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Preparation, optimization and characterization of controlled release mucoadhesive microspheres containing highly variable drug Itraconazole in reducing gastric variability as compared to innovator formulation

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ABSTRACT

Oral candidiasis is one of the most common, treatable oral mucosal infections seen in persons with human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS). Oral candidiasis can be a frequent and significant source of oral discomfort, pain, loss of taste, and aversion to food. Candida albicans carriage and a history of oral candidiasis are other significant risk factors for oral candidiasis. For the normal healthy patient, the treatment of oral candidiasis is relatively simple and effective. Itraconazole (ITCZ), a poorly soluble drug is quiet effective in treatment of oral candidiasis. ITCZ belong to class IV of biopharmaceutical classification system and falls in category of highly variable drugs. A controlled release formulation of ITCZ has been developed in the form of mucoadhesive microspheres. A 3^2 factorial design has been constructed to extract best formulation. Parameters such as peppas model, hixon-crowell model, first order, zero order and matrix diffusion were studied. The optimized formulation was studied for pharmacokinetic behavior in terms of AUC, C_{max} and t_{max}. The results shows that when the drug is released in a controlled manner the intra patient variability has been considerably reduced as compared to the drug released in immediate fashion. The C_{max}, AUC and t_{max} for test and reference formulations was found to be 89 to 112.1 and 73.2 to 136.2, 79.9 to 106.4 and 81.6 to 141.4 and 90.1 to 118 and 68.3 to 88.4 respectively.

INTRODUCTION

Oral candidiasis is one of the most common, treatable oral mucosal infections seen in persons with human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS) [1]. Oral candidiasis can be a frequent and significant source of oral discomfort, pain, loss of taste, and aversion to food. Candida albicans carriage and a history of oral candidiasis are other significant risk factors for oral candidiasis [2]. The infection is caused by Candida albicans, a dimorphic fungal

organism that typically is present in the oral cavity in a non-pathogenic state in about one-half of healthy individuals. Normally present as a yeast, the organism, under favorable conditions, has the ability to transform into a pathogenic (disease causing) hyphael form. Conditions that favor this transformation include broad-spectrum antibiotic therapy, xerostomia, immune dysfunction (secondary to systemic diseases such as diabetes or the use of immune suppressant medications), or the presence of removable prostheses. Unless the patient is severely immunocompromised, the infection is generally limited to the superficial mucosa and skin. Invasive candidiasis infection is rare, with disseminated disease even more so. This superficial nature of the infection makes oral candidiasis so amenable to treatment. Several antifungal agents can be used topically. For topical agents, successful therapy depends on adequate contact time (2 minutes) between the agent and the oral mucosa. Treatment duration varies from 7 to 14 days, with therapy minimally continued for 2 to 3 days beyond the last clinical signs and symptoms. Topical agents have the benefit of few side effects at normal therapeutic doses because of their lack of gastrointestinal absorption. However, sucrose containing topical agents can be carcinogenic when used over prolonged time periods [3], such that adjunctive topical fluoride therapy may be needed. Systemic antifungals have the advantage of once-daily dosing and simultaneous treatment of fungal infections at multiple body sites. However, these antifungals have more side effects, and selection requires consideration of important drug interactions. The dental hygienist can play an important role in the education of patients to prevent recurrence. For many years, amphotericin B deoxycholate remained the mainstay of treatment for IFIs [4]. Systemic prescription antifungal agents include ketoconazole [5], fluconazole [6], and Itraconazole [7, 10].

The major limitations of its usage are the substantial adverse effects such as fever, chills, nausea and vomiting, electrolyte abnormalities and, most importantly, nephrotoxicity [8]. In the 1990s, the introduction of the two azoles fluconazole and itraconazole represented a considerable advance in antifungal therapy. However, the use of fluconazole is hampered by its narrow spectrum, and the use of itraconazole is limited due to absorption problems [9, 10]. New therapeutic agents have now been developed that provide better antifungal activities and lower toxicities. Mucoadhesive buccal films and controlled release oral preparations can be a better option for drug delivery of antifungal agents [11, 12, 13].

Bioequivalence studies are generally conducted by comparing the *in vivo* rate and extent of drug absorption of a test and a reference drug product in healthy subjects. In a standard *in vivo* bioequivalence study design, participants receive a single dose of test and reference products on separate occasions with random assignment to the two possible sequences of product administration. Samples of an accessible biologic fluid such as blood or urine are analyzed for drug concentrations, and pharmacokinetic measures such as area under the curve (AUC) and peak concentration (C_{max}), are obtained from the resulting concentration-time profiles. To evaluate bioequivalence, the U.S. Food and Drug Administration (FDA) has employed a testing procedure termed *the two one-sided tests procedure* to determine whether the average values for the pharmacokinetic measures from the test and reference products are comparable. This procedure involves the calculation of a confidence interval for the ratio between the average values of the test and reference product. In the U.S., a test product is considered to be bioequivalent to a reference product if the 90% confidence interval of the geometric mean ratio of AUC and C_{max} between the test and reference fall within 80-125%. Currently, the bioequivalence limits of 80-125% have been applied to almost all drug products by

the FDA. An approach to prepare sustained release preparations using polymers can be useful in reducing variability between subjects [14].

MATERIALS AND METHODS

The drug Itraconazole, Carbopol 934P, Ethyl Cellulose and Hydroxy propyl Methyl Cellulose was procured as a gift samples from Zydus Cadila Healthcare ltd. Ahmedabad, India. Other reagents were of Analytical grade.

Preparation of bioadhesive Microspheres:
ITCZ gastro retentive microspheres were prepared by emulsification method. 5.0 gm of Ethyl cellulose was dissolved in 60 ml of Dichloromethane and 40 ml of dehydrated alcohol (90%). To this solution mixture 3.0 gm of Itraconazole and 1.2 gm of Carbopol 934P powder was added under magnetic stirring and mixture was blended for 24 hr. Then the suspension was slowly dispersed in 250 ml of light liquid paraffin containing 7.5 gm Span 80 at a stirring rate of 600 rpm. After 30 min. of emulsification, solvents were evaporated gradually with the help of water-circulating vacuum pump until the microspheres were formed. The system temperature was kept at 20°C all through the process. The microspheres were washed with petroleum ether and vacuum dried at room temperature. Microspheres with diameter range 400 to 1000 µm were obtained.

Factorial design and Optimization:
Design of experiment (DOE) has been widely used in pharmaceutical field to study the effect of formulation variables and their interactions on response variables. In this study, a 3^2 full factorial design was used. The polynomial equations were used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e. positive or negative). The high value of correlation coefficient for the dependent variables indicates a good fit. A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses as per equation

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \beta_{11} X_1^2 + \beta_{22} X_2^2$$

Where, Y is the dependent variable, β_0 is the arithmetic mean response of nine runs.

A 3^2 full factorial design was constructed where the mucoadhesive polymer concentration (X_1) and stirring speed (X_2) were taken as independent variables. Percent microencapsulation efficiency, particle size, time taken to release 50% (t_{50}) of drug was taken as the response variables (dependent variables) (Table 1 and 2)

Table 1. Factorial combinations of various mucoadhesive miocrospheres.

Coded factor	Level	Mucoadhesive Polymer Conc. (mg) (X_1)	Stirring speed (rpm) (X_2)
-1	Low	500	500
0	Medium	1000	1000
1	High	1500	1500

Table 2. Factorial combinations of ITCZ-HPMC5CP based microspheres

Std No.	Formulation ID	Run No.	Factor1 A: Mucoadhesive Polymer Conc. (mg)	Factor2 B: Stirring speed (rpm)	Factor coded
1	ITCZ-HPMC5CP1	9	1500	1000	(1, 0)
2	ITCZ-HPMC5CP2	7	500	1500	(-1, 1)
3	ITCZ-HPMC5CP3	4	1500	500	(1, -1)
4	ITCZ-HPMC5CP4	6	1000	1500	(0, 1)
5	ITCZ-HPMC5CP5	8	500	500	(-1, -1)
6	ITCZ-HPMC5CP6	3	1000	1000	(0, 0)
7	ITCZ-HPMC5CP7	5	1500	1500	(1, 1)
8	ITCZ-HPMC5CP8	2	1000	500	(0, -1)
9	ITCZ-HPMC5CP9	1	500	1000	(-1, 0)

Evaluation parameters for Microspheres:

1. Shape and surface morphology: The surface characteristics were examined by means of Scanning electron microscopy (SEM Philips XL-30 equipped with an image analysis system). Photographs of each freshly prepared batch were taken with a Canon Power Shot A60 digital camera with 1600 · 1200 pixel of magnification.

2. Determination of particle size and size distribution: Particle size was determined by optical microscopy method using calibrated ocular eyepiece. Effects of process variables i.e., drug concentration, polymer concentration, stirring rate and stirring time on particle size and size distribution was studied.

3. Microencapsulation efficiency: Entrapment efficiency was determined after removal of surface anchored drug. The surface anchored drug was removed by dispensing accurately weight amount of microspheres in 10 ml of PBS pH 7.4 for 10 min. with occasional shaking. The suspension was centrifuged at 3000 rpm for 5 min. and the supernatant was kept aside. The sedimented microspheres were retreated in the same manner and supernatant of this centrifuge was mixed with first supernatant and drug concentration was determined spectrophotometrically.

4. *In vitro* drug release: Drug release study was carried out using modified USP dissolution test apparatus. The scheme of using simulated fluids at different pH was 1st hr – simulated gastric fluid pH 1.2, 2nd and 3rd hr – mixture of SIF and SGF pH 4.5, 4th and 5th hr – SIF pH 6.8 and 6th hr – pH SIF 7.5. Cross linked microspheres bearing drug were suspended in dissolution media at 37±0.1°C. Samples were withdrawn periodically and compensated with same amount of fresh dissolution media. The samples were analyzed for drug content by measuring absorbance using UV spectrophotometer.

5. Drug release kinetics: To describe the kinetics of drug release from the mucoadhesive microspheres, mathematical models such as zero order, first order, Higuchi's, Hixson-Crowell's and Peppas models were used. The criterion for selecting the most appropriate model was chosen on the basis of a goodness-of-fit test.

***In vivo* studies:**

The critical survey of various analytical methods revealed that with regard to sensitivity, reproducibility and feasibility of estimating the drug both in dosage forms as well as in biological medium, the HPLC based methods are superior. Therefore, HPLC method was selected for estimation of Itraconazole in blood plasma because of the advantage that the method could be used for the determination of the drug. Accurately weighed 5 mg of Itraconazole were weighed in Citizen electronic balance 9 New Delhi, India) and transferred separately in clean and dry 50 ml volumetric flasks and dissolved in the minimum volume of methanol. The volume was made upto 100 ml with water. One ml of above solution was taken in 10 ml volumetric flask, and 200 µl of plasma was added to it. The content extracted with 2.5 ml of acetone by centrifugation (Remi, India) at 2000 rpm for 10 min. two ml of supernatant was taken in a boiling tube and vacuum evaporated at 45°C in vacuum oven. The residue was dissolved by adding 0.5 ml of mobile phase [Buffer solution : Acetonitrile = 50 : 50 v/v], mixed thoroughly and centrifuged again for 10 min for 2000 rpm. An aliquot (0.5 ml) of organic layer was evaporated and residue was again dissolved in 2 ml of mobile phase. The sample solution was filtered through 0.2 µm filter (Millipore, India) and injected in the loop of HPLC. The HPLC instrument (Shimadzu, Japan) comprising of pump LC-10AT-vp equipped with universal injector 77251 (Rheodyne) with an injection volume of 20 µl, SPD-10A-vp with variable wavelength UV-Visible detector (Shimadzu) and Shimadzu class-vp software version 5.03, A C-18 reverse phase column (Luma, particle size -5 µ, column size 250 x 4 mm) was used. The flow rate was kept at 2 ml/min and absorbance was measured at 265 nm for the drug. The collected blood samples after each interval were centrifuged at 5000 rpm for 10 minutes to separate the plasma. To 150 µl of plasma, equal volumes of acetonitrile was added and kept for 30 minutes. The mixture was centrifuged at 5000 rpm for 10 minutes and the supernatant was filtered through 0.22 µm membrane filters (Millipore, India).The plasma concentration of drug was determined using HPLC method as described previously. The plasma concentration was recorded and shown graphically in Figure 1 – 12. A bioequivalence study (six treatment, six period, single dose, parallel study) on formulations (ITCZ-HPMC5CP – test formulation and Sporanox – reference) was carried out in healthy rabbits. 1ml blood samples were collected for a period of 24 hrs making 24 hrs from each subject during the course of study. The pre dose blood sample in each period was collected within a period of approx 1.5h before dosing and post dose. Samples were collected within 2 min of scheduled time. The withdrawn blood samples were centrifuged at refrigerated temperature to separate plasma. All plasma samples were transferred to suitable labeled tubes and rechecked to ensure transfer of plasma to correct tube. The plasma samples were stored below -15°C until analysis.

RESULT AND DISCUSSION

Response surface analysis: A 3^2 full factorial design was constructed where the mucoadhesive polymer concentration (X_1) and stirring speed (X_2) were taken as independent variables. Percent microencapsulation efficiency, particle size, time taken to release 50% of drug (t_{50}) was taken as the response variables for microsphere formulations.

SEM micrographs of the optimized microsphere formulation were reported in Fig. 13. Few of the microspheres exhibited irregular shape and crumpled surface. They seemed to be hollow microspheres, which collapsed during the preparation process. The microspheres shown in Fig. exhibited spherical shape and smooth surface. The results showed that the drug/polymer ratio affected the morphological characteristics of the microspheres. As the polymer ratio increased more spherical microspheres with smoother surface were obtained.

The results of particle size analysis shows that the stirring speed, polymer concentration have marked influence on the particle size of microspheres obtained. As polymer concentration is increased particle size is reduced with the formation of irregular shape microspheres whereas stirring speed exhibits directly proportionality with the size of microspheres. The maximum and minimum range for microspheres was found to be in the range of

***In vitro* drug release study**:

In vitro drug release study is performed to calculate in vivo behaviour of drug. A number of pharmacoepial methods have been proposed for dosage form based drug dissolution studies. As per ICH guidelines, pH 1.2, 4.5 and 6.8 were used to predict in vivo drug dissolution behaviour of modified release drug products. Mucoadhesive microspheres were evaluated in 0.1N HCl. HPMC is widely used as matrix forming polymer, the property owes to its hydrophilic nature and rapid gelling tendency. DSC studies were performed to evaluate compatibility of drug with polymer. Drug release behavior depends primarily on drug:polymer concentration (1:1, 1:2 and 1:3). At low drug:polymer ratio (1:1) formulations ITCZ-HPMC5CP1 shows drug release of 60.91. For formulation codes ITCZ-HPMC5CP4 drug release was found to be 68.53. For formulation codes ITCZ-HPMC5CP7 77.03. For drug polymer ratio (1:2) formulation codes ITCZ-HPMC5CP2 drug release was found to be 58.39. For formulation codes ITCZ-HPMC5CP6 68.57. For formulation codes ITCZ-HPMC5CP9 76.25. For drug polymer concentration (1:3) for formulation codes ITCZ-HPMC5CP4, 52.82. For formulation codes ITCZ-HPMC5CP7, drug release was 55.23. For formulation codes ITCZ-HPMC5CP9 drug release was 74.84 for 12 hrs.

Table 3. Analysis of Coefficient of Regression for estimation of HPMC based microspheres

Parameter	Estimate		
	Microencapsulation efficiency	Particle size	Drug release (t_{50})
Coefficient factor	ITCZ-HPMC5CP		
Intercept	79.06	179.4	10.06
A	-0.45	-4.51	0.58
B	2.44	-39.97	-1.45
AB	7.09	2.23	-0.45
A^2	-4.01	4.72	0.017
B^2	-5.27	-2.29	-1.18
R-squared	0.9857	0.7628	0.8835
Adjusted R-squared	0.9619	0.3676	0.6895

The Correlation Coefficient of Microencapsulation Efficiency of ITCZ-HPMC5CP was 0.9857 for particle size it was 0.8835 and for drug release was 0.7628 and was good indicator of fit and factors such as Stirring speed and Polymer concentration greatly control the process.

Drug release Kinetics study: On all the dissolution profiles obtained, kinetic analysis was performed and the data was evaluated after fitting to Zero order, First order, Higuchi, Peppas and Hixson-crowell models. Values observed were correlation coefficient, (k) release rate constant, residual sum of squares (RSS) and (n) value in case of peppas model. Criteria for selecting most appropriate model was based on best reliability of fit indicated by R value nearer to one calculated from ANOVA of release data after fitting to each dissolution model. When drug release is concentration dependent, first order model is an indicator. Zero order model is independent of concentration of drug. Matrix model is applicable when matrix polymer is used and peppas model is used when release mechanism is not well known Fickian diffusion exists when $n<0.5$, but at $n>0.5$ non-fickian diffusion mechanism is observed. On the basis of R value, the best fit model for ITCZ-PVPHPMC5CP were peppas model (ITCZ-HPMC5CP1, 2, 3, 4, 5, 6, 8 and 9) and Hixson crowell model (ITCZ-HPMC5CP7).

Numerical Optimization:
The results of Numerical Optimization revealed that the solutions obtained are based on overall ANOVA, Diagnostic case statistics and desirability of the model. The desirability is an objective function that ranges from zero (outside the limit values) to one (at the goal). The Numerical optimization finds a point that maximizes the desirability function. A desirability value of one doesn't always reflects the good optimization conditions because it is completely dependent on how closely the lower and upper limit that are set relative to the actual optimum conditions. The goal of optimization is to find good set of conditions that will meet all goals. The formulations were selected on the basis of goals set for all responses obtained, criteria of attaining maximum microencapsulation efficiency, lowest possible particle size, best degree of swelling, better mucoadhesion capacity and maximum time to reach half quantity of drug for sustain drug release. The lower and upper limits of responses for microencapsulation efficiency of ITCZ-HPMC5CP were 60.42 to 79.32. Particle size analysis results for above formulations were in range of 125.65 to 228.15. t_{50} range for above formulations were 6.9 to 11.4. The best solutions of numerical optimization for ITCZ-HPMC5CP with highest desirability value of 0.689. The statistics of most desired numerical optimization revealed that the 95% Confidence interval low (95% CI low) and 95% Confidence interval high (95% CI high) is in the range where process average fall into 95% of the time of Microencapsulation Efficiency, Particle Size and t_{50}. The 95% Confidence interval low (95% CI low) and 95% Confidence interval high (95% CI high) for Microencapsulation Efficiency, Particle Size and t50 for ITCZ-HPMC5CP was 75.54% to 81.36%, 119.63m to 184.64m and 7.55h to 10.41h respectively. The 95% Predictable interval low (95% PI low) and 95% Predictable interval high (95% PI high) for Microencapsulation Efficiency, Particle Size and t50 for ITCZ-HPMC5CP was 73.51% to 83.40%, 87.58m to 216.68m and 6.14h to 11.81h respectively.

Table 4. Results of Drug Release Kinetics of ITCZ-HPMC5CP microspheres

Model	Kinetic parameters	Formulations								
		a	b	c	d	e	f	g	h	i
Zero order	R	0.9810	0.9774	0.9769	0.9860	0.9832	0.9798	0.9809	0.9799	0.9822
	k	105.57	106.82	109.98	102.31	103.03	106.02	102.05	103.19	105.29
	RSS	92	100	78	92	106	95	137	127	88
First order	R	0.9964	0.9954	0.9964	0.9932	0.9944	0.9963	0.9912	0.9938	0.9963
	k	-1.43	-1.41	-1.41	-1.49	-1.47	-1.43	-1.51	-1.48	-1.44
	RSS	19	28	15	30	30	18	62	37	14
Matrix	R	0.9737	0.9778	0.9772	0.9686	0.9708	0.9724	0.9723	0.9696	0.9688
	k	66.81	65.77	63.43	70.27	69.38	66.38	70.49	69.10	67.01
	RSS	127	98	76	206	182	129	198	191	153
Peppas	R	**0.9975**	**0.9966**	**0.9983**	**0.9981**	**0.9967**	**0.9979**	0.9920	**0.9963**	**0.9985**
	k	**81.84**	**78.81**	**80.67**	**85.25**	**82.61**	**82.19**	78.17	**81.59**	**84.53**
	RSS	**8**	**10**	**3**	**9**	**15**	**7**	51	**19**	**5**
Hixon-Crowell	R	0.9953	0.9927	0.9929	0.9969	0.9961	0.9952	**0.9942**	0.9951	0.9969
	k	-0.42	-0.42	-0.43	-0.43	-0.43	-0.43	**-0.43**	-0.43	-0.43
	RSS	29	42	27	22	32	28	**59**	42	18

Table 5. Results of Numerical Optimization of ITCZ-HPMC5CP microspheres

Number	polymer concentration	stirring speed	Entrapment efficiency	Particle size	t50 release	Desirability
1	1500	1304.92	78.4523	152.132	8.97685	0.689
2	1500	1300	78.4213	152.525	8.99111	0.689
3	1499.93	1311.01	78.49	151.646	8.9591	0.689

Table 6. Results of Statistics of Numerical Optimization of ITCZ-HPMC5CP microspheres

Response	Prediction	SE Mean	95% CI low	95% CI high	SE Pred	95% PI low	95% PI high
Solution 1							
Entrapment efficiency	78.4523	0.92	75.54	81.36	1.55	73.51	83.4
Particle size	152.132	13.29	119.63	184.64	26.38	87.58	216.68

t50 release	8.97685	0.58	7.55	10.41	1.16	6.14	11.81
Solution 2							
Entrapment efficiency	78.4213	0.91	75.51	81.33	1.55	73.48	83.36
Particle size	152.525	13.25	120.11	184.94	26.36	88.02	217.03
t50 release	8.99111	0.58	7.57	10.42	1.16	6.16	11.83
Solution 3							
Entrapment efficiency	78.49	0.92	75.57	81.41	1.55	73.54	83.44
Particle size	151.646	13.33	119.02	184.27	26.41	87.03	216.26
t50 release	8.9591	0.59	7.53	10.39	1.16	6.12	11.8

Table 7. Kinetic parameters for in vivo performance of Innovator and selected formulations (Arithmetic mean ± SD)

Parameter	Ratio	90_Lower	90_Upper	Geo mean Test	Geo mean Ref	% CV Test	% CV Ref
Cmax (Maximum Plasma concentration) (ng/ml)							
Cmax (Test)	99.9	89	112.1	63	63.1	8.3	6.3
Cmax (Reference)	100.2	73.7	136.2	50.5	50.5	25.4	19.9
AUC (Area under the Curve) (ng/ml.h)							
AUC (Test)	92.2	79.9	106.4	413.1	448.1	20.8	17.7
AUC (Reference)	107.4	81.6	141.4	294	273.8	29.6	26.7
t_{max} (Time to reach maximum plasma concentration) (hr)							
t_{max} (Reference)	77.7	68.3	88.4	3.78	4.86	8.8	17.2
t_{max} (Test)	103.1	90.1	118	4.06	3.94	12.6	11.6

No. of subjects: 16

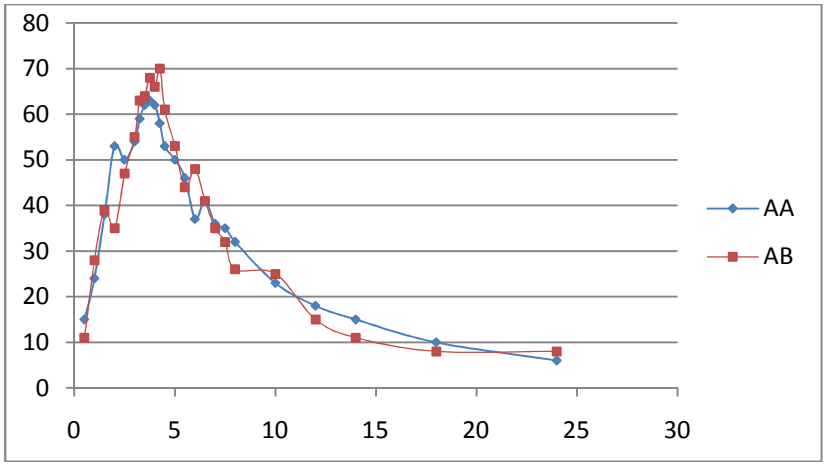

Figure 1. In vivo behavior of (Parallel study design) Sporanox Capsules 100 mg in Subject 1.

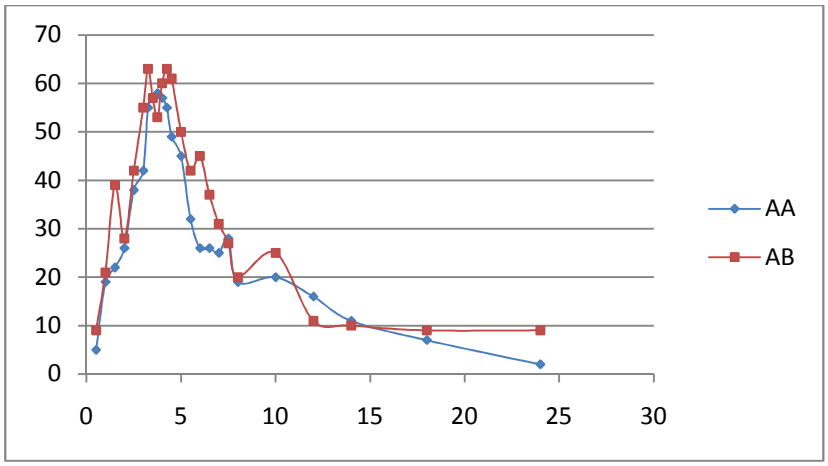

Figure 2. In vivo behavior of (Parallel study design) Sporanox Capsules 100 mg in Subject 2.

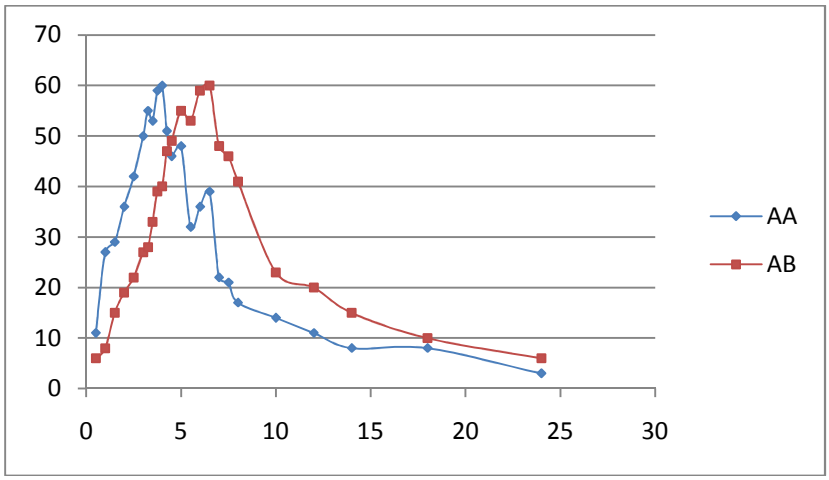

Figure 3. In vivo behavior of (Parallel study design) Sporanox Capsules 100 mg in Subject 3.

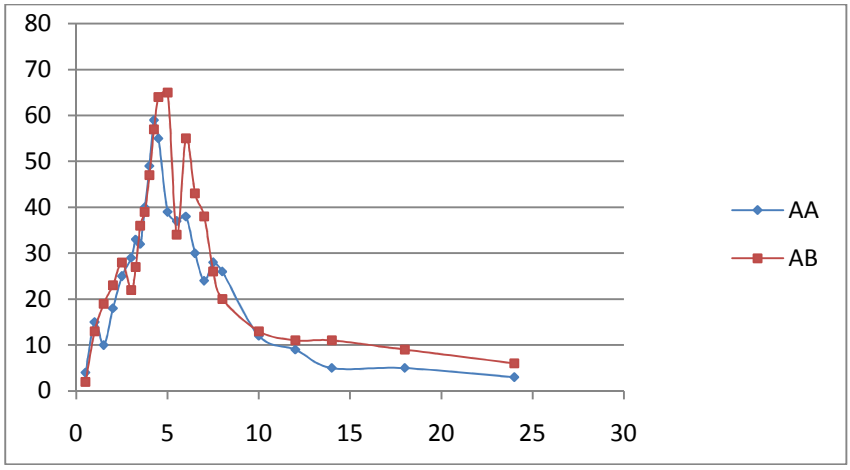

Figure 4. In vivo behavior of (Parallel study design) Sporanox Capsules 100 mg in Subject 4.

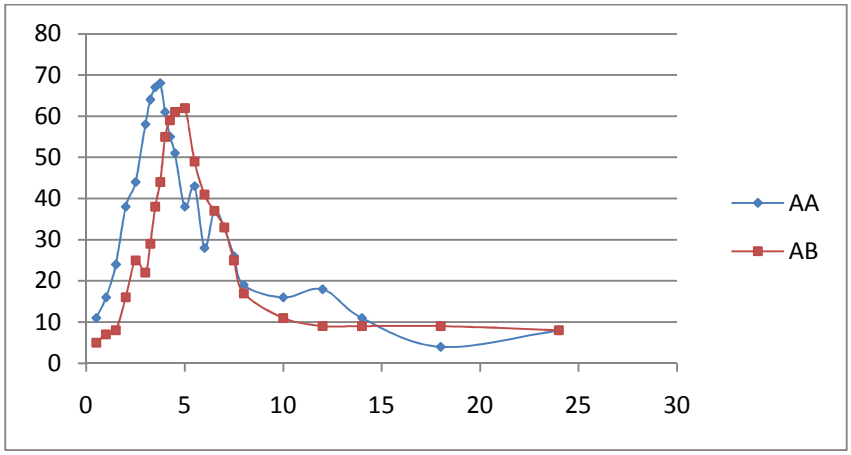

Figure 5. In vivo behavior of (Parallel study design) Sporanox Capsules 100 mg in Subject 5.

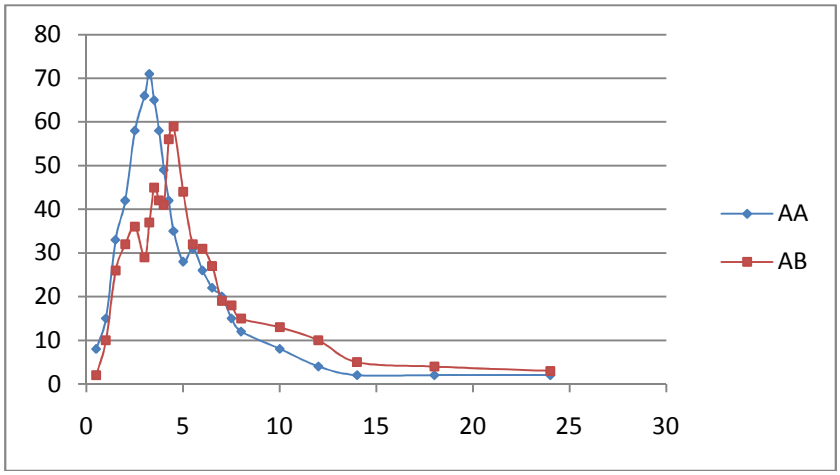

Figure 6. In vivo behavior of (Parallel study design) Sporanox Capsules 100 mg in Subject 6.

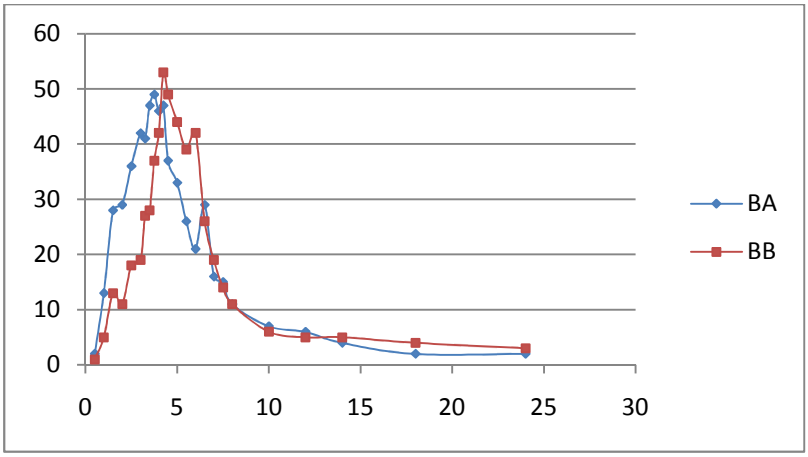

Figure 7. In vivo behavior of (Parallel study design) ITCZ-HPMC5CP in Subject 1.

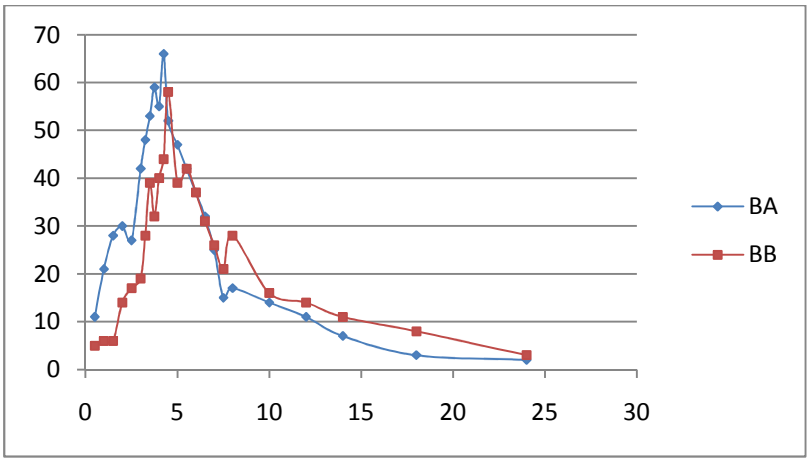

Figure 8. In vivo behavior of (Parallel study design) ITCZ-HPMC5CP in Subject 2.

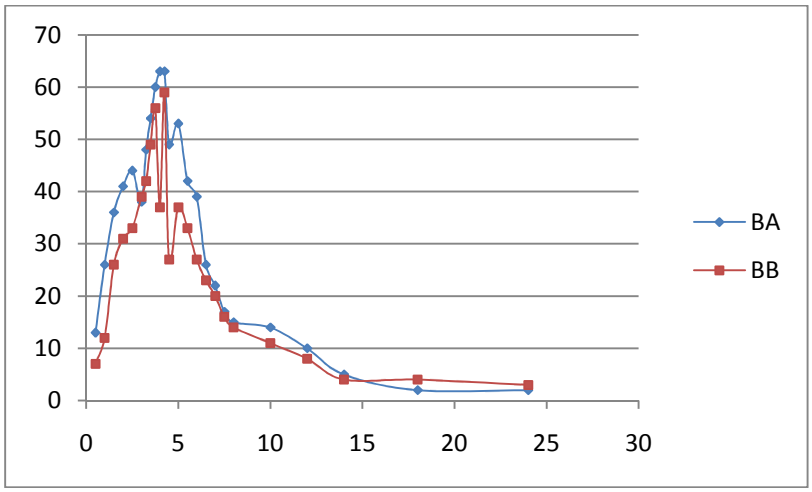

Figure 9. In vivo behavior of (Parallel study design) ITCZ-HPMC5CP in Subject 3.

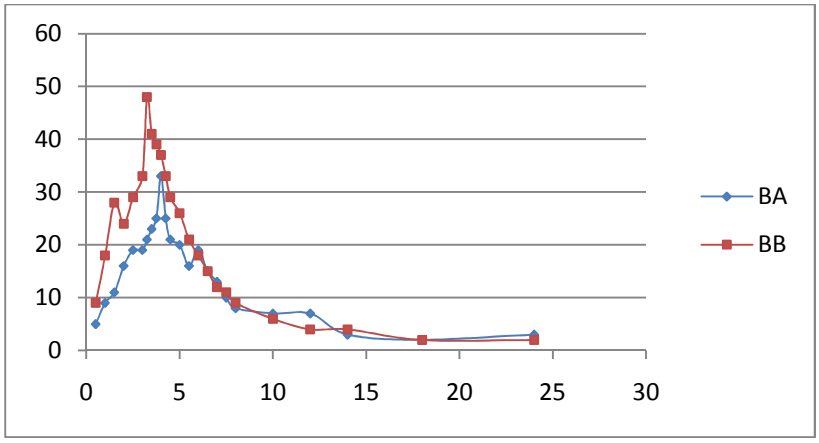

Figure 10. In vivo behavior of (Parallel study design) ITCZ-HPMC5CP in Subject 4.

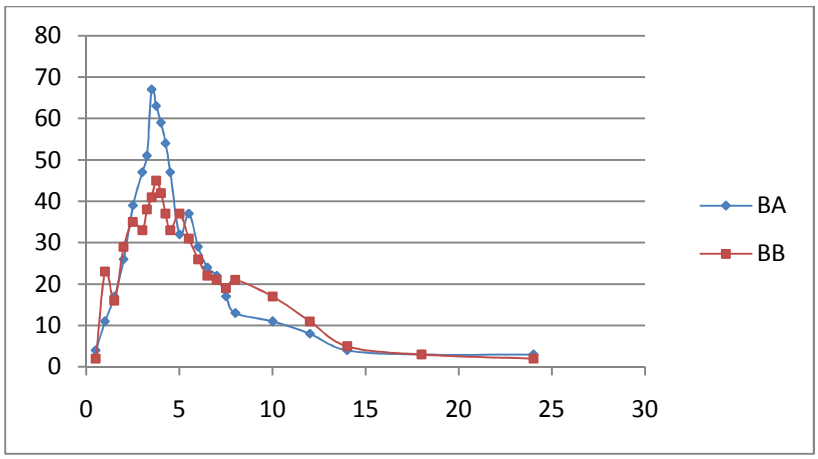

Figure 11. In vivo behavior of (Parallel study design) ITCZ-HPMC5CP in Subject 5.

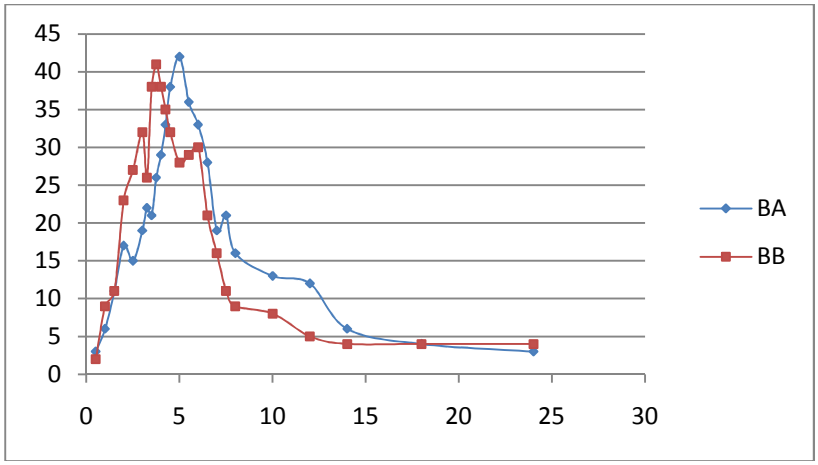

Figure 12. In vivo behavior of (Parallel study design) ITCZ-HPMC5CP in Subject 6.

Table 7 shows kinetic behavior of test and reference samples. The result shows that the proposed modified release formulation shows less variability as compared to immediate release marketed innovator product (Sporanox® Capsules 100 mg). The present study thus illustrates the need for designing of dosage form in such a way so as to release the drug in a controlled manner reducing the intrapatient and interpatient variabililty. The variability of Itraconazole the drug used in

research work can be reduced by modifying its release behavior. The results were independent of dosage form design provided the drug is getting released over an extended period of time.

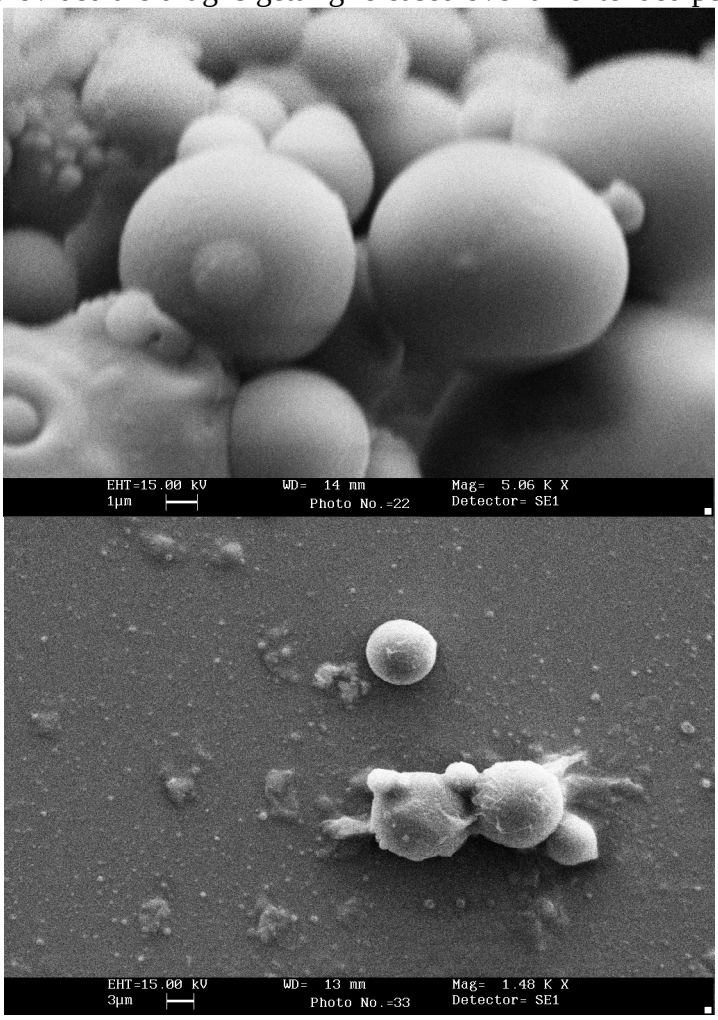

Figure 13. SEM photographs of Microspheres

CONCLUSION

Oral Candidiasis is caused by Candida Albicans, a dimorphic fungal organism that typically is present in the oral cavity in a non-pathogenic state in about one-half of healthy individuals. Itraconazole one of the drug used in the treatment of oral candidiasis exhibits poor aqueous solubility and permeability. At the same time the drug belongs to the category of highly variable drug. Currently available marketed preparation (Innovator) for Itraconazole includes Sporanox Capsules 100 mg which is a immediate release preparation. The studies carried out shows significant difference between the results obtained for both innovator and developed formulation. The in house developed formulation exhibits better results as far as C_{max} and AUC are concerned indicating that for a highly variable drug such as Itraconazole delivering a drug in a controlled manner might be a better approach to reduce intra patient variability.

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