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| RESEARCH ARTICLE

Formulation, In-vitro and Antifungal Activity of Fluconazole by Absorbant Solid Dispersion

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| ABSTRACT

Fluconazole is a antifungal drug used for numerous systemic and artificial fungal infections. However, it has many boundaries when directed in the form of oral solid dosage forms due to its poor aqueous solubility and dissolution profile, which is a major effort in reaching adequate oral bioavailability. Adsorbent solid dispersion (ASD) is one of the highly promising methods for ameliorating the wettability and solubility of medications having low aqueous solubility. The current research aims to improve the dissolution and solubility profile of fluconazole using the ASD approach. Polyethylene glycol 6000 (PEG 6000), Poloxamer 188 and Poloxamer 407 were applied as water- soluble polymeric carriers to trap the drug in an amorphous state and improve dissolution profile. In addition, Aerosil 200 and Aerosil 300 were utilized as highly porous carriers (adsorbents) to drastically increase the drug's contact area with dissolution media. Six adsorbent solid dispersion formulas (ASDF1 - ASDF6) were prepared using the melting method in a ratio of 0.25:0.25:0.25 (drug: carrier: adsorbent). The prepared mixtures were evaluated for saturated solubility, drug content, percentage yield, in-vitro release and antifungal activity. The prepared formulations showed an improvement in the drug's solubility. The greatest result was achieved with formulation Flu4(Poloxamer407, Aerosil 3000 and Fluconazole), which showed an increase in solubility associated with pure fluconazole. This enhancement is attributed to the alteration of the drug into an amorphous state and the massive surface area providing by the porous carriers.

| KEYWORDS

Fluconazole, Adsorbent solid dispersions, PEG 6000, Poloxamer 407, Poloxamer 188, Aerosil 300, Aerosil 200.

| ARTICLE INFORMATION

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1. Introduction

Oral digestion is the highly suitable and greatest extensively utilized approach of drug delivery due to its ease of management, good patient agreement, cost efficiency, limitations of sterility and elasticity in design of pharmaceutical dosage form. Solubility is the crucial rate determining criterion for orally transported medications to obtain effective drug level in systemic circulation for therapeutic response. The two major common reasons for insufficient oral systemic availability are weak aqueous permeability and solubility. In addition , one of the greatest restrication in oral dosage form design is the poor bioavailability . Consequently, for pharmaceutical formulation researchers, the problematic of solubility is a key issue .Poor solubility is a critical concern, which is equivalent to the formulation development of modern chemical units. Any medication that must be absorbed must be present at the absorption site in the form of solution . Amphotericin B and azoles have been the first line in the treatment for fungal infections in recent years . However, because of side effects like nephrotoxicity and infusion responses , the use of amphotericin B has been limited . As a appropriate additional to amphotericin B, Fluconazole has developed in the treatment of various systemic and superficial fungal diseases[1].

Fluconazole is antifungal medication used for a different of fungal infections . It is a triazole agent that basic in nature with pKa value of 2.03 at 37 °C and is also high polar drug. The triazole and fluoride atoms are responsible for the weak basic and polarity. Fluconazole interplay with 14-demethylase, a CYT P-450 enzyme accountable for catalyzing the alteration of lanosterol to ergosterol[2]. As ergosterol represents an important part of the fungal cellular membrane, fluconazole prevents the combination

of ergosterol to elevate cellular penetrability. Other functions of the drug are to prevent formation of yeasts through stop endogenous respiration. Notably, the loss of sterols correlates with the build up of sterols in fungus and is the main reason for fluconazole s alleged fungistatic action. fluconazole inhibition of mammalian demethylation is less complicated, it aids the body in combating the substances that cause fungal infections. However, when used as oral tablets and suspensions, it still has a lot of drawbacks [3].

Solid Dispersion (SD) approach has emerged as one of the innovative promising techniques for enhancing the solubility of weakly-soluble drugs. Solid dispersions include dispersion of the medication in a carrier matrix, usually a hydrophilic polymer, which improves the medication's dissolution and minimizes particle size, thereby increasing the rate of wettability . Over the previous five years, essential developments have been made in solid dispersion. This is true, especially in the formulation of weakly-soluble drugs. The modification of amorphous solid dispersions, which enhance medication solubility by transforming the crystalline medicines into an amorphous state, is one noteworthy extension. Recent research emphasizes the significance of polymeric carriers including hydroxypropyl methylcellulose ,polyvinylpyrrolidone and new-generation polymers like Soluplus in order to stabilize amorphous drug particles, inhibit recrystallization and improving solubility and bioavailability. Its success is largely dependent on the quality of the carrier and the preparation of solid dispersions [4].

The goal of this study is to use the ASD method to enhance the solubility of fluconazole. To effectively formulate fluconazole, several key excipients are utilized to enhance its solubility and dissolution profile. PEG 6000 is a hydrophilic, water-loving polymer that acts as a matrix to trap fluconazole; as it solidifies, it forces the drug into an amorphous, non-crystalline state that dissolves much faster in water. Working alongside this, Aerosil 200 serves as a highly porous, lightweight carrier with a surface area of 200 m^2/g, allowing the drug to deposit as a thin film onto its massive surface and inside its pores, which drastically increases the drug's contact area with dissolution fluids. Similarly, Aerosil 300 is the exact same type of porous carrier but possesses a larger surface area of 300 m^2/g, providing even more physical space for the drug to spread out and potentially offering an even faster dissolution rate than the 200 variant. To further aid the dissolution process, Poloxamer 188, a non-ionic surfactant or surface-active agent, is employed to dramatically improve wettability by lowering the surface tension between the hydrophobic drug and water, allowing the fluid to penetrate and dissolve the drug quickly without it clumping back together. Finally, Poloxamer 407, a surfactant similar to 188 but with a higher molecular weight, also improves wetting and solubility while offering excellent micelle-forming and gel-forming capabilities at certain concentrations, which helps keep the dissolved drug stable and prevents it from precipitating.

2. Materials and Method

2.1. Materials

Fluconazole as pure drug, Poloxamer407, Poloxamer188, Aerosil2000, Aerosil 3000 and PEG6000 were purchased from Hangzhou, Hyperchem. China.

2.2. Method

2.2.1. Preparation of ASD of Fluconazole

For preparing the fluconazole solid dispersion , Fusion method was using , weighing the amount of fluconazole, PEG6000, Poloxamer 407 and Poloxamer 188 properly with a weight 0.250 mg for each. A water bath was set to a certain temperature (70°C), each polymer is located in a mortar and then in the water bath until it melts . The designed amount of Fluconazole were added gradually with through mixing by a pestle, and was included in the molten carrier with a ratio of 0.250:0.250 with constant stirring until uniform mixture was got. Mesh number 70, 212 µm used for sieving the powder after it has been dried at room temperature[5]. The formulated solid dispersions are illustrated in table1.

Formulation of adsorbent solid dispersion (ASD) of fluconazole .The powder of mixture for fluconazole and polymer (PEG6000,Poloxamer 407 and Poloxamer) was heated again in the water bath , Once uniform slurry was achieved , Aerosil 2000 and Aerosil 3000 were added in a weight 0.25 mg for each with the same ratio (0.250:0.250:0.250) very carefully and gradually to the mortar with continuous stirring until a mass obtained. The mass for each mixture was permitted to cool at ambient temperature. Finally, were sieved again using the same sieve to obtain a uniform size powder as shown in table2[6].

Table 1. Structure of various SD formulations of Fluconazole

Formulation code	Fluconazole (g)	poloxamer 188(g)	poloxame r 407(g)	PEG6000 (g)
SD1	0.25	0.25	---------	----------
SD2	0.25	----------	0.25	----------
SD3	0.25	----------	----------	0.25

Table 2. Structure of different ASD formulas of FLU.

formulation code	Arosil200(mg)	Arosil300(mg)
ASDF1(polox188/FLU)	0.25	
ASDF2 (polox188/FLU)		0.25
ASDF3 (polox407/FLU)	0.25	
ASDF4 (polox407/FLU)		0.25
ASDF5 (PEG6000)	0.25	
ASDF6 (PEG6000)		0.25

2.2.2. Physical mixture (PM)

The PM was produced by homegenuous blending of medication, adsorbent and vehicle with similar ratios ASD . The mixture was transported through a Mesh number 70 sieve Mikron 212 to obtain uniformly sized particles.

2.2.3. Saturated solubility determination

An excessive quantity of FLU, SD and ASD were incorporated to ten ml of water; the prepared samples were sited in shaker water bath apparatus at room temperature for fourty eight hours. Then, filtration of the samples was carried out using a 0.45µm disposable filter syringe and subsequently diluted. Finally , UV spectrophotometer was used to analyze the diluted and determine the dissolved quantity of FLU[7].

2.2.4. Percent yield (PY %) measurement:

The Percent yield was determined for every category of ASD , which was measured according to the equation (1)[8].

$$PY\% = \frac{Actual\ weight\ of\ SDF}{Theoretical\ weight\ of\ SDF} \times 100 \text{.....(1)}$$

2.2.5. Quantification of drug loading of ASD

An precisely weighed amount of ASD equal to 10 mg of FLU was obtained and solubilized in a 10 ml of organic solvent methanol and volume was diluted. Based on this, 1ml of the solution was sampled and subjected to further diluted with methanol. The mixture was analyzed for medication content using UV spectrophotometry technique [9]. The percent of medication content in the ASD was obtained using the following equation 2[10].

$$Drug\ content\ \ \% = \frac{Actually\ gained\ weight\ of\ FLU}{Theoretical\ weight\ of\ FLU} \times 100 \text{.....(2)}$$

2.2.6. In-vitro studies

Dissolution investigations of fluconazole and ASD equal to 150mg of fluconazole were performed in RC-3 Dissolution Tester a multi-vessel dissolution tester that typically supports USP Apparatus 2 (Paddle method) . Buffer solution was prepared from dissolving KH2PO4 (6.805 g) and NaoH(0.896) in distilled water to reach a ph that equals 6.8 (checked by HI2211 ph/oRP meter). The temperature should be at 37±0.5 °C and the speed of rotation is 75rpm. The specific weight to each formula(pure drug, ASDF1,ASDF2,ASDF3,ASDF4,ASDF5,ASDF6) placed in the vessel of the device , After turning on the device, we will wait at specific time intervals (5,10,15,30,60,90 min) and 5ml were withdrawn from each sample and followed by replacement with fresh phosphate buffer media at the regular intervals .The samples were filtered using the filter syringe 0.5 um and then were examined by UV spectrophotometer at 261 nm[11].

2.2.7. Antifungal activity:

An agar well diffusion approach was used to evaluate the biological activity as previously reported. In this study, blinding was worked for agar well diffusion. The selected strains for this investigation were candida tropicalis and candida albicans. The choice of different candida species was influenced by strong activity of FLU against candida in comparison to other antifungals agents. For comparision, the antifungal activity of optimized formula of SDF, physical mixture, marketing FLU and free FLU. In the center of the sterile petri dish, a predetermined amount of fresh fungal culture was pipeted. The petri dish containing the inoculum was then filled with melted , chilled muller hinton agar for fungus and properly mixed. A sterile cork borer with a diameter of 6 mm was used to make wells into agar plates containing the inoculum after solidification. The inhibition zone diameter was measured after 24 hours incubation period at 37 °C to assess the activity. This process was carried out as previously described[12,13].

3. Results and Discussion

3.1. Saturation solubility of ASDFs

Table 3 demonstrations the solubility findings FLU ASDFs. Additional enhancement in solubility was achieved when FLU formulated as ASDFs in comparison to pure drug as as result of adsorption of FLU on the polar adsorbent carrier and rise the surface area of FLU that subjected to the solvent media , in which the medication is attach [14]to the adsorbent carrier and thus cannot agglomerated which promotes in improved solubility and wettability of the FLU. The solubility improvement of the

numerous adsorbents carrier is higher in aerosol 300 than aerosil200 in the occurrence of any water-soluble carrier. The outcomes may be due to the variations in adsorption volume of two adsorbents to the FLU. Highest solubility was got with Aerosil 300 as a result of its high disintegration efficiency in an aqueous media and high surface area(SA) [15]. Consequentely , the greatest surface area(SA) of FLU that showing to the dissolution medium was gotten upon adsorbed onto adsorbed on Aerosil 300. Formula ASDF4 demonstrated the greatest solubility 6.25 mg/ml compared to 0.485 mg/ml for pure drug resulting that ASD technique enhances the solubility by 12 compared with the pure drug.

3.2. Percentage yield (PY %) and content determination for prepared ASDF

The formula ASDFs illustrated greater percent yield within the range of 85-70%. The finding suggesting the appropriateness of the technique (melting adsorption approach) with the used material for such preparations.

In contrast, the medication level in each the formulations was shown to be within 98-100% w/w, which is in match with U.S.P criteria (98-100%). The findings of percent yield and medication amount are demonstrated in table 3.

Table 3. the comprehensive summary of the drug content, percentage yield, and solubility parameters(n=3±SD)

Formula	Saturated solubility mg/ml	Drug content	Percentage yield
FLU in water	0.485±0.01	--------	---------
FLU in buffer	0.261±0.01	---------	---------
ASDF1	2.67±0.03	80%±1.21	84±1.02
ASDF2	3.75±0.03	98%±2.99	94±1.55
ASDF3	2.16±0.05	92%±2.65	95±1.98
ASDF4	6.25±0.01	99%±1.02	95±0.99
ASDF5	5.96±0.01	90%±1.22	90±1.66
ASDF6	5.82±0.06	95%±1.87	92±1.65

3.3. In-vitro dissolution investigations

Acomparative in-vitro dissolution of the unprocessed (pure) drug and (ASDF1-ASDF6) was assesed. An enhancement in the dissolution test was observed (figure 1) by ASDF4 in comparison with other ASDFs, and pure drug. This outcome may result from increased solubility through hydrogen bond formation between the medication and Aerosil 300, micellar solubilisation of FLU in poloxamer407, increased wettability and amorphisation of FLU[16].

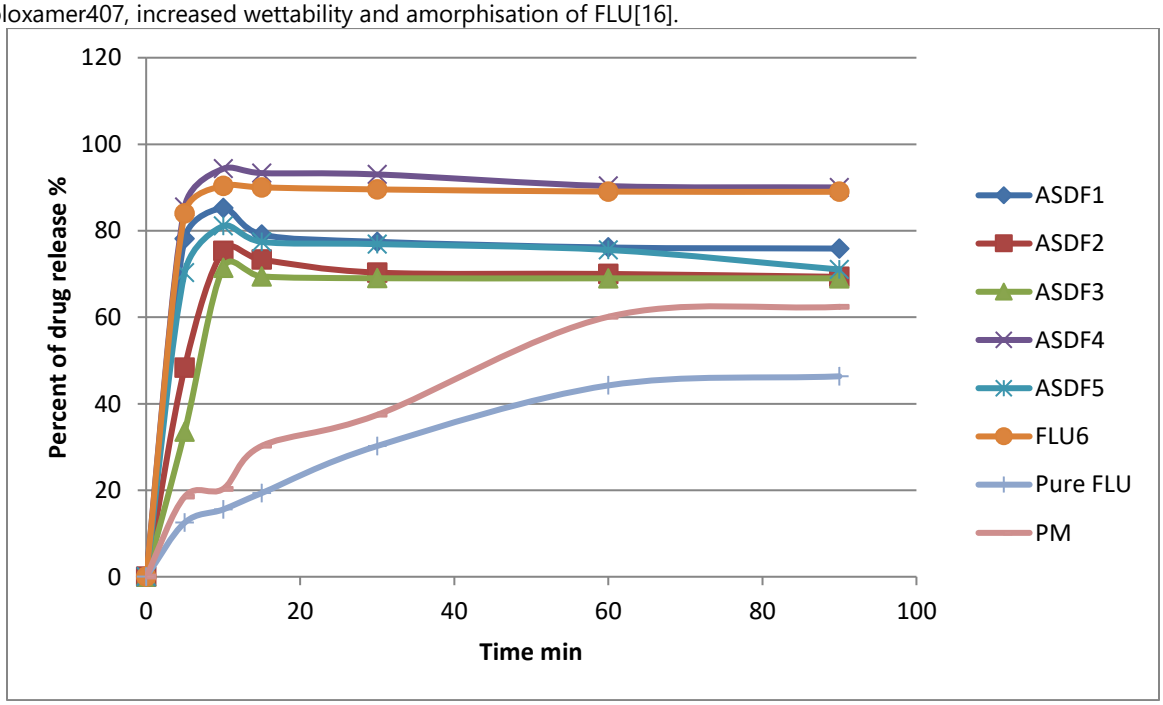

Figure 1: Comparative in-vitro dissolution profile (release)of fluconazole, PM and ASDFs at phosphate buffer 6.8 and 37°C±0.5

3.4. Assessment of biological activity:

The agar well diffusion method against Candida albicans and Candida tropicalis was used to avaluate the antifungal activity of the selected formula (ASDF4) . In comparision to pure FLU, physical mixture and marketed capsule, it demonstrated improved antifungal activity. Notably, they produced 10 mm inhibition zone in diameter against Candida tropicalis and candida albican, while pure drug exhibited no detectable inhibition zone (0 mm) under the same conditions as demonstrated in figure 2 .

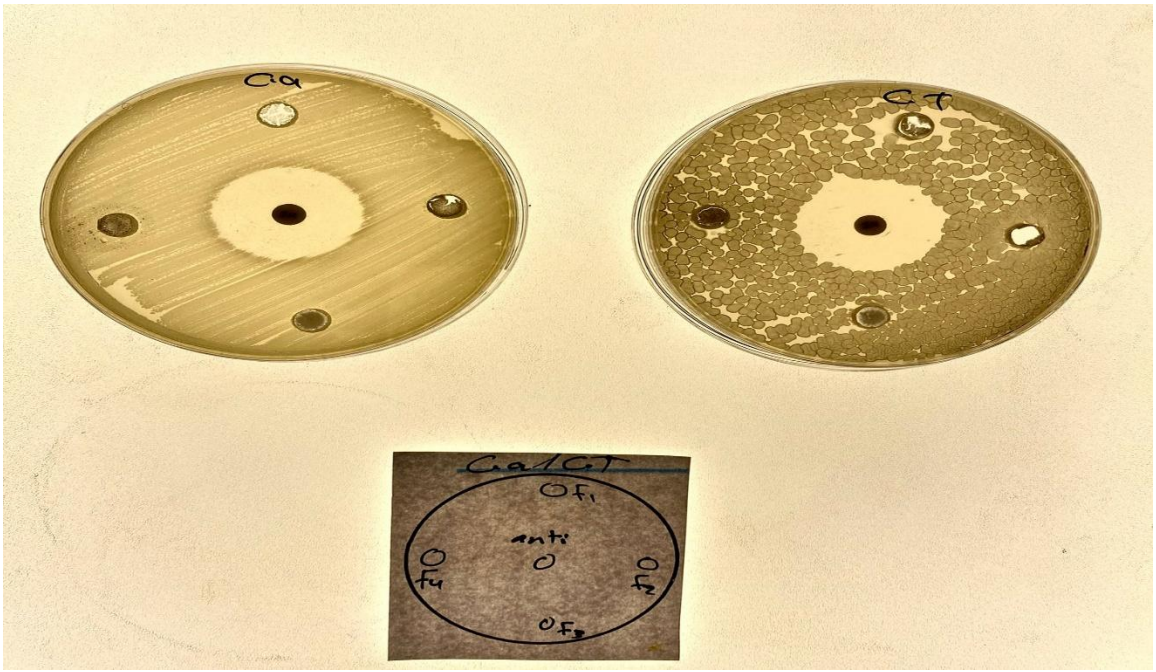

Figure 2 : The agar well diffusion technique for the selected formulaF1:ASDF4 , physical mixture: F2, marketed capsule: F3 and pure drugF4 against candida albicans and candida tropicalis.

4. Conclusion

An enhancement in dissolution and solubility of FLU was increased by formulating it as adsorbent solid dispersion by melt technique using polar transporters carrier and adsorbents in a ratio of 0.25:0.25:0.25(drug: carrier: adsorbent). All ASDFs formula enhanced the solubility of FLU could be due to improved wettability and condensed crystallinity of the FLU, which result to advance medication solubility and dissolution profile. However, greater solubility with improved dissolution and antifungal activity was achieved by ASDF4 using hydrophilic carrier poloxamer 407 and Aerosil 300 as an adsorbent with large surface area.

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