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Enhancement of Dissolution Rate of Poorly Soluble Drug Mefenamic Acid by Solid Dispersion

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ABSTRACT

The object of this article is to investigate enhancement of the dissolution rate of Mefenamic acid (MA) using solid dispersion method. A series of solid dispersions of the drug MA using poly ethylene glycol 6000 (PEG 6000) , poly vinyl pyrrolidone K-30 (PVP K-30), hydroxyl propyl methyl cellulose (HPMC) and micro crystalline cellulose (MCC) as carriers were prepared following the kneading and solvent evaporation methods. Dissolution studies using the USP XIV apparatus were performed for solid dispersions of MA. The FTIR spectra of samples were taken on the FTIR spectrophotometer using the KBr disk to identify the physicochemical interaction between drug and carrier, hence its effect on dissolution. IR spectroscopy showed no change in the structure of MA. Powder x-ray diffractometry was carried out to find out the changes in crystalline nature of the MA. The samples were analyzed by DSC using a Mettler Toledo S R System. Solid dispersions at 2:2:6 ratio of MA: HPMC: MCC, a 6.94 fold increase in the dissolution rate of MA was observed. Solid dispersions, prepared using HPMC showed greater improvement in dissolution profile of MA prepared by solvent evaporation technique. Thus, the solid dispersion technique can be successfully used for improvement of dissolution rate of MA.

Keywords: Mefenamic acid (MA), solid dispersion (SD), dissolution rate.

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INTRODUCTION

The rate and extent of dissolution of the drug from any solid dosage form determines the rate and extent of absorption of the drug [1, 2]. In case of poorly water soluble drug, dissolution rate is rate limiting step in the process of drug absorption, Potential bioavailability problem relevant with extremely hydrophobic drug is may be due to erratic and incomplete absorption from GIT [3]. Potential absorption problem occur if the aqueous solubility is less than 1mg/ml. Several techniques have been developed for the solubility enhancement of poorly soluble drugs such as solid dispersion [4-8], inclusion complex [9,10], ultra rapid freezing process [11],melt sonocrystallization [12], solvent change method [13],melt granulation technique [14], supercritical solvent, supercritical and cryogenic technique, cosolvent approach. Numerous solid dispersion systems have been demonstrated in the pharmaceuticals literature to improve the dissolution properties of poorly water soluble drugs, which was introduced in the early 1970's is a multicomponent system, such as nimesulide, ketoprofen, tenoxicam, nifedipine, nimodipine, ursodeoxycholic acid, and albendazole. Various hydrophilic carriers, such as polyethylene glycols, polyvinylpyrrolidone, hydroxypropyl methylcellulose, gums, sugar, mannitol and urea have been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs [15]. Francis et al [16] in their patent describes the no. of the drugs from which solid dispersion can be prepared. Because of poor aqueous solubility, MA may possess dissolution related absorption problem, hence an attempt was made to improve the dissolution of MA through the solid dispersion technique.

MATERIALS AND METHODS

Mefenamic acid was a gift sample from M/s.Sigma Laboratories, Mumbai, methanol (Qualigens) and polyvinyl pyrrolidone (PVP K_{30}) was a gift sample from M/s. Sun Pharma Ind. Ltd., Mumbai. All other materials used were of pharmacopoeial grade and were procured from commercial sources.

Preparation of solid dispersions

Preparation of Solid Dispersions Employing Superdisintegrant MCC

Solid dispersions of MA in superdisintegrant MCC were prepared by solvent evaporation method. The required quantities of MA were dissolved in methanol to get a clear solution in a dry mortar. The super disintegrant MCC (passed through 120 No. mesh) was then added to clear drug solution and dispersed. The solvent was removed by continuous trituration. Trituration was continued until a dry mass was obtained. The mass obtained was further dried at 50^0 C for 4 hours in an oven. The product was crushed, pulverized and shifted through mesh no.100. Solid dispersions in the superdisintegrant MCC were prepared at a ratio of MA, MCC namely 1:4 respectively.

Preparation of Solid Dispersions Employing Combined Carriers

The required quantities of MA and water soluble carriers (PEG, PVP, HPMC) were dissolved in the solvent to get a clear solution in a dry mortar. The super disintegrant MCC was then added to the drug solution and dispersed. The solvent was then evaporated by continuous trituration. Trituration was continued until a dry mass was obtained. The mass obtained was further dried at 50^0 C for 4 hours in an oven. The product was crushed, pulverized and shifted through mesh N0.100. Various solid dispersions prepared with their composition are listed in Table 1.

Table1. Composition of various solid dispersions prepared

S No	Composition		
	Drug	Carriers	SD Code
1	Mefenamic acid	(2)PEG (2), MCC (6)	MA-PEG-MCC,226
2	Mefenamic acid	(2) PVP(2), MCC(6)	MA-PVP-MCC,226
3	Mefenamic acid	(2) HPMC (2), MCC	MA-HPMC-MCC,226
4	Mefenamic acid	(1)MCC(4)	MA-MCC,14

Estimation of Mefenamic Acid

A spectrophotmetric method based on the measurement of absorbance at 279 nm in phosphate buffer pH7.4 was used in the present study for the estimation of Mefenamic acid [23]. The method was validated for reproducibility, accuracy, precision and linearity by analyzing six individually weighed samples of MA. The stock solution of MA was subsequently diluted to a series of dilution containing 5, 10, 15 and 20 *µg/ml* of solution, using phosphate buffer of pH7.4. The absorbance of these solutions was measured in UV-VIS spectrophotometer (ELICO SL-159) .The method obeyed Beer's law in the concentration of 0-20 *µg/ml.*

Estimation of Mefenamic acid in the solid dispersions prepared

From each batch, 4 samples of 50 mg of SD's each were taken and analyzed for the drug Mefenamic acid. 50 mg of dispersions were weighed into a 100 ml volumetric flask. Methanol was added and mixed the contents thoroughly to dissolve the drug from the dispersion. The solution was then filtered and collected carefully into another 100 ml volumetric flask. The solution was made up to volume with the solvent. The solution was suitably diluted with appropriate dissolution fluid and assayed at 279 nm for MA. The results are given in Table 2.

Fourier-transform infrared spectroscopy (FTIR)

Fourier transform infrared spectra of Pure Drug & solid dispersions of MA with HPMC and MCC are shown in (Figure 4). The spectra of pure drug showed peaks at 3310.23cm^{-1}(N-H stretch), 1649.70cm^{-1}(C=O stretch), 1575.30cm^{-1} (N-H bending), 1507-08cm^{-1} (C=C stretch), 751.38cm^{-1}(aromatic stretch).

X-ray diffractometry

The XRD patterns of the MA, HPMC and MCC solid dispersions are shown in (Figure 5). It has been observed that the diffraction patterns of the solid dispersions are somewhat diffused compared to diffraction patterns of MA. It also indicates that the crystallinity of the solid dispersions are less than that of the MA.

Differential scanning Calorimetry (DSC)

The DSC patterns for MA with HPMC and MCC solid dispersions are shown in (Figure 6). DSC thermogram of MA exhibits endothermic peaks at 229.41^{o}C corresponding to its melting point and is confirmed by literature data [26,27]. Solid dispersion of MA,HPMC,MCC showed endothermic peak at 229.22 which shows a weak interaction in the physical mixture.

Dissolution Rate Studies on Solid Dispersions

Dissolution rate of MA acid were studied using an USP XXIII six station dissolution rate test apparatus (Electro Lab). Paddle stirrer at a speed of 50 rpm and temperature of 37^{0} ± 1^{0}C were used in each test. Drug or solid dispersion of drug equivalent to 100 mg of MA was used in each dissolution rate test. Samples of dissolution medium i.e., phosphate buffer pH7.4 (5ml) were withdrawn through a filter (0.45 µ) at different time intervals, suitably diluted, and assayed for Mefenamic acid. The dissolution experiments were conducted in triplicate. The results are given in Table 3. Dissolution rates of MA and its solid dispersions followed first order kinetics (Table 4). Dissolution parameters such as T_{50}, DE_{30}, K_1, Percent of MA dissolved in 10 minutes are given in Table 5.

Table 2: Mefenamic Acid Content of Various Solid Dispersions Prepared

S.No	SD Code	Percent Mefenamic acid Content (X ± S.D)
1	MA-PEG-MCC,226	19.57 ± 0.84 (0.94)
2	MA-PVP-MCC,226	19.77 ± 0.22 (0.85)
3	MA-HPMC-MCC,226	19.97 ± 0.49 (0.68)
4	MA-MCC,14	19.89 ± 0.32 (1.01)

Table 3: Dissolution Profiles of Mefenamic Acid Solid Dispersions

Time in Min.	Percent Mefenamic acid dissolved (X ± SD, n=3)				
	MA	MA-PEG-MCC 226	MA-PVP-MCC 226	MA-HPMC-MCC 226	MA-MCC 14
5	12.39±0.3	45.7±0.3	35.9±0.3	72.9±0.3	9.9±0.2
10	18.66±0.8	49.7±0.8	48.5±0.1	77.1±0.4	11.7±0.4
20	24.22±0.6	61.5±0.3	63.5±0.1	85.4±0.5	21.2±0.6
30	28.83±0.7	71.0±0.2	74.9±0.2	89.7±0.4	27.1±0.7
40	32.25±0.3	75.6±0.4	80.9±0.2	91.9±0.6	36.2±0.5
60	36.05±0.4	88.1±0.2	88.9±0.3	97.9±0.5	47.7±0.4
90	39.21±0.5	95.5±0.2	92.8±0.8	100.3±0.6	64.1±0.3
120	41.62±0.3	100.2±0.3	96.5±0.3	100.6±0.5	73.2±0.4

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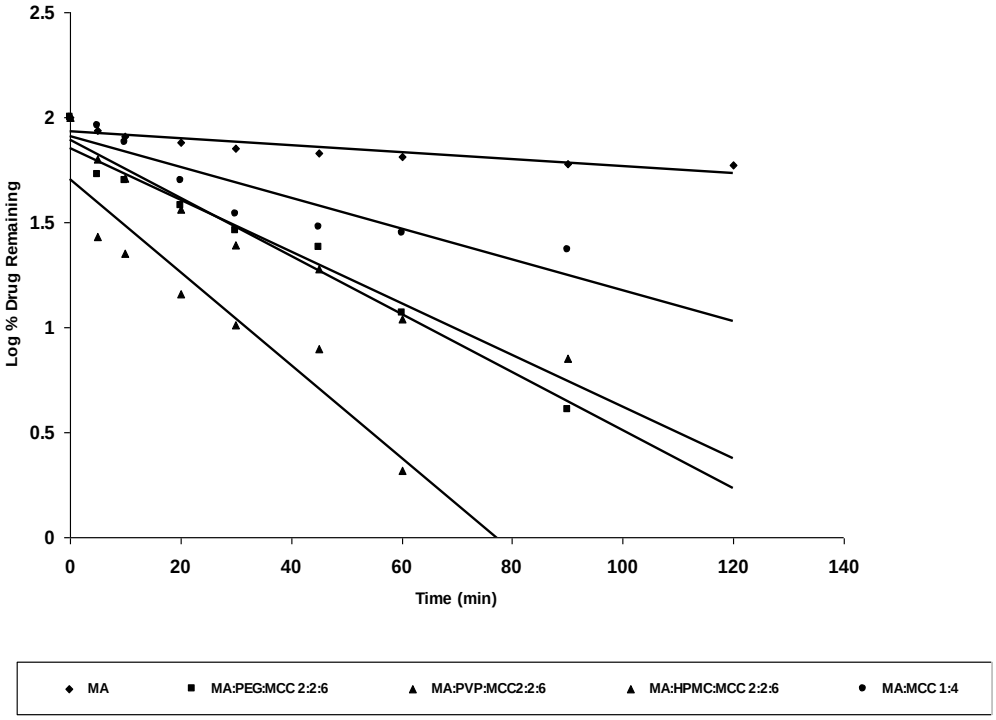

Fig.2 First Order Dissolution Plots of Mefenamic acid and its Solid Dispersions

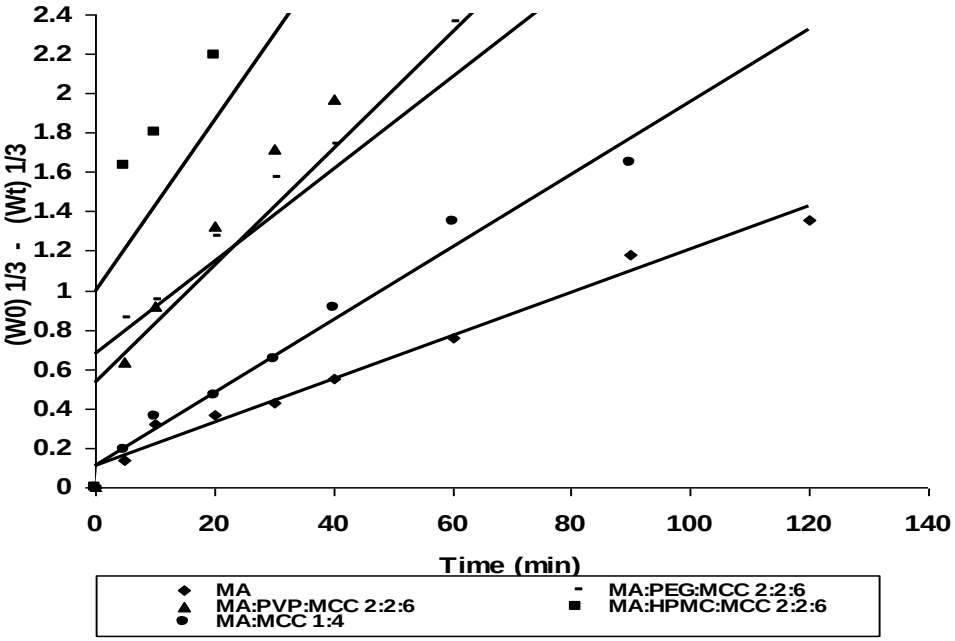

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Fig 3. Hixson-Crowell Dissolution Plots of Mefenamic acid and its Solid Dispersions

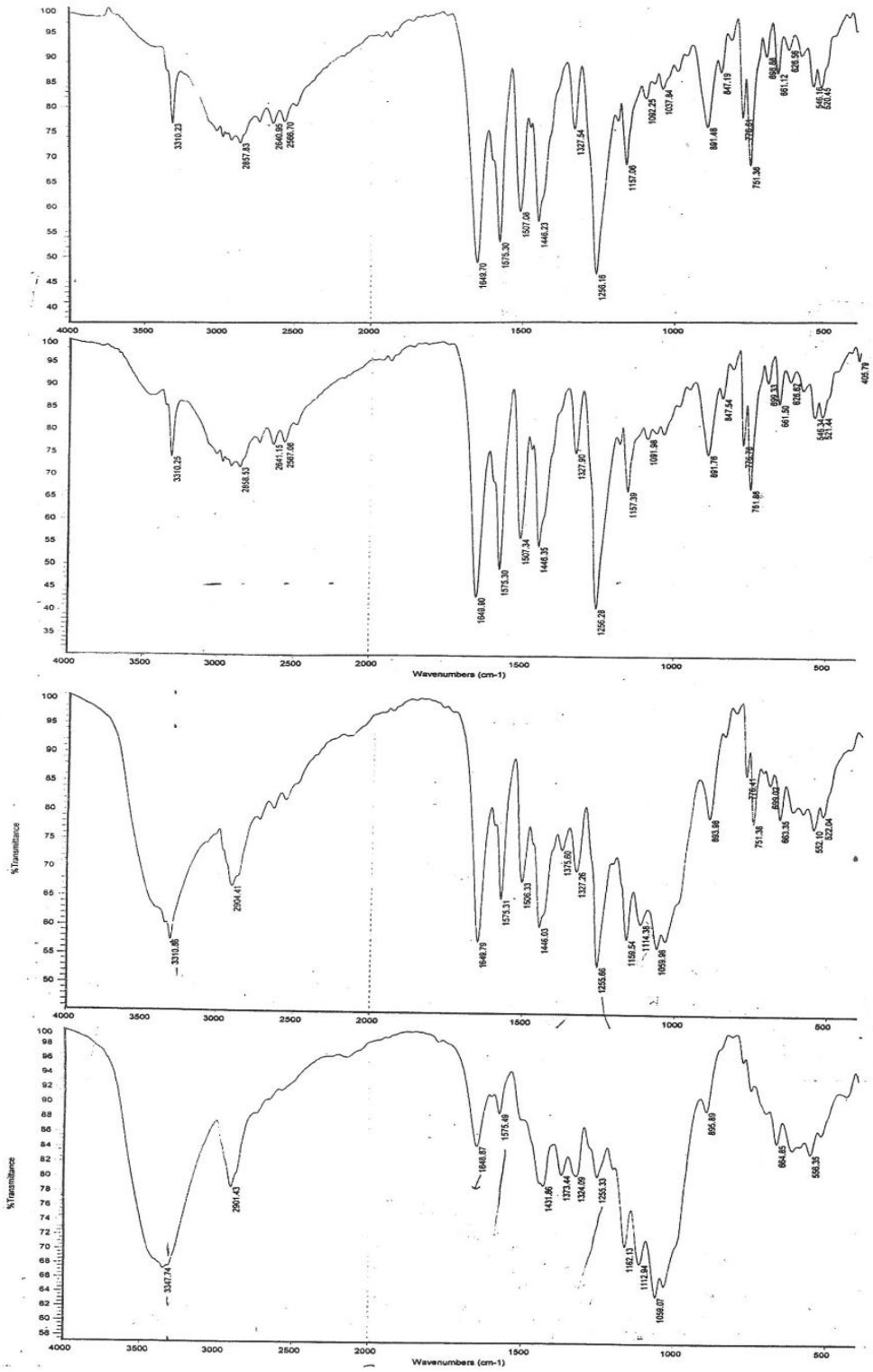

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Figure 4: FTIRSpectra of (I) MA (II) MA: HPMC (III) MA: HPMC: MCC (IV) MA:MCC Solid Dispersions (From top to bottom)

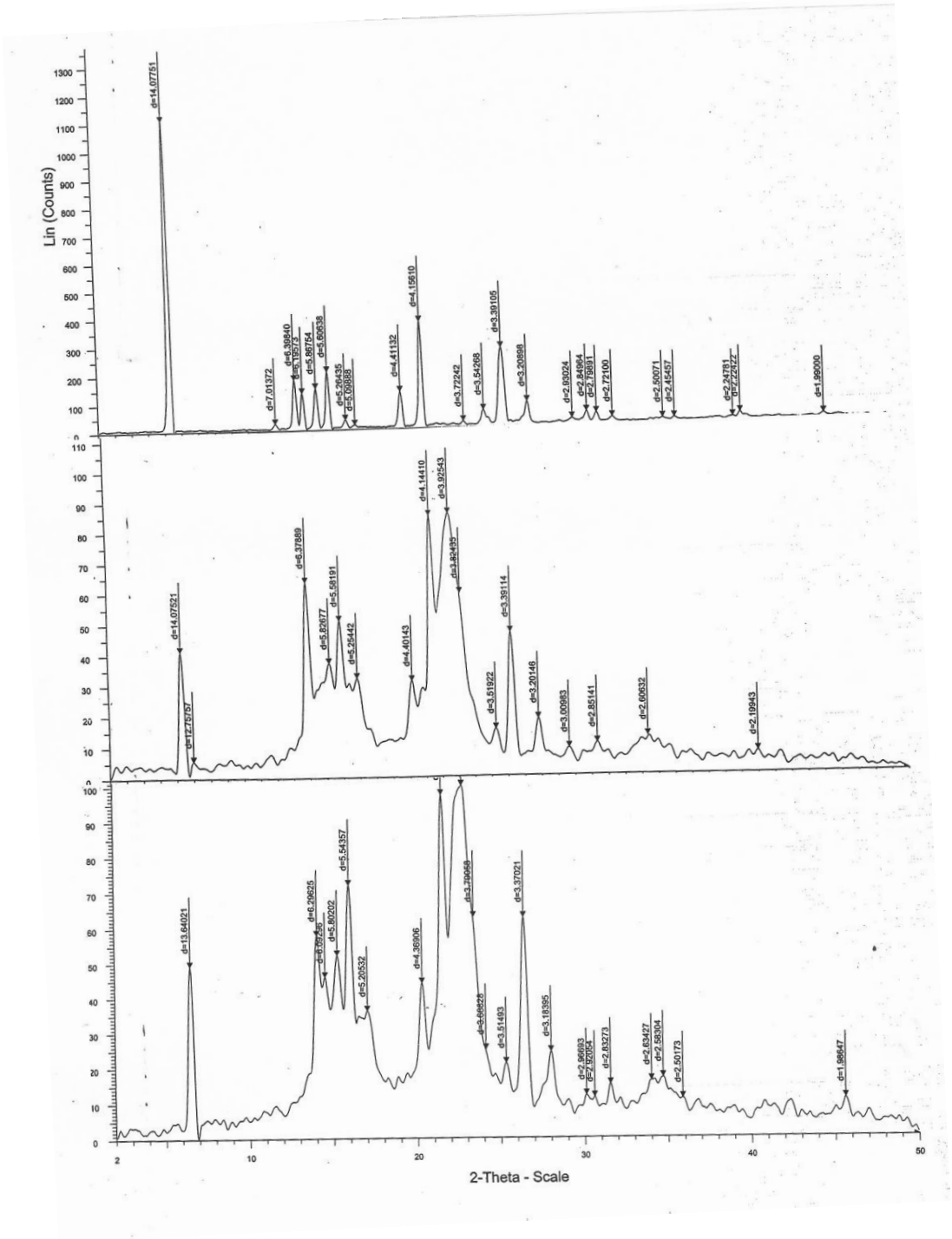

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Fig5: XRD Graphs of (I) MA (II) MA: HPMC (III) MA: HPMC: MCC Solid Dispersions (From top to bottom)

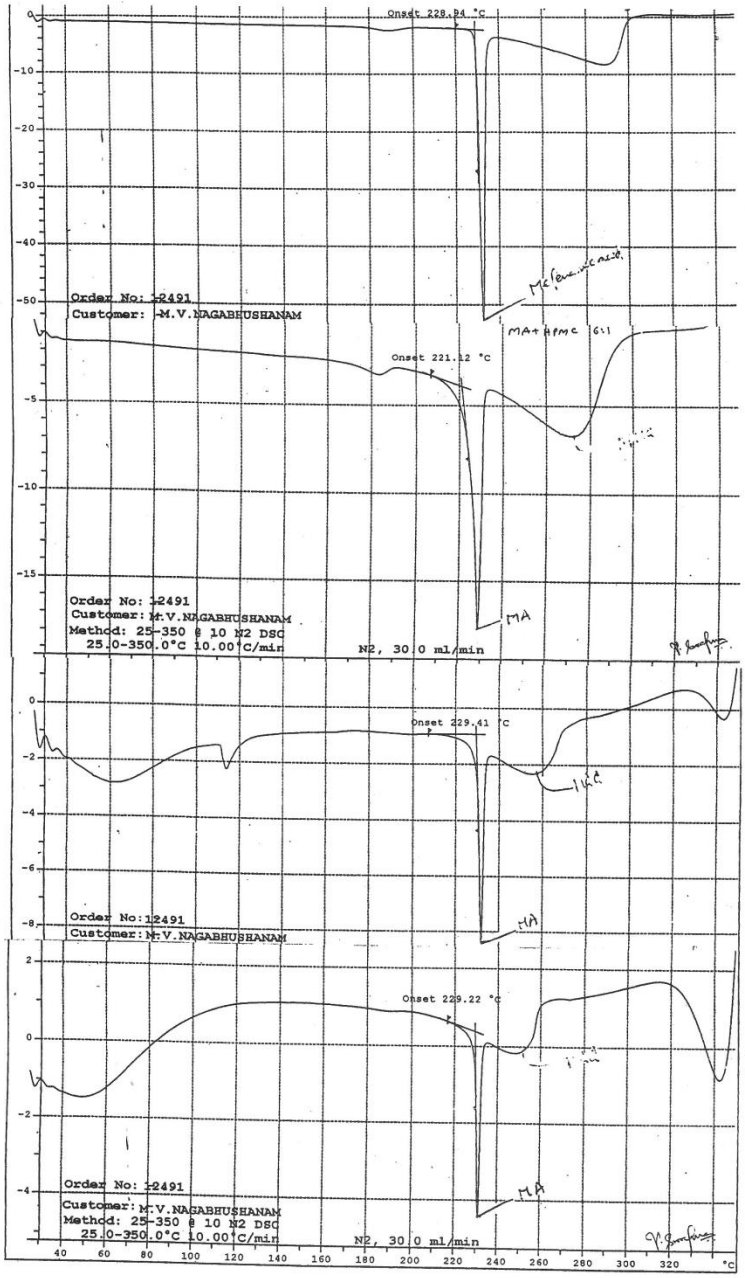

Fig 6 : DSC Thermograms of (I) MA (II) MA: HPMC (III) MA: HPMC: MCC (IV) MA:MCC Solid Dispersions

Table 5 Correlation Coefficient (r) values of Mefenamic Acid Solid Dispersions as per Zero order, First Order and Hixson-Crowell Cube Root Models

S.NO	SOLID DISPERSION	CORRELATION Coefficient (r) Value		
		Zero order	First order	Hixson-Crowell
1	MEFENAMIC ACID	0.991	0.976	0.989
2	MA-PEG-MCC.226	0.84	0.989	0.966
3	MA-PVP-MCC, 226	0.81	0.973	0.938
4	MA-HPMC-MCC, 226	0.617	0.953	0.879
5	MA-MCC, 14	0.985	0.905	0.997

Table 6. Dissolution Parameters of Mefenamic acid and its Solid Dispersions in Superdisintegrants

S.NO	SOLID DISPERSION	Dissolution Parameters			
		T_{50}	DE_{30} (%)	K_1	No. of folds increase in $K_1(min^{-1})$
1	MEFENAMIC ACID	>60	19.6	0.0072	--
2	MA-PEG-MCC.226	10	52.4	0.030	4.17
3	MA-PVP-MCC, 226	11	52.1	0.020	2.78
4	MA-HPMC-MCC, 226	03	74.8	0.05	6.94
5	MA-MCC, 14	20	34.9	0.0168	2.33

Analysis of Dissolution Data of Solid Dispersions as per Hixson-Crowell's cube root law

The dissolution data of MA and their solid dispersions were also analyzed as per Hixson-Crowell's [24] cube root equation. Hixson-Crowell introduced the concept of changing surface area during dissolution and derived the "cube-root law" to nullify the effect of changing surface area and to linearize the dissolution curves. Hixson-Crowell's cube root law is given by the following equation. $(W_o)1^{/3} - (W_t)^{1/3} = Kt$, where W_o is initial mass and W_t is the mass remained at time 't'. The cube root equation is applicable to the dissolution of monodisperse powder consisting of uniform sized particles. A plot of $(W_o)^{1/3} - (W_t)^{1/3}$ versus time will be linear when dissolution occurs from monodisperse particles of uniform size. Hixson-Crowell plots of the dissolution data were found to be linear (Fig.3) with all solid dispersions. This observation indicated the drug dissolution from all the solid dispersions is occurring from discretely suspended or deposited (monodisperse) particles. This might have also contributed to the enhanced dissolution rate of the solid dispersions. The correlation coefficient (r) values of the first order release model are found to be (0.9075 to 0.9940) slightly higher when compared to the Hixson-Crowell's cube root model. Hence the release of drug from the preparations followed predominantly first order kinetics compared to Hixson-Crowell cube root law. Correlation coefficient values in the analysis of dissolution data as per zero order, first order and Hixson-Crowell cube root are given in Table.3. Another parameter suitable for evaluation of *in vitro* dissolution has been suggested by Khan [25] by parameter Dissolution efficiency (DE). DE is defined as the area under the dissolution curve up to a certain time 't' expressed as percentage of the area of the rectangle described by 100% dissolution in the same time.

$$\text{Dissolution Efficiency (DE)} = \left[\frac{\int_o^t y.dt}{y_{100}t} \right] 100$$

The index DE_{30} would relate to the dissolution of drug from a particular formulation after 30 minutes and could be compared with DE_{30} of other formulations. Summation of the large dissolution data into a single figure DE enables ready comparison to be made between a large numbers of formulations.

RESULTS AND DISCUSSION

All the dissolution parameters given in Table 6 indicated rapid and higher dissolution of MA from all solid dispersions when compared to MA pure drug. MA-HPMC-MCC (2:2:6) solid dispersion gave rapid and higher dissolution than the pure drug. A 6.94 fold increase in the dissolution rate of MA was obtained with this solid dispersion when compared to pure drug. Combined carriers gave much higher enhancement in the dissolution rate of MA than water dispersible carriers alone. Solid dispersions of super disintegrants gave rapid and higher dissolution of MA when compared to pure drug as well as its solid dispersion in water soluble PVP. In each case, the K_1 and DE_{30} values were increased. A 6.94 fold increase in the dissolution rate of MA was observed with MA-HPMC-MCC solid dispersion. All the solid dispersions in combined carriers gave much higher rates of dissolution, several times higher than the dissolution rate of pure drug. MA-HPMC-MCC solid dispersion gave a 6.94 fold increase in the dissolution rate of MA whereas solid dispersion of MA in MCC alone (MA-MCC 14) gave only 2.33 fold increase. Thus combination of super disintegrants with water soluble carrier HPMC resulted in a greater enhancement in the dissolution rate of MA.

CONCLUSION

Thus superdisintegrant MCC was found to be useful as a carrier in Mefenamic acid solid dispersions alone and in combination with HPMC to enhance the solubility, dissolution rate and dissolution efficiency.

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