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PREPARATION AND CHARACTERIZATION OF MICROPARTICLES OF TENOXICAM

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Abstract: The aim of the present study was to improve the solubility and dissolution rate of Tenoxicam by preparing microparticles by spray drying technique using chloroform and water as solvents systems. Tenoxicam microparticles were prepared by spray drying using chloroform and water as solvents systems to improve solubility and dissolution rate. The prepared microparticles were evaluated for solubility and in-vitro dissolution. The prepared microparticles were characterized by DSC, FT-IR, XRD and SEM. Dissolution profile of the prepared microparticles was compared with its recrystallized and commercialized sample. Prepared microparticles exhibited decreased in crystallinity. The solubility of microparticles exhibited one and half fold increases than the commercial Tenoxicam and dissolution showed 63 % release in 60 min. Consequently, from the above result it can be concluded that spray dried technique is a useful technique to improve the solubility and dissolution of poor water soluble drug like Tenoxicam.

Keywords: Spray drying, Crystals, Tenoxicam, Crystallinity, Solubility, Dissolution.

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INTRODUCTION

Tenoxicam, 4-hydroxy - 2 - methyl -N-2- pyridinyl - 2H - thieno - [2,3e]1,2-thiazine-3-carboxamide-1,1-dioxide (Figure 1a) is a non-steroidal anti-inflammatory drug (NSAID), acting as preferential inhibitor of cyclooxygenase-2 and inhibitor of prostaglandin synthesis. It is very effective as analgesic and anti-inflamatory drug for the systemic treatment of rheumatoid arthritis, osteoarthritis and other joint diseases (1, 2). However, being a lipophilic drug (Log P=2.4), tenoxicam is sparingly soluble in water (0.076 mg/mL at 25°C) (3), so that its dissolution may be the rate determining step in the absorption process.

Consideration of the modified Noyes-Whitney equation provides some hints as to how the dissolution rate of very poorly soluble compounds might be improved to minimize the limitations to their oral availability. There have been numerous efforts to improve drug dissolution rates. These include (a) reducing the particle size to increase the surface area; (b) using water-soluble carriers to form inclusion complexes; (c) solubilization in surfactant systems; (d) using pro-drugs and drug derivatization; and (e) manipulation of the solid state of drug substances to improve the drug dissolution i.e. by reducing the crystallinity of drug substances through formation of solid dispersions. However, there are practical limitations to these techniques (4). Although particle size reduction is commonly used to increase the dissolution rate, there is a practical limit to the size reduction that can be achieved by such commonly used methods as controlled crystallization and grinding. The use of very fine powders in a dosage form may also be problematic because of handling difficulties and poor wettability. Salt formation is not feasible for neutral compounds and the synthesis of appropriate salt forms of drugs which are weakly acidic or weakly basic may often not be practical. Even when salts can be prepared, an increased dissolution rate in the gastrointestinal tract may not be achieved in many cases because of the reconversion of salts into aggregates of their respective acid or base forms. The solubilization of drugs in organic solvents or in aqueous media by the use of surfactants and co-solvents leads to liquid formation that is usually undesirable from the viewpoints of patient acceptability and marketing (5). Solid dispersions have been widely used to enhance the solubility, dissolution rate, and bioavailability of poorly soluble drugs (6,7,8,9). There are different types solid dispersion systems categorized according to the physical states of the drug and the carrier in the systems. It may be a molecular solid solution, a dispersion of amorphous or crystalline drug particles in an amorphous carrier matrix, or a combination of a solution and dispersion of solids.

The enhancement in the dissolution rate is obtained by one or a combination of the following mechanisms: eutectic formation, increased surface area of the drug due to precipitation in the carrier, formation of true solid solution, improved wetability and drug precipitation as a metastable crystalline form or a decrease in substance crystallinity. The type of solid dispersion formed depends on both the carrier-drug combination and the method of manufacture.

Spray drying is one of the techniques of preparing solid dispersion and is widely used as an alternative to milling to reduce particle size (10,11,12,13). The large surface area of the resulting particle should result in an enhanced solubility and dissolution rate, consequently, improved bioavailability.

The aim of the present study was to improve the solubility and dissolution rate of Tenoxicam by spray drying technique using chloroform and water as solvents system.

MATERIALS AND METHODS

Materials

All chemicals and buffers used were of analytical grade.

Preparation of crystals

Preparation of spray dried crystals of Tenoxicam (SD)

Tenoxicam (3 g) was dissolved in 25 ml of chloroform and water (4:1) system until a clear solution was obtained. The resulted solution was spray dried using Mini Spray Dryer LSD -48; (Jay instrument & systems Pvt. Ltd. Mumbai) at a Feed rate of 12%, an vacuum in the system -65 MM WC, Atomization pressure rate 1.5 kg/cm^2 , Aspirator level at 35%, inlet temperature at 105±5°C and outlet temperature at 45 ±5°C. The formed microparticles were separated using cyclone separator, collected and stored in a desiccator at ambient temperature until use.

Preparation of Recrystallized crystals (RS)

Tenoxicam (3 g) was dissolved in 25 ml of chloroform and water (4:1) and heating at 45^{0}C. The drug solution was maintained at room temperature with occasional stirring. The crystals of Tenoxicam were collected by filtration and were dried at 45^{0}C for 12 hours.

Evaluation of crystals

Determination of residual solvents in different crystals by gas chromatography

GC studies were carried out on SHIMADZU model 2014 (Shimadzu Technologies, Japan) coupled with a split/split less injector, operated in a split-mode and FID. The computer with GC solutions software has been used to control the gas chromatograph. Rtx-5 capillary column (cross bond 5%di-phenyl/95%di-methyl-polysiloxane) with a length of 30 meters coil and an internal diameter of 0.25 mm was used throughout the study.

Differential scanning calorimetry (DSC)

A DSC study was carried out to detect possible polymorphic transition during the crystallization process. DSC measurements were performed on a DSC DuPont 9900, differential scanning calorimeter with a thermal analyzer.

Fourier transform infrared (FTIR) spectroscopy

The FTIR spectral measurements were taken at ambient temperature using a Shimadzu, Model 8033 (USA). About 2 mg of the pure drug, recrystallized and spray dried crystals were used separately. Pure drug and all the prepared crystals were dispersed in KBr powder and the pellets were made by applying 6000 kg/cm2 pressure.

X-ray analysis

X-Ray powder diffraction patterns were used to detect possible polymorphic transition during the crystallization process. X-Ray powder diffraction patterns were recorded using Rigaku Miniflex II X-ray Diffractometer with Ni filtered radiation of wavelength 1.5406 Å (Cu Target). Samples were scanned in the 2θ range of 0-50o. The scanning speed used for the recording was 3o/min with step size of 0.02o.

Scanning electron microscopy (SEM)

Scanning electron microscopic (Joel- LV-5600, USA, with magnification of 250x) photographs were obtained to identify and confirm crystals nature and morphological characters of the crystals.

Solubility studies of crystals

The solubility of all Tenoxicam crystals in water and pH 7.2 phosphate buffer was determined by taking excess quantity of crystals and adding to screw- capped 50 ml glass vials filled with water and pH 7.2 phosphate buffer. The vials were shaken for 24 hours on mechanical shaker. The solution was filtered through Whatmann filter paper No.1 and the drug concentration was determined spectrophotometrically at 375 nm.

Dissolution studies of crystals

The dissolution of Tenoxicam commercialized sample, recrystallized sample and spray dried crystals was determined by using USP dissolution apparatus XXIV-Type II (Electro Lab, Mumbai). Dissolution medium (900ml) consisted of pH 7.2 Phosphate buffer and 10 ml of dissolution medium was withdrawn at every 10 min interval for 1 h. The amount of dissolved drug was determined using UV spectrophotometric method (UV 1601 A Shimadzu, Japan) at 375 nm.

Determination of the physical stability

To determine the physical stability of spray dried crystals, a stability study of prepared crystals was carried out at 40°C and 60% relative humidity for 6 months according to the ICH guidelines. The prepared crystals were packed in high density polyethylene (HDPE) container and placed in stability chamber. The samples were withdrawn at the interval of 0, 1, 3 and 6 months and evaluated for appearance, characterization by FT-IR and dissolution release and compared with initial results.

RESULT AND DISCUSSION

The prepared microparticles were collected and were found to be free-flowing and white to off white in color. The percentage yield of spray dried crystals was found to be in the range of 82-88 %. This small yield could be increased by addition of solid substance or in large scale production (14). Drug content for the microparticles was found to be in the range of 98 %±0.13 (Table-3).

Recrystallization of Tenoxicam was done to find out the changes in crystal lattice, being induced by solvents that can influence the physicochemical properties of the substance. Hence the mechanical, micromeritic and dissolution properties of spherical crystals were compared with commercial sample and recrystallized sample. Recrystallization of Tenoxicam was carried out using same solvent composition as was used for spray dried technique.

The DSC thermograms showed a sharp endothermic peak for all the Tenoxicam crystals. This one step melt might be due to only one crystal form (Triclinic) of the Tenoxicam formed during the crystallization process, thus indicating that Tenoxicam did not undergo any crystal modification. The temperature range of the endothermic peak of all the Tenoxicam crystals lies in the range of 207°C to 214°C (Fig. 1). In DSC curve, commercial sample of Tenoxicam had a sharp endothermic peak at 214.8°C with enthalpy of 167.56 J/g that corresponded to the melting point of Tenoxicam. Melting points show slight variation as the nature of the crystals might have been affected by the solvent. The melting endotherm for agglomerated Tenoxicam was 207°C with decreased enthalpy of (156.65 J/g) indicating decreased crystallinity of Tenoxicam in microparticles.

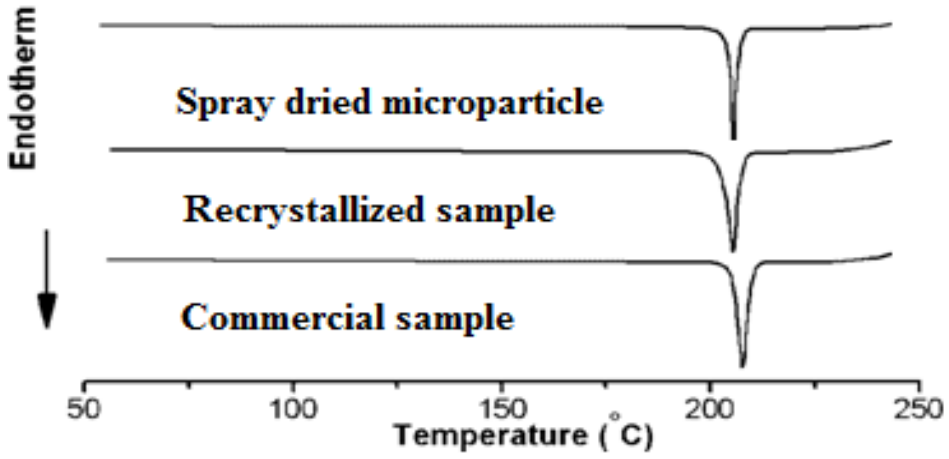

Fig. 1 DSC Spectrum of pure drug, recrystallized sample and spray dried crystals

The FTIR spectra of pure Tenoxicam, recrystallized crystals and spray dried microparticles are shown in Fig 2. FTIR spectroscopy has been successfully used for exploring the differences in molecular conformations, crystal packing and hydrogen bonding arrangements for different

solid-state forms of an organic compound. Spectral variations originate due to alteration in bonds that exhibit characteristic vibrational frequencies, leading to frequency shifts and splitting in absorption peaks. Infrared spectra of commercial Tenoxicam, recrystallized sample, spherical agglomerates showed characteristic peaks at 3447 cm-1, which is assigned for the O-H stretching vibration and two bands at 3155 and 3090 cm-1, which are due to the N-H stretching and aromatic C-H vibrations. In addition, a strong band was observed at 1636 cm-1, which was attributed to the amide carbonyl stretching band (C=O) as showed in (Fig. 2). Specific changes in IR spectra are not very clear and could be due to variations in the resonance structure, rotation of a part of a molecule on certain bonds. Alteration could be due to minor distortion of bond angles, or even a result of the presence of solvents of crystallization.

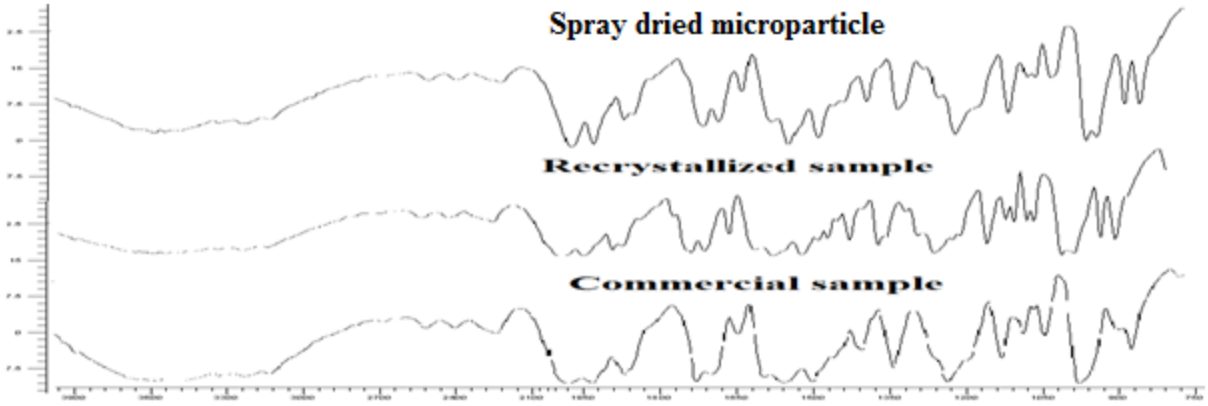

Fig. 2 FT-IR Spectrum of pure drug, recrystallized sample and spray dried crystals

X- Ray diffraction was used to analyze potential changes in the inner structure of Tenoxicam nanocrystals during the formulation of the spray dried microparticles. The extent of such changes depends on the chemical nature and physical hardness of the active ingredient. The powders X-ray dif-fraction patterns of the pure drug, recrystallized and spray dried microparticles are shown in Figure 3. The results of the DSC were further conformed by X-ray diffraction studies (Figure 3). The characteristic peak of the Tenoxicam appeared in the 2ϑ range of 10–50^{o}, The X-Ray diffraction pattern for Tenoxicam and spray dried microparticles are presented in Fig.3 and showed marked crystallinity as evident from the sharp peaks at 2θ angles. The degree of crystallinity is seen to be decreased and it depends on the processing method. The XRPD of spray dried microparticles shows further decrease in degree of crystallinity as evident from the decreased in intensity peaks. The reason for this could be that spray drying is an energy intensive process where solution passes from state of relative unsaturation to super saturation in a fraction of seconds. Further rapid evaporation of solvent from the supersaturated atomized droplets of the solution seemingly interferes with the crystal building process leading to amorphization of the drug. These results could explain the observed enhancement of solubility and rapid dissolution of Tenoxicam in prepared microparticles.

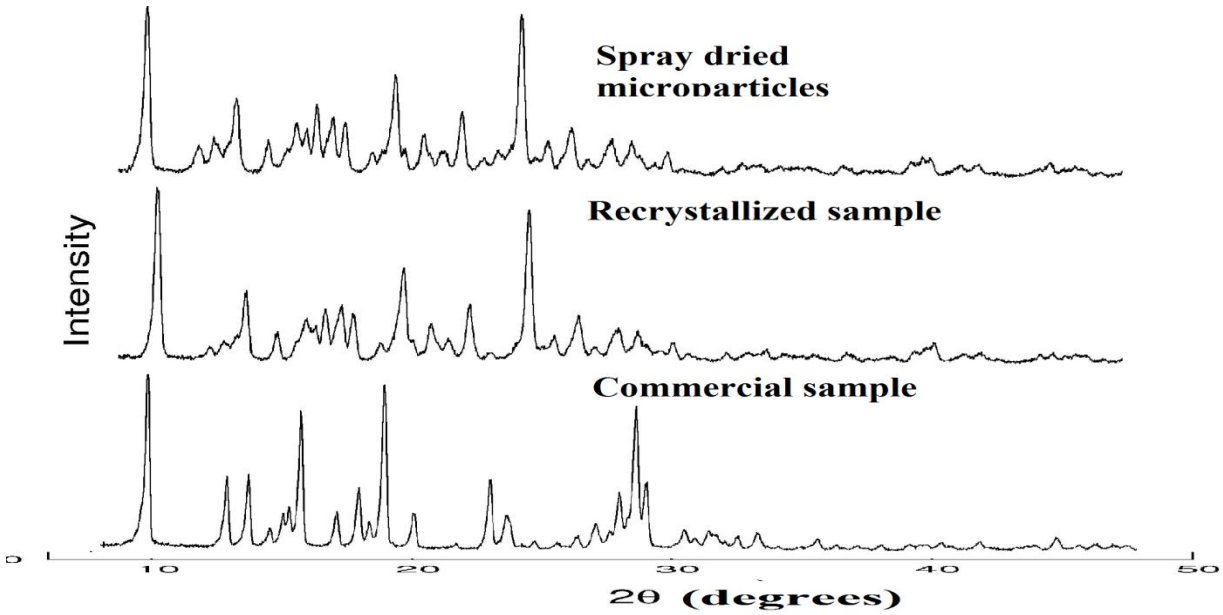

Fig 3 X- Ray diffractogram of pure drug, recrystallized sample and spray dried crystals

The SEM image of the pure drug, recrystallized crystals and spray dried crystals are shown in Fig. 4. The Tenoxicam crystals in the recrystallized samples were broken into much smaller ones and irregular size (11-24 µm) and the shape of prepared spray dried crystals are uniform and spherical in shape with small in size (5-13 µm) (Table-3).The spherical shape of spray dried microparticles does not lead to cake formation during storage because of less point of contact thereby increasing the stability of the spray dried microparticles formulation, which is an advantage over other shapes. This could be therefore, indicate that Tenoxicam particle size has been reduced, which also accelerates solubility and dissolution.

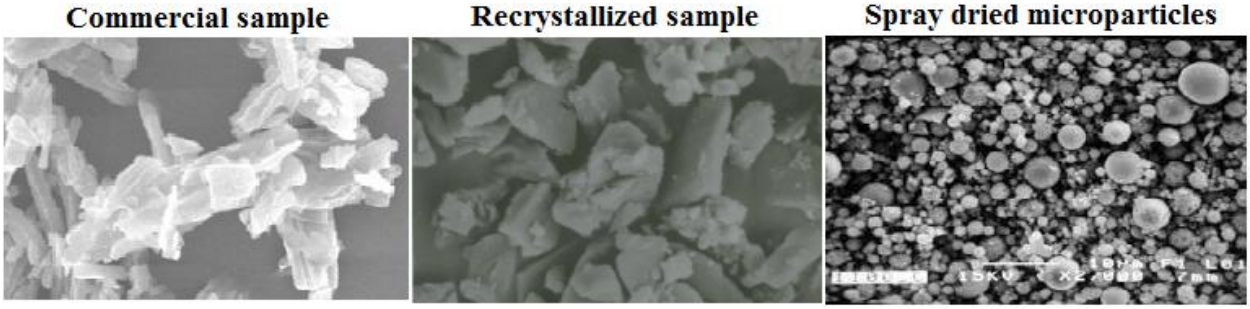

Fig 4 SEM of pure drug, recrystallized sample and spray dried crystals

Increase in the solubility of Tenoxicam from spray dried microparticles (0.230 mg/mL) was found to be one and half fold times higher than the solubility of the pure drug (0.092 µg/mL), suggesting the presence of less crystallinity form of Tenoxicam in the spray dried microparticles, indicating super-saturation obtained from the prepared crystals. Increase in the solubility of Tenoxicam from the recrystallized crystals was 0.113 mg/mL when compare to pure drug. This

could be due to the reduction in crystallinity or wetting effect of the prepared crystals. The solubility results for the different crystals are shown in Table 1. The higher solubility of Tenoxicam from spray dried microparticles may be due to the increased surface area, wettability and reduction in crystallinity in prepared spray dried crystals.

Table 1: Solubility, Percentage yield, Drug content and Particle size of prepared crystals

Formulations code	Solubility of Tenoxicam (mg/ ml) SD±3	Percentage yield%	Drug content SD ±3	Particle size determination (µm) SD±3
Pure drug	0.092	--	--	--
Recrystallized crystals	0.113	97-99	98.47±0.02	11-24
Spray dried crystals	0.230	82-88	98.24±0.13	5-13

The dissolution of pure Tenoxicam, recrystallized crystals and spray dried microparticles in pH 7.2 phosphate buffer shown in Fig. 5, the dissolution profiles were plotted as the % release from the prepared spray dried microparticles, recrystallized crystals and pure Tenoxicam versus time in minute. The rate of dissolution of pure Tenoxicam was slow compared with Tenoxicam from its recrystallized crystals and spray dried microparticles in 60 min. The % release from sprays dried microparticles showed more release compared to other drug samples. There was a significant difference in the drug release between the spray dried microparticles and recrystallized crystals. The increase in dissolution from the spray dried microparticles and recrystallized crystals were probably due to the wetting and reduction in crystallinity of drug, thus leading to a higher dissolution rate then pure Tenoxicam. The large surface area of the resulting spray dried Microparticles should result in an enhanced dissolution rate and thereby improve the bioavailability.

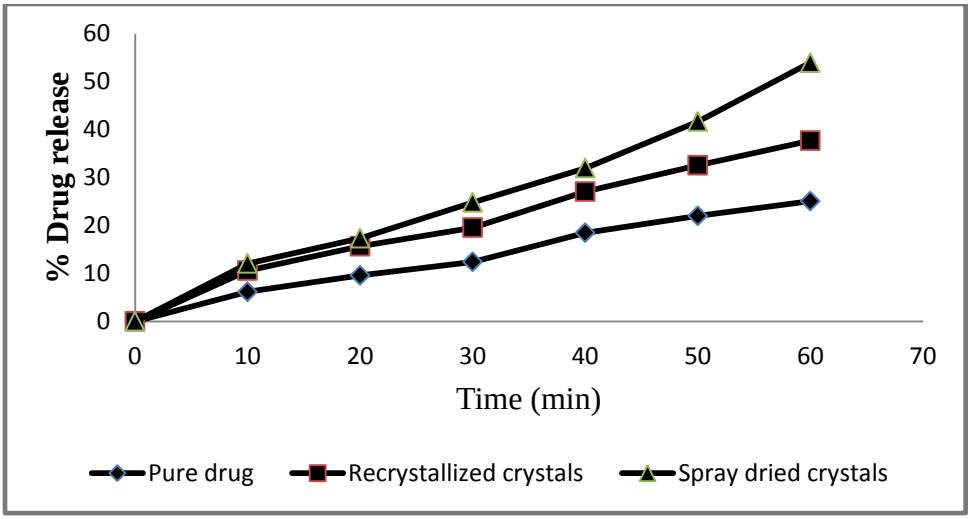

Fig 6 Dissolution release of pure drug, recrystallized crystals and microparticles

The best way to guarantee stability is by maintaining their physical state and molecular structure. The results of the stability study of prepared spray dried crystals of Tenoxicam stored at 40 ^{0}C and 75% relative humidity for 6 month. The influence of physical stability on the prepared crystals was investigated. Prepared microparticles of Tenoxicam were stable and complied with all the properties when compared to initial results of prepared microparticles of Tenoxicam.

CONCLUSION

In this present study, an increased solubility and dissolution rate of Tenoxicam were achieved by preparing crystals by spray drying technique using chloroform and water as solvents system. DSC, FT-IR and XRD studies showed that there is no change in the crystal structure of Tenoxicam during the spray drying process and showed that spray dried microparticles exhibited decreased in crystallinity. The solubility and dissolution of the spray dried microparticles was improved significantly compared with its recrystallized crystals and commercialized sample of Tenoxicam. The Tenoxicam spray dried microparticles showed highest % of drug release and solubility compare to other crystals of Tenoxicam. Stability results showed that prepared spray dried microparticles stable for 6 month as per ICH guidelines. Hence, , from the above result it can be concluded that spray dried microparticles of Tenoxicam is a useful technique to improve the solubility and dissolution of poorly water soluble drug like Tenoxicam.

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REFFRENCEES

1. Larrucea E, Arellano A, Santoyo S, Ygartua P. Study of the Complexation Behavior of Tenoxicam with Cyclodextrins in Solution: Improved Solubility and Percutaneous Permeability. Drug Dev Ind Pharm 2002; 28(3): 245-252.

2. Aigner Z, Kezsmarki A, Kata M, Novak C, Istvan E. Investigation of tenoxicam and γ cyclodextrin binary and ternary complexes. J. Incl. Phenom. Macrocycl. Chem 2002; 42: 227-233.

3. Kurkov VS. Ukhatskaya VE, Loftsson T. Drug/cyclodextrin: beyond inclusion complexation. J Incl Phenom Macrocycl Chem 2010; 69: (3-4), 297-301;

4. Kapsi SG, Ayres JW. Processing factors in development of solid solution formation of celecoxib for enhancement of drug dissolution and bioavailability. Int. J. Pharm 2001; 229: 193-203.

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

6. Juppo AM, Boissier C, Khoo C. Evaluation of solid dispersion particles prepared with SEDS. Int. J. Pharm 2003; 250: 385-401.

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

8. Sekiguchi K, Obi N. Studies on absorption of eutectic mixture. I. A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. Chem. Pharm. Bull 1961; 9: 866-872.

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

10. Maury M, Murphy K, Kumar S, Shi L, Lee G. Effects of process variables on the powder yield of spray-dried trehalose on a laboratory spray-dryer. Eur. J. Pharm. Biopharm 2005; 59: 565-573.

11. Amal AE, Ebtessam AE. Dissolution of ibuprofen from spray dried and spray cooled particles. Pak. j. pharm. Sci 2010; 23(3): 284-290.

12. Maa YF, Nguyen PA, Sit K, Hsu CC. Spray drying performance of bench-top spray dryer for protein aerosol powder preparation. Biotech. Bioeng 1998; 60: 301-309.

13. Mudit D, Kini AG, Kulkarni PK. Preparation and characterization of microparticles of piroxicam by spray drying and spray chilling methods. Res. Pharma. Sci 2010; 5(2): 89-97.

14. Mudit D, Kulkarni PK, Kini AG. Spherical agglomeration of Ketoprofen by solvent change method. Int. jour. Pharm. Research & review 2010; 4(3): 129-135.

15. Mudit D, Kulkarni PK. Preparation and Characterization of Spherical Agglomerates of Piroxicam. Lat. Am. J. Phar 2011; 30(7): 1383-8.

16. Mudit D, Kulkarni PK. Lyophilization monophase solution technique for improvement of the solubility and dissolution of piroxicam. Res Pharm Sci 2012; 7(1): 13–21.