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RESEARCH ARTICLE

FORMULATION AND *IN VITRO* CHARACTERIZATION OF METOCLOPRAMIDE LOZENGES BY USING THE QUALITY BY DESIGN (QBD) APPROACH

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Abstract

Objective: Conventional dosage forms may not be suitable for all patients, especially those facing difficulty with swallowing, which results in reduced adherence to medication, impacting treatment outcomes. This study aimed to formulate and characterize metoclopramide lozenges using the quality-by-design approach to provide a patient-friendly alternative.
Materials and Method: Formulations were optimized using response surface methodology and a Design Expert, focusing on metoclopramide, citric acid, and carboxymethyl cellulose, with hardness and dissolution as primary response variables. The experimental design involved 20 runs, six replications of the central point, and a quadratic model for improved model fitting, with adjustments made through transformation and numerical hill-climbing algorithms.
Results and Discussion: Formulations of metoclopramide lozenges were obtained through a systematic quality-by-design approach. Using numerical optimization, the formulation with the highest desirability score of 1.00 was selected, yielding a hardness of 14.55 kg and a dissolution time of 1.25 minutes. The optimal coded values were 1.53223 grams for Metoclopramide (A), 4.84302 grams for Citric acid (B), and 18.5048 grams for carboxymethyl cellulose (C). The optimized formulation was subjected to *in vitro* testing to validate its performance, yielding a hardness ranging from 13.98 to 15.00 kg/cm^2 and a dissolution time ranging from 1.11 to 2.23 minutes. The effectiveness of the QbD approach was confirmed as outcomes closely aligned with the targeted responses.
Conclusions: The Quality by Design approach was found effective in optimizing the formulation of metoclopramide lozenges. Using the Design of Expert and Response Surface Methodology, an optimized formulation was obtained with the desired hardness and dissolution rate.
Keywords: Design expert, metoclopramide lozenges, optimized formulation, QbD approach, response surface methodology.

INTRODUCTION

Formulations are designed for easy patient administration through oral tablets, capsules, solutions, and injections, catering to specific patient needs and preferences. These delivery systems offer flexibility in treatment options based on individual patient conditions or requirements[1]. Formulation design is a systematic process that improves drug characteristics through strategies like dissolution, stability, and absorption. It significantly impacts treatment results and drug delivery effectiveness, reducing side effects and improving patient compliance. The oral route is preferred for patient compliance but has disadvantages for the elderly, pediatric, tremors, intellectual disabilities, and impaired swallowing ability[2,3] are oral dosage forms for patients who cannot swallow solid dosages or slow-release drugs. They contain vitamins

and antibiotics and come in various shapes. They provide local or systematically administered drug levels through the oral cavity, dissolve gently in the mouth, and are used to administer analgesics, sedatives, cleaning agents, antitussives, antimicrobials, antihistamines, and aromatics[4].

The Quality by Design (QbD) approach, replacing the Quality by Testing (QbT) method, focuses on chemistry, control, manufacturing, and safety in drug product formulation design. The QAD approach ensures product safety, effectiveness, and quality by scientifically understanding formulation and process factors influencing product quality[5,6].

QbD, or "quality by planning", is a systematic approach that focuses on target product design, offering benefits like reduced side effects, faster launches, and regulatory flexibility. It uses scientific ideologies and quality risk management to enhance product understanding, reduce manufacturing costs, improve FDA interaction, and enable continuous improvement in drug product manufacturing operations. The FDA endorses the Design of Experiments (DoE) method for its systematic approach, superior findings, and cost-effective description of input factors' impacts in industrial and research settings. Justin-Besancon and colleagues developed metoclopramide in 1964. This drug prevents vomiting by blocking dopamine effects, enhancing acetylcholine release, and sensitizing muscarinic receptors. Metoclopramide, a drug with a short half-life of 4 hours in humans and 60-90 minutes in rats and dogs, is easily absorbed and quickly eliminated. It works quickly after intravenous and intramuscular injections and is soluble in ethanol and water. Its metabolism involves N-deethylation, which is either eliminated in urine or converted to sulfate or glucuronide in bile. Impaired renal function prolongs its half-life, necessitating larger dialysis doses[7,8].

The study aims to improve patient compliance by eliminating first pass metabolism and preventing nausea and vomiting. A new antiemetic tablet has been developed, bypassing the liver for increased bioavailability and effectiveness. Metoclopramide's oral formulation has a bioavailability of around 40.7%. However, it can vary between 30 and 100%. Metoclopramide lozenges are a versatile and easy-to-use option for managing symptoms, particularly beneficial for those experiencing nausea or difficulty keeping pills down. The study focuses on formulation studies using the QbD approach, which improves product quality and optimized formulation, lowers development risks, and increases regulatory compliance[9].

MATERIALS AND METHODS

The ingredients, carboxymethylcellulose (CMC), citric acid, metoclopramide, sorbitol, fructose, mannitol, natural flavour, sodium bicarbonate, magnesium stearate, and French vanilla flavour, were purchased from Sigma Aldrich, Germany. We used each ingredient exactly as it was provided to us without any purification.

The method used in design expert:

RSM response surface methodology is utilized for process optimization experiments. It provides statistical tools for designing and analyzing experiments, producing predictive models, and specialized software for response surface maps, aiming for high yield and cost-effectiveness[10].

Central composite design:

Formulation process was studied using a standard RSM design called a central composite design (CCD). It's well suited for fitting a quadratic surface, which usually works well for process optimization[11].

Response surface method for process optimization:

After completing the initial discovery steps and advancing through the breakthrough phase in current experimentation strategy, we strategically identified three variables with their quantities Metoclopramide (A) 1.8 g, Citric Acid (B) 5 ml, and CMC (C) 20 mg—as the most promising candidates for optimization for 100 lozenges. Hardness and Dissolution were measured as the primary response variables for metoclopramide lozenges. The results indicate that y1 corresponds to hardness (N/mm^2) of 10–20 $kg/N/mm^2$ and y2 to dissolution (min) of 1–1.5 min. The central composite design (CCD) emerged as the preferred choice in RSM design, owing to its flexibility and suitability for current study[12].

The centre point in this CCD is replicated six times—not simply resampled or retested, but entirely rerun. This approach ensures a genuine measure of error, capturing natural variations from start to finish. The number of replicates is selected to encompass a broad region where the standard error of prediction remains relatively stable[12]. The results presented in Table 1 from the 20 run design originate from an authentic experiment. This experiment serves as the foundation for showcasing the effectiveness of this contemporary RSM in generating valuable predictive models[12].

Analysis

Model Selection

A quadratic model was applied to the experimental results, supported by software tailored for RSM. However, upon diagnosing the residuals, which represent the disparities between actual and predicted Hardness and Dissolution, it became evident that a notable enhancement could be achieved by initially taking the inverse of the responses (1/y). Such transformations, frequently involving logarithms, are commonly utilized to enhance statistical properties, thereby validating a model within the factorial region of the RSM experiment[13].

Statisticians use coded factors to avoid round-off problems when using actual units of measure. Maintaining model hierarchy prevents misleading impressions about factors' significance, as they may make a difference at a higher order or in concurrence with other factors. However, some statisticians advocate for maintaining the entire quadratic polynomial as standard practice, as it helps avoid unforeseen inaccuracies in predictive modeling[13].

Optimization

Pharmaceutical experimenters used numerical hill-climbing algorithms to optimize hardness and

dissolution in metoclopramide lozenges. These optimized values were then delivered to a second group for formulation, ensuring maximum desirability in evaluation parameters. This approach helps optimize diagnostic models and achieve desired outcomes[14].

Verification of experiment:

Another group verified the Experiment by formulating lozenges and evaluating their parameters using QbT[14].

Expert design software

Design-expert simplifies the use of powerful multifactor testing tools, providing a smooth method for advancing the study and guaranteeing its outstanding success[15].

It is a statistical software program designed especially for experiment design (DoE). Design experts provide comparative testing, screening, characterization, optimization, resilient parameter design, mixture designs, and integrated designs[15].

Design of experiments

Design-Expert software enhances products and processes by efficiently screening essential factors and components. It allows users to set flags, explore contours on interactive 2D graphs, and visualize response surfaces with rotatable 3D plots. It also enables users to maximize desirability for all responses, identifying the' sweet spot' meeting all specifications. Design-Expert simplifies the application of powerful multifactor testing tools, making the process user friendly[16].

Physicochemical Characterization

Friability

To determine the friability of the sample tablets, they were weighed and placed in the tester. Once the device was turned on and ran for four minutes at 25 rpm, it was removed and weighed again[17].

Disintegration time

A disintegration test involves placing a tablet in a device with a liquid medium, such as water or simulated gastric fluid. The device agitates the liquid at a constant temperature to simulate bodily conditions. The time taken for the tablet to dissolve fully is recorded[18].

Weight variation

Twenty tablets were taken in, and a digital weighing scale was used to calculate each tablet's individual and total weight. The total weight was used to calculate the average weight of one tablet[19].

Determination of drug content

Twenty lozenges were finely powdered to ensure the drug's complete solubility. A 100 mL volumetric flask containing 50 ml of 6.8 phosphate buffer was then added to the powder, which was weighed precisely and allowed to stand for 30 minutes with intermittent sonication. Distilled water was added until the mixture reached its full volume. A UV-visible spectrophotometer was used to measure the absorbance at λ_{max} 234 nm after the solution had been appropriately diluted.[19]

Hardness

The USP method was used to determine the hardness of 20 core and coated tablets. The tablets were tested using a Monsanto hardness tablet tester, with a load applied and the point of fracture calculated. Ten tablets were used for the test, and the hardness was measured[20].

Dissolution time

For each formulation, three *in vitro* release tests (n=3) were carried out using a paddle-based USP type II dissolution test device. A 900 ml solution of 0.1N HCl was used as the dissolving medium, and the device was run at 50 rpm at 37±2°C[21,22].

***In vitro* drug release**

Scientists simulate digestion by placing lozenges in a vessel containing a liquid simulating stomach fluid. A rotating paddle keeps the fluid warm (37°C) and mixed (50 rpm). They periodically withdraw small samples and dilute them tenfold for analysis with a UV-visible instrument at 234 nm. This allows them to track how much drug is released from the tablet over time. By calculating the percentage of drugs released at each sampling point, they create a "release profile" that reveals how quickly the medication leaves the tablet[23].

Release kinetics

The DD-Solver add-in program is utilized to apply various kinetic models, such as zero-order, first-order, Korsmeyer, and Peppas, to calculate a drug's release kinetics from its dosage form. The drug release behaviour and pattern are then evaluated[24].

RESULTS

Formulation and process development

Better process understanding and control are vital to minimizing product waste due to manufacturing failure and producing products of desired quality with reduced end-product testing. These objectives were accomplished by identifying process variables for preparing robust Metoclopramide Lozenges. Subsequent process development studies confirmed the criticality of the process parameters. Critical process parameters are the process inputs that, when varied beyond the proven acceptable ranges (PAR), significantly affect the CQA; therefore, they must be controlled within predetermined limits. Critical process factors named as A=Metoclopramide, B=Citric Acid, and C=CMC, having units as gram, milliliter, and milligram, respectively. The Coded value for metoclopramide quantity was 1.20 as low and 1.80 as high, the Coded value for Citric Acid was 3.00 as low and 4.00 as high, and the Coded value for CMC was 15.00 as low and 20.00 as high, having mean value as 1.50, 4.00, and 17.50 respectively (Table 2) and having standard deviation as 0.2543, 0.847, and 2.12 respectively.

Optimization of Responses

Numerical optimization is crucial when analyzing multiple factors with multiple responses, providing valuable insights when combined with graphical analysis. However, subject-matter knowledge is crucial for success. To avoid defining impossible criteria, set broad acceptable ranges and narrow them down as you learn about factor levels' impact on responses.

Therefore, by utilizing the values of these crucial factors (ingredients), desired outcome can be attained, namely, an optimized response rate of 14.55 kg hardness and 1.25 minutes dissolution.

Table 1: Design matrix.

Run	Space Type	Factor 1 A:Metoclopramide G	Factor 2 B:Citric Acid Ml	Factor 3 C:CMC Mg	Response 1 Hardness N/mm²	Response 2 Dissolution min
1	Center	1.5	4	17.5	10	1
2	Axial	2.00454	4	17.5	11	1.1
3	Axial	1.5	5.68179	17.5	12	1.2
4	Axial	1.5	4	13.2955	13	1.3
5	Factorial	1.2	5	20	14	1.4
6	Factorial	1.8	5	15	15	1.5
7	Axial	1.5	2.31821	17.5	16	1
8	Factorial	1.2	3	20	17	1.1
9	Factorial	1.8	5	20	18	1.2
10	Factorial	1.8	3	15	19	1.3
11	Center	1.5	4	17.5	20	1.4
12	Center	1.5	4	17.5	10	1.5
13	Factorial	1.8	3	20	11	1
14	Center	1.5	4	17.5	12	1.1
15	Factorial	1.2	5	15	13	1.2
16	Factorial	1.2	3	15	14	1.3
17	Center	1.5	4	17.5	15	1.4
18	Axial	0.995462	4	17.5	16	1.5
19	Axial	1.5	4	21.7045	17	1
20	Center	1.5	4	17.5	18	1.1

Table 2: Factors.

Factor	Units	Type	Subtype	Minimum	Maximum	Coded Low	Coded High	Mean	Std. Dev.
A	G	Numeric	Continuous	0.9955	2.00	-1 ↔ 1.20	+1 ↔ 1.80	1.50	0.2543
B	Ml	Numeric	Continuous	2.32	5.68	-1 ↔ 3.00	+1 ↔ 5.00	4.00	0.8478
C	Mg	Numeric	Continuous	13.30	21.70	-1 ↔ 15.00	+1 ↔ 20.00	17.50	2.12

Table 3: Optimized responses.

Responses	Optimized Value	A: Metoclopramide	B: Citric Acid	C: CMC
Hardness	14.55 (N/mm²)	1.53223 (g)	4.84302 (ml)	18.5048 (mg)
Dissolution	1.25 (Minutes)			

The responses, along with their optimized values, are shown in Table 3. While the software proposed numerous solutions, we opted for the one with the highest desirability score, which is 1.00.

Ingredients (Factors)

A = Metoclopramide ……. Grams (g)

B = Citric Acid……. Milliliter (ml)

C=CMC……Milligrams (mg)

3D Surface of Responses

When fitting a quadratic model with two or more continuous predictors, it becomes beneficial to provide a graphical representation of the fitted surface. Given the particular significance of surface visualization in response-surface methods, the function "3D Graphs" was devised and integrated into the RSM package in pursuit of this.

Development of optimized formulation

The lozenge formulation, comprising Metoclopramide, citric acid, CMC, and all other components, undergo wet granulation, followed by drying the granules in an oven at 40°C for 6 hours. Subsequently, these granules were directly compressed into tablets using a press, with an average weight of 3000 mg, as detailed in Table 2[25].

***In vitro* analysis on the optimized formulation**

The optimized formulation, after development, was subjected to *in-vitro* laboratory testing to evaluate the optimized responses due to the optimized concentration are as follows:

Physicochemical Characterization

Weight variation

The weight variation of the formulations was determined to be within pharmacopeial limits, ranging from 2999.3±1.58 mg to 3000.7±2.6 mg. The results are indicated in Table 4.

Friability

The friability of all formulations is no more than one, indicating all formulations comply with the official limits. The results are indicated in Table 4.

Disintegration Time

The disintegration time ranges between 2 and 8 minutes, as described in Table 4, indicating a good disintegration time for drug release.

Drug Content

After an assay, the drug content percentage of each lozenge ranged from 98.13±1.71 to 99.81±1.48, as indicated in Table 4.

Hardness test and Dissolution test

The 10 lozenge sample was subjected to a hardness and dissolution test to evaluate its hardness and dissolution time.

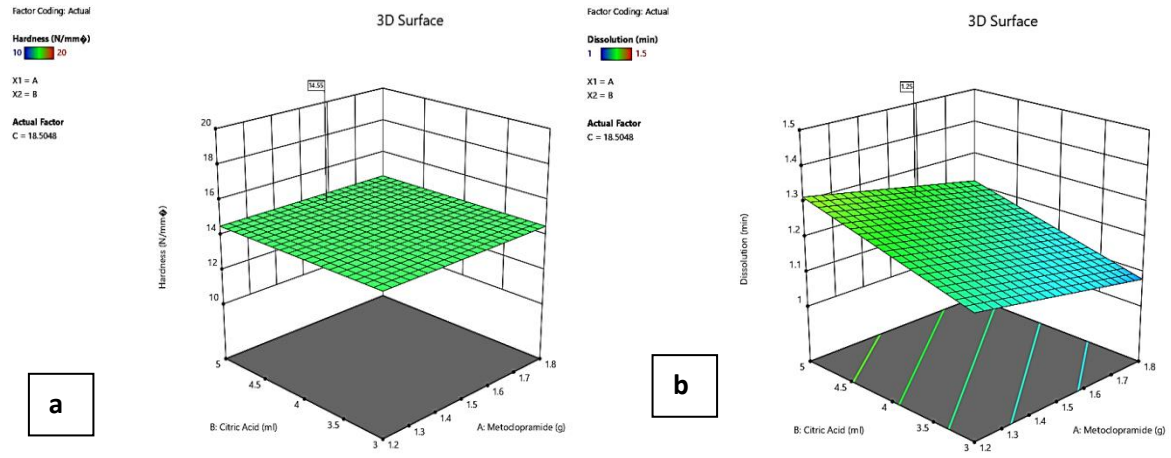

Figure 1: 3D Surface Modelling of a) Hardness and b) Dissolution.

Table 4: Physicochemical characterization.

Formulation	Friability	Weight variation	Disintegration (minutes)	Drug Content (%)
F1	0.5	2999.3 ±2.7	2	98.17±1.62
F2	0.6	3000.7 2.6	4	99.44±1.93
F3	0.4	2999.3±2.3	6	99.26±2.08
F4	0.8	2999.6±2.5	4	98.13±1.71
F5	0,7	3000.5±1.53	3	98.88±1.62
F6	0.6	2999.6±2.8	2	99.17±1.28
F7	0.8	2999.8±1.88	8	99.81±1.48
F8	0.5	3000.2±2.2	2	98.33±1.58
F9	0.6	2999.5±2.8	7	99.18±1.71
F10	0.4	2999.3±1.58	5	99.26±2.08

As shown in Table 5, the hardness of the sampled lozenges ranged from 13.98 to 15.00 kg/cm^2, and the dissolution time ranged from 1.11 to 2.23 minutes. These values are close to the optimized hardness responses, indicating precise optimization of formulation concentration through Quality by Design (QBD)[22]. Additionally, 3D surface modeling of hardness and dissolution was carried out, and the results are displayed in Figure 1.

***In vitro* drug release**

The drug-release characteristics of metoclopramide were evaluated using *in vitro* drug-release tests on metoclopramide lozenges. The dissolution rate of the medication increased steadily across all formulations (F1 to F7) over a 30 minute period. Most formulations, except F4, achieved 90% drug release after 30 minutes, with a relatively rapid initial release period followed by a slow-release pattern.

Table 5: Hardness and dissolution test on the optimized formulation.

Sample	Hardness (N/mm^2)	Dissolution time (Minutes)
Lozenges-1	15.00	1.44
Lozenges-2	13.98	1.91
Lozenges-3	14.44	1.11
Lozenges-4	14.91	1.76
Lozenges-5	14.56	1.44
Lozenges-6	13.76	2.23
Lozenges-7	14.79	0.98
Lozenges-8	14.43	1.54
Lozenges-9	14.23	1.36
Lozenges-10	14.57	1.88

Notably, formulation F6 demonstrated the highest drug release over the 30 min period, reaching 95.17%, as shown in Figure 3.

Release kinetic

The *in vitro* dissolution rate pattern was calculated using various mathematical model coefficients. The value of r^2, which helps in understanding the nature of metoclopramide lozenges, is shown in Table 6. The r^2 value for first-order kinetics is 0.9769, and for zero-order kinetics, it is 0.9347. The r^2 value was close to 1 for first order kinetics, confirming that the metoclopramide lozenges followed first-order kinetics and showed immediate drug release. In the Korsmeyer-Peppas model, all formulations had an n value between 0.296 and 0.664, demonstrating Fickian release and first-order kinetics.

DISCUSSION

Metoclopramide lozenges are a new drug delivery method for treating nausea and vomiting in patients who cannot swallow pills. They work by locally delivering active molecules in the oral cavity, bypassing traditional ingestion and resulting in faster action and improved patient compliance by passing traditional ingestion, resulting in faster action and improved patient compliance. Response Surface Methodology (RSM) was used to develop and evaluate formulations with Generate Expert. Process optimization for formulation processes was done using central composite design (CCD). Metoclopramide, citric acid, and carboxymethylcellulose were the main

ingredients focused on, with hardness and dissolution as the primary factors considered for optimization. Increasing the quantity of carboxymethylcellulose enhances the dissolution rate of metoclopramide hydrochloride. The study uses numerical hill-climbing algorithms to optimize hardness and dissolution in metoclopramide lozenges. The results from the 20 run design demonstrate the effectiveness of this contemporary RSM in generating predictive models, ensuring maximum desirability in evaluation parameters.

This approach helps optimize diagnostic models and achieve desired results. The formulation for the lozenges, which includes metoclopramide, citric acid, CMC, and other ingredients chosen for their unique properties, is granulated moist and then dried for six hours at 40°C in an oven. Then, using a press, these granules were immediately crushed into lozenges, each weighing 3000 mg on average, ensuring consistent dosage and ease of administration.

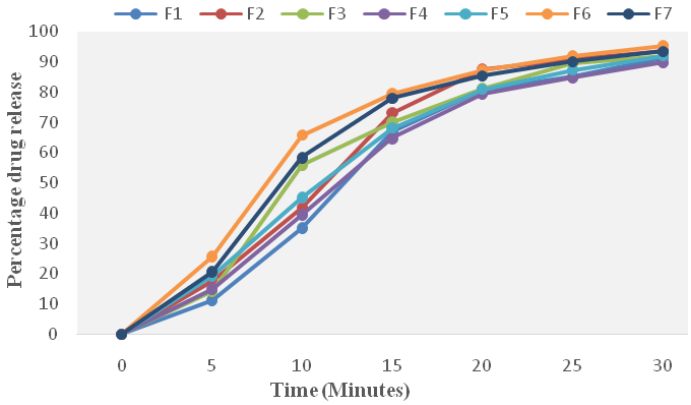

Figure 2: *In-vitro* percentage drug release.

Following development, *in-vitro* laboratory testing was conducted on the optimized formulation to assess the optimized responses resulting from the optimized concentration. In their work "Response surface methodology (RSM) as a tool for optimization in analytical chemistry", Bezerra *et al.*, noted similar results of response optimization[26]. The formulation with the greatest desirability score of 1.00 was chosen by numerical optimization, resulting in a hardness of 14.55 kg and a dissolve time of 1.25 minutes. A hardness and dissolution test were conducted to assess the hardness and dissolving time of the 10 lozenge sample. The hardness of the examined lozenges varied from 13.98 to 15.00 kg/cm^2. In their study on the formulation and evaluation of theophylline lozenges, Pravalika L *et al.*, noted similar patterns for hardness[27].

Table 6: Release kinetics.

Formulation	Zero Order		First Order		Korsmeyer	
	K0	R (Squre)	K1	R (Squre)	kKP	n
F1	3.473	0.9330	0.065	0.9306	6.034	0.424
F2	3.705	0.9056	0.076	0.9433	8.837	0.322
F3	3.652	0.8756	0.076	0.9561	10.441	0.664
F4	3.446	0.9347	0.065	0.9578	12.741	0.400
F5	3.575	0.9183	0.071	0.9722	9.257	0.296
F6	3.899	0.7810	0.095	0.9769	17.285	0.450
F7	3.790	0.8292	0.086	0.9691	13.845	0.585

The dissolve time of the examined lozenges varied from 1.11 to 2.23 minutes. In their development and evaluation of novel lozenges containing marshmallow root extract, Niko Benbassat *et al.*, noted similar results in dissolution studies[28]. These data demonstrate accurate formulation concentration optimization using Quality by Design (QBD) since they are near the optimal hardness responses.

Numerical optimization chose the formulation with the greatest desirability score of 1.00, resulting in a hardness of 14.55 kg and a dissolve time of 1.25 minutes. The ideal coded values are as follows: 4.84302 grams for citric acid (B), 18.5048 grams for carboxymethyl cellulose (CMC) (C), and 1.53223 grams for metoclopramide (A). Most formulations, except F4, achieved 90% drug release after 30 minutes, with a relatively rapid initial release period followed by a slow-release pattern. Notably, formulation F6 demonstrated the highest drug release over the 30-minute period, reaching 95.17%. The r^2 value was close to 1 for first-order kinetics, confirming that the metoclopramide lozenges followed first-order kinetics and showed immediate release effects.

Results showed a strong alignment with the intended responses, confirming the effectiveness of the QbD approach. This suggests that the quality of the product was consistently maintained throughout the development process. It also indicates that the QbD approach can be a reliable method for ensuring product quality and consistency. Furthermore, these findings demonstrate the importance of implementing QbD principles in pharmaceutical development to meet

regulatory requirements and customer expectations. Overall, the study highlights the significant impact of utilizing a QbD approach on improving product quality and reducing risks in the manufacturing process. Future research should focus on optimizing formulation parameters and conducting *in vivo* studies to evaluate the efficacy of metoclopramide lotions. This will provide a better understanding of the QBD approach's potential benefits. Various administration methods and dosage forms could enhance the effectiveness of metoclopramide lozenges.

Additionally, investigating stability and shelf life under different storage conditions is crucial for ensuring quality and efficacy.

Limitations of the study

The study's limitations include the lack of long-term stability testing of the lozenges and potential variability in results due to differences in manufacturing processes. Additionally, the study did not assess the impact of different storage conditions on the performance of the metoclopramide lozenges. Future research could focus on conducting long-term stability testing to assess the durability of the lozenges over time. Furthermore, investigating the effects of various storage conditions on the performance of metoclopramide lozenges could provide valuable insights for optimizing their quality and efficacy.

CONCLUSIONS

This study demonstrated the significant benefits of the quality-by-design (QbD) approach. This methodology facilitated the elucidation of various two-way interactions between independent variables, which the conventional one-factor-at-a-time method cannot accomplish. The ability to pinpoint the relationship between critical material and process attributes culminates in process control and continuous improvement. Hence, by implementing the Design of Expert approach, formulation parameters are studied and optimized using the response surface method. This systematic approach allows us to determine optimal parameters and predict desirable outcomes. Optimization helps us save time and reduce resource wastage. The QbD approach offers a promising future for pharmaceutical development. Hence, DOE saved time and hassle by allowing quality testing to be done and provided much better and more sophisticated means for process optimization.

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DATA AVAILABILITY

The data will be available to anyone upon request from the corresponding author.

AUTHOR'S CONTRIBUTION

Mustafa MA: Conceived and designed, manuscript drafting. **Mahmood A:** methodology. **Shahzad S:** conceptualization, literature search. **Kanwal N:** Ideas, experimental studies. **Rasheed N:** Conceived and designed, manuscript writing. **Mahmood M:** editing, data analysis. **Umair Amjad:** collected, analyzed data, wrote manuscript. **Saeed MA:** data analysis. **Ahsan MS:** Methodology, experimental studies. **Raza SMA:** material collection. **Pervaiz MH:** data curation, investigation. **Hanif R**: methodology. **Ahmad R:** conceptualization. All authors revised the article and approved the final version.

CONFLICT OF INTEREST

None to declare.

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