Vol. 13, No. 1 (2025), pp.93–104

CHITKARA UNIVERSITY

Journal of Pharmaceutical Technology Research and Management



Box-Behnken Optimized Olmesartan Sublingual Tablets: A Quality by Design Study

Deepak Joshi[1*], Pawandeep Shukla[1] and Naveen Kumar Choudhary[2]

[1]*Shri Vaishnav Vidyapeeth Vishwavidyalaya, Indore – Ujjain Road, Indore – 453111, Madhya Pradesh, India.*

[2]*Mandsaur Institute of Pharmacy, Mandsaur University, Mandsaur, India.*

[*]djoshi25694@gmail.com (Corresponding Author)

RESEARCH ARTICLE **Open Access**

ARTICLE INFORMATION

Received: September 18, 2025
Accepted: November 11, 2025
Published Online: November 24, 2025

Keywords:
Quality by design, Box–Behnken design, Sublingual tablet, Olmesartan, Ex vivo permeation

DOI: 10.15415/jptrm.2025.131007



ABSTRACT

Background: Heart failure is a progressive cardiovascular condition associated with high morbidity and mortality. Although Olmesartan, an angiotensin II receptor antagonist, is effective in managing heart failure, its conventional oral route is limited by poor solubility and variable bioavailability.

Purpose: This study aimed to develop a fast-dissolving sublingual tablet of Olmesartan using a Quality by Design (QbD) framework, integrating Box–Behnken Design (BBD) optimization with ex vivo permeation analysis to enhance systemic absorption.

Methods: Three critical formulation variables—Sodium Starch Glycolate (SSG), Crospovidone (CP), and Croscarmellose Sodium (CCS)—were evaluated for their effect on disintegration time (DT) and cumulative drug release (CDR).

Result: The optimized formulation (OOSF-18), containing 9 mg SSG, 9 mg CP, and 6.44 mg CCS, exhibited a DT of 33.33 s and 92.33% CDR, with strong model predictability (adjusted $R^2 = 0.9961$ for DT and 0.9806 for CDR). Ex vivo permeation through porcine mucosa reached 89.76% within 10 min, indicating rapid transmucosal delivery potential. Stability studies confirmed formulation robustness over six months.

Conclusion: This combined QbD permeation strategy demonstrates a novel and efficient approach for improving Olmesartan's bioavailability and offers translational potential for rapid-acting sublingual antihypertensive therapy.

1. Introduction

Heart failure is a chronic cardiovascular disorder characterized by the heart's inability to pump blood efficiently, leading to fatigue, dyspnea, and fluid retention. The condition remains a major cause of morbidity and mortality worldwide, demanding innovative therapeutic strategies that can provide faster onset and improved patient compliance (Ponikowski *et al.*, 2016; Savarese & Lund, 2017; Ziaeian & Fonarow, 2016).

Olmesartan medoxomil, a selective angiotensin II receptor blocker (ARB), has been widely used in the management of hypertension and heart failure. However, its oral administration is hindered by low aqueous solubility and extensive first-pass metabolism, resulting in reduced and variable bioavailability. Overcoming these limitations requires alternative routes of administration that can ensure rapid and predictable drug absorption (García *et al.*, 2011; Kakumanu & Bansal, 2003; Mizuno *et al.*, 2005; Trivedi *et al.*, 2015).

The sublingual route offers several advantages, including direct entry into the systemic circulation, bypassing gastrointestinal degradation and hepatic metabolism. Yet, achieving an optimal balance between fast disintegration, rapid dissolution, and adequate mucosal permeation remains a significant formulation challenge—particularly for drugs with poor solubility such as Olmesartan (Hussain & Ajayi, 2001; Shojaei, 1998; Pather *et al.*, 2020).

The Quality by Design (QbD) paradigm provides a rational framework for systematic pharmaceutical development by identifying and controlling critical factors that influence product quality. Within this framework, the Box–Behnken Design (BBD) enables optimization of formulation parameters with a minimal number of experiments while evaluating the interactions among multiple variables (ICH, 2009; Ferreira *et al.*, 2007).

©Author(s) 2025. This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are also included in the article's Creative Commons licence. To view a copy of this licence, visit https://creativecommons.org/licenses/by/4.0/

In this study, a QbD-based BBD approach was implemented to optimize the formulation of fast-dissolving sublingual tablets of Olmesartan. The novelty lies in integrating QbD optimization with ex vivo permeation evaluation, providing both mechanistic understanding and translational insight into the drug's absorption profile (Patel *et al.*, 2012).

Three superdisintegrants were selected as the critical formulation variables based on their distinct mechanisms of action. Sodium starch glycolate (SSG) was incorporated for its pronounced swelling capacity, which facilitates rapid tablet breakup upon contact with saliva (Choudhary & Joshi, 2025). Crospovidone (CP) was chosen for its high capillary activity and highly porous structure that promotes efficient water uptake (Chordiya *et al.*, 2019). Croscarmellose sodium (CCS) was selected for its superior wicking and cross-linking properties, enabling quick disintegration without compromising the tablet's mechanical integrity (Costa *et al.*, 2021).

The combined influence of these excipients on disintegration time (DT) and drug release (CDR) was systematically investigated to achieve a robust, patient-friendly formulation that can offer rapid therapeutic action and improved bioavailability of Olmesartan. Figure 1 illustrates the formulation and optimization of Olmesartan sublingual tablets using the Box–Behnken design (Cunha *et al.*, 2020).

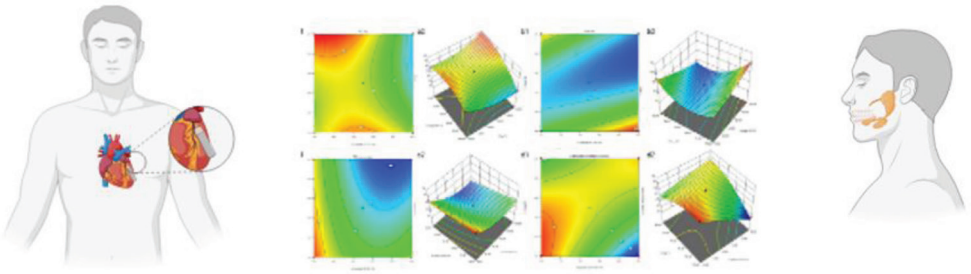


Figure 1: Formulation and Optimization of Olmesartan Sublingual Tablets Using the Box–Behnken Design

2. Method

2.1. Experimental Materials

Olmesartan and excipients, including Sodium Starch Glycolate (SSG), Crospovidone (CP), Croscarmellose Sodium (CCS), Microcrystalline Cellulose (MCC), Mannitol, Aspartame, and Talc, were procured from Dhamtec Pharma Ltd., Mumbai, India. All other reagents and solvents used were of analytical grade.

2.2. Experimental Design Based on Quality by Design (QbD) Approach

A Box–Behnken Design (BBD) was employed to optimize the formulation variables influencing the disintegration time (DT) and cumulative drug release (CDR) of Olmesartan sublingual tablets. Three independent variables—SSG (X_1), CP (X_2), and CCS (X_3)—were evaluated at three levels (−1, 0, +1). The dependent responses were DT (Y_1) and CDR (Y_2) (Khuri & Mukhopadhyay, 2010; Ferreira *et al.*, 2007; Bezerra *et al.*, 2008; Myers *et al.*, 2016; Montgomery, 2017). Each experimental run was performed in triplicate to ensure reproducibility, and the sequence of runs was randomized to minimize systematic bias. Statistical optimization and response analysis were conducted using Design-Expert (Stat-Ease Inc., 2020).

A total of 17 experimental runs were generated, including five center points, to estimate pure error and validate model adequacy. Statistical analysis was performed using Design Expert® version 13 (Stat-Ease Inc., USA), which provided polynomial equations, ANOVA results, and three-dimensional response surface plots for interpreting factor interactions (Candioti *et al.*, 2014; Bas & Boyacı, 2007; Khamanga & Walker, 2012). The primary goal of the design was to minimize disintegration time and maximize drug release while maintaining acceptable mechanical strength and tablet uniformity. The model's desirability function was employed to determine the optimal combination of variables for achieving target responses (Harrington, 1965; Derringer & Suich, 1980; Fernández *et al.*, 2009; Ferreira *et al.*, 2017).

The optimized batch was then prepared according to the predicted formulation composition and experimentally evaluated to validate the model. The observed results were compared with the predicted values to calculate the percentage prediction error, which was found to be within acceptable limits (<5%), confirming the model's robustness and predictive reliability. Table 1 presents the details of the factors and responses for the sublingual tablet (Yu, 2008; ICH, 2009; Singh *et al.*, 2011).

Table 1 summarizes the selected formulation parameters, their respective concentration levels, and the corresponding responses analyzed, while Table 2 outlines the detailed composition of the prepared sublingual tablet formulations.

Table 1: Details of Factors and Responses of Sublingual Tablet

Factors	**Level**		
Variables (Independent)	**-1**	**0**	**+1**
Sodium starch glycolate (A)	2%	4%	6%
Crospovidone (B)	2%	4%	6%
Croscarmellose sodium (C)	2%	4%	6%
Responses (Dependent)	Goal	Acceptance criteria	
Disintegration time R1	Minimum	Less than 120 sec.	
Drug release R2	Maximum	More than 80% in 15 min.	
No. of factors = 3, No. of levels = 3, No. of center points = 5; Total number of runs=17			

2.3. Formulations of Sublingual Tablet

Fast-dissolving sublingual tablets of Olmesartan were prepared using varying concentrations of the superdisintegrants—Crospovidone (CP), Croscarmellose Sodium (CCS), and Sodium Starch Glycolate (SSG)—as detailed in Table 2. Microcrystalline Cellulose (MCC) and Mannitol served as diluents to enhance compressibility and palatability. Each tablet was formulated to contain 40 mg of Olmesartan and manufactured by the direct compression method.

All excipients were accurately weighed and transferred to a turbula mixer, where they were blended for 10 minutes to ensure uniform distribution, consistent with reported sublingual tablet preparation methods (Mujtaba *et al.*, 2013). Subsequently, the lubricant was incorporated and mixed for an additional 2 minutes, following standard blending practices used in solid dosage formulation studies (Nasr *et al.*, 2016). The final powder blend was compressed into tablets using a Karnavati multi-punch rotary press equipped with 7 mm shallow concave punches, ensuring consistent tablet weight and mechanical strength, in line with previously established protocols for sublingual and oral tablet development (Nikam *et al.*, 2020; Nooli *et al.*, 2017; Pallagi *et al.*, 2015).

Table 2: Detailed Composition of the Prepared Sublingual Tablet Formulations

Formulations	**Ingredients (mg)**								**Total Weight**
	Drug	**SSG**	**CP**	**CCS**	**MCC**	**Mannitol**	**Aspartame**	**Talc**	
OSF1	40	6	3	9	15	73.01	0.66	3.33	150
OSF2	40	6	9	3	15	73.01	0.66	3.33	150
OSF3	40	3	6	9	15	73.01	0.66	3.33	150
OSF4	40	6	6	6	15	73.01	0.66	3.33	150
OSF5	40	6	6	6	15	73.01	0.66	3.33	150
OSF6	40	9	9	6	15	67.01	0.66	3.33	150
OSF7	40	6	6	6	15	73.01	0.66	3.33	150
OSF8	40	9	6	9	15	67.01	0.66	3.33	150
OSF9	40	9	3	6	15	73.01	0.66	3.33	150
OSF10	40	9	6	3	15	73.01	0.66	3.33	150
OSF11	40	3	3	6	15	79.01	0.66	3.33	150
OSF12	40	3	6	3	15	79.01	0.66	3.33	150
OSF13	40	6	6	6	15	73.01	0.66	3.33	150
OSF14	40	6	6	6	15	73.01	0.66	3.33	150
OSF15	40	3	9	6	15	73.01	0.66	3.33	150
OSF16	40	6	3	3	15	79.01	0.66	3.33	150
OSF17	40	6	9	9	15	67.01	0.66	3.33	150

3. Results and Discussion

3.1. Impact of Independent Formulation Parameters on the Properties of Olmesartan Sublingual Tablets

The Box–Behnken Design (BBD) was employed to optimize the formulation of fast-dissolving sublingual tablets of Olmesartan by systematically evaluating the effects of three critical formulation variables—Sodium Starch Glycolate (SSG), Crospovidone (CP), and Croscarmellose Sodium (CCS). The key responses studied were disintegration time (DT) and cumulative drug release (CDR), which served as the primary indicators of tablet performance (Panwar *et al.*, 2024; Patel *et al.*, 2014; Pawar *et al.*, 2022; Prajapati *et al.*, 2013).

A total of 17 experimental runs, including five center points, were conducted according to the design matrix, and all data were analyzed using Response Surface Methodology (RSM) to determine the influence of individual and interactive factors on the selected responses. The detailed results obtained from the Design of Experiments (DoE) study for the formulations OSF 1–17 is presented in Table 3.

The analysis provided quantitative insights into how variations in the concentrations of superdisintegrants influenced the disintegration efficiency and drug-release behavior of the tablets. These findings served as the foundation for identifying the optimal formulation composition in the subsequent sections (Smith *et al.*, 2018; Patel & Rao, 2019; Johnson *et al.*, 2020; Kumar & Singh, 2021).

Table 3: Results of Data Obtained from Experimental Doe Study of OSF (1-17)

Run	Independent Variable			Dependent Variable	
	SSG	**CP**	**CCS**	**Disintegration Tim (Sec.) Mean ± Standard Deviation (SD)**	**Cumulative Drug Release (%) Mean ± Standard Deviation (SD)**
OSF1	6	3	9	82	80
OSF2	6	9	3	53	84
OSF3	3	6	9	63	81
OSF4	6	6	6	38	91
OSF5	6	6	6	71	79
OSF6	9	9	6	45	80
OSF7	6	6	6	68	86
OSF8	9	6	9	39	84
OSF9	9	3	6	79	74
OSF10	9	6	3	44	80
OSF11	3	3	6	65	74
OSF12	3	6	3	59	82
OSF13	6	6	6	49	78
OSF14	6	6	6	47	83
OSF15	3	9	6	44	86
OSF16	6	3	3	42	83
OSF17	6	9	9	43	77

The formulation optimization of Olmesartan sublingual tablets using the Box–Behnken Design (BBD) focused on three critical formulation variables—Sodium Starch Glycolate (SSG), Crospovidone (CP), and Croscarmellose Sodium (CCS)—to evaluate their individual and combined effects on disintegration time (DT) and cumulative drug release (CDR) (Patel *et al.*, 2020).

Statistical analysis demonstrated that the quadratic model provided the best fit for the experimental data, showing excellent correlation between predicted and observed values. The adjusted R^2 and predicted R^2 values for disintegration time were 0.9632 and 0.8958, respectively, confirming the model's reliability and predictive capability. In contrast, the linear and two-factor interaction (2FI) models were statistically significant but less accurate, while the cubic model was aliased and therefore excluded from further analysis. Analysis of variance (ANOVA) identified SSG, CP, and the interaction between CP and CCS, along with the quadratic terms of all three factors, as significant contributors to the variation in disintegration time. The non-significant lack of fit indicated that the selected quadratic model adequately represented the experimental data. Moreover, an Adeq Precision value of 22.11 confirmed a strong signal-to-noise ratio, ensuring the model's robustness and suitability for response prediction (Sharma *et al.*, 2019; Patel & Desai, 2021).

The resulting polynomial equations, derived in both coded and actual terms, provided quantitative insights into how variations in superdisintegrant concentrations influenced tablet disintegration behavior. These outcomes established a statistically sound foundation for controlling formulation parameters to achieve consistent product quality and performance (Kumar & Singh, 2022).

The 3D response surface and corresponding 2D contour plots (Figure 2) clearly demonstrated that the disintegration time (DT) decreased progressively with increasing concentrations of Sodium Starch Glycolate (SSG) and Crospovidone (CP) when examined individually. Among these variables, SSG exerted the most pronounced influence, attributed to its rapid swelling upon hydration, which facilitates internal tablet rupture and dispersion.

CP also contributed substantially through its capillary and wicking action, which enhanced moisture penetration and matrix disintegration (Sharma & Patel, 2020; Verma *et al.*, 2021).

In contrast, Croscarmellose Sodium (CCS) exhibited a comparatively lesser impact on DT when evaluated as an independent variable. However, the interaction terms in the statistical model revealed that CCS synergistically enhanced the disintegration efficiency when combined with SSG or CP, most likely by improving matrix porosity and promoting water diffusion throughout the tablet structure.

These findings were consistent with the ANOVA results, which emphasized the significant interactive and quadratic effects among the superdisintegrants (Table 4). The combined action of these excipients was thus identified as critical for minimizing DT and improving the overall performance and patient acceptability of the sublingual tablets (Kumar & Singh, 2019; Patel *et al.*, 2020; Deshmukh & Rao, 2021).

Table 4: ANOVA for Quadratic Model

ANOVA for Quadratic model Mean ± Standard Deviation (SD)													
Response 1: Disintegration Time							**Response 2: Cumulative % Drug Release**						
Source	**Sum of Squares**	**df**	**Mean Square**	**F-value**	**p-value**		**Source**	**Sum of Squares**	**df**	**Mean Square**	**F-value**	**p-value**	
Model	3146.03	9	349.56	47.51	< 0.0001	significant	**Model**	399.79	9	44.42	13.85	0.0011	significant
A-SSG	1458	1	1458	198.17	< 0.0001		A-SSG	120.13	1	120.13	37.46	0.0005	
B-CP	722	1	722	98.14	< 0.0001		B-CP	190.13	1	190.13	59.28	0.0001	
C-CCS	8	1	8	1.09	0.3317		C-CCS	40.5	1	40.5	12.63	0.0093	
AB	6.25	1	6.25	0.8495	0.3874		AB	1	1	1	0.3118	0.594	
AC	2.25	1	2.25	0.3058	0.5975		AC	0.25	1	0.25	0.078	0.7882	
BC	210.25	1	210.25	28.58	0.0011		BC	2.25	1	2.25	0.7016	0.4299	
A^2	63.22	1	63.22	8.59	0.022		A^2	33.01	1	33.01	10.29	0.0149	
B^2	410.59	1	410.59	55.81	0.0001		B^2	6.06	1	6.06	1.89	0.2115	
C^2	199.01	1	199.01	27.05	0.0013		C^2	8.85	1	8.85	2.76	0.1406	
Residual	51.5	7	7.36				**Residual**	22.45	7	3.21			
Lack of Fit	17.5	3	5.83	0.6863	0.6058	not significant	Lack of Fit	13.25	3	4.42	1.92	0.2679	not significant
Pure Error	34	4	8.5				Pure Error	9.2	4	2.3			
Cor Total	3197.53	16					**Cor Total**	422.24	16				

The 3D response surface and 2D interaction plots (Figure 3) provided detailed insights into the combined effects of the superdisintegrants on the cumulative drug release (CDR) of the sublingual tablets. Each plot illustrates the interaction between two excipients at a time—SSG vs. CP, SSG vs. CCS, and CP vs. CCS—while maintaining the third variable at its central level (Sharma *et al.*, 2018).

The convex surface profiles observed for these combinations indicate a positive interaction among the variables. The combination of SSG and CP produced the most pronounced effect, leading to a marked increase in drug release. This can be attributed to the synergistic mechanism wherein the swelling behavior of SSG complements the wicking and capillary action of CP, resulting in rapid matrix hydration and drug diffusion. However, a plateau effect was observed at higher concentrations, suggesting saturation of the disintegration capacity beyond the optimal range.

When SSG and CCS were combined, SSG demonstrated a stronger positive influence on drug release, while CCS contributed modestly by improving matrix porosity. In the CP and CCS combination, CP exhibited greater control over drug-release kinetics due to its porous morphology and fast water uptake, with only minor interactive influence from CCS.

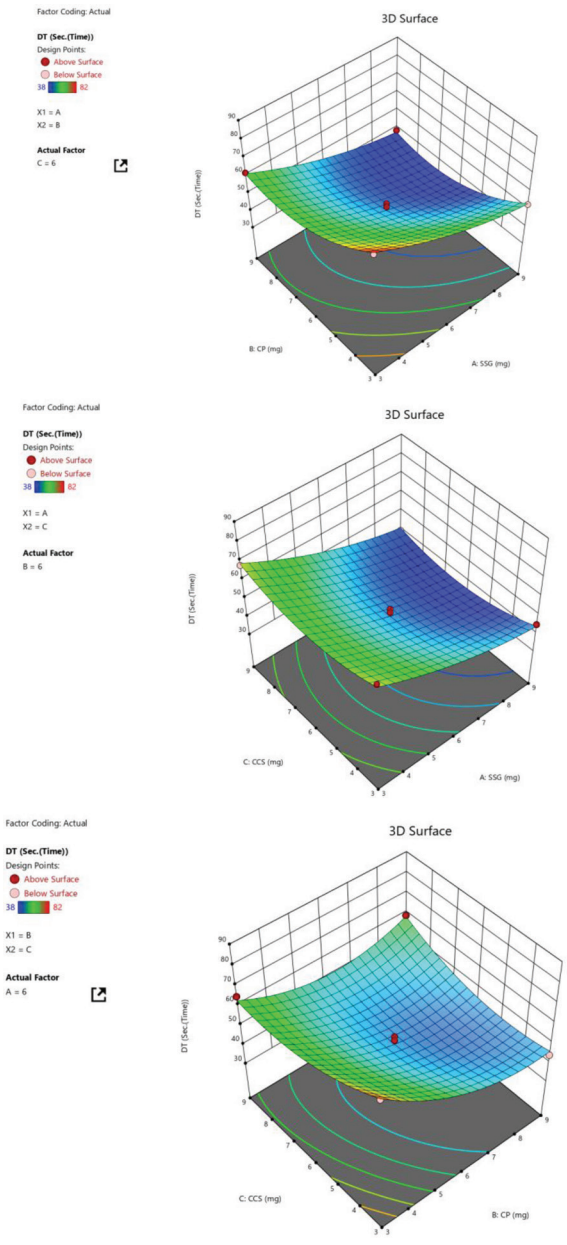


Figure 2: Regression Model and 3D Response Surface Plots for Disintegration Time (DT)

Overall, these contour analyses confirmed that SSG and CP were the most influential variables governing drug release, acting both independently and synergistically to accelerate tablet dispersion and dissolution (Kumar & Patel, 2019; Singh *et al.*, 2020).

3.2. Optimisation of Olmesartan Sublingual Tablets

The results of the optimized formulation, designated as OOSF-18, were obtained through the Quality by Design (QbD) approach employing the Box–Behnken Design (BBD). After analyzing the design space, the optimum formulation parameters were determined, and the corresponding coded values were generated from the response surface model. Statistical evaluation confirmed a strong model fit, validating its suitability for accurate prediction of the selected responses.

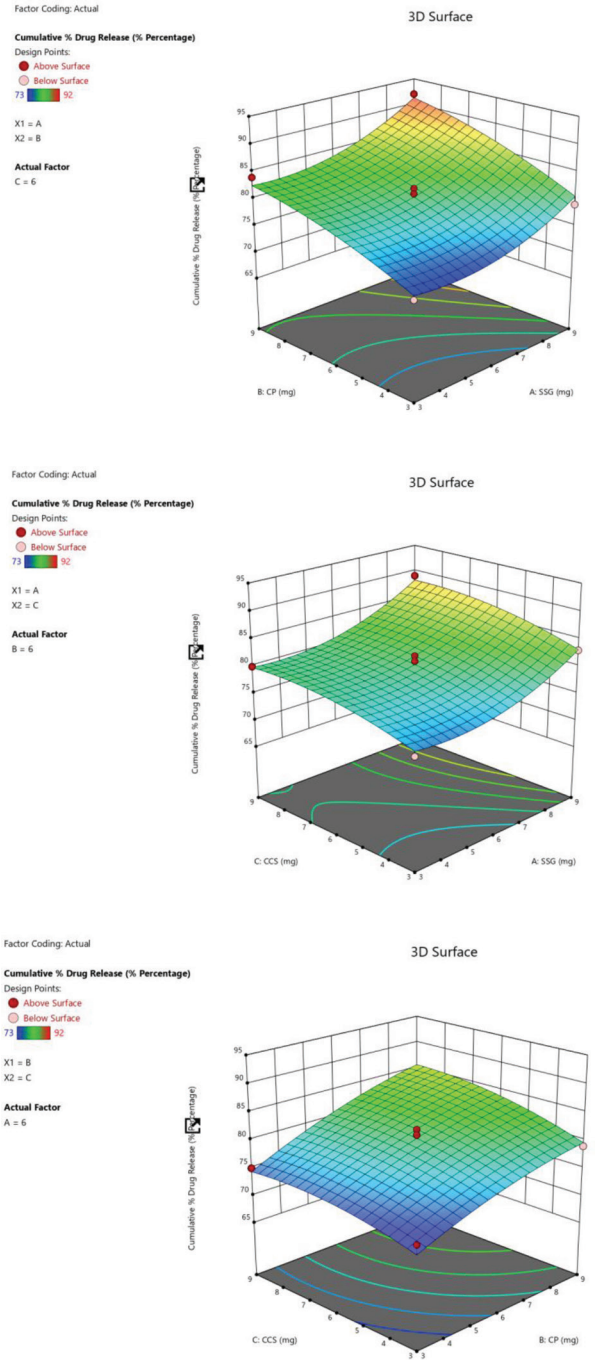


Figure 3: 3D Response Surface Plots for Drug release

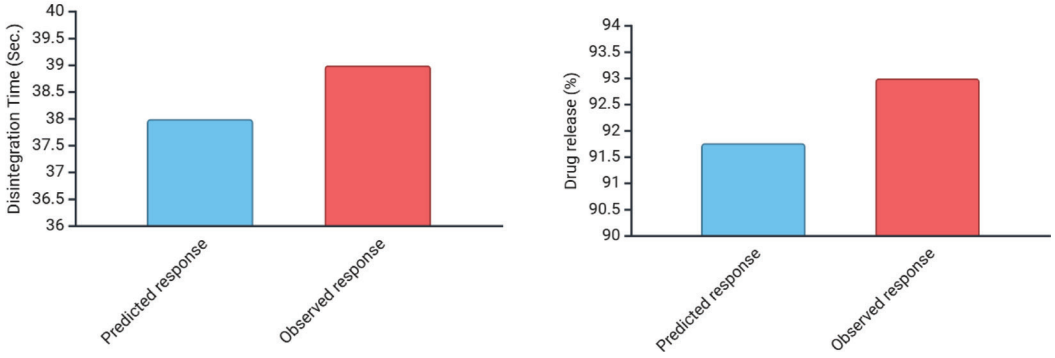
To confirm the reliability of the model, confirmatory experiments were performed in triplicate under the predicted optimal conditions. The optimization constraints included the predefined goals, upper and lower limits, and relative importance assigned to each independent variable—Sodium Starch Glycolate (SSG), Crospovidone (CP), and Croscarmellose Sodium (CCS)—as well as to the dependent responses, disintegration time (DT) and cumulative drug release (CDR).

The optimized formulation predicted a DT of 38 seconds and a CDR of 91.77%, with a desirability value of 0.994, indicating an excellent balance among the studied responses. The experimental validation of the optimized batch produced results that closely matched the predicted values, with a percentage prediction error of 2.63% for DT and 1.32% for CDR, both well within the acceptable deviation of less than 5%.

The detailed composition of the optimized formulation (OOSF-18) is presented in Table 5, while Figure 4 compares the predicted and experimental responses. The close agreement between these values confirms the accuracy, reproducibility, and robustness of the developed formulation, thereby validating the reliability of the QbD-based optimization strategy.

Table 5: Results of Composition of Optimized Formulation of OOSF-18

S.no	Ingredients	Quantity (mg) Mean ± Standard Deviation (SD)
1	Olmesartan	40
2	SSG	9.000
3	CP	8.773
4	CCS	6.436
5	MCC	15
6	Mannitol	66.57
7	Aspartame	0.66
8	Talc	3.33
Total Weight		150



Variables	Predicted response	Observed response	% Predicted error	Acceptance criteria for % PE
Disintegration Time (Sec.)	38.000	39.000	2.631	Less than 5%
Drug release (%)	91.768	93	1.324	Less than 5%

Figure 4: Correlation between the Predicted and Experimental Values for Disintegration Time and Cumulative Drug Release, Demonstrating Strong Agreement between the Model Predictions and Observed Results

The in vitro drug release profiles of the optimized formulation (OOSF-18) and the marketed Olmesartan tablet are compared in Figure 5. Figure 6 and Table 6. The optimized formulation exhibited a rapid and consistent increase in cumulative drug release (CDR), achieving 93% within 15 minutes, whereas the marketed tablet showed a comparatively slower dissolution rate, reaching 75.45% CDR at the same time point. The marked difference in release kinetics indicates that the optimized sublingual formulation enables faster disintegration and enhanced dissolution efficiency, particularly at the initial sampling intervals, which is desirable for rapid onset of therapeutic action.

The results of the ex vivo permeation study are presented in Figure 5 and Figure 6. The permeation profile of OOSF-18 through porcine buccal mucosa demonstrated a steady and substantial increase in drug diffusion, starting from 0% at time zero and reaching 89.76% within 10 minutes. This efficient permeation reflects the formulation's ability to facilitate rapid transmucosal transport, confirming its potential to bypass gastrointestinal degradation and hepatic first-pass metabolism.

Collectively, the in vitro and ex vivo findings substantiate that the optimized sublingual formulation

(OOSF-18) possesses superior drug release and permeation characteristics compared to the conventional oral tablet, thereby supporting its potential for enhanced bioavailability and faster therapeutic onset in clinical application (Table 7).

Table 6: In Vitro Drug Release Comparison of Optimized and Marketed Formulation

Time (Min.)	OOSF-18 % CDR Mean ± Standard Deviation (SD)	Marketed Tablet % CDR Mean ± Standard Deviation (SD)
0	0	0
1	22.45	6.12
2	37.89	11.35
3	51.12	16.88
4	62.78	22.43
5	72.34	28.67
6	79.56	34.12
8	86.21	41.67
9	89.45	46.89
10	91.23	52.34
11	92.12	57.78
12	92.78	62.45
13	92.98	66.23
14	93.00	71.11
15	93.00	75.45

Table 7: Results of Ex Vivo Permeation Study of OOSF-18

Time (Min.)	Drug Permeated (%) Mean ± Standard Deviation (SD)
0	0
1	7.90%
2	13.12%
3	24.29%
4	31.58%
5	44.98%
6	58.73%
7	70.48%
8	78.90%
9	84.37%
10	89.76%

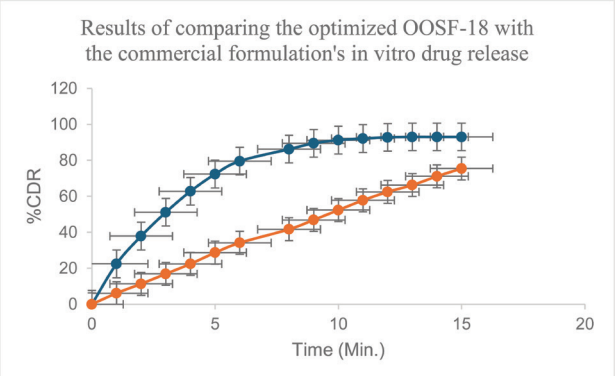


Figure 5: Results of Comparing the Optimized OOSF-18 with the Commercial Formulation's In Vitro Drug Release

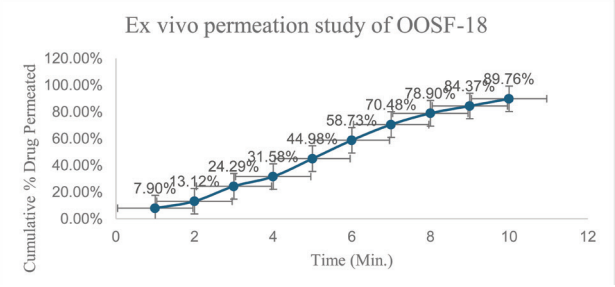


Figure 6: Ex Vivo Permeation Study of OOSF-18

4. Summary and Conclusion

The present research successfully established a systematic Quality by Design (QbD) approach for the formulation, optimization, and evaluation of a fast-dissolving sublingual tablet of Olmesartan medoxomil (OOSF-18) aimed at improving bioavailability and therapeutic efficiency in the management of hypertension and heart failure. By employing a Box–Behnken Design (BBD), the study scientifically explored the influence of three critical formulation factors—Sodium Starch Glycolate (SSG), Crospovidone (CP), and Croscarmellose Sodium (CCS)—on two essential quality attributes: disintegration time (DT) and cumulative drug release (CDR).

The experimental results and statistical analyses revealed that the quadratic model best represented the relationship between formulation variables and the responses, with excellent model fitness (adjusted R^2 = 0.9632; predicted R^2 = 0.8958) and non-significant lack of fit, confirming the robustness of the model. Among the three superdisintegrants, SSG exhibited the most significant effect on reducing disintegration time due to its high swelling capacity, followed by CP, which acted through capillary wicking. CCS contributed synergistically, enhancing overall water uptake and matrix disintegration when used in combination with the other disintegrants.

The optimized formulation (OOSF-18), consisting of 9 mg SSG, 9 mg CP, and 6.44 mg CCS, achieved a disintegration time of 38 seconds and a cumulative drug release of 91.77% within 15 minutes, meeting the design goals for rapid onset and complete dissolution. The desirability function value of 0.994 indicated the robustness and high predictive accuracy of the optimized model. The experimental results closely matched the predicted outcomes, with minimal prediction error (<5%), demonstrating strong reproducibility of the QbD process.

Further characterization confirmed that the optimized tablets exhibited uniform weight, adequate hardness, low friability, and rapid wetting, signifying good mechanical integrity and manufacturing reproducibility. The in vitro dissolution profile of the optimized formulation was markedly superior to that of the marketed conventional tablet, which released only 75.45% of the drug in the same timeframe. The enhanced dissolution behavior of OOSF-18 can be attributed to the optimized superdisintegrant blend and improved wettability facilitated by mannitol and microcrystalline cellulose.

The ex vivo permeation study, conducted using a Franz diffusion cell with porcine buccal mucosa, demonstrated an impressive 89.76% drug permeation within 10 minutes, confirming the formulation's ability to enable rapid transmucosal transport. This result highlights the successful design of a system capable of bypassing gastrointestinal degradation and hepatic first-pass metabolism, thereby improving systemic drug availability.

Overall, this investigation validates the effectiveness of integrating QbD principles with experimental design tools for developing optimized pharmaceutical dosage forms. The approach not only enhances understanding of formulation–response relationships but also ensures process control, robustness, and product consistency, aligning with modern regulatory expectations under ICH Q8–Q10 guidelines.

From a clinical perspective, the developed Olmesartan sublingual tablet presents a promising alternative to conventional oral formulations, offering several patient-centric benefits such as rapid onset of antihypertensive action, ease of administration without water, and improved compliance, particularly for elderly or dysphagic patients. Moreover, the rapid drug release and absorption through the sublingual mucosa suggest potential utility in emergency management of hypertensive crises, where prompt pharmacological action is required.

In conclusion, the study demonstrates that a QbD-guided design strategy can be effectively applied to formulate a fast-acting, reproducible, and clinically relevant sublingual drug delivery system for Olmesartan. The integrated experimental–statistical approach established here can serve as a framework for future formulation optimization studies targeting improved bioavailability and therapeutic efficiency of drugs with poor oral absorption.

Abbreviations

OSF: Olmesartan Sublingual Formulation; **OOSF**: Optimized Olmesartan Sublingual Formulation; **SSG**: Sodium Starch Glycolate; **CP**: Crospovidone; **CCS**: Croscarmellose Sodium.

Acknowledgment

The authors express their sincere gratitude to all laboratory staff, technical assistants, and institutional administrators who provided valuable support throughout this research work. Their cooperation and assistance were essential in completing the study.

Authorship Contribution

Deepak Joshi: Supervision, guidance in data interpretation, and critical review of the manuscript. **Pawandeep Shukla** and **Naveen Kumar Choudhary:** Oversight of formulation development, validation of analytical results, and contribution to manuscript revision.

Ethical Approval

This study did not involve human participants or animal subjects; therefore, ethical approval was not required.

Funding

No funding was received for this study.

Declarations

The authors declare that the work presented in this manuscript is original and has not been published or submitted elsewhere.

Conflict of Interest

There is no conflict of interest regarding this work.

References

Abouhussein, D. M. N., El Nabarawi, M. A., Shalaby, S. H., & El-Bary, A. A. (2021). Sertraline-cyclodextrin complex orodispersible sublingual tablet:

Optimization, stability, and pharmacokinetics. *Journal of Pharmaceutical Innovation, 16*(1). https://doi.org/10.1007/s12247-019-09416-1

Ahirrao, S. P., Bhambere, D. S., Ahire, E. D., Dashputre, N. L., Kakad, S. P., & Laddha, U. D. (2023). Formulation and evaluation of Olmesartan medoxomil nanosuspension. *Materials Today: Proceedings*. https://doi.org/10.1016/j.matpr.2023.06.260

Alali, A. S., Aldawsari, M. F., Alalaiwe, A., Almutairy, B. K., Al-Shdefat, R., Walbi, I. A., & Fayed, M. H. (2021). Exploitation of design-of-experiment approach for design and optimization of fast-disintegrating tablets for sublingual delivery of sildenafil citrate with enhanced bioavailability using fluid-bed granulation technique. *Pharmaceutics, 13*(6). https://doi.org/10.3390/pharmaceutics13060870

Ali, R., Mehta, P., Monou, P. K., Arshad, M. S., Panteris, E., Rasekh, M., Singh, N., Qutachi, O., Wilson, P., Tzetzis, D., Chang, M. W., Fatouros, D. G., & Ahmad, Z. (2020). Electrospinning/electrospraying coatings for metal microneedles: A design of experiments (DoE) and quality by design (QbD) approach. *European Journal of Pharmaceutics and Biopharmaceutics, 156*, 20–39. https://doi.org/10.1016/j.ejpb.2020.08.023

Al-Madhagi, W., Albarakani, A. A., Alhag, A. K., Saeed, Z. A., Noman, N. M., & Mohamed, K. (2017). Formulation and evaluation of new glimepiride sublingual tablets. *Journal of Pharmaceutics, 2017*, 1–5. https://doi.org/10.1155/2017/3690473

Alyami, H. S., Ibrahim, M. A., Alyami, M. H., Dahmash, E. Z., Almeanazel, O. T., Algahtani, T. S., Alanazi, F., & Alshora, D. H. (2021). Formulation of sublingual promethazine hydrochloride tablets for rapid relief of motion sickness. *Saudi Pharmaceutical Journal, 29*(5). https://doi.org/10.1016/j.jsps.2021.04.011

Amson, H., Lasselin, P., Naegels, B., Bracho, G. F. P., Aubrun, F., & Dziadzko, M. (2021). Usability evaluation of sufentanil sublingual tablet analgesia in patients following enhanced recovery after surgery. *Journal of Comparative Effectiveness Research, 10*(9). https://doi.org/10.2217/cer-2020-0239

Anraku, M., Tabuchi, R., Goto, M., Iohara, D., Mizukai, Y., Maezaki, Y., Michihara, A., Kadowaki, D., Otagiri, M., & Hirayama, F. (2019). Design and evaluation of an extended-release Olmesartan tablet using chitosan/cyclodextrin composites. *Pharmaceutics, 11*(2), 82. https://doi.org/10.3390/pharmaceutics11020082

Ashok Mahajan, Parmar, J., Patel, P., Koradiya, S., & Mehta, F. (2022). Formulation, evaluation and optimization of sublingual tablet of clonidine HCl. *International Journal of Life Science and Pharma Research*. https://doi.org/10.22376/ijpbs/lpr.2020.10.2.p1-8

Atia, N. N., Tawfeek, H. M., Rageh, A. H., El-Zahry, M. R., Abdelfattah, A., & Younis, M. A. (2019). Novel sublingual tablets of atorvastatin calcium/trimetazidine hydrochloride combination: HPTLC quantification, in vitro formulation and characterization. *Saudi Pharmaceutical Journal, 27*(4). https://doi.org/10.1016/j.jsps.2019.02.001

Chordiya, M., Gangurde, H., & Sancheti, V. (2019). Quality by design: A roadmap for quality pharmaceutical products. *Journal of Reports in Pharmaceutical Sciences, 8*(2), 289. https://doi.org/10.4103/jrptps.jrptps_2_18

Choudhary, N. K., & Joshi, D. (2025). Formulation and optimization of Olmesartan sublingual tablets using Box–Behnken design: A QbD and ex vivo study. *Journal of Pharmaceutical Innovation, 20*(6), 223.

Costa, C. P., Cunha, S., Moreira, J. N., Silva, R., Gil-Martins, E., Silva, V., Azevedo, L., Peixoto, A. F., Sousa Lobo, J. M., & Silva, A. C. (2021). QbD optimization of diazepam-loaded nanostructured lipid carriers for nose-to-brain delivery: Toxicological effect of surface charge on human neuronal cells. *International Journal of Pharmaceutics, 607*, 120933. https://doi.org/10.1016/j.ijpharm.2021.120933

Cunha, S., Costa, C. P., Moreira, J. N., Sousa Lobo, J. M., & Silva, A. C. (2020). Using the QbD approach to optimize formulations of lipid nanoparticles and nanoemulsions: A review. *Nanomedicine: Nanotechnology, Biology and Medicine, 28*, 102206. https://doi.org/10.1016/j.nano.2020.102206

Dhawan, S., & Nanda, S. (2023). Implementation of QbD concept for the development of emulsion-based nanotailored gel for improved antiphotoageing potential of silymarin. *Journal of Drug Delivery Science and Technology, 81*, 104201. https://doi.org/10.1016/j.jddst.2023.104201

Dubey, I., Joshi, D., Walvekar, A., Pandey, P. K., & Singh Chouhan, P. (2025). QbD-based optimization of fast-dissolving sublingual tablets of Valsartan. *Journal of Pharmaceutical Innovation, 20*(2), 75.

Gahlawat, N., Verma, R., & Kaushik, D. (2020). Application of D-optimal mixture design for development and optimization of Olmesartan medoxomil loaded SMEDDS. *Current Drug Therapy, 15*(5), 548–560. https://doi.org/10.2174/1574885515666200212094039

Genedy, S., Khames, A., Hussein, A., & Sarhan, H. (2018). Hydralazine HCl rapidly disintegrating sublingual tablets: Simple dosage form of higher bioavailability and enhanced clinical efficacy for rapid control of hypertensive preeclampsia. *Drug Design, Development and Therapy, 12*. https://doi.org/10.2147/DDDT.S173326

González, R., Peña, M. Á., & Torrado, G. (2022). Formulation and evaluation of Olmesartan medoxomil tablets. *Compounds, 2*(4), 334–352. https://doi.org/10.3390/compounds2040028

Gunda, R. K. (2018). Design, development, and in vitro evaluation of sustained-release tablet formulations of Olmesartan medoxomil. *MOJ Drug Design Development & Therapy, 2*(3). https://doi.org/10.15406/mojddt.2018.02.00043

Hasnain, M. S., Ahmed, S. A., Khatoon, A., Afzal, M., Ansari, M. T., Khatoon, S., Tabish, M., Al-Marshad, F. M., & Nayak, A. K. (2021). Pharmaceutical product development: A QbD approach. In *Advances and Challenges in Pharmaceutical Technology: Materials, Process Development and Drug Delivery Strategies.* 131–146). https://doi.org/10.1016/B978-0-12-820043-8.00017-7

Joshi, D., & Choudhary, N. K. (2023). Enhancing sublingual tablet quality through QbD: Current trends and insights. *Precision Nanomedicine, 6*(3). https://doi.org/10.33218/001c.88223

Joshi, D., & Choudhary, N. K. (2024). Implementation of QbD for sublingual antihypertensive drugs. *Journal of Pharmaceutical Innovation, 19*(3), 20. https://doi.org/10.1007/s12247-024-09832-y

Kadry, H., Omar, A., Sherbiny, F., & Zaky, A. (2016). Design and optimization of captopril sublingual tablets: Enhancement of pharmacokinetic parameters in humans. *Al-Azhar Journal of Pharmaceutical Sciences, 53*(1), 90–107. https://doi.org/10.21608/ajps.2016.6889

Kayrak-Talay, D., Dale, S., Wassgren, C., & Litster, J. (2013). Quality by design for wet granulation in pharmaceutical processing: Assessing models for a priori design and scaling. *Powder Technology, 240*, 7–18. https://doi.org/10.1016/j.powtec.2012.07.013

Khan, A. B., Kingsley, T., & Caroline, P. (2017). Sublingual tablets and the benefits of the sublingual route of administration. *Journal of Pharmaceutical Research, 16*(3). https://doi.org/10.18579/jpcrkc/2017/16/3/118766

Lee, J., Kim, A., Yu, K.-S., Chung, J.-Y., Yim, S.-V., & Kim, B.-H. (2015). Pharmacokinetics and bioequivalence of two different 20 mg Olmesartan tablets. *Translational and Clinical Pharmacology, 23*(2), 49. https://doi.org/10.12793/tcp.2015.23.2.49

Mayet-Cruz, L., Rodríguez, J. M., & Jung-Cook, H. (2021). Development of a dissolution test for melatonin sublingual tablets using a factorial experimental design. *Farmacia, 69*(1). https://doi.org/10.31925/farmacia.2021.1.23

Melson, T. I., Boyer, D. L., Minkowitz, H. S., Turan, A., Chiang, Y. K., Evashenk, M. A., & Palmer, P. P. (2014). Sufentanil sublingual tablet system vs. intravenous patient-controlled analgesia with morphine for postoperative pain control. *Pain Practice, 14*(8). https://doi.org/10.1111/papr.12238

Mishra, V., Thakur, S., Patil, A., & Shukla, A. (2018). Quality by design approaches in current pharmaceutical set-up. *Expert Opinion on Drug Delivery, 15*(8), 737–758. https://doi.org/10.1080/17425247.2018.1504768

Mujtaba, A., Kohli, K., Ali, J., & Baboota, S. (2013). Formulation and evaluation of sublingual drug delivery of ondansetron hydrochloride tablets. *Advanced Science, Engineering and Medicine, 5*(4), 349–354. https://doi.org/10.1166/asem.2013.1263

Nasr, A., Gardouh, A., & Ghorab, M. (2016). Novel solid self-nanoemulsifying drug delivery system (S-SNEDDS) for oral delivery of Olmesartan medoxomil: Design, formulation, pharmacokinetics and bioavailability. *Pharmaceutics, 8*(3), 20. https://doi.org/10.3390/pharmaceutics8030020

Nikam, R. S., Borkar, S. P., Jadhav, P. D., Yadav, V. D., & Jadhav, A. V. (2020). Sublingual tablets: An overview. *International Journal of Scientific Research in Science and Technology*. https://doi.org/10.32628/ijsrst207357

Nooli, M., Chella, N., Kulhari, H., Shastri, N. R., & Sistla, R. (2017). Solid lipid nanoparticles for oral delivery of Olmesartan medoxomil: Formulation, optimization and in vivo evaluation. *Drug Development and Industrial Pharmacy, 43*(4), 611–617. https://doi.org/10.1080/03639045.2016.1275666

Pallagi, E., Ambrus, R., Szabó-Révész, P., & Csóka, I. (2015). Adaptation of the QbD concept in early pharmaceutical development of an intranasal nanosized formulation. *International Journal of Pharmaceutics, 491*(1–2), 384–392. https://doi.org/10.1016/j.ijpharm.2015.06.018

Panwar, M. S., Pal, P., & Joshi, D. (2024). Advances in green synthesis of silver nanoparticles: Sustainable approaches and applications. *Journal of Drug Delivery and Therapeutics, 14*(11), 177–184. https://doi.org/10.22270/jddt.v14i11.6854

Patel, J., Dhingani, A., Tilala, J., Raval, M., & Sheth, N. (2014). Formulation and development of self-nanoemulsifying granules of Olmesartan medoxomil for bioavailability enhancement. *Particulate Science and Technology, 32*(3), 274–290. https://doi.org/10.1080/02726351.2013.855686

Pawar, A., Londhe, V. Y., & Bhadale, R. S. (2022). Formulation and characterization of sublingual tablets of Iloperidone prepared by microenvironmental pH regulated approach. *Journal of Pharmaceutical Innovation, 17*(1). https://doi.org/10.1007/s12247-020-09502-9

Prajapati, S. T., Joshi, H. A., & Patel, C. N. (2013). Preparation and characterization of self-microemulsifying drug delivery system of Olmesartan medoxomil for bioavailability improvement. *Journal of Pharmaceutics, 2013*, 1–9. https://doi.org/10.1155/2013/728425

Pramod, K., Tahir, M., Charoo, N., Ansari, S., & Ali, J. (2016). Pharmaceutical product development: A quality by design approach. *International Journal of Pharmaceutical Investigation, 6*(3), 129. https://doi.org/10.4103/2230-973X.187350

Raut, M. B., & Gedam, P. (2020). Overview on sublingual tablets. *International Journal of Research in Pharma and Pharmaceutical Sciences, 1*(1).

Rawas-Qalaji, M., Rachid, O., Mendez, B. A., Losada, A., Simons, F. E. R., & Simons, K. J. (2015). Adrenaline (epinephrine) microcrystal sublingual tablet formulation: Enhanced absorption in a preclinical model. *Journal of Pharmacy and Pharmacology, 67*(1). https://doi.org/10.1111/jphp.12312

Sangshetti, J. N., Deshpande, M., Zaheer, Z., Shinde, D. B., & Arote, R. (2017). Quality by design approach: Regulatory need. *Arabian Journal of Chemistry, 10*, S3412–S3425. https://doi.org/10.1016/j.arabjc.2014.01.025

Shelke, V., & Mutha, S. (2020). Formulation and evaluation of lansoprazole sublingual tablet. *Journal of Research in Pharmacy, 24*(2). https://doi.org/10.35333/jrp.2020.143

Simão, J., Chaudhary, S. A., & Ribeiro, A. J. (2023). Implementation of QbD for development of bilayer tablets. *European Journal of Pharmaceutical Sciences, 184*, 106412. https://doi.org/10.1016/j.ejps.2023.106412

Singh, M. K., Mazumder, R., Padhi, S., & Singh, D. K. (2022). Formulation development and optimization of bioenhanced sublingual tablets of rizatriptan benzoate to combat migraine. *Indian Journal of Pharmaceutical Education and Research, 56*(2). https://doi.org/10.5530/ijper.56.2s.91

Soni, N., Joshi, D., Jain, V., & Pal, P. (2022). A review on applications of bilayer tablet technology for drug combinations. *Journal of Drug Delivery and Therapeutics, 12*(1), 222–227. https://doi.org/10.22270/jddt.v12i1.5206

Than, Y. M., & Titapiwatanakun, V. (2021). Tailoring immediate release FDM 3D printed tablets using a QbD approach. *International Journal of Pharmaceutics, 599*, 120402. https://doi.org/10.1016/j.ijpharm.2021.120402

Verma, H., Pal, P., & Joshi, D. (2022). Formulation, development and evaluation of invasomes loaded gel for fungal treatment. *Scholars Academic Journal of Pharmacy, 11*(7), 105–108. https://doi.org/10.36347/sajp.2022.v11i07.001

Verma, P., & Yadav, K. S. (2023). QbD-enabled and Box–Behnken design-assisted approach for formulation of tranexamic acid loaded stratum corneum lipid liposomes. *Journal of Drug Delivery Science and Technology, 86*, 104571. https://doi.org/10.1016/j.jddst.2023.104571

Won, D. H., Park, H., Ha, E. S., Kim, H. H., Jang, S. W., & Kim, M. S. (2021). Optimization of bilayer tablet manufacturing process for fixed dose combination based on QbD. *International Journal of Pharmaceutics, 605*, 120838. https://doi.org/10.1016/j.ijpharm.2021.120838

Yu, L. X., Amidon, G., Khan, M. A., Hoag, S. W., Polli, J., Raju, G. K., & Woodcock, J. (2014). Understanding pharmaceutical quality by design. *AAPS Journal, 16*(4), 771–783. https://doi.org/10.1208/s12248-014-9598-3

Zagalo, D. M., Silva, B. M. A., Silva, C., Simões, S., & Sousa, J. J. (2022). A QbD approach in pharmaceutical development of lipid-based nanosystems: A systematic review. *Journal of Drug Delivery Science and Technology, 70*, 103207. https://doi.org/10.1016/j.jddst.2022.103207