

FORMULATION STUDIES ON SOLID DISPERSIONS OF MEFENAMIC ACID IN SUPERDISINTEGRANTS

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ABSTRACT

The feasibility of formulating the solid dispersions of mefenamic acid into tablet dosage forms is evaluated. All the tablets formulated employing solid dispersions of mefenamic acid in superdisintegrants gave rapid and higher dissolution of mefenamic acid when compared to that of mefenamic acid plain tablets. The increasing order of dissolution rate of formulated tablets with various carriers was Croscarmellose (CC)>Pregelatinised starch (PGS)> Primojel(PJ)> Crospovidone (CP). The same order of performance was observed with tablets formulated employing superdisintegrants alone and in combination with PVP. A 2.75 fold increase in the dissolution rate of mefenamic acid was observed with tablets formulated employing its solid dispersions in CC (MAF4) when compared to plain tablets (MAF1). A 6.97 fold increase in the dissolution rate of mefenamic acid was observed with tablets formulated employing its solid dispersions in combined carriers CC and PVP (MAF8) when compared to its plain tablets (MAF1).

Keywords: *Mefenamic Acid; Solid Dispersion; Dissolution rate; Solubility; polyvinylpyrrolidone; pregelatinised starch.*

INTRODUCTION

The poor dissolution characteristics of relatively insoluble drugs have long been a problem to Pharmaceutical Industry. A number of modern drugs are poorly soluble in water and aqueous fluids. Their absorption and bioavailability require an improvement in the dissolution rate and efficiency. Among the various methods for improving the dissolution rate and bioavailability, solid dispersion technologies were found to be very successful with a number of drugs. Solid dispersions of a number of poorly soluble drugs such as phenylbutazone¹, indomethacin², tolbutamide³, griseofulvin⁴, ketoprofen⁵, sulfathiazole⁶ etc., exhibited faster dissolution rates and improved bioavailability. Water soluble substances such as urea⁷⁻⁹, polyethyleneglycols^{3,10-12}, polyvinylpyrrolidone¹³⁻¹⁵, sugars such as dextrose¹⁶⁻¹⁹ sucrose^{20,21}, succinic acid²², bile acids^{19,23}, Surfactants²⁴⁻²⁷, cellulose polymers such as hydroxypropyl methylcellulose²⁸, hydroxypropyl cellulose²⁸ and modified starches such as dextrin^{29,30}, α -cyclodextrin^{29,30} and hydroxyethyl starch^{29,30} etc. are used as carriers for preparing solid dispersions.

Most of the Non-steroidal anti inflammatory drugs belong to class II category under Biopharmaceutical Classification System (BCS) i.e., they are inherently highly permeable through biological membranes, but exhibit low aqueous solubility. They need enhancement in solubility and dissolution rate for improving their oral bioavailability.

In the present investigation studies were carried out on solid dispersions of mefenamic acid using water

dispersible superdisintegrants, a new class of tablet excipient, alone and in combination with PVP, for enhancing the dissolution rate. Mefenamic acid, an anthranilic acid derivative, is a non-steroidal anti-inflammatory drug(NSAID)³¹. It is used in mild to moderate pain including headache, dental pain, postoperative and postpartum pain, dysmenorrhoea, osteoarthritis. The usual dose by mouth is 500 mg three times daily. Mefenamic acid is absorbed from the gastro intestinal tract. Peak plasma concentration occurs at about 2 to 4 hours after ingestion. Rate of absorption and/or extent of bioavailability for such insoluble hydrophobic drug is controlled by rate of dissolution in gastro-intestinal fluids³². Solid dispersions³³ were prepared by employing common solvent and solvent evaporation method. Water dispersible superdisintegrants, a new class of tablet excipient were evaluated as carriers, alone and in combination with PVP, for enhancing the dissolution rate and bioavailability of mefenamic acid.

MATERIALS AND METHODS

Mefenamic acid was a gift sample from M/s. Sigma Laboratories, Mumbai, methanol (Qualigens) and , polyvinylpyrrolidone (PVP K30) was a gift sample from M/s. Sun Pharma Ind. Ltd., Mumbai. Primojel, crospovidone, croscarmellose, lactose, potato starch, talc, magnesium stearate were procured from commercial sources. All other materials used were of pharmacopoeial grade.

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PREPARATION OF SOLID DISPERSIONS

Preparation Employing Superdisintegrants

Solid dispersions of mefenamic acid (MA) in superdisintegrants (pregelatinised starch) were prepared by solvent evaporation method. The required quantities of drug were dissolved in methanol to get a clear solution in a dry mortar. The super disintegrant (passed through 120 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° C for 4 hours in an oven. The product was crushed, pulverized and shifted through mesh no.100. In each case solid dispersions in the superdisintegrants were prepared at a drug:excipient ratio of 1:4.

Preparation Employing Combined Carriers

The required quantities of drug and water soluble carrier (PVP) were dissolved in the solvent to get a clear solution in a dry mortar. The super disintegrant 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° C for 4 hours in an oven. The product was crushed, pulverized and shifted through mesh NO.100. Composition of various solid dispersions prepared is given in Table 1.

Table 1. Various solid dispersions composition

Sl. No.	Composition		
	Drug	Carriers	SD Code
1.	Mefenamic Acid (1)	PJ (4)	MA-PJ, 14
2.	Mefenamic Acid (1)	CP(4)	MA-CP, 14
3.	Mefenamic Acid (1)	CC(4)	MA-CC, 14
4.	Mefenamic Acid (1)	PGS(4)	MA-PGS, 14
5.	Mefenamic Acid (1)	PJ(3.2) PVP (0.8)	MA-PJ-PVP
6.	Mefenamic Acid (1)	CP(3.2) PVP (0.8)	MA-CP-PVP
7.	Mefenamic Acid (1)	CC(3.2) PVP (0.8)	MA-CC-PVP
8.	Mefenamic Acid (1)	PGS(3.2) PVP (0.8)	MA-PGS-PVP

Figure in parentheses () indicate ratio

Estimation of mefenamic acid

Spectrophotometric method based on the measurement of absorbance at 279 nm in phosphate buffer pH 7.4 was used in the present study for the estimation of mefenamic acid³⁴. The method was validated for reproducibility, accuracy, precision and linearity by analyzing six individually weighed samples of mefenamic acid. The stock solution of mefenamic acid was subsequently diluted to a series of dilution containing 5, 10, 15 and 20 µg/ml of solution, using phosphate buffer of pH 7.4. The absorbance of these solutions was measured in UV-VIS spectrophotometer (ELICO SL-159). The method obeyed Beer's law in the concentration range of 0-20 µg/ml.

Estimation of mefenamic acid in solid dispersions

From each batch, 4 samples of 50 mg were taken and analyzed for mefenamic acid. 50 mg of dispersion was weighed and transferred 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 phosphate buffer of pH 7.4 and assayed at 279 nm for mefenamic acid. The results are given in Table 2.

Table 2. Mefenamic Acid Content of Various Solid Dispersions

Sl.No.	SD Code	Percent Mefenamic Acid Content ($\bar{x} \pm s.d.$)
1.	MA-PJ, 14	19.8 ± 0.17 (0.86)
2.	MA-CP, 14	19.8 ± 0.42(1.23)
3.	MA-CC, 14	19.2 ± 0.18 (0.96)
4.	MA-PGS, 14	19.9 ± 0.31 (0.65)
5.	MA-PJ-PVP	19.2 ± 0.32 (1.24)
6.	MA-CP-PVP	19.6 ± 0.19 (0.98)
7.	MA-CC-PVP	19.7 ± 0.12 (0.64)
8.	MA-PGS-PVP	19.8 ± 0.17 (0.86)

Tablet formulation by direct compression

Solid dispersions of mefenamic acid (MA) in superdisintegrants and combined carriers exhibited several times higher dissolution rates and dissolution efficiency values than the corresponding pure drugs. The feasibility of formulating these solid dispersions into tablet dosage forms is evaluated. As the superdisintegrants employed as carriers in solid dispersions lose their swelling characteristics when dried during wet granulation method, these dispersions were formulated into compressed tablets by direct compression method. All these solid dispersions in superdisintegrants and combined carriers were found to be sufficiently free flowing for direct compression. Tablets each containing 100 mg of mefenamic acid were prepared as per the formulae given in Table 3.

Table 3. Formulae of Mefenamic Acid Tablets Prepared Employing its Solid Dispersions in Super Disintegrants

Ingredient (mg/Tablet)	Formulation									
	MAF ₁	MAF ₂	MAF ₃	MAF ₄	MAF ₅	MAF ₆	MAF ₇	MAF ₈	MAF ₉	MAF ₁₀
Mefenamic Acid	100	-	-	-	-	-	-	-	-	-
MA-PJ 14	-	500	-	-	-	-	-	-	-	-
MA-CP 14	-	-	500	-	-	-	-	-	-	-
MA-CC 14	-	-	-	500	-	-	-	-	-	-
MA-PGS 14	-	-	-	-	500	-	-	-	-	-
MA-PJ-PVP	-	-	-	-	-	500	-	-	-	-
MA-CP-PVP	-	-	-	-	-	-	500	-	-	-
MA-CC-PVP	-	-	-	-	-	-	-	500	-	-
MA-PGS-PVP	-	-	-	-	-	-	-	-	500	-
Lactose	400	-	-	-	-	-	-	-	-	-
Potato Starch	25	25	25	25	25	25	25	25	25	25
Talc	5	5	5	5	5	5	5	5	5	5
Magnesium Stearate	5	5	5	5	5	5	5	5	5	5
Total Weight (mg)	535	535	535	535	535	535	535	535	535	535

All ingredients were blended in a closed dry plastic container. The blend of powders was compressed into tablets to a hardness of 6-8 kg/sq.cm. On a 'Cadmach' single punch tablet machine. In each case 50 tablets were prepared.

Evaluation of Tablets

The tablets were evaluated for hardness, friability, disintegration, content of active ingredient and dissolution rate. Disintegration times were determined in 'Thermonic' tablet disintegration test machine (USP) using distilled water. Hardness of the tablets was tested using a 'Monsanto' hardness tester. Friability of the tablets was determined in a 'Roche' friabilator. The results are given in Table 4.

Table 4. Evaluation of Tablets of Mefenamic Acid Tablets

Sl. No.	Tablet Formulation	Hardness (kg/sq.cm)	Friability (%)	Disintegration Time (min)	Drug Content (mg/tablet)
1.	MAF ₁	7.0	0.40	4.0	98.9
2.	MAF ₂	8.0	0.45	2.5	99.6
3.	MAF ₃	7.0	0.41	3.0	99.4
4.	MAF ₄	7.5	0.35	2.0	98.8
5.	MAF ₅	8.0	0.30	2.0	99.2
6.	MAF ₆	8.0	0.32	1.5	99.6
7.	MAF ₇	8.5	0.28	2.5	98.9
8.	MAF ₈	7.5	0.25	1.5	99.1
9.	MAF ₉	7.0	0.38	1.5	99.2

Content of Active Ingredient

Ten tablets were weighed, powdered and mixed thoroughly. Four samples of tablet powder, each equivalent to 20 mg drug were weighed accurately and taken in a boiling test tube. In each case, mefenamic acid present in the tablet powder was extracted with 4 x 10 ml quantities of methanol and the extracts were collected into a 100 ml volumetric flask. The volume was made up to the mark with methanol. The solution was subsequently diluted with phosphate buffer pH 7.4 and assayed for mefenamic acid at 279 nm. The results are given in Table 4.

Dissolution Rate Study

Dissolution rate of mefenamic acid tablets was studied using an USP XXIII 6 station dissolution rate test apparatus (Electro Lab) with a paddle stirrer. The dissolution rate was studied in 900 ml of phosphate buffer pH 7.4 at a speed of 50 rpm and a temperature of 37 $\pm$ 1°C. Samples of dissolution medium (5ml) were withdrawn through a filter (0.45 μ) at different time intervals, suitably diluted, and assayed for mefenamic acid at 279 nm. The dissolution experiments were conducted in triplicate. The dissolution profiles of various tablets are shown in Fig. 1.

RESULTS AND DISCUSSION

All formulated tablets were of good quality fulfilling official (I.P.) and other requirements with regard to content of active ingredient, hardness, friability and disintegration time. All the tablets formulated employing solid dispersions in superdisintegrants gave rapid and higher dissolution of mefenamic acid when compared to that of mefenamic acid plain tablets (i.e. tablets formulated employing mefenamic acid and lactose as diluent, MAF1).

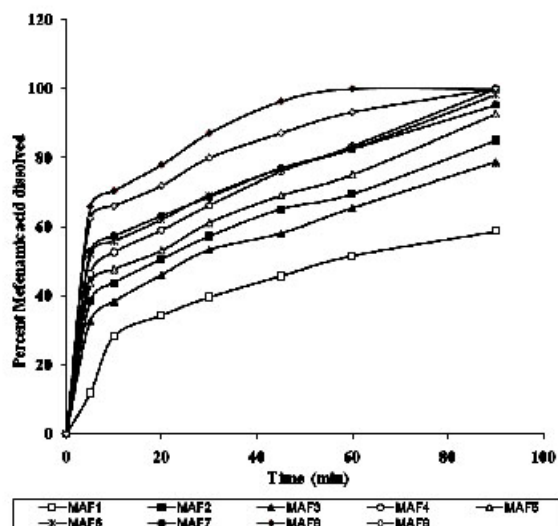


Fig. 1 : Dissolution Profiles of Mefenamic Acid Tablets Formulated Employing Mefenamic acid and its Solid Dispersions in Superdisintegrants.

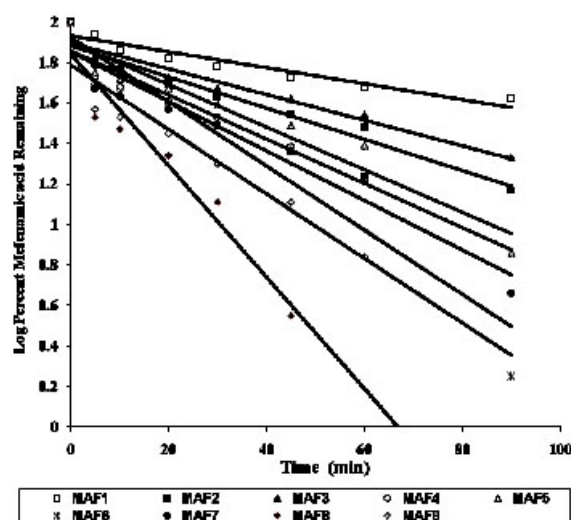
The dissolution data were fitted into zero order, first order models to assess the kinetics and mechanism of dissolution. The kinetic model that best fits the dissolution data was evaluated by comparing the correlation coefficient (*r*) values obtained in various models. The model that gave higher '*r*' value is considered as the best fit model. The correlation coefficient (*r*) values obtained in the analysis of dissolution data as per different models are given in Table 5. The '*r*' values were higher in the first order model than those in the zero order models with all the tablet formulations prepared from solid dispersions of mefenamic acid indicating that the dissolution of mefenamic acid from all the solid dispersions followed first order kinetics. Mefenamic acid dissolution from all the tablets followed first order kinetics with correlation coefficient '*r*' above 0.9398 (Table 5). The first order dissolution plots of various tablets are shown in Fig.2. The dissolution parameters estimated from the dissolution data of various tablets are summarized in Table 6. All dissolution parameters (*K*₁, DE₃₀, T₅₀ and percent dissolved in 10 min) indicated rapid and

Table 5. The Correlation Coefficient (*r*) Value in the Analysis of Dissolution Data of Mefenamic Acid Tablets as per Zero Order and First Order Models

Tablet Formulation No.	Solid Dispersion Employed	Correlation Coefficient (<i>r</i>) Value	
		Zero Order	First Order
MAF1	Pure drug	0.9868	0.9923
MAF2	MA-PJ 14	0.8817	0.9676
MAF3	MA-CP 14	0.8997	0.9724
MAF4	MA-CC 14	0.8863	0.9660
MAF5	MA-PGS 14	0.8848	0.9646
MAF6	MA-PJ PVP	0.8469	0.9398
MAF7	MA-CP PVP	0.8296	0.9700
MAF8	MA-CC PVP	0.7375	0.9666
MAF9	MA-PGS PVP	0.7818	0.9534

Table 6 : Dissolution Parameters of Mefenamic Acid Tablets formulated Employing Solid Dispersions of Mefenamic acid

Sl. No.	Formulation	Dissolution Parameter				Increase in K_1 (No. of Folds)
		T_{90} (min)	T_{50} (min)	DE ₃₀ (%)	K_1 (min ⁻¹)	
1.	MAF 1	59.0	> 90	16.65	0.0091	-
2.	MAF 2	19.5	> 90	43.87	0.0176	1.93
3.	MAF 3	27.4	> 90	39.31	0.0146	1.60
4.	MAF 4	8.50	77.5	51.66	0.0251	2.75
5.	MAF 5	15.6	85.55	47.14	0.0241	2.64
6.	MAF 6	4.70	81.56	54.84	0.0364	4.00
7.	MAF 7	4.50	83.66	55.70	0.0281	3.08
8.	MAF 8	3.50	41	69.14	0.06346	6.97
9.	MAF 9	3.85	53	64.25	0.0370	4.06

**Fig. 2 : First Order Dissolution Plots of Mefenamic acid Tablets Formulated**

higher dissolution of mefenamic acid from tablets formulated employing its solid dispersions when compared to plain tablets, MAF1.

The dissolution rate (K_1) of mefenamic acid from the tablets formulated employing solid dispersions in superdisintegrants was found to be several times higher (1.6 - 6.97 fold increase) with various tablets when compared to plain tablets (Table 6). Tablets formulated with solid dispersions in croscarmellose sodium (CC) alone (MAF4) and in combination with PVP (MAF8) gave highest enhancement in the dissolution rate of mefenamic acid from tablets. A 2.75 and 6.97 fold increase in the dissolution rate was observed with formulations MAF4, MAF8 respectively when compared to plain tablets MAF1.

The increasing order of dissolution rate of Mefenamic acid from the tablets observed with various superdisintegrants was CC > PGS > PJ > CP. The same order of performance was observed in both the series of tablets formulated (i.e. employing superdisintegrants alone, superdisintegrants with PVP). The increasing order of dissolution rates of tablets formulated from solid dispersions of mefenamic acid are comparable

with solid dispersions of Nifedipine-Crospovidone³⁵, Nilvadipine-Croscarmellose sodium³⁶, Nilvadipine-crospovidone³⁶, Ibuprofen-PVP³⁷, Rofecoxib-PVP³⁷. The tablets formulated from solid dispersions of mefenamic acid provide rapid dissolution rate by one or more of the following mechanisms.

- (i) **Particle size reduction:** Solid dispersions achieve faster dissolution rates as the drug undergoes micronization while depositing over the surface of the excipient. As mefenamic acid and carriers (CC, CP, PJ, PGS) are dispersed at molecular level in a solid dispersion it releases very fine particles of the drug when the carrier molecules readily dissolve in the aqueous fluids.
- (ii) **Improving the wettability of the particles:** Wetting of powders is the primary condition for them to disperse and dissolve in body fluids³⁸. The presence of water-soluble carrier (PVP) improves the wettability of hydrophobic drug particles.
- (iii) **Conversion of crystalline drugs into amorphous form:** Solid dispersions of mefenamic acid may convert a crystalline drug into amorphous form. Since the amorphous form is the highest energy form of a pure compound it produces faster dissolution.
- (iv) **Solubilizing effect of the carriers** (PVP, PJ, CP, CC, PGS)

CONCLUSION

The dissolution rate and dissolution efficiency of mefenamic acid could be enhanced several times by their solid dispersion in super disintegrants alone and in combination with PVP. Superdisintegrants particularly croscarmellose sodium, pregelatinized starch, primojel and crispidone were found to be good carriers giving solid dispersions with enhanced dissolution rate and efficiency. These solid dispersions in superdisintegrants could be compressed into tablets. Mefenamic acid tablets formulated employing their solid dispersions in super disintegrants also exhibited enhanced dissolution rate and efficiency, several times higher than those of plain tablets. These tablets were quite stable with regard to various other characteristics and enhanced dissolution rate. Thus, solid dispersion in superdisintegrants is recommended as an effective and efficient technique for enhancing the dissolution rate, dissolution efficiency of mefenamic acid. Superdisintegrants are inert safe and non-toxic excipients that are currently used in compressed tablet formulations as disintegrants. These can be used as efficient carriers in solid dispersion techniques to enhance the dissolution rate of insoluble and poorly soluble drugs.

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