RESEARCH PAPER

Formulation and Characterization of Olanzapine Loaded Nanoparticles by Selecting Box–Behnken Design

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ABSTRACT

Schizophrenia and bipolar disorder are a chronic psychiatric disorder which requires long-term pharmaco-therapy. Olanzapine, a BCS Class II drug, exhibits poor water solubility and extensive first-pass metabolism, which leads to low and variable bioavailability and dose-dependent side effects. The present study was aimed to develop and optimize olanzapine-loaded polymeric nanoparticles to enhance drug solubility, control release, and improve therapeutic efficacy. Nanoparticles were prepared by selecting the oil-in-water emulsion solvent evaporation method with glyceryl monostearate as the polymer and polyvinyl alcohol (PVA) as the stabilizer. A Box-Behnken design was opted to study the effects of formulation variables polymer concentration, surfactant concentration, and lipid content on selected dependent variables like particle size(nm), entrapment efficiency(%), and in-vitro drug release(%). The optimized formulation (F5) exhibited optimum particle size with the 121nm, high entrapment efficiency with 93% and invitro drug release with 94% controlled drug release. Statistical analysis confirmed the significance of the obtained models, with glyceryl monostearate significantly influencing particle size and PVP concentration playing a key role in drug encapsulation and release rate. The study of the drug release rates achieved in vitro with this delivery system demonstrated a zero order release (R^2=0.9974) of drug for 12 hours and released drug from the nanoparticles when compared to remaining formulations. From the evaluation of the results for the kinetic modelling, it was determined that the release of drug from the polymeric nanoparticles involved a combination of diffusion and erosion mechanisms and that the overall Korsmeyer-Peppas kinetic model had the highest correlation coefficient (n=1.03). Overall, this delivery system demonstrated enhanced physico-chemical properties and controlled drug delivery ability, therefore having potential to enhance both the oral bioavailability of olanzapine and the solubility of olanzapine. This delivery system has the potential to be used in combination with in situ gels for the development of advanced drug delivery systems.

Keywords: Olanzapine, Polymeric based Nanoparticles, Box-Behnken Design, Controlled Drug Release, Novel drug delivery

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INTRODUCTION

Schizophrenia and bipolar disorder are considered as chronic psychiatric disorders that can severely impact the cognitive and social abilities of patients if not treated. The atypical antipsychotic drug olanzapine has strong antagonistic effects on both D_2 dopamine and 5 HT_2 serotonin receptors, and is effective in treating both the positive and negative effects of psychotic disorders[1]. Although the oral form of olanzapine is clinically useful, it has low and inconsistent bioavailability related to the large amount of drug that is metabolized before it reaches the bloodstream. Additionally, dosing, weight gain, and metabolic disturbances are considered dose-dependent adverse effects associated with the systemic route of administration. The barriers of making olanzapine available in reasonable doses lead to new ways of delivering the drug in order to improve its therapeutic effectiveness as well as to minimize side effects and frequency of dosing. Olanzapine (an atypical antipsychotic) received a Biopharmaceutics Classification System (BCS) Classification II assignment because of its low solubility in aqueous solutions and high permeability [2]. Low water solubility decreases how much drug becomes available for the body to use and together with extensive first pass metabolism and dose-dependent adverse drug reactions limits how much olanzapine can be administered by way of the oral route. In order to overcome the challenges presented by these limitations, new nanotechnology-based strategies are currently being investigated as tools to improve the

availability of olanzapine through enhancing solubility, protecting the drug from degradation, and controlling the duration of the drug's action. However, because of the small size of nanoparticles, their ability to remain at the administration site is limited, which will ultimately make it impossible to completely absorb olanzapine via an oral route[3].

Drug-encapsulated nanoparticles to create longer contact times with the target area, provide extended-release of drug, improve bioavailability, and decrease dosing frequency. The primary goal of this research was to optimize formulation variables to produce a stable drug delivery system and overcome drawback of solubility and dose frequency by provideing sustained release, with a more significant pharmacokinetic profile and improved patient adherence. Later systematic physico-chemical characterisation and *in vitro* evaluation were conducted to assess the potential of this olanzapine nanoparticles.

MATERIALS AND METHODS

Materials

Olanzapine was procured from Himedia Lab LTD, Hyderabad, INDIA. Glyceryl monosterate,Tween80, polyvinyl alcohol (PVA; MW 30,000–70,000 Da), dichloromethane (DCM), ethanol, and all other chemicals were of analytical grade. Deionized water was used throughout the study.

Preparation of Olanzapine-Loaded Nanoparticles

Emulsion-Solvent Evaporation Method

Olanzapine loaded nanoparticles were prepared by selecting the oil-in-water (O/W) emulsion solvent evaporation method [10]. A known quantity of olanzapine (100 mg) and then tween 80 were dissolved in a suitable solvent like 10 mL dichloromethane to form an organic phase. The aqueous phase consisted of 50 mL of 1% w/v PVA solution. The organic phase was added dropwise into the aqueous phase under high-speed homogenization at 10,000 rpm for 5 min. The resulting emulsion was subjected to stirring at room temperature for 4h to evaporate the organic solvent. Nanoparticles were subjected to centrifugation for 20 min, washed thrice with cold deionized water, and freeze-dried with mannitol (5% w/v) as a cryoprotectant[11]. rug loaded nanoparticles were stored in a desiccator until further use.

Experimental design and Optimization

To systematically optimize the formulation variables and understand their effects on key responses, a Box–Behnken design (BBD) was employed. This response surface methodology enables efficient exploration of the interactions between independent variables, such as polymer concentration, surfactant level, and solvent, with a reduced number of experimental runs compared to box-behnken design[12,13]. The BBD method allows to find the best formulation settings that easily predicts the influence of independent and dependent variables.

CHARACTERIZATION OF OLANZAPINE-LOADED NANOPARTICLES

Determination of Particle Size (nm) and Zeta Potential (mV)

Dynamic light scattering (DLS) was utilised to characterise the particle size, zeta potential and polydispersity index (PDI) of olanzapine-loaded nanoparticles on a Zetasizer Nano ZS (Malvern Instruments, UK). Prior to analysis, samples were diluted using de-ionised water in order to minimise multiple scattering effects during measurement. A total of three measurements were taken for particle size, particle size distribution (PDI) and zeta potential with values reported as mean value +/- standard deviation. The values for each of these measurements were critical for predicting the stability, uniformity and potential aggregation behaviour of nanoparticles[14,15]. Zeta potential (ZP) measurements were performed in order to predict the long term colloidal stability of the nanoparticles. Nanoparticles which have a ZP greater than ±25 mV are considered to be stable due to electrostatic repulsion and this minimizes the possibility of aggregation throughout storage[16,17].

Determining Encapsulation Efficiency

The encapsulation efficiencies (EE%) of the olanzapine loaded nanoparticles were calculated by dissolving an accurately weighed sample of nanoparticles in acetonitrile in order to release olanzapine from the polymeric matrix. The acetonitrile solution was then filtered (0.45 µm) and analysed using UV spectrophotometry at λmax of 254 nm[18], in order to calculate the encapsulation efficiency by the following formula:

EE% = (actual drug content)/(total drug added) x 100

Higher values for EE% indicate the ability of drug to be entrapped within the polymeric matrix which is critical for sustained drug delivery from the nanoparticles[19].

In-vitro drug release studies

To assess *in-vitro* drug release, olanzapine-loaded nanoparticles were placed in Franz diffusion cells containing vertically oriented dialysis membranes. The membranes were pre-soaked in phosphate-buffered saline (PBS, pH 7.4) for 12 hours to ensure hydration

prior to the start of the experiments and mounted between the donor and receptor chambers of the Franz diffusion cells. The receptor chambers were filled with PBS (pH 7.4) at a temperature of 37 ± 0.5°C, and continuously stirred with a magnetic stirrer at 600 rpm to establish and sustain sink conditions. A precise amount of olanzapine-loaded nanoparticles (the equivalent of 10 mg of drug) was placed into the donor chambers. Samples (1 mL) were withdrawn from the receptor chambers at pre-determined time points (0.5, 1, 2, 4, 6, 8, 12h) and immediately replaced with the same volume of fresh dissolution media to sustain volume and sink conditions. The collected samples were filtered through a 0.45 µm membrane and the olanzapine concentration was determined by UV-Visible spectroscopy at λmax 254 nm. Cumulative percentages of drug released were calculated and plotted against time to generate release profiles of olanzapine from nanoparticles [20,21].

Results and Discussion

A total of 15 experimental runs were generated with the selected design BBD, and the results were fitted to a quadratic polynomial model and equations were generated for all the three dependent variables.

Preformulation Studies

Organoleptic Properties: The sample was identified and described by the specifications of the COA (certificate of analysis) supplied by the manufacturer, as shown in Table 1, which shows the physical identification findings for the selected drug, Olanzapine.

Table 1: Organoleptic properties of Olanzapine

Drug name	Parameter	Specification as per COA	Observation
Olanzapine (OLG)	Colour	Yellow powder	Yellow powder
	Appearance	Crystalline	Crystalline
	Odour	Odourless	Odourless

Determination of Melting Point: Olanzapine melting point was found to be 192±2.65°C by melting point analysis, which, when coincidences with the drug's standard reported melting point of 190-195°C, demonstrated its purity.

Determination of Solubility: The selection of the right solvent for the preparation of Olanzapine (OLG) nanoparticles was mainly based on the solubility in respective solvents. The solubility of OLG was determined in different solvents such as PEG 400, dimethyl sulfoxide (DMSO), distilled water, ethanol, methanol, and phosphate buffer pH 6.4 and 7.4 (PBS). Table 2 , shows about the olanzapine solubility study results. The Indian Pharmacopoeia (IP) served as the basis for the solubility terminology employed.

Table 2: Solubility analysis of Olanzapine

S. No	Solvent	Concentration (mg/mL)	Inference
1	Water	0.012±2.31	Insoluble
2	Ethanol	11.031±3.52	Soluble
3	Methanol	18.79±3.91	Soluble
4	PEG 400	41.68±5.42	Soluble
5	DMSO	35.44±5.01	Soluble
6	Phosphate buffer solution pH 6.4	0.248±6.34	Slightly Soluble
7	Phosphate buffer solution pH 7.4	0.402±5.39	Slightly Soluble

*Values represent mean ± standard deviation (n=3)

Table 3: Box–Behnken design matrix with experimental responses

		Factor 1	Factor 2	Factor 3	Response 1	Response 2	Response 3
Std	Run	A: PVP	B: Tween 80	C: Glyceryl Monostearate	Particle size	Entrapment efficiency	*In-vitro* drug release
		Mg	%	Mg	Nm	%	%
5	2	50	0.5	150	240	80	83
3	5	50	0.75	200	243	85	79
7	7	50	0.5	250	169	86	81
1	8	50	0.25	200	170	80	82
9	1	100	0.25	150	121	93	94
16	3	100	0.5	200	210	87	84
13	4	100	0.5	200	212	80	82
14	6	100	0.5	200	218	84	86
17	9	100	0.5	200	185	88	86
12	12	100	0.75	250	208	81	76
10	14	100	0.75	150	195	90	88
15	16	100	0.5	200	199	81	87
11	17	100	0.25	250	196	86	89

2	10	150	0.25	200	205	76	79
4	11	150	0.75	200	225	82	89
6	13	150	0.5	150	175	89	91
8	15	150	0.5	250	201	87	85

Effect of Formulation Variables on Particle Size (Y_1)

Particle size is a critical quality attribute of Olanzapine-loaded nanoparticles, as it directly influences the drug release, stability, bioavailability, and overall therapeutic performance. In the present study, the influence of three formulation variables on particle size was evaluated using a Box–Behnken Design (BBD). A quadratic response surface model was selected to establish the relationship between the selected factors and the measured responses, which was selected based on sequential model sum of squares and lack-of-fit analysis.

Polynomial Equation for response(Y1)

The results of the multiple regression analysis for the response Y1 (particle size) showed that the coefficients associated with factors A (PVP), B (Tween 80), and C (Glyceryl monostearate) exhibit a positive sign in the linear terms of the quadratic model. This indicates that an increase in the levels of these independent variables leads to an increase in particle size, with factor C showing a particularly strong influence. The fitted polynomial equation for particle size (Y1) has shown in equation 1. Positive sign and negative sign in the equation indicates increase and decrease in the effect.

Particle Size(Y1) = 208.20+5.50A+2.50B+32.25C+1.00AB−22.00AC+7.00BC−13.35A2+10.65B2−11.85C2

Where: A=PVP, B=Tween80, C = Glyceryl monostearate

The final quadratic polynomial equation describes how each formulation factor influences particle size and helps in predicting the response within the experimental range. The constant term (208.20) represents the average particle size at the center levels of all variables and it can be termed as coefficient value. The linear coefficients indicate that glyceryl monostearate (C) has the strongest positive effect on increasing particle size, while PVP (A) and tween 80 (B) show only minor direct effects. The interaction terms demonstrate how pairs of factors work together; among them, the AC interaction is the most influential with showing that the combined levels of PVP and Glyceryl monostearate significantly reduce particle size. The quadratic terms (A^2, B^2, C^2) reveal curvature in the response surface, meaning that particle size does not change in a straight-line manner but instead reaches optimal values at intermediate levels of the factors.

Among the variables, glyceryl monostearate (C) showed the most significant effect on particle size, followed by the interaction and quadratic terms which contributed to curvature in the response surface.

The three-dimensional response surface and contour plots clearly illustrate the relationship between the independent variables and particle size. This interaction is depicted clearly in Figure 1., where the combined effects of the factors on the particle size are represented.

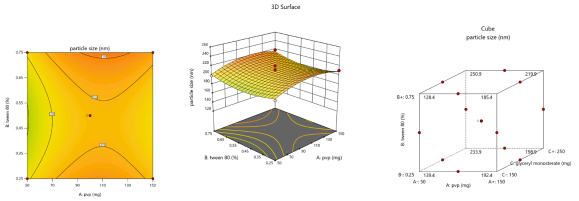

Figure 1: Contour plot, 3D surface, Cube Plots for Particle Size

Table 4: Analysis of variance for the response Y1

Source	Sum of Squares	Df	Mean Square	F-value	p-value	
Model	12526.58	9	1391.84	16.04	0.0007	Significant
A-pvp	242.00	1	242.00	2.79	0.1388	
B-tween 80	50.00	1	50.00	0.5763	0.4725	
C-glyceryl monostearate	8320.50	1	8320.50	95.91	< 0.0001	
AB	4.00	1	4.00	0.0461	0.8361	
AC	1936.00	1	1936.00	22.32	0.0021	
BC	196.00	1	196.00	2.26	0.1765	
A^2	750.41	1	750.41	8.65	0.0217	
B^2	477.57	1	477.57	5.50	0.0514	
C^2	591.25	1	591.25	6.82	0.0349	
Residual	607.30	7	86.76			

Lack of Fit	294.50	3	98.17	1.26	0.4014	not significant
Pure Error	312.80	4	78.20			
Cor Total	1313.88	16				

The ANOVA results shown in the table 2, confirmed that the quadratic model was statistically significant with a Model F-value of 16.04 and a corresponding p-value of 0.0007, indicating that the model successfully predicts particle size based on the selected formulation components. There is only a 0.07% probability that such a high F-value could arise due to random noise. The lack-of-fit was not significant (F = 1.26, p = 0.4014), demonstrating that the model fits the experimental data well and that the residual variation is primarily due to experimental error rather than model inadequacy.

Significance of Individual Model Terms

The results of the linear terms indicate that glyceryl monostearate (C) had a highly significant ($p < 0.0001$) effect on the size of the particle, with the interpretation that the size of the particle would increase significantly as the lipid concentration increased. The increase in particle size due to increased lipid concentration is due to the increased viscosity created and increased growth of the particles during their formation due to the higher lipid concentration. The linear terms of the PVP (A) and Tween 80 (B) did not have a statistically significant ($p > 0.05$) effect on particle size compared to that of glyceryl monostearate (C). The high R^2 values provide assurance that the model adequately captures most of the variance in particle size.

Effect of Formulation Variables on Entrapment Efficiency (Y2)

The entrapment efficiency of Olanzapine-loaded nanoparticles is an important quality characteristic since it indicates the percentage of the drug has entered into the carrier system successfully and impacts drug load, drug release profile, and drug therapeutic effect. In this research, the influence of formulation variables on entrapment efficiency was examined using a Box-Behnken Design (BBD). A quadratic model was chosen to explain how the independent variables relate to entrapment efficiency. The final quadratic polynomial equation for entrapment efficiency in coded form is:

Entrapment Efficiency (Y_2) = 85.18 + 3.25A – 0.375B – 2.88C + 1.2600AB – 13.00AC + 9.00BC + 13.35A^2 – 11.95B^2 + 4.77C^2.

The quadratic polynomial defines quantitatively how the formulation factors PVP (A), Tween 80 (B), and glyceryl monostearate (C) relate to the entrapment efficiency of Olanzapine-loaded nanoparticles. The intercept term of 85.18 indicates the calculated entrapment efficiency at the mid-range of all three formulation factors. PVP's positive (linear) coefficient, +3.25, indicates increasing the polymer concentration significantly increases the entrapment efficiency. This increase in entrapment efficiency may be attributed to enhanced matrix formulation and improved drug-polymer contact, resulting in improved entrapment of Olanzapine within the nanoparticle system.

Tween 80 (B) also has a negative coefficient, though not as large as that of glyceryl monostearate (C) (–0.375 vs. –2.88). While both decrease the entrapment efficiency of a drug, Tween 80's negative coefficient indicates that its negative effect on entrapment efficiency is only present when the concentration of Tween 80 is high enough to promote increased partitioning of the drug into the external aqueous phase. Glyceryl monostearate's negative coefficient suggests that higher lipid concentrations will substantially decrease the amount of drug retained in nanoparticle formulation due to increased fluidity of the lipid phase, which may lead to expulsion of the drug during solidification of the nanoparticles. The interaction terms are able to explain the overall effects of the formulation variables as well. The quadratic terms indicate curvature in the response surface. The positive coefficient for A^2 (+13.35) indicates a significant curvature effect as a result of increasing the concentration of PVP. This implies that, at some point, the concentration of polymer will be optimal for drug entrapment and will lead to an increase in the amount of drug that is entrapped. The negative coefficient for B^2 (–11.95) indicates that increasing amounts of Tween 80 will adversely affect drug entrapment efficiency due to increased solubilization of the drug.

The positive C^2 term (+4.77) indicates a mild curvature effect of glyceryl monostearate, suggesting that moderate lipid levels are favourable for achieving optimal entrapment efficiency.

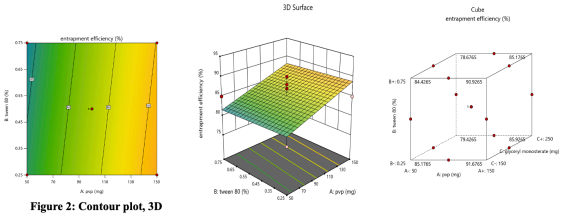

Figure 2: Contour plot, 3D surface, Cube Plots for Entrapment efficiency

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Table 5: Analysis of variance for the response Y2

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	151.75	3	50.58	3.64	0.0420	Significant
A-pvp	84.50	1	84.50	6.08	0.0284	
B-tween 80	1.12	1	1.12	0.0809	0.7805	
C-glyceryl monostearate	66.12	1	66.12	4.76	0.0481	
AB	16.00	1	16.00	0.8338	0.3827	
AC	121.00	1	121.00	6.31	0.0309	
BC	6.25	1	6.25	0.3257	0.5808	
Residual	180.72	13	13.90			
Lack of Fit	135.52	9	15.06	1.33	0.4180	not significant
Pure Error	45.20	4	11.30			
Cor Total	332.47	16				

Twenty-seven percent of the response variance can be attributed to the average (F-value) of the linear effects of (1) increasing amount of PVP, (2) increasing amount of glyceryl monostearate, and (4) interactions between PVP and glyceryl monostearate (0.0284 ≤ p-vals: Fvalues; 6.08 ≤ F-values). This suggests that these three variables can be used to make statistically significant changes in entrapment efficiency of Olanzapine-loaded nanoparticles using these variables in their respective amounts as long as they were combined correctly. As an example, the interaction between PVP and glyceryl monostearate resulted in an additive effect on entrapment efficiency of Olanzapine-containing nanoparticles by establishing an additive effect of increasing PVP concentration along with increasing concentration of glyceryl monostearate.

In examining the interaction effects, the AC interaction terms (PVP-glyceryl monostearate) were statistically significant with respect to the effects of both the polymer and the lipid concentrations on entrapment efficiency showing strong combined effects (F=6.31, p=0.0309). However, the AB and BC interaction terms were not statistically significant (p>0.05), indicating that the combined effects of PVP-Tween 80 and Tween 80-glyceryl monostearate on the response were weaker than those observed for PVP-glyceryl monostearate. The adjusted R^2 value (0.3310) would indicate moderate explanatory power for the model after accounting for the number of terms to the model. The predicted R^2 value (0.0227) is relatively low and does not compare closely with the adjusted R^2, indicating that the relative lack of precision in making predictions can be due to actual experimental variability or low higher-order predictability.

Effect of Formulation Variables on *In-vitro* Drug Release (Y3)

The *in-vitro* drug release of Olanzapine loaded nanoparticles is an important attribute of the carrier system, as it determines how quickly and how much drug will be available and so impacts how well the drug will perform in the body and how often it will need to be given. The effect of formulation parameters on the in-vitro drug release was assessed with a Box-Behnken Design (BBD) and a quadratic model was created to assess the relationships between the selected independent variables and the in-vitro drug release. The final model for *in-vitro* drug (Y3) is:

***In-vitro* drug Release (Y3) = 84.59 + 2.75A + 0.0000B - 2.00C + 3.25AB - 1.75AC - 3.25BC**.

The overall coefficient from this equation (84.59) measures the average (%) of drug release when each formulation is set to its mid-level. This number shows the base level of performance of drug release for this type of system. The positive coefficient of factor A (+2.75) shows that as this variable gets larger the amount of drug released gets larger (likely due to increased drug diffusion, decreased matrix resistance, or increased wettability of the nanoparticles).

Since the coefficient for factor B is zero, this means that factor B does not independently influence drug release in the concentration range examined. Despite this, it is possible that factor B still influences drug release via an interaction with one or more of the other factors. Factor C has a negative coefficient of -2.00; therefore, as factor C increases, drug release decreases.

This effect may be related to increased hydrophobicity or increased structural rigidity of the matrix, both of which will impede the diffusion of the drug out of the nanoparticles. The positive interaction between factors A and B (+3.25) indicates potential synergistic effects; thus when A and B are increased together, the release of drug is greater than would be expected based upon the release of drug due to factor A alone or the release of drug due to factor B alone.

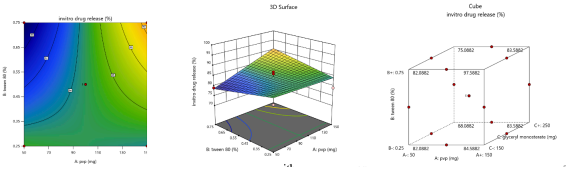


Figure 3: Contour plot, 3D surface, Cube Plots for *invitro* release

Table 6: Analysis of variance for the response Y3

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	189.25	6	31.54	3.81	0.0307	Significant
A-pvp	60.50	1	60.50	7.30	0.0222	
B-tween 80	2.842E-14	1	2.842E-14	3.430E-15	1.0000	
C-glyceryl monostearate	32.00	1	32.00	3.86	0.0778	
AB	42.25	1	42.25	5.10	0.0475	
AC	12.25	1	12.25	1.48	0.2520	
BC	42.25	1	42.25	5.10	0.0475	
Residual	82.87	10	8.29			
Lack of Fit	66.87	6	11.14	2.79	0.1703	not significant
Pure Error	16.00	4	4.00			
Cor Total	272.12	16				

The model produced a statistically significant outcome. The model F-value of 3.81 and a p-value of 0.0307 showed that formulation variables significantly influence how much drug is released in vitro. A lack of fit value of 2.79 with an accompanying p-value of 0.1703 showed that the model fits the experimental data sufficiently well and that the differences between the actual and predicted values can be attributed to random experimental error. These statistical data support the conclusion that the 2FI model adequately classifies in vitro drug release data throughout the designed experimental conditions. Individual factor contributions to the model The analysis of variance indicated that factor A (PVP) was a statistically significant factor affecting drug release in vitro ($F = 7.30$; $P < 0.05$). The high F-value indicates that variability in concentration of PVP is important to the control of release of drug from the matrix, likely affecting matrix morphology, diffusion of drug from the matrix, and polymer/polymer interactions within the matrix. Tween 80 (factor B) does not have a statistically significant effect upon in vitro drug release ($p = 1.0000$). Therefore, Tween 80 does not have an independent effect on release from the matrix within the concentration ranges used in this experiment; this corresponds to the low coefficient of Tween 80 in the polynomial equation.

Factor C (glyceryl monostearate) was shown to negatively influence (though not significantly) drug release ($p = 0.0778$). However, since its p-value is only marginally below the cut-off for statistical significance at 5%, the lower value strongly indicates that a moderate decrease in drug release is a consequence of glyceryl monostearate increasing the hydrophobic nature of the matrix and the resistance of the matrix to diffusion from the matrix to the release medium. Both of the two interaction terms AB (PVP × Tween 80) and BC (Tween 80 × glyceryl monostearate) were statistically significant ($F = 5.10$, $p = 0.0475$), suggesting that the combination of these factors (PVP and Tween 80, and Tween 80 and glyceryl monostearate) have a synergistic effect on enhancing drug release.

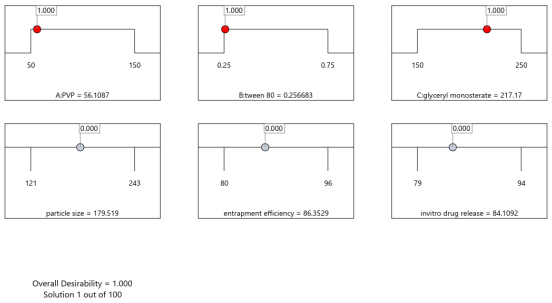


Figure 4: Ramp Solutions of the optimized formulation

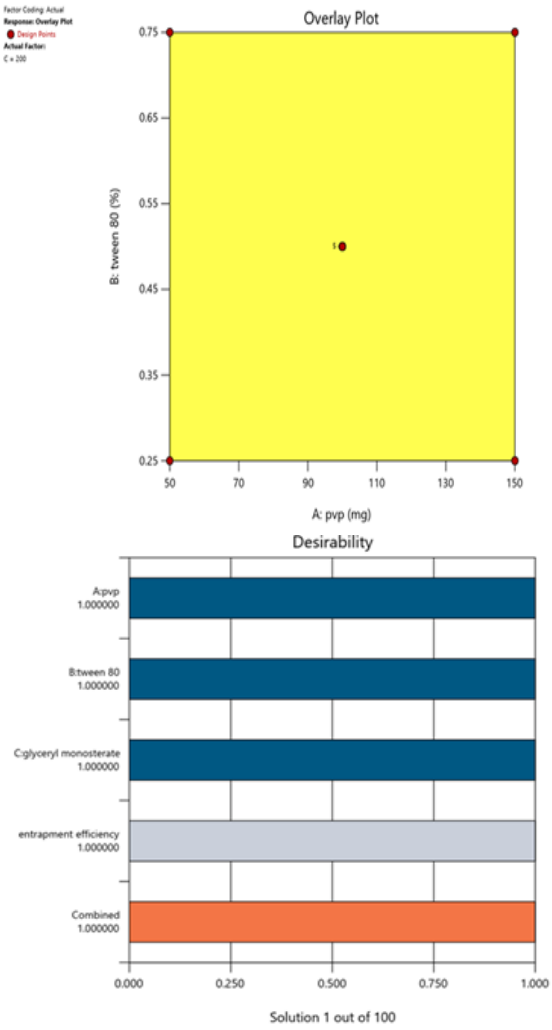
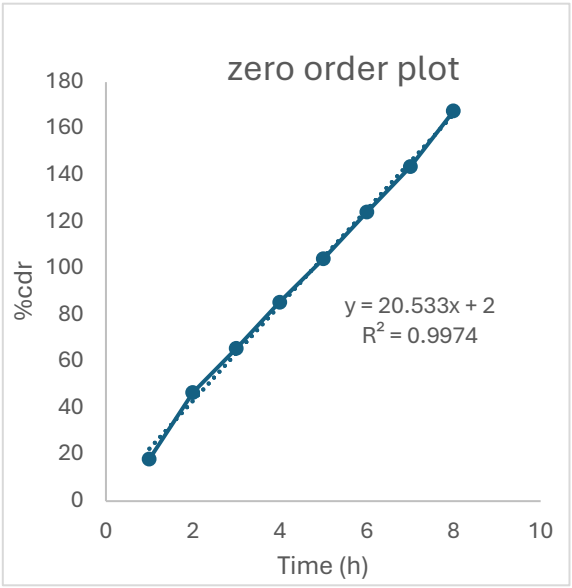
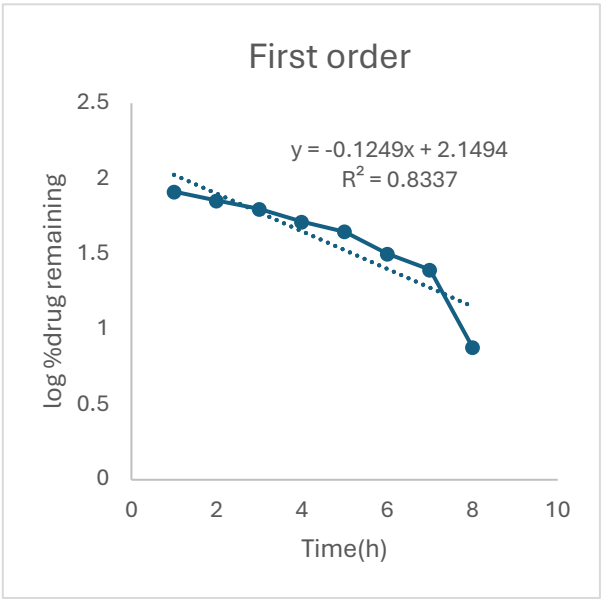


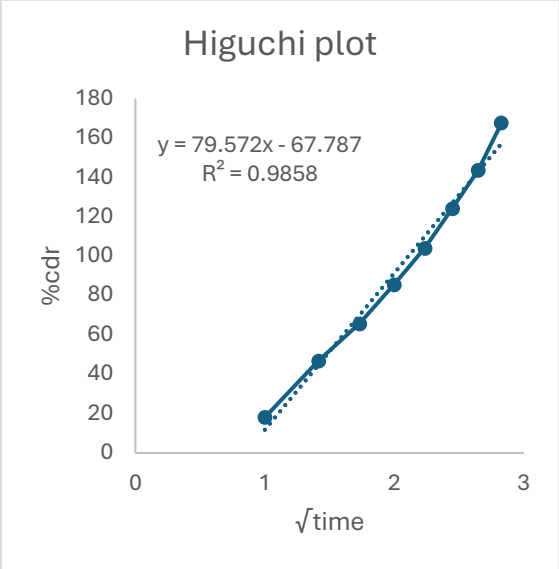
Figure 5: Overlay plot and desirability plot of optimized formulation

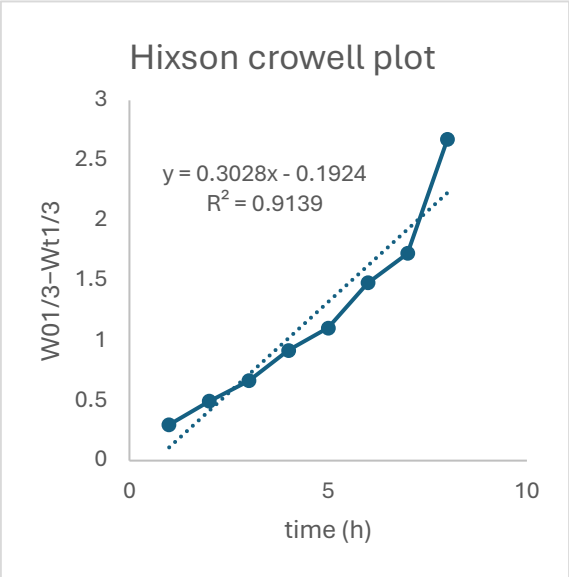
Kinetic Modelling of Optimized Formulation (F5) for Release Kinetics

There are many different models to evaluate the relationship between drug release and its formulation (F5). These include zero-order, first-order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas. A comparison of all these models will be done by looking at R^2 or coefficient of determination values for the fit of each model to the data. The zero-order model produced the best fit with an $R^2 = 0.9974$ which means there is an almost perfect linear correlation of cumulative drug release over time. Therefore the drug is released at a constant rate which does not depend on concentration, something that is very beneficial when designing a controlled drug delivery system.









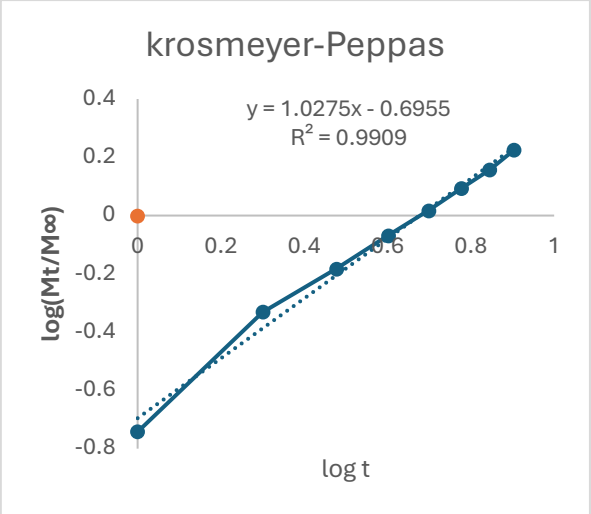


Figure 7: Kinetic modelling plots for optimized formulation (F5)

The correlation coefficient for the first order plot of the release rate of olanzapine from the optimized formulation was relatively low (R^2 = 0.8337), suggesting that drug release was not primarily dependent on concentration; therefore, first-order kinetics was not a sufficient descriptor of the release behaviour. Conversely, the Higuchi plot exhibited an excellent linear correlation (R^2 = 0.9858), indicating that drug release was primarily controlled by a diffusion-controlled mechanism. The results imply that olanzapine diffuses out of the nanoparticle matrix into the dissolution medium, supporting matrix diffusion's contribution to drug release. Additionally, the linear correlation with the Hixson-Crowell model (R^2 = 0.9139) indicates that changes in surface area and diameter contribute to the overall release process, suggesting that both diffusion and either matrix erosion or structural reorganization of the nanoparticles are likely to affect drug release. The Korsmeyer-Peppas plot also provided an excellent fit (R^2 = 0.9909), as displayed in Figure 7. The release exponent ($n \approx 1.03$, slope of the plot) indicates that the drug release mechanism was a Super Case II transport mechanism, demonstrating that drug release is influenced by a combination of diffusion, polymer relaxation and matrix erosion; such behaviour is typical for controlled-release systems utilising a polymeric matrix.

CONCLUSION

The current study successfully developed an optimized formulation of olanzapine-loaded nanoparticles using Box-Behnken design to assess the effect of formulation factors on particular characteristics of nanoparticles on independent variables like; particle size, encapsulation efficiency and *invitro* drug release studies. Among independent variables, glyceryl monostearate had a significant impact on particle size, while the concentration of PVP was the primary determinant on improving drug loading and controlling the overall drug-release rate from the final drug product. Statistically, all models performed adequately and produced a good correlation, and a lack of proper fit; therefore, meeting the criteria for using each of these general models of drug release for formulating olanzapine-loaded nanoparticles. The final formulation of olanzapine-loaded nanoparticles was in the nanosize range with 121nm, displayed encapsulation and loading efficiencies with sustained drug release profile. Drug release kinetics followed zero-order kinetics meaning there was a continuous/controlled release profile supported by diffusion and erosion mechanisms

that were established through kinetic modelling. This novel nanoparticle system represents a drug product with improved drug release profile and increased formulation stability and solubility by providing an opportunity to increase therapeutic effects while also decreasing dosing frequency. This approach provides a promising strategy for effective delivery of olanzapine and can be further extended to advanced drug delivery systems such as in situ gels for improved patient compliance.

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