FORMULATION AND EVALUATION OF MEFENAMIC ACID SOLID DISPERSIONS USING PEG-4000

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ABSTRACT

Mefenamic acid (MA) solid Dispersions were prepared employing methanol as a common solvent using PEG-4000 as a drug carrier with two different techniques namely, melting method and solvent evaporation in varied ratios. The prepared solid dispersions were evaluated and compared with that of pure drug (mefenamic acid) in respect to the dissolution rate and dissolution efficiency. It is noted that solid dispersions of mefenamic acid showed a remarkable increase in dissolution rate and dissolution efficiency. An increase in the dissolution rate was observed with an increase in PEG-4000 concentration with regarding to solvent evaporation method. Dissolution rate of mefenamic acid was found to be increased 8.14 folds with mefenamic acid- PEG-4000 solid dispersion (1:2) ratio, in case of solvent evaporation method, and 6.51 folds with mefenamic acid- PEG-4000 solid dispersion (1:1) ratio. PEG-4000 can be used in order to raise the dissolution rates of poorly soluble drugs such as mefenamic acid.

Keywords: Mefenamic Acid, Solid Dispersion, Melting Technique, Solvent Evaporation

INTRODUCTION

Drugs belonging to class II category under Biopharmaceutical classification system (BCS) are generally known for the characteristic features of inherently high permeability through biological membranes, and low aqueous solubility. Most of the NSAIDs come under this category. Rate of dissolution in gastro-intestinal fluids governs the rate of absorption and / or extent of bioavailability for such hydrophobic and insoluble drugs. Mefenamic acid is one among from the list of such drugs¹, which is a non-steroidal anti-inflammatory, anthranilic acid derivative². It is commonly used in treating pains including menstrual pain, osteoarthritis, headache, dental pain, dysmenorrhea, postoperative and postpartum pain. The usual dose is 500 mg, given three times a day. Mefenamic acid is known to decrease inflammation and uterine contractions where the mechanism of action is not known yet. Absorption of mefenamic acid is seen in the gastro intestinal tract. It is reported that after about 2 to 4 hours of ingestion, plasma concentrations reach peaks². Our present study aims at formulating the solid dispersion, in order to enhance the dissolution rate of MA using two different techniques. In the present study solid dispersions were prepared using a common solvent through melting technique and solvent evaporation methods in varied ratios. Studies were conducted on mefenamic acid so as to enhance the dissolution rates and bioavailability PEG-4000 issued as the drug carrier. The solid dispersions prepared were characterized for drug content, infrared spectral studies, differential scanning calorimetric studies, and in-vitro release studies. From the obtained results, it was observed that solid dispersion formulated showed an improved dissolution rate in comparison with the pure drug.

MATERIALS AND METHODS:**Materials**

Mefenamic acid was a gift sample from M/s. Sigma Laboratories, Mumbai, methanol (qualigens) and , peg-4000 was purchased from SD fine chemicals limited. All other materials used were of pharmacopoeia grade and were procured from commercial sources.

Method**Preparation of solid dispersions³****Preparation of solid dispersions employing soluble carriers (PEG-4000)**

Solid Dispersions of Mefenamic Acid were prepared by solvent evaporation method employing methanol as solvent. The required quantity of carrier was dissolved in the solvent to get a clear solution. The solvent was then removed by evaporation at constant mixing with the application of slight heat to ensure the easy evaporation of the solvent. The mass obtained was crushed pulverized and shifted through mesh no. 30. Solid dispersions were prepared in the ratios of drug carrier 1:1, 1:1.5, 1:2.

Preparation of solid dispersions using melting technique

Solid Dispersions of Mefenamic Acid were prepared by melting technique employing methanol as solvent. Carrier was dissolved in a china dish, placing it on a hot plate to get a clear solution and then drug was slowly added to the polymer solution, then this was allowed to cool on a waterbath in order to solidify the obtained solid dispersion. then the prepared mass was crushed pulverized and shifted through mesh no.30 . Solid dispersions were prepared in the ratios of drug carrier namely 1:1, 1:1.5, 1:2.

Evaluation**DSC**

Thermal analysis was performed on the drug, physical mixtures, and the best formulations from the two techniques in order to know if there is any change in the melting point of drug after the formulation which ensures the stability of the drug when the heat is applied.

Infra-red spectrum

Infra-red studies were carried out to rule out interaction between drug and carrier used in formulation of solid dispersion by potassium bromide disc method using Infra-red spectrophotometer.

Table 1: Composition of solid dispersions

Formulation	Drug	Carrier	Ratio (Drug:Carrier)
Solvent Evaporation			
F ₁	Mefenamic acid	Peg-4000	1:1
F ₂	Mefenamic acid	Peg-4000	1:1.5
F ₃	Mefenamic acid	Peg-4000	1:2
Melting Technique			
F ₄	Mefenamic acid	Peg-4000	1:1
F ₅	Mefenamic acid	Peg-4000	1:1.5
F ₆	Mefenamic acid	Peg-4000	1:2

Table 2: Calibration curve of Mefenamic acid

Concentration($\mu\text{g/ml}$)	Absorbance
2	0.067
4	0.148
6	0.228
8	0.303
10	0.381
12	0.470

Table 3: Drug content of the solid dispersions

Formulation	Trail-I	Trail-II	Trail-III	Avg $\pm$ Deviation
F ₁	98.26	99.01	97.38	98.21667 $\pm$ 0.815864
F ₂	95.10	97.22	96.29	96.20333 $\pm$ 1.062654
F ₃	95.26	97.14	96.27	96.22333 $\pm$ 0.940868
F ₄	96.37	97.09	101.09	98.1833 $\pm$ 2.542859
F ₅	98.01	95.26	96.00	96.42333 $\pm$ 1.423037
F ₆	95.69	97.53	95.01	96.07667 $\pm$ 1.303738

Table 4: Release kinetics of the formulations

Formulation Code	Zero Order		First Order		Hixson-Crowell	
	K _{slope}	Regression	K _{slope}	Regression	K _{slope}	Regression
Pure Drug	0.1262	0.9548	-0.0006	0.9577	-0.002	0.9568
F ₁	0.7413	0.9397	-0.005	0.9605	-0.0152	0.9549
F ₂	0.5717	0.6002	-0.0036	0.5248	-0.0114	0.5527
F ₃	0.8551	0.9174	-0.0091	0.8338	-0.0232	0.9056
F ₄	0.7552	0.6036	-0.0069	0.7069	-0.0188	0.6685
F ₅	0.6225	0.5875	-0.0054	0.6817	-0.015	0.6488
F ₆	0.6962	0.7046	-0.0063	0.8241	-0.0173	0.7863

Figure 1: Calibration curve of Mefenamic Acid **Figure 2: FT-IR of Mefenamic Acid** **Figure 3: FT-IR of physical mixture**

Figure 4: FT-IR of F₃

Figure 5: FT-IR of F₄

Figure 6: DSC Thermograms of Pure Drug, Physical Mixture, F₃, F₄

Figure 7: In-vitro release studies of Pure Drug, F₁, F₂, F₃

Figure 8: In-vitro release studies of Pure Drug, F₄, F₅, F₆

Figure 9: First Order release of Pure Drug, F₁, F₂, F₃, F₄, F₅, F₆ Figure 10: Hixson Crowell plot of Pure Drug, F₁, F₂, F₃, F₄, F₅, F₆

Estimation of mefenamic acid

A spectrophotometric method based on the measurement of absorbance at 279nm in phosphate buffer pH 7.4 was used in the present study for the estimation of mefenamic acid. The method was validated for reproducibility, accuracy, precision and linearity by analyzing x individually weighed samples of mefenamic acid. The stock solution of mefenamic acid was subsequently diluted to a series of dilution containing 2, 4, 6, 8, 10 and 12µg/ml of solution, using phosphate buffer of pH 7.4. The absorbance of these solutions was measured in UV-VIS spectrophotometer (shimadzu 1800). The method obeyed Beer's law in the concentration of 0-12µg/ml.

Drug content

From each batch of preparation 50mg of solid dispersions was taken and analyzed for the drug mefenamic acid. Weighed dispersions were 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 7.4 PH buffer. The solution was suitably diluted with dissolution fluid and assayed at 279nm for mefenamic acid.

Dissolution studies of solid dispersions

Dissolution rate of mefenamic were studied to compare the rate of dissolution of solid dispersions with that of pure drug Mefenamic acid using a eight station dissolution rate test apparatus (Electro Lab). The test was performed in USP paddle apparatus using 900ml phosphate buffer solution at pH 7.4 and temperature 37± 0.5 °C.

RESULTS AND DISCUSSION

FT-IR

Infra-red spectral analysis revealed that there were no interactions between pure drug and solid dispersion. The results are shown in figures 2-5.

DSC

DSC was performed for pure drug, Physical mixture, F₃ and F₄ and no interactions were found between the drug and the polymer and there was no change in the melting point of the drug found, which is evident from the DSC thermograms shown in figure 4.

Drug content

Drug content of the formulations was witnessed to be 96.07667%, 96.20333%, 96.22333%, 98.1833%, 96.42333%, 98.21667% for the formulations F₁, F₂, F₃, F₄, F₅, F₆ with a standard deviation of 0.815864%, 1.303738%, 0.940868%, 2.542859%, 1.423037%, 1.062654% respectively. 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 in to the polymer. Therefore, the methods and the polymer used in this study finds to be reproducible for preparation of solid dispersion.

In-vitro studies

In-vitro dissolution studies were performed for pure drug, formulations F₁, F₂, F₃, F₄, F₅, and F₆. The release was found to be 10.23%, 60.06%, 47.05%, 91.86%, 78.13%, 73.51%, 75.08% respectively. There was a very low release with the pure drug which was then increased with solid dispersions. Release rate was found to be the highest in case of F₃ in case of solvent evaporation method formulations and F₄ in case of melting method formulations. There was a decrease in release in case of the formulations with ratio (1:1.5). An increase of 6.51 folds was observed with F₄ and highest rise of 8.14 folds was seen with the formulation F₃. Though there was an increase in the dissolution rate of the formulations formulated through melting technique, highest increase in the dissolution rate was found to be with the formulation formulated through solvent evaporation method.

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

The dissolution data of Pure drug (mefenamic acid) and the solid dispersions were analysed as per Hixson-Crowell's 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. $(W_0)^{1/3} - (W_t)^{1/3} = Kt$, where W_0 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 $(W_0)^{1/3} - (W_t)^{1/3}$ 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 (Figure 8) with all the formulations. 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 regression values of the first order release model are found to be higher in comparison to the Hixson-Crowell's cube root model for F_1 , F_4 , F_5 , F_6 . Hence the release of drug from the preparations followed predominantly first order kinetics compared to Hixson-Crowell cube root law. But F_2 , F_3 followed Hixson-Crowell cube root law. Slope and regression values of dissolution data as per zero order, first order and Hixson-Crowell cube root are given in Table 4.

CONCLUSION

There was a drastic increase in the dissolution of mefenamic acid with use of PEG-4000 as polymer. This ensures that PEG-4000 could be effectively used as a polymer in order to increase the dissolution profile of poorly soluble drugs such as mefenamic acid.

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