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OPTIMIZATION OF FAST MELTING OLANZAPINE TABLETS USING SOLID DISPERSION AND RESPONSE SURFACE METHODOLOGY

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ABSTRACT

Background: Olanzapine is a poorly water-soluble, anti-psychotic drug that belongs to the class of thiobenzodiazepines, which has a bioavailability of 60 – 65%. The purpose of this research work is to enhance the solubility of olanzapine by the solid dispersion technique using different water-soluble carriers, using a phase solubility study using a 2^4 factorial design, and to incorporate the solid dispersion of olanzapine to formulate fast-melting tablets using different superdisintegrants. **Methodology**: The fast-melting tablets were prepared using the wet granulation technique and optimized through a 2^3 full factorial design. The independent variables are sodium starch glycolate (X1), sodium carboxymethyl cellulose (X2), and the method of preparation of the solid dispersion (X3). The dependent variables are hardness (Y1), friability (Y2), disintegration time (Y3), and in vitro drug release studies (Y4). The kinship between independent and dependent variables was demonstrated using contour diagrams. Additionally, the prepared fast-melting tablets were analysed for their weight variation, drug content uniformity, and other dependent variables. **Results and Discussion:** The fast-melting tablets (batch F6) were considered desirable based on their drug content (99.5% & drug release of 99.3% in 20 minutes, following first–order and Higuchi kinetics. The difference factor $f1$ and similarity factor $f2$ were found to be 2.43% and 83%, respectively, for the optimized formulation FM2, and the drug release was greater than that of the marketed product. **Conclusion:** It is evident that the optimized formulation FM2 appears to be a promising system that facilitates the rapid release of olanzapine compared to other formulations.

INTRODUCTION

Olanzapine is a relatively new benzodiazepine atypical antipsychotic medicine that belongs to the class of thiobenzodiazepines. It has proven efficacy against the positive and negative symptoms of schizophrenia and bipolar disorder. Schizophrenia represents the most prevalent type of severe mental illness and is considered a severe brain disorder that cannot be cured and may have fatal ramifications if left untreated. Olanzapine exhibits poor water solubility, belongs to the biopharmaceutics classification system class II (characterized by low solubility & high permeability), and approximately 93% of the plasma protein is bound, undergoing substantial pre-systemic processing in the liver, resulting in relatively poor oral bioavailability [1]. Solid dispersion is the most widely used technique for enhancing the solubility and bioavailability of poorly soluble active therapeutic ingredients,

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as it is an easy and cost-effective approach. Solid dispersion involves one or more active substances in an inert carrier or matrix, utilizing the solid-state melting solvent technique. It can be used to improve the dissolution rate of drugs with low water solubility, thereby enhancing their oral bioavailability, improving the compound's surface wetting properties, and increasing the interfacial area available for drug dissolution. A broad range of water-soluble carriers has been employed to increase the aqueous solubility of the active therapeutic ingredient from a solid dispersion. When added to solid dispersion, several poorly soluble therapeutic drugs have been shown to increase in solubility, dissolution rate, and oral absorption [2].

Fast-melting formulations are a new class of products that offer additional benefits over other dosage forms, combining the benefits of both liquid and conventional tablet formulations. They offer the convenience of a tablet format while also addressing the disadvantage of s***w***allowing. Additionally, it provides a far more accurate dosage than the main alternative, ***or***al liquids. This formulation is specifically intended for individuals who are dysphasic, elderly, young, travelling, or psychotic and who refuse to consume traditional oral formulations or are unable to swallow them due to problems of swallowing or dysphagia, which are prevalent across all age groups. Fast-melting or fast-disintegrating tablets dis***solve*** in the mouth without chewing. The need for chewing has garnered considerable attention over the last decade. The fast-melting tablet is also known as a rapid dissolving, quick-melting, fast-dispersion, or orodispersible tablet [3].

Orodispersible is a term recently introduced by the European Pharmacopoeia. Tablets, when placed in the mouth, dissolve or disperse within less than three minutes before ingestion. This type of formulation is suitable for antipsychotics, cardiovascular, analgesics, and anti-allergy medications. When such a tablet is placed on the tongue, the medicine is quickly dispersed or dissolved in the saliva. This results in a faster sort of action and better bioavailability of the drug compared to the standard tablet dosage form. For formulating the fast-melting tablet, a variety of technologies are employed, and these methods are based on enhancing porosity in the tablet by incorporating superdisintegrants or water-soluble excipients [4]. The carriers used for the solid dispersion technique are polyvinyl pyrrolidone K-30, polyethylene glycol 4000, Urea, and carboxymethyl cellulose, based on their solubilizing property, along with other functions such as disintegration, crystallization inhibition, and promoting amorphization [2]. Fast-dissolving tablets enable faster dissolution in saliva, facilitating pre-gastric absorption, reduced first-pass metabolism, and potentially quicker therapeutic action. The use of various carrier combinations, co-processing techniques, or multi-functional excipients in this research work is novel, enabling the achievement of a robust, palatable, and stable formulation.

MATERIAL AND METHODS

Materials

Olanzapine was received as a gift sample from Micro Labs, Bangalore, India. Polyvinyl pyrrolidone K-30, magnesium stearate, and talc were purchased from Molychem, Mumbai. Sodium carboxy methyl cellulose, mannitol, and sodium starch glycoate were obtained from Yarrow Chem, Mumbai. All other chemicals used were of analytical grade.

Methods

Phase solubility

Phase solubility analysis was conducted by adding a constant level of the drug and increasing the quantity of various carriers according to the specified ratios in screw-capped bottles. The bottles were shaken in a Rotary flask shaker and incubated at 37°C for 48 hours. After 48 hr, the solutions were filtered using Whatman filter paper. The filtrate was diluted and analysed spectrophotometrically at 250 nm [5].

$$\boldsymbol{Concentration} = \left[\frac{\mathbf{1}}{\boldsymbol{slope}}\right] \times \boldsymbol{absorbance}$$

Experimental Study Design for Optimization of Phase Solubility [5]

The 2^4 factorial design was employed to optimize responses and determine the optimum process parameters with two variables at four levels. The carriers (X1) PEG 4000, CMC, PVP K 30, and urea, along with carrier ratios of 1:1, 1:2, 1:3, and 1:4 (X2), were considered as independent variables in the phase solubility method (Table 1). Each variable was studied at four levels, as given in Table 1. The dependent variables selected were Ka (Y1), complexation efficiency (Y2), ΔG (Y3), and solubility (Y4) as in Table 2. Minitab® Statistical Software (Version 17.1) was used to perform the statistical analysis of values. The high solubilizing carrier was chosen for further study.

Table 1: Independent Variables

Code	Independent Variables	Level (-1)	Level (0)	Level (+1)	Level (+2)
X1	Carriers	CMC	Urea	PEG 4000	PVP K 30
X2	Carrier ratio	1:1	1:2	1:3	1:4

Table 2: Dependent Variables

Code	Dependent Variables
Y1	Ka
Y2	Complexation Efficiency
Y3	ΔG
Y4	Solubility

Preparation of Solid Dispersion: Olanzapine was made into a solid dispersion using the kneading and melting methods.

Kneading method: Accurately weighed drug and excipients were placed in a mortar. A sufficient quantity of water–ethanol mixture (1:1) was added to the blend and kneaded vigorously to obtain a paste-like consistency, which was then dried in a hot air oven, pulverized, and passed through sieve #80 to get a free-flowing powder. The same procedure was repeated for other formulations also [6].

Melting method: The drug and the excipients were weighed accurately. The excipients were melted, and the drug was added to them. It was mixed well and flash-cooled in an ice bath and then stored overnight in a desiccator. After being ground with a mortar and pestle, the obtained solid dispersion was sieved through an 80-mesh sieve and stored in a desiccator for further use. [6]

Experimental Study Design for Optimization of Fast-Melting Tablets [7]: Response surface methodology is a tool used to analyze the impact of independent variables on dependent variables, utilizing a combination of statistical and mathematical techniques. The 2^3 factorial design was employed to optimize responses and determine the optimal process parameters with three variables at two levels. The two superdisintegrants Sodium starch glycolate (X1) and Sodium carboxymethyl cellulose (X2), and the method of preparation of solid dispersion (X3) were considered as independent variables in the preparation of fast-melting tablets of Olanzapine by the wet granulation method. Each variable was studied at two levels (−1 and +1) (Table 3), as given in the formulation (Table 5). The dependent variables (Table 4) selected were particle size analysis (Y1), swelling index (Y2), drug entrapment efficiency (Y3), and percentage drug release (Y4). Minitab® Statistical Software (Version 17.1) was used to perform the statistical analysis. The best-optimized formulation can be further explored in a field of study. The statistical model incorporating interactive and polynomial terms was used to evaluate the response.

$$Y = b0 + b1X1 + b2X2 + b3X3 + b12X1X2 + b13X1X3 + b23X2X3 + b123X1X2X3$$

Table 3: Independent Variables

Code	Independent Variables	Level (-1)	Level (+1)
X1	Sodium Starch Glycolate	10 mg	20 mg
X2	Sodium carboxymethyl cellulose	10 mg	20 mg
X3	Method of preparation of solid dispersion	Kneading	Melting

Table 4: Dependent Variables

Code	Dependent Variables
Y1	Hardness
Y2	Friability
Y3	Disintegration time
Y4	% drug release

Evaluation of granules

Bulk density [8]**:** The bulk density was calculated utilizing the following formula, & which is represented in g /ml: (BD = M/Vb). In this case, M is the mass of the powder, and Vb is the bulk volume.

Angle of Repose [9]

The funnel method was used to calculate the angle of repose. The precisely weighed mixture was poured into a funnel. The drug-excipient mixture was allowed to freely flow through the funnel to the top after the height of the funnel was adjusted such that the tip of the funnel just touched the top of the heap.

Using the following formula, the powder cone's diameter was measured, and the angle of repose was determined.

$$Tan\ \theta = \frac{h}{r}$$

h is the height of the pile, ***r*** is the radius of the pile's base

Table 5: Composition of Fast-Melting Olanzapine Tablet

F. Code	OLZ – SD equivalent (mg)	PVP K-30 (mg)	MCC (mg)	SSG (mg)	SCMC (mg)	Vanillin (mg)	Mannitol (mg)	Talc (mg)	Mag. Stearate (mg)	Method of Preparation	Weight per tablet (mg)
F1	20	80	40	10	0	2	3	2	3	Kneading	160
F2	20	80	40	20	0	2	3	2	3	Kneading	170
F3	20	80	40	0	10	2	3	2	3	Kneading	160
F4	20	80	40	0	20	2	3	2	3	Kneading	170
F5	20	80	40	10	0	2	3	2	3	Melting	160
F6	20	80	40	20	0	2	3	2	3	Melting	170
F7	20	80	40	0	10	2	3	2	3	Melting	160
F8	20	80	40	0	20	2	3	2	3	Melting	170

Tapped density [10]: Tapped density (TD) was determined by measuring the mass (M) of a known quantity of powder and its tapped volume (Vt) after subjecting the powder in a graduated cylinder to a fixed number of mechanical taps on a tapped density tester. The tapped density was calculated using the formula:

$$\boldsymbol{Tapped\ Density = M \times Vt(g/ml)}$$

Where Vt is the tapped volume in mL and M is the mass in g.

Void volume [10]: This parameter reflects the inter-particulate space present in the powder bed before and after tapping. Void volume (Vo) was obtained from the difference between the bulk volume (Vb) and tapped volume (Vt) as:

$$\boldsymbol{Vo = Vb - Vt}$$

Porosity [10]: The total porosity (ε) was calculated as the ratio of void volume to bulk volume, expressed in percentage, using the following formula. Higher porosity values indicate greater inter-particle spaces.

$$\boldsymbol{\varepsilon = \frac{Vo}{V} \times 100}$$

Where V is the total volume and V_0 is the tapped volume.

Carr's Index [11]: Carr's Index, an indicator of powder compressibility, was calculated from bulk density and tapped density values using the following equation. Carr's Index value below 15% typically indicates good flow, while values above 25% suggest poor flow.

$$\boldsymbol{Carr's\ Index}\ (\%) = \frac{\boldsymbol{Tapped\ Density - Bulk\ Density}}{\boldsymbol{Tapped\ Density}} \times \boldsymbol{100}$$

Hausner ratio [11]: The Hausner ratio was calculated as the ratio of tapped density to bulk density. An HR ≤ 1.25 is generally considered indicative of good flowability, while values > 1.25 indicate poor flow characteristics due to higher inter-particle friction.

$$\boldsymbol{Hausner\ Ratio = \frac{Tapped\ Density}{Bulk\ Density}}$$

Scanning Electron Microscope

The surface morphology of Olanzapine**,** PVP K-30 solid dispersion, and physical mixtures was examined by means of a Hitachi (Japan) scanning electron microscope. The powders were fixed to a brass stub using double-sided adhesive tape and made electrically conductive by recoating, in a vacuum, with a thin layer of platinum (approximately 3-5 nm) for 100 s at 30 W. The pictures were taken at an excitation voltage of 15 kV and a magnification of 100 µm [12].

Evaluation of Tablets

The weight variation [10]

The average weight of twenty tablets was calculated after they were chosen at random. Then, the weight of each tablet was measured and compared to the average. The weight variation test is passed if the comparative variation falls within the specified limitations.

Thickness [10]: A direct method can be used to measure thickness using vernier calipers. The thickness of the tablets was measured by placing the tablet between the vernier caliper's two arms, which allowed us to measure the thickness accurately.

Hardness [13]

The Monsanto Hardness Tester was used to determine the crushing strength, also known as hardness, which is the force needed to shatter the tablet in a radial direction. The indicator reading is set to zero, and the test tablet is maintained in a fixed or moving position. Afterwards, the screw knob was moved forward, progressively increasing the stress applied to the tablet's edge until it broke the scale reading. The amount of pressure needed in kg/cm² to shatter the tablet was then noted.

Friability [11]

Friability was determined by calculating the weight loss of a tablet during a four-minute tumble at 25 rpm in a friabilator. The weight loss of the tablets due to fracture or abrasion was recorded and referred to as % friability. The percentage friability (% F) was determined by employing the given formula,

$$\% \boldsymbol{F} = \frac{\boldsymbol{W - Wo}}{\boldsymbol{Wo}} \times \mathbf{100}$$

Where, Wo= Initial weight of the tablet, W = Weight of the tablet after the test.

Drug Content **[14]**

The drug content of the fast-melting tablets was determined by UV spectrophotometry using a double-beam UV-Vis spectrophotometer. The analytical wavelength (λmax) was first identified by scanning a suitably prepared standard solution of the pure drug over the range of 200–400 nm, and the assay was performed at the resulting λmax. For sample preparation, ten tablets were weighed to obtain the average tablet weight; tablets were powdered, and an amount of powder equivalent to one tablet was accurately weighed and transferred to a 100 mL volumetric flask, extracted with 50 mL of the chosen diluent, sonicated for 15–30 min to ensure complete dissolution, and made up to volume. The solution was filtered through a 0.45 µm syringe filter and appropriately diluted with diluent to fall within the calibration range. A series of calibration standards was prepared from a primary stock and measured to construct a linear calibration curve. Sample absorbance was measured against the diluent blank, and drug content was calculated from the regression equation.

In vitro Disintegration Time [3]

The solvent that enters the tablet's pores causes the super disintegrants to swell, providing enough hydrodynamic pressure to dissolve the tablet completely and quickly.

In vitro Drug Release Study [15]

Dissolution Parameters: Medium: pH 6.8 buffer solution; Apparatus: USP – Type II (Paddle); RPM: 50; Temperature: 37 ± 0.5℃; Medium Volume: 900 ml

Procedure: In vitro release studies were carried out using a USP XXIII paddle dissolution test apparatus. 900 mL of pH 6.8 buffer solution was placed in a dissolution vessel, and the medium's temperature was maintained at 37 °C ± 0.50 °C. The speed was 50 rpm. Samples were withdrawn at predetermined time intervals, and the same volume of fresh medium was replaced. The samples were analysed for drug content against a pH 6.8 buffer as a blank at a maximum of 251 nm using a UV spectrophotometer.

Comparison with the marketed product [16]

The in vitro dissolution profile of the optimized formulation, FM2, was compared with that of the marketed formulation in pH 6.8 phosphate buffer. The comparison was performed using model-independent mathematical approaches, specifically the difference factor (f_1) and similarity factor (f_2), as recommended by the US FDA and EMA guidelines.

The difference factor (f_1) was calculated using the formula:

$$f1 = \{[\sum_{t=1}^{n}(Rt - Tt)]/[\sum_{t=1}^{n} Rt]\} * 100$$

The similarity factor (f_2) was calculated using the formula:

$$f2 = 50 * \log\{[1 + (\frac{1}{n})\sum_{t=1}^{n}(Rt - Tt)^2]^{-0.5} * 100\}$$

Where n is the number of time points, R_t is the percentage of drug dissolved from the reference (marketed) product at time t, and T_t is the percentage of drug dissolved from the test formulation (FM2) at the same time point.

According to regulatory criteria, an f_2 value between 50 and 100 indicates similarity between two dissolution profiles, whereas an f_1 value less than 15 suggests minor differences in drug release. The in vitro dissolution profile of the optimized formulation, F6, was compared with that of the marketed formulation at a pH of 6.8. The similarity factor & dissimilarity factor are calculated. Dissolution tests were conducted under the conditions specified in the IP (9th Ed., 2022).

RESULTS & DISCUSSION

The investigation into enhancing the solubility of Olanzapine through various carriers provides valuable insights into

improving drug delivery systems for better therapeutic outcomes. By employing phase solubility analysis, this study elucidates the role of carriers and carrier ratios in enhancing solubility-related parameters such as dissociation constant, complexation efficiency, Gibbs free energy & solubility. The results suggest that the water-soluble carrier PVP K30 (Table 6 & Figure 1) enhances the solubility of Olanzapine to a greater extent when compared to other carriers like urea, PEG 4000, and carboxy methyl cellulose.

Furthermore, response surface methodology allows for the optimization of formulation parameters to maximize solubility enhancement. Therefore, PVP K30 is selected as a carrier for enhancing solubility in the preparation of a solid dispersion.

Table 6: Phase Solubility data

Phase solubility code	Carrier	Slope	Intercept	Ka	CE	Δ G (kJ / mol)	Solubility of 1:4 (µg/ml)
PS 1	PEG 4000	2270	-87.18	0.01148	-1.0004	-152.8	13.81
PS 2	CMC	5363	-207.5	0.00482	-1.0002	-182.47	7.56
PS 3	PVP K30	1738	-69.59	0.01438	-1.0006	-145.09	31.26
PS 4	Urea	2501	-99.78	0.01003	-1.0004	-157.42	11.7

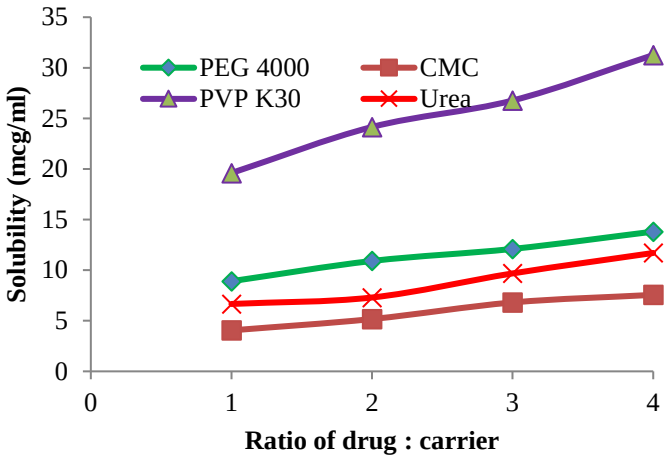

Figure 1: Phase Solubility Curves

REGRESSION EQUATIONS OF PHASE SOLUBILITY STUDIES

$$Y1 - Ka = -0.0375 + 0.000753\,X1\,Carriers + 0.03053\,X2\,Carrier\,ratio$$

X1 (Carriers): This is the first independent variable, representing the amount of carriers. The coefficient is 0.000753, suggesting that for each unit increase in the amount of carriers (X1), the difference between Y1 and Ka increases by 0.000753 units. This implies that increasing the amount of carriers leads to a slight increase in the difference between Y1 and Ka.

X2 (Carrier ratio): This is the second independent variable, representing the carrier ratio. The coefficient is 0.03053, suggesting that for each unit increase in the carrier ratio (X2), the difference between Y1 and Ka increases by 0.03053 units. This implies that increasing the ratio of carriers to solute leads to a more substantial increase in the difference between Y1 and Ka.

The intercept term (-0.0375) represents the value of Y1 - Ka when both the amount of carriers (X1) and the carrier ratio (X2) are zero. So, this equation suggests that both the amount of carriers and the carrier ratio contribute positively to the difference between Y1 and Ka (Figure 2). Increasing either one leads to an increase in this difference, with the carrier ratio having a larger impact per unit increase compared to the amount of carriers.

$$Y2 - CE = 3.501 - 0.0000\,X1\,Carriers - 3.001\,X2\,Carrier\,ratio$$

X1 (Carriers)**:** This is the first independent variable, representing the amount of carriers. However, the coefficient is zero (0.0000), which means that changes in X1 do not contribute to changes in Y2-CE. In other words, the amount of carriers does not affect the difference between Y2 and CE.

X2 (Carrier ratio)**:** This is the second independent variable, representing the carrier ratio. The coefficient is -3.001, suggesting that for each unit increase in the carrier ratio (X2), the difference between Y2 and CE decreases by 3.001 units. This implies that increasing the ratio of carriers to solute leads to a decrease in the difference between Y2 and CE.

The intercept term (3.501) represents the value of Y2 - CE when both the amount of carriers (X1) and the carrier ratio (X2) are zero. This equation suggests that while the number of carriers doesn't affect the difference between Y2 and CE, the carrier ratio does (Figure 3). Increasing the carrier ratio leads to a decrease in the difference between Y2 and CE.

$$Y3 - \Delta G = 551 + 2.9\,X1\,Carriers - 478\,X2\,Carrier\,ratio$$

The coefficient of X1 (2.9) suggests that for each unit increase in the amount of carriers (X1), the change in Gibbs free energy

(Y3 - ΔG) is expected to increase by 2.9 units. This implies that adding more carriers leads to an increase in the change in Gibbs free energy.

The coefficient of X2 (-478) indicates that for each unit increase in the carrier ratio (X2), the change in Gibbs free energy (Y3 - ΔG) is expected to decrease by 478 units. This suggests that increasing the ratio of carriers to solute results in a decrease in the change in Gibbs free energy.

The intercept term (551) represents the expected change in Gibbs free energy when both the amount of carriers (X1) and the carrier ratio (X2) are zero. This equation suggests that both the amount of carriers and the carrier ratio affect the change in Gibbs free energy (Figure 4). Increasing the amount of carriers leads to an increase in the change in Gibbs free energy, while increasing the carrier ratio leads to a decrease in the change in Gibbs free energy.

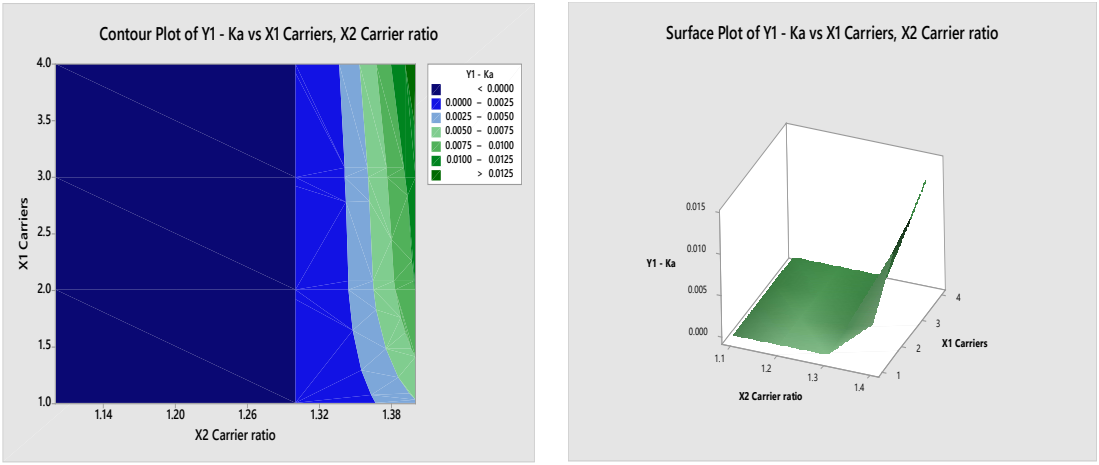

Figure 2: Contour & Surface plot of Y1 (Ka) Vs X1 (Carriers) & X2 (Carrier ratio)

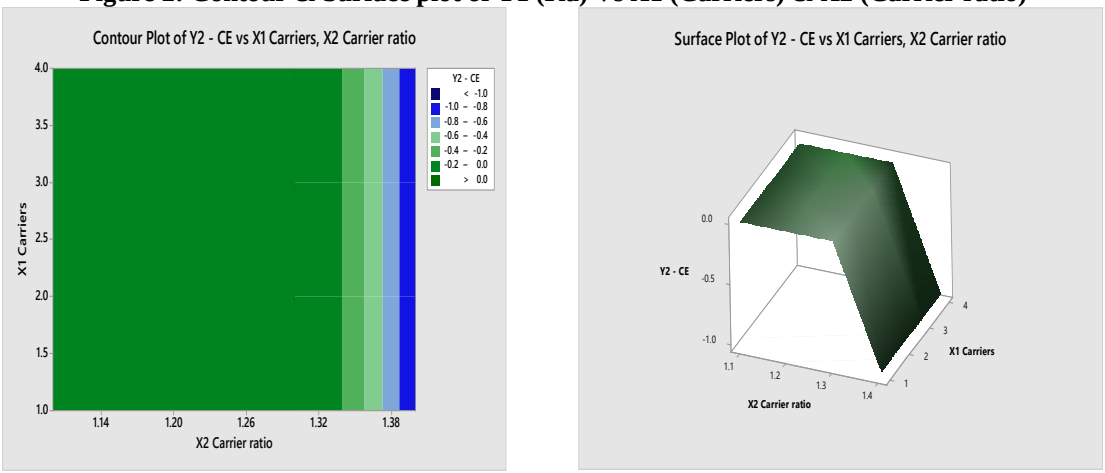

Figure 3: Contour & Surface plot of Y2 (Complexation Efficiency) Vs X1 (Carriers) & X2 (Carrier ratio)

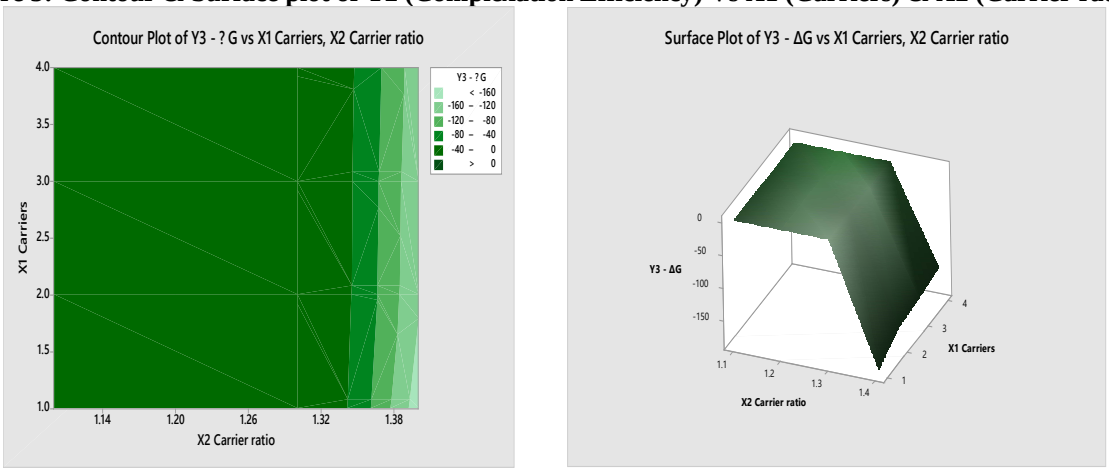

Figure 4: Contour & Surface plot of Y3 (ΔG) Vs X1 (Carriers) & X2 (Carrier ratio)

$$Y4 - Solubility = -28.4 + 6.123\ X1\ Carriers + 20.80\ X2\ Carrier\ ratio$$

The coefficient of X1 (6.123) suggests that for each unit increase in the amount of carriers (X1), the change in solubility (Y4 - Solubility) is expected to increase by 6.123 units. This implies that adding more carriers leads to a positive change in solubility. The coefficient of X2 (20.80) indicates that for each unit increase in the carrier ratio (X2), the change in solubility (Y4 - Solubility) is expected to increase by 20.80 units. This implies that increasing the ratio of carriers to solute results in a greater positive change in solubility.

The intercept term (-28.4) represents the expected change in solubility when both the amount of carriers (X1) and the carrier ratio (X2) are zero. So, this equation suggests that both the amount of carriers and the carrier ratio have positive effects on the change in solubility (Figure 5). Increasing either one leads to an increase in solubility, with the carrier ratio having a larger impact per unit increase compared to the amount ofcarriers.

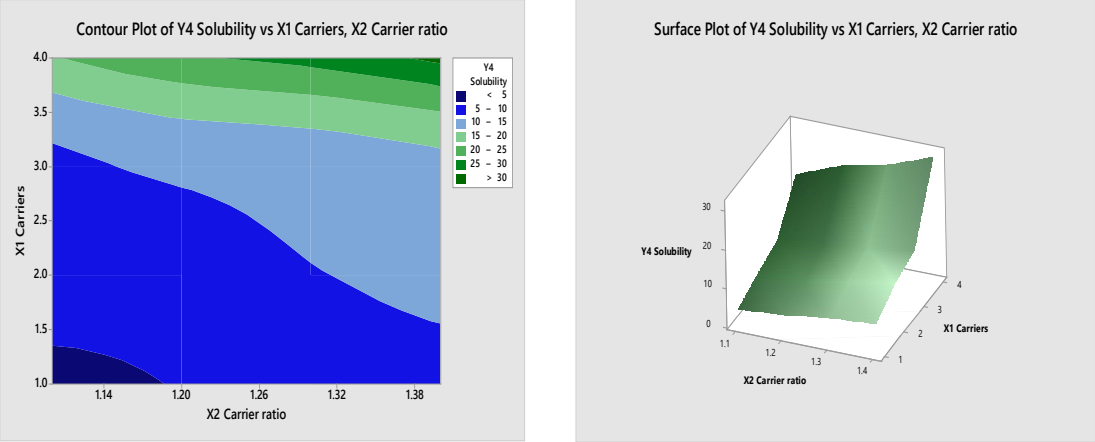

Figure 5: Contour & Surface plot of Y4 (Solubility) Vs X1 (Carriers) & X2 (Carrier ratio)

Surface Morphology

The SEM image of PS 3 (Olanzapine: PVP K 30 solid dispersion) reveals particles with heterogeneous surface morphologies, featuring a mixture of spherical & irregularly shaped particles with distinct surface topography. The most prominent particle in the centre exhibits a rough, granular surface texture, suggesting a high concentration of surface-deposited polymer-drug aggregation. The surface appears densely coated with fragmented structures, indicative of drug crystallization or phase separation during bead formation. Surrounding particles show varying degrees of surface roughness, with more compact and less textured surfaces, possibly representing partially covered drug particles. The absence of smooth surfaces and the presence of micro-cracks on many of the particles suggest a fast melting mechanism (Figure 6).

Particle Size Distribution

The particle size distribution analysis revealed that the particles ranged from approximately 3.2 µm to 285 µm, with a mean particle size of about 29.1 µm. The median particle size (D50) was found to be 15.4 µm, while the interquartile range (IQR) extended from 6.3 to 30.9 µm, indicating that the majority of particles were distributed within this size range. The D90 value showed that 90% of the particles measured below 42.2 µm. The largest particles observed were approximately 44.4 µm in length along their longest axis, and several notable elongated fragments measuring between 38 and 44 µm were also present, highlighting the heterogeneous size and morphology of the solid dispersion system.

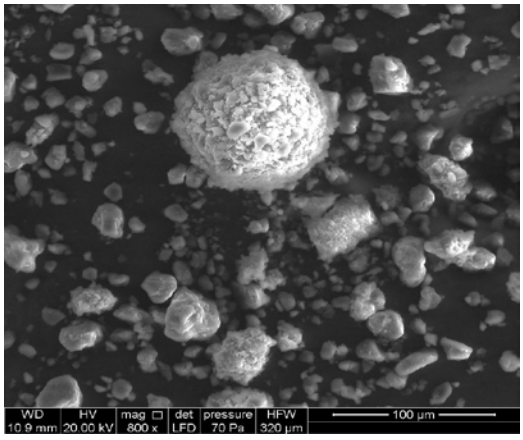

Figure 6: SEM image of PS 3

Morphological Observations

The morphological analysis of the solid dispersion revealed distinct structural variations among the particles. A central large spherical particle of approximately 280 µm was observed, characterized by a rough, granular surface with evident polymer–drug aggregation, along with signs of fragmented

crystallites and possible phase separation. In addition, irregular particles ranging from 10 to 50 µm displayed a mixed morphology, with surfaces ranging from compact to semi-rough, and some appeared partially coated with PVP, indicating a heterogeneous dispersion of the polymer. Smaller microparticles measuring less than 10 µm were also noted, which are likely formed as fast-quenched drug–polymer fragments and appeared more spherical with smoother surfaces compared to the larger aggregates. Furthermore, surface cracks and pronounced roughness were observed across multiple particles, suggesting a rapid melting and solidification mechanism during the bead formation process. The fast-melting tablets were prepared using the wet granulation method, which involved solid dispersions of Olanzapine with PVP K-30 (prepared by the kneading & melting method) and super disintegrants, including sodium starch glycolate and sodium carboxymethyl cellulose. The physical properties of all formulations were evaluated (Table 7) before compression, including angle of repose, bulk density, tapped density, compressibility index, and Hausner ratio. The angle of repose value ranged from 25° 46" to 270° 17". The results were found to be below 30°, indicating that the blend had good flow ability. The bulk density and tapped density ranged from 0.554 to 0.578 and 0.623 to 0.654, respectively. The compressibility index ranged from 11.59 to 14.8. The blend was found to have free-flowing property, as the result was found to be below 20%. The Hausner ratio ranged from 1.11 to 1.14. The result indicates that the value of the free-flowing properties of the granules was below 1.2.

Table 7: Pre-compression parameters of Olanzapine fast melting tablets

F. code	Angle of Repose (°) ± SD	Bulk density (gm/cc) ± SD	Tapped density (gm/cc) ± SD	Carr's index ± SD	Hausner's ratio ± SD
FK1	26.72 ± 0.34	0.572 ± 0.01	0.647 ± 0.01	13.11 ± 0.38	1.13 ± 0.02
FK2	25.91 ± 0.28	0.562 ± 0.01	0.628 ± 0.01	11.74 ± 0.35	1.11 ± 0.01
FK3	26.23 ± 0.29	0.578 ± 0.02	0.645 ± 0.01	11.59 ± 0.34	1.11 ± 0.01
FK4	27.17 ± 0.31	0.571 ± 0.01	0.644 ± 0.02	12.78 ± 0.37	1.12 ± 0.01
FM1	25.84 ± 0.27	0.576 ± 0.01	0.654 ± 0.01	13.54 ± 0.39	1.13 ± 0.01
FM2	25.46 ± 0.25	0.554 ± 0.01	0.636 ± 0.01	14.80 ± 0.41	1.14 ± 0.01
FM3	26.58 ± 0.30	0.556 ± 0.02	0.623 ± 0.01	12.05 ± 0.36	1.12 ± 0.01
FM4	25.75 ± 0.26	0.558 ± 0.01	0.635 ± 0.02	13.79 ± 0.38	1.13 ± 0.01

The results of all these tests were satisfactory (Table 8). The hardness of tablets in all batches ranged from 3.9 to 4.2 kg/cm^2. All the formulations passed the weight variation test, as per the pharmacopeial limit of ±5 %. The percentage friability of all batches ranged from 0.2% to 0.5%, which was well below the pharmacopeial limit of <1%. Drug content was also found to be uniform among all the formulations and ranged from 96.7 to 99.5%. To determine the kinetic drug release, the data were analyzed using different models. The optimized formulation FM2 was considered the best among all the formulations based on both drug content and % drug release within 20 minutes.

Table 8: Post-compression parameters of Olanzapine Fast Melting Tablets

Batch No	Hardness (kg/cm^2) ± SD	Friability (%) ± SD	Weight variation (mg) ± SD	Disintegration time (min) ± SD	Drug Content % ± SD
FK1	4.10 ± 0.06	0.20 ± 0.02	160.2 ± 1.2	63 ± 1.2	96.8 ± 0.4
FK2	3.90 ± 0.04	0.50 ± 0.03	170.3 ± 1.4	55 ± 1.0	98.2 ± 0.6
FK3	4.00 ± 0.07	0.40 ± 0.02	160.2 ± 1.3	63 ± 1.1	97.5 ± 0.5
FK4	4.20 ± 0.05	0.30 ± 0.02	170.5 ± 1.5	57 ± 1.1	98.3 ± 0.4
FM1	4.10 ± 0.06	0.20 ± 0.02	160.3 ± 1.4	59 ± 1.0	97.4 ± 0.6
FM2	3.90 ± 0.05	0.50 ± 0.03	170.1 ± 1.3	50 ± 1.0	99.5 ± 0.5
FM3	4.20 ± 0.04	0.20 ± 0.02	160.2 ± 1.2	61 ± 1.1	96.7 ± 0.4
FM4	4.00 ± 0.07	0.30 ± 0.02	170.3 ± 1.5	55 ± 1.0	98.6 ± 0.6

The fast-melting tablets of Olanzapine were prepared by the wet granulation technique using solid dispersions of Olanzapine, sodium starch glycolate, sodium CMC, microcrystalline cellulose, and vanillin. The magnesium stearate and talc were

used as a lubricant and glidant, respectively. The prepared tablets of all formulations were subjected to various evaluation parameters, including weight variation, hardness, friability, drug content, in vitro disintegration time, and in vitro dissolution study (Table 9).

Table 9*:* In vitro drug release of Olanzapine fast-melting tablets

Time (min)	FK1	FK2	FK3	FK4	FM1	FM2	FM3	FM4
0	0	0	0	0	0	0	0	0
5	50.6 ± 1.2	52.2 ± 1.0	50.8 ± 1.3	52.8 ± 1.1	50.5 ± 1.2	56.8 ± 1.0	51.3 ± 1.3	53.4 ± 1.1
10	62.4 ± 1.4	64.3 ± 1.2	63.1 ± 1.3	64.7 ± 1.1	62.7 ± 1.4	69.5 ± 1.2	62.6 ± 1.3	65.8 ± 1.2
15	77.9 ± 1.5	80.9 ± 1.4	76.6 ± 1.6	81.1 ± 1.3	77.2 ± 1.5	83.1 ± 1.3	75.3 ± 1.6	81.2 ± 1.4
20	94.7 ± 0.8	98.1 ± 0.7	94.5 ± 0.9	97.8 ± 0.8	94.9 ± 0.8	99.3 ± 0.6	95.4 ± 0.9	97.1 ± 0.7
25	100	100	100	100	100	100	100	100

The In vitro release data of all formulations (FK1–FK4 and FM1–FM4) were fitted to different kinetic models, namely zero-order, first-order, Higuchi, and Korsmeyer–Peppas, to elucidate the mechanism of drug release.

Model fitting was carried out using linear regression analysis, and the best-fit model was selected based on the coefficient of determination (R^2). Among the tested models, the first-order model consistently demonstrated higher R^2 values (0.9027–0.9329) compared to the zero-order model (0.8408–0.8939), indicating that drug release was concentration-dependent. The Higuchi model also exhibited excellent correlation ($R^2 > 0.98$ for all formulations), suggesting that the release process was predominantly diffusion-controlled from the polymeric matrix. Korsmeyer further supported this observation through Peppas' analysis, where the release exponent (n) values were below 0.89, confirming a Fickian diffusion mechanism. Taken together, the results indicate that drug release from all formulations followed first-order kinetics with a diffusion-controlled mechanism consistent with the Higuchi model. Model comparison using adjusted R^2 values, along with information criteria (AIC/BIC), reinforced these findings by favouring the Higuchi model as the best fit across all formulations (Table 10).

Table 10: Kinetics of drug release of Olanzapine Fast Melting Tablets

F. Code	Zero-order (R^2)	First-order (R^2)	Higuchi's (R^2)	Korsmeyer – Peppa (R^2)	Possible Drug Release mechanism
FK1	0.8935	0.9105	0.9935	0.8791	First order
FK2	0.8790	0.9175	0.9900	0.8763	First order
FK3	0.8918	0.9041	0.9931	0.8779	First order
FK4	0.8751	0.9243	0.9898	0.8745	First order
FM1	0.8939	0.9092	0.9933	0.8792	First order
FM2	0.8408	0.8683	0.9828	0.8636	First order
FM3	0.8912	0.9027	0.9898	0.8769	First order
FM4	0.8693	0.9329	0.9902	0.8722	First order

REGRESSION EQUATIONS

$$Y1\ Hardness = 4.200 - 0.01400X1\ SSG - 0.00600X2\ SCMC + 0.0000X3\ MOP$$

Intercept (4.200)**:** This is the base hardness value when all the predictors (X1, X2, X3) are zero. It represents the hardness of the material, unaffected by SSG, SCMC, or MOP. Coefficient of X1 SSG (-0.01400)**:** For each unit increase in SSG, the hardness of the material decreases by 0.01400 units, assuming other factors are held constant. This suggests that higher values of SSG are associated with lower hardness. Coefficient of X2 SCMC (-0.00600) (Figure 7)**:** For each unit increase in SCMC, the hardness decreases by 0.00600 units, assuming other factors are held constant. This suggests that higher values of SCMC are associated with lower hardness—coefficient of X3 MOP (0.0000) (Figure 8)**.** Since the coefficient for X3 MOP is zero, it means that MOP does not affect the hardness according to this model.

The intercept (4.200) represents baseline hardness when SSG (X_1), SCMC (X_2), and MOP (X_3) are zero. Increasing SSG by 1 unit decreases hardness by 0.014 units; increasing SCMC decreases hardness by 0.006 units. MOP shows no measurable

effect (coefficient = 0). Contour plots (Figures 7–8) confirm a negative gradient with SSG and SCMC, and no curvature along the MOP axis.

Summary: This model predicts that the hardness of the material decreases with increases in SSG and SCMC, and that MOP has no effect on the hardness. The intercept provides a baseline value for hardness when the predictors are zero.

- Model fit**:** $R^2 = 52\%$, Adj $R^2 = 16\% \rightarrow$ weak, not statistically significant.
- Conclusion**:** No variable significantly influences hardness (Table 11)

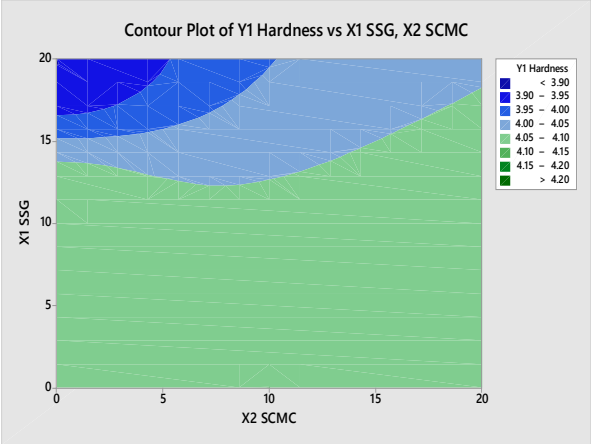

Figure 7: Contour plot of Y1 Hardness Vs X1 SSG, X2 SCMC

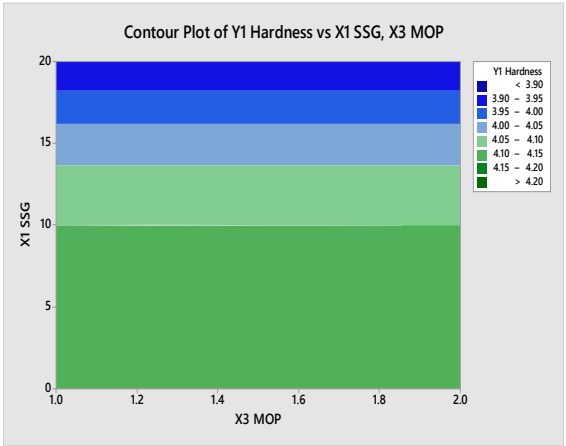

Figure 8: Contour plot of Y1 Hardness Vs X1 SSG, X3 MOP

The intercept (4.200) represents baseline hardness when SSG (X_1), SCMC (X_2), and MOP (X_3) are zero. Increasing SSG by 1 unit decreases hardness by 0.014 units; increasing SCMC decreases hardness by 0.006 units. MOP shows no measurable effect (coefficient = 0). Contour plots (Figures 7–8) confirm a negative gradient with SSG and SCMC, and no curvature along the MOP axis.

Summary: This model predicts that the hardness of the material decreases with increases in SSG and SCMC, and that MOP has no effect on the hardness. The intercept provides a baseline value for hardness when the predictors are zero.

- Model fit**:** $R^2 = 52\%$, Adj $R^2 = 16\% \rightarrow$ weak, not statistically significant.
- Conclusion**:** No variable significantly influences hardness (Table 11)

Table 11: ANOVA of Y1 Hardness

Source	DF	F-Value	P-Value
Regression	3	1.44	0.355
X1 (SSG)	1	2.97	0.160
X2 (SCMC)	1	0.55	0.501
X3 (MOP)	1	0.00	1.000
Error	4		

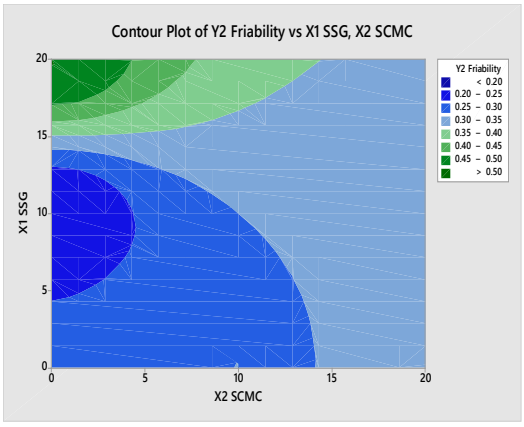

Figure 9: Contour plot of Y2 Friability Vs X1 SSG, X2 SCMC

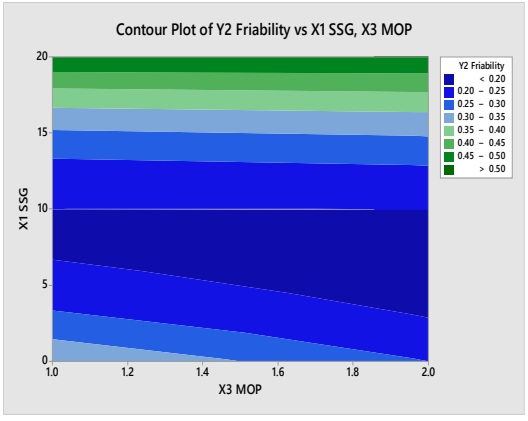

Figure 10: Contour plot of Y2 Friability Vs X1 SSG, X3 MOP

$$Y2\ Friability = 0.175 + 0.01800X1\ SSG + 0.01200X2\ SCMC - 0.0500X3\ MOP$$

Intercept (0.175): This is the base level of friability when all predictors (X1, X2, and X3) are zero. It represents the friability

of the material, unaffected by SSG, SCMC, or MOP. Coefficient of X1 SSG (0.01800): For each unit increase in SSG, the friability of the material increases by 0.01800 units, assuming other factors are held constant. This suggests that higher values of SSG are associated with increased friability. Coefficient of X2 SCMC (0.01200) (Figure 9): For each unit increase in SCMC, the friability increases by 0.01200 units, assuming other factors are held constant. This indicates that higher values of SCMC also lead to increased friability. Coefficient of X3 MOP (-0.0500) (Figure 10): For each unit increase in MOP, the friability decreases by 0.0500 units, assuming other factors are held constant. This suggests that higher values of MOP are associated with reduced friability. The intercept (0.175) is the baseline friability. SSG increases friability by 0.018 units per unit increase, and SCMC increases it by 0.012 units. MOP reduces friability by 0.050 units per unit increase. Contour plots (Figures 9–10) show upward slopes with SSG/SCMC and a downward slope with MOP.

Summary: According to this model, friability increases with higher values of SSG and SCMC, while it decreases with higher values of MOP. The intercept provides a baseline friability value when all predictors are at zero.

- Model fit: R^2 = 59.1%, Adj R^2 = 28.5%.
- Near significance: X1 SSG (p = 0.089, borderline effect).
- Conclusion: Moderate explanatory power; trend but not statistically strong (Table 12)

$$\boldsymbol{Y3\ Disintegration\ Time = 73.63 - 0.8050X1\ SSG - 0.6450X2\ SCMC - 3.250X3\ MOP}$$

Table 12: ANOVA of Y2 Friability

Source	DF	F-Value	P-Value
Regression	3	1.93	0.267
X1 (SSG)	1	5.01	0.089
X2 (SCMC)	1	2.23	0.210
X3 (MOP)	1	0.43	0.550
Error	4		

Intercept (73.63)**:** This is the baseline disintegration time when all predictors (X1, X2, X3) are zero. It represents the disintegration time of the material, unaffected by SSG, SCMC, or MOP. Coefficient of X1 SSG (-0.8050)**:** For each unit increase in SSG, the disintegration time decreases by 0.8050 units, assuming other factors remain constant. This indicates that higher levels of SSG are associated with faster disintegration.

Coefficient of X2 SCMC (-0.6450) (Figure 11)**:** For each unit increase in SCMC, the disintegration time decreases by 0.6450 units, assuming other factors remain constant. This means that higher SCMC also results in faster disintegration. Coefficient of X3 MOP (-3.250) (Figure 12)**:** For each unit increase in MOP, the DT decreases by 3.250 units, assuming other factors remain constant. This suggests that MOP has a substantial effect, with higher values leading to a significant reduction in DT. Baseline disintegration time is 73.63 s. SSG reduces DT by 0.805 s/unit, SCMC by 0.645 s/unit, & MOP by 3.250 s/unit, indicating MOP has the most substantial effect. Contour plots (Figures 11 & 12) show pronounced decreases along the MOP axis and moderate declines with SSG and SCMC.

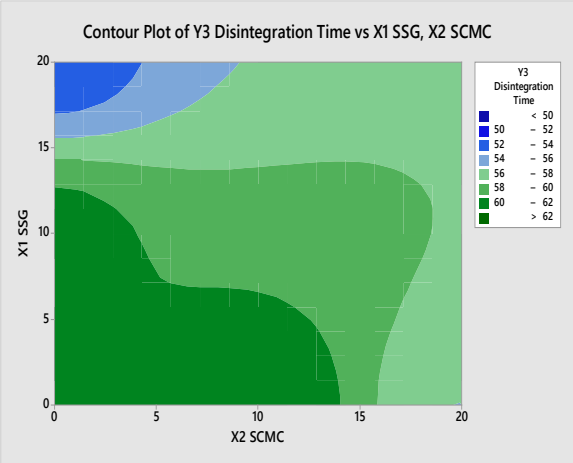

Figure 11: Contour plot of Y3 DT Vs X1 SSG, X2 SCMC

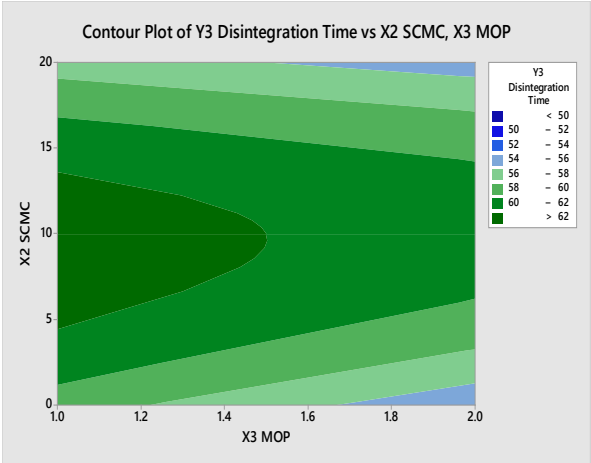

Figure 12: Contour plot of Y3 DT Vs X2 SCMC, X3 MOP

Summary: According to this model, disintegration time decreases with increases in SSG, SCMC, and MOP. The negative coefficients indicate that higher values of these predictors are associated with faster disintegration times. The intercept of 73.63 provides the starting point for disintegration time when all predictors are at zero.

- Model fit**:** R^2 = 97.3%, Adj R^2 = 95.3% → excellent fit.
- All factors significant (p < 0.01).
- Conclusion: Strong predictive model (Table 13)

Table 13: ANOVA of Y3 Disintegration

Source	DF	F-Value	P-Value
Regression	3	48.47	0.001
X1 (SSG)	1	123.21	0.000
X2 (SCMC)	1	79.10	0.001
X3 (MOP)	1	22.09	0.009
Error	4		

$$Y4\%\ drug\ release = 91.075 + 0.3435 \cdot X1\ (SSG) + 0.2965 \cdot X2\ (SCMC) + 0.400 \cdot X3\ (MOP)$$

Intercept (91.075): This is the baseline percentage of drug release when all three variables (X1X1X1, X2X2X2, and X3X3X3) are zero. It represents the starting point of drug release in the absence of the factors SSG, SCMC, and MOP. Effect of SSG (X1X1X1)**:** The coefficient for SSG is 0.3435. This means that for each unit increase in SSG, the drug release percentage increases by 0.3435%, assuming the other factors remain constant. A higher value of SSG generally contributes to a higher drug release. Effect of SCMC (X2X2X2) (Figure 13)**:** The coefficient for SCMC is 0.2965. This indicates that for each unit increase in SCMC, the drug release percentage increases by 0.2965% when other factors are held constant. Thus, SCMC also positively impacts drug release, though slightly less than SSG. Effect of MOP (X3X3X3) (Figure 14)**:** The coefficient for MOP is 0.400. This suggests that for each unit increase in MOP, the drug release percentage increases by 0.400%, assuming the other variables are constant. MOP has the highest effect on drug release among the three variables. Baseline release is 91.075%. SSG increases drug release by 0.3435%/unit, SCMC by 0.2965%/unit, and MOP by 0.4000%/unit, with MOP showing the highest positive influence. Contour plots (Figures 13 & 14) indicate simultaneous increases in release when any variable is raised.

Summary: The above equation indicates that the amounts of SSG, SCMC, and MOP positively influence drug release. The intercept provides the baseline release, while each coefficient represents the incremental increase in drug release for each unit increase in the respective variable.

- Model fit**:** R^2 = 93.4%, Adj R^2 = 88.4%.
- Significant variables**:** X1 SSG and X2 SCMC (p< 0.01) (Table 14)
- MOP not significant (p = 0.415).

Table 14: ANOVA of Y4 % Drug Release

Source	DF	F-Value	P-Value
Regression	3	18.84	0.008
X1 (SSG)	1	55.35	0.002
X2 (SCMC)	1	41.24	0.003
X3 (MOP)	1	0.83	0.415
Error	4		

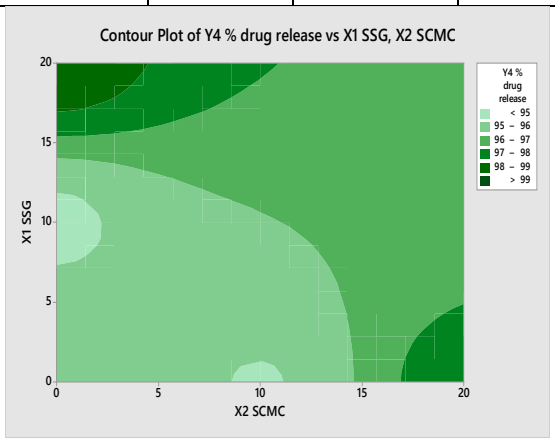

Figure 13: Contour plot of Y4 % drug release Vs X1 SSG, X2 SCMC

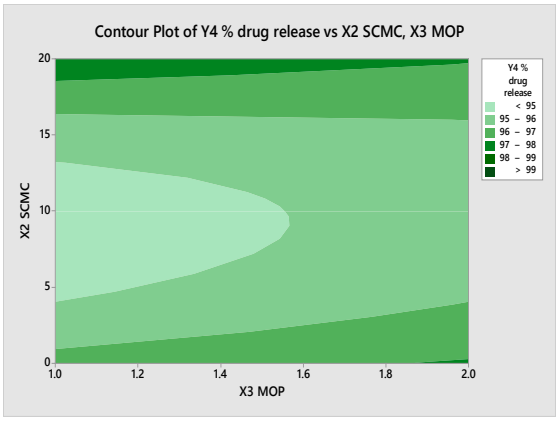

Figure 14: Contour plot of Y4 % drug release Vs X2 SCMC, X3

Model adequacy & residual diagnostics conclusions from ANOVA

1. Lack-of-fit test

** Y1 & Y2**:** Lack-of-fit likely present (low R^2, high error variance).

** Y3 & Y4**:** Adequate models (high R^2,very low residual error).

2. Residual diagnostics

** Y1 & Y2**:** Residuals show high scatter, weak normality assumption - unreliable predictions.

** Y3 & Y4**:** Residuals likely small, random, with no systematic pattern - strong reliability.

COMPARISON WITH THE MARKETED PRODUCT

The in vitro dissolution profile of the optimized formulation FM2 [Table 15] was compared with that of the marketed formulation at pH 6.8. The similarity factor $f2$ was found to be 83% and the difference factor $f1$ was found to be 2.43 for the formulation FM2 and the marketed formulation, indicating that the drug release rate of the FM2 formulation was higher than that of the marketed formulation (Table 16 & Figure 15). The value of $f2$ from 50 to 100 shows similarity in *in vitro* release profiles, and the value of $f1$ below 15% shows that drug release profiles are similar to each other.

Table 15: Formulation of the finally optimized batch FM2

Composition	Weight (mg)
Olanzapine	20
PVP K-30	80
MCC	40
SSG	20
SCMC	0
Vanillin	2
Mannitol	3
Magnesium stearate	3
Talc	2
Total (mg)	170

Table 16: In vitro comparative drug release of formulation FM2 with the marketed product

Time (mins)	FM2 (%)	Marketed product %
0	0	0
5	56.8	54.4
10	69.5	67.3
15	83.1	81.6
20	99.3	96.2
25	100	99.5

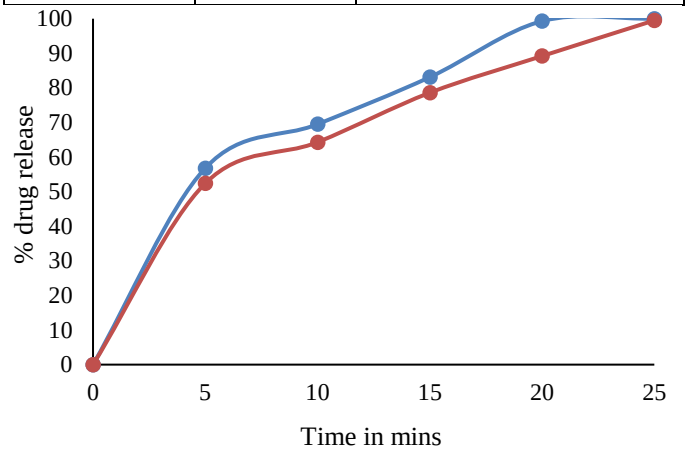

Figure 15: Drug release comparison with the marketed product

For quantitative comparison, dissolution efficiency % and mean dissolution time were calculated for FM2 and the marketed product. FM2 exhibited a dissolution efficiency % of 84.7% and a mean dissolution time of 11.9 minutes, while the marketed product showed a dissolution efficiency % of 82.9% and a mean dissolution time of 12.2 minutes. These values indicate that FM2 provided slightly more efficient and faster drug release than the marketed formulation. However, statistical comparisons using Student's t-test at individual time points (5–25 min) and one-way ANOVA across the complete release profiles revealed no significant differences ($p > 0.05$) between FM2 and the marketed product. These results confirm that the optimized formulation (FM2) follows first-order kinetics with a diffusion-controlled release mechanism as described by the Higuchi model. Furthermore, its dissolution performance was statistically comparable to that of the marketed product, establishing FM2 as a suitable alternative with equivalent release characteristics.

CONCLUSION

The present study reports on the development of fast-melting tablets for oral administration of Olanzapine. The results demonstrated that the release of the drug is influenced by the solid dispersion of Olanzapine and the superdisintegrants sodium starch glycolate & sodium carboxymethyl cellulose.

It can be conclusively stated that the fast-melting tablet FM2 appears to be an anticipatory system for the fast release of Olanzapine. From the results, it can be concluded that the use of superdisintegrant sodium starch glycolate and the solid dispersion of Olanzapine with PVP K-30, prepared by the melting method, exhibits a greater drug release rate than the other formulations. The release kinetics of FM2 indicate drug release by first-order kinetics, with Higuichi following a diffusion mechanism. The dependent variables, disintegration and In vitro dissolution time, were influenced by the independent variables, sodium starch glycolate and melting method. The difference factor $f1$ and similarity factor $f2$ was found to be 2.43% and 83%, respectively, for the optimized formulation FM2, and the drug release was greater than that of the marketed product.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Revathi Sundaramoorthi contributed to formulation methodology, statistical data interpretation using software, manuscript editing, and supervision. Jenifer Sathappan and Senthil Rajan Sivakumar contributed to the review of literature and experimentation. Anitha Pavadai contributed to experimentation and manuscript writing. All authors contributed to the completion of the manuscript.

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