

PREPARATION AND EVALUATION OF SOLID DISPERSION OF TERBINAFINE HYDROCHLORIDE

K. ArunPrasad^{1*}, N. Narayanan¹, G. Rajalakshmi²

1. Department of Pharmaceutics, Madras Medical College, Chennai.

2. Department of Pharmaceutics, SRM College of Pharmacy, SRM University, Kattankulathur, Kancheepuram district, Chennai-603203.

*Email: aarunkap@yahoo.co.in

ABSTRACT

The study was aimed to formulate solid dispersion tablet of Terbinafine Hydrochloride by using carriers polyethylene glycol 6000 (by melting method) and polyvinyl pyrrolidone K 30 (by solvent method) in the drug carrier ratio of 1:1, 1:2 and 1:3. The prepared solid dispersions were characterized for their drug content, thermal studies, infrared spectral studies, differential scanning calorimetric studies, aqueous solubility studies and in-vitro release studies. From the results, it was clear that solid dispersion formulation showed improved dissolution rate than pure drug and physical mixture. The solid dispersion showing better release profile was chosen to formulate into a tablet dosage form of weight 600 mg. The tablets compressed were evaluated for its physical parameters like thickness, hardness, weight variation, friability, drug content and disintegration tests. The dissolution profile of formulated tablet was compared with the marketed product and the formulated tablet showed better release profile than the marketed product.

Keywords: Solid dispersion, Differential scanning calorimetric studies, Terbinafine HCl, dissolution and carriers.

INTRODUCTION

The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion but it is problematic if the drug is poorly soluble or poor membrane penetrability¹. Although salt formation, solubilization, particle size reduction have commonly used to increase dissolution rate and thereby oral absorption and bioavailability of low water soluble drugs²⁻⁴, there is practical limitation to these techniques. Among numerous ways of enhancing drug dissolution solid dispersion of drug in a water soluble polymer is one of the promising technique⁵. Solid dispersion (SD) is defined as the dispersion of one or more active ingredients in inert carriers at solid state prepared by fusion, solvent or solvent fusion methods⁶⁻⁸.

Terbinafine hydrochloride is a synthetic alkylamine drug with broad spectrum of antifungal activity^{9, 10, 11}. It is used for immediate relief in Jock itch (burning sensation in groin area, thigh folds or anus, genital areas etc.) or Tinea cruris (fungal infection in groin area) and in various types of onychomycosis or Tinea unguium (fungal infection of nail bed, matrix or plate, toenails are mostly affected). It occurs mainly due to *Trichophyton rubrum*, *Candida albicans*, *Trichophyton mentageophytis* and *Epidermophytion floccosum*. Terbinafine hydrochloride is highly lipophilic and only slightly soluble in water, so to improve the dissolution, solid dispersion technique is selected¹².

Solid dispersion technique has been used for a wide variety of poorly aqueous soluble drugs such as Nimesulide, Ketoprofen, Tenoxicam, Nifedipine, Aceclofenac, Valdecoxib using various hydrophilic carriers like polyethylene glycol, polyvinylpyrrolidone, hydroxypropylmethyl cellulose, sugar, mannitol, urea etc.¹³

In this study Terbinafine hydrochloride was used as model drug and polyethylene glycol 6000 and

polyvinylpyrrolidone K 30 were used as carriers in 1:3 ratios. Administering the drug in solid dispersion enhances the dissolution and immediate release, as oral administration of drug is used in killing dermatophytes like trichophyton, microsporus canis of skins and nails.

MATERIALS AND METHODS

Materials

Terbinafine hydrochloride was supplied by Dr. Reddy's laboratory and polyethylene glycol 6000 from fluka chemicals and polyvinylpyrrolidone K 30 from BASF India. All other chemicals and reagents used were of analytical grade.

Preparation of solid dispersion¹⁴

Solid dispersion of terbinafine hydrochloride was prepared by melting and solvent method. The composition is shown in table No:1.

Table 1: Composition of Solid Dispersion

Formulation Code	Carrier	Drug: carrier	Method
SD PEG1 SD PEG2 SD PEG3	PEG 6000	1:1 1:2 1:3	Solid dispersion (Melting method)
SD PVP 4 SD PVP 5 SD PVP 6	PVP K 30	1:1 1:2 1:3	Solid dispersion (solvent evaporation method)
PM PEG 1 PM PEG 2 PM PEG 3	PEG 6000	1:1 1:2 1:3	Physical mixture
PM PVP 1 PM PVP 2 PM PVP 3	PVP K 30	1:1 1:2 1:3	Physical mixture

In melting method the drug and carrier polyethylene glycol 6000 were mixed in 1:1, 1:2, and 1:3 ratios in a china dish and heated on a paraffin bath. The mixture was poured on a tile and cooled. The resulted solidified mass was dried pulverised and passed through sieve # 100.

In solvent evaporation method, the drug and carrier polyvinylpyrrolidone K 30 were mixed in 1:1, 1:2 and 1:3 ratios in methanol. Solvent was removed by evaporation under reduced pressure. The mass was pulverised and passed through sieve # 100.

Preparation of physical mixtures

For the sake of comparison, physical mixtures having the same composition of the solid dispersions were prepared by simply triturating the drugs and the polymers in a porcelain mortar. The mixtures were then sieved (420 μm) and stored in amber-glass capped containers.

Evaluation of Solid Dispersion

Estimation of drug content: The formulation equivalent to 50 mg of terbinafine hydrochloride was weighed and diluted suitably with distilled water. The absorbance was measured at 283 nm and the amount of drug in each formulation was calculated.

Differential Scanning Calorimetry: Differential scanning calorimetry was performed by Differential scanning calorimeter 60 shimadzu to obtain suitable thermograms. The accurately weighed sample was placed in an aluminium pan and an empty aluminium pan was used as reference. The experiment was performed under nitrogen flow, at a scanning rate 30^oC/min. in range of 50-350^oC.

Infra red spectrum: Infra red studies was carried out to rule out interaction between drug and carrier used in formulation of solid dispersion by potassium bromide disc method using Infra red spectrophotometer.

Thermal studies: It was carried out to ascertain the effect of heating on stability of the drug. It is based on thaw point melt method by heating drug in capillary melting point tube and allowing it to solidify. The melting point of rapidly solidifying mass was noted.

Aqueous solubility studies:¹⁵ It was carried out to determine solubility of terbinafine hydrochloride alone in aqueous medium and also in presence of carriers like polyethylene glycol 6000 and polyvinyl pyrrolidone K30. This was done by dissolving excess drug in different flasks containing different concentration of carrier in distilled water. The flasks were shaken thoroughly for 6 hours and kept aside for 24hours. The suspensions were filtered, diluted suitably and absorbance was measured at 283nm.

Dissolution Studies: The invitro dissolution studies were done to compare the rate of dissolution of solid dispersions with that of pure drug Terbinafine hydrochloride and physical mixtures. The test was performed in USP paddle apparatus using 900ml phosphate buffer solution at pH 7.4 and temperature 37 \pm 1^oC

Tablet preparation and characterization:

Composition containing equivalent of 500 mg of terbinafine hydrochloride were compressed on single

punch rotary tableting press using 12.7mm round flat beveled punch by direct compression technique. Composition of the tablet is given in table no: 2.

Prepared tablets were evaluated for hardness (Monsanto hardness tester) friability (Roche friabilator), weight variation and drug content. In vitro dissolution studies were carried out in USP paddle apparatus using 900ml phosphate buffer pH 7.4. The drug release profile of formulated tablet was compared with marketed tablet. Stability studies were also conducted at 40^oC for periodic time intervals.

Table 2: Composition of the tablet formulated with Solid dispersion

S.No	Ingredients	Qty/Tablet (in mg)	Qty/Batch (in gm)
1.	Solid dispersion (equivalent to Terbinafine Hydrochloride)	500	25
2.	Micro Crystalline Cellulose (Avicel- pH 102)	82.64	4.132
3.	Croscarmellose Sodium (Acdisol)	12.40	0.62
4.	Colloidal Silicon Dioxide (Aerosil 200)	1.86	0.093
5.	Magnesium Sterate	3.10	0.155
6.	Total weight	600	30000

RESULTS AND DISCUSSION

Drug content analysis

Drug content of the solid dispersions was found to be between 94.52 % and 104.83%. All the physical mixtures and solid dispersions showed the presence of high drug content and low standard deviations of the results. It indicates that the drug is uniformly dispersed in the powder formulation. Therefore, the method used in this study appears to be reproducible for preparation of solid dispersion.

The occurrence of any interaction between a drug and polymers in the formulation can be predicted by conducting the differential scanning calorimetry studies. The thermograms of solid dispersions display the characteristic features of the drug. This indicates no possible interaction between the polymers and Terbinafine Hydrochloride. The results are shown in figure no: 1.

Infra red spectral analysis showed that there were no interactions between pure drug and solid dispersion. The results are shown in figure no: 2.

Thermal study was carried out to ascertain the decomposition of drug. This indicated that there was no change in the melting point of Terbinafine hydrochloride after thermal studies. Thermograms of solid dispersion displayed characteristic features of pure drug. The results are tabulated in table no: 3.

Figure 1: Differential Scanning Calorimetric studies of Terbinafine hydrochloride and polymers

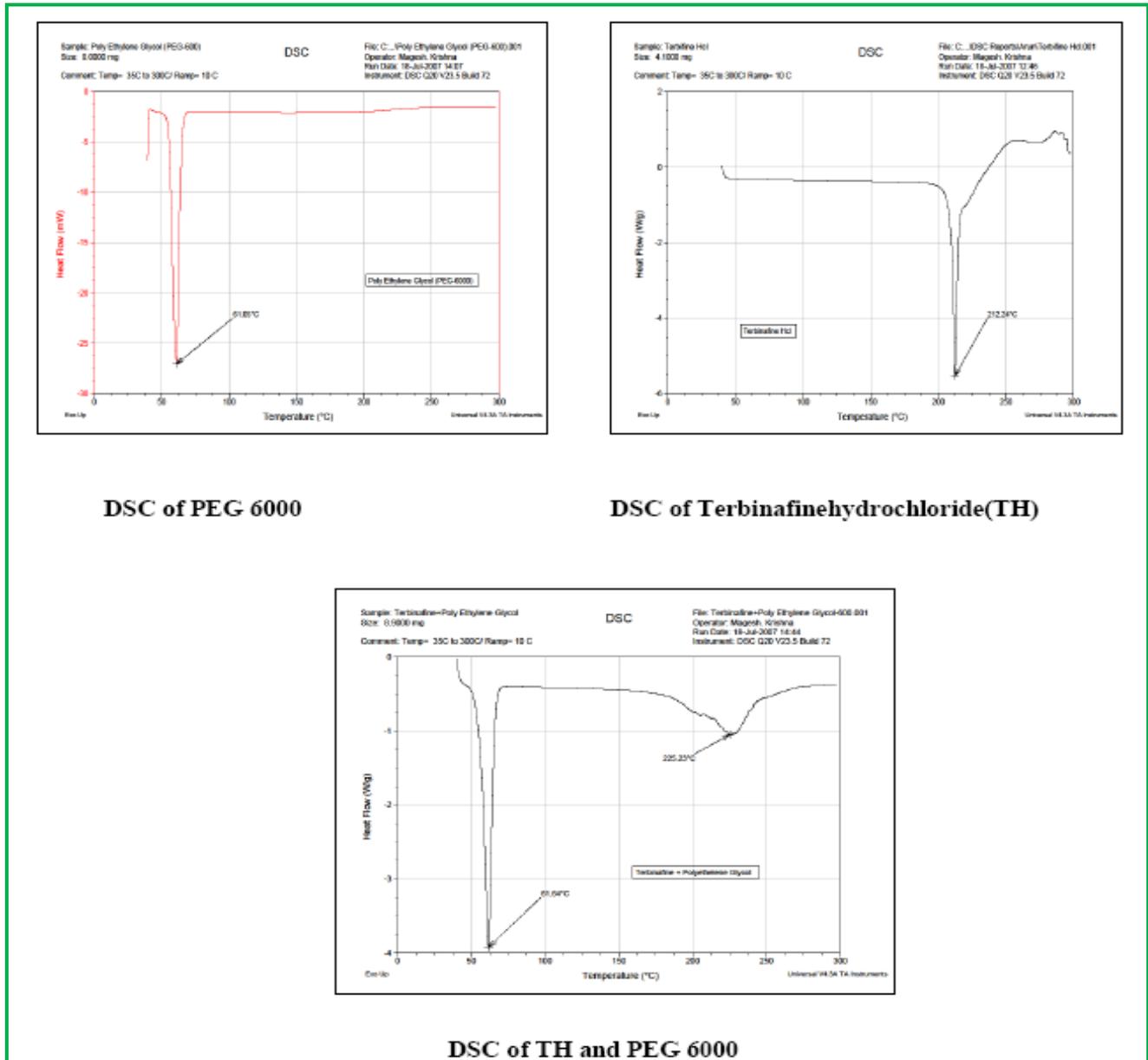


Figure 2: Infrared spectrum of Terbinafine hydrochloride and PEG 6000.

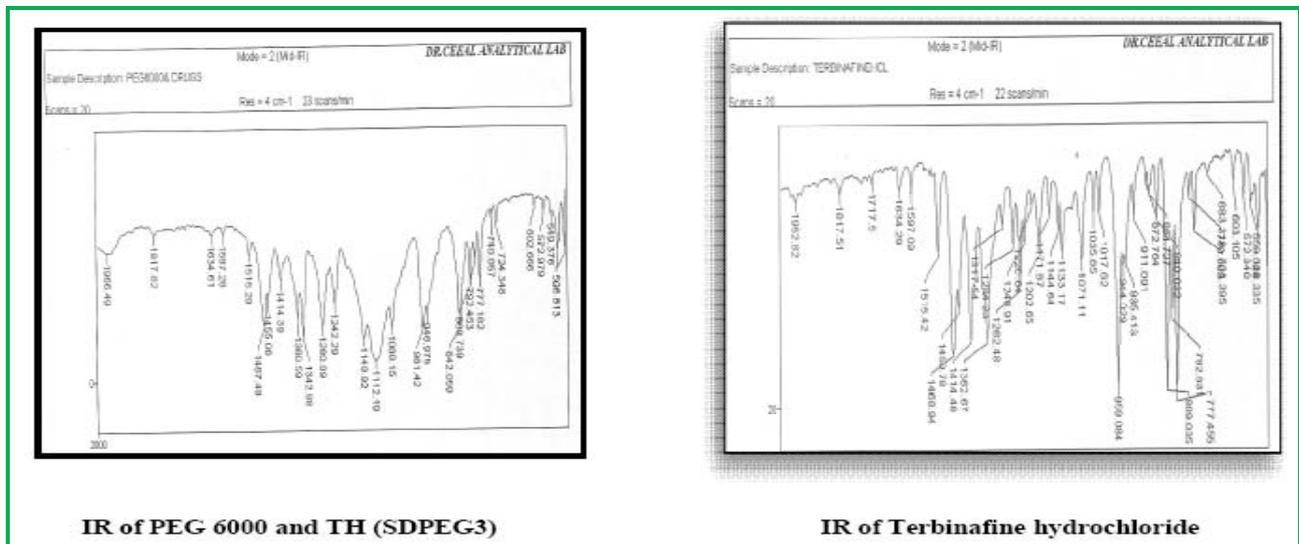


Table 3: Thermograms of solid dispersion

S.No	Melting point of Terbinafine HCl (Before thermal studies) in °C	Melting point of Terbinafine HCl (After thermal studies) in °C
1.	205	206
2.	205	205
3.	205	205

Aqueous solubility studies indicated that solubility of terbinafine hydrochloride increased in presence of carriers when compared to solubility of drug in distilled water. The fast and rapid dissolution of drug observed in solid dispersions due to the presence of drug in amorphous form. The amorphous form is the highest energy of pure compound and produces faster dissolution. The other factors like absence of aggregation, good wettability and dispersability might have also contributed to the increase in dissolution rate. The results of aqueous solubility studies are given in table no:4.

Table 4: Solubility studies of Terbinafine hydrochloride in distilled water

Name of the Carrier	Solubility studies of Terbinafine hydrochloride in different concentrations of carrier			
	0.25%	0.50%	0.75%	1%
PEG 6000	0.634	0.652	0.632	0.644
PVP K 30	0.645	0.648	0.635	0.635

In vitro dissolution studies indicated that as concentration of carrier increases, dissolution of drug improved. The results of drug release from solid dispersion and physical mixtures of PEG 6000 are shown in figure no: 3 and 4 respectively. The formulation code SDPEG3 (Terbinafine hydrochloride: PEG 6000 = 1:3) showed 95.7 % release in 35 minutes than other PEG solid dispersions whereas the physical mixtures of same formulation released 96.75 % in 60 minutes, pure drug in 90 minutes. In case of formulation SDPVP3 (with drug and PVP K30 1:3) showed 98.7 % in 1 hour, physical mixture of the same ratio showed only 93% release. Compared with the pure drug and physical mixture, the dissolution was found to increase in the following order.

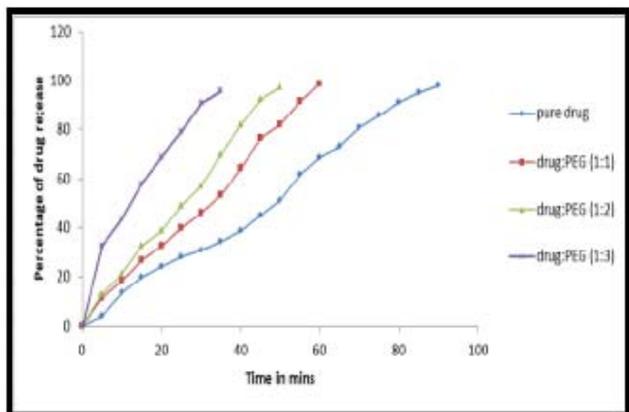


Figure 3: In vitro release studies of Solid dispersions of TH with PEG 6000

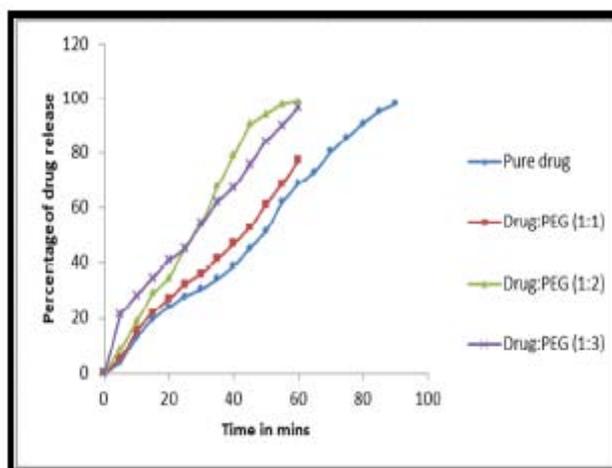


Figure 4: In vitro release studies of Physical mixture of TH with PEG 6000

Pure drug < Physical mixture < solid dispersion

This may be due to the presence of polymer, which increases wetting, and dissolution of the drug. Even though the polymer is present in the physical mixture the dissolution rate was lesser than solid dispersion. This increase in dissolution rate of solid dispersion was attributed to molecular/ colloidal dispersion of drug in mixture. Higher the proportion of carrier there was a steep increase in dissolution rate of drug. The release of drug from solid dispersion and physical mixture using PVP K 30 is given in figure no: 5 and 6 respectively.

Solid dispersion showing better release was formulated into tablet dosage form and evaluated for its parameters. All parameters were within the specified I.P. limits. The thickness and diameter of the tablets were found to be 3.51 and 12.7mm. Weight variation was within the I.P. limits ($\pm 5\%$). The hardness of the different formulations ranged from 6 to 7 kg/cm². All the formulations exhibited less than 1% friability. The drug content analysis of Terbinafine Hydrochloride in all the formulations was found to be (98.6 % w/w) within the I.P. limits ($\pm 5\%$). The time taken for the tablets to disintegrate was evaluated in all the formulations and found to be 8min 31 sec. (I.P. limits uncoated tablet is < 15min).

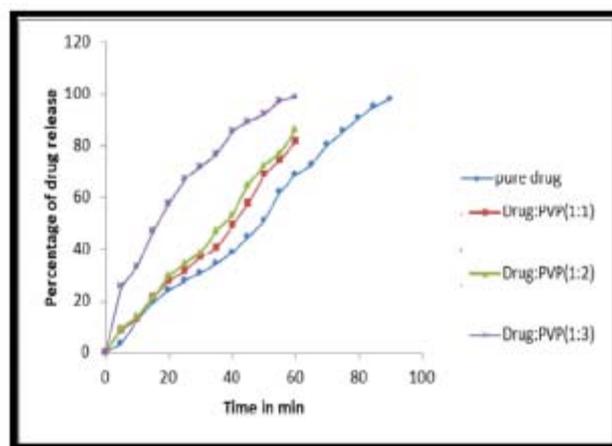


Figure 5: In vitro release studies of Solid dispersion of TH with PVP K 30

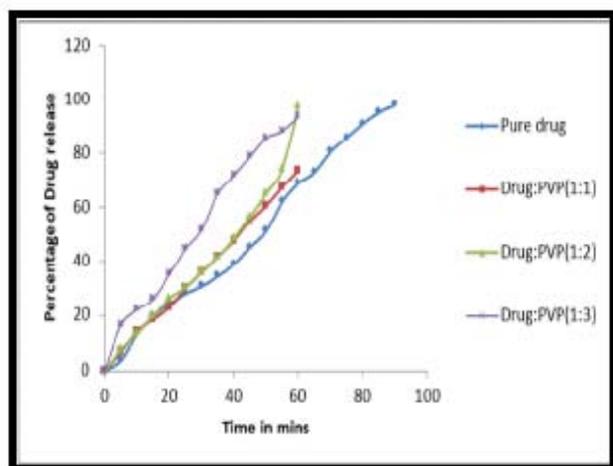


Figure 6: In vitro release studies of Physical mixture of TH with PVP K 30

Stability studies were carried out at 40°C for a month to assess their short-term stability. The insignificant change in the physical appearance and the drug content in all formulations being stored at 40°C indicate that the formulations could provide a minimum shelf life of 2 years. Stability studies were also performed. The results were promising; it indicates the solid dispersion was stable.

The formulated tablets showed a complete drug release in 45 minutes whereas the marketed product was found to release only 65% of the drug in 45 minutes. The results are shown in figure no: 7. Hence the formulated solid dispersion tablets can be prescribed for acute fungal infections.

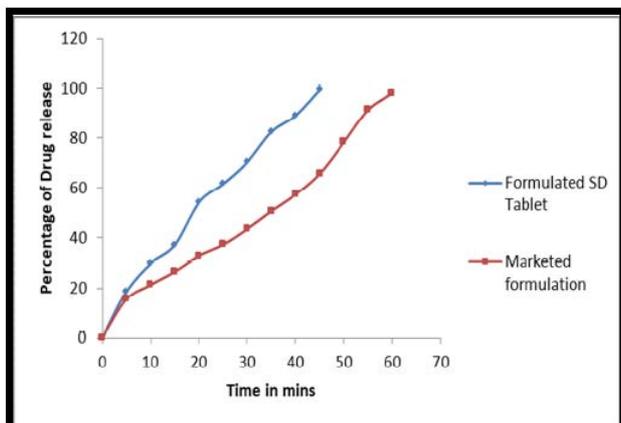


Figure 7: Comparison of In vitro release profile of formulated tablet and marketed tablet

CONCLUSION

Terbinafine hydrochloride an antifungal drug used in treatment of onychomycosis provide a better therapy if drug is released effectively and this is achieved by formulating drug in term solid dispersion as tablet. It could be considered as better choice of treatment in onychomycosis with fast release, achieving good patient compliance

REFERENCES

1. Dhirendra K, Lewis S, Udupa N and Atin K, Solid dispersions: A Review, Pak. J.Pharm. sci, 22(2), 2009; 234-246.
2. Noyes AA, Whitney WR, The rate of solution of solid substances in their own solutions. J Am chem Soc 1897, 19; 930-4.
3. Nernst W. Theoric der Reaktions-geschwindigkeit in heterogenous system. Zeitschrift-F Physik chemie 1904, 47:525.
4. Galia E, Nicolaidis E, Horters D, Lobenberg R, Reppasc, Dressman B Evaluation of various dissolution media for predicting invivo performance of class I & II drugs, Pharm Res 1998, 15; 698-705.
5. Brahmarkar D.M ,Sunil B,Jaiswal, Bioavailability and Bioequivalence, Biopharmaceutics and pharmacokinetics A treatise,II edtn, Vallabh prakashan,2009,349-357.
6. Damian F, Blaton N, Naesens L, et al. Physicochemical characterization of solid dispersions of the antiviral agent UC-781 with Polyethylene glycol 6000 and Gelucire 44/14. Eur. J. Pharm. Sci. 2000; 10: 311-322.
7. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersions systems J. Pharm. Sci 1971; 60: 1281-1302.
8. Ford JL, The Current states of Solid dispersions. Pharm Acta Helv. 1986; 61: 69-88.
9. Andrews Diseases of the skin clinical dermatology, 297-307.
10. American Academy of family physicians, Feb 2001.
11. AHFS, Drug information, American Society of Health System – Pharmacists 2004, 3331-3333.
12. Rang and Dales Pharmacology, Antifungal drugs, Churchill living stone Elsevier, Philadelphia, 2007, 48,696.
13. Aftab Modi and Pralhad Tayade, Enhancement of dissolution profile by solid dispersion (kneading) technique, AAPS pharm sci tech 2006, 7(3), article 68.
14. Jain Rupal, Jani Kaushal, Setty C. Mallikarjuna, Patel Dipti, Preparation and evaluation of Solid dispersions of Aceclofenac ,Int.J.Pharm Sci and Drug Research,2009,1(1):32-35.
15. Higuchi T and Connors K.A, Advanced analytical chemical instrumentation, 1965, 4; 117
