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Research Article

ENHANCEMENT OF SOLUBILITY OF POORLY WATER SOLUBLE DRUG – METRONIDAZOLE BY HYDROTROPY

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ABSTRACT

Metronidazole is an oral synthetic antiprotozoal and antibacterial agent, 2-methyl-5nitroimidazole-1-ethanol ($C_6H_9N_3O_3$). It is physically available in white to pale yellow crystals or crystalline powder with 159-163^{0}C melting point. It is sparingly soluble in Water and in Alcohol; slightly soluble in ether and chloroform. In the present investigation different concentrated solutions of urea (a hydrotropic agent) were employed to enhance the aqueous solubility of Metronidazole which is a poorly water-soluble drug. Here hydrotropic phenomenon i.e solvent evaporation technique and melting method were employed to prepare solid dispersions of Metronidazole. Solid dispersions were evaluated for dissolution rate and a marked increase in dissolution rate was observed. Marked increase in Metronidazole release during drug dissolution profile was found with its solid dispersions as it is poorly water soluble drug. As a hydrotropic agent Urea was used to prepare solid dispersion so that the solubility of Metronidazole could be increased.

Keywords: *Metronidazole, Urea, Hydrotropy, solid Dispersion, Dissolution*

INTRODUCTION

Metronidazole is an oral synthetic antiprotozoal and antibacterial agent, 2-methyl-5nitroimidazole-1-ethanol ($C_6H_9N_3O_3$). It is physically available in white to pale yellow crystals or crystalline powder with 159-163^{0}C melting point. It is sparingly soluble in Water and in Alcohol; slightly soluble in ether and chloroform. Metronidazole is a nitroimidazole antibiotic medication used mainly in the treatment of infections caused by susceptible organisms, particularly anaerobic bacteria and protozoa. Metronidazole is an antibiotic, amebicide, and antiprotozoal [1].

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It is well absorbed orally with a plasma elimination half-life ranging from 6–7 hours.[2]

Metronidazole, taken up by diffusion, is selectively absorbed by anaerobic bacteria and sensitive protozoa. Once taken up by anaerobes, it is non-enzymatically reduced by reacting with reduced ferredoxin, which is generated by pyruvate oxido-reductase. Many of the reduced nitroso intermediates will form sulfinamides and thioether linkages with cysteine-bearing enzymes, thereby deactivating these critical enzymes. As many as 150 separate enzymes are affected. In addition or alternatively, the metronidazole metabolites are taken up into bacterial DNA, and form unstable molecules. This function only occurs when metronidazole is partially reduced, and because this reduction usually

happens only in anaerobic cells, it has relatively little effect upon human cells or aerobic bacteria. [3]

Solid dispersion technique can be used to improve the dissolution rate ,solubility and absorption of a number of insoluble drugs [4]. Now days, the most importance is given to enhance the dissolution rate of the poorly soluble drugs, so, it increases the bioavailability of drug. Solid dispersion is one of the techniques used to increase the dissolution rate of the lipophilic drugs [5, 6, and 7]. Solid dispersions are prepared by solvent or co-precipitation method where both guest solute and solid carrier solvent are dissolved in a common volatile solvent such as alcohol. The liquid solvent is removed by evaporation under reduced pressure or by freeze drying which results in amorphous precipitation of guest in a crystalline carrier [8, 9]. Solid dispersions are two-component systems which consist of a hydrophilic carrier in which the drug is incorporated. The drug is incorporated in the hydrophilic carrier which may be molecularly dispersed or may occur as Nano crystals or amorphous nanoparticles. The enhancement in dissolution rate of the drug can be ascribed to-

(a) An increasing solubility of the drug because of its amorphous state or small particle size (Kelvin's law) [10-13]

(b) An increased surface area available for drug dissolution because of the small size of the drug particles [14,15]

(c) An improvement in wetting of the drug caused by the hydrophilic carrier [16,17]

MATERIALS AND METHODS

Instruments: Shimadzu UV-Visible recording spectrophotometer was used.

USP XXIV type II apparatus (Peddle Type) was employed for dissolution.

Chemicals: Metronidazole was obtained from Unisule Pvt Ltd, Sonipat, Haryana as a generous gift. Whereas Urea was of analytical grade.

Determination of Metronidazole release:

Calibration Curve: Firstly 100 mg of Metronidazole was dissolved in 5ml of 25%w/v urea solution prepared using distilled water and then the volume was made up to 100 ml. This was placed as stock solution for calibration of Metronidazole. Then various dilutions from this stock solution were prepared using stock solution i.e 2µg/ml, 4µ/ml, 6µ/ml……..10mcg/ml. Now these solutions were observed in UV-Visible spectrophotometer for calibration curve at wavelength 277nm.

Method for Preparation of Hydotropic Solid Dispersion of Metronidazole:

Here physical methods of solid dispersion were used to prepare solid dispersions of Metronidazole.

Solvent evaporation method:

Preparation of urea solution: 10gm of urea was dissolved in 40ml of distilled water i.e 25% w/v.

Preparation of solid dispersion in urea solution: 100mg of metronidazole was taken in a 50 ml conical flask and 2ml (contains 500mg urea) of urea solution was added and stirring was done. Most of the water was removed from the solution by maintaining the temperature 50°C. When semisolid consistency was attained it was transferred to china dish and kept in an oven at 90°C±2^{0}C for complete drying. Dried mass was powdered and passed through 80-mesh sieve. The ratio of the Drug: Carrier was 1:5. This solid dispersion was stored in dessicator. In the similar way various solid dispersions having ratio of the Drug: Carrier 1:10 and 1:15 were prepared.

Melting method:

This procedure involves the preparation of physical mixture of 100 mg Metronidazole and urea in three different Drug: Carrier ratios i.e 1:5, 1:10 and and 1:15 in china dish subsequently heated directly until it melted. Then the melted mixture was solidified rapidly in an ice-bath under vigorous stirring. The

final solid mass was crushed, pulverized in Pesle Mortar and sieved by 80 no sieve.

Table 1: Formulations of prepared Metronidazole solid Dispersions

Batch code	*Method of Preparation of Solid Dispersion*	*Ratio Drug: Hydrotropic agent*
E1	Solvent evaporation method	1:5
E2	Solvent evaporation method	1:10
E3	Solvent evaporation method	1:15
M1	Melting method	1:5
M2	Melting method	1:10
M3	Melting method	1:15

EVALUATION

Dissolution Study: The dissolution rate for various solid dispersions (Solvent evaporation and Melting method) were carried out in USP XXIV type II apparatus (Peddle Type) using 900ml of phosphate Buffer (pH 6.8). The temperature was maintained at 37±0.5°C and speed of paddle was adjusted to 50rpm. 5ml of samples (aliquots) were withdrawn at different time intervals. Same volume of fresh phosphate Buffer (pH 6.8) was replaced after each with drawl of aliquot. Aliquots were double diluted with phosphate Buffer (pH 6.8) and analysed using Shimadzu UV-Visible recording spectrophotometer at 277nm.

Table 2: Comparative study of Dissolution Profile of Metronidazole Solid Dipersion in Different Ratios (Solvent Evaporation Method):

Time (Minutes)	*Percentage Cumulative Drug Release*		
	Drug: Urea (1:5) Batch Code E1	*Drug: Urea (1:10) Batch Code E2*	*Drug: Urea (1:15) Batch Code E3*
10	20.419	26.775	33.919
20	24.25	40.169	42.981
30	27.928	42.214	47.824
40	32.622	47.913	55.023
50	42.209	52.992	62.425
60	45.452	55.673	70.179
70	48.94	57.448	75.235
80	51.605	62.358	79.896
90	54.834	66.142	88.873

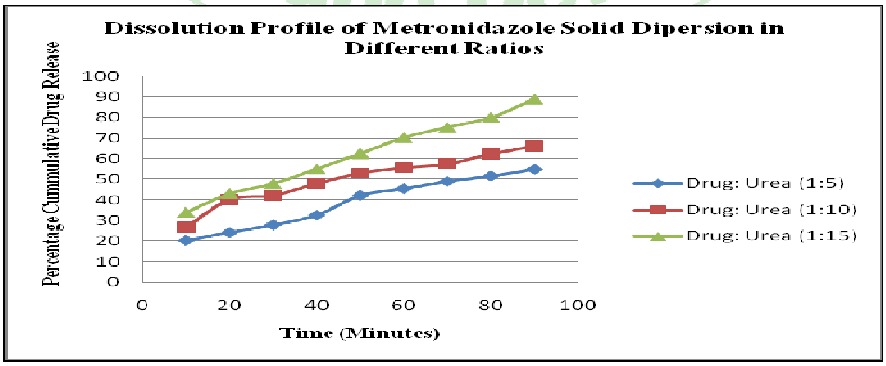
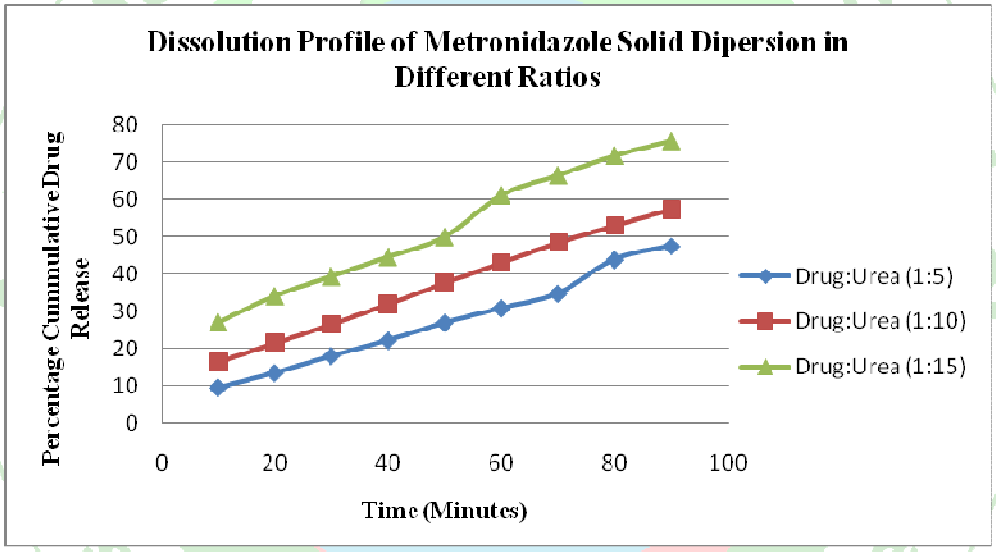


Table 3: Comparative study of Dissolution Profile of Metronidazole Solid Dipersion in Different Ratios (Melting Method):

Time (Minutes)	*Percentage Cumulative Drug Release*		
	Drug: Urea (1:5) Batch Code E1	*Drug: Urea (1:10) Batch Code E2*	*Drug: Urea (1:15) Batch Code E3*
10	9.563	16.481	26.944
20	13.506	21.55	34.094
30	18.068	26.553	39.338
40	22.201	31.93	44.501
50	26.9	37.645	49.879
60	30.809	42.968	60.995
70	34.777	48.406	66.324
80	43.859	52.941	71.567
90	47.491	57.307	75.539



RESULTS AND DISCUSSION

Solid dispersions of Metronidazole were prepared by solvent evaporation and melting method using Urea as a hydrotropic agent. The highest solubility was shown in Batch E3 (prepared by solvent evaporation method) where the ratio of drug & urea was 1:15 whereas secondly marked higher increase was found in Batch M3 (prepared by melting method) where the ratio of drug & urea was 1:15. After reviewing the data collected by dissolution of different batches of solid dispersions it was found that solubility and dissolution rate of poorly soluble drug Metronidazole can be increased by formulating solid dispersions. Here solid dispersions confirmed a higher dissolution rate than pure drug. The dissolution study was carried out in phosphate buffer (pH 6.8) at 37±0.5°C upto 90 minute and the rate of dissolution was found to be increased in solid dispersion in comparison to pure drug.

On comparing the dissolution profiles of the solvent evaporation and melt dispersion method, it was found that solvent evaporation method was better than the melting method with respect to dissolution profiles. So it was concluded that dissolution of poorly soluble drug can be promisingly increased by the solid dispersion methods.

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