Original Article

Formulation, Characterization And Evaluation Of Oral Dosage Form Of Itraconazole To Enhance Solubility

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DOI: 10.47750/pnr.2022.13.S10.287

Abstract

In this present study solubility of antifungal Itraconazole drug was enhanced with solid dispersion by using PEG6000 and PVP K30 as a carrier in different ratios followed formation of a compressed tablet. Tablets were prepared by compression method and evaluation parameters were screened for drug content, disintegration hardness of tablet and dissolution rate. In vivo study was also performed for determination of drug absorption. Tablets prepared by solid dispersion have been better rate of solubility and dissolution.

Keywords:- Solubility, Antifungal, Soli dispersion Method, Compression

INTRODUCTION:

Solubility is the property of a solid, liquid, or gaseous chemical substance called solute to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the solute in the solvent. Solid dispersion technologies enhance the solubility and dissolution of drugs and thereby improve the oral bioavailability of poorly water soluble drugs (Patil, Gaikwad, 2009). Thus, drug's acceptability and bioavailability will depends on enhancement of solubility and dissolution that reduces dose required for showing fast onset of action (Chauhan, Shimpi, Paradkar, 2005)

Ketoconazole is hydrophobic BCS Class II imidazole derivative used as an antifungal agent. They are used to treat Tinea pedia (Athelete's foot) and effective against several fungal strains such as Candida albicans. These are available in oral and topical dosage form. These has poor 0.00931 mg/ml respectively and bioavailability is very less. To resolve the problem of poor solubility, solid dispersion with hydrophilic carrier is prepared and converted to a conventional dosage form such as tablet.

METHOD:

Preparation of physical mixture:

Physical mixtures of APIs and polymer at different mass ratios (1:1, 1:3, 1:5 for PEG6000 and 1:2, 1:3 and 1:4 with PVPK 30) were prepared in a glass mortar with trituration up to 10 minutes. This physical mixture was sieved with 0.25 nm sieve the physical mixtures were stored in desiccators with silica gel to reduce effect of hygroscopicity.

Preparation of solid dispersions by fusion method:

Solid dispersions of APIs at different mass ratios (1:1,1:3 1:5 for PEG 6000 and 1:2, 1:3 and 1:4 with PVPK 30) were prepared by using melt or fusion method. Polymer like PEG 6000 and PVP K30 was placed in a porcelain dish and melted by heating up to 70 °C. In this molten mass, appropriate amount of drugs was added and stirred to form a homogenous dispersion. The solution was cooled on an ice bath and stored in desiccators for 24 h. It was then scrapped, pulverized and passed through a sieve. The prepared solid dispersions were then filled in glass bottles, sealed and stored in desiccators until further use.

Saturation solubility

Saturation solubility of the complexes was determined by equilibrating an excess of complex in different media. Itraconazole such as acidic buffer (pH 1.2), Phosphate buffer (pH 6.8), Methanol and distilled water was used to dissolve for 48 hours on a mechanical shaker at room temperature. At equilibrium after 2 days, aliquots were withdrawn, followed

by centrifugation at 4000 rpm for 10 minutes, filtration (0.22-mm pore size, Whatmann) and a spectrophotometric assay for drug content at 258 nm.

Preparation of tablet:

Tablet is a solid dosage form. Tablet was formed through direct compression method. The Drug: Polymer ratio having higher saturation solubility in a particular solvent was forwarded for the final formulation. API complex were compressed into tablets using a tablet punching machine. Excipients such as Sprayed dried lactose (SDL) used as a binder ,Sodium Starch Glycolate (SSG) used as a disintegrating agent ,magnesium stearate as a lubricant and talc as a glidant were added as per the composition. Tablets were prepared by the direct compression method. The prepared tablets were evaluated for weight variation, hardness, friability, content uniformity, disintegration time and in vitro dissolution and In Vivo study.

Table 1: Composition of tablet

	F1	F2	F3	F4
Ketoconazole complex	96.7	96.7	96.7	92.7
Spray dried lactose	20.5	19.5	18.5	16.5
Sodium Starch Glycolat	6.8	7.8	8.8	11.8
Magnesium Stearate	05	05	05	07
Talc	01	01	01	02
Total weight	130	130	130	130

RESULT AND DISCUSSION:

Preformulation studies:

Preformulation studies of drug were determined on the basis of melting point, colour, and FTIR and UV analysis.

Standard Calibration Curve of Itraconazole (λ_{max} =258 nm): Standard Itraconazole was scanned and absorbance was measured between 200- 400mm against blank solution showed wavelength maximum at 258 nm

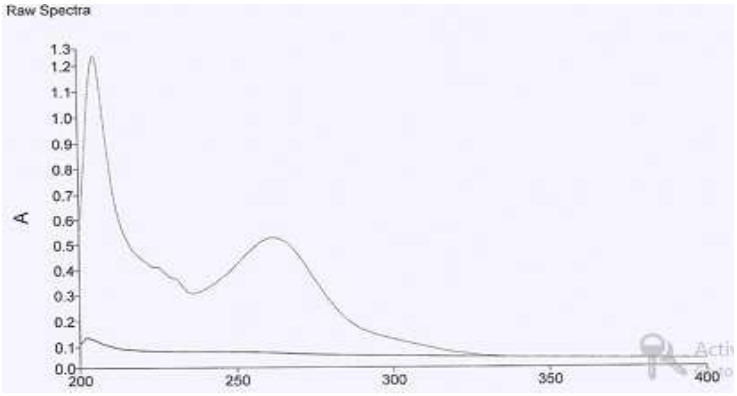

Figure 1: Maximum wavelength of Itraconazole

Table 2: Absorbance of Itraconazole

Conc(µg/ml)	Absorbance
10	**0.61**
20	**1.09**
30	**1.49**
40	**2.05**
50	**2.42**
60	**2.97**
r^2	0.997

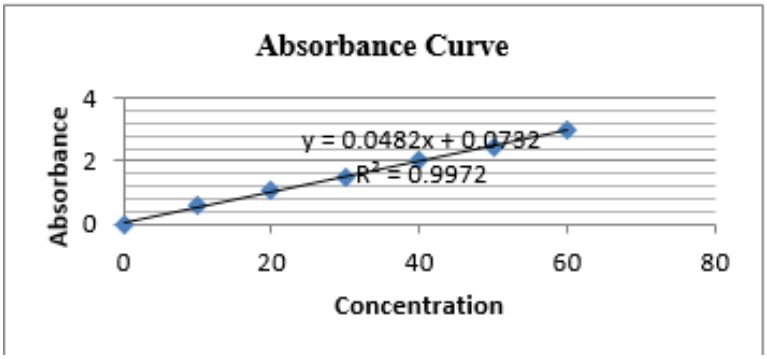

Figure 2: Calibration curve for Itraconazole

FTIR of Itraconazole:

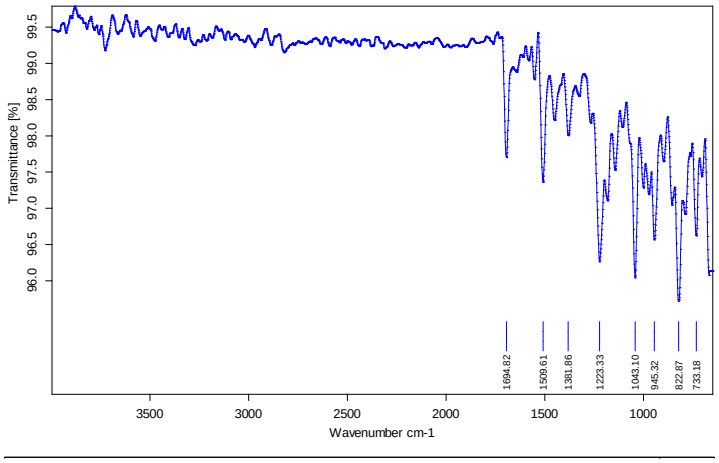

Figure 3: FTIR of Itraconazole

Physical Parameter of Tablet

1) **Hardness** – Hardness of tablet was determined by using Monsanto hardness apparatus.

Table 3: Hardness of Tablet

Sample No.	Hardness
F1	3.8±0.8
F2	3.9±0.8
F3	4.2±0.3
F4	4.1±0.5

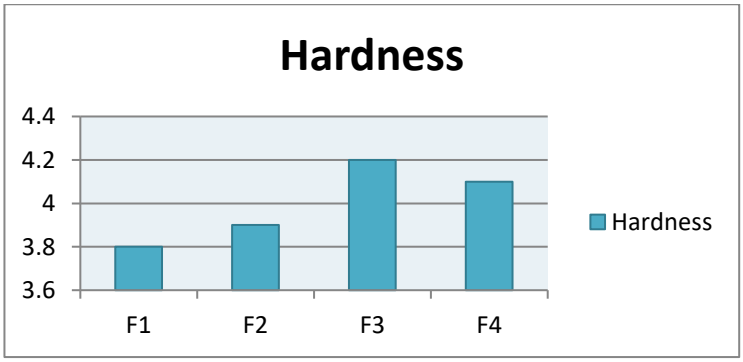

Figure 4: Plot for Hardness

2) **Friability:** Friability of tablets was determined by Roche friabilator and was found less than 1%

Table 4: Friability

Sample	Drug Complex(KTZ)
F1	0.53±0.1
F2	0.69±0.12
F3	0.56±1.1
F4	0.72±0.23

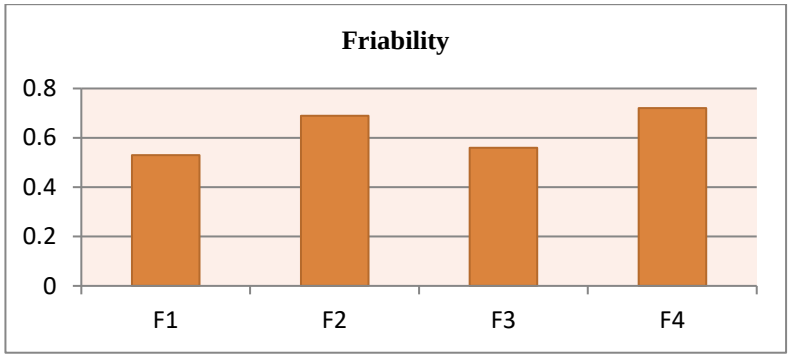

Figure 5: Plot for Friability

3) **Weight Variation:** Weight variation of tablets was observed. Average tablet weight of the formulation obtained had a range of 68.3-71.9 mg.

Table 5 Weight Variation

Formulation	F1	F2	F3	F4
Weight Variation	69.5±0.14	69.4±1.1	70.78±0.2	71.9±0.24

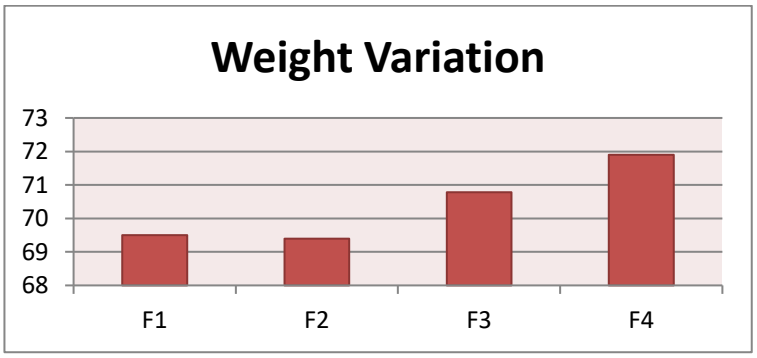

Figure 6: Weight variation

4) **Drug Content:** The drug contents were found to be more than 99% of theoretical value.

Table 6: Determination of Drug Content

Tablet formulation	Drug Content
F1	99.2±0.8
F2	99.8±1.1
F3	99.7±1.1
F4	99.1±1.2

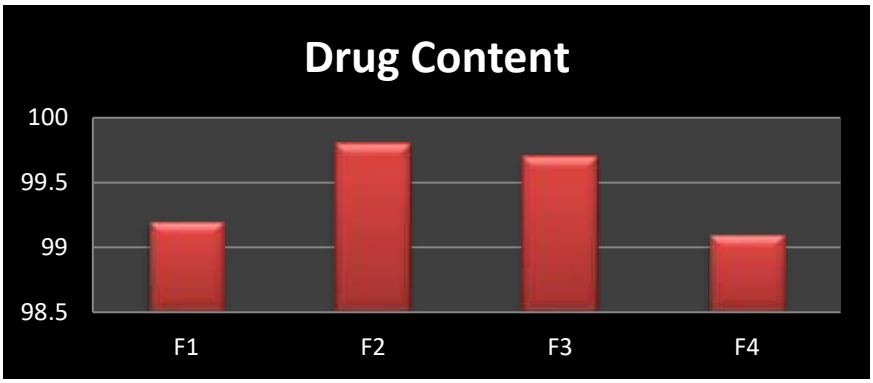

Figure 7: Plot for Drug Content

5) **Disintegration Time:** Disintegration time was determined by disintegration apparatus and varies from 2.9 to 4.5 min.

Table7 Disintegration time

Tablet formulation	Disintegration Time(Min)
F1	3.0
F2	2.9
F3	4.5
F4	3.9

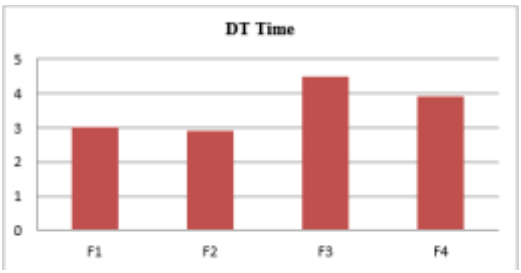

Figure: 8 Disintegration time

Dissolution profile: Dissolution profile study was performed for all the formulation and it was shows that F1 has better drug release as compared to others.

Table 8: In vitro Drug release

	Formulation				
S.NO.	Time (MIN)	**F1**	**F2**	**F3**	**F4**
1	5	49.52	38.94	39.57	43.12
2	10	58.92	49.12	48.13	56.76
3	15	66.89	55.34	55.85	65.9
4	20	76.97	65.43	62.97	72.67
5	25	80.67	69.45	70.86	78.98
6	30	84.91	73.78	75.89	81.89
7	45	89.89	82.85	78.99	84.69
8	60	92.89	89.34	82.09	87.89
9	120	97.10	95.90	90.13	90.35

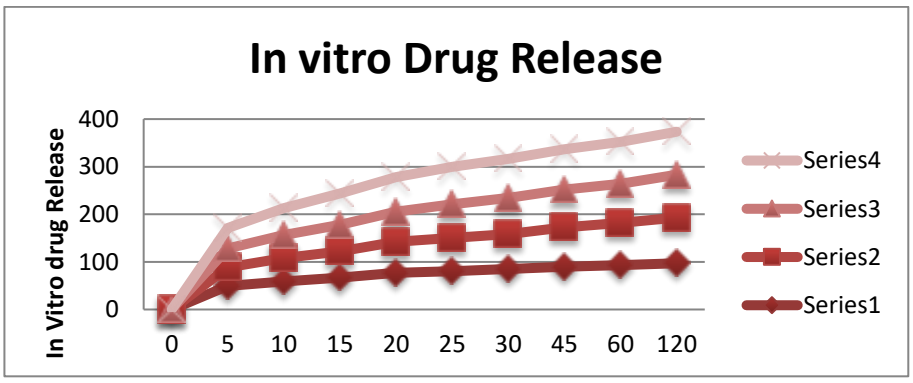

Figure: 9 In Vitro Drug release

Stability studies: Stability study of formulations was determined as per ICH guidelines at different Temperatures.

Table 9: Stability studies

S. No	Days	%drug remaining 27±2^{0}c/60±5% RH	%drug remaining 42±2^{0}c/60±5% RH
1	0	100±0	100±0
2	30	99.9±.003	99.4±.041
3	45	98.8±.027	98.2±.036
4	90	97.6±.012	97.1±.02

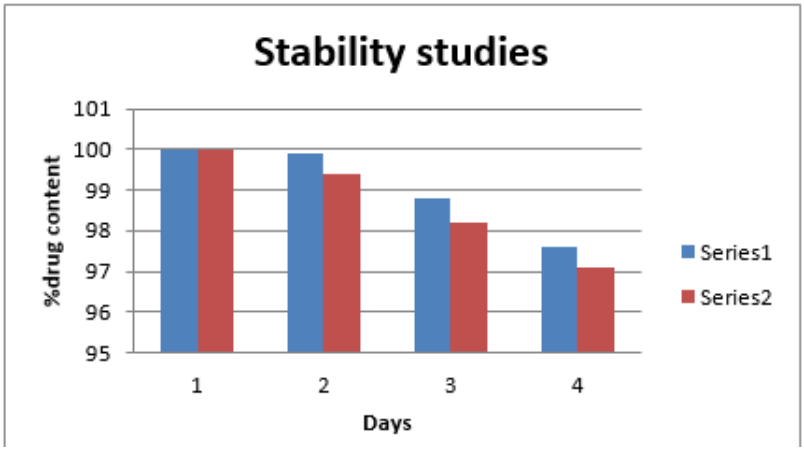

Figure 10: Stability studies

CONCLUSION:

This study includes the formation of oral dosage form tablet of BCS Class II antifungal drug having low water solubility .Due to low solubility dissolution of drug is low and also cause several side effects .so to reduce this solubility enhancement methods are applied by using hydrophilic carrier such as PEG6000 and PVP K30 in different proportions. As per results F2 has better dissolution profile as compared to others it has PEG6000 as a dispersion carrier. All the parameters of dosage form was determined such as hardness of tablet, its drug content disintegration time and stability studies and all the parameters follows standards as per given in Indian Phamacopoeia.

REFERENCES:

1. Chiou, Win Loung, and Sidney Riegelman. "Pharmaceutical applications of solid dispersion systems." Journal of pharmaceutical sciences 60.9 (1971): 1281-1302.
2. Vasconcelos, Teofilo, Bruno Sarmento, and Paulo Costa. "Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs." Drug discovery today 12.23-24 (2007): 1068-1075.
3. Jagdale, S. C., et al. "Preparation and characterization of Metformin hydrochloride− Compritol 888 ATO solid dispersion." Journal of Young Pharmacists 3.3 (2011): 197-204.
4. Kalivoda, Adela, Matthias Fischbach, and Peter Kleinebudde. "Application of mixtures of polymeric carriers for dissolution enhancement of fenofibrate using hot-melt extrusion." International journal of pharmaceutics 429.1-2 (2012): 58-68.
5. Jagtap, S., Magdum, C., Jadge, D. and Jagtap, R., 2018. Solubility enhancement technique: a review. Journal of Pharmaceutical Sciences and Research, 10(9), pp.2205-2211.
6. Sinko, P.J., 2011. Micromeritics. In Martin's Physical Pharmacy and Pharmaceutical Sciences: Physical Chemical and Biopharmaceutical Principles in the Pharmaceutical Sciences: Sixth Edition (pp. 442-468). Wolters Kluwer Health Adis (ESP).
7. Gupta, J. and Devi, A., 2019. Solubility EnhancementTechniquesforPoorly Soluble Pharmaceuticals: A Review. Indian Journal of Pharmaceutical and Biological Research, 7(02), pp.09-16.
8. Gupta, J. and Devi, A., 2019. Solubility Enhancement Techniques for Poorly Soluble Pharmaceuticals: A Review. Indian Journal of Pharmaceutical and Biological Research, 7(02), pp.09-16.
9. Blagden, N., de Matas, M., Gavan, P.T. and York, P., 2007. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. Advanced drug delivery reviews, 59(7), pp.617-630.
10. Singh, M.C., Sayyad, A.B. and Sawant, S.D., 2010. Review on various techniques of solubility enhancement of poorly soluble drugs with special emphasis on solid dispersion. J Pharm Res, 3(10), pp.249-250.
11. Noor, R., Hasan, S.M.F. and Khalid, F., 2018. Pharmaceutical techniques for the fabrication of poor water soluble drugs–a review. Baqai Journal of Health Sciences, 21(1), pp.77-86.
12. Brahmankar, D.M. and Jaiswal, S.B., 2005. Biopharmaceutics and pharmacokinetics: A treatise. Vallabhprakashan.
13. Leuner, C. and Dressman, J., 2000. Improving drug solubility for oral delivery using solid dispersions. European journal of Pharmaceutics and Biopharmaceutics, 50(1), pp.47-60.
14. Kumar, S. and Singh, P., 2016. Various techniques for solubility enhancement: An overview. The Pharma Innovation, 5(1, Part A), p.23.
15. Kumar, R.S. and Yagnesh, T.N.S., 2016. Solid dispersions: An approach to enhance solubility of poorly soluble drugs. Indo Am J Pharm Res, 5(11), pp.7036-56.
16. Song, I.S., Cha, J.S. and Choi, M.K., 2016. Characterization, in vivo and in vitro evaluation of solid dispersion of curcumin containing d-α-Tocopheryl polyethylene glycol 1000 succinate and mannitol. Molecules, 21(10), p.1386.
17. Craig, D.Q., 2002. The mechanisms of drug release from solid dispersions in water-soluble polymers. International journal of pharmaceutics, 231(2), pp.131-144.
18. Vasconcelos, T., Sarmento, B. and Costa, P., 2007. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug discovery today, 12(23-24), pp.1068-1075.
19. Dhiman, S., Kaur, P. and Arora, S., 2012. Solid Dispersions: Opportunity in Drug Delivery System. Drug Invention Today, 4(10).
20. Tagalpallewar, V.R., Ughade, M.A., Indurwade, N.H., Kubare, P.G. and Chintawar, A.A., "Enhancement of Solubility of poorly water soluble drug by solid dispersion.
21. Joshi, M., Tiwari, G., Tiwari, R., Agarwal, N. and Goyal, A., 2012. Solid dispersion: an updated review. Journal of drug discovery and development, 1(1), p.4.
22. Manogna, K., Nagaveni, P. and Thyagaraju, K., 2017. Enhancement of solubility of poorly soluble drugs by solid dispersion: An overview. Indian Journal of Pharmaceutical and Biological Research, 5(04), pp.17-23.