Improvement of the Dissolution Rate of Piroxicam by Surface Solid Dispersion

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ABSTRACT

In order to improve the dissolution behavior of piroxicam, the surface solid dispersion of the drug in microcrystalline cellulose and in potato starch was prepared by coevaporation method. The in vitro dissolution study was performed according to the USP method. The samples were characterized by X-ray diffractometry. It was found that the dissolution rate and the dissolution parameters of the drug from the surface solid dispersion were higher than those of the intact drug. The degree of the dissolution rate enhancement depended on the nature and the amount of the carrier, i.e., the higher amount of the carrier used, the higher dissolution rate was obtained. The dissolution rate of the drug in potato starch based surface solid dispersion was significantly higher than that in the microcrystalline cellulose based. The surface adsorption of the drug particles onto the surface of the carrier was observed in their physical mixtures. This phenomenon had lowered the dissolution rate of the drug. The extent of the surface adsorption was more significant in piroxicam-microcrystalline cellulose system. According to the results, potato starch is the carrier of choice for preparing the piroxicam surface solid dispersion.

Key words: Piroxicam, Microcrystalline cellulose, Avicel PH101, Potato starch, Surface solid dispersion

INTRODUCTION

The effort to improve the dissolution and solubility of a poorly water-soluble drug remains one of the most challenging tasks in drug development. Several methods have been introduced to overcome this problem. However, these methods possess their own drawbacks which limit their applications in pharmaceutical field .

Solid dispersion technique has been extensively used to increase the solubility of a poorly water-soluble drug (Ford, 1986; Serajuddin, 1999; Dressman and Leuner, 2000). According to this method, a drug is thoroughly dispersed in a water-soluble carrier by suitable method of preparation. The mechanism by which the solubility and the dissolution rate of the drug is increased includes: firstly, the particle size of a drug is reduced to submicron size or to molecular size in the case where the solid solution is obtained. The particle size reduction generally increases the rate of dissolution; secondly, the drug is changed from crystalline to amorphous form, the high energetic state which is highly soluble; finally,

the wettability of the drug particle is improved by the dissolved carrier. Despite these promising advantages, the application of solid dispersion in pharmaceutical industry has certain limitation. Only a few solid dispersion products are commercially available. This is due to their poor physical characteristics for dosage form formulation. The solid dispersions prepared by using water-soluble carrier such as polyethylene glycol are soft and tacky mass which is difficult to handle, especially in the capsule-filling and tablet making process, e.g., pulverization, sieving and mixing.

The surface solid dispersion technique was then introduced in order to overcome these shortcomings. Unlike the conventional solid dispersion, the carriers used in the surface solid dispersion are the water-insoluble, porous materials with hydrophilic property. They can immediately disperse upon contact with water, rendering rapid release of drug particles into the medium. The dissolution of the drug particles is facilitated by the same mechanisms exhibited by the conventional solid dispersion. Surface solid dispersion had been demonstrated as a successful method to improve the dissolution rate and the solubility of many drugs (Nakai et al., 1976; Alsaidan et al., 1998; Kerc et al., 1998; Chowdary and Roa, 2000).

Piroxicam is an anti-inflammatory drug. It is widely used to combat the musculoskeletal and joint disorders (Kathleen, 1999).The bioavailability problem arises from its low water solubility and dissolution rate in the acid medium in which the absortion takes place. Oral piroxicam administration is characterized by slow absorption. The maximum serum level is attained at about 2 hours after taken orally. There have been some attempts to improve its bioavailability. The dispersed tablet design was introduced to facilitate rapid disintegration. The improvement of the dissolution and biovailability of the drug by conventional solid dispersion and the inclusion complex formation with cyclodextrin were demonstrated (Basan et al., 2001; Yuksel et al., 2003; Jug and Becirevic, 2004).

In the present study, the surface solid dispersion technique was applied in order to improve the dissolution rate of piroxicam. The carriers used were microcrystalline cellulose (Avicel PH101) and potato starch. The samples were prepared at various drug-to-carrier weight ratios by coevaporation method. The X-ray diffractometry was used to characterized the state of the drug and carriers.

MATERIALS AND METHODS

Materials

Piroxicam was purchased from Sigma, Germany. The carriers used, microcrystalline cellulose (Avicel PH101) and potato starch were from Fluka Chemie AG, Switzerland. The solvents used were analytical reagent grade from Labscan, Ireland.

Preparation of physical mixtures

The accurately-weighed amount of piroxicam and either carrier at 1:1, 1:2, 1:5 and 1:10 drug-to-carrier weight ratios were thoroughly blended, using vortex mixer. The physical mixtures were freshly prepared prior to analysis.

Preparation of surface solid dispersions

The surface solid dispersions of piroxicam and carriers were prepared by coevaporation method. The required amount of piroxicam was dissolved in dichloromethane. The carrier was dispersed in the drug solution. The mixtures were sonicated for 15 minutes to ensure the intimate mixing. The solvent was removed, using rotary vacuum evaporator at 50˚C. The residue obtained was dried at 50˚C overnight. The dried mass was pulverized and passed through 80/170 mesh sieves. The products were kept in desiccator for further study.

Dissolution studies

The dissolution of the samples was studied, using dissolution apparatus II (USP) paddle method. The dissolution medium was 900 ml of distilled water, maintained at 37±0.5˚C. The stirring speed was 100 rpm. The accurately-weighed sample, equivalent to 20 mg of piroxicam was placed over the dissolution medium. A 5.0 ml sample solution was withdrawn at appropriate time intervals through 0.45 μm millipore filter. An equal volume of fresh dissolution medium was immediately replaced. The concentration of piroxicam at each sampling time was analyzed spectrophotometrically at 339 nm. The experiments were triplicately performed. The mean concentration of the drug was plotted against time.

X-ray diffraction

X-ray diffraction patterns of the samples were recorded, using X-ray diffractometer, Semens-D500, Germany with Cu-Kα (Ni-filter), radiation (λ= 1.5418 ˚A). The experiments were carried out at room temperature under the following conditions: voltage 20 kV, current 20 mA, 2θ angle range 10-60 with scanning speed, 5˚/minute.

Release of drug from surface solid dispersions

The required amount of surface solid dispersions, equivalent to 20 mg of piroxicam, was placed into a screw-capped vial containing 10 ml of dichloromethane. The mixture was stirred for one hour at room temperature, using magnetic stirrer. The solubility of piroxicam in dichloromethane and the stirring time were preliminarily determined to ensure the complete release of the drug. The content in each vial was filtered through 0.45 μm membrane filter and analyzed for the drug content by spectrophotometer.

RESULTS AND DISCUSSION

According to the dissolution profiles shown in Figure 1, the dissolution rates of the drug from the physical mixtures were lower than those of the intact drug. This was due to the surface adsorption of the drug particles onto the surface of the carriers which subsequently retarded the dissolution of the drug. This phenomenon was more pronounced in drug-Avicel PH101 physical mixture. The difference in their particle size and porosity was responsible for this finding. The particle size of Avicel PH101 is extremely small with high porosity, thus exerting large surface area for adsorption (Levis and Deasy, 2001). The results corresponded with the data obtained from the release study, which showed the higher amount of the drug retained by Avicel PH101 than by potato starch. Figure 2 and Figure 3 illustrate the dissolution profiles of the drug from surface solid dispersions in Avicel PH101 and in potato starch respectively. It can be noted that the dissolution rate of the drug increased according to

the increasing amount of the carriers. In the case of Avicel PH101, the amount of the carrier used should be at least ten times (by weight) higher than the drug in order to overcome the effect of surface adsorption. This finding corresponded with the previous report that the 1:9 weight ratio of piroxicam to Avicel PH101 was sufficient to exhibit higher dissolution rate and anti-inflammatory effect in rats (Barzegar-Jalali et al., 2002). However, in their study, only Avicel PH101 was used as carrier. For the surface solid dispersion of drug in potato starch, the higher dissolution rate than the intact drug was observed at as low concentration as 1:1 weight ratio, signifying its superiority to Avicel PH101 as the carrier for piroxicam surface solid dispersion.

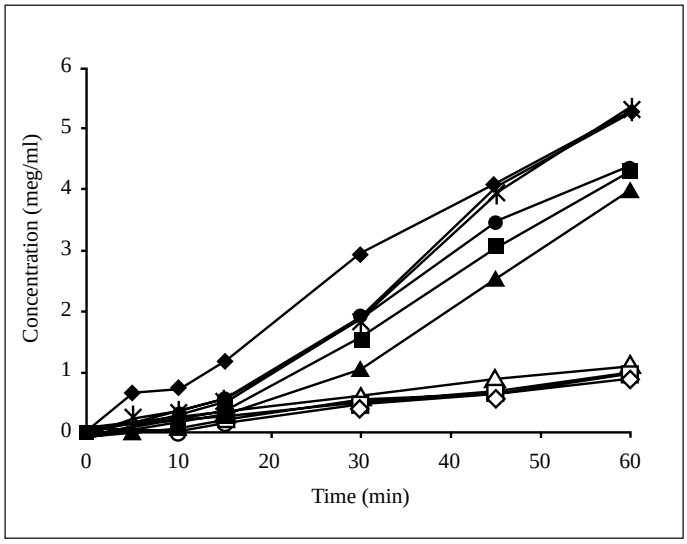

Figure 1. Dissolution profiles of piroxicam, intact drug (∗) compared to its physical mixtures in Avicel PH 101 (opened symbols) and in potato starch (solid symbols), in water at 37˚C, at various weight ratios: ● 1:1; ▲ 1:2; ■ 1:5; ◆ 1:10

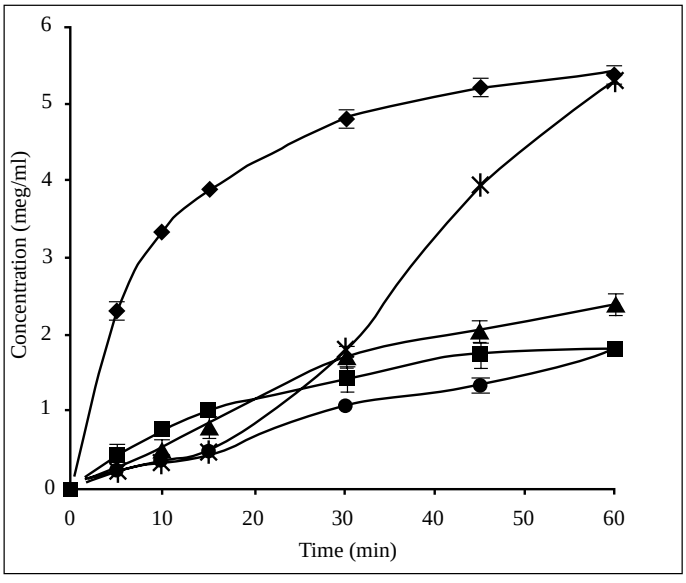

Figure 2. Dissolution profiles of piroxicam, intact drug (∗) compared to its surface solid dispersion in Avicel PH 101 in water at 37˚C, at various weight ratios: ● 1:1; ▲ 1:2; ■ 1:5; ◆ 1:10

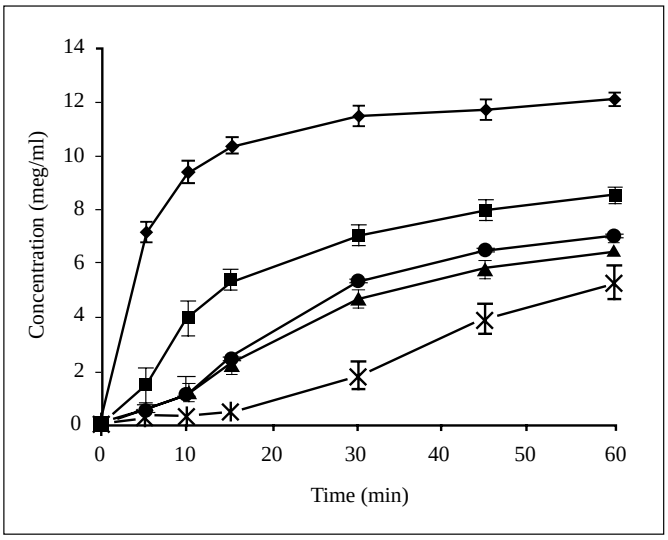

Figure 3. Dissolution profiles of piroxicam, intact drug (∗) compared to its surface solid dispersion in potato starch in water at 37˚C, at various weight ratios: ● 1:1; ▲ 1:2; ■ 1:5; ◆ 1:10

The dissolution parameters of the drug in all samples are summarized in Table 1. The surface adsorption of the drug occurred significantly in the physical mixtures of both carries. The $t_{10\%}$ of the physical mixtures was greater than that from the surface solid dispersions, signifying the higher extent of the drug entrapment by the carriers. The relative dissolution rate (RDR) of the drug in surface solid solution containing potato starch was six times higher than the intact drug whereas it was two times as shown by the Avicel PH101 system. These parameters also indicated the higher efficacy of the potato starch than Avicel PH 101 when used as the surface solid dispersion for piroxicam. RDR is the ratio of the drug concentration dissolved from the physical mixtures or surface solid dispersions to that from the intact drug at 30 minutes

Table 1. The dissolution parameters, the relative dissolution rate (RDR) and the time required for the 10% of the drug to be dissolved ($t_{10\%}$) of all samples.

Samples	Physical mixtures		Surface solid dispersions	
	RDR	$t_{10\%}$	RDR	$t_{10\%}$
Piroxicam, intact drug	1.0	>60	1.0	>60
Drug: Avicel PH 101 1:1	0.24	>60	0.58	>60
Drug: Avicel PH 101 1:2	0.31	>60	0.95	37
Drug: Avicel PH 101 1:5	0.28	>60	0.78	37
Drug: Avicel PH 101 1:10	0.26	>60	2.65	3
Drug: Potato starch 1:1	1.04	44	2.93	13
Drug: Potato starch 1:2	0.57	38	2.58	13
Drug: Potato starch 1:5	0.83	34	3.88	5
Drug: Potato starch 1:10	1.60	25	6.34	1.6

The higher efficiency of potato starch in improving the dissolution rate of the drug can be explained by its higher degree of amorphousness as shown by X-ray diffractograms in Figure 4. The more intense peaks represent the higher degree of crystallinity as exhibited by the intact drug and Avicel PH101. Because of the high degree of the amorphous state, the potato starch can swell in water more readily than Avicel PH 101, a microcrystalline substance, thus providing the more favorable microenvironment for the drug to be dissolved.

The X-ray diffractograms (Figure 5 and Figure 6) demonstrate the decrease in the intense peaks of the drug when the concentration of the carrier increased, implying that the drug was partially changed to the amorphous form.

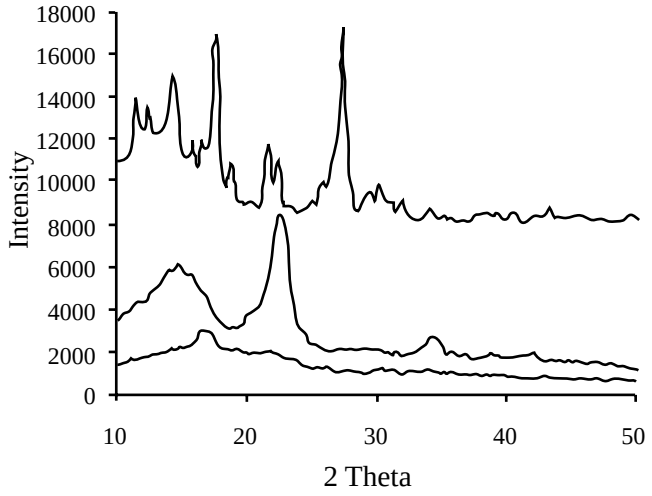

Figure 4. X-ray diffractograms of piroxicam, mtact (apper); Avicel PH101 (middle) and potato starch (lower curve)

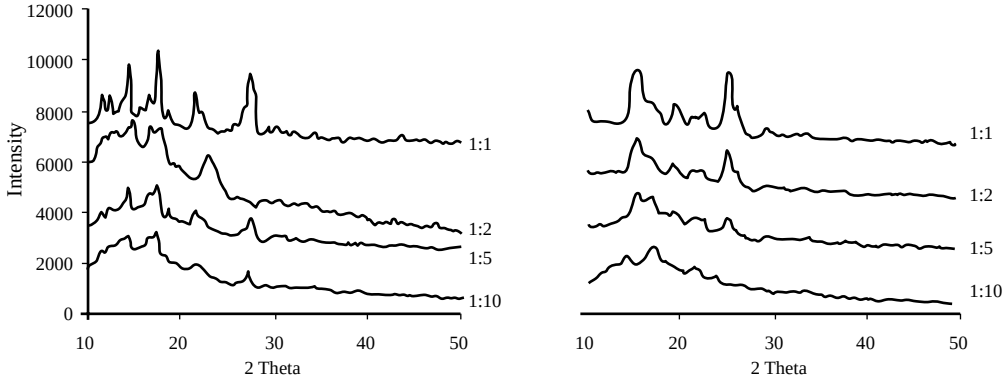

Figure 5. X-ray diffractograms of piroxicam, compared to its physical mixtures (left) and surface solid dispersions (right) in Avicel PH101 at various weight ratios

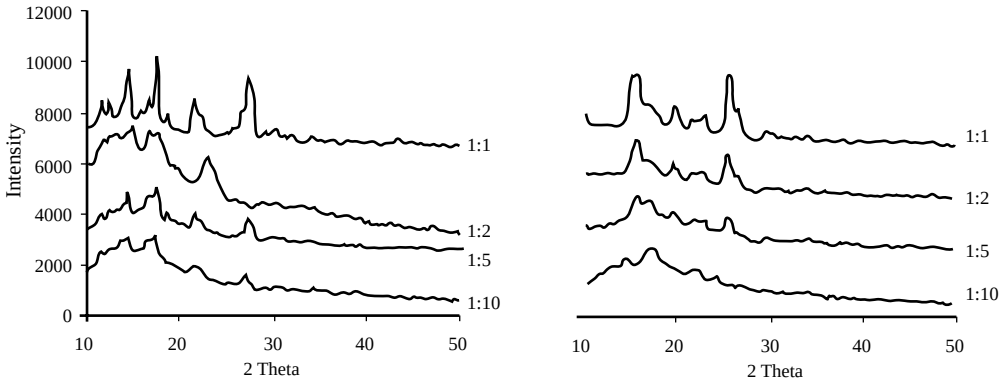

Figure 5. X-ray diffractograms of piroxicam, compared to its physical mixtures (left) and surface solid dispersions (right) in potato starch at various weight ratios

CONCLUSIONS

The surface solid dispersion technique had been shown as a successful approach to improve the dissolution rate of piroxicam. The nature and the amount of the carrier used played an important role in the enhancement of the dissolution rate. The increase in the dissolution rate would provide the rapid onset of action after the drug is taken orally. It is very interesting to note that the carriers used in this study are obtained from natural source and are commonly used as excipients in tablet and capsule formulation. It is also important to mention the adverse effect found when the drug was simply mixed with the carrier. The adsorption of the drug particles onto the porous surface of the carrier resulted in the slower dissolution rate. This is known as pharmaceutical incompatibility. However, when the two components are mixed and prepared as surface solid dispersion, the improvement of the dissolution rate can be obtained.

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