International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 3, Issue 1, 2011

Research Article

DISSOLUTION ENHANCEMENT OF MEFENAMIC ACID USING SOLID DISPERSIONS IN CROSPOVIDONE

M.V.NAGABHUSHANAM [1*], A.SUDHA RANI

*[1]Principal, D.C.R.M. Pharmacy College, Inkollu, Prakasam (Dt.,) A.P. Pin: 523 167 India. Email :priya_narendra @ rediffmail.com

Received: 26 April 2010, Revised and Accepted: 16 Oct 2010

ABSTRACT

Solid Dispersions of mefenamic acid (MA), with a water soluble polymer (PVP) and a super disintegrant namely, crospovidone (CP), were prepared by common solvent and solvent evaporation methods employing methanol as solvent. Solid Dispersions prepared were evaluated for dissolution rate and dissolution efficiency in comparison to the corresponding pure drug mefenamic acid. Solid dispersions of mefenamic acid showed a marked enhancement in dissolution rate and dissolution efficiency. The order of increasing dissolution rate was observed with increase in crospovidone ratio. At 1:4 ratio of mefenamic acid-CP a 2.26 fold increase in the dissolution rate of mefenamic acid was observed with mefenamic acid-CP (1:4) solid dispersion. The solid dispersions in combined carriers gave much higher rates of dissolution than super disintegrants alone. MA-CP-PVP solid dispersion gave a 3.47 fold increase in the dissolution rate of mefenamic acid. Superdisintegrants alone or in combination with PVP could be used to enhance the dissolution rate of poorly soluble drug mefenamic acid.

Keywords: Mefenamic Acid, Solid Dispersions, Dissolution rate, Solubility, Polyvinyl pyrrolidine, crosspovidone.

INTRODUCTION

Mefenamic acid, an anthranilic acid derivative, is an non-steroidal anti-inflammatory drug(NSAID)[1]. It is used in mild to moderate pain including headache, dental pain, postoperative and postpartum pain, dysmenorrhea, osteoarthritis. The usual dose by mouth is 500 mg three times daily. Mefenamic acid is absorbed from the gastro intestinal tract. Peak plasma concentrations occur about 2 to 4 hours after ingestion. Most of the NSAIDs 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. Rate of absorption and / or extent of bioavailability for such insoluble hydrophobic drug is controlled by rate of dissolution in gastro-intestinal fluids[2]. The present study aims at enhancing the dissolution rate of MA. In the present investigation solid dispersions[3] were prepared by employing common solvent and solvent evaporation methods. Studies were carried out on mefenamic acid with an objective of enhancing their dissolution rates and bioavailability. Water dispersible super disintegrants, a new class of tablet excipients 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 , polyvinyl pyrrolidone (PVP K_{30}), crospovidone were gift samples 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 soluble carriers (PVP)

Solid Dispersions of Mefenamic Acid were prepared by common solvent method employing methanol as solvent for mefenamic acid solid dispersions . The required quantities of drug and carrier were weighed and dissolved in the corresponding solvent in a round bottom flask to get a clear solution. The solvent was then removed by evaporation under reduced pressure (vacuum) at 60^0 C with constant mixing. The mass obtained was crushed pulverized and shifted through mesh no.100 . Solid dispersion was prepared in the ratio of drug carrier namely 8:2.

Preparation of solid dispersions employing superdisintegrants

Solid dispersions of mefenamic acid (MA) in superdisintegrant crospovidone were prepared by solvent evaporation method. The required quantities of MA was dissolved in methanol to get a clear solution in a dry mortar. The super disintegrant crospovidone (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 50^0 C for 4 hours in a oven. The product was crushed, pulverized and shifted through mesh no.100. In each case solid dispersions in the superdisintegrant were prepared at three different ratios of drug excipient namely 1:1, 1:2 and 1:4 respectively.

Preparation of solid dispersions 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 superdisintegrant 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.

Estimation of Mefenamic acid

A spectrophotmetric 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 acid[4]. 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 of 0-20 *µg/ml.*

Estimation of Mefenamic acid solid dispersions prepared

From each batch, 4 samples of 50 mg 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.

Table1: Various solid dispersions and their composition

S No.	Composition		
	Drug	Carriers	SD Code
1.	Mefenamic Acid (8)	PVP (2)	MA-PVP, 82
2.	Mefenamic Acid (1)	CP (1)	MA-CP, 11
3.	Mefenamic Acid (1)	CP(2)	MA-CP, 12
4.	Mefenamic Acid (1)	CP(4)	MA-CP, 14
5.	Mefenamic Acid (1)	CP(3.2) PVP (0.8)	MA-CP-PVP

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 mefenamic acid. The results are given in Table 2.

Table 2: Mefenamic acid content of various solid dispersions prepared

S No.	SD Code	Percent Mefenamic acid content ($\bar{x}$ ± s.d.,)
1.	MA-PVP, 82	79.5 ± 0.74 (0.93)
2.	MA-CP, 11	49.3 ± 0.38 (0.7)
3.	MA-CP, 12	32.5 ± 0.20(1.01)
4.	MA-CP, 14	19.8 ± 0.41 (1.26
5.	MA-CP-PVP	19.6 ± 0.19 (0.98)

Dissolution Rate Studies on Solid Dispersions

Dissolution rate of mefenamic 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 $37^0 \pm 1^0$C were used in each test. Drug or solid dispersion of drug equivalent to 100 mg of mefenamic acid was used in each dissolution rate test.

Samples of dissolution medium phosphate buffer pH 7.4 (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.

Table 3: Dissolution profiles of Mefenamic acid solid dispersions

Time (min)	Percent Mefenamic acid dissolved ($\bar{x}$ ± s.d., n = 3)					
	MA	MA-CP 11	MA-CP 12	MA-CP14	MA-CP-PVP	MA-PVP 82
5	12.39±0.63	24.11±1.85	28.81±0.93	33.51±1.67	53.79±1.85	21.75±1.88
10	18.66±0.38	29.67±1.89	35.36±1.86	39.81±0.77	58.61±2.22	26.22±1.67
20	24.2±0.56	39.07±1.86	40.93±1.67	46.37±1.85	64.55±2.43	31.41±1.86
30	28.83±0.69	44.51±1.70	46.86±2.23	53.54±1.66	69.12±1.48	36.98±1.85
45	32.25±0.71	51.07±2.61	53.41±2.03	61.08±1.69	77.78±1.67	40.94±2.04
60	36.05±0.54	56.26±1.66	59.85±1.13	68.50±1.90	84.58±1.49	46.01±1.70

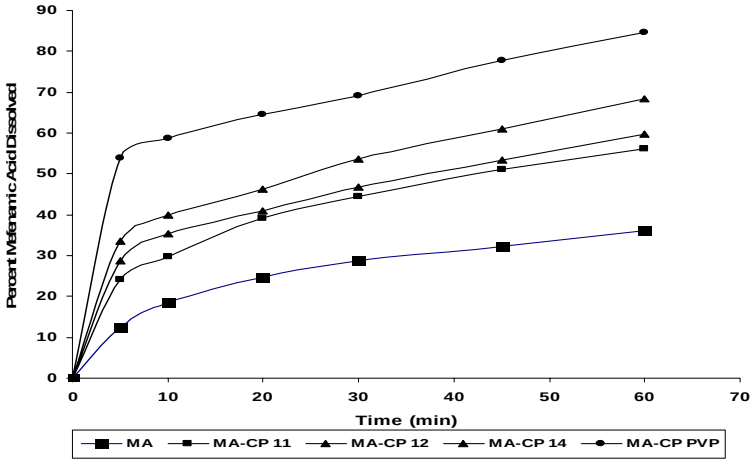

Fig. 1: Dissolution profiles of Mefenamic acid and its solid dispersions in comparison to mefenamic acid pure drug

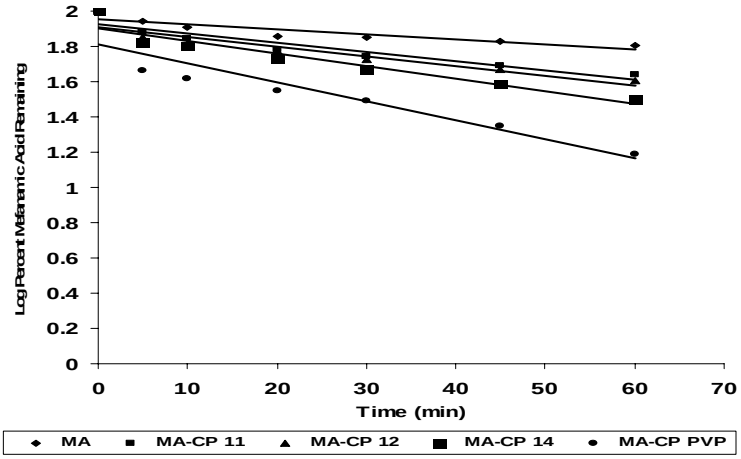

Fig. 2: First order dissolution plots of Mefenamic acid and its solid dispersions

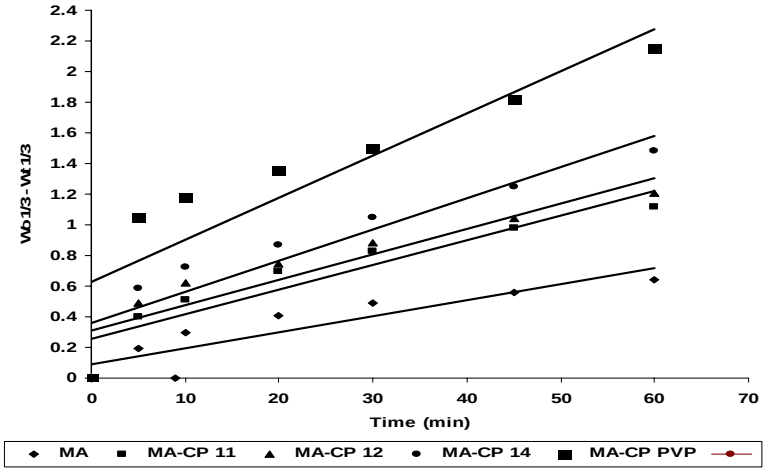

Fig. 3: Hixson-crowell dissolution plots of Mefenamic acid and its solid dispersions

Table 4: The correlation coefficient (r) values in the analysis of dissolution data of Mefenamic acid solid dispersions as per zero order, first order and Hixson-Crowell cube root models

Sl. No.	Solid dispersion	Correlation coefficient (r) value		
		Zero order	First order	Hixson-Crowell
1.	Pure Drug	0.9875	0.9940	0.9920
2.	MA -PVP, 82	0.8763	0.9075	0.9061
3.	MA -CP 11	0.8957	0.9422	0.9300
4.	MA -CP 12	0.8707	0.9369	0.9150
5.	MA -CP 14	0.8725	0.9401	0.9273
6.	MA -CP PVP	0.7805	0.9684	0.8846

Table 5: Dissolution parameters of Mefenamic acid and its solid dispersions in superdisintegrants

Sl. No.	Solid dispersion	Dissolution Parameter			
		T_{50} (min)	% Dissolved in 10 min	DE_{30} (%)	K_1 (min^{-1})
1.	Mefenamic Acid	> 60	10.63	19.60	0.0072
2.	MA-CP 11	43	26.29	31.87	0.0121
3.	MA-CP 12	40	30.69	35.09	0.0128
4.	MA-CP 14	26	34.89	39.91	0.0163
5.	MA-CP PVP	4.10	58.61	56.65	0.0250
6.	MA-PVP 82	> 60	26.20	26.81	0.0087

Dissolution rates of mefenamic acid and its solid dispersions followed first order kinetics.(Table4)

Analysis of dissolution data of solid dispersions as per hixson-crowell's cube root law

The dissolution data of mefenamic acid and their solid dispersions were also analyzed as per Hixson-Crowell's[5] 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. Another parameter suitable for evaluation of *in vitro* dissolution has been suggested by Khan[6] by a paramter Dissolution efficiency (DE). DE is defined as the area under the dissolution curve upto 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. First order dissolution rate constants (K_1) calculated from the slopes of the first order liner plots, dissolution efficiency (DE_{30}) values, T_{50} (time for 50% dissolution) and percent dissolved in 10 minutes are given in Table 2.

RESULTS AND DISCUSSION

All the dissolution parameters given in Table 2 indicated rapid and higher dissolution of mefenamic acid from all solid dispersions when compared to mefenamic acid pure drug. Mefenamic acid-PVP (8:2) solid dispersion gave rapid and higher dissolution than the pure drug. A 1.20 fold increase in the dissolution rate of mefenamic acid was obtained with this solid dispersion when compared to pure drug. Water dispersible superdisintegrants gave much higher enhancement in the dissolution rate of mefenamic acid than water soluble carriers. Solid dispersions of superdisintegrants gave rapid and higher dissolution of mefenamic acid 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 as the concentration of carrier (superdisintegrant) in the soli dispersion was increased. At 1:4 ratio of MA:CP, the order of increasing dissolution rate with various superdisintegrants was 1:4>1:2>1:1. A 2.26 fold increase in the dissolution rate of mefenamic acid was observed with mefenamic acid-CP (1:4) 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. PVP combined superdisintegrants gave higher dissolution rates than superdisintegrants alone. MA-CP-PVP solid dispersion gave a 3.47 fold increase in the dissolution rate of mefenamic acid whereas solid dispersion of mefenamic acid in CP alone (MA-CP 14 solid dispersion) gave only 2.26 fold increase. Thus combination of superdisintegrants with water soluble carrier PVP resulted in a greater enhancement in the dissolution rate of mefenamic acid.

CONCLUSION

Thus superdisintegrant crosspovidone was found to be useful as a carrier in mefenamic acid solid dispersions alone and in combination with PVP to enhance their solubility, dissolution rate and dissolution efficiency.

ACKNOWLEDGEMENTS

The authors would like to express sincere thanks to the Management of D.C.R.M. Pharmacy College for their encouragement and providing necessary facilities in carryout this research work. The authors would also express sincere thanks to M/s. Sigma Laboratories, Mumbai for generous gift of mefenamic acid samples.

REFERENCES

1. Sweet Mann S C, Martindale- The Extra Pharmacopoeia, 33rd ed. The Pharmaceutical Press, London; 2005.
2. Guirguis M and Jammali F. J Pharm Pharmaceut Sci 2001; 77: 4.
3. Sekiguchi K and Obi N, Chem Pharm Bull 1961; 866:9. .
4. Teresa H, Ado, Jan Pawlaczyk, J of Inclusion Phenomena and Macrocyclic Chemistry, 1999; 35:3.
5. Hixon AW, and Crowell J H, Ind Eng Chem 1931; 923:23.
6. Khan K A, Rhodes C T, Pharma Acta Helv 1972; 594 : 47.