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A Study to Improve the Solubility and Dissolution of Itraconazole Using Peg Solid Dispersions

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Abstract

Itraconazole is a broad-spectrum triazole antifungal drug extensively used in the treatment of systemic and superficial fungal infections. However, its therapeutic effectiveness is limited by its poor aqueous solubility and slow dissolution rate, which result in low and variable oral bioavailability. The present study was undertaken to improve the solubility and dissolution characteristics of itraconazole by formulating solid dispersions using polyethylene glycol (PEG) as a hydrophilic carrier. Solid dispersion technology is a widely accepted approach for enhancing the dissolution of poorly water-soluble drugs by increasing wettability, reducing particle size, and converting the drug into an amorphous or less crystalline state. Itraconazole solid dispersions were prepared using suitable drug-to-polymer ratios by the fusion method. The prepared formulations were evaluated for percentage yield, drug content, saturation solubility, and in vitro dissolution studies. Drug–polymer compatibility was assessed using Fourier Transform Infrared Spectroscopy (FTIR), while Differential Scanning Calorimetry (DSC) and Powder X-ray Diffraction (PXRD) were used to characterize the physical state of the drug. The dissolution profiles of the solid dispersions were compared with those of the pure drug and physical mixtures to determine the extent of enhancement.The results indicated that PEG-based solid dispersions significantly improved the solubility and dissolution rate of itraconazole compared with the pure drug. The enhanced performance was attributed to improved wettability, reduced crystallinity, and uniform dispersion of the drug within the hydrophilic polymer matrix. The optimized formulation exhibited the highest drug release and dissolution efficiency, suggesting its potential to improve oral bioavailability and therapeutic efficacy.

Keywords: Itraconazole, Solid Dispersion, Polyethylene Glycol (PEG), Solubility Enhancement, Dissolution Rate, Poorly Water-Soluble Drugs, Oral Bioavailability, FTIR, DSC, PXRD.

I. Introduction

Itraconazole is a broad-spectrum triazole antifungal drug widely used for the treatment of systemic and superficial fungal infections caused by fungi such as Candida, Aspergillus, and dermatophytes. It exhibits excellent antifungal activity by inhibiting the synthesis of ergosterol, an essential component of the fungal cell membrane. Despite its proven therapeutic efficacy, the clinical performance of itraconazole is significantly limited by its poor aqueous solubility and slow dissolution rate. According to the Biopharmaceutics Classification System (BCS), itraconazole belongs to Class II drugs, which are characterized by low solubility and high

permeability. For such drugs, dissolution is the rate-limiting step in drug absorption, making solubility enhancement essential for improving oral bioavailability.

Poor water solubility is a major challenge in pharmaceutical formulation development, as it can result in incomplete drug dissolution, variable absorption, delayed onset of action, and inconsistent therapeutic outcomes. Since itraconazole is practically insoluble in water, only a small fraction of the administered dose dissolves in gastrointestinal fluids, leading to reduced and unpredictable bioavailability. Consequently, considerable research has focused on developing formulation strategies that enhance the solubility and dissolution characteristics of itraconazole.Among the various techniques available, solid dispersion has emerged as one of the most effective approaches for improving the dissolution of poorly water-soluble drugs. Solid dispersion involves dispersing the drug within a hydrophilic carrier, thereby reducing particle size, improving wettability, increasing surface area, and in many cases converting the drug from a crystalline to an amorphous form. These changes enhance the drug's contact with the dissolution medium and significantly improve its dissolution rate. As a result, solid dispersion technology has become an important strategy for enhancing the oral delivery of BCS Class II drugs.

Polyethylene glycol (PEG) is one of the most commonly used hydrophilic carriers for preparing solid dispersions because of its excellent water solubility, biocompatibility, low toxicity, and ease of processing. PEG is available in different molecular weights, such as PEG 4000 and PEG 6000, and has been widely employed to improve the dissolution behavior of poorly soluble drugs. It enhances drug wettability, reduces crystallinity, and promotes rapid drug release in aqueous media. Moreover, PEG-based solid dispersions can be prepared using simple techniques such as the fusion (melting) method and solvent evaporation method, both of which are suitable for laboratory and industrial-scale production.The evaluation of itraconazole solid dispersions involves physicochemical characterization and in vitro dissolution studies to determine the extent of solubility enhancement. Analytical techniques such as Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), and Powder X-ray Diffraction (PXRD) are commonly used to assess drug–polymer compatibility and changes in crystallinity. Dissolution studies provide valuable information regarding the release profile of the drug and help identify the optimum drug-to-polymer ratio for maximum dissolution enhancement.

The present study focuses on improving the solubility and dissolution of itraconazole using PEG-based solid dispersions. By incorporating itraconazole into a hydrophilic polymer matrix, the study aims to overcome the limitations associated with poor aqueous solubility and enhance the drug's dissolution behavior. Improved dissolution is expected to increase oral bioavailability, reduce variability in drug absorption, and enhance therapeutic effectiveness. The findings of this study may contribute to the development of more efficient oral formulations of itraconazole and provide valuable insights into the application of solid dispersion technology for other poorly water-soluble drugs.

II. Review of Literature

Madhavi, Nimmathota et al., (2023). Using a variety of permeation enhancers, this study aims to improve the bioavailability of poorly absorbed medications in appropriate dose forms. The methods included kneading solid dispersions (SDs) and simply combining polymers PEG 6000 and PEG 20,000 to create physical mixtures (PMs), which were then tested for several physicochemical properties. Several polymers were used to transform optimised SDs into gels, which were then tested for penetration in both laboratory and animal models. The drug proportion in both SDs and PMs was determined to be within the acceptable range. The results showed that PEG-6000 had the greatest SD and PM dissolving rate (99.78% within 240 min) when compared to PEG 20000. Oleic acid was shown to produce the greatest drug release (92.9% within 8 hours) in both in vitro and ex vivo permeation trials, as confirmed by the researchers. Research on the interactions between the pharmaceuticals and the excipients confirmed that the formulations that were created were compatible with each other. Itraconazole PEG-6000 gel showed encouraging benefits on optimal skin penetration, according to the data.

Sid, Dounia et al., (2020). This study aims to improve the hydro solubility behaviour of a weakly basic, poorly soluble medication, namely itraconazole (ITZ). The co-evaporation approach is used to create binary inclusion complexes of ITZ and β-cyclodextrin (β-CD) in molar ratios of 1:2. We check how it dissolves and how it compares to the pure medication. Adding the extremely water-soluble polymer polyvinylpyrrolidone (PVP) to the ITZ/ β-CD complex synthesis allows for the production of ternary complexes. In fact, all of the formulations and pure ITZ undergo solid state examination using techniques including differential scanning calorimetry (DSC), powder X-ray diffraction (pX-RD), and Fourier transforms infrared (FT-IR) spectroscopy. According to solubility experiments, the solubility of ITZ produced with β-CD or β-CD and PVP was found to be enhanced with all three formulations. In contrast to the rapid and widespread release of ITZ produced by the ternary inclusion complexes, the findings demonstrate that the pure drug has a poor dissolving characteristic. Polyvinylpyrrolidone, itraconazole, and β-cyclodextrin are the main ingredients.

Kumar, Anuj et al., (2020). By making insoluble pharmaceuticals more soluble, solid dispersions improve medication bioavailability and dissolution rate. Solid dispersions are prepared using a variety of techniques, including kneading, co-precipitation, hot-melt extrusion, fusion, solvent, and many more. To increase the drug's solubility, Solid Dispersions has used a variety of carriers. Using itraconazole, poloxamer, Sporanox, citric acid, and PVP to create solid diffusions, this study aims to regain itraconazole bioavailability without crystalline alteration and to circumvent the drawbacks of adaptive solid diffusion techniques. Hemmi Pharma, BASF Chemical, and Korea-Hanssen Pharm are among the chemical suppliers that provide itraconazole, poloxamer, and Sporanox chemical, respectively. Researchers have tested the effects of solid diffusion on itraconazole solubility by manipulating the characteristics of carriers. Additionally, the stability and solubility have been studied and assessed using commercially available compounds like Sporanox, which contains 100 mg of itraconazole. To prove the stability of the dispersion method, it is essential to track the drug's crystalline form for at least six months. To improve bioavailability and enhance drug solubility

without crystalline modification, a new formulation was devised. This highlights the relevance of solubility.

Janssens, Sandrien et al., (2008). The crystallinity of PEG 6000 was decreased by combining it with PVP K25, PVPVA 64, and HPMC 2910 E5 using spray drying and extrusion. The co-spray drying process with HPMC 2910 E5 resulted in the maximum decrease of crystallinity in PEG 6000. Next, the mix was supplemented with the model medicine itraconazole, and the ternary solid dispersions that resulted were studied. Phase separation, usually leading to recrystallisation of either PEG 6000 or Itraconazole, occurs when PEG 6000 is added to the Itraconazole/HPMC 2910 E5 system, according to this study's findings. In comparison to the binary 20/80 w/w Itraconazole/HPMC 2910 E5 solid dispersion, the medication was much more amorphous and dissolved better in all ternary dispersions containing 20% Itraconazole. Compared to the binary 40/60 w/w Itraconazole/HPMC 2910 E5 dispersion, the drug's solubility was reduced in all ternary dispersions containing 40% Itraconazole, and it was largely crystalline. The findings demonstrate that when Itraconazole is in a highly amorphous form, the drug release is enhanced when PEG 6000 is added to HPMC 2910 E5.

Ye, Guanhao et al., (2007). The purpose of this research was to determine if itraconazole pellets in a solid dispersion may increase the drug's rate of solubility. Also investigated were the effects of high shear palletisation process parameters on pellet size and dissolving rate, among other pellet attributes. Mixtures of itraconazole with the hydrophilic polymer Eudragit E100 were made using a simple fusion technique. The resulting powders were then studied using X-ray powder diffraction and differential scanning calorimetry. Consequently, a lab-scale high shear mixer was used to create solid dispersions that included pellets. Applying a central composite design to optimise crucial process factors, such kneading time and impeller speed, and statistically modelling the results improved product quality. The solid dispersion of itraconazole, which was generated with a drug-to-polymer ratio of 1:2, was shown to be in an amorphous form. The answers were significantly impacted by both of the tested factors. The dissolving rate was about 30 times faster for powdered solid dispersion and 70 times faster for pellets made utilising the best parameter values compared to the pure medication. To improve the solubility of itraconazole, a solid dispersion made via a simple fusion process might be considered. Central composite design is an excellent method for optimising the palletisation process in high shear mixers.

III. Materials and Methods

Jubilant Life Sciences Limited provided the itraconazole as a complimentary sample. Jubilant Life Sciences Lmt. supplied the croscarmellose sodium, sodium starch glycolate, and cross povidone; LOBA Chemie supplied the microcrystalline cellulose, magnesium stearate, and talc; and Central Drug House supplied the mannitol.

Preparation of Standard Calibration curve

In a volumetric flask, 10 millilitres of methanol was mixed with 10 milligrams of itraconazole, a pure drug, to create a 1000µg/ml solution. Make a note of it and refer to it as product A. One way to create a solution with a concentration of 20µg/ml is to transfer 1ml of the stock solution into a volumetric flask and dilute it with methanol until it reaches 50ml. Please note "stock B

solution" on the label. Divide the stock B solution into equal portions and transfer 2 mL, 3 mL, 4 mL, 5 mL, 6 mL, and 7 mL to separate 10 mL volumetric flasks. Next, make 4µg/ml, 6µg/ml, 8µg/ml, 10 millilitre, 12 millilitre, and 14 milligram solutions by diluting the mixture to 10 millilitres with methanol. Using a UV spectrophotometer, the solution with the highest concentration was examined in the next step; the ʎmax was found to be 261nm. With the wavelength set at 261 nm, record the absorbance at each concentration. The absorbance of each concentration was specified, as indicated in table no. 1.

Preparation of solid dispersion of Itraconazole: -

Using various carriers, such as PEG 4000 and PEG 6000, in a water bath, the solid dispersion of itraconazole may be created using the melting or melt evaporation methods. For formulations, the necessary drug-to-carrier ratio was prepared by adding the relevant amounts of drug and carriers (PEG 4000, PEG 6000, and methyl cellulose) using the melting process. Afterwards, the medication and carrier were melted by heating the combination under controlled conditions while stirring constantly. The mixture was placed in an ice bath to chill and solidify after melting. The solid dispersions were ground and sieved (#100) before being dried in a desiccator. A appropriate liquid solvent is used to dissolve the medicine in the melt evaporation process. A china dish is used to melt the polyethylene glycol. The medication solution is mixed directly into the melted polyethylene glycol, which is then evaporated to provide a transparent, solvent-free film.

Preparation of tablets and its characterisation

Using the direct compression technique, 120 mg of itraconazole was made into dispersible tablets. Before adding the magnesium stearate and talc, make sure all the ingredients are blended evenly.

Evaluation of tablets

The table below displays the results of the various tests performed on the tablets, including those for hardness, friability, drug content, wetting time, in vitro dispersion time, and in vitro dissolution.

Hardness

The procedure followed by the test was conventional. Using either the Monsanto hardness tester or the Fizer hardness tester (Cadmach, India), the tablets' hardness was ascertained. Three tablets at random from each formulation were tested for hardness by pressing them diagonally between the tablet hardness tester's plungers until they shattered. The unit of measurement for the scale reading was kg/cm2.

Friability Test

The Roche friabilator was used to assess the tablet's friability. Twenty weighted tablets were spun at 25 revolutions per minute for four minutes, or up to one hundred rotations. After removing the pills, they were dusted and weighed again. Reduce your weight by no more than one percent. This percentage of friability was determined using the following formula:

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

Drug content

Two crushed pills containing 200 milligrams of itraconazole were mixed with distilled water and then weighed. Following filtration, the fluid was appropriately diluted. Spectroscopic analysis was performed at 261 nm to determine the drug content. We measured the absorbance of each sample three times. Find out how much medication.

IV. Result and Discussion

Solid Dispersion:

Drug content

Table no. 5 shows that the solid dispersions' percentages varied between 60% and 75.58 percent. Statistical analysis revealed that all solid dispersions had high drug concentrations and small standard deviations. As expected, the powdered form of the drug was dispersed uniformly. This study suggests that the method for producing solid dispersion may be repeated.

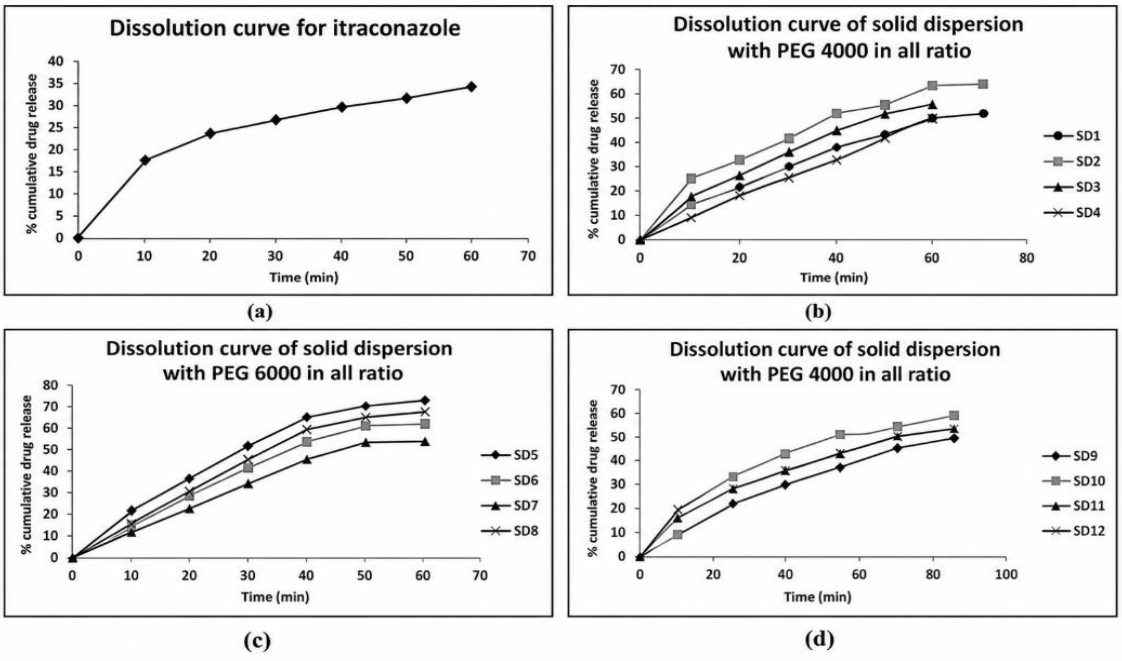
Aqueous solubility Research found that compared to the drug's solubility in pure water, itraconazole's solubility in carriers was much higher. Because the medication is present in an amorphous state in solid dispersions, they dissolve quickly. The amorphous form has the most energy of any pure chemical and dissolves quickly. The increase in dissolving rate can have been caused by other aspects as well, such as the lack of aggregation, excellent wettability, and dispersibility. Table 5 shows the water solubility of all solid dispersion ratios.

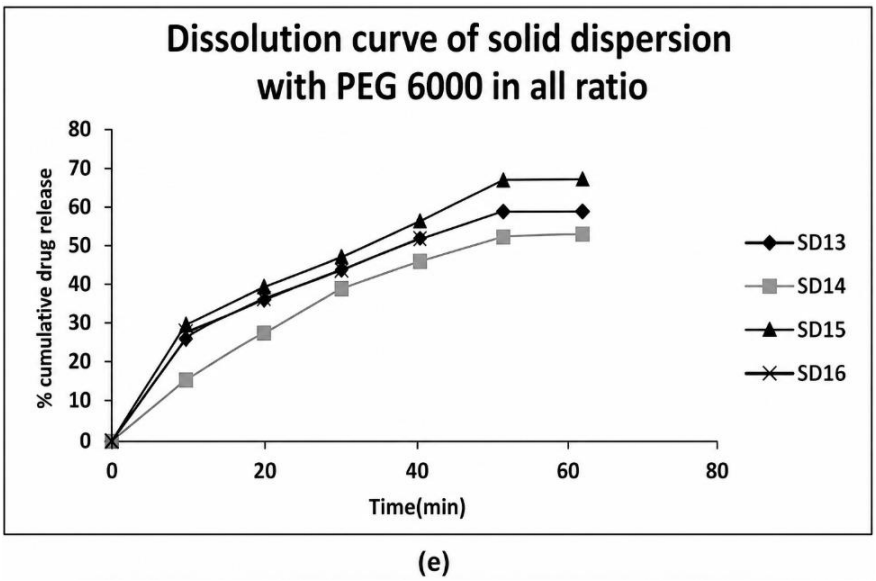
In vitro dissolution studies shown that increasing the carrier concentrations resulted in better drug solubility. Findings of the drug release from the PEG 6000 solid dispersion are shown in Table no:П5. In Figure 3, we can see a graph showing the maximum drug release from the solid dispersion as a function of time and percentage of drug release. The SD8 formulation (Itraconazole: PEG 6000=1:4) increased drug release in 40 minutes by 70.12% compared to other solid dispersions of PEG and pure medicine. In order to formulate a solid dispersion tablet with enhanced release, the following criteria were considered.

Table 5- Evaluation of solid dispersion

Formulation Name	Theoretical Yield	Practical Yield	% Practical Yield	Amount of Drug Present in SD (mg)	% Purity	Time (min)	% Drug Release
SD1	100 mg	98 mg	98.0%	49.00	61.75	60	52.28
SD2	150 mg	148 mg	98.6%	49.33	66.57	60	65.86

SD3	200 mg	188 mg	94.0%	47.00	63.00	40	51.28
SD4	250 mg	245 mg	94.0%	49.00	62.25	50	55.72
SD5	100 mg	94 mg	94.0%	47.00	63.50	40	62.63
SD6	150 mg	148 mg	94.0%	46.94	68.82	50	59.73
SD7	200 mg	186 mg	93.0%	46.50	61.25	50	52.37
SD8	250 mg	249 mg	99.6%	49.80	75.85	40	70.12
SD9	100 mg	94 mg	94.0%	47.00	60.00	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	48.00
SD12	250 mg	248 mg	99.2%	49.60	64.25	60	57.51
SD13	100 mg	96 mg	96.0%	48.00	60.99	40	56.56
SD14	150 mg	148 mg	98.6%	49.33	61.84	50	57.86
SD15	200 mg	196 mg	98.0%	49.00	63.75	50	68.17
SD16	250 mg	244 mg	97.6%	48.80	64.75	40	55.95





(e)

Figure 3- 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).

Post-compression Parameters

The newly created tablets were put through their paces using a variety of governmental criteria and additional measures. Results for hardness, friability, weight fluctuation, thickness dispersion time, and disintegration are shown in Table no. 6.

Table 6-Evaluation of formulated dispersible tablet of Itraconazole.

Parameter	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/cm^2)	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

From 4.70 kg/cm2 to 6.87 kg/cm2, the tablets' hardness levels were arranged in that sequence. The results of the mean hardness tests are shown in Table no. 7.

Friabilities ranging from 0.291 to 0.428 were observed in all of the formulations. The results were found to be exactly within the allowed range (1%), in every single formulation that was considered. The content homogeneity of each formulation was examined, and the findings, together with the weight variances, are shown in the table. All of the tablets passed the weight variation test, with an average percentage of fluctuation that was found to be within the ± 7.5% pharmacopoeial limitations. It was found by the data to be between 118.45 mg and 121.52 mg.

The findings demonstrated that when it came to wetting the tablets, sodium starch glycolate and crosscarmellose sodium were more successful than crosspovidone. After sodium starch glycolate and crosscarmellose sodium, the most dispersible components were found to be crosspovidon.

In vitro dissolution studies

The in vitro dissolution investigations were conducted on all nine formulations using the tablet dissolution tester USP XXIII. At 261 nm, the samples were analysed after being removed at various intervals of time. The average quantity of itraconazole in each pill was used to determine the cumulative medication release. Figure 4 shows the results of the in vitro drug release as well as the cumulative percentage of drug release versus time for the formulations F1–F3, F4–F6, and F7–F9. There was a linear relationship between the concentration of superdisintegrant and the rate of disintegration. At the end of 45 minutes, the drug release was 69.53% in Formulation F1, 72.82% in Formulation F2, and 90.71% in Formulation F3, where the concentration of Crosspovidone increased from 1% w/w to 2% w/w. The drug release at the end of 35 minutes was 57-94% for Formulation F4, 67-84% for Formulation F5, and 60.94% for Formulation F6, all of which included increasing amounts of Crosscarmellose sodium from 1% w/w to 2% w/w. By the end of 35 minutes, formulations F7, F8, and F9—which included sodium starch glycolate in increasing percentages from 1% w/w to 2% w/w—had reported drug releases of 53.25%, 81.08%, and 74.50%, respectively. Formulation F3 had the fastest drug release of all the formulations, at around 90.71 percent in 45 minutes. Crosspovidone, followed by Crosscarmellose, then Sodium starch glycolate, was the order of superdisintegrants' relative effectiveness in increasing the rate of tablet dissolving. At the conclusion of 45 minutes, Figure no. 4 shows that, in comparison to the other formulations, F3 had a drug release rate of 90.68%.

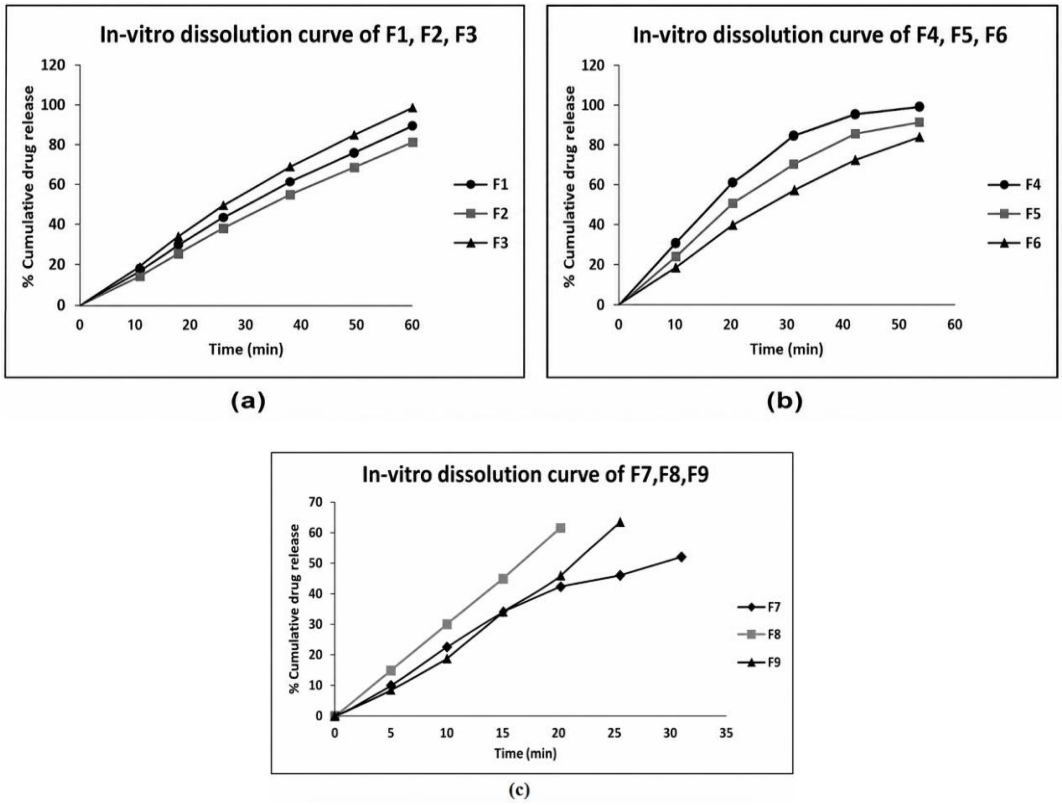


Figure 4-showing in-vitro dissolution curve between %cumulative drug release and Time(min) of formulation (a). F1, F2, F3; (b)F4, F5, F6; (c)F7, F8, F9

V. Conclusion

The present study successfully demonstrated that the solubility and dissolution rate of itraconazole, a poorly water-soluble antifungal drug, can be significantly enhanced through the preparation of solid dispersions using polyethylene glycol (PEG 4000 and PEG 6000). The solid dispersion technique effectively improved the wettability and dispersion of itraconazole, resulting in increased drug solubility and a faster dissolution profile compared with the pure drug. The prepared solid dispersions were evaluated for percentage yield, drug content, purity, solubility, dissolution behaviours, and tablet quality parameters such as weight variation, hardness, friability, wetting time, and dispersion time. All formulations complied with pharmacopeial limits for tablet quality, indicating satisfactory manufacturing characteristics. Among the prepared solid dispersions, formulations containing PEG 6000 exhibited comparatively better enhancement in solubility than PEG 4000, owing to the higher hydrophilicity and dissolution-promoting ability of PEG 6000.The optimized solid dispersion formulation demonstrated the highest solubility (138.7 µg/mL) and achieved superior drug release (70.12%) compared to the remaining formulations. The improvement in dissolution can be attributed to the reduction in drug crystallinity, increased surface area, enhanced wettability, and improved molecular dispersion of itraconazole within the hydrophilic polymer matrix. The formulated fast-dissolving tablets prepared using the optimized solid dispersion also exhibited acceptable physical properties, including uniform weight variation, adequate hardness, low friability, satisfactory drug content, rapid wetting time, and short dispersion time, confirming their suitability for oral administration.

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