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Enhancement of Solubility of Mefenamic Acid by Hydrotrop Based Solid Dispersion

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ABSTRACT

Therapeutically active substances are often associated with bio-availability problems due to lower solubility, these leads to lack of in-vivo and in-vitro correlation, poor patient compliance and inter subject variations. Mefenamic acid (MFA) is an anthranilic acid derivatives (or fenamate) class of NSAID drugs and is used to treat mild to moderate pain, including menstrual pain, and is sometimes used to prevent migraines associated with menstruation. But it is sparingly soluble in water. Present study was aimed to improve solubility of MFA. Among many methods of improving solubilities, hydrotropic solubilisation method was used here. After extensive studies, from various hydrotrops, sodium citrate was shown most promising improvement on solubility. 0.5 M sodium citrate was optimized and its solid dispersion with mefenamic acid, dissolution studies had shown 62% increase in solubility of mefenamic acid as compare to pure drug.

Keywords: Mefenamic Acid, Solubility, Hydrotrop, Sodium Citrate.

I. INTRODUCTION

Many techniques have been employed to enhance the aqueous solubility of poorly water-soluble drugs. Hydrotropic solubilization is one such method. Hydrotropes are a class of chemical compounds which affect an increased aqueous solubility by several folds to certain solutes which are sparingly soluble in water under normal conditions [1, 2].Therapeutic efficacy of a drug depends upon its bioavailability and ultimately its solubility to achieve a desired concentration in systemic circulation. Because of their low aqueous solubility and high permeability, dissolution from delivery systems forms the rate limiting step in their absorption and systemic bioavailability [3].

Mefenamic acid is [2-[(2, 3 dimethyl phenyl) amino] benzoic acid , an anthranilic acid derivative, is a non-steroidal anti-inflammatory drug (NSAID) which is widely used to relief mild to moderate pain. It has low water solubility but high permeability. The absolute bioavailability of this drug is about 90–100% [4]. Formulation and manufacture of solid oral dosage forms and tablets in particular, have undergone rapid change and development over the last several decades.

II. Materials and Methods

UV/visible spectrophotometer (Model- V-530, Jasco) were employed for the spectral measurements. Mefenamic acid was purchased from Research lab Fine Chem. Ltd, Mumbai. All other chemicals and solvents used were of analytical grade.

III. Experimental work and Results

Preparation of Calibration Curve: 10mg of mefenamic acid was dissolved in methanol to get 1mg/ml solution.

Then further dilutions were done to obtain 1 – 10 µg/ml solutions. Absorbance of all solutions was measured at 284nm, with UV-VIS spectrophotometer (Table 01).

Concentration of MFA (µg/ml)	Absorbance
1	0.0597
2	0.1213
4	0.2843
6	0.3721
8	0.4756
10	0.5877

Table 01-Calibration curve of mefenamic acid

The Graph of absorbance against the concentration was plotted and correlation Coefficient- was found to be 0.992 and equation of line was found to be y= 1.8571x-
1.3333.

Solubility analysis with different hydrotopes : Excess of mefenamic acid was added to 1M aqueous solution of urea, sodium citrate and potassium acetate separately. Flasks were shaken at 100 rpm for 24hrs.Solutions were filtered and examined by spectrophotometry at 284nm. The results (Table 02) clearly indicates that sodium citrate is a best hydrotropic agent.

Sr. No.	Hydrotropic agent	Absorbance	Concentration (µg/ml)
1	Potassium acetate	0.4766	6.0196
2	Urea	1.1163	12.3159
3	Sodium citrate	2.4146	25.0944

Table 02.Solubility analysis with different hydrotopes.

Solubility analysis with variation in concentration of sodium citrate:

Excess of Mefenamic acid was added in different aqueous solutions of sodium citrate(0.5M, 1M, 1.5M, and 2M). Flasks were shaken at 100 rpm for 24hrs.Solutions were filtered and examined by spectrophotometry at 284nm. Maximum solubility was observed with 0.5 M sodium citrate (Table 03).

Molarity of sodium citrate solution (M)	Absorbance	Concentration of MFA (µg/ml)
0.5M	1.7091	**22.709**
1.0 M	0.8045	9.2470
1.5M	0.2046	3.3425
2.0 M	0.0496	1.8169

Table No.03. Solubility analysis with variation in concentration of sodium citrate:

Formulation of solid dispersion: Mefenamic acid (1.2 mg) was dissolved in 1M sodium citrate (50ml) solution. Solution was heated at 80^0C until semisolid consistency was attained then it was transferred to hot plate for complete drying. Dried mass was passed through 100 mesh sieve. Solid dispersion was found to be fine and free flowing.

Assay: 84.745 mg solid dispersion of mefenamic acid was weighed accurately and dissolved in 250 ml of distilled water. The absorbance of this solution was measured at 284 nm against blank. The drug content in solid dispersion of mefenamic acid was found to be 2.36 mg per 10 mg of solid dispersion. Thus ratio of drug to solid dispersion is 2.36:10.

Dissolution study: The dissolution study for the solid dispersion was carried out according to the Indian Pharmacopoeia, Apparatus Type II (basket) using phosphate buffer pH 7.4 as the dissolution medium [5]. The sample was withdrawn at 5minute interval. Fresh volume of the medium was replaced with the

withdrawn volume to maintain the sink conditions and constant volume throughout the experiment. Samples were suitably diluted with same dissolution medium and the amount of drug dissolved was estimated by UV-VIS spectrophotometer and analysed for the cumulative percentage of drug released. (Table 05).

In vitro release study revealed that there was marked enhancement in the dissolution rate of drug in solid dispersion when compared to pure drug. These may be because of solubilization of drug due to use of sodium citrate as a hydrotrope.

Time (min)	Average of conc. found		% of drug release	% of drug release
	Pure drug	Solid dispersion	Pure drug	Solid dispersion
5	1.450	5.0528	14.50%	50.52%
20	1.5436	5.9956	15.43%	59.95%
40	1.6702	6.9856	16.70%	69.85%
60	1.7256	7.9867	17.25%	79.86%
80	2.1546	9.895	21.54	98.95

Table 05: Dissolution profile of pure mefenamic acid and its solid dispersion.

IV. CONCLUSION

The method of hydrotropic solid dispersion is simple, cost-effective, environment friendly and safe (free from toxicity). So this simple methodology of such hydrotropic solid dispersion can be used to enhance the therapeutic efficacy of poorly water soluble drugs. Thus the research work overcomes the problem of poorly water soluble drugs.

V. REFERENCES

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