RESEARCH PAPER

DEVELOPMENT, OPTIMIZATION AND EVALUATION OF APREPITANT-MEDICATED CHOCOLATE AS A PATIENT-FRIENDLY ORAL DRUG DELIVERY SYSTEM FOR THE MANAGEMENT OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

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Abstract
Aprepitant is a neurokinin-1 (NK1) receptor antagonist widely used for the prevention of chemotherapy-induced nausea and vomiting (CINV). However, its poor aqueous solubility and conventional dosage forms may limit patient acceptability and therapeutic performance. The present study aimed to develop a palatable chocolate-based oral dosage form of aprepitant with improved patient compliance while maintaining its pharmaceutical quality and antiemetic efficacy. Nine aprepitant-medicated chocolate formulations (F1–F9) were prepared using the chocolate tempering method by varying the concentrations of cocoa butter, carob powder, and milk powder. The formulations were evaluated for physical appearance, organoleptic properties, melting point, hardness, loss on drying (LOD), drug content, and in vitro drug release. The optimized formulation was further assessed for antiemetic activity using the copper sulfate-induced emesis model and compared with the standard antiemetic drug, domperidone. Formulations F1–F6 exhibited smooth texture, glossy appearance, and good sensory acceptability, whereas F7–F9 showed fat bloom, oiling, and poor organoleptic characteristics. Drug content ranged from 93.8 ± 2.0% to 99.1 ± 0.4%, while cumulative drug release after 60 min ranged from 75.6 ± 0.25% to 97.1 ± 0.32%. Formulation F6 demonstrated the most desirable physicochemical properties, including a melting point of 32.2 ± 0.1°C, hardness of 3.8 ± 0.32 kg/cm², low moisture content (0.76 ± 0.03%), drug content of 99.0 ± 0.4%, and the highest drug release (97.1 ± 0.32%). In the in vivo antiemetic study, the optimized formulation produced dose-dependent inhibition of emesis, with 73.31% inhibition at 20 mg/kg, exceeding the activity observed with domperidone (66.96%). The developed aprepitant-medicated chocolate formulation demonstrated excellent physicochemical properties, high drug content, rapid drug release, favorable sensory characteristics, and significant antiemetic activity. The optimized formulation offers a patient-friendly alternative oral dosage form with potential advantages in improving compliance and therapeutic effectiveness for the management of chemotherapy-induced nausea and vomiting.

Keywords: Aprepitant; Medicated chocolate; Chocolate-based drug delivery system; Cocoa butter; Carob powder; Drug release; Antiemetic activity; Chemotherapy-induced nausea and vomiting (CINV); Patient compliance; Oral drug delivery.

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.Introduction

Chemotherapy-induced nausea and vomiting (CINV) remains one of the most distressing adverse effects experienced by cancer patients undergoing chemotherapy (Gupta et al., 2021). Despite significant advances in antiemetic therapy, uncontrolled nausea and vomiting can adversely affect nutritional status, quality of life, treatment adherence, and overall therapeutic outcomes. Effective management of CINV is therefore essential to improve patient comfort and ensure successful completion of chemotherapy regimens (Gautam et al., 2023).

Aprepitant is a selective neurokinin-1 (NK1) receptor antagonist that blocks the binding of substance P in the central nervous system and is widely used in combination with 5-hydroxytryptamine-3 (5-HT3) receptor antagonists and corticosteroids for the prevention of acute and delayed CINV (Navari, 2004). Owing to its unique mechanism of action, aprepitant has demonstrated superior efficacy in reducing delayed emesis compared with conventional antiemetic agents. However, aprepitant belongs to the Biopharmaceutics Classification System (BCS) Class II and exhibits poor aqueous solubility, which may limit its dissolution rate and oral bioavailability. Furthermore, conventional capsule formulations may not be suitable for pediatric, geriatric, or dysphagic patients who experience difficulty swallowing solid oral dosage forms (Nazlı et al., 2023).

Novel oral drug delivery systems have gained considerable attention for improving patient compliance while enhancing drug performance. Among these, medicated chocolates represent an attractive alternative because of their pleasant taste, ease of administration, high patient acceptability, and ability to mask the unpleasant taste of drugs (Naqvi et al., 2022). Chocolate-based dosage forms possess a lipid-rich matrix that melts rapidly at body temperature, facilitating drug release in the oral cavity and gastrointestinal tract. In addition, chocolate formulations are particularly suitable for pediatric and geriatric populations due to their palatability and convenience. The incorporation of pharmaceutical excipients within a chocolate matrix also enables the development of stable and elegant dosage forms with desirable organoleptic properties (Al-Kabariti et al., 2024).

Cocoa butter is the principal structural component of chocolate and exhibits excellent melting characteristics, remaining solid at room temperature while melting near body temperature. Carob powder has emerged as a valuable cocoa substitute owing to its pleasant flavor, natural sweetness, dietary fiber content, and antioxidant constituents. Milk powder contributes to improved texture, creaminess, and taste masking, while soya lecithin acts as an emulsifying agent that enhances the homogeneity and stability of the formulation. Appropriate optimization of these ingredients is critical for achieving acceptable mechanical strength, melting behavior, sensory characteristics, and drug release (Balcázar-Zumaeta et al., 2026).

Several investigations have explored medicated chocolate formulations as patient-friendly oral dosage forms for drugs intended for pediatric and special patient populations (HS et al., 2025). However, limited information is available regarding the formulation of aprepitant into a chocolate-based delivery system. Therefore, the development of an optimized aprepitant-medicated chocolate may provide an effective strategy to improve patient compliance without compromising pharmaceutical quality or therapeutic efficacy.

In the present study, aprepitant-medicated chocolates were prepared by the conventional chocolate tempering method using cocoa butter, carob powder, milk powder, soya lecithin, and chocolate essence. The formulations were evaluated for physicochemical characteristics, organoleptic properties, melting point, hardness, moisture content, drug content, and *in vitro* drug release. The optimized formulation was further investigated for its antiemetic activity using a copper sulfate-induced emesis model to assess its therapeutic potential as a patient-friendly oral dosage form for the management of chemotherapy-induced nausea and vomiting.

Material and Methods

Material

Aprepitant was obtained as a gift sample from Bioplus Life Science, Bangalore, India. Cocoa butter was procured from Arboreal Bioinnovations Private Limited, New Delhi, India, carob powder from Tungal Farms, Karnataka, India, soya lecithin from HiMedia Laboratories Pvt. Ltd., Mumbai, India, and chocolate essence from Fab Flavours & Fragrances Private Limited, New Delhi, India. Methanol, ethanol, hydrochloric acid, sodium hydroxide, and monopotassium phosphate of analytical reagent (AR) grade were purchased from S. D. Fine Chem. Ltd., Mumbai, India, while chloroform (AR grade) was procured from Chem Pure Pvt. Ltd., Mumbai, India. All chemicals and reagents used in the study were of analytical grade and were used as received without further purification.

Methods

Formulation of Aprepitant chocolates

F1-F9 Aprepitant chocolates were formulated using the procedure described by Reddy et al., (2017), where precise amounts of each ingredient were used as per formulations. Cocoa butter has been melted at temperatures ranging from 45-48°C, cooled to 27-28°C, and tempered at 30-32°C. Then, Soya Lecithin and Chocolate essence was added, followed by 125mg of Aprepitant in combination with a portion of Carob and Milk powder. Other powders and sugar were added gradually. Deaeration of this homogenous solution and casting into molds was carried out. Air bubbles were released and chocolates were set at room temperature (18-20°C) or chilled briefly. Chocolates were then demolded and wrapped in moisture-proof packages for storage at temperatures between 15-25°C.

Table 1: Formulation ingredient of Aprepitant Chocolates

Sr. No.	**Ingredient (per chocolate)**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	Aprepitant	0.04	0.04	0.04	0.04	0.04	**0.04**	0.04	0.04	0.04
2	Coco a	2.0	2.0	2.5	2.5	3.0	**3.0**	4.0	4.0	4.0

	butter									
3	Carob powder	0.5	1.0	0.5	1.5	1.0	**1.5**	2.0	1.0	2.0
4	Milk powder	0.5	0.5	0.5	–	–	**–**	0.5	–	–
5	Sugar	1.0	1.0	1.0	1.0	1.0	**1.0**	1.0	1.0	1.0
6	Soya lecithin	0.2	0.2	0.2	0.2	0.2	**0.2**	0.2	0.2	0.2
7	Chocolate essence	1 drop	1 drop	1 drop	1 drop	1 drop	**1 drop**	1 drop	1 drop	1 drop

Evaluation of Aprepitant chocolates

Evaluation of the prepared formulations of chocolate was carried out using the following criteria:

Physical Appearance

Surface smoothness was determined based on grittiness or stickiness, and color, appearance, and smells were evaluated (Viswanath *et al.,* 2015).

Drug Content Determination

Use a UV, chocolates were dissolved in 20 mL ethanol and then sonicated, centrifuged at 2500 rpm for 15 minutes, and filtered (Vasani and Shah, 2016). Absorbance reading was performed at λmax 210 nm by using ethanol as a blank.

Disintegration Test

Performed using a USP disintegration tester at 37 ± 0.5°C and 60 rpm. Three smaller chocolates (with same API concentration as other formulations) were put into distilled water and time to disintegrate was recorded. (Prasanna *et al.,* 2016).

Melting Point

The formulations were placed in porcelain dishes, immersed in a water bath set up on a tripod stand and heated (Sunil *et al.,* 2010). The temperature at which complete melting of the formulations occurs was noted using a thermometer.

Hardness

The hardness of the chocolates was measured using Monsanto hardness tester and was reported in kg/cm² (Yogesh *et al.,* 2021). The chocolates were made small-sized to fit into the tester. Hardness values were obtained in triplicates and the mean was obtained.

Loss on Drying (LOD)

This gravimetric method was used to measure weight loss as a result of presence of water or volatile matter (Mayank and Jain, 2012). Samples were placed in porcelain dishes, weighed, heated in a hot-air oven and weighed periodically until a constant weight was attained.

***In Vitro* Drug Release**

The chocolates were evaluated using USP II apparatus in 500 mL pH 7.4 saline phosphate buffer solution at 37 ± 0.5°C, 100 rpm for 60 minutes (Pawar *et al.,* 2019). Samples (5 mL) were withdrawn after 60 minutes, filtered, and analyzed by UV spectrophotometry to evaluate the percentage of drug released.

***In-vivo* antiemetic activity of prepared Aprepitant chocolates**

Animal

For the antiemetic experiment, young healthy chicks (7-10 days old) weighing 40-50 g of either sex were used. The chicks were bought from a reputable poultry farm and maintained under standard laboratory conditions of regulated temperature (25±2°C), relative humidity (55-65%) and 12 hours light/dark cycle. Food and water were provided ad libitum except during fasting. The chicks were acclimatized in the laboratory for three days before the experiment. The chicks were fasted for 24 hours before conducting the experiment.

Acute Toxicity Studies

Based on OECD methods, the toxicity of Aprepitant-medicated chocolate formulation was evaluated by using two different dosages, i.e., (10 mg/kg and 20 mg/kg) p.o to chicks (N=6) and their behavioral effects as well as mortality rate were observed for 48 hours within 2 weeks (Chemicals, 2005).

Experimentation

The animals were randomly divided into 4 groups, with N = 6 chicks per group.

Group, I was the disease control group, which was administered copper sulfate (50 mg/kg p.o.);

Group II received medicated Aprepitant-medicated chocolate formulation at 10 mg/kg;

Group III received Aprepitant-medicated chocolate formulation at 20 mg/kg.

Group IV was the standard treatment group, which was administered Domperidone (10 mg/kg, p.o.).

Determination of the Antiemetic Effect

The anti-emetic property of the medicated chocolate of Aprepitant was determined using an established in-vivo model for testing anti-emetic drugs, specifically the copper sulfate induced chick emetic model. The test was done as already detailed but with a few changes. The chicks were individually isolated in

clear observation cages and given some time to adapt for around 10 minutes before the experiment. Group I, which acted as the disease control, was administered copper sulfate (50 mg/kg p.o.). Medicated chocolate formulation containing Aprepitant (10 mg/kg and 20 mg/kg for Group II and Group III chicks, respectively, and Domperidone: 10 mg/kg, p.o., for Group IV) was orally administered to the chicks. All the groups were administered with copper sulfate (50 mg/kg, p.o.) 10 minutes after its administration as an emetic agent. The chicks were then observed for 10 minutes after the administration of copper sulfate, and the number of retching movements was noted down for every chick. The efficiency of Aprepitant medicated chocolate formulation as an antiemetic was determined on the basis of comparison of mean retches of the treatment groups and negative control group. The less the number of retches, the more antiemetic (Bokhari *et al.,* 2020). The percentage inhibition of emesis was calculated using the formula:

Inhibition (%) = (A-B/A) x 100

Where A = Frequency of retching in the negative control group, and B = Frequency of retching in the test group.

Statistical Analysis

The data is expressed as mean ± SEM. The one-way ANOVA and Dunnett's multiple comparison test were applied to statistically analyze the data. The different treatment groups were compared with the disease control group. Statistical analyses were performed using GraphPad Prism version 8.0.2 (GraphPad Software, San Diego, CA, USA). A significance level of $p < 0.05$ was applied.

Stability Study

The stability study for the optimized formulation of Aprepitant chocolates was done following the ICH guidelines Q1A (R2) for the evaluation of stability of the formulation under accelerated storage conditions. The optimized formulation was packed in air and moisture-resistant bottles and stored in a stability chamber maintained at 40±2°C temperature and 75±5% relative humidity for duration of three months. Samples were collected after predetermined intervals of 0, 1, 2, and 3 months and tested for different physicochemical parameters such as appearance, drug content, disintegration time, and *in vitro* drug release from the formulation. The values obtained at different intervals were compared with that of freshly prepared samples to see if there is any change in the quality parameters of the formulation during storage. The formulation was said to be stable if there were no significant changes observed in the quality parameters or in drug content or dissolution of the optimized formulation during the study period.

Results and Discussion

Aprepitant-medicated chocolates were successfully formulated by the conventional chocolate tempering technique using cocoa butter as the lipid base, with carob powder and milk powder incorporated as functional excipients. The formulation composition was systematically varied to evaluate the influence of cocoa butter, carob powder, and milk powder on the physicochemical properties and performance of the medicated chocolates. The composition of all experimental formulations (F1–F9) is presented in Table 1.

The physical appearance of the formulations demonstrated that the concentration of cocoa butter and the presence of milk powder markedly influenced the surface characteristics and texture of the chocolates. Formulations F1–F6 exhibited smooth texture, glossy appearance, and acceptable consistency, indicating successful tempering and proper crystallization of cocoa butter. In contrast, formulations F7–F9, containing a higher concentration of cocoa butter (4.0 g) and increased levels of carob powder, showed undesirable characteristics such as surface oiling, fat bloom, stickiness, and poor structural integrity (Table 2). These observations suggest that excessive lipid content adversely affected the stability of the chocolate matrix by promoting fat migration and improper crystal formation.

Organoleptic evaluation further supported the physical characterization results. Formulations F1, F3, F5, and F6 showed pleasant taste, smooth mouthfeel, and high overall acceptability, whereas F7–F9 exhibited greasy mouthfeel, oily aftertaste, and poor sensory acceptance (Table 3). The incorporation of milk powder improved creaminess and masked the bitter taste of aprepitant, while excessive carob powder negatively influenced the sensory attributes.

The physicochemical evaluation confirmed that all optimized formulations possessed acceptable quality characteristics (Table 4). The melting points of F1–F6 ranged from 31.8 ± 0.2 to 33.1 ± 0.3°C, which is suitable for oral chocolate formulations, allowing the product to remain stable at room temperature while melting readily in the oral cavity. Conversely, formulations F7–F9 exhibited comparatively lower melting points (29.0–30.2°C), indicating reduced thermal stability due to the higher cocoa butter content.

Drug content analysis demonstrated uniform distribution of aprepitant throughout the chocolate matrix. Formulations F1–F6 exhibited drug content between 97.3 ± 0.8% and 99.1 ± 0.4%, whereas formulations F7–F9 showed comparatively lower drug content (93.8–95.5%), possibly due to non-uniform dispersion of the drug in the softer lipid

matrix. These findings indicate that appropriate optimization of excipient composition is essential to achieve satisfactory content uniformity.

The in vitro drug release study revealed that the composition of the chocolate matrix significantly affected drug dissolution. Among all formulations, F6 exhibited the highest cumulative drug release (97.1 ± 0.32% at 60 min), followed closely by F3 (96.5 ± 0.32%) and F1 (95.0 ± 0.45%) (Table 4). The improved dissolution observed in these formulations may be attributed to the balanced proportions of cocoa butter, carob powder, and milk powder, which promoted rapid disintegration of the chocolate matrix and enhanced drug diffusion. In contrast, F7–F9 exhibited considerably lower drug release (75.6–82.1%), likely due to excessive lipid content forming a hydrophobic barrier that retarded penetration of the dissolution medium.

Mechanical strength analysis demonstrated hardness values ranging from 3.7 to 4.8 kg/cm² for F1–F6, indicating adequate structural integrity for handling, packaging, and transportation. The reduced hardness observed in F7–F9 (2.2–2.8 kg/cm²) correlated with their softer texture and inferior physical appearance. Similarly, loss on drying values remained below 1% for F1–F6, indicating minimal moisture uptake and better storage stability, whereas F7–F9 showed comparatively higher moisture content (1.30–1.65%), which may further contribute to quality deterioration during storage.

Based on the collective physicochemical, organoleptic, and dissolution characteristics, Formulation F6 demonstrated the most desirable performance and was considered the optimized formulation. This formulation exhibited excellent appearance, high drug content, optimum hardness, low moisture content, and the highest in vitro drug release, indicating a well-balanced formulation capable of delivering aprepitant efficiently.

The optimized aprepitant-medicated chocolate formulation was further evaluated for antiemetic activity using the copper sulfate-induced emesis model. The formulation produced a dose-dependent reduction in the number of retches compared with the control group (Table 5). Administration of the medicated chocolate at 10 mg/kg reduced retching by 49.30%, while the 20 mg/kg dose achieved 73.31% inhibition of emesis, which was greater than that observed with the standard drug domperidone (66.96% inhibition). The superior antiemetic activity at the higher dose suggests efficient oral delivery of aprepitant through the chocolate matrix and confirms that the formulation retained the pharmacological efficacy of the drug. The optimized formulation (F6) remained stable under accelerated storage conditions of 40 ± 2°C and 75 ± 5% RH for three months. No significant changes were observed in the physical appearance, drug content, melting point, hardness, moisture content, or in vitro drug release. Drug content remained above 98%**,** and cumulative drug release after 60 minutes remained greater than 96% throughout the study period. These findings indicate that the optimized aprepitant chocolate formulation possesses good physicochemical stability and complies with the acceptance criteria recommended by ICH Q1A(R2**)** (Table 6).

Table 2: Physical Appearance and Texture

Formulation	Color	Texture	Surface appearance
F1	Light brown	Smooth, creamy	Glossy
F2	Medium brown	Slightly firm	Glossy
F3	Light–medium	Smooth	Glossy
F4	Medium–dark	Smooth, dense	Glossy
F5	Medium brown	Firm, smooth	Glossy
F6	Medium–dark	Smooth, creamy	Glossy
F7	Dark brown	Very oily, soft	Dull, oil bloom
F8	Dark brown	Very soft, greasy	Surface oiling
F9	Very dark	Sticky, uneven	Dull, fat & sugar bloom

Table 3: Results of Organoleptic evaluation

Formulation	Taste	Mouthfeel	Aftertaste	Acceptability
F1	Sweet, creamy	Soft	Pleasant	Excellent
F2	Moderately	Firm	Slight bitter	Good

	sweet			
F3	Sweet, balanced	Smooth	Pleasant	Very Good
F4	Cocoa-forward	Dense	Mild bitterness	Good
F5	Balanced	Firm	Pleasant	Very Good
F6	Sweet, creamy	Smooth	Pleasant	Excellent
F7	Excessively fatty	Greasy mouthfeel	Lingering oily aftertaste	Poor
F8	Greasy	Unpleasant coating	Oily	Poor
F9	Overly bitter + oily	Gritty/sticky	Off taste	Very poor

Table 4: Results of evaluation parameters

Formulation	Melting Point (°C)	Drug Content (% w/w)	% Release @ 60 min	Hardness (kg/cm²)	LOD (%)
F1	31.8± 0.2	98.5 ± 0.6	95.0± 0.45	4.2±0.3	0.85± 0.05
F2	32.6± 0.3	97.3 ± 0.8	90.2± 0.36	4.8±0.4	0.92± 0.07
F3	32.0± 0.4	99.1 ± 0.4	96.5± 0.32	3.9±0.3	0.78± 0.03
F4	32.4± 0.2	98.2 ± 0.5	92.8± 0.25	3.7±0.6	0.80± 0.07
F5	33.1± 0.3	98.7 ± 0.5	94.6± 0.15	4.6±0.22	0.88± 0.06
F6	**32.2± 0.1**	**99.0 ± 0.4**	**97.1± 0.32**	**3.8±0.32**	**0.76± 0.03**
F7	29.8± 0.3	94.6 ± 1.8	78.4± 0.36	2.5±0.36	1.45± 0.04
F8	30.2± 0.4	95.5 ± 1.5	82.1± 0.33	2.8±0.36	1.30± 0.05
F9	29.0± 0.2	93.8 ± 2.0	75.6± 0.25	2.2±0.25	1.65± 0.04

Table 5: Antiemetic effect of aprepitant-medicated chocolate formulation

Group	Treatment	Dose (mg/kg, p.o.)	No. of Retches (Mean ± SEM)	Inhibition of Emesis (%)
I	Copper sulfate (control)	50	36.83 ± 1.42#	0.00
II	Aprepitant-medicated chocolate formulation	10	18.67 ± 1.08*	49.30
III	Aprepitant-medicated chocolate formulation	20	9.83 ± 0.74***	73.31
IV	Domperidone	10	12.17 ± 0.89***	66.96

Data expressed as Mean ± SEM (n = 6 animals/group). P < 0.001 vs. copper sulfate control.

Table 6: Accelerated Stability Study of Optimized Aprepitant Chocolate Formulation (F6)

Storage Period	Appearance	Storage Condition: 40 ± 2°C / 75 ± 5% RH				
		Drug	Melting	Hardness	LO	Drug

		Content (%)	Point (°C)	(kg/cm²)	D (%)	Release at 60 min (%)
Initial (0 Month)	Smooth, glossy, no visible defects	99.0 ± 0.4	32.2 ± 0.1	3.8 ± 0.32	0.76 ± 0.03	97.1 ± 0.32
1 Month	No significant change	98.8 ± 0.5	32.1 ± 0.2	3.8 ± 0.28	0.78 ± 0.04	96.8 ± 0.41
2 Months	No significant change	98.5 ± 0.6	32.0 ± 0.2	3.7 ± 0.30	0.80 ± 0.04	96.5 ± 0.38
3 Months	Slight dullness, no fat bloom	98.2 ± 0.7	31.9 ± 0.3	3.7 ± 0.29	0.83 ± 0.05	96.1 ± 0.45

Conclusion

Aprepitant-medicated chocolates were successfully formulated using the chocolate tempering method and demonstrated satisfactory physicochemical properties, including acceptable appearance, drug content, hardness, melting point, and moisture content. Among the developed formulations F6 exhibited the best overall performance with the highest drug release and excellent organoleptic characteristics. The optimized formulation also showed significant dose-dependent antiemetic activity, indicating that the chocolate-based delivery system effectively retained the therapeutic efficacy of aprepitant. These findings suggest that medicated chocolates represent a promising, patient-friendly oral dosage form with the potential to improve compliance and provide effective management of chemotherapy-induced nausea and vomiting.

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