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Research Article

PREPARATION AND CHARACTERIZATION OF SPRAY DRIED MICROPARTICLE AND CHILLED SPRAY DRIED PARTICLE OF KETOPROFEN BY SPRAY DRYING METHOD

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ABSTRACT

Ketoprofen, an anti-inflammatory drug, exhibits poor water solubility and flow properties, poor dissolution and poor wetting. Consequently, the aim of this study was to improve the dissolution of ketoprofen. Microparticles containing ketoprofen were produced by spray drying and spray chilling technology to enhance dissolution rate. The prepared formulations were evaluated for in vitro dissolution and solubility. The produced drug particles were characterized by scanning electron microscopy (SEM), differential scanning calorimeter (DSC), x-ray diffraction (XRD) and Fourier transform infrared spectroscopy (FT-IR). Dissolution profile of the spray dried micropartical was compared with chilled spray micropartical, pure sample and recrystallized sample. Spray dried micropartical exhibited decreased crystallinity, but for spray chilled particles there was evidence of polymorphic changes in the drug and improved micromeritic properties. The dissolution of the Spray dried micropartical was improved compared with spray chilling micropartical, recrystallized and pure sample. Consequently, it is believed that spray drying of Ketoprofen is a useful tool to improve wettability, solubility and hence the dissolution behavior of poorly water soluble drugs, in contrast to spray chilling technique.

Key words: Spray drying, spray chilling, ketoprofen, dissolution,crystallinity.

INTRODUCTION

Formulation and manufacture of solid oral dosage forms, and tablets in particular, have undergone rapid change and development over the last several decades. One of the most revolutionary technologies is that of direct compression. Direct compression is economical, facilitates processing without the need of moisture, heat and involves small number of processing steps. In direct tabletting method, it is necessary to increase flowability and compressibility of the bulk powder in order to retain a steady supply of powder mixture to the tabletting machine and sufficient mechanical strength of the compacted tablets. In addition to increasing efficiency of the manufacturing process it is also important to increase bioavailability of the drug by improving the solubility of the bulk drug powder. Spray dried [1] micropartical is one of such techniques to improve the micromeritic properties and dissolution of drug.

Consequently, many hydrophobic drugs show erratic and incomplete absorption from the gastrointestinal tract of animals and humans, which may lead to therapeutic failure. Thus, one of the major challenges to drug development today is poor solubility, as an estimated 40% of all newly developed drugs are poorly soluble or insoluble in water [2, 3, 5, 6]. As a result, much research has been conducted into methods of improving drug solubility and dissolution rates to increase the oral bioavailability of hydrophobic drugs. Various techniques such as melt adsorption, supercritical fluid processes, using different composion of solvents to prepared the micropartical to improve the dissolution rate of poorly water soluble drugs. and amorphous state to improve their dissolution[1,8,20]. Manipulation of the solid state by decreasing crystallinity of drug substances through formation of solid dispersion is one of the methods used for promoting drug dissolution [6, 9]. The solid dispersion technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly water soluble active pharmaceutical ingredients because it is simple, economic, and advantageous technique. The concept of solid dispersion covers a wide range of systems. 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 wettability, 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 [3, 19]. Microwaves irradiation was used recently for the preparation of solvent-free solid dispersions and for enhancement of release of the poorly soluble drug, Spray drying is one such technique of preparing solid dispersion and is widely used as an alternative to milling to reduce particle size. Spray chilling or spray congealing is another form of solid dispersion where the melted mass is atomized into droplets, which quickly solidify in a cool air [7]. The advantage in spray chilling is that no additional manufacturing step is needed to pulverise the solid dispersion. In pharmacy, spray chilling has been used to prepare sustained-release formulations, to improve stability [14, 18] and to mask the unpleasant taste [22]. The technique also has the advantages of being free from organic solvents compared to spray drying. The method has also been used by the food industry, for example, to encapsulate vitamins and minerals [4]. ketoprofen was chosen as a hydrophobic drug. Ketoprofen 2- (benzoyl-3-phenyl) propionic acid is one of the safest and most potent non-steroidal anti-inflammatory drugs being widely used in the market. The drug used to treat rheumatoid arthritis, osteoarthritis, and mild to moderate pain. It has low aqueous solubility and hence poor dissolution. The present work was conducted to improve the wetability , solubility and hence the dissolution of ketoprofen using spray drying and spray chilling techniques.

MATERIALS AND METHODS

Materials

Ketoprofen was obtained as a gift sample from Micro labs, Bangalore, India. Chloroform was procured from Merck, Mumbai, India. All chemicals and buffers used were of analytical grade.

Preparation of microparticles

Microparticles prepared by spray drying

Spray dried particles consisted of Ketoprofen only was prepared by dissolving the drug in the mixture of iso propyl alcohol/water (45:55 (v/v) ratio) solution. The 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 kg/cm^2 , Aspirator level at 35%, inlet temperature at 84 ±2°C and outlet temperature at 38 ±1°C. The formed microparticles were separated using cyclone separator, collected and stored in a desiccator at ambient temperature until ready to be used.

Microparticles prepared by spray chilling

Spray chilled particles were prepared by melting the drug at 92°C. The melt was kept at 92°C and atomized with a pneumatic nozzle (Mini Spray Dryer LSD -48; Jay instrument & systems Pvt. Ltd. Mumbai). Air kept at 20°C. The inner diameter of the pneumatic nozzle was o.1mm, the capillary length was 5mm and the pressure

was 1 Kg/cm^2. The particles were collected using cyclone separator and stored in a desiccator.

Recrytallized microparticals prepared

Changes in crystal lattice, being induced by solvents, 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 ketoprofen was carried out using same solvent composition as was used for spray drying. ketoprofen was dissolved in 45 ml of acetone and 55 ml of iso propyl alcohol with occasional stirring for 30 min . The crystals of ketoprofen were collected by filtration and were dried at 45^{0}C.

Evaluation of microparticles

Determination of percentage yield and Drug content

The percentage yield of each formulations was determined according to the total recoverable final weight of microparticles (prepared by spray drying and spray chilling) and the total original weight of ketoprofen.

Microparticals[7] (50 mg) were triturated with 10 ml of water. Allowed to stand for 10 min with occasional swirling and methanol was added to produce 100 ml. After suitable dilution, measured at 260 nm. Drug content was determined from standard plot.

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). Samples were dispersed in KBr powder and the pellets were made by applying 5 ton pressure. FTIR spectra were obtained by powder diffuse reflectance on FTIR spectrophotometer.

X-ray analysis

X-Ray powder diffraction patterns were obtained at room temperature using a Philips X' Pert MPD diffractometer, with Cu as anode material and graphite monochromator, operated at a voltage of 40 mA, 45 kV.The process parameters used were set as scan step size of 0.0170 (2θ).

Scanning electron microscopy (SEM)

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

Micromeritic properties

Particle size of recrystallized sample, pure samples and spray chilling particle were determined by microscopic method using calibrated ocular micrometer and size of microparticles (prepared by spray drying) were determined using Malvern Mastersizer 2000 version 5.1 (Malvern, UK.).

The samples of spray dried microparticles were dispersed in 1:20 with methanol and measured at temperature of 37°C. Apparent particle densities of microparticles (prepared by spray drying and spray chilling) were measured using a Pycnometer. Carr's index was determined from powder volumes at the initial stage and after 1250 tappings to constant volume (Electolab, Mumbai). The angle of repose of microparticles (prepared by spray drying and spray chilling) and commercial crystals was measured by fixed funnel method.

Mechanical Property

Mechanical Propertie[8-10] like tensile strength of microparticles (prepared by spray drying and spray chilling) were determined by compressing 500 mg of microparticals using hydraulic press at different ton/cm^2 for 1 min. The compacts stored in desiccator for overnight to allow elastic recovery. The thickness and diameter were measured for each compact. The hardness of each compact was then measured using Pfizer hardness tester. The tensile strength (σ) of the compact (ton/cm^2) was calculated using following equation.

$$\sigma = 2F/\pi Dt$$

Where, F, D and t are hardness (ton), compact diameter (cm) and thickness (cm), respectively.

Solubility studies

The solubility[12] of ketoprofen microparticles (prepared by spray drying and spray chilling) in water was determined by taking excess quantity of microparticals in 50 ml to screw- capped glass vials filled with water. The vials were shaken for two hours on mechanical shaker. The solution was filtered through Whatmann filter paper No.1 and drug concentration was determined at 260 nm.

Dissolution studies of microparticals

The dissolution[7] of ketoprofen pure sample, microparticles (prepared by spray drying and spray chilling) and recrystallized sample was determined by using USP dissolution apparatus XXIV-Type II (Electro Lab, Mumbai). Dissolution medium was 900 ml 7.4 Phosphate buffer. The amount of dissolved drug was determined using UV spectrophotometric method (UV 1601 A Shimadzu, Japan) at 260 nm.

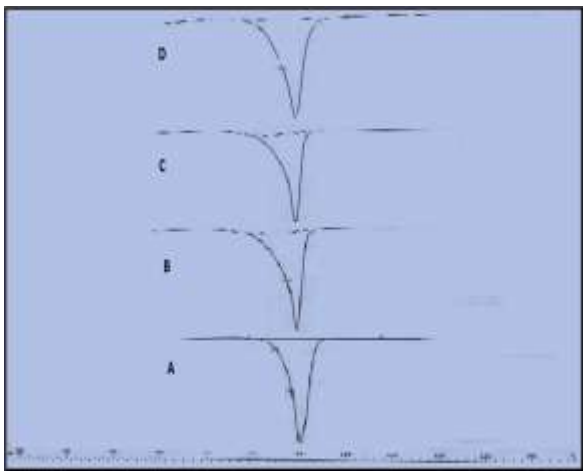


Figure -1: Shown (DSC) of A -Pure Drug, B -Recrystalized Drug, C-Chilled Drug Particle , D-Spray Dried Microparticle

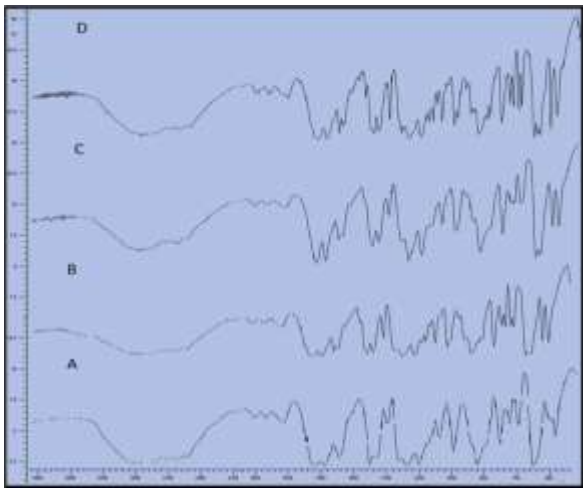


Figure -2: Shown (FT-IR) of A -Pure Drug, B -Recrystalized Drug, C-Chilled Drug Particle , D-Spray Dried Microparticle

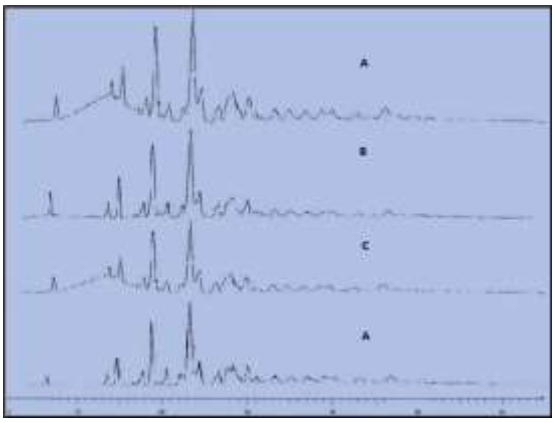
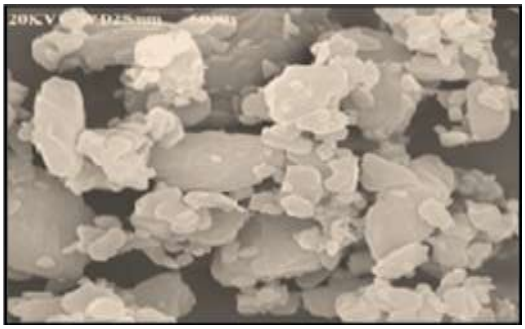
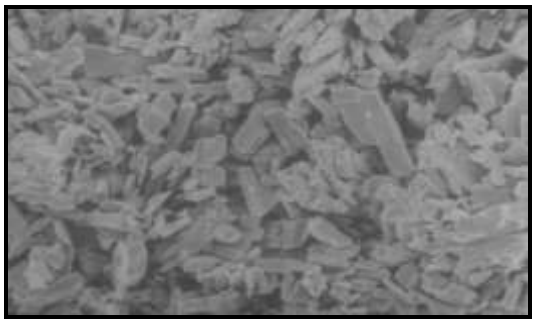


Figure -3: Shown (XRD) Figure of A -Pure Drug, B -Recrystalized Drug, C-Chilled Drug Particle , D-Spray Dried Microparticle

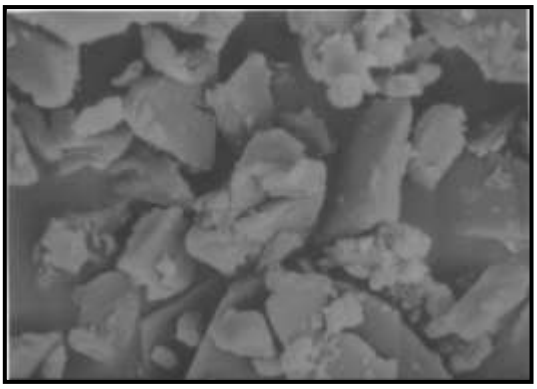


A

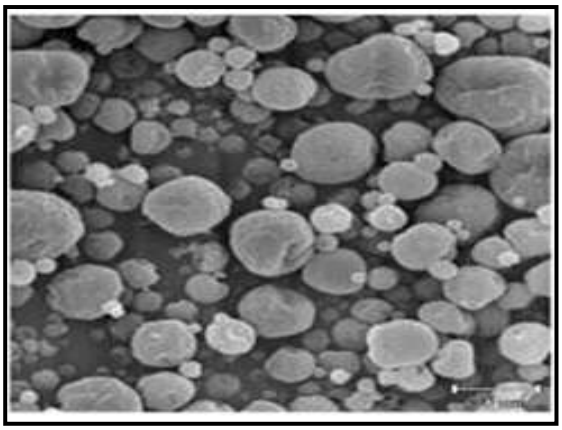


B

Figure -4: Shown (SEM) of A -Pure Drug, B -Recrystalized Drug, C-Chilled Drug Particle , D-Spray Dried Microparticle



C



D

Figure -5: Shown Tenstile Strength of P.S-Pure Drug Sample, C.S-Chilled Partical Samlpe, Sd.S-Spray Dried Sample

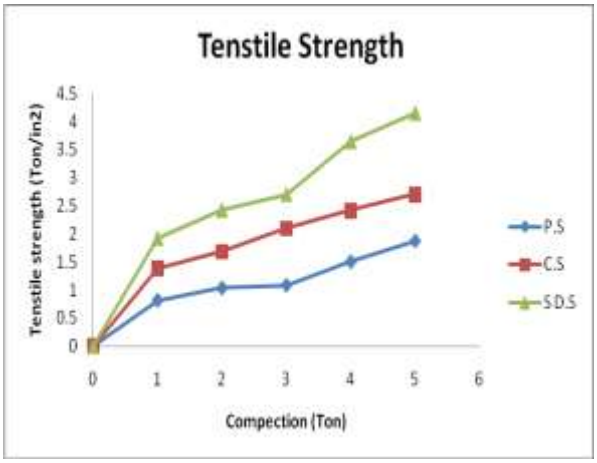


Figure -5: Shown Tenstile Strength Fo P.S-Pure Drug Sample, C.S-Chilled Partical Samlpe, Sd.S-Spray Dried Sample

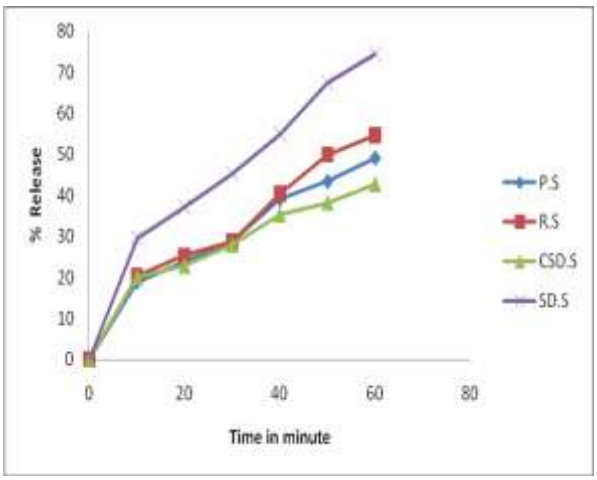


Figure -6: Shown Dissolution: of P.S-Pure Drug Sample, Recrystallized Sample, Csd.S-Chilled Spray Dried Partical Samlpe, Sd.S-Spray Dried Microparticle Sample

Table -1: Shown Different Cell Parameters Obtained For Ketoprofen Particle Crystals From Xrd Data.

	A	B	C	A	β	γ	Unit cell volume
Pure sample	12.0789	12.271	16.225	94.31	71.67	143.4	1223.21
Recrystallized Sample	6.8862	7.4854	15.915	91.75	64.04	82.19	875.38
Chilled spray dried particle	6.7732	9.925	15.481	92.74	73.06	78,35	823.09
Spray dried microparticle	6.8634	10.890	14.494	96.27	83.42	54.97	725.79

a, b, c – three sides of cell expressed in A^0.
α, β, γ - three angles of the cell expressed in degrees

Table -2: Shown Micrometrics Property Of Pure Drug Sample, Recrystallized Sample, And Chilled Spray Dried Partical Samlpe, Spray Dried Microparticle Sample

Properties	Pure sample	Recrystallized Sample	Chilled spray dried particle	Spray dried particle
Particle size (μm)	3-6	8-14	25-43	7-11
Flow rate (gm/Sec)	No flow	No flow	No flow	2.84
Angle of repose	41.01	32.31	29.48	28.07
Tapped density (gm/ml)	0.9302±0.006	0.5753±0.043	0.5380±0.052	0.2159±0.05
Bulk density(gm/ml)	0.6692±0.003	0.4178±0.06	0.3839±0.002	0.1892±0.004
Carr's index	28.05	27.37	23.81	12.37
Porosity (%)	0.3844	0.6952	0.6852	0.9086

RESULTS AND DISCUSSION

The solvents chosen for the spray drying were Iso propyl alcohol (IPA) and Acetone. These both the solvent were miscible in any proportion with each other.

The spray dried formulations collected and powders were free-flowing and white. The percentage yield of spray dried ketoprofen was found to be 67%. Drug content for the spray dried formulation was found to be 98±0.002. The percentage yield for spray chilled ketoprofen particles was found to be 83%. Such yields are higher compared to spray dried products. Drug content for spray chilled ketoprofen partical was found to be 96±0.001.

The DSC thermograms (fig. 1) shows a sharp endothermic peak for all the ketoprofen crystals. This one step melt might be due to only one crystal form (Triclinic) of the ketoprofen formed during the crystallization process, thus indicating that ketoprofen did not under go any crystal modification. The temperature range of the endothermic peak of all the ketoprofen crystals lies in the range of 93^0 to 96^0. Melting points show slight variation as the nature of the crystals might have been affected by the solvent. The melting endotherm for spray dried micropartical of ketoprofen was 96.53° with decreased enthalpy of (162.17 J/g) indicating decreased crystallinity. The DSC thermograms of spray chilled ketoprofen showed melting endotherm at the characteristic endothermic peak for the drug at 93.39°C with enthalpy of 127.54 J/g. this may assume of the formation of another polymorphic structure of ketoprofen during the process of spray chilling.

Pure sample, Recrystallized sample and spray dried micropartical of the ketoprofen samples have exhibited general characteristic peaks at 2983-2930 cm^{-1} (Aromatic C-H stretch carboxylic acid O-H stretch), 1695-1649 cm^{-1} (C=O stretch), 1595 cm^{-1} (Aromatic C=C stretch), 1437 cm^{-1} (CH-CH_3 deformation), 2891 cm^{-1} ((C-H) stretch plus O-H deformation), 1690 cm^{-1} (Carboxylic O-H out of plane deformation), 860-640 cm^{-1} (C-H out of plane deformation for substituted aromatic) (fig. 2).In case of chilled spray dried particle showed some different characteristic peak for FR-IR could be due variations in the resonance structure, rotation of a part of a molecule or certain bonds. Alteration could be due to minor distortion of bond angles, formation of new polymorph due to heating or even a result of the presence of a solvent of spray drying.

The DSC scans and FT-IR studies for spray chilled ketoprofen formulations support the idea of formation of new polymorph.

All the samples showed similar peak positions (2θ) in X-ray diffraction, formation of different polymorphs of ketoprofen was ruled out. However relative intensities of XRD peaks were modified (fig. 3). This could be attributed to the markedly different crystal habits of the samples (Table 1). Therefore the relative abundance of the planes exposed to the X-ray source would have been altered, producing the variations in the relative intensities of the peak or may be due to differences in particle sizes.

Particle of pure sample are of the smallest size (3-6 μm) and they have irregular shapes. Recrystallization produced crystals with intermediate size (8-14 μm). The particle formed by spray chilled are large size compare to pure, recrystallized and spray dried micropartical with size of (25-43) μm. Microparticals formed by spray drying, The resultant Micropartical had a smooth surface (fig's. 4). Microparticals obtained were spherical in shape with small size (7-11) μm. The Micrometrics properties of Pure Sample, Recrystallized Sample, Chilled spray dried particle and spray dried micropartical of ketoprofen shown below: (Table 2).

Spray dried microparticals exhibited superior compressibility characteristics compared to pure sample and chilled spray dried particle (fig. 5). It could be due to the fact that during the process of compression fresh surfaces are formed by fracturing crystals. Surface freshly prepared by fracture enhanced the plastic inter particle bonding, resulting in a lower compression force required for compressing the agglomerates under plastic deformation compared to that of single crystal.

The solubility of ketoprofen spray dried microparticles in water was found (0.837to be greater than the (0.172) pure sample but In the case of chilled spray dried particle, the solubility in water (0.183) was not found significance compare to spray dried micropartical.

The dissolution profiles of ketoprofen (fig. 6) exhibited improved dissolution behaviour for spray dried micropartical than pure sample, recrystallized sample and chilled spray dried partical. The reason for this faster dissolution could be linked to the better wettability of the micropartical. The amount of drug dissolved in 60 min greatly varied for spray dried micropartical.

The DSC and FT-IR studies for spray chilled Ketoprofen formulations give the idea of formation of new polymorph with less solubility characteristics compared to the spray dried micropartical. Therefore, based on these results together with the assumption of formation of melt-solidified bonds could explain the low dissolution from particles prepared by spray chilling technique. Hence spray chilling is not a suitable technique to improve dissolution of ketoprofen.

CONCLUSION

Spray dried micropartical of Ketoprofen were prepared by spray drying techniqueand chilled spray dried partical to improve the dissolution rate. Spray dried micropartical exhibited decreased crystallinity and improved micromeritic properties. DSC and XRD studies showed that there is no change in the crystal structure of ketoprofen during the spray drying process i.e., polymorphism has not occurred. The dissolution of the spray dried micropartical was improved compared with pure sample, Recrystallized sample and chilled spray dried partical. spray chilled partical of ketoprofen reduced the drug release compared to the spray dried micro particle may be due to the formation of a new polymorph as indicated from the FTIR and DSC data or the formation of new bonds.

Hence this spray drying technique can be used for formulation of tablets of ketoprofen by direct compression with directly compressible tablet excipients.

REFERENCES

1. Chowdary KPR and Hymavathi. Enhancement of dissolution rate of meloxicam. *Ind. J. Pharm Sci* R (2001).63(2): 150-154.
2. Corrigan DO, Corrigan OI and Healy AM Predicting the physical state of spray dried composites:salbutamol sulphate/lactose and salbutamol sulphate/polyethylene glycol co-spray dried systems. *Int. J. Pharm*., (2004). 273: 171-182.
3. Craig DQM The mechanisms of drug release from solid dispersions in water-soluble polymers. *Int. J. Pharm*., (2002). 231: 131-144.
4. Gibbs BF, Kermasha S, Alli I and Mulligan CN . Encapsulation in the food industry: A review. *Int. J. Food Sci. Nutr.*,(1999) 50: 213-224.
5. Kamble R, Maheshwari M, Paradkar AR and Kadam S .Melt solidification technique: Incorporation of higher wax content in ibuprofen beads. *AAPS PharmSciTech*., (2004) 5(4): Article 6.
6. Kapsi SG and Ayres JW . Processing factors in development of solid solution formulation of itraconazole for enhancement of drug dissolution and bioavailability. *Int. J. Pharm*.,(2001) 229: 193-203.
7. Killeen MJ . The process of spray drying and spray congealing. *Pharm. Eng.,(1993)* 13: 56-64.
8. Paradkar AR, Pawar AP, Chordiya JK, Patil VB and Ketkar AR. Spherical crystallization of celecoxib. Drug Dev Ind Pharm,(2002) 28(10):1213-1220.
9. Chourasia MK, Vijaya R, Jain N, Jain SK, Jain S. and Jain NK., Preparation and characterization of Spherical crystal agglomerates for direct tabletting by spherical crystallization technique. Indian Drugs,(2004) 41(4):214-220.
10. Takeo Kuriki, and Kawashima.Y, Hirofumi Takeuchi, Tomoaki Hino, and Toshiyuki Niwa. Modification of tolbutamide by solvent change technique. III. Micromeritic properties, dissolution rate of tolbutamide spherical agglomerates prepared by QESD method and SC method. Chem Pharm Bull, (1990) 38(3):733-739.
11. Maa YF, Nguyen PA, Sit K and Hsu CC . Spray drying performance of bench-top spray dryer for protein aerosol powder preparation. *Biotech. Bioeng.(1998),* 60: 301-309.
12. Nocent M, Bertocchi L, Espitalier F, Baron M, Courraze G. Definition of a solvent system for spherical crystallization of salbutamol sulfate by quasi-emulsion diffusion (QESD) method. J Pharm Sci, (2004) 90(10):1620-1627.
13. Maury M, Murphy K, Kumar S, Shi L and Lee G (2005). 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.
14. Amal a. E and Ebtessam A E, Dissolution of ibuprofen from spray dried and spray chilled particles; Pak. J. Pharm. Sci., (2010) 23, no.3, pp.284-290.
15. Newa M, Bhandari KH, Li DX, Kwon TH, Kim JA, Yoo, BK, Woo JS, Lyoo WS, Yong CS and Choi HG . Preparation, characterization and in vivo evaluation of ibuprofen binary solid dispersions with poloxamer 188.(2007) *Int. J. Pharm*., 343: 443-450.
16. Newa M, Bhandari KH, Lee DX, Sung JH, Kim JA, Yoo BK, Woo JS, Choi HG and Yong CS . Enhanced dissolution of ibuprofen using solid dispersion with polyethylene glycol 20000. *Drug Development and Industrial Pharmacy*.(2008) 34: 1013-1021.
17. Paradkar AR, Maheshwari M, Ketkar AR and Chauhan B . Preparation and evaluation of ibuprofen beads by melt solidification technique. *Int. J. Pharm*.,(2003) 255: 33-42.
18. Schwendeman SP, Tobio M, Joworowicz M, Alonso MJ and Langer R . New strategies for the microencapsulation of tetanus vaccine. *J. Microencapsulation*.(1998) 15: 299-318.
19. Serajuddin ATM . Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. *J. Pharm. Sci.*,(1999) 88: 1058-1066.
20. Vasconcelos T, Sarmento B and Costa P . Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. *Drug Discov. Today*,(2007) 12: 1068-1075.
21. Yajima T, Umeki N and Itai S . Optimum spray congealing conditions for masking the bitter taste of chlarithromycin in wax matrix. *Chem. Pharm. Bull.*,(1999) 47: 220-225.