RESEARCH ARTICLE

Preparation of solid dispersions of ornidazole using mixed hydrotropic solubilization technique and their characterization

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Abstract

Aim: The aim of the study was to determine the aqueous solubility of ornidazole using different hydrotropic agents then prepare a solid dispersion of ornidazole by mixed hydrotropic solubilization technique and their characterization. **Materials and Methods**: Equilibrium solubilities of ornidazole in different aqueous mediums were determined at room temperature. The volumetric flask was shaken on mechanical shaker for 12 h so that equilibrium solubility can be achieved and the solution was allowed to equilibrate undisturbed for 24 h. For the preparation of hydrotropic solid dispersion containing ornidazole and hydrotropic blend, minimum quantity of distilled water at 68°C–70°C contained in a 200 ml beaker was used to dissolve the urea and nicotinamide. Then, ornidazole was added to this beaker (at 35°C–40°C) and a Teflon-coated magnetic bead was dropped in it. Magnetic bead was stirring in a beaker using a magnetic stirrer, maintaining the temperature at 35°C–40°C. The prepared solid dispersions of ornidazole have been characterized by X-ray diffraction (XRD), differential scanning calorimetry (DSC), and infrared (IR) studies. **Results and Discussion**: The hydrotropic blend urea and nicotinamide (1:1 ratio) have been found to increase aqueous solubility of poorly water-soluble drug ornidazole. This mixed hydrotropic blend was used to prepare solid dispersion of ornidazole. DSC thermogram, XRD, and IR spectra showed that there is no interaction between drug and hydrotropic agents. **Conclusion**: Solid dispersions are containing a blend of urea and nicotinamide as water-soluble hydrotropic carriers show fast release of drug as compared with the pure bulk drug sample and physical mixture. The proposed techniques would be economical, convenient, and safe.

Key words: Mixed-hydrotropic solubilization, nicotinamide, ornidazole, urea

INTRODUCTION

Solid dispersion technique[1-9] has been utilized to increase the dissolution and thereby the rate of absorption and/or total bioavailability of poorly water-soluble drugs. The common methods of making solid dispersions are solvent evaporation, fusion, and fusion-solvent methods. Hydrotropic solid dispersion (HSD) technique[9] prohibits the use of organic solvent. Hydrotropic agents are water-soluble, whereas the drug is poor water soluble. However, in the presence of a large amount of hydrotropic agent in water, the drug gets solubilized. Then, water is removed by suitable evaporation technique to get a solid mass (a solid dispersion). Then, so formed solid dispersions shall be denoted as HSDs. Ornidazole is a 5-nitroimidazole derivative drug which has antimicrobial action. It is used in the treatment of protozoal infections, and also in the treatment and prophylaxis of anaerobic bacterial infections.[10]

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MATERIALS AND METHODS

Material

Ornidazole was received as a gift sample from IPCA Laboratories Limited (Ratlam, India). Urea (Merck Ltd., Mumbai), Nicotinamide, Sodium ascorbate, Sodium gluconate, and trisodium citrate dihydrate (Qualigens Fine Chemicals, Mumbai) were used. All other chemicals and solvents were of analytical grade.

Determination of Equilibrium Solubility

Equilibrium solubilities of ornidazole in different aqueous mediums [Table 1] were determined at room temperature. For determining solubility, accurately measured 3 ml of a particular blend of hydrotropic agent was taken in a 10 ml volumetric flask, and an excess amount of drug was added, and mechanically shaken until saturated solution was formed. The volumetric flask was shaken on a mechanical shaker for 12 h so that equilibrium solubility can be achieved and solution was allowed to equilibrate undisturbed for 24 h. Then, solution was centrifuged at 2000 rpm for 5 min in ultracentrifuge, and then the solution was filtered through Whatman Grade 41 filter. Aliquot was suitably diluted with purified water and analyzed using UV spectrophotometer at 319 nm.[11]

Enhancement ratios insolubility [Table 2] were determined by following formula:

$$\text{Enhancement ratio} = \frac{\text{Solubility of drug in hydrotropic solution}}{\text{Solubility of drug in distilled water}}$$

Selection of Ratios of Drug and Carrier in Physical Mixture (PM) and HSD

There was a significant enhancement in solubility of drug using a blend of urea and nicotinamide in the ratio of 1:1. Therefore, optimized combination of hydrotropes was selected for the preparation of solid dispersion. Finally, ratios of drug: Carrier (a blend of urea and nicotinamide in 1:1 ratio) used for solid dispersions were 1: 2, 1:4, and 1:6.

Preparation of HSDs of Ornidazole

For preparation of 10 g HSD containing ornidazole and hydrotropic blend (10% w/w urea and 10% w/w nicotinamide) in 1:2 ratio, ornidazole (3.3331 g), urea (3.3432), and nicotinamide (3.3323) were accurately weighed. Minimum quantity of distilled water at 68°C–70°C contained in a 200 ml beaker was used to dissolve the urea and nicotinamide. Then, ornidazole was added to this beaker (at 35°C–40°C) and a

Table 1: Equilibrium solubility of ornidazole in different media

Solvent	pH of solvent system	Solubility* (g/100 ml)	Solubility enhancement ratio
Distilled water	7.01	1.51	-
10% w/v sodium ascorbate solution	7.21	1.61	1.06
10% w/v sodium gluconate solution	5.82	1.23	0.81
10% w/v trisodium citrate solution	8.81	0.67	0.45
10% w/v urea	8.71	3.02	2.01
20% w/v urea	9.13	4.61	3.07
10% w/v nicotinamide	7.22	3.68	2.45
20% w/v nicotinamide	6.71	9.02	6.01
10% (urea+nicotinamide)	8.43	11.16	7.44

*Average of three determinations

Table 2: Dissolution profile of pure drug, OUVB3 1:6 PM, 1:2 and 1:4 HSD in distilled water (*n*=3)

Time (min)	Cumulative percent drug dissolved (mean±SD)				
	Pure drug	OUVB^3 1:6 PM	OUVB^3 1:2	OUVB^3 1:4	OUVB^3 1:6
5	7.929±0.023	22.345±0.057	65.592±0.056	100.914±0.045	101.138±0.042
10	15.871±0.056	32.467±0.088	77.458±0.093	100.393±0.076	100.987±0.095
15	21.847±0.067	45.346±0.097	76.788±0.092	96.316±0.045	98.473±0.048
20	30.837±0.098	66.342±0.076	80.504±0.023	93.009±0.084	96.830±0.073
30	43.336±0.078	76.138±0.059	89.693±0.035	91.860±0.075	94.821±0.083

HSD: Hydrotropic solid dispersion, SD: Standard deviation, OUVB^3: Ornidazole urea nicotinamide

Teflon-coated magnetic bead was dropped in it. Magnetic bead was stirring in a beaker using a magnetic stirrer, maintaining the temperature at 35°C–40°C until ornidazole got completely solubilized. Stirring was continued till the semisolid mass remained in beaker. Semisolid mass was spread on watch glasses in thin layers for quick drying. All the watch glasses were kept in oven, maintained the temperature at 40°C for drying. When the mass became dry, it was transferred in pestle mortar and triturated, again kept in oven for drying. After drying, the powder of solid dispersion was passed through sieve number 100 and was kept for 6 days in a desiccator containing blue silica gel. After this, the HSD powder was stored in air-tight glass bottles. Same procedure was repeated to prepare HSDs containing ornidazole and hydrotropic blend (urea: Nicotinamide - 1:1) in ratios of 1:4 (using 2.0101 g ornidazole) and 1:6 (using 1.4292 g ornidazole).

PM of Ornidazole

Drug:carrier ratio 1:6 was used for preparation of PM. Ornidazole (1.4312 g), urea (4.2946 g), and nicotinamide (4.3011 g) were accurately weighed and mixed for 10 min using glass pestle and mortar with trituration. Then, powder was passed through sieve number 100. After this, the PM was stored in air-tight glass bottles.

Determination of Drug Content in Ornidazole Formulations (HSD and PM)

Solid dispersion/PM containing about 10 mg of ornidazole was accurately weighed and transferred to a 500 ml volumetric flask. About 450 ml of distilled water was added, and flask was shaken to dissolve the formulation completely. Then, volume was made up to the mark with distilled water, and the absorbance of this solution was measured at 319 nm against reagent blank. In each case, analysis was performed in triplicate. The drug content [Table 3] was determined using regression equation:

$Y = 0.03288\ X + 0.03216.$

Powder X-ray Diffraction (XRD) Studies of Formulated HSD and PM

The powder XRD spectra of the prepared HSDs and the PMs were obtained using RU-H_3R, horizontal Rotaflex rotating anode X-ray generator instrument, Rigaku, Tokyo.

Differential Scanning Calorimetry (DSC)

To obtain the DSC thermograms of the drug, solid dispersion and PM, TA Instruments-2910 modulated DSC (USA) was employed. To take DSC thermograms, 4 mg of drug or formulation of drug was weighed accurately and placed in one of the matched aluminum pan. The sample pan and the reference pan both were sealed and placed on the heating cell and covered with a glass bell jar. Heating at a rate of 10°C/min with a continuous purge of nitrogen (45 cc/min) was done with recording of energy changes in the sample with respect to the reference in the temperature range of 50°C–170°C.

Fourier-transform Infrared (FTIR) Spectroscopy

FTIR spectroscopy of drug, solid dispersion and PM were done using FTIR spectrophotometer (Shimadzu FTIR

Table 3: Drug contents of physical mixtures and hydrotropic solid dispersions (n = 3)

Drug: Hydrotropic blen	Percent drug content (mean ± SD)	
	PM	HSD
OUN 1 : 2	-	33.345±0.054
OUN 1 : 4	-	20.104±0.075
OUN 1 : 6	14.279±0.081	14.521±0.087

PM: Physical mixture, HSD: Hydrotropic solid dispersion, SD: Standard deviation, OUN: Ornidazole Urea Nicotinamide

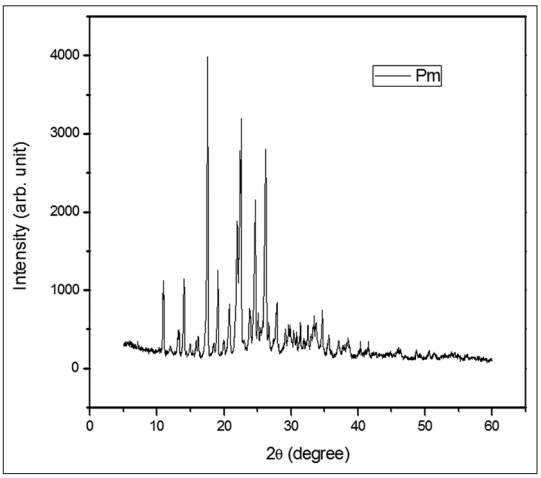

Figure 1: X-ray diffraction spectra of ornidazole

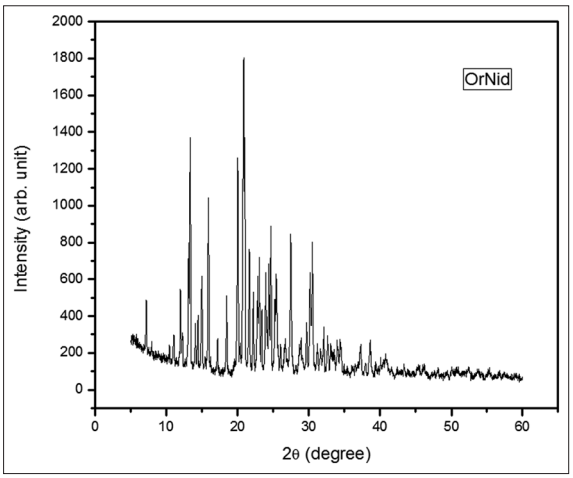

Figure 2: X-ray diffraction spectra of physical mixture

IRAffinity-1, Japan). The samples were scanned over wavenumber region of 4000–400/cm at resolution of 4/cm.

Dissolution Rate Studies of Drug and Its Formulations

Dissolution rates of bulk drug sample of ornidazole, PM (1:6), and HSD containing drug: Hydrotropic blend of 1:2, 1:4, and 1:6 ratios were studied using USP XXIV (type II) dissolution rate test apparatus. Bulk drug sample, PM, and HSDs equivalent to 100 mg drug were used to perform dissolution rate studies. Distilled water was used as dissolution medium. The stirrer was adjusted to rotate at 50 rpm. A temperature of 37 ± 0.5°C was maintained throughout the experiments. Samples (10 ml) of dissolution medium were withdrawn at known time intervals and replaced with same volume of distilled water after each withdrawal. The samples were analyzed for drug contents by measuring the absorbances of appropriately diluted sample solutions with distilled water at 319 nm wavelength. Calculations for amounts of drug released were done using regression equation Y = 0.03288 X + 0.03216.

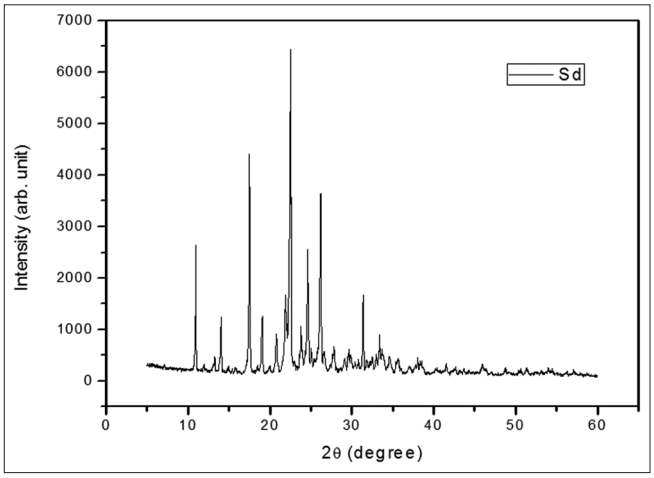

Figure 3: X-ray diffraction spectra of solid dispersion

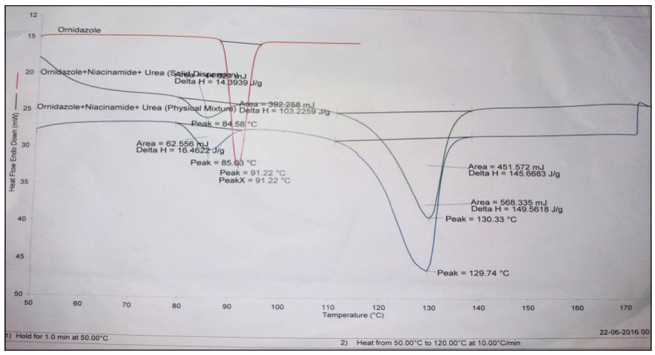

Figure 4: Differential scanning calorimetry curve of ornidazole, physical mixture, and solid dispersion

RESULT AND DISCUSSION

The results of the solubility data [Table 1] showed that the solubility of ornidazole increases synergistically by mixed hydrotropy. It also showed that solubility of ornidazole was increased more than 7 times in hydrotropic blends.

XRD diffraction patterns [Figures 1-3] of solid dispersion and PM (HSDs $OUVB_3$ 1:6 and PM $OUVB_3$ 1:6), exhibited same peaks at 2θ of 13.3, 15.8, 20.8, and 30.4 as in the case of pure ornidazole drug. Since the XRD diffraction patterns of PM and HSD are moral as same this indicates that there is no chemical interaction between drug and hydrotropic agents (by making the HSD). This study confirmed that HSDs were not present in amorphous form; rather they were of crystalline nature.

DSC thermogram [Figure 4] of ornidazole showed a single sharp endotherm, having an onset of 88.4°C, a maximum at 90.1°C, and a return to baseline at 93.7°C. This endotherm shows the melting of ornidazole. The DSC curve of PM and solid dispersion both showed same endothermic peak which indicates that there is no complex formation between drug and hydrotropic agents in HSD.

The infrared spectra [Figures 5-7] of ornidazole obtained, exhibit peaks at 3174.1, 1536.9, 1361, and 1269.5/cm.

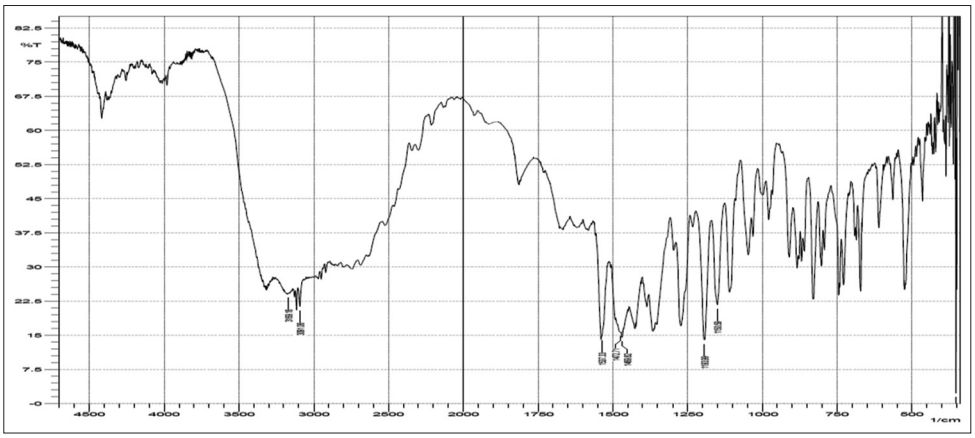

Figure 5: Infrared spectra of ornidazole

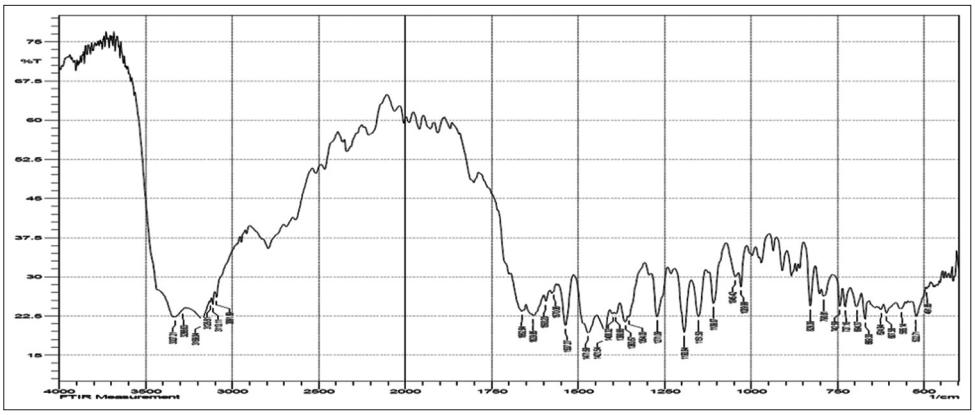

Figure 6: Infrared spectra of physical mixture

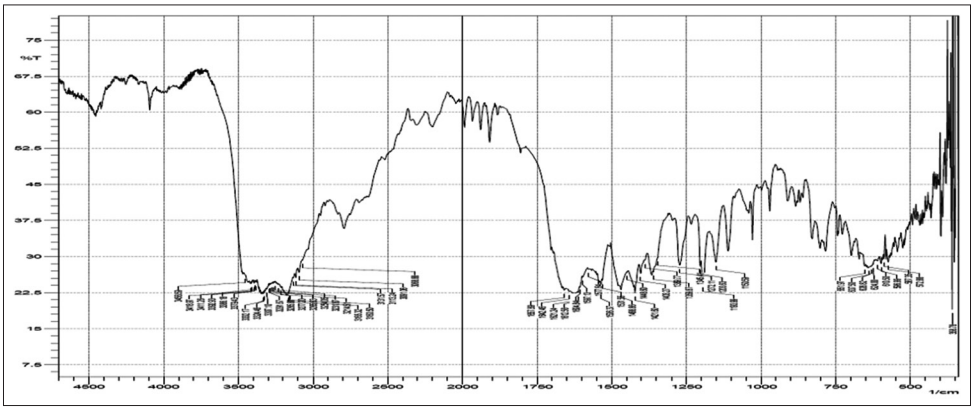

Figure 7: Infrared spectra of solid dispersion

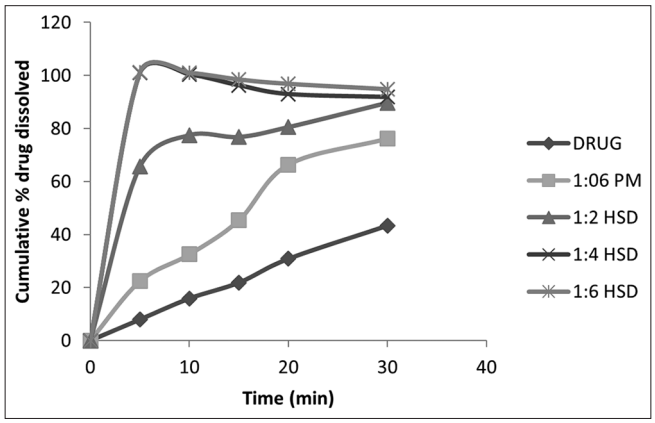

Figure 8: Dissolution profile of pure drug, ornidazole urea nicotinamide 1:6 physical mixture, 1:2 and 1:4 hydrotropic solid dispersion in DW

Same peaks were observed in PM and solid dispersion of ornidazole. It shows that there is no interaction between drug and hydrotropic agents.

From the results [Table 2 and Figure 8] of dissolution rate study, it is evident that the bulk drug sample exhibited poor drug release profiles. Initial rates of dissolution of drug from HSDs were very quick as compared with initial rates of dissolution from bulk drug sample. It also showed that 1:4 and 1:6 HSD were dissolved completely within 1 min. While on the other hand, pure drug and PM were not dissolved completely even after 30 min.

CONCLUSION

The solid dispersions of ornidazole were developed using the concept of mixed hydrotropic solubilization technique. Solid dispersions containing blend of urea and nicotinamide as water-soluble hydrotropic carriers show the fast release of drug as compared with the pure bulk drug sample and PM; the quick onset of action and better extent of absorption is expected after oral administration of these HSDs. The proposed techniques would be economical, convenient, and safe. Thus, the study opens the chances of preparing mixed HSD of poorly water-soluble drugs.

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