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Preparation and Characterization of Piroxicam/Poloxamer Solid Dispersion Prepared by Melting Method and Solvent Method

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ABSTRACT – Solid dispersions of piroxicam were prepared by melting method using poloxamer as a carrier. The results of DSC and XRD studies showed that the amorphous form of piroxicam coexisted with the crystalline form in the solid dispersions. However, the ratio of crystalline form of piroxicam in the solid dispersion prepared by melting method decreased in comparison with the same ratio of the solid dispersion prepared by solvent method. As the ratio of poloxamer in the solid dispersion increased, the ratio of the amorphous form of piroxicam in the solid dispersion increased. The dissolution rate of piroxicam from the solid dispersions was significantly higher than that from piroxicam powder. In comparison to the solid dispersion prepared by solvent method, the dissolution rate of piroxicam from the solid dispersion prepared by melting method was higher. As the ratio of poloxamer in the solid dispersion prepared by melting method increased, the initial dissolution rate decreased, however, the total amount dissolved at the end of the study increased.

Key words – Piroxicam, Solid dispersion, Melting method, Poloxamer, Dissolution rate

Piroxicam is one of the oxicam derivatives with anti-inflammatory, analgesic, and antipyretic activity. It has been used in various musculoskeletal and joint disorders such as osteoarthritis, rheumatoid arthritis.[1] Although its relatively long half-life permits the administration of a single daily dose,[1] the absorption of piroxicam after oral administration can be significantly affected by its dissolution in the gastrointestinal tract because piroxicam is classified as Class II drug according to the Biopharmaceutics Classification System (BCS).[2] To improve the dissolution rate of piroxicam, several methods have been attemped including solid dispersion,[2-4] salt formation with ethanolamines,[5] inclusion complex with cyclodextrin,[6] and lipid-based formulation.[7]

Alternative way to improve the drug dissolution rate is the use of emulsifying agents. Its driving forces were suggested to be the improvement of wetting characteristics and the drug solubilization.[8] Poloxamer is nonionic polyoxyethylene-polyoxypropylene copolymers and has been used as the multipurpose excipients including emulsifying agent, solubilizing agent, stabilizing agent, wetting agent, or tablet binder.[9] It is not only regarded as nontoxic and nonirritant material[9] but also has relatively low melting point. The low melting point allows us to prepare solid dispersion by melting method. When poloxamer is used as a solid dispersion carrier, the drug dissolution rate is expected to be enhanced in virtue of its solubilizing ability and its role as a solid dispersion carrier. Recently, poloxamer-containing microparticles of griseofulvin, a poorly water-soluble drug, were prepared by spray drying method and the formed microparticles enhanced the drug dissolution rate and the oral absorption owing to emulsifying ability of poloxamer.[10]

To our knowledge, only two piroxicam/poloxamer solid dispersions were reported in the literature.[11-12] However, the solid dispersion reported by Shin and Cho was not for an oral drug delivery system but for a topical delivery system using poloxamer gel formulation. Fathy and El-Badry prepared and characterized the solid dispersions using solvent method to enhance the dissolution rate of piroxicam. Through their study, they suggested that the improved dissolution rate of piroxicam in the solid dispersion might be due to the conversion of its crystalline form into the amorphous form. However, when their X-ray diffraction patterns were considered, the characteristic peaks of piroxicam still appeared regardless of the ratios of piroxicam/poloxamer used to prepare solid dispersion. It suggests that some portion of piroxicam in the solid dispersion existed as a crystalline form. Moreover, the solvent method for preparing solid dispersion has some disadvantages including the toxicity of residual solvent and the environmental pollution of the used organic solvents. Although the dissolution rate of piroxicam in pH 1.2 medium was significantly improved, it is more important to investigate the dissolution rate of piroxicam at neutral pH. Piroxicam is a zwitterionic drug and the solubility increases at both acidic and basic pH, while the solubility is extremely low at neutral pH.

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The present study focuses on the characterization of piroxicam/poloxamer solid dispersion prepared by melting method and the comparison with the results obtained from the solvent method. The melting method using poloxamer as a carrier is subjected to an elevated temperature for a relatively short duration time and can be used to process some of the thermolabile drugs through hot melt extrusion.[8]

Experimental

Materials

Piroxicam was obtained from Jeil Pharm. Co. (Seoul, Korea). Micronized poloxamer 407 (Lutrol® micro 127) was obtained from BASF Korea (Seoul, Korea). All other chemicals were of reagent grade or above and were used without further purification.

Preparation of solid dispersions by melting method

Piroxicam and poloxamer were sieved through 150-μm mesh and mixed together using predetermined ratios of piroxicam/poloxamer (1/1, 1/3 and 1/5). The resulting mixture was placed into a beaker that was immersed in the oil bath at 80°C with continuous stirring. The molten state products were kept in a vacuum oven for 12 h at room temperature. The hardened product was ground using a mortar and a pestle, and sieved through 150-μm mesh.

Preparation of solid dispersion by solvent method

Piroxicam (300 mg) was dissolved in 5 ml of methylene chloride and the same amount of poloxamer was dissolved in 5 ml of 95% ethanol. These two solutions were mixed together and the solvents were removed at room temperature with stirring. The resulting product was further dried in vacuum oven for 12 h at room temperature. The dried product was pulverized and sieved through 150-μm mesh.

Preparation of physical mixtures

To prepare the physical mixtures, piroxicam and poloxamer were sieved through 150-μm mesh and mixed together using predetermined ratios of piroxicam/poloxamer (1/1 and 1/3).

X-ray diffraction (XRD) patterns

X-ray powder diffraction was performed at room temperature with an X-ray diffractometer (X'Pert PRO MPD, PANalytical Co., Holland). Monochromatic Cu Kα-radiation ($\lambda = 1.5418$ Å) was obtained with a Ni-filtration and a system of diverging and receiving slides of 0.5° and 0.1 mm, respectively. The diffraction pattern was measured with a voltage of 40 kV and a current of 30 mA over a 2θ range of 5-35° using a step size of 0.02° at a scan speed of 1 s/step.

Differential scanning calorimetry (DSC)

Thermal analysis was carried out using a DSC unit (Pyris 6 DSC, Perkin Elmer, Boston, MA, USA). Indium was used to calibrate the temperature scale and enthalpic response. Samples were placed in aluminum pans and heated at a scanning rate of 10°C/min.

To observe the mechanism of crystallization in the solid dispersion, the physical mixture of the ratio of 1/1 (piroxicam/poloxamer) was placed in aluminum pans and heated at a scanning rate of 10°C/min from room temperature to 205°C and cooled at a scanning rate of 1°C/min from 205°C to room temperature.

Dissolution studies

Drug dissolution tests were carried out using a dissolution tester (DST 810, Labfine, Inc., Suwon, Korea). Test samples containing 20 mg of piroxicam were placed in a USP dissolution apparatus II containing 900 ml of distilled water at 37°C (paddle method at 100 rpm). Aliquots of the medium (5 ml) were withdrawn at predetermined time intervals and equivalent amounts of distilled water were added. Samples were then filtered through 0.45-μm Millipore filter. Filtered samples were analyzed by HPLC (Shimadzu Scientific Instruments, Kyoto, Japan) at a wavelength of 320 nm and a flow rate of 1 ml/min (mobile phase; methanol:water:phosphoric acid=700:299:1).

To investigate the effect of poloxamer concentration on the dissolution of piroxicam, 20 mg of piroxicam was placed in a USP dissolution apparatus II containing 900 ml of poloxamer aqueous solution (1, 2, 4 and 10 mg/ml) at 37°C (paddle method at 100 rpm). Aliquots of medium (5 ml) were withdrawn at predetermined time intervals and equivalent amounts of the same medium were added. Samples were then filtered through 0.45 μm Millipore filter. Filtered samples were analyzed in the same way as described previously.

Solubility of piroxicam in poloxamer solution

An excess amount of piroxicam powder sieved through 150-μm mesh was added to 5 ml of the various concentrations of poloxamer aqueous solution (0, 1, 2, 4 and 10 mg/ml) in a 20 ml screw-capped glass vial. The vials were placed in a shaking incubator at 37°C for 24 h. Samples were filtered through 0.45-μm Millipore filter and diluted with an appropriate volume of mobile phase for the HPLC analysis. The diluted samples were assayed using HPLC system.

Results and Discussion

Figure 1 shows the XRD patterns of piroxicam, poloxamer, physical mixtures and the solid dispersions with various ratios of piroxicam and poloxamer. Piroxicam showed a high crystallinity with its characteristic diffraction angles (2θ) of 8.66, 14.55, 17.74, 21.77, and 27.44. Poloxamer also showed two characteristic diffraction angles (2θ) of 19.06 and 23.22. In the physical mixtures, both of piroxicam and poloxamer peaks appeared as expected. Although the crystalline peaks of piroxicam appeared in the solid dispersions prepared by melting method, the intensities of piroxicam crystalline peaks decreased in comparison with those of the physical mixtures. The results suggested that the amorphous form of piroxicam coexisted with the crystalline form in the solid dispersions. To confirm the results obtained from XRD study, further study was performed using DSC.

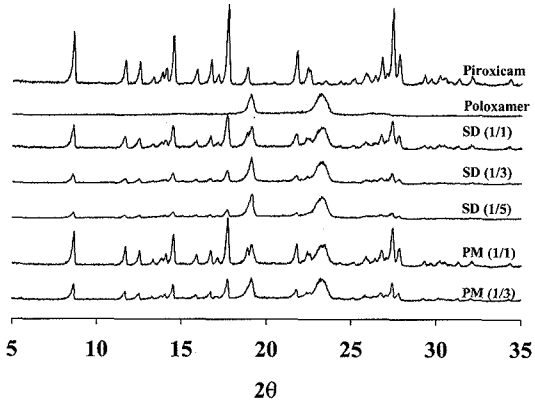

Figure 1–X-ray diffraction patterns of piroxicam, poloxamer, physical mixtures and solid dispersions with various ratios of piroxicam and poloxamer.

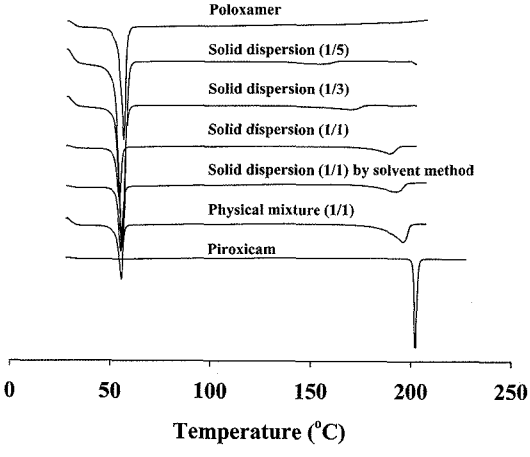

Figure 2–DSC thermograms of piroxicam powder, poloxamer, the physical mixture, the solid dispersion by solvent method and the solid dispersions with various ratios of piroxicam and poloxamer.

Figure 2 shows the DSC thermograms of piroxicam, poloxamer, physical mixture, solid dispersion prepared by solvent method, and solid dispersions prepared by melting method. The melting peak of piroxicam appeared at 202.4°C and that of poloxamer appeared at 56.5°C. The melting peak of piroxicam in the physical mixture with the ratio of 1/1 (piroxicam/poloxamer) and that in the solid dispersion with the same ratio prepared by solvent method appeared at 196.0 and 192.5°C, respectively. As the ratio of poloxamer in the solid dispersion prepared by melting method increased, the melting peak of piroxicam shifted to lower temperature and the area of fusion peak of piroxicam broadened and decreased as shown in Figure 2 and Table I. These results confirmed that the amorphous form of piroxicam coexisted with the crystalline form in the solid dispersions. Moreover, the heat of fusion of piroxicam in the solid dispersion prepared by solvent method was higher than that in the solid dispersion with same ratio prepared by melting method. This suggests that the ratio of crystalline form of piroxicam in the solid dispersion prepared by solvent method was higher than that in the solid dispersion with same ratio prepared by melting method.

When the solid dispersion was prepared by solvent method, all the drug particles were completely dissolved. Therefore, the melting peak of piroxicam appeared in the solid dispersion prepared by solvent method must be due to recrystallization of the drug during drying process. In order to elucidate the fate of piroxicam during the process of melting method, the process of the preparation of solid dispersion by melting method was simulated using DSC as shown in Figure 3. Since poloxamer melts at 56.5°C, some of piroxicam could be dissolved in poloxamer solution as was reported in our previous work using felodipine.[13] It was noted that felodipine dissolved in the melted poloxamer solution during the DSC measurement, thereby the

Table I–*Comparison of the Heat of Fusion and Melting Point in the Piroxicam Powder, the Physical Mixture, the Solid Dispersion by Solvent Method and the Solid Dispersions with Various Ratios of Piroxicam/Poloxamer by Melting Method*

Ratio of piroxicam/poloxamer	Heat of fusion (ΔH) (J/g)	Melting point (°C)
Piroxicam powder	119.8	202.4
1/1 (physical mixture)	79.8	196.0
1/1 (by solvent method)	47.7	192.5
1/1 (by melting method)	37.9	189.2
1/3 (by melting method)	12.5	170.0
1/5 (by melting method)	5.7	155.3

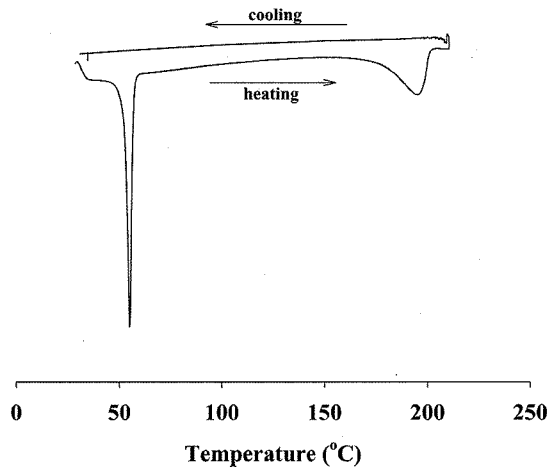

Figure 3–DSC thermogram of the physical mixture with the ratio of 1/1 (piroxicam/poloxamer). Sample was heated at a scanning rate of 10°C/min from room temperature to 205°C and cooled at a scanning rate of 1°C/min from 205°C to room temperature.

melting peak of felodipine did not appear. In case of piroxicam, the melting peak still appeared, however, the size of the melting peak was reduced due to partial dissolution of piroxicam in poloxamer melt. During the cooling process, the drug recrystallization peak did not appear. This result indicated piroxicam dissolved in poloxamer melt would not convert back to crystalline form and remained as amorphous form during the cooling process. It coincides with the results of melting temperature shift and reduced heat of fusion peak with increasing ratio of poloxamer in the solid dispersion prepared by melting method since more piroxicam is expected to dissolve as the content of poloxamer increased.

Figure 4 shows the drug dissolution profiles of piroxicam powder, physical mixture, solid dispersion prepared by solvent method, and solid dispersions prepared by melting method. The presence of poloxamer had significant effect on the dissolution of piroxicam. The dissolution rate of piroxicam from the physical mixture was significantly improved when compared to that of piroxicam powder. The dissolution rate of piroxicam was further increased by the preparation of solid dispersion. The dissolution rates of piroxicam from solid dispersions were significantly higher than that from physical mixture. When the dissolution rate of piroxicam from solid dispersion prepared by solvent method was compared to that from solid dispersion prepared by melting method using same ratio of piroxicam to poloxamer, it was found that melting method provided faster dissolution rate, indicating melting method is more efficient way of preparing piroxicam solid dispersion. These results were in good agreement with the previous DSC results where more amorphous form was identified in the solid dispersion prepared by melting method. It has been reported that the formulation containing more amorphous form of drug has higher drug dissolution.[12] Unexpectedly, the dissolution rate of piroxicam in the initial phase decreased as the ratio of poloxamer in the solid dispersion increased. Initially, the solid state poloxamer in the solid dispersion seemed to hinder the drug release, resulting in slower dissolution rate. To confirm this, the effect of poloxamer concentration in the dissolution medium on the dissolution rate of piroxicam was compared and the results are shown in Figure 5. As the concentration of poloxamer in the medium increased, the dissolution rate of piroxicam increased in entire range. Since the poloxamer was completely dissolved before placing piroxicam in the medium, the drug dissolution was not hindered and the drug dissolution rate proportionally increased with the con-

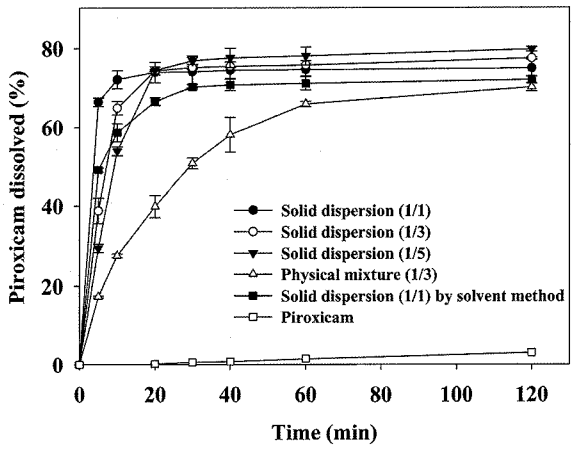

Figure 4–Dissolution rate of piroxicam from piroxicam powder, the physical mixture, the solid dispersion by solvent method and the solid dispersions with various ratios of piroxicam/poloxamer by melting method (n=3).

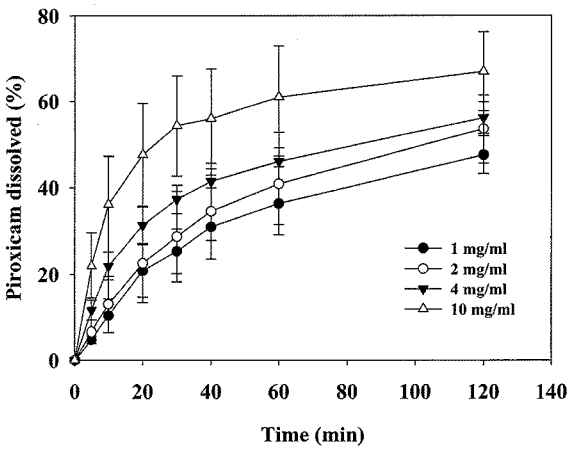

Figure 5–Dissolution rate of piroxicam in the various concentration of poloxamer aqueous solution (n=3).

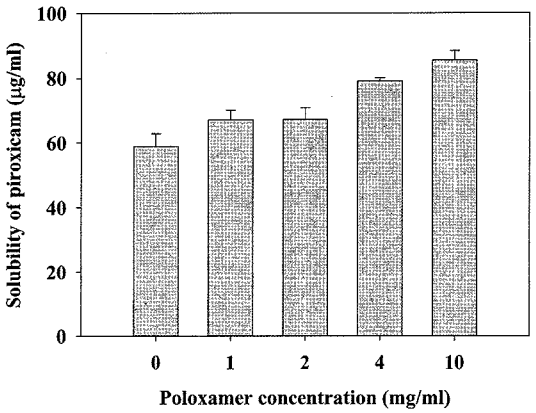

Figure 6–Solubility of piroxicam in various concentrations of poloxamer aqueous solution (n=3).

centration of poloxamer increased. Piroxicam in the solid dispersions exists both in crystalline and amorphous form. The amorphous form of piroxicam may dissolve almost at the same time with poloxamer. The dissolution of the crystalline form of piroxicam may be affected by the emulsifying ability of poloxamer, which was confirmed by the increased dissolution rate of physical mixture when compared with piroxicam alone. Poloxamer can enhance the solubility and/or wettability of the drug. In order to clarify the main mechanism of the dissolution of crystalline form, the solubility of piroxicam was measured in various concentrations of poloxamer solution (Figure 6). The solubility of piroxicam increased only slightly with increasing concentration of poloxamer. The results indicated that the main mechanism of enhanced dissolution was mainly due to the improved wettability of the drug surface by poloxamer.

Conclusions

Solid dispersions of piroxicam were prepared by melting method using poloxamer as a carrier. The results of DSC and XRD studies showed that the amorphous form of piroxicam coexisted with the crystalline form of piroxicam in the solid dispersions. The dissolution rate of piroxicam from the solid dispersions was significantly higher than that from piroxicam powder and physical mixture. These results indicated that melting method is better than solvent method and it can be used to obtain faster dissolution rate and to resolve environmental issues of organic solvent.

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