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Research Article

SOLUBLITY ENHANCEMENT OF MICONAZOLE BY FORMULATION OF HYDROTROPIC SOLID DISPERSIONS

Anu Kaushik*, Rakesh Kumar Jat

Institute of Pharmacy, Shri Jagdishprasad Jhabarmal Tibrewala University Jhunjhunu Rajasthan, 313001, India

ABSTRACT

In the present research work mixed hydrotropic solubilization phenomenon is used to enhance the solubilization of poorly water soluble drugs. Bulk drug samples were identified by the observed IR spectra and the melting points determination. Sodium benzoate, niacinamide and urea are the hydrotropes were selected for the solubility enhancement of drugs Solubility enhancement ratios for selected poorly water-soluble drugs were determined. Results showed that remarkable increase in aqueous solubility of Miconazole in presence of large concentration of hydrotropes. Marketed Miconazole tablets determined by spectrophotometric analysis using hydrotropic solubilization techniques. Validation of the proposed analysis methods is confirmed by satisfactorily low values of statistical parameters viz., standard deviation, percent coefficient of variation and standard error.

Keywords: Solubility enhancement, hydrotropes, Solid dispersion, Miconazole.

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***Address for Correspondence**
Institute of Pharmacy, Shri Jagdishprasad Jhabarmal Tibrewala University Jhunjhunu Rajasthan, 313001, India Email: anu171417@gmail.com

INTRODUCTION

In the present research work mixed hydrotropic solubilization phenomenon is used to enhance the solubilization of poorly water soluble drug (Miconazole). The solubility of drugs of pharmaceutical formulation in water is very great problem of present day. There are so many techniques or methods are used nowadays to increase the solubility of different pharmaceutical preparations[1]. Use of Solid dispersion[2,3], cyclodextrin[4] and polysaccharide chitosans[5], dendrimers [6], preparation of buffers, Liquisolid techniques[7], complex formation, chelation and salting in are different procedures to increase the solubility of active constituents. Different solubilization techniques have various advantage and disadvantage in the formulations. Hydrotropic solubilization is one of the techniques that are used to increase aqueous solubility of different dosages forms in pharmaceutical industry.

In hydrotropic solubilization a large amount of hydrotropic agents like urea, sodium benzoate, sodium citrate, sodium salicylate, sodium alginate, nicotinamide, glycine etc are used in parts by agitating the solution vigorously adding agents after regular intervals. The hydrotropes forms agglomerates with drugs to dissolve and salting in phenomena takes place in the mechanism. The hydrotropes are eco-friendly, cheap and harmless to the preparations as compared to organic solvents such as chloroform, methanol, petroleum ether etc. that are toxic to environment, very costly, inflammable and evaporable. The organic solvents are hazardous to environment as compared to hydrotropes.

Mixed hydrotropic solubilization is now more advanced version of hydrotropic solubilization. In this technique two or more hydrotropes are taken in different ratios to increase the solubility of the drug. Itself pharmaceutical ingredient also acts as hydrotropes to increase the solubility of other drugs. The hydrotropes form agglomerates and increase the solubility of different pharmaceutical formulations by salting in mechanism.

From literature survey, it is evident that urea has been extensively employed to make solid dispersions of a large number of poorly water-soluble drugs (by fusion or common solvent technologies). As evident from solubility studies, urea has been found to enhance aqueous solubility of Miconazole significantly. Therefore, this poorly water-soluble drugs and urea as a model hydrotropic agent selected to prepare hydrotropic solid dispersions for solubility enhancement study. The prepared solid dispersions have been characterized by DSC, XRD and IR studies. They have

been studied for dissolution rate enhancement effect and stability as well.

METHODS

Identification of bulk drug samples

The bulk drug samples were identified by matching their IR spectra. The instrument used for this purpose was, FTIR-8400 S, Shimadzu Corporation (Japan). Further, confirmation of drugs was done by observing their melting points (by Thiele's tube method). The observed melting points of these drugs were matching with the reported melting points.

Selections of hydrotropes for poorly water-soluble drugs

From the literature survey evident that more is the concentration of hydrotropes, more is the aqueous solubility of drugs. Therefore, concentrated aqueous solutions of some hydrotropes were utilized in this study. 2 M sod. Benzoate (2 M SB), 2 M sod. Salicylate, 2 M niacinamide (2 M NM), (2 M SS), 4 M sodium acetate (4 M SA), 10 M urea and 1.25 M sodium citrate (1.25 M SC) (10 M UR) were used as hydrotropic solutions.

In order to select best hydrotropes for various drugs, an approximate solubility determination method was employed. This process is a modified form of the process used by Simamora *et al*[8]. When the determined solubility enhancement ratio was at least 5, such hydrotropic solution was selected for that drug (Table 1).

Table 1: Hydrotropes selected for poorly water-soluble drugs

Drugs	Selected hydrotropic solution
Miconazole	2 M Sodium benzoate
Miconazole	2 M Niacinamide
Miconazole	10 M Urea

Determination of interference of hydrotropic agents in the spectrophotometric estimation of drugs[9]

A UV-visible recording spectrophotometer (model UV-160 A; Shimadzu, Japan) with 1 cm matched silica cells was employed for spectrophotometric determinations. For determination of interference of hydrotropes in the spectrophotometric estimation of miconazole, the absorbance of the Std solutions of drugs were measured in distilled water only and in the presence of the highest concentration of the hydrotropic agent employed for spectrophotometric analysis/formulation aim in the this study. Absorbances of drug were recorded against respective reagent blanks at appropriate wavelengths and results are presented in Table 2.

Determination of interference of formulation additives in the spectrophotometric estimation of drugs

For determination of interference of formulation additives in the spectrophotometric estimation of miconazole, the absorbance of the standard solutions of drugs were determined in presence of maximum concentrations of formulation additives employed for formulation purpose in the present investigation. The absorbance were recorded against respective reagent blanks at appropriate wavelengths and results are presented in table 2 and 3

Regression Equation for Miconazole in Distilled Water

50 mg miconazole bulk drug was accurately weighed and transferred to a 500 ml volumetric flask. Distilled water (450 ml) was added and flask was shaken vigorously to dissolve the drug. Absorbance values of these solutions were noted at 320 nm against distilled water blank. These values of absorbance of standard solutions were used to obtain regression equation (Table 4).

Regression Equations for Miconazole in Presence of Hydrotropic Agents (Sodium benzoate, Niacinamide and Urea)

50 mg of drug was accurately weighed and transferred to a 500 ml volumetric flask. Twenty ml of 2 M sod benzoate solution was incorporated and then drug was added in this solution and dissolved by shaking. Absorbance values of these solutions were measured at 320 nm against their respective reagent blanks. The values of absorbance of std solutions were utilized to get reg. eq. (Table 4) for the determination of miconazole in presence of sod. benzoate.

Essentially same procedure was repeated using 2 M niacinamide and 10 M urea solutions in place of 2 M sodium benzoate solution to obtain regression equation (Table 3) for the estimation of miconazole in presence of niacinamide and urea.

The regression equations so obtained, the wavelengths selected and the concentrations of various hydrotropic solutions used (Beer's ranges) are shown in Table 4.

Equilibrium solubility determinations at room temperature

A method was employed for determination of equilibrium solubility at room temperature. Filtrates of saturated solutions of miconazole were measured on spectrophotometer, determining the absorbance of diluted solutions (with distilled water) against the respective reagent blanks at their appropriate wavelengths (Table 4). Solubility so determined have been shown in Table 5.

Enhancement ratios (Table 5) in solubility were determined by following formula -

Enhancement ratio=

Solubility in hydrotropic solution/Solubility in distilled water

Spectrophotometric analyses of marketed tablet formulations of miconazole using hydrotropic solubilization technique

20 marketed tablets of miconazole (formulation-I) were weighed and ground to a fine powder. An accurately weighed tablet powder equivalent to 50 mg of

miconazole was transferred to a 25 ml volumetric flask. Then 20 ml of 2 M sodium benzoate solution was added and the flask was shaken for about 10 min to solubilize the drug present in tablet powder and the required volume was made up by adding distilled water. Filtrate was collected, and first few ml of solution was rejected then this filtered solution was divided in 2 parts A and B.

To check its chemical stability and to observe precipitation, Part A was kept at room temp for 48 hours, if any. Further, Part B filtrate was diluted by addition of distilled water and was analyzed on uv-spectrophotometer against reagent blank by noting the absorbance at 320 nm. The drug content of the tablet formulation-I was calculated using reg. eq. (Table 4). The results of analysis are presented in Table 6. After 48 hours, filtrate of part A was analyzed in the same way, to test the chemical stability of drug in presence of hydrotrops (Na-benzoate).

After first analysis, same procedure was repeated for five times more. In these cases, filtrates were not divided in two parts. Filtrates were analyzed in fresh conditions only. Using the same procedure the drug contents of tablet formulation-I were calculated and results of analysis are presented in Table 6. The statistical evaluation of results of analysis is presented in Table 7.

Recovery studies of marketed miconazole tablet formulations using hydrotropic solubilization technique

In order to validate the proposed method, the recovery studies were performed. For this, pre-analyzed tablet powder equivalent to 50 mg of miconazole was accurately weighed and transferred to a 25 ml volumetric flask. Then, 10 mg of miconazole bulk drug sample was added to this volumetric flask, as spiked drug. Then, 20 ml of 2 M sodium benzoate solution was added and the flask was shaken for about 10 min and the volume was made up to the mark with distilled water. After stirring the contents of flask for mixing of contents, contents were filtered using Whatman filter #41. Then, First few ml of collected filtered solution was rejected. The filtrate was appropriately diluted by addition of distilled water and absorbance of this solution was measured at 320 nm against respective reagent blank. The recovery studies were performed for six times (using 10 mg spiked drug) and the results of recovery analysis are presented in Table 8. Similar recovery studies were performed using 20 mg of miconazole bulk drug sample as the spiked drug and results are presented in Table 8.

Just like marketed tablets of formulation-I, the marketed tablets of formulation-II was subjected to analysis (using 2 M sodium benzoate solution) and the results are presented in table 6, 7 and Table 8..

Another hydrotropic agent, 2 M niacinamide solution was also used for spectrophotometric estimation of marketed tablet formulations (I and II) of miconazole in the same manner as in the case of 2 M sodium benzoate solution method, as per the conditions mentioned in Table 4.33. The results of analysis are presented in table 6, 7 and Table 9.

Preparation of Hydrotropic Solid Dispersions of Miconazole[10. 11]

Accurately weighed 5.0 g miconazole and 20.0 g urea were employed to prepare solid dispersion containing miconazole and urea in ratio of 1:4 (MU 1:4HSD). Similarly, 5.0 g miconazole, 30.0 g urea and 5.0 g miconazole, 40.0 g urea were used to prepare solid dispersions containing miconazole and urea in ratios of 1:6 (MU 1:6 HSD) and 1:8 (MU 1:8 HSD), respectively.

Preparation of Physical Mixtures of Miconazole

To prepare physical mixture containing miconazole and urea in ratio 1:8 (AU 1:8 PM), accurately weighed 5.0 g miconazole and 40.0 g urea were triturated intensely for 10 min using glass pestle and mortar. Then, powder mass was shifted through sieve # 100.

Determination of Drug Content in Miconazole in physical mixtures (PM) and hydrotropic solid dispersions (HSD) [10. 11]

Powdered solid dispersion containing about 10 Mg of miconazole (drug) was weighed and transferred to a 500 ml vol flask. About 450 ml of distilled water was added and content of this flask was stirred to dissolve the solid dispersion completely. Now volume was produced up to the required volume with dist water and the absorbance was noted at 320 nm against reagent blank. In each case, analysis was carried out in triplicate. The drug content was determined using regression equation Y = 0.0551 X – 0.0075 (Table 4). The results of analysis are presented in Table 12.

IR studies of formulations of drugs

A large number of solid dispersions have been characterized by IR studies to assess the possibility of interaction between drugs and water-soluble carriers. Attempts were made to assess the possibility of interaction of hydrotropic agent, urea with drug miconazole by conducting IR studies on the prepared drug formulations, HSD and PM both.

DSC studies of drugs and their formulations

A large number of solid dispersions have been characterized by DSC studies to assess the possibility of interactions between drugs and water-soluble carriers. Attempts were made to assess the possibility of interaction of hydrotropic agent, urea with miconazole by conducting DSC studies.

In order to obtain the DSC thermograms of the drugs and their formulations (HSD and PM), a thermal analysis instrument, TA Instruments-2910 modulated DSC (USA) was employed. To carry out these studies, 1-4 mg of drug or formulation of drug was weighed accurately and placed in one of the matched aluminium 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^{O}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

80-200^{O}C.

Powder X-ray diffraction studies of drugs and their formulations

The powder X-ray diffraction spectra of urea, miconazole, the prepared HSD and PM were found using RU-H3R, Horizontal Rotaflex rotating anode X-ray generator instrument, Rigaku (Rigaku International Corporation, Tokyo). The powder was spread on a graticule and pressed in such a way that powder did not fall on keeping the graticule vertical. The graticule was placed in sample holder and exposed to C_uK_α-radiation (40 KV, 50 MA), $2\theta = 5^\circ$ to 40° at a scanning speed 4°/min and step size 0.02° 2θ. The X-ray diffractograms so obtained are presented in Fig. 1 to Fig. 6. The major characteristic X-ray diffractogram peaks are presented in Table 13.

Dissolution rate studies of drugs and their formulations

Dissolution rates of bulk drug samples miconazole, dissolution medium. Bulk drug samples, physical mixtures and hydrotropic solid dispersions equivalent to 200 mg drug were used to perform dissolution rate studies. The stirrer was adjusted to rotate at 50 rpm. A temperature of 37 ± 0.5^{O}C was maintained throughout the experiments. Calculations for amounts of drugs released were done using respective reg. equations (Table 4). The observation of dissolution studies are shown in the Fig. 7.

Stability studies of drug formulations

The physical mixtures (of drugs with urea) were subjected to chemical stability and the chemical stabilities. The percent residual drug for each formulation at different time intervals is recorded in Table 14.

RESULTS AND DISCUSSION

Bulk drug samples were identified by the observed IR spectra and the melting points determination. Based on an approximate solubility determination method, suitable hydrotropes were selected for the poorly water-soluble drugs (Table 1).

It is evident from Table 2 that there is no or negligible interference on the absorbance values of drug solutions in presence of hydrotropic agents. Also, it is evident from Table 3 that there is no or negligible interference on the absorbance values of drug solutions in presence of formulation additives.

physical mixtures containing drug:urea of 1:8 ratio of miconazole an

For spectrophotometric estimations of miconazole, the regression equations were determined (Table 4). The observed values of R (correlation coefficient) were approaching 1, indicating good linear relationships.

Solubility enhancement ratios for selected poorly water-soluble drugs were determined (Table 5) and ranged in between 5.1 to 10.9 and 6.1 to 7.1.

Table 2: Interference studies for hydrotropic agents

Drug	Solvent system used	Concentration of drug used (µg/ml)	Concentration of hydrotropes used (µg/ml)	Wavelength (nm)	Absorbance against respective blank
Miconazole	DW	20	-	320	1.089
Miconazole	DW + SB	20	2300	320	1.090
Miconazole	DW + NM	20	1950	320	1.087
Miconazole	DW + UR	20	4800	320	1.072

SB-Sodium benzoate, NM-Niacinamide, UR-Urea, SC-Sodium citrate, DW-Distilled water

Table 3: Interference studies for formulation additives

Drug	Solvent system used	Concentra- tion of drug used (µg/ml)	Concentration of additive used (µg/ml)	Wave length (nm)	Absorbance against respective blank
Miconazole	DW	20	-	320	1.089
Miconazole	DW + Glycerin	20	100	320	1.079
Miconazole	DW + Sucrose	20	200	320	1.083

DW-Distilled water

Table 4: Optical characteristics for uv-spectrophotometric determination of drugs using different solvent systems

Drug	Solvent system	Wavelength used (nm)	Beer's range (µg/ml)	Regression equation	R
Miconazole		320	5 – 30	.0548 X – 0.0017	0.9999
Miconazole	+ SB	320	5 – 30	.0548 X – 0.0015	0.9998
Miconazole	+ NM	320	5 – 30	.0551 X – 0.0021	0.9998
Miconazole	+ UR	320	5 – 30	.0551 X – 0.0075	0.9996

DW-Distilled water, SB-Sodium benzoate, NM-Niacinamide, UR-Urea, SC-Sodium citrate

Table 5: Solubility of drug in different aqueous systems at room temperature

Drug	Solvent system	Method of analysis used	Solubility (% w/v)	Temperature (^{0}C)	Solubility enhancement ratio
Miconazole	DW	SPM	0.728	28 ± 1	-
Miconazole	2 M SB	SPM	3.783	28 ± 1	5.2
Miconazole	2 M NM	SPM	7.941	28 ± 1	10.9
Miconazole	10 M UR	SPM	3.682	28 ± 1	5.1

DW-Distilled water, SB-Sodium benzoate, NM-Niacinamide, UR-Urea, SC-Sodium citrate, SA-Sodium acetate, SS-Sodium salicylate, TM-Titrimetric method, SPM-

In the present investigation Miconazole having poor aqueous solubility has been selected as model drugs. Hydrotropic solubilization phenomenon has been used to analyze these drugs without the help of organic solvents.

As evident from Table 5, there is remarkable increase in aqueous solubility of Miconazole in presence of large concentration of hydrotropes. Thus, it was thought worthwhile to make use of hydrotropic solubilization techniques for the development of new spectrophotometric analytical techniques.

Spectrophotometric analyses of marketed tablet formulations of miconazole using hydrotropic solubilization technique

The statistical evaluation of results of analysis is presented in Table 7.

Recovery studies of marketed miconazole tablet formulations using hydrotropic solubilization technique

The recovery studies were performed for six times (using 10 mg spiked drug) and the results of recovery analysis are presented in Table 8. Similar recovery studies were performed using 20 mg of miconazole bulk drug sample as the spiked drug and results are presented in Table 8.

Just like marketed tablets of formulation-I, the marketed tablets of formulation-II was subjected to analysis (using 2 M sodium benzoate solution) and the results are presented in Table 6, 7 and Table 8.

Another hydrotropic agent, 2 M niacinamide solution was also used for spectrophotometric estimation of marketed tablet formulations (I and II) of miconazole in the same manner as in the case of 2 M sodium benzoate solution method (Section 4.7 and 4.8), as per the conditions mentioned in Table 4.33. The results of analysis are presented in 6, 7 and Table 9.

Table 6: Results of spectrophotometric analysis of miconazole tablet formulations SBM-Sodium benzoate method, NMM-Niacinamide method

Amount of drug present in tablet powder analyzed (mg)	Amount found (mg)				Percentage estimated			
	Formulation-I		Formulation-II		Formulation-I		Formulation-II	
	SBM	NMM	SBM	NMM	SBM	NMM	SBM	NMM
50	49.76	51.42	50.29	49.03	99.52	102.84	100.58	98.06
50	50.56	50.24	49.63	49.96	101.12	100.48	99.26	99.92
50	49.90	51.06	49.33	50.31	99.80	102.12	98.66	100.62
50	50.04	49.93	50.16	49.39	100.08	99.86	100.32	98.78
50	50.69	50.65	49.36	49.26	101.38	101.30	98.72	98.52
50	49.86	51.03	50.18	48.93	99.72	102.06	100.36	97.86

Table 7: Statistical evaluation of spectrophotometric analysis of miconazole tablet formulations

Tablet formu-lation	SBM				NMM			
	Mean % estimated	Standard deviation	% Coeff. of variation	Stan- dard error	Mean % estimated	Standard deviation	% Coeff. of variation	Stan-dard error
I	100.27	0.784	0.782	0.320	101.44	1.120	1.104	0.457
II	99.65	0.872	0.875	0.356	98.96	1.086	1.097	0.443

SBM-Sodium benzoate method, NMM-Niacinamide method.

Table 8: Results of recovery studies of spectrophotometric analysis of miconazoletablet formulations using sodium benzoate solution (n=6)

Tablet formulation	Drug present in pre-analyzed tablet powder taken (mg)	Pure drug added (spiked) (mg)	% Recovery estimated (mean ± S.D.)	% Coeff. of variation	Standard error
I	50	10	98.87 ± 1.321	1.336	0.539
I	50	20	99.22 ± 0.912	0.919	0.372
II	50	10	100.37 ± 0.773	0.770	0.316
II	50	20	101.77 ± 1.103	1.084	0.450

Table 9: Results of recovery studies of spectrophotometric analysis of miconazole tablet formulations using niacinamide solution (n=6)

Tablet formulation	Drug present in pre-analyzed tablet powder taken (mg)	Pure drug added (spiked) (mg)	% Recovery estimated (mean ± S.D.)	% Coeff. of variation	Standard error
I	50	10	98.88 ± 0.762	0.771	0.311
I	50	20	99.49 ± 2.339	2.351	0.955
II	50	10	99.67 ± 1.050	1.053	0.429
II	50	20	98.59 ± 0.950	0.963	0.388

Table 7 denotes that the mean percent estimations of miconazole tablets determined by spectrophotometric analysis using hydrotropic solubilization techniques (by use of 2 M sodium benzoate solution and 2 M niacinamide solution) ranged from 98.96 to 101.44. Observed values of mean percent estimation are very close to 100, indicating the accuracy of the proposed methods. Low values of standard deviation (0.784 to 1.120), percent coefficient of variation (0.782 to 1.104) and standard error (0.320 to 0.457) validated the proposed methods of analysis. Table 8 and Table 9 show that mean percent recoveries estimated using the proposed methods ranged from 98.59 to 101.77, which are again very close to 100, indicating the accuracy of the proposed method. Validation of the proposed analysis methods is confirmed by satisfactorily low values of statistical parameters viz., standard deviation (0.762 to 2.339), percent coefficient of variation (0.770 to 2.351) and standard error (0.311 to 0.955).

Like above explanation, the other proposed methods employed for spectrophotometric estimations of marketed tablets of miconazole are very well validated (Table 10, 11).

Table 10: Observed values of mean percent estimation, standard deviation, percent coefficient of variation and standard error, obtained in spectrophotometric analysis of marketed tablets of drugs using proposed hydrotropic solubilization techniques

Tablets analyzed	Method of analysis	Mean % estimated	Standard deviation	% Coeff. of variation	Standard error	Reference table number
Miconazole	SBM	100.27, 99.65	0.784, 0.872	0.782, 0.875	0.320, 0.356	4.30
Miconazole	NMM	101.44, 98.96	1.120, 1.086	1.104, 1.097	0.457, 0.443	4.30

SBM-Sodium benzoate method, NMM-Niacinamide method, URM-Urea method

Table 11: Ranges of mean percent recoveries, standard deviation, percent coefficient of variation and standard error, obtained in spectrophotometric analysis of marketed tablets of drugs using proposed hydrotropic solubilization techniques

Tablets analyzed	Method of analysis	Range of mean % recovery estimated	Range of standard deviation	Range of % coeff. of variation	Range of standard error	Refer- ence table number
Miconazole	SBM	98.87 to 101.77	0.773 to 1.321	0.770 to 1.336	0.316 to 0.539	4.31
Miconazole	NMM	98.59 to 99.67	0.762 to 2.339	0.771 to 2.351	0.311 to 0.955	4.32

SBM-Sodium benzoate method, NMM-Niacinamide method, URM-Urea method

From literature survey, it is evident that urea has been extensively employed to make solid dispersions of a large number of poorly water-soluble drugs (by fusion or common solvent technologies). As evident from solubility studies (Table 5), urea has been found to enhance aqueous solubility of miconazole significantly. Therefore, this poorly water-soluble drug and urea as a model hydrotropic agent selected to prepare hydrotropic solid dispersions for solubility enhancement study. The prepared solid dispersions have been characterized by DSC, XRD and IR studies. They have been studied for dissolution rate enhancement effect and stability as well.

Determination of Drug Content in physical mixtures (PM) and hydrotropic solid dispersions (HSD)

The drug content was determined using regression equation Y = 0.0551 X – 0.0075 (Table 4). The results of analysis are presented in Table 12.

Table 12: Drug contents of physical mixtures and hydrotropic solid dispersions (n=3)

Drug	Drug : Urea ratio	Percent drug content (mean ± S.D.)	
		PM	HSD
Miconazole	1 : 4	18.93 ± 0.981	18.75 ± 0.808
	1 : 6	13.83 ± 0.638	13.89 ± 0.930
	1 : 8	10.99 ± 1.386	10.91 ± 1.008
	1 : 10	8.82 ± 0.898	8.64 ± 1.061
	1 : 12	7.44 ± 1.333	7.39 ± 1.218

PM-Physical mixture, HSD-Hydrotropic solid dispersion

IR studies of formulations of drugs

A large number of solid dispersions have been characterized by IR studies to assess the possibility of interaction between drugs and water-soluble carriers. Attempts were made to assess the possibility of interaction of hydrotropic agent, urea with drugs miconazole by conducting IR studies on the prepared drug formulations, HSD and PM both (Fig. 5.1 to Fig. 5.9). The instrument used for this purpose was, FTIR-8400 S, Shimadzu Corporation, Japan. Formulations containing highest proportion of urea were employed for these studies.

DSC studies of drugs and their formulations

A large number of solid dispersions have been characterized by DSC studies to assess the possibility of interactions between drugs and water-soluble carriers.

Powder X-ray diffraction studies of drugs and their formulations

The powder X-ray diffraction spectra of urea, miconazole, the prepared HSD and PM were found using RU-H3R, Horizontal Rotaflex rotating anode X-ray generator instrument, Rigaku (Rigaku International Corporation, Tokyo). The X-ray diffractograms so obtained are presented in Fig. 1 to Fig. 6. The major characteristic X-ray diffractogram peaks are presented in Table 13.

Dissolution rate studies of drugs and their formulations

Calculations for amounts of drugs released were done using respective reg. equations (Table 4). The observation of dissolution studies are shown in the Fig 7.

Chemical Stability Testing of Hydrotropic Solid Dispersions and Physical Mixtures of Drugs

The physical mixtures (of drugs with urea) were subjected to chemical stability and the chemical stabilities. The percent residual drug for each formulation at different time intervals is recorded in Table 14.

Table 13: X-ray diffraction peaks (major) for miconazole and urea systems (2θ values)

	onazole	1:8 PM	1:8 HSD
8.98	12.34	12.48	10.70
20.80	13.92	14.02	22.04
21.96	21.70	21.72	22.46
23.62	24.92	22.12	24.58
24.36	27.50	22.56	29.32
26.52	29.42	24.74	31.70
27.96	33.44	29.46	35.64
28.34	-	31.82	37.16
30.32	-	35.72	-
31.34	-	-	-
35.26	-	-	-
39.42	-	-	-

Table 14: Chemical stability data of miconazole hydrotropic solid dispersions and physical mixture

Condition	Time (months)	Percent residual drug in formulations (mean ± S.D.)			
		MU 1:4HSD	MU 1:6 HSD	MU 1:8 HSD	MU 1:8 PM
Room temperature	1	99.69 ± 1.339	99.88 ± 0.699	99.90 ± 0.599	99.82 ± 1.339
Room temperature	3	99.52 ± 0.699	99.72 ± 1.387	99.79 ± 0.769	99.65 ± 0.699
Room temperature	6	99.38 ± 1.089	99.24 ± 1.488	99.48 ± 1.337	99.53 ± 0.760
40^oC/75% RH	1	99.46 ± 0.779	99.61 ± 0.919	99.52 ± 0.941	99.39 ± 0.951
40^oC/75% RH	3	99.16 ± 0.831	99.02 ± 1.380	98.89 ± 1.137	98.97 ± 0.888
40^oC/75% RH	6	97.44 ± 1.530	97.89 ± 1.209	97.77 ± 0.843	97.86 ± 1.677
55^oC	1	99.38 ± 2.376	99.36 ± 0864	99.15 ± 0.763	99.28 ± 0.921
55^oC	3	98.45 ± 0.665	98.27 ± 1.490	98.42 ± 1.088	98.39 ± 0.776
55^oC	6	96.16 ± 0.843	96.05 ± 0.677	96.21 ± 1.320	96.81 ± 1.144

The IR spectrum of miconazole showed absorption bands at 3215 cm^{-1}corresponding to OH group, at 1515 cm^{-1} and 1560 cm^{-1} corresponding to – NO_2 and at 1180 cm^{-1} and 1360^{-1} cm^{-1} corresponding to C-N group. The IR spectra of MU 1:8 PM and MU 1:8 HSD both showed absorption bands corresponding to the functional groups of miconazole and urea (both). These studies indicate that there is no chemical interaction between miconazole and urea.

The DSC curves of urea, miconazole, exhibited endothermic peaks at 135.73^oC, 162.87^oC, 127.46^oC, respectively corresponding to their melting points. DSC curves of MU 1:8 PM (Fig. 5.12) and MU 1:8 HSD showed endothermic peaks at 131.80^oC and 133.58^oC, respectively. The endothermic peak at 162.87^oC observed in case of miconazole, was absent in case of DSC curves of the two formulations of miconazole (MU 1:8 PM and MU 1:8 HSD). Both endothermic peaks at 131.80^oC (for MU 1:8 PM) and 133.58^oC (for MU 1:8 HSD) are very close to the endothermic peak of urea (at 135.73^oC). Also, the endothermic peaks at 131.80^oC for physical mixture of miconazole and urea (MU 1:8 PM) and at 133.58^oC for hydrotropic solid dispersion of miconazole and urea (MU 1:8 HSD) are very close to each other. This fact clearly rules out any chemical interaction between miconazole and urea (the hydrotropic agent).

Fig. 1 to Fig. 6 show the characteristic X-ray diffraction patterns recorded for urea and miconazole, the prepared hydrotropic solid dispersion formulations and the physical mixture formulations. The X -ray diffractograms of urea and miconazole exhibited a series of intense peaks, which were indicative of their crystalline characters. XRD diffraction patterns of the hydrotropic solid dispersions MU 1:8 HSD, TU 1:8 HSD, and the physical mixtures MU 1:8 PM, PM, TU 1:8 PM also exhibited a series of intense peaks which are characteristic peaks of urea and the respective drug. The peaks found in case of hydrotropic solid dispersions and the respective physical mixtures are quite comparable. This study confirmed that hydrotropic solid dispersions were not present in amorphous form; rather

they are of crystalline nature.

From figures (Fig. 7) of dissolution profiles, it is evident that the bulk drug samples exhibited poor drug release profiles. Initial rates of dissolution of drugs from hydrotropic solid dispersions were very quick as compared to initial rates of dissolution from bulk drug samples. Physical mixtures also showed slightly better drug release profiles compared to drug release profiles from respective bulk drug samples. Drug release profiles from hydrotropic solid dispersions were still better than the drug release profiles from physical mixtures. Also, it is indicated that as the proportion of water-soluble carrier (urea) was increased in solid dispersions there was improvement in dissolution behavior. As the initial rates of dissolution of drugs from hydrotropic solid dispersions were significantly high as compared to initial dissolution rates from bulk drug samples, the quick onset of action and better extent of absorption is expected after oral administration of these hydrotropic solid dispersions.

Hydrotropic solid dispersion formulations and physical mixture formulations of miconazole were subjected to stability studies at room temperature, 40°C/75% RH and 55°C for six months (Table 14). The initial drug contents of formulations were considered as 100.00%. To determine chemical stability at room temperature, 40°C/75% RH and 55°C, the residual drug contents of these formulations were determined after 1, 3 and 6 months of storage.

The residual drug content after storage for 6 months at room temperature in all formulations was above 98% (much above 90.00%), showing very good chemical stabilities at room temperature. The residual drug contents after storage for 6 months at 40°C/75% RH in all formulations was above 96% (much above 90.00%), showing good chemical stabilities at moderate temperature. The residual drug content after storage for 6 months at 55°C in all formulations was above 90.00%, showing good chemical stabilities at a higher temperature.

The physical mixtures (of drugs with urea) were subjected to chemical stability and the chemical stabilities observed were very comparable to the chemical stabilities of corresponding hydrotropic solid dispersions indicating that the chemical stability was not influenced by making respective solid dispersions (with urea).

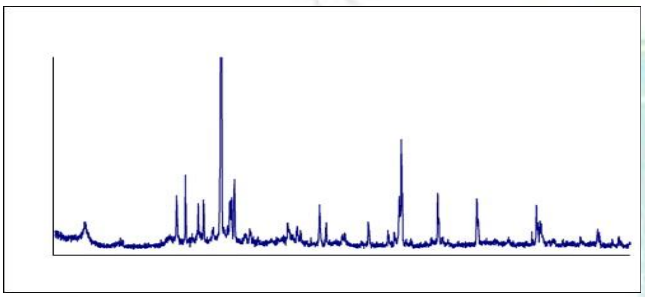

Figure 1: X-ray diffractogram of urea

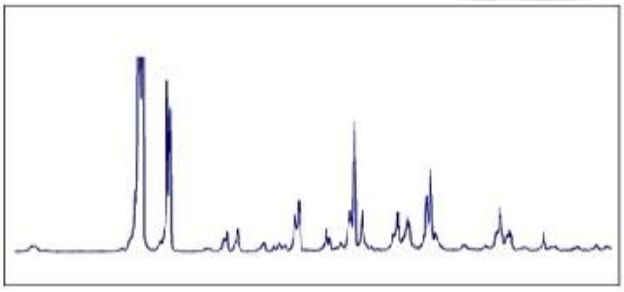

Figure 2 X-ray diffractogram of miconazole

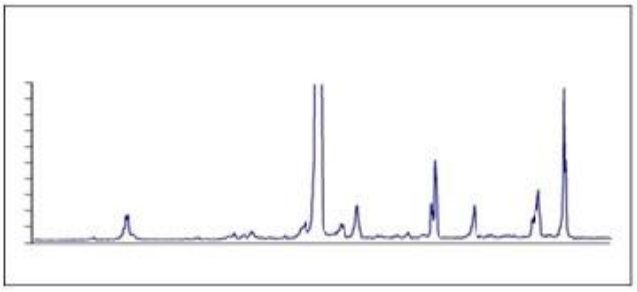

Figure 3: X-ray diffractogram of miconazole:urea, 1:8 hydrotropic solid dispersion

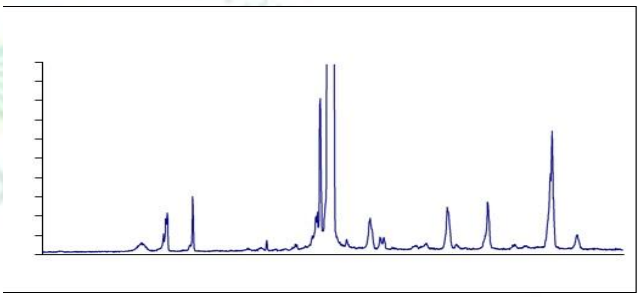

Figure 4: X-ray diffractogram of miconazole:urea, 1:8 physical mixture

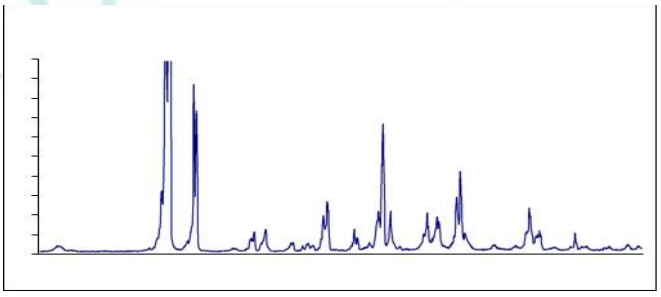

Figure 5: X-ray diffractogram of miconazole

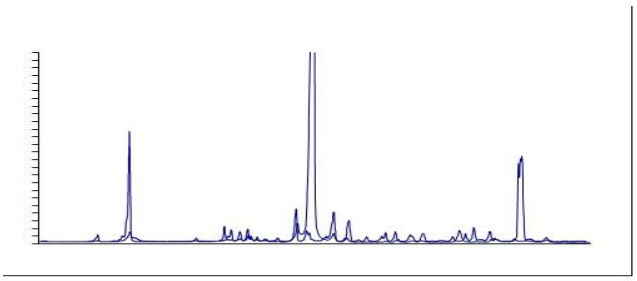

Figure 6: X-ray diffractogram of urea

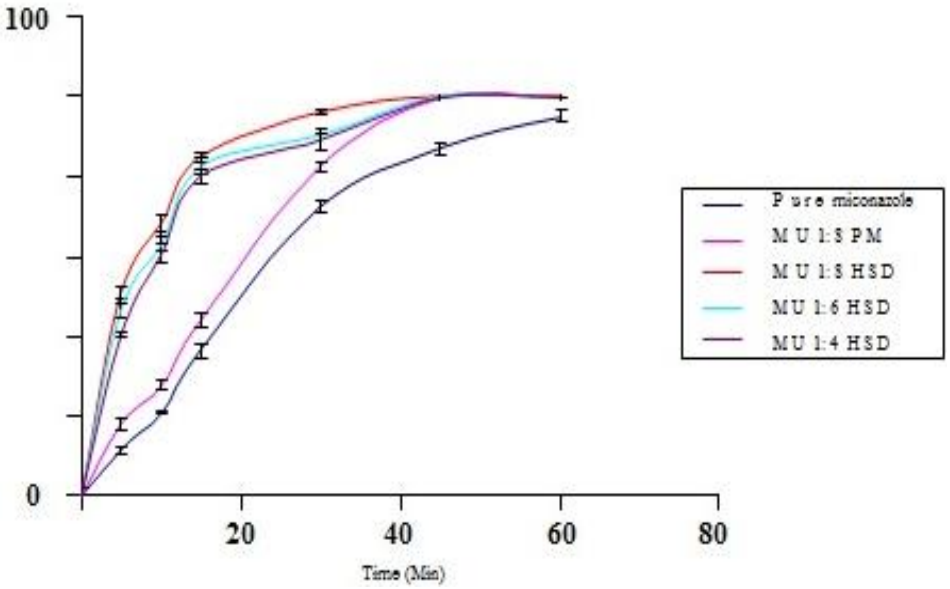

Figure 7: Dissolution profiles of pure miconazole and its formulations in distilled water

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