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Ketoconazole Solubility Enhancement: Different Techniques and its Comparison

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Abstract

Four techniques namely melt sonocrystallization, solid dispersion, hydrotrophy and inclusion complex with cyclodextrin were used for the solubility enhancement. The order of the techniques for the solubility enhancement was found hydrotrophy>inclusion complex>solid dispersion>sonocrystallization method. Enhancement in the solubility by the hydrotrophy method was found to be 12.159 fold increases while by inclusion compound, solid dispersion, and melt-sonocrystallization method was found to be 9.644, 7.349, and 5.517 fold respectively. Dissolution study of the four formulations prepared by the four different techniques was also performed. On the basis of data of drug dissolution profile of all four formulations (aqueous suspension) it was found that the formulation prepared by the hydrotropy method showed the best release profile that is 83.16%. While release from the suspension prepared by inclusion compound, solid dispersion and melt-sonocrystallization method were found to be 61, 73 and 58% respectively. Thus on the basis of this study we can say that the hydro trophy technique is the best technique for the solubility enhancement of the ketoconazole.

Key words: ketoconazole, melt-sonocrystallization, solid dispersion, stress degradation, hydrotrophy

Contents

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1. Introduction

Amongst all the diseases afflicting mankind, one of the major classes of diseases which are also fatal many a times is fungal infections. Hence, antifungal therapy forms a very important and essential part of modern pharmacotherapeutic applications of medicines. Fungal infections (mycoses) are widespread in the population; they are generally associated with the skin (e.g. 'athlete's foot') or mucous membranes (e.g. 'thrush'). In temperate climates and in otherwise healthy people, they are mainly benign, being more of a nuisance than a threat. However, they become a more serious problem when the immune system is compromised or when they gain access to the systemic circulation. When this occurs, fungal infections can be fatal. Human fungal infections have increased dramatically in incidence and severity in recent years (since the 1970's).

One of the contributory factors has been the widespread use of broad-spectrum antibiotics, which eliminate or decrease the non-pathogenic bacterial populations that normally compete with fungi. Other causes include the recent advances in surgery, the spread of AIDS and the use of immunosuppressant or cancer chemotherapy agents. The result has been an increased prevalence of opportunistic infections, i.e. infections that rarely cause disease in healthy individuals. Older people, diabetics, pregnant women and burn wound victims are particularly at risk of fungal infections such as candidiasis (Desmukes 2000). Primary fungal infections, rare in many parts of the temperate world, are also now encountered more often because of the increase in international travel. Also, the appearance of azole resistant organisms, as well as the rise in the number of patients at risk for mycotic infections, has created new challenges. Also, fungal infections are usually more difficult to treat than bacterial infections, because fungal organisms grow slowly and because fungal infections often occur in tissues that are poorly penetrated by antimicrobial agents (Scherer *et al*., 2002).

2. Materials and Methods

Materials

Ketoconazole received as a gift sample from Ranbaxy Research Lab.(Gurgaon, India), β-cyclodextrinreceive from Sigma-Aldrich (Bangalore, India),PEG 6000, Ethyl alcohol, Octanol, Methanol, Acetone received from S.D. Fine Chemicals, Ltd**.** (Mumbai, India), PEG 4000receive from IOL Chemical Limited (Mumbai, India), Dichloromethane received from CDH labs (New Delhi, India).

Method

Melt-sonocrystallization

Particle size reduction and particle engineering techniques are being developed to modify the physicochemical, micromeritic and biopharmaceutical properties of the drug. Numbers of particle design techniques is reported, such as spherical crystallization, extrusion spheronization, and melt solidification, spray drying, past illation, solution atomization and crystallization by sanitation (SAXS), where simultaneous crystallization and agglomeration occur. It is used to enhance dissolution of hydrophobic drugs and to study its effect on crystal properties of drug. It forms drug agglomerates with number of shallow circular pits on the surface and leads to increase in solubility. (Okumura *et al.,* 1982) Ultrasound (US) was introduced in the traditional process of pharmaceutical technology, few years ago. For instance, several workers reported US assisted compaction and US spray congealing of variety of systems where physical modification of structure of drug or excipient was done to improve drug release and compaction properties of drug. Besides these effects on solid, US may also act on a liquid or melt mixtures causing cavitations and extreme molecular motion, which divides the drop of material into number of micro drops of narrow size range. One of the mechanical effects cause by ultrasonification is disaggregation or de agglomeration of the particle assembling. Cavitations is an important phenomenon of ultrasonicator. The energy produced due to the collapse of bubbles at very high temperature was responsible for breaking of particles. The so generated shock waves can cause the particle to collide to one another with great force since these are similar charge particles; problem of agglomeration is greatly reduced. There are reports on application of ultrasonic (US) energy during crystallization, i.e. sonocrystallization. US energy has been used to achieve nucleation for moderate super saturation during crystallization process or terminal treatment to achieve de-agglomeration to obtain desired crystal habit. Studied US assisted compaction of various drugs with excipient such as cyclodextrin and eudragit. Significant changes in the crystal properties were observed due to US treatment (Albertini*et al.,* 1999). The effect of application of US energy on the properties of melt sonocrystallized (MSC) valdecoxib was characterized by scanning electron microscopy (SEM), differential scanning calorimetery (DSC), X-ray powder diffraction (XRPD), infrared spectroscopy and saturated solubility studies.

Solid Dispersions

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug; the matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles therefore, based on their molecular arrangement. Six different types of solid dispersions can be distinguished (Lang *et al.,* 1978). Certain combinations can be encountered in the same sample; some molecules are present in clusters while some are molecularly dispersed. Confusingly, in various studies the designation of solid dispersions is based on the method of preparation. However, since different preparation methods can result in the same subtypes or similar preparation methods can result in different subtypes, it can be argued that solid dispersions should preferably be designated according to their molecular arrangement. Moreover, not the preparation method but the molecular arrangement governs the properties of solid dispersions. Therefore, it is essential to use terms that indicate the molecular arrangement in the solid dispersion. Knowledge about the molecular arrangement will enlarge comprehension of the properties and behavior of solid dispersions. Furthermore, it will facilitate optimization of their properties required for a specific application. For example, the mechanism underpinning the dissolution of solid dispersions is poorly understood. (Casiraghi*et al.,* 2002) Many case studies showed accelerated dissolution of hydrophobic compounds

using solid dispersions but mechanisms are rarely discussed due to lack of knowledge about the mode of incorporation of the hydrophobic drug in the matrix, despite numerous efforts to clarify this. (Duncan, 2002) All three situations result in different drug concentrations at the dissolving interface. Still it has not been fully elucidated how this affects dissolution behavior of solid dispersions. Secondly, the physical and chemical stability of the matrix or the incorporated drug depends on the mode of incorporation, for example if drug molecules are present in amorphous nano particles, crystallization requires only rotational rearrangement. On the other hand, for a molecularly dispersed drug, translational diffusion is necessary before crystallization can occur by rotational rearrangements. The physical state of the matrix is also important for the chemical stability of the drug; the crystallinity of the matrix influences the translational and rotational rearrangements of the drug necessary for degradation reactions. The influence of drug load and method of preparation on dissolution behavior and stability of solid dispersions can only be understood and predicted when the relation between these characteristics and the mode of incorporation is known.

Carriers for Solid Dispersions

The solubility of etoposide, glyburide, itraconazole, ampelopsin, valdecoxib, celecoxib, halofantrine can be improved by solid dispersion using suitable hydrophilic carriers.(Derle*et al.,* 2010).

Table 1. Examples of Carriers

S. No.	Chemical Class	Examples
1	Acids	Citric acid, Tartaric acid, Succinic acid
2	Sugars	Dextrose, Sorbitol, Sucrose, Maltose, Galactose, Xylitol
3	Polymeric Materials	Polyvinylpyrrolidone, PEG-4000, PEG-6000, Carboxymethyl cellulose, Hydroxypropyl cellulose, Sodium alginate
4	Surfactants	Polyoxyethylene stearate, Poloxamer, Deoxycholic acid, Tweens and Spans

Preparation of Solid Dispersion

Various preparation methods for solid dispersions have been reported:

A. Fusion method

B. Solvent Evaporation Method

C. Melt agglomeration

D. Surface-active Carriers

Characterization of Solid Dispersion

Table 2. Characterizations of Solid Dispersions

S. No.	Characterization	Methods	Significance
1	Drug-carrier Miscibility	Hot stage microscopy DSC (conventional modulated) pXRD (conventional and variable temp), NMR 1H spin lattice relaxation time	To find out the complex formation between drug and carrier.
2	Drug-carrier interactions	FT-IR spectroscopy, Raman spectroscopy and Solid state NMR studies	To find out the integration between drug and carrier and formation of inclusion complex.
3	Physical structure	SEM Surface area analysis	To find out the particle size and shape.
4	Surface properties	Dynamic vapour sorption, Inverse gas chromatography, Atomic force microscopy and Raman microscopy	To study the morphology and degree to study the morphology and degree of crystallinity.
5	Amorphous content	Polarized light optical microscopy Hot stage microscopy, Humidity stage microscopy, DSC (MTDSC), ITC, pXRD	To find out the amorphous form of drug.
6	Stability	Humidity studies Isothermal Calorimetry DSC (Tg, temperature recrystallisation) Dynamic vapour sorption Saturated solubility studies	To find out the degree of crystallinity
7	Dissolution enhancement	Dissolution, Intrinsic dissolution, Dynamic solubility and Dissolution in bio-relevant media	To find out the rate and extent of dissolution

3. Result and Discussion

A typical Pre formulation programme should begin with the description of the organoleptic properties of the drug substance.

Identification and Characterization of Drug

Physical Appearance

Colour: White to off-white.
Odour: Odourless.
State: Crystalline Powder.
Physical appearance was found to be in agreement of the reported data (IP 2007).

Melting Point

The melting point was found to be 148° C by capillary method which showed agreement with the reported as 148-152° C which are shown in (IP 2007).

Partition Coefficient

The partition coefficient of ketoconazole in n-Octanol/ distilled water was found to be 4.35

UV Spectrum of ketaconazole in different medium

UV Spectrum of ketaconazole in distilled water at λmax 244

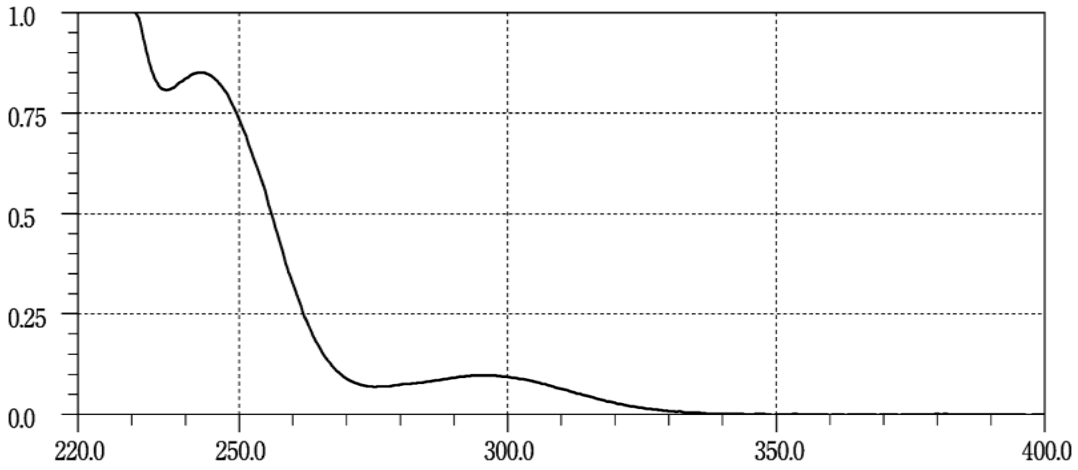

Figure 1. UV Spectrum of Ketoconazole in distilled water

UV Spectrum of ketaconazole in DCM at λmax 244.2

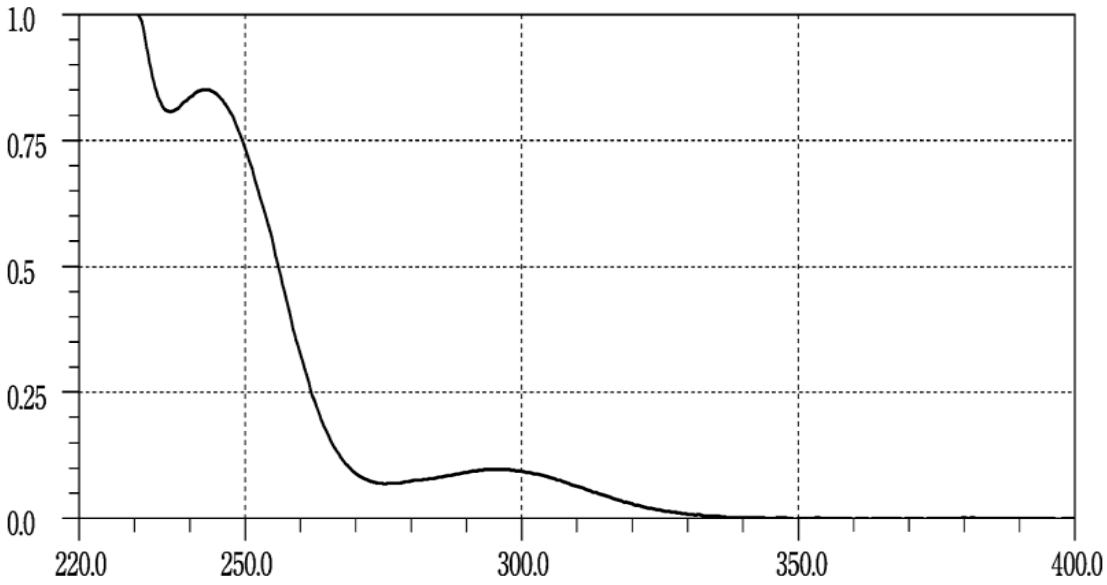

Figure 2. UV Spectrum of Ketoconazole in DCM

IR Spectrophotometry

The infra-red spectrum of drug sample was (FTIR- 8400S, Shimadzu, Kyoto- Japan) found to be in agreement with the reported reference spectra of the IR (IP 1996). CH2 , C-H, C=O, C-N, C=C functional group showed 1465, 3000-2850, 1680-1630, 1350-1000 cm^{-1} in official data where as it is found as 1460, 2964, 1647, 1201 in sample which showed in agreement with official data which showed the sample is pure.

Solubility Study

Table 3. Solubility of the ketoconazole in different solvent systems

S. No	Solvent	Absorbance	Concentration (mg/ml)
1	Dichloromethane	0.081	5.091
2	Distilled Water	0.115	1.88
3	Octanol	0.059	3.864

Ketoconazole showed highest solubility in DCM (5.091 mg/ml). This was agreement with the I.P 2007.

Preparation of calibration curve in dichloromethane (DCM)

Table 4. Absorbance of ketoconazole solution in dichloromethane at λ max 244.2 nm.

S. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.174
3	15	0.285
4	20	0.391
5	25	0.489
6	30	0.585
7	35	0.733
8	40	0.814

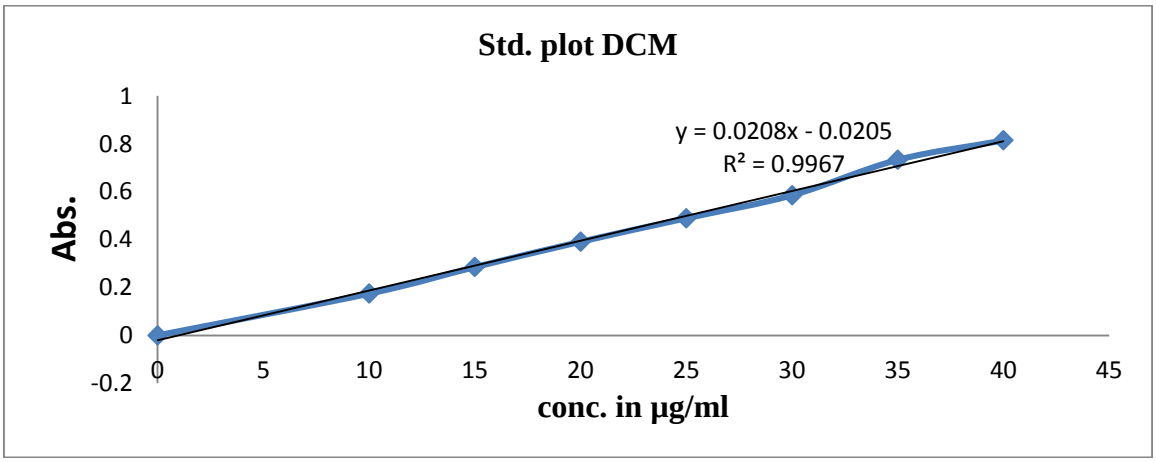

Figure 3. Standard Graph of Ketoconazole in dichloromethane (DCM) at λmax 244.2 nm.

Preparation of calibration curve in distilled water

Table 5. Absorbance of ketoconazole solution in distilled water at λ max 244 nm

S. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.305
3	15	0.402
4	20	0.531
5	25	0.621
6	30	0.756
7	35	0.831
8	40	0.956

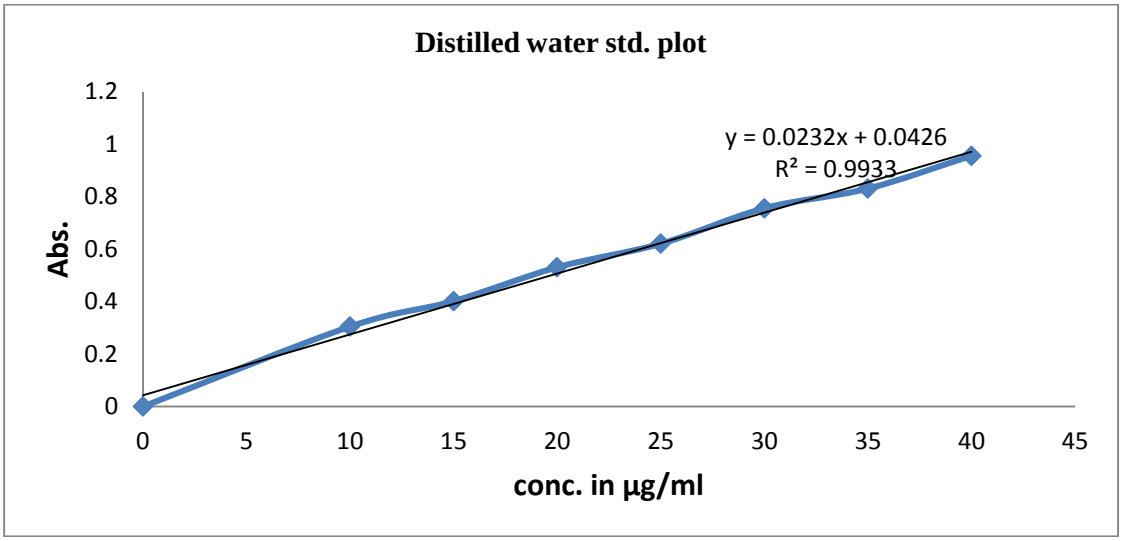

Figure 4. Standard Graph of Ketoconazole in distilled water at λmax 244nm.

Preparation of calibration curve in octanol

Table 6. Absorbance of ketoconazole solution in octanol at λ max 244.4 nm

S. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.189
3	15	0.263
4	20	0.375
5	25	0.472
6	30	0.563
7	35	0.693
8	40	0.783

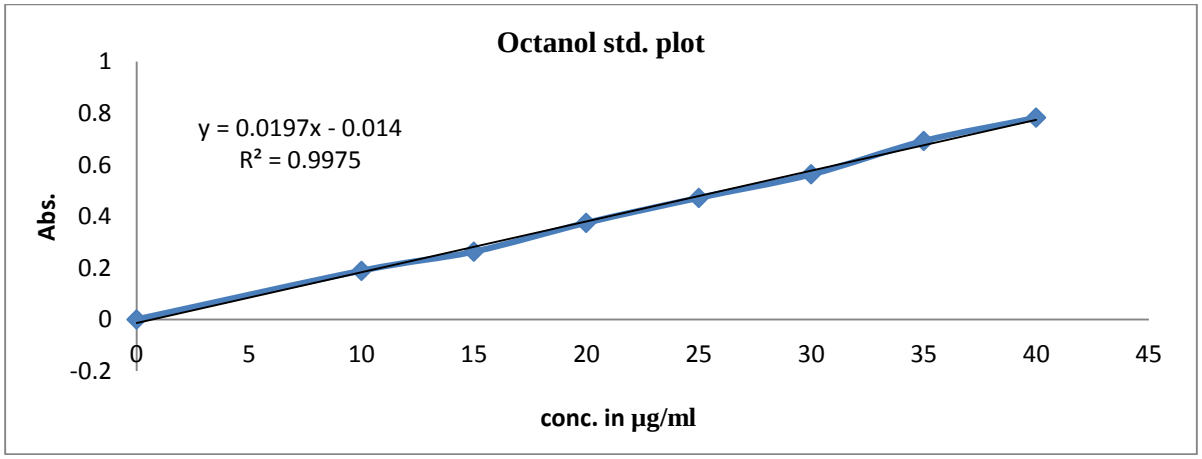

Figure 5. Standard Graph of Ketoconazole in octanol at λmax 244.4 nm.

Drug Polymer Compatibiliy Study

Physical Appearance: There was gas formation, caking, colour change was present hence we can say that no incompatibility was present.

IR spectroscopy: The reference IR Spectra of β-cyclodextrin is referred from the (*IoanaStanculescu et al* 2010). They obtained the IR spectra by KBr pellet technique in interaction study of polychloro biphenyl and β-cyclodextrin. They showed the IR spectra which are approximately obtained during my research study.

IR Spectrum of PEG-6000 The reference IR spectra of the PEG 6000 are obtained from the (*Divyatheja et al* ; 2012), in a solubility enhancement study of the rifampicin and other excipient, they showed the IR spectra which are approximately same obtained during my research study.For the incompatibility study of the drug and excipient individual spectra was compared with the pure spectra and was found that there is no incompatibility between the drugs and various selected excipient which are used in the formulation

Evaluation of Suspension

Techniques for the evaluation of heterogeneous systems are generally complex and are far from being completely satisfactory sedimentation method employed for evaluation of suspension is discussed below:

Sedimentation volume: It considers the ratio of the ultimate height (Hu) of the sediment to the initial height (Ho) of the total suspension as the suspension settles in a cylinder under standard conditions. The suspensions of formulations prepared from different techniques I, II, III and IV were filled in 100 ml graduated cylinder and kept undisturbed for 24 hour and initial height(Ho) was measured. The ultimate height (Hu) was measured at different time intervals. The Hu/Ho ratio is plotted versus time.

Table 7. Rare of sedimentation

Time (Hr)	Type I			Type II			Type III			Type IV		
	Ho (cm)	Hu (cm)	Hu/Ho	Ho (cm)	Hu (cm)	Hu/Ho	Ho (cm)	Hu (cm)	Hu/Ho	Ho (cm)	Hu (cm)	Hu/Ho
0	20	20	1	20	20	1	20	20	1	20	20	1
0.5	20	20	1	20	19.8	0.99	20	20	1	20	20	1
1	20	20	1	20	19.8	0.99	20	20	1	20	20	1
2	20	20	1	20	19.6	0.98	20	19.4	0.97	20	20	1
4	20	19.8	0.99	20	19.4	0.97	20	19.4	0.97	20	19.6	0.98
8	20	19.8	0.99	20	19.2	0.96	20	18.8	0.94	20	19.4	0.97
10	20	19.4	0.97	20	19	0.95	20	18.6	0.93	20	19.4	0.97
12	20	19.4	0.97	20	19	0.95	20	18.4	0.92	20	19.4	0.97
24	20	19.4	0.97	20	19	0.95	20	18.4	0.92	20	19.4	0.97

The sedimentation studies showed that all the suspension were stable indicated by the plot of Hu/Ho ratio versus time figure 3.16. As shown in figure the plot become horizontal after 4 hours for all the formulations. The Hu/Ho ratio for suspension of type I, II, III, and IV formulation after 24 hours were 0.97, .095, 0.92 and 0.97 respectively and all suspension passed the test of stability testing because of the acceptable Hu/Ho value.

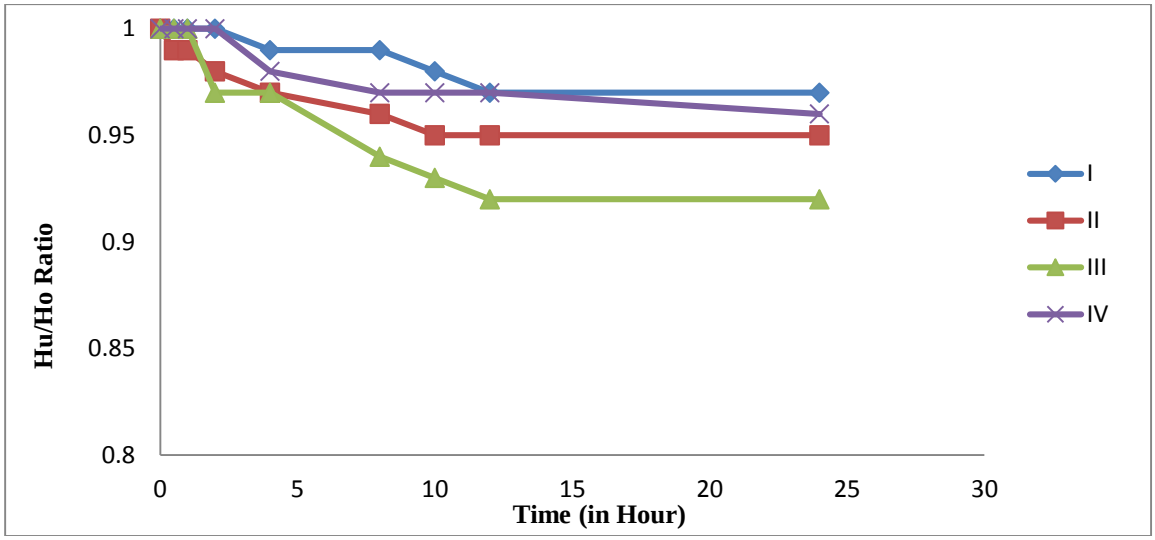

Figure 6. Plot of Hu/Ho ratio versus time for the evaluation of suspension indicating the stability of the suspensions

Where, I= Melt Sonocrystallization Technique, II= Solid Dispersion Technique, III= Hydrotropy Technique and IV= Inclusion Complex Formation Technique.

***In Vitro* Release Study**

Four formulations prepared by four different solubility enhancement techniques (melt crystallization, solid dispersion, hydrotrophy, inclusion complex formation were checked for their dissolution profile to assess the best formulation. A 2 % aqueous suspension of ketoconazole was prepared for the *in vitro* release study. Release study was performed in distilled water by dialysis membrane method. 1 ml of the formulation was taken in dialysis bag and it was kept inside the basket type of dissolution apparatus (Type 1 dissolution apparatus). Volume of dissolution media (distilled water) 900 ml. Temperature was kept 37± 0.5°C and speed of the basket was 100 rpm. Sampling was done at 0, 0.5, 1, 2, 4, 6, 8, 12 and 24 hrs by withdrawing 2 ml of the sample and replacing with 2ml of solvent. The analysis of sample was done by taking absorbance with UV spectrophotometer (Schimadzu, Japan). Concentration of the drug in sample was calculated from the calibration curve prepared in distilled water, by the extrapolation method.

Comparison of Drug Release Profile of Four Suspensions of Different Techniques of Solubility Enhancement

Table 7. Showing the comparison of drug release profile of four suspensions of different techniques of solubility enhancement

Times (hrs)	Hydro trophy (% drug rlease)	Melt sonocry. (% drug rlease)	Solid Dispersion (% drug rlease)	Inclusioncomplex (% drug rlease)	Control (% drug rlease)
0	0	0	0	0	0
05	7.5	6.3	6.66	11.94	2.3
1	15.9	11.7	12.06	18.12	3.1
2	24.54	16.98	18.42	24.72	4.22
4	36.18	22.32	23.88	31.32	5.6
6	49.08	27.72	29.7	37.2	8.6
8	53.78	32.82	32.94	47.94	10.2
12	60.48	41.22	41.88	57.9	16.11
24	83.16	58.68	61.02	73.62	17.34

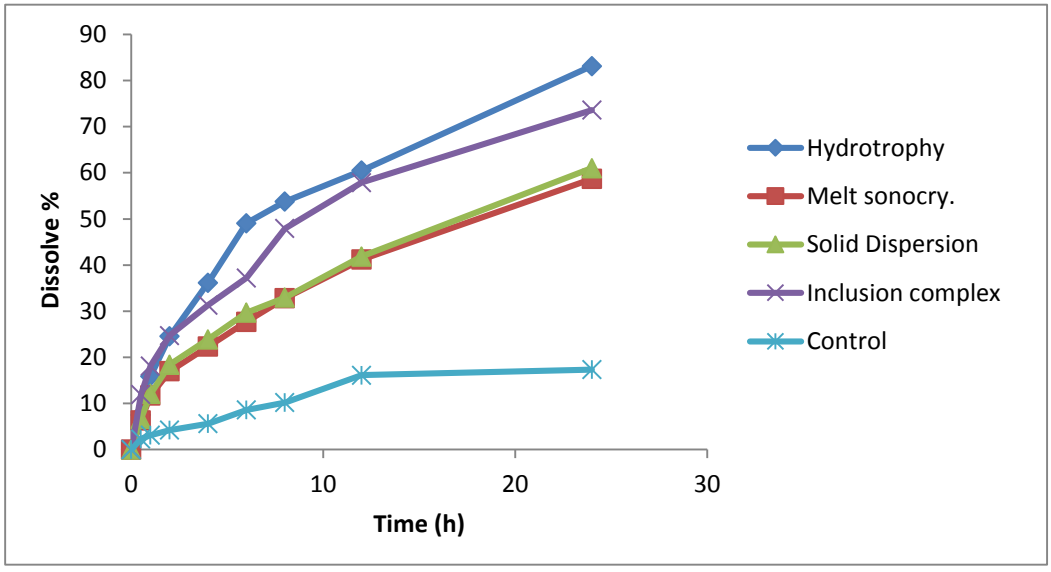

Figure 7. Comparative dissolution by different techniques

Result: On the basis of the dissolution study it was clear that the formulation which was prepared by the hydrotrophy method showed the best result for the solubility as well as for *in vitro* release study i.e. 12.159 fold increase in solubility and 83.16% release of the ketoconazole from the from its suspension was observed.

4. Conclusion

Four techniques namely melt sonocrystallization, solid dispersion, hydrotrophy and inclusion complex with cyclodextrin were used for the solubility enhancement. The order of the techniques for the solubility enhancement was found hydrotrophy>inclusion complex>solid dispersion>sonocrystallization method. Enhancement in the

solubility by the hydrotrophy method was found to be 12.159 fold increases while by inclusion compound, solid dispersion, and melt sonocrystallization method was found to be 9.644, 7.349, and 5.517 fold respectively. Dissolution study of the four formulations prepared by the four different techniques was also performed. On the basis of data of drug dissolution profile of all four formulations (aqueous suspension) it was found that the formulation prepared by the hydrotropy method showed the best release profile that is 83.16%. While release from the suspension prepared by inclusion compound, solid dispersion, and melt sonocrystallization method were found to be 61, 73 and 58% respectively. Thus on the basis of this study we can say that the hydro trophy technique is the best technique for the solubility enhancement of the ketoconazole.

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