

A Systematic QbD-Based Approach for the Development of Baclofen ODTs: Integration Risk Assessment and Factorial Design for Enhanced Patient Compliance

Nuha Mohammed Abdulkhaleq^{1*}, Noor Yousif Fareed², Ghada Hamid Najji³, Zainab M. Abdulkhaleq⁴, Zaid M Abdul Khalik⁵

¹Department of Pharmaceutics, College of Pharmacy, Al-Mustafa University College, Baghdad, Iraq.

²Department of Pharmaceutics, College of Pharmacy, University of Basrah, Basrah, Iraq.

³Department of Pharmaceutics, College of Pharmacy, University of Babylon, Babylon, Iraq.

⁴Department of Pharmaceutical Chemistry, College of Pharmacy, Al-Mustafa University College, Baghdad, Iraq.

⁵Baghdad College of Medical Science, Baghdad, Iraq.

*Correspondence to: Nuha Mohammed Abdulkhaleq (E-mail: nuha.pharm@almustafauniversity.edu.iq)

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Abstract

Objective: The current study aimed to prepare baclofen as an orally disintegrating tablet (ODT) to facilitate swallowing in patients with dysphagia. The research utilized the Quality by Design (QbD) framework to identify key formulation variables and optimize the mechanical and physiological properties of baclofen ODT tablets.

Methods: The study begins with risk assessment using the Ishikawa scheme to explore the different process, formulation and environmental factors affecting ODTs. Then, a Plackett-Burman screening design (PBSD) was used to identify the critical independent variables affecting the critical quality attributes (CQAs) of Baclofen ODTs represented by disintegration time (D), hardness(H), and friability (F). Then, a 3² full factorial design was used to optimize the concentrations of significant variables identified by the PBSD.

Results: The most influential factors affecting the quality of Baclofen ODT were successfully identified via Ishikawa analysis. These factors were subsequently quantified through the PBSD and resulted in the finding that Croscarmellose Sodium (CCS) and Microcrystalline Cellulose (MCC) concentrations were the primary determinants of tablet performance. A factorial design was constructed, and 9 formulations were produced. The factorial regression equations developed for friability, hardness, and disintegration time were all statistically significant. Both PBSD and factorial analysis showed that increasing the concentration of CCS significantly prolonged disintegration via gelling-induced pore-blocking. Conversely, increased MCC levels compromised mechanical integrity, resulting in reduced hardness and elevated friability. Numerical optimization identified F3 as the optimum formula since it displayed the highest desirability function (0.74). The optimum formula (F3) has a disintegration time of 22 seconds, a hardness of 5.8 Kg/cm², and its friability values was 0.25%, respectively.

Conclusion: The study successfully replaced the traditional trial and error concept for ODTs development by adopting a systematic QbD approach. The employment of PBSD coupled with factorial optimization ensured a systematic workflow which can efficiently validate the structural and functional performance of the optimized ODTs.

Keywords: Baclofen, orally disintegrating tablet, factorial design, disintegration time, direct compression method

Introduction

The selection of oral solid dosage forms remains the gold standard choice in pharmacotherapy. This is attributed to their described characteristics such as patient preferability, industrial scalability and their inherent chemical stability. Despite these advantages, significant noncompliance exists specifically among patients with dysphagia.

Orally Disintegrating Tablets (ODTs) have been developed to supply the need for a water-independent administration route that ensures rapid drug release upon contact with saliva.¹ According to the definition proposed by FDA, ODT formulation must disintegrate within 30 seconds to bypass the obstacles associated with traditional swallowing, thereby enhancing therapeutic safety and patient compliance.²

Initial development of ODTs served special patient groups with difficulty in swallowing represented by pediatric and elderly patients with Parkinson's disease, schizophrenia, or gastric reflux. However, owing to ODT properties such as quick disintegration, pleasant taste and greater stability compared to oral liquid formulations, their application has expanded greatly.^{3,4}

The primary limitations of ODTs is attributed to their diminished mechanical strength making them prone to capping and surface erosion during shipping.⁵ While numerous manufacturing techniques are available for ODTs formulation—including lyophilization, phase transition, and sublimation—direct compression remains the most prevalent technique owing to its cost-effectiveness, simplicity and industrial familiarity.⁵ This method relies on a precise formulation of excipients, such as diluents, disintegrants, and flavoring agents, which must meet stringent criteria regarding aqueous solubility, rheological behavior, and particle size distribution to ensure compressibility.⁶

The industrial transition from the empirical “trial-and-error” workflows toward sophisticated mathematical modeling based scientific methodologies has become an obligation in today's world. This transition ensures both reproducibility and consistency of the resultant pharmaceutical products.⁷ The quality by design (QbD) framework evolved as a central counterpart in this development in a systematic formulation development program. This starts with predefined objectives and provides a fundamental understanding of both the product and the manufacturing process, evidence-based methodologies and systematic quality risk management.⁸

The Ishikawa (fishbone) diagram is an integral part of QbD that underlies under the classification of qualitative risk assessment, which serves to map and illustrate the complex landscape of formulation and process variables potentially influencing the Critical Quality Attributes (CQAs).⁹ Additionally, Plackett-Burman screening design moved beyond qualitative assumptions to quantitatively filter these variables, allowing for the identification of the “vital few” factors that significantly impact CQAs.¹⁰ On the other hand, a 3² Full Factorial Design is implemented as the core multivariate optimization strategy to provide high-resolution data following this screening.¹¹ This approach is important for understanding complex, non-linear relationships and synergy effects among the most important independent variables at three different levels.¹²

Baclofen is a skeletal muscle relaxant used for reducing spasms and alleviating pain associated with conditions such as multiple sclerosis, spinal cord injuries, fibromyalgia, and myofascial pain.¹³ It acts by a mechanism that involves acting as a GABA agonist at GABA-B receptors within the brain and spinal cord, which results in the hyperpolarization of neurons and the inhibition of substance P release to reduce pain.¹³ Regarding its physicochemical properties, baclofen has a molecular weight of 213 g/mol, a boiling point of 364°C, and a melting point ranging from 372 to 376°C. The drug is slightly soluble in water (5.4 mg/ml) and insoluble in organic solvents like acetone and methanol, but it exhibits high solubility in dilute acids and alkalis.¹⁴ The structure of baclofen is shown in Figure 1.¹⁴

Despite the numerous published work regarding formulation of Baclofen as an ODT, there is limited application to the mathematical models and poor utilization to a systematic DoE approach to evaluate the impact of MCC and CCS on critical quality attributes. The novelty of this work relies on the development of regression equations to optimize the mechanical properties and disintegration time of Baclofen ODT formulations. This research aimed to employ a structured DoE approach to investigate the effect of variables on the performance of Baclofen ODTs by two steps approach consisting from risk assessment (fishbone diagram and PBSD) and factorial optimization. The obtained mathematical models can predict the important CQA leading to enhance the functional and structural properties of Baclofen ODTs.

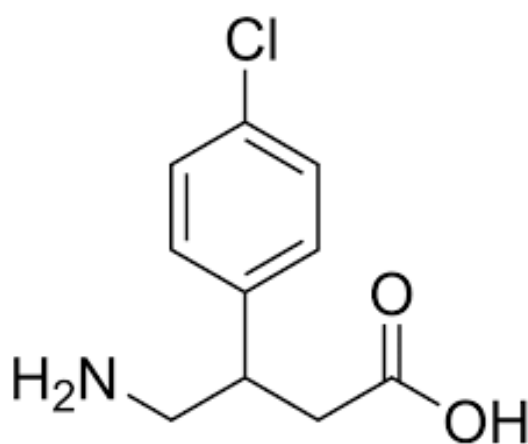


Fig. 1 Chemical structure of Baclofen.¹⁴

Materials and Methods

Materials

Baclofen was purchased from Macklin Biochemical Co., Ltd. Croscarmellose sodium (CCS), Microcrystalline cellulose (MCC), and mannitol were generously provided as gift samples by Pioneer Pharmaceutical Industries, Iraq. Hydrochloric acid (HCl) was obtained from Thomas Baker Chemicals Pvt. Ltd. (India).

Preliminary Risk Assessment (Fishbone Diagram)

Based on existing knowledge from literature review and experimental findings, a fishbone diagram was created in which all risk factors influencing the CQAs of Baclofen ODTs were included. The risk factors were classified into 3 main categories: environmental factors, critical process parameters, and formulation factors. On the other hand, for Baclofen ODTs, the CQA were identified as friability, hardness and disintegration time which ensures the desired product performance.

Plackett–Burman Screening Design (PBSD)

According to the constructed Ishikawa (fishbone) diagram, several independent variables were selected from the CMAs and CPPs which are known for their strong influence on the quality of Baclofen ODTs. These factors were further investigated by the PBSD as illustrated by Table 1.

Formulation Optimization Using 3² Full Factorial Design

A 3² full factorial design was conducted to further investigate the optimal concentration of the two major (MCC and CCS concentrations) variables that emerged from the PBSD. The investigated variables and their perspective levels are shown in Table 2.

Preparation of ODT Batches

The required quantity Baclofen, CCS, MCC and mannitol for each formula was accurately weighted and passed through sieved number 40 mesh to ensure particle size uniformity. The mixture was blended for 7 minutes, after which Magnesium

Table 1. The independent variables with their respective levels used in PBSD

Independent variables	Codes	Low level(-1)	High level(+1)
MCC concentration (%)	A	15	40
CCS concentration (%)	B	2	4
Compression force (psi)	C	4000	5000
Mixing time (minutes)	D	5	15
Lubricant concentration (%)	E	0.5	1
Lubrication time (minutes)	F	2	4

Stearate was added for the final lubrication phase and mixed for 3 minutes. Direct compression was performed using a single-punch table press machine (Model TDP-5, Shanghai Tianfeng Pharmaceutical Machinery Co., Ltd., Shanghai, China) equipped with 6 mm flat-faced punches. The employed compression force was adjusted to 4500 psi. The complete formulation table is illustrated in Table 3.

Pharmacopeial Evaluation and Quality Control

All formulated ODTs were evaluated according to USP/ BP standards to ensure compliance with pharmaceutical requirements:

Friability

Twenty tablets were randomly selected from each formulation and introduced into the drums of the friability tester from Biobase in Jinan, China. The drums in the device were spun 100 times for 4 minutes, at a rate of 25 rotations per minute. According to the standards of Ph. Eur. 10, A weight loss of less than 1% was set as the acceptance criterion.¹⁵

Tablet Hardness

It is the tablet-breaking force per unit area. Hardness determines the tablet's resistance to chipping, abrasion, and breaking during storage, transformation and handling before use. The crushing strength ($n = 10$) was determined using a Monsanto hardness tester to ensure the tablets could withstand handling.¹⁵

Disintegration Time

Fast-disintegrating tablets dissolve in the mouth due to saliva; however, the USP and IP have no tablet disintegration test to imitate *in vivo* settings. In this research, six tablets were randomly selected from each formulation and introduced into the test chambers of the USP Disintegration Apparatus in phosphate buffer 6.8 at $37 \pm 2^\circ\text{C}$. In compliance with FDA guidelines for ODTs, the target disintegration time was set at <30 seconds.¹⁶

Physicochemical Evaluation of the Optimized Formulation

The evaluation was conducted in two sequential phases: the characterization of the powder blend (pre-compression) and the assessment of the finished tablets (post-compression).

Pre-compression (Micromeritic) Characterization

To assess the powder properties of the created ODT formulation powder combination, the values of the angle of repose, flow time, compressibility index, and Hausner's ratio for the optimized formulation were calculated and examined in compliance with the European Pharmacopoeia.⁵

Post-compression Characterization

Weight variation test

Twenty tablets were chosen at random, weighed separately, and the average weight of all the tablets was then determined.

Table 2. Independent factors with their levels and dependent quality attributes with their optimization constraints for the 3^2 factorial design

Variable	Code	Unit	levels			Continuous
Independent variables			Low level(-1)	Medium level(0)	High level(+1)	
MCC concentration	X1	%	15%	27.5%	40%	yes
CCS concentration	X2	%	2	3	4	yes
Dependent variables	Code	Unit	Constraints		Research goal	
			Lower	Upper		
Disintegration time	Y1	minutes	15	30	Minimize	
Hardness	Y2	Kg/cm ²	4	5.5	maximize	
Friability	Y3	%	0	1	Maximize	

Table 3. Quantitative composition of Baclofen ODT batches (F1–F9) optimized via 3^2 full factorial designs

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Baclofen	10	10	10	10	10	10	10	10	10
MCC	40	15	40	27.5	40	27.5	15	15	27.5
CCS	2	3	4	2	3	4	2	4	3
Mg-stearate	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Mannitol Q.S.	100	100	100	100	100	100	100	100	100

*Final table weight is 100 mg, MCC was used in 3 levels constitute 15, 27.5 and 40%, CCS was also used in 3 levels constitute 2, 3 and 4%.

To make sure that variations were within the USP-permitted bounds, the weight of each tablet was compared to the average weight of tablets.¹⁵

Content uniformity test

Using spectroscopic techniques, the Baclofen content of twenty randomly chosen pills was ascertained. A volumetric flask containing 100 ml of phosphate buffer (pH 6.8) was filled with the powdered medication and excipients after the tablets were crushed in a mortar. Prior to concentration measurement using a UV spectrophotometer (Shimadzu1700, Shimadzu Corporation, Kyoto, Japan) at 276 nm, the sample was meticulously combined, filtered, and diluted as needed. There were no drugs in the blank phosphate buffer.¹⁷

In-vitro drug release study

USP Apparatus II (Paddle) was used to conduct dissolution trials ($n = 6$) at 50 rpm in 500 mL of 0.1N HCl, pH 1.2, at $37 \pm 0.5^\circ\text{C}$. Five millilitre aliquots were taken out at regular intervals, filtered, and examined using UV-Vis Spectroscopy at 276 nm. $Q > 80\%$ in 30 minutes was the desired release.¹⁸

Statistical Analysis and Optimization

The data were analyzed using analysis of variance (ANOVA) at a 95% confidence level ($P < 0.05$). The desirability function was utilized to perform numerical optimization, identifying the optimal formulation component where all pharmacopeial requirements were simultaneously satisfied.

Results

Cause-and-Effect Relationship for Baclofen ODTs Utilizing the Ishikawa Diagram

A methodical visual depiction that qualitatively investigates the main causative factors and their secondary causes influencing product quality is the Ishikawa fishbone diagram. The Ishikawa (fishbone) diagram showing the possible causal connections between formulation and process variables and the CQAs of Baclofen ODTs is shown in Figure 2. The graphic directs the selection of variables for ensuing Plackett–Burman screening and optimization studies by highlighting excipient concentrations and critical process parameters as the most significant factors influencing friability, hardness, and disintegration time.

Identification of Significant Factors (Plackett-Burman Screening Design)

The screening phase began with the evaluation of six independent variables to identify those with the most significant impact on the CQA of Baclofen ODTs. Plackett-Burman experimental matrix and results are shown in Table 4.

The Pareto chart analysis obtained from the PBSO is illustrated in Figure 3 below. The chart for the disintegration time shows that both MCC and CCS concentration crossed both the t -value and bonferroni limits. The orange

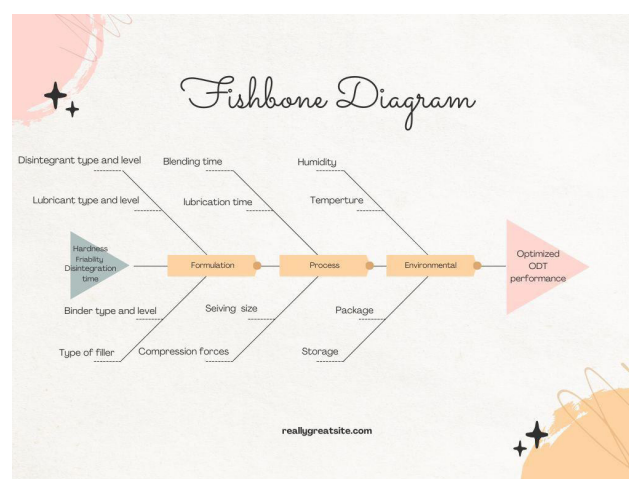


Fig. 2 The Ishikawa (fishbone) diagram that shows the possible causal connections between the CQAs of Baclofen ODTs and formulation and process variables.

bar indicates a positive effect, meaning that increasing the concentration of MCC leads to a significant increase (prolongation) in disintegration time. Similarly, a positive effect was obtained from CCS indicating that increasing the concentration of CCS leads to a significant increase (prolongation) in disintegration time.

On the other hand, the pareto chart for the hardness shows that only MCC concentration crossed both the t -value and bonferroni limits. The blue bar indicates a negative effect, meaning that increasing the concentration of MCC leads to a significant decrease in hardness.

In case of friability, only variables exceeding the t -value and Bonferroni limit are MCC concentrations which showed a positive effect on friability (orange bar). Meaning that increasing the concentration of MCC leads to a significant increase in friability.

Factors such as mixing time and lubrication time were found to be statistically insignificant within the tested ranges. Consequently, these were fixed at their mid-levels for the subsequent optimization phase to simplify the process.

Statistical Analysis of the 3² Factorial Design

The interaction between the two "vital" factors was further explored using a 3² full factorial design as shown in Table 5.

Statistical validation of the experiment's results was achieved using ANOVA as shown in Table 6. According to the obtained results, all of the quadratic models developed for disintegration time, hardness and friability were found to be significant (P -value < 0.05 , $R^2 > 0.95$). Furthermore, the R^2 values for all of the three responses were > 0.95 indicating strong agreement between the actual and predicted values.

The second-order quadratic polynomial equations were obtained for disintegration time, hardness and friability as shown in Equations 1–3. The inclusion of the second-order polynomial terms (A² and B²) indicates a non-linear response surface. This curvature suggests that the influence of MCC and CCS on disintegration and hardness is not constant throughout all of the prepared formulas, but rather changes

Table 4. Plackett-Burman screening design experimental matrix and results

Run	MCC	CCS	Mixing time	Lubricant concentration	Lubrication time	Compression force	Disintegration time	Hardness	Friability
1	40	2	5	1	4	5000	21.2	2.8	0.92
2	15	4	5	1	4	4000	37.5	5.5	0.24
3	15	2	15	1	4	5000	17.8	5.6	0.21
4	15	2	5	0.5	2	4000	18.1	5.4	0.25
5	15	4	15	0.5	2	4000	38.4	5.5	0.22
6	40	4	15	1	4	5000	45.6	2.9	0.89
7	15	4	5	1	2	5000	39.2	5.6	0.21
8	40	2	15	1	2	4000	22.8	2.8	0.9
9	40	2	15	0.5	4	4000	21.5	2.7	0.95
10	40	4	5	0.5	2	4000	44.9	2.9	0.91
11	15	4	5	0.5	4	5000	36.9	5.6	0.23
12	40	2	15	0.5	2	5000	23.1	2.8	0.88

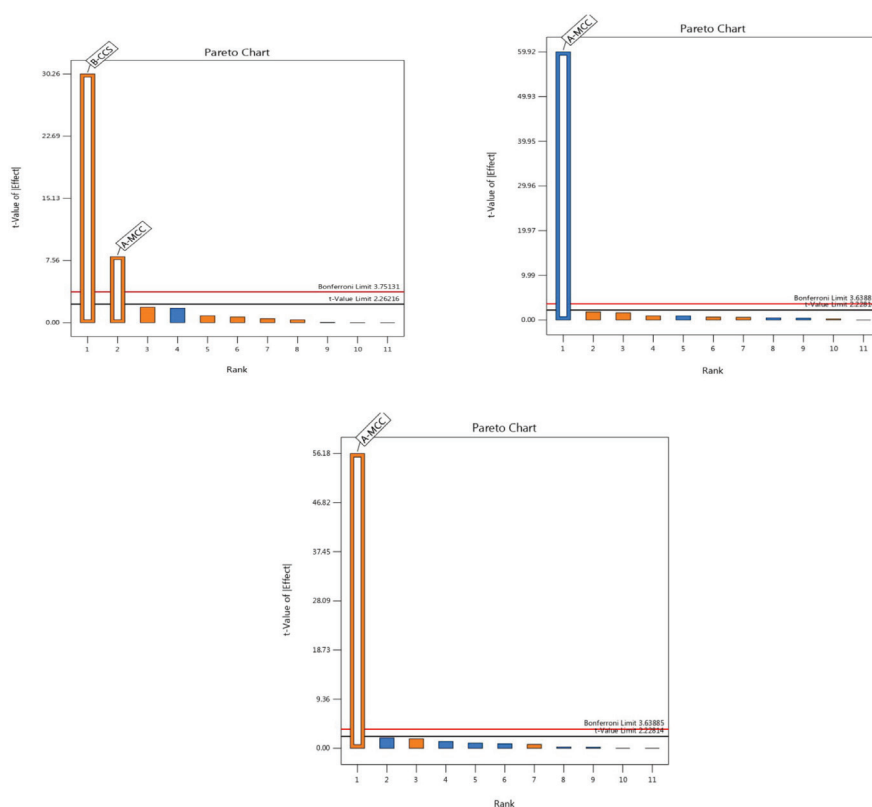


Fig. 3 Pareto charts illustrating the standardized effects of formulation and process variables according to the PBSO on the CQAs of Baclofen ODTs. Orange bar indicates positive effects while the blue bar indicates negative effect.

Table 5. Experimental matrix and results for the 3² full factorial design of Baclofen ODTs

Formula	F1	F2	F3	F4	F5	F6	F7	F8	F9
CCS concentration (%)	+1	-1	+1	0	+1	0	-1	-1	0
MCC concentration (%)	-1	0	+1	-1	0	+1	-1	+1	0
Disintegration time (minutes)	48	28	22	45	32	20	55	18	30
Hardness (Kg/cm ²)	5.2	2.8	5.8	4.2	5.4	4.5	2.6	3	4.1
Friability (%)	0.38	0.95	0.25	0.55	0.32	0.4	0.98	0.88	0.52

in intensity as the concentrations reach their higher or lower limits.

$$D = 33.11 + 0.5556A1 - 1.44A2 + 16.22B1 - 3.11B2 \quad \text{Equation (1)}$$

$$H = 4.18 - 1.38A1 + 0.0889A2 \quad \text{Equation (2)}$$

$$F = 0.5811 + 0.35561A1 - 0.0911A2 \quad \text{Equation (3)}$$

Factor A represents MCC concentration, Factor B represents CCS concentration. A1 and B1 are the linear terms representing the main effects of A and B respectively. A2 and B2 are the quadratic or polynomial terms representing the curvature in the relationship.

The developed regression model for disintegration time (Equation 1) shows that factor B (CCS concentration) has the most dominant effect on the disintegration time owing to its large positive linear coefficient (16.22). Accordingly, the disintegration time is increased (prolonged) by increasing CCS concentration. On the other hand, the effect of factor A (MCC concentration) is determined by its positive linear correlation (+0.5556), which is suggestive of prolongation of the disintegration time as a result of increasing MCC concentration under these specific conditions.

Regarding the mathematical models developed for hardness (Equation 2), it is also seen that the only factor A (MCC concentration) is dominant and it has a significant negative impact (−1.38) on tablet hardness. Accordingly, the hardness of ODT is decreased as a result of increasing MCC concentration. The final model developed for friability (Equation 3). It is clear that only factor A (MCC concentration) is effective and it has a significant positive impact (0.3556) on tablet friability. Accordingly, the friability of ODT is increased as a result of increasing MCC concentration.

Numerical Optimization and Desirability

The desirability function (D) was used as a tool from Design Expert to perform numerical optimization for identifying the optimal formulation. The goal for this step was to minimize disintegration time while maximizing mechanical stability. According to the required optimization parameters, the software identified a solution with a desirability score of 0.746. The optimal levels were determined to be 40% MCC and 4% CCS, as illustrated in Figure 4. According to the desirability ramps, the values for the predicted CQAs will be 5.46 kg for

hardness (H), 0.316% for friability (F), and 20.88 seconds for disintegration time (D).

Validation and Model Confirmation

The final step in the QbD approach is to ensure the validity of the produced models for CCA. This was achieved by comparing the experimental results of the optimized formulation (Run #3) against the values predicted by the Design-Expert software to yield the % Relative Error, which is calculated based on equation 4 below. The results of the validation were summarized in Table 7.

$$\% \text{Relative error} = \frac{\text{Predicted value} - \text{Experimental value}}{\text{Predicted value}}$$

Equation (4)

According to the obtained results, the % relative error for the disintegration time and hardness were 5.36% and 6.23% respectively. These values are located within the typical $\pm 10\%$ and regarded as acceptable ranges. However, in case of friability, the model exhibited a high percentage of error (20.89%). This finding is attributed to the extremely low values involved (Predicted 0.316% vs. Experimental 0.25%) where even small variation in the test condition results in a large mathematical percentage.

Characterization and Quality Control of the Optimized Baclofen ODT

It is essential to prove that the optimized formulation (F3) adheres to the standard pharmacopoeial requirements of ODT preparations. The results of the pre-compression and post-compression tests are illustrated in Table 8. Based on the results for the angle of repose (28.69°) and Hausner ratio (1.14), the powder mixture exhibited excellent flowability. On the other hand, Car's index value (8.64 $\pm$.01) indicated a good compressibility, which are regarded as essential requirements for the direct compression method. Additionally, the results of the post-compression test showed acceptable weight variation and content uniformity results according to USP requirements of exceeding 90%.

The *in vitro* dissolution study for the optimized formulation (F3) showed a unique dissolution kinetics as seen in

Table 6. ANOVA outcome for the 3² full factorial design of Baclofen ODT

Source	F-value	df	P-value	R ²	Adjusted R ²	Predicted R ²	Adequate precision
Model D	22.73	4	0.0052	0.9579	0.9157	0.7867	11.05
A-A	0.3233	2	0.7410	–	–	–	–
B-B	45.14	2	0.0018	–	–	–	–
Residual	–	4	–	–	–	–	–
Model H	90.87	2	<0.0001	0.9680	0.9574	0.9281	19.033
A-A	90.87	2	<0.0001	–	–	–	–
Residual	–	6	–	–	–	–	–
Model F	69.94	2	<0.0001	0.9589	0.9452	0.9075	16.2097
A-A	69.94	2	<0.0001	–	–	–	–
Residual	–	6	–	–	–	–	–

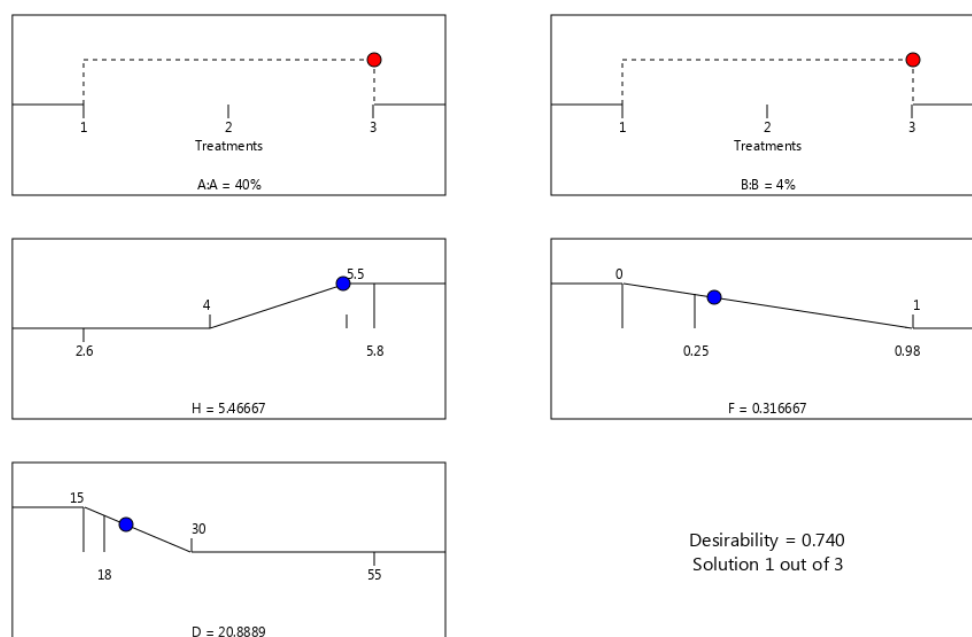


Fig. 4 Optimization of the 3^2 factorial design based on the desirability function.

Table 7. Predicted vs. experimental values for the optimized Baclofen ODT

Response	Predicted value	Experimental value	% Relative error
Disintegration time (s)	20.88	22	5.36%
Hardness (kg)	5.46	5.8	6.23%
Friability (%)	0.316	0.25	20.89%

Table 8. Physicochemical characterization of optimized Baclofen ODT (F3)

Phase	Parameter	Experimental result (Mean $\pm$ SD)	Quality standard /Limit
Precompression	Angle of repose ($^{\circ}$)	28.69 ± 0.01	Excellent flow (25–30) $^{\circ}$
	Bulk density (g/mL)	0.42 ± 0.2	-
	Tapped density (g/mL)	0.48 ± 0.15	-
	Car's index	$8.64 \pm .01$	Good compressibility (11–15%)
	Hausner's ratio	1.14 ± 0.15	Good flow (1.12–1.18)
Post compression	Weight variation (mg)	$99.06 \pm 0.01\%$	Complies (USP $\pm 7.5\%$)
	Content uniformity (%)	$97.25 \pm 1.63\%$	90–110%

Figure 5. This rapid release profile, reaching over 99% dissolution within ten minutes, significantly exceeds the pharmacopeial requirements for immediate-release dosage forms.

Discussion

To overcome the limitations associated with formulation development utilizing the trial and error approach, modern technology was shifted into the systematic Design of Experiments (DoE) framework. However, the major dilemma in ODT formulation is the classical hardness-disintegration paradox which was addressed in several studies using the DoE

approach.¹⁹ The current study aimed to utilize a risk assessment protocol coupled with a two step DoE approach to optimize the disintegration time of Baclofen ODTs without compromising its mechanical strength.

An constructed Ishikawa diagram was performed based on an extensive literature review and successfully addressed the potential risks across formulation, environmental, and processing categories. Furthermore, it greatly enhanced the isolation of high-impact variables for further examination by the PBSD.

The generated pareto charts from the PBSD served to identify the statistical significance of a given independent

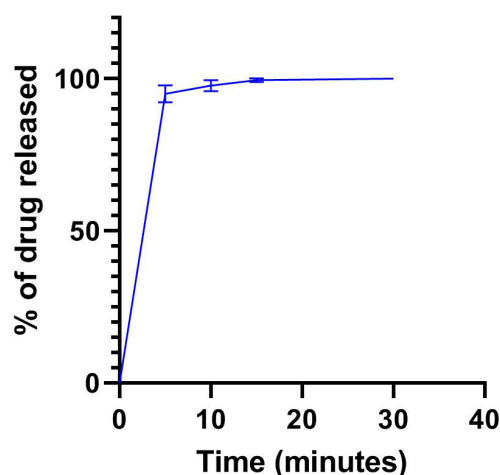


Fig. 5 Dissolution profiles of the optimized Baclofen ODT formulations.

variable depending on the threshold limits of both the t -value and Bonferroni corrections. Furthermore, the pareto charts also showed whether the investigated factors had a positive or negative correlation with the CQA. Analysis confirmed that CCS and MCC concentrations were the dominant factors, justifying their use in the final 3^2 factorial optimization.

Analysis of the variance for the CQAs of Baclofen ODTs generated by 3^2 full factorial designs confirmed that all of the developed quadratic regression equations were significant ($P < 0.05$). This indicates that the observed variations in tablet properties are not due to random chance but are directly controlled by the concentrations of CCS and MCC as indicated by their regression equations.

According to the equation obtained for disintegration time in the full factorial design, both factor A (MCC concentration) and factor B (CCS concentration) carries a positive sign, indicating that increasing their amount leads to prolongation in the disintegration time. This result is compatible with that obtained from the pareto chart of PBSD. Furthermore, CCS has a larger coefficient than MCC indicating its more predominant effect on the disintegration time. The efficacy of CCS as a super disintegrant is driven by extensive polymer expansion and fluid absorption.²⁰ Despite being insoluble in water, the well-known tablet disintegrant CCS swells significantly (4–8 times its original volume) upon contact with water.¹⁹ However, behind certain concentration limits, CCS significant swelling (4–8 times its original volume) causing the formation of viscous gel layer that hinders tablet disintegration.¹⁹

Additionally, statistical analysis also showed that factor A (MCC concentration) is the primary driver for tablet mechanical properties represented by hardness and friability as indicated by their equations (2 and 3). Despite its effect being contradictory to its binding properties, there are several mechanisms that can explain this phenomenon. MCC is known for its plastic deformation and its use in high concentration lead to a disruption in the interparticle bonding network among the basic components of the formulation and interfered with its ability to form a cohesive matrix through hydrogen bonding.²¹ Additionally, the high porosity and low bulk density of MCC without sufficient compression force can result in reduction in the tensile strength manifested as softer tablets.²² The case is similar for friability and increasing MCC

concentration is coupled with increased friability percentage since it causes a compromised tensile strength as documented by another research.²³

The good flowability and compressibility characteristics of the powder blend for the optimized formulation (F3) resulted in ODTs with high content uniformity and small weight variation with limits that are acceptable by the pharmacopoeial guidelines. Furthermore, the optimized formulation (F3) successfully passed the dissolution test which is coupled by achieving the required balance between the enhanced mechanical properties (hardness and friability) and rapid disintegration. These findings confirm the effectiveness of the 3^2 factorial design as a powerful tool in the achievement of a high-performance, and robust Baclofen delivery system.

Limitation of the Current Study

Despite the excellent predictability of the mathematical models obtained from the current study, a relatively high prediction of error was obtained for friability (20.89%). This is related to the low experimental values for friability so that even a minor deviation increases the percentage of error. Accordingly, this limitation does not affect the practical reliability of the optimized formulation.

Conclusion

The research design was very successful in using two stages of systematic DoE approach to create an optimized ODT of Baclofen which can be an effective solution for patients with dysphagia. The optimized ODT successfully balanced between the rapid disintegration and mechanical integrity. Additionally, the optimized ODTs meet all the quality control requirements for weight variation, content uniformity and dissolution. The findings of the current study supports the implementation of the QbD approach to generate high quality pharmaceutical products.

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Data Availability Statement

All data results obtained from experimental procedures or analysis during this study are included in this article.

Ethics Statements

The authors declare that all procedures followed in the current study were performed *in vitro* and that no ethical approval was required from an ethics committee.

Conflict of Interest

The authors declare that there were no conflicts of interest regarding the publication of this paper.

Author's Contribution

The authors confirm their contribution to the paper as follows: study conception and design: Noor Yousif Fareed and Nuha Mohammed Abdulkhaleq, Experimental work: Nuha Mohammed Abdulkhaleq, Zainab M. Abdulkhaleq and Zaid M Abdul Khalik, Results interpretation: Noor Yousif Fareed and Nuha Mohammed Abdulkhaleq. Statistical analysis and draft manuscript writing, Noor Yousif Fareed and Ghada

Hamid Naji. All authors reviewed the results and approved the final version of the manuscript.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used Grammarly and quillbot to improve the grammatical flow and refine the linguistic expression of the manuscript. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the scientific content and integrity of the published work. ■

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