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Enhancement of dissolution rate of nifedipine using sucrose ester coprecipitates

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Summary

The dissolution rate enhancement properties of sucrose esters were evaluated. Coprecipitates of nifedipine with different sucrose esters were prepared and drug dissolution and the stability of drug dissolution were studied. The use of sucrose palmitate of high HLB value dramatically improved the dissolution rate, especially when a drug/ester ratio of 1 : 14 was used. Increasing the drug/ester ratio produced a more amorphous product, progressively increasing the dissolution rate. Although the results are promising, the use of sucrose esters is probably very much restricted due to their hydrolytic instability during storage and the progressively increasing crystallinity of the coprecipitate.

Introduction

It is well known that the poor bioavailability of some drugs is related to their poor dissolution rate (Sugimoto et al., 1980; Fatah et al., 1986). Several techniques are used to increase their dissolution rate such as decreasing the particle size, the use of wetting agents, coprecipitates and solid solutions (Sugimoto et al., 1980; Sumnu, 1986; Meshal, 1990). Recently, the use of sucrose laurate was proposed as a solubilising agent (Fattah, 1986). The introduction of sucrose esters in pharmaceutical formulation is recent (Lerk, 1991). They have the advantage of low toxicity and biodegradation (Chester, 1973). We report on the use of coprecipitates of sucrose esters in order to increase the dissolution rate of nifedipine, chosen as a model drug. Nifedipine is a poorly water soluble drug of very low bioavailability when orally administered in crystalline form.

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Materials and Methods

Nifedipine was purchased from Sigma Chemical Co. (St. Louis, MO, U.S.A.). The following excipients were used: Avicel PH 102 (FMC Int., Wallingstown, Ireland), Explotab (Edward Mendell, U.K.), magnesium stearate (Flandria, Zwijnaarde, Belgium), PVP K-30 (BASF, Ludwigshafen, Germany), Tween 20 (Flandria, Zwijnaarde, Belgium), dicalcium phosphate dihydrate (C.N. Schmidt, Amsterdam, The Netherlands),

TABLE 1

Specifications of sucrose esters

Reference no.	Product name	HLB value	Manufacturer
F 160	sucrose palmitate	15	Croda, France
F 140	sucrose palmitate	13	Croda, France
F 110	sucrose palmitate	11	Croda, France
P 1570	sucrose palmitate	15	Ryoto, Japan
P 1670	sucrose palmitate	16	Ryoto, Japan
S 1570	sucrose stearate	15	Ryoto, Japan
S 1170	sucrose stearate	11	Ryoto, Japan
L 1695	sucrose laurate	16	Ryoto, Japan

lactose anhydrous (De Melkindustrie Veghel, Veghel, The Netherlands) and Crospovidone (GAF Corp., New York, U.S.A.).

Sucrose esters were received from Croda (Croda GmbH, Mettelal, Germany) and from Ryoto Co. (Mitsubishi-Kasei Food Corp., Tokyo, Japan). Table 1 shows the different sucrose esters used in this study.

Preparation of coprecipitates

Coprecipitates were prepared by the solvent method. Nifedipine-sucrose ester mixtures were prepared using the following ratios: 1:3, 1:6, 1:9 and 1:14 (w/w). Nifedipine/P 1670 and L 1695 mixtures were prepared in a 1:14 ratio only. The sucrose esters and the nifedipine were dissolved in a minimal volume of solvent. Isopropanol and chloroform (analytical grade, Novolab, Gent, Belgium) were used in separate experiments. The solvent was removed on a water bath at 40°C under a gentle nitrogen stream. The residual solvent was removed under vacuum at 50°C over a duration of 12 h. Next the coprecipitates were pulverised with a mortar and pestle. The powder fraction below 90 μm was collected and stored at ambient temperature, 25% RH and protected from light prior to the dissolution experiments

Tablets containing 10 mg nifedipine were compressed with P 1570, S1570 and F 160-nifedipine coprecipitates (1:14). Tablets, containing Explotab or Crospovidone 4% and 8% of total formula as disintegrating agent and 1.5% of magnesium stearate, were compressed with increasing amounts of Avicel pH 102 from 33 to 68% (w/w) of total formula, or dicalcium phosphate and lactose as filling agents.

Tablets were made by direct compression on an eccentric compression machine (Korsch, Type EKO) fitted with 8 or 13 mm flat punches. The tablets had a hardness of 6 kg on Heberlein.

The dissolution rate determination of nifedipine was run in 900 ml of water using the paddle method as described in USP XXII. The paddle was operated at 150 rpm. At 5 min intervals, over a 1 h period, 5 ml were withdrawn, 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 studies were run four times. The calibration curve specifications were $y = 0.0109x(\pm 0.00109) + 0.00325(\pm 0.002)$ $(n = 6)$. The tablet disintegration test was performed as described in the Eur.Pharm. The medium used was 0.1 N HCl. To characterize the powders and the coprecipitates X-ray diffractometry was used (Philips, Type PW 1051, CuKα (40 kV, 20 mA), Eindhoven, The Netherlands).

The stability of the dissolution rate of the coprecipitates was studied after storage at ambient temperature and 25, 65 and 85% RH, respectively, for 6 months. The stability study was performed with F 160, P 1570 and S 1570 coprecipitates for a drug-sucrose ester ratio of 1:14. Free fatty acid levels in the coprecipitate and fatty acid distribution were determined by gaschromatography as described by Lerk (1991).

Results and Discussion

Sugar esters are mainly applied in the food industry as emulsifying agents, crystallization inhibitors and antibacterial compounds. The application of sucrose esters in pharmaceutical formulations had remained unknown until recently when Lerk (1991) reported the use of sucrose laurate and palmitate in drug formulations.

The rate-limiting step in the absorption process for drugs of low solubility is generally the dissolution rate rather than the diffusion rate across the gut wall. The use of solid dispersions of drugs is one of the several techniques that can

be used to improve the dissolution properties of poorly soluble drugs.

Coprecipitates of nifedipine with different sucrose esters were prepared and drug dissolution and the stability of drug dissolution were studied.

Fig. 1 shows the influence of the chemical type of sucrose-esters and of the HLB value on the drug dissolution rate. Sucrose esters with HLB values of 11 and 13 showed a markedly lower dissolution profile than esters with an HLB value of 15. Furtermore, the dissolution rate appeared to be influenced by the chemical nature of the esters. The dissolution rate of nifedipine was higher for a palmitate than for a stearate ester, both with an HLB value of 15. The origin of the stearate esters did not influence the dissolution profile. Coprecipitates made with sucrose esters of HLB value 16, namely, laurate and palmitate esters, could not be isolated due to their highly hygroscopic character.

This phenomenon has previously been described for sucrose laurate by Lerk (1991). It has already been shown that the solvent used for the preparation of a coprecipitate might affect the drug dissolution rate, e.g., as reported for griseofulvin (Chiou and Riegelman, 1969; Chiou and Niazi, 1976). Other authors reported no influence of solvent on the dissolution profile as for nifedipine (Sumnu et al., 1986). In this study isopropanol and chloroform were used as solvents. Fig. 2 shows the dissolution profile for sucrose stearate (F 160; S 1570) and sucrose palmitate (P 1570) coprecipitates as a function of solvents used for a drug/sucrose ester ratio of 1:14. The palmitate ester (P 1570) with an HLB value of 15 made with isopropanol clearly shows a faster dissolution rate as more than 95% dissolved in 30 min.

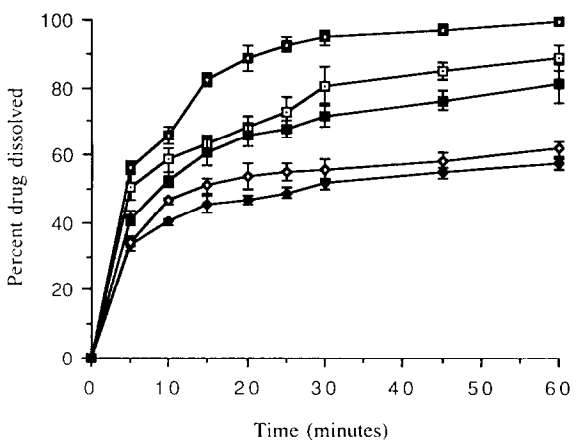


Fig. 1. Mean dissolution profile ($n = 4$; $\pm$SD) for nifedipine-sucrose ester coprecipitates. The drug/sucrose ester ratio was 1:14 and the particle size of the coprecipitates was below 90 μm. The coprecipitate was prepared from isopropanol. The following sucrose esters were used: S1570 (HLB 15) (stearate ester) (⊡), S 1170 (HLB 11) (stearate ester) (◆), P 1570 (HLB 15) (palmitate ester) (■), F140 (HLB 13) (stearate ester) (◇) and F160 (HLB 15) (stearate ester) (■).

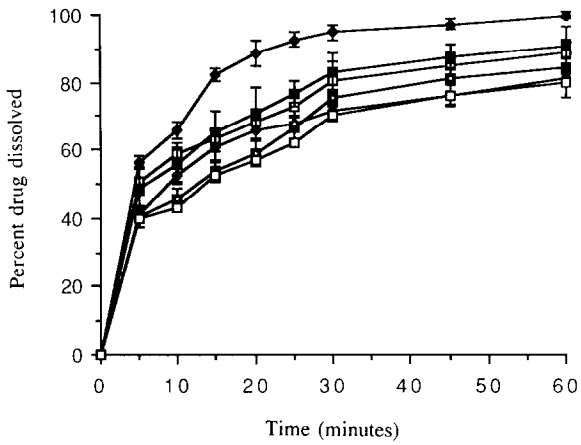


Fig. 2. Mean dissolution profile ($n = 4$; $\pm$SD) for nifedipine-sucrose ester coprecipitates. The drug/sucrose ester ratio was 1:14 and the coprecipitates were prepared from isopropanol and chloroform. The following sucrose esters were used: S 1570 (iso) (⊡), S 1570 (chloro) (■), P 1570 (iso) (◆), P 1570 (chloro) (■), F 160 (iso) (◇) and F 160 (chloro) (□).

Fig. 3a depicts the dissolution profile for sucrose palmitate (HLB 15) (P 1570) coprecipitates made in chloroform with an increasing drug/ester ratio of 1:3; 1:6; 1:9 and 1:14 (w/w), respectively. Increasing the ratio showed a positive effect on the drug dissolution rate ranging from 58% for the 1:3 ratio to 91% for the 1:14 ratio after 30 min, respectively. Increasing the drug/ester ratio resulted in a more amorphous product (Fig. 3b), progressively increasing the dissolution rate. This effect appeared to be independent of the composition of the sucrose esters as an analogous influence was observed for sucrose stearate (S 1570).

The influence of particle size on the dissolution rate of drugs has been previously shown for some solid dispersions, such as griseofulvin-succinic acid, tolbutamide-PVP and chlorthiazide-PVP, dextrose and sucrose (Chiou and Riegelman, 1969; Chiou and Niazi, 1976; Salama et al., 1981). The influence of particle size on drug dissolution was shown for a nifedipine/P 1570 coprecipitate prepared with isopropanol as 90 and 60% of the drug was dissolved for a particle size fraction below 90 μm and between 125–180 μm, respectively.

Tablets were prepared with coprecipitates F 160, P 1570 and S 1570 with microcrystalline cellulose, dicalcium phosphate and α-lactose monohydrate. The disintegration time of the tablets did not fulfill the requirements of the Eur.Pharm. for rapidly disintegrating tablets, even when the type of disintegrant or their concentration was altered. Increasing the amount of microcrystalline cellulose to a concentration of 68% (total weight of tablet 500 mg) allowed the disintegration of tablets made with S 1570 and P 1570 within 5 min, while the test still failed for tablets made with F 160 (> 15 min).

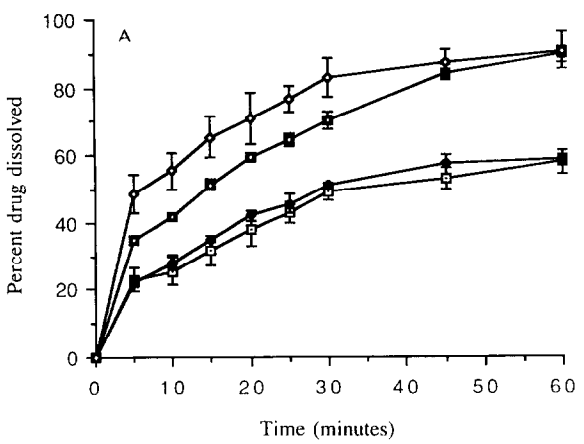


Fig. 3. (a) Mean dissolution profile ($n = 4$; $\pm$SD) of nifedine-P 1570 coprecipitates prepared with different ratios of drug/sucrose ester from chloroform: 1:3 (⊡), 1:6 (♦), 1:9 (■) and 1:14 (◇). (b) X-ray diffraction patterns of pure nifedipine (1) and of nifedipine-P 1570 coprecipitates prepared with different ratios of drug/sucrose ester from chloroform: 1:3 (2), 1:6 (3), 1:9 (4) and 1:14 (5).

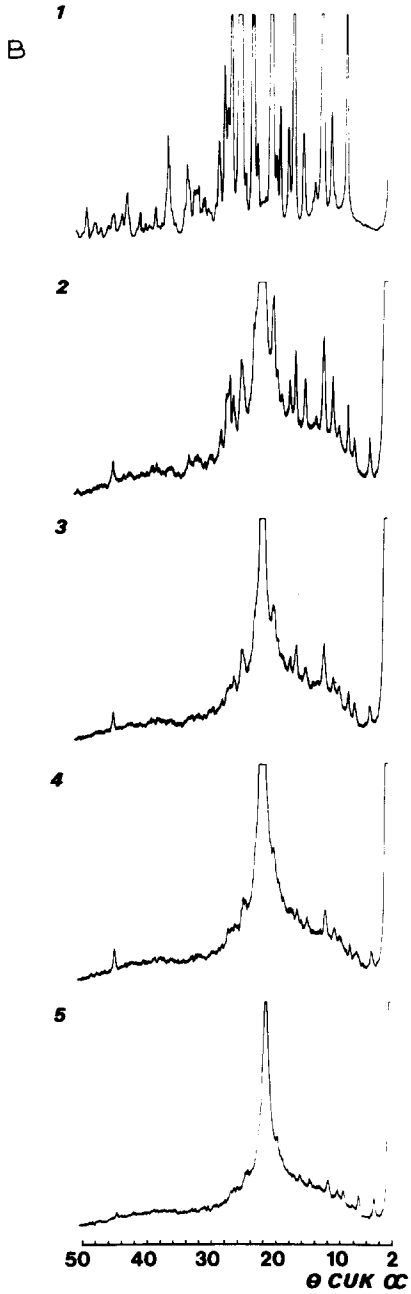


Fig. 3 (continued).

F 160, F 1570 and S 1570 coprecipitates (1:14) made from isopropanol were stored at ambient temperature, at three different RH levels of 25, 65 and 85%, respectively, for a duration of 6 months.

TABLE 2

Free fatty acid levels (%; w/w) for pure sucrose esters and coprecipitates (1:14) prepared in isopropanol after storage for 6 months at 65% RH and ambient temperature

	Time zero	6 months
P 1570	1.9	
Nifedipine/P 1570 [a]		5.68
F 160	2.3	
Nifedipine/F 160 [a]		4.92
S 1570	2.7	
Nifedipine/S 1570 [a]		4.29

[a] Data recalculated as 100% sucrose ester.

Fig. 4a shows the dissolution profile and Fig. 4b the X-ray diffraction patterns of P 1570 coprecipitates (1:14; made from isopropanol) and stored at different humidity levels. The dissolution rate decreased for increasing humidity levels and dropped from 95% after 30 min to approx. 35% after 6 months when stored at 85% RH. No progressive increase in crystallinity of the coprecipitates was observed for storage at 65% RH (Fig. 4b). Experiments with S 1570 and F 160 coprecipitates showed similar trends. The determination of free fatty acids in the coprecipitates stored at 65% RH clearly indicated an increase in free fatty acid levels due to hydrolytic instability of the sucrose esters (Table 2. The same free fatty acid levels were achieved for the sucrose esters at 85% RH after 2 months. The poor stability in dissolution rate could be due to the

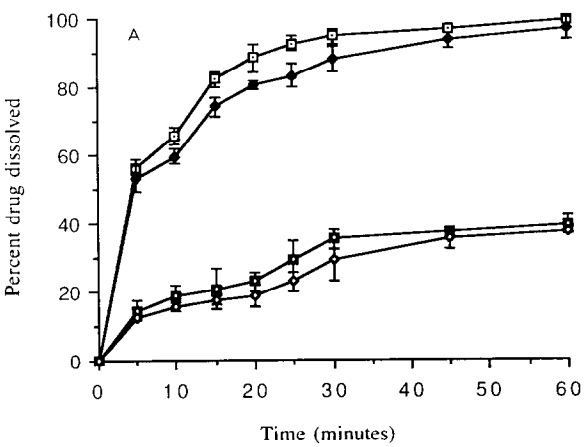
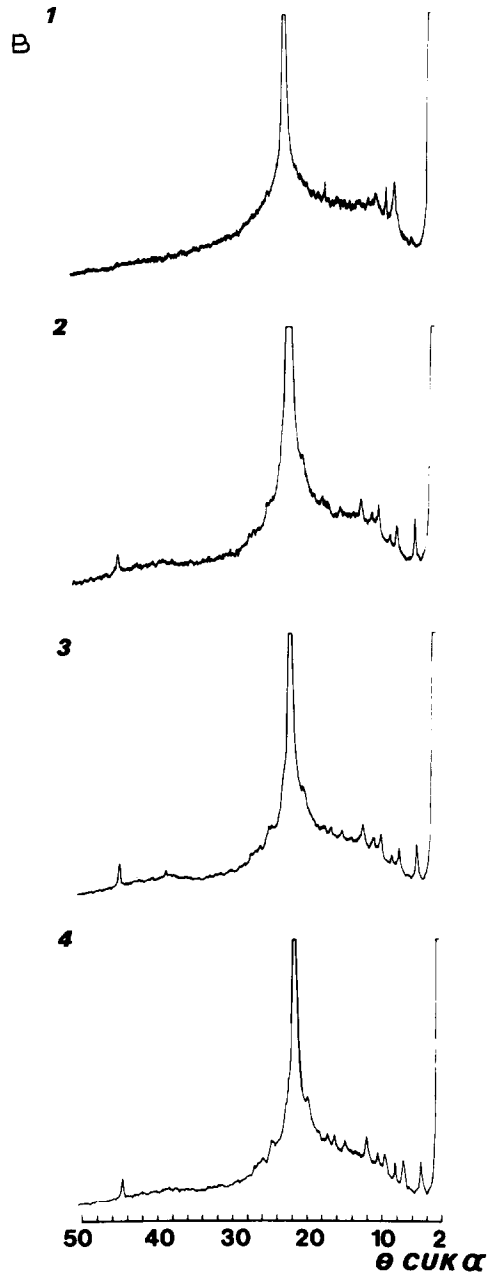


Fig. 4. (A) Mean dissolution profiles ($n = 4$; ± SD) of nifedipine-P 1570 coprecipitate (1:14; isopropanol) directly after preparation (⊡) and after 6 months storage at ambient temperature and 25% RH (♦), 65% RH (■) and 85% RH (◇). (B) X-ray diffraction patterns of nifedipine-P 1570 coprecipitate (1:14; isopropanol) after preparation (1) and after 6 months storage at ambient temperature and 25% RH (2), 65% RH (3) and 85% RH (4).



hydrolytic instability of the sucrose esters when stored at higher RH.

It can be concluded that, although some sucrose esters especially sucrose palmitate of high HLB value, show promise as candidates for the formulation of coprecipitates in order to increase the dissolution rate of drugs, their use is probably restricted due to their hydrolytic instability during storage especially at high RH.

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