INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA):IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Research Article

Formulation Development Of Solid Dispersion Adsorbate To Enhance Solubility, Dissolution And Flow Properties Of Clotrimazole Using 32 Factorial Design

Bhavin D. Pandya*, Krena N. Patel, Jinal H. Boradhara, Vaishnavi D. Shah, Vishwa A. Vyas

Department of Pharmaceutics, Babaria Institute of Pharmacy, BITS Edu Campus, Varnama, Vadodara, Gujarat, India.

ARTICLE INFO

Received: 13 June 2024
Accepted: 17 June 2024
Published: 09 July 2024

Keywords:
Solid, Dispersion, Adsorbate, Solubility, Dissolution, Clotrimazole, Factorial, Design

DOI:
10.5281/zenodo.12746233

ABSTRACT

The study aimed to improve the solubility and flow properties of clotrimazole, a Biopharmaceutical Classification System (BCS) Class II drug, using the solid dispersion adsorbate technique. The solid dispersion of clotrimazole with poloxamer 188 was prepared through the melting method and subsequently adsorbed onto sylysia 350, a porous carrier. A 3^2 factorial design and response surface methodology were employed to establish the optimal formulation variables, such as the ratio of clotrimazole to poloxamer 188 and the ratio of sylysia 350 to the solid dispersion. The prepared clotrimazole solid dispersion adsorbate granules were evaluated for their dissolution and flow properties and characterized using differential scanning calorimetry (DSC), X-ray diffraction (XRD), Fourier-transform infrared spectroscopy (FTIR), Scanning Electron Microscopy (SEM) and accelerated stability analysis. Optimal solid dispersion adsorbate granules containing an equivalent of 10 mg of clotrimazole were manufactured into tablets using the wet granulation method, alongside plain clotrimazole tablets for comparison. The study found that clotrimazole was spontaneously solubilized in poloxamer 188, as indicated by the negative Gibbs free energy values. Dissolution studies, conducted in 0.1 N hydrochloric acid in accordance with USFDA guidelines, showed that the optimized formulation released over 85% of the drug within 30 minutes, significantly faster than the pure clotrimazole tablets. Furthermore, after one month of storage at 40°C and 75% relative humidity, the solid dispersion adsorbate granules exhibited no change in drug release, indicating that sylysia

***Corresponding Author:** Bhavin D. Pandya
Address: *Department of Pharmaceutics, Babaria Institute of Pharmacy, BITS Edu Campus, Varnama, Vadodara, Gujarat, India.*
Email : pandyabhavin3264@gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

350 effectively prevented the conversion of clotrimazole from its amorphous to crystalline form, thus enhancing its physical stability. Therefore, the solid dispersion adsorbate technique proves to be a promising approach for enhancing the solubility and flow properties of poorly water-soluble drugs.

INTRODUCTION

Candidiasis is a fungal infection caused by a yeast (a type of fungus) called Candida. Candida normally lives on skin and inside the body, such as the mouth, throat, gut, and vagina. Candida can cause infections, if it grows out of control or if it enters deep into the body. For example, it can cause infections in the bloodstream or internal organs like the kidney, heart, or brain [1]. Clotrimazole is an USFDA approved broad-spectrum antifungal agent used for the treatment of a wide variety of dermatophyte infections and oral, local and systemic candidiasis [30]. Clotrimazole kills individual Candida or fungal cells by altering the permeability of fungal cell wall. It binds to phospholipids in the cell membrane and inhibits the biosynthesis of ergosterol and other sterols required for cell membrane production which leads to the death of fungal cell via loss of intracellular elements [27]. Clotrimazole is a class-II drug of biopharmaceutical classification system with very low aqueous solubility (0.00049 mg/ml), high permeability, pKa of 4.7, and log P of 6.1 in octanol/water. It has a low bioavailability, with an absolute oral bioavailability of less than 10% in humans. Clotrimazole has been observed to have inadequate absorption due to its low water solubility and dissolution rate [2, 27]. Several researchers have sought to enhance solubility and dissolution properties of clotrimazole by developing inclusion complexes with beta-cyclodextrin, clotrimazole ufosomes, cubosomes, proniosomal gel, microemulsion based in-situ gel, microemulsion based vaginal gel, emulgel, transdermal spray, solid lipid nanoparticles for solubility and bioavailability enhancement [27–37]. A solid dispersion is a dispersion of active substances in an inert carrier or matrix that has been created using the melting, solvent, or melting-solvent process. Some of the downsides of solid dispersion include difficulties pulverizing, low compressibility, and poor flow characteristics. Furthermore, the high-energy amorphous state of the medication in solid dispersion tends to return to the less soluble crystalline form during storage [9]. The solid dispersion adsorbate method may solve these issues. Solid dispersion adsorbate is a process in which solid dispersion is adsorbed onto a porous carrier (with a very large surface area) to create a free-flowing powder and boost dissolving rates and hence bioavailability. Commercially available porous carriers (Aerosil, Sylysia, Florite, and Aerogel) with varying properties such as particle size, pore size, and specific surface area are commonly used to encapsulate poorly soluble drug substances [14, 15]. In the current investigation, Sylysia 350 served as a porous carrier (adsorbent). Sylysia 350 is amorphous silicon dioxide having a pore volume of 1.60 ml/g. It is a dry, tasteless, odourless, white micronized porous powder with 3.9 μm particle size. It has a high specific surface area of around 300 m2/g and an adsorption capacity of about 310 ml/100g, making it a useful material for adsorption of high proportions of drugs. Sylysia 350 has several uses in the pharmaceutical area, for example, it has been employed as a floating carrier to construct low-density floating systems, to prepare liquisolid systems with increased flow property and compressibility, to mask the unpleasant taste by adsorption on its porous surface, and to increase the dissolution and solubility of low aqueous drug in solid dispersion [17, 26]. Poloxamer 188 was empirically chosen as a carrier for solid dispersion because to its low temperature of melting (about 60°C), surfactant characteristics, and oral safety[1]. When it comes to developing formulations, traditional trials take more time, effort, and money. Experimental designs are

beneficial for producing formulations that require fewer experiments and determining the relative relevance of different factors. As a result, the major goal of the current study is to increase clotrimazole solubility by solid dispersion (melting). The secondary goal is to transform the melt dispersion into flowable and compressible granules by adsorbing it onto a porous carrier (sylysia 350) using a 32 factorial design, and then to produce a clotrimazole tablet formulation that dissolves quickly.

MATERIALS AND METHODS

MATERIALS

Clotrimazole was acquired as a gift sample from chemdyes corporation in Rajkot. Fuji silysia chemicals, Japan, sent a gift sample of sylysia 350 (amorphous silicon dioxide). Suvidhinath laboratories supplied poloxamer 188, polyvinyl pyrrolidone K-30, isopropyl alcohol, spray-dried lactose, sodium starch glycolate, magnesium stearate, and talc. All other compounds were analytical grade.

PHASE SOLUBILITY STUDIES

Phase solubility studies were studied as described according to Higuchi and Connors [4, 5]. The solubility of clotrimazole with poloxamer 188 and PVP K30 was investigated. Beaker solutions containing 5%, 10%, 15%, and 20% of each polymer were prepared. An excess amount of clotrimazole was added to 5 ml of each solution. The solutions were shaken in an environmental shaker at 250C for 24 hours. Samples were filtered via whatman filter paper and analysed spectrophotometrically (Shimadzu U-1800, Japan) for dissolved drug at 264 nm. The apparent (1:1) stability constant was determined from the phase solubility graph using the Higuchi and Connors phase-solubility study method. Poloxamer 188 and polyvinyl pyrrolidone K-30 were dissolved separately in water to create an aqueous carrier solution (5, 10, 15, and 20% w/v). An excess of clotrimazole was added to 5 ml of each polymer solution. The solutions were agitated on a shaker at 250C for 24 hours. The samples were filtered via Whatman filter paper and analyzed spectrophotometrically (Shimadzu U-1800, Japan) for dissolved drug at 264 nm. The apparent stability constant, Ks, was estimated using the phase solubility graph. The Gibbs free energy (ΔG0tr) of clotrimazole from pure distilled water to polymer solution was determined using the following formula equation: Where, S0/SS is the ratio of the solubility of clotrimazole in distilled water to that of polymer solution.

PRELIMINARY SCREENING FOR SELECTION OF CARRIER

The melting method was used to conduct preliminary investigations for screening the ratio of carrier (Poloxamer 188) and clotrimazole for solid dispersion. Different carrier-to- clotrimazole ratios (0:1, 1:1, 3:1, 5:1, and 7:1) were examined. Poloxamer 188 (chosen based on screening investigations) was melted in a china dish over a water bath. Clotrimazole was then distributed in the molten carrier material while stirring continuously. The molten material was rapidly cooled to room temperature in order to produce solid dispersion. The resulting solid dispersion was collected and kept in desiccators until further examination. Clotrimazole solid dispersions corresponding to 10 mg were packed into capsules, and the in-vitro dissolving test was performed using the method outlined in the in-vitro dissolution tests.

PRELIMINARY SCREENING FOR SELECTION OF ADSORBENT

Preliminary investigations were conducted to find a suitable adsorbent in order to improve the flow characteristics of the clotrimazole solid dispersion. Sylysia 350 and sylysia 550 were chosen as adsorbents due to their superior adsorptive abilities. Poloxamer 188 and clotrimazole in solid dispersion were preserved at the same ratio (3:1). Clotrimazole solid dispersion was adsorbed onto

adsorbent in various ratios (sylysia 350/sylysia 550) to produce solid dispersion adsorbate granules. The resultant solid dispersion adsorbate granules were assessed for angle of repose using the fixed funnel technique.

CHARACTERIZATION OF SOLID DISPERSION BY FTIR

Clotrimazole, the carrier (Poloxamer 188), the adsorbent (Sylysia 350), and the solid dispersion adsorbate were all analyzed using Fourier Transform Infrared (FTIR). The produced samples were examined using an FTIR instrument (Agilent Cary 360) at the Babaria Institute of Pharmacy in Vadodara, and the FTIR spectra were recorded. The spectra were collected in the wave number range of 4000 to 400 cm-1.

Table 1. Design layout of 32 factorial batches.

Independent variables

	Coded value		Decoded value	
Formulation	**X_1**	**X_2**	**X_1[a]**	**X_2[b]**
F_1	-1	-1	2:1	1
F_2	-1	0	2:1	2
F_3	-1	+1	2:1	3
F_4	0	-1	3:1	1
F_5	0	0	3:1	2
F_6	0	+1	3:1	3
F_7	+1	-1	4:1	1
F_8	+1	0	4:1	2
F_9	+1	+1	4:1	3
F_{10}[c]	-	-	2.5:1	1.5

a - Solid dispersions were prepared using the ratio of carrier and drug (X1).

b - One part of these solid dispersion was adsorbed onto the different ratios of sylysia 350 (X2).

c - Check point batch for validation of model.

PREPARATION OF SOLID DISPERSION ADSORBATE GRANULES

Clotrimazole solid dispersion adsorbate granules were made using the melting method. Table 1 explains the composition of the carrier (poloxamer 188), adsorbent (sylysia 350), and clotrimazole. Poloxamer 188 was melted in a china dish over a water bath. Clotrimazole was dispersed in the molten carrier material by continuous stirring to achieve solid dispersion. The resulting solid dispersion was then adsorbed onto the sylysia 350 (pre-heated to 60°C) to produce solid dispersion adsorbate granules. The solid dispersion adsorbate granules were allowed to cool till room temperature.

EXPERIMENTAL DESIGN

According to the literature review, two independent parameters, the ratio of carrier (poloxamer 188) and clotrimazole in solid dispersion and the ratio of adsorbent (sylysia 350) to solid dispersion, are predicted to have a substantial impact on the dissolution and flow characteristics of the produced system [4, 5]. Thus, in the current study, a two-factor, three-level (32) design was adopted to measure impact of two independent variables. As a result, formulation components such as the ratio of carrier (Poloxamer 188) and clotrimazole in solid dispersion (X1) and the ratio of adsorbent (sylysia 350) to solid dispersion (X2) were chosen as independent variables. Table 1 shows that a total of nine

formulations were created. The dependent variables chosen were Q30 (cumulative % drug release at 30 minutes, Y1) and angle of repose (Y2). The response were calculated using the following statistical model, which included both interactive and polynomial terms:

$$Y = b0 + b1X1 + b2X2 + b12X1X2 + b11X21 + b22X22;$$

Where, Y is dependant, b0 is the arithmetic mean response of all trials, and b1, b2, b12, b11, and b22 are the estimated coefficients for the associated factors X1, X2, X1X2, X12, and X22, representing the average effect of altering one component at a time from low to high value. The interaction term (X1X2) depicts how the response varies when two factors are altered concurrently. The polynomial terms (X12, X22) are used to examine nonlinearity. The polynomial equation and all significant values were derived using design expert software.

STATISTICAL ANALYSIS

Design Expert software version 7.0.0 (Stat-Ease, Inc., Minneapolis, MN) was used to simulate the impact of independent factors on replies. Polynomial equations were created for the dependent variables, Q30 and angle of repose. The obtained polynomial equations were simplified by eliminating nonsignificant components. The experimental findings were confirmed using an analysis of variance and the F-test. The optimal formulation was chosen using graphical optimization with the overlay plot.

VALIDATION OF EXPERIMENTAL DESIGN

Additional checkpoint trials (F10) were carried out to confirm the experimental design. The polynomial equations predicted the values for Q30 and angle of repose. The anticipated and experimental values of the responses were compared for statistical significance using the t-test with a 95% confidence interval. The proportion of relative error between predicted and experimental values for each answer was computed.

CHARACTERIZATION OF SOLID DISPERSION ADSORBATE

IN-VITRO DISSOLUTION STUDIES

In-vitro dissolution testing of developed formulations were performed in 900 ml of 0.1 N hydrochloric acid according to the Indian Pharmacopoeia. The dissolving medium was maintained at 37 ± 0.50C and 100 rpm [3]. Aliquots of 10 ml were taken at regular intervals, filtered, and spectrophotometrically analyzed at 264 nm using a UV visible spectrophotometer (UV-1800, Shimadzu, Japan).

X-RAY POWDER DIFFRACTION

The spectra of clotrimazole, poloxamer 188, sylysia 350 and optimized solid dispersion adsorbate formulation (F5) were obtained from X-ray powder diffraction studies using philips X-Ray diffractometer (Model: X'PERT MPD, Holland). The samples were ground into powders with a mortar and pestle and the cross section of samples was exposed to X-ray radiation. The scanning angle ranged from 20 to 700 of 2θ.

DIFFERENTIAL SCANNING CALORIMETRY

The differential scanning calorimetry studies of optimized formulation (F5), clotrimazole, carrier (poloxamer 188), and adsorbent (sylysia 350) were carried out by using DSC60 Shimadzu, Japan. The thermal characteristics of the samples were studied at a scanning rate of 200C/min, encompassing a temperature range of 30-4000C in an inert environment flushed with air at a rate of 10 ml/min.

FORMULATION OF TABLETS

Clotrimazole solid dispersion adsorbate tablets were manufactured using the wet granulation technique. The tablets were made using standard amounts of commonly employed excipients as described in the literature [4, 5]. Table 2 shows the composition of solid dispersion adsorbate and

plain clotrimazole tablets. The optimized composition of solid dispersion adsorbate granules (F5) corresponding to 10 mg was appropriately mixed with spray dried lactose and sodium starch glycolate for 10 minutes. In the prepared powder mixture, 5% w/v of polyvinyl pyrrolidone (PVP K-30) was added, passed the granules from sieve no. 60, dried it 70°C temperature in tray dryer and made the granules by wet granulation method. Magnesium stearate and talc were added to the prior mixture, mixed for an additional 5 minutes, then compressed using a rotary tablet compression machine. Tablets with an average weight of 500 mg were manufactured. The tablets were subjected to a variety of assessment tests, including hardness, friability, and weight variation, as per normal protocols.

Table 2. Formulation of tablets.

Ingredients	Solid dispersion adsorbate tablets (mg)	Plain clotrimazole tablets (mg)
Solid dispersion adsorbate–equivalent to 10 mg of drug	120[a]	10
Polyvinyl pyrrolidone K-30 in isopropyl alcohol	5% w/v	5% w/v
Spray dried lactose	340	450
Sodium starch glycolate	20	20
Magnesium stearate	5	5
Talc	10	10
Total weight	500	500

a- Optimized composition of solid dispersion adsorbate granules (F5) equivalent to 10 mg of clotrimazole.

STABILITY STUDIES

The optimized composition of clotrimazole solid dispersion adsorbate underwent accelerated stability testing for one month in a stability chamber at 40 ± 20C and 75 ± 5% RH, following ICH guidelines [4]. The optimized composition of clotrimazole solid dispersion adsorbate was put in vials and sealed with rubber plugs and aluminium closures. Following the stability period, the samples were collected and tested for all in-vitro parameters. The similarity factor (f2) was employed to assess the release of drug.

RESULTS AND DISCUSSION

PHASE SOLUBILITY STUDIES

To evaluate the best carrier for solid dispersion production, phase solubility tests were performed on clotrimazole in two polymeric carriers (poloxamer 188 and polyvinyl pyrrolidone K-30) (Figure 1). The solubility of clotrimazole in water was practically found to be 0.47 µg/ml. The solubility of clotrimazole in polymer solution was increased when the concentration of polymeric carrier increased from 5 to 20%. The findings are consistent with the previously published literature. The curves obtained were AL type. The regression coefficient (r2) values of clotrimazole for poloxamer 188 and polyvinyl pyrrolidone K-30 were 0.9936 and 0.9913, respectively. The stability constant value was greater in poloxamer 188 than in polyvinyl pyrrolidone K-30. The values of the stability constant are determined by slope values. The higher the slope values, the stronger the polymer's ability to solubilize the medication. Thus, the results show that clotrimazole solubility has a favourable linear relationship with poloxamer 188 when compared to polyvinyl pyrrolidone K-30. Negative Gibbs

free energy transfer values (Table 3) indicated that clotrimazole was solubilized spontaneously in polymer solution. The greatest result was achieved for poloxamer 188 when compared to polyvinyl pyrrolidone K-30. As a result, poloxamer 188 served as a carrier for the solid dispersion.

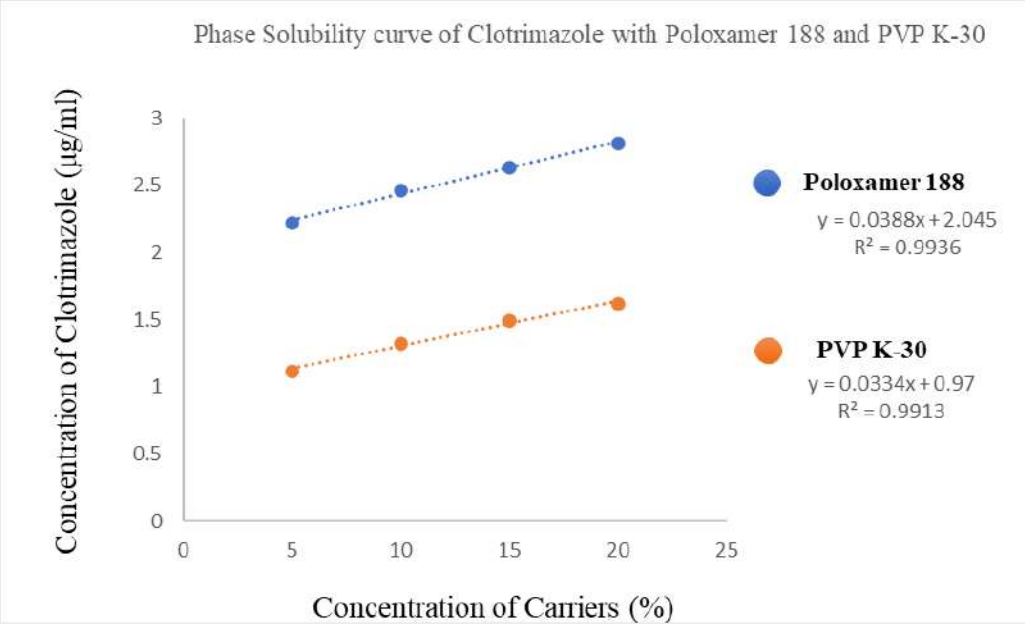


Figure 1. Phase solubility studies of clotrimazole

Table 3. Gibb's free energy (ΔG0tr) and stability constant for clotrimazole in different carriers

Concentration of Carrier (%)	ΔG^0_{tr} KJ/mol at 25^{0}C	
	Poloxamer 188	PVP K30
5	-552.48	-148.68
10	-668.42	-264.94
15	-870.46	-488.84
20	-1875.88	-872.73
K_a	0.0295	0.0174

PRELIMINARY STUDIES FOR SCREENING OF RATIO OF CARRIER (POLOXAMER 188) AND CLOTRIMAZOLE IN SOLID DISPERSION

According to the Indian Pharmacopoeia, the time required to release 85% of the drug from traditional clotrimazole formulation should not exceed 30 minutes [3]. Figure 2 depicts in-vitro dissolving experiments of clotrimazole solid dispersions comprising various ratios of poloxamer 188 and clotrimazole. The cumulative proportion of drug release rose as the carrier-to-drug ratio grew from 1:1 to 7:1. The formulation with a carrier-to-drug ratio of 1:1 did not meet the Indian Pharmacopoeia standards, however ratios of 3:1, 5:1, and 7:1 did meet the Indian Pharmacopoeia standards for drug release of clotrimazole. While there was no significant difference in drug release between 3:1, 5:1, and 7:1 carrier to drug ratios, and to restrict the bulk volume required for the manufacture of solid dispersion adsorbate tablets, a 1:3 drug to carrier ratio was chosen for the adsorbent. The results confirm that as the carrier-to-drug ratio in solid dispersion improved, the time to release the drug molecules decreased. This decrease in time might be attributed to greater hydrophilic lipophilic balance (HLB) value of poloxamer 188 (when compared to other grades of poloxamer) and

improved capacity to solubilize the poorly aqueous soluble drug.

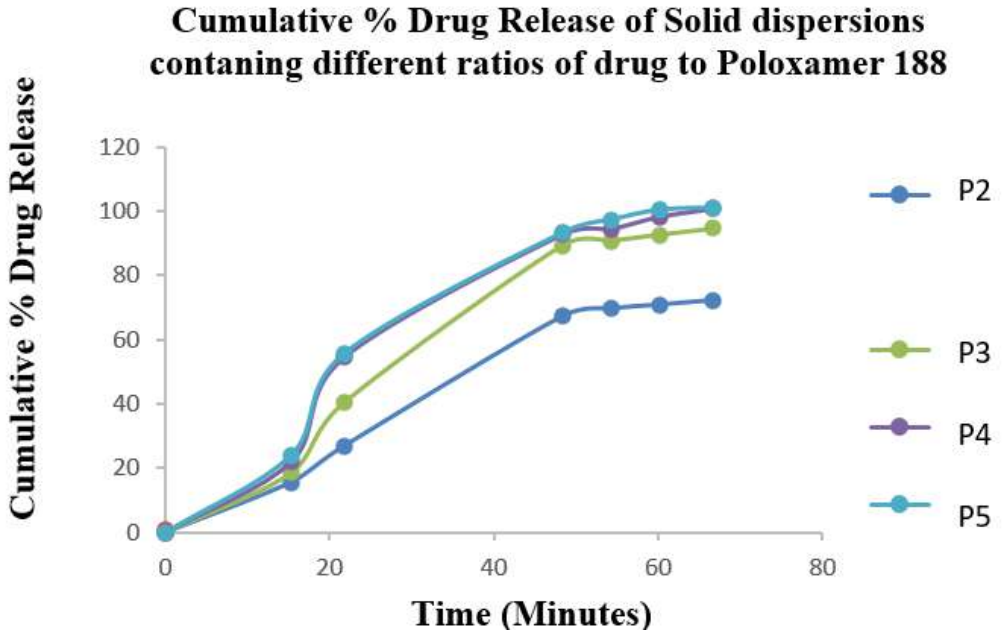


Figure 2. Effect of different ratios of poloxamer 188 and clotrimazole in solid dispersion on drug release; P2 – 1:1, P3 – 3:1, P4 – 5:1, P5 – 7:1.

CHARACTERIZATION OF SOLID DISPERSION ADSORBATE BY FTIR SPECTROSCOPY

The FTIR spectrum of pure clotrimazole (Figure 3 (a)) has prominent distinctive peaks at 745.5 cm-1 (C–Cl stretching, halogen), 1207.7 cm-1 (C–N, stretching, strong), 3056.4 cm-1 (C=C–H aryl stretching vibration of benzene ring), 1431.3 cm-1 (C–N bending aromatic ring). The poloxamer 188 has distinctive peaks at 2875.6 cm-1, 1340 cm-1, and 1097.7 cm-1 due to stretching of the O-H, C-H, and C-O groups, respectively (Figure 3 (b)). FTIR spectra of sylysia 350 in (Figure 3 (c)). Figure 3 (d) shows the FTIR spectra of a solid dispersion adsorbate. The complete absence of drug-specific peaks in the FTIR spectrum of clotrimazole solid dispersion adsorbate demonstrates complete adsorption of clotrimazole solid dispersion on sylysia 350.

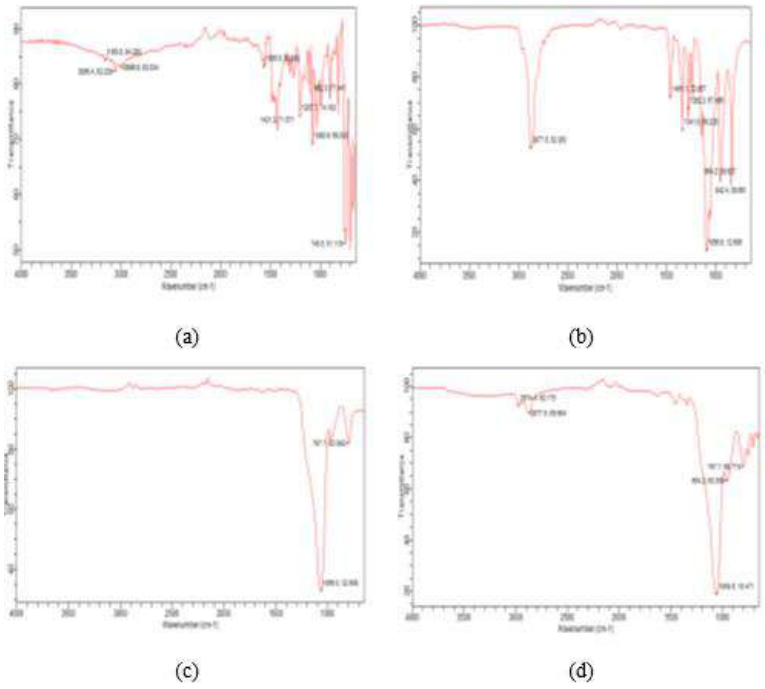


Figure 3. FTIR spectra of (a) Pure clotrimazole, (b) Poloxamer 188, (c) Sylysia 350 and (d) Clotrimazole Solid dispersion adsorbate.

PRELIMINARY STUDIES FOR SELECTION OF RATIO OF ADSORBENT TO SOLID DISPERSION

Preliminary screening was conducted to find an appropriate adsorbent to improve the flow characteristics of the solid dispersion. The prepared solid dispersion proved difficult to pulverize, with poor flow and compressibility. Sylysia 350 and sylysia 550 were chosen as an adsorbent due to their excellent adsorptive properties. Figure 4 shows the results of these studies as adsorbed over sylysia 350 (a colloidal silicon dioxide); angle repose values decreased significantly while flow qualities improved (angle of repose less than 25 indicates acceptable flow properties) as compared to sylysia 550. This can be due to the adsorption capacity of colloidal silicone dioxide particles (310 ml/100g), which allows for more adsorption on its surface when compared to sylysia 550 [15]. Furthermore, at a greater adsorbent to solid dispersion ratio (3:1), there was no notable change in angle of repose values, and additional ratios were not investigated in order to keep the bulk volume of tablet formulation to a minimum.

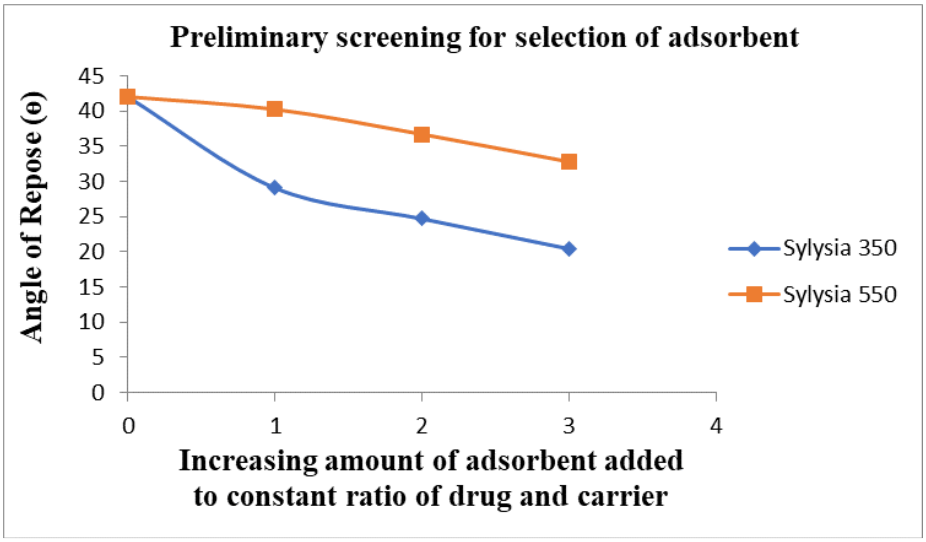


Figure 4. Effect of different adsorbents on angle of repose.

FULL FACTORIAL DESIGN

EFFECT OF FORMULATION VARIABLES ON Q30 (Y1)

The estimated equation between response Y1 to the converted factor is presented in following equation. The polynomial equation for Q30:

$$Y1 = +88.10+5.00X1+0.27X2+0.12X1X2–6.70X12–0.50X22$$

The sign of b12 is positive, indicating that the combined impact of X1 and X2 is positive for the Q30 variable. The analysis of variance findings show that the model is significant ($P<0.05$). Concerning Y1, the findings of multiple regression analysis revealed that coefficients b1 and b2 both had positive signals. The magnitude of component X1 is greater than that of factor X2. The positive coefficient values imply that when the carrier-to-drug ratio in solid dispersion increases, so does Q30. However, the amount of adsorbent employed to absorb one component of the solid dispersion has no influence on Q30. Poloxamer 188 increases the dissolution rate of clotrimazole. It is a non-ionic in amphiphilic surfactant that forms micelles in aqueous solutions. When the solid dispersion adsorbate comes into contact with the dissolution media, Poloxamer 188 is hydrated into the polymer solution, causing drug particles to solubilize and release into the dissolution medium. Similar findings were obtained for lurasidone hydrochloride, a class-II drug of biopharmaceutical classification system, and the solid dispersion adsorbate of lurasidone hydrochloride employing poloxamer 188 demonstrated higher solubility and dissolution rate.[5]

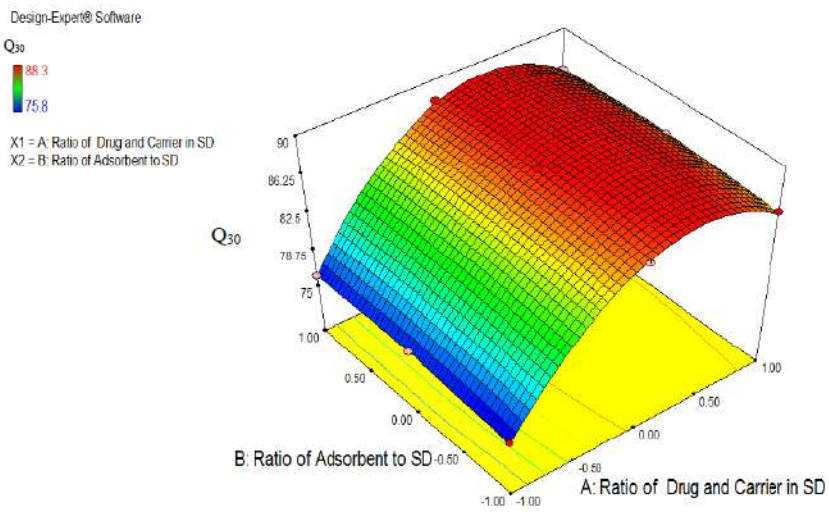


Figure 5. 3D response surface plot for Q30 (Y1) of factorial batches F1 to F9.

EFFECT OF FORMULATION VARIABLES ON ANGLE OF REPOSE (Y2)

The estimated equation between response Y2 to the converted factor is presented in the equation below. The polynomial equation for angle of repose. (Y2):

$$Y2 = +25.92+1.29X1–6.50X2–1.72X1X2+0.53X12+4.15X22$$

The ANOVA results show that the model is statistically significant ($P < 0.05$). Concerning Y2, results of the multiple regression analysis suggest that coefficient b1 is positive and coefficient b2 is negative. Factor X2 has a greater magnitude (6.50) than factor X1. It was revealed that, of the two independent factors, selected factor X2 has a substantial influence on angle of repose. The negative X2 coefficient implies that as the amount of adsorbent utilized to adsorb one part of the solid dispersion rises, the angle of repose decreases. Except for F1, F4, and F7, all formulas F2, F3, F5, F6, F8, and F9 have an angle of repose of less than 30 degrees. It has been found that angles of repose less than 30 suggest favourable flow characteristics. In formulations F1, F4, and F7, the solid dispersion mass formed did not adhere to the surface of sylysia 350. This showed increased angles of repose, as well as a sticky solid mass with poor flow characteristics. The results demonstrate that as the amount of adsorbent employed to adsorb one part of solid dispersion increased, the angle of repose decreased.

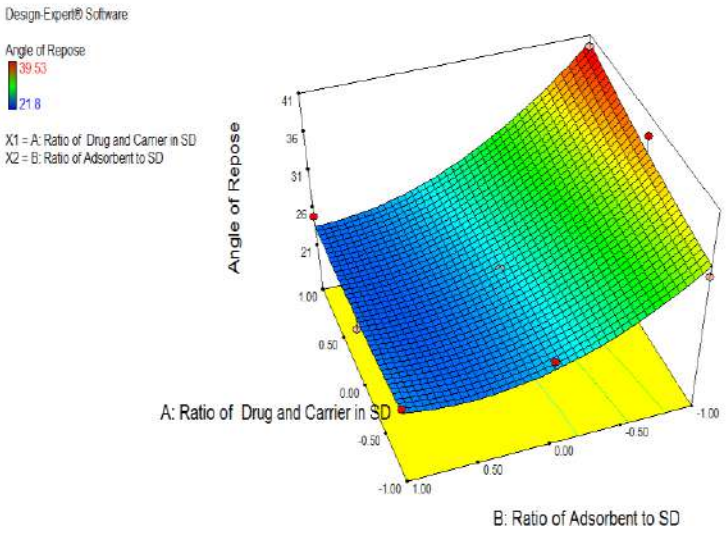


Figure 6. 3D response surface plot for angle of repose (Y2) of factorial batches F1 to F9.

CHECK POINT BATCH

The checkpoint batch (F10) was made up to evaluate the model and establish the function of the obtained polynomial equation in forecasting the response. The theoretical values were obtained by putting the values into the polynomial equation. The experimental and anticipated values were then compared using a 95% confidence interval and represented as a percentage bias. The results are shown in Table 4. The model was verified since the percentage bias value was less than 5% and there was not a significant variance between the two sets of data.

Table 4: Observed response of 32 factorial design (average ± SD, n = 3).

Formulation	Ratio of carrier to drug	Ratio of adsorbent to solid dispersion	Q_{30}	Angle of Repose (ɵ)
F_1	2:1	1	75.8±0.72	32.61±0.24
F_2	2:1	2	76.3±0.32	26.19±0.18
F_3	2:1	3	76.1±0.82	24.96±0.27
F_4	3:1	1	87.0±0.55	38.61±0.22
F_5	3:1	2	88.3±0.67	25.64±0.15
F_6	3:1	3	88.0±0.75	21.80±0.26
F_7	4:1	1	85.8±0.32	39.53±0.28
F_8	4:1	2	86.3±0.63	26.98±0.21
F_9	4:1	3	86.1±0.71	25.01±0.23
F_{10}[a]	2.5:1	1.5	82.23±0.42	25.93±0.67
F_{10}[b]	2.5:1	1.5	84.13	26.27

a Observed values of check point batch

b Predicted values from polynomial equation

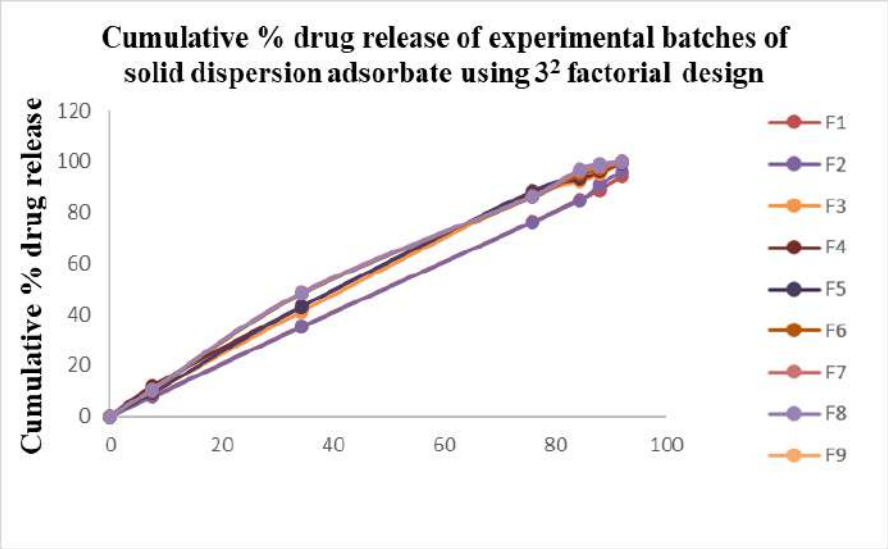


Figure 7. In-vitro drug release profiles of factorial batches F1 to F9.

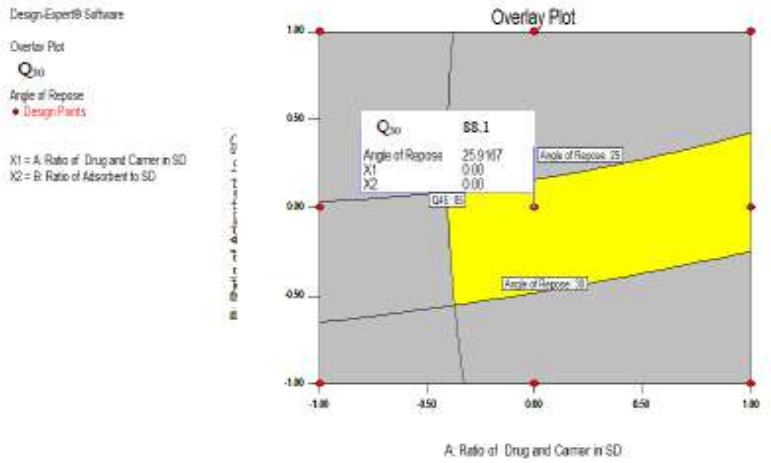


Figure 8. Overlay plot for optimization of solid dispersion adsorbate granules.

The values X1 (carrier-drug ratio in solid dispersion) and X2 (adsorbent-solid dispersion ratio) should be kept to a minimum. As a result, formulation F5 was chosen as the optimal formulation. The overlay plot projected F5 as the optimal batch.

SELECTION OF OPTIMIZATION BATCH

A graphical optimization (overlay plot) was utilized to optimize all of the replies with various goals. Constraints on dependent and independent variables were used to get the optimal formulation. The limitations were Q30 minimum (According to Indian Pharmacopoeia, 85% cumulative percentage of drug release should occur within 30 minutes) and angle of repose maximum value 25 (values less than 25 imply excellent flow characteristics). These limitations were universal to all formulations. The optimum values for independent variables were estimated using design expert software. Figure 8 shows an overlay plot. The yellow section of the overlay plot represents the design space. The optimum batch would be displayed in the top corner of the design space based on the limitations applied. However, in order to maintain the bulk volume of solid dispersion adsorbate granules to a minimum, we aimed to keep both independent variables X1 (carrier-to-drug ratio in solid dispersion) and X2 (adsorbent-to-solid dispersion ratio) to a minimum. As a result, formulation F5 was chosen

as the optimal formulation. The overlay plot projected F5 as the optimal batch.

EVALUATION OF OPTIMIZED FORMULATION OF SOLID DISPERSION ADSORBATE OF CLOTRIMAZOLE

DIFFERENTIAL SCANNING CALORIMETRY (DSC) STUDIES

Figure 9 shows the DSC thermograms for clotrimazole, poloxamer 188, sylysia 350, and optimized formulation of solid dispersion adsorbate of clotrimazole (F5). Clotrimazole showed a single abrupt endothermic peak at about 1470C, which corresponded to its melting temperature and indicated its crystalline form (Figure 9 (a)). Thermal breakdown of clotrimazole may account for the endothermic peak around 1600C. Poloxamer 188 exhibited a pronounced endothermic peak at 61.160C (Figure 9 (b)), which corresponds to its melting point. DSC thermograph of sylysia 350 showed no endothermic peak at 4000C (Figure 9 (c)). The removal of the drug melting peak in solid dispersion adsorbate granules (Figure 9 (d)) was due to drug solubility in the melted carrier.

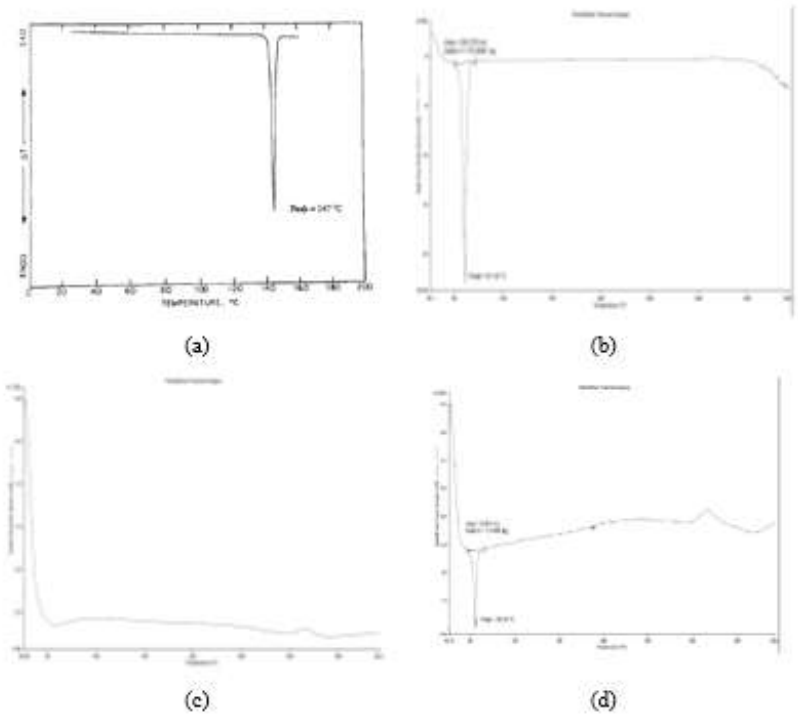


Figure 9. DSC thermographs of (a) Clotrimazole, (b) Poloxamer 188, (c) Sylysia 350 and (d) solid dispersion adsorbate granules; formulation (F5).

X-RAY DIFFRACTION STUDIES

The X-ray diffraction pattern of pure clotrimazole revealed prominent peaks at 2θ values of 9.324○, 9.363○, 10.376○, 12.490○, 16.819○, 18.877○, 19.567○, 19.960○, 20.828○, 22.595○, 23.098○, 24.448○, 25.196○, 27.612○, 28.269○ showing its crystalline nature. Poloxamer 188 has two distinct peaks with 2θ values of 19.68○ and 23.65○ on an amorphous background. Sylysia 350 did not exhibit any distinguishing peaks because it is amorphous in nature. The optimized solid dispersion adsorbate formulation shows only one sharp peak at 2θ value of 12.713○. The results concluded that the formation of the amorphous form and which has indicated that more solubility as compared to crystalline form.

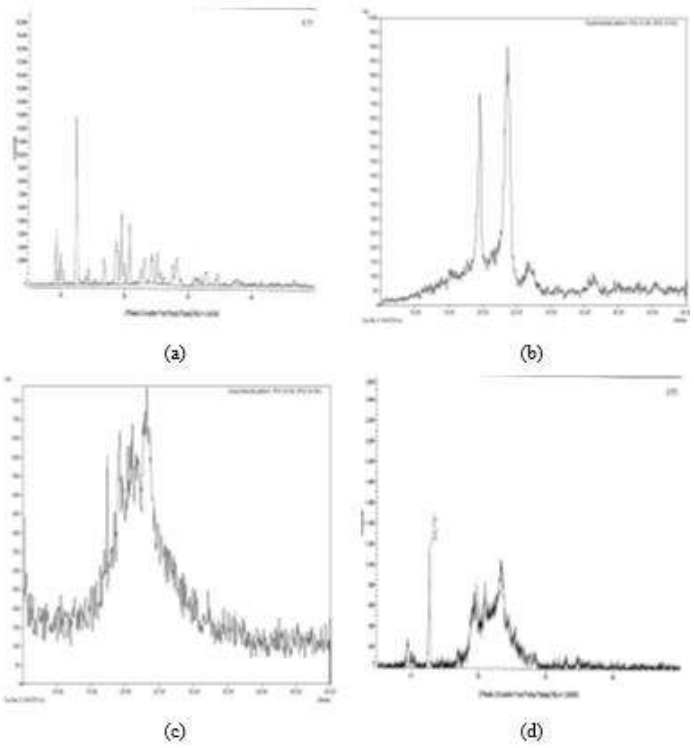
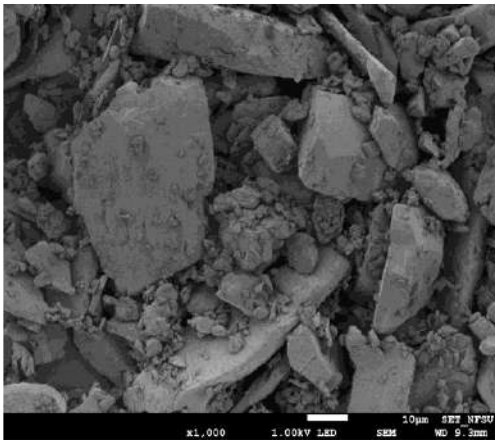


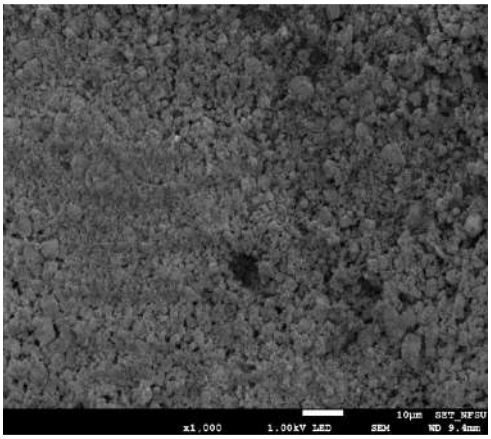
Figure 10. X–ray diffraction pattern of (a) Clotrimazole, (b) Poloxamer 188, (c) Sylysia 350 (d) Solid dispersion adsorbate granules; formulation F5.

SCANNING ELECTRON MICROSCOPE (SEM) STUDY

The surface morphology of the clotrimazole powder (Figure 11 (a)) revealed irregular-shaped crystalline particles in agglomerates. It has been claimed that sylysia 350 is a porous silicone dioxide with many inter and intra particle holes on its surface, providing a high surface area for adsorption. Figure 11 (b) depicts a SEM micrograph of solid dispersion adsorbate granules, confirming the full adsorption of molten poloxamer 188 and clotrimazole solid dispersion on the porous surface of sylysia 350. This observation implies that the solid dispersion adsorbate did not exhibit particle agglomeration, resulting in a free-flowing solid dispersion with increased surface area.



(a)



(b)

Figure 11. SEM micrographs of clotrimazole powder (a) and optimized formulation of solid dispersion adsorbate granules (b).

CHARACTERIZATION OF SOLID DISPERSION ADSORBATE TABLET

The wet granulation method was used to make tablets of solid dispersion adsorbate granules (equal to 10 mg of clotrimazole). These tablets were evaluated using a variety of factors, and the results are shown in Table 5. Tablets made from solid dispersion adsorbate granules released more than 85% of the drug in 30 minutes, compared to pure clotrimazole powder tablets. When compared to tablets made from plain clotrimazole, solid dispersion adsorbate granules increased cumulative percentage drug release by nearly twice as much. The value of Q30 increased from 48.30% for plain clotrimazole tablet to 87.93% for solid dispersion adsorbate tablet. The angle of repose, which reflected flow characteristics, increased from 48.370 for plain clotrimazole powder to 25.640 for solid dispersion adsorbate granules. This results revealed that the solid dispersion adsorbate approach improved both solubility and flow property of clotrimazole.

Table 5. Physical characteristics (pre-compression and post-compression parameters) of optimized solid dispersion adsorbate tablets.

Parameter	Result
Bulk density (gm/ml)	0.178±0.15
Tapped density (gm/ml)	0.192±0.27
Carr's index (%)	7.29±0.11
Hausner's ratio	1.07±0.21
Angle of repose (θ) in (^{0})	25.64±0.15
Weight variation (mg)	498±0.06
Diameter (mm)	12±0.00
Thickness (mm)	4.15±0.23
Hardness (kg/cm2)	4.8±0.56
Friability (%)	0.36±0.28
Disintegration time (min)	2.43±0.21
Drug content (%)	99.86±0.25
Q_{30} (%)[a]	87.93±0.67
Q_{30} (%)[b]	48.30±0.54

a Q30 of solid dispersion adsorbate tablets

b Q30 of plain clotrimazole tablets

STABILITY STUDIES

Accelerated stability experiments were conducted for one month at 400C and 75% relative humidity to examine the effect of aging on the formulations. The drug release was assessed prior to and following stability trials, and the similarity factor (f2) was computed. When the (f2) value exceeds 50, the two curves are deemed statistically comparable. The similarity factor (f2) was calculated to be 87.81%. In a few investigations, it has been observed that the amorphous state of the drug in solid dispersion reverts to a less soluble crystalline form after storage. Solid dispersion adsorbate tablets remained unchanged after one month of storage at 40°C and 75% relative humidity, confirming that sylysia 350 inhibited the conversion of clotrimazole from amorphous to crystalline form and increased physical stability of the amorphous state

.

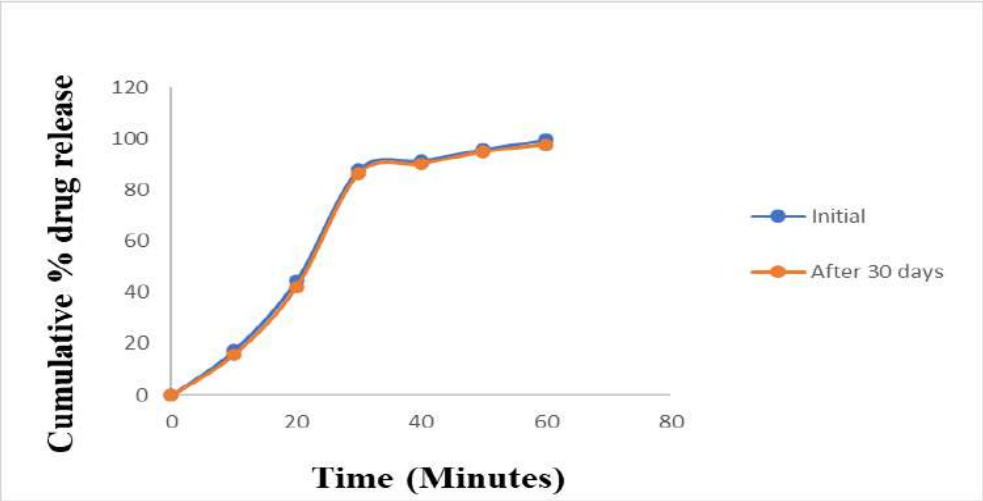


Figure 12. In–vitro drug release profile of clotrimazole solid dispersion adsorbate tablet before and after stability studies.

CONCLUSION

This study proved that the solid dispersion adsorbate approach is a successful technique to enhance dissolution and flowability of clotrimazole. The solid dispersion adsorbate granules comprising carrier, drug, and adsorbent can be compacted into tablets without the normal processing issues associated with solid dispersion technique. The improved formulation, which contained clotrimazole, poloxamer 188, and sylysia 350 in a 1:3:2 ratio, met the Indian Pharmacopoeia criterion of releasing more than 85% of the cumulative drug release within 30 minutes. Furthermore, age did not influence the drug release or physical stability of clotrimazole.

REFERENCES

1. Singh A, Verma R, Murari A, Agrawal A, “Oral candidiasis: An overview” Journal of Oral and Maxillofacial Pathology, 2014, 18 (1), 81–85.
2. Hoogerhekk JG, Wyka BE, “Analytical Profiles of Drug Substances” The American Pharmaceutical Association, 1982, 11, 226–255.
3. Indian Pharmacopoeia vol. II, Indian Pharmacopoeia commission Ghaziabad, 2022, pp 1935–1939.
4. Mahajan AN, Surti N, Patel PR, Patel A, Shah DA, Patel VB, “Melt Dispersion Adsorbed onto Porous Carriers: An Effective Method to Enhance the Dissolution and Flow Properties of Raloxifene Hydrochloride” Assay and

Drug Development Technologies, 2020, 18 (6), 1–13.

5. Mahajan A, Surti N, Koladiya P, "Solid dispersion adsorbate technique for improved dissolution and flow properties of lurasidone hydrochloride: characterization using 32 factorial design" Drug Dev. Industrial Pharmacy, 2017, 1, 8.
6. Rahman M, Khalipha A, Azad A, Hossain S, Haque S, "Methods of solubility and dissolution enhancement for poorly water soluble drugs: a review" WJPPS, 2014, 3 (5), 107–116.
7. Chowdary K, Kumar P, "Recent Research on Formulation Development of BCS class – II Drugs – a review" Int. Res J Pharm. App Sci, 2013, 3 (1), 173–176.
8. Vemula V, Lagishetty V, Lingala S, "Solubility enhancement techniques" Int. J Pharm. Sci. Rev. Res., 2010, 5 (1) 41–47.
9. Das S, Roy S, Kalimuthu Y, Khanam J, Nanda A, "Solid Dispersions: An Approach to Enhance the Bioavailability of Poorly Water soluble Drugs" Int. J of Pharmacol Pharm Tech., 2012, 1 (1), 37–42.
10. Kumar A, Murthy G, Rani P, "A Concise review on oral pH independent controlled drug delivery system" WJPPS, 2014, 3 (11), 315, 316.
11. Patel V, Dave R, "Evaluation of Colloidal Solid Dispersions: Physiochemical Considerations and In Vitro Release Profile" AAPS Pharm Sci. Tech., 2013, 14 (2), 620, 621.
12. Hanada M, Jermain S, Williams III R, "Enhanced Dissolution of a Porous Carrier Containing Ternary Amorphous Solid Dispersion System Prepared by a Hot Melt Method" Journal of Pharmaceutical Sciences, 2017, (107), 362, 370.
13. Pandya R, Mehta T, Gohel M, "Solid dispersion Adsorbate – A Novel Technique for dissolution enhancement of Febuxostat," IJPSR, 2015, 6 (10), 4236, 4242.
14. Shah H, Shah V, Bhutani S, Parikh D, Mehta T, "Dissolution improvement of Nebivolol hydrochloride using solid dispersion adsorbate technique" Asian Journal of Pharmaceutics, 2015, 49, 54.
15. Jammula S, Patra N, Swain S, Panigrahi K, Patro A, Beg s, Dinda S, Rao M, "Improvement in the dissolution rate and tableting properties of cefuroxime axetil by melt-granulated dispersion and surface adsorption" Acta Pharmaceutica Sinica B, 2013, 113, 121, 122.
16. Kaushik S, Pathak K, "Solid Dispersion Adsorbates – A Novel Method for Enhancement of Dissolution Rates of Felodipine" Int. J. Pharm. Sci. Rev. Res., 2013, 21 (1), 310, 313.
17. Patel B, Parikh R, Swarnkar D, "Enhancement of dissolution of Telmisartan through use of solid dispersion technique surface solid dispersion," Pharm Bioall Sci., 2012, 64, 67.
18. Parmar K, Shah S, Sheth N, "Studies in Dissolution Enhancement of Ezetimibe by Solid Dispersions in Combination with a Surface Adsorbent" Dissolution Technologies, 2011, 55, 60.
19. Patel N, M.Pharm. Thesis, "Development and Characterization of Ternary Solid Dispersion Granules of Poorly Water Soluble Drugs: Diflunisal and Mefenamic acid" The University of Toledo, August 2011.
20. Kaushik D, Singh N, Arora A, "Enhancement of Dissolution Profile of Gliclazide by Solid Dispersion Adsorbates" Lat. Am. J. Pharm., 2011, 30 (10), 2057, 2060.
21. Vadher A, Parikh J, Parikh R, Solanki A, "Preparation and Characterization of Co-Grinded Mixtures of Aceclofenac and Neusilin US2 for Dissolution Enhancement of

Aceclofenac" AAPS Pharm Sci Tech, 2009, 10 (2), 606, 613.

22. Bahl D, Bogner R, "Amorphization of Indomethacin by Co-Grinding with Neusilin US2: Amorphization Kinetics, Physical Stability and Mechanism" Pharmaceutical Research, 2006, 23 (10), 2317, 2324.
23. Chauhan B, Shimpi S, Paradkar A, "Preparation and evaluation of Glibenclamide-polyglycolized glycerides solid dispersions with silicon dioxide by spray drying technique" European Journal of Pharmaceutical Sciences 26, 2005, 219–229.
24. Gupta M, Tseng Y, Goldman D, Bogner R, "Hydrogen Bonding with Adsorbent during Storage Governs Drug Dissolution from Solid-Dispersion Granules" Pharmaceutical Research, 2002, 19 (11), 1663, 1671.
25. Bogner R, Gupta M, Tseng Y, Goldman D, "Enhanced Drug Dissolution and Bulk Properties of Solid Dispersions Granulated with a Surface Adsorbent" Pharmaceutical Development and Technology, 2001, 6 (4), 563–572.
26. Hasenzahl S, Meyer J, Heym J, Use of Granular Materials based on pyrogenically produced Silicon Dioxide in Pharmaceutical Compositions, U. S. Patents, EP1439858B1, 2004.
27. Bolla PK, Meraz CA, Rodriguez VA, Deaguero I, Singh M, Yellepeddi VK and Renukuntla J, "Clotrimazole loaded ufosomes for topical delivery: formulation development and in-vitro studies" Molecules, 2019, 24, 1–15.
28. Balata G, M. Mahdi, Bakera RA, "Improvement of solubility and dissolution properties of clotrimazole by solid dispersions and inclusion complexes" Indian Journal of Pharmaceutical Sciences, 2011, 517–526.
29. Hashem FM, Shaker DS, Ghorab MK, Nasr M, Ismail A, "Formulation, characterization, and clinical evaluation of microemulsion containing clotrimazole for topical delivery" AAPS PharmSciTech, 2011, 12 (3), 879–886.
30. Harish NM, Prabhu P, Charyulu RN, Gulzar MA, Subrahmanyam CVS, "Formulation and evaluation of in-situ gels containing clotrimazole for oral candidiasis" Indian Journal of Pharmaceutical Sciences, 2009, 421–427.
31. Bachhav YG, Patravale VB, "Microemulsion-based vaginal gel of clotrimazole: formulation, in-vitro evaluation and stability studies" AAPS PharmSciTech, 2009 (10) 2, 476–481.
32. Paradkar M, Thakkar V, Soni T, Gandhi T, Gohel MC, "Formulation and evaluation of clotrimazole transdermal spray" Drug Dev Ind Pharm, 1–8.
33. Madhushri M, Thakur RS, Jadhav KK, Patel RN, "Formulation and evaluation of solid lipid nanoparticles containing clotrimazole" Am. J. PharmTech Res. 2012, 2 (3), 1–16.
34. Thomas L, Viswanad V, "Formulation and optimization of clotrimazole-loaded proniosomal gel using 32 factorial design" Sci. Pharm. 2012, 731–748.
35. Omar SM, Ismail A, Hassanin KD, Dawoud SH, "Formulation and evaluation of cubosomes as skin retentive system for topical delivery of clotrimazole" JAPR, 2019, 3 (2), 68–82.
36. Shahin M, Hady SA, Hammad M, Mortada N, "Novel jojoba oil-based emulsion gel formulations for clotrimazole delivery" AAPS PharmSciTech, 2011, 12 (1), 239–247.
37. Prabagar B, Yoo BK, Woo JS, Kim JA, Rhee JD, Piao MG, Choi HG, Yong CS, "Enhanced bioavailability of poorly water-soluble clotrimazole by inclusion with beta-cyclodextrin" Arch Pharm. Res. 2007, 30 (2) 249–254

HOW TO CITE: Bhavin D. Pandya , Krena N. Patel, Jinal H. Boradhara, Vaishnavi D. Shah, Vishwa A. Vyas, Formulation Development Of Solid Dispersion Adsorbate To Enhance Solubility, Dissolution And Flow Properties Of Clotrimazole Using 32 Factorial Design, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 7, 594-613. https://doi.org/10.5281/zenodo.12746233