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Research Article

SOLUBLITY ENHANCEMENT OF FLUCONAZOLE BY FORMULATION OF HYDROTROPIC SOLID DISPERSIONS

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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 and ranged in between 5.1 to 10.9 and 6.1 to 7.1. Results showed that remarkable increase in aqueous solubility of Fluconazole in presence of large concentration of hydrotropes. Marketed fluconazole 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

Introduction

In the present research work mixed hydrotropic solubilization phenomenon is used to enhance the solubilization of poorly water soluble drug (fluconazole). 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 salycilate, 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

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technologies). As evident from solubility studies, urea has been found to enhance aqueous solubility of fluconazole 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

It is evident from the literature survey that more is the concentration of hydrotropes, more is the aqueous solubility of poorly water-soluble drugs. Therefore, concentrated aqueous solutions of some hydrotropic agents were utilized in this research. 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 having poor aq solubility, an approximate solubility determination method was employed. This process is a modified form of the process used by Simamora et al.. From the variation in 2 observations (of weight), an approximate solubility was measured and solubility increment ratios (solubility in aqueous hydrotropic solution/solubility in water) were measured for all selected drugs for all six hydrotropic solutions. When the determined solubility enhancement ratio was at least 5, such hydrotropic solution was selected for that drug[8] (Table 1).

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 hydrotropic agents in the spectrophotometric estimation of fluconazole, 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. Absorbance of drug was 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 fluconazole, 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 Equations for Fluconazole in Distilled Water

50 mg Fluconazole 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 are shown in Table 4.

Regression Equations for, Fluconazole, in Presence of Hydrotropic Agents

50 mg of Fluconazole 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 Fluconazole 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 4) for the estimation of Fluconazole in presence of niacinamide and urea.

Equilibrium solubility determinations at room temperature

Filtrates of saturated solutions of fluconazole 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 has been shown in Table 5. Enhancement ratios in solubility were determined by following formula -

Enhancement ratio= Solubility in hydrotropic solution/Solubility in distilled water

Spectrophotometric analysis of marketed tablet formulations of fluconazole

20 marketed tablets of fluconazole (formulation-I) were weighed and ground to a fine powder. An accurately weighed tablet powder equivalent to 50 mg of fluconazole 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 (selected wavelength). The drug content of the tablet formulation-I was calculated using reg. eq. Y = 0.0548 X- 0.0015 (Table 6). The results of analysis are presented in Table 7. After 48 hours, filtrate of part A was analyzed in the same way, to test the chemical stability of drug in presence of hydrotropes (Na-benzoate).

Application of hydrotropic solubilization techniques in formulation of hydrotropic solid dispersions of Fluconazole

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.

Preparation of hydrotropic solid dispersions (HSD) and physical mixtures (PM) of selected drugs

Preparation of Hydrotropic Solid Dispersions of Fluconazole[10, 11]

Accurately weighed 5.0 g fluconazole and 20.0 g urea were employed to prepare solid dispersion containing fluconazole and urea in ratio of 1:4 (TU 1:4HSD). Same procedure was repeated to prepare hydrotropic solid dispersions containing fluconazole and urea in ratios of 1:6 (TU 1:6 HSD) and 1:8 (TU 1:8 HSD) using accurately weighed 5.0 g fluconazole, 30.0 g urea and 5.0 g fluconazole, 40.0 g urea, respectively.

Preparation of Physical Mixtures

To prepare physical mixture containing fluconazole and urea in ratio 1:8 (TU 1:8 PM), accurately weighed 5.0 g fluconazole 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 physical mixtures (PM) and hydrotropic solid dispersions (HSD) [10, 11]

Powdered solid dispersion/physical mixture containing about 10 mg of fluconazole was accurately weighed and transferred to a 500 ml volumetric flask. About 450 ml of distilled water was taken and beaker was content was stirred to dissolve the solute. Now volume was produced up to the required with distilled water and the absorbance of this solution was determined at 318 nm against reagent blank. In each case, testing was carried out in triplicate. The drug content was determined using Reg Eq

Y=0.0339 X + 0.0075 (Table 3.4). The data of this testing are shown in Table 12.

IR studies of formulations of drugs

Attempts were made to assess the possibility of interaction of hydrotropic agent, urea with drugs fluconazole, by conducting IR studies on the prepared drug formulations, HSD and PM both. 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

Attempts were made to assess the possibility of interaction of hydrotropic agent, urea with drugs fluconazole, 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 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^{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. Various DSC thermograms (melting isotherms) are shown in Fig. 1.

Powder X-ray diffraction studies of drugs and their formulations

The powder X-ray diffraction spectra of urea and fluconazole, the prepared hydrotropic solid dispersions and the physical mixtures 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 $C_uK\alpha$-radiation (40 KV, 50 MA), $2\theta = 5^{o}$ to 40^{o} at a scanning speed 4^{0}/min and step size 0.02^{o} 2θ. The X-ray diffractograms so obtained are presented in Fig. 2 to Fig. 5. 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 fluconazole, physical mixtures containing drug: urea of 1:8 ratio of fluconazole and urea of 1:12 ratio and all hydrotropic solid dispersions of drug were studied using USP XXIV (type II) dissolution rate test apparatus (Model-TDT 6P, Electrolab, Mumbai, India) using a paddle stirrer. Distilled water (900 ml) was used as 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 presented in Table 14 to 18 and shown in the Fig. 6.

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 solubility enhancement of drugs (Table 1).

Table 1: Hydrotropes selected for Fluconazole

Drug	Selected hydrotropic solution
Fluconazole	2 M Sodium benzoate
Fluconazole	2 M Niacinamide
Fluconazole	10 M Urea

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.

Table 2: Interference studies for hydrotropic agents

Drug	Solvent system used	Concentration of drug used (μg/ml)	Concentration of hydrotrope used (μg/ml)	Wavelength (nm)	Absorbance against respective blank
Fluconazole	DW	30	-	318	1.019
Fluconazole	DW + SB	30	3450	318	1.018
Fluconazole	DW + NM	30	2925	318	1.022
Fluconazole	DW + UR	30	7200	318	1.019

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
Fluconazol	DW	30	-	318	1.019
Fluconazol	DW +	30	150	318	1.014
Fluconazol	DW +	30	300	318	1.016

DW-Distilled water

For spectrophotometric estimations of fluconazole, 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 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
Fluconazole	DW	318	5 – 25	Y = 0.0337 X + 0.0115	0.9995
Fluconazole	DW + SB	318	5 – 25	Y = 0.0337 X + 0.0094	0.9994
Fluconazole	DW + NM	318	5 – 25	Y = 0.0338 X + 0.0100	0.9989
Fluconazole	DW + UR	318	5 – 25	Y = 0.0339 X + 0.0075	0.9995

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

Application of hydrotropic solubilization techniques in formulation of hydrotropic solid dispersions of Fluconazole

In the present investigation drug (Fluconazole) 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. Drug has been analyzed by spectrophotometric analysis.

Various organic solvents like methanol, chloroform, acetone, dimethyl formamide and ethanol have been employed for solubilization of drugs having poor aq solubility to perform their titrimetric analyses. Demerits of organic solvents include Costly, toxicity and impurity. As evident from Table 5, there is remarkable increase in aqueous solubility of Fluconazole in presence of large concentration of hydrotropes.

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

Drug	Solvent system	Method of analysis used	Solubility (% w/v)	Temperature (^oC)	Solubility enhancement ratio
Fluconazole	DW	SPM	0.538	28 ± 1	-
Fluconazole	2 M SB	SPM	3.302	28 ± 1	6.1
Fluconazole	2 M NM	SPM	3.794	28 ± 1	7.1
Fluconazole	10 M UR	SPM	3.821	28 ± 1	7.1

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

Table 6: Results of spectrophotometric analysis of fluconazole tablet formulations

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	50.88	51.16	49.03	50.08	101.76	102.3	98.06	100.16
50	49.86	50.21	50.91	48.92	99.72	100.4	101.8	97.84
50	51.43	50.76	49.43	48.67	102.86	101.5	98.86	97.34
50	50.27	50.61	50.76	50.22	100.54	101.2	101.5	100.44
50	50.96	50.83	49.38	49.54	101.92	101.6	98.76	99.08
50	50.36	50.55	50.54	49.33	100.72	101.1	101.0	98.66

SBM-Sodium benzoate method, NMM-Niacinamide method

Table 7: Statistical evaluation of spectrophotometric analysis of fluconazole 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	101.25	1.357	1.340	0.544	101.37	0.631	0.622	0.258
II	100.02	1.636	1.636	0.668	98.92	1.235	1.248	0.504

SBM-Sodium benzoate method, NMM-Niacinamide method

Table 8: Results of recovery studies of spectrophotometric analysis of fluconazole tablet 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	98.69 ± 1.444	1.463	0.589
I	50	20	99.39 ± 2.062	2.075	0.842
II	50	10	100.75 ±	1.339	0.551
II	50	20	98.66 ± 0.945	0.958	0.386

Table 9: Results of recovery studies of spectrophotometric analysis of fluconazole 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	98.93 ± 0.930	0.940	0.380
I	50	20	98.33 ± 1.299	1.321	0.530
II	50	10	101.41 ± 0.873	0.861	0.356
II	50	20	99.77 ± 1.433	1.436	0.585

Table 7 denotes that the mean percent estimations of fluconazole tablets determined by spectrophotometric analysis using hydrotropic solubilization techniques (by use of 2 M sodium benzoate solution and 2 M niacinamide solution) ranged from 100.02 to 101.25. Observed values of mean percent estimation are very close to 100, indicating the accuracy of the proposed methods. Low values of standard deviation (0.631 to 1.235), percent coefficient of variation (0.622 to 1.248) and standard error (0.258 to 0.504) validated the proposed methods of analysis. Table 8 and Table 9 show that mean percent recoveries estimated using the proposed methods ranged from 98.39 to 101.41, 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 (0.631 to 1.235), percent coefficient of variation (0.861 to 2.075) and standard error (0.356 to 0.842).

Like above explanation, the other proposed methods employed for spectrophotometric estimations of marketed tablets of fluconazole, 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
Fluconazole	SBM	101.25, 100.02	1.357, 1.636	1.340, 1.636	0.544, 0.668	4.39
Fluconazole	NMM	101.37, 98.92	0.631, 1.235	0.622, 1.248	0.258, 0.504	4.39

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	Range of standard deviation	Range of % coeff. of variation	Range of standard error	Reference table number
Fluconazole	SBM	98.66 to 100.75	0.945 to 2.062	0.958 to 2.075	0.386 to 0.842	4.40
Fluconazole	NMM	98.33 to 101.41	0.873 to 1.433	0.861 to 1.436	0.356 to 0.585	4.41

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

Application of hydrotropic solubilization techniques in formulation of hydrotropic solid dispersions of drugs having poor solubility

As evident from solubility studies (Table 7, urea has been found to enhance aqueous solubility's of fluconazole, 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.

Determination of Drug Content in Formulations (HSD and PM)

The drug content was determined using reg eq Y=0.0339 X + 0.0075 (Table 3.4). The data of this testing are shown in Table 12.

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

Drug	Drug : Urea ratio	Percent drug content (mean ± S.D.)	
		PM	HSD
Fluconazole	1 : 4	19.11 ± 1.016	18.88 ± 0.772
	1 : 6	14.05 ± 2.313	14.13 ± 0.891
	1 : 8	10.88 ± 0.733	10.54 ± 1.321
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

The IR spectrum of fluconazole showed absorption bands at 1180 cm^{-1} and 1360 cm^{-1} corresponding to C-N group and at 1515 cm^{-1} and 1560 cm^{-1} corresponding to NO_2 group. The IR spectrum of urea showed absorption bands at 3261 cm^{-1} corresponding to NH_2-CO- and at 1621 cm^{-1} and 1678 cm^{-1} corresponding to group. The IR spectra of TU 1:8 PM (Fig. 5.2) and TU 1:8 HSD both showed absorption bands corresponding to the functional groups of fluconazole and urea (both). These studies indicate that there is no chemical interaction between fluconazole and urea.

Similarly, the single endothermic peaks at 132.05^{O}C for fluconazole and urea physical mixture (TU 1:8 PM) and at 131.71^{O}C for fluconazole and urea hydrotropic solid dispersion (TU 1:8 HSD) are very comparable and also close to the endothermic peak for urea at 135.73^{O}C, indicating that there is no chemical interaction between fluconazole and urea and the reason for only one peak may be the dissolution of fluconazole in melted urea.

DSC Studies of drugs and their formulations

Various DSC thermograms (melting isotherms) are shown in Fig. 1

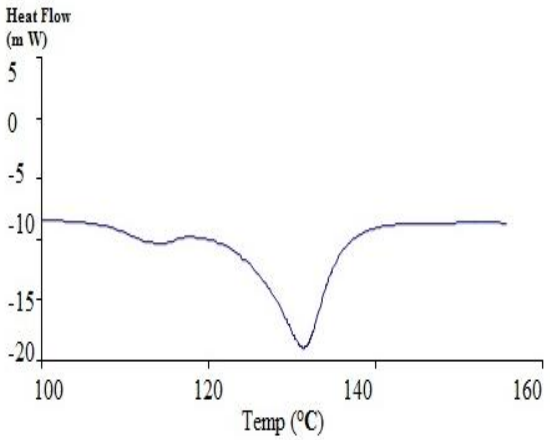

Figure 1: DSC curve of fluconazole:urea, 1:8 PM

Powder X-ray diffraction studies of drugs and their formulations

The X-ray diffractograms so obtained are presented in Fig. 2 to Fig. 5 . The major characteristic X-ray diffractogram peaks are

presented in Table 13.

Fig. 2 to Fig. 5 show the characteristic X-ray diffraction patterns recorded for urea and fluconazole, the prepared hydrotropic solid dispersion formulations and the physical mixture formulations. The X -ray diffractograms of urea and fluconazole exhibited a series of intense peaks, which were indicative of their crystalline characters. XRD diffraction patterns of the hydrotropic solid dispersions TU 1:8 HSD and the physical mixtures 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.

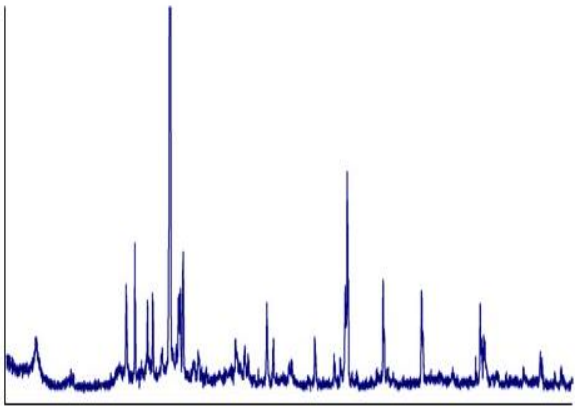

Figure 2: X-ray diffractogram of urea

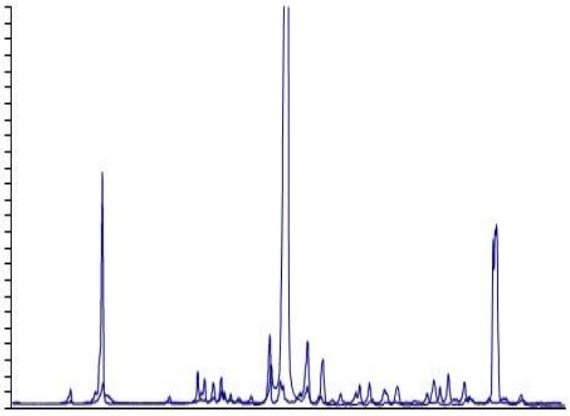

Figure 3: X-ray diffractogram of fluconazole

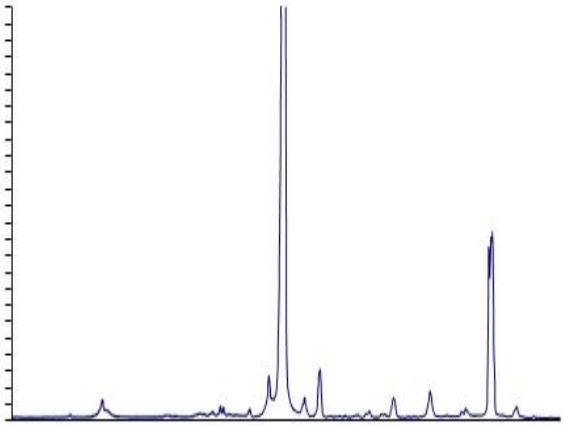

Figure 4: X-ray diffractogram of fluconazole:urea, 1:8 physical mixture

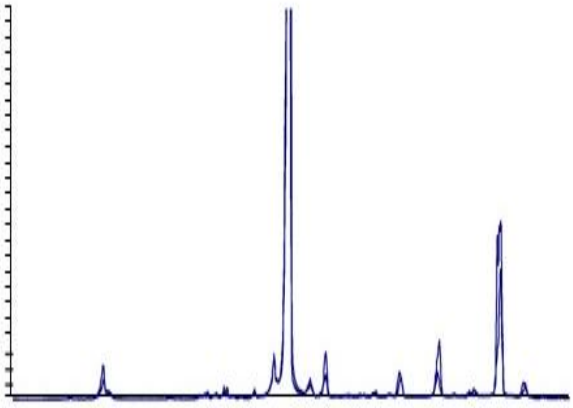

Figure 5: X-ray diffractogram of fluconazole:urea, 1:8 hydrotropic solid dispersion

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

Urea	Fluconazole	TU 1:8 PM	TU 1:8 HSD
8.98	10.68	10.76	10.76
20.80	16.78	21.46	21.46
21.96	18.32	22.50	22.50
23.62	21.38	24.70	24.72
24.36	22.20	29.46	29.46
26.52	23.80	31.74	31.84
27.96	24.72	35.68	35.66
28.34	27.76	-	-
30.32	31.76	-	-
31.34	32.80	-	-
35.26	35.68	-	-
39.42	-	-	-

Dissolution rate studies of drugs and their formulations

The observation of dissolution studies are presented in Table 14 to 18 and shown in the Fig. 6.

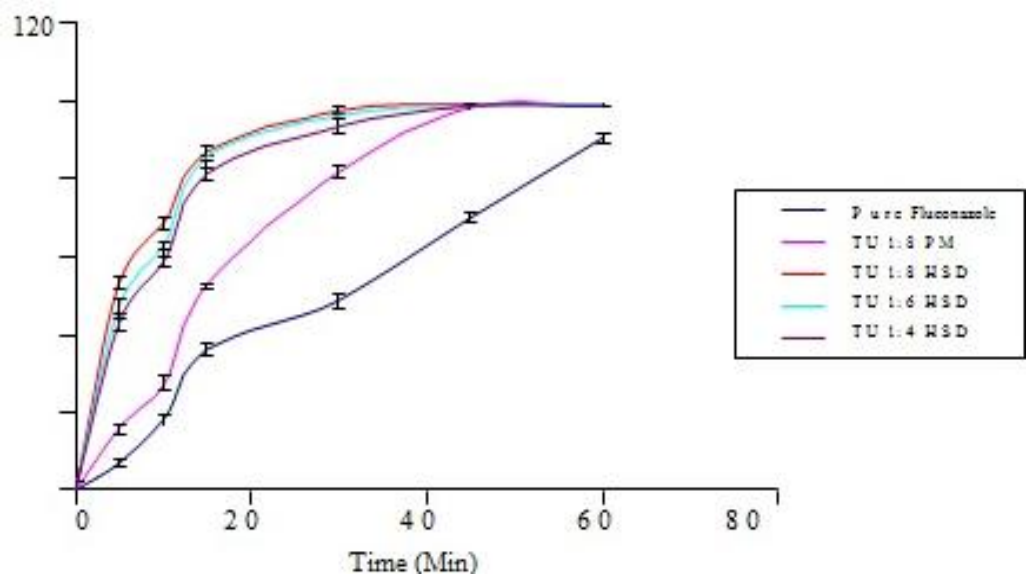

Figure 6: Dissolution profiles of pure fluconazole and its formulations in distilled water

Table 14: Dissolution profile of fluconazole pure drug in distilled water

S. No.	Time (min)	Cumulative percent drug dissolved			
		I	II	III	Mean ± S.D.
1	5	6.21	7.59	6.99	6.93 ± 0.694
2	10	18.34	16.73	19.46	18.18 ± 1.356
3	15	35.59	34.66	37.85	36.03 ± 1.640
4	30	48.76	50.38	46.90	48.68 ± 1.741
5	45	69.02	70.84	70.36	70.07 ± 0.943
6	60	90.46	89.32	91.88	90.55 ± 1.282

Table 15: Dissolution profile of physical mixture of fluconazole and urea (1:8) in distilled water

S. No.	Time (min)	Cumulative percent drug dissolved			
		I	II	III	Mean ± S.D.
1	5	15.77	14.22	17.03	15.67 ± 1.407
2	10	25.73	29.49	29.49	27.42 ± 1.909
3	15	52.66	52.05	53.44	52.77 ± 0.697
4	30	81.75	83.28	80.39	81.81 ± 1.446
5	45	98.11	98.33	98.88	98.44 ± 0.397
6	60	98.31	99.72	99.43	99.15 ± 0.165

Table 16: Dissolution profile of hydrotropic solid dispersion of fluconazole and urea (1:8) in distilled water

S. No.	Time (min)	Cumulative percent drug dissolved			
		I	II	III	Mean ± S.D.
1	5	53.33	54.93	52.03	53.43 ± 1.452
2	10	68.86	70.06	66.94	68.62 ± 1.574
3	15	86.49	88.55	85.95	87.00 ± 1.372
4	30	97.50	98.77	96.88	97.72 ± 0.963
5	45	99.53	98.44	99.22	99.06 ± 0.562
6	60	99.44	99.33	98.89	99.22 ± 0.291

Table 17: Dissolution profile of hydrotropic solid dispersion of fluconazole and urea (1:6) in distilled water

S. No.	Time (min)	Cumulative percent drug dissolved			
		I	II	III	Mean ± S.D.
1	5	47.69	49.36	45.05	47.37 ± 2.173
2	10	62.88	65.33	61.43	63.21 ± 1.971
3	15	85.09	85.31	86.58	85.66 ± 0.804
4	30	96.49	95.88	97.37	96.58 ± 0.749
5	45	99.62	98.37	98.51	98.83 ± 0.685
6	60	99.59	99.16	99.43	99.39 ± 0.217

Table 18: Dissolution profile of hydrotropic solid dispersion of fluconazole and urea (1:4) in distilled water

S. No.	Time (min)	Cumulative percent drug dissolved			
		I	II	III	Mean ± S.D.
1	5	42.18	44.43	41.06	42.56 ± 1.716
2	10	58.92	60.39	57.76	59.02 ± 1.318
3	15	81.33	83.05	79.93	81.44 ± 1.563
4	30	93.43	91.69	95.11	93.41 ± 1.710
5	45	98.72	98.33	99.52	98.86 ± 0.607
6	60	98.89	99.21	98.47	98.86 ± 0.371

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 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). The percent residual drugs for each formulation at different time intervals are recorded in Table 19.

Table 19: Chemical stability data of fluconazole hydrotropic solid dispersions and physical mixture (n=3)

Condition	Time (months)	Percent residual drug in formulations (mean ± S.D.)			
		TU 1:4 HSD	TU 1:6 HSD	TU 1:8 HSD	TU I:8 PM
Room temperature	1	99.63 ± 0.668	99.76 ± 2.307	99.69 ± 1.330	99.81 ± 1.337
Room temperature	3	99.47 ± 1.035	99.52 ± 0.913	99.59 ± 0.883	99.72 ± 2.004
Room temperature	6	99.33 ± 1.297	99.31± 0.599	99.22 ± 0.699	99.08 ± 1.360
40^{o}C/75% RH	1	99.52 ± 0.677	99.60 ± 0.730	99.77 ± 1.290	99.55 ± 0.666
40^{o}C/75% RH	3	98.73 ± 0.820	98.58 ± 0.673	98.68 ± 1.333	98.40 ± 0.790
40^{o}C/75% RH	6	97.61 ± 0.379	97.65 ± 1.490	97.81 ± 0.786	97.85 ± 1.119
55^{o}C	1	98.83 ± 0.722	99.03 ± 1.008	98.94 ± 0.991	98.79 ± 1.357
55^{o}C	3	97.15 ± 1.390	97.21 ± 0.688	97.44 ± 1.399	97.66 ± 1.930
55^{o}C	6	94.26 ± 0.831	94.08 ± 1.799	94.01 ± 0.801	94.22 ± 2.337

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