



FORMATION AND CHARACTERIZATION OF SOLID DISPERSION OF PIROXICAM

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ABSTRACT

Solid dispersions of a poorly water-soluble drug piroxicam in Polyvinylpyrrolidone (PVP) were prepared by spray drying techniques. The physicochemical properties of the products and drug– polymer interactions were characterized by Scanning Electron Microscopy, Particle Size Analysis, Fourier transform infrared spectroscopy, Determination of drug content etc. Piroxicam was found amorphously dispersed in solid dispersion systems with the drug to polymer weight ratio of 1:4. Spectra data indicated the formation of hydrogen bonding between the drug and the polymer. The techniques evaluated in this work resulted in improved dissolution of piroxicam. PVP processing could provide an effective pharmaceutical formulation technology to improve the bioavailability of poorly water-soluble drug.

Keywords: Solid dispersion; piroxicam, *In-vitro* dissolution study, Spray drying method.

INTRODUCTION

In order to enhance the bioavailability of poorly water-soluble drugs, an increasing number of pharmaceutical formulation technologies are being developed to address this challenge of drug product development. These include micronization, formation of complexes [1] and solid dispersions [2-4], etc. The therapeutic usage of solid dispersions has been the focus of many recent studies, [5-6] and several successful examples have been commercialized in pharmaceutical market. In solid dispersions drug molecules or very fine drug crystals are dispersed in a biocompatible or water-soluble matrix. A number of water soluble polymers such as hydroxypropylcellulose, hydroxypropyl methylcellulose (HPMC), polyethylene glycol (PEG) and Polyvinylpyrrolidone (PVP) have been used as carriers for solid dispersions [7-9]

conventionally, solid dispersions are prepared by fusion method and solvent evaporation [10].

Fusion method, also called melt method, is precluded for many situations because of its high processing temperature, usually about 150°C, at which many active pharmaceutical ingredients. On the other hand, solvent evaporation method circumvents the difficulties encountered with fusion method by working at milder conditions. However, excess usage of organic solvents and complication of product purity during the processing still hamper the application of solvent evaporation techniques. Among many derivatives of solvent evaporation method, spray drying technique has been proven a powerful tool for preparing solid dispersions of drug and polymers [11-12] because of its simplicity and effectiveness. While further improvement is needed to make this technique sufficiently practical, alternative technologies are under

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development in pursuit of high product quality and low environmental impact. In the late 80's, supercritical fluids (SCF) started attracting interests in the pharmaceutical industry as an alternative to conventional processes [13-14]. The most common SCF is supercritical carbon dioxide (scCO₂) which is nontoxic, nonflammable and available in large quantities. Owing to its mild critical temperature (31.06⁰C) and low critical pressure (7.38 MPa), scCO₂ is suitable to precipitate heat-sensitive drugs. A variety of scCO₂ techniques have been developed with different working principles, such as rapid expansion of supercritical solutions (RESS), gas antisolvent precipitation (GAS), supercritical antisolvent precipitation (SAS), precipitation with compressed fluid antisolvent (PCA), solution-enhanced dispersion by supercritical fluids (SEDS), precipitation from gas-saturated solutions (PGSS), etc [15-18]. These techniques were proven to effectively control particle size and reduce residual solvent content; and in some examples crystal habit, morphology and polymorphic form of the processed drug could be controlled as well [17]. Among numerous SCF techniques, PCA is of special interest because of its wide adaptability and mild operating condition, which makes it more promising for pharmaceutical applications. Solid dispersions have been prepared using PCA processes, and most of the final products showed improved physicochemical and pharmaceutical properties [19]. The spray drying processing can produce particles with controlled micrometric properties, [20] the adverse effects of this technique on the crystalline and stability of pharmaceutical substances drive us to further exploit the potential of PCA processing as a supplementary technology of forming pharmaceutical solid dispersions. Piroxicam is a biopharmaceutical Classification System (BCS) class II pharmaceutical with well-defined polymorphic characterization [21] Its structure contains one O–H and one N–H group which can possibly form hydrogen bonds with the carbonyl group in the PVP repeat unit. Many studies have been conducted on its crystal form modification and formulation with other pharmaceutical-related materials. In a recent study, solid dispersions of pharmaceutical compounds in various excipients were prepared using spray drying processing [22–25] we prepared solid dispersions containing piroxicam and excipient (PVP K25) and their physicochemical properties were characterized by Fourier transform infrared spectroscopy (FTIR), and scanning electron microscopy (SEM), particle size analysis and determination of drug content etc. In addition, the dissolution mechanisms of the solid dispersions were also discussed.

MATERIALS AND METHODS

MATERIALS:

Piroxicam was purchased from Sun pharmaceuticals Ltd, Mumbai. Polyvinylpyrrolidone K25

(PVP, MW=24, 000 g/mol) was obtained from International Specialty products, Inc. (ISP), Wayne, NJ. Carbon dioxide (99.7%) was supplied by GT&S, Inc., Allentown, PA. Ethanol was purchased from Reachem Lab. Chemicals Pvt.Ltd.Chennai and dichloromethane (99.95%) and acetone from VWR International, West Chester, PA. All chemicals and reagents were used without further purification.

PREPARATION OF SOLID DISPERSIONS OF PIROXICAM WITH PVP K25:

Spray Drying Process [26]

Solutions of piroxicam and its mixtures with PVP K25 (weight ratio=1:1,1:2,1:3,1:4) in mixture of ethanol and acetone were fed into a mini-spray-dryer Buchi Mini Spray Dryer 290 (Flawil, Switzerland) with a co-axial nozzle with co-current flow. The total concentration of the solutions was 5 w/v%. The inlet temperature at the drying chamber was maintained around 110±2⁰C and outlet temperature was 60±5⁰C. The aspirator setting was 35 m³/h. The spray feed rate was 5.5 mLmin⁻¹. The spray-dried powders were prepared in duplicate. Yields of 60% and higher amount were obtained. In addition, physical mixtures (PM) of piroxicam and PVP K25 with weight ratio of 1:1, 1:2, 1:3, and 1:4 were prepared by mixing the two components until a homogenous mixture was obtained.

Characterization of Formulated solid dispersion [26-28] Scanning Electron Microscopy (SEM)

A scanning electron microscope (SEM, model JEOL JSM-6701F.Japan) was used to examine the particle size and morphology at 20 kV accelerating voltage. The samples were fixed by mutual conductive adhesive tape on aluminum stubs and covered with a 250 Å film of gold-palladium using a sputter coater.

Particle Size Analysis

Particle size distribution was measured using a laser diffraction size analyzer (LS 13 320, Beckman, Fullerton, CA). Samples were suspended in silicone oil and treated by ultrasonication for 1 min. Dispersed samples were then fed into the analyzer.

Fourier Transform Infrared Spectroscopy (FTIR)

Infrared spectra were collected on a Thermo Nicolet FT-IR spectrometer (Avatar 360, Madison, WI). KBr pellets were prepared and scanned over a range of 400–4000 cm⁻¹. The spectra were obtained by averaging 32 scans at a resolution of 2 cm⁻¹.

Determination of Drug content

The content of piroxicam in the solid dispersion samples was determined using UV-Vis spectrophotometer (PERKIN ELMER). A 10 mg sample was dissolved in 100 mL methanol, and then 1 mL of the stock solution was diluted to 50 mL with simulated gastric fluid (SGF) without pepsin. Drug content was calculated from the absorbance measured at 334 nm.

Invitro Dissolution Studies

The dissolution rate of piroxicam samples was measured in a Distek 2100C dissolution test system

(Distek, North Brunswick, NJ) using simulated gastric fluid (SGF) without pepsin at pH 1.2 and USP apparatus II (paddle) method. In each dissolution vessel, quantities of samples equivalent of 10 ± 0.2 mg piroxicam were added to 500 mL dissolution medium. Bath temperature and paddle rotation speed were set at $37 \pm 0.2^\circ\text{C}$ and 50 rpm, respectively. The amount of drug dissolved was assayed spectrophotometrically at 334 nm at regular intervals.

RESULTS AND DISCUSSION

Scanning Electron Microscopy (SEM)

Scanning electron microscopy (JEOL JSM-6701F, Japan) was carried out to study their Morphological characteristics of Solid dispersions of piroxicam (ratio 1:4).

Particle Size Analysis

Particle size determination was done by using a laser diffraction size analyzer. Size distribution plays an important role in determining the release characteristics of the solid dispersion. Smaller the solid dispersion, faster will be the release rate of the drug from the solid dispersion, while larger the size, more sustained or controlled will be the release of the drug. The particle size ranges of four formulations are as follows. The particle size is formulated batches of solid dispersion were found to be in the range of 41.78– 43.42 μm .

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR is a very powerful technique in detecting presence of interaction in drug-carrier solid dispersions. The appearance or disappearance of peaks and/or the shift of their positions are often an indication of interactions such as hydrogen bonding. Piroxicam contains one hydrogen donor (–OH and –NH) whose characteristic absorption bands are n O–H at 3339 cm^{-1} for form I and 3381 cm^{-1} . Also, a broad well defined band was observed in the spectrum of PVP K25 in $1600\text{--}1700\text{ cm}^{-1}$ assigned to the carbonyl stretching vibration. Within each pyrrole ring of the PVP polymer, the carbonyl group is more favorable in hydrogen bonding over the tertiary amine because of the steric hindrance of the latter group. The spectrum of physical mixture was simple summation of pure drug and PVP K25, revealing no perceptible interaction between the two components.

Determination of drug content

The drug content in the solid dispersion was determined by the procedure described earlier. The drug content of the different batches is as follows

The solid dispersion of formulations F-IV has highest mg of the drug content followed by the formulations F-I, F-II, F-III, respectively.

IN-VITRO DISSOLUTION STUDY

The dissolution of solid dispersions of piroxicam and PVP K25 of products prepared by spray drying method, to enhance the dissolution of piroxicam more prominently. There are possible mechanisms responsible for dissolution of solid dispersions: drug-controlled and carrier controlled dissolution.

FIG.1. Scanning Electron Microscopy of formulation F-IV ratio (1:4)

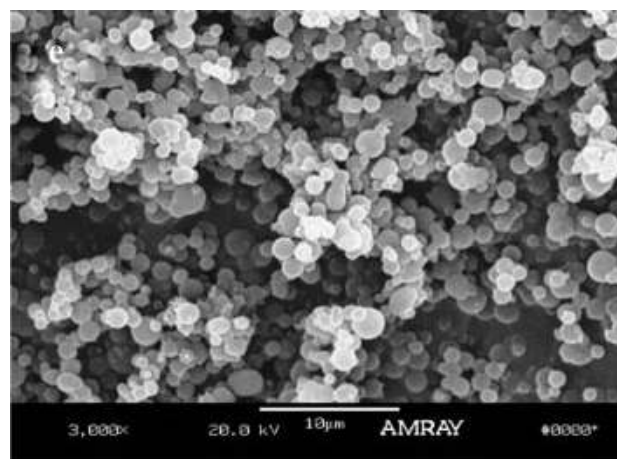
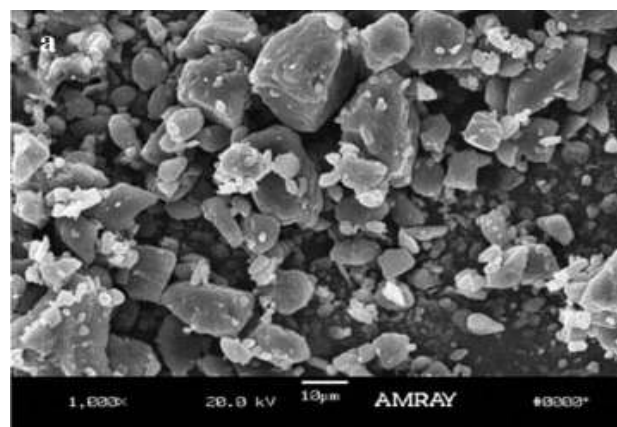


Table: 1: Particle size analysis of different batches of solid dispersion

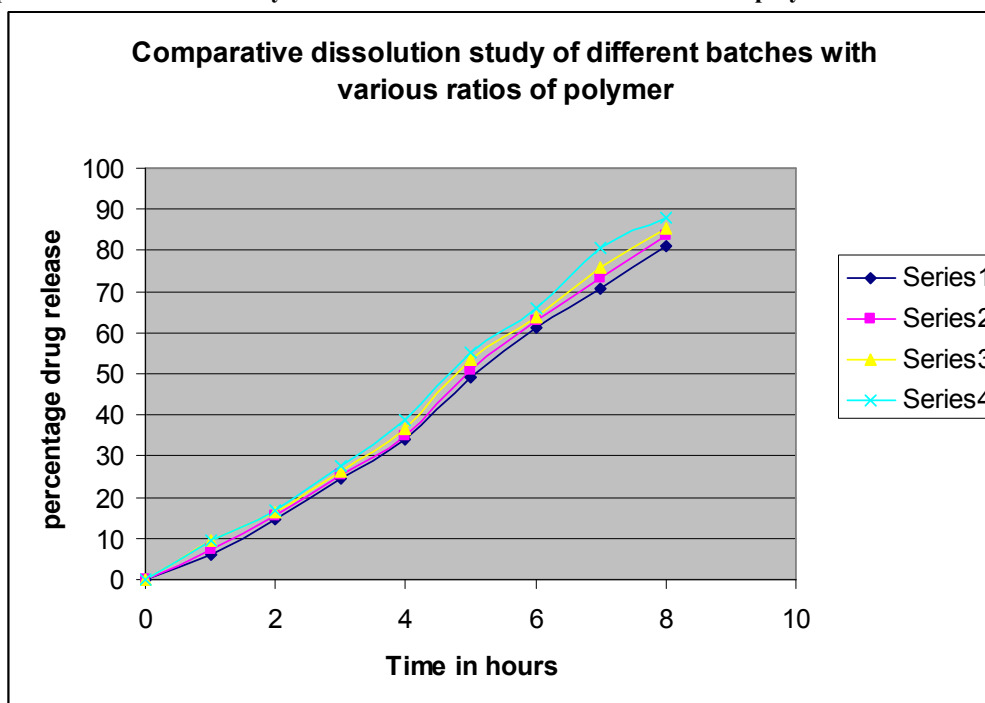
S.No	Formulations	Ratio (core: coat)	Particle size (μm)
1	F-I	1:1	41.78
2	F-II	1:2	42.24
3	F-III	1:3	42.79
4	F-IV	1:4	43.42

Table: 2 Drug content of Different formulation

S.No	Formulations	Ratio (core: coat)	Drug content (mg)
1	F-I	1:1	62
2	F-II	1:2	68
3	F-III	1:3	79
4	F-IV	1:4	83

Table: 3. Comparative dissolution study of different batches with various ratios of polymer

S. No	Time in hours	% of drug release F-I (Ratio 1:1)	% of drug release F-II (Ratio 1:2)	% of drug release F-III (Ratio 1:3)	% of drug release F-IV (Ratio1:4)
1	0	0.000	0.000	0.000	0.000
2	1	6.046	7.234	9.651	9.476
3	2	14.584	15.674	16.380	16.752
4	3	24.596	25.505	26.432	27.431
5	4	34.211	35.035	36.450	38.760
6	5	49.187	51.062	53.434	55.255
7	6	61.290	62.796	63.977	65.753
8	7	70.684	73.410	75.792	80.485
9	8	81.069	83.632	85.551	88.130

Figure:3. Comparative Dissolution study of different batches with various ratios of polymer

CONCLUSION

The spray drying techniques were evaluated for their potential use in the preparation of rapidly dissolving dosage forms of piroxicam, a BCS Class II API, with PVP K25. Solid dispersions of piroxicam with PVP K25 were prepared and characterized by Fourier transform infrared spectroscopy, scanning electron microscopy, and *invitro* dissolution tests. Solid dispersions obtained in a technique were lack of crystallinity and dissolved quickly in pH 1.2 simulated gastric fluids without pepsin. The amorphous piroxicam was dispersed in PVP K25 through hydrogen bonding in a solid dispersion. Spray drying technique is

capable of preparing solid dispersions with faster dissolution because of the smaller size of its products. Because the processing is more powerful in controlling the particle size and the physical transformation nature of this technique will not interfere with the interactions between drug and carrier, it is possible to utilize this method to control the *in vitro* performance without complicating the stability issue. It can be expected that the improvement in piroxicam dissolution rate will increase its bioavailability, but further efforts must be made to verify dissolution mechanism of the piroxicam/PVP K25 formulations.

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