RESEARCH PAPER

DEVELOPMENT AND OPTIMIZATION OF APREPITANT MEDICATED CHOCOLATES BY BOX–BEHNKEN EXPERIMENTAL DESIGN

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ABSTRACT
The present study aimed to develop and optimize Aprepitant medicated chocolates using a Box–Behnken experimental design to enhance drug delivery and patient compliance. Aprepitant, a poorly water-soluble drug used in the management of chemotherapy-induced nausea and vomiting, was incorporated into a chocolate-based dosage form to improve palatability and bioavailability. The formulation variables selected for optimization were cocoa butter (X_1), carob powder (X_2), and milk powder (X_3), while drug content and in-vitro drug release were considered as dependent responses. A total of 13 formulations were prepared as per the Box–Behnken design and evaluated for physicochemical properties, drug content, and in-vitro drug release. The drug content of all formulations ranged from 93.25% to 99.12%, indicating uniform distribution of the drug. In-vitro drug release studies showed a maximum release of 98.25% within 60 minutes. Among all formulations, F12 was identified as the optimized formulation, exhibiting desirable drug content, maximum drug release, good mechanical strength, and excellent organoleptic properties. The optimized formulation showed close agreement between predicted and experimental values, confirming the reliability of the statistical model. Overall, the study demonstrates that medicated chocolates can serve as an effective and patient-friendly dosage form for Aprepitant, offering improved drug release and acceptability.
Keywords: Aprepitant, Medicated chocolates, Box–Behnken design, Drug content, In-vitro drug release, Optimization, Oral drug delivery, Patient compliance.
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Introduction

Oral drug delivery remains the most preferred route of administration due to its convenience, patient compliance, and cost-effectiveness (Baryakova et al., 2023). However, conventional oral dosage forms such as tablets and capsules may present challenges for certain patient populations, including pediatric, geriatric, and patients experiencing nausea or vomiting (Lopez et al., 2015).

To overcome these limitations, medicated confectionery dosage forms such as chocolates have emerged as an innovative and patient-friendly alternative, offering improved palatability, ease of administration, and enhanced compliance (Hanwate et al., 2026).

Medicated chocolates are solid dispersions of drug in a chocolate base, which not only masks the unpleasant taste of drugs but also provides a smooth mouthfeel and rapid melting at body temperature (Pillai et al., 2024). The lipid-based matrix of chocolate can enhance the solubility and bioavailability of poorly water-soluble drugs by promoting dissolution and absorption. Additionally, chocolates can serve as an effective carrier for drugs requiring rapid onset or improved patient acceptability (Rabie et al., 2026).

Aprepitant is a neurokinin-1 (NK1) receptor antagonist widely used in the prevention of chemotherapy-induced nausea and vomiting (CINV). Despite its therapeutic efficacy, Aprepitant exhibits poor aqueous solubility and variable bioavailability, which may limit its clinical performance (Hargreaves et al., 2011). Therefore, the development of an alternative dosage form such as medicated chocolates can improve its solubility, mask its taste, and enhance patient compliance, especially in patients who have difficulty swallowing conventional dosage forms.

Optimization of formulation variables is a critical step in the development of an efficient dosage form. Statistical tools such as the Box–Behnken design provide a systematic and reliable approach to evaluate the effects of multiple formulation variables and their interactions on significant quality attributes. This design reduces the number of experimental trials while ensuring accurate optimization through the development of predictive mathematical models.

In the present study, Aprepitant medicated chocolates were developed and optimized using Box–Behnken experimental design. The effects of selected independent variables on key responses such as drug content, hardness, and drug release were investigated. The optimized formulation was further evaluated for its physicochemical properties and in-vitro drug release behavior to assess its potential as a novel and effective oral drug delivery system.

Material and Methods

Material

Aprepitant was used as the active pharmaceutical ingredient for the preparation of medicated chocolates. Cocoa butter was employed as the primary lipid base, while carob powder and milk powder were used as functional excipients to enhance taste, texture, and uniformity. Soya lecithin was incorporated as an emulsifying agent, and chocolate essence was added for flavor enhancement. Sugar was used as a sweetening agent to improve palatability. Organic solvents and all other reagents used in the study were of analytical grade and used without further purification.

Methods

Preparation of Aprepitant Chocolates as per Box–Behnken Design

Aprepitant chocolates were prepared according to the experimental runs generated by a Box–Behnken design, employing three independent formulation variables at three levels: cocoa butter concentration (X_1), carob powder concentration (X_2), and milk powder concentration (X_3), while all other ingredients were kept constant (Reddy et al., 2017). The dependent variables selected for optimization were drug content and in-vitro drug release, both targeted for maximization.

For each experimental run, the required quantities of ingredients were accurately weighed as per the design matrix. Cocoa butter (X_1) was melted using a water bath at 45–48 °C, followed by controlled cooling to 27–28 °C and subsequent reheating to 30–32 °C to achieve proper tempering. Soya lecithin and chocolate essence were added to the tempered cocoa butter under continuous stirring.

Aprepitant was first premixed with a portion of the variable solid phase components, namely carob powder (X_2) and/or milk powder (X_3), to ensure uniform drug distribution. This premix was gradually incorporated into the molten cocoa butter while maintaining the working temperature. The remaining quantity of carob powder, milk powder, and sugar was added slowly with continuous mixing to obtain a homogeneous chocolate mass.

The prepared mixture was subjected to gentle deaeration to remove entrapped air and then poured into pre-warmed chocolate molds corresponding to individual Box–Behnken experimental runs. The molds were tapped lightly to eliminate air bubbles and allowed to set at 18–20 °C, with brief refrigeration when required to facilitate solidification. The solidified chocolates were carefully demolded, wrapped in moisture-resistant packaging material, and stored at 15–25°C until further evaluation.

Table 1: Formulation variable using box behnken design

Independent Variable	Low (−1)	Medium (0)	High (+1)
Cocoa butter (g)	2.0	3.0	4.0
Carob powder (g)	0.5	1.25	2.0
Milk powder (g)	0	0.25	0.5
Dependent variable			
Drug Content (%)	Maximize		
In-vitro drug release (%)	Maximize		

Table 2: Box–Behnken Design Layout with Independent Formulation Variables

F. Code	std	Run	Factor 1 A: Cocoa butter	Factor 2 B: Carob powder	Factor 3 C: Milk powder
F1	5	1	2	1.25	0
F2	10	2	3	2	0
F3	1	3	2	0.5	0.25
F4	14	4	3	1.25	0.25
F5	6	5	4	1.25	0
F6	8	7	4	1.25	0.5
F7	11	8	3	0.5	0.5
F8	7	9	2	1.25	0.5
F9	12	11	3	2	0.5
F10	3	12	2	2	0.25
F11	2	13	4	0.5	0.25
F12	9	14	3	0.5	0
F13	4	16	4	2	0.25

Final Equation in Terms of Coded Factors

Drug Content (%) = 96.776 − 0.175A + 0.355B − 0.015C + 1.3675AB + 0.8825AC − 1.2225BC − 0.4993A² − 0.5593B² + 1.4908C².

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.

Final Equation in Terms of Actual Factors

Drug Content (%) = 99.616 − 0.3412(Cocoa butter) − 0.8811(Carob powder) − 14.426(Milk powder) 1.8233(Cocoa butter × Carob powder) + 3.5300(Cocoa butter × Milk powder) − 6.5200(Carob powder × Milk powder) − 0.4993(Cocoa butter)² − 0.9942(Carob powder)² + 23.8520(Milk powder)²

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. This equation should not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor and the intercept is not at the center of the design space.

Final Equation in Terms of Coded Factors

In-Vitro Drug Release (%) = 95.024 + 0.3325A − 0.5825B − 0.9500C + 0.4500AB − 0.4500AC − 0.6500BC − 2.3120A² + 1.7880B² − 0.4120C²

In-Vitro Drug Release (%) = 95.024 + 0.3325A − 0.5825B − 0.9500C + 0.4500AB − 0.4500AC − 0.6500BC − 2.3120A² + 1.7880B² − 0.4120C²

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.

Final Equation in Terms of Actual Factors

In-Vitro Drug Release (%) = 79.511 + 13.9045(Cocoa butter) − 9.6567(Carob powder) + 9.2293(Milk powder) 0.6000(Cocoa butter × Carob powder) − 1.8000(Cocoa butter × Milk powder) − 3.4667(Carob powder × Milk powder) − 2.3120(Cocoa butter)² + 3.1787(Carob powder)² − 6.5920(Milk powder)²

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. This equation should not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor and the intercept is not at the center of the design space.

Evaluation of Formulation

Physical Appearance: The surface texture of each formulation was examined for grittiness or stickiness, along with visual inspection of color, appearance, and odor (Viswanath *et al.,* 2015).

Drug Content Determination: Using a UV spectrophotometer, chocolates were dissolved in 20 mL ethanol, sonicated, centrifuged at 2500 rpm for 15 minutes, and filtered (Vasani and Shah, 2016). The supernatant was analyzed at λ_{max} 210nm using ethanol as a blank.

Disintegration Test: Performed using a USP disintegration tester at 37 ± 0.5°C and 60 rpm. Three smaller chocolates (same API concentration as main formulations) were placed in distilled water, and disintegration time was recorded (Prasanna *et al.,* 2016).

Melting Point: Formulations were placed in porcelain dishes, submerged in a water bath on a tripod stand, and heated (Sunil *et al.,* 2010). The melting temperature was recorded using a thermometer once complete melting occurred.

Hardness: Chocolate strength was determined using a Monsanto hardness tester, expressed in kg/cm² (Yogesh *et al.,* 2021). Smaller-sized chocolates of each formulation were prepared to fit into the tester, and hardness measurements were taken in triplicate, with the mean value calculated.

Loss on Drying (LOD): This thermogravimetric test determined weight loss due to water or volatile matter (Mayank and Jain, 2012). Samples were weighed in porcelain dishes, heated in a hot-air oven, and reweighed at intervals until constant weight was achieved.

***In Vitro* Drug Release:** Using USP II apparatus, chocolates were tested in 500 mL pH 7.4 saline phosphate buffer at 37 ± 0.5°C, 100 rpm, for 60 minutes (Pawar *et al.,* 2019). Samples (5 mL) were collected at 5-minute intervals, replaced with fresh medium, filtered, and analyzed via UV spectrophotometry to determine cumulative drug release.

Results and Discussion

The present study successfully demonstrated the formulation and optimization of Aprepitant medicated chocolates using the Box–Behnken experimental design, where the effects of cocoa butter (X_1), carob powder (X_2), and milk powder (X_3) were systematically investigated (Table 1 and Table 2).

The results of drug content and percentage drug release presented in Table 3 indicate that all

formulations exhibited satisfactory drug content ranging from 93.25% to 99.12%, confirming uniform distribution of Aprepitant within the chocolate matrix. Formulation F2 showed the highest drug content (99.12%), whereas F11 exhibited the lowest value (93.25%). These minor variations may be attributed to differences in mixing efficiency and excipient composition; however, all formulations remained within acceptable limits.

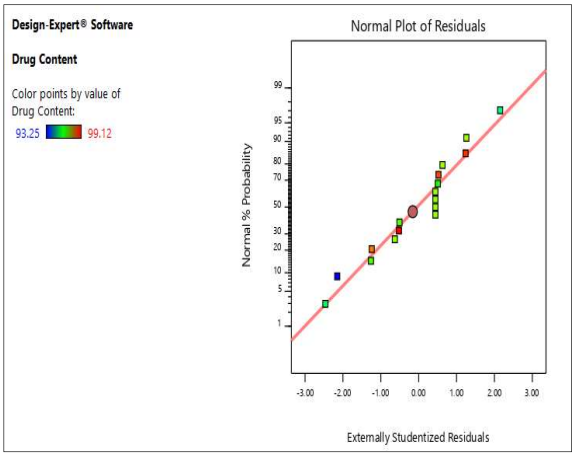
The in-vitro drug release profiles summarized in Table 5 showed a gradual and time-dependent increase in drug release for all formulations. At 60 minutes, drug release ranged from 91.45% to 98.25%. Among all formulations, F12 exhibited the highest drug release (98.25%), indicating superior dissolution behavior. This observation is also consistent with the results reported in Table 3**,** confirming the optimized performance of F12. The enhanced release may be due to an optimal balance of hydrophilic and lipophilic components, which improved drug dispersion and wettability.

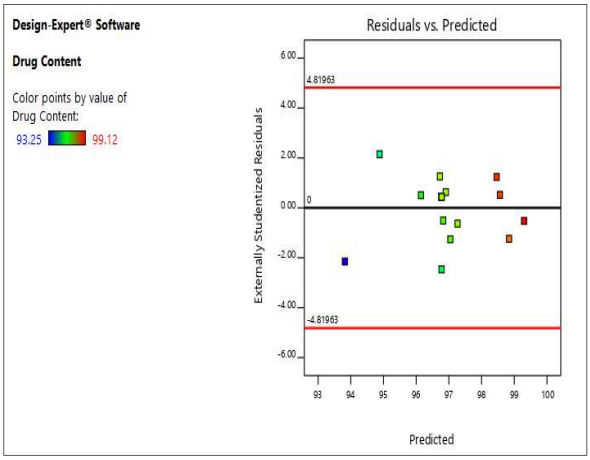
The physicochemical and organoleptic evaluation parameters provided in Table 4 revealed that all formulations possessed acceptable melting point, hardness, and moisture content. Formulation F12 exhibited the highest hardness (3.8 kg/cm²) and lowest loss on drying (2.18%), indicating better mechanical strength and stability. In addition, F12 demonstrated excellent organoleptic properties such as pleasant taste, smooth mouthfeel, and absence of aftertaste, which are crucial for improving patient compliance. In contrast, formulations like F3, F5, and F6 showed bitterness and grittiness, which may reduce acceptability.

The response surface methodology and graphical analysis illustrated in Figure 1 and Figure 2 clearly depict the influence of formulation variables on drug content and drug release. The contour and 3D surface plots indicate that an optimal combination of cocoa butter, carob powder, and milk powder is essential to achieve desirable formulation characteristics. Cocoa butter influenced the structural integrity and release profile, while carob powder and milk powder contributed to taste masking and improved dispersion of the drug.

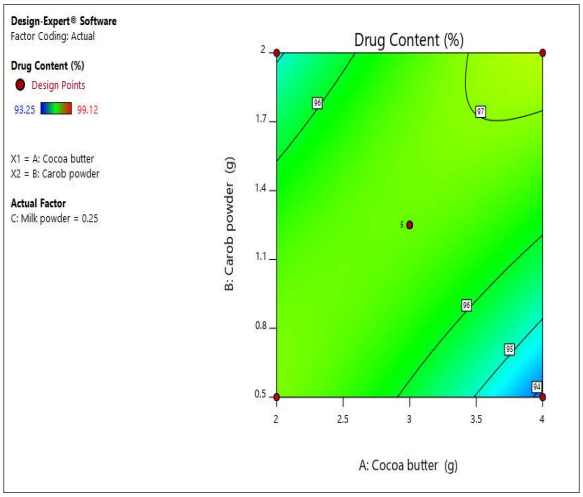
The comparison of predicted and experimental responses for the optimized formulation F12, as shown in Table 6, demonstrated close agreement between the predicted and observed values. The predicted drug content and drug release values were very close to the experimental results, confirming the validity and reliability of the Box–Behnken design model in optimization.

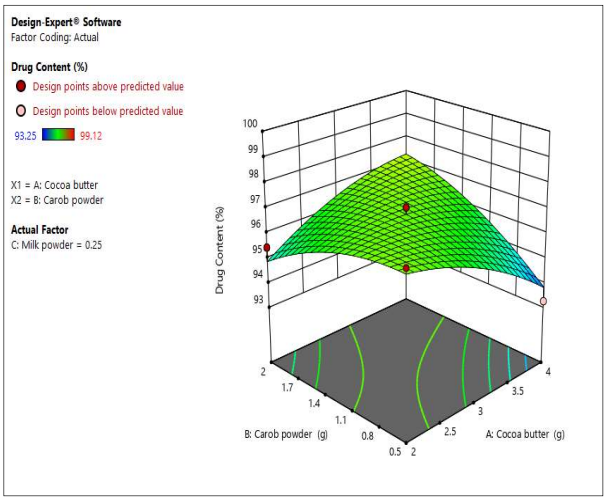
The study confirms that formulation F12 is the optimized batch, exhibiting high drug content, maximum drug release, desirable physicochemical properties, and excellent organoleptic characteristics. The findings highlight that the Box–Behnken design is an effective tool for formulation optimization, and medicated chocolates represent a promising and patient-friendly dosage form for the delivery of Aprepitant.





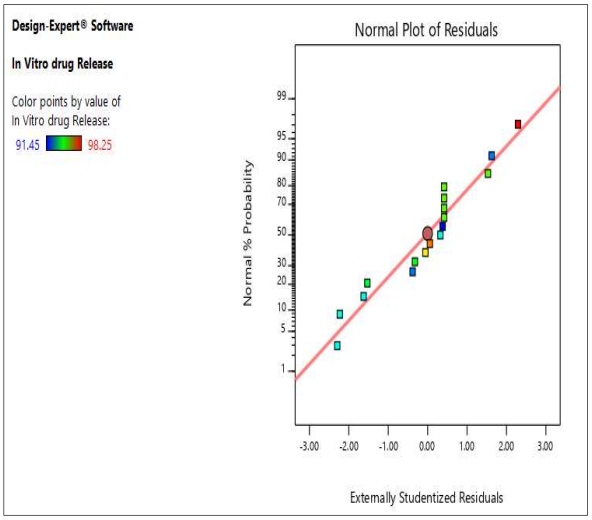
Graph of normal plots for residuals **Graph of normal plots for residuals vs prdicted**

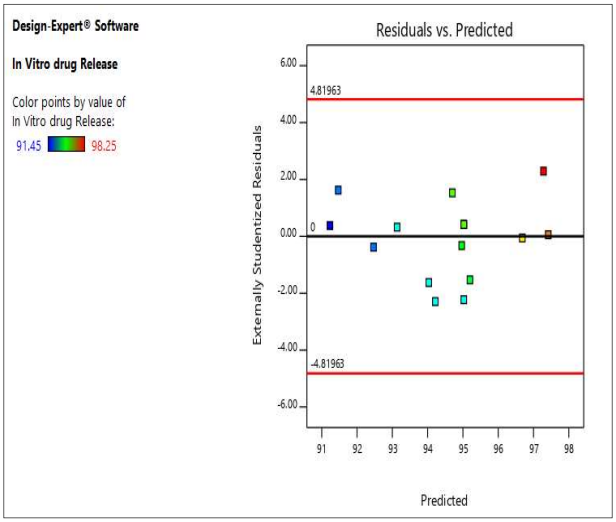




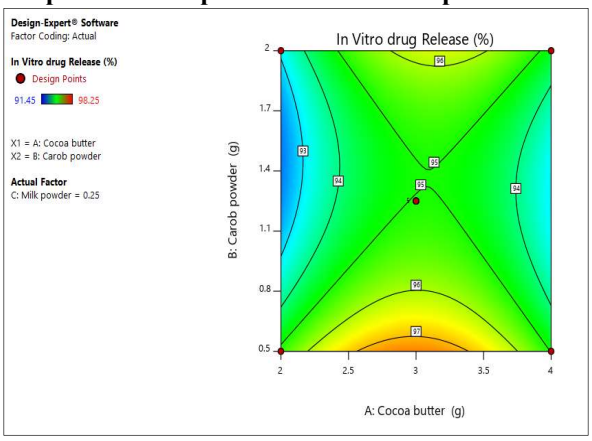
Contour plots of cocoa butter vs carob powder 3D plots of cocoa butter vs carob powder

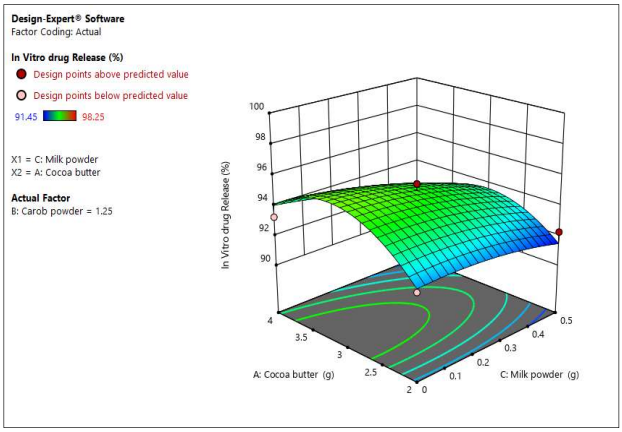
Figure 1: Different graphs for drug content obtained by DOE





Graph of normal plots for residuals Graph of normal plots for residuals vs prdicted





Contour plots of cocoa butter vs carob powder
3D plots of cocoa butter vs milk powder
Figure 2: Different graphs for In-vitro drug Release obtained by DOE

Table 3: Results of Drug Content and % Drug release

F. Code	Drug Content	% Drug release after 60min
F1	98.45	92.25
F2	99.12	97.45
F3	97.12	94.45
F4	97.05	95.45
F5	97.12	93.25
F6	98.85	91.45
F7	98.74	96.65
F8	96.65	92.25
F9	96.65	93.25
F10	95.45	93.32
F11	93.25	94.78
F12	**96.32**	**98.25**
F13	97.05	95.45

Table 4: Evaluation Parameters of Formulations F1–F13

Formulation	Melting Point (°C)	Hardness (kg/cm²)	LOD (%)	Taste	Mouthfeel	Aftertaste	Overall Acceptability
F1	158–160	3.2	2.45	Slightly bitter	Acceptable	Slight bitterness	Acceptable
F2	159–161	3.4	2.38	Slightly bitter	Smooth	Mild	Acceptable
F3	157–159	3.1	2.52	Bitter	Slightly gritty	Bitter	Fair
F4	160–162	3.5	2.30	Slightly bitter	Smooth	Minimal	Good
F5	158–160	3.3	2.41	Bitter	Slightly rough	Bitter	Fair
F6	156–158	3.0	2.60	Bitter	Gritty	Bitter	Poor
F7	160–162	3.6	2.28	Slightly bitter	Smooth	Minimal	Good
F8	158–160	3.2	2.47	Slightly bitter	Acceptable	Mild	Acceptable
F9	159–161	3.4	2.35	Slightly bitter	Smooth	Minimal	Good
F10	158–160	3.3	2.40	Slight bitterness	Acceptable	Mild	Acceptable
F11	160–162	3.5	2.32	Slightly bitter	Smooth	Minimal	Good
F12	**161–163**	**3.8**	**2.18**	**Pleasant**	**Very smooth**	**No aftertaste**	**Excellent**
F13	159–161	3.4	2.36	Slightly bitter	Smooth	Minimal	Good

Table 5: In-vitro drug release profile (%) of formulation F1 to F13

Ti	F1	F2	F3	F4	F5	F6	F7	F8	F9	F1	F1	F1	F1

me (min)										**0**	**1**	**2**	**3**
15	23.06	24.36	23.61	23.86	23.31	22.86	24.16	23.06	23.31	23.33	23.70	**24.56**	23.86
30	46.13	48.73	47.23	47.73	46.63	45.73	48.33	46.13	46.63	46.66	47.39	**49.13**	47.73
45	69.19	73.09	70.84	71.59	69.94	68.59	72.49	69.19	69.94	69.99	71.09	**73.69**	71.59
60	92.25	97.45	94.45	95.45	93.25	91.45	96.65	92.25	93.25	93.32	94.78	**98.25**	95.45

Table 6: Comparison of Predicted and Experimental Responses of Optimized Formulation (F12)

Response Parameter	Predicted Value (%)	Experimental (Actual) Value (%)
Drug release (%)	96.14	96.32
% Drug release after 60 min	97.28	98.25

Conclusion

The present study successfully demonstrated the development and optimization of Aprepitant medicated chocolates using the Box–Behnken experimental design. The selected formulation variables cocoa butter, carob powder, and milk powder were found to significantly influence drug content and in-vitro drug release. All formulations exhibited acceptable physicochemical properties and uniform drug distribution. Among them, formulation F12 was identified as the optimized batch, showing high drug content, maximum drug release, desirable mechanical strength, and excellent organoleptic characteristics such as pleasant taste and smooth mouthfeel. The optimized formulation also showed close agreement between predicted and experimental responses, confirming the reliability of the statistical model. The study highlights that medicated chocolates can serve as a novel, patient-friendly, and effective oral dosage form for Aprepitant, particularly for patients who have difficulty swallowing conventional dosage forms. Additionally, the Box–Behnken design proved to be a valuable tool for systematic optimization, reducing experimental trials while ensuring accurate results.

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