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Original article

ENHANCING THE DISSOLUTION OF POLYMORPHS I AND II OF MEFENAMIC ACID BY SPRAY DRYING

Mudit DIXIT[1]*, Ashwini G KINI[1], Parthasarthi K KULKARNI[1]

J.S.S University, J.S.S College of Pharmacy, Department of Pharmaceutics, Mysore 570015, Karnataka, INDIA

Abstract

Mefenamic acid, 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 both the form of mefenamic acid (1 & II). Microspheres containing mefenamic acid (Form 1 & II) were produced by spray drying using isopropyl alcohol and water in the ratio of 40:60 (v/v) as solvent system. The prepared formulations were evaluated for in vitro dissolution and solubility. The prepared 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 microspheres was compared with pure sample and recrystallized sample. Spray dried microspheres of both form of mefenamic acid exhibited decreased crystallinity and improved micromeritic & mechanical properties. The dissolution of the spray dried microspheres (Form 1 & II) were improved compared with recrystallized and pure sample of mefenamic acid. Consequently, it was believed that spray drying of mefenamic acid is a useful tool to improve dissolution, Hence this spray drying technique can be used for formulation of tablets of mefenamic acid by direct compression with directly compressible tablet excipients.

Key words: *Spray drying, Mefenamic acid, Form 1 & II, Solubility dissolution,Crystallinity.*

Püskürtülerek Kurutma ile Mefenamik Asit'in I ve II Polimorflarının Disolüsyonunun Artırılması

Antienflamatuvar bir ilaç olan mefenamik asit, suda düşük çözünürlük ve akış özelliği ile düşük disolüsyon ve ıslanma özellikleri gösterir. Buna dayanarak, bu çalışmada mefenamik asit'in her iki formunun da (Form I & II) disolüsyonunun artırılması amaçlanmıştır. Mefenamik asit (Form I & II) içeren mikroküreler, solvan sistemi olarak 40:60 (v/v) oranında izopropil alkol ve su kullanılarak püskürterek kurutma yöntemiyle hazırlanmıştır. Hazırlanan formülasyonlar in vitro disolüsyon ve çözünürlük açısından değerlendirilmiştir. İlaç partiküllerinin karakterizasyonu taramalı electron mikroskobu (SEM), diferansiyel taramalı kolorimetre (DSC), X-ışını kırınımı (XRD) ve Fourier transform infrared spektroskopi (FTIR) yardımıyla yapılmıştır. Püskürtülerek kurutulmuş mikrokürelerin disolüsyon profili saf ve yeniden kristallenmiş örneklerin profilleriyle karşılaştırılmıştır. Mefenamik asit'in her iki formuyla hazırlanan püskürtülerek kurutulmuş mikrokürelerde kristallenme azalmış, mikromeritik ve mekanik özellikleri iyileşmiştir. Püskürtülerek kurutulan mikrokürelerin (Form I & II) disolüsyonu yeniden kristallenmiş ve saf mefenamik asit örneklerine kıyasla artmıştır. Sonuç olarak, mefenamik asit'in püskürtmeyle kurutulmasının, disolüsyonun artırılması için yararlı bir yaklaşım olduğu düşünülmektedir. Püskürterek kurutma tekniği, mefenamik asitin uygun eksipiyanlarla birlikte doğrudan basım yardımıyla tabletlerinin formülasyonu için kullanılabilir.

Anahtar kelimeler: *Püskürterek kurutma, Mefenamik asit, Form I & II, Çözünürlük, Disolüsyon, Kristallenme.*

***Correspondence:** E mail: muditdixit911@yahoo.com; Tel: +919035508450.

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 (1). 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 drying is one of such techniques to improve the micromeritic properties and dissolution of drug.

Polymorphs are solid crystalline phases of a drug compound, resulting from at least two different molecular arrangements of the compound in the solid state. The various physical properties of drugs showing polymorphism, for example, crystal habit, intermolecular interaction, particle density, thermodynamic activity, solubility, dissolution rate and chemical and physical stability, have been reported (2-6). The differences of physical properties may affect the reproducibility of the manufacturing process of dosage forms and their performance. In addition, the solubility can affect the drug absorption and therefore its bioavailability (7,8). The pharmaceutical applications of polymorphs have also been reviewed (9). Since polymorphs have different lattice energies, the more energetic ones seek to revert to the most stable or the latest energetic form. Hence, polymorphs can transform to other crystal forms during manufacturing processes, including grinding, kneading and tabletting (10-15) is also widely known that the storage conditions, such as temperature, humidity or pharmaceutical excipients, affect the stability of metastable crystal forms (15-19). It is therefore important to characterize the polymorph and clarify the physicochemical properties of bulk drugs during the manufacturing processes and storage period. Mefenamic acid is a non-steroidal anti-inflammatory drug and widely used as an antipyretic analgesic and anti rheumatic drug. It has been reported that mefenamic acid has two polymorphs, forms I and II, and that they showed different solubility and stability. Form II exhibited higher solubility than form I in several solvents (20,21). The dissolution profile of form II showed supersaturation accompanying the decrease down to the solubility of form I due to the transformation to form I. Conversely, form I transformed to form II at high temperature (142.5–150 ◦C) and this transformation followed the zero-order reaction mechanism (Polany-Winger equation) (22). The purpose of this study was to more precisely investigate the stability of forms I and II at high humidity and in water and ethanolic suspensions, assuming the effect of the addition of kneading solvents in the granulation process. The kinetic transformation of form II to form I using several solid-state reaction models was also discussed. 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(23-25). Mefenamic acid was chosen as a poorly water soluble drug and it has two polymorph (form 1& 2). Mefenamic acid N-2-3-xylylanthranilic 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 mefenamic acid (form 1 & II) using spray drying techniques.

MATERIALS AND METHODS

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

Mefenamic acid Form 1 preparation

Form I crystals were prepared by saturating 50 mL of acetone with an excess amount of the drug. The un-dissolved drug was filtered off and the saturated acetone solution was cooled slowly in an ice bath. This solution was left overnight, and the recrystallized crystals were filtered, washed with water and dried at room temperature.

Mefenamic acid Form II preparation

Form II crystals were prepared from dissolve the excess amount of drug dissolve in *N*, *N*-di-methylformamide. After the crystals were dissolved in this solvent, the hot solution was cooled to −40 ◦C. The solution was maintained at this temperature until most of the mefenamic acid was crystallized and then the crystals were filtered and dried at 70 ◦C. All other chemicals used were of analytical grade.

Preparation of Microspheres

Microspheres prepared by spray drying

Spray dried particles consisted of mefenamic acid was prepared by dissolving the 5 gm drug samples (commercial sample, form 1 & form 2 one by one) in the mixture of isopropyl alcohol/water (40:60 (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 115 ±2°C and outlet temperature at 45 ±1°C. The formed microspheres were separated using cyclone separator, collected and stored in a desiccator at ambient temperature for further use.

Preparation of recrytallized sample of mefenamic acid

Changes in crystal lattice, being induced by solvents, can influence the physicochemical properties of the substance. Hence the mechanical, micromeritic and dissolution properties of microspheres were compared with commercial sample and recrystallized sample. Recrystallization of mefenamic acid was carried out using same solvent composition as was used for spray drying mefenamic acid was dissolved in 40 ml of isopropyl alcohol and 60 ml of water with occasional stirring for 30 min . The crystals of mefenamic acid were collected by filtration and were dried at 45^{0}C.

Evaluation of Microspheres

Determination of percentage yield and drug content

The percentage yield of each formulation was determined according to the total recoverable final weight of microspheres and the total original weight of mefenamic acid.
Microspheres (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, samples were measured at 332 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 sizes of recrystallized sample, commercial samples, spay dried microspheres determined by microscopic method using calibrated ocular micrometer. Apparent particle densities of microspheres 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 microsphere and commercial crystals was measured by fixed funnel method.

Mechanical Property

Tensile strength

Tensile strength of microspheres was determined by compressing 500 mg of microspheres 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.

Heckle's equation

Mefenamic acid commercial sample and prepared samples were compressed at compaction pressure of 0.5, 1, 1.5, 2, 2.5 and 3 tons for 1 min using a hydraulic press. The densification behavior of powders was studied using Heckle's equation,

$$\ln (1/1\text{-}D) = KP + A$$

Where, D is the relative density of compressed powder bed at applied pressure P,
K is the slope of the straight liner portion of the Heckle plot and the reciprocal of K is the mean yield pressure (P_Y).

Solubility studies

The solubility of different mefenamic acid samples in water was determined by taking excess quantity of microspheres 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 332 nm.

Dissolution studies of microspheres

The dissolution of mefenamic acid commercial sample, microspheres of form 1 & II 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 332 nm.

Determination the physical stability

To determine the physical stability of microspheres samples were placed in a climate chamber of 20^0C and 45% relative humidity (RH). After 90 days, the % crystallinity of mefenamic acid in the samples was determined by means of differential scanning calorimetry (DSC).

RESULT AND DISCUSSION

The solvents chosen for the spray drying were Isopropyl alcohol (IPA) and water. These both solvents were miscible in any proportion with each other. The prepared forms of mefenamic acid were used for the preparation of microspheres by spray drying.

The spray dried microspheres formulations of mefenamic acid form 1 & II collected and powders were free-flowing. The percentage yield of spray dried mefenamic acid form-1 was found to be 63%. The percentage yield for spray dried microspheres of mefenamic acid form- II was found to be 68%. This small yield can be increase by adding of solid substance or in large scale production as it was small scale preparation. Drug content for the spray dried microspheres formulation of mefenamic acid form 1 & II was found to be 96±0.013 & 98±0.012 respectively.

The DSC thermogram (Figure 1) shows a sharp endothermic peak for all the mefenamic acid. This one step melt might be due to only one crystal form (Triclinic) of the mefenamic acid formed during the crystallization process, thus indicating that mefenamic acid did not undergo any crystal modification in case of both the forms of mefenamic acid (i.e. form I & II). The temperature range of the endothermic peak of all the mefenamic acid crystals lies in the range of $230\text{-}235^0$. Melting points show slight variation as the nature of the crystals might have been affected by the solvent. The mefenamic acid commercial sample melted at 235.79°C with enthalpy of 173.5 J/g. In case of recrystallized sample there is no much change as compare to commercial sample.DCS profiles of form I showed two endothermic peaks at 170 and 231 ◦C due to the transformation to form II and the melting of form II, respectively (22).Form II exhibited only an endothermic peak at 233 ◦C The melting endotherm for spray dried microspheres of mefenamic acid form I was 170 °C with decreased enthalpy of (129.34 J/g) indicating decrease crystallinity. The DSC thermograms of spray dried microspheres mefenamic acid form- II showed melting endotherm at the characteristic endothermic peak for the drug at 231°C with enthalpy of 156.37 J/g indicating decreased crystallinity but compare to form-1 is less. The decrease in crystallinity as follows: pure drug sample > recrystallized > microspheres of form I of mefenamic acid > microspheres of form II of mefenamic acid.

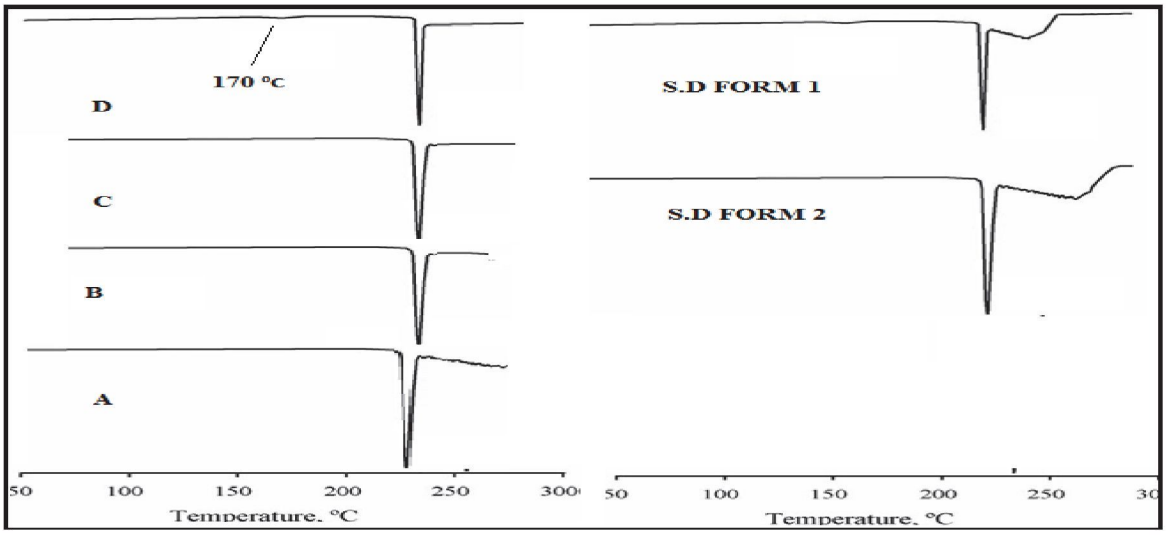

Figure 1. DSC thermograms of commercial mefenamic acid (A), recrystallized sample (B), form II (C), form I (D), spray dried microspheres of form I and spray dried microspheres of form II.

Infrared spectra of all the samples mefenamic acid commercial showed characteristic peaks at 1255 cm^{-1} (-OH group bending and vibrations of COOH), 1647 cm^{-1} (N-H stretching vibration), 1572 cm^{-1} (C=O stretching), 1504 cm^{-1} (Aromatic C-H plane deformation), 1163 cm^{-1} (Aromatic-O-CH_3) and 757 (Aromatic C-C vibration for ortho substitution). The IR absorption bands in the FTIR spectrum of all crystals of mefenamic acid were similar (Figure 2). These unassociated changes at the molecular level shows that there are no differences between the internal structure and conformations of these samples. This agrees with the conclusion of Adhiyaman and Sanat about crystal modification (15). Mefenamic acid has two polymorphic forms, the stable polymorph I and the metastable polymorph II. The FTIR absorption spectra of form I and II, shows characteristic difference in the detailed shape and intensities of some of the major absorption bands that can be used to identify each polymorph specifically in the region of wave number between 3350 cm-1 and 3300 cm-1, the NH stretching frequency occur at (3310-3250) cm-1 for form I and at 3347 cm-1 for form II (23). All FTIR absorption profiles of mefenamic acid for crystalline samples are consistent with those of polymorph I.

Fig. 3 shows the XRD patterns of forms I and II. The characteristic XRD peaks of form I were observed at 6.4°, 21.5° and 26.6° (2θ), while those of form II were observed at 11.9°, 18.0°, 24.1° and 25.6° (2θ). These results coincided with those reported previously (21). Therefore, the quantitative analysis was performed by using these peak intensities of form II. In spray dried formulation, all the samples showed similar peak positions (2θ) in X-ray diffraction, formation of different polymorphs of mefenamic acid was ruled out. However relative intensities of XRD peaks were modified (Figure 3). This could be attributed to the markedly different crystal habits of the samples. 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.

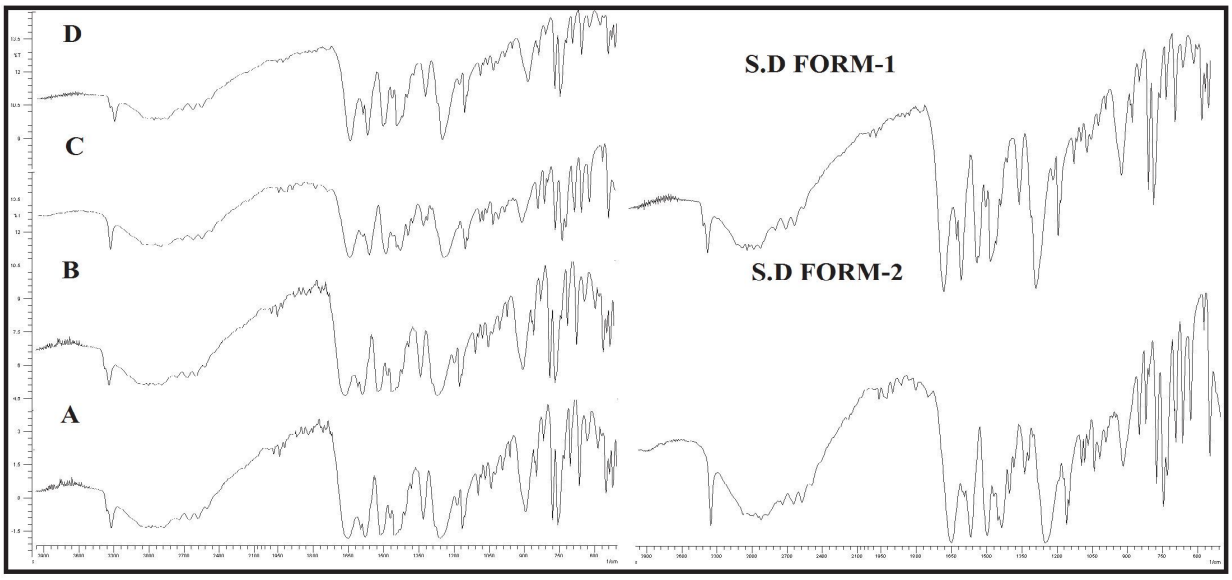

Figure 2. FTIR spectra of commercial mefenamic acid (A), recrystallized sample (B), form II (C), form I (D), spray dried microspheres of form I and spray dried microspheres of form II.

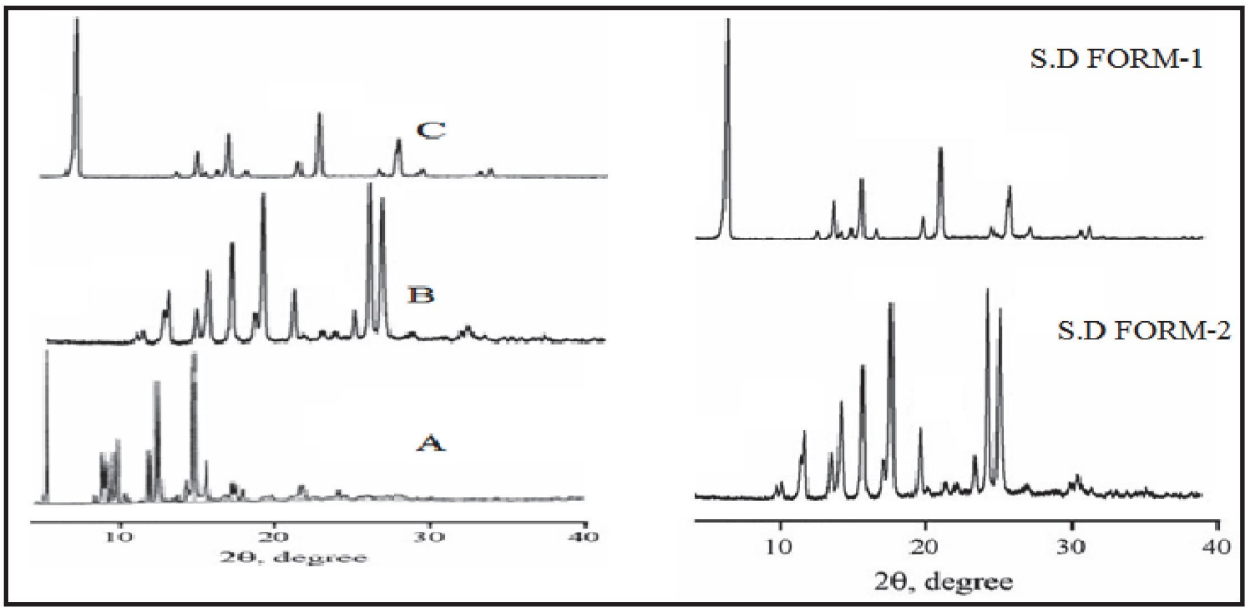

Figure 3. X-ray patterns of commercial mefenamic acid (A), recrystallized sample (B), form II (C), form I (D), spray dried microspheres of form I and spray dried microspheres of form II.

SEM photographs of forms I and II crystals were presented in Figure 4. Forms I and II crystals were stick- and cube-shaped particles, respectively, indicating that they were quite different in their particle morphology. Particle of pure sample are of the smallest size (4-8 µm) and they have irregular shapes. Recrystallization produced crystals with intermediate size (5-18 µm). The particle formed by microspheres of mefenamic acid of form I & II formed by spray drying technique are small in size (6-11) µm and (5-12) µm respectively, and the resultant

microspheres had a smooth surface (Figure 4). Microspheres obtained were spherical in shape. Because of the spherical shape there are less chances of forming a cake and lump during the storage because spherical shape particle has less point of contact and more void space.

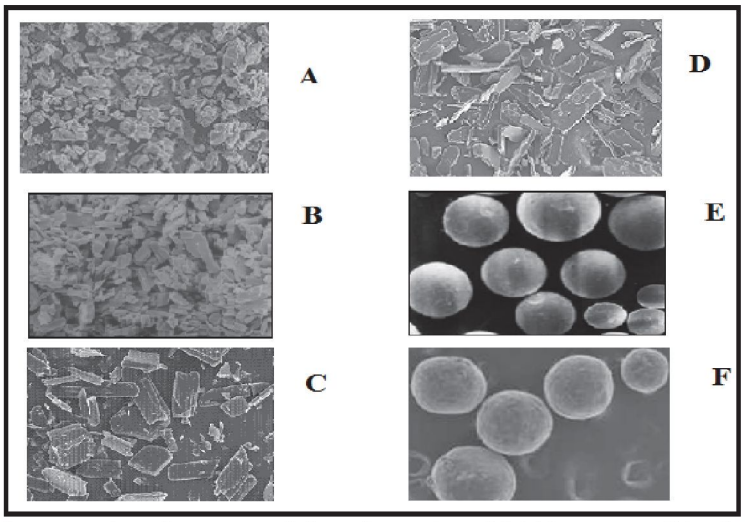

Figure 4. SEM photographs of commercial mefenamic acid (A), recrystallized sample (B), form II (C), form I (D), spray dried microspheres of form I and spray dried microspheres of form II

The micrometrics properties of pure sample, recrystallized sample, and spray dried microspheres of both forms (I & II of mefenamic acid shown in Table 1).

Table 1. Micrometrics property of mefenamic acid of different samples.

Properties	Form I	Form II	Microspheres Form I	Microspheres Form II
Particle size (μm)	4-8	5-18	6-11	5-12
Flow rate (gm/Sec)	No flow	No flow	1.32	2.84
Angle of repose	38.50	34.13	30.32	27.24
Tapped density (gm/mL)	0.8179±0.013	0.5684±0.043	0.5252±0.052	0.2063±0.05
Bulk density(gm/mL)	0.6166±0.012	0.4268±0.06	0.3642±0.002	0.1916±0.004
Carr's index	27.17	25.18	23.78	11.19
Porosity (%)	18	22	29	37

Spray dried microspheres of both form (I & II) of mefenamic acid exhibited superior compressibility characteristics compared to pure samples and recrystallized samples (Figure 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. Tensile strength of the mefenamic

acid exhibited compressibility as follows: pure sample of form I & II > spray dried microspheres form I > spray dried microspheres form II.

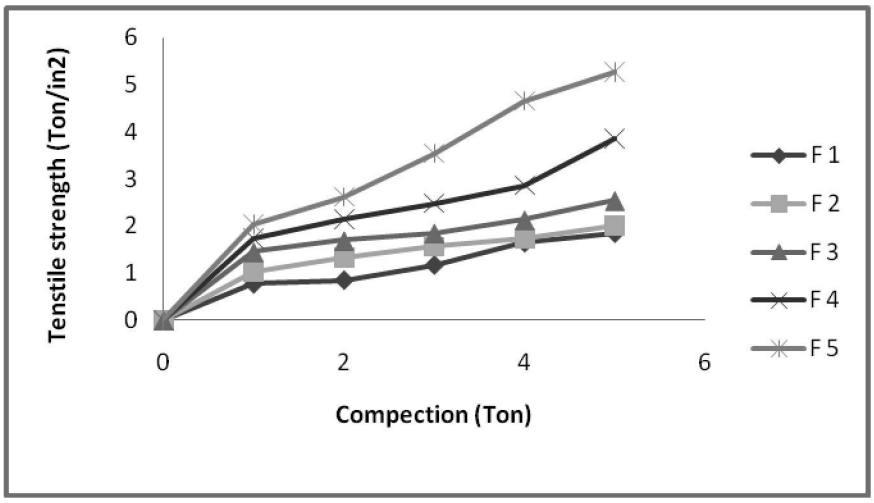

Figure 5. Tenstile strength of different sample of mefenamic acid, commercial sample (F1), pure form I (F2), pure form II (F3), spray dried form I (F4) and spray dried form II (F5)

Heckle profile of commercial sample and prepared crystals are shown in Figure 6, and characteristic values of P_Y, D_A, D'_0 and D'_B and elastic recovery are reported in Table 2. At early compression phase below 25 Mpa, the compression of prepared crystals beginning at lower relative density, while the initial rearrangement phase without pressure increase for commercial sample this corresponds to different D'_0 values. D'_B is greater for prepared crystals; indicate a greater brittle fracture tendency of these materials. Elastic recovery is relatively high for a brittle material, but it must be noted that tablets survive the decompression phase and show no sign of capping. Prepared mefenamic acid microspheres of different forms exhibited higher porosity compared to commercial sample, hence require lower compression force for compressing under plastic deformation compared to commercial sample.

The solubility of mefenamic acid spray dried microspheres of form 1 & II in water was found to be (0.0526) & (0.0836) respectively. This was higher than recrystallized sample (0.0094) and pure sample (0.0083). According to above result spray drying technique is a good method to increasing the solubility of poorly water soluble drug.

Table 2. Heckle's parameters and elastic recovery of mefenamic acid.

Parameters	F1	F2	F3	F4	F5
P_Y	68.5 ± 4.02	68.52±3.55	68.61 ± 3.95	69.2 ± 3.65	69.4 ± 5.15
D'_0	0.573 ±0.006	0.493±0.049	0.494 ± 0.045	0.495 ± 0.052	0.496 ±0.008
D_A	0.712 ±0.002	0.713±0.027	0.715 ± 0.003	0.723 ± 0.024	0.728 ±0.004
D'_B	0.138 ±0.005	0.188±0.004	0.191 ± 0.028	0.204 ± 0.003	0.229 ±0.012
Elastic recovery (%)	4.78 ± 0.25	4.79±0.49	4.80 ± 0.31	4.815 ± 0.483	4.83 ± 0.451

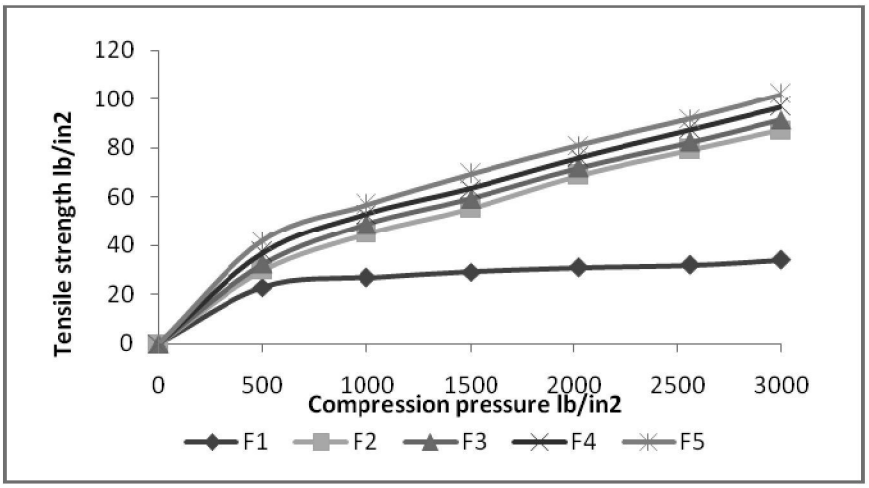

Figure 6. Heckle's profile of different samples of mefenamic acid, commercial sample (F1), pure form I (F2), pure form II (F3), spray dried form I (F4) and spray dried form II (F5).

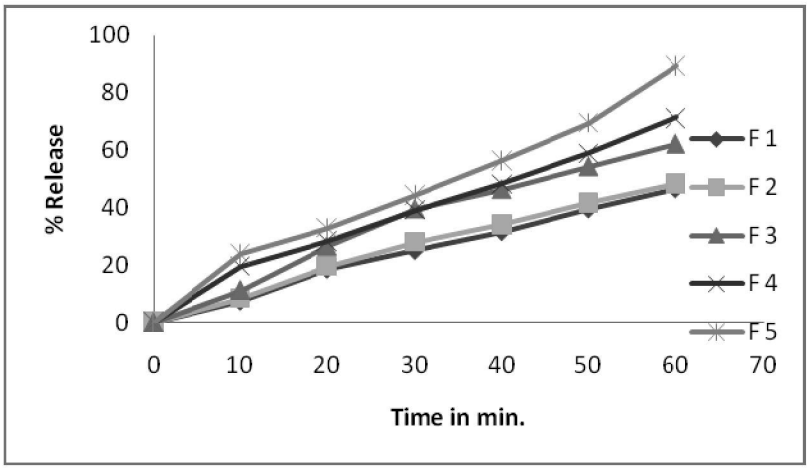

Figure 7. Dissolution profiles of commercial sample (F1), pure form I (F2), pure form II (F3), spray dried form I (F4) and spray dried form II (F5).

The dissolution profiles of mefenamic acid (Figure 7) exhibited improved dissolution behavior for spray dried microspheres of form I & II than recrystallized sample and pure sample. The reason for this faster dissolution could be linked to the better wettability of the microspheres. The amount of drug dissolved in 60 min greatly varied for spray dried microspheres.

The dissolution behavior of microspheres must remain unchanged during storage. The best way to guarantee this is by maintaining their physical state and molecular structure. For optimal stability of amorphous microspheres, the molecular mobility should be as low as possible. However, microspheres, partially or fully amorphous, are thermodynamically unstable and will have a natural tendency to crystallize, because the crystalline state has a lower energy compared to amorphous material. However, amorphous material can be kinetically stable, which implies that the equilibrium state, i.e. crystalline, is not reached within the timeframe of the experiment or shelf life of the product. Therefore, the physical state should be monitored because changes therein are likely to alter the drug release.

The results of the stability study of microspheres stored at 20 ^{0}C and 45% relative humidity for 90 days were shown in Table 3. The influence of microspheres on the physical stability of mefenamic acid was investigated. The drug fusion enthalpy of Form microspheres was decreased from 129.34 to 128.57 J/g after storage with a subsequent decrease of mefenamic acid crystallinity, whereas in case of form microspheres, the drug fusion enthalpy was decreased from 156.37 to 155.74 J/g after storage, it also indicated decrease of mefenamic acid crystallinity. Above result shows that microspheres of both form I & II of mefenamic acid were stable after 90 days at 20 ^{0}C and 45% relative humidity.

Table 3. Thermotropic parameters of pure mefenamic acid and its microspheres containing form I & II before and after storage for 90 days at 20 ^{0}C and 45% relative humidity.

Formulations	Peak ^{0}C		ΔH J/G	
	a	b	a	b
Pure drug sample	235.79	235.78	175.55	175.55
Spray dried Form I	170	169.89	129.34	128.57
Spray dried Form II	231	230.45	156.37	155.74

a: Immediately after preparation, **b:** After storage for 2 month at 20 ^{0}C and 45 % relative humidity

CONCLUSION

When incorporating metastable polymorph crystals in the dosage forms, it is essential to investigate the solubility, dissolution and other property to ensure pharmaceutical quality and bioavailability. Form II crystals have higher solubility than that of form I and it is therefore preferable to use form II for pharmaceutical preparations. Spray dried microspheres of mefenamic acid (Form I & II) were prepared by spray drying technique. Spray dried microspheres of both form 1 & II decreased crystallinity and improved micromeritic properties. DSC and XRD studies showed that there is no change in the crystal structure of mefenamic acid of both the forms during the spray drying process. The dissolution of the spray dried microspheres of both the form 1 & II was improved compared with pure samples of mefenamic acid. But the solubility, dissolution, micromeritic and mechanical property of microspheres containing mefenamic acid form II more comparable to Form 1 and pure drug sample. And because of this reason form II used in pharmaceutical formulation. It was observed that form I & II of mefenamic acid microspheres was stable after 90 days. Hence this spray drying technique can be used for formulation of tablets of mefenamic acid by direct compression with directly compressible tablet excipients.

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