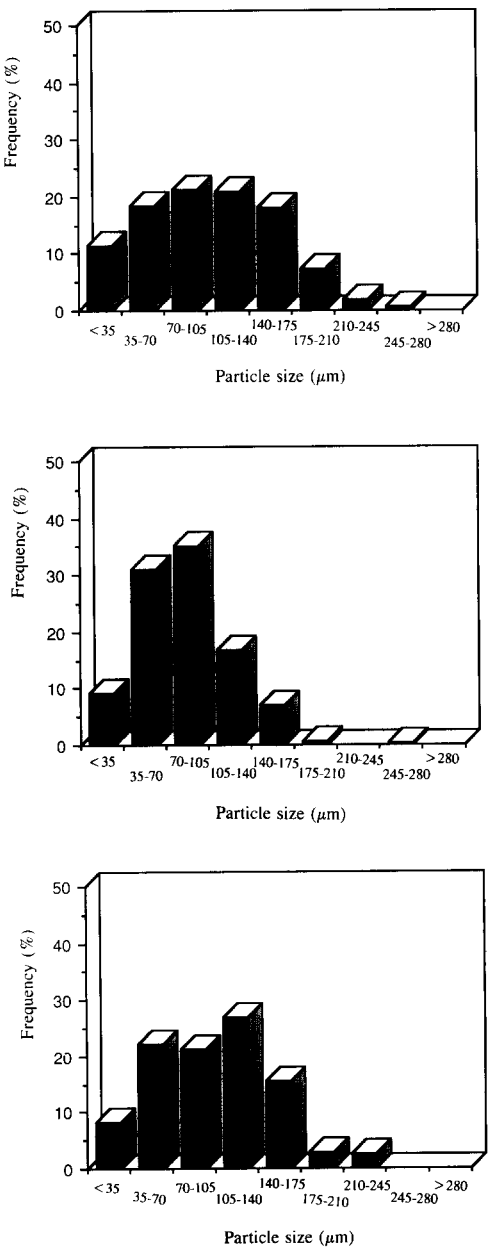

Fig. 4. Influence of 0.5% (a), 1% (b)and 4% (c) *N*-octenylsuccinate starch in the prewetting solution on the particle size distribution of nifedipine-microcrystalline granules.

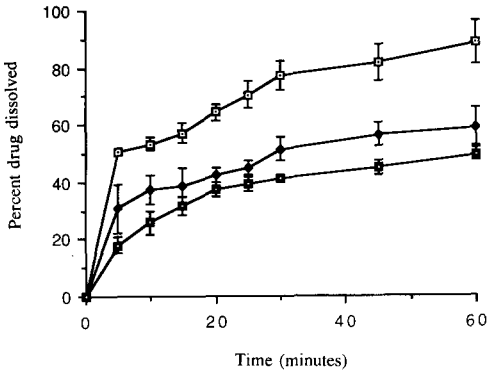

Fig. 5. Influence of the volume of wetting fluid on the mean dissolution profile ($n = 4$; ±SD) of nifedipine from tablets containing a nifedipine-microcrystalline powder blend prewetted with 1% CL490. Fluid phase volume was 70% (⊡——⊡), 80% (♦——♦) and 95% (■——■) of dry weight.

tion rate. Only 40% drug dissolved in 1 h, being very similar to the dissolution profiles obtained with the prewetting process using sodium laurylsulfate-PVP. In contrast, prewetting the drug-microcrystalline powder blend with a 1% aqueous dispersion of the modified starch dramatically improved the dissolution rate, showing 90% drug dissolved in 1 h. The two different batches of modified starch gave very similar results, indicating that the product efficacy and the reproducibility of the product's performance can be guaranteed batch by batch. Fig. 3 shows the influence of the concentration of starch CL 487 on the dissolution rate. An optimum in drug dissolution rate was reached when a 1% dispersion was used during the prewetting process. The use of a 0.25 or a 0.5% dispersion yielded a dissolution rate of approx. 45 or 60% after 1 h, respectively. Increasing the concentration beyond 1% progressively decreased the dissolution rate from approx. 85% after 1 h for a 2% dispersion to approx. 65% for a 3% dispersion and approx. 60% for a 4% dispersion, respectively. A possible explanation for this phenomenon is that for a starch ester concentration below 1% the wetting of the drug was inadequate. Besides, as can be seen from Fig. 4, a concentration of starch ester in the prewetting solution below or above 1% influenced the particle size distribution. The drug dissolution rate seemed very sensitive to small changes in particle size. When the fraction above 90 μm was used for a powder prewetted with 1% *N*-octenylsuccinate ester the dissolution rate dropped dramatically from 90 to 50% after 1 h. The disintegration time seemed hardly affected by an increasing concentration of modified starch. A maximal disintegration time of 180 s was observed for tablets made of prewetted powder blend using a 4% starch ester dispersion (Table 1).

TABLE 1

Disintegration time of tablets compressed with a prewetted powder blend prepared with aqueous dispersions of N-octenylsuccinate starch esters

	Concentration (w/v) of the aqueous *N*-octenylsuccinate ester dispersion used in prewetting	Disintegration time (s) (±SD; $n = 6$)
CL 487	1%	92 (±8)
	2%	93 (±1)
	3%	156 (±7)
	4%	158 (±12)
CL 490	1%	113 (±7)
	2%	140 (±11)
	3%	160 (±3)
	4%	180 (±3)

TABLE 2

Particle size distribution of dicalcium phosphate dihydrate granulated with aqueous dispersions of N-octenylsuccinate ester (CL 490)

	Particle size				
	> 1000 μm	1000–710 μm	710–500 μm	500–250 μm	< 250 μm
5% CL 490	9.4	12.8	16.5	44.5	16.8
6% CL 490	8.3	11.5	14.5	46.2	19.4
10% CL 490	6.9	11.7	16.0	46.3	19.1

The volume of wetting fluid appeared to have a critical influence on the dissolution rate (Fig. 5). An increase in volume from 70 to 95% of dry weight dramatically decreased the dissolution rate from 90 to 60% in 1 h. Similar results were obtained with the second batch of the octenylsuccinate ester. This phenomenon could again be correlated with an increase in powder particle size after the wetting stage.

The tablets prepared with a powder blend prewetted with a 1% CL 487 dispersion showed an excellent dissolution profile stability when stored for 6 months at 25, 65 and 85% RH, respectively.

It was previously shown (Visavarungroj and Remon, 1991) that pregelatinized waxy corn starch has excellent binding properties. Dicalcium phosphate granules were prepared with increasing concentrations of CL 487 aqueous dispersions in order to evaluate the binding capacity of the starch derivative. As shown in Table 2, it is obvious that even for highly concentrated *N*-octenylsuccinate ester dispersion (e.g., 10%, w/v) the binding efficacy of the original dried waxy corn starch was completely lost. Moreover, the granule friability was nearly 100%.

It can be concluded that a low substituted *N*-octylsuccinate ester of waxy corn starch can be considered as a powerful dissolution enhancer of drugs in solid dosage forms. Investigations are underway on their ability to act as a stabiliser and a wetting agent in aqueous suspension formulations.

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