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Original Article

Quality by Design Based Development and Optimization of Orodispersible Tablets of Propranolol Hydrochloride

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ABSTRACT

Purpose: This study aims to develop orodispersible tablets that dissolve rapidly in the mouth, using a tasteless combination of Kyron T-314 and propranolol hydrochloride, and to apply the Quality by Design methodology. **Materials and Methods:** The QbD method was used to understand the process better and expand the design space. This included using a quality target product profile and critical quality attributes, as well as conducting risk assessments. The research goal was to use Orodispersible tablets to speed the onset of action of propranolol hydrochloride. A 32-factorial design was used to develop Orodispersible tablets containing propranolol hydrochloride. In this design, two independent variables, HPMC as a binder and Kyron T-314 as a super disintegrant, were used at each level. **Results:** Response surface methodology successfully optimized the formulation using HPMC and Kyron T-314 as independent variables. The optimized formulation had a wetting time of 11.85 s, a friability of 0.46%, and 91.31% drug release within 15 min (Q15). The developed models demonstrated outstanding goodness of fit (R^2=0.9892-0.9982), indicating the optimization process's reliability. Experimental validation revealed a good fit between the predicted and observed responses, supporting the reliability of the optimization model. **Conclusion:** Validation of the optimisation study confirmed the robustness of response surface methodology as a predictive tool. The study illustrates the optimal formulation of Orodispersible tablet containing propranolol hydrochloride through the Quality by Design methodology.

Keywords: Critical Material Attributes, Critical Quality Attributes, Drug Resin Complex, Quality by Design.

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INTRODUCTION

QbD is a strategy being implemented in many industries such as pharmaceuticals, manufacturing and product development to ensure the continuous supply of high-quality products. It uses a proactive and systematic method of integrating quality aspects in the life cycle of a product from design to production. This is facilitated by strategic planning and utilisation of existing data. Although there are challenges associated with risk management, QbD has demonstrated its effectiveness in reducing the variability of the final product and anticipating regulatory approval.[1,2] QbD principles are delineated in ICH guidelines, including Q8, Q9, and Q10. These guidelines have provided fundamental frameworks for comprehending QbD. They focus on the importance of scientific principles, risk assessment, and management of the product life cycle through different methodologies.[3,4] When products transition from the early stages of research and development to production, it can be very unpredictable. This is generally because people do not realize the entire reason for failures. QbD is an all-encompassing approach encompassing all steps involved in drug development, production, and delivery.[5,6] Orodispersible Tablets (ODTs) are an innovative technology designed to disintegrate quickly, even without water, within seconds, and provide enhanced convenience for patients. Tablets and capsules may have some difficulties with some patient groups, including the elderly, children, people with mental challenges, and people with swallowing difficulties. To overcome such problems, much work has been done on the development of Orodispersible Tablets (ODTs).[7] For various types of medications, especially therapeutic ones that require rapid peak plasma levels to achieve the desired pharmacological action, Oral Disintegrating Tablets (ODTs) have been developed.[8] Orodispersible tablets disintegrate rapidly in the oral cavity, allowing rapid dispersion before swallowing and thereby improving patient compliance. This increased bioavailability can be seen in several different categories of medications, such as antipsychotics, analgesics, antiallergics, cardiovascular medications, and Erectile Dysfunction (ED)

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medications.[9] While ODTs are convenient for many people, creating them can be difficult, especially if the active ingredient has an unpleasant taste. Flavouring agents, sweeteners, amino acids, polymer coatings, complexation with ion-exchange resins, and inclusion complexes with cyclodextrins are among the strategies used to mask the flavor.[10,11] The drug propranolol hydrochloride blocks all β- adrenergic receptors. Some of the effects of this receptor blocker are making the blood vessels smaller, stopping angiogenic factors like VEGF and bFGF from working, killing endothelial cells, and eliminating the renin-angiotensin-aldosterone system from working. Propranolol hydrochloride exhibits a relatively long duration of action and is generally administered once or twice daily depending on the clinical indication. It is important to note that abrupt discontinuation of propranolol can lead to worsened angina and an increased risk of myocardial infarction. Many drugs, including propranolol, have a salty and bitter taste. To address this issue, Ion Exchange Resins (IER) are employed to create tasteless complexes, either through batch or column processes.[12]

Super disintegrants like Polacrilin potassium, Sodium Starch Glycolate (SSG), and croscarmellose sodium are commonly used to accelerate tablet disintegration. These ingredients rapidly decompose, facilitating the quick disintegration of the tablets.[13,14] A systematic optimization strategy based on Response Surface Methodology (RSM) was employed to simultaneously optimize the concentrations of Kyron T-314 and Hydroxypropyl Methylcellulose (HPMC), with the objective of achieving rapid wetting, minimal friability, and enhanced drug release. Multiple critical quality attributes were optimized simultaneously using a desirability function rather than evaluating formulation variables independently. Statistical model validation, residual diagnostics, overlay plot analysis, and numerical optimization were integrated to establish a robust design space capable of consistently producing tablets with the desired quality attributes. This comprehensive QbD framework provides a scientifically justified formulation strategy and contributes to a better understanding of the combined influence of superdisintegrant and binder concentrations on the performance of propranolol hydrochloride orodispersible tablets. The study aimed to investigate the combined effects of Kyron T-314 and HPMC on the formulation characteristics of propranolol hydrochloride orodispersible tablets, using a 3^2 Central Composite Design (CCD).[15] Therefore, the present study employed a Quality by Design (QbD) approach combined with response surface methodology to optimize propranolol hydrochloride orodispersible tablets using Kyron T-314 as a superdisintegrant and HPMC as a binder, to achieve rapid wetting, low friability, and enhanced drug release.

MATERIALS AND METHODS

Materials

Propranolol hydrochloride from Liberates Chemicals in Surat, Gujarat; Polacrilin potassium (Kyron T- 314) was obtained from Coral Pharmaceutical Pvt. Ltd., in Ahmedabad; Hydroxypropyl methyl cellulose was purchased from Loba Chemicals in Mumbai, India; sodium saccharine, talc, magnesium stearate, and mannitol were obtained from Sigma Laboratories Pvt. Ltd., in Mumbai. The solvents used in this investigation were all laboratory-grade.

Methods

Preparation of Taste Masking Drug Polymeric Complex (DRC)

The resin was immersed in 25 mL of distilled water, where it expanded. The drug was then added to the resin solution. The drug and resin were forcibly mixed using a magnetic stirrer set to maximum speed. Following agitation, the drug-resin slurry was filtered through Whatman filter paper, and the resulting residue was identified as DRC. To remove H+ ions, the complex was rinsed with 75 mL of double-distilled water. Several formulations were designed to optimize key characteristics, including swelling time, stirring duration, and drug-to-resin ratio.[13,15]

Experimental Design

QbD Tools

Quality by design approach for making drug products, a quality target product profile was created to help make tablets that dissolve in the mouth. This was done to enhance patient compliance and achieve the desired therapeutic outcome.[16,17] To meet the QTPP criteria, such as dosage form, drug delivery route of administration, dose, and stability studies, along with critical quality attributes, were identified. These attributes included wetting time, friability, and the amount of drug release within 15 min (Q_{15}).

Experimental Design

A 3^2 CCD was utilized to explore the effects of two primary independent variables, HPMC as a binder and Kyron T 314 as a super disintegrant, on various dependent responses (WT, Fr, Q15). These responses included percentage Fr, WT, and Q_{15} (Sharma S and Singh K 2020). Polynomial equations were formulated to articulate the relationship between the independent variables (HPMC and Kyron T 314) that can be changed to obtain the desired response. The polynomial equation is as follows:

$$Y = b0 + b1\ X1 + b2\ X2 + b3\ X1\ X2 + b4\ X12 + b5\ X22 + b6\ X12\ X2 + b7\ X1X22 \quad (1)$$

In this equation, y is a response variable, and b0 is the mean answer from all thirteen experiment runs. The main independent factors, marked as X1 and X2, show what usually happens when you change just one factor from its lowest to its highest value.

When you only need to do a few tests, the 3^2 Central Composite Design (CCD) is the best way to determine how different variables (main effects) affect each other. In this study, the 3^2 CCD was selected as it offered a more suitable approach due to the absence of prior knowledge regarding response surface values. Therefore, the 3^2 CCD was chosen for the optimization of formulations.[18]

After conducting formulation trials, levels of HPMC at 2.5, 5, and 7.5 mg were selected, while Kyron T-314 levels were set at 5, 7.5, and 10 mg (Table 1). The research involved the creation of thirteen formulations through nine potential combinations, with the central point repeated four times. Mean values were then calculated for subsequent analysis.[19-22] Utilising Design Expert-13 (Version 13.0.5.0, Stat-Ease), the researchers obtained the following results: A significance test was conducted on the model. Four compositions (VC1-VC4) were selected as validating criteria and evaluated using the response surface approach. A thorough comparison was made between the observed and predicted responses.[20]

The optimization objective was to identify the formulation providing the best overall balance among the selected critical quality attributes. Wetting time and friability were assigned the goal of minimization, whereas the percentage drug release at 15 min (Q_{15}) was assigned the goal of maximization. Factor levels were maintained within the investigated experimental ranges, and equal importance was assigned to all responses. The desirability value (D), ranging from 0 to 1, was calculated by combining the individual desirability functions for each response, where a value approaching 1 indicated the highest degree of simultaneous optimization. The formulation exhibiting the maximum desirability was selected as the optimized formulation and subsequently validated experimentally by comparing predicted and observed response values.

Risk-Assessment Analysis

Risk-assessment studies were conducted to find the essential material properties that could affect the drug product's most important quality properties (CQAs) in ODT formulation.[21,22] Using the trial version of Minitab 18 software, an Ishikawa fishbone diagram (Figure 1) was made to make this study easier. A Risk Estimation Matrix (REM) was created to give three different amounts of risk: high, medium, and low. This was done for a qualitative risk assessment. This matrix helped figure out possible cause-and effect links between CMAs and how they might affect the CQAs of ODTs (Tables 2 and Table 3 for more information). A failure mode and effects analysis was also performed to look at risk factors and find failure modes related to the dose form.

$$\text{RPN} = \text{Severity(S)} \times \text{Occurrence (O)} \times \text{Detection (D)}$$

The Risk Priority Number (RPN) was calculated by giving each CMA a rank order score for how bad it was, how often it happened, and how easy it was to find. These ranking scores, which ranged from 1 to 10, were determined based on prior knowledge, experience, and extensive brainstorming exercises.[23,24]

The ICH guidelines Q8 and Q9 define a risk-based approach. This includes assessment of potential hazards relating to different aspects of method development and implementation. These factors could include small differences in method parameters (such as reagents, instruments, analysts and laboratories and environmental parameters [e.g. temperature and humidity]), as well as time. In order to evaluate these risks a variety of techniques

Table 1: 3^2 Central composite design layout, experimental runs, and their actual combinations.

Batch No	Coded Value		Actual Value	
	Factor X1 (HPMC)	Factor X2 (Kyron T 314)	Factor X1 (HPMC) mg	Factor X2 (Kyron T 314) mg
F1	-1	-1	2.5	5
F2	0	-1	5	5
F3	1	-1	7.5	5
F4	-1	0	2.5	7.5
F5	0	0	5	7.5
F6	1	0	7.5	7.5
F7	-1	1	2.5	10
F8	0	1	5	10
F9	1	1	7.5	10
F10	0	0	5	7.5
F11	0	0	5	7.5
F12	0	0	5	7.5
F13	0	0	5	7.5

Note: The concentration ranges of HPMC and Kyron T-314 were selected based on preliminary screening studies.

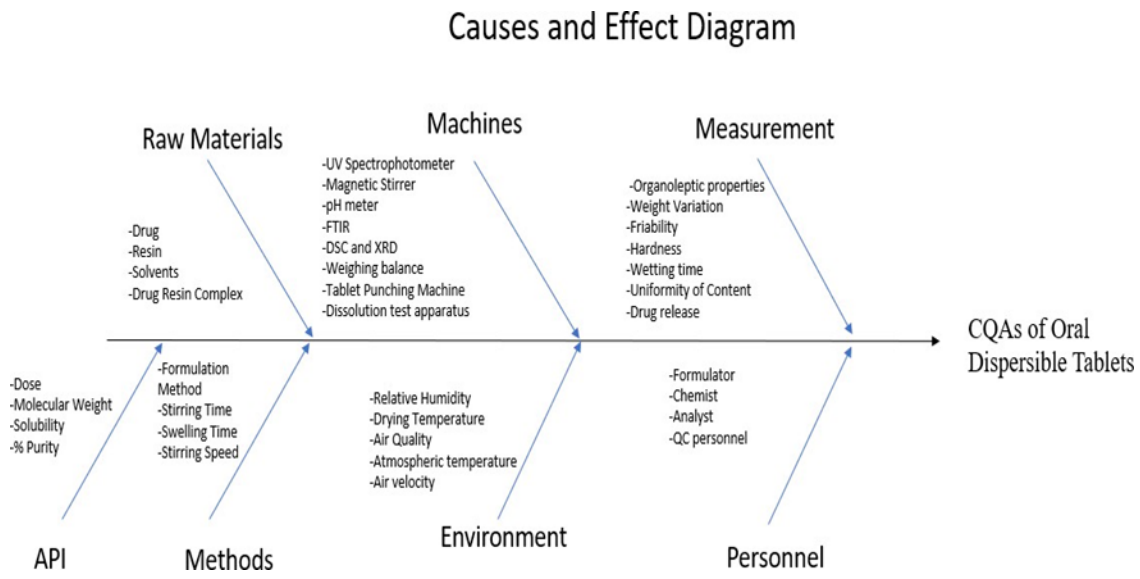


Figure 1: Ishikawa fishbone diagram depicting critical quality attributes for Orodispersible tablet formulations.

Table 2: Risk Estimation Matrix (REM) for initial risk assessment of Orodispersible tablets.

Critical Quality Attributes	Amount of HPMC	Amount of Kyron T 314
Wetting Time (WT)	Medium	Medium
Friability (Fr)	High	High
Drug Release (Q15)	High	High

may be implemented to analyse data and identify potential sources of variability such as experimental design, system analysis and methods. A different strategy may be considered for fit in the event that this strategy is not successful, based on a similar risk evaluation procedure. Three kinds of risk-based approaches are possible: Factors that pose a high level of risk necessitate meticulous management. Examples of critical components of the methodology include sample preparation techniques, data analysis methods, and so forth. In order to ensure reliability and robustness, these factors are generally considered during the development of a method. Potential noise factors: These are factors that have the potential to generate variability, but they are not as critical as high-risk factors. While they may not need much control, they still need to be considered and monitored to minimise their impact on the method. Factors for exploration: These are variables that can be studied experimentally to determine acceptable ranges. Exploring these parameters helps us to improve this approach and make it more robust.[4,25]

Differential Scanning Calorimetry (DSC)

DSC analysis was performed to examine the thermal characteristics of the prepared formulation and ascertain its pure form. The investigations employed an SDT Q 600 V20.9 build 20 DSC, analysing both the pure drug and a drug combination.[26]

X-ray Diffraction Studies

XRD examination of the drug and the formulated tablet was performed using a Shimadzu diffractometer, model XRD-6100, utilising nickel-filtered CuKα radiation with a wavelength of 1.54 Å, at a temperature of 25°C. The scanning range for 2θ extended from 2° to 80° in increments of 0.02°, with the apparatus functioning at 40 kV and 30 mA.[27]

Drug Polymers / Excipients Compatibility Study by using FTIR Spectroscopy

Drug-polymer interactions were analyzed using FTIR (PerkinElmer Spectrum IR, version 10.7.2). Samples were prepared by mixing propranolol hydrochloride with KBr at a 1:100 ratio and scanned over 4000-450 cm^{-1}. The spectra were examined for any shifts or changes indicating physical interactions between the drug and excipients.[28,29]

Formulation of Orodispersible Tablets Using 3^2 Central Composite Designs

The development approach for orally dispersible tablets in batches F1 to F13 started with direct compression, which used a drug resin complex to add 10 mg of propranolol hydrochloride. The diluent was Microcrystalline Cellulose (MCC), with a binder (hydroxypropyl methylcellulose), Polacrilin potassium (Kyron T-314) as the super disintegrant, mannitol as the soothing agent, talc as the anti-adherent, saccharin as the sweetener, and magnesium stearate as the lubricant. Each ingredient was precisely measured, and all components were sifted through a 100# sieve before being blended. The powder mix was then compressed using a single-punch tablet machine (Table 4).

Evaluation of Tablets

Evaluation parameters of Powder Blend

The angle of rest is the steady angle in three dimensions that is measured in relation to the flat base. It can be seen in the cone-shaped pile of stuff that appears when powder is poured through a funnel-shaped container. If the angle of rest is less than 40°C, it means the substance can flow easily. If it's more than 40°C, it means the substance sticks together.

The Compressibility Index (CI) is a measure used to assess the flowability of a powder. It quantifies the propensity of a powder to compact under pressure. The compressibility index is often determined using the accompanying equation:

$$\text{Compressibility Index (\%)} = [(\text{Tapped Density} - \text{Bulk Density}) / \text{Tapped Density}] \times 100$$

A substance that has a compressibility index of less than 20% is frequently regarded as having desirable flowability. Since it reflects particle friction, the Hausner ratio, which is defined as the ratio of tapped bulk density to aerated bulk density, is a valuable indicator of cohesion. The material is solid and challenging to fluidise when the Hausner ratio reaches 1.4. Nevertheless, a free-flowing powder is indicated by ratios below 1.25.[30]

Evaluation Parameters Post-Compression for Prepared Orodispersible Tablets

Thickness, Hardness, Friability, and Weight Variation of Prepared Tablets

A Vernier caliper was used to measure tablet thickness, a Pfizer hardness tester to assess hardness, and a Roche friabilator to measure friability. USP states that the weight variation test involves weighing 20 tablets individually, estimating the mean attractive weight, and then comparing it to the mean.

Wetting Time

A tablet's internal structure and the hydrophilic nature of the formulation's excipients are reflected in the time it takes to become fully wetted. Wetting time is a crucial factor influencing tablet disintegration and is strongly connected with contact angle; a shorter wetting time is often associated with a higher rate of tablet disintegration. Five circular tissue sheets, each with a diameter of 10 cm, were placed in a Petri dish of comparable size to determine the wetting time. The dish was then gently filled with a specified volume (10-20 mL) of a water-soluble dye solution, such as eosin, to guarantee that the tissue layers were uniformly moist. The soaking time was measured by slowly placing a tablet in the middle of the tissue paper and timing how long it took to reach the surface. The following formula was then used to determine the tablet's water absorption ratio:[31]

$$R = \frac{Wa - Wb}{Wb} \times 100$$

Disintegration Time

A disintegration test instrument was used to assess the disintegration time of the orodispersible tablets. These tablets usually dissolve in a minute; patient disintegration times have been reported to range from 5 to 30 sec. One tablet is placed in each of the six tubes for the evaluation, and then a disc is added to each tube. However, there are drawbacks to the traditional approach to testing these tablets' disintegration; ideally, the test should mimic the oral cavity's natural breakdown process using saliva. The medium was kept at 37°C and agitated at 100 revolutions per minute in a 1-L cylindrical vessel containing 900 mL. Orodispersible tablets were placed in a basket sinker positioned between 6 and 8.5 cm from the bottom of the vessel.[27,31]

Dissolution Studies

The prepared propranolol hydrochloride tablets were subjected to a 15-min dissolution study using a USP paddle-through dissolution apparatus (Electrolab TDP-08L, India). 900 mL of phosphate buffer (pH 6.8) was used as the dissolving medium in the device, which was kept at 37±0.5°C with a stirring speed of 50 rpm. Throughout the research, 1 mL aliquots were taken at regular intervals. Each time, 1 mL of phosphate buffer (pH 6.8) was added to compensate for the amount removed, keeping the total volume at 900 mL. A UV-vis spectrophotometer (Shimadzu 1800, Japan) was used to measure the absorbance of the samples at 228 nm after proper dilution and filtration.[32,33]

Accelerated Stability Analysis

According to the International Council for Harmonization (ICH) guideline Q1A (R^2), an accelerated stability study was conducted on the optimized propranolol hydrochloride orodispersible tablet formulation. Tablets were kept out of direct sunlight for six months in well-sealed packaging at 40±2°C and 75±5% Relative Humidity (RH). Critical quality features, such as wetting time, friability, and cumulative drug release after 15 min (Q15), were assessed at

Table 3: FMEA analysis summary indicating RPN scores for material attributes that affect the CQAs.

Sl. No.	CMAs	Name of Factors	Severity (S)	Occurrence (O)	Detection (D)	RPN	Likely risk on CQAs
1.	CMAs	HPMC	6	7	5	210	WT, Fr, Q15
2.		Kyron T 314	8	8	5	320	WT, Fr, Q15
Risk Ranking	0 to 150	Green	151 to 300	Yellow	301 to 512	Red	

Table 4: Composition of propranolol hydrochloride Orodispersible tablets.

Ingredients	Formulations code												
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
DRC (equivalent to 10 mg)	45	45	45	45	45	45	45	45	45	45	45	45	45
Mannitol	20	20	20	20	20	20	20	20	20	20	20	20	20
HPMC	2.5	5	7.5	2.5	5	7.5	2.5	5	7.5	5	5	5	5
Kyron T-314	5	5	5	7.5	7.5	7.5	10	10	10	7.5	7.5	7.5	7.5
MCC (Avicel pH101)	63	60.5	58	60.5	58	55.5	58	55.5	53	58	58	58	58
Saccharine	10	10	10	10	10	10	10	10	10	10	10	10	10
Talc	3	3	3	3	3	3	3	3	3	3	3	3	3
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Flavour (Vanilla)	Q S	Q S	Q S	Q S	Q S	Q S	Q S	Q S	Q S	Q S	Q S	Q S	Q S
Total Weight (mg) q.s.	150	150	150	150	150	150	150	150	150	150	150	150	150

predefined intervals (0, 3, and 6 months). The performance and physical stability of the optimized formulation under accelerated storage conditions were evaluated by comparing the observed results with the original values. Every measurement was carried out three times.[29,34,35]

Statistical Analysis

All experiments were conducted in triplicate, and the results are presented as mean±Standard Deviation (SD). Statistical analysis and formulation optimization were performed using Design-Expert® software (Version 13, Stat-Ease Inc., Minneapolis, MN, USA).

RESULTS

Precompression Studies on Powder Blend

The tapped and bulk densities of the powder mix were assessed, revealing that the compressibility index for all formulations ranged from 12.33% to 13.56%. The findings indicated that the flow qualities were satisfactory. Hausner's ratio, ranging from 1.12 to 1.16 across all formulations, indicated that the materials exhibited good flow properties. The angle of repose for the whole formulation mix ranged from 25.2° to 28.3°, indicating that all formulations exhibited favourable flow characteristics (Table 5).

Characterization of Drug and Prepared Tablet

X-ray Diffraction (XRD)

The X-ray diffractogram indicates that propranolol HCl is crystalline, as evidenced by strong, distinct peaks. The diffractogram of Polacrilin potassium (Kyron T-314) resin showed broad peak widths, indicating an amorphous nature. The diffractogram of the formulated tablet exhibits a semi-crystalline peak, indicating it is a drug-resin combination. Researchers discovered that complexation produces a novel solid with reduced crystallinity (Figures 2A and 2B).

Differential Scanning Calorimetry (DSC)

The DSC curves indicate that pure propranolol HCl has an endothermic peak at 166.02°C, commencing at 163.03°C and concluding at 167.62°C. The formulated tablet has an endothermic peak at 166.14°C (ranging from 161.79 to 167.74°C). The drug's integration into the resin resulted in a decrease in peak height and a smooth endothermic curve. This signifies that there is no significant interaction between the medicine and the complex; the resin does not materially modify the drug characteristics throughout the complexation process (Figures 3A and 3B).

FTIR Spectroscopy

The FTIR spectrum of pure propranolol hydrochloride showed characteristic absorption peaks at 3624-3740 cm^{-1} (O-H stretching), 1685-1700 cm^{-1} (C=O stretching), 1546-1549 cm^{-1} (aromatic C=C/C-N stretching), 1408-1441 cm^{-1} (C-H bending), and 1019-1021 cm^{-1} (C-O stretching). The formulated tablet retained these characteristic peaks with only slight shifts in peak position and intensity, indicating good compatibility between propranolol hydrochloride and the excipients, with no evidence of significant chemical interaction (Figure 4). These findings confirm the compatibility of the drug with the selected excipients and demonstrate that the formulation process did not alter the chemical integrity of propranolol hydrochloride.

Experimental Design

Data Analysis

Data analysis revealed that the WT, Fr, and Q15 values are substantially influenced by the independent factors chosen. Equations 2-4 yield the ANOVA results (Table 6) for WT, Fr, and Q15 for various dependent variables, such as:

WT = 22.6-5X1-13X2-0.5 X1X2+4.4 X12+6.4X22+0.5 X12X2+1.5 X1X22-5.9 X12X22 (2)

Fr=0.65-0.04X1-0.24X2-0.007X1X2+0.04X12+0.02X22+0.01X12X2+0.01X1X22-0.05X12X22 (3)

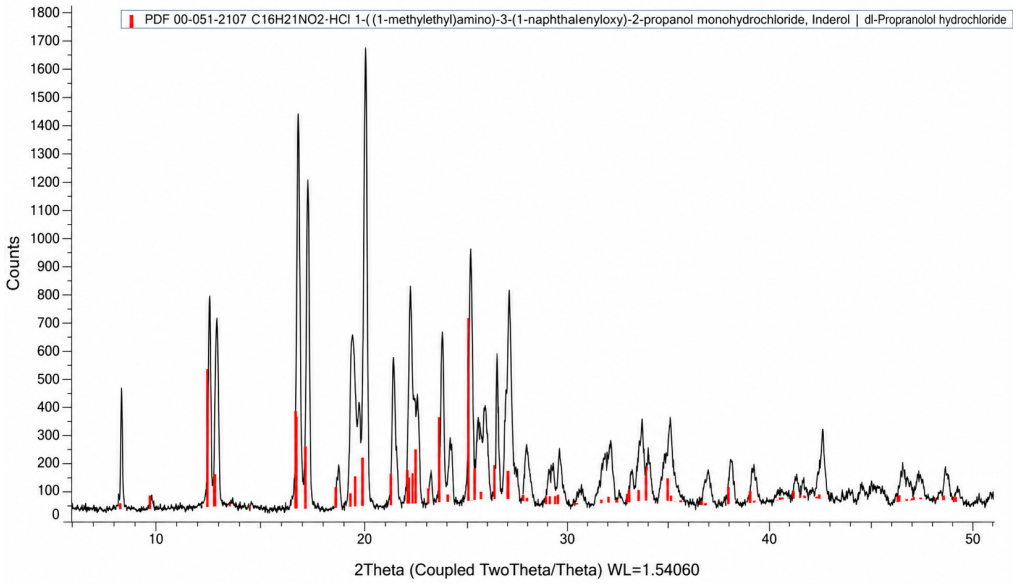
Q15= 93.6-1.52X1+0.49X2+0.18X1X2+0.01X12+1.52X22+0.21X12X2-2.2X1X22+0.53X12X22 (4)

Residual diagnostic analysis was performed to evaluate model adequacy using internally studentized residuals, normal probability plots, and residual-versus-predicted plots. One experimental run exhibited an unusually high residual value together with a comparatively large Cook's distance, indicating disproportionate influence on model fitting. Model refinement following exclusion resulted in improved goodness-of-fit and enhanced predictive capability without altering the overall interpretation of the experimental outcomes.

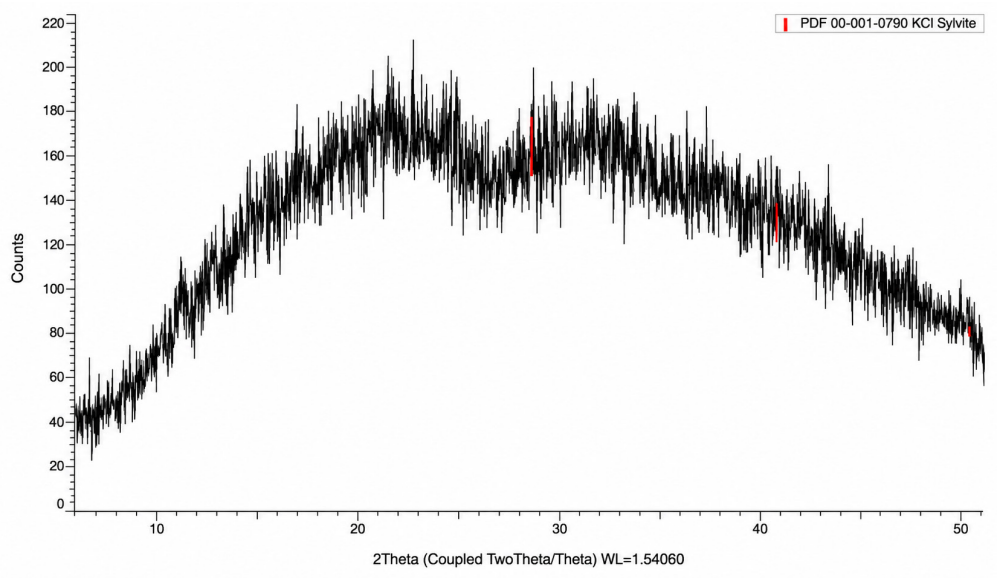
Table 5: Evaluation of powder blend micromeritics.

Formulations	Bulk Density (g/mL)	Tapped Density (g/cm^3)	Carr's Index	Hausner's Ratio	Angle of Repose (ϴ)
F1	0.51±0.04	0.61±0.11	12.33±0.15	1.12±0.07	26.5±0.15
F2	0.50±0.03	0.6±0.09	13.38±0.13	1.11±0.06	25.5±0.13
F3	0.53±0.07	0.63±0.10	12.45±0.16	1.05±0.03	25.7±0.13
F4	0.54±0.06	0.62±0.12	13.38±0.13	1.11±0.06	27.2±0.18
F5	0.59±0.10	0.67±0.17	12.43±0.15	1.11±0.06	28.3±0.20
F6	0.57±0.09	0.65±0.15	13.34±0.12	1.08±0.04	26.1±0.14
F7	0.53±0.04	0.59±0.08	13.44±0.13	1.14±0.08	26.5±0.13
F8	0.51±0.03	0.58±0.07	13.56±0.14	1.12±0.07	25.2±0.12
F9	0.58±0.09	0.67±0.17	13.26±0.12	1.16±0.09	26.1±0.13
F10	0.50±0.03	0.62±0.12	12.43±0.12	1.05±0.03	26.1±0.14
F11	0.51±0.03	0.62±0.12	12.44±0.16	1.06±0.04	26.3±0.12
F12	0.50±0.03	0.63±0.12	12.44±0.15	1.05±0.03	26.1±0.14
F13	0.50±0.03	0.63±0.12	12.43±0.16	1.06±0.04	26.2±0.11

Note: Mean±SD (n=3).



(A)



(B)

Figure 2: X-ray diffraction patterns of (A) pure propranolol hydrochloride and (B) optimized orodispersible tablet demonstrating reduced crystallinity following drug-resin complex formation.

Response Surface Analysis

Experimental findings show that parameters such as WT (Wetting Time), Fr (Friability), and Q15 (Drug Release at 15 min) are affected by Kyron T 314 and HPMC factors. WT has shown a more or less linear decrease with the increase of Kyron T 314 level and HPMC level, as shown in Figure 5A. On top of that, the contour plot shows a stable linear reduction in WT caused by a combination of these variables. Figure 5B shows that the Fr of an Orally Disintegrating Tablet (ODT) decreases sharply as the HPMC level decreases; the addition of Kyron T 314 also contributes to this effect to a lesser degree. Similarly, in Figure 5C, Q15 of ODT shows a rapid increase with increasing levels of Kyron T 314 and HPMC. These results highlight the substantial role both independent factors play in the release of the drug.

A residual normality plot was used to detect outliers, and one data point was removed from the total of 13 runs. The quadratic model was then fitted to the collected data, and the fit is displayed in the executive summary of the plot (Figure 6), where information on the model's quality and consistency can be found. Regression analysis was conducted on the response parameters (wetting time, Friability, and Q_{15}), and the statistical models were found to be significant.

The high R^2 values of 0.9982, 0.9982 and 0.9892 indicate excellent fits between the data and the model for wetting time and Friability, respectively, and Q15. Moreover, the goodness of the prediction value of 0.845, which is ideally greater than 0.5, indicates high predictive power and allows confident predictions about the effects of changes in material attributes on response variables. In the models, we have F values of 32.82, 262.12, and 55.32 for WT, Fr, and Q15, respectively, which again support the importance of these models. Furthermore, values of $p<0.05$ indicate that the model terms are significant. However, sufficient reliability, which determines the signal-to-noise ratio, is also important, with a ratio greater than 4 being desirable.

Overlay Plot for Optimized Batch

The overlay plot generated by the Design Expert software illustrates the optimized desired value area (depicted as the darker region in Figure 7). This confirms that the optimized products fall within this designated area. The overlay plot was designed by keeping the value of WT (11 - 30.22 sec), Fr (0.70982 - 1), and Q15 (93.81 - 99.39%). The shaded region represents combinations of HPMC and Kyron T-314 concentrations predicted to produce acceptable wetting time, friability, and Q15 values. The formulation exhibiting the highest overall desirability was selected for experimental validation.

Validation of Response Surface Methodology

A plot was generated using the Design Expert software, with the darker shaded area indicating the optimal range of values. This visualization confirms that the product has been optimized within this designated area. (VC1 to VC4 Table 7). These batches were evaluated for WT, Fr, and Q15, and a graph is plotted between observed and predicted values (Figure 8).

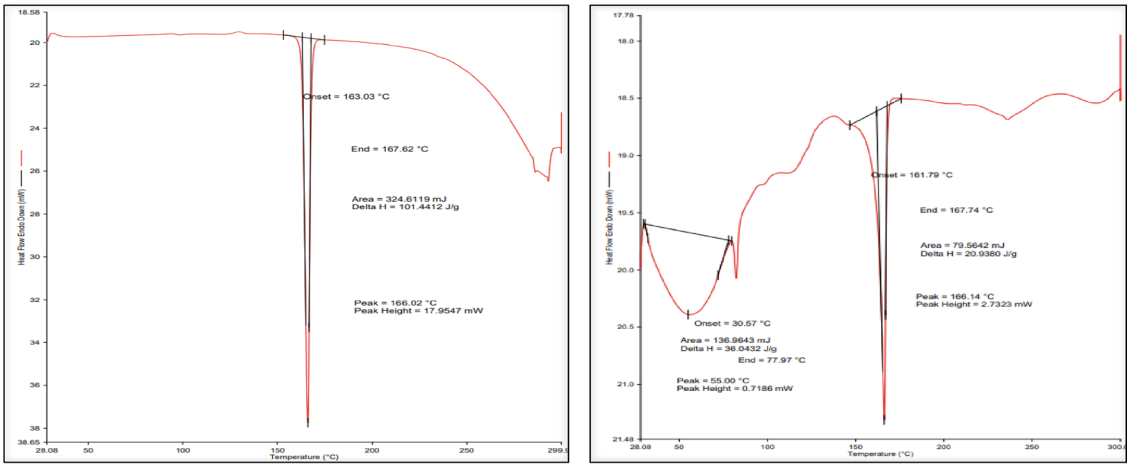
Thickness, Hardness, Friability, and Weight variation

The thickness of the granules was measured using a Vernier calliper, and the results are presented in Table 8. In the acceptable range of ±5% of the standard value, the average thickness of the prepared tablets was between 1.1 and 1.2 mm. The tablets' firmness was assessed using a Pfizer hardness analyser. The

Table 6: Analysis of variance for a statistical model.

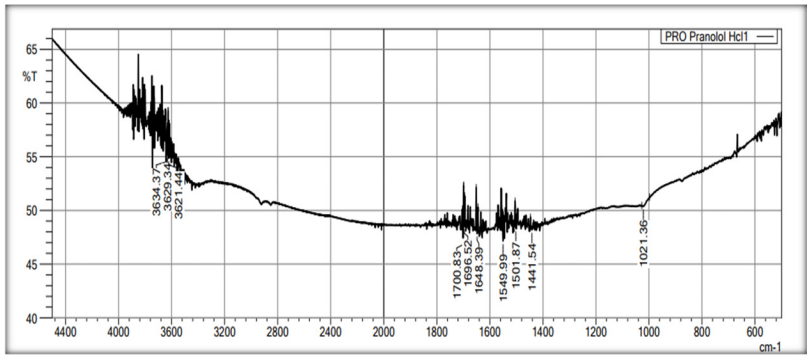
Response	Sum of Squares	d_f	Mean Squares	F-value	*p*-value	R^2	Adequate Precision
WT	1132.15	8	165.82	32.82	0.0006	0.9982	19.172
Friability (Fr)	0.31	7	0.050	262.12	<0.0002	0.9982	56.732
Drug Release (Q15)	638.23	8	93.92	55.32	0.0003	0.9892	25.432

Values are presented as mean±SD (n=3). Statistical significance was determined using one-way ANOVA, with p<0.05 considered statistically significant.

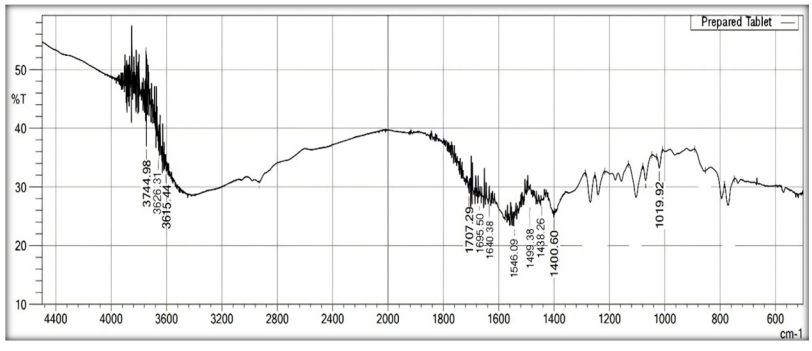


(A) (B)

Figure 3: Differential scanning calorimetry thermograms of (A) pure propranolol hydrochloride and (B) optimized orodispersible tablet indicating the absence of significant drug-excipient interactions.

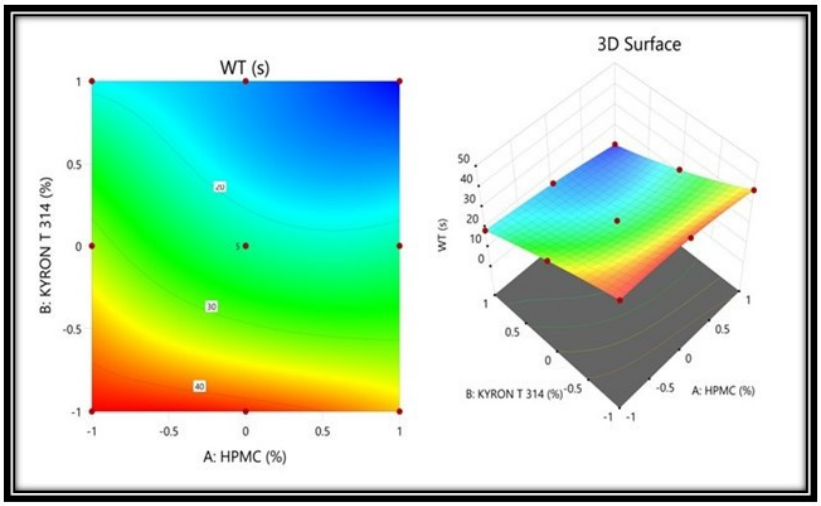


(A)

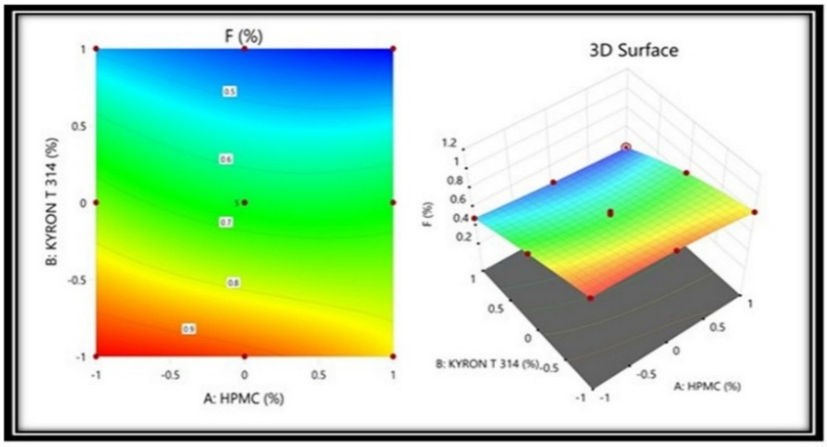


(B)

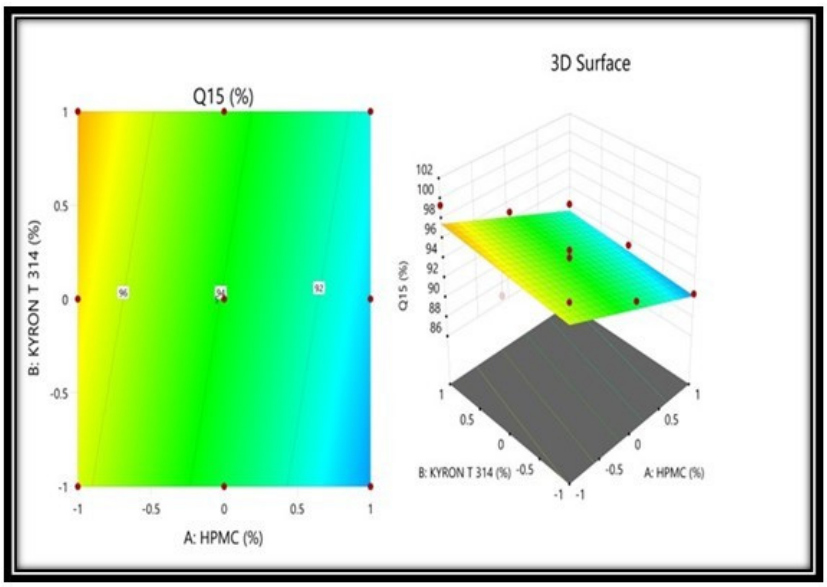
Figure 4: FTIR Spectra (A) Propranolol Hydrochloride, (B) Prepared tablet.



(A)



(B)



(C)

Figure 5: Three-dimensional response surface and corresponding contour plots illustrating the effects of HPMC (X1) and Kyron T-314 (X2) on (A) wetting time, (B) friability, and (C) percentage drug release at 15 min (Q15). Response surfaces demonstrate the interaction between formulation variables.

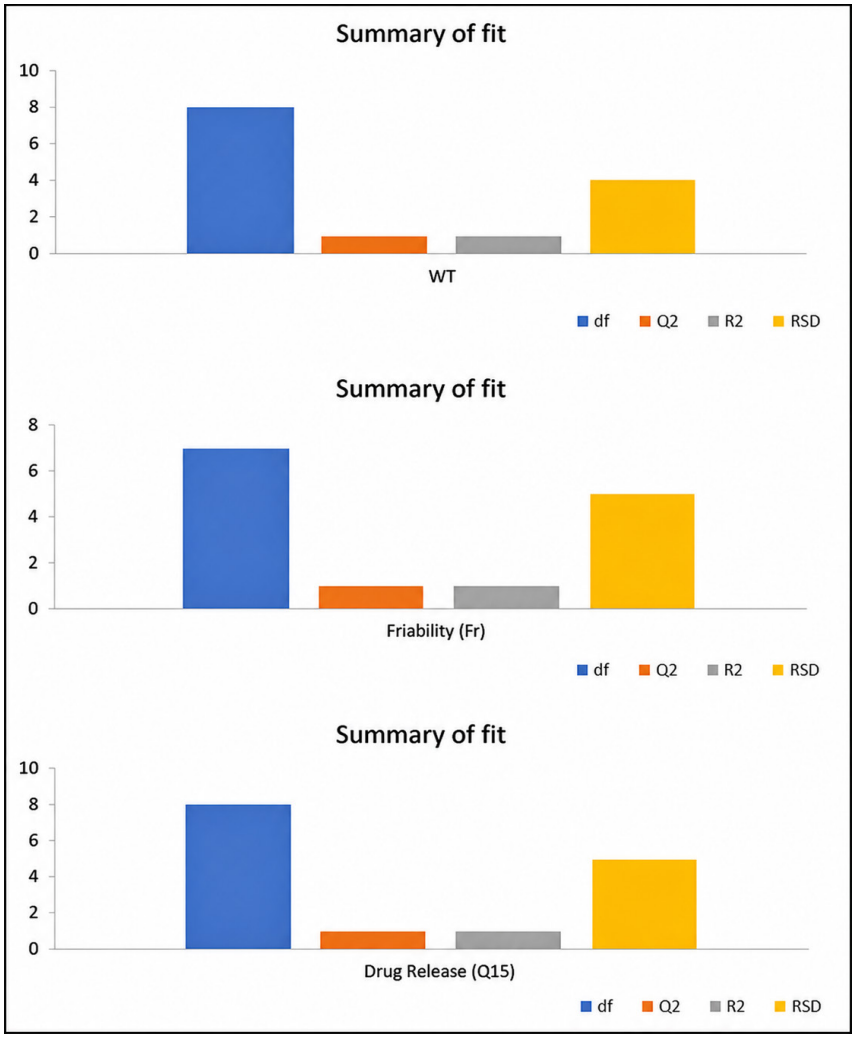


Figure 6: Statistical summary of the fitted quadratic models showing model adequacy, goodness-of-fit (R^2), predictive ability (Q^2), reproducibility, and model validity obtained from Design-Expert software.

Indian Pharmacopoeia (IP) standards were met by the hardness values, which ranged from 3.1 to 3.6 kg/cm² (Table 8). The tablets' friability was assessed using a Roche friability instrument. The average friability of all formulations was between 0.39% and 0.96%, which is below the IP limit of 1%. Therefore, the granules possess an adequate mechanical strength. The prepared tablets were also evaluated for variation in weight and the results are presented in Table 8. The weight deviation percentage fell within the permitted limit specified in the monograph, namely 5%.

Wetting Time

The wetting time of the formulated tablets was assessed, and the results are shown in Table 8. The findings indicated that the wetting time of the formulated tablets ranged from 0.11 to 0.43 sec.

In vitro Disintegration Time

The disintegration time of Orodispersible tablets was assessed using a disintegration test device (single test, Glab India). The disintegration time of the tablet was assessed, and the results are shown in Table 7. The findings indicated that the disintegration period of the formulated tablets ranged from 30 to 37 sec (Table 8).

Dissolution Studies

The release study of formulated propranolol hydrochloride tablets was assessed using a dissolving test with specifications of 1.1 to 1.2 mm. It is advisable to keep tablet thickness within a±5% range of the standard value as determined by the USP paddle type device (Electrolab TDP-08L, India). Nine formulations (F1 to F9) were developed using a binder (HPMC) and superdisintegrants (Kyron T 314) at varying doses (Table 8). The findings indicated that the drug release from the formulated tablets ranged from 91.55% to 95.49%. Formulation F6 had the maximum drug release at 95.49% (Figure 9).

Accelerated Stability Analysis

The optimized propranolol hydrochloride orodispersible tablet formulation was subjected to an accelerated stability study under ICH Q1A (R^2) storage conditions (40±2°C/75±5% RH) for six months. The formulation remained physically stable throughout the study period, with no observable changes in appearance, color, or tablet integrity. Minor changes were observed in wetting time, friability, and percentage cumulative drug release (Q15); however, these variations were within acceptable pharmacopeial limits and were not statistically significant ($p>0.05$). Wetting time increased slightly from 11.85±0.24 s to 12.21±0.33 s, while friability increased marginally from 0.46±0.02% to 0.49±0.03% after six months. Similarly, the percentage cumulative drug release at 15 min decreased slightly from 91.31±0.54% to 90.63±0.72% (Table 9). These findings demonstrate that the optimized formulation maintained its critical quality attributes during accelerated storage, indicating satisfactory physical stability and robustness.

DISCUSSION

The Orodispersible tablets of propranolol HCl were formulated and optimized by utilizing DOE. In the Quality- by-Design (QbD) approach, various batches of Orodispersible Tablet (ODTs) were formulated using varying concentrations of independent variables such as Hydroxypropyl Methylcellulose (HPMC) and Kyron T 314 through direct compression methods. FTIR studies were conducted on the drug molecules and the formulated tablets with the excipients to ascertain their compatibility.[36] FTIR peaks of the drug molecules corresponded with those of the prepared tablets, confirming no interaction between the components. The previously reported X-ray diffraction pattern of propranolol hydrochloride is distinguished by sharp diffraction peaks, confirming the crystalline nature of the drug.[36,37] Additionally, the X-ray diffractogram of this work exhibited solid and robust peaks, confirming the crystalline nature of propranolol HCl. The diffractogram of Polacrilin potassium (Kyron T-314) resin showed diffused peak levels, confirming an amorphous nature.[38] However, the propranolol HCl pure drug demonstrates an endothermic peak at 166.02°C (with a beginning at 163.03°C

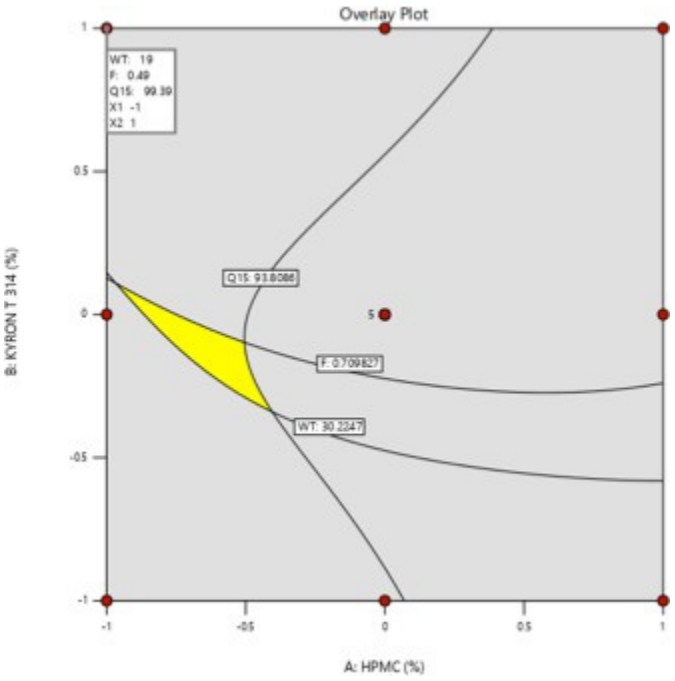


Figure 7: Overlay plot generated using Design-Expert software showing the optimized design space (shaded region) satisfying predefined criteria for wetting time, friability, and Q15.

Table 7: Validation of response surface methodology.

Batch No	HPMC	Kyron T 314	Response	Predicted Value	Observed Values	Percentage Error
Optimized batch	3.85	14.62	Fr	0.462	0.465	-6.122
-	-	-	WT	11.854	11.855	-0.0058
-	-	-	Q15	91.23	91.31	-6.035
VC1	2.675	12.72	Fr	0.446	0.445	-8.333
-	-	-	WT	12.841	12.84	-2.059
-	-	-	Q15	97.25	97.18	0.072
VC2	2.75	12.72	Fr	0.421	0.42	-6.66
-	-	-	WT	12.624	12.622	1.284
-	-	-	Q15	96.88	96.95	-0.0722
VC3	3.725	12.75	Fr	0.455	0.453	0
-	-	-	WT	11.452	11.224	2.049
-	-	-	Q15	97.95	98.05	-0.1019
VC4	3.925	13.3	Fr	0.414	0.412	-4.6511
-	-	-	WT	11.152	10.874	2.5758
-	-	-	Q15	98.75	98.89	-0.1415

Values are presented as Mean±SD (n=3). Statistical significance was determined using one-way ANOVA, with $p<0.05$ considered statistically significant.

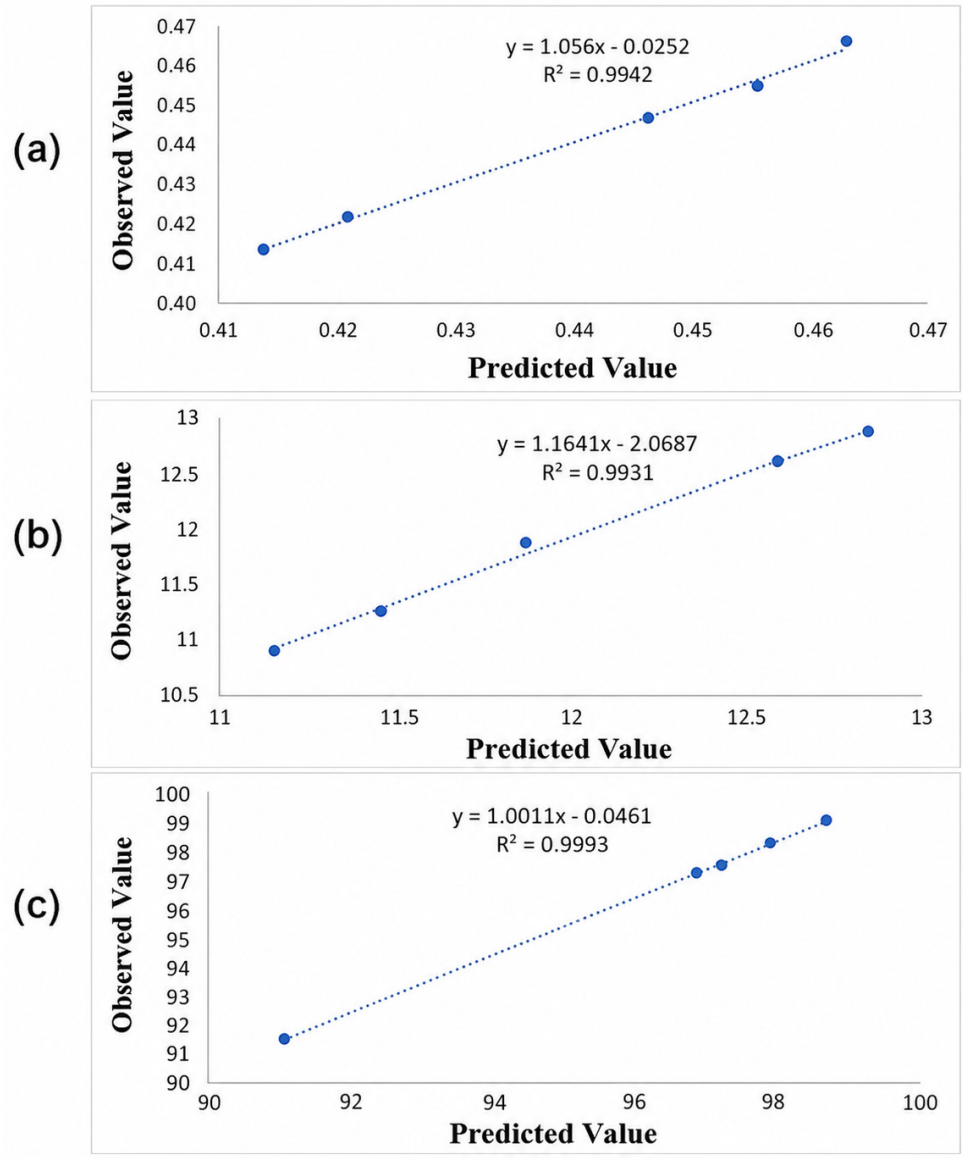


Figure 8: Comparison between predicted and experimentally observed responses for (A) friability, (B) wetting time, and (C) Q15 demonstrating good agreement and successful model validation.

and an end set at 167.62ºC).[39] In comparison, the prepared tablet shows an endothermic peak at 166.14ºC (the beginning is 161.79ºC and the ending is 167.74ºC). Optimizations of tablet formulations were performed using a 32 CCD design. The results for the response parameters, namely WT and Fr, were subjected to regression analysis, and statistically significant regression models were identified.[40,41] The obtained responses (wt, fr, and Q15) showed a strong correlation between the dependent and independent variables. The observed reduction in wetting time with increasing concentrations of Kyron T-314 can be attributed to its superior swelling capacity and rapid water uptake, which facilitate faster penetration of the dissolution medium into the tablet matrix. Similar observations have been reported in previous studies investigating ion-exchange resin-based superdisintegrants, where rapid hydration accelerated tablet disintegration and improved drug release. Conversely, increasing HPMC concentration tended to prolong wetting time because of the formation of a more cohesive polymeric network that delayed water penetration. Tablet friability was predominantly influenced by the concentration of HPMC, which acted as an effective binder by enhancing interparticle adhesion and improving mechanical strength. Increasing HPMC concentration reduced friability by producing a more compact tablet structure. However, excessive binder concentrations may adversely affect tablet disintegration; therefore, optimization was necessary to achieve an appropriate balance between mechanical integrity and rapid disintegration. Similar relationships between binder concentration and tablet strength have been reported in previous studies on QbD-based orodispersible tablet formulations. Drug release at 15 min (Q15) was governed by the combined effects of Kyron T-314 and HPMC. Increasing Kyron T-314 promoted rapid tablet disintegration through swelling and wicking mechanisms,

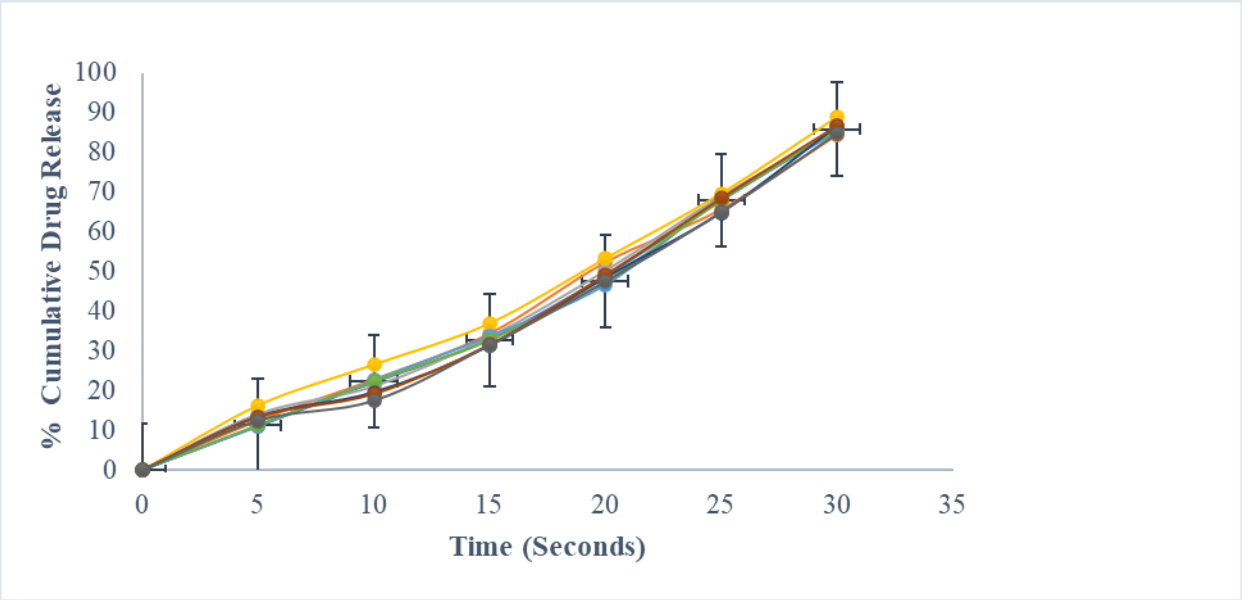


Figure 9: Comparative dissolution profiles of propranolol hydrochloride orodispersible tablet formulations (F1-F13) showing percentage cumulative drug release over 15 min.

Table 8: Evaluation of propranolol hydrochloride orodispersible tablets.

Formulations	Thickness (mm)	Hardness (Kg/cm^2)	Weight Variation (mg)	*In vitro* Disintegration Time (sec)	WT (Sec)	Fr (%)	Q_{15} (%)
F1	1.1±0.04	3.2	Pass	37±0.32	22±0.76	0.66±1.12	91.55±0.46
F2	1.1±0.07	3.5	Pass	34±0.29	11±1.05	0.39±0.83	92.28±0.26
F3	1.2±0.05	3.3	Pass	30±0.31	23±0.48	0.7±1.01	92.61±1.04
F4	1.1±0.02	3.1	Pass	31±0.28	22±0.76	0.67±1.13	94.2±0.92
F5	1.2±0.06	3.4	Pass	35±0.28	16±0.97	0.43±0.44	95.07±0.96
F6	1.1±0.12	3.4	Pass	33±0.27	37±1.29	0.83±0.27	95.49±0.28
F7	1.1±0.10	3.1	Pass	32±0.29	23±0.48	0.65±0.49	93.65±0.90
F8	1.2±0.25	3.1	Pass	35±0.38	42±0.53	0.92±0.42	94.08±0.92
F9	1.2±0.05	3.6	Pass	36±0.39	22±0.76	0.63±0.49	94.98±0.93
F10	1.1±0.10	3.1	Pass	36±0.38	32±0.15	0.74±1.01	94.59±0.92
F11	1.1±0.10	3.1	Pass	35±0.34	19±1.03	0.49±0.47	94.39±1.07
F12	1.1±0.10	3.1	Pass	36±0.38	23±0.48	0.62±0.48	93.84±0.91
F13	1.1±0.10	3.1	Pass	35±0.33	43±0.58	0.96±0.09	94.35±1.04

Values are presented as mean±SD (n=3).

Table 9: Accelerated Stability Study of the Optimized Propranolol Hydrochloride Orodispersible Tablet Formulation.

Characteristics	Storage Condition (40°C±2°C /75%±5% RH)			
Parameters	Initial	After 1 Month	After 3 Months	After 6 Months
Wetting Time (s)	11.85±0.24	11.96±0.27	12.08±0.29	12.21±0.33
Friability (%)	0.46±0.02	0.47±0.02	0.48±0.03	0.49±0.03
% Cumulative Drug Release (Q_{15})	91.31±0.54	91.08±0.58	90.87±0.65	90.63±0.72

resulting in enhanced dissolution. In contrast, higher HPMC concentrations produced a denser polymeric matrix that moderately slowed drug release by delaying medium penetration. The optimized formulation successfully balanced these opposing effects, achieving rapid drug release while maintaining acceptable tablet strength. These findings are consistent with previously reported studies demonstrating that simultaneous optimization of superdisintegrant and binder concentrations is essential for obtaining high-performance orodispersible tablets developed using Quality by Design principles. This F distribution is dependent on the Degrees of Freedom (d_f) for the variance for both the numerator and denominator of the F ratio. The model results in the following F values: 32.82 for WT, 262.12 for Fr, and 55.32 for Q15. The high R^2 values suggest that these models are important. A *p*-value <0.05 indicates that model terms are significant, supporting the significance of the models created for WT, Fr, and Q15 (Sharma V and Chopra H 2012). A ratio greater than 4 indicates good signal-to-noise reliability. The WT, Fr, and Q15 for all 13 batches (F1-F13) exhibited wide variation. The hardness of the formulations (F1 to F13) obtained ranged from 3.1 to 3.6 kg/cm^2; thus, good mechanical strength was obtained, while the thickness of the formulations obtained was 1.1 to 1.2 mm. The weight variation and friability testing were passed regulatory norms. *In vitro* dissolution experiments were conducted on all formulations for 30 sec, and the results showed maximum drug loading, similar to that of the optimized formulation. The optimized batch was validated by setting four separate batches based on the optimized value from the overlay plot shown in Figure 5. Comparing observed values with predicted responses showed that the models were valid and provided close agreement. This research demonstrates the use of Central Composite Design (CCD) optimization strategies to improve the product development process and offers a practical way to save time and produce a better formula. These methods have the potential to improve the development of ODTs and provide avenues for future research. A limitation of the present investigation is the absence of accelerated and long-term stability studies of the optimized formulation. Although the optimized formulation demonstrated satisfactory pharmaceutical performance immediately after preparation, its long-term physical and chemical stability remains to be established.

CONCLUSION

Orodispersible tablets dissolve easily in the mouth without the need for water and allow rapid drug release within minutes, with effects for treatment. ODTs provide a promising drug delivery system for the drug Propranolol hydrochloride, which is supposed to be used for treating conditions such as elevated blood pressure, atrial fibrillation, myocardial infarction, and migraine. Given the bitter taste of propranolol hydrochloride, taste masking was achieved using an ion-exchange resin, Kyron T 314. Using the direct compression technique, varying concentrations of HPMC and Kyron T 314 were used to produce batches of ODTs. The formulation hardness (F1 to F13), which ranged from 3.1 to 3.6 kg/cm^2, showed favorable mechanical strength, and the formulations ranged in thickness from 1.1 to 1.2 mm. Weight variation and friability tests matched the official standards. *In vitro* dissolution studies were carried out for all formulations within a 30-sec timeframe. The outcomes pinpointed the optimized formulation showcasing the highest drug loading. This study demonstrates the utility of Central Composite Design (CCD) optimization techniques in streamlining product development, saving time, and yielding superior formulations. These methods have the potential to enhance the development of ODTs and open avenues for further research.

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ABBREVIATIONS

ABS: Absorbance; **bFGF:** Basic Fibroblast Growth Factor; **BP:** British Pharmacopoeia; **CCD:** Central Composite Design; **CMAs:** Critical Material Attributes; **Conc.:** Concentration; **CQAs:** Critical Quality Attributes; **cm:** Centimetre; **DOE:** Design of Experiments; **DRC:** Drug-Resin Complex; **DSC:** Differential Scanning Calorimetry; **FMEA:** Failure Mode and Effects Analysis; **Fr:** Friability; **FTIR:** Fourier Transform Infrared Spectroscopy; **g:** Gram; **HCl:** Hydrochloride; **HPMC:** Hydroxypropyl Methylcellulose; **IER:** Ion Exchange Resin; **IP:** Indian Pharmacopoeia; **kg:** Kilogram; **MCC:** Microcrystalline Cellulose; **mg:** Milligram; min: Minutes; **mL:** Millilitre; **mm:** Millimetre; **µg:** Microgram; **ODT:** Orodispersible Tablet; **pH:** Negative logarithm of hydrogen ion concentration; **Q15:** Drug Release at 15 Min; **QbD:** Quality by Design; **QTPP:** Quality Target Product Profile; **REM:** Risk Evaluation Matrix; **RPN:** Risk Priority Number; **RSM:** Response Surface Methodology; **sec:** Seconds; **SSG:** Sodium Starch Glycolate; **USP:** United States Pharmacopeia; **UV:** Ultraviolet; **VEGF:** Vascular Endothelial Growth Factor; **WT:** Wetting Time; **XRD:** X-ray Diffraction.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

AR: Writing - original draft, Software, Methodology, Investigation, Formal analysis, Data curation. **VS:** Conceptualization, Writing - reviewing and editing, Software, Methodology, Investigation, Formal analysis. All authors reviewed the results and approved the final version of the manuscript.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not applicable.

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