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FORMULATION AND EVALUATION OF MEFENAMIC ACID SOLID DISPERSION USING DIFFERENT CARRIERS

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ABSTRACT

The main objective of this study was to formulate and evaluate the dissolution rate of mefenamic acid solid dispersions in which Urea, polyvinylpyrrolidone K30 (PVP K30) and polyethylene glycol 4000 (PEG 4000) were used as carrier for each of the formulations and compared with each other based on enhancement of bioavailability. The dissolution rate and dissolution efficiency of the prepared solid dispersions were evaluated in comparison to the corresponding pure drug. Mefenamic acid-urea (1:3) solid dispersion showed rapid and higher dissolution than the pure drug. Thus urea was found to be useful as a carrier in Mefenamic Acid solid dispersions compared to polyvinylpyrrolidone K30 and polyethylene glycol 4000 and it enhances the solubility, dissolution rate and dissolution efficiency.

KEYWORDS: Mefenamic acid, solid dispersion, carrier, solvent evaporation, dissolution rate and solubility.

INTRODUCTION

Medications having limited water solubility and high membrane permeability are classified as Class II drugs under the Biopharmaceutical Classification System (BCS). The drugs which are having poor water solubility they often show poor oral bioavailability due to the low levels of absorption. Thus such drugs exhibit dissolution rate limited absorption. The main ways for improving dissolution is to increase the surface area available for dissolution

include reducing the solid compound's particle size, enhancing the wetting characteristics of the compound surface, reducing the boundary layer thickness, ensuring sink conditions for dissolution and enhancing the drug's apparent solubility under physiologically relevant conditions. The oral absorption and bioavailability of BCS Class II medications can therefore be enhanced by the use of solid dispersion technology.[1]

Solid dispersion is a solubilization approach that focuses mostly on drug-polymer two-component systems, where drug dispersion and its stabilization are crucial for formulation development. The fundamental idea behind improving the poorly soluble medicine with solid dispersion is completely removing the drug's crystalline structure and its molecular dispersion in a hydrophilic polymeric carrier. The carrier dissolves when the solid dispersion is in contact with water, and the medicine then releases as minute colloidal particles. This enhances the surface area of the dissolution rate and, consequently, the bioavailability of medications that are weakly water soluble. By reducing particle size and increasing particle porosity, a drug in a hydrophilic hydro soluble carrier accelerates dissolution. Therefore, by modifying these medications' drug release profiles, it is possible to increase their bioavailability and minimize their side effects.[2]

Mefenamic acid (MA), an anthranilic acid derivative, is a non-steroidal anti-inflammatory drug (NSAID) and short (2h) plasma half life drug. It is used as antipyretic, analgesic and antirheumatic for the treatment of headache, dental pain, postoperative and postpartum pain, dysmenorrhea and osteoarthritis. The usual dose orally is 500mg three times daily. Mefenamic acid is absorbed from the gastrointestinal tract. Peak plasma concentrations occur about 2 to 4 hour after ingestion. Most of the NSAIDs belong to class II category under biopharmaceutical classification system (BCS), since they are inherently highly permeable through biological membranes, but exhibit low aqueous solubility. Rate of absorption and/or extent of bioavailability for such hydrophobic drugs are controlled by rate of dissolution in gastrointestinal fluids. Solid dispersions are one of the most promising strategies to improve the oral bioavailability of poorly water soluble drugs. By reducing drug particle size to the absolute minimum and hence improving drug wettability, bioavailability may be significantly improved. The present study aims at enhancing the dissolution rate and bioavailability of mefenamic acid with the solid dispersions by employing common solvent and solvent evaporation methods. Water dispersible super disintegrants, a new class of tablet excipients

were evaluated as carriers, for enhancing the dissolution rate and bioavailability of mefenamic acid.[3]

MATERIALS AND METHODS

Collection of Materials

All the chemicals used were of standard pharmaceutical grade. Mefenamic acid received as a gift sample from VerGO Pharma Research Laboratories Pvt.Ltd., Goa, India. Urea was procured from Medilise Chemicals, Kerala, India. PVP K3O and PEG 4000 were obtained from Yarrow chemical products, Mumbai. Ethanol and other solvent used were of analytical grade.

Preparation of solid dispersions of mefenamic acid by solvent evaporation method[4]

Solid Dispersions of Mefenamic Acid were prepared by solvent evaporation method using ethanol as solvent. A sufficient volume of ethanol was used and it was continuously stirred to dissolve the necessary amount of mefenamic acid and the carrier in 1:1 and 1:3 ratios. At 45 the solvent from the solution was evaporated while the mixture was continuously stirred to produce dry mass. The dried substance was ground, put through a 44-mesh sieve and kept in desiccators until it was employed in subsequent experiments.

Table 1: Compositions of mefenamic acid solid dispersions.

Formulation code	Drug (mg)	Urea (mg)	PVP-K30 (mg)	PEG 4000 (mg)	Ethanol (ml)	Ratio (drug: carrier)
F1	100	100	-	-	10/ q.s	1:1
F2	100	-	100	-	10/ q.s	1:1
F3	100	-	-	100	10/ q.s	1:1
F4	250	750	-	-	10/ q.s	1:3
F5	250	-	750	-	10/ q.s	1:3
F6	250	-	-	750	10/ q.s	1:3

Evaluation

Estimation of mefenamic acid[5]

Estimation of mefenamic acid was carried out using a spectrophotometric method based on the measurement of absorbance at 279nm in 7.4pH buffer. An absorption maxima of mefenamic acid was determined using 7.4pH buffer. Beer's range was found to be in the range from 0-20 µg/ml.100 mg of Mefenamic acid was accurately weighed and taken in a 100 ml volumetric flask. From the working standard solution, the suitable aliquots of 1000 µg/ml solution were diluted up to the mark with buffer to get the concentrations range of 5, 10, 15

&20µg/ml for mefenamic acid. The absorbance of these solutions was measured at 279 nm by UV spectrophotometer, using 7.4pH buffer as blank. The absorbance values were plotted against concentration to obtain the standard.

Drug Content[5]

From each batch of preparation 50mg of solid dispersions was taken and analyzed for the drug mefenamic acid. Weighed dispersions were transferred into a 100ml volumetric flask. Ethanol was added and contents were mixed thoroughly to dissolve the drug from the dispersion. The solution was then filtered and collected carefully into another 100ml volumetric flask. The solution was made up to volume with solvent 7.4pH buffer. The solution was suitably diluted with dissolution fluid and assayed at 279nm for mefenamic acid.

In -vitro dissolution studies of solid dispersions[4]

Solid dispersions' in vitro release profile was assessed using the USP dissolving device (Type-II). 900 ml of pH 7.4 buffer maintained at 37±0.5 served as the dissolution media. The capsule containing the medication, physical mixture, or solid dispersion was placed in the dissolution apparatus' basket and rotated at a speed of 50 rpm. At predetermined intervals, 1ml samples were taken out and subjected to spectrophotometric analysis at 279nm. Fresh buffer solution was used in replacement of the removed samples.

RESULTS AND DISCUSSION

Standard graph of mefenamic acid by UV- Visible spectrophotometry

A simple, fast and precise UV spectrophotometric method for estimation of mefenamic acid was carried out. Absorbance was read at 279 nm using 7.4pH buffer as blank. Beer's range was obeyed between 0-20µg/ml.

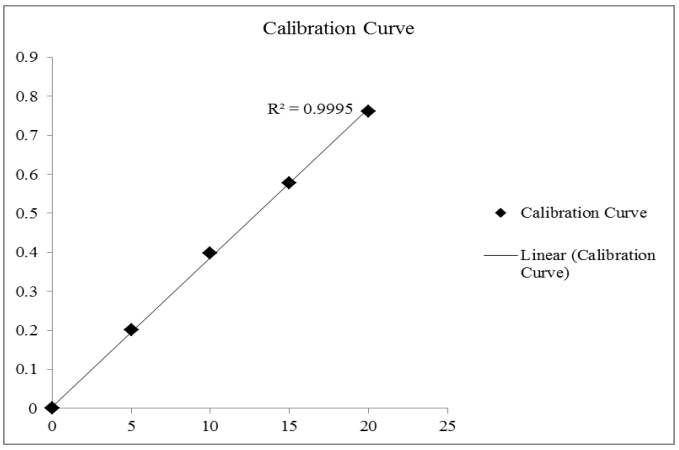

Fig. 1: Calibration curve of mefenamic acid by UV –visible spectrophotometry.

Drug content

All the solid dispersions indicated the presence of high drug content and low standard deviations of the results, which specifies that the drug is uniformly dispersed into the carrier. Therefore, the methods and the carrier used in this study finds to be reproducible for preparation of solid dispersion.

In-vitro drug release study

Drug release study for the drug and all the formulations containing drug were performed in simulated gastric fluid (pH 7.4) at 37 ± 2°C. There was a very low release with the pure drug. Drug release form these solid dispersions were increased and dependent on the type of carrier and concentration of carrier used. F1, F4 and F6 formulations having high solubility which will show the highest drug release from the solid dispersion than F2, F3 and F5 formulations. Urea is a humectant with high water solubility and its helps to draw the water to striatum corneum of body tissue. These properties are responsible for enhancing the bioavailability of the drug in the body. While formulation F4 containing urea shows the high solubility ensuring the sink condition, consequently shows an increase in bioavailability of the drug.

Table 2: Solubility of formulation after 90 minutes.

Time			%CDR				
	Drug	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0	0
10	15.25	19.75	15.5	18	17	17.75	18.55
20	21.5001	28.2502	21.5001	25.5002	26.0001	21.0001	27.0002
30	23.5004	37.2505	25.5004	33.7504	35.5004	30.2504	36.5005
40	26.2569	48.5009	33.5006	40.5008	49.5008	37.0007	47.2509
50	31.5009	53.2514	45.501	48.0013	58.5014	40.5011	56.0014
60	35.4801	60.752	54.5015	53.2518	69.502	49.5016	66.002
70	39.7517	72.7527	63.0021	64.7524	77.0028	57.0021	76.2527
80	43.0021	81.5035	70.2528	74.5031	85.5037	68.5028	81.5036
90	48.5026	88.0044	78.0036	83.0039	92.0046	79.5035	86.5045

Table 3: Release kinetics of the formulations.

Formulation Code	Zero Order		First order	
	K_{slope}	Regression	K_{slope}	Regression
Drug	0.4625	0.9482	-0.003	0.9738
F1	0.7070	0.7571	-0.009	0.9413
F2	0.8435	0.9918	-0.007	0.9578
F3	0.8620	0.9893	-0.008	0.9350
F4	1.0142	0.9903	-0.011	0.9414
F5	0.7951	0.9820	-0.007	0.9124
F6	0.9471	0.9851	-0.009	0.9729

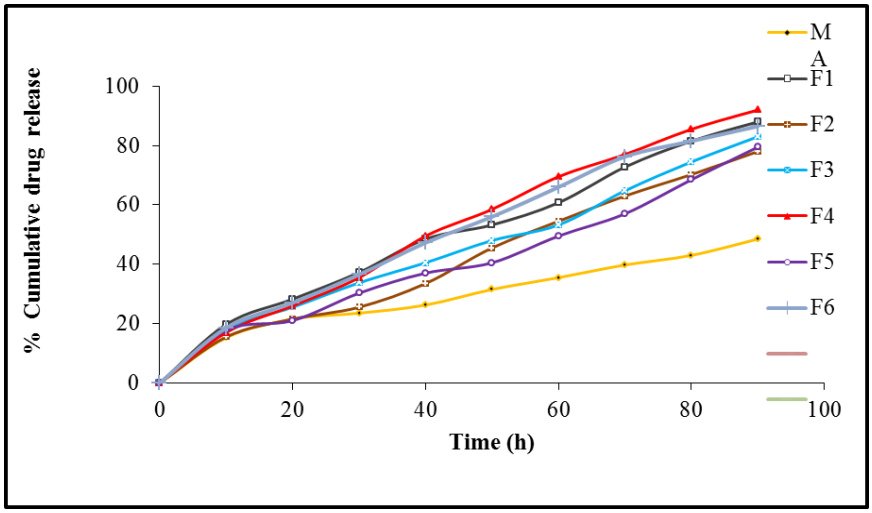

Fig. 2: Graph of %CDR of in-*vitro* drug release.

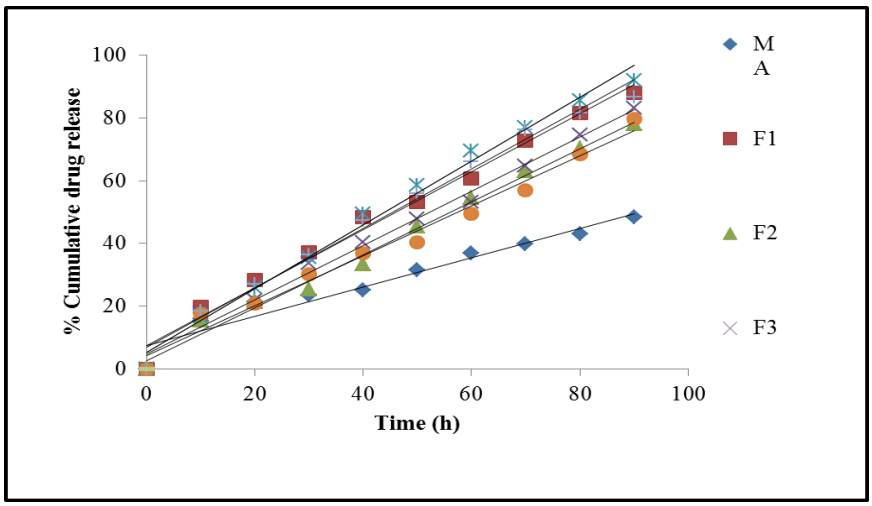

Fig. 3: Graph of zero order kinetics.

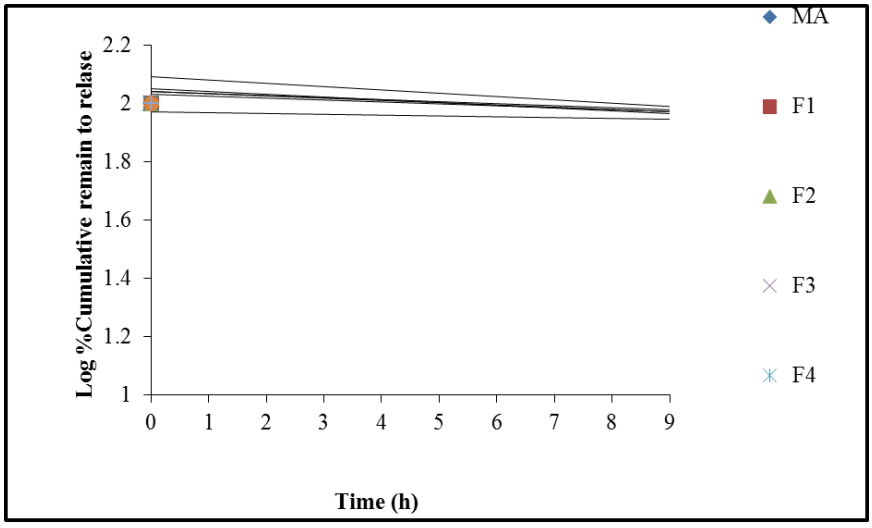

Fig. 4: Graph of first order kinetics.

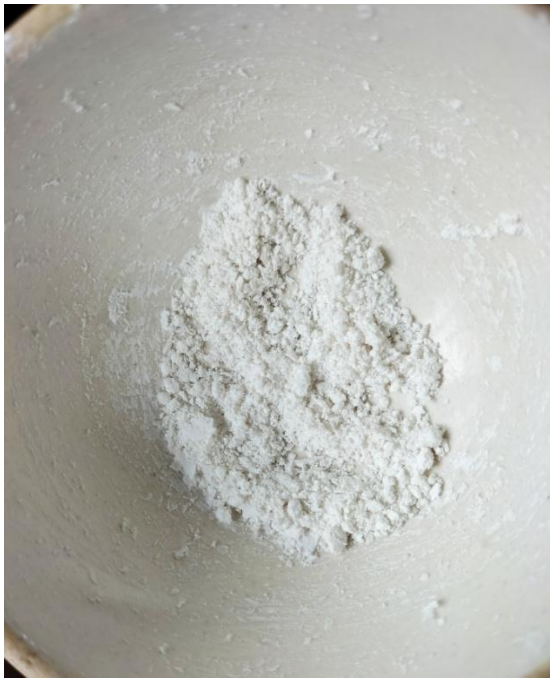

Fig. 5: Preparation of mefenamic acid solid dispersion.

CONCLUSION

All the dissolution parameters indicated rapid and higher dissolution of mefenamic acid from all solid dispersions when compared to mefenamic acid pure drug. Mefenamic acid-urea (1:3) solid dispersion showed rapid and higher dissolution than the pure drug and all other prepared solid dispersions, based on the in-vitro evaluation. Thus urea was found to be useful as a carrier in Mefenamic acid solid dispersions and it enhances the solubility, dissolution rate and dissolution efficiency of mefenamic acid. Designed solid dispersions were seemed to be promising as alternative dosage form for mefenamic acid delivery.

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