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Ibuprofen–phospholipid solid dispersions: Improved dissolution and gastric tolerance

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ABSTRACT

Solid dispersions of ibuprofen with various phospholipids were prepared, and the effect of phospholipids on the *in vitro* dissolution and *in vivo* gastrointestinal toxicity of ibuprofen was evaluated. Most phospholipids improved the dissolution of ibuprofen; dimyristoylphosphatidyl-glycerol (DMPG) had the greatest effect. At 45 min, the extent of dissolution of ibuprofen from the ibuprofen–DMPG system (weight ratio 9:1) increased about 69% compared to ibuprofen alone; the initial rate of dissolution increased sevenfold. Increasing the DMPG content from 9:1 to 4:1 in this system did not significantly increase the rate and the extent of dissolution. X-ray diffraction and scanning electron micrograph indicated a smaller crystallite size of ibuprofen with fairly uniform distribution in the ibuprofen–DMPG solid dispersion. A small amount of carrier phospholipid significantly increases the rate and the extent of dissolution, which may increase the bioavailability of ibuprofen. The number of ulcers >0.5 mm in size formed in the gastric mucosa of rats following ibuprofen, DMPG, DMPC and DPPC solid dispersions (ibuprofen and phospholipid weight ratio 4:1) were 8.6 ± 6.2, 3.9 ± 5.3, 5.3 ± 4.9 and 9.1 ± 7.4, respectively. Solid dispersion of ibuprofen with DMPG was significantly less irritating to the gastric mucosa than ibuprofen itself (one-way ANOVA, $p < 0.05$). Solid dispersion of ibuprofen and DMPG decreases the gastric side effects of ibuprofen.

1. Introduction

When a drug is administered orally in a solid dosage form such as a tablet, capsule, or suspension it must be released from the dosage form and dissolved in the gastrointestinal fluids before it can be absorbed. If the rate of dissolution of the drug is significantly slower than the rate of absorption, the dissolution of the drug becomes the rate-limiting step in the absorption process. Different formulation approaches have been used to improve the oral absorption of drugs with low water solubility by increasing the dissolution rate or solubility (Dhirendra et al., 2009).

Solid dispersions with water-soluble carriers require a large proportion of the carrier to be effective. It would be advantageous to use a minimum amount of carrier that gives rapid dissolution of a drug from a solid dosage form. Phospholipids have the advantage of increasing the dissolution rate of drugs with low aqueous solubility, but at a much lower carrier concentration (Mirza et al., 2010; Sosada et al., 2006; Vudathala and Rogers, 1992). In aqueous media, phospholipids disperse spontaneously to form spherical bilayer structures (liposomes) that can entrap or sequester solutes. The entrapped drug in the bilayer structures can then be transported to the stationary or diffusion layer and subsequently to the site of absorption to yield more rapid and higher absorption. This behavior can also be utilized for the controlled release of drugs (Vudathala and Rogers, 1992).

Ibuprofen, a common NSAID, is widely used for treatment of osteoarthritis, rheumatoid arthritis, primary dysmenorrhea, mild to moderate pain and fever (Insel, 1996). It is relatively insoluble in water (Greenhalgh et al., 1999; Glowka, 2000). Ibuprofen is 80% absorbed after oral administration. The time for peak plasma concentration (t_{max}) for ibuprofen is approximately 2 h and it has a short plasma half-life of 2 h (Insel, 1996). Several reports have shown a variation in the absorption rate and potential bioinequivalence problems associated with ibuprofen solid dosage forms (Gillespie et al., 1982; Stead et al., 1983). To improve dissolution rate of ibuprofen several formulation approaches such as microcapsules (Adeyeye and Price, 1994), inclusion complexes (Ghorab and Adeyeye, 2001), prodrugs (Murtha and Ando, 1994), and solid dispersions (Geppi et al., 2005; Moneghini et al., 2008; Newa et al., 2008a, 2008b, 2008c) were used. Similar to other NSAIDs, ibuprofen has potentially serious gastrointestinal (GI) side effects. These side effects may be ameliorated when ibuprofen is combined with a phospholipid. The adverse reactions, variable absorption, and short

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plasma half-life have led this drug to be considered as a good candidate for formulation with phospholipids. The purpose of this study was to characterize the release of ibuprofen from phospholipid solid dispersion and investigate the effect of phospholipids on the GI toxicity of ibuprofen in the rat.

2. Materials and methods

2.1. Materials

Phospholipon 100 and phospholipon 100H (100H) were gifts from American Lecithin Company (Oxford, CT). Dimyristoylphosphatidylglycerol (DMPG), dimyristoylphosphatidylcholine (DMPC), dipalmitoylphosphatidylcholine (DPPC), distearoylphosphatidylcholine (DSPC), and ibuprofen were purchased from Sigma Chemicals (St. Louis, MO). Fisher Scientific HPLC grade solvents were used throughout the study.

2.2. Preparation of phospholipid solid dispersions and physical mixture

Solid dispersions of ibuprofen and phospholipids were prepared by solvent method (Chiou and Riegelman, 1971) using chloroform or ethanol as solvent. Weighed amounts of the phospholipid and ibuprofen (ratio of 1:15, 1:9 and 1:4) were added to the solvent and dissolved with gentle stirring; solvated ibuprofen was prepared without phospholipids. The solvent was removed at room temperature under nitrogen. Further drying was accomplished in a vacuum dissector overnight. Physical mixtures were prepared by gently triturating appropriate quantities of ibuprofen and the phospholipid using a mortar and pestle. Solid dispersions, solvated ibuprofen and physical mixtures were passed through an 80-mesh sieve prior to dissolution study. Solid dispersions of DPPC and DMPC, regardless of the solvent used, appeared as ribbon-like particles after sieving due to their waxy consistency.

2.3. Dissolution studies

The dissolution studies were carried out using VK7000 dissolution test apparatus and VK8000 automatic sample collector (VanKel Industries, Inc., Edison, NJ). The dissolution flasks were immersed in the water bath equipped with an external temperature control unit. An USP standard paddle continuously stirred the dissolution medium (900 ml of distilled deionized water) at 100 rpm at 37 °C. Sieved samples (25 mg of ibuprofen or ibuprofen equivalent solid dispersions) were dispersed on the surface of the dissolution medium at the beginning of the study. A sink condition was always maintained in the dissolution medium. Samples were taken at designated intervals by the automatic sample collector and the concentration of ibuprofen present in the dissolution medium was determined using an HP 8452A diode array spectrophotometer (Hewlett Packard, Palo Alto, CA) at 220 nm wavelength.

2.4. Powder X-ray diffraction (PXRD)

Powder X-diffraction (PXRD) patterns were obtained using an XDS2000 automated powder diffractometer (SCINTAG, CA). Samples (~50 mg) were run as a smear mount on a glass slide. The X-rays were Cu Kα radiation (λ = 1.54060 Å), 40 kV, 30 mA, 0.03°/step and 1° 2θ/min.

2.5. Scanning electron microscopy

A JSM-6701F field emission scanning electron microscope (JEOL, Peabody, MA) was used to compare the particle shape and size of ibuprofen, solvated ibuprofen, ibuprofen–DMPG physical mixture and ibuprofen–DMPG solid dispersion. Photomicrograph of ibuprofen was taken at 500x magnification and for solvated ibuprofen; ibuprofen–DMPG physical mixture and ibuprofen–DMPG solid dispersion were taken at 1800× magnification.

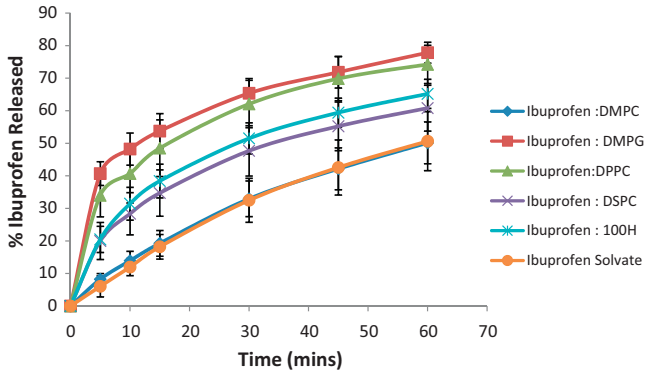

Fig. 1. Dissolution profile of chloroform treated ibuprofen and various phospholipid solid dispersions of ibuprofen (ibuprofen:phospholipid 9:1) at 37 °C in distilled water.

2.6. Gastrointestinal toxicity study in rats

Solid dispersions of ibuprofen and phospholipids (weight ratio 4:1) were prepared in chloroform as described earlier. DMPG, DMPC and DPPC were used as phospholipids. Ibuprofen and solid dispersions were suspended in 1.0% hydroxyl propyl methyl cellulose prior to administration. Male Sprague-Dawley rats (weight 295–510 g) were used to study the gastrointestinal toxicity (Shanbhag et al., 1992). All animal procedures were conducted in accordance to The Guide for the Care and Use of Laboratory Animals (National Academic Press 1996), accredited by AAALAC (American Association for the Assessment and Accreditation of Laboratory Animal Care). The animals were euthanized in accordance with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association. Briefly, doses equivalent to 150 mg/kg of ibuprofen was administered orally for 4 days by gavage. Control group rats were treated with saline. Rats were fasted for 8 h before dosing and 4 h after dosing. Four hours after the last dose, rats were sacrificed. The stomach and the first 4-cm of the duodenum were removed. The stomach was opened along the lesser curvature, washed with water and the mucus wiped off. A 2 × 2 binocular magnifier was used to examine the number of lesions formed. The total number of ulcers and ulcers >0.5 mm in size were counted.

2.7. Statistics

One-way ANOVA was performed to find any statistically significant effect ($p = 0.05$). If a difference is noted least significant difference (LSD) method was applied to compare the treatment groups.

3. Results and discussion

3.1. Solid dispersions prepared in chloroform

Among all the phospholipids used, DMPG exerted the greatest effect on both the rate and extent of dissolution of ibuprofen (Fig. 1). Compared to the solvated drug, the ibuprofen–DMPG system (weight ratio of 9:1) increased the initial dissolution rate within first 5 min approximately sevenfold (from 1.2 to 8.1 percent released per min). The extent of dissolution in the dissolution

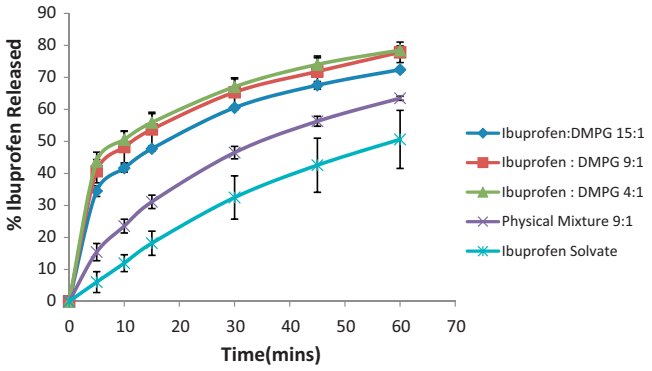

Fig. 2. Dissolution profile of ibuprofen and ibuprofen–DPMG solid dispersions at different ratios in comparison to physical mixture (ibuprofen:DMPG 9:1) at 37 °C in distilled water. Ibuprofen and ibuprofen–DPMG solid dispersions were prepared from chloroform.

medium at 45 min was increased from approximately 43% to 72% of the total drug used. Except for DMPC, all other phospholipids (DPPC, DSPC, and 100H) increased the dissolution of ibuprofen when compared to the solvated drug alone.

In aqueous solution at 37 °C, phospholipids with transition temperatures (T_c) lower than 37 °C (DMPG and DMPC) would be expected to increase dissolution of ibuprofen more than phospholipids with T_c greater than 37 °C (DPPC and DSPC). The highest dissolution rates were obtained with DMPG and DPPC and the lowest dissolution rates were from DMPC. Possible reasons for this are discussed in Section 3.2.

Because the ibuprofen–DMPG solid dispersions prepared from chloroform gave the highest dissolution and because they formed fine, non-waxy particles, this system was used to study the effects of different ratios of drug to phospholipid. Fig. 2 shows the effect of different ratios of ibuprofen to DMPG on the dissolution of ibuprofen. Increasing the DMPG content in this system from 15:1 to 4:1 resulted in only a 9% increase in extent of dissolution at 45 min; however, the initial rate of dissolution at 5 min increased by 27%. There were no significant differences in dissolution between 4:1 and 9:1 ratios of ibuprofen to DMPG. This indicates that a small amount of the carrier phospholipid was enough for a significant increase in the rate and extent of dissolution.

3.2. Solid dispersions prepared in ethanol

Since trace amounts of chloroform may remain after vacuum drying, a less toxic solvent, ethanol was used in preparing the solid dispersion. Fig. 3 shows the dissolution profile of ibuprofen solid dispersions prepared from ethanol. Similar to chloroform,

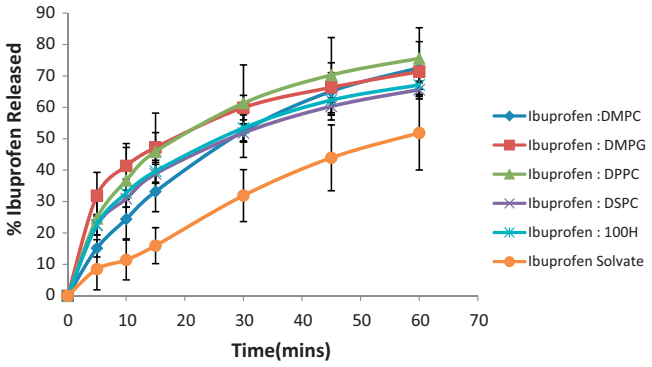

Fig. 3. Dissolution profile of ethanol treated ibuprofen and various phospholipid solid dispersions of ibuprofen (ibuprofen:phospholipid 9:1) at 37 °C in distilled water.

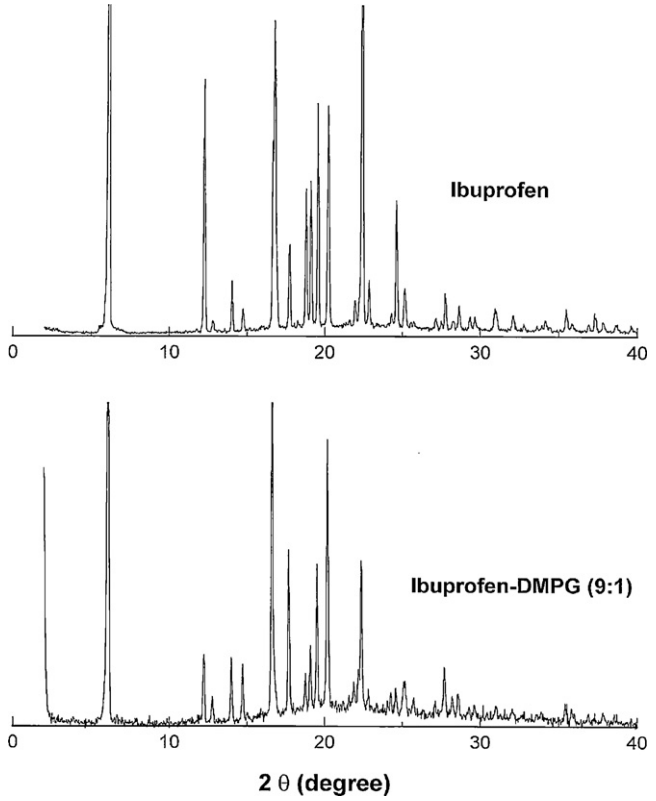

Fig. 4. Powder X-ray diffraction spectra of chloroform treated ibuprofen (top) and ibuprofen–DMPG solid dispersion (bottom) prepared from chloroform (ibuprofen:DMPG 9:1).

phospholipid solid dispersions prepared from ethanol showed improved dissolution of ibuprofen. Again, the ibuprofen–DMPG showed the similar effect on the dissolution of ibuprofen (up to 45 min); but at a slightly lower rate and extent of dissolution. As mention in Section 3.1, DMPC showed no improvement in dissolution of ibuprofen when the solid dispersions were prepared in chloroform; however, when prepared in ethanol, the ibuprofen–DMPC system showed dissolution equal to the ibuprofen–DMPG system. Ibuprofen is an anionic compound due to the carboxylic acid group. Thus, the type of functionality on the drug and the ability of a solvent to form hydrogen bonds could influence the way zwitterionic phospholipid solid dispersions are formed.

Another explanation is that ibuprofen is chemically associating with the zwitterionic phospholipids through intermolecular bonding. This type of association has been reported to occur between aspirin and DPPC (Lichtenberger et al., 1995). Once formed, the physiochemical properties of both compounds are changed. This could also explain the high dissolution rate of ibuprofen from DPPC, despite its T_c greater than 37 °C. This demonstrates the importance of the drug-solvate and the electronic nature of the drug on the formation of the solid dispersions and subsequent drug dissolution from solid dispersions. Further study would be needed to verify these premises.

3.3. Powder X-ray diffraction

Powder X-ray scans of ibuprofen and ibuprofen–DMPG solid dispersion were made to determine if there is a loss or modification of the pure drug's crystal structure after it is formed into a phospholipid solid dispersion, and to determine if any new crystalline phases may have formed. Fig. 4 shows that there is virtually no difference in crystallinity between the two. This would indicate that for ibuprofen, the enhanced dissolution is due to the increased

surface area of the drug crystallites after formation of the solid dispersions and not due to a change from a crystalline to an amorphous state.

3.4. Scanning electron microscopy

Fig. 5A, B and C shows that the ibuprofen, solvated ibuprofen and physical mixture of ibuprofen and phospholipids(DMPG) are anhedral crystals of various sizes and Fig. 5D shows that the particles of ibuprofen–DMPG solid dispersion consist of a sponge-like amalgam with a significant reduction of the drug's crystallite size. Solid dispersions of ibuprofen with DMPG greatly increase surface area of the ibuprofen crystals. This allows faster solvating of the drug and faster breakup of the solid dispersions.

An attempt was made to determine crystallite size using EDS X-ray mapping. Phosphorous is present in the phospholipid, but not in ibuprofen so the distribution of phosphorous in the solid dispersions was mapped at several magnifications, assuming that crystallites of ibuprofen would appear as areas depleted of phosphorous. No phosphorous-depleted area was identified down to the micron scale on the solid dispersions. This could be because the crystallites are less than a micron in size, or because the crystallites are heavily coated with the phospholipid, or both.

When placed into an aqueous medium, phospholipids rapidly form liposomal structures as part of the dispersion process. This effectively increases the saturation concentration of drug in the diffusion layer during the dissolution process through the release of substantially entrapped quantities of finely dispersed drug from the lipid bilayer or from the aqueous compartments. This may be another reason for the increased dissolution of ibuprofen from the ibuprofen–DMPG solid dispersion.

Table 1
Ulcerogenic activity (number of ulcers) in rats produced by ibuprofen and ibuprofen solid dispersion formulations using phospholipids[a] (mean ± SD, $n \geq 12$).

	Ulcers > 0.5 mm	Total ulcers
Ibuprofen	8.6 ± 6.2	13.4 ± 8.9
Ibuprofen–DMPG	3.9 ± 5.3[a]	5.9 ± 6.4[a]
Ibuprofen–DMPC	5.3 ± 4.9	8.8 ± 7.3
Ibuprofen–DPPC	9.1 ± 7.4	13.9 ± 10.6

[a] $p < 0.05$, one-way ANOVA. Least significant difference (LSD) method was applied to compare the treatment groups. Ibuprofen–DMPG treated group is significantly different than ibuprofen treated group. Also, ibuprofen–DMPG treated group is significantly different than ibuprofen–DPPC treated group.

3.5. Gastrointestinal toxicity study in rats

The number (mean ± SD) of ulcers >0.5 mm in size formed in the gastric mucosa following ibuprofen, and solid dispersions with DMPG, DMPC and DPPC are shown in Table 1. Solid dispersion of ibuprofen with DMPG was significantly less irritating to the gastric mucosa than ibuprofen itself (one-way ANOVA, $p < 0.05$). Similar

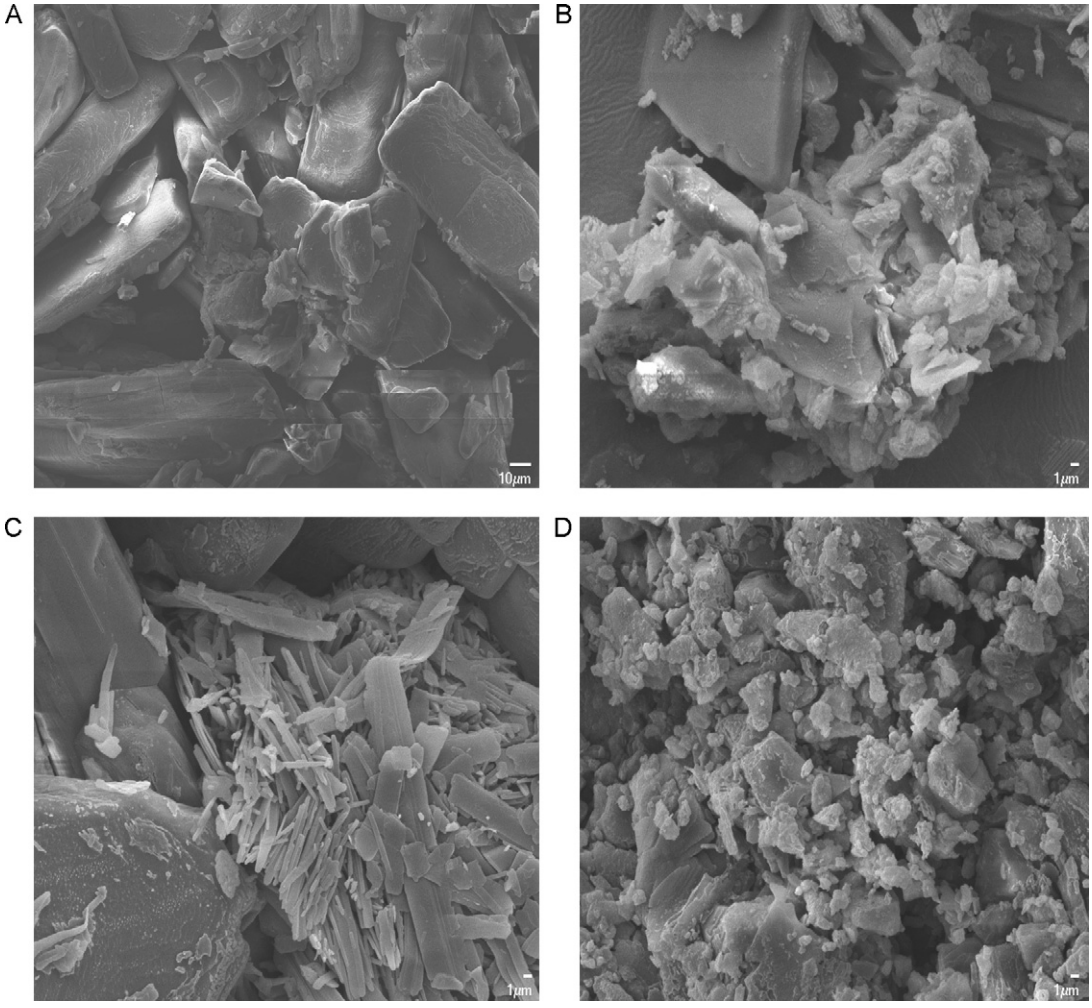

Fig. 5. Scanning electron micrographs of (A) ibuprofen only, (B) ibuprofen solvated in $CHCl_3$, (C) ibuprofen:DMPG 9:1 physical mixture, and (D) ibuprofen:DMPG 9:1 solid dispersion.

result was obtained when total number of ulcers was compared between the groups. No detectable ulcer was found in the intestinal mucosa.

It has also been shown that solid dispersions of nonsteroidal anti-inflammatory drugs (NSAIDs) with zwitterionic phospholipids reduce the incidence of gastrointestinal (GI) tract bleeding and ulceration (Lichtenberger et al., 1995). The proposed explanation for this is that NSAIDs, when combined with a phospholipid, have less ability to interact with the extracellular phospholipid lining of the mucus layer and greater lipid solubility and movement across membranes. In addition, drugs susceptible to GI degradation or solubility changes will have some protection within the bilayer structures (Porter et al., 2008) and may reduce GI toxicity. Liposome encapsulation of drugs has been shown to reduce the toxic side effects of drugs (Oussoren et al., 1998; Minones et al., 2002).

Our previous studies (Mirza et al., 2010) have demonstrated that solid dispersions of piroxicam, an NSAID, formulated with phospholipids improve the bioavailability of the drug. The increased dissolution of ibuprofen from phospholipid solid dispersion may improve the bioavailability of Ibuprofen in addition to reducing the GI toxicity.

4. Conclusion

The rate and extent of dissolution of ibuprofen from solid dispersions of either DMPG or DPPC in low concentration (10%, w/w, phospholipid) are significantly increased when prepared from chloroform or ethanol. The improved dissolution behavior of drug–phospholipid solid dispersions is likely to originate from substantial increase in the drug's total surface area during the dissolution process. Solid dispersion of ibuprofen and DMPG significantly decreases the gastric side effects of ibuprofen. Drug formulations using phospholipids, either alone or as a mixture with other inert ingredients, could have the twofold advantage of improved bioavailability and/or decreased GI toxicity.

References

Adeyeye, C.M., Price, J.C., 1994. Development and evaluation of sustained-release ibuprofen–wax microspheres. II. In vitro dissolution studies. Pharm. Res. 11, 575–579.

Chiou, W.L., Riegelman, S., 1971. Pharmaceutical applications of solid dispersion systems. J. Pharm. Sci. 60, 1281–1302.

Dhirendra, K., Lewis, S., Udupa, N., Atin, K., 2009. Solid dispersions: a review. Pak. J. Pharm. Sci. 22, 234–246.

Geppi, M., Guccione, S., Mollica, G., Pignatello, R., Veracini, C.A., 2005. Molecular properties of ibuprofen and its solid dispersions with Eudragit RL100 studied by solid-state nuclear magnetic resonance. Pharm. Res. 22, 1544–1555.

Ghorab, M.K., Adeyeye, M.C., 2001. Enhancement of ibuprofen dissolution via wet granulation with beta-cyclodextrin. Pharm. Dev. Technol. 6, 305–314.

Gillespie, W.R., DiSanto, A.R., Monovich, R.E., Albert, K.S., 1982. Relative bioavailability of commercially available ibuprofen oral dosage forms in humans. J. Pharm. Sci. 71, 1034–1038.

Glowka, F.K., 2000. Stereoselective pharmacokinetics of ibuprofen and its lysinate from suppositories in rabbits. Int. J. Pharm. 199, 159–166.

Greenhalgh, D.J., Williams, A.C., Timmins, P., York, P., 1999. Solubility parameters as predictors of miscibility in solid dispersions. J. Pharm. Sci. 88, 1182–1190.

Insel, P., 1996. Analgesic-antipyretic and antiinflammatory agents. In: Hardman, J. (Ed.), Goodman & Gilman's The Pharmacological Basis of Therapeutics. , 9th ed. McGraw-Hill, New York, p. 639.

Lichtenberger, L.M., Wang, Z.M., Romero, J.J., Ulloa, C., Perez, J.C., Giraud, M.N., Barreto, J.C., 1995. Non-steroidal anti-inflammatory drugs (NSAIDs) associate with zwitterionic phospholipids: insight into the mechanism and reversal of NSAID-induced gastrointestinal injury. Nat. Med. 1, 154–158.

Minones Jr., J., Conde, O., Minones, J., Patino, J.M.R., Seoane, R., 2002. Amphotericin B–dipalmitoyl phosphatidyl glycerol interactions responsible for the reduced toxicity of liposomal formulations: a monolayer study. Langmuir 18, 8601–8608.

Mirza, S., Miroshnyk, I., Habib, M., Brausch, J., Hussain, M.D., 2010. Enhanced dissolution and oral bioavailability of piroxicam formulations: modulating effect of phospholipids. Pharmaceutics 2, 339–350.

Moneghini, M., Bellich, B., Baxa, P., Princivalle, F., 2008. Microwave generated solid dispersions containing ibuprofen. Int. J. Pharm. 361, 125–130.

Murtha, J.L., Ando, H.Y., 1994. Synthesis of the cholesteryl ester prodrugs cholesteryl ibuprofen and cholesteryl flufenamate and their formulation into phospholipid microemulsions. J. Pharm. Sci. 83, 1222–1228.

Newa, M., Bhandari, K.H., Kim, J.A., Yoo, B.K., Choi, H.G., Yong, C.S., Woo, J.S., Lyoo, W.S., 2008a. Preparation and evaluation of fast dissolving ibuprofen–polyethylene glycol 6000 solid dispersions. Drug Deliv. 15, 355–364.

Newa, M., Bhandari, K.H., Kim, J.O., Im, J.S., Kim, J.A., Yoo, B.K., Woo, J.S., Choi, H.G., Yong, C.S., 2008b. Enhancement of solubility, dissolution and bioavailability of ibuprofen in solid dispersion systems. Chem. Pharm. Bull. (Tokyo) 56, 569–574.

Newa, M., Bhandari, K.H., Oh, D.H., Kim, Y.R., Sung, J.H., Kim, J.O., Woo, J.S., Choi, H.G., Yong, C.S., 2008c. Enhanced dissolution of ibuprofen using solid dispersion with poloxamer 407. Arch. Pharm. Res. 31, 1497–1507.

Oussoren, C., Eling, W.M., Crommelin, D.J., Storm, G., Zuidema, J., 1998. The influence of the route of administration and liposome composition on the potential of liposomes to protect tissue against local toxicity of two antitumor drugs. Biochim. Biophys. Acta 1369, 159–172.

Porter, C.J., Pouton, C.W., Cuine, J.F., Charman, W.N., 2008. Enhancing intestinal drug solubilisation using lipid-based delivery systems. Adv. Drug Deliv. Rev. 60, 673–691.

Shanbhag, V.R., Crider, A.M., Gokhale, R., Harpalani, A., Dick, R.M., 1992. Ester and amide prodrugs of ibuprofen and naproxen: synthesis, anti-inflammatory activity, and gastrointestinal toxicity. J. Pharm. Sci. 81, 149–154.

Sosada, M., Gorecki, M., Pasker, B., 2006. Influence of rapeseed phospholipids on ibuprofen dissolution from solid dispersions. Pharmazie 61, 677–680.

Stead, J.A., Freeman, M., John, E.G., Ward, G.T., Whiting, B., 1983. Ibuprofen tablets: dissolution and bioavailability studies. Int. J. Pharm. 14, 59–72.

Vudathala, G.K., Rogers, J.A., 1992. Dissolution of fludrocortisone from phospholipid coprecipitates. J. Pharm. Sci. 81, 282–286.