ENHANCEMENT SOLUBILITY AND DISSOLUTION OF MEFENAMIC ACID BY MODIFIED STARCH

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ABSTRACT

The objective of the present research work is to enhance the dissolution profile of the mefenamic acid by Modified Starch as a carrier. Starch citrate was prepared by reacting the citric acid with starch at elevated temperature. Starch citrate was exhibited good flow properties and it had good swelling property without pasting when heated in water was consider to be promising carrier for solid dispersions for enhancing the dissolution rate of poorly water soluble drugs. Starch citrate was characterized by Fourier transform infrared spectroscopy (FTIR), Differential scanning calorimetry (DSC) and X-ray diffraction (XRD) and these results were suggesting that structure of starch had been modified. Mefenamic acid is a non-steroidal anti-inflammatory drug belongs to the Biopharmaceutics classification system (BCS) class II drug. Dissolution rate is the rate determining step in the bioavailability of the mefenamic acid. Dissolution profile of the mefenamic acid was improved by solid dispersion technique. Solid dispersions were prepared by solvent evaporation method. Prepared solid dispersions were characterized by Fourier transform infrared spectroscopy (FTIR), Differential scanning calorimetry (DSC) and Scanning electron microscopy (SEM). In vitro dissolution studies were carried by using USP (XXIV) type II apparatus. Results of the Fourier transform infrared spectroscopy and Differential scanning calorimetry were revealed that there were no interactions between the drug and polymer. Mean dissolution rate of the pure drug was improved from 0.6391to 4.740. A 4.740 fold improvement in the mean dissolution rate of mefenamic acid was observed. Initial dissolution rate and dissolution efficiency of mefenamic acid were also found to improved. It was concluded that Starch citrate is promising carrier for dissolution enhancement of poorly water soluble drugs.

Keywords: Mefenamic acid, Starch citrate, Solid dispersions, Dissolution rate.

INTRODUCTION

Nearly about 40% of the newly discovered drugs are lipophilic and failed to reach market due to the poor water solubility [1]. Solubility and dissolution rate is the rate determining step for bioavailability of the BCS class II drugs. The bioavailability problem of the BCS class II drugs can be overcome by increasing the solubility and dissolution rate of the drug in the gastrointestinal fluids [2]. Several pharmaceutical formulation technologies are being developed for the solubility and dissolution rate of poorly water soluble drugs such as micronization, nano suspension, supercritical fluid process, solid dispersions, solid solutions, sonocrystalisation, co solvency and hydrotropy etc [3].

Solid dispersions are one of the techniques used to enhance the dissolution rate and oral absorption of the poorly water soluble drugs [4]. In the solid dispersions, the drug is molecularly dispersed or may exist in amorphous state and this may result in the enhancement of the solubility and dissolution rate as compared with the crystalline substance [5].

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 [6]. Even though various carriers are available for the improvement of dissolution profile of the drugs continues development of new carriers is needed. Chowdary et al., [7, 8] has reported starch citrate is a noval carrier for solid dispersions and also as a disintegrant in tablet formulation.

Mefenamic acid is a NSAID belongs to the BCS class II drug. Dissolution rate is the rate determining step in the bioavailability of the mefenamic acid. The main aim of the present research work is preparation of the potato starch citrate as a novel carrier for the solid dispersions and the dissolution profile of the mefenamic acid has been improved

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by using starch citrate. Solid dispersions were prepared by solvent evaporation method [9]. The prepared solid dispersions were characterized by Fourier transform infrared (FTIR) spectroscopy, Differential scanning calorimetry (DSC) and Scanning electron microscopy (SEM).

MATERIAL AND METHODS

Mefenamic acid was a gift sample from A to Z pharmaceuticals, Chennai, Potato starch and Methanol were purchased from S.D. Fine Chem. Ltd, Mumbai and Citric acid was purchased from Microfine chemicals. All other chemicals and solvents used were of analytical grade.

Preparation of Starch Citrate

Potato Starch citrate was prepared based on the method reported by Chowdary et al., [7, 9]. 20 g of the citric acid was dissolved in 20 ml of the distilled water. The pH of the citric acid solution was adjusted to 3.5 with 10 M sodium hydroxide solution and finally the volume of the solution was made up to 50 ml by adding distilled water. The citric acid solution was mixed with 50 g of potato starch in a stainless steel tray and conditioned for 16 h at room temperature (28^0C). The tray was then placed in a hot air oven and dried at 60^0C for 6 h. The resulting mixture was ground and further dried in hot air oven and dried at 130^0C for 2 h. From the dried mixture the unreacted citric acid was removed by washing the product with distilled water. The washed product was dried at 50^0C to remove water/moisture completely. The dried starch citrate was ground and sized.

Characterization of Starch Citrate
Physicochemical properties

The physicochemical properties like solubility, pH, melting point, viscosity, swelling index, test for gelling property, density, bulk density, angle of repose, compressibility index of starch citrate were determined based on method of chowdary et al [10].

Fourier Transform Infrared spectroscopy

The FTIR spectra of starch, citric acid and starch citrate were obtained on a Thermo-IR 200 FTIR Spectrophotometer. The KBr pellet technique was used to prepare the samples. The spectrum was recorded in the spectral region from 4000 to 400cm^{-1}.

Differential scanning calorimetry

DSC analysis of the starch, citric acid and starch citrate were performed using Mettler Toledo DSC 822e. The samples were weighed and encapsulated in a flat bottomed aluminum pans. Liquid nitrogen was used as coolant. The samples were scanned at 10^0C/min over temperature range of 0-300^{0}C.

X-ray diffraction

The solid state properties of the starch and starch citrate were carried by XRD by using XPERT-PRO X-ray diffractometer. The diffraction pattern was recorded at room temperature over a range 3 to 80 (2θ).

Preparation of Solid Dispersions

Solid dispersions of mefenamic acid were prepared by solvent evaporation method. The solid dispersions were prepared in 1:1, 1:2, 1:3 and 1:4 ratios of drug: carrier. Required amount of mefenamic acid was taken into a dry mortar and sufficient amount of methanol was added to get clear drug solution. Starch citrate was then added and mixed. The thick slurry was kneaded for complete evaporation of methanol and then dried at 55°C until dry. The dried mass was pulverized and sieved through mesh no. 80. and stored in desiccator.

Table 1. Formulation of Mefenamic acid solid dispersions

Formulation	Ratio	Mefenamic acid (g)	Starch citrate (g)
P1	1:1	1	1
P2	1:2	1	2
P3	1:3	1	3
P4	1:4	1	4

Evaluation of Solid Dispersions
Fourier Transform Infrared

The FTIR spectra of starch citrate, Mefenamic acid and solid dispersions were obtained on a Thermo-IR 200 FTIR Spectrophotometer which was employed to characterize the possible interactions between the drug and carrier in the solid state. The KBr pellet technique was used to prepare the samples. The spectrum was recorded in the spectral region from 4000 to 400cm^{-1}.

Differential scanning calorimetry

DSC analysis of the starch citrate, Mefenamic acid and solid dispersions were performed using Mettler Toledo DSC 822e. The samples were weighed and encapsulated in a flat bottomed aluminum pans. Liquid nitrogen was used as coolant. The instrument was calibrated with Indium. The samples were scanned at 10^0C/min over temperature range of 0-300^{0}C.

Scanning electron microscopy

Morphology and surface morphology of the pure drug and solid dispersions was studied by scanning electron microscope by using scanning electron microscope (SSM-840, Jeol Corporation, Japan). The SEM images were recorded at different magnifications.

Drug content

50 mg equivalent of mefenamic acid was weighed and transfer in to 50 mL of volumetric flask. Methanol was added and mixed the contents thoroughly to dissolve the drug from the solid dispersions and kept aside for 1 h. The solution was filtered. From the filter solution 1 mL was withdrawn into 100 mL volumetric flask. The volume was

made up to 100 mL with methanol and assayed at 279 nm for mefenamic acid.

In-Vitro dissolution study

In-vitro dissolution studies were carried out for pure drug and solid dispersions by using USP (XXIV) type II apparatus. Dissolution studies were carried using pH 7.4 phosphate buffers as a dissolution medium, temperature $37^0C\pm0.5^0C$ and the paddle rotation speed of 50 rpm. 50 mg equivalent of mefenamic acid of the prepared solid dispersions was placed in the basket of the dissolution medium. Aliquot of 5 mL were withdrawn at different intervals up to 60 minutes and a 5 mL of the fresh medium was added to replace the sample that was withdrawn. The samples were filtered through 0.45μ membrane filter and the filtrate was diluted suitably and analysed for mefenamic acid at 279 nm by UV.

Dissolution parameters

The dissolution data of the pure drug and solid dispersions were subjected to calculation of dissolution parameters like DE, MDR, and IDR. DE was calculated as described by Khan et al (10). Dissolution parameters were calculated as follows

$$D.E. = \frac{\int_0^t y \times dt}{y_{100} \times t} \times 100$$

IDR= % dissolved/min

$$MDR = \frac{\sum_{j=1}^{n} \Delta M_j / \Delta t}{n}$$

RESULTS AND DISCUSSION
Starch citrate

Citric acid can form reactive anhydride upon heating by loosing water molecule. The reactive anhydride can react with starch which is present in the reaction mixture to form starch citrate. The reaction involved in the preparation was shown in the Fig.1.

Fig 1.   Chemical reaction involved in the preparation of the starch citrate
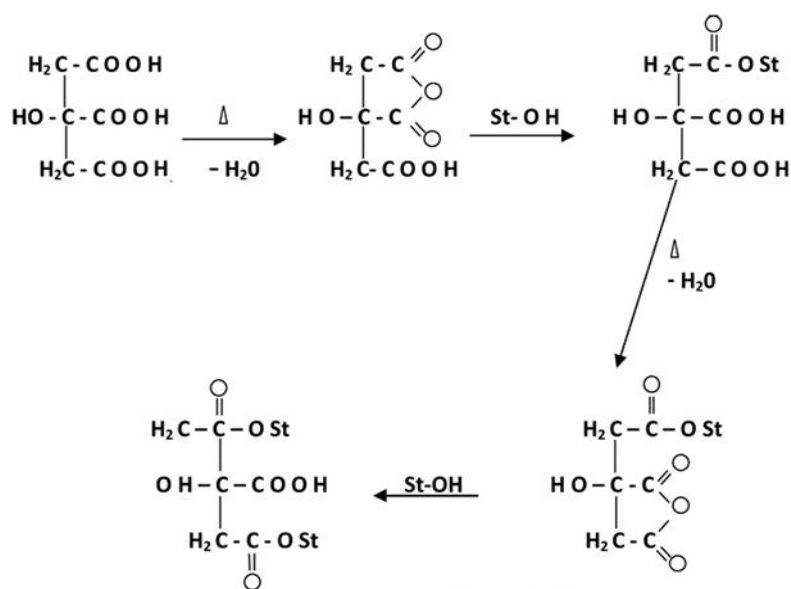

Table 2. Physical properties of the Potato Starch citrate prepared

S.NO	Property	Result
1	Solubility	Insoluble in all aqueous and organic solvents
2	pH(1% w/v aqueous dispersion)	4.78
3	Melting point	Charred at 210^oc
4	Viscosity (1% w/v aqueous dispersion)	0.9906 cps
5	Swelling index	1100
6	Gelling property	No gelling and the swollen particles of starch citrate separated from water. Where as in the case of starch, it was gelatinized and formed gel
7	Density	0.605 g/cc
8	Angle of Repose	20.04^o
9	Compressibility Index	8.33%

Fig 2. Microscopic images of (A) Starch and (B) Starch citrate
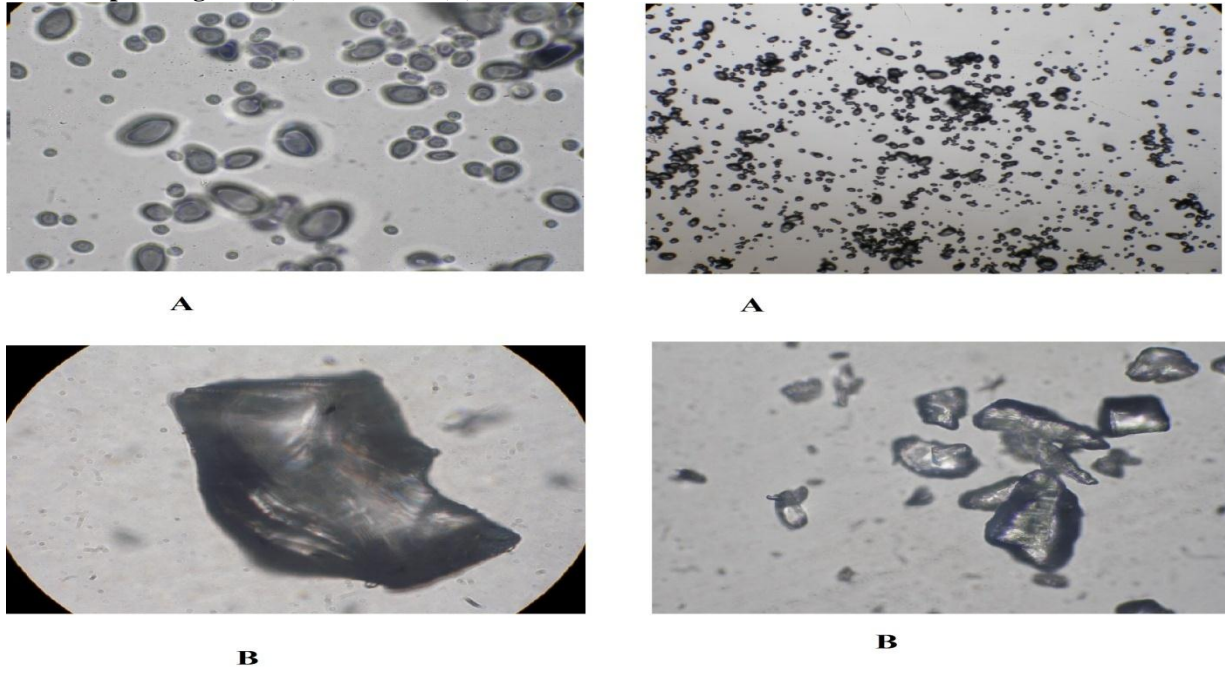

A

A

B

B

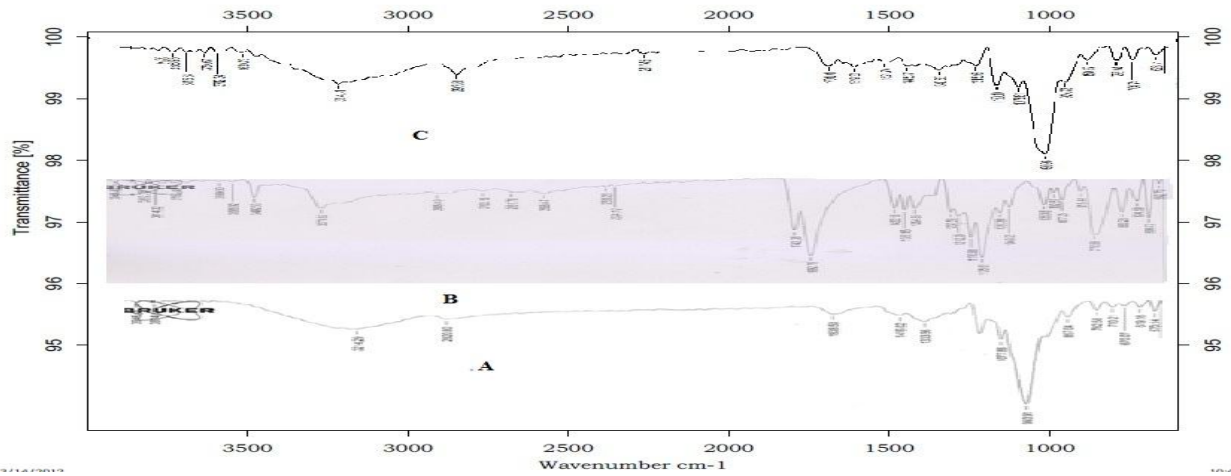**Fig 3. FTIR spectra of the (A) Citric acid, (B) Starch and (C) Starch citrate**

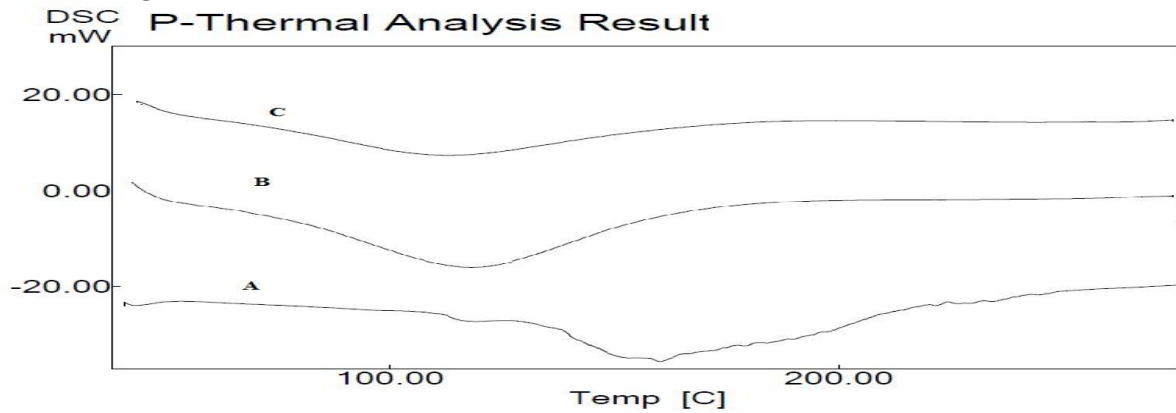**Fig 4. DSC thermograms of (A) Citric acid, (B) Starch and (C) Starch citrate**

Fig.5. X-Ray Diffractograms of (A) Starch and (B) Starch citrate
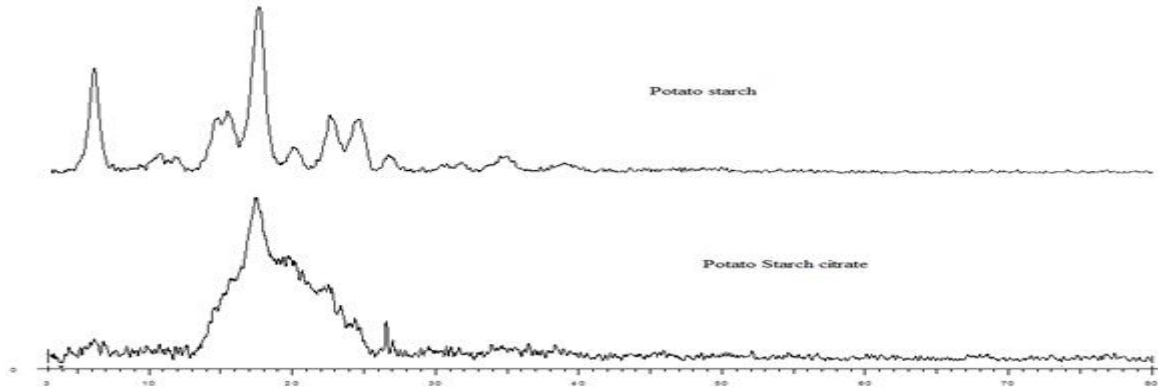

Fig 6. FTIR spectra of the (A) Starch citrate (B) Mefenamic acid, (C) Physical mixture and (D) solid dispersions
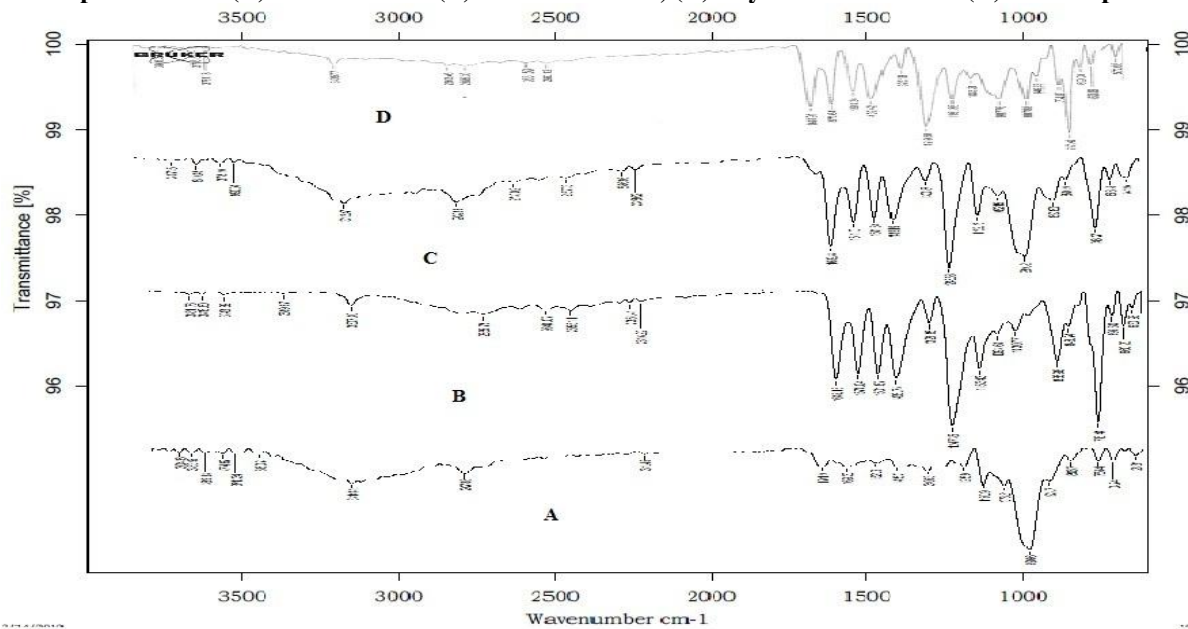

Fig.7. DSC thermograms of (A) Mefenamic acid , (B) P2 Solid dispersions, (C) P4 solid dispersions and (D) Starch citrate
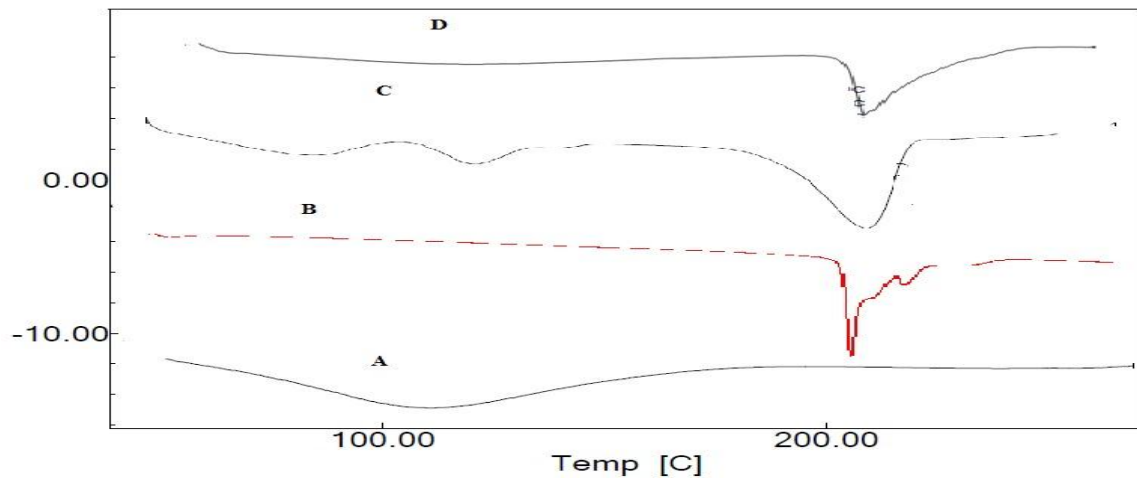
Fig 8. Scanning electron photomicrographs of (A) Mefenamic acid, (B) Starch citrate, (C) P2 solid dispersions and (D) P4 solid dispersions
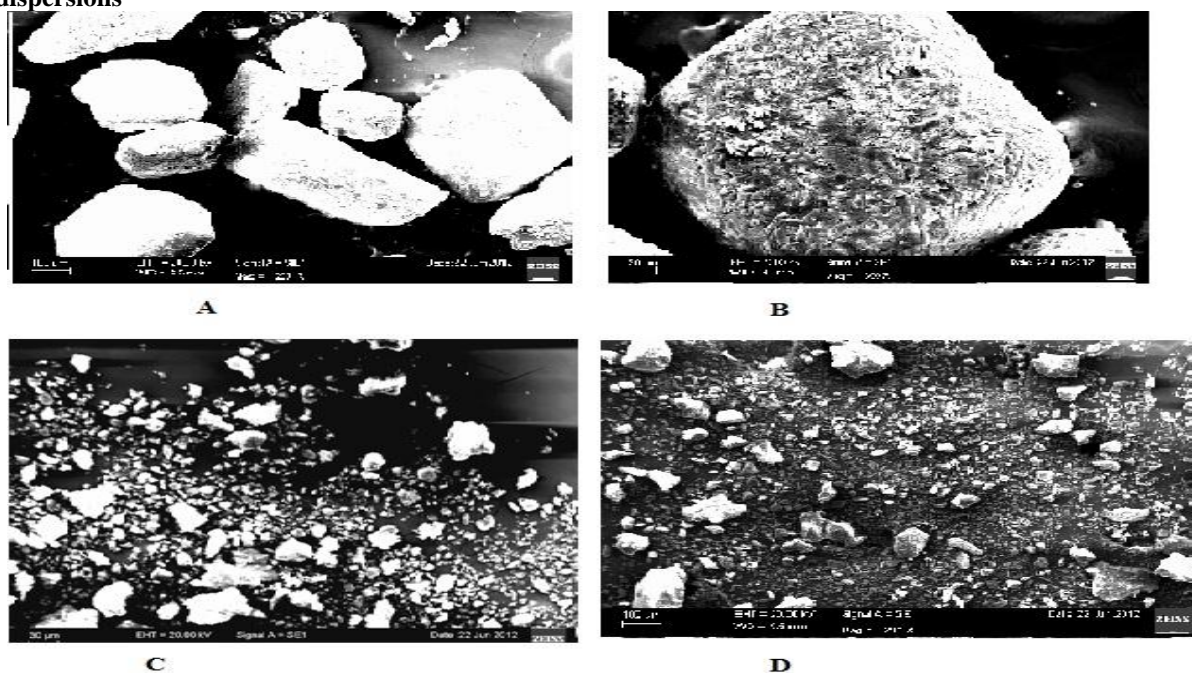

Fig 9. *In-Vitro* dissolution profile of the pure drug (Mefenamic acid) and Solid dispersions
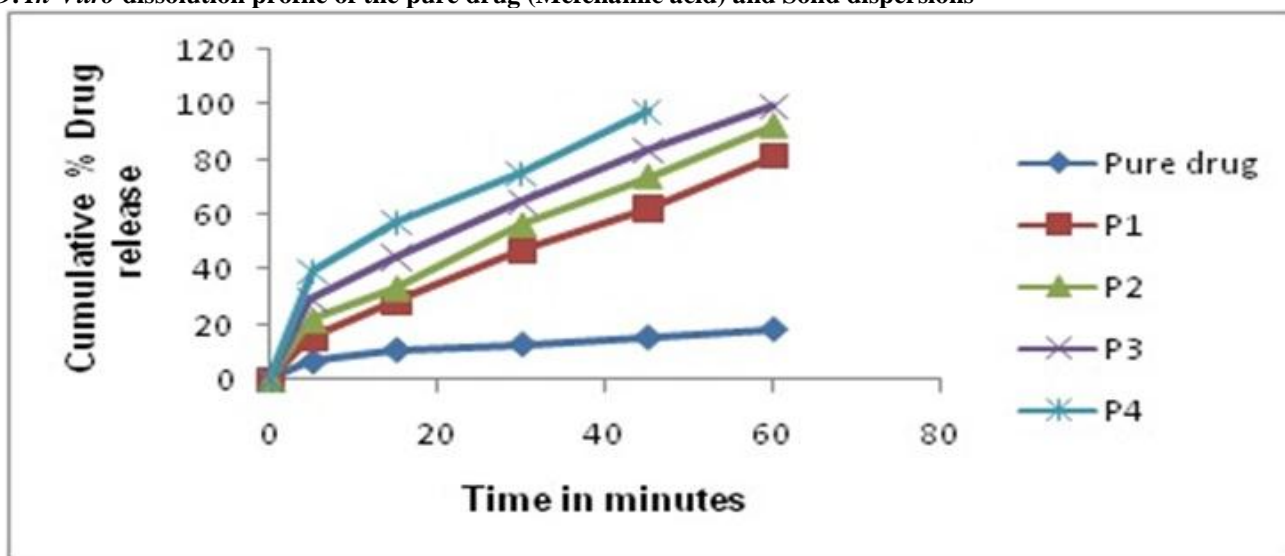

Table 3. Drug content of solid dispersions

S.NO.	Formulation	% Drug content
1	P1	96.157
2	P2	99.473
3	P3	95.684
4	P4	98.562

Physicochemical properties

      Physicochemical properties of the starch citrate were shown in the Table.2. Native potato starch was found to be simple granules (round and polygonal) in shape. The

starch granules consist of semicrystalline structure [11]. The prepared starch citrate was found to be off white color and semicrystalline nature. The semicrystalline nature further conformed by DSC. The melting point of the starch citrate was determined by using meting point apparatus. Native starch and starch citrate was not having any meting point but charred at 238^0C, 222^0C. The results of DSC further conformed that the native starch and starch citrate does not having melting point. Native starch was hydrolyzing upon heating and converted to gel/ paste and it was not found in case of the starch citrate. The swelling property of the starch citrate in water was compared with starch and it was found

that starch citrate had 1100% swelling in water. Starch citrate was found to be insoluble in water, aqueous buffers of pH 1.2, 4.5, 7.4 and organic solvents. Starch citrate was exhibited good flow properties.

Chemically modified starch had good swelling property without pasting when heated in water was consider to be promising carrier for solid dispersions for enhancing the dissolution rate of poorly water soluble drugs.

Fourier Transform Infrared spectroscopy

FTIR spectra of the starch, citric acid and starch citrate were shown in Fig.3. The starch shows significant peaks at 3214.29 cm^{-1} indicates OH Stretching, 2920.80 cm^{-1}. The starch citrate shows significant peaks at 3379.37 cm^{-1} indicates OH Stretching, 1705.09 cm^{-1} indicates C=O stretching, 1146.86 cm^{-1} indicates C-O-C stretching. The C=O stretching, C-O-C stretching characteristic bonds were absent in the starch.

Differential Scanning Calorimetry

The DSC thermograms of the starch, citric acid and starch citrate were shown in the Fig.4. There was no endothermic peaks were observed in starch and starch citrate. The citric acid was showing the melting point at 156.56^{0}C. The results of the DSC conformed that the structure of the starch and starch citrate were not totally crystalline in nature.

X-ray diffraction

The X-ray diffractogram pattern of potato starch and potato starch citrate were shown in the fig.5. The X-ray diffraction studies can be used to predict the crystallinity of the potato starch and potato starch citrate. The XRD of the potato strach showed intense peaks at 2θ values of 5.881, 16.945, 17.024, 17.123, 17.262, 17.319, 17.433, 17.6, 17.739. The potato starch citrate showed intense peaks at 16.686, 16.806, 17.101, 17.366, 17.471, 17.799 and 18.057. In case of potato starch the intense peaks were at a paticular 2θ values and in case of the starch citrate intensity of the peaks were decreased but it was spread over region of the 2θ values. The XRD of the potato starch and potato starch citrate were found to be different and indicates that the crystalinty of the starch and starch citrate were found to be different. The crystalinty structure was increased in case of the potato starch citrate. The change in the crystalinity may be due to the addition of the citric acid to the starch.

Evaluation of the solid dispersions
Fourier Transform Infrared

The FTIR spectra of the mefenamic acid, starch citrate and solid dispersions were shown in the Fig.6. The mefenamic acid was shown significant peaks at 3307.40 cm^{-1} indicates N-H stretching, intense bands at 1570.04 cm^{-1} indicates N-H bending, 1645.18 cm^{-1} indicates C=O stretching, 746 cm^{-1} indicates aromatic stretching. These characteristic peaks were also observed in FTIR spectrum of solid dispersions formulation suggesting that there were no interactions between the drug and polymer.

Differential Scanning Calorimetry

The DSC thermograms of mefenamic acid, starch citrate and solid dispersions were shown in the Fig.7. Mefenamic acid was shown a sharp endothermic peak at 230^{0}C. In case of the solid dispersions the endothermic peak was observed at 217^{0}C. There was a slight shift in the endothermic peak towards lower temperature with lower intensity (broad peak). Low intensity peak of endothermic peak indicates that some amount of drug is still present in the crystalline state. Broad peak indicates that the some amount of the drug was partly dissolved in carrier.

Scanning Electron Microscopy

The SEM images of the mefenamic acid, starch citrate and solid dispersions were shown in the Fig.8. Mefenamic acid was appeared as crystalline and the size of the crystals was found to be different. In case of solid dispersions still the drug was appeared as a crystalline but the size of the crystals was reduced to greater extent.

Drug content

The drug content was found in the range of the 95.684 to 99.473. The drug content values were shown in the table.3. P2 formulation was shown highest drug content. These results were suggesting that the acceptability of present method of preparation of the solid dispersions.

In-Vitro dissolution study

The dissolution study was carried out for the prepared solid dispersions of mefenamic acid and pure drug in pH 7.4 phosphate buffer. The dissolution profile of the pure drug and solid dispersions were reported in the Fig.9 and the dissolution parameters were presented in the table.4. At the end of 60 min pure drug showed a maximum release of 18% of the drug where as solid dispersion of 1:1, 1:2 and 1:3 showed 81.2%, 92.13% and 99.473 respectively. P4 formulation was shown 97.342% drug release at 45min. DE_{45} of pure drug, P1, P2, P3 and P4 was found in the order of the 8.483, 30.631, 36.512, 42.947 and 50.684 and a 5.974 fold increase in DE_{45} of mefenamic acid was found in P4 when compared with the pure drug. IDR of the pure drug was found to be 1.283 and it was improved up to 7.910. P4 formulation of the solid dispersions was shown highest IDR. MDR of the pure drug was improved from 0.6391 to 4.740. A 4.740 fold improvement in the MDR of mefenamic acid was found in P4 when compared with pure drug. The dissolution parameters were improved by increasing the concentration of carrier. Values of $T_{50\%}$ were presented in the table. Time taken by the P4 formulation to release 50% of drug was found to be 10.96 minutes.

CONCLUSION

In the present study the starch citrate was prepared

by reacting the citric acid with starch at elevated temperature. Prepared starch citrate was found to be insoluble in water, organic solvents, acidic and alkaline pH. Starch citrate was exhibited good flow properties. Starch citrate was characterized by FTIR, DSC and XRD and these results were suggesting that structure of starch had been modified. Chemically modified starch had good swelling property without pasting when heated in water was consider to be promising carrier for solid dispersions for enhancing the dissolution rate of poorly water soluble drugs. Results of the FTIR and DSC were revealed that there were no interactions between the drug and polymer. DSC and SEM results confirmed the decrease crystallinity of the mefenamic acid. DE and MDR had been enhanced by increasing the concentration of starch citrate in the formulation. It was concluded that starch citrate is a promising carrier for dissolution enhancement poorly water soluble drugs.

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