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Formulation and Evaluation of Mefenamic Acid Solid Dispersions Employing Starch Citrate-A New Solubility Enhancer

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ABSTRACT

Solid dispersions refer to the group of solid products consisting of at least a hydrophilic carrier and hydrophobic drug. Drug is molecularly dispersed in amorphous form. Solubility and dissolution rate is the rate determining step for bioavailability of mefenamic acid, a BCS class II drug. In this paper, preparation of starch citrate and evaluation of it, as a solubility enhancer by formulating solid dispersion using mefenamic acid will be discussed. For evaluation, as solubility enhancer, of starch citrate *in vitro* evaluation of solid dispersion (prepared by physical method, solvent evaporation method and kneading method) was done. Starch citrate found to be a novel carrier and solubility enhancer of poorly soluble drugs.

Keywords: Mefenamic acid, Starch citrate, Solid dispersion & *In vitro* studies, physical method, solvent evaporation, kneading method

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1. INTRODUCTION

Several pharmaceutical techniques are being developed for the enhancement of solubility and dissolution rate of poorly water soluble drugs. Solid dispersion is one of the novel techniques among micronization, nanosuspension, supercritical fluid process, solid dispersion, solid solution, sonocrystallization, co-solvency and hydrotrophy in enhancing the solubility of poorly soluble drugs. Solid dispersion is one of the pharmaceutical techniques for increasing the dissolution, absorption and therapeutic efficacy of drug.[1] Here, one or more active ingredients dispersed in an inert carrier matrix at solid state to prepare a fusion at melting state. In the solid dispersion, the drug is molecularly dispersed in amorphous state and result in the enhancement of solubility and dissolution rate as compared to the crystalline substance.[2,3] There are several carriers available for enhancement of the solubility and dissolution rate such as polymers, superdisintegrants, cyclodextrins, carbohydrates, surfactants, hydrotropes, polyglycolized glycerides, acids and dendrimers.[4] Even though various carriers are available for the improvement of dissolution rate of the drug, there is need of development of new carriers. Mefenamic acid is an NSAID belongs to BCS class II drug which is poorly soluble drug. It is white to off-white crystalline powder. The elimination half-life of mefenamic acid is approximately 2 hours. It acts by binding the prostaglandin synthetase receptor COX-1 and COX-2 followed by inhibiting prostaglandin synthetase.[5, 6] As mefenamic acid belongs to BCS class II drug it suffers from bioavailability problems which can be overcome by increasing the solubility and dissolution rate in the gastrointestinal fluid. The main aim of the present research work is to prepare starch citrate, as a novel solubility enhancer of poorly soluble drugs.

2. MATERIALS AND METHODS

2.1 Materials

Mefenamic acid was a kind gift from A to Z pharmaceuticals, Chennai. Citric acid was procured from microfine chemicals. Potato starch, methanol and all other solvents of analytical grade were purchased from SD fine chem. Ltd. Mumbai. Distilled water was used throughout the experimentation.

2.2 Methods

2.2.1 Preparation of starch citrate[7, 8]:

Starch citrate was prepared by dissolving 10 g of citric acid in 25ml of distilled water. The pH of citric acid solution was adjusted to 3.5 by adding drop wise 10M sodium hydroxide and the volume of this solution was made up to 50 ml by adding distilled water. In the next step, 25 g of potato starch was added to the above prepared solution and kept for conditioning at room temperature for 16 hours. After 16 hours mixture was dried at 60°C in hot air oven for six hours.

The unreacted citric acid was removed by washing the mixture with distilled water followed by drying at 50°C which results in removal of moisture entirely.

2.2.2 Characterization of starch citrate

The prepared starch citrate was evaluated for solubility, pH, melting point, viscosity, swelling index, gelling property, moisture, particle size, density, bulk density, angle of repose and compressibility index.

Solubility

In aqueous (water, aqueous buffers of pH 1.2, 4.5, and 7.4) and nonaqueous solvents (alcohol, dichloromethane, chloroform, acetone, and petroleum ether) the solubility of prepared starch citrate was checked.

pH

The pH of 1% w/v slurry was measured by pH meter.

Melting point

Melting point was determined by using melting point apparatus.

Viscosity

The viscosity of 1% dispersion in water was measured using Ostwald viscometer.

Swelling index

In two graduated test tubes having 10 ml of water and liquid paraffin respectively, 200 mg of starch citrate was added, mixed to form dispersion. The test tubes containing dispersion are allowed to stand for 12 hours. After 12 hours the volume of sediment was recorded and calculated by using the given formula:

$$S.I = \frac{\text{Volume of sediment in water} - \text{Volume of sediment in light liquid paraffin}}{\text{Volume of sediment in light liquid paraffin}} \text{ X } 100$$

Test for gelling property

Gelling property evaluation was done by heating the 7% w/v dispersion of starch and starch citrate in a water bath at 100 ºC for 30 min.

Particle size

Particle size was evaluated by standard sieving method.

Density

Benzene as a liquid, density (g/cc) was evaluated by liquid displacement method.

Bulk density

Loose bulk density was measured by taking an accurate weight amount of sample taken in a 50 ml of measuring cylinder and measure the volume of packing. Loose bulk density determined by using the formula

$$\text{LBD} = \frac{\text{Mass of powder}}{\text{Volume of packing}}$$

Tapped bulk density was measured by tapping the measuring cylinder filled with the sample on a plane surface and record the tapped volume. Tapped bulk density determined by using the formula

$$\text{TBD} = \frac{\text{Mass of powder}}{\text{Tapped volume of packing}}$$

Percentage compressibility index

Carr's compressibility determines the percentage compressibility of the powder blend. The Formula for the calculation of Carr's Compressibility Index is

$$\%\ \text{Carr's Index} = \frac{(\text{TBD} - \text{LBD})}{\text{TBD}} \text{ X } 100$$

Where, TBD= Tapped bulk density; LBD= Loose bulk density.

Angle of repose

The angle of repose is measured to determine the frictional force of loose powder blend, the maximum angle between the powder surface and the horizontal plane. Calculated by the formula

$$\tan\theta = \frac{h}{r}$$

$$\theta = \tan^{-1}\frac{h}{r}$$

Where θ=angle of repose; h=height; r=radius

2.2.3 Preparation of solid dispersion[9]

Mefenamic acid solid dispersion employing starch citrate was prepared by three different methods, i.e., physical mixing, solvent evaporation, and kneading method in different ratios as shown in table 1.

Physical mixing

Drug (Mefenamic acid) and starch citrate were taken in a ratio of 1:1,1:2,1:3 in a clean motor and mixed by using the spatula, and then the powder blend was shifted through sieve no.100 and stored in airtight container in a desiccator.

Solvent evaporation

Drug (Mefenamic acid) and starch citrate were taken in a ratio of 1:1, 1:2, and 1:3. The drug was dissolved in methanol to get a clear solution in a china dish. The starch citrate was then added to clear drug solution and dispersed. By heating, at 50°C on a heating mantel, the solvent was removed and sieved (#100) and kept in a desiccator.

Kneading method

Mefenamic acid and starch citrate were mixed geometrically to which methanol added. The mixture was stirred to form thick slurry and further kneaded to facilitate evaporation of methanol. The resultant product was dried (at 55°C), pulverized, sieved and stored in a desiccator until further use.

Table 1: Composition table of mefenamic acid solid dispersion:

Formulation	Ratio	Mefenamic acid	Starch citrate
P1 Physical mixing	1:1	1	1
	1:2	1	2
	1:3	1	3
P2 Solvent evaporation	1:1	1	1
	1:2	1	2
	1:3	1	3
P3 Kneading method	1:1	1	1
	1:2	1	2
	1:3	1	3

2.2.4 Determination of drug content[11]

The solid dispersion containing mefenamic acid equivalent to 50 mg was weighed and transferred to 50 ml of volumetric flask. Methanol was added to mix the contents thoroughly to dissolve the drug from solid dispersion. After keeping aside for 1 hour, the solution was filtered, transferred 1 ml into a 100 ml volumetric flask and by using phosphate buffer pH7.4 volume was makeup and analyzed using UV spectrophotometer 279 nm.

2.2.5 *In Vitro* dissolution studies

In vitro drug dissolution studies were performed using USP type II dissolution apparatus with pH 7.4 phosphate buffer maintained at 37°C±5°C used as dissolution medium. The prepared solid dispersion was placed in the dissolution media at the speed of 50 rpm. Aliquot of 5 ml was withdrawn from dissolution medium and replaced with fresh dissolution media at different time intervals up to 60 minutes. The samples obtained were filtered (0.45 micron) and the drug was measured by UV spectrophotometer at 279 nm.

3. RESULTS AND DISCUSSION

The starch citrate prepared was found to be white amorphous free-flowing powder. The physical and micromeritics properties of the starch citrate are given in table 2. It was insoluble in all aqueous and organic solvents tested. The pH of 1.0% aqueous dispersion was found to be 7.72. Starch citrate exhibited good swelling in water. The swelling index was found to be 1500. All micrometric properties indicated good flow properties needed manufacturing of tablets. The density of starch citrate was found to be 0.645g/cc. The angle of repose and compressibility index showed good flow properties of starch citrate.

Solid dispersion prepared using mefenamic acid, and starch citrate found to be colorless, free-flowing and amorphous. The percent of mefenamic acid dissolved from solid dispersion obtained from *in vitro* dissolution study were given in table 3.

Table 2: Physical and micromeritics properties of the starch citrate prepared

Parameters	Observation
Solubility	Insoluble in all aqueous and organic solvents tested
pH (1% w/v aqueous dispersion)	7.72
Melting Point	Charred at 210º C
Viscosity(1% w/v aqueous dispersion)	1.01cps
Swelling index	1500
Gelling property	No gelling at 100^{0}C. Where as in the case of starch, it was gelatinized and formed gel.
Particle Size	152 µm (80 mesh)
Density	0.645g/cc
Bulk Density	0.834 g/cc
Angle of Repose	21.04^0
Compressibility Index	8.81%

Table 3: Cumulative percent dissolved of mefanamic acid

Formulation/Time	5 (min)	10 (min)	15 (min)	30 (min)	45 (min)	60 (min)
F0	2.812 ±0.82	4.554 ±0.92	6.352±0.84	8.48±0.75	9.662±0.95	11.446±1.1
F1	12.112±1.2	21.818±1.26	25.382±0.86	37.836±1.36	38.218±1.42	48.386±1.24
F2	14.092±0.65	25.668±0.86	35.766±1.34	46.968±0.74	57.338±1.82	69.036±0.54
F3	14.12±0.55	26.95±0.62	37.32±0.98	47.87±1.23	59.268±1.32	71.084±0.77
F4	15.728±1.55	33.30±0.52	44.394±0.44	47.246±1.63	57.32±1.85	69.316±1.93
F5	22.492±0.22	35.066±0.78	47.626±0.63	48.16±0.51	58.586±0.48	79.85±0.22
F6	33.20±1.24	48.252±0.23	58.992±0.31	61.086±0.37	72.092±0.93	81.228±0.97
F7	34.006±0.69	57.002±0.40	61.418±0.51	74.952±1.64	83.284±1.54	91.38±1.42
F8	35.76±0.042	66.396±1.74	77.368±0.02	83.39±0.88	99.76±0.98	-
F9	40.292±0.31	82.16±0.05	99.212±0.59	-	-	-

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n dissolution studies, percentage drug dissolved from prepared solid dispersion by different methods (physical mixing, solvent evaporation and kneading method) at 5, 10, 15, 30, 45 and 60 minutes are calculated and dissolution profile for different formulation are given in below figure 1. There is increase in solubility of mefenamic acid after it was prepared into solid dispersion. The solid dispersions of mefenamic acid showed an increased rate of dissolution in comparison to pure drug. After comparing the dissolution profile of all formulations, it was found that the dissolution rate increases to the maximum extent in kneading method compared to other methods in the ratio of 1:3 (mefenamic acid: starch citrate) as showed in figure 2.

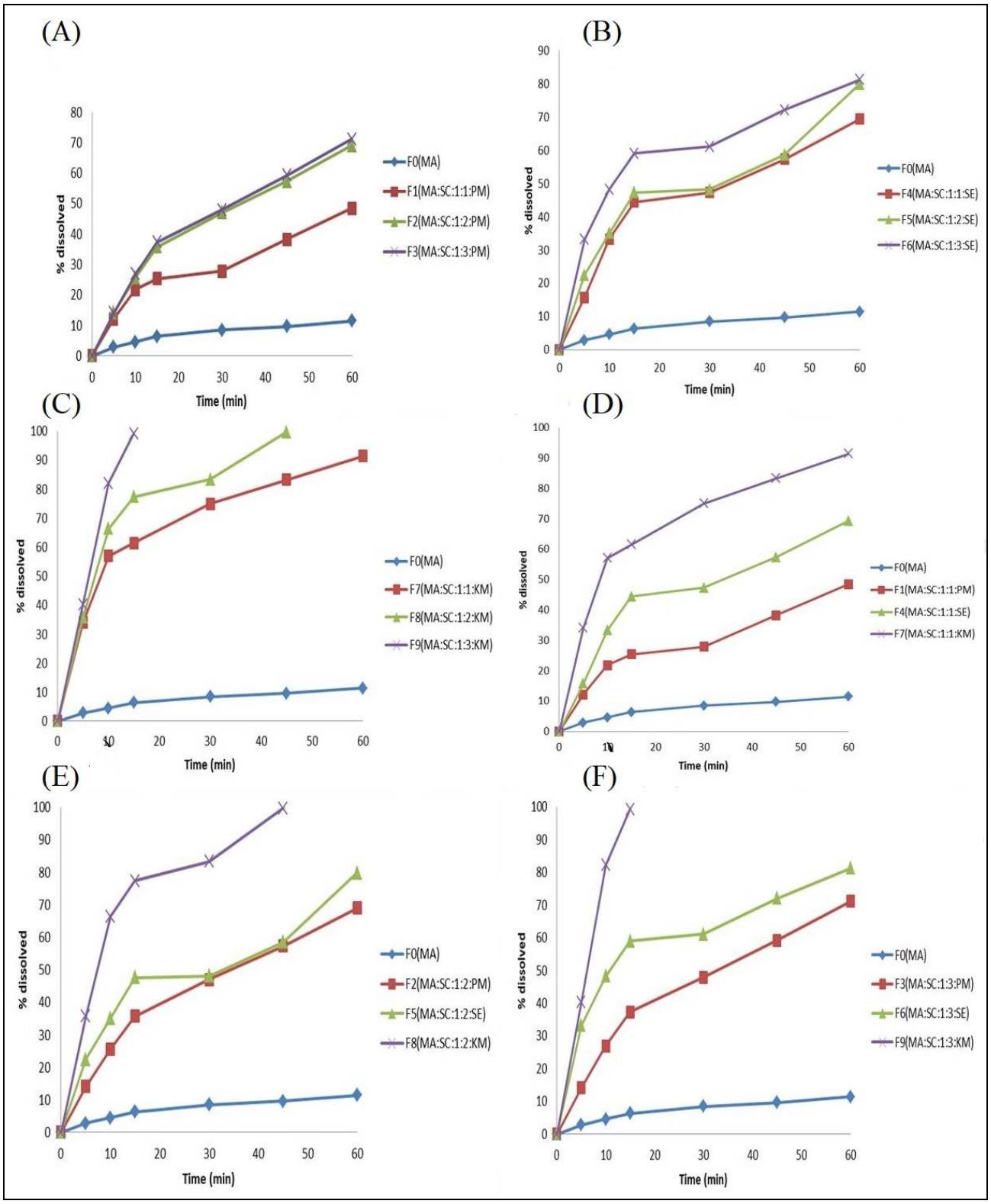

Figure 1: Dissolution profiles of mefenamic acid of solid dispersions (A: dissolution profile by physical mixing method, B: dissolution profile by solvent evaporation method, C: dissolution profile by Kneading method, D: dissolution profile of solid dispersion in 1:1 ratio, E: dissolution profile of solid dispersion in 1:2 ratio, F: dissolution profile of solid dispersion in 1:3 ratio).

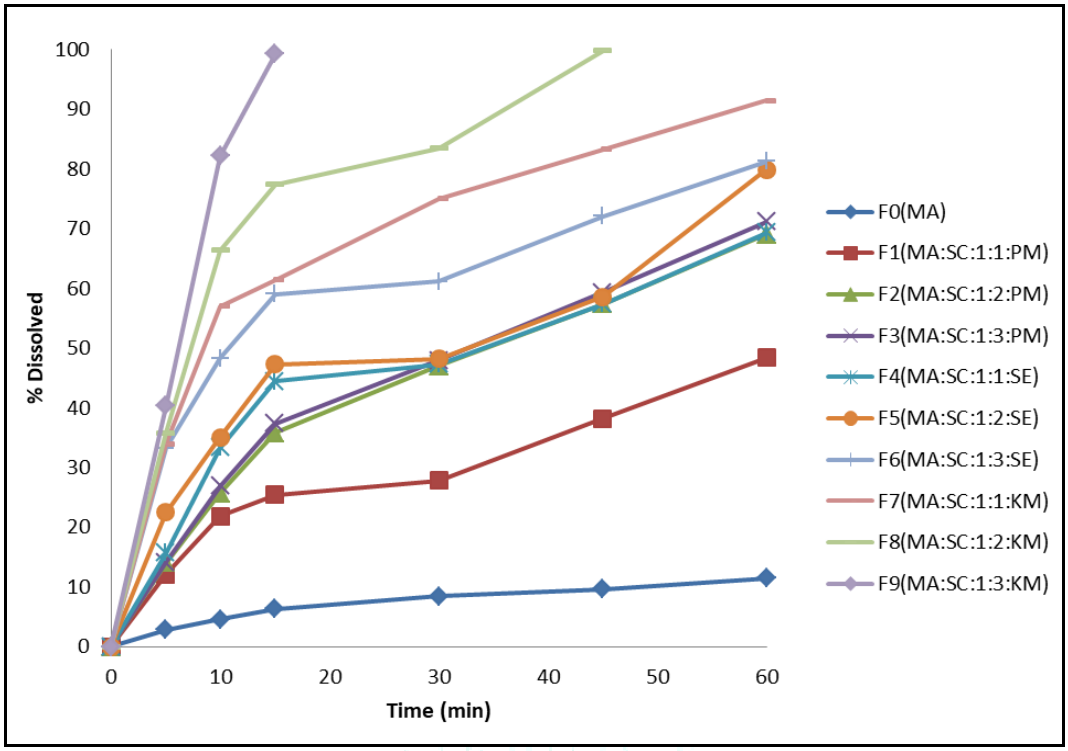

Figure 2: Dissolution profiles of Mefenamic acid of solid dispersions by different methods, (Physical mixing, solvent evaporation and kneading method) in different ratios.

4. CONCLUSION

In this research starch citrate was prepared by reacting citric acid with starch at elevated temperature. The formed starch citrate exhibited good flow property and found to be insoluble in water and organic solvents. As per the *in-vitro* dissolution profiles starch citrate can enhance the solubility of mefenamic acid to a greater extent when it is used as a carrier in kneading method of solid dispersion preparation in the ratio of 1:3. Therefore, starch citrate can be used as a novel carrier for solubility enhancement of poorly soluble drugs.

Financial & competing interests' disclosure

The authors confirm that this article content has no conflict of interest.

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