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Effect of chitosan and chitosan glutamate enhancing the dissolution properties of the poorly water soluble drug nifedipine

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Abstract

In this study, a significant effect of chitosan increasing nifedipine dissolution has been demonstrated. This effect was dependent on the polymer:drug mixing weight ratio, the chitosan type and the method used to disperse the drug within the polymer. The greater the chitosan content the higher the drug dissolution was, up to a maximum corresponding to a polymer:drug ratio of 3:1. Significant differences within the various tested chitosans were observed. The lower the M_w the more important the polymer effect was which, in turn, was more noticeable for the glutamate salt than for the chitosan base. The various chitosan:nifedipine solid mixtures were ordered, according to the efficiency of improving the drug dissolution, as follows: solid dispersion > kneaded mixture > co-ground mixture > physical mixture. The drug dissolution enhancement was attributed to the decreased drug crystallinity and size and polymer wetting effect. Co-grinding of chitosan along with nifedipine in a 3:1 ratio, which leads to solid mixtures exhibiting a significantly improved dissolution profile without requiring the addition of organic solvents or high temperatures for its preparation, appears to be the more simple and convenient method.

Keywords: Chitosan; Chitosan glutamate; Co-ground mixture; Dissolution enhancement; Nifedipine; Solid dispersion

1. Introduction

Dissolution is frequently the rate-limiting step in gastrointestinal absorption and the bioavailability of poor water-soluble drugs from solid dosage forms. The potent well-known va-

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sodilator nifedipine (NF) is a representative example of the type of drugs that display this kind of behavior. NF is practically insoluble in water (Syed Laik Ali, 1989), and as a consequence it can exhibit low bioavailability after oral administration. Therefore, the improvement of NF dissolution from its oral solid dosage forms is an important issue for enhancing its bioavailability and therapeutic efficiency. Various strategies have been conducted in order to increase the NF dissolution; mainly via the use of solid dispersions with polyethylene glycol, urea, lactose and polyvinylpyrrolidone (Sugimoto et al., 1980; Sumnu, 1986; Morimoto et al., 1987) or complexes with cyclodextrins (Torres-Labandeira et al., 1992). However, the practical applicability of these systems has remained limited mainly due to the difficulty of incorporating them into solid dosage forms.

In the last few years, chitosan (CS) has been considered to be one of the most promising biopolymers for drug delivery purposes because of its interesting properties. CS (β-(1–4)-2-amino-2-deoxy-D-glucose) is the *N*-deacetylated product of the polysaccharide chitin, which is one of the most abundant polymers in nature since it is the principal component of crustaceans shells and insects (Muzarelli, 1977). CS is specifically biodegraded by the enzyme lysozyme which is concentrated in the mucosa, is mucoadhesive (Lehr et al., 1992) and enhances the penetration of macromolecules across the different human mucosae such as the intestinal and nasal (Illum et al., 1994; Borchard et al., 1996). It exhibits good biocompatibility and safety after parenteral administration (Hirano et al., 1990); and has been approved as a food ingredient, a fact that suggests the acceptability of this new excipient for oral drug administration (Weiner, 1993). From a technological point of view, CS has been demonstrated to be an excellent direct compression adjuvant (Nagai et al., 1984; Upadrashta et al., 1992) and a good vehicle for enhancing the dissolution properties and bioavailability of a number of poor water-soluble drugs (Sawayanagi et al., 1982, 1983; Shiraishi et al., 1990; Acartürk et al., 1993; Genta et al., 1995). Several types of chitosan are commercially available which differ in the molecular weight, deacetylation degree and presence of free or substituted by acid/amino groups (chitosan base or chitosan salt).

Taking all this into account, this study was carried out to investigate the feasibility of CS enhancing the NF dissolution. CS was selected because of its interesting properties, mainly oral biocompatibility and proved enhancing effect of several drugs dissolution as well as its direct compression feasibility. In this respect, it is interesting to point out that the final goal of our work is to use the developed CS:NF mixtures to prepare tablets by a direct compression technique. The effect of various formulation and process variables including CS-to-NF mixing weight ratio, type of CS and method used to disperse NF along with the CS on the drug dissolution was investigated. Differential scanning calorimetry (DSC) and X-ray diffraction techniques were used to explain the results.

2. Materials and methods

2.1. Materials

The following chemicals were obtained from commercial suppliers and used as received: chitosan base (CS; supplier's specification: degree of deacetylation was $>80\%$ and molecular weights were 50, 150 and 300 kDa for Sea cure®123 (low-M_w grade), Sea cure®223 (medium-M_w grade), and Sea cure®320 (high-M_w grade)), CS glutamate (supplier's specification: degree of deacetylation was $>80\%$, and molecular weights were 150 and 350 kDa, for Sea cure®G110 (medium-M_w grade) and Sea cure®G210 (high-M_w grade)) (Pronova Lab., Drammer, Norway); nifedipine (NF; Sigma, Madrid, Spain); ethanol, hydrochloric acid (Probus, Badalona, Spain) and sodium chloride (Merck, Darmstadt, Germany). Distilled water was used throughout this study.

All experiments were carried out under light-protected conditions to prevent the photodecomposition of nifedipine.

2.2. Preparation of drug:polymer solid mixtures

Drug:polymer solid mixtures were prepared by homogeneously incorporating NF within CS or CS glutamate in varying weight ratios using different methods: (i) physical mixtures (PM) of drug and polymer were obtained by simply blending with an spatula the previously sieved (100 μm) medium-M_w CS glutamate and NF in a polymer:drug ratio of 2:1; (ii) co-ground mixtures (GM) of CS (low-, medium- and high-M_w grades) or CS glutamate (medium- and high-M_w grades) and NF in various weight ratios (polymer:drug = 1:1, 2:1, 3:1, 4:1, 6:1 and 8:1, w/w) were obtained by co-grinding for 20 min in a ceramic mortar and sieving through a 100-μm mesh sieve; (iii) a kneaded mixture (KM) in a polymer:drug weight ratio of 2:1 was prepared by kneading the required amounts of medium-M_w CS glutamate and drug with 1.5-times their amount of water:ethanol (1:6) in a ceramic mortar (polymer/drug mixture weight, 0.50 g; wetting liquid, 0.75 g) (the kneaded mixture was subsequently oven-dried for 48 h at 50°C and sieved through a 100-μm mesh sieve); (iv) solid dispersions (SD_I, SD_{II}) in a polymer:drug weight ratio of 2:1, were obtained by a casting/drying technique. Polymer solutions (0.33%, w/w) were prepared by dissolving medium-M_w CS glutamate in distilled water at room temperature. The NF was directly dispersed (method I) or first dissolved in a small volume of ethanol (ethanol:water, 1:6) and then added (method II) to the CS glutamate aqueous solution. The drug-containing polymer solutions were cast on glass petri dishes (diameter, 14.50 cm) and the solvent dried for 48 h at 50°C (area of casting, 165.13 cm^2; casting weight, 100 g; total solids content, 0.5 g; drug, 0.167 g). The film obtained was then crushed, pulverized and sieved through a 100-μm mesh sieve. All samples were stored in a desiccator (containing silica gel) at room temperature until the assay.

2.3. Characterization of the solid mixtures

Thermal analysis was performed using a Shimadzu DSC-50 system with a differential scanning calorimeter equipped with a computerized data station (scanning rate, 10°C/min; temperatures range, 35–250°C). Powder X-ray diffraction patterns were carried out with a Philips X-ray diffractometer (PW 1710 BASED) using Cu Kα radiation.

In vitro dissolution studies of the pure drug and the polymer:drug solid mixtures were performed according to the solid dispersed amount method (Nogami et al., 1969) using the USP23 paddle apparatus. The samples, containing 5 mg of NF or its equivalent in solid mixture, were placed in 500 ml of the dissolution medium (simulated gastric juice without enzymes) in a glass beaker at 37 ± 0.5°C and stirred at 100 rpm. At predetermined time intervals, samples of 5 ml were taken and replaced with fresh medium. The concentration of the NF dissolved was determined by UV spectrophotometry at 340 nm after appropriate filtration. All samples were analyzed in triplicate. The percent of drug dissolved after 15 min (D_{15}) and the dissolution efficiency after 240 min (DE_{240}), which was calculated according to the method of Khan (1975), were used to characterize the initial and total drug dissolution, respectively.

2.4. Investigated variables

The investigated variables (polymer:drug mixing ratio, type of polymer and method used to incorporate the drug within the polymer) are summarized in Table 1, which also shows the studied levels.

2.5. Statistical analysis

One-way analysis of variance (ANOVA) with the least-significant difference (LSD) test for multiple comparisons (Statgraph program; Statistical Graphics, Version 7.0) was performed to determine the effect of the investigated variables on the dissolution parameters D_{15} and DE_{240}. Differences were considered to be significant at a level of $p < 0.05$.

Table 1
Processing variables in the preparation of chitosan:nifedipine solid mixtures

Variable	Investigated levels	Kept constant
Polymer:drug mixing ratio	1:1, 2:1, 3:1, 4:1, 6:1, 8:1	Sea cure G110 co-ground mixture
Type of chitosan	Salt (glutamate)	
	Medium-M_w: Sea cure G110	Polymer:drug, 3:1 co-ground mixture
	High-M_w: Sea cure G210	
	Base	
	Low-M_w: Sea cure 123	
	Medium-M_w: Sea cure 223	
	High-M_w: Sea cure 320	
Preparation method	Physical mixture, PM; co-ground mixture, GM; kneaded mixture, KM; solid dispersion (method I), SD_I; solid dispersion (method I), SD_{II}	Polymer:drug, 2:1 Sea cure G110

3. Results and discussion

The first objective of this study was to identify the polymer:drug mixing weight ratio at which the polymer effect was noticeable. Polymer:drug mixtures were prepared by co-grinding medium-M_w CS glutamate and NF in weight ratios varying from 1:1 to 8:1.

The DSC thermograms of NF, CS glutamate and their co-ground mixtures (Fig. 1) revealed that CS glutamate exhibited a broad and small endothermic peak owing to its amorphous character; while NF showed an endothermic peak at 175°C due to melting. On grinding with the polymer, the drug melting endotherm showed a broadening; however, the peak did not disappear. The thermograms showed no evidence of the formation of a solid complex or any chemical interaction between drug and polymer.

The crystallinity of NF in the co-ground (2:1, 3:1) mixtures was compared with that of ground NF by means of powder X-ray diffractometry. Fig. 2 depicts the X-ray diffraction patterns of the pure drug, low-M_w CS, medium-M_w CS glutamate and their respective polymer:drug co-ground mixtures. NF exhibited a characteristic X-ray diffraction pattern, which almost disappeared in its co-ground mixtures with the amorphous polymers, the diffractometry patterns of the co-ground 3:1 mixtures being similar to those of polymers. This indicated an important decrease in the crystallinity of the drug. The amorphization of NF was higher for the 3:1 mixture than for the 2:1 CS glutamate:mixture, which would explain the differences later observed in the dissolution profiles.

The in vitro dissolution profiles of NF in the acidic release medium, shown in Fig. 3, clearly indicated that the co-grinding of NF with CS glutamate markedly enhanced the dissolution rate of the drug compared with that of the NF alone for all polymer:drug ratios. The higher the polymer content, the faster was the dissolution. At 15 min, there was almost 0% dissolved of the pure drug, compared to nearly 15, 30 and 60% for the 1:1, 3:1 and 8:1 CS:NF ratio. Analysis of variance ($p < 0.05$) performed on D_{15} (initial dissolution) (Fig. 4) indicated the existence of significant differences between pure drug and all CS glutamate:NF mixtures. The least-significant difference test allowed us to order the formulations as follows: NF < CS:NF 1:1 < CS:NF 2:1–4:1 < CS:NF 6:1–8:1. It is important to point out that a nearly linear dependence ($r^2 = 0.960$) was found between D_{15} and the polymer content; therefore this was an important factor in controlling the initial dissolution rate of NF. For longer periods of time, the dissolution parameter DE_{240} increased with the CS glutamate content and reached a maximum at the 3:1 ratio. ANOVA ($p < 0.05$) of DE_{240} confirmed that differences were significant and the LSD test grouped the formulations according to its efficacy as follows: NF < CS:NF 1:1 < CS:NF 2:1 < CS:NF 3:1–8:1. The polymer effect was suppressed at a ratio of 3:1; and further

increases in polymer content showed no effect on drug dissolution.

From the results of this study it was concluded that the co-grinding of NF with CS glutamate remarkably enhanced drug dissolution, this being dependent on the polymer:drug ratio. The NF dissolution was at an optimum at a ratio of 3:1 of polymer:drug. The enhancement of the NF dissolution rate by co-grinding it with CS glutamate, compared to that of the pure drug, could presumably be explained by a combination of two factors: (i) a decrease in crystallinity and size of

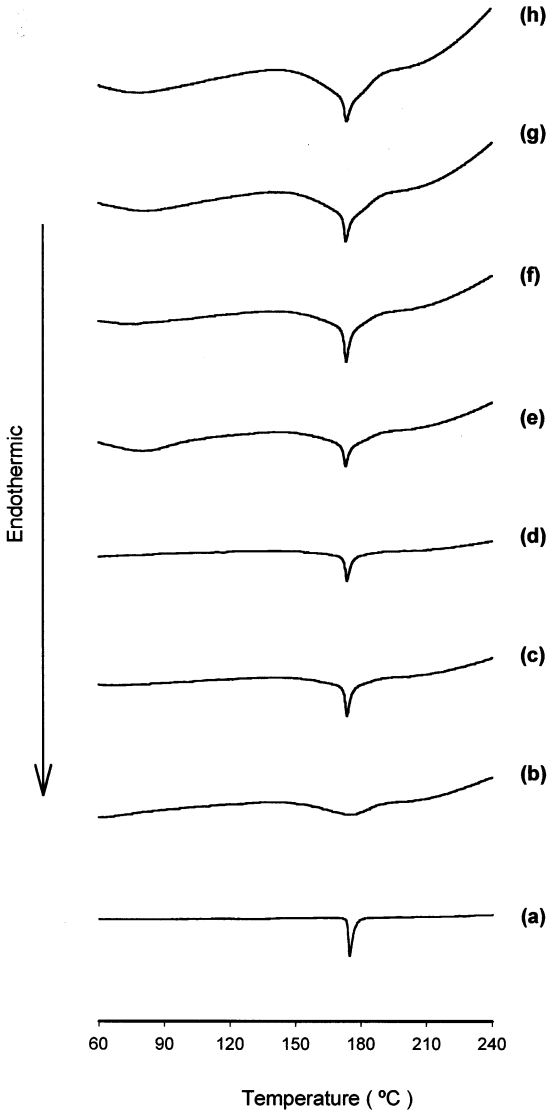

Fig. 1. Differential scanning calorimetry of the polymer:drug co-ground mixtures. Key: (a) NF; (b) CS glutamate; (c) 1:1, (d) 2:1, (e) 3:1, (f) 4:1, (g) 6:1 and (h) 8:1 CS glutamate:NF. CS glutamate, medium-M_w chitosan glutamate, Sea cure G110; NF, nifedipine.

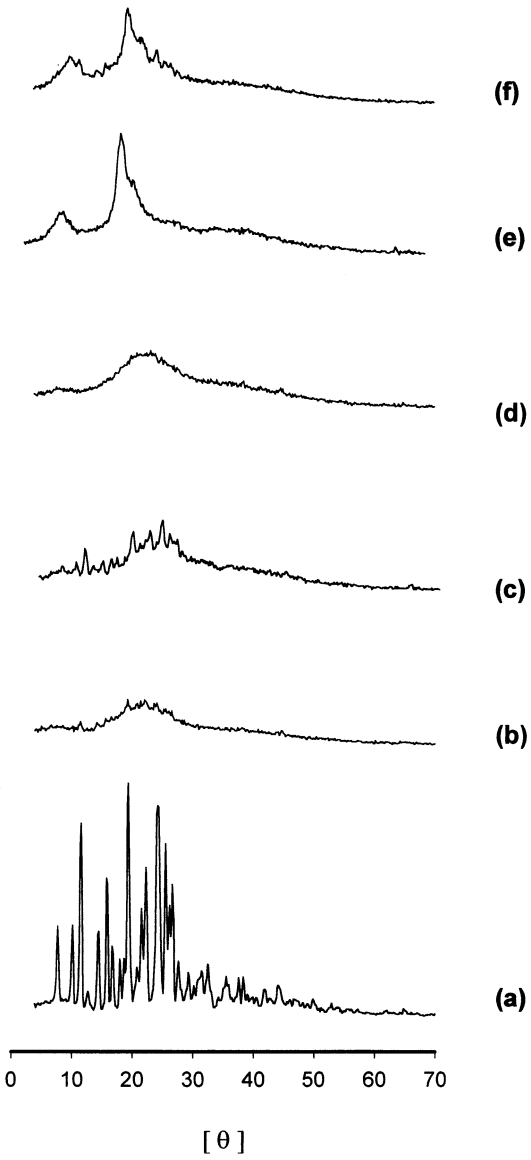

Fig. 2. Powder X-ray diffraction patterns of (a) NF; (b) CS glutamate; (c) CS glutamate:NF (2:1) co-ground mixture; (d) CS glutamate:NF (3:1) co-ground mixture; (e) CS and (f) CS:NF (3:1) co-ground mixture. low-M_w chitosan, Sea cure 123; CS glutamate, medium-M_w CS glutamate, Sea cure G110; NF, nifedipine).

the drug crystals in the co-ground mixture, which was confirmed from the powder X-ray diffraction patterns; and (ii) an improved drug wettability (Sawayanagi et al., 1982, 1983; Imai et al., 1991; Acartürk et al., 1993). CS is highly soluble in low pH; upon contact with the acidic dissolution medium, its amino groups become ionized, the polymer rapidly takes up water and swells to a great extent before it dissolves completely. The co-grinding process of NF with the water-soluble polymer, improves the surface hydrophilicity of the drug powder, because of the rapid dissolution of CS glutamate which allowed water to surround and dissolve NF and reduce aggregation of drug particles (Wan and Pang, 1995).

After identifying the optimum polymer:drug mixing ratio, the second part of this work was focused on the investigation of the effect of the type of CS on NF dissolution from co-ground CS:NF (3:1) mixtures. The CS selected differed in the M_w and optional substitution of its amino groups by glutamic acid. Their particular characteristics were summarized in Table 1. In the previous study, differences in drug dissolution were found to be non-significant for CS:NF ratios

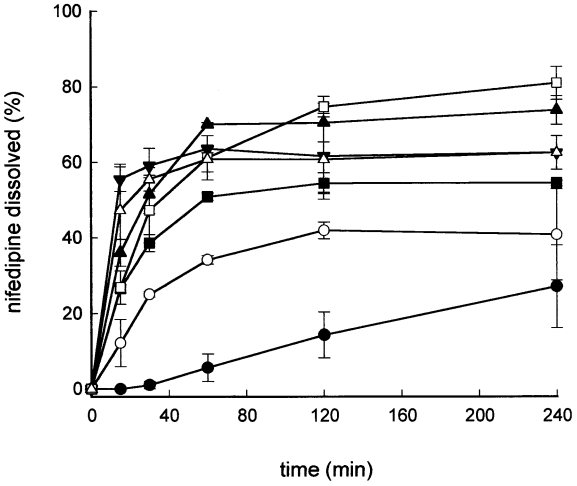

Fig. 3. Effect of the polymer:drug mixing ratio on NF dissolution from the co-ground mixtures. Key: (●) NF and (○) 1:1, (■) 2:1, (□) 3:1, (▲) 4:1, (△) 6:1 and (▼) 8:1 CS glutamate:NF. CS glutamate, medium-M_w chitosan glutamate, Sea cure G110; NF, nifedipine; data shown are the mean ± standard deviations, $n = 3$.

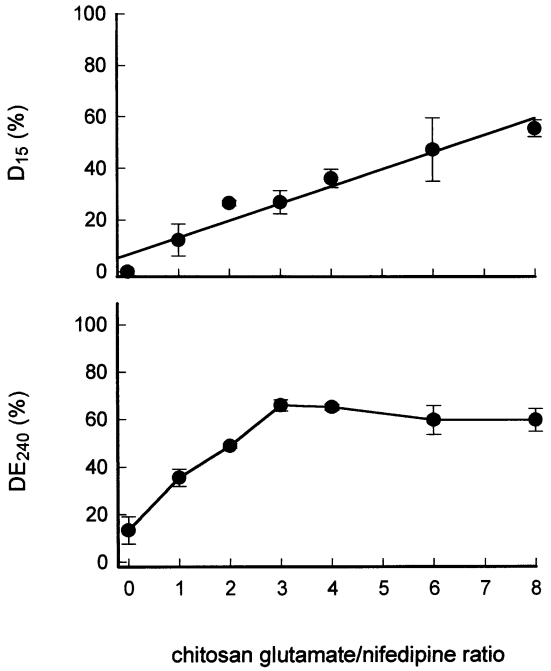

Fig. 4. Effect of the polymer:drug mixing ratio on the percentage of nifedipine dissolved after 15 min (D_{15}) and dissolution efficiency after 240 min (DE_{240}) from the co-ground mixtures (polymer, medium-Mw chitosan glutamate, Sea cure G110; data shown are the mean ± standard deviations, $n = 3$).

above 3:1. Therefore the 3:1 ratio, which is the proportion that showed the strongest effect on NF dissolution while including less polymer content, was selected for this study.

Fig. 5 depicts the dissolution profiles of NF alone and from its co-ground mixtures with Sea cure 123, 223 320 (low-, medium- and high-M_w CS base; carrying free amino-groups, NH_2), Sea cure G110 and G210 (medium- and high-M_w CS glutamate; with substitution by glutamic acid–amino groups, NH_{3+}). All types of CS led to an enhancement of the NF dissolution rate compared to that of the pure drug; there being important differences within the different types of CS. ANOVA ($p < 0.05$) performed on the parameters D_{15} and DE_{240} (Fig. 6) demonstrated that the differences were significant; and according to the LSD test, the systems were classified as follows: G210–G110–123 > 223 > 320-NF (for D_{15}); and G110 > G210 > 123–223 > 320 > NF (for DE_{240}). On comparing the results of both LSD tests it can

be concluded that the effect of the type of CS is more critical in the initial step of drug dissolution.

The trend found was that for the two types of CS (base and salt), the lower the M_w, the faster was the drug dissolution. This behavior was predictable taking into account the relationship between M_w and viscosity of polymer solution (Adusumilli and Bolton, 1991). Upon contact with the acidic medium, CS swells and forms a gel. The diffusion of the drug through the gel into the release medium would be retarded by increasing the viscosity of the polymer, and hence of the gel (Imai et al., 1991). On the other hand, the CS glutamate led to a faster drug dissolution than CS. The explanation to this behavior was found in the differences in the wetting rate, solubilities and swelling capacity of the various CS: the CS glutamate salt would rapidly wet and dissolve upon its incorporation into the dissolution medium, whereas the CS base, less water soluble, would take more time to dissolve. The different X-ray diffraction patterns would also explain differences found in drug dissolution. As was previously shown in Fig. 2, the various CS exhibited different X-ray diffraction patterns, the CS glutamate salt as well as their co-ground mixtures with NF are more amorphous than those of CS base.

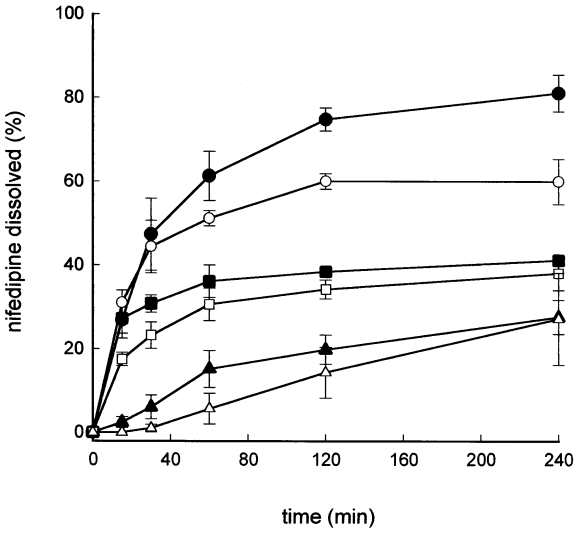

Fig. 5. Effect of the type of CS on NF dissolution from polymer:drug (3:1) co-ground mixtures. Key: (●) medium-M_w CS glutamate (Sea cure G110); (○) high-M_w CS glutamate (Sea cure G210); (■) low-M_w CS (Sea cure 123); (□) medium-M_w CS (Sea cure 223); (▲) high-M_w CS (Sea cure 320) and (△) pure NF. CS, chitosan; NF, nifedipine; data shown are the mean ± standard deviations, $n = 3$.

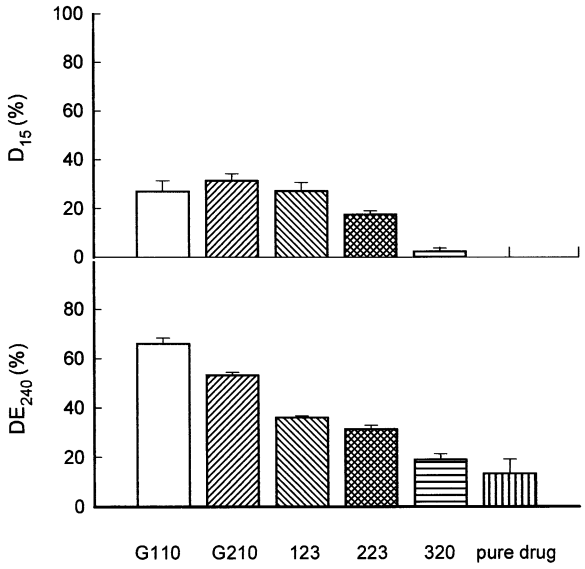

Fig. 6. Effect of the type of chitosan on the percentage of nifedipine dissolved after 15 min (D_{15}) and dissolution efficiency after 240 min (DE_{240}) from polymer:drug (3:1) co-ground mixtures. Key: Sea cure G110 and G210, medium- and high-M_w chitosan glutamate; Sea cure 123, 223 and 320, low-, medium- and high-M_w chitosan (data shown are the mean ± standard deviations, $n = 3$.

It was expected that the method used to disperse NF within CS could be a main factor affecting the enhancement of drug dissolution. Therefore, the third part of this work was focused on the selection of the most suitable procedure to obtain efficient CS:NF solid mixtures. The investigated methods were described in Section 2. The chosen polymer was medium-M_w CS glutamate, which had showed the highest effect on drug dissolution. The selected CS:NF ratio was 2:1, in an attempt to further decrease the CS content and hence, the final drug/excipient mass weight.

Thermograms depicted in Fig. 7 indicated again no evidence of any solid complexation or chemical interaction between drug and polymer for all systems; and the diffraction patterns of all CS:NF mixtures showed fewer and less intense peaks than that of pure drug. The diffraction intensity of NF

in the co-ground, kneaded and solid dispersions was smaller than that of the physical mixture (Fig. 8), which would explain their increased dissolution rate (Fig. 9). ANOVA ($p < 0.05$) performed on the parameters D_{15} and DE_{240} (Fig. 10) demonstrated the existence of significant differences; and the LSD test allowed us to order the systems according to their efficacy on drug dissolution, as follows: NF-PM < KM–SD_I < SD_{II} (for D_{15}); and NF-PM < GM–KM < SD_I < SD_{II} (for DE_{240}).

The non-existence of significant differences among the physical mixture and the pure drug would discard any wetting effect of CS at the polymer:drug ratio (2:1) used in this study; and

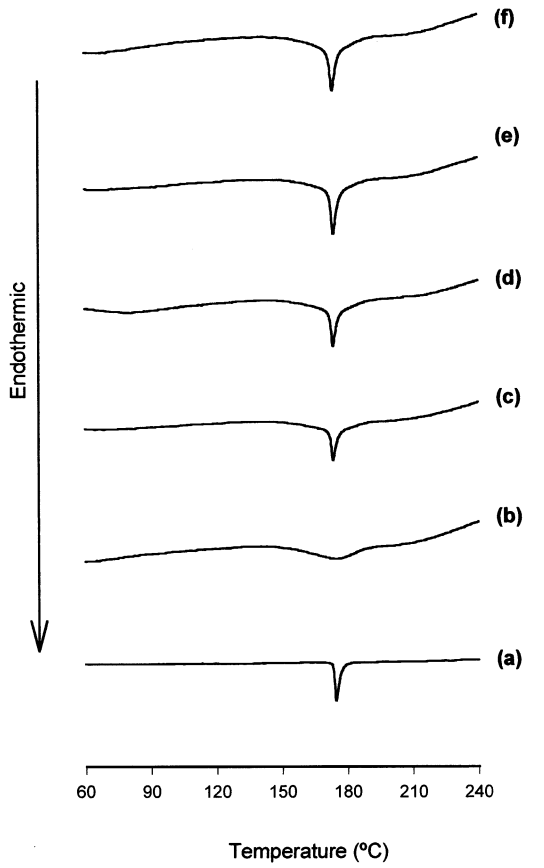

Fig. 7. Differential scanning calorimetry of the polymer:drug (2:1) mixtures prepared using different methods. Key: (a) nifedipine; (b) medium-*M*dw chitosan glutamate (Sea cure G110); (c) co-ground mixture; (d) kneaded mixture; (e) solid dispersion (method I) and (f) solid dispersion (method II).

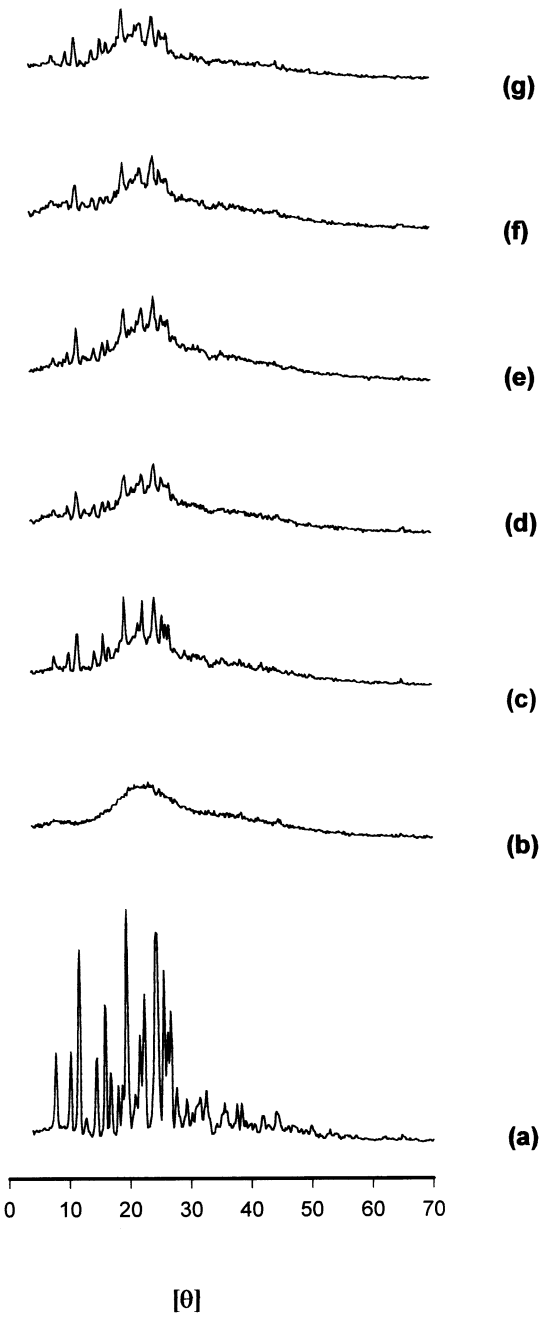

Fig. 8. Powder X-ray diffraction patterns of the polymer:drug (2:1) mixtures prepared using different methods. Key: (a) nifedipine; (b) medium-M_w chitosan glutamate (Sea cure G110); (c) physical mixture; (d) co-ground mixture; (e) kneaded mixture; (f) solid dispersion (method I) and (g) solid dispersion (method II).

the significant differences found between the physical and the co-ground mixture, definitively demonstrated the importance of the reduction of NF crystal size within the CS. On the other hand, the improved dissolution rate of NF from the solid dispersions might predominantly be due to a more intimate dispersion of NF within the CS. In particular, it was observed that the solid dispersions prepared by method II (SD_{II}, dissolution of NF in ethanol and addition to the CS aqueous solution) exhibited the significantly fastest dissolution rate; which suggests that a solid solution of the drug within the polymer might be formed during the solvent evaporation.

Based on the above discussed data, it was concluded that CS strongly affected the dissolution of the poorly water-soluble drug NF, the medium-M_w CS glutamate type being particularly useful. It was proved that all solid mixtures of NF with CS showed a remarkably rapid dissolution rate compared to pure drug and physical mixture. The enhanced dissolution of NF from the solid mixtures could be mainly attributed to amorphization

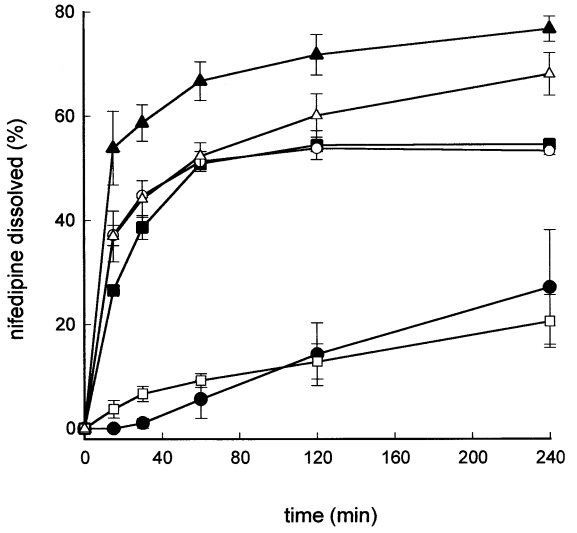

Fig. 9. Effect of the method used to prepare the polymer:drug (2:1) solid mixtures on the dissolution of nifedipine. Key: (●) pure drug; (□) physical mixture; (■) co-ground mixture; (○) kneaded mixture; (△) solid dispersion (method I); and (▲) solid dispersion (method II) (polymer, medium-M_w chitosan glutamate, Sea cure G110; data shown are the mean ± standard deviations, $n = 3$).

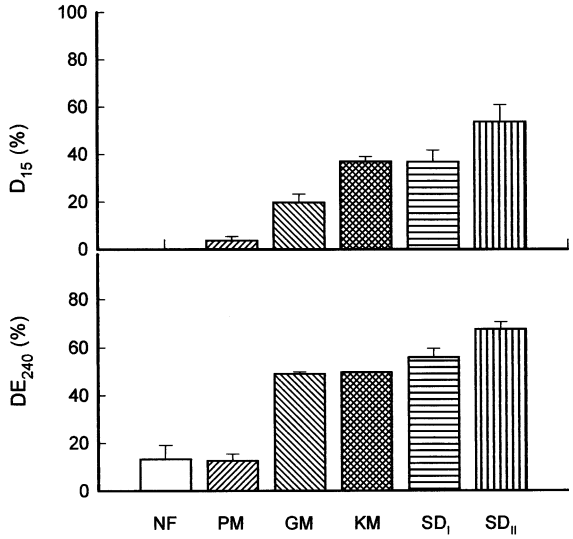

Fig. 10. Effect of the method used to prepare the polymer:drug (2:1) solid mixtures on the percentage of nifedipine dissolved after 15 min (D_{15}) and dissolution efficiency after 240 min (DE_{240}). Key: NF, nifedipine; PM, physical mixture; GM, co-ground mixture; KM, kneaded mixture; SD_I, solid dispersion (method I); SD_{II}, solid dispersion (method II) (polymer, medium-M_w chitosan glutamate, Sea cure G110; data shown are the mean ± standard deviations, $n = 3$).

of the drug (as was demonstrated by X-ray diffractometry); however, a contribution role of improved wettability, reduced aggregation and increased surface area can not be discarded for some polymer:drug ratios. The simply co-grinding of NF along with CS in a 3:1 CS:NF ratio, which leads to solid mixtures exhibiting a significantly improved dissolution profile without using organic solvents or high temperatures, appears to be the easier and most convenient method from a practical point of view.

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