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Research Article

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

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ABSTRACT

The study aimed to improve the solubility and flow properties of clozapine, a Biopharmaceutical Classification System (BCS) Class II drug, using the solid dispersion adsorbate technique. The solid dispersion of clozapine 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 clozapine to poloxamer 188 and the ratio of sylysia 350 to the solid dispersion. The prepared clozapine 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), and accelerated stability analysis. Optimal solid dispersion adsorbate granules containing an equivalent of 25 mg of clozapine were manufactured into tablets using the direct compression method, alongside plain clozapine tablets for comparison. The study found that clozapine was spontaneously solubilized in poloxamer 188, as indicated by the negative Gibbs free energy values. Dissolution studies, conducted in an acetate buffer at pH 4.0 in accordance with USFDA guidelines, showed that the optimized formulation released over 85% of the drug within 45 minutes, significantly faster than the pure clozapine 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 350 effectively prevented the conversion of clozapine 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

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flow properties of poorly water-soluble drugs.

INTRODUCTION

Schizophrenia is a widespread mental condition and one of the leading causes of mental impairment. Psychotherapy and antipsychotics are first-line therapies that should be continued forever to reduce the chance of recurrence[1]. Clozapine is a USFDA-approved antipsychotic agent used to treat schizophrenia. Clozapine is a class-II drug of biopharmaceutical classification system with very low aqueous solubility (0.0118 mg/ml), high permeability, pKa of 7.5, and log P of 3.23 in octanol/water. It has a low bioavailability, with an absolute oral bioavailability of 27-50% in humans. Clozapine has been observed to have inadequate absorption due to its low water solubility and dissolution rate[31]. Several researchers have sought to enhance solubility and dissolution properties of clozapine by developing inclusion complexes with beta-cyclodextrin, clozapine liquisolid tablets, solid lipid nanoparticles, nanoparticles, nanocapules, and solid dispersion by solvent evaporation[24-36]. 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[5]. 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[10, 11]. 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[13]. 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 clozapine 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 clozapine tablet formulation that dissolves quickly.

MATERIALS AND METHODS

MATERIALS

Clozapine 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, 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[1]. The solubility of clozapine 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 clozapine 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 293 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 clozapine 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 293 nm. The apparent stability constant, Ks, was estimated using the phase solubility graph. The Gibbs free energy (ΔG0tr) of clozapine from pure distilled water to polymer solution was determined using the following formula equation:

$$\Delta G^0_{tr} = -2.303RT \log\left[\frac{S_0}{S_s}\right]$$

Where, S0/SS is the ratio of the solubility of clozapine in distilled water to that of polymer solution. The melting method was used to conduct preliminary investigations for screening the ratio of carrier (Poloxamer 188) and clozapine for solid dispersion. Different carrier-to-clozapine 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. Clozapine 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, sieved, and kept in desiccators until further examination. Clozapine solid dispersions corresponding to 25 mg were packed into capsules, and the in-vitro dissolving test was performed using the method outlined in the in-vitro dissolution tests.

CHARACTERIZATION OF SOLID DISPERSION BY FTIR

Clozapine, 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.

PRELIMINARY SCREENING FOR SELECTION OF ADSORBENT

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

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

Clozapine solid dispersion adsorbate granules were made using the melting method. Table 1 explains the composition of the carrier (poloxamer 188), adsorbent (sylysia 350), and clozapine. Poloxamer 188 was melted in a china dish over a water bath. Clozapine 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 clozapine 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. 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 Clozapine 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 Q45 (cumulative % drug release at 45 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, Q45 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 Q45 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 acetate buffer (pH 4.0) according to the United States Pharmacopoeia. The dissolving medium was maintained at 37 ± 0.50C and 100 rpm. Aliquots of 10 ml were taken at regular intervals, filtered, and spectrophotometrically analyzed at 293 nm using a UV visible spectrophotometer (UV-1800, Shimadzu, Japan).

X-RAY POWDER DIFFRACTION

The spectra of clozapine, 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), clozapine, 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

Clozapine solid dispersion adsorbate tablets were manufactured using the direct compression technique. The tablets were made using standard amounts of commonly employed excipients as described in the literature. Table 2 shows the composition of solid dispersion adsorbate and plain clozapine tablets. The optimized composition of solid dispersion adsorbate granules (F5) corresponding to 25 mg was appropriately combined with spray dried lactose and sodium starch glycolate for 10 minutes. Magnesium stearate was added to the prior mixture, mixed for an additional 5 minutes, then crushed using a rotary tablet compression machine. Tablets with an average weight of 600 mg were manufactured. The tablets were submitted 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 clozapine tablets (mg)
Clozapine	300[a]	25
Spray dried lactose	258	533
Sodium starch glycolate	24	24

Magnesium stearate	6	6
Talc	12	12
Total weight	600	600

a - Optimized composition of solid dispersion adsorbate granules (F5) equivalent to 25 mg of clozapine

STABILITY STUDIES

The optimized composition of clozapine solid dispersion adsorbate underwent accelerated stability testing for one month in a stability chamber at 40 ± 20C and 75 ± 5% RH, following ICH guidelines. The optimized composition of clozapine solid dispersion adsorbate was put in USP type-I 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 clozapine in two polymeric carriers (poloxamer 188 and polyvinyl pyrrolidone K-30) (Figure 1). The solubility of clozapine in water was 1.76 µg/ml. The solubility of clozapine 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 clozapine for poloxamer 188 and polyvinyl pyrrolidone K-30 were 0.98 and 0.975, 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 clozapine 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 clozapine 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.

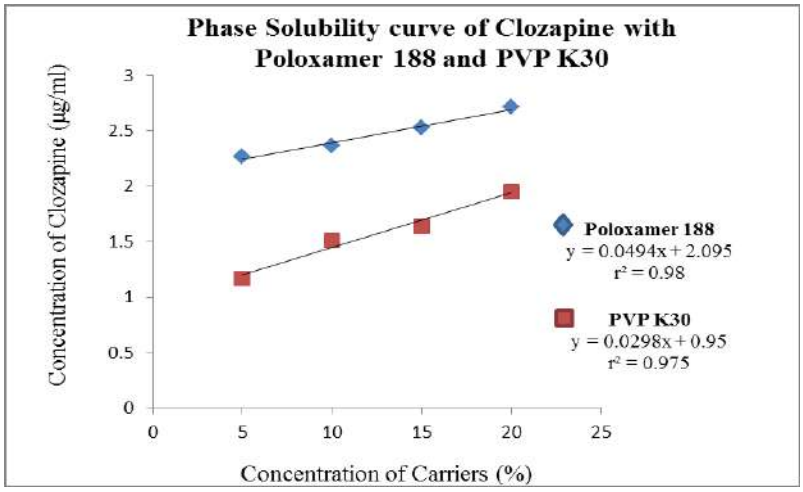


Figure 1. Phase solubility studies of clozapine.

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

Concentration of Carrier (%)	ΔG^0_{tr} KJ/mol at 37^0C	
	Poloxamer 188	PVP K30
5	-676.58	-159.68
10	-776.42	-278.94
15	-950.46	-381.84
20	-2575.88	-1038.73
K_a	0.0295	0.0174

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

According to the USP, the time required to release 85% of the drug from traditional clozapine formulation should not exceed 45 minutes. Figure 2 depicts in-vitro dissolving experiments of clozapine solid dispersions comprising various ratios of poloxamer 188 and clozapine. 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 USP standards, however ratios of 3:1, 5:1, and 7:1 did meet the USP standards for drug release of clozapine. 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.

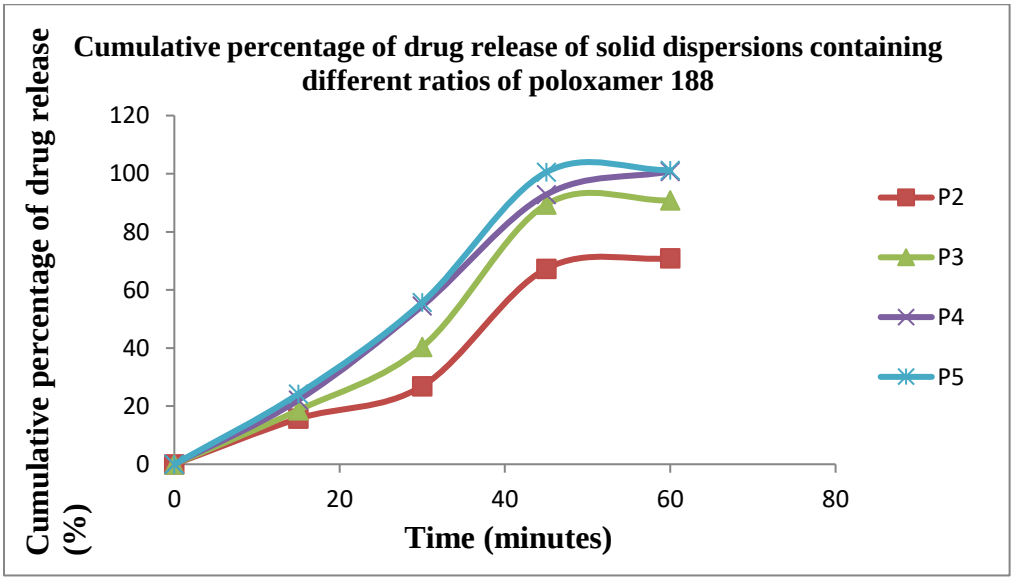


Figure 2. Effect of different ratios of poloxamer 188 and clozapine in solid dispersion on drug release; P2 – 1:1, P3 – 3:1, P4 – 5:1, P5 – 7:1.

CHARACTERIZATION OF SOLID DISPERSION ADSORBATE BY FTIR SPECTROSCOPY

The FTIR spectrum of pure clozapine (Figure 3(a)) has prominent distinctive peaks at 3281.9 cm-1 (N-H stretch), 2929.7 cm-1 (C-H stretch), 903.9

cm-1 (C-H Bending out of plane, aromatic), 1451.8 cm-1 (C-H Bending, methyl), 1589.7 cm-1 (N-H bending), and 2842.1 cm-1 (C-H stretch). 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 clozapine solid dispersion adsorbate demonstrates complete adsorption of clozapine solid dispersion on sylysia 350.

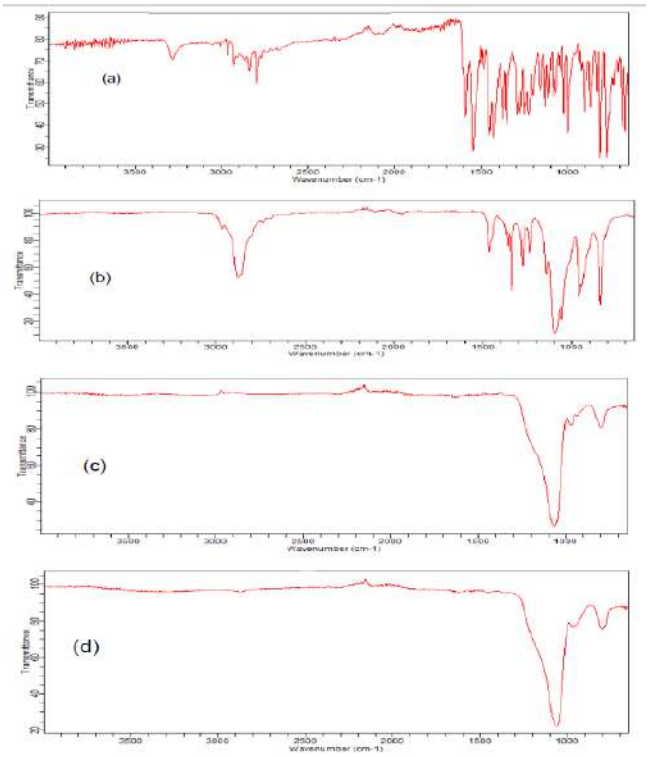


Figure 3. FTIR spectra of (a) pure Clozapine, (b) Poloxamer 188, (c) Sylysia 350 and (d) Clozapine Solid dispersion adsorbate.

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. 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.

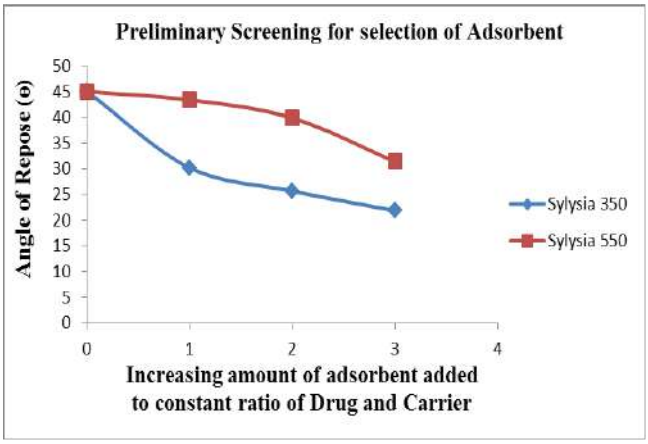


Figure 4. Effect of different adsorbents on angle of repose.

FULL FACTORIAL DESIGN

EFFECT OF FORMULATION VARIABLES ON Q45 (Y1)

The estimated equation between response Y1 to the converted factor is presented in following equation. The polynomial equation for Q45:

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

The sign of b12 is positive, indicating that the combined impact of X1 and X2 is positive for the Q45 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 Q45. However, the amount of adsorbent employed to absorb one component of the solid dispersion has no influence on Q45. Poloxamer 188 increases the dissolution rate of clozapine. 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.[1]

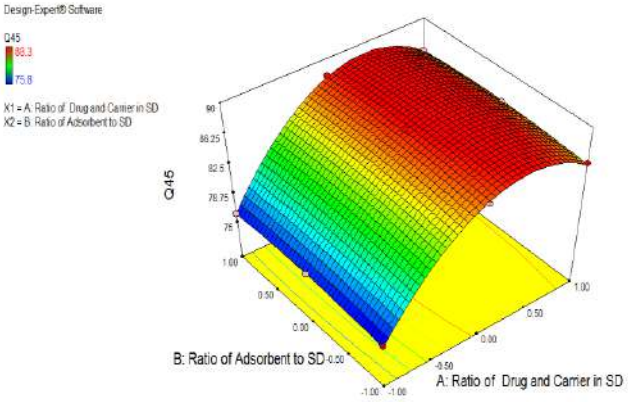


Figure 5. 3D response surface plot for Q45 (Y1) of factorial batches F1 to F9.

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.

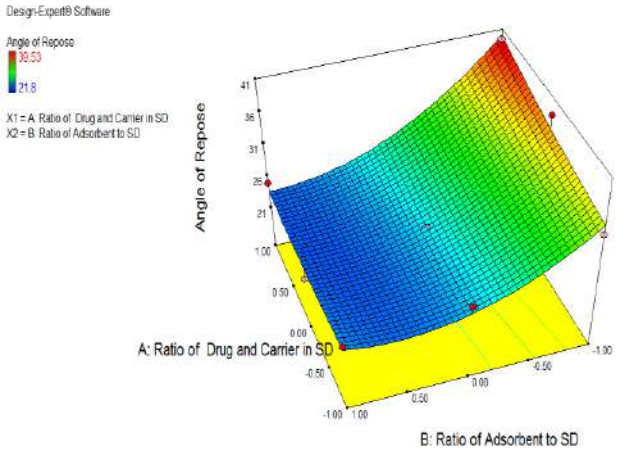


Figure 6. 3D response surface plot for angle of repose (Y2) of factorial batches F1 to F9.

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_{45}	Angle of Repose (θ)
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
% Bias	2.25	1.29		

a Observed values of check point batch

b Predicted values from polynomial equation

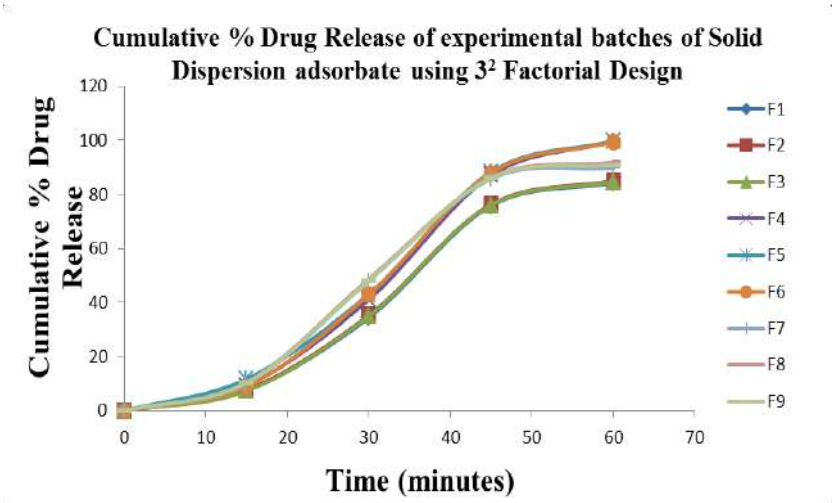


Figure 7. In-vitro drug release profiles of factorial batches F1 to F9.

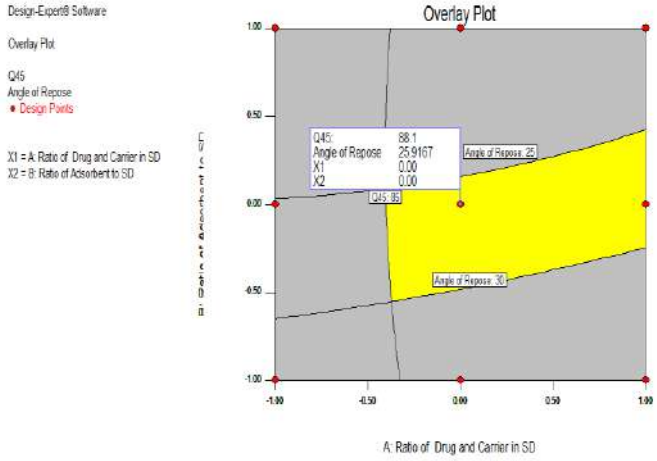


Figure 8. Overlay plot for optimization of solid dispersion adsorbate granules.

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 Q45 minimum (according to USP, 85% cumulative percentage of drug release should occur within 45 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 CLOZAPINE

DIFFERENTIAL SCANNING CALORIMETRY (DSC) STUDIES

Figure 9 shows the DSC thermograms for clozapine, poloxamer 188, sylysia 350, and optimized formulation of solid dispersion adsorbate of clozapine (F5). Clozapine showed a single abrupt endothermic peak at about 187.150C, which corresponded to its melting temperature and indicated its crystalline form (Figure 9(a)). Thermal breakdown of clozapine may account for the endothermic peak around 3200C. Clozapine has been observed to experience thermal deterioration at temperatures ranging from 300 to 4000C. 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.

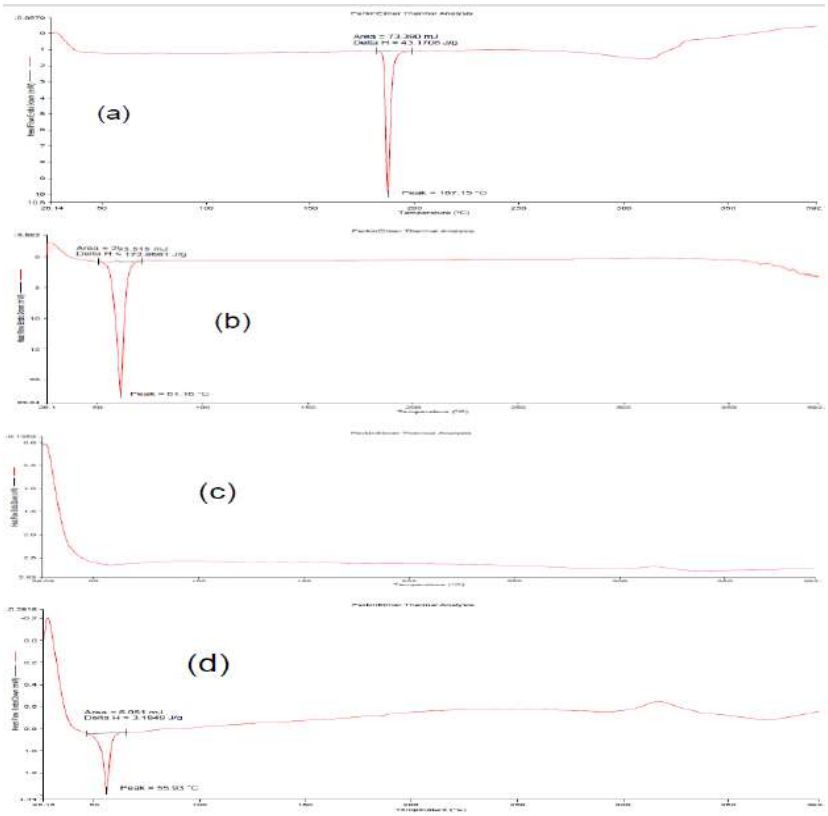


Figure 9. DSC thermographs of (a) Clozapine, (b) Poloxamer 188, (c) Sylysia 350 and (d) solid dispersion adsorbate granules; formulation (F5).

X-RAY DIFFRACTION STUDIES

The X-ray diffraction pattern of pure clozapine revealed prominent peaks at 2θ values of 10.26○, 16.82○, 16.94○, 17.11○, 17.24○, 18.93○, 19.04○, 20.79○, 23.36○, and 29.49○, 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 improved solid dispersion adsorbate formulation did not exhibit the strong, clear diffraction peaks. The results concluded that the creation of the amorphous form, which has a higher solubility than the crystalline form.

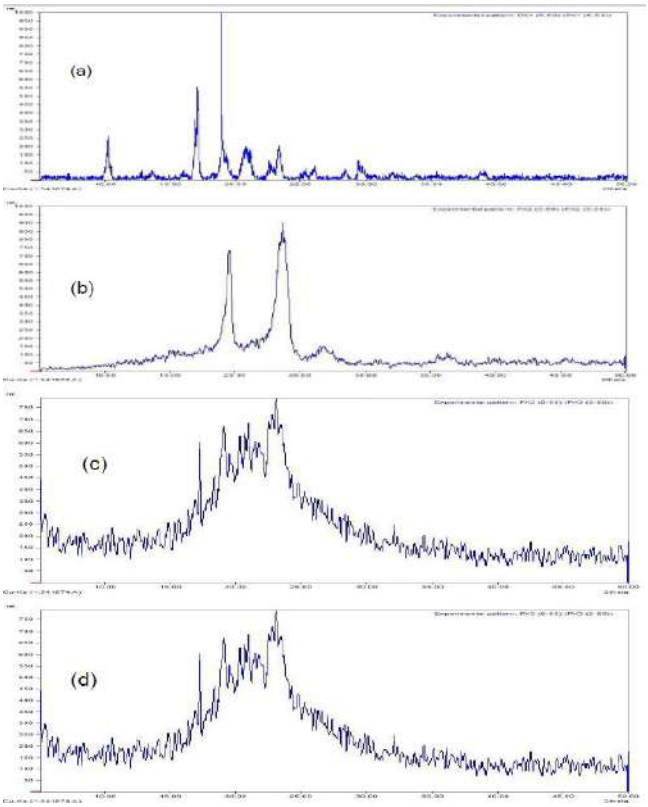
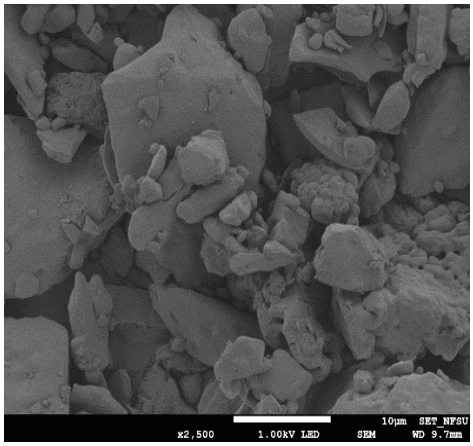


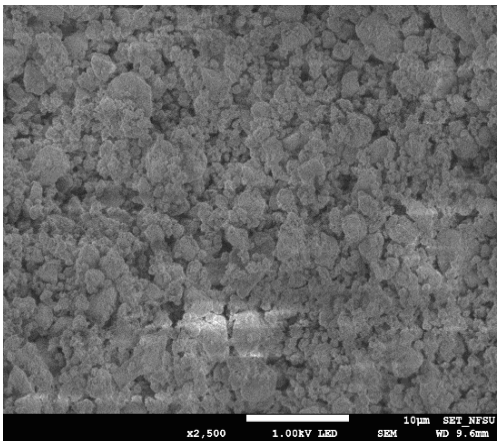
Figure 10. X–ray diffraction pattern of (a) Clozapine, (b) Poloxamer 188, (c) Sylysia 350 (d) Solid dispersion adsorbate granules; formulation F5.

SCANNING ELECTRON MICROSCOPE (SEM) STUDY

The surface morphology of the clozapine 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[13]. Figure 11 (b) depicts a SEM micrograph of solid dispersion adsorbate granules, confirming the full adsorption of molten poloxamer 188 and clozapine 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)

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)	598±0.06
Diameter (mm)	12±0.00
Thickness (mm)	5.15±0.23
Hardness (kg/cm^2)	4.8±0.56
Friability (%)	0.36±0.28
Disintegration time (min)	2.43±0.21
Drug content (%)	99.86±0.25
Q_{45} (%)[a]	87.93±0.67
Q_{45} (%)[b]	48.3±0.31
Solubility (mg/ml)	1.088±0.41

a Q45 of solid dispersion adsorbate tablets

b Q45 of plain clozapine tablets

CHARACTERIZATION OF SOLID DISPERSION ADSORBATE TABLET

The direct compression method was used to make tablets of solid dispersion adsorbate granules (equal to 25 mg clozapine). 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 45 minutes, compared to pure clozapine powder tablets. When compared to tablets made from plain clozapine, solid dispersion adsorbate granules increased cumulative percentage drug release by nearly twice as much. The value of Q45 increased from 48.30% for plain clozapine tablet to 87.93% for solid dispersion adsorbate tablet. The angle of repose, which reflected flow characteristics, increased from 48.370 for plain clozapine powder to 25.640 for solid dispersion adsorbate granules. This results revealed that the solid dispersion adsorbate

approach improved both clozapine solubility and flow characteristics.

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 clozapine from amorphous to crystalline form and increased physical stability of the amorphous state.

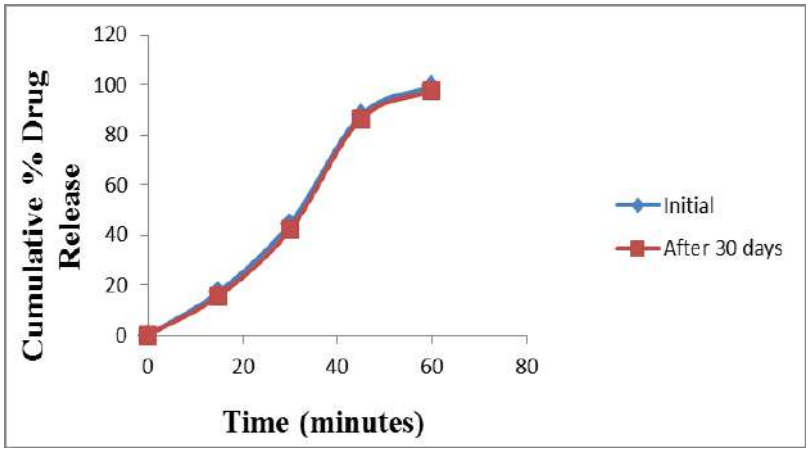


Figure 12. In–vitro drug release profile of clozapine solid dispersion adsorbate tablet before and after stability studies.

CONCLUSION:

This study proved that the solid dispersion adsorbate approach is a successful technique to enhance dissolution and flowability of clozapine. The solid dispersion adsorbate granules comprising carrier, drug, and adsorbent can be compacted into tablets without the normal processing issues associated with solid dispersion tableting. The improved formulation, which contained clozapine, poloxamer 188, and sylysia 350 in a 1:3:2 ratio, met the USP criterion of releasing more than 85% of the cumulative drug release within 45 minutes. Furthermore, age did not influence the drug release or physical stability of clozapine.

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