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Research Article

Individual and combined effect of PVP, PEG 6000 and some other diluents on the solubility and dissolution rate of Itraconazole tablets

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ABSTRACT

Itraconazole, an Anti-fungal drug, which is poorly soluble in water. It requires Enhancement in dissolution rate for enhancing its oral bioavailability by several techniques. The prepared Itraconazole tablets possess good physico-chemical characteristics and the *in vitro* dissolution and release rate kinetics were originated acceptable. Deviations were found in dissolution rate, efficiency for the Itraconazole tablets. The factors viz., used of Poly ethylene glycol 6000, Poly Vinyl Pyrrolidone and Dicalcium Phosphate, as A, B and C respectively and the combined factors also observed. Formulations F_3 and F_7 gave good dissolution rate and efficiency values. Addition of PVP 2% resulted in increased dissolution rate of Itraconazole tablets. A grouping of Poly ethylene glycol 6000, Poly Vinyl Pyrrolidone and Dicalcium Phosphate was suggested for making Itraconazole tablets with good dissolution characteristics.

Keywords: Itraconazole; DE; PVP; PEG; DCP.

INTRODUCTION

Itraconazole, a widely given Anti-fungal drug, it has poor solubility in water and has less bioavailability by oral route. The bioavailability of Itraconazole is dissolution rate limited.A few components identified with medication and dose frame incredibly impact the oral bioavailability of Itraconazole from tablet dose structure. Itraconazole requires Enhancement in disintegration rate for upgrading its oral bioavailability. In this study micronization technique is utilized to upgrade the solvency, disintegration rate and bio accessibility of inadequately tablets. (Chaumeil, 1998; Ahad 2011; Martin, 2011; Jinno et al, 2006; Yellela, 2010; Jounela et al, 1975; Vemula et al, 2010; Nishihata et al, 1993).

Factorial experiments

In factorial analyses as the descriptive word factorial demonstrates the impacts of a few elements of variety are considered and explored all the while, the medications being every one of the blends of various elements under study. To discover the viability of different medicines, viz., distinctive levels of Potash or Nitrogen we may lead two basic tests, one for Potash and other for Nitrogen. A progression of examinations in which stand out element is fluctuated at once would be both protracted and excessive may even now unacceptable in view of systemic changes in the general back ground conditions. By and large if the levels of different variables are equivalent the s^n factorial analysis implies a test with n calculate, each at s levels where n is any positive whole number more noteworthy than or equivalent to 2, e.g. 2^3 test implies an investigation with 3 elements at 2 levels each 3^2 test implies a trial means a trial with 2 variables at 3 levels each. (Shah and Pathak2010).

2^2 Designs

The four treatments can be counted as follows:

$a_0 b_0$ or '1': Factors A and B, both at first level.

$a_1 b_0$ or a: A at second level and B at first level

$a_0 b_1$ or b: A at first level and B at second level

$a_1 b_1$ or ab: A and B both at second level

Materials and methods

Materials: Itraconazole was gift sample from (M/S NatcoPharma.Ltd, Hyd.) Lactose, Di calcium phosphate, Poly Ethylene Glycol 6000, Polyvinyl Pyrrolidone, Crospovidone, Talc, Magnesium stearate were procured from SD Fine chemicals, Mumbai, India. The remaining chemicals of AR quality.

Methods:

Estimation of Itraconazole

A λ_{max}225 nm in 0.1 N HCl was utilized for Itraconazole estimation.

Preparation of Standard Solutions

100 mg of Itraconazole was dissolved in methanol by

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taking it in volumetric flask (100 ml) and the volume was made up to the mark with methanol.

Procedure

The standard Itraconazole solution was suitably diluted with 0.1N HCl for getting 2,4,6,8 and 10 µg. The absorbance was determined by using UV-VIS double beam Spectrophotometer (CT 60, Mumbai, India) at 225 nm. By using these readings (Table 2) standard graph was plotted (Prasad et al, 2010).

Estimating Solubility

An excess quantity (100mg) of Itraconazole was added to 25ml stoppered conical flask containing 15ml of methanol and were shaken for 24h at 28±1^{0}C (RT) using a Rotary flask Shaker. Samples were taken at every 2 hours; filtered using a 0.45µ membrane filter and the absorbance was determined by using UV-VIS double beam Spectrophotometer at 225 nm. These procedures were performed for four times.

Preparation Itraconazole tablets

The required quantities of drug, PEG 6000, PVP and DCP were mixed, melted on water bath. The formed mass was passed from # 14 or 16 for granules. These granules were lubricated with talc, magnesium stearate and Crospovidone were added in a closed Polyethylene bag. The tablet granules were compressed into tablets on a rotary multi station tablet punching machine (m/s Cemach, Hyderabad, India) (Katdare et al, 1987; Reverchon et al, 2004). These values were shown in table1.

Uniformity of content

Ten tablets were weighed and powdered. Tablet powder equal to 50mg of Itraconazole was taken into bubbling test tube and separated with 4 X 10ml amount methanol. The Methanolic concentrates were gathered into 50 ml of volumetric carafe and the volume was made up to 50 ml with methanol. The arrangement was hence weakened with phosphate cradle pH 7.4 and Assayed for Drug content by UV Spectrophotometric system.

Hardness

Monsanto (Cemach, Hyderabad, India) hardness tester was utilized and the hardness of five tablets was estimated.

Friability

Roche Friabrilator is adopted for 100 rpm within 4 min. The loss on friability was mathematically expressed as follows.

$$F = \frac{W_{Final} - W_{Intial}}{W_{Intial}} \times 100$$

Where,

F= friability (%), W_{Intial}= Initial weight and W_{Final} = Final weight

Disintegration time

Instrument: Tablet disintegration apparatus

Speed: 30 cycles per minute

Temperature: 37±2^{0}C

Disintegration media: Simulated saliva fluid of pH 6.8

Dissolution rate

Instrument: USP-II dissolution test apparatus (DISSO-2000, LabIndia)

Dissolution media: 900ml of 0.1N HCl

Paddle speed: 50rpm

Temperature: 37 ±0.5^{0}C

Sample size: (5ml)

λ_{max}: 225nm

Number of trials (n): 4

RESULTS AND DISCUSSION

All the tablets prepared were evaluated for physicochemical characteristics. The Hardness of Itraconazole tablets was found to be 4.3 to 4.8. Kg/cm^2. The loss in the Friability was within 1% in all the preparations. The drug content was in 100± 5% of the labeled claim. The prepared tablets passed all the official tests prescribed in Pharmacopoeia.

The *in vitro* dissolution of Itraconazole tablets indicates, increase in drug dissolution by the addition of PVP was observed.

The dissolution parameters like., T_{50}, K_1 and DE_{30} were subjected to ANOVA to know the significance of individual and combination possessions of the factors A, B and C diluents.

To evaluate the individual and combined effects of the 3 factors (PEG 6000, PVP and type of diluents) on $k_1$and DE_{30} was performed by 2^3–factorial design. The three factors involved and their level tested are shown in table 9.

Calibration curve for Itraconazole was sown in tabulated in table 2 and shown in fig 1. The slope was found to be 0.049x+0.0038 with regression value of 0.999. The in process control tests for Itraconazole tablets were shown in table 3. The prepared tablets *in vitro* dissolution data was shown in table 4 and 5. The dissolution data histograms were shown in fig 2 and 3.

Disintegration effectiveness (DE30) for every situation was computed. The dissolution parameters of the tablets were given in table 6. The after effects of ANOVA are given in tables 7 and 8.ANOVA of K1 and DE_{30} values showed that the individual and joined impacts of three variables on disintegration rate and productivity of Itraconazole tablets were exceedingly critical (P<0.01).The consequences of ANOVA of T_{50} qualities demonstrated that the Individual and Combined

Table 1: Formulation of Itraconazole Tablets

Ingredient (mg/tablet)	Formulation							
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
Itraconazole	50	50	50	50	50	50	50	50
PEG6000	21	42	21	42	21	42	21	42
PVP	-	-	4.2	4.2	-	-	4.2	4.2
Lactose	124.4	103.4	122.2	97	-	-	-	-
DCP	2	2		-	124.4	103.4	118	97
Crospovidone	-	-	-	8.4	2	2	8.4	8.4
Talc	8.4	8.4	8.4	4.2	8.4	8.4	4.2	4.2
Magnesium Stearate	4.2	4.2	4.2	4.2	4.2	4.2	4.2	4.2
Tablet Weight (mg)	210	210	210	210	210	210	210	210

Table 2: Calibration Curve for the Estimation of Itraconazole

Itraconazole Concentration (µg/ml)	Absorbance
0	0.000±0.00
2	0.107±0.0001
4	0.197±0.0001
6	0.291±0.0001
8	0.397±0.0002
10	0.497±0.0002

Table 3: In process control tests for Itraconazole tablets

Formulation	Drug Content (mg/Tablet)	Friability (%)	Hardness (Kg/cm^2)	Disintegration Time (min)
F_1	48.2±0.21	0.8±0.01	4.3±0.2	3.20±0.20
F_2	49.2±0.23	0.6±0.03	4.5±0.3	3.40±0.19
F_3	49.6±0.32	0.6±0.04	4.5±0.2	3.45±0.18
F_4	48.4±0.34	0.6±0.03	4.8±0.3	3.90±0.17
F_5	50.5±0.29	0.5±0.05	4.4±0.2	4.10±0.19
F_6	50.2±0.31	0.6±0.06	4.3±0.4	4.54±0.18
F_7	48.2±0.33	0.7±0.05	4.6±0.5	3.62±0.19
F_8	49.2±0.35	0.8±0.07	4.2±0.3	3.75±0.20

All values mentioned as mean ±SD; Number of trials (n)=3

Table 4: Dissolution Profiles of Itraconazole tablets (F1 –F4)

Time (min)	Drug Dissolved (Mg)				% Drug Dissolved				% Drug Remaining			
	F1	F2	F3	F4	F1	F2	F3	F4	F1	F2	F3	F4
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100	100	100	100
5	4.18	4.16	3.77	3.08	8.35	8.31	7.53	6.16	91.65	91.69	92.47	93.84
10	7.09	5.47	5.96	3.36	14.18	10.95	11.91	6.72	85.82	89.05	88.09	93.28
20	7.83	7.29	7.37	5.21	15.66	14.59	14.73	10.43	84.34	85.41	85.27	89.57
30	9.48	7.57	8.83	6.74	18.96	15.14	17.67	13.47	81.04	84.86	82.33	86.53
40	10.82	8.59	9.67	7.29	21.64	17.18	19.34	14.59	78.36	82.82	80.66	85.41
50	11.19	10.54	10.80	8.83	22.38	21.08	21.60	17.67	77.62	78.92	78.40	82.33
60	13.88	11.39	11.39	9.67	27.76	22.79	22.79	19.34	72.24	77.21	77.21	80.66

impacts of all the three elements aside from consolidated impact of AC (PEG-sort of diluents) on the Dissolution rate and Efficiency were very noteworthy ($P<0.01$).Factors as Per 2^3 Factorial Designs was shown I table 9. Formulations containing DCP as diluents gave higher Dissolution Efficiency values than those definitions utilizing Lactose as diluents. This might be because of quick dispersible nature of DCP, which may have helped in fast scattering of medication particles giving higher disintegration.

CONCLUSION

All the Itraconazole tablets were of good quality as per the standard test for tablets perfumed. Much varieties were seen in the Dissolution rate (K1) and Dissolution Efficiency (DE30) of the tablets arranged because of Formulation variables (i.e., Factors A, B and C). The Individual and Combined impacts of Factor A (PEG6000) Factor B (PVP) and the Combined impacts of Factors AB, AC and BC on the Dissolution rate (K1) of Itraconazole tablets were exceedingly significant

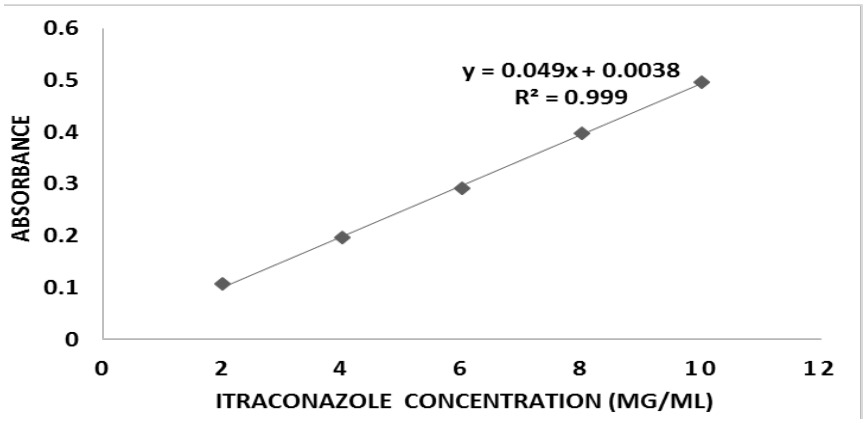

Figure 1: Calibration curve of Itraconazole

Table 5: Dissolution profiles of Itraconazole tablets (F5 –F8)

Time (min)	Drug dissolved (mg)				% drug dissolved				% drug remaining			
	F5	F6	F7	F8	F5	F6	F7	F8	F5	F6	F7	F8
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100	100	100	100
5	3.08	4.75	5.31	4.88	6.16	9.50	10.61	9.76	93.84	90.50	89.39	90.24
10	3.36	5.64	6.55	6.07	6.72	11.28	13.10	12.14	93.28	88.72	86.90	87.86
20	5.21	7.63	8.83	8.68	10.43	15.25	17.67	17.37	89.57	84.75	82.33	82.63
30	6.74	8.22	9.48	9.76	13.47	16.44	18.96	19.52	86.53	83.56	81.04	80.48
40	7.29	9.24	10.86	10.82	14.59	18.48	21.71	21.64	85.41	81.52	78.29	78.36
50	8.83	9.67	12.60	11.64	17.67	19.34	25.20	23.27	82.33	80.66	74.80	76.73
60	9.67	11.10	14.03	12.73	19.34	22.19	28.06	25.46	80.66	77.81	71.94	74.54

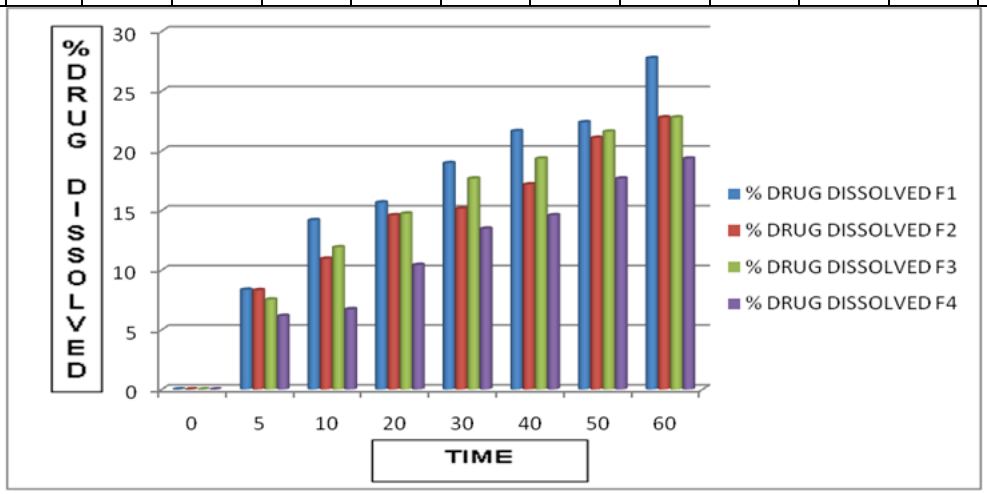

Figure 2: A histogram of In Vitro Dissolution Profiles of Itraconazole Tablets (F1-F4)

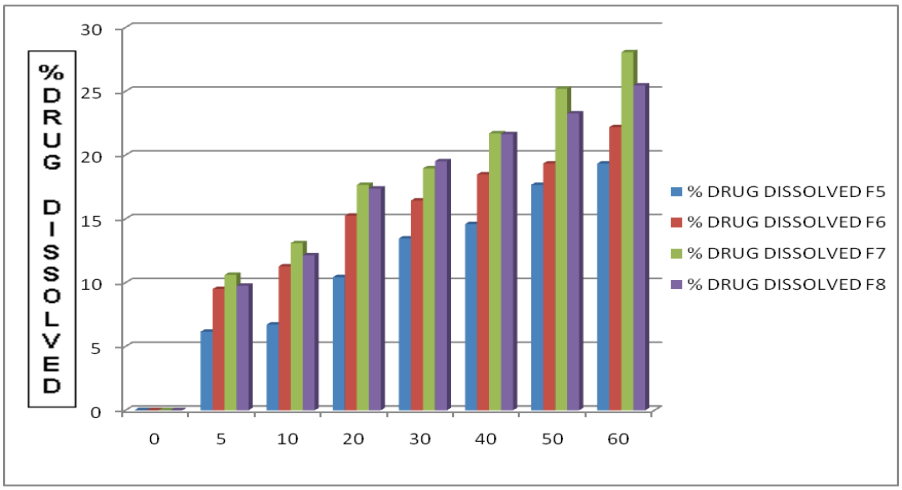

Figure 3: A histogram of In Vitro Dissolution Profiles of Itraconazole Tablets (F5-F8)

(P<0.01). The Individual impacts of element A (PEG 6000), element C (Type of diluents) and joined impacts of components AC and BC on the DE30 were additionally very significant(P<0.01). Formulations F3 and F7 gave higher Dissolution rate (K1) and Dissolution Efficiency (DE30) values among all and these plans are considered as the best details of Itraconazole. Expansion of PVP 2% brought about expanded disintegration rate of Itraconazole tablets. Tablet containing DCP as Diluents alongside PEG and PVP gave higher disintegration rate (K1) and proficiency (DE30) than those containing lactose as diluents. A blend of PEG and PVP alongside DCP as diluents is prescribed for definition of Itraconazole tablets with higher Dissolution rate and Efficiency.

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