ISSN:2230-7346
Available online http://WWW.JGTPS.COM
Research Article *Journal of Global Trends in Pharmaceutical Sciences*

Vol.2, Issue 1, pp 43-54, January–March 2011

PREPARATION AND INVITRO EVALUATION OF SOLID DISPERSION OF PIROXICAM WITH HPMC K100M BY USING SPRAY DRYING TECHNIQUE

A.Arunachalam[1], M.Karthikeyan[2], S.AshutoshKumar[2], S.Manidipa[2], Kishore Konam[3], Pottabathula hari Prasad[4], S.Sethuraman*[5], R.Senthilraj[6]

1. Department of Pharmaceutics, Sasikanthreddy College of Pharmacy, Nellore, A.P, India

2. Department of Pharmaceutics, AKRG College of Pharmacy, West Godavari, A.P, India.

3. Department of Pharmaceutical Analysis and QA, Sree Nagarjuna College of Pharmacy, Kadipikonda, Warangal, A.P, India.

4. Department of Industrial Pharmacy, Swami Ramananda Tritha Institute of Pharmaceutical Sciences, Nalgonda, A.P, India.

5. Department of Chemistry, SCSVMV University, Kanchipuram, Tamilnadu, India.

6. Department of Pharmaceutical Biotechnology, Vikas College of Pharmacy, Jangaon, Warangal, A.P, India.

Corresponding author E-Mail:sethuqcexecutive@gmail.com

ABSTRACT

Solid dispersions of a poorly water-soluble drug piroxicam in hydroxypropyl methylcellulose (HPMC) were prepared by spray drying technique. The physicochemical properties of the products and drug– polymer interactions were characterized by Scanning Electron Microscopy, Particle Size Analysis**,** and 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.

The techniques evaluated in this work resulted in improved dissolution of piroxicam. The conclusion sis a HPMC used to prepared effective pharmaceutical formulation of solid dispersion and to improve the bioavailability of poorly water-soluble drug.

KEY WORDS:

Solid Dispersion; Piroxicam, HPMC, Spray drying method, Characterization, *In-Vitro* dissolution study.

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 150^0C, 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 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 (31.06^0C) 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 METHOD:

MATERIALS:

Piroxicam was purchased from Sun Pharmaceuticals Ltd, Mumbai. HPMC K100M, Loba Chemie Pvt. Ltd; Mumbai. 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 HPMC K100M:

Spray Drying Process:[26]

Solutions of piroxicam and its mixtures with HPMC K100M (weight ratio=1:1, 1:2, 1:3, and 1:4) in mixture of ethanol and acetone were fed into a mini-spray-dryer Bu¨ chi 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 ± 2^0C and outlet temperature was 60 ± 5^0C.

The aspirator setting was 35 m^3/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 HPMC K100M 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: [26-30]

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 A° 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 ultra sonication 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.

***In-vitro* 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±0.2^{0}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).

Figure: 1

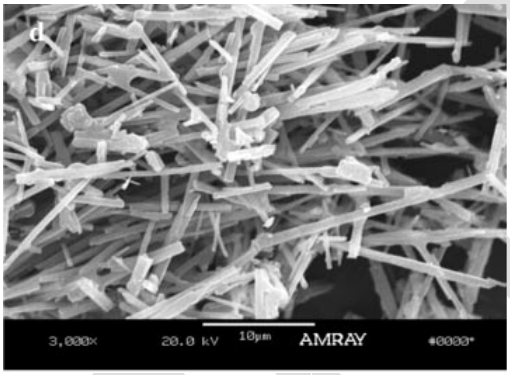
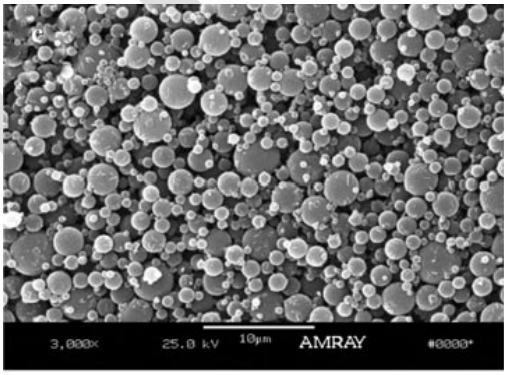


Figure: 2



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.

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	39.34
2	F-II	1:2	40.52
3	F-III	1:3	41.76
4	F-IV	1:4	42.47

The particle size is formulated batches of solid dispersion were found to be in the range of 39.34– 42.47 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 HPMC K100M in 1600– 1700 cm^{-1} assigned to the carbonyl stretching vibration. Within each pyrrole ring of the HPMC 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 HPMC K100M, 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.

TABLE: 2 Drug Content of four different batches:

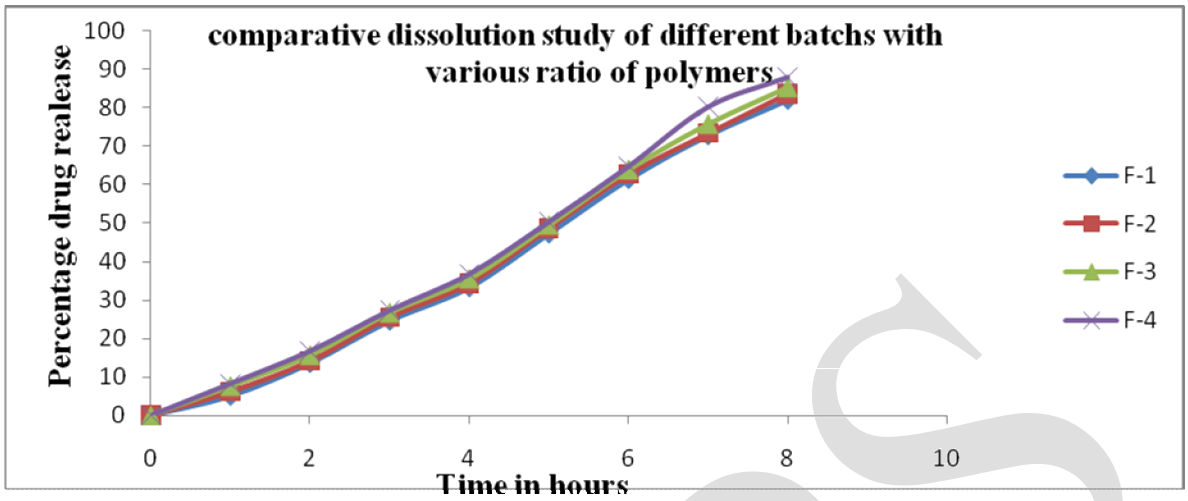
S.no	Formulations	Ratio (core: coat)	Drug content (mg)
1	F-I	1:1	58
2	F-П	1:2	63
3	F-III	1:3	71
4	F-IV	1:4	78

IN-VITRO DISSOLUTION STUDY:

The dissolution of solid dispersions of piroxicam and HPMC 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.

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	5.047	6.204	7.649	8.286
3	2	13.564	14.198	15.670	16.756
4	3	24.534	25.565	26.762	27.321
5	4	33.216	34.345	35.546	36.768
6	5	47.183	48.762	49.534	50.355
7	6	61.290	62.796	63.977	64.753
8	7	72.684	73.460	75.798	80.235
9	8	81.879	83.762	85.361	87.960



CONCLUSION:

The spray drying techniques were evaluated for their potential use in the preparation of rapidly dissolving dosage forms of piroxicam, with HPMC K100M. Solid dispersions of piroxicam with HPMC K100M 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 crystalline and dissolved quickly in pH 1.2 simulated gastric fluids without pepsin. The amorphous piroxicam was dispersed in HPMC K100M 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.

REFERENCES:

1. Perrut M. 2003. Supercritical fluids applications in the pharmaceutical industry. Stp Pharma Sci 13: 83–91.
2. Ruan LP, Yu BY, Fu GM, Zhu DN. 2005. Improving the solubility of ampelopsin by solid dispersions and inclusion complexes. J Pharmceut Biomed 38:457– 464.

3. Chiou WL, Riegelman S. 1971. Pharmaceutical applications of solid dispersion systems. J Pharm Sci 60:1281–1302.

4. Leuner C, Dressman J. 2000. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm 50:47–60.

5. Serajuddin ATM. 1999. Solid dispersion of poorly water-soluble drugs: Early promises, subsequent problems, and recent breakthroughs. J Pharm Sci 88:1058–1066.

6. Sethia S, Squillante E. 2003. Solid dispersions: Revival with greater possibilities and applications in oral drug delivery. Crit Rev Ther Drug 20:215– 247.

7. Kanaze FI, Kokkalou E, Niopas I, Georgarakis M, Stergiou A, Bikiaris D. 2006. Dissolution enhancement of flavonoids by solid dispersion in PVP and PEG matrixes: A comparative study. J Appl Polym Sci 102:460–471.

8. Karavas E, Georgarakis E, Sigalas MP, Avgoustakis K, Bikiaris D. 2007. Investigation of the release mechanism of a sparingly water-soluble drug from solid dispersions in hydrophilic carriers based on physical state of drug, particle size distribution and drug-polymer interactions. Eur J Pharm Biopharm 66:334–347.

9. Kumar SGV, Mishra DN. 2006. Preparation, characterization and in vitro dissolution studies of solid dispersion of meloxicam with PEG 6000. J Pharm Soc Jpn 126:657–664.

10. Habib MJ. 2001. Pharmaceutical Solid Dispersion Technology. 1st edition. Lancaster, PA: Technomic Pub. 97 p.

11. Majerik V, Charbit G, Badens E, Horvath G, Szokonya L, Bosc N, Teillaud E. 2007. Bioavailability enhancement of an active substance by supercritical antisolvent precipitation. J Supercrit Fluid 40: 101–110.

12. Paradkar A, Ambike AA, Jadhav BK, Mahadik KR. 2004. Characterization of curcumin-PVP solid dispersion obtained by spray drying. Int J Pharm 271:281–286.

13. Bahrami M, Ranjbarian S. 2007. Production of micro- and nano-composite particles by supercritical carbon dioxide. J Supercrit Fluid 40:263– 283.

14. McHugh MA, Krukonis VJ. 1994. Supercritical fluid extraction: Principles and practice. 2nd edition. London: Butterworth-Heinemann. 512 p.

15. Del Valle EMM, Galan MA. 2005. Supercritical Fluid technique for particle engineering: Drug delivery applications. Rev Chem Eng 21:33–69.

16. Foster N, Mammucari R, Dehghani F, Barrett A, Bezanehtak K, Coen E, Combes G, Meure L, Ng A, Regtop HL, Tandya A. 2003. Processing pharmaceutical compounds using dense gas technology. Ind Eng Chem Res 42:6476–6493.

17. Knez Z, Weidner E. 2003. Particles formation and particle design using supercritical fluids. Curr Opin Solid St M 7:353–361.

18. Kompella UB, Koushik K. 2001. Preparation of drug delivery systems using supercritical fluid technology. Crit Rev Ther Drug 18:173–199.

19. Majerik V, Horvath G, Szokonya L, Charbit G, Badens E, Bosc N, Teillaud E. 2007. Supercritical antisolvent versus coevaporation—Preparation and characterization of solid dispersions. Drug Dev Ind Pharm 33:975–983.

20. Sacchetti M, Van Oort MM. 2007. Spray-drying and supercritical fluid particle generation techniques. In: Hickey AJ, editor. Inhalation aerosols: Physical and biological basis for therapy. 2nd edition. Boca Raton, FL: CRC. pp. 307–346.

21. Vrecer F, Srcic S, Smid-Korbar J. 1991. Investigation of piroxicam polymorphism. Int J Pharm 68: 35–41.

22. Jun SW, Kim MS, Jo GH, Lee S, Woo JS, Park JS, Hwang SJ. 2005. Cefuroxime axetil solid dispersions prepared using solution enhanced dispersion by supercritical fluids. J Pharm Pharmacol 57: 1529–1537.

23. Liu H, Zhou LL, Wei LL, Hong G, Nie SF, Yang XG, Tang R, Pan WS. 2007. Preparation of budesonidepoly (ethylene oxide) solid dispersions using supercritical fluid technology. Drug Dev Ind Pharm 33: 959–966.

24. Muhrer G, Meier U, Fusaro F, Albano S, Mazzotti M. 2006. Use of compressed gas precipitation to enhance the dissolution behavior of a poorly water-soluble drug: Generation of drug microparticles and drug-polymer solid dispersions. Int J Pharm 308:69–83.

25. Won DH, Kim MS, Lee S, Park JS, Hwang SJ. 2005. Improved physicochemical characteristics of felodipine solid dispersion particles by supercritical anti-solvent precipitation process. Int J Pharm 301:199–208.

26. KE WU, 2008 Formation and Characterization of Solid Dispersions of Piroxicam and Polyvinylpyrrolidone Using Spray Drying and Precipitation with Compressed Antisolvent, journal of pharmaceutical sciences, vol. 98, no. 7, 2422-2431.

27. Vrecer F, Vrbinc M, Meden A. 2003. Characterization of piroxicam crystal modifications. Int J Pharm 256:3–15.

28. Tantishaiyakul V, Kaewnopparat N, Ingkatawornwong S. 1996. Properties of solid dispersions of piroxicam in polyvinylpyrrolidone K-30. Int J Pharm 143:59–66.

29. Taylor LS, Zografi G. 1997. Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. Pharm Res 14:1691–1698.

30. Van den Mooter G, Augustijns P, Blaton N, Kinget R. 1998. Physico-chemical characterization of solid dispersions of temazepam with polyethylene glycol 6000 and PVP K30. Int J Pharm 164:67–80.