Influence of Polyvinyl Pyrrolidone Addition during Crystallization on the Physicochemical Properties of Mefenamic Acid Crystals

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ABSTRACT

Crystallization of mefenamic acid in the presence of polyvinyl pyrrolidone was carried out in an effort to improve its physicochemical properties. Mefenamic crystals were prepared as follows: A supersaturated solution of mefenemic acid using absolute ethanol as a solvent was prepared. Then an aqueous polymeric solution of polyvinyl pyrrolidone (PVP) was added, cooled, and filtered. The concentration of the polymer varied as follows 0, 1, 5, 12.5, and 25%. The collected crystal properties were tested using optical microscopy, differential scanning calorimetry (DSC), Fourier transform infra red spectroscopy (FTIR), and x-ray powder diffraction. Solubility, dissolution, and wetability properties of the crystal were also evaluated. A result showed that the crystallized samples were mainly composed of mixture of polymorph I and II and as the concentration of PVP increases proportions of Polymorph I in the mixture increases. Enhancement of the dissolution rate was achieved in all crystallized samples and as the concentration of PVP was increased, dissolution rate increased. The wetability of the formed crystal improved as the concentration of the PVP was increased. Wetability results explained the improvement in dissolution rate despite the formation of large crystals mainly composed of the more stable polymorph (Form I).

Keywords: Crystallization, Mefenamic acid, Polyvinyl pyrrolidone, Dissolution, Polymorph.

INTRODUCTION

Crystallization is a critical process used to obtain raw material with desirable properties. Control of the crystallization process is a challenge since it influences powder properties[1]. A lot of trials were done to improve the physicochemical properties of raw materials by crystallization technique in which incorporation of materials such as surfactants [2, 3], polymers [4, 5], and other additives such as small molecules, sugars, salts and amino acids [6, 7, 8] was conducted. It has been recognized that the presence of soluble substances during crystallization can influence the kinetic of crystal nucleation, growth, morphology and dissolution [9]. Crystal technology was employed to obtain crystal with different characteristics such as particle size [4, 10], compression and mechanical properties [11, 12], dissolution characteristics [2, 3, 4, 6], crystal yield [13, 14] and morphology [15, 16].

Mefenamic acid is a nonsteroidal anti–inflammatory drug (NSAID) [17]. It is a member of the femate group [18]. Mefemanic acid is practically insoluble in water and, it is indicated in large doses (adult dose usually 250-500 mg). Its dissolution can be considered the rate-limiting step for absorption from the gastrointestinal tract [19]. Mefenamic acid exists in two polymorphic forms, form I, which is the stable polymorph and form II the metastable one [20]. Form II has higher saturation solubility than form I, but in the dissolution media, form II was found to be unstable and converted into form I [21, 22]. Thus, the limiting step in mefenamic acid dissolution

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is attributed to the poor solubility polymorph I. In addition, mefenamic acid showed variation in its physicochemical properties depending on its source [17, 23, 24]. Mefenamic acid tends to stick to surfaces and is difficult to handle during granulation and tableting due to its inherent property of high hydrophobicity [17]. Many attempts were carried out in an effort to improve the physicochemical properties of mefenamic acid. Some of the efforts include: preparation of the drug in solid dispersion in egg albumin (25) and in polyethylene glycol (26), crystallization from different solvents [22, 27] and formation of inclusion complex with β-cyclodextrin[28].

In this work, crystallization of mefenamic acid in the presence of polyvinyl pyrrolidone was carried out. Polyvinyl pyrrolidone is hydrophilic polymer widely used in pharmaceuticals in order to enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds by making solid dispersions [29, 30] or by using it as additive during crystallization [31, 32].

Experimental

Materials

Mefenamic acid was supplied kindly by Al-Hikma Pharmaceuticals Amman, Jordan, Polyvinyl Pyrrolidone (PVP) average molecular weight 1,300,000, K 85-95 (Across organics, Geel, Belgium), Absolute ethanol (Scharlau, Barcelona, Spain), Potassium dihydrogen orthophosphate (Scharlau, Barcelona, Spain), Sodium hydroxide (Frutarom LTD, Cleveland, UK), and Potassium bromide (Fluka chemie AG, Buchs Switzerland). Also, only deionized and distilled water was used in the experiments.

METHODS

Preparation of mefenamic acid crystals

Mefenamic acid crystals were recrystallized as follows: Ten grams of mefenamic acid were placed in a 500 ml conical flask, followed by the addition of 250 ml absolute ethanol, and then placed on a steam bath (approximate temperature 100^{o}C) (Nickel Elect, UK). The solution was stirred continuously until it became clear. In another 100 ml beaker, the required amount of polyvinyl pyrrolidone - according to Table 1 for each sample was weighed and added to 40 ml of distilled deionized water.

Table (1): The Concentration of the Polyvinylpyrrolidone (PVP) in the Aqueous Solution and Final Crystallization Solution

Labeled	Aqueous concentration (% w/v)	Final concentration (% w/v)
1% PVP	1.0	0.138
5% PVP	5.0	0.690
12.5% PVP	12.5	1.724
25% PVP	25.0	3.448

After obtaining a clear supersaturation solution of mefenamic acid, it was removed from the steam bath and the aqueous polyvinyl pyrrolidone solution was added to mefenamic acid solution, stirred by glass rod for 30 seconds over the steam bath again and transferred directly to the refrigerator (White House, No frost, Japan). The temperature inside the refrigerator was approximately 5^{o}C $\pm$ 2. After 24 hours, the crystals were collected by filtration using bucchnar funnel. The crystals were washed using absolute ethanol to remove alcohol soluble impurities and dried for 24 hours in a Pyrex dessicator containing fresh silica gel.

Crystal properties of mefenamic acid raw material as well as all crystallized samples were evaluated using differential scanning calorimetry (DSC), Fourier transform infra red and x-ray powder diffraction. The samples were also tested for crystal purity, dissolution properties, water solubility and wetability as follows:

Crystal purity

In order to evaluate crystal purity, mefenamic acid was assayed in mefenamic acid raw material, sample was crystallized in the absence of PVP and at different concentrations of PVP as follows: Sample of 10 mg was dissolved in 500ml of water. Half milliliter sample was placed inside HPLC vials.

Analysis of mefenamic acid was determined using HPLC method and using USP mefenamic acid reference standard as a calibrating standard. The system was composed of Shimadzu 10AVP system controller, GGU-14A degasser, SIL-10AD VP auto injector, LC-10AD liquid chromatography pump and SPD-10AVP diode array detector. Phenomenox C18 250x4.6mm 5Micron chromatography column was used. The mobile phase used was a mixture of acetonitrile and 0.5 mM Acetate buffer (65:35) at a flow rate of 1 mL/min. The injected volume was 20 µl. Mefenamic acid was detected at UV wavelength of 280nm.

Differential scanning colarimetery

Differential scanning calorimetry measurements were performed using Quick cooling differential scanning calorimeter DSC-50Q (Shimadzu, Japan) equipped with a Shimadzu TA-50WSI instrument controller and a Shimadzu professional computer. The instrument was calibrated at the temperature of 156.60°C using pure indium (99.999%). Samples weighing approximately 5 mg were hermetically placed, sealed in crimped aluminum sample pans to prevent moisture loss during heating. The samples were scanned from 25°C to 350°C at a heating rate of 15°C/minute. An empty pan sealed in the same way was used as a reference.

Fourier Transformed Infra Red Spectroscopy (FTIR)

The FTIR spectrometer, Nicolet Avatar 5.1 ESP 360 S (Thermo Scientific, USA) was used to obtain the FTIR spectra; the FTIR data were analyzed using Omnic software on Windows 95. The blank used was KBr. Each sample was diluted by mixing 0.1 g of the sample with 0.9 g of KBr. The mixture was placed in the instrument for analysis as powder without compression using diffuse reflectance cells.

X-Ray Powder Diffraction

X-ray Powder diffraction patterns of all samples were determined using a Philips PW3040 diffractometer X'Pert MPD, (Philips, Netherlands) with Cobalt radiation. The sample tubes were filled completely with sample and then measured at a generator tension of 40 kV and a generator current of 40 mA. Finally, after running the sample on slow chart speed, all peaks on the chart corresponding to 2θ values were located and their values were written into the data chart and analyzed accordingly. The X-ray powder diffraction patterns for all samples were also performed.

The x-ray powder diffraction patterns for mefenamic acid polymorph I and II was studied (33). Depending on the presence of characteristic peaks for each form, one can differentiate between form I and II. The presence of peak at 2θ=7° is characteristic for form I, while the presence of peak 2θ=18° is characteristic for form II. In order to quantify the proportions of form I and form II, relative intensities of the characteristic peak of form I at 2θ=7° and the characteristic peak of form II at 2θ=18° was determined for the different crystallized samples.

In Vitro Dissolution Testing

Type II dissolution apparatus DT 60 (Erweka, Germany) was used to study the dissolution properties of the crystals. One hundred milligram of each of mefenamic acid raw material or other crystallized samples was filled into hard gelatin capsule of size 5. The dissolution profile of each capsule was studied in 540 ml of dissolution medium using a paddle apparatus according to USP 23 at a paddle speed of 100 rpm and a temperature of 37°C. The medium consisted of phosphate buffer of pH 7.5. Samples were taken at 0.25, 0.5, 1, 2, 3, and 4 hours. At each interval, 5 ml sample was taken, filtered using Millipore filters 0.45µm (Orange Scientific N.V./S.A. 1410 Waterloo, Belgium) and diluted as needed. Another 5 ml of the fresh buffer was added to the medium for replacement. The

concentration of the drug was determined using ultraviolet spectroscopy at wavelength of 333 nm using Photodiode Array Photometer, (MultiSpec-1501, Shimadzu, Japan). The color of the capsule shell and/or the presence of polymers did not interfere with the ultraviolet spectroscopy at the above wavelength.

Solubility determination

The solubility of mefenamic acid and other crystallized samples was determined in phosphate buffer of pH 7.5 and at temperature of 25°C. Samples in excess of the amount required for saturation solubility (about 100 mg) was added to 100 ml of the phosphate buffer in a 100 ml conical flask, covered with parafilm. The samples were shaken in Clifton shaking bath, (Nickel Electro, UK), for a period of time in excess to that required for equilibrium (24 hours). After equilibration, the solutions were filtered rapidly through Millipore filters 0.45µm, (Orange Scientific N.V./S.A. 1410 Waterloo, Belgium) and diluted as needed. The concentration of the drug was determined spectrophotometrically at a wavelength of 333nm using Shimadzu UV1201 spectrophotometer (Shimadzu, Japan).

Contact angle

Compressed discs were needed in order to measure the contact angle. Five hundred milligram of each crystal form was compressed using RKM 50, Universal testing machine, (Roell & Korthaus, Germany) applying force of 44 KN with a highly polished stainless steel punch and die of a 1/2 inch diameter. Samples that exhibited non-uniform surfaces or where sticking or picking occurred were not used. Each disc was placed on the ShadowMaster instrument (ShadowMaster, Germany) and then a drop of 5.0 µl of deionized distilled water was placed on the disc using a micropipette, Transferpette®, from a height of 1 cm perpendicular to the disc. The contact angle then was read using a magnification of 20 times. Each sample was tested 6 times as mentioned earlier.

Polarizing optical microscopy

Photographs were taken using Fuji Film Superia (200 CA135-36, iso 200/24°) for each sample, few milligrams were spread and placed on a glass slide under polarizing optical microscope (Ortholux Iipol-BK) with a total magnification of 200 times.

RESULTS AND DISCUSSION

Evaluation of the crystals

Mefenamic acid raw material as well as crystallized samples from aqueous solution containing different concentrations of polyvinyl pyrrolidone were prepared and evaluated using differential scanning calorimetry (DSC), Fourier transform infra red, and x-ray powder diffraction. The crystal purity, dissolution properties, water solubility and wetability were also evaluated. The evaluation results are as follows:

Crystal purity

Since the amount of additives (PVP) was too little to be quantified using the available analytical methods, mefenamic acid content was determined in the prepared crystals and raw materials. The percentage of drug in the samples ranged between 98.6% and 99.6 for samples crystallized in PVP solutions of concentrations that ranged between 1% and 25%. Mefenamic acid raw material drug content was 98.2% while drug concentration in the sample crystallized in the absence of PVP was 99.6%. The results demonstrate that the level of PVP in the crystals was small and less than 2%, thus the prepared crystals are mainly composed of mefenamic acid. The results also showed that the prepared crystal have higher drug content or equal to that of the raw material. This phenomenon may be attributed to the crystallization process which can be utilized for purification purposes.

Differential scanning calorimetry

Figure (1) shows the DSC thermograms of mefenamic acid crystals. It is known that mefenamic acid has two known polymorphic forms, the stable polymorph (form I) and the metastable polymorph (form II) (22). Differentiation between these two polymorphs was studied by using the DSC technique (17). It was

found that the metastable form II showed only one endothermic peak corresponding to the melting point at about 230°C. While the stable form I displayed two endothermic peaks, the first peak corresponds to the transition of form I to form II. It was affected by the experimental conditions such as the heating rate. This peak was found to be at 179°C (heating rate at 40°C/min), 190°C (5°C/min) or between 215 – 220°C (2°C/min) (17, 20, 22). The second peak corresponds to the fusion of form II, which was found to be at about 230°C. Both polymorphic forms decompose after fusion and the drug decarboxlates completely at about 300°C.

All samples show the two major endothermic peaks that correspond to the stable polymorph I. The first peak lies between 169 – 184°C and the second peak between 226.56 – 228.18°C. These variations might be due to the presence of polymers and due to the crystallization conditions.

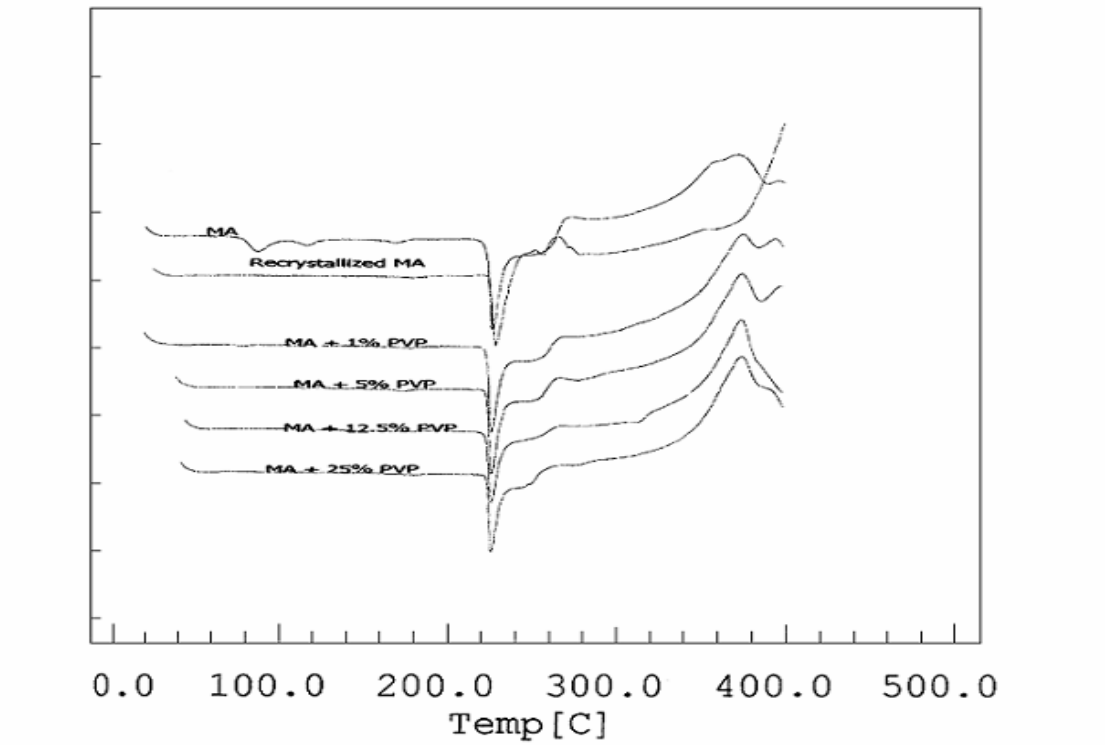

Figure (1): Differential scanning calorimtery thermograms of mefenamic acid raw material, crystal prepared in the absence of PVP and crystals prepared in various concentrations of PVP

In the DSC thermogram for mefenamic acid powder, additional peaks appeared around 100°C. The peak before 100°C represents the adsorbed water, while the peak appeared after 100°C represents the occluded water.

DSC thermogram of PVP k90 has only one fusion peak at about 150°C when scanned from ambient temperature to 300°C. This peak did not appear separately in the DSC thermograms of mefenamic acid samples crystallized in the presence of PVP K-90. This might be due to the minute amount of PVP present at surface of mefenamic acid crystals (less than 2%) coupled with a broad endothermic peak of the polymer.

Fourier transform infrared

Infrared spectra of mefenamic acid were used in order to differentiate between polymorph I and

polymorph II (22). The two polymorphs of mefenamic acid differ in their –NH stretching frequencies, the –NH stretching frequency occurs at 3313 cm^{-1} for form I while for form II it occurs at 3347 cm^{-1}. Figure (2) shows the FTIR spectrum of mefenamic acid crystals.

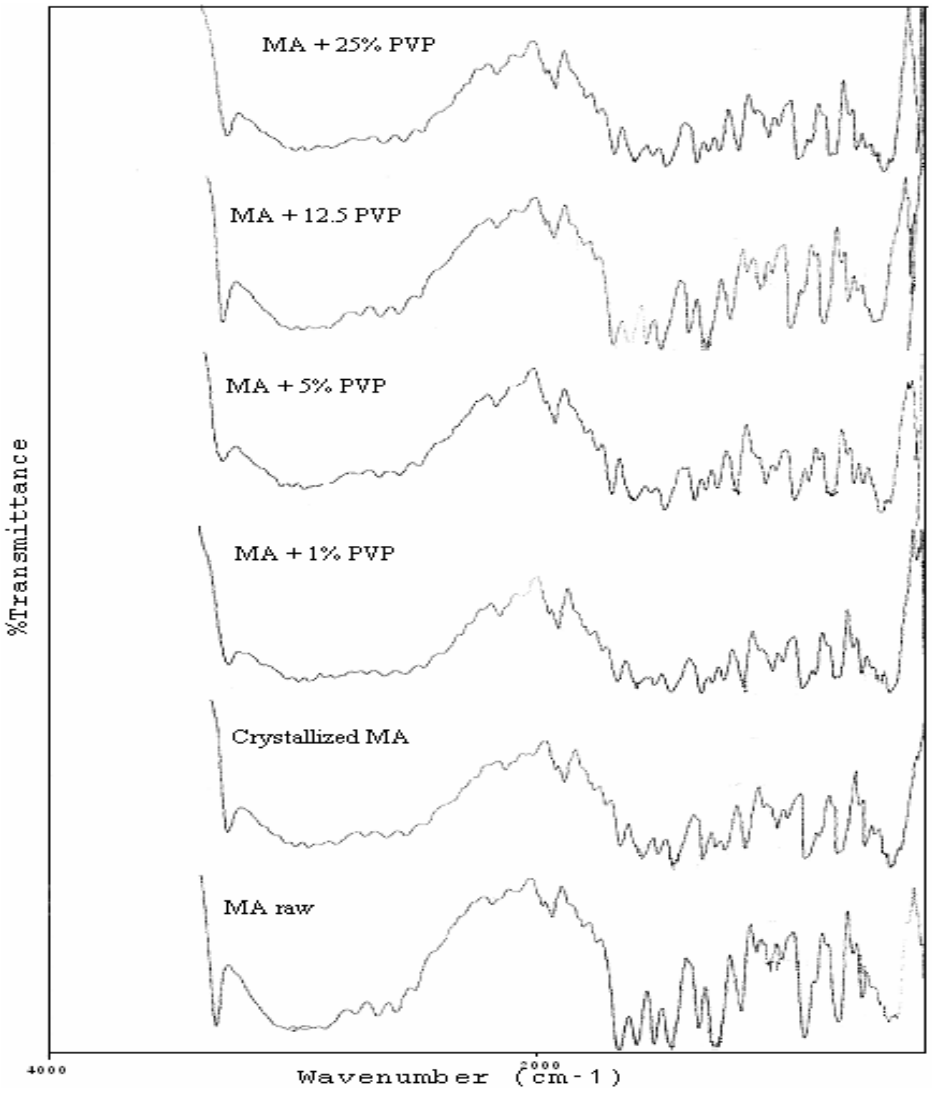

Figure (2): FTIR of mefenamic acid raw material, sample crystallized in the absence of PVP and samples crystallized in different concentrations of PVP

All samples appear to have form I; since the -NH stretching frequencies occur between 3308.14-3316.17cm^{-1}; which correspond to the stable polymorph (form I).

X-ray powder diffraction

X-ray diffraction was noted to be able to differentiate between crystal forms of a drug as it were not sufficiently identified by FTIR and DSC.

The x-ray powder diffraction patterns for mefenamic acid polymorph I and II was studied (33). Depending on the presence of characteristic peaks for each form, one can differentiate between form I and II. The presence of a peak at 2θ=7° is characteristic for form I, while the presence of peak 2θ=18° is characteristic for form II.

Figure (3) shows the X-ray powder diffraction pattern for mefenamic acid crystals. The results confirmed the presence of the two polymorphs (form I and form II) as the characteristic peak for form I and the characteristic peak for form II appeared in all crystallized samples.

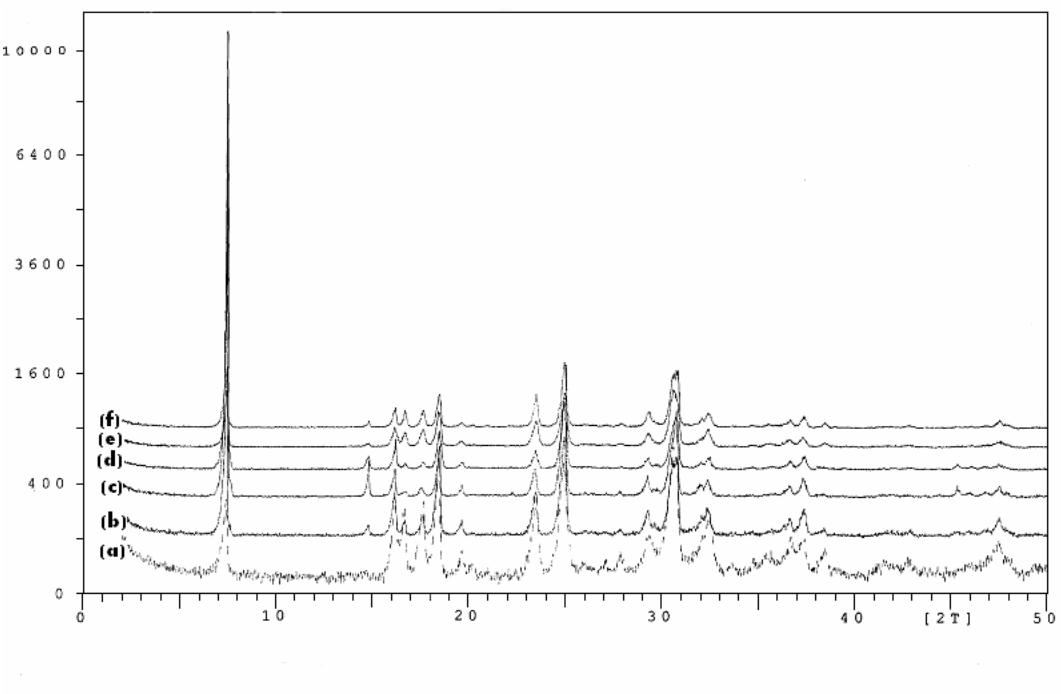

Figure (3): X-ray powder diffraction of mefenamic acid raw material, sample crystallized in the absence of PVP and samples crystallized at different concentrations of PVP a. raw MA b. MA crystallized in the absence of PVP c. MA crystallized in 1% PVP d. MA crystallized in 5% PVP e. MA crystallized in 12.5% PVP f. MA crystallized 25% PVP

Based on the intensity of the characteristics peaks of polymorph I (2θ=7°) and II (2θ=18°), it can be concluded that polymer I is predominate over polymorph II in all prepared crystals. No attempt was made to separate pure polymorph I or II.

Dissolution properties

Figure (4) shows the dissolution profile of mefenamic acid, samples that were crystallized in the absence of PVP and that crystallized in the presence of different concentrations of PVP. The first step in the dissolution process was the disintegration of the hard gelatin capsule, which was completed within 5 minutes in all samples.

Dissolution rate of mefenamic acid raw material (the original powder) increased slowly and did not reach a plateau until the end of the experiment. The amount of mefenamic acid dissolved after four hour was approximately 35 mg out of the 100 mg placed in the dissolution apparatus. Crystallized mefenamic acid showed a higher rate of drug release. The amount of mefenamic acid released was 58 mg after 4 hours for samples crystallized in the absence of PVP. This enhancement may

be due to the effect of the solvent used during the crystallization process (absolute ethanol), which causes hydrophilization of the mefenamic acid surface (34). Thus, mixing a hydrophobic drug thoroughly with ethanolic carrier solution caused surface hydrophilization, improved wettability, and enhanced dissolution rate.

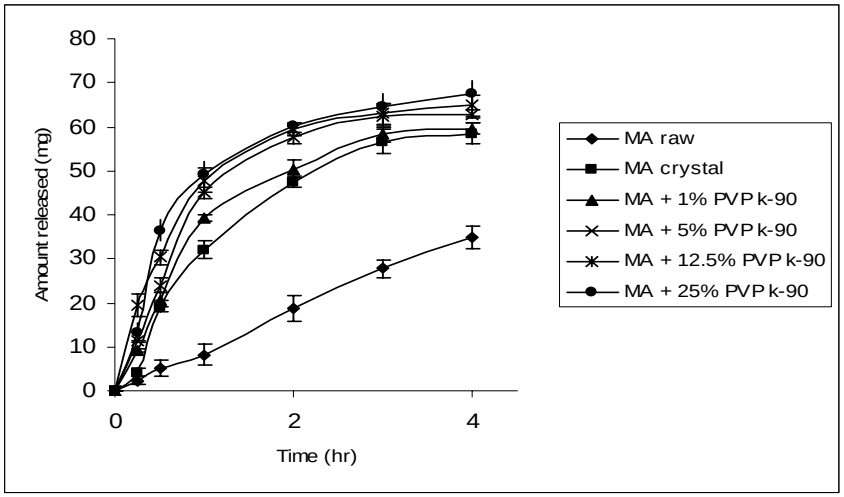

Figure (4): Dissolution profile of mefenamic acid raw material, sample crystallized in the absence of PVP and samples crystallized in different concentrations of PVP

Crystallization of mefenamic acid in the presence of PVP showed further improvement in the dissolution of the drug and as the concentration of PVP in the crystallization medium increased, dissolution rate of the drug increased. Despite the increase in the proportions of the more stable and less water soluble form I in the formed crystals, high dissolution rate were obtained. This might be due to precipitation or adsorption of small amount of PVP on the hydrophobic surface of mefenamic acid crystals since mefenamic acid is a very hydrophobic drug and PVP is a very hydrophilic polymer, the precipitation of PVP will increase wettability of mefenamic acid crystals. The presence of the polymer during crystallization process might also cause defects in the crystal structure and the crystal would become thermodynamically unstable and, hence, dissolve faster.

Equilibrium solubility

The equilibrium solubility was tested in phosphate buffer (pH 7.5). Table 2 shows the results of the solubility study.

Table (2): Equilibrium solubility of mefenamic acid raw material, crystallized sample in the absence of PVP and crystallized sample in the presence of different concentration of PVP.

Sample	Equilibrium Solubility (μg/ml)	Standard Deviation (SD)
Mefenamic acid	84.387	1.448
Crystallized mefenamic acid	93.643	3.380
Crystallized mefenamic acid + 1% PVP K-90	89.490	1.941
Crystallized mefenamic acid + 5% PVP K-90	86.260	2.072
Crystallized mefenamic acid + 12.5% PVP K-90	89.188	2.953
Crystallized mefenamic acid + 25% PVP K-90	89.146	2.056

In this study, there were no major differences in the solubility between processed samples. But as noticed from the table, when comparing each sample with the raw material, there are differences between the crystallized samples and the raw material. This was confirmed statistically using student T-test. So, crystallization in presence of polymers enhances the dissolution rate with slight increase in the solubility. This may be due to the crystallization process and the presence of polymers. It was thought that surfactant present inside and/or outside the crystals enhances the solubility of the drug in the diffusion layer during dissolution, and the amount of surfactant in the crystal was low to affect the solubility.

Contact angle

Contact angle between a solid flat surface and minute droplet of water is a measure of the wettability of solid. Mefenamic acid raw material and all crystallized samples were compressed into discs; and then, wettability of these samples was determined. The results are presented in table (3).

Table (3): Contact angle mefenamic acid raw material, crystallized sample in the absence of PVP and crystallized samples in the presence of different concentrations of PVP.

Sample	Contact angle (°)	Standard Deviation (SD)
Mefenamic acid	79.2	0.75
Crystallized mefenamic acid	74.0	0.89
Crystallized mefenamic acid + 1% PVP K-90	69.2	0.52
Crystallized mefenamic acid + 5% PVP K-90	63.3	0.52
Crystallized mefenamic acid + 12.5% PVP K-90	61.3	1.17
Crystallized mefenamic acid + 25% PVP K-90	60.8	0.41

It is well known that as the contact angle decreased, the wettability will be improved. The results showed that the mefenamic acid is the least wettable, because of its highest contact angle value. Crystallized mefenamic acid has lower contact angle and so improved wettability; which explains its improved dissolution over the mefenamic acid raw material.

All crystallized samples with PVP K-90 have lower contact angle values and better wettability than the mefenamic acid and the crystallized mefenamic acid.

Wettability for samples crystallized with the PVP also increased as the PVP concentration increased. The 25% PVP dissolution profile was close to that of 12.5%, and the wettability for the 25% was close to that for the 12.5%.

We conclude that wettability for all crystallized samples was improved, which explain the dissolution improvement compared to the original powder.

Polarizing optical microscopy

Usually, particle size reduction increases the surface area that is exposed to the dissolution medium, which enhances dissolution rate. Therefore, it is important to determine particle size and morphology. Mefenamic acid raw material, crystallized sample in absence of PVP and sample crystallized in the presence of different concentrations of PVP were visualized using polarizing optical microscope. Figure (5) presents the microscopical view of mefenamic acid crystals using polarized plane light (PPL).

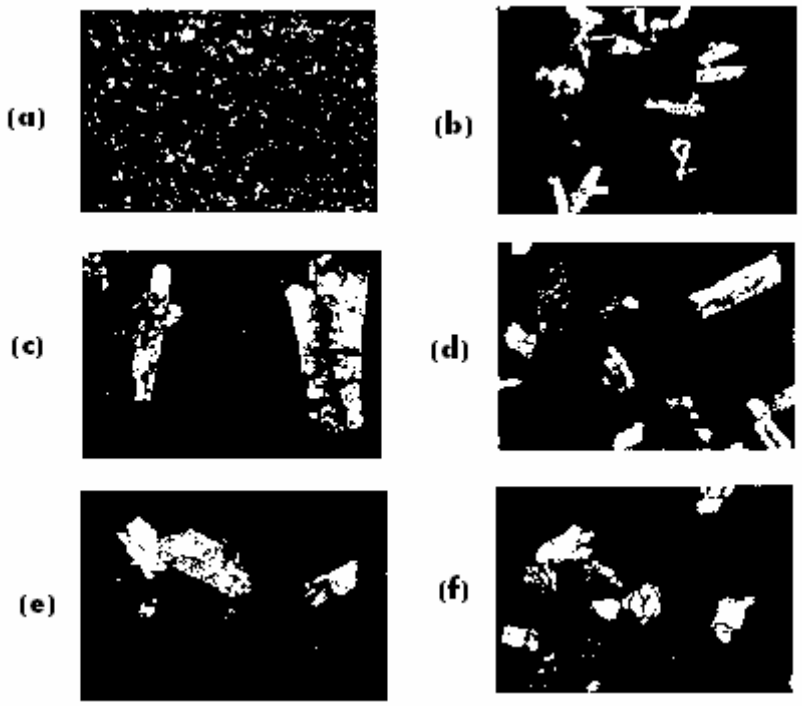

Figure (5): Polarizing optical microscopy photo of mefenamic acid (MA) raw material, sample crystallized in the absence of PVP and samples crystallized at different concentrations of PVP a. raw MA b. MA crystallized in the absence of PVP c. MA crystallized in 1% PVP d. MA crystallized in 5% PVP e. MA crystallized in 12.5% PVP f. MA crystallized 25% PVP

The results demonstrate that Mefenamic acid raw material has small crystalline granular shape. On the other hand, Crystallization of mefenamic acid in absolute ethanol and from aqueous solution gave crystals that are smaller and of plate- or prismatic-shape.

Using PVP K-90 in concentrations of 1, 5 and 12.5% during crystallization also gave plates crystals, small granules appeared with the 12.5%. The 25% PVP gave bipyramidal habits. Since mefenamic acid is a hydrophobic drug; any increase in size results in decreased particle-particle interaction, decreased surface area & increase dissolution. Other crystallized samples in presence of PVP have large crystals with the presence of similarity in shape.

CONCLUSION

Crystallization of Mefenamic acid in the presence of a water-soluble polymer such as polyvinyl pyrrolidone (PVP) leads to crystals comprise of higher percentage of the more stable polymorph (form I) coupled with a larger crystal size. The crystals have better wettability than the starting powder due to the sorption of small amount of the polymer on the surface of the crystals leading to better dissolution characteristics. The enhancement in the dissolution of mefenamic acid crystals was more obvious with the use of higher concentrations of the polymer during crystallization.

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تأثير إضافة البولي ڤينيل بيرو ليدون خلال البلورة على خصائص بلورات حامض الميفنمك

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ملخـص

بلورة حامض الميفنمك بوجود مبلمر البولي ڤينيل بيرو ليدون من أجل الحصول على حامض الميفنمك بخواص فيزيوكيميائية أفضل. تم تحضير بلورات حامض الميفنمك كما يلي: تم تحضير محلول مشبع لحامض الميفنمك في الكحول الأيثيلي المطلق ثم إضافة محلول مائي يحوي على البولي ڤينيل بيرو ليدون ثم تبريده وفلترته. هذا وقد غير تركيز المبلمر كما يلي: 0، 1، 5، 12.5، 25%. تم فحص البلورات الناتجة باستخدام الميكروسكوب الضوئي وماسح التباين المسعري والأشعة تحت الحمراء والأشعة السينية. وكذلك دراسة خواص الذائبية والانحلال والتبلل للبلورات الناتجة. أظهرت النتائج أن البلورات تتكون من خليط من متعدد الأشكال 1 و2 بحيث كلما ازداد تركيز المبلمر ازدادت نسبة متعدد الأشكال 1 في الخليط. تم أيضا ملاحظة زيادة معدل الانحلال في كل العينات التي تم بلورتها، وكلما ازداد تركيز المبلمر ازدادت سرعة انحلال الدواء. لوحظ أيضا زيادة درجة تبلل البلورات الناتجة كلما ازداد تركيز المبلمر وهذا يفسر زيادة سرعة انحلال الدواء من البلورات بالرغم من كبر حجمها وزيادة نسبة متعدد الأشكال 1 الثابت.

الكلمـات الدالـة: البلورة، حامض الميفنمك، البولي ڤينيل بيرو ليدون، الانحلال، متعدد الأشكال.

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