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Improvement of Solubility and Oral Bioavailability of Itraconazole by its Oral Solid Dosage Form Fabrication Using Suitable Pharmaceutical Excipients

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Conflicts of Interest: **Nil**
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ABSTRACT

The objective of this study was to develop fast dissolving Itraconazole tablets using suitable excipients to improve solubility and enhance the oral absorption of Itraconazol and match *in vitro* drug dissolution profile with Sporonax. The combination of the various solubilizer and hydrophilic surfactants like Poloxamer 188, polysorbate 80 and Polyoxyl 35 castor oil (HLB 12-14) were used in the present study. Nine formulations (A1, A2, A3, B1, B2, B3, C1, C2, and C3) were prepared and characterized. Combinations having different HLB values were evaluated, as the major solubility enhancing excipients and surfactants which also facilitate the lymphatic absorption. The formulations were so designed that they form colloidal emulsion on contact with water or GI fluids. This colloidal emulsion also increases the permeability through GI membrane. The optimized tablet formulations were suitably packaged in HDPE and subjected to accelerated stability testing as per the ICH guidelines.

The optimized composition of tablet formulation C3 containing Poloxamer 188 and polysorbate 80, in ratio 2:1 and lactose monohydrate (as the diluents) which was designed in the present study to arrive at a formulation that shows comparable *in vitro* dissolution rate to Sporonax. Accelerated stability study on the optimized composition in HDPE packaging further demonstrated no adverse changes occur in the formulation when evaluated for parameters such as disintegration time, drug content and *in vitro* dissolution.

Keyword: Itraconazol, fast dissolving tablet, Poloxamer 188, polysorbate 80, Polyoxyl 35

Introduction

Oral formulation has been the preferred and most common route of drug delivery around the globe. The popularity of this dosage form is owing to its ease of administration and good patient compliance. From drug development and formulation perspective, a solid dosage form offers superior stability compared to intravenous formulation. Therefore, most of the new chemical entities (NCE) under development these days are intended to be used in solid dosage form that originate an effective and reproducible in vivo plasma concentration after oral administration. But for many drugs, formulation of solid dosage form can be an inefficient mode for administration as approximately 40% or more of the NCE being generated through drug discovery programs have problem in water solubility. [1]

Solubility also plays a major role for other dosage forms like parenteral formulations as well. Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for achieving required pharmacological response. Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Low aqueous solubility is the major problem

encountered with formulation development of new chemical entities as well as generic development. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. Water is the solvent of choice for liquid pharmaceutical formulations. Most of the drugs are either weakly acidic or weakly basic having poor aqueous solubility.[2]

More than 40% NCEs (new chemical entities) developed in pharmaceutical industry are practically insoluble in water. These poorly water soluble drugs having slow drug absorption leads to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. For orally administered drugs solubility is the most important one rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. Problem of solubility is a major challenge for formulation scientist. [3]

The improvement of drug solubility thereby its oral bio-availability remains one of the most challenging aspects of drug development process especially for oral-drug delivery system. There are numerous approaches available and reported in literature to enhance the solubility of poorly water-soluble drugs.[4] The techniques are chosen on the basis of certain aspects such as properties of drug under consideration, nature of excipients to be selected, and nature of intended dosage form. [5]

MATERIAL AND METHODS

Itraconazole was procured from M/s Themis Laboratories Pvt. Ltd., Thane (manufactured by Cadila Healthcare Ltd, Batch no: PX/001/7010, Mfg. Jun. 2010).

The various excipients used in the preparation of immediate-release tablets of Itraconazole with their intended function are indicated in table 1.

Table 1: Excipient for Preparation of Itraconazole

S.N.	Excipients	Trade Name	Make	Function in Formulation
1.	Poloxamer 188	Lutrol®F 68	BASF	Solubilizer/emulsifier
2.	Medium chain triglycerides	Captex® 335	Abitec	Surfactant
3.	Polyoxyl 35 castor oil	Cremophor® EL	BASF	Surfactant
4.	Polysorbate 80	Tween® 80	Merck	Surfactant
5.	Spray dried lactose	Lactopress®	DMV	Diluent
6.	Magnesium stearate	Synpro®	Ferro	Lubricant/antiadherent
	Citric acid			Acidifying agent

The various equipments used in the present study with their purpose are indicated in table 2.

Table 2: Equipments Used in the Preparation of Itraconazole Tablet

S.N.	Equipment	Purpose
1	Material holding tank equipped with facility for spraying molten mass	To melt the lipid, to maintain constant temperature and for spraying
2	Vibratory sifter and sieves of various size	Sieving and grading of granules
3	Fluid bed equipment	To spray the granules
4	Blender	Blending
5	Tablet machine	Compression of tablets

Physical characteristics and other details of reference product used in this study are mentioned in table 3.

Table 3: Details of Reference Product Used in Study

S.N.	Reference Product	Details
1	Brand name	Sporanox
2	Strength	100 mg
3	Manufactured by	Johnson and Johnson
4	Lot no	----------
5	NDC No.	----------
6	Appearance	White to uncoated tablet
7	Thickness	----------
8	Weight	----------
9	Tablet hardness	----------

Methods

Preparation of itraconazole granules and tablets

The various steps involved in the formulation of immediate release Itraconazole tablets were as under –

- Preparation of molten mass of Itraconazole and suitable hydrophilic surfactants and/or lipids.
- Spray congealing the above molten mass in a top spray fluid processor.
- Sieving the spray congealed mass through 80 mesh.
- Blending the spray congealed particles with extra granular excipients.
- Compression into tablets.

The qualitative and quantitative composition of different prototype formulation was as under.

1. ***Prototype Formulation A:*** These prototypes contained combination of Poloxamer 188 as surfactant and solubility enhancer, medium chain triglycerides as the lipidic excipient ,citric acid as acidifying agent, Magnesium Stearate as lubricant and spray dried lactose as the diluent.

2. ***Prototype Formulation B:*** These prototypes contained combination of Poloxamer 188 and polyoxyl 35 castor oil as hydrophilic surfactants and solubility enhancing excipients, citric acid as acidifying agent and spray dried lactose as the diluent.

3. ***Prototype Formulation C:*** These prototypes contained combination of Poloxamer 188 and polysorbate 80 as hydrophilic surfactants and solubility enhancing excipients, citric acid as acidifying agent and spray dried lactose as the diluent.

Physicochemical Evaluation of Tablet

Average weight of tablets, Tablet hardness, Tablet thickness, Friability (100 revolutions), dissolution etc.

Magnified photographs of rapid-release spray congealed Itraconazole granules of all the formulation prototypes were taken using digital microscope Intelplay QX3 attached to a personal computer. The photographs were used to examine the surface morphology of spray congealed particles.

Results and Discussion

In the present study, an attempt was to fabricate and evaluate fast dissolving Itraconazole tablets with the prime objective of enhancing the solubility of Itraconazole and match *in vitro* drug dissolution profile with Sporonax. The combination of the various solubilizer and hydrophilic surfactants like Poloxamer 188, polysorbate 80 and Polyoxyl 35 castor oil (HLB 12-14) were used in the present study.

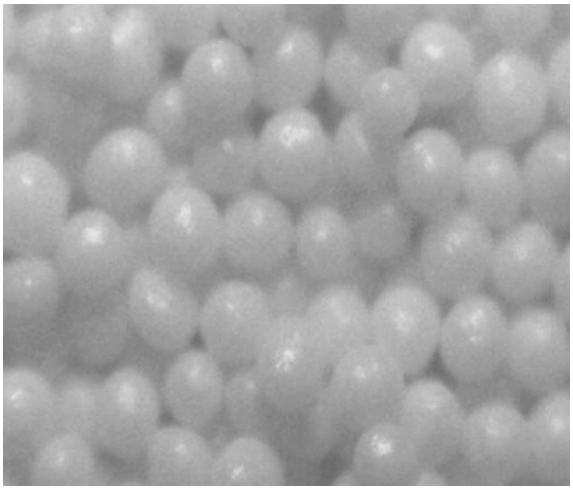
Combinations having different HLB values were evaluated, as the major solubility enhancing excipients and surfactants which also facilitate the lymphatic absorption. The formulations were so designed that they form colloidal emulsion on contact with water or GI fluids. This colloidal emulsion also increases the permeability through GI membrane.

The optimized tablet formulations were suitably packaged in HDPE and subjected to

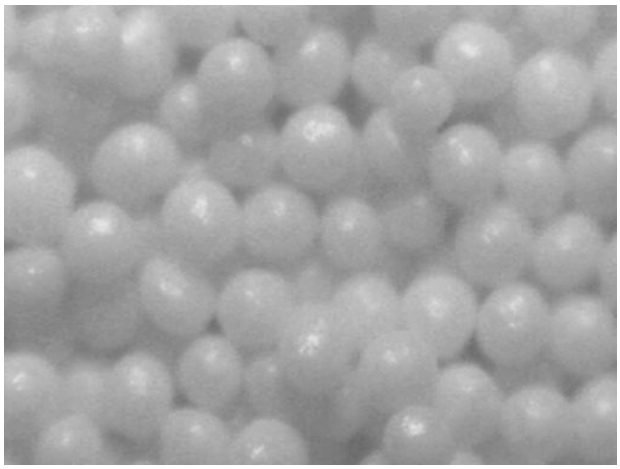
accelerated stability testing as per the ICH guidelines. The subsequent paragraph discusses the results obtained from the present investigations.

Stereomicrography of Spray Congealed Itraconazole Particles

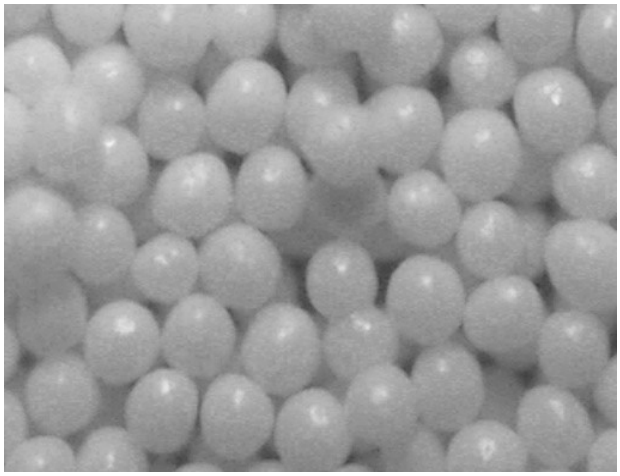
Stereophotomicrography of rapid-dissolving Itraconazole spray congealed particles revealed that pellets with all the 4 solid dispersion compositions had smooth and glossy surface. However, the surface of pellets coated with poloxamer alone was glossier owing to presence of waxy but hydrophilic surfactant (formulation C). The smooth surface morphology of the pellets is an indication of uniformity and integrity of drug-polymer deposition on the inert core pellets (i.e. freedom from flaws). *See* figures 1.A to 1.C.



Pellets A



Pellets B



Pellets C

Figure 1. Stereomicrographs of fast dissolving Itraconazole spray congealed particles (magnification 200 X)

Physical Attributes of Prototype Itraconazole Tablets

Average weight, tablets thickness, tablet hardness, percent friability and Disintegration time of the prepared prototypes are presented in table 4. Water was used as the immersion fluid for testing the disintegration time of the Itraconazole immediate release tablets; previously maintained at temperature of 37^0C.

Table 4: Physical Characteristics of Itraconazole rototype Tablets

Parameter of Tablets	Unit	Prototype Formulations A1	A2	A3	B1	B2	B3	C1	C2	C3
Average Weight	mg	700	700	700	700	700	700	700	700	700
Average Thickness	mg	5.37	5.23	5.35	5.34	5.39	5.41	5.35	5.37	5.38
Hardness	Kp	5-6	5-6	5-6	6-7	6-7	6-7	6-7	6-7	6-7
Friability (100 revol.)	%	0.18	0.14	Nil	0.2	0.21	0.12	0.03	0.12	0.06
Disintegration Time	min	12-14	12-14	13-18	11-15	12-16	14-20	12-16	13-17	14-19

All the prepared tablets formulations of Itraconazole had satisfactory physical characteristics and were mechanically strong enough to withstand the rigours of handling, packaging, storage and transportation. Furthermore, they also disintegrate in less than 30 minutes.

Particle Size of Itraconazole Prototypes Aqueous Dispersion

The particle size distribution of the Itraconazole granules aqueous dispersion has been presented in percentile form in table 5 through 7. Particle size of prototypes C were considered as the optimized formulation since they provided smallest particle size D_{90} (514) nm which qualify the colloidal dispersion benchmark.

Table 5: Particle Size Distribution of Prototype A Aqueous Dispersions

Particle size distribution	Prototype A formulations A1	A2	A3
D i (10) nm	1400	1800	1600
D i (50) nm	Above 2000	Above 2000	Above 2000
D i (90) nm	Above 2000	Above 2000	Above 2000

Table 6: Particle Size Distribution of Prototype B Aqueous Dispersions

Particle size distribution	Prototype B formulations B1	B2	B3
D i (10) nm	1000	1200	1800
D i (50) nm	Above 2000	Above 2000	Above 2000
D i (90) nm	Above 2000	Above 2000	Above 2000

Table 7: Particle Size Distribution of Prototype C Aqueous Dispersions

Particle size distribution	Prototype C formulations C1	C2	C3
D i (10) nm	1400	1100	199
D i (50) nm	2000	1500	339
D i (90) nm	Above 2000	2000	514

***In Vitro* Dissolution of Prototype Itraconazole Tablets**

In vitro drug dissolution of Itraconazole formulation of prototypes A, B and C along with Sporonax are given in table 8, 9 and 10 respectively.

Table 8: Comparison of Dissolution Profile of Prototype A Formulations with Sporonax

Sampling interval (min)	% Dissolution Sporonax *vs* Prototype A*			
	Sporonax	A1	A2	A3
15	39.59	25.23	38.23	39.01
30	60.0	31.7	46.45	47.89
45	73.6	36.7	50.22	51.62
60	86.8	41.7	54.07	55.87
90	100.01	45.67	56.87	57.04
f_2 value	-	**20.8**	**28.36**	**29.07**

** Results are mean of 6 readings*

Table 9: Comparison of Dissolution Profile of Prototype B Formulations with Sporonax

Sampling interval (min)	% Dissolution Sporonax *vs* Prototype B*			
	Sporonax	B1	B2	B3
15	39.59	30.23	30.83	30.01
30	60.0	41.1	45.4	48.9
45	73.6	48.9	57.0	60.42
60	86.8	53.1	60.17	64.0
90	100.01	58.9	62.17	66.12
f_2 value	-	**27.74**	**31.64**	**34.62**

** Results are mean of 6 readings*

Table 10: Comparison of Dissolution Profile of Prototype C Formulations with Sporonax

Sampling interval (min)	% Dissolution Sporonax *vs* Prototype C*			
	Sporonax	C1	C2	C3
15	39.59	36.43	37.71	39.11
30	60.0	50.1	53.9	56.29
45	73.6	61.22	68.72	71.5
60	86.8	67.07	77.45	84.0
90	100.01	73.19	82.59	98.73
f_2 value	-	**39.02**	**50.89**	**79.55**

** Results are mean of 6 readings*

Figure 2, 3 and 4 illustrates the *in vitro* dissolution profile of Itraconazole prototype A, B and C formulations respectively. It can be seen that the in vitro dissolution curve of formulation C3 is nearly superimposable to that obtained with reference product.

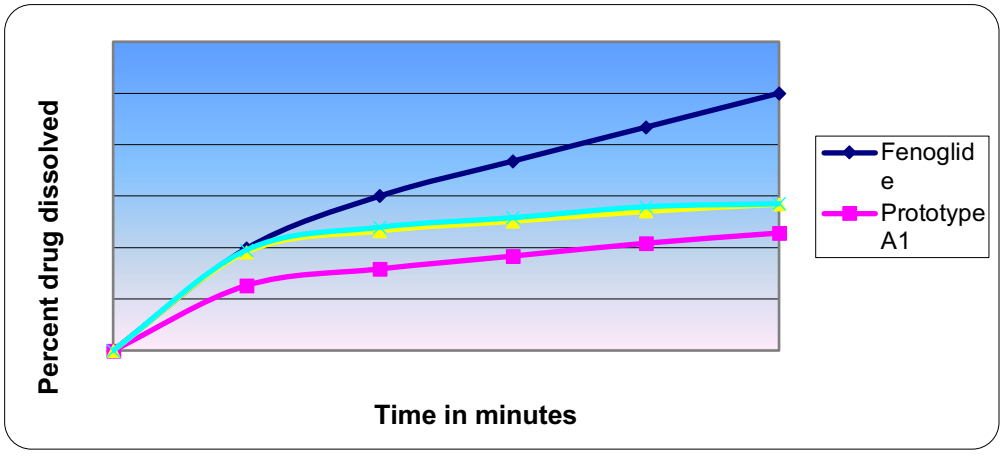


Figure 2. Comparative *in vitro* dissolution profile of prototype A versus Sporonax

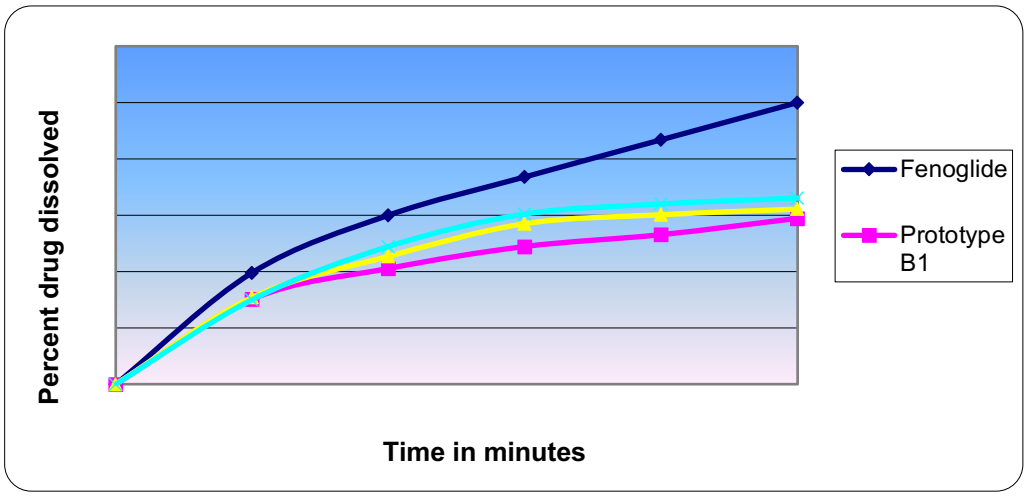


Figure 3. Comparative *in vitro* dissolution profile of Prototype B versus Sporonax

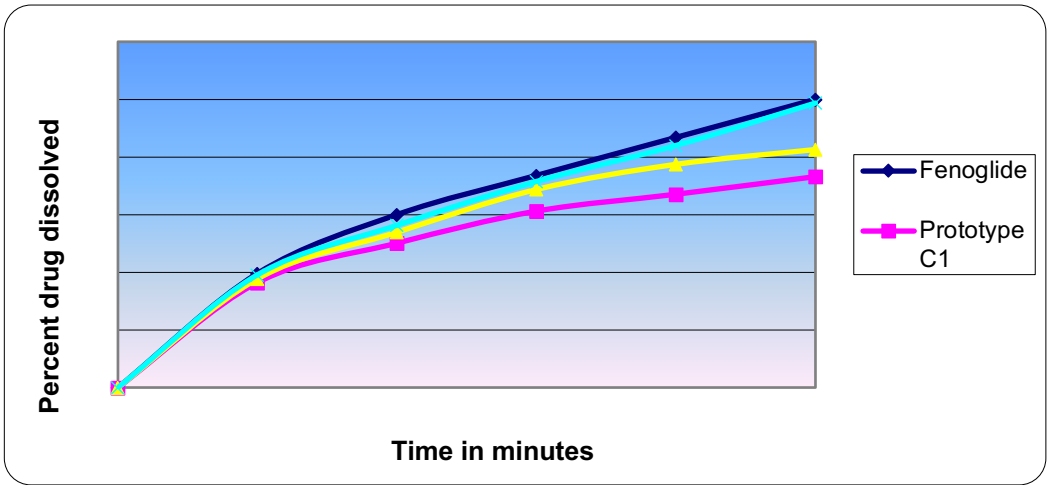


Figure 4. Comparative *in vitro* dissolution profile of Prototype C versus Sporonax

A direct influence of combination of solubilizer and hydrophilic surfactants type and their amount on the release profile of Itraconazole tablets was observed. All the tested prototype formulations A1 through A3 containing combination of the Poloxamer 188 (constant quantity) as the surfactant and (varying quantity) of medium chain triglycerides (lipidic vehicle) demonstrated that drug release was dependent upon concentration of surfactant. The ones that contained lesser surfactant (formulation A1) showed slower drug release. In case of formulation A3, which contained greater amount of surfactant as compared to formulation A1, an improved dissolution trend was observed as expected. However, the improvement in drug dissolution was inadequate in comparison to reference product.

Prototype B formulations were designed with an intent to obtain enhanced drug release which will be comparable to Sporonax using combination of Poloxamer 188 (constant quantity) and polyoxyl 35 castor oil (variable) as surfactants but surprisingly the dissolution of these prototypes was also slow.

In case of prototype C formulations that contained combination of Poloxamer 188 (constant quantity) and polysorbate 80 (variable) as surfactant having HLB around 14, all the tested prototype formulations C1 through C3 demonstrated enhancement of drug release. Drug release was dependent upon the content of the surfactant. Formulation C1 which contained the lowest surfactant content showed a protracted drug release, formulation C2 that contained intermediate quantity of surfactant demonstrated higher drug release compared to

C1 while the last prototype, formulation C3, containing highest content of surfactant showed enhanced drug release and comparable with Sporonax. Thus the system containing the combination of Poloxamer and polysorbate 80 having ratio about (1:0.52) gives D i (90) nm 514 nm and drug release was comparable with Sporonax

All the prototype formulation on dissolution formed emulsions which gives drug release comparable to Sporonax in 15 minutes. However, as the time increases, dissolution rate of drug remains constant or increases marginally until 90 minutes in case of prototypes A and B. This indicates that upon contact with dissolution media, formulations A1 to A3 and B1 to B3 form emulsions which have poor thermodynamic stability and eventually drug particle size in dispersion increases. This was not observed in the case of the prototype C3 formulation where the drug dissolution enhances with time indicating good thermodynamic stability of microemulsion or drug dispersion produced on contact with aqueous fluids.

Similarity factors (f_2 values) were also determined for all the prepared prototype of Itraconazole formulations in order to derive conclusion with regards to closeness of drug release of a given formulation to the drug release shown by innovator product Sporonax Although all the C-type formulations were better in comparison to A and B type designs, which became evident from f_2 values, formulation C3 was the best of all since its f_2 value was the greatest.

Stability Studies on Optimized Prototype Itraconazole Tablets

After one and three months of storage at 40˚C and 75% RH in HDPE container, the moisture content of Itraconazole tablet formulation remained almost at the initial level of less than 2.0% w/w (at 60˚C). Itraconazole content and *in-vitro* dissolution of stability samples were analysed and showed little or no change in drug release. Itraconazole content of prototype C3 stored at elevated storage condition as given in table 11 which is indicative of good stability of the dosage form in HDPE container.

Table 11: Stability Data of ItraconazoleTablets Prototype C3

Time	Appearance	Assay	% Drug release in minutes				
			15	30	45	60	120
Initial	White to off-white colour capsule shape tablet	99.83	39	56	56	80	98
1M, 40°C/75%RH	No change	98.80	38	55	55	80	98
3M, 40°C/75%RH	No change	98.91	38	55	55	79	97

**M: Month*

The combination of the solubilizer Poloxamer 188 and various lipids/surfactants like medium chain triglycerides, polysorbate 80 and polyoxyl 35 castor oil were used in the present study to prepare Itraconazole particles by spray congealing, with the objective of producing drug-excipient particles having improved dissolution rate in aqueous milieu. Combinations of Poloxamer and different surfactant having different HLB values were evaluated, as the major solubility enhancing excipients which also facilitate the lymphatic absorption and avoid first-pass hepatic metabolism. Citric acid creates micro environment which helpful in improving dissolution of drug. The formulation were so designed that they form stable colloidal emulsion (nanosized) on contact with water or GI fluids which increases drug solubility facilitates permeability through GI membrane.

However, the major deciding factor in the selection of optimum formulation was size distribution of particles produced on dilution with aqueous fluids and their stability (preferably nanosized) and the *in vitro* drug dissolution rate. It can be concluded that

formulation containing poloxamer 188, polysorbate 80 ratio about (2:1) provides the smallest and stable particle size of dispersed formulation.

Poloxamer 188 (HLB >24) forms eutectic mixture with Itraconazole in molten state which become less viscous on addition of polysorbate 80. This sprayable molten mass was spray congealed in fluidized counter-cooled air chamber. Spray congealed granules are then sieved and mixed with spray-dried lactose and lubricant and compressed into tablets. The molten mixture of Poloxamer and Itraconazole and polysorbate 80 forms eutectic mixture with Itraconazole and on spray congealing of the molten mass, the molecular arrangement of drug and solubilizing excipients favour increase surface free energy of particles that are formed in aqueous dispersion that have comparatively improved thermodynamically stability and which eventually facilitates improved *in vitro* drug dissolution rate. Both Poloxamer and polysorbate 80 improve wettability coupled with micellar solubilization and stabilizes emulsion on contact with water or GI fluids. Polysorbate 80 (HLB 15) proved to be better than Cremophor EL (HLB 12-14) in providing the optimized formulation. Polysorbate 80 is relatively more hydrophilic and less viscous as compared to polyoxyl 35 castor oil which might have favoured better rate of drug dissolution of the product and hence prototype C3 was considered the best of all formulations designed.

Conclusions

Thus, the optimized composition of tablet formulation C3 containing Poloxamer 188 and polysorbate 80, in ratio 2:1 and lactose monohydrate (as the diluents) which was designed in the present study to arrive at a formulation that shows comparable *in vitro* dissolution rate to Sporonax. Accelerated stability study on the optimized composition in HDPE packaging further demonstrated no adverse changes occur in the formulation when evaluated for parameters such as disintegration time, drug content and *in vitro* dissolution.

References

1. Kumar, N, Jain, A K, Singh, C, Agrawal, K, Nema, R K, Development, characterization and solubility study of solid dispersion of terbinafide HCl, Int J Pharm sci, Nanotech, 2008,1, 171-176.
2. Vemula, VR, Lagishetty, V, Lingala, S, Solubility enhancement techniques, International Journal of Pharmaceutical Sciences Review and Research, 2010, 5(1), 41–51.
3. Lipinski C.A, Lombardo F, Dominy B.W, Feeney P.J, Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings, Adv. Drug Deliv. Rev. 23 (1997) 3–25
4. Sharma, D, Soni, M, Kumar S, Gupta GD, Solubility enhancement—eminent role in poorly soluble drugs, Research Journal of Pharmacy and Technology, 2009,2(2),220–224.
5. Kumar, A, Sahoo, SK, Padhee, K, Kochar, PS, Sathapathy, A, Pathak, N, Review on solubility enhancement techniques for hydrophobic drugs, Pharmacie Globale, 2011,3(3),001–007.
6. Hite, M, Turner, S, Federici, C. Part 1: Oral delivery of poorly soluble drugs, Pharmaceutical Manufacturing and Packing Sourcer Summer, 2003, 38-40.
7. Hauss D.J, Oral lipid-based formulations – enhancing the bioavailability of poorly water soluble drugs, Informa Healthcare, New York, 2007.
8. Yogesh, S, Thorat, Indrajeet, D, Gonjari, and Avinash, H, Hosmani, Solubility Enhancement Technique: A Review on conventional and novel approaches, IJPSR, 2011, 2(10), 2501-2513.
9. Guidance for industry, "Dissolution testing for immediate release solid oral dosage forms,"FDA,August 1997.
10. Yasir Mohd, Asif Mohd ,Kumar Ashwin, Biopharmaceutical Classification System:An Account, International Journal of PharmTech Research Vol.2, No.3, (July-Sept 2010)1681-1690.
11. Patel, M., Patel, S., Patel, N., Patel, M., A review of novel oral lipid Oral based

formulation for poorly soluble drugs, ***Int. J. Pharm. Sci. Nanotech***., 2011,3,4,1182-1192.
12. Khar R K, Pandita D, "Biopharmaceutical classification system and its importance, "The Indian Pharmacist. March 2005, 25-30.
13. Mark, G, Pharmaceutical preformulation and formulation. A practical guide from candidate drug selection to commercial dosage form, Interpharm./CRC, New York, 2004,21- 95.
14. Rawlins, E.A., Bentley's text book of pharmaceutics, 8th ed., 1992,11.
15. Brahmankar, D.M., Jaiswal, S.B., *Biopharmaceutics and Pharmaceutics – A Treatise*, Vallabh Prakashan, Delhi, 1995
16. Testa B, Caldwell J, Prodrugs revisited: The ''ad hoc'' approach as acomplement to ligand design, Med. Res. Rev. 16 (1996) 233–241.
17. Lachman, L, Lieberman, H, Kanig, JL, The Theory And Practise of Industrial Pharmacy, 3rd edition, Lea & Febiger, 1986, 457-478.
18. The United States Pharmacopeia, USP 30-NF 25, 2007
19. Amidon, GL, Lennernäs, H, Shah, VP, Crison, JR., A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability, Pharmaceutical Research, 1995, 12(3), 413–420.
20. Brahmankar D.M., Jaiswal, Sunil B., Bio pharmaceutics and Pharmacokinetics A Treatise, Vallabh prakashan, 2009, 349-353.