Effect of low melting hydrophilic carriers on the solubility and dissolution rate of Piroxicam using solid dispersion technique

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Abstract: The present study was aimed to enhance the solubility and dissolution rate of Piroxicam, a poorly water soluble drug from BCS class II. Solid dispersions (SDs) of Piroxicam Solutol and Gelucire were prepared by applying fusion method. The prepared SDs were tested for their aqueous solubility and dissolution rate. These dispersions were characterized by PXRD and FTIR for any physical or chemical change, respectively. From the results it was revealed that the solubility value of drug was increased by 20-25 times (with Solutol) and 6-10 times (with Gelucire). Dissolution rate of piroxicam was 7-8 times quicker in SDs with Solutol while with Gelucire a slow drug release in first 20 min was noted that was further enhanced by adding a ternary component, i.e. silica. The real time stability studies show that the solid dispersions are quite stable after 6 months in terms of solubility and dissolution rate. The study concludes that binary solid dispersion with Solutol has effectively increased the solubility of piroxicam that in turn has increased its dissolution rate, therefore useful in enhancing the bioavailability of this poorly soluble drug. In case of piroxicam: Gelucire solid dispersion; a ternary component is required to achieve quick release of drug.

Keywords: Piroxicam, binary dispersion, ternary dispersion, solid dispersion, solubilizer.

INTRODUCTION

Solubility is the amount of solute in the solvent that result in a homogenous scheme or solution (Savjani *et al.*, 2012), while dissolution is the rate of this solution formation. In majority of studies dynamic solubility of drugs has been reported as it represents the equilibrium/saturated solubility of that compound in given medium (Szafraniec *et al.* 2017, Hussain *et al.*, 2018). Both these parameters are necessary for the absorption of drugs and to achieve anticipated plasma concentration of drug subsequently pharmacological action (Savjani *et al.*, 2012). More than 40% of newly chemical entities (NCEs) discovered in pharmaceutical development are virtually insoluble in aqueous medium because of their lipophilic nature (Patel *et al.*, 2012; Ventosa-Andres *et al.*, 2010). Poor solubility of drugs especially of BCS class II (those having low solubility but high permeability) is the great challenge for the formulation scientists in designing the oral dosage forms (Savjani *et al.*, 2012).

Solid dispersion (SD) is one of the popular technique (Kumar *et al.*, 2016; Han, Yi Rang *et al.*, 2019) used for solubility enhancement, owing to the fact that it is a simple, economical and easy method. This technique improves the solubility and/or dissolution rate of drugs by: Particle size reduction, solubilization improved wetting, reduction in crystallinity and/or amorphous phase (Karatas *et al.*, 2005).

SDs are the dispersion of one or more hydrophobic active pharmaceutical ingredients (APIs) in an inert hydrophilic carrier or matrix in solid state (Mogal *et al.*, 2012). The goal of this study is to enhance the solubility and/or dissolution rate of piroxicam by preparing its solid dispersion in different low melting hydrophilic carriers. Fusion method of solid dispersion was used in this study, as this is simple and economical method which requires only drug and carrier and can easily be prepared in laboratory (Das *et al.*, 2012).

MATERIALS AND METHODS

Piroxicam (a non-steroidal anti-inflammatory drug) was provided by Fynk Pharmaceuticals (Pvt.) Ltd. Lahore, Pakistan as a kind gift (Two types low melting hydrophilic solubilizers including; Gelucire 44/14 (Gattefosse, France) and Solutol HS-15 (BASF GmbH, Germany) were used in this study. Colloidal Silicon (Aerosil-200, China) was purchased from local supplier.

Preparation of physical mixture

For the purpose of comparison with SDs, physical mixtures (PM) of piroxicam and Gelucire 44/14 (formulation G1) or Solutol HS-15(S1) in 1:1 ratio were prepared by mixing drug and polymers and in mortar and pestle.

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Preparation of solid dispersion

Binary SDs of piroxicam and Solutol HS-15 or Gelucire 44/14 in 1:1, 1:2 and 1:3 ratios (formulations S2-S4 and G2-G4, respectively See table 1) were prepared by fusion method as described in literature (de los Santos *et al.*, 2017). For the purpose, the weighed amount of either polymer was added in a glass beaker and heated to melting on a hot plate stirrer. The drug was then incorporated in the molten polymer and mixed with spatula to form a uniform dispersion. The prepared SDs were cooled at ambient temperature and stored in a desiccator. Ternary solid dispersion containing silica (formulation G5) was also prepared to evaluate the effect of ternary component on the drug-carrier binary mixture.

Solubility studies

The solubility of intact drug and in PMs and SDs was determined by shake flask technique. An excess amount of drug or its solid dispersions was added in a 50ml conical flask containing 20 ml of distilled water. The flasks were shaken on orbital flask shaker, Heidolph, Germany) until equilibrium was achieved. The soluble amount of drug was determined by UV spectrophotometric method at 355 nm.

Dissolution testing

Drug release from prepared solid dispersions were carried out in paddle dissolution apparatus (Type II). The dissolution medium (pH 1.2) was maintained at 37^{o}C with stirred at 50 rpm. Piroxicam filled capsules (appropriately weighed) were added in the dissolution vessels. 5ml samples were taken at fixed time intervals and an equal volume of the fresh medium was added after each sample. The samples were assayed to determine drug content at pre-defined time spans.

Powder X ray diffraction (PXRD)

PXRD studies of piroxicam alone and its solid dispersions was conducted using Brukers D8 diffractometer. The sample holders were spun with in the x-ray beam where Cu-filter was used to create the radiations at 35 kV and 40 mA. The samples were measured over the 2θ range between 4 to 25° over the step size of 0.017° (Lim *et al.*, 2013).

FTIR

The piroxicam and its solid dispersions were analyzed through FTIR (Bruker FTIR spectrophotometer). The resolution was set at 2 cm^{-1}. The wavelength range was 4000 to 500 cm^{-1}.

RESULTS

Solubility studies

The results show that the solubility of piroxicam in distilled water was 0.047mg/mL. The PM with Solutol and Gelucire have shown slightly higher solubility (~3 times) while SDs with both these hydrophilic carriers have shown 0.86, 1.01 and 1.13 mg/ml solubility with 1:1, 1:2 and 1:3 ratios with Solutol. On the other hand, SDs with Gelucire have depicted 0.29, 0.37 and 0.47mg/ml solubility values with same drug to polymer ratios (fig. 1). It was also observed that there was a linear increasing trend of solubility was increasing the polymer concentration (Lee *et al.*, 2010).

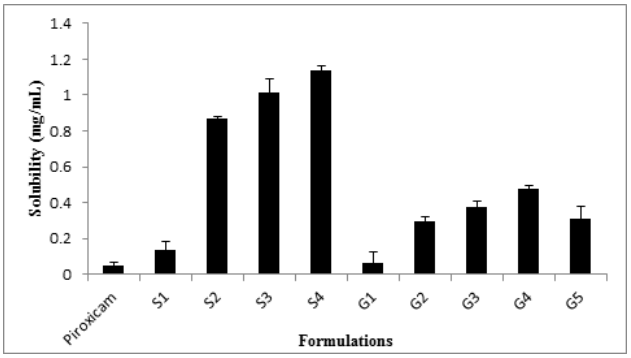

Fig. 1: Solubility of piroxicam, physical mixture and solid dispersions of piroxicam with Solutol and Gelucire.

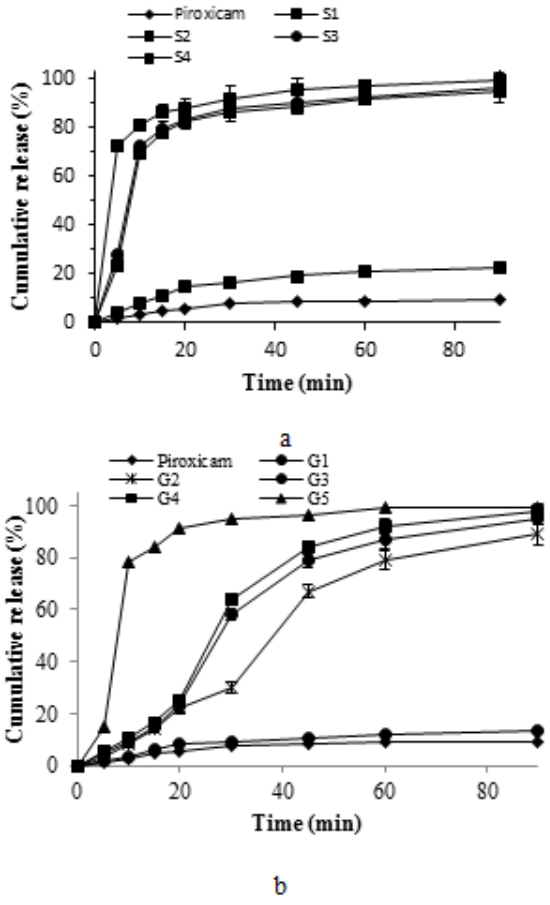

Fig. 2: Figure showing % release of piroxicam and its physical mixture and solid dispersion with Solutol HS-15 (a) and Gelucire 44/14 (b) in simulated gastric fluid pH 1.2

Table 1: Composition of formulations describing the quantity of drug and carriers per 2g of physical mixture or solid dispersions

Formulation code	Ratio	Quantity of Piroxicam (g)	Quantity of Solutol (g)	Quantity of Gelucire (g)
S1 (PM)	1:1	1	1	-
S2 (SD)	1:1	1	1	-
S3 (SD)	1:2	0.67	1.33	-
S4 (SD)	1:3	0.5	1.5	-
G1 (PM)	1:1	1	-	1
G2 (SD)	1:1	1	-	1
G3 (SD)	1:2	0.67	-	1.33
G4 (SD)	1:3	0.5	-	1.5
G5 (TSD)	Ternary SD	0.32	-	1.28 0.4 (Colloidal silica)

*PM physical mixture, SD solid dispersion, TSD ternary solid dispersion

Dissolution studies

The dissolution studies have shown only 7-10% release of the piroxicam in dissolution medium. The physical mixture with Solutol has almost similar release profile, however, solid dispersions with Solutol exhibited >80% drug release in first 30 min (fig. 2a).

The SDs with Gelucire on the other hand, exhibited slow release of piroxicam in first 20 min followed by a faster release i.e. >60% at 30 min of dissolution. The incorporation of colloidal silica in these SDs (i.e. formulation G5) has resulted in quick release of drug that reaches ~80% in first 10 min (fig. 2b).

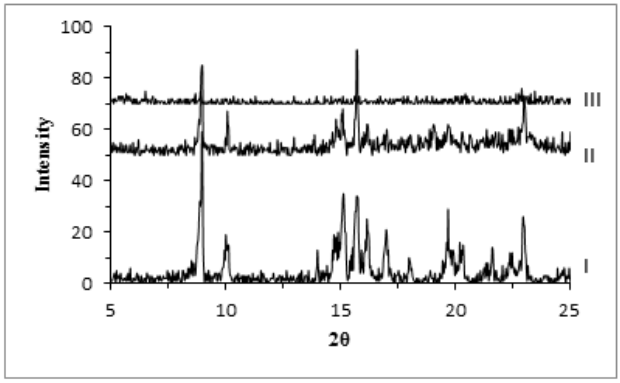

Fig. 3: PXRD patterns of piroxicam (I) and its solid dispersions with Gelucire (II) and Solutol (III)

Powder x-ray diffraction

The characteristic peaks of piroxicam (I in fig. 3) were seen at the diffraction angle of 2θ at 9.0º, 10.01º, 15.14º, 15.74º, 22.97º and 25.85º. The diffraction pattern of solid dispersion of piroxicam with Gelucire 44/14 (II) showed peaks at 2θ of 8.99º, 15.74º and 23º. The PXRD pattern of the solid dispersion of piroxicam with solutol HS-15 (III) showed two peaks at the diffraction angle 2θ of 8.9º and 22.0º with very low intensity.

FTIR results

The IR spectrum of piroxicam showed that the stretching of groups at the specific wave numbers are in close agreement as described by (Mihalić *et al.*, 1986). The IR spectrum of solid dispersion with gelucire 44/14 and solutol HS-15 showed that there was no interaction present between the drug and the hydrophilic carrier.

DISCUSSION

Among different techniques being used for the enhancement of solubility and dissolution rate of poorly soluble drugs; the fusion method using low melting hydrophilic carriers is very useful method. The reason of increase in solubility in SDs was due to the loss in crystallinity of drug (PXRD results) and the wetting and solubilization of drug by both hydrophilic carriers as these have interfacial tension lowering property (Ayşegül Karataş *et al.*, 2005, Rajebahadur *et al.*, 2006). The enhancement in the dissolution rates was also linked with enhanced solubility by both polymers (Ayşegül Karataş et al., 2005). The slow release of drug in first 20 min with Gelucire indicated the formation of aggregates and the addition of silica in such formulation enhances the drug release rates (i.e. >80% within 10 minutes). The possible explanation is; the silica has amended the dispersibility of drug: Gelucire solid dispersions and facilitated the penetration of elution medium into the mixture. This leads to better wetting of drug hence fast dissolution resulted as compared with that of binary dispersion

CONCLUSION

This study establishes that the use SD technique with selected solubilizers can effectively enhance the solubility and/or dissolution of Piroxicam. Binary solid dispersion with Solutol has effectively increased the solubility of piroxicam that in turn has increased its dissolution rate, therefore useful in enhancing the bioavailability of this poorly soluble drug. In case of piroxicam: Gelucire solid dispersion a ternary component is required to achieve quick release of drug.

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