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QbD Assisted Approach for studying the impact of Formulation and Process Variables on Release Kinetic of Antiepileptic Formulation

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ABSTRACT

The present study adopts a Quality by Design (QbD) assisted approach to systematically evaluate the impact of formulation and process variables on the release kinetics of antiepileptic drug formulations, specifically sublingual and bilayer tablets. Two distinct formulations strategies were developed: a sublingual tablet for rapid onset of action and a bilayer tablet designed to deliver both immediate and sustained release profiles. Critical formulation variables, including the concentration of superdisintegrants (Croscopovidone), binders (PVP K30), and diluents (Microcrystalline Cellulose), along with key process parameters, were identified through risk assessment and optimized using Design of Experiments (DoE). Response surface methodology and contour plots were utilized to investigate the interaction effects on critical quality attributes, including friability and in vitro drug release. The drug release profiles from both formulations were analyzed using different kinetic models, namely zero-order, first-order, Higuchi, and Korsmeyer-Peppas to better understand the underlying release mechanisms.

1. Introduction

Epilepsy is a long-term neurological condition marked by repeated seizures and impacts around 50 million individuals globally. Effective management of epilepsy relies heavily on consistent therapeutic drug levels in the bloodstream to prevent seizures and maintain quality of life. However, achieving and maintaining these therapeutic levels can be challenging due to variations in drug absorption, metabolism,

and patient compliance. Antiepileptic drugs (AEDs) require carefully controlled release to ensure sustained therapeutic effect while minimizing side effects. Traditional formulation approaches may not provide the desired level of control over drug release, leading to fluctuations in plasma concentration and reduced efficacy. This calls for a more systematic and robust development strategy, where both formulation and

process variables are optimized to achieve the desired drug release profile.^[1,2]

Sublingual tablets offer a promising approach for rapid onset of action, especially in emergency conditions such as epileptic seizures. These tablets are placed under the tongue, allowing the drug to be absorbed directly into the bloodstream through the mucosal membrane, bypassing first-pass metabolism. This route is particularly useful for antiepileptic therapy, where quick relief is often essential.^[3,4]

Drug release kinetics plays a crucial role in understanding how the drug is released from the dosage form over time. It helps in predicting the onset, intensity, and duration of the drug's therapeutic effect. Analyzing release kinetics through models such as Zero-order, First-order, Higuchi, and Korsmeyer-Peppas provides insights into the mechanism of drug release, which is vital for optimizing the performance of sublingual formulations.^[5, 6]

Quality by Design (QbD) is a modern, science-based approach recommended by regulatory authorities like the FDA and ICH (International Council for Harmonisation). QbD emphasizes understanding the formulation and manufacturing process to ensure predefined product quality. It involves identifying Critical Quality Attributes (CQAs), Critical Material Attributes (CMAs), and Critical Process Parameters (CPPs) through risk assessment and design of experiments (DoE).^[7, 8]

In the context of antiepileptic sublingual tablets, QbD enables the systematic evaluation of formulation components such as superdisintegrants (e.g., Crospovidone), binders (e.g., PVP K30), and diluents (e.g., Microcrystalline Cellulose), along with process variables that can influence drug release kinetics and disintegration time. Applying statistical tools and response surface methodology (RSM) allows the development of a robust formulation that meets the desired release characteristics.^[9]

This study utilizes a Quality by Design (QbD) based approach to examine how formulation and process parameters influence the release kinetics of a sublingual antiepileptic formulation. Using a systematic design of experiments, this work aims to identify optimal conditions that result in a stable, effective, and patient-friendly dosage form. The findings contribute toward the development of reliable formulations that ensure

consistent and rapid therapeutic outcomes in epilepsy management.^[10, 11]

1. Materials and Methods

3.1 Materials

Pregabalin was obtained from Elixir Pharma Chem Pvt. Ltd. Ahmedabad, India. Crospovidone was obtained from Loba Chemie Pvt. Ltd, PVP K30 was obtained from Loba Chemie Pvt. Ltd, Micro crystalline cellulose was obtained from Loba Chemie Pvt. Ltd, Mannitol was obtained from Loba Chemie Pvt. Ltd, Aerosil was obtained from Loba Chemie Pvt. Ltd, Magnesium stearate was obtained from Loba Chemie Pvt. Ltd, Mumbai, India.

3.2 Selection of material needed to sublingual tablet

We prepared three dummy batches, each containing a different super-disintegrant: Crospovidone, Croscarmellose Sodium, and Sodium Starch Glycolate. After completing the quality control (QC) tests, we analyzed the results. The batch containing Crospovidone showed the best performance in terms of disintegration time. Based on these results, we selected Crospovidone for the final formulation.

3.3 Experimental Design

A Quality by Design (QbD) approach was implemented using a Design of Experiments (DoE) framework to systematically evaluate the impact of formulation and process variables on the performance of the sublingual antiepileptic tablet. The Box-Behnken Design (BBD) was chosen for its effectiveness in evaluating quadratic response surfaces while requiring a reduced number of experimental trials. The independent variables (factors) included concentrations of Crospovidone (superdisintegrant), PVP K30 (binder), and MCC (diluent), while the dependent responses were disintegration time, friability and *in vitro* drug release. Statistical analysis, including ANOVA and response surface plots, was performed using software such as Design-Expert® to determine the significance and interaction of variables. This design helped in identifying the optimal formulation conditions for achieving rapid disintegration and enhanced drug release, essential for the effectiveness of sublingual delivery.^[12-15] Shown in Table

1

Table 1: Independent Variables and their corresponding levels

S.No.	Independent Variables		Low (-1)	High (+1)
1.	Crospovidone	mg	2	5
2.	MCC	mg	40	50
3.	PVPK30	mg	0.5	5

3.4 Method

Pregabalin sublingual tablets were formulated using superdisintegrants such as Crospovidone, a binder like PVP K-30, a diluent such as microcrystalline cellulose, a sweetener

like mannitol, and a lubricant such as magnesium stearate. All components were thoroughly mixed and passed through a #44 mesh sieve to ensure uniform particle size. The resulting blend was then compressed into tablets using a single-punch rotary

tablet compression machine. Each formulation contained 100 mg of the drug and was appropriately punched into tablet form.^[16,17]

3.5 Pre-formulation Evaluation

1. UV Analysis of pregabalin

Calibration Curve in Phosphate Buffer pH 6.8

A standard stock solution of drug was prepared by dissolving accurately weighed 100 mg of drug in 10 ml of phosphate buffer pH6.8 (Solution A, i.e., 10000 µg/ml) From this solution, further dilutions of 1000, 2000, 3000, 4000, 5000 µg/ml were prepared. Absorbance of each of the above dilution was measured at the detection wavelength.

2. FTIR Spectroscopy

The FTIR spectrophotometer was used to record the FTIR spectra of Pregabalin at room temperature in the 4000-400 cm⁻¹ ranges. The sample was made by grinding it with dry KBr powder and compressing the powder in a hydraulic press.^[18]

3. X-Ray Diffraction (XRD)

Crystallinity of Pregabalin was evaluated by using X-ray diffractometer, using Nifiltered Cu-K a radiation source.^[18]

4. Differential Scanning Calorimetry (DSC)

Thermal analysis of Pregabalin, was carried out using differential scanning calorimetric method. Samples equivalent to approximately 2 mg Pregabalin was placed in thermetically sealed aluminium pans and heated over the temperature range of 25°C-250°C at a constant rate of 40°C/min under a nitrogen purge (20 ml/min).^[18]

3.6 Pre-compression Evaluation

The flow properties for Bulk density, Tapped density, Hausner's ratio, Carr's index, Angle of repose were evaluated.^[19, 20]

3.7 Evaluation of Pregabalin sublingual tablets

1. Thickness

The tablet thickness was measured using a digital vernier caliper. To assess thickness uniformity, three tablets were randomly selected from each batch, and their thicknesses were recorded.^[21]

2. Hardness

The hardness of the tablet was determined by using a Monsanto. For measurement of hardness, 3 tablet were randomly selected from each batch, and their hardness was measured.^[21]

3. Friability

A Roche Friabilator was used to test the tablets' friability. Six weighted tablets were put through a combination of shock and abrasion in the Friabilator's plastic chamber rotating at 25 r.p.m. for four minutes. After that, the pills were dusted and weighed again.^[22]

4. Weight Variation

Each formula's twenty randomly chosen tablets were weighed separately. The standard deviation was computed and the average weight was established. The weight of 80–250 mg tablets shouldn't differ by more than $\pm 7.5\%$ from the stated value.^[23]

5. In Vitro drug release

An in-vitro dissolution study of the sublingual tablet was performed using a USP dissolution apparatus type II (paddle type). The dissolution medium comprised 300 mL of phosphate buffer (pH 6.8), maintained at 37°C $\pm$ 0.5°C with a rotation speed of 50 rpm. Each tablet was carefully placed in the vessel, and at predetermined time intervals, 5 mL aliquots were withdrawn, filtered, and analyzed for Pregabalin content using a Shimadzu-1800 spectrophotometer at 210 nm.^[24]

6. Disintegration Time

The USP Disintegration test device was used to determine the tablet's disintegration time in water at 37 $\pm$ 20 C. One liter of phosphate buffer pH 6.8 was utilized as the disintegration medium, and six pills from each batch were added. It was observed how long it took for all six tablets to completely dissolve. All of the tablets should ideally dissolve within two minutes.^[25]

7. Drug Content Uniformity

Drug content uniformity was assessed to ensure the even distribution of the drug within the tablet. This involved dissolving each tablet completely by stirring it in a volumetric flask filled with 10 ml of 6.8 pH phosphate buffer. The filtered solution was then utilized for measuring the absorbance at 210 nm to estimate the drug concentration, employing a Shimadzu 1800 UV-Spectrophotometer.^[26]

8. Wetting Time

To determine wetting time in sublingual tablets, place a tablet on absorbent paper in a petri dish containing a small amount of water, and measure the time it takes for the tablet to become completely wetted using a stopwatch.^[27]

9. Water Absorption Ratio

In sublingual tablet formulation, the water absorption ratio (R) is determined by measuring the weight increase after a tablet absorbs water, calculated as

$$10. R = 100 * (W_a - W_b) / W_b,$$

where W_a is the weight after absorption and W_b is the weight before. [28]

According to the Design of Experiments (DoE) analysis, the Box-Behnken Design (BBD) proposed a set of 15 experimental trials outlined in the Table 2, accompanied by corresponding responses for evaluation.

2. Results and Discussions

4.1 Development of Sublingual tablet by BBD

Table 2: The Box-Behnken Designed Composition of Sublingual Tablet of Pregabalin.

Batch No.	Independent Variable			Response Variable		
	Super-disintegrants (mg)	Binder (mg)	Diluent (mg)	In-Vitro drug release (%)	Friability (%)	Disintegration (sec)
MQA2 01	2	50	2.75	93.81	0.16%	18
MQA2 02	3.5	45	2.75	91.64	0.16%	30
MQA2 03	5	50	2.75	92.13	0.16%	21
MQA2 04	5	45	5	96.21	0.33%	20
MQA2 05	3.5	45	2.75	89.99	0.08%	26
MQA2 06	2	40	2.75	92.06	0.08%	36
MQA2 07	2	45	5	92.58	0.16%	25
MQA2 08	3.5	40	5	94.45	0.33%	13
MQA2 09	3.5	45	2.75	95.77	0.16%	12
MQA2 10	3.5	50	0.5	91.79	0.08%	29
MQA2 11	3.5	50	5	92.94	0.33%	25
MQA2 12	5	40	2.75	93.69	0.08%	15
MQA2 13	3.5	40	0.5	94.96	0.16%	13
MQA2 14	5	45	0.5	97.51	0.16%	35
MQA2 15	2	45	0.5	92.15	0.16%	26

2.2. Statistical analysis of Sublingual Tablet formulation

The fit summary and ANOVA analysis (Table 3) of the Sublingual Tablet offer important insights into the influence of various factors on the response variables, aiding in the

identification of significant factors. This data is essential for optimizing the formulation of the Sublingual Tablet to meet desired quality standards.

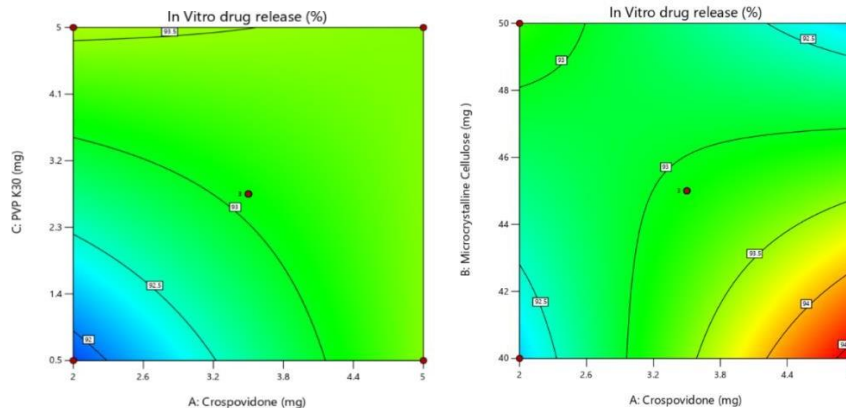
Table 3: Model fitting and ANOVA of the measured response variables designed by the software for Sublingual**Tablet formulation**

Response variable	Model	Sequential p-value	Lack of fit p-value	Adjusted R ²	Predicted R ²	Remark
In-Vitro Drug Release (R1)	Linear	<0.0001	0.2540	0.8010	0.7146	Suggested
	2F1	0.8324	0.1953	0.7531	0.4569	-
	Quadratic	0.1754	0.2494	0.8414	0.2292	-
	Cubic	0.2494	-	0.9310	-	Aliased
Friability (R2)	Linear	<0.0001	-	0.9914	0.9914	Suggested
	2F1	0.1117	-	0.9965	0.9902	-
	Quadratic	0.3101	-	0.9971	0.9833	-
	Cubic	-	-	1.0000	-	Aliased
Disintegration	Linear	0.0001	0.4334	0.8551	0.7702	Suggested
	2F1	0.9064	0.3338	0.8134	0.4912	-
	Quadratic	0.3230	0.3379	0.8427	0.2867	-
	Cubic	0.3379	-	0.9055	-	Aliased

2.3. Effect of independent variable on In-Vitro Drug Release

The 2D and 3D contour plot images in Fig. 1 [A] and Fig. 2 [A] respectively showed that increasing the ratio of Crospovidone and PVPK30 led to an increase in drug release,

ranging from 89.99 to 97.51 %. Additionally, Figures 1 [B] and 2 [B] showed that effect of drug release remained consistent with respect to Crospovidone, resulting in increased drug release.



[A]

[B]

Figure 1. [A] 2D contour plot visually represents the influence of Crospovidone and PVP K30 on the Drug release parameter and

[B] 2D contour plot visually represents the influence of Crospovidone and MCC on the Drug release parameter.

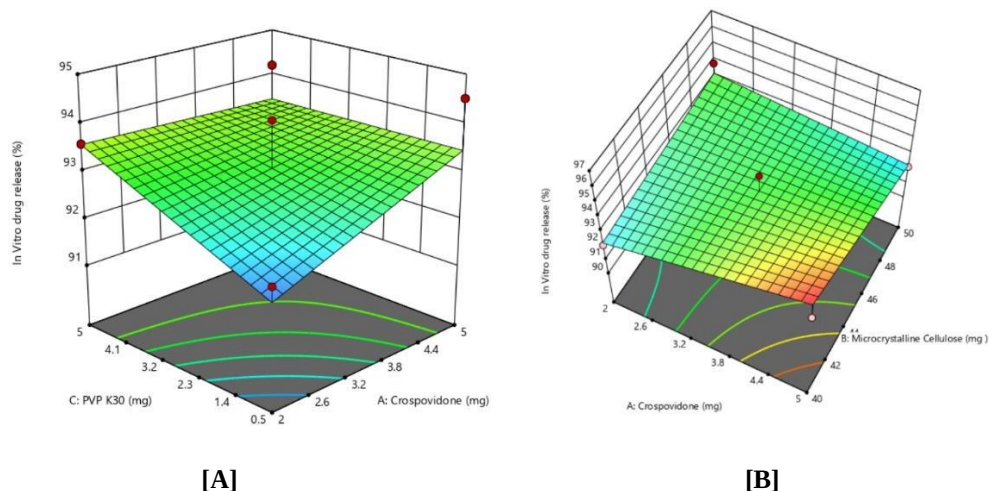


Figure 2. [A] 3D contour plot visually represents the influence of Crospovidone and PVP K30 on the Drug release parameter and [B] 3D contour plot visually represents the influence of Crospovidone and MCC on the Drug release parameter.

4.4. Effect of independent variable on Friability

The 2D and 3D contour plot images in Figures 3 [A] and 4 [A] revealed that increasing the ratio of MCC and Crospovidone increased the ratio of friability, raising it from 0.08 to 0.33%.

Figures 3 [B] and 4 [B] demonstrated that the appropriate combination of Microcrystalline Cellulose and PVP K30 ensured a stable tablet formulation with minimal friability.

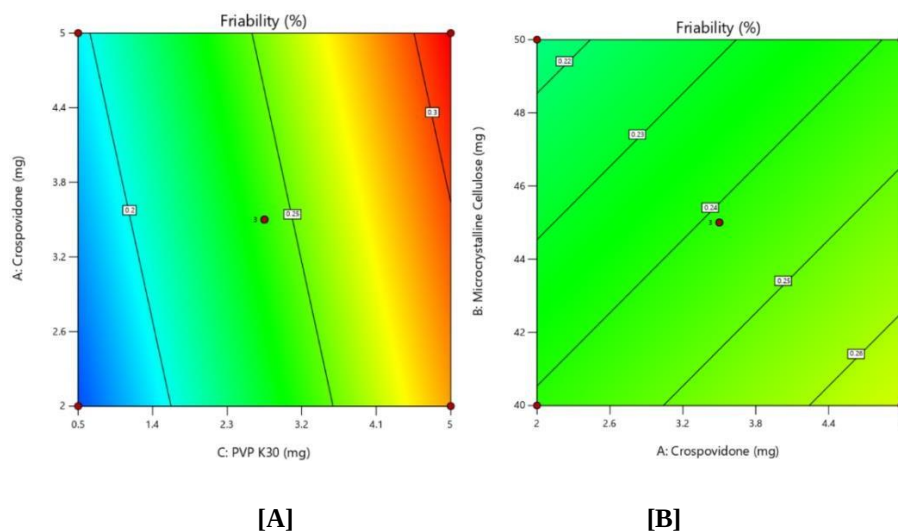


Figure 3. [A] 2D contour plot visually represents the influence of PVP K30 and MCC on the Friability parameter [B] 2D contour plot visually represents the influence of Crospovidone and MCC on the Friability parameter

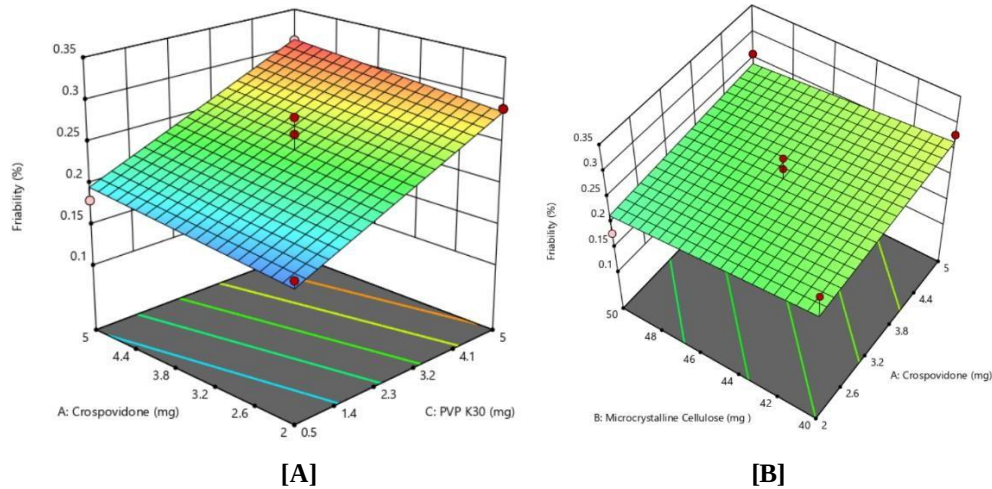


Figure 4. [A] 3D contour plot visually represents the influence of Crospovidone and PVP K30 on the Friability parameter
[B] 3D contour plot visually represents the influence of MCC and Crospovidone on the Friability parameter

4.5. Effect of independent variable on Disintegration

The 2D and 3D contour plot images in Fig. 5 [A] and Fig. 6 [A] showed that increasing the amount of Crospovidone and Microcrystalline Cellulose (MCC) leads to a longer disintegration time, ranging from 13 to 29 seconds. This means the tablet takes more time to break down as the

concentration of these two ingredients goes up. Similarly, Figures 5 [B] and 6 [B] showed that the disintegration time remained steady with increasing amounts of PVP K30, but overall, higher levels of PVP K30 resulted in a slower disintegration process.

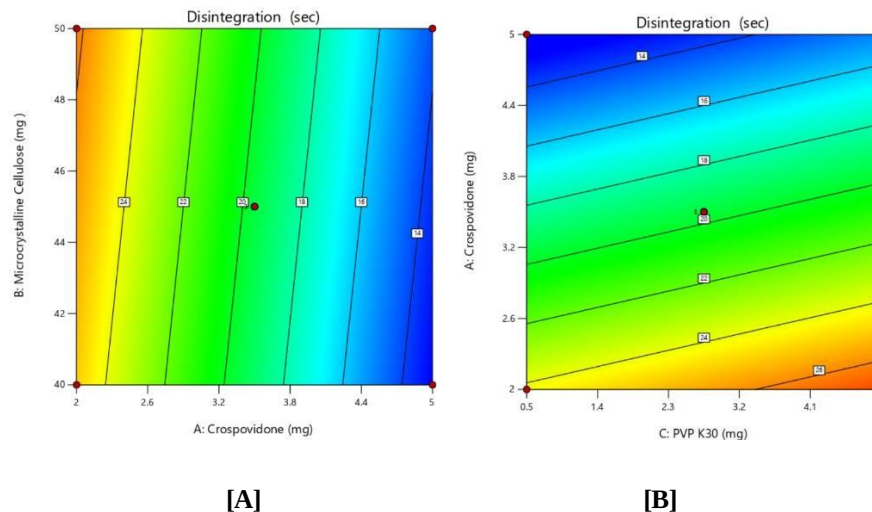


Figure 5. [A] 2D contour plot visually represents the influence of Crospovidone and MCC on the Disintegration parameter
[B] 2D contour plot visually represents the influence of PVP K30 and crospovidone on the Disintegration parameter

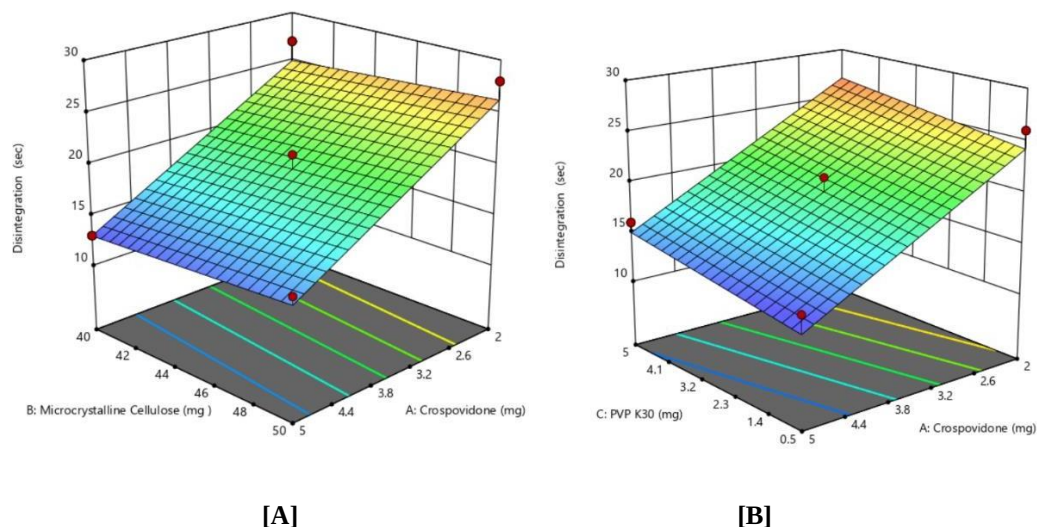


Figure 6. [A] 3D contour plot visually represents the influence of Crespovidone and MCC on the Disintegration parameter [B] 3D contour plot visually represents the influence of PVP K30 and Crespovidone on the Disintegration parameter

4.6. Perturbation graph

A. In-Vitro Drug Release

The perturbation graph for Drug release indicated that MCC (B) has a more significant impact on drug release compared to crespovidone (A) and PVP K30 (C) as shown in Figure 7[A].

B. Friability

The perturbation graph for Friability indicated that MCC (B) had a more significant impact on drug release compared to crespovidone (A) and PVP K30 (C) as shown in Figure 7[B].

C. Disintegration

The perturbation graph for Friability indicated that crespovidone (A) had a more significant impact on drug release compared to MCC (B) and PVP K30 (C) as shown in Fig.7[C].

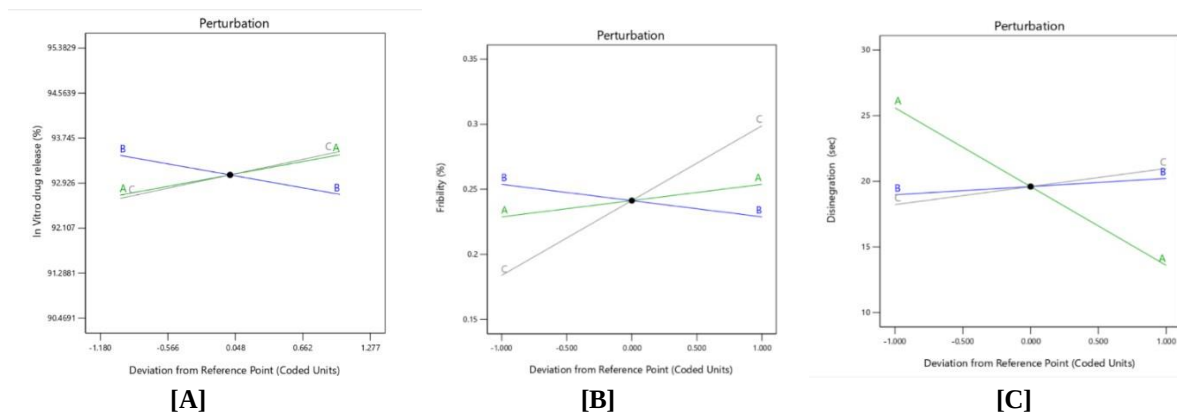


Figure 7. Perturbation graph

4.7. Pre-formulation Evaluation

1. UV Analysis of pregabalin

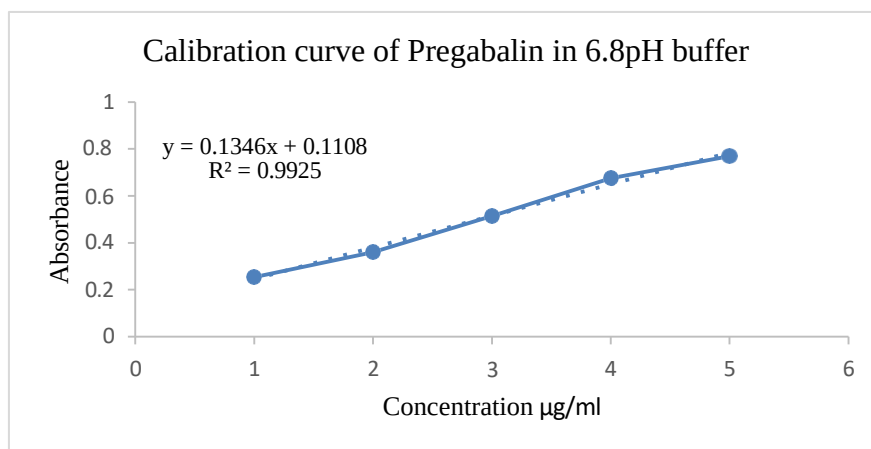
Calibration Curve of Pregabalin in 6.8 pH Phosphate buffer.

The calibration curve for Pregabalin was established using Phosphate buffer, and absorbance values within the range of 1000-5000 $\mu\text{g/ml}$ were recorded, as outlined in Table no. 4. Additionally, the standard calibration curve

for Pregabalin was depicted in Figure 8. Through least square regression analysis, it was found that there was a linear response within the range of 1000-5000 $\mu\text{g/ml}$, with a regression coefficient (R^2) value 0.992. The liner equation resulting from the analysis was, where y denotes the absorbance (A), and x represents the concentration of Pregabalin in $\mu\text{g/ml}$.

Table 4: Calibration Curve of Pregabalin in PBS pH 6.8.

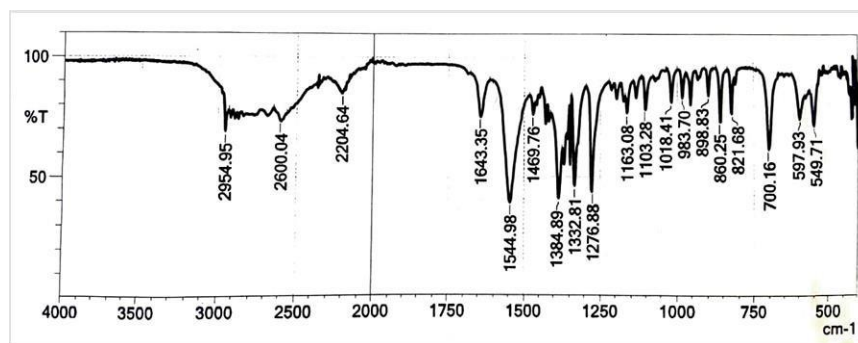
S. No.	Concentration $\mu\text{g/ml}$	Absorbance at 210nm
1.	1000 $\mu\text{g/ml}$	0.2542
2.	2000 $\mu\text{g/ml}$	0.3601
3.	3000 $\mu\text{g/ml}$	0.5140
4.	4000 $\mu\text{g/ml}$	0.6755
5.	5000 $\mu\text{g/ml}$	0.7697

**Figure 8. Calibration curve of Pregabalin**

2. FTIR

The IR spectra analysis of Pregabalin, identified as (3S)-3-(aminomethyl)-5-methylhexanoic acid, confirmed the presence of characteristic functional groups. The absorption peak at 2954.95 cm^{-1} corresponded to C-H stretching, indicating alkyl group vibrations. The peak at 2600.4 cm^{-1} represents O-H stretching of the carboxylic acid group, showing a broad peak due to hydrogen bonding. The C-H bending vibrations of methylene groups are observed at

1469.76 cm^{-1} , showing medium intensity. The COOH C-O stretching at 1276.88 cm^{-1} further confirmed the presence of carboxylic acid functionality. Additionally, the NH_2 N-H bending at 1643.35 cm^{-1} signified the presence of a primary amine group, which was crucial in Pregabalin's structure and activity. These IR spectral characteristics validated the chemical identity and structural integrity of Pregabalin as shown in Figure 9.

**Figure 9. FTIR of pure API****Table 5: FTIR Interpretation of pregabalin**

Wavenumber (cm^{-1})	Type of Vibration	Assignment	Interpretation
2954.95	C-H Stretching	Alkyl group	Indicates the presence of alkyl group vibrations
2600.04	O-H Stretching (broad)	Carboxylic acid (COOH)	Broad peak due to hydrogen bonding in the -OH group

			of carboxylic acid.
1643.35	N–H Bending	Primary amine (NH ₂)	Indicates the presence of a primary amine group, crucial to Pregabalin's activity.
1469.76	C–H Bending	Methylene (CH ₂) group	Medium intensity peak due to bending vibrations in methylene groups.
1276.88	C–O Stretching	Carboxylic acid (COOH)	Confirms the presence of the carboxylic acid functional group.

3. XRD (X-Ray Diffractometer studies)

XRD patterns of Pregabalin were shown in Figure 10, The XRD analysis of Pregabalin confirmed its high crystallinity with distinct diffraction peaks. The data obtained in this study contributed to the understanding of its solid-state characteristics, which was crucial for pharmaceutical

formulation and stability studies. The X-ray diffractogram of pregabalin confirms its crystalline structure, indicated by several sharp and intense peaks (Figure 10). The XRD pattern of pure pregabalin at 2 θ reveals characteristic peaks at 9.4, 19.04, 24, 36, 38, 42, and 49.9.

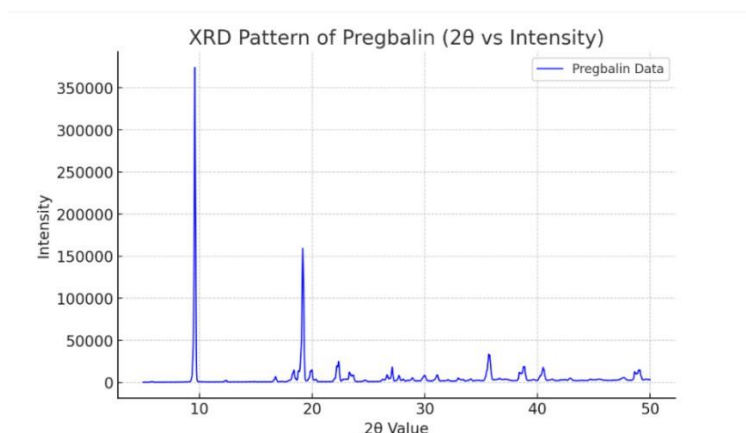


Figure 10. X-ray diffraction patterns of Pregabalin

Table 6: XRD Interpretation of pregabalin

2 θ (degrees)	d-spacing (Å)	Relative Intensity (a.u.)	Observations
9.4	9.41	100	Strong, sharp peak
19.04	4.66	85	Major crystalline reflection
24.00	3.71	75	Distinct peak
36.00	2.49	60	Moderate intensity
38.00	2.36	55	Moderate crystalline signal
42.00	2.15	45	Lower intensity
49.90	1.83	50	Minor sharp peak

4. DSC (Differential Scanning Calorimetry)

The DSC analysis of pure Pregabalin (Figure 11) was conducted to determine its thermal behavior, including melting point, phase transition and potential degradation. A

heating rate 40°C/min from 50°C to 300°C, revealed a sharp endothermic peak at 214.80°C with an enthalpy change (ΔH) OF 447.4236J/g.

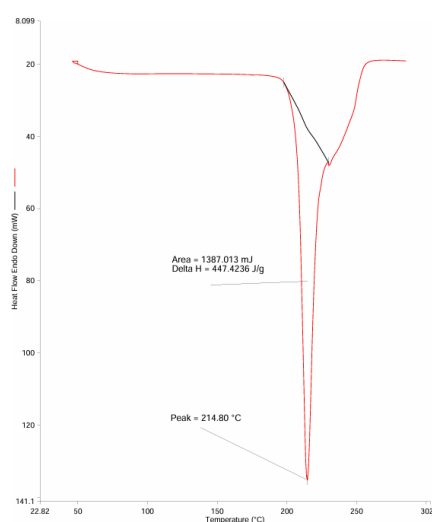


Figure 11. DSC of Pregabalin

4.8. Pre-compression Evaluation

Table 7: Flow properties of all batches of powder blend

Batch No.	Bulk Density (g/ml)	Tapped Density (g/ml)	Hausner's Ratio	Compressibility Index (%)	Angle of Repose (o)
MQA201	0.264±0.01	0.335±0.03	1.268±0.5	18.19±0.5	29.55±0.5
MQA202	0.312±0.03	0.413±0.04	1.223±0.3	20.02±0.4	29.54±0.5
MQA203	0.320±0.12	0.332±0.05	1.201±0.2	19.04±0.3	30.19±0.5
MQA204	0.430±0.44	0.412±0.03	1.231±0.1	20.04±0.4	31.08±0.5
MQA205	0.332±0.22	0.430±0.05	1.271±0.6	21.11±0.5	29.31±0.5
MQA206	0.274±0.05	0.441±0.02	1.301±0.6	18.05±0.2	28.33±0.5
MQA207	0.294±0.02	0.321±0.01	1.221±0.2	19.05±0.5	28.32±0.5
MQA208	0.314±0.04	0.425±0.05	1.242±0.4	12.24±0.6	29.15±0.5
MQA209	0.284±0.06	0.405±0.02	1.252±0.4	14.05±0.1	30.25±0.5
MQA210	0.362±0.25	0.329±0.04	1.324±0.6	18.22±0.2	31.22±0.5
MQA211	0.325±0.15	0.334±0.05	1.265±0.5	16.55±0.3	29.58±0.5
MQA212	0.272±0.04	0.420±0.03	1.227±0.4	20.15±0.4	28.05±0.5
MQA213	0.270±0.03	0.410±0.05	1.265±0.6	11.35±0.6	28.65±0.5
MQA214	0.402±0.25	0.390±0.02	1.256±0.3	17.10±0.2	30.32±0.5
MQA215	0.345±0.22	0.442±0.04	1.241±0.1	18.85±0.2	28.42±0.5

4.9. Post-compression Evaluation

Table 8: Post-compression Evaluation

S. No	Thickness (mm)	Hardness (Kg/cm ²)	wetting time(min.sec.)	Water absorption ratio (%)	% Drug content	Weight variation
1.	2.79	3.3	4.38	42.07	93.14	105.5
2.	2.80	3.1	2.58	48.88	91.43	103.8
3.	2.78	3.2	2.10	52.67	93.29	106.5
4.	2.82	3.2	1.45	49.20	94.57	107.3

5.	2.79	3.3	3.21	43.4	95.14	103.5
6.	2.83	3.2	4.42	40.47	95.71	105.6
7.	2.75	3.2	3.52	33.67	100.86	106.8
8.	2.89	3.1	4.02	28.64	97.43	106.5
9.	2.86	3.2	3.44	53.01	96.71	105.5
10.	2.81	3.1	3.28	48.13	98.29	103.5
11.	2.74	3.1	4.10	44.13	99.71	104.9
12.	2.78	3.2	2.10	50.96	99.14	106.2
13.	2.87	3.2	3.21	51.30	97.14	107.28
14.	2.79	3.1	1.30	40.63	101.92	107.93
15.	2.79	3.2	4.20	31.93	100.57	107.9

4.10. In-Vitro Dissolution studies

The In-Vitro dissolution studies were conducted for the prepared for the prepared formulation, as discussed in table 9. The corresponding graph was represented in Figure 12.

Table 9: %Cumulative drug release of formulations MQA201-215

Batches	Time (Min)						
	5 min	10 min	15min	20 min	30 min	45 min	60 min
MQA201	84.70	88.90	91.01	92.27	93.26	93.34	93.81
MQA202	75.39	80.92	84.64	87.82	90.81	91.68	91.87
MQA203	84.59	87.92	89.75	90.97	92.15	92.65	92.79
MQA204	83.78	89.31	92.60	95.67	95.80	96.03	96.21
MQA205	74.61	78.92	83.57	88.84	89.62	90.01	90.05
MQA206	78.26	84.99	90.02	90.18	91.85	91.02	92.06
MQA207	73.59	79.98	82.64	86.12	88.92	89.07	89.58
MQA208	82.82	88.35	92.07	93.18	94.01	94.27	94.45
MQA209	78.58	85.17	90.26	93.82	94.85	95.25	95.77
MQA210	76.26	83.99	87.52	89.89	90.18	91.05	91.79
MQA211	81.66	85.96	89.64	90.08	91.28	92.81	92.94
MQA212	75.92	86.34	91.40	92.41	92.77	93.64	93.69
MQA213	80.70	86.23	90.47	92.97	93.79	94.66	94.96
MQA214	83.88	88.42	91.58	95.28	96.92	97.34	97.51

MQA215	79.59	82.92	89.05	90.97	92.15	92.59	92.79
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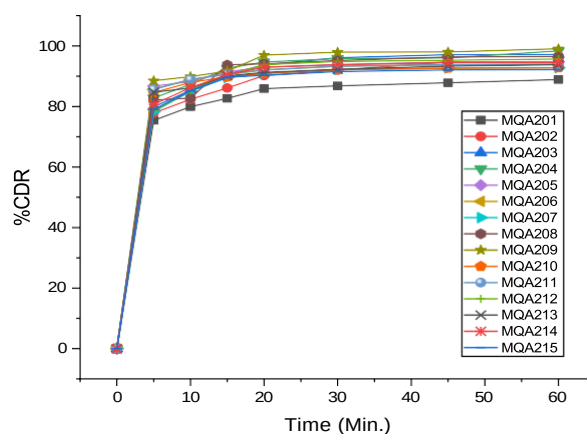


Figure 12. *In-Vitro* drug release profile of formulation (MQA201 to MQA215)

4.11. Release kinetics

4.11.1. Zero Order

The graph [Figure 13.] represented the zero-order drug release kinetics of the sublingual tablet formulation over a period of 60 minutes. The x-axis denotes time (minutes), while the y-axis represents the cumulative percentage of drug released. Multiple formulations (MQA201 to MQA215) were analyzed

to evaluate the release profile. The observed trend demonstrated a linear increase in drug release over time, indicating that the release rate remained constant and independent of drug concentration. This characteristic was crucial for maintaining a steady therapeutic effect and ensuring consistent drug absorption through the sublingual mucosa.

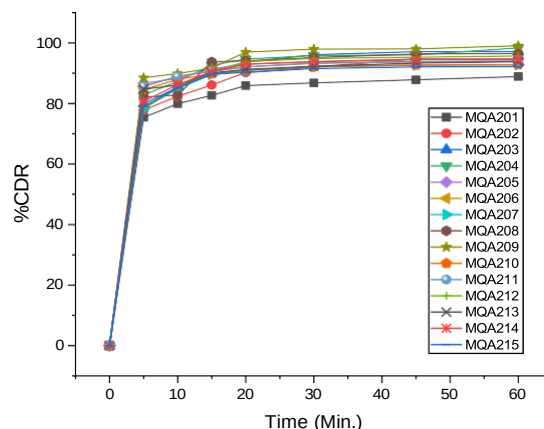


Figure 13. Formulation of MQA201 to MQA215 Zero order kinetics

4.11.2. First Order

The graph [Figure 14.] illustrated the first-order drug release kinetics of a sublingual tablet formulation over a period of 60 minutes. The x-axis represented time (minutes), while the y-axis denoted the logarithm of the cumulative percentage of drug remaining. The downward slope in the graph suggests that the drug release is concentration-dependent, meaning that as the drug dissolved, the release rate gradually decreased over time.

This behaviour aligned with the first-order kinetic model, where the drug release rate is proportional to the amount of drug still available in the tablet. Such a release pattern was commonly observed in formulations where drug dissolution and diffusion mechanisms governed the release process. For sublingual tablets, a first-order kinetic model indicated that the drug was rapidly released initially, followed by a gradual decline, which may be beneficial for achieving rapid onset of action in therapeutic applications.

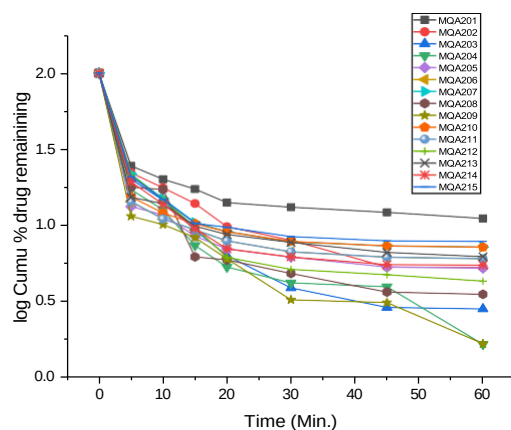


Figure 14. Formulation of MQA201 to MQA215 First Order model

4.11.3. Higuchi

The above graph [Figure 15.] represented the **Higuchi drug release kinetics** of a sublingual tablet formulation, where the x-axis denotes the **square root of time (SQRT of time)**, and the y-axis represents the **cumulative percentage of drug released**. The Higuchi model describes drug release from a matrix system based on **Fickian diffusion**, indicating that the

release rate is governed by the drug's diffusion through the formulation.

For sublingual tablets, Higuchi kinetics play a crucial role in determining drug availability at the absorption site, ensuring optimal therapeutic efficacy. The results confirmed that the sublingual tablet formulations exhibited diffusion-mediated release, which could be tailored to enhance drug bioavailability.

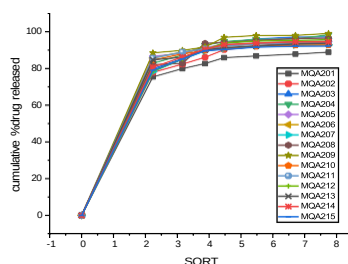


Figure 15. Formulation of MQA201 to MQA215 Higuchi model

4.11.4. Korsmeyer-peppas

The graph (Figure 16.) represented the Korsmeyer-Peppas model for drug release kinetics of a sublingual tablet formulation. The x-axis denoted log time, while the y-axis

represented log cumulative drug release (log %CDR). This model was commonly used to describe drug release mechanisms from polymeric systems, particularly when multiple release phenomena were involved.

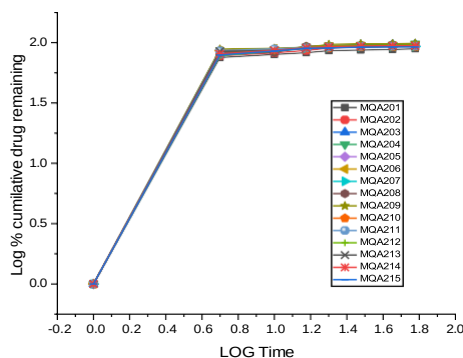


Figure 16. Formulation of MQA201 to MQA215 Korsmeyer-Peppas model

4.11.5. Hixson

The graph (Figure 17.) represented the Hixson-Crowell cube root model, which described drug release from dosage forms where dissolution and erosion of the tablet surface occurred simultaneously. The x-axis represented time (minutes), while the y-axis showed the difference in cube root of the initial drug content (W_0) and remaining drug content (W) at time t .

For the sublingual tablet formulation, the data suggested that as the tablet dissolved, its surface area decreased, leading to a gradual reduction in the release rate. This information was crucial for optimizing the formulation to ensure consistent and predictable drug release, improving bioavailability and therapeutic efficacy.

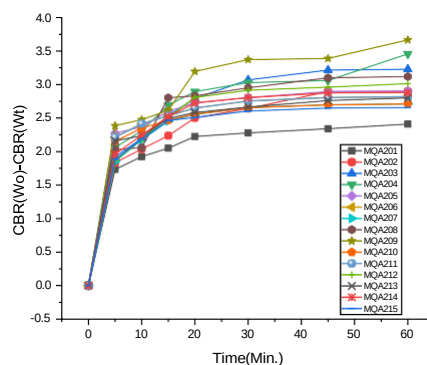


Figure 17. Formulation of MQA201 to MQA215 Hixson-Crowell cube root model

Table 10: The table presents R^2 values for different drug release models across various batches of Sublingual tablet

Batches	R^2 Value					
	Zero order	First order	Higuchi	Korsmeyer-Peppas R^2	Korsmeyer-Peppas n value	Hixson-Crowell cube root
MQA201	0.7638	0.8238	0.8779	0.9585	0.0671	0.8047
MQA202	0.8597	0.9601	0.9441	0.9836	0.0864	0.9325
MQA203	0.7739	0.9265	0.8865	0.9632	0.0832	0.8823
MQA204	0.6788	0.7898	0.8088	0.9129	0.0675	0.7539
MQA205	0.7918	0.8675	0.8905	0.9467	0.0391	0.8429
MQA206	0.7741	0.8566	0.884	0.9706	0.0377	0.8309
MQA207	0.6471	0.7523	0.7838	0.9047	0.0669	0.7177
MQA208	0.6392	0.765	0.7427	0.8128	0.0728	0.7182
MQA209	0.766	0.8143	0.8446	0.8711	0.0509	0.7979
MQA210	0.7579	0.8357	0.8775	0.9655	0.0381	0.8116
MQA211	0.7741	0.8566	0.8884	0.9706	0.0377	0.8309
MQA212	0.6822	0.7946	0.8136	0.9206	0.0804	0.7579
MQA213	0.7893	0.8623	0.8846	0.9374	0.044	0.8383
MQA214	0.6888	0.797	0.8191	0.9259	0.0634	0.7622
MQA215	0.6346	0.7292	0.7711	0.894	0.0594	0.9677

4.12. Optimized batch of Sublingual tablet (MQA216)

After analyzing the response data statistically and considering the defined constraints for each response variable, such as in-vitro drug release, friability, and disintegration time at various time points, the Design Expert software (Stat-Ease Inc.,

Minneapolis, MN) proposed a formulation composition. This suggestion was based on achieving the highest desirability value, as detailed in Tables 11 and 12 and illustrated in Figure 18.

Table 11: Desirable objectives of response variables for optimized formulation of Sublingual tablet

S.No.	Response variables	Criteria
1.	<i>In-vitro</i> drug release %	Minimum
2.	Friability	Minimum
3.	Disintegration	Maximum

Table 12: Software predicted values of responses with maximum desirability of optimized formulation of Sublingual tablet

Measured responses		
Response variable	Software predicted value	Experimentally observed value
1. <i>In-vitro</i> drug release %	93.46	92.42
2. Friability	0.28	0.31
3. Disintegration	26	24

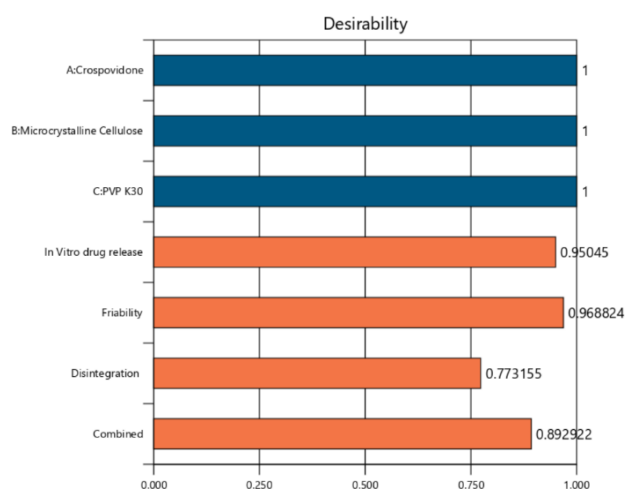


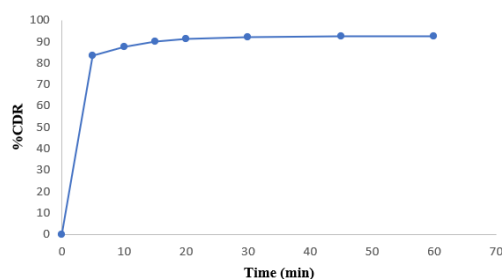
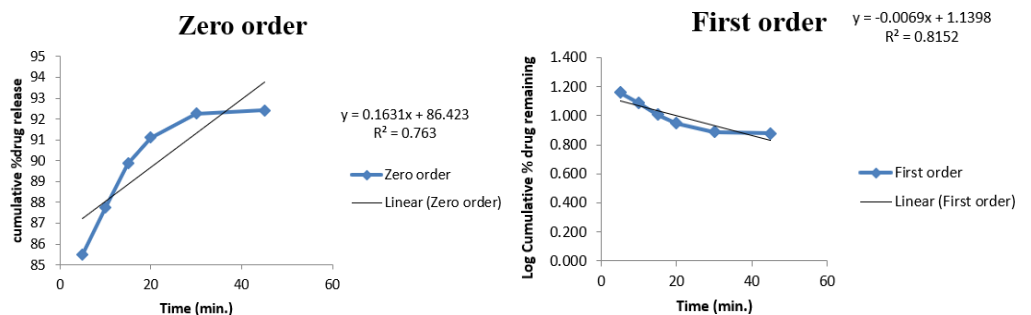
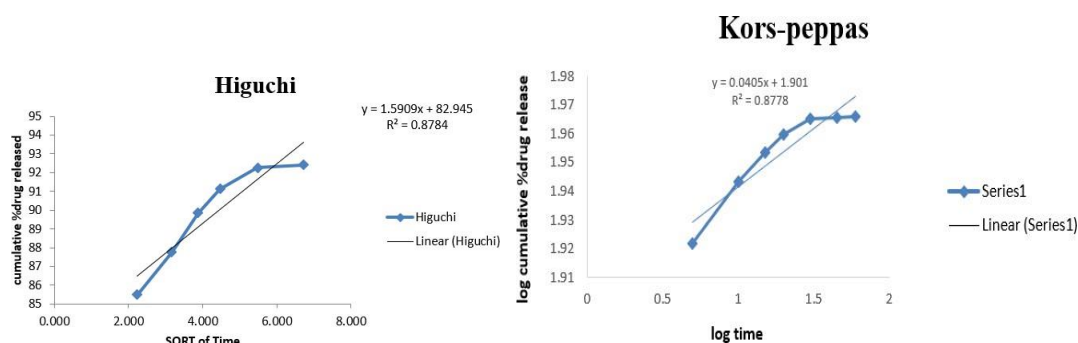
Figure 18. Desirability of Independent or Response Variables Depicted in Bar Graph

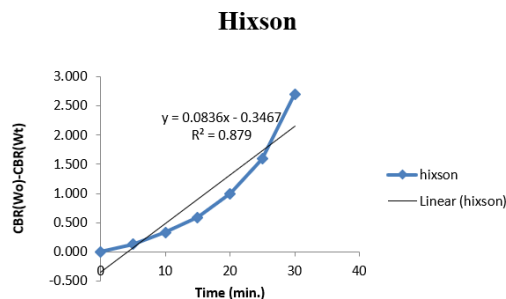
For ease of comprehension, a summary of the data for the optimized batch (MQA216) is provided in Table 13.

Table 13: QC parameter of optimized batch

S. No.	Parameters	Observation
1.	Thickness	2.73 mm
2.	Hardness	3.4 Kg/cm ²
3.	Friability	0.21 %

4.	Disintegration time	24sec
5.	% Drug content	96%
6.	Weight variation	103.4
7.	wetting time	2.5 sec
8.	Water absorption ratio	49.13%
9.	<i>In-Vitro</i> Drug release	92.42%

In-Vitro* Drug release MQA216****Figure 19. *In-Vitro* drug release profile of formulation (MQA216)*4.13. Release Kinetics of optimized batch****[A] Formulation of MQA216 Zero order [B] Formulation of MQA216 First order****[C]Formulation of MQA216 Higuruchi model [D] Formulation of MQA216 Korsmeyer Peppas model**



[E] Formulation of MQA216 Hixson-Crowell cube root model
Figure 20. Release kinetics graphs of optimized Sublingual tablet (MQA216)

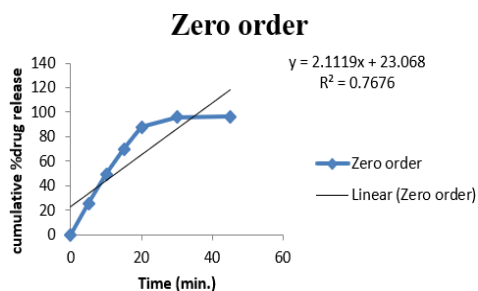
The drug release kinetics of the sublingual tablet formulation were analyzed using different mathematical models, [Figure 20.] including Zero-Order, First-Order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell models. The Zero-Order model [Figure 20. A] ($R^2 = 0.763$) demonstrated a steady increase in cumulative % drug release over time, suggesting a constant release rate. Although this was ideal for sustained-release formulations, it was not suitable for sublingual tablets, as they require rapid absorption. The First-Order model [Figure 20. B] ($R^2 = 0.9732$) displayed a logarithmic decrease in cumulative % drug remaining, indicating a concentration-dependent release mechanism. This suggested that drug release is faster initially and slowed down over time, which partially aligned with sublingual drug absorption, as sublingual formulations dissolve quickly and follows first-order kinetics. The Higuchi model [Figure 20. C] ($R^2 = 0.8784$), which plots cumulative % drug release against the square root of time, suggested a diffusion-controlled release mechanism, typically observed in matrix-based or polymeric formulations. However, since sublingual tablets are designed for rapid dissolution rather

than prolonged diffusion, this model does not fully represent sublingual drug kinetics. The Korsmeyer-Peppas model [Figure 20. D] ($R^2 = 0.8778$) analyzed drug release based on polymeric systems, implying a combination of diffusion and polymer relaxation. This mechanism was not relevant for conventional sublingual formulations, as they do not rely on polymer-controlled release systems. Lastly, the Hixson-Crowell model [Figure 20. E] ($R^2 = 0.879$) accounted for drug release from system undergoing dissolution accompanied by shape change. However, sublingual tablets primarily disintegrated rather than gradually erode, making this model less applicable to the observed release behavior.

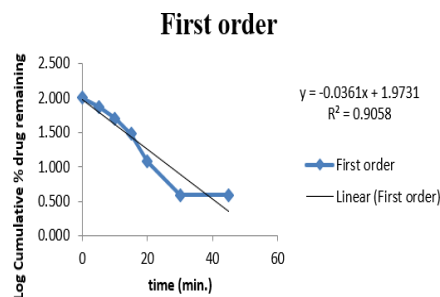
Among these models, the First-Order models best fitted the sublingual tablet formulation, as they represented the rapid dissolution and absorption required for immediate therapeutic action. In contrast, the Higuchi and Korsmeyer-Peppas models suggest diffusion- or polymer-controlled release mechanism, which were more suitable for sustained or modified-release formulations rather than for the fast onset of action needed in sublingual drug delivery.

4.16. Release kinetics graph of bilayer tablet

A. Immediate release layer



[A] Formulation of IR Zero order



[B] Formulation of IR First order

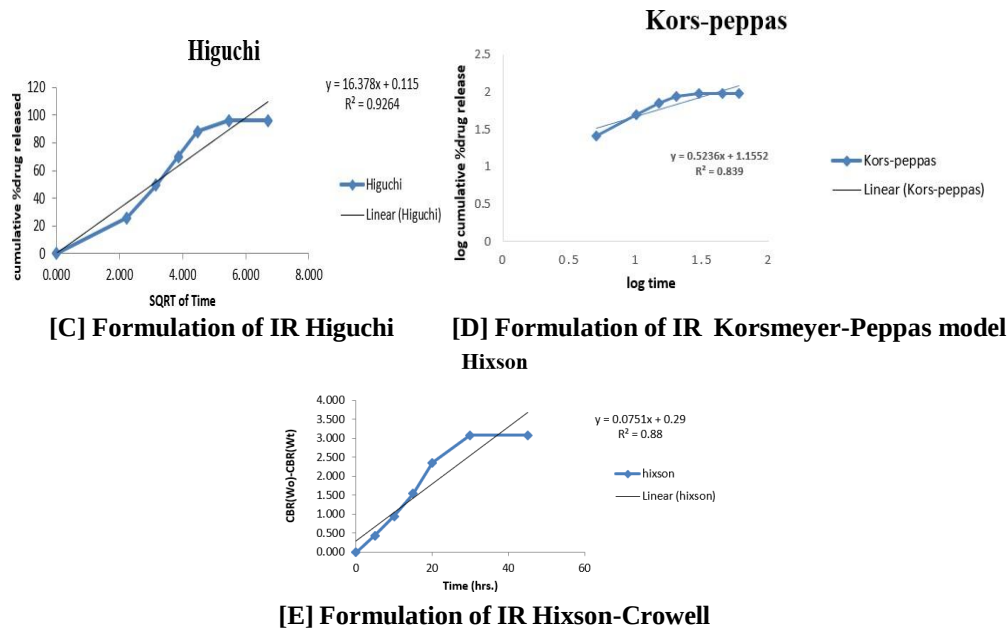
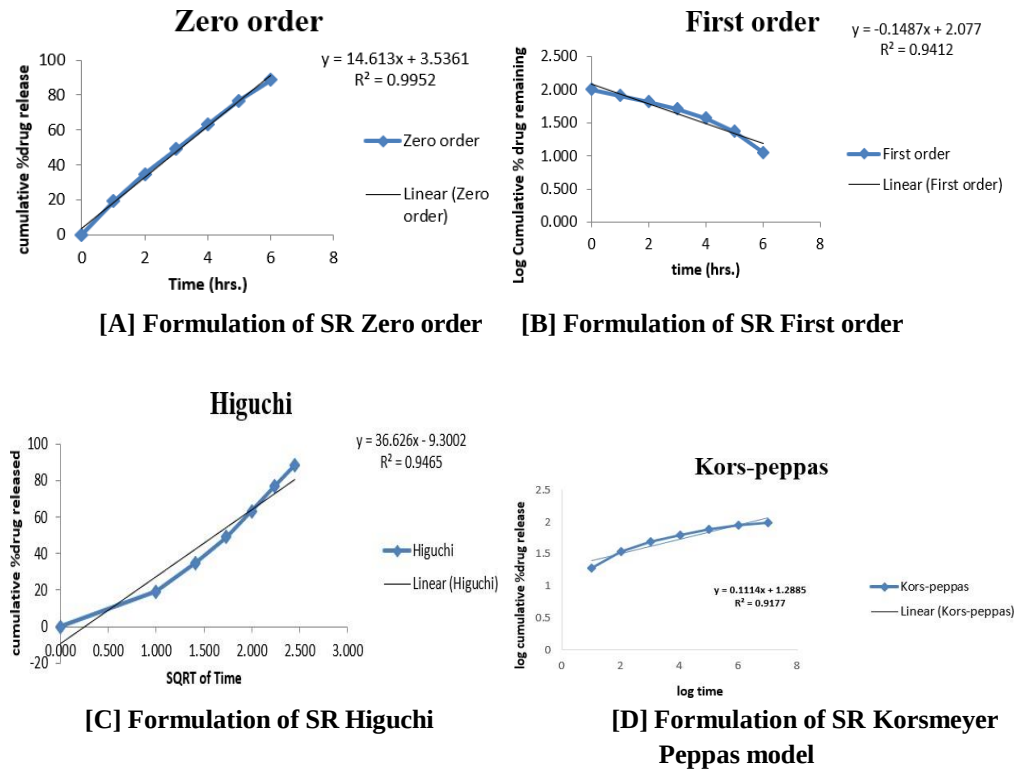
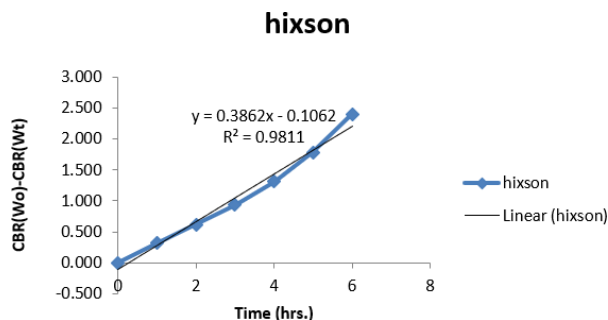


Figure 21. Release kinetics graphs of Bilayer tablet (IR)

B. Sustain release layer





[E] Formulation of SR Hixson-Crowell

Figure 22. Release kinetics graphs of Bilayer tablet (SR)

The bilayer tablet formulation was developed to achieve and understand a biphasic drug release profile [Figures 21 and 22], comprising an immediate-release (IR) layer for rapid onset of action and a sustained-release (SR) layer to maintain prolonged therapeutic levels. Kinetic analysis of the IR layer, as illustrated in the first set of graphs, revealed the best fit with the Higuchi model ($R^2 = 0.9264$), indicating a diffusion-controlled release mechanism. The first-order model ($R^2 = 0.9058$) also demonstrated a strong correlation, suggesting concentration-dependent release. In comparison, the Hixson-Crowell model ($R^2 = 0.88$) showed moderate correlation, while the Korsmeyer-Peppas ($R^2 = 0.839$) and zero-order ($R^2 = 0.7676$) models were less predictive, pointing to limited anomalous transport and time-independent release behaviour in the IR phase, respectively. For the SR layer, kinetic evaluation showed excellent linearity with the zero-order model ($R^2 = 0.9984$), confirming a steady and concentration-independent drug release over time. High correlation with the Higuchi model ($R^2 = 0.9924$) further supported a diffusion-based release, while the Hixson-Crowell model ($R^2 = 0.98$) indicated the involvement of surface area reduction due to erosion. The first-order model ($R^2 = 0.9446$) and Korsmeyer-Peppas model ($R^2 = 0.9177$) n value is 0.116 which show Fickian diffusion controlled also showed good fits, suggesting minor contributions from concentration-dependent release and a diffusion mechanism, respectively.

The bilayer Pregabalin tablet achieves its desired dual-release functionality through well-defined kinetics in both layers. The IR layer follows primarily Higuchi and First-order kinetics with a mixed (anomalous) mechanism, ensuring rapid onset, while the SR layer adheres to Zero-order and diffusion-based release, supporting prolonged therapeutic effect.

4.14. Comparison of *In-Vitro* drug release of optimized Sublingual tablet VS Bilayer tablet and capsule

Figure 23. presented the *in-vitro* drug release profiles of different formulations, illustrating the percentage of cumulative drug release (%CDR) over time. The comparative evaluation of drug release profiles between the sublingual and bilayer tablet formulations clearly highlights the differences in their release behavior and therapeutic potential. The sublingual formulation exhibited a very rapid onset, achieving over 90% drug release within just 15 minutes, indicating efficient absorption through the highly vascularized sublingual mucosa. This rapid release makes it highly suitable for conditions requiring immediate therapeutic action, such as pain management or emergency interventions. In contrast, the bilayer tablet, which combines an immediate-release (IR) layer and a sustained-release (SR) layer, demonstrated a more controlled and biphasic release profile. While the IR portion of the bilayer tablet released approximately 96% of the drug within 30 minutes, the SR layer extended the release up to 7 hours, ensuring prolonged therapeutic levels. Thus, the sublingual tablet is optimal for fast onset, but the bilayer tablet provides the advantage of both immediate relief and sustained drug action, reducing the need for frequent dosing. From a clinical perspective, the choice between the two depends on the desired therapeutic objective: for rapid symptom control, the sublingual tablet is ideal, whereas for maintaining prolonged plasma concentrations, the bilayer formulation is more effective and offers better patient compliance. These study may help to further investigation such formulation.

Table 14: *In-Vitro* Drug release

Time (min.)	MQA216	Bilayer (IR)	Time (hr.)	Bilayer (CR)
5	83.50	30.73	1	19.26
10	87.76	60.34	2	34.77
15	89.86	81.08	3	49.16
20	91.12	88.02	4	63.09

30	92.26	96.14	5	76.68
45	92.42	96.15	6	88.67
60	92.44	96.16	7	97.51

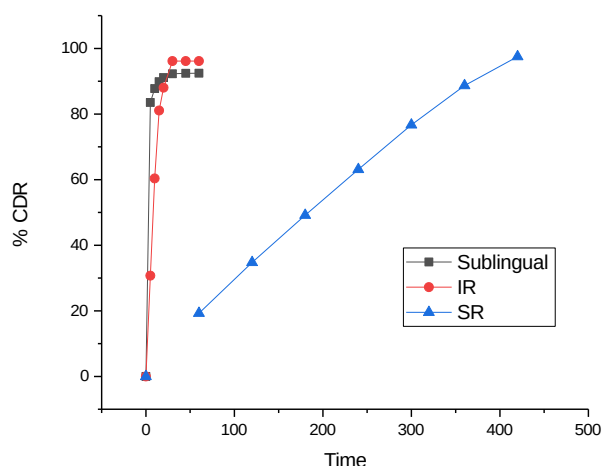


Figure 23. Drug release of Sublingual and bilayer tablet

4.15. Comparison of Release kinetics of optimized sublingual tablet vs Bilayer tablet

The release kinetics of sublingual and bilayer tablets differ significantly due to their formulation design and intended therapeutic purpose. Sublingual tablets were characterized by an immediate or burst drug release, often not fitting neatly into conventional kinetic models due to their rapid dissolution and direct absorption through the sublingual mucosa, bypassing first-pass metabolism. They loosely aligned with first-order kinetics, where the release is concentration-dependent. In contrast, bilayer tablets were engineered to exhibit dual-release kinetics, typically consisting of one immediate-release layer and another sustained- or delayed-release layer. This allowed the drug to follow more structured kinetic models such as Zero-order (constant release), Higuchi (diffusion-controlled), or Korsmeyer-Peppas (polymer-based diffusion/erosion) depending on formulation specifics. The comparative evaluation of the drug release kinetics between the sublingual and bilayer tablet formulations reveals notable differences in their performance and release mechanisms. The sublingual formulation exhibits a rapid and almost immediate drug release, reaching over 90% release within the first 20 minutes, as evidenced by its steep curve and plateau in the initial timeframe. This fast onset is beneficial for conditions requiring prompt therapeutic action. However, its release kinetics show moderate fitting across models, with the First order model ($R^2 = 0.9732$) and Higuchi model ($R^2 = 0.8784$) demonstrating a better correlation, suggesting that release is dissolution driven and anomalous transport mechanisms primarily govern the drug release.

In contrast, the bilayer tablet, comprising both an immediate-release (IR) and a sustained-release (SR) layer, offers a biphasic release profile. The IR layer achieves around 96% release within the first 45 minutes, which is comparable to the sublingual form in rapidity. However, it shows better kinetic alignment with the First-order ($R^2 = 0.9058$), Higuchi ($R^2 = 0.9264$), and Korsmeyer-Peppas ($R^2 = 0.839$) models, indicating a combination of concentration-dependent release and matrix diffusion. The SR layer demonstrates a highly linear Zero-order release ($R^2 = 0.9984$), alongside strong fits with Higuchi ($R^2 = 0.9924$) and Korsmeyer-Peppas ($R^2 = 0.9177$) n value is 0.116 which show Fickian diffusion controlled, highlighting controlled and consistent release over time through erosion and polymer relaxation mechanisms. Overall, while the sublingual formulation is ideal for rapid relief, the bilayer tablet offers a superior therapeutic profile by combining immediate relief with sustained drug levels. Its controlled release behaviour supports better compliance and long-term efficacy, making it the preferred choice for chronic conditions requiring both immediate and prolonged drug action.

5. Conclusion

A sublingual tablet of Pregabalin was successfully developed using a Quality by Design (QbD) approach. The optimized batch (MQA216) demonstrated rapid disintegration (24 seconds), low friability (0.21%), and high in-vitro drug release (92.42% within 20 minutes). The formulation met all predefined quality parameters and achieved a high desirability score of 0.8923, confirming its reliability, safety, and effectiveness for immediate sublingual drug delivery.

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