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Characterization and dissolution behavior of nifedipine and phosphatidylcholine binary systems

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Abstract

Physicochemical properties and the dissolution behavior of binary systems of nifedipine (NIF) and dipalmitoylphosphatidylcholine (DPPC) or dimyristoylphosphatidylcholine (DMPC) as physical mixtures, solid dispersions and ground mixtures at 9:1 w/w were investigated. The drug and formulations were characterized by powder X-ray diffraction, Fourier transform infrared spectroscopy (FTIR) and differential thermal analysis (DTA). The dissolution and solubility of NIF was increased in the order physical mixture < solid dispersion < ground mixture. The powder X-ray diffraction patterns and FTIR spectra indicated absence of major crystalline or molecular changes of NIF or the PCs. The fraction of NIF dissolved after 1 h was approximately 30 and 34% from NIF/DMPC and NIF/DPPC ground mixtures, respectively, and the dissolution was only slightly reduced from NIF/DPPC, 9.75:0.25 w/w systems. The crystal lattice parameter, *c*, of DPPC and DMPC in the solid dispersion was longer than that of PC alone but each was considered to be in an amorphous state in the ground mixture because of the absence of an X-ray diffraction peak. Full-width at half-maximum (half width) of the X-ray diffraction peak of NIF in the ground mixture was greater than NIF in the physical mixture or solid dispersion, suggesting that the lattice distortion of NIF crystals was increased by grinding. Thermal analysis confirmed the crystalline state of DPPC and DMPC in the physical mixture and the solid dispersion but an amorphous state in the ground mixture. Thus, an increase in lattice distortion of NIF crystals due to grinding and an amorphous state of DPPC or DMPC in the ground mixtures are considered mainly responsible for the larger increase in dissolution rate and extent of dissolution of NIF after 1 h compared to the solid dispersion formulation.

Keywords: Nifedipine; Dissolution; Physical mixture; Solid dispersion; Ground mixture; Phosphatidylcholine; Crystal lattice distortion

1. Introduction

Nifedipine (NIF) is a practically water-insoluble drug used therapeutically as a calcium-channel blocker for systemic and coronary vasodilation. Poorly water-soluble drugs that undergo dissolution rate-limited gastrointestinal absorption gen-

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erally show increased bioavailability when dissolution is improved by formulation techniques. In particular, solid dispersions of poorly water-soluble drugs and phosphatidylcholine (PC) systems have been studied (Venkataram and Rogers, 1984; Vudathala and Rogers, 1992; Biswas et al., 1993). With only a small amount of phospholipid (e.g., 5–20 percent by weight) improved dissolution and absorption characteristics of griseofulvin, fludrocortisone or carbamezapine were found. Furthermore, the effect of aging of the solid dispersions on the dissolution rate and on the residual organic solvent in the coprecipitates were reduced with the incorporation of about 5% cholesterol (Vudathala and Rogers, 1991).

Pharmaceutical properties of solid dispersions of NIF and some enteric coating agents have been investigated (Sugimoto et al., 1982; Hasegawa et al., 1985a) and improved bioavailability as well as sustained release characteristics were found (Hasegawa et al., 1985b). The dissolution and absorption characteristics of NIF/polyethylene glycol/PC solid dispersions have also been investigated (Law et al., 1992).

In the present report, the pharmaceutical properties of physical mixtures, solid dispersions and ground mixtures of NIF with small amounts of PCs have been investigated. Possible mechanisms of the improvement of NIF dissolution from these formulations have been discussed with respect to certain identified physicochemical characteristics of NIF and the PCs in these systems.

2. Materials and methods

Nifedipine was purchased from Sigma Chemical Corp. (St Louis, MO). Dipalmitoylphosphatidylcholine (DPPC) and dimyristoylphosphatidylcholine (DMPC) were obtained from Princeton Lipids Inc. (Princeton, NJ). Water was double-distilled and other chemicals used were reagent grade.

2.1. Preparation of NIF/PC systems

2.1.1. Solid dispersion

Solid dispersions of NIF/PC were prepared as coprecipitates by the solvent method using chloroform. Solutions of NIF and DPPC or DMPC monohydrate were prepared in 20 ml of chloroform, the solvent was removed under reduced pressure at 40°C and further dried overnight in a vacuum oven. The coprecipitates were sieved (125 mesh, US-standard sieves) just prior to experimentation from storage under vacuum after about 15 h.

2.1.2. Physical mixture

The appropriate weights of NIF and DPPC or DMPC monohydrate (125 mesh) were placed in a screw-capped bottle and mixed by hand-shaking for 10 min.

2.1.3. Ground mixture

The appropriate weights of NIF and DPPC or DMPC monohydrate were ground in a mortar for 1 h then sieved (125 mesh). NIF crystals were similarly treated for testing as a control.

The composition of NIF/DPPC or NIF/DMPC mixtures used was 9:1 w/w, unless otherwise stated. All sample powders were put in light-resistant bottles and stored in a refrigerator until required for use.

2.2. Powder X-ray diffraction

A RAD type powder X-ray diffraction system (Rigaku Co.) was used. Graphite-monochromated cobalt Kα line (1.7903 Å) was used as an X-ray source. A fixed-time step-scanning method was employed. The step width was 0.02° (2θ) with a fixed time of 1 s at each step. Full-width at half-maximum (FWHM) of the diffraction peak was defined as the half width of the peak obtained by dividing the peak area by the peak height.

2.3. Differential thermal analysis (DTA)

A Fisher Thermalizer (series 300 QDTA, Fisher Scientific Co.) was used. The sample was sealed in an aluminum pan and heated at 25°C/min using an empty pan as reference. The chart temperature was calibrated using the melting points (onset temperatures) of indium and tin determined under

the same conditions. The heat of fusion (ΔH_f) of the NIF crystal was calculated by comparing the area under the melting peak of NIF with that of a known amount of indium. The area under the endothermic peak was obtained by the cutting and weighing method.

2.4. Fourier transform infrared spectroscopy (FTIR)

A Nicolet 5DX system (Nicolet Co.) was used. Measurements were carried out using the KBr disk method. Ten spectra were obtained for each sample and averaged.

2.5. The dissolution test

A spin-filter dissolution test apparatus equipped with a nominal 1-μm stainless steel filter screen was used (Shah et al., 1973). The filter was rotated at 200 rpm in 700 ml of dissolution medium consisting of simulated gastric fluid USP without pepsin and containing 0.001% Tween 80 at 37°C. Sample powders equivalent to 30 mg of NIF were dispersed in the dissolution medium, which was continuously circulated through the filter and a microcell in the spectrophotometer (Beckman, model 25). Concentrations of NIF in the dissolution medium were obtained from absorbances at 235 nm and a calibration curve. As shown previously (Venkataram and Rogers, 1984; Vudathala and Rogers, 1992), small amounts of phospholipid in the dissolution media, presumably existing as small vesicles, did not interfere with the absorbances of NIF (i.e., equivalent concentrations of PCs dispersed in the dissolution medium had zero absorbance).

2.6. Determination of NIF solubility

An excess amount of sample powder (20 mg) was added to 20 ml of the dissolution medium in a light-resistant screw-capped bottle. The bottles were agitated for 60 h in a water-bath maintained at 37°C (previously determined to have reached apparent equilibrium in the medium in which all of the PC would have dissolved). Samples were removed, filtered (Whatman No. 5 filter paper) and the NIF concentration was determined analytically as before after appropriate dilution.

3. Results

The dissolution profile of NIF crystals exhibited a relatively slow rate of dissolution in which only about 18% of the initial amount of drug had dissolved in 60 min yielding a concentration of 7.7 mg/l (Fig. 1, Table 1). Grinding the NIF increased the initial dissolution rate over 5 min (IDR) 3-fold but the concentration in the medium after 60 min increased only slightly (5%). Combining NIF and DPPC increased the IDR 2-fold from physical mixtures, 4-fold from solid dispersions, and about 3-fold from ground mixtures (compared to ground NIF). NIF/DMPC binary systems behaved similarly (Fig. 2), except that the IDR was increased 5-fold from the solid dispersion. Concentrations of NIF in solution after 60 min increased in the order physical mixture < solid disperison < ground mixture and were approxi-

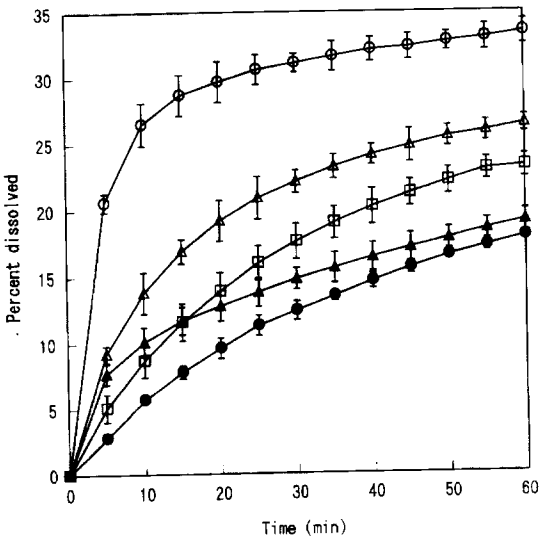

Fig. 1. Dissolution profiles of NIF and NIF/DPPC (9:1 w/w) systems: (○), ground mixture; (△), solid dispersion; (□), physical mixture; (▲), ground NIF; (●), NIF crystals. Mean ± SD (n = 3).

Table 1
Comparison of dissolution properties of NIF and NIF/PC binary systems at 37°C

NIF/PC (9:1 w/w)	Initial dissolution Rate (IDR) (mg/l/min)	Conc. NIF after 60 min (mg/l)
NIF crystals	0.2	7.7
Ground NIF	0.6	8.1
DPPC		
Physical mixture	0.4	10.1
Solid dispersion	0.8	11.4
Ground mixture		
9:1 w/w	1.8	14.6
9.5:0.5 w/w	1.3	12.9
9.75:0.25 w/w	1.3	12.0
DMPC		
Physical mixture	0.4	8.8
Solid dispersion	1.0	11.8
Ground mixture	2.1	13.3

Dissolution medium was simulated gastric fluid, USP without pepsin containing 0.001% Tween 80.

mately 30, 50 and 80% higher using DPPC compared to 15, 50 and 65% higher using DMPC, than from NIF alone (Table 1). However, the fraction of the dose of NIF dissolved after 1 h from, for example the ground mixtures, was only 30 and 34% from NIF/DMPC and NIF/DPPC, 9:1 w/w systems, respectively.

The dissolution of NIF as a function of the weight ratio of NIF:DPPC in ground mixtures is shown in Fig. 3. Although the dissolution of NIF decreased as the fraction of DPPC was reduced (Table 1) it was observed that even 2.5% DPPC improved the dissolution rate of NIF 2-fold and the extent of dissolution after 1 h by 50%. This suggests that the same mechanisms responsible for the dissolution behavior of NIF ground mixture

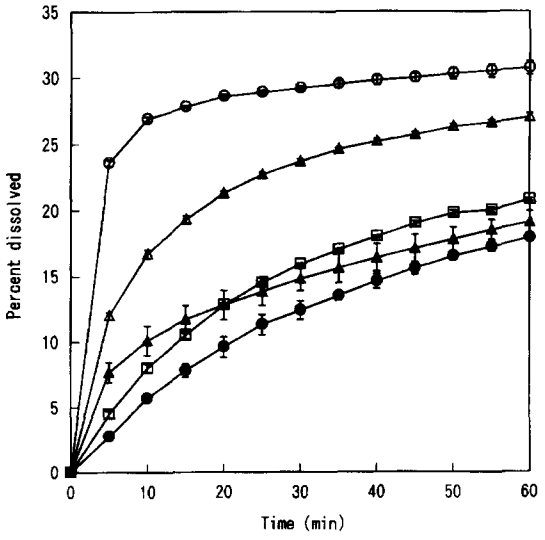

Fig. 2. Dissolution profiles of NIF and NIF/DMPC (9:1 w/w) systems. (○), ground mixture; (Δ), solid dispersion; (□), physical mixture; (▲), ground NIF; (●), NIF crystals. Mean ± SD (n = 3).

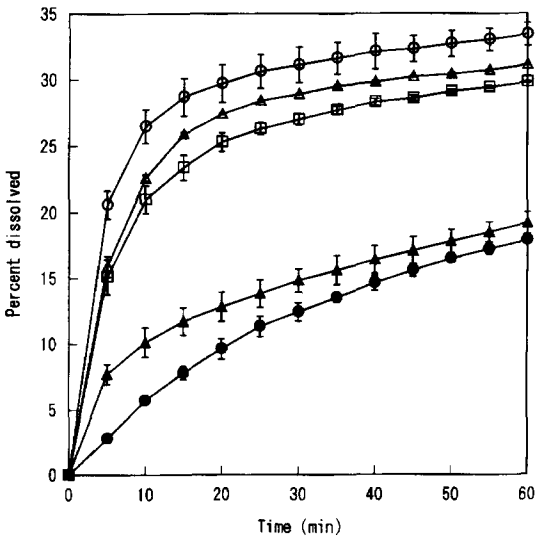

Fig. 3. Effect of DPPC concentration on the dissolution rate of NIF/DPPC ground mixtures. (○), (9:1 w/w); (Δ), (9.5:0.5 w/w); (□), (9.75:0.25 w/w); (▲), ground NIF; (●) NIF crystals. Mean ± SD (n = 3).

Table 2
Solubility of NIF and NIF from NIF/PC (9:1 w/w) systems in dissolution medium at 37°C[a]

Formulation	Solubility (μg/ml)	
	DMPC	DPPC
NIF alone	15.2 (0.7)	15.2 (0.7)
Physical mixture	15.5 (1.1)	15.8 (2.4)
Solid dispersion	20.5 (1.0)	20.5 (0.6)
Ground mixture	27.1 (2.3)	35.6 (5.3)

[a]Dissolution medium was simulated gastric fluid, USP without pepsin and containing 0.001% Tween 80. Standard deviation in brackets (n = 3).

containing 10% DPPC operate with only 2.5% DPPC.

The solubility data of NIF from each formulation in the dissolution medium shown in Table 2 indicate that the presence of the PC had no effect on the solubility of NIF from physical mixtures but solubility increased in the order physical mixture < solid dispersion < ground mixture. The solubility from ground mixtures of NIF/DPPC was about 30% higher than from NIF/DMPC.

Physical characterization of NIF, PC, and NIF/PC binary systems by powder X-ray diffraction is described in typical diffraction patterns shown in Fig. 4 and relevant parameters given in Table 3 and Table 4. Characteristic peaks shown for each compound or formulation indicate that neither grinding or coprecipitation of NIF caused any significant molecular or crystal lattice structural change of NIF. Reflection plane indices were estimated from NIF lattice parameters, $P2_1/c$, given by Triggle et al. (1980) as follows: a = 10.923 Å; b = 10.326 Å; c = 14.814 Å; β = 92.70°, and are indicated adjacent to each peak in Fig. 4, patterns a, b and c. The following lattice parameters ($P2_1$) of the crystal structure of DMPC dihydrate have been reported (Pearson and Pascher, 1979): a = 8.72 Å, b = 8.92 Å, c = 55.4 Å and β = 97.40°. The c axis lattice parameter is very large because PCs form a hydrogen-bonded dimer structure in the crystal lattice. The diffraction pattern of DMPC in Fig. 4 exhibited diffraction peaks at 17.61 (5.82°), 13.21 (7.76°), 8.81 (11.66°) and 6.65 Å (15.46°) in d-spacing attributable to

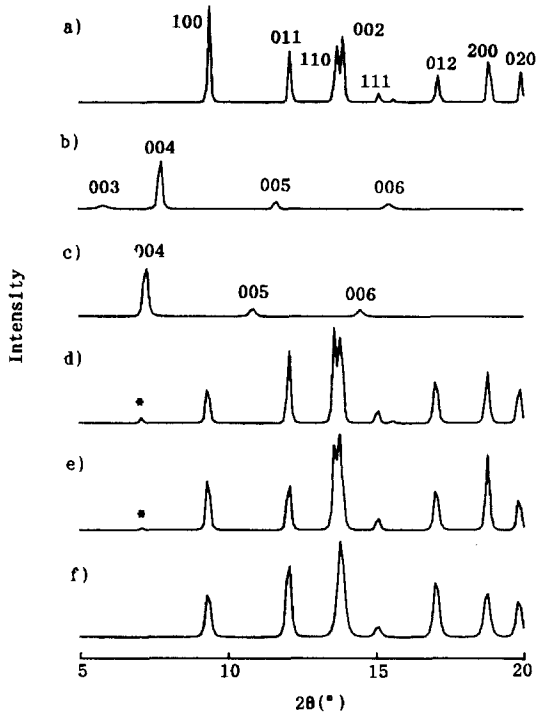

Fig. 4. Powder X-ray diffraction patterns of: (a) NIF crystals; (b) DMPC; (c) DPPC; (d) NIF/DPPC (9:1 w/w) physical mixture; (e) NIF/DPPC (9:1 w/w) solid dispersion; (f) NIF/DPPC (9:1 w/w) ground mixture. Numbers adjacent to the peaks represent the reflection plane indices. *The diffraction peak of DPPC crystals.

the 003, 004, 005 and 006 reflections, respectively. The diffraction pattern of DPPC exhibited diffraction peaks at 14.13 (7.26°), 9.45 (10.86°) and 7.09 Å (14.50°) in d-spacing, attributable to the 004, 005 and 006 reflections, respectively. Also, as can be seen in Fig. 4, diffraction peaks of DPPC

Table 3
Length of c axis of DPPC and DMPC crystals from powder X-ray diffraction

Sample	c axis[b] (Å)
Intact DPPC	56.52
DPPC in solid dispersion[a]	59.86
Intact DMPC	52.84
DMPC in solid dispersion[a]	55.13

[a]NIF/DPPC, 9:1 w/w.
[b]Calculated from the diffraction angle of the 004 reflection.

Table 4
FWHM of 100 and 011 reflections of NIF in NIF/DPPC and NIF/DMPC (9:1 w/w) systems from powder X-ray diffraction

Sample	FWHM of 100 reflection($2\theta°$)	FWHM of 011 reflection($2\theta°$)
NIF crystals	0.169	0.158
NIF/DPPC		
physical mixture	0.186	0.217
solid dispersion	0.233	0.235
ground mixture	0.339	0.318
NIF/DMPC		
physical mixture	0.196	0.214
solid dispersion	0.234	0.256
ground mixture	0.335	0.297

FWHM, full-width at half-maximum.

occurred in the diffraction pattern of NIF/DPPC physical mixture and solid dispersion, indicating that DPPC in these systems existed in a crystalline state. On the other hand, the diffraction pattern of the ground mixture had no peak corresponding to DPPC, indicating that DPPC existed in an amorphous state. Similar results were obtained for the NIF/DMPC systems.

The lattice parameters, c (c-axis) of each PC alone or in NIF/PC solid dispersion estimated from peak positions corresponding to 004 reflections are given in Table 3. The lengths of the c-axis of PCs in the solid dispersions were larger than for the PCs alone and the c-axis of DMPC in the solid dispersion agreed closely with the c-axis of DMPC dihydrate (Pearson and Pascher, 1979), suggesting that crystalline DMPC in the solid dispersion had a dihydrate structure.

FWHM of the 100 and 011 reflections of NIF crystals in the NIF/DPPC and NIF/DMPC systems are summarized in Table 4. The observed increase in FWHM can arise from either an increase in the lattice distortion or a decrease in crystallite size (Klug and Alexander, 1974; Fukuoka et al., 1993). FWHM of the 100 and 011 reflections of NIF crystals in NIF/DPPC or NIF/DMPC systems were in the order NIF crystals < solid dispersion < ground mixture. These results suggest that the lattice distortion of NIF crystals in the ground mixture was larger than that in the solid dispersion.

The FTIR spectra of NIF and NIF/PC systems (not shown) were essentially identical indicating that there were no major crystal structure or molecular changes of NIF or of PCs as a result of grinding or coprecipitation.

Typical DTA thermograms of the NIF/DPPC systems are depicted in Fig. 5. The main endothermic peak of NIF had an onset temperature of 174°C (cf. 174°C Law et al., 1992; 172–174°C, Merck Index, 1989) which shifted to 166–168°C in the binary mixtures. Likewise, peak temperatures of the formulations were 176–177°C (cf. 182°C). Pure DPPC produced an endothermic peak at about 70°C which also appeared in the thermograms of the NIF/DPPC physical mixture and solid dispersion systems, but not the ground mixture. Similar thermotropic changes were observed in the NIF/DMPC binary systems. These results suggest that the DPPC or DMPC in the physical mixture and the solid dispersion was in a crystalline state, whereas either PC in the ground mixture was in an amorphous state.

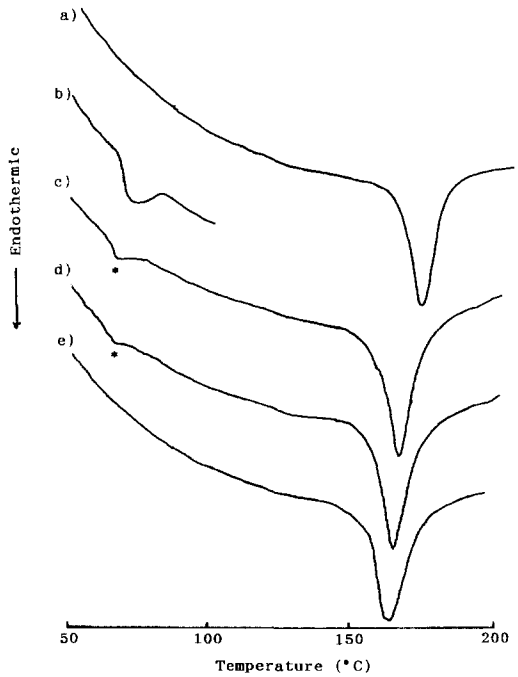

Fig. 5. DTA thermograms of NIF, DPPC and NIF/DPPC (9:1 w/w) systems. (a) NIF crystals; (b) DPPC; (c) physical mixture; (d) solid dispersion; (e) ground mixture. *The endothermic peak of DPPC.

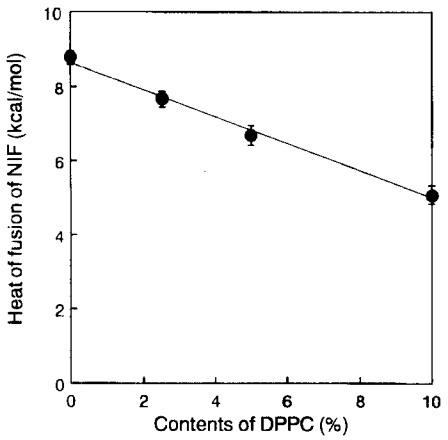

Fig. 6. Heats of fusion of NIF crystals in NIF/DPPC physical mixtures as a function of the DPPC concentration.

Fig. 6 depicts the effect of DPPC concentration on the ΔH_f of NIF in NIF/DPPC physical mixtures. ΔH_f decreased linearly with DPPC concentration from 8.8 for pure NIF to about 5 kcal/mol for 9:1 w/w NIF/DPPC systems (as well as solid dispersions, ground mixtures and NIF/DMPC systems), suggesting that some of the NIF may have dissolved in the DPPC during the heating process. Thus, DTA was not sufficiently sensitive to provide any additional detailed information about the physicochemical characteristics of NIF crystals in the NIF/PC systems.

4. Discussion

The dissolution rate of NIF was improved from the solid dispersion or ground mixture formulations with PC and the ground mixture was superior to the solid dispersion. The mechanism of improvement of the dissolution rate was considered as follows. As previously reported, solid dispersions of poorly water-soluble drugs with small amounts of PCs resulted in faster dissolution rates than from physical mixtures (Venkataram and Rogers, 1984) due to reduced crystallinity in the solid dispersion state. Furthermore, PCs were described as forming colloidal aggregates (liposomes) in the dissolution medium in which drug partitioned and dissolved during dissolution. In a similar fashion, these same mechanisms are considered to apply with respect to the improved dissolution of NIF from NIF/PC solid dispersions in this study.

The dissolution rate of NIF from NIF/PC ground mixtures is strongly dependent on the physicochemical states of both NIF and the PCs. The evidence indicates that, in the ground mixtures, an amorphous state of the PCs existed and the lattice distortion of NIF crystals was larger than in the solid dispersion. On the basis of this information, grinding poorly water-soluble drugs with small amounts of PCs appears to have the effect of increasing the lattice distortion of crystalline drugs. Also, the observed higher IDR of ground NIF compared to NIF crystals (Table 1) may be due to increased crystal lattice distortion. Because amorphous PCs are considered to dissolve faster than crystalline PCs, liposomes (or myelinic structures) of PCs should develop faster at the crystal-liquid interface (Venkataram and Rogers, 1984) from ground mixtures than from solid dispersions. Subsequently, partitioning and solubilization of NIF in liposomes would be expected to occur based on the solubility data in Table 2. The lower increase in dissolution from physical mixtures after 1 h is indicative of the crystalline states of both NIF and PC which undergo dissolution and dispersion independent of each other. Since NIF solubility was not increased by PC in the physical mixtures (Table 2), the observed improvement in dissolution of NIF could be due to wetting of the NIF crystals (Chou and Riegelman, 1971).

The results of the PC concentration-dependent dissolution (Fig. 3, Table 1) also suggest that the amount dissolved is determined by the amount incorporated in liposomes at early dissolution times rather than equilibration of free drug in solution with pre-formed liposomes at later times. The marginally lower fraction of NIF dissolved after 1 h from ground mixtures containing 2.5 compared to 10% DPPC is indicative of fewer liposomes formed from the lower concentration of DPPC giving rise to a slightly lower uptake of NIF.

Fujii et al. (1988a, 1988b, 1991a, 1991b) have reported the dissolution of phenytoin, NSAIDs,

phenobarbital, and benzodiazepines from solid dispersions with hydrogenated soybean PC at mole fractions of drug of 0.75 and 0.25 and lower, in which the drug occurred in an amorphous state. Dissolution from the solid dispersions was greater than the free drug or physical mixtures in all cases but little difference was observed between the 0.75 and 0.25 mole fractions. The dissolution rate and fraction of carbamazepine dissolved was increased from 10:1 weight ratio or lower coprecipitates with lecithin (Biswas et al., 1993) but, also in this case, the drug was described as existing in an amorphous state in the solid dispersions.

Combining lecithin with drug:polyethylene glycol solid dispersions has also been shown to be effective in increasing the dissolution properties of NIF (Law at al., 1992) as well as miconazole (Pedersen and Rassing, 1990). Nifedipine or egg PC at only 5% concentration was either dissolved or dispersed in the polyethylene glycol in an amorphous state and the increased NIF dissolution was attributed to uptake of drug by liposomes (Law et al., 1992),

It is apparent that high drug:PC ratios provide a greater efficient use of drug and require smaller amounts of carrier which, using lecithins, represent a significant cost saving. Ground mixtures of drug with microcrystalline cellulose or cyclodextrins have been reported to have anomalous properties with respect to sublimation (Nakai et al., 1978), chemical stability (Nakai et al., 1982), molecular state (Nakai et al., 1984), drug absorption (Yamamoto et al., 1976) and solid-state reaction (Fukuoka et al., 1994). In the present study, this technique using DPPC or DMPC yielded superior dissolution behavior because of an amorphous state of the PC and a lattice distortion of the crystalline structure of NIF, which was not observed to the same extent with the physical mixture or solid dispersion formulations. Ground mixtures are easier to prepare under controlled conditions than coprecipitates and, at least for some crystalline drugs and PCs, could represent a better approach to improve dissolution.

Acknowledgements

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