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Development of dissolution medium for poorly water soluble drug mefenamic acid

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ABSTRACT

Mefenamic acid, a non steroidal anti-inflammatory drug is poorly water soluble. Addition of surfactant to the dissolution medium improves the dissolution of pure drug by facilitating the drug release process at the solid/liquid interface and micelle solubilization in the bulk. In the present study a dissolution medium was developed. The composition of the dissolution medium was selected on the basis of solubility data of Mefenamic acid at 37^0 C. The solubility data revealed that water consisting of 2% w/v sodium lauryl sulphate shall be suitable dissolution medium. The discriminating power of the selected dissolution medium (2% w/v sodium lauryl sulphate in water.) relative to the other dissolution medium was evaluated. The results further justified that the usage of 2% w/v sodium lauryl sulphate in water serves as most suitable dissolution medium for Mefenamic acid.

Keywords: Solubility, Dissolution Rate, Sodium Lauryl Sulphate, Mefenamic acid.

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INTRODUCTION

Mefenamic acid is a potent nonsteroidal anti inflammatory drug (NSAID) of the enolic acid class, which shows preferential inhibition of cyclooxygenase- 2(COX -2) and inhibits the prostaglandin synthesis. It is highly prescribed in the treatment of rheumatoid arthritis, osteoarthritis and other joint disorders. However, its oral bioavailability is very low, probably due to poor solubility in water and insufficient dissolution rate [1]. The results of present work appeared to have more significance in comparison with the reported literature. Literature reported that the rate constants of the dissolution profiles of Mefenamic acid and inclusion complexes showed the highest dissolutions of 93.12% and 93.91% from 1:1 and 1:1 complexes of Mefenamic acid β-CD and HP- β-CD respectively in phosphate buffer. In the case of 0.1N HCl, the highest dissolution of 94.56% and 95.2% were obtained from the complexes of Mefenamic acid with β-CD and HP- β-CD respectively and this shows no much improvement in the dissolution of Mefenamic acid with β-CD and HP- β-CD complexes[2].

Although cyclodextrins increasing the solubility of poorly soluble drugs, they have certain disadvantages. Certain types of cyclodextrins have specific toxicity in pre-clinical models potentially thereby limiting their use in toxic studies. Sometimes the complexed drug with cyclodextrins will not dissociates rapidly, in such cases, the pharmacokinetics of the poorly soluble drug may be altered as release is not immediate [3]. Thus it is necessary to develop an alternative dissolution medium to overcome these problems.

Drugs that are practically insoluble (solubility less than 0.01%) are of increasing therapeutic interest, as it is a well recognized fact that when administered orally, they may present serious problems of bio-availability. Since their dissolution rate can be the rate limiting step in the in vivo absorption process, there is a definite need for the development of an appropriate dissolution test [4].

Approaches usually used in the design of dissolution media for poorly water soluble drugs include:

a) Bringing about drug solubility by increasing the volume of the aqueous sink or removing the dissolved drug.

b) Solubilization of the drug by co-solvents, up to 40% and by anionic or non-ionic surfactants by adding to the dissolution medium in post micellar concentrations.

c) Alteration of pH to enhance the solubility of insoluble drug molecules [5, 6]. The last two approaches seen less cumbersome and have been more widely employed in pharmacopoeial dissolution tests [7]. The objective of the present study is to develop suitable dissolution medium, which satisfies sink condition, for testing Mefenamic acid formulations by adding co-solvents or surfactants. The discriminating power of selected dissolution medium was evaluated using prepared formulations.

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MATERIALS AND METHODS

MATERIALS

Mefenamic acid was a gift sample from Blue cross laboratories, Nasik, India. Sodium lauryl sulphate, Tween 80, and other chemicals were procured from SD fine chemicals, Mumbai.

METHOD

Preparation of Mefenamic acid capsules

A batch of 10 capsules was prepared by filling the mixture of Mefenamic acid and excipients in hard gelatin capsules. Each capsule is equivalent to 100mg of Mefenamic acid. Mefenamic acid is lubricated with 0.5% w/w magnesium stearate and 0.5% w/w talc.

The prepared capsules were characterized by performing dissolution studies.

CHARACTERIZATION

Solubility study

The apparent solubility of Mefenamic acid in water and in presence of co-solvent or surfactant in water was determined at 37^0c. Mefenamic acid (25mg) was added to 25ml of water in a conical flask. The conical flasks were kept on a shaker incubator maintained at 37 ± 0.5^0c for 48hrs. After shaking, the solution was filtered through whatman filter paper and the filtrate was assayed spectrophotometerically at 285 nm against the respective blank solutions. The results are shown in table – 1

Based on the results suitable dissolution medium was selected and dissolution studies are performed using the selected medium.

Dissolution study

Dissolution studies were performed using USP dissolution apparatus II at 37 ± 0.5^0 C and at 50 rpm. Water and water containing SLS of different concentration used as dissolution medium. At regular intervals 5ml of samples are withdrawn and sink conditions are maintained by replacing with the same quantity replaced with dissolution medium. The samples are analyzed spectrophotometrically at 285nm. The dissolution profile of the Mefenamic acid in selected medium is compared with the dissolution profile of Mefenamic acid and inclusion complexes.

The dissolution data is given in table - 2 and graphically presented in Figure - 1.

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RESULTS AND DISSCUSSION

Since Mefenamic acid is water insoluble hence the solubility studies were carried out in different mediums. The data revealed that the solubility of Mefenamic acid is least in water and its solubility is maximum in water containing 2 % w/v of SLS.

As on increasing the pH of water, the solubility of Mefenamic acid is increased. The solubility is further increased on addition of co-solvent and surfactants. Surfactants enhance the solubility of Mefenamic acid in water than the co-solvent (methanol).

Among two surfactants, SLS has shown better results than the tween- 80. Hence, water containing SLS has selected as dissolution medium. The solubility of Mefenamic acid in water containing various concentrations of SLS has been studied. Among all concentrations of SLS, the solubility of Mefenamic acid is more in water containing 2% w/v SLS.

Dissolution studies of Mefenamic acid capsules was carried out using water containing SLS as dissolution medium and the results were compared with dissolution profile of Mefenamic acid and inclusion complexes.

Literature reported that the rate constants of the dissolution profiles of Mefenamic acid and inclusion complexes were the highest dissolution of 93.12% and 93.91% obtained from 1:1 and 1:1 complexes of Mefenamic acid β-CD and HP-β-CD respectively in phosphate buffer. In the case of 0.1N HCL,the highest dissolution of 94.56% and 95.2% were obtained from the complexes of Mefenamic acid with β-CD and HP-β-CD respectively. The dissolution profile of Mefenamic acid in water containing 2% w/v has shown better results than the inclusion complexes of Mefenamic acid.

The improved dissolution profile of Mefenamic acid in surfactant containing SLS may be due to the fact the surfactants enhances the dissolution of pure drug by facilitating the drug release process at the solid/ liquid interface and micelle solubilisation in the bulk [8].

CONCLUSION

Thus from above results it was concluded that 2 %w/v SLS in water is considered as suitable dissolution medium for routine in-vitro dissolution testing of conventional Mefenamic acid formulations.

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Table -1: Solubility data of Mefenamic acid in different solvents

S.No	SOLVENTS	SATURATION SOLUBILITY(µg/ml)
1.	Water	4.18
2.	P^H 1.2	6.21
3.	P^H 6.8	7.01
4.	P^H 7.4	8.29
5.	P^H 8.0	7.42
6.	5% v/v Methanol in Water	6.33
7.	10% v/v Methanol in Water	13.62
8.	0.25% v/v Tween 80 in Water	90.15
9.	0.5% v/v Tween 80 in Water	112.04
10.	1% v/v Tween 80 in Water	214.78
11.	0.1% w/v SLS in water	10.41
12.	0.25% w/v SLS in water	80.12
13.	0.5% w/v SLS in water	201.28
14.	1% w/v SLS in water	401.11
15.	1.5% w/v SLS in water	503.33
16.	2% w/v SLS in water	852.3

Table – 2: Percentage CDR of Mefenamic acid in different dissolution media

S.No	Time (Min)	Water	0.25%SLS	0.5%SLS	1%SLS	1.5%SLS	2%SLS
1	0	0	0	0	0	0	0
2	5	3	16.8	22.56	30	38.88	42.48
3	10	3.624	19.2	28.8	37.68	46.08	46.08
4	15	3.888	21.36	36.48	45.12	51.36	51.36
5	30	4.2	25.2	40.8	50.16	56.4	56.4
6	45	5.4	27.6	48.96	55.44	60	61.92
7	60	6.912	30.96	51.36	61.68	66.72	70.56
8	75	7.44	32.88	59.28	66	69.6	77.52
9	90	8.088	34.56	60.72	68.88	77.28	83.76
10	105	9.792	35.04	61.92	73.68	79.68	92.4
11	120	12.192	35.76	62.16	75.36	81.12	96.24

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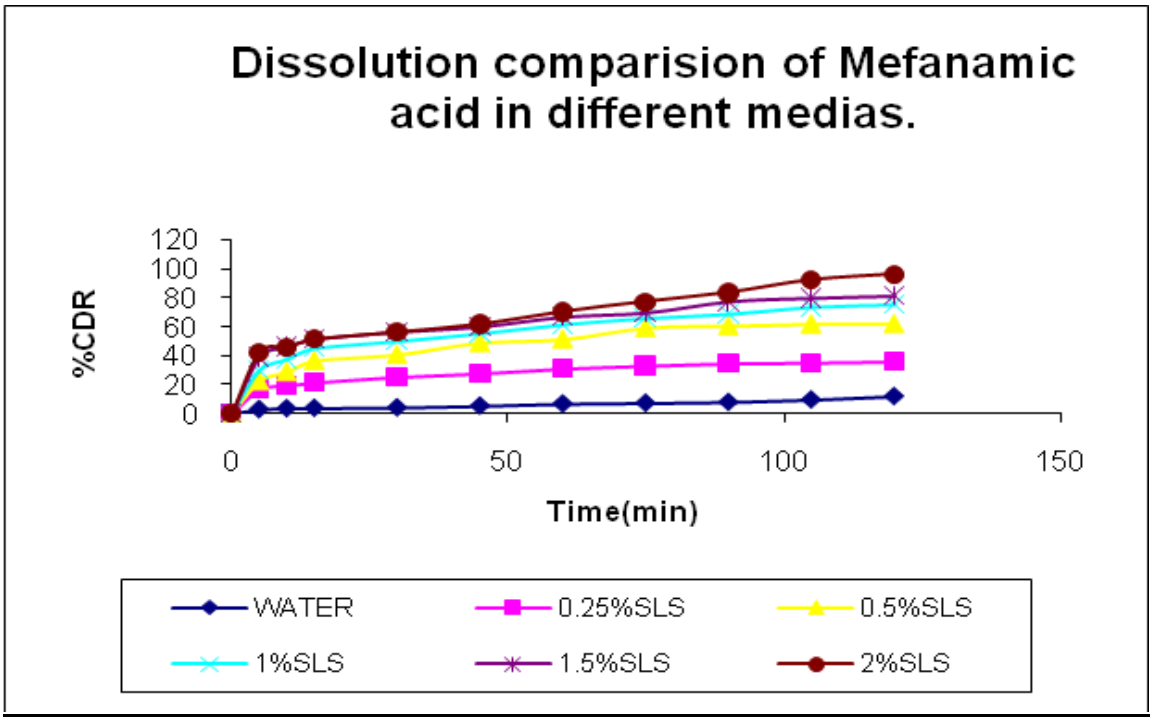
Fig-1: Dissolution comparisons of Mefenamic acid in different Medias.



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