

## Dissolution Enhancement of Poorly Water Soluble Drugs by Co-precipitation in the Presence of Additives and Stabilizers

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### ABSTRACT

Mefenamic acid and Astemizole are models of drugs with poor aqueous solubility. The dissolution rates of Mefenamic acid and Astemizole were enhanced by the precipitation of both drugs in the presence of aqueous surfactant (SAA) (Cremophor®) and polymer solution (PEG 20,000). The highest dissolution rate for both drugs was achieved by precipitation in the presence of (Cremophor®), followed by precipitation in the presence of (PEG 20,000). The precipitated crystals were characterized using IR, DSC, SEM and X-ray powder diffraction. Mefenamic acid precipitates were of smaller size with no habit change, while in the case of astemizole there was a decrease in the crystallinity compared with the original powder. No changes in the polymorphic forms for both drugs were noticed during precipitation process.

**Keywords:** Mefenamic acid, Astemizole, precipitation, crystallization.

### INTRODUCTION

Developing novel techniques to improve the dissolution and bioavailability is of great importance in the development of pharmaceutical formulations, particularly those containing an active ingredient that is poorly soluble in water<sup>1</sup>. A common method for increasing the dissolution rate is forming of a high specific surface area by micronization. The process is usually used to obtain small particles by the disruption of large crystals. Chaumeil describes the improvement in dissolution rate and in bioavailability by micronization of sparingly water-soluble drugs using jar mills and fluid energy mills<sup>2</sup>.

Cospite and Dominici<sup>3</sup> describe a better clinical efficacy for micronized diosmin compared with the nonmicronized drug. However, several disadvantages resulting from the preparation process exist. In this context, the micronization process using mills is extremely inefficient<sup>4</sup>. Because high energy input can induce disruptions in the crystal lattice which can lead to physical or chemical instability. In addition, disordered regions in the resulting product are thermodynamically unstable. Ticehurst et al.<sup>5</sup> describe a method of micronizing revatropate hydrobromide in a jet mill. Disordered structures were detected and analyzed by dynamic vapor sorption analysis. Amorphous or disordered material will recrystallize, especially when water from the atmosphere is adsorbed. Because of a reduction of the glass transition temperature, the energy threshold to recrystallization is decreased<sup>6</sup>.

The conversion of crystalline solid surfaces into partially amorphous solid surfaces leads to a dynamic nature of the micronized drug<sup>7</sup>. In addition to this,

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disordered structures in the material can also influence the performance in formulations<sup>8</sup>. Surface energy changes influence processing properties such as the powder flow. Micronized powders with a higher energetic surface show poorer flow properties<sup>9-10</sup>. Due to their high specific surface, micronized particles are often agglomerated. Another milling technique is the high pressure homogenization. Nanosuspensions can be produced using milling by high pressure homogenizers<sup>11-12</sup>. The drug crystals, which have a starting size that is preferably as small as possible, are suspended in an aqueous surfactant solution. Ideally completely amorphous particles are obtained. Milling and solution-based techniques have been reviewed extensively. However, mechanical micronization by milling was found to alter the flow and compressibility of crystalline powders and cause formulation problems.<sup>13</sup>

As a disadvantage of all milling processes the product can be afflicted with impurities due to abrasion.

On the other hand, controlled precipitation is a particle engineering technology that creates crystals of nano-structured drug particles with rapid dissolution rate. In this technology the drug is dissolved in a suitable solvent then precipitated in the presence of crystal growth inhibitor to form drug nanoparticles. Particles prepared by controlled precipitation have the advantage of a narrower particle size distribution as compared to other methods<sup>14</sup>. One of the advantages of these methods is the possibility of designing in certain beneficial characteristics such as enhancing dissolution rate by the inclusion of surfactant or increasing the stability of amorphous material by the incorporation of sugars<sup>15-17</sup>.

In this work, two drugs (acidic and basic) are used as a model drugs; Mefenamic acid, which was selected as a model for acidic drugs, and Astemizole, as a model for basic ones. Both drugs show poor aqueous solubility and enhancement for their dissolution rate is required since dissolution rate is an *in vitro* predictor of *in vivo* bioavailability. Both drugs were precipitated from their solutions in the presence of additives (PEG and Cremophor<sup>®</sup>) by changing the pH of the media using HCl for mefenamic acid and NaOH for Astemazole.

## MATERIALS AND METHODS

Mefenamic acid (MA), Astemizole (AST) and Cremophor<sup>®</sup> EL (Poly oxyl 35 castor oil) were obtained as a generous gift from the Jordanian Pharmaceutical Manufacturing (JPM, Amman, Jordan). Polyethylene glycol (PEG MWT 20,000) (SERVA, GmbH & Co. lot 04031). All the other chemicals in this work were of analytical grade.

### 1- Preparation of mefenamic acid and astemizole crystals by precipitation

One gram of mefenamic acid or astemizole was dissolved in either 50 ml of (1 M NaOH or 1 M HCl) to form either sodium mefenamate or Astemizole.HCl soluble salts. The second step was the precipitation of mefenamic acid or astemizole by (1 M HCl or 1 M NaOH) till a pH of 7.4 was reached. These samples were taken as control.

Fifty ml of mefenamic acid solution in 1 M NaOH or fifty ml of astemizole solution in 1M HCl as prepared above were added to fifty ml of 1% cremophor<sup>®</sup> or 1% PEG 20,000 (all of pharmaceutical grade) and the drugs were then precipitated by 1 M HCl or 1 M NaOH till a pH of 7.4 was reached.

All samples were filtered, and the collected precipitants were dried for 24 hrs at room temperature and stored before any further use in tightly closed jars in desiccators.

### 2- Determination of the drug content:

An accurate amount of the precipitants corresponding to about 10 mg (mefenamic acid or astemizole) were extracted with 100 ml ethanol (96%). After filtration and appropriate dilution with distilled water, the concentration of both drugs (mefenamic acid and astemizole) were measured spectrophotometrically at  $\lambda = 281$  nm for astemizole and  $\lambda = 333$  nm for mefenamic acid, respectively. The assays were carried out in triplicate and the average drug contents were determined.

### 3- Dissolution Studies

The *in vitro* drug release studies from the various formulations prepared were carried out using the USP dissolution test apparatus II (Ereweka, Germany), paddle

method at  $100 \pm 1$  rpm. The dissolution media was 500 ml phosphate buffer solution (pH 7.4) which was chosen based on preliminary experiments to study the release of both drugs at  $37 \pm 0.5^\circ\text{C}$ . Ten milligrams of astemizole or mefenamic acid were placed in a transparent hard gelatin capsule size 5; five milliliter samples were withdrawn at various intervals and filtered through  $0.45\mu\text{m}$  millipore filter. Samples were then analyzed for drug concentration using a UV spectrophotometer (Shimadzu, Japan) at  $\lambda = 281$  nm for astemizole and  $\lambda = 333$  nm for mefenamic acid, respectively. The mean of three determinations was used to calculate the drug release from each formulation.

#### **4- Characterization of Mefenamic acid (MA) and Astemizole (AST) precipitates:**

##### **I- Scanning Electron Microscopy (SEM)**

The external morphology of astemizole and mefenamic acid samples was observed with a scanning electron microscope (Polaron E 6100 vacuum coater, UK) (Camera SU30, Semprobe, France).

The samples were mounted on a metal stub with a double sided adhesive tape and then coated under vacuum with a gold layer using a metallizer.

##### **II- Differential Scanning Calorimetry (DSC)**

Thermograms were recorded using a Differential Scanning Calorimetry (DSC-50 Q Shimadzu, Japan, equipped with a Shimadzu TA-50 WSI instrument controller and a Shimadzu professional computer). The samples were weighed in aluminum pans sealed with a crimper. Thermograms were recorded under nitrogen atmosphere (20ml/min) from ambient to  $300^\circ\text{C}$  at a heating rate of  $10^\circ\text{C}/\text{min}$ .

##### **III- Infrared Spectroscopy (IR)**

IR spectra were recorded with an IR spectrometer (BUCK Scientific- Model 500 IR Spectrometer connected to Buck Model 500 EZ Scan Software version (2.10).

Each sample was diluted by mixing 0.5 mg of the sample with 100 mg KBr, and then placed for analysis as powder without compression. The samples were analyzed using diffuse reflectance cells.

##### **IV- Powder X-Ray Diffractometry (PXRD)**

The PXRD patterns of samples were recorded with (PW 3040 diffractometer Xpert MPD, Phillips, Netherlands) with cobalt radiation at 40 mefenamic acid with  $2\theta$  increasing at a rate of  $3^\circ/\text{min}$  in a continuous mode. Counts were actuated for 1 s at each step. The samples were placed into an aluminum holder and the instrument was operated between initial and final  $2\theta$  (5- 50), respectively, in an increment of  $0.05^\circ$ , generator tension of 40kv and a generator current of 40 mA.

#### **RESULTS AND DISCUSSION:**

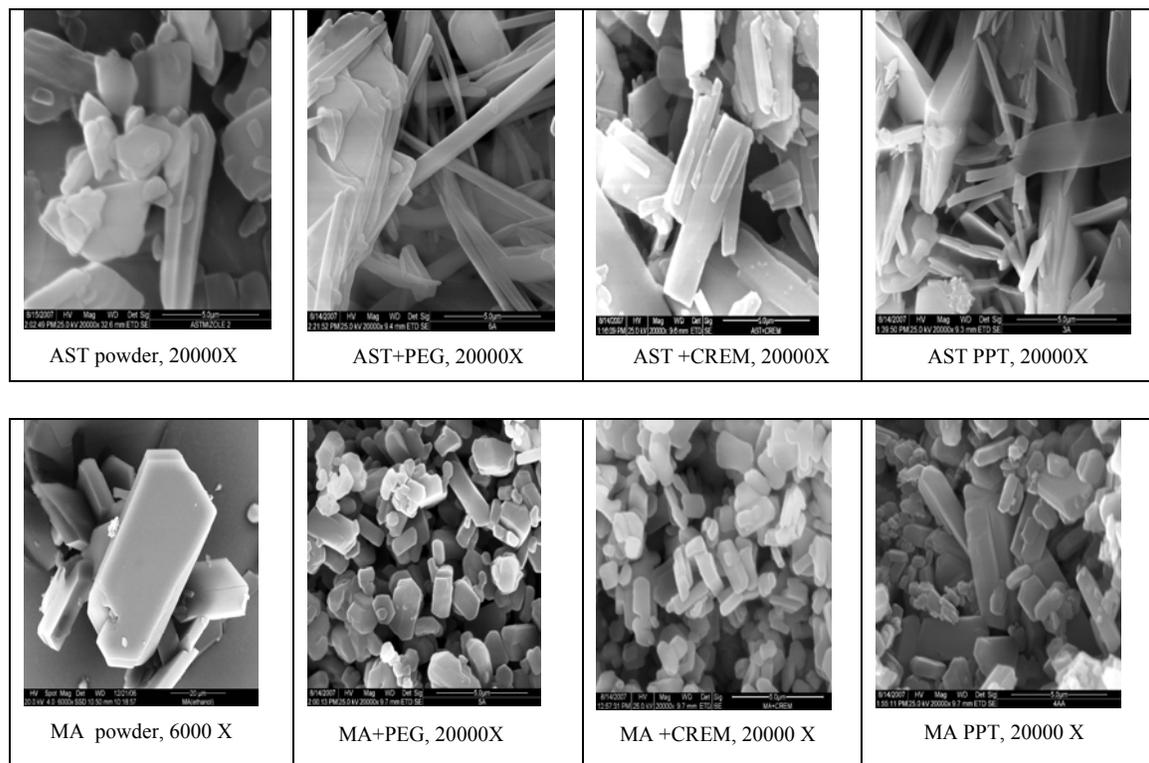
##### **Determination of the drug content of the coprecipitates:**

The samples prepared by acid-base precipitation were analyzed for their drug content, and percentage of drugs recovered from the different co-precipitates were calculated and found to be within the range of 99.99-100.2%. This result was expected since the amount adsorbed from the surfactant and polymer was too little to be detected by the available analytical methods.

##### **Characterization of Mefenamic Acid (MA) and Astemizole (AST) precipitates:**

###### **I-Scanning Electron Microscope (SEM)**

Figure 1 shows the scanning electron micrographs (SEM) of untreated and precipitated mefenamic acid and Astemizole (AST) with or without Cremophor<sup>®</sup> or PEG. It is clear from the figure that the untreated mefenamic acid powders have large plate shaped crystals, while precipitates obtained in the presence or absence of Cremophor<sup>®</sup> (CREM) SAA or (PEG) polymer have smaller plates.



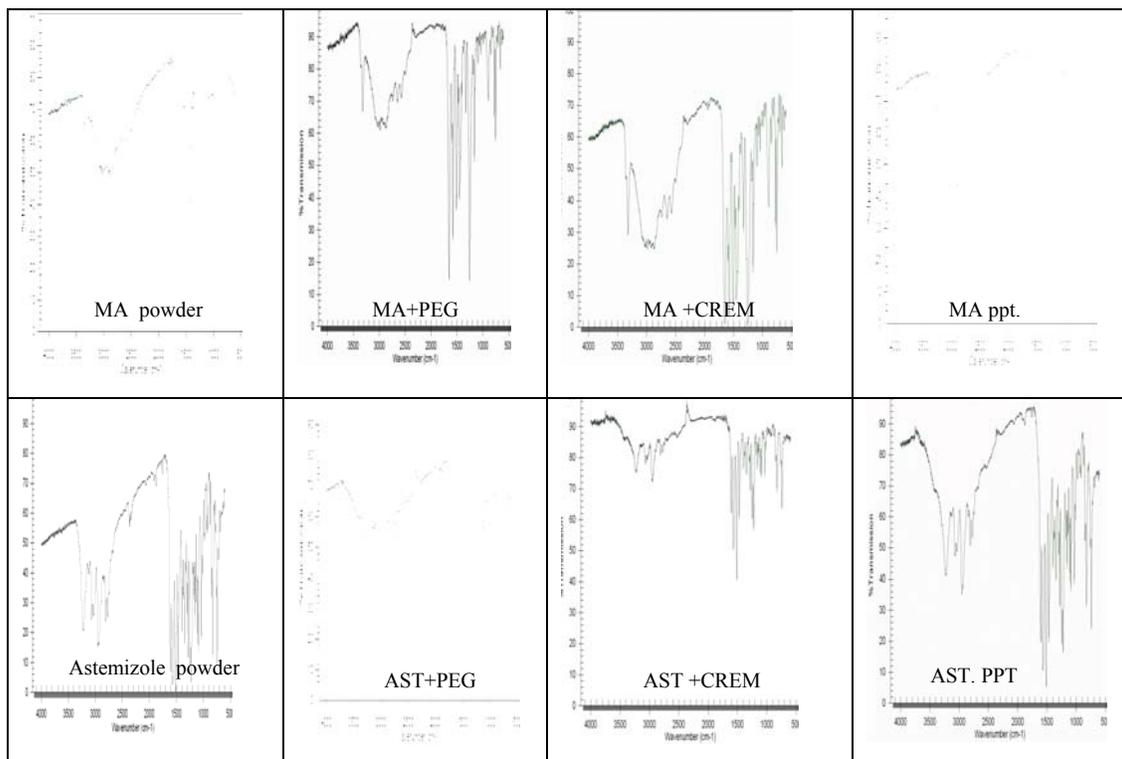
**Fig (1): Comparative scanning electron micrographs of both pure untreated (mefenamic acid and astemizole) and treated ones**

The results also showed that the size of crystals produced using CREM and PEG have the smaller size than that of the precipitated mefenamic acid without the addition of any additives. The size of the precipitates is in the following order; mefenamic acid (untreated starting material) is larger than mefenamic acid ppt (without additives) which is also larger than mefenamic acid with either PEG or CREM., it can be concluded that the precipitation method decreases the crystal size due to incomplete growth and that it is the preferential adsorption method of surface active agent molecule or polymer molecule on the crystal face which inhibits the growth from one face and produces elongated crystals<sup>18</sup>.

Regarding Astemizole crystals, no major changes in the particle size or the shape were noticed.

## II- Infrared Results

The IR spectra of all modified precipitates (Figure 2) were identical and the main absorption bands of mefenamic acid appeared in all of the spectra. This indicates that there were no difference between the internal structure and conformation of these samples. In the case of Astemizole powder, the spectra for both astemizole powder and astemizole precipitated without additives were identical while those precipitated with additives showed significant decrease in the intensities of certain absorption peaks.



**Fig (2): Comparative IR spectra for both pure untreated (mefenamic acid and astemizole) and treated powders.**

### III- DSC Results:

The DSC data for mefenamic acid (untreated) and the modified crystals are shown in figure (3). It should be noted that the DSC thermograms of all modified crystals showed only slight variation, however the modified precipitates obtained from precipitation in the absence of surface active agent or polymer showed a slight endothermic peak, this could be due to entrapment of the stabilizer or desolvation of the crystals (Gordon chaw, 1992). No differences were observed between the melting points of the precipitates and the commercial powder of astemizole.

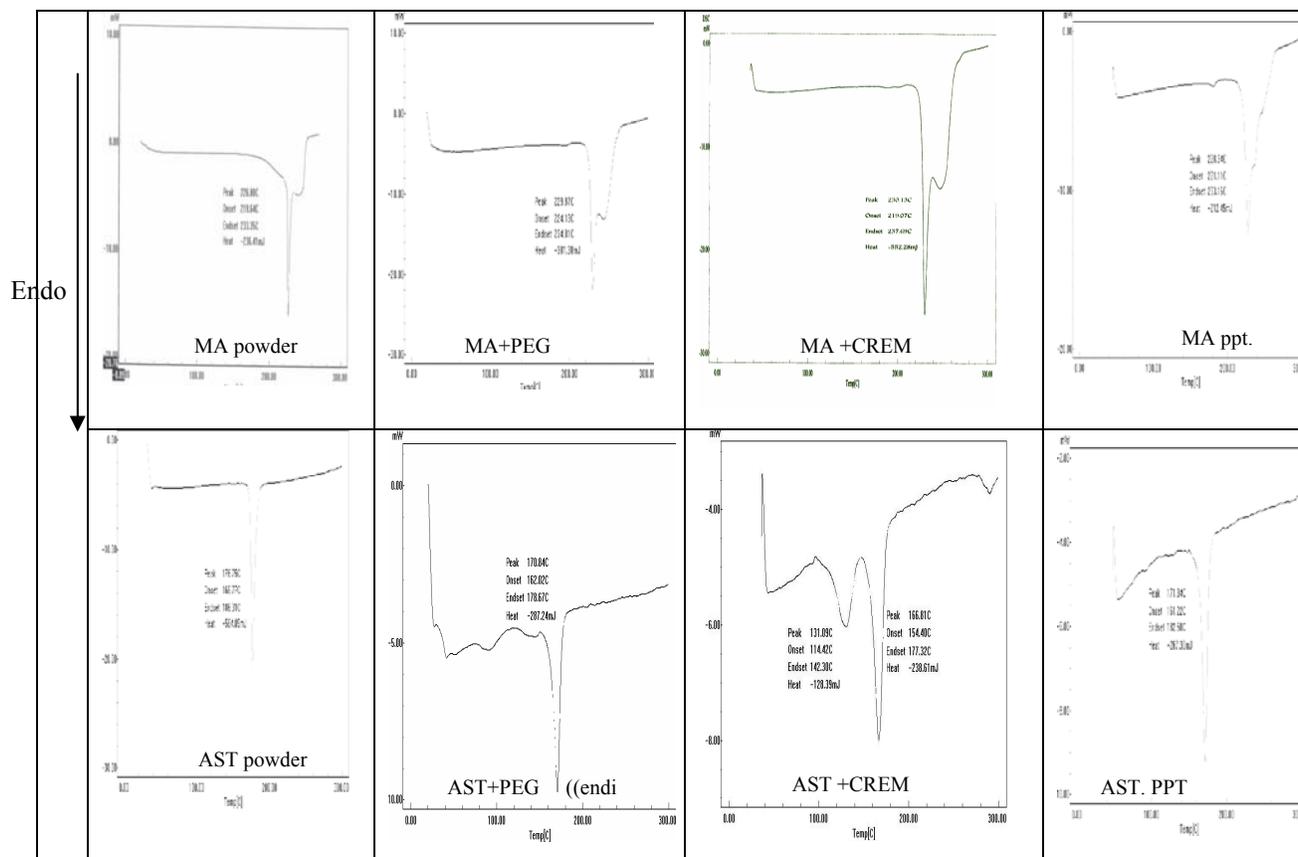
### IV- X-Ray Results:

XRD spectra of all crystals of mefenamic acid and astemizole are presented in figure (4). Sharp peaks at diffraction angles ( $2\theta$ ) were obtained in the case of

untreated mefenamic acid and the treated ones.

The presence of these sharp peaks indicates no significant difference in the entire diffraction pattern between treated and untreated mefenamic acid samples, although a decrease in the crystallinity between the untreated powder and precipitated crystals is obvious. In the case of astemizole, the X-ray patterns of the precipitated ones have a significant decrease in the crystallinity compared with the starting material.

Results from SEM photos, IR spectroscopy, X-ray powder diffraction and DSC lead to the conclusion that there are no changes in the chemical entities and polymorphic forms of both drugs. Reduction in the particle size of mefenamic acid and a decrease in the crystallinity of astemizole were the major changes occurred to both drugs as a result of precipitation process in the presence of additives.



Fig(3): Comparative differential scanning calorimetric thermographs of both pure untreated (mefenamic acid and astemizole) powders and treated ones

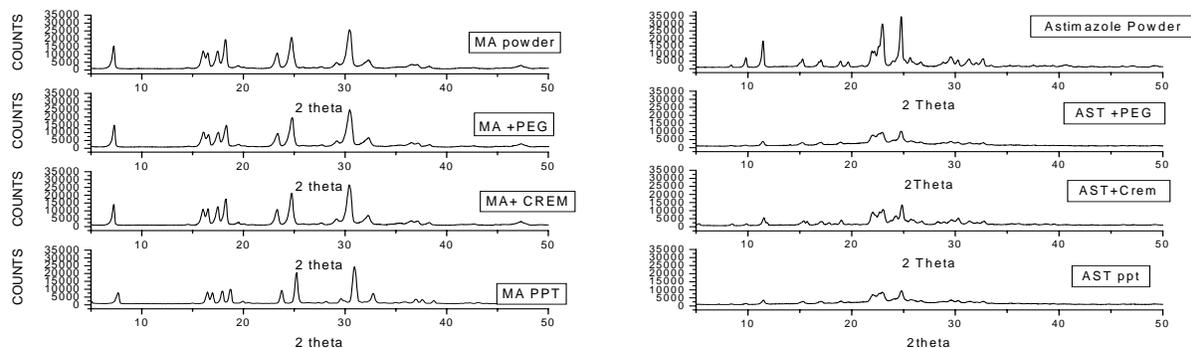
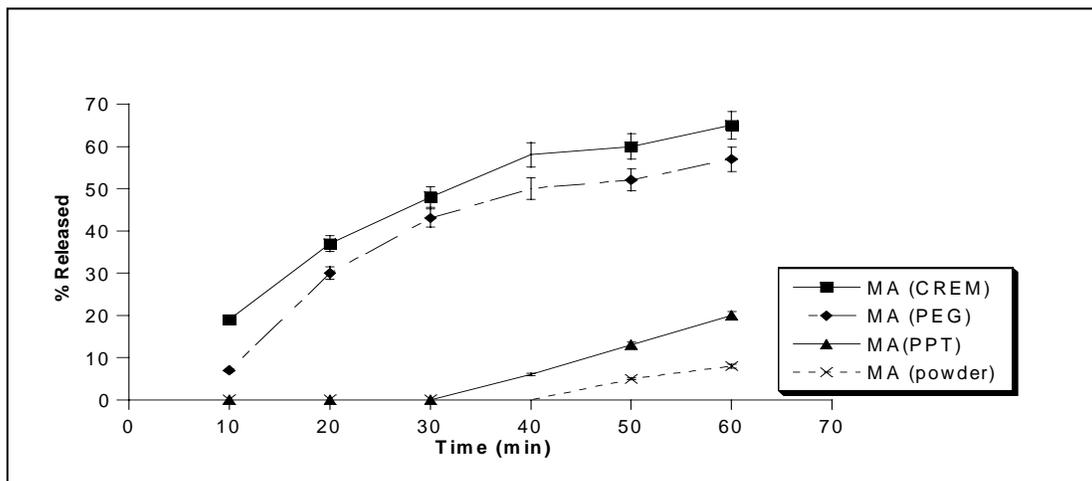


Fig (4): Comparative x-ray powder diffraction pattern of both pure untreated (mefenamic acid and astemizole) powders

**Dissolution Studies**

The dissolution profiles of Mefenamic acid and Astimazole crystals prepared by precipitation were shown in figure (5) and (6). All precipitated samples gave higher dissolution rate than control (precipitated crystal without additives and untreated powders). Mefenamic acid crystals

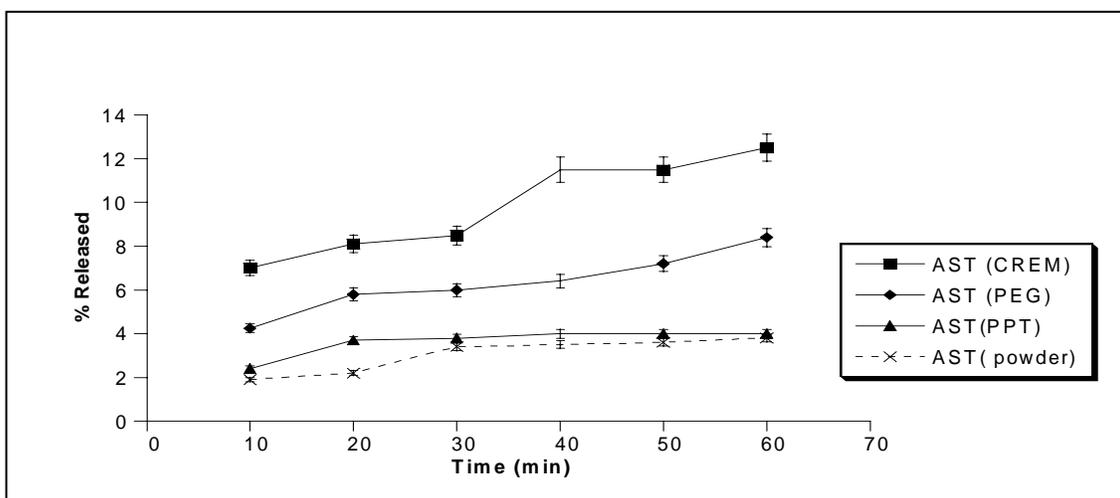
precipitated in the presence of Cremophor<sup>®</sup>, the non ionic surfactant, showed the highest dissolution rate followed in order by that precipitated in the presence of PEG, precipitated crystals without any additives and untreated mefenamic acid powder.



**Fig (5): Dissolution profile of pure Mefenamic Acid (MA) powder and treated ones**

Astimazole dissolution profiles have exactly the same trend like that of mefenmanic acid. The dissolution rate of Astimazole crystals precipitated with Cremophor<sup>®</sup> is greater than that precipitated with PEG which is greater

than the precipitated crystals without any additives. On the other hand, the untreated astemizole powder has the lowest dissolution rate.



**Fig (6): Dissolution profile of pure Astemizole powder and treated ones**

The enhancement of dissolution rate of mefenamic acid and astemizole is probably due to the following mechanisms, firstly, adsorption of Cremophor® and PEG on the surfaces of both drugs. This adsorption on the hydrophobic surfaces would increase the wettability of the crystals and thereby increase their dissolution rate. The increase in the wettability after precipitation process was evident by the observation that the prepared precipitates sink to the bottom of the vessel during dissolution, while the untreated powders float on the surface of the dissolution medium. Secondly, reduction in the particle size of mefenamic acid crystals during the precipitation process which is evident from SEM photos. While in the case of astemizole, a decrease in the degree of crystallinity was obvious in the X-ray patterns, leading to a more amorphous solid form.

In addition to the above proposed mechanisms, the presence of additives, Cremophor® and PEG, during the precipitation process might cause some defects in the structure of crystals and they would become

thermodynamically unstable and hence, dissolve faster.

### CONCLUSION

The dissolution rates of acidic and basic drugs (mefenamic acid and astemizole) can be greatly enhanced by the precipitation in the presence of additives or stabilizers. The characterization of the crystals using DSC, IR, X-ray, and SEM ruled out any polymorphic changes of both drugs. The enhancement in the dissolution rates is probably due to reduction in the particle size especially for mefenamic acid, loss in crystallinity of powders and the increase in the wettability of the crystals.

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(Astemizole)

(Mefenamic Acid)

(PEG 20000)

(Cremophor)

(PEG 20,000)

(Cremophor)

.DSC,IR,SEM,X-RAY (diffraction)

(Astemizole)

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