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Formulation And Evaluation Of Solid Dispersion Of Itraconazole Incorporated Dispersible Tablet

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ABSTRACT

The purpose of this study is to formulate the solid dissipation incorporated dispersible tablet of Itraconazole by using carriers polyethylene glycol 6000 and 4000(by melting system and solvent melting sinking system) in the medicine carrier rate of 11, 12 and 13. The set solid dissipations was compared and characterized for their medicine content, thermal studies, infrared spectral studies, discriminational scanning calorimetric studies, waterless solubility studies and in- vitro release studies. From the results, it was clear that solid dissipation expression of cut- 6000 in the rate 13 prepared by melting system showed bettered dissolution rate than pure medicine. The solid dissipation showing better release profile was chosen to formulate into a tablet lozenge form of weight 120 mg. Itraconazole is a triazole antifungal agent used for fungal infections. It has a broader diapason of fungal exertion. Itraconazole dispersible tablet was prepared by direct contraction system using microcrystalline cellulose as a direct compressible vehicle. Croscarmellose sodium, crosspovidone and sodium bounce gllycolate were used as a superdisintegrants in different proportion for the expression. The decomposition time and dissolution parameter was dropped with adding the attention of superdisintegrants. The tablets prepared were estimated for weight variation, hardness, decomposition time, frangibility and dissolution.

Keywords: Itraconazole, Dispersible tablet, Super disintegrant

Introduction

The oral route of medicine administration was preferred as the most common system of delivery due to convenience and ease of ingestion but utmost of the pharmaceutical lozenge forms are designed for oral administration when direct consumption is desired. Further psychiatric instances, hospitalised or bedridden cases with habitual conditions finds difficulty to swallow the solid oral lozenge. It was anticipated that ODTs can address similar critical issues. [1] ODTs are solid lozenge form that provides the rapid-fire decomposition or dissolution of solids to present as a result or suspense form indeed when placed in the mouth under limited bio-fluid. Odts can also has an adverse effective if the medicine is inadequately answerable or poor membrane penetrability. Although swab conformation, solubilization, flyspeck size reduction has generally used to increase dissolution rate and thereby oral immersion and bioavailability of low water answerable medicines, there's practical limitation to these ways. There are number of ways for enhancing the medicine dissolution. Solid

dissipation of medicine in a water answerable polymer is one of the promising fashions. It's defined as the dissipation of one or further active constituents in inert carriers at solid state prepared by emulsion, solvent or solvent emulsion styles. (2) Dispersible medicine delivery is fleetly gaining acceptance as an important new medicine delivery technology. Super disintegrants are added in the expression to grease break- up and disintegrate fleetly in to lower patches when placed in water or in mouth. These super disintegrants has a property of swelling and due to its swelling property, it exerts a pressure in the external direction or radial direction, due to which the tablet burst or the immersion of water is accelerated leading to an enormous increase in the volume of grains to promote decomposition. (3)

Itraconazole, which was first synthesized in 1980, demonstrates a broad diapason of exertion against a number of fungal species similar as dermatophytes, Malassezia furfur, Candida species, Aspergillus species, and Histoplasma capsulatum etc. It is an antifungal drug. The medium of action of Itraconazole is analogous to that of ketoconazole, which involves the inhibition of cell membrane ergo sterol conflation. (4) still, Itraconazole differs from ketoconazole in that it demonstrates a high degree of lipophilicity and a lack of endocrine-affiliated side goods. Itraconazole is an extremely weak base (Pka = 3.7) which was nearly unionized at physiological pH. Since Itraconazole was answerable only in extreme acidic conditions, only an oral lozenge expression is presently available for use. Solid dissipation fashion has been used for a wide variety of inadequately waterless answerable medicines similar as Itraconazole, Ketoconazole, Nimesulide, Aceclofenac, Valdecoxib using colourful hydrophilic carriers like polyethylene glycol, polyvinylpyrrolidone, hydroxypropyl methyl cellulose, sugar, mannitol, ureaetc.In this study Itraconazole was used as model medicine and polyethylene glycol 6000 and 4000 were used as carriers in 14 rates.(5)

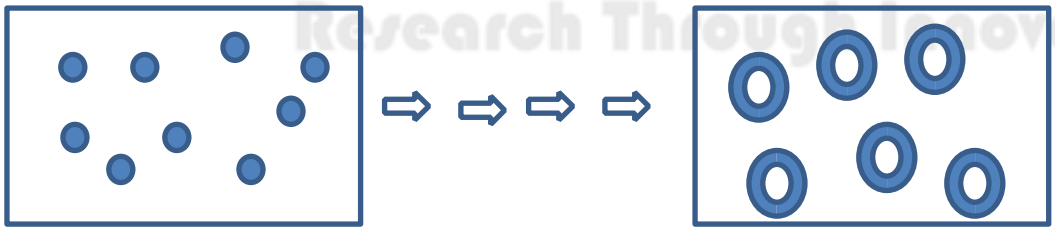
MECHANISM OF DRUG RELEASE:

Overall Mechanism of drug release of ODT:

According to official publication European Pharmacopoeia the ODT should be disperses or disintegrates in less than three minutes. The fundamental approach used in development of ODT is the use of super disintegrants like sodium starch glycol ate (Primo gel, Explotab) carboxymelhylcellulose (Croscarmellose), cross povidone, Polyvinylpyrrolidone (Polycladose

) etc. which provides rapid disintegration of tablet after putting in water, and release the drug in it. Bioavailability of certain drugs may be increased due to absorption of drugs in oral cavity and may be due to pregastric absorption of saliva which contains dispersed drugs which pass down into the stomach. The amount of drug which is subject to undergo first pass metabolism is reduced.[7]

Fig no:1-Mechanism of odts



granules with superdisintegrants in aqueous medium

swelling of granules due to superdisintegrants

MATERIALS AND METHODS

Itraconazole was obtained as a gift sample from jubilant life sciences limited. Crosscarmellose sodium, Sodium starch glycolate and Crosspovidone was purchased from Jubilant Life Sciences Lmt. Microcrystalline cellulose, Magnesium stearate and Talc was obtained from LOBA Chemie, Mannitol from cental drug house.

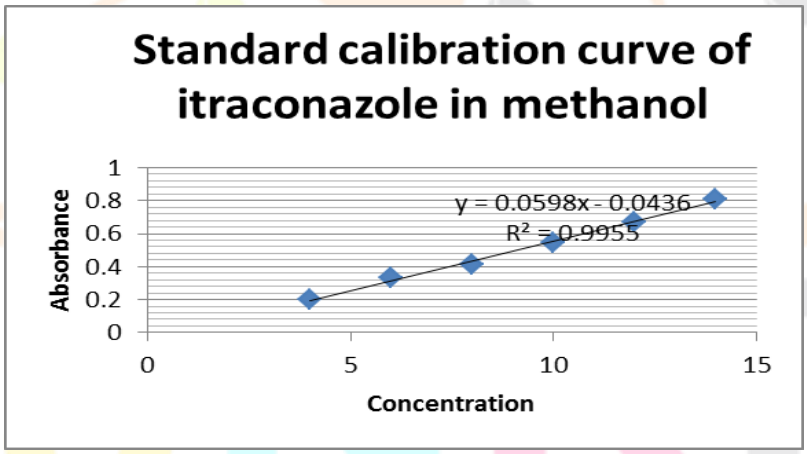
Preparation of Standard Calibration curve

Accurately weighed 10mg of pure drug of itraconazole and dissolved with methanol in 10ml volumetric flask to prepare 1000µg/ml solution. Label it as stock A solution. From stock a solution pipette out 1ml and dilute with methanol up to 50ml in volumetric flask to form 20µg/ml solution. Label this as stock B solution. Prepare the aliquotes by pipetting out 2ml,3ml,4ml,5ml,6ml,7ml from stock B solution, dilute up to 10ml with methanol in 10ml volumetric flask to prepare 4µg/ml,6µg/ml,8µg/ml,10µg/ml,12µg/ml,14µg/ml solution.

Then analysed the highest concentration solution in UV spectrophotometer to determine the ʎmax i.e found to be 261nm. Set the wavelength at 261nm and note the absorbance of all the concentration. The absorbance of all the concentration was described in table no.1. **TABLE NO:-1-Data table for standard calibration curve**

Concentration(µg/ml)	Absorbance(nm)
4	0.201
6	0.331
8	0.411
10	0.544
12	0.671
14	0.807

Fig no:2- Standard Calibration curve of Itraconazole in Methanol



Preparation of solid dispersion of Itraconazole:-

The solid dispersion of Itraconazole can be prepared by using the melting method and melt evaporation method with the help of different carriers i.e:- PEG 4000,PEG 6000 in a water bath.

In **melting method** briefly appropriate amount of drug and carriers (PEG 4000, PEG 6000 and Methyl cellulose) were added to prepare required drug to carrier ratio for formulations .Then the mixture was heated under controlled temperature to melt drug and carrier with continuous stirring. The melted preparation was cooled to solidify in an ice bath. The solid dispersions prepared was pulverized and sifted (#100) and stored in a desiccators.[8]

In **melt evaporation method**, the drug is dissolved in a suitable liquid solvent. The polyethylene glycol is melted in a china dish. After melting the poly ethylene glycol, the drug solution is directly incorporated into the melt of

polyethylene glycol, which is then evaporated until a clear solvent free film is left.[9] The data were given in table no.2

Table no:-2- Formulation table for solid dispersion

Carrier	Drug:Carrier Ratio	Formulation Name	Method
PEG-4000	1:1	SD1	Melting Method
	1:2	SD2	
	1:3	SD3	
	1:4	SD4	
PEG-6000	1:1	SD5	Melting method
	1:2	SD6	
	1:3	SD7	
	1:4	SD8	
PEG-4000	1:1	SD9	Melt Evaporation
	1:2	SD10	
	1:3	SD11	
	1:4	SD12	
PEG-6000	1:1	SD13	Melt Evaporation method
	1:2	SD14	
	1:3	SD15	
	1:4	SD16	

Evaluation of Solid Dispersion[10] Estimation of drug content:

The formulation equivalent to 20 mg of Itraconazole was weighed and diluted suitably with distilled water. The absorbance was measured at 261 nm and the amount of drug in each formulation was calculated.The percentage purity was of each solid dispersion was calculated and shown in table no:6 **Dissolution Studies:**

The invitro dissolution studies were done to compare the rate of dissolution of solid dispersions with that of pure drug Itraconazole and physical mixtures. The test was performed in USP paddle apparatus using 900ml water and temperature 37+ 1°C.(shown in table no.6) **Aqueous solubility studies**:

It was carried out to determine solubility of Itraconazole alone in aqueous medium and also in presence of carriers like polyethylene glycol 6000 and 4000. This sudy was done by dissolving the excess of drug in different flasks containing different concentration of carrier in distilled water.[11]The flasks was shaken thoroughly for 6 hours and kept aside for 24hours. The suspensions were filtered, diluted suitably and absorbance was measured at 261 nm.(shown in table no.5)

Preparation of tablets and its characterisation[12]

Dispersible tablets containing 120mg of Itraconazole was prepared from direct compression method. All the ingredients were mixed uniformly followed by addition of magnesium stearate and talc.

Table no.3: formulation table of dispersible tablet of Itraconazole

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Itraconazole	60	60	60	60	60	60	60	60	60
Crosspovidone	3	4.5	6	-	-	-	-	-	-
Crosscarmellose Sodium	-	-	-	3	4.5	6	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	3	4.5	6
Microcrystalline cellulose	28.5	28.5	28.5	28.5	28.5	28.5	28.5	28.5	28.5
Manitol	26.7	25.2	23.7	26.7	25.2	23.7	26.7	25.2	23.7
Talc	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Magnesium stearate	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6

Evaluation of tablets[13]

All the tablets were evaluated for different parameters as hardness, friability, drug content, wetting time, *Invitro* dispersion time, and *In vitro* dissolution study and presented in table no.7

Weight variation

Weight variation was done as per standard procedure. Twenty tablets were taken from each of the formulation(F1-F9) and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet is determined from the collective weight and find out % variation as per table no-4 **Table no:4- weight variation of tablets (IP 2007)**

Average weight of tablets (mg)	Maximum % difference allowed
80 or less	10
80 – 250	7.5
More than 250	5

Hardness

The test was done as per the standard method. The hardness of tablets was determined by using the Fizer hardness tester (Cadmach,India) or by Monsanto hardness tester. The hardness of three randomly selected tablets from each formulation was determined by placing the tablet diagonally between two plungers of tablet hardness tester and applying pressure until the tablet broke.The reading on the scale was noted down in kg/cm2.

Friability test

The friability of tablets was measured by using Roche friabilator .Twenty tablets were weight and rotated at 25rpm for 4 min. or upto 100 revolutions. The tablets were taken out, dusted and reweighed. The weight loss should not be more than 1%.The percentage friability was calculated by the formula given below :

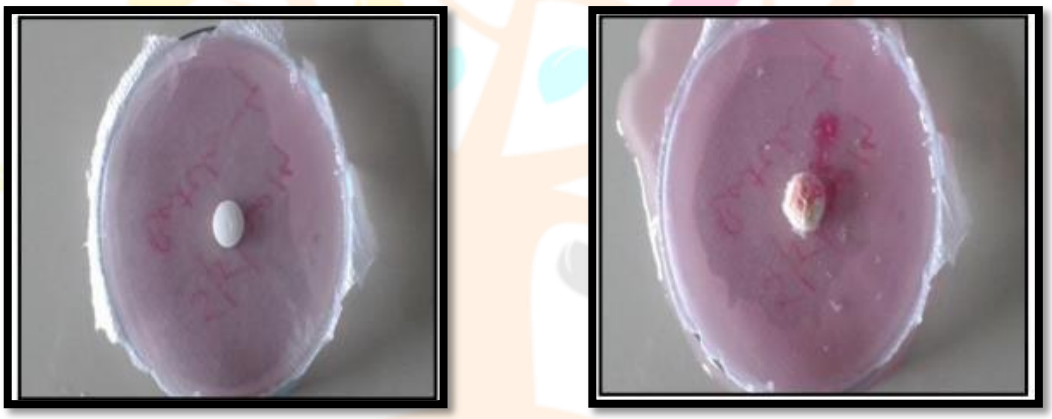
$$\%\boldsymbol{Friability} = [(\boldsymbol{Initial\ weight} - \boldsymbol{Final\ weight}) \times \mathbf{100}] \div \boldsymbol{Initial\ weight}$$

Drug content

Two tablets were powdered and the blend equivalent to 200 mg of Itraconazole was weighed and dissolved in distilled water. The solution was filtered and suitably diluted. The drug content was analysed spectroscopically at 261 nm. Each sample was analysed in triplicate and note the absorbance. Calculate the amount of drug.

Wetting time

A piece of tissue paper (10.75×12 mm).folded twice was placed in a culture dish (d=6.5 cm) containing 6 ml of water. A tablet from each of the formulation was put on the paper and the time required for the water to diffuse from the wetted paper throughout the entire tablet was then recorded using the stopwatch(as shown in fig no.3). The results are shown in table no.7



(a) (b)

Figure no:3- showing tablet(a)before wetting(b)after wetting

***In vitro* dispersion time**

Tablet was added to 10 ml of water at 37±0.5°C and the time required for complete dispersion of a tablet from each of the formulation was measured.

***In vitro* drug release**

In vitro drug release of itraconazole from dispersible tablets was determined using USP Dissolution Testing Apparatus II (Paddle type) (Disso2000, Labindia).The dissolution test was performed using 900 ml of water at 37 ± 0.50C. The speed of rotating paddle was set to be at 100 rpm. At a predetermined time interval (5 min); 5 ml samples 156 were withdrawn, filtered through Whatman filter paper. Absorption of solution was checked by UV spectrophotometer at 261 nm and drug release was determined from standard curve.

RESULT AND DISCUSSION

Solid Dispersion:

Drug content of the solid dispersions was found to be between 60 % and 75.58%(shown in Table no.6). All the solid dispersions showed the presence of high drug content and low standard deviations of the results. It indicates that the drug was uniformly dispersed in the powder formulation. Therefore, the method used in this study appears to be reproducible for preparation of solid dispersion.

Aqueous solubility studies indicated that solubility of Itraconazole increased in presence of carriers when compared to solubility of drug in distilled water. The fast and rapid dissolution of drug seen 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 aqueous solubility of all the ratio of solid dispersion is shown in table no.5

In vitro dissolution studies indicated that as the concentration of carrier increases , dissolution of drug improved. The results of drug release from solid dispersion of PEG 6000 are shown in table no:-6 . A graph is plotted against %drug release vs time which shows the maximum release of drug from the solid dispersion(shown in fig no.4).The formulation code SD8(Itraconazole: PEG 6000=1:4) showed 70.12% drug release in 40 min than other solid dispersion of PEG and pure drug. Solid dispersion showing better release was formulated into tablet dosage form and evaluated for its following parameters.

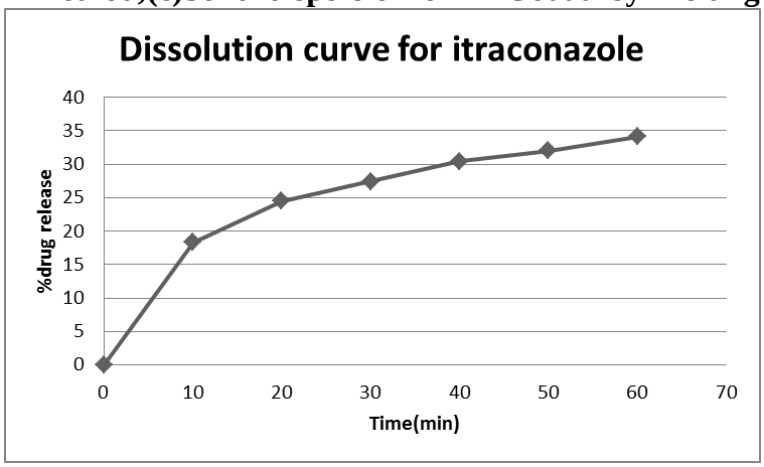
Table no.5- Aqueous solubility of drug and drug with polymer(PEG4000 and PEG 6000) in different ratio

Drug concentration(%w/v)	Polymer(PEG4000) concentration(%w/v)	Polymer(PEG6000) concentration(%w/v)	Solubility(µg/ml)
1	0	0	10
1	1	0	48.7
1	2	0	75.1
1	3	0	128.5
1	4	0	98.6
1	0	1	37.3
1	0	2	64.5
1	0	3	138.7
1	0	4	102.6

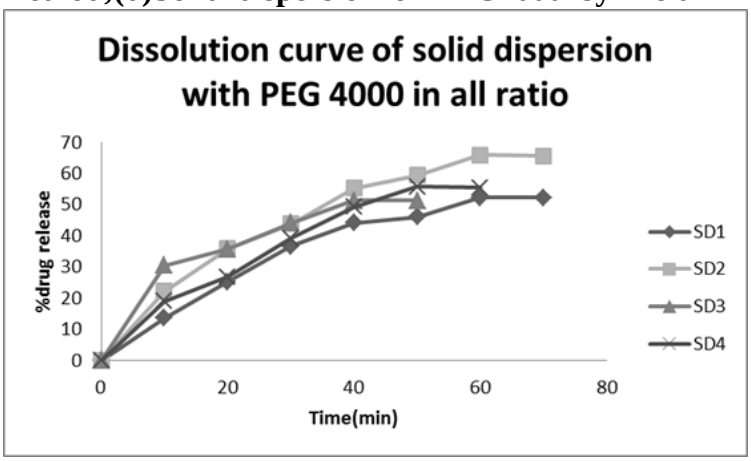
Table no.6- Evaluation of solid dispersion

Formulation Name	Theoritical yield	Practical yield	%Practical yield	Amount of drug present in SD(mg)	%Purity	Time(min)	%Drug release
SD1	100 mg	98 mg	98 %	49	61.75	60	52.28
SD2	150 mg	148 mg	98.6%	49.33	66.57	60	65.86
SD3	200 mg	188 mg	94%	47	63	40	51.28
SD4	250 mg	245 mg	94 %	49	62.25	50	55.72
SD5	100 mg	94 mg	94%	47	63.5	40	62.63
SD6	150 mg	148 mg	94%	46.94	68.82	50	59.73
SD7	200 mg	186 mg	93%	46.5	61.25	50	52.37
SD8	250 mg	249 mg	99.6%	49.8	75.85	40	70.12
SD9	100mg	94 mg	94%	47	60	70	53.87
SD10	150 mg	149 mg	99.33%	49.66	63.02	50	60.51
SD11	200 mg	197 mg	98.57%	49.25	65.18	40	48
SD12	250 mg	248 mg	99.2%	49.6	64.25	60	57.51
SD13	100 mg	96 mg	96%	48	60.99	40	56.56
SD14	150 mg	148 mg	98.6%	49.33	61.84	50	57.86
SD15	200 mg	196 mg	98%	49	63.75	50	68.17
SD16	250 mg	244 mg	97.6%	48.8	64.75	40	55.95

Figure no:4- Dissolution curve of (a)Pure drug Itraconazole;(b)Solid dispersion of PEG4000 by melting method;(c)Solid dispersion of PEG6000 by melting method;(d)Solid dispersion of PEG4000 by melt evaporation method;(e)Solid dispersion of PEG6000 by melt evaporation method plotted against %drug release vs Time(min).



(a)



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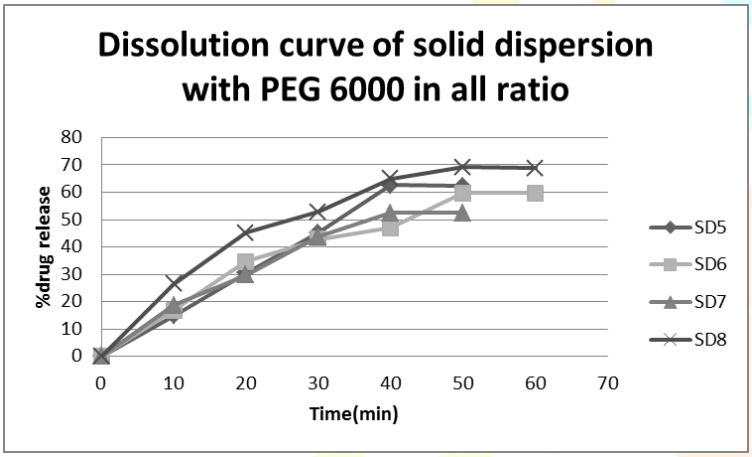

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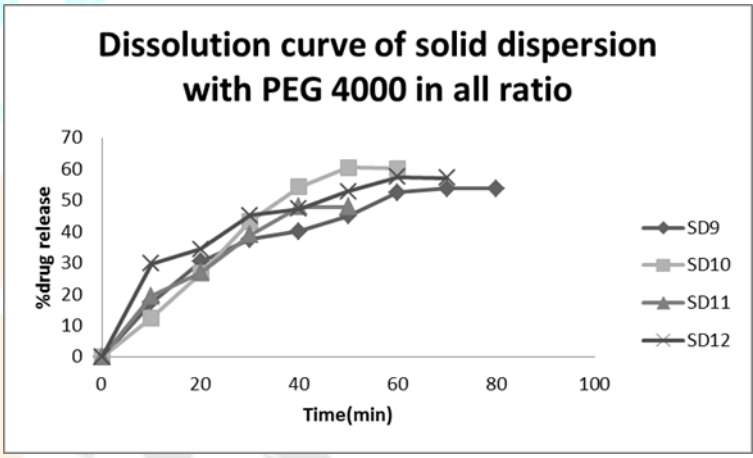
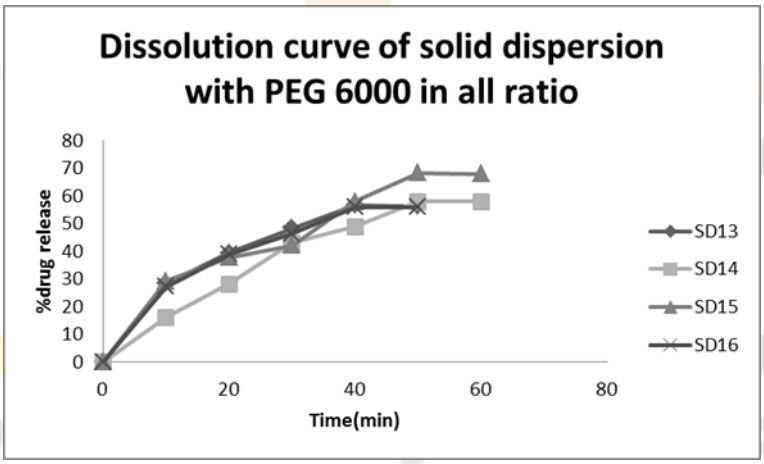


(d)



(e)

Post-compression Parameters

The formulated tablets were evaluated according to various official specifications and other parameters. Hardness, friability, weight variation, thickness dispersion time and disintegration were performed and all the results are tabulated in table no.7

The hardness of the tablets was found in the range of 4.70 kg/cm^2 to 6.87 kg/cm^2, respectively. The mean hardness test results are tabulated in Table no.7 as shown below.

Friability of the all the formulation was in the range of 0.291 to 0.428. The obtained results were found to be well within the approved range (<1%) in all designed formulations. The content uniformity was performed for all the formulations and the weight variation for all the formulations is shown in Table no.7. All the tablets passed the weight variation test; average percentage weight variation was found within the pharmacopoeial limits of ± 7.5 %. The obtained results were found to be 118.45mg to 121.52mg.

The wetting time of tablets was found to be crosspovidone ≤ sodium starch glycolate crosscarmellose sodium. While dispersion time was found crosspovidone ≤ sodium starch glycolate ≤ crosscarmellose sodium.

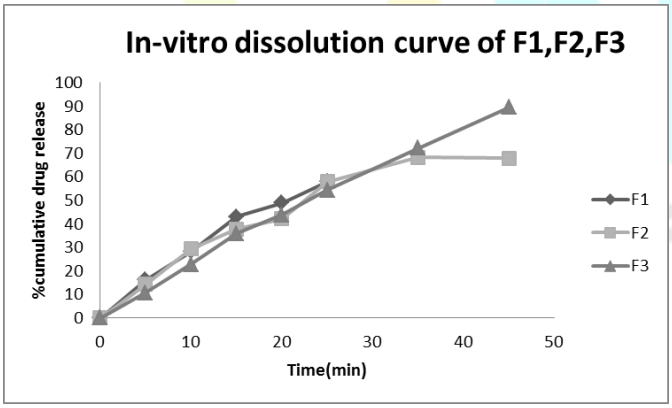
Table no:7-Evaluation of formulated dispersible tablet of Itraconazole.

Parameter	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Weight Variation(mg)	119.5	121.27	118.45	120.5	119.34	121.52	119.6	120.45	118.5
Hardness (kg/cm2)	3.71	3.81	3.92	3.89	3.66	3.68	3.50	3.42	3.48
Friability (%)	0.426	0.352	0.428	0.357	0.293	0.361	0.293	0.291	0.426
Drug Content (%)	93.28	93.70	97.06	88.66	90.76	92.86	86.98	88.66	91.60
Wetting Time (sec)	49.1	45.6	44.4	51.8	57.3	55.6	49.3	48.8	47.9
Dispersion Time(sec)	56.6	52.3	48.2	64.6	62.8	59.5	53.1	55.7	50.2
% cumulative drug release (min)	69.53	69.21	90.71	57.94	66.84	69.78	53.25	81.08	74.85

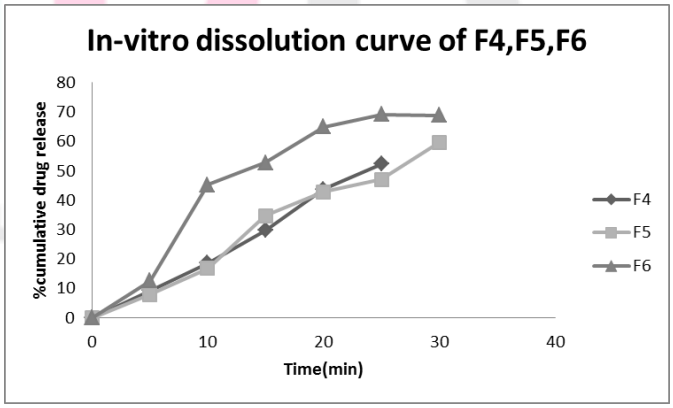
In vitro dissolution studies

All the nine formulations were subjected for the in vitro dissolution studies using tablet dissolution tester USP XXIII. The samples were withdrawn at different time intervals and analyzed at 261 nm. Cumulative drug release was calculated on the basis of mean amount of Itraconazole present in the respective tablet. The plots of cumulative % drug release V/s. time and the results obtained in the in vitro drug release for the formulations F1 to F3, F4 to F6 and F7 to F9 are shown in Figure 6. The dissolution rate was found to increase linearly with increasing concentration of superdisintegrant. Formulations F1, F2 and F3 which contained increasing concentrations of Crosspovidone from 1 % w/w to 2 % w/w, have recorded drug release 69.53%, 72.82% and 90.71% respectively, at the end of 45 minutes. Formulations F4, F5 and F6 which contained increasing concentrations of Crosscarmellose sodium from 1 % w/w to 2 % w/w, have recorded drug release 57.94 %, 66.84% and 69.78% respectively, at the end of 35 minutes. Formulations F7, F8 and F9 contained increasing concentrations of sodium starch glycolate from 1 % w/w to 2 % w/w, have recorded drug release 53.25%, 81.08% and 74.85% respectively, at the end of 35 minutes. In all the formulations the drug release of formulation F3 was nearby 90.71% in 45 min. The relative efficiency of different superdisintegrants to improve the dissolution rate of tablets was in order, Crosspovidone> Crosscarmellose>Sodium starch glycolate.

In comparative study of the formulations F3 showed 90.68% drug release respectively at the end of 45 minutes, graphical representation is shown in Figure no.5



(a)



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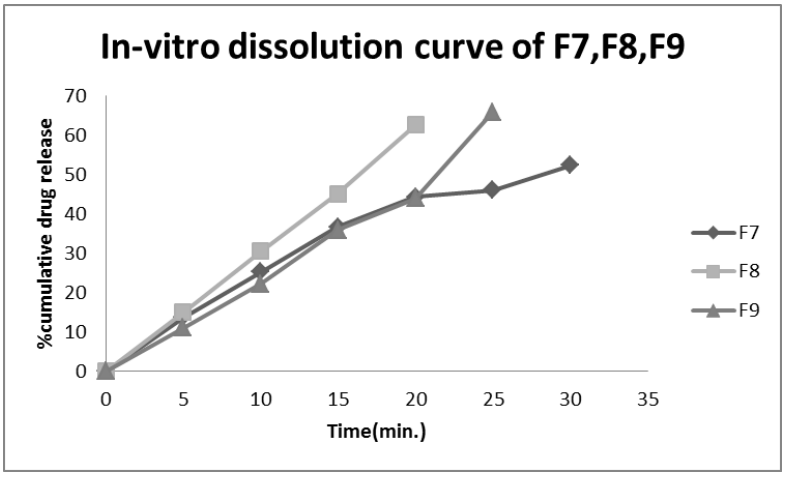

(c)

Figure no:5-showing in-vitro dissolution curve between %cumulative drug release and Time(min) of formulation (a).F1,F2,F3; (b)F4,F5,F6; (c)F7,F8,F9

CONCLUSION

From the results obtained it can be concluded that the dispersible tablet with the solid dispersion of Itraconazole can be formulated using different superdisintegrants like, Croscarmellose Sodium, Crospovidone, Sodium Starch Glycolate by Direct Compression technique and was found to be disintegrate in less than 2 minute, which provide faster effect and better patient compliance.

The formulated tablets shows compliable results for various physiochemical parameters viz. hardness, friability, weight variation, content uniformity and disintegration. The in vitro studies revealed that formulation F3 showed maximum drug release. From the above it can be concluded that the formulation F3 containing 2% Crospovidone is the best formulation which release upto 90.71% in 45 min.

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