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Influence of rapeseed phospholipids on ibuprofen dissolution from solid dispersions

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The dissolution profiles of ibuprofen (IB) from solid dispersions prepared by the solvent evaporation method, containing the rapeseed lecithin ethanol soluble fraction (LESF) or rapeseed phosphatidylcholine (RPC) have been determined. The effect of incorporation of PEG 4,000 or PEG 8,000 in the solid dispersions on the controlled-release of IB was also investigated. Dissolution studies conducted in double-distilled water using the paddle dissolution apparatus showed that the initial dissolution rate (IDR) within the first 5 min and the maximum percent of dissolved IB of IB/LESF were double of those of IB/RPC (both in ratio 4 : 1 w/w). The low amounts of LESF markedly increased dissolution of IB. Increasing of LESF concentration from 0 to 10 and 20% in solid dispersions produced 60 and 100% improvement of IB maximum dissolution level respectively, to compare with that of IB alone. PEG 4,000 caused the slightly decreasing in IB dissolution rate, while PEG 8,000 markedly improved the dissolution of IB in examined conditions.

1. Introduction

Several new pharmaceutical dosage forms and formulations like solid dispersions have been studied and evaluated to increase dissolution rate and bioavailability of poorly water-soluble drugs (Serajuddin 1999; Leuner and Dressman 2000; Garekani et al. 2003). The phospholipid carriers, used to date as solubilizers and to form a drug matrix in solid dispersions include the synthetic 1,2-diacyl-*sn*-glycerophosphocholine with defined fatty acids as well as natural and chemically modified egg and soya phosphatidylcholine (Fujii et al. 1991a, b; Vudathala and Rogers 1992; Habib et al. 1998; Prabhu et al. 2001; Abdul-Fattah and Bhargava 2002). For these carriers, the efficiency of dissolution of a poor water-soluble drug essentially depends on the fatty acid profile in the phospholipid molecules (Vudathala and Rogers 1992). Rapeseed lecithin ethanol soluble fraction (LESF) and pure rapeseed phosphatidylcholine (RPC) prepared from 00-type rapeseed varieties low in erucic acid and glucosinolates are less sensitive to oxidation in comparison to native soya constituents, and have the potential to be used not only in technical fields but also in pharmacy and cosmetic industry (Sosada et al. 1992; Sosada 1997). The rapeseed phospholipids contain mostly oleic (C 18 : 1) and linoleic (C 18 : 2) acids, 58% and 29% respectively. In contrast, the principal component of soya phospholipid fatty acids is linoleic acid (C 18 : 2; 65%), with a lower level of oleic acid (13%) (Sosada et al. 1992).

The purpose of this study was to use solid dispersions, based on rapeseed phospholipids prepared by the solvent evaporation method, to improve the dissolution rate of ibuprofen (IB), the (*R*,*S*)2-(4-isobutylphenyl)-propionic acid, a compound that is poorly water soluble and is widely used as one of the best tolerated nonsteroidal anti-inflammatory drugs. The effect of incorporation of selected polyethylene glycols in the solid dispersions on the controlled-release of the drug was additionally investigated.

2. Investigations, results and discussion

A comparison of the dissolution profiles of IB alone and as the solid dispersions IB/RPC and IB/LESF (4 : 1) in double-distilled water at 37 °C is shown in Fig. 1. As expected, the dissolution of IB depends on the presence of rapeseed phospholipids in examined formulations. IB alone dissolved relatively rapid in the first 5 min and than leveled off only at about 45 μg/ml. This observation might

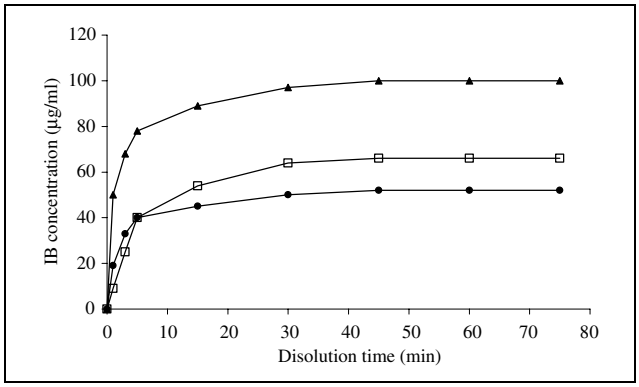

Fig. 1: Dissolution profiles of IB/phospholipid solid dispersions (4 : 1) in water at 37 °C. IB/RPC (□), IB/LESF (▲), no phospholipid (●)

Table 1: Dissolution of IB, IB/RPC and IB/LESF solid dispersions

No.	Formulation	% Dissolved (75 min)[a]	IDR[a, b] (mg/ml/min)
1	IB	10.0 ± 0.5	8.1 ± 0.1
2	IB/RPC (4 : 1)	14.5 ± 0.6[c]	7.9 ± 0.1
3	IB/LESF (4 : 1)	20.3 ± 0.4[c]	15.6 ± 0.1[c]
4	IB/LESF (8.5 : 1.5)	18.2 ± 0.8[c]	14.5 ± 0.1[c]
5	IB/LESF (9 : 1)	16.0 ± 0.5[c]	13.3 ± 0.2[c]

[a] Mean ± SD; n = 3
[b] Initial dissolution rate within first 5 min
[c] Value significantly different from that obtained for IB ($p < 0.05$, t-test)

be attributed to the fact that the fine particles of a solid dispersion have dissolved at first, leaving the slowly dissolving less fine particles behind. The slightly decrease in pH values from 5.5 to 4.4 observed in the experimental medium during the run, due to dissolution of the weak acid (IB) could also explain the faster IB dissolution in the first 5 min of the run and the next lowering in IB dissolution rate. When IB is incorporated into solid dispersions, the dissolution of IB from the formulations studied was significantly higher than that of pure IB. The maximum concentrations of IB achieved in solution for IB/RPC and IB/LESF leveled off at 65 and 90 μg/ml respectively. A comparison of the quantitative dissolution behavior of IB under different phospholipid compositions is given in Table 1. The results show that the initial dissolution rate (IDR) within the first 5 min and the percent of dissolved IB after 75 min of IB/LESF were double of those of IB/RPC and the values were significantly different ($p < 0.0023$) from that obtained for IB and IB/RPC. Significantly faster IB dissolution from IB/LESF dispersions might be attributed to the better solubilizing effects of LESF on the active drug, to compare with RPC. It is speculated that pure RPC is a less effective solubilizer compare to LESF. The second one is a complex mixture of the zwitterion phosphatidylcholine and the acidic phospholipids, mostly phosphatidylethanolamine. In consequence, the LESF has a different phospholipid fatty acid profile and hydrophilicity compared to RPC. For that reason it could be suggested that LESF as a complex solubilizer has much better solubilizing properties to IB than RPC. Based on the above results, the dissolution of IB/LESF solid dispersion was considered to be optimum. The LESF concentration also exerted a notable effect on the dissolution of IB from solid dispersions. Fig. 2 shows that low amounts of LESF markedly increased dissolution of IB. Increasing the LESF concentration from 0 to 10 and to 20% in solid dispersions produced 60 and 100% improvement of IB maximum dissolution level (after 75 min) respectively, compared with that of IB alone. A similar behavior was observed for IDR where a 20% addition of LESF to the formulation gives a two-fold increment in dissolution rate compared to pure IB (Table 1). This is interpreted in a way that the quantity of LESF that can be included in the IB-phospholipid crystalline structure plays an important role in the dissolution process and the phospholipid concentration effects only to a certain limit depending on the character of solid dispersion components. The IB formulations with LESF concentration above 20% were semi-fluid and in consequence impossible to powder and test using the methods of this study. The advantageous influence of phospholipid solid dispersions on the dissolution of another nonsteroidal inflammatory drug – flurbiprofen has been confirmed (Habib et al. 1998). The results obtained for flurbiprofen and dimyristoyl phosphatidylglycerol solid dispersions suggested that less than a 20 : 1 ratio of drug to phospholipid was required to disperse flurbiprofen. Increasing the phospholipid content did not improve markedly the dissolution rate to any significant extent (Habib et al. 1998). Similar phenomenon was also observed in our investigations.

Fig. 3 describes the dissolution profiles of IB observed for solid dispersions IB/LESF with incorporated polyethylene glycols PEG 4,000 or PEG 8,000. The dissolution results presented in Fig. 3 and Table 2 provide some evidence of how the addition of polyethylene glycols with different molecular weight at low concentration can alter the physical state and dissolution behavior of IB/LESF (4 : 1 by weight) solid dispersion. At a LESF/PEG ratio of 20 : 1, only PEG 8,000 caused an increase in IB maximum dissolution level from 20 to 29% after 75 min comparing to IB/LESF without polymer, whereas PEG 4,000 with an IDR value about 15% lower, markedly decreased the dissolution rate of IB from the solid dispersions examined. These results suggest that polyethylene glycols slightly reduced the interaction of LESF in the phospholipid solid dispersions, thereby resulting in a slower dissolution rate. On the other hand, polyethylene glycol (PEG 10,000) alone or in talc-PEG system was shown to be useful as a carrier for ibuprofen (Khan and Jiabi 1998).

The effects of a PEG 8,000 concentration on the dissolution of IB/RPC/PEG 8,000 and IB/LESF/PEG 8,000 solid dispersions can be observed in Fig. 4 and Table 2. From the dissolution profiles obtained in the experiments it

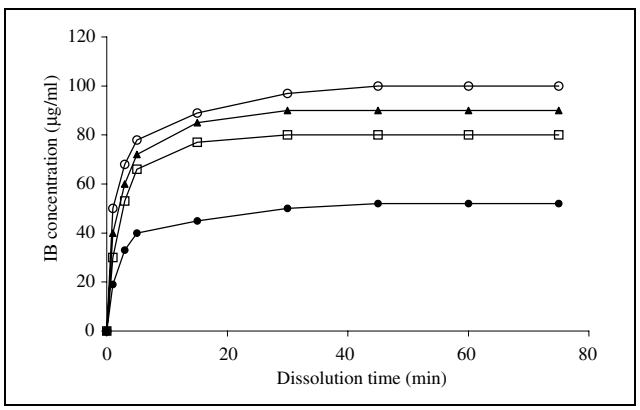

Fig. 2: Dissolution profiles of IB/LESF solid dispersions in water (37 °C) at weight ratios of 4 : 1 (○), 8.5 : 1.5 (▲), 9 : 1 (□), no phospholipid (●)

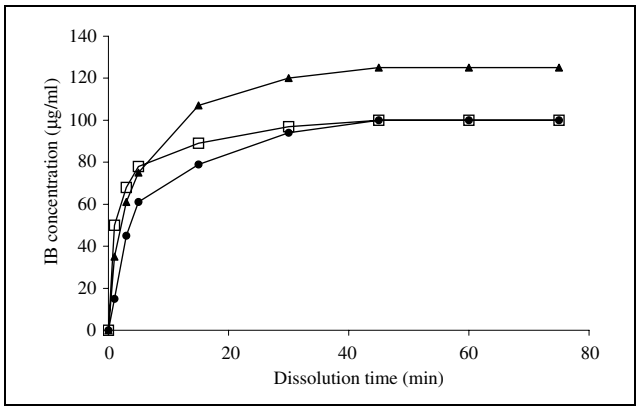

Fig. 3: Dissolution profiles of IB/carrier (4 : 1) solid dispersions in water at 37 °C, where the carrier is LESF/PEG mixture 20 : 1 by weight. PEG 4000 (●), PEG 8000 (▲), no polyethylene glycol (□)

Table 2: Effect of incorporation of polyethylene glycols (PEG 4000; PEG 8000) in IB/RPC and IB/LESF (4 : 1) solid dispersions on the dissolution of IB

No.	Formulation	Phospholipid/PEG weight ratio	% Dissolved (75 min)[a]	IDR[a, b] (μg/ml/min)
1	IB/LESF	1 : 0	20.3 ± 0.4	15.6 ± 0.2
2	IB/LESF/PEG 4,000	20 : 1	22.3 ± 0.6[c]	13.0 ± 0.7[c]
3	IB/LESF/PEG 8,000	200 : 1	27.4 ± 0.5[c]	14.6 ± 0.2[c]
4	IB/LESF/PEG 8,000	20 : 1	28.0 ± 0.6[c]	15.0 ± 0.1[c]
5	IB/LESF/PEG 8,000	2 : 1	28.5 ± 0.9[c]	15.9 ± 0.1[c]
6	IB/RPC/PEG 8,000	200 : 1	17.0 ± 0.3[c]	5.3 ± 0.2[c]
7	IB/RPC/PEG 8,000	20 : 1	18.1 ± 0.4[c]	8.2 ± 0.1[c]
8	IB/RPC/PEG 8,000	2 : 1	21.6 ± 0.2[c]	13.1 ± 0.1[c]

[a] Mean ± SD, n = 3
[b] Initial dissolution rate within first 5 min
[c] Value significantly different from that obtained for IB ($p < 0.05$, paired t-test)

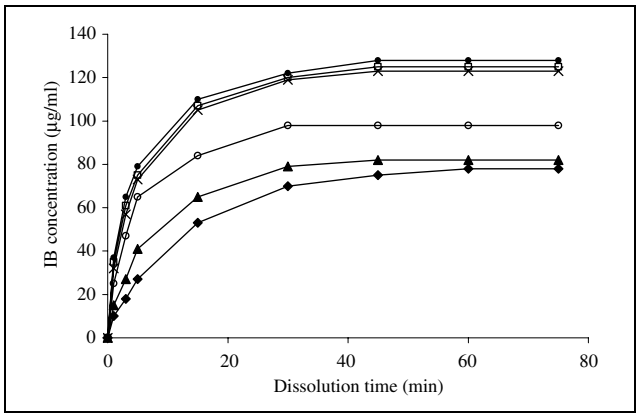

Fig. 4: Dissolution profiles of IB/carrier (4 : 1) solid dispersions in water at 37 °C, where the carrier is LESF/PEG 8,000 at weight ratios of 200 : 1 (×), 20 : 1 (□), 2 : 1 (●) and RPC/PEG 8000 at ratios of 200 : 1 (◆), 20 : 1 (▲), 2 : 1 (○)

could be supposed that the effect of PEG 8000 incorporated in the phospholipid matrix in ratios 1 : 200, 1 : 20 and 1 : 2 depends markedly on the kind of phospholipid used (LESF or RPC). The incorporation of PEG 8,000 to RPC in concentration from about 0.5 to 33% (w/w) slightly improved the dissolution of IB. In this case the IB maximum dissolution level increased by about 30% and the increment of IDR was a little above double, while PEG 8,000 for the identical concentrations incorporated in rapeseed phospholipid mixture (LESF) gives practically no effect on the dissolution of IB. The differences in dissolution behavior of polyethylene glycols used in the study suggest that PEG 4,000 reduced the interaction of phospholipids in the solid dispersions more than PEG 8,000. The results obtained by other authors (Vudathala and Rogers 1992) also confirm the significant effect of polymers (polyvinylpyrrolidone, dextran, polylactic acid) incorporated in fludrocortisone/phospholipid solid dispersions on the dissolution behavior of the examined drug.

In conclusion, the results show that solid dispersions of rapeseed phospholipids (LESF and RPC) have a positive effect on the dissolution of IB, a compound which is practically insoluble in water. The dissolution of this drug significantly depends both on the kind of phospholipid used (a native mixture or a pure phosphatidylcholine), and on the drug/carrier ratio. Taking the examined formulations into consideration, the best dissolution effect was observed for LESF solid dispersion in IB/LESF ratio of 4 : 1 (w/w). The effect of incorporation of PEG 4,000 and PEG 8,000 in IB/carrier systems on IB dissolution was not consistent. Polyethylene glycol with the lower molecular weight (PEG 4,000) in a concentration of about 5% (by weight of a carrier) caused a slightly decrease in IB dissolution rate and the maximum dissolution level in this case was practically unchanged. On the other hand, polyethylene glycol with higher molecular weight (PEG 8000) markedly improved the dissolution of IB in examined conditions.

Summarizing, the results obtained in these investigations show the possibility of the application of high drug-containing solid dispersions using rapeseed phospholipids to improve the dissolution behavior of poorly water-soluble drugs and the possibility of modifying drug release by the incorporation of small amounts of polyethylene glycols.

3. Experimental

3.1. Substances

Ibuprofen of pharmaceutical grade was a generous gift of Terpol SA (Sieradz, Poland). Crude commercial rapeseed lecithin free of erucic acid and glucosinolates (00-type rapeseed) containing 63% acetone insolubles was obtained from Kama Foods (Brzeg, Poland). This lecithin was deoiled with acetone and fractionated with 95% ethanol to obtain rapeseed LESF by the method described elsewhere (Sosada et al. 1993). RPC was prepared from rapeseed LESF according to Singleton et al. (Singleton et al. 1965), using neutral aluminum dioxide type 507C (Fluka AG, Buchs, Switzerland) and chloroform/methanol mixture 9 : 1 (v/v). LESF containing 56.4% phosphatidylcholine, 13.2% phosphatidylethanolamine, 2.5% phosphatidylinositol, determined by HPLC (Sosada et al. 2003) and in total 98% acetone insolubles (Ja 4-4b American Oil Chemists' Society method) was used in the experiments. RPC with 98.1% phosphatidylcholine was also used. Polyethylene glycols (PEG 4000 and PEG 8000) were obtained from Fluka AG (Buchs, Switzerland). All other solvents and reagents were of analytical grade and were used without further purification. For statistical analysis STATISTICA PL version 6.0 for Windows was used.

3.2. Preparation of solid dispersions by the solvent evaporation method

Single-component solid dispersions (IB/LESF in ratios 4 : 1, 8.5 : 1.5, 9 : 1 and IB/RPC in ratio 4 : 1) contained appropriate parts by weight of IB and part of either the LESF or RPC. Multicomponent solid dispersions with phospholipids and polyethylene glycols (IB/LESF/PEG 4,000, IB/LESF/PEG 8,000 and IB/RPC/PEG 8,000) contained 4 parts by weight of IB and 1 part of a phospholipid and polyethylene glycol mixture (2 : 1, 20 : 1 or 200 : 1 by weight).

Accurately weighed amounts of IB and rapeseed phospholipids (and polyethylene glycol when included) were dissolved in chloroform (chloroform/solid in ratio 1 : 1 by weight). After the components had been dissolved, chloroform was evaporated by continuous stirring in ambient temperature under a gentle stream of nitrogen during about 15 min to constant weight of solids and disappearance of the characteristic odour of chloroform. The solid dispersions obtained were dried under vacuum (40 °C, 13 hPa, 12 h), sieved through a 60-mesh screen and stored in a desiccator at room temperature and protected from light.

3.3. Analysis of solid dispersions

The drug content in solid dispersions was determined by an UV spectrophotometric method using the JASCO Spectrophotometer model V-530 (Tokyo, Japan), dissolving 10 mg in 20% (v/v) methanol/water solution,

determining the absorbance of a suitably diluted solution at 264 nm, and interpolating concentrations (μg/ml) from a standard calibration curve (prepared for concentrations range 0–300 μg/ml).

3.4. Dissolution studies

The dissolution studies were carried out using the Polish Pharmacopoeia VI dissolution test apparatus with the paddle method. The dissolution medium (900 ml double-distilled water) was maintained at a temperature of 37 ± 0.5 °C and stirred at 600 rpm by an adjustable, constant-speed motor. A sample of solid dispersion representing 450 mg IB was introduced into the dissolution flask and the pH value was controlled during the run using a digital pH-meter CP-215 (Elmetron, Poland). At predetermined intervals (1, 3, 5, 15, 30, 45, 60 and 75 min) 10 ml of the test solution was withdrawn from the flask and immediately filtered through a 0.20 μm membrane filter (Sartorius AG, Goettingen, Germany). The same volume of freshly redistilled water was added to the test solution. An 8 ml sample of the filtrate was put into a volumetric flask (volume of 10 ml) and 2 ml of methanol was added. IB concentration was determined by UV method as described above. The presence of small amounts of phospholipids or polyethylene glycols in the formulations did not interfere with the analysis of IB. All determinations were done in triplicate and averaged.

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