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Development of ginger oleoresin-enriched marshmallow candy as a nutraceutical for managing pediatric chemotherapy-induced nausea and vomiting

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ABSTRACT

Objective: Chemotherapy-induced nausea and vomiting (CINV) significantly impact pediatric cancer patients, affecting treatment adherence and quality of life. This study aimed to develop gingerol-enriched marshmallow candy as a nutraceutical to alleviate CINV, offering a palatable and effective antiemetic formulation for children.
Methods: A central composite experimental design was employed to optimize the formulation. The various parameters, including textural attributes (hardness, springiness, and cohesiveness), weight variation, disintegration time, *in vitro* release, moisture content, water activity coefficient, and stability, of the marshmallows were evaluated to ensure the efficacy and quality of the product.
Results: The study identified an optimal formulation comprising ginger powder extract (4% w/w), gelatin (6% w/w), gum acacia (2.5% w/w), and agar (2.5% w/w). This composition demonstrated excellent textural characteristics, rapid disintegration, and efficient gingerol release in simulated conditions. The marshmallow candy also exhibited high acceptability in terms of stability and potential usability as a pediatric nutraceutical.
Conclusion: The ginger oleoresin-enriched marshmallow candy presents a novel and appealing delivery system for managing CINV in pediatric patients. Its favorable sensory and functional properties could improve compliance and enhance the overall treatment experience for children undergoing chemotherapy.

1. Introduction

Nutraceuticals are biologically active compounds that provide both nutritional and medicinal benefits, including antioxidants, dietary fibers, inorganic minerals, phytochemicals, prebiotics, probiotics, and herbs that aid in the treatment of numerous ailments.[1] A growing "green wave" in the market reflects increasing awareness of the potential harms of synthetic drugs and the acceptance of traditional systems of medicine, such as Ayurveda, Siddha, Unani, and Chinese medicine.[2] Moreover, the global health crises, such as the COVID-19 pandemic, have further fueled interest in nutraceuticals across all age groups.[3] The need for pediatric-friendly delivery systems for nutraceuticals and medications has become increasingly critical. Children often struggle to swallow tablets or capsules, while syrups and suspensions may be incompatible due to taste or dosage issues.[4,5] Lozenges pose a risk of accidental swallowing and choking[4] leading to the demand for palatable and safer alternatives like gummies, chewable tablets, and marshmallows that combine taste with safety and compliance.[4] Marshmallow candies are unique chewing confections with a foamy texture that appeals greatly to children, yet their potential as delivery systems for loading nutraceuticals remains underexplored. By incorporating herbs with pungent or bitter tastes, such candies can effectively mask flavors while being molded into attractive shapes, sizes, and colors.

Chemotherapy, combined with surgery and radiation, is a key pillar in cancer treatment. However, its effectiveness comes with the downside of significant side effects, as it affects both malignant and healthy

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cells. Among these side effects, nausea and vomiting stand out, affecting nearly 48% of patients and severely diminishing their quality of life, nutritional intake, and immune function, ultimately impacting treatment success. While antiemetic medications are available, only around 26% of patients report satisfactory relief from these drugs, and they can lead to side effects such as headaches and drowsiness.[6,7] This has led to a growing interest in complementary therapies using natural products with minimal side effects.[8] The fame of Indian Ayurvedic treatments has opened up avenues for some very popular food spices and herbs, such as ashwagandha, turmeric, ginger, tulsi, pepper, garlic, etc. Ginger (*Zingiber officinale* Roscoe) is well-known and has been extensively researched for its ability to relieve chemotherapy-induced nausea and vomiting (CINV). Ginger, a common household spice, possesses a wide range of health benefits, including antiemetic, anti-inflammatory, and antioxidant properties.[9–11] Furthermore, it can be used as an anti-inflammatory and pain-relieving agent in the treatment of arthritis.[11,12] It has the potential to control diabetes, dyslipidemia, cardiovascular disease, migraine, and asthma.[11,13–15] It also has a protective effect on peptic and duodenal ulcers and can be used to treat stomach upset, colitis, and inflammatory bowel disease.[11,16] The free radical foraging ability of ginger is attributable to its ability to act as an anti-oxidant and shield against cancer.[17,18] Other popular uses of ginger include curing the common cold, flu-like syndrome, and anxiety.[13,19] The major phytoconstituents present in ginger root powder extract are gingerols and shogaols, which are responsible for its antiemetic properties.[20,21] It blocks 5-HT_3 receptors, and its antioxidant effect due to free-radical scavenging action in the gut suggests that it is helpful for decreasing the occurrence and severity of chemotherapy-stimulated nausea and vomiting.[21–24] Consequently, incorporating ginger into pediatric-friendly marshmallow candies represents a novel strategy to enhance compliance and reduce the severity of CINV in children undergoing chemotherapy. This study aimed to develop and optimize gingerol-enriched marshmallow candy using a central composite design, evaluating its potential as a palatable, effective delivery system for improving pediatric patient well-being during chemotherapy. Although various ginger-containing formulations have been developed, such as tablets,[25] capsules,[26] emulsion,[27] chewing gum,[28] lozenges,[29] gum mixtures (available from: https://www.emergenc.com/products/botanicals/gummies/turmeric-gingergummies/), hard candy,[30] nanoemulsions,[31] and nanoparticles,[32] ginger oleoresin-loaded marshmallow candies specifically targeting pediatric populations have not yet been explored.

2. Materials and methods

2.1. Materials

Ginger rhizome was purchased from the local market of Aurangabad and was further authenticated by the Department of Botany, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, Maharashtra, India. Gum acacia (briefly named as acacia), agar, gelatin with a bloom strength of 220, and citric acid were obtained from Fisher Scientific, India. Refined sugar and urban plaster pure corn syrup wereprocured from retail stores.

2.2. Preparation of ginger root powder extract

One hundred grams of ginger rhizome was washed, cleaned and dried, cut into fine disc-like slices, and crushed into a coarse powder.[33] Further extraction with 95% ethanol (500 mL) was performed via the maceration technique.[27,34] The solvent was evaporated via a rotary evaporator with the bath temperature maintained at 60 °C and pressure at 175 mbar to obtain a thick pasty mass.[35,36] The paste was suspended in distilled water to allow the resins to precipitate out.[37,38] The resins were separated by filtration, and the remaining residue was vacuum-dried in a vacuum drying oven at 40 °C under 100 mbar pressure until the desired dryness was achieved.[18,33] The dried mass was then ground using a mortar and pestle to produce a fine ginger powder, which was subsequently passed through a 50-mesh sieve for experimental use.[39]

2.3. Characterization of gingerol obtained from ginger powder extract

2.3.1. Thin-layer chromatography plate method

A chromatographic thin plate (5 × 8 cm) was coated with a surface thickness of 0.3 mm, and the sample was spotted 1 cm from the bottom using capillary tubes. The mobile phase was hexane:diethyl ether (70:30). A 10 µL aliquot of the ethanolic extract (as reported in the preparation section) was used and compared against the reference standard.[37]

2.3.2. Fourier transform infrared (FTIR) and ultraviolet (UV) spectroscopy

To identify the characteristic functional groups in the extract, FTIR studies were performed. Five milligrams of the extract were blended with potassium bromide (KBr). Furthermore, the mixture was pressed to form a thin pellet. The screening was performed from 400 to 4000 cm^{-1}. The extract (100 mg) was dissolved in methanol, and the volume was adjusted to 100 mL to obtain 1000 ppm as a stock solution. Furthermore, a 10 µg/mL solution was prepared, which was screened in the range of 200–400 nm by means of a UV spectrophotometer to determine λ_{max}.[37]

2.4. Formulation of ginger oleoresin-enriched marshmallow candy

A central composite design was used to develop ginger-infused marshmallows with various acacia and agar concentrations. Eleven batches, including three center points, were prepared as per Tables 1 and 2. Ginger powder extract (4% w/w), gelatin (6% w/w), sucrose (32% w/w), corn syrup (31% w/w), and citric acid (1% w/w) were kept constant, with distilled water added to reach 100% w/w. All the ingredients were weighed according to the required batch size. Initially, sugar was added to water, and the mixture was placed in a sand bath (116 °C) for boiling. After the dissolution of sugar, corn syrup was added, and the mixture was heated for an additional 2 min[40]. Simultaneously, gelatin, agar, and acacia were dissolved in a small portion of distilled water and were kept aside for an hour until they swelled.[41] The swollen gummy base was then added to the sugar-corn syrup solution and boiled to 114 °C until it reached the soft ball stage.[42] The boiling solution was removed from the flame and poured into a vessel, which was blended continuously via a hand blender (Philips HR3705/10) for 6 min until the volume of the mixture tripled and became light and fluffy. The required quantity of ginger powder was subsequently added and blended well to obtain a homogeneous mixture. The mixture was then poured into prepared starch molds, dusted with a mixture of cornstarch/castor sugar on the top, left to set at 25 °C for 4 h, and subsequently dried in a hot air oven maintained at 38–40 °C.[43] The prepared marshmallow samples were stored in a desiccator until further evaluation.

2.5. Evaluation of ginger oleoresin enriched marshmallow candy

2.5.1. Physiochemical characterization

The final products underwent thorough analysis to assess their key attributes, including moisture content, water activity (a_w), and soluble solid content (°Brix). The moisture content was determined via the gravimetric method, where samples were dried in a vacuum oven at 60

Table 1
Central composite experimental design with coded values for formulation variables.

Formulation variables	Levels		
	-1	0	+1
A-Concentration of acacia (% w/w)	0.5	1.5	2.5
B-Concentration of agar (% w/w)	2.5	3.5	4.5

Table 2
Formulation batches for ginger oleoresin enriched marshmallow candies designed via central composite experimental design.

Ingredients (% w/w)	Batches										
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Acacia	0.5	0.5	0.5	1.5	1.5	1.5	2.5	2.5	2.5	1.5	1.5
Agar	2.5	3.5	4.5	2.5	3.5	4.5	2.5	3.5	4.5	3.5	3.5

°C until a constant weight was achieved. A dew point hygrometer was employed to measure the water activity (a_w). The soluble solid content (measured in °Brix) was assessed via a refractometer at a temperature of 20 °C.[44] All the measurements were conducted in triplicate to ensure the reliability and accuracy of the results.

2.5.2. Weight variation, thickness, diameter, and gingerol content

A weight variation test was performed on 20 ginger marshmallow samples by weighing the individuals and calculating the average weight. The % weight deviation was calculated via the following equation (Equation (1)). The thickness and diameter were measured via a Vernier caliper. The gingerol content was determined by treating marshmallow with 20 mL of water and heating it at 70 °C for 5 min. The resulting solution was decanted via a Buchner funnel.[45] The filtrate was collected and further diluted with methanol, and the gingerol content was estimated at 282 nm via a UV spectrophotometer.[37,46]

$$\%\ \boldsymbol{deviation} = \frac{(\boldsymbol{individual\ weight} - \boldsymbol{average\ weight})}{\boldsymbol{individual\ weight}} \times \mathbf{100} \qquad \text{Equation 1}$$

2.5.3. Texture profile test

The texture profile analysis of all formulated marshmallow batches was conducted using a CT3 texture analyzer (Brookfield Engineering, UK) to evaluate hardness, springiness, and cohesiveness. The instrument was equipped with a 75 mm diameter compression plate and set to a test speed of 1 mm/s, return speed of 1 mm/s, and 75% deformation with a 0.07 N load.[47]Hardness was determined as the peak force required during the first compression cycle. Springiness was calculated as the sample's ability to recover its shape after the first compression, measured by the distance recovered between the two cycles. Cohesiveness was assessed as the ratio of the area under the second compression curve to that under the first, indicating the structural integrity of the sample.

2.5.4. Disintegration time

The disintegration time of ginger-incorporated marshmallow in pH 6.8 phosphate buffers at 37 °C was determined via a USP disintegration apparatus. The test was conducted in a manner similar to disintegration tests performed for chewable tablets and lozenges.[48–52] An evaluation was performed to understand how quickly these ginger-containing marshmallows broke down in a simulated oral environment.

2.5.5. In vitro dissolution

The Type II USP dissolution test apparatus, which is a paddle-type apparatus, was used for this study. The test was performed at 50 revolutions per minute (rpm) and at a controlled temperature of 37 ± 0.5 °C. The dissolution medium used for these studies was a pH 6.8 buffer. During the dissolution study, a marshmallow was placed in each flask of the dissolution apparatus. Samples of 5 mL were withdrawn from the dissolution medium at predetermined time intervals over a 60-min period. To ensure that the dissolution study maintains sink conditions, an equal volume of the dissolution medium was replaced each time when a sample was withdrawn. By measuring the absorbance at 248 nm via a UV–Vis spectrophotometer, the cumulative percentage of gingerol dissolved from the marshmallows was determined.[53] The data obtained from the dissolution studies were fitted to various mathematical models via PCP Disso Version 2.08 software to describe the drug release kinetics.

2.5.6. Multiple regression analysis of factorial batches

Multiple regression was implemented to derive the relationships between multiple independent variables (X1, X2, etc.) and a dependent variable (Yi). Polynomial equations are used to model the relationships between the factors and the response variable. The response parameters, such as hardness, disintegration time, and dissolution rate, were statistically analyzed via one-way analysis of variance (ANOVA). Response surface plots and optimization studies were generated using Design Expert 13 software to analyze the influence of independent variables (factors) on the response parameters. This approach facilitated a clearer understanding of the relationships and aided in identifying optimal formulation conditions.

2.5.7. Stability studies

The optimized batch (F7) was subjected to a three-month stability study under accelerated stored conditions at 25 ± 2 °C and 60% ± 5% relative humidity[45,54] in a sealed glass jar as per ICH guidelines.[55] Quality attributes such as water activity, hardness, springiness, cohesiveness, disintegration time, and *in vitro* drug release were measured before and after the study. Statistical analysis via the Mann–Whitney test ($P \leq 0.05$) was conducted to determine whether the storage conditions significantly impacted these quality attributes.[46]

3. Results

3.1. Characterization of gingerol obtained from ginger powder extract

3.1.1. Thin-layer chromatography plate (TLC) method

The TLC technique was employed to detect the presence of gingerol by observing its separation characteristics on silica gel grade A as the stationary phase. Through visual examination, we observed distinct spots that were clearly visible. However, when exposed to long-wavelength UV light at 365 nm, these spots displayed a vibrant fluorescent blue color. To confirm the identity of the compounds in the ethanolic extract, we compared the R_f (retention factor) values of these spots with those of reference standards (Standard Ginger Extract Powder, Sunthi, Phyto life Sciences P. Ltd., Ahmedabad, Gujarat, India). Notably, the R_f value obtained for the test sample was 0.48, which closely matched the R_f value of the reference standard (Fig. 1). These findings support the authentication of the presence of gingerol in the ethanolic extract as previously reported.[38,56]

3.1.2. Fourier transform infrared (FTIR) and ultraviolet (UV) spectroscopy

The FTIR spectra depicted in Fig. 2a illustrate the distinct functional groups of gingerol, acacia, agar, and gelatin. In the spectrum of gingerol, an O-H stretching band is observed around 3529 cm^{-1}, indicative of its hydroxyl group, and C-H stretching vibrations are observed at 3025 cm^{-1} and 2845 cm^{-1}, associated with aliphatic chains. The sharp peak at 1736 cm^{-1} corresponds to the C=O stretching vibration of the ketone group. Additionally, peaks near 1632 cm^{-1} and 1364 cm^{-1} are characteristic of aromatic vibrations, highlighting the presence of the aromatic ring structure in gingerol.[38,57]For acacia, the broad O-H stretching band is identified at 3412 cm^{-1}, along with C-H stretching at 2935 cm^{-1} and C=O stretching at 1625 cm^{-1}, characteristic of polysaccharides and their functional properties.[58,59] Agar exhibits a strong O-H stretching band at 3385 cm^{-1} and C-H stretching at 2945 cm^{-1}, along with distinct peaks at 1700 cm^{-1} corresponding to C=O stretching.[60] Gelatin shows its

Fig. 1. TLC images of ethanolic extract of *Zingiber officinale*. S: standard; T: test sample.

characteristic, C-H stretching at 2986 cm^{-1}, N-H stretching band at 3312 cm^{-1}, along with amide-specific peaks like the amide I band at 1670 cm^{-1} and amide II band at 1565 cm^{-1}.[61] In the physical mixture containing gingerol, acacia, agar, and gelatin, the spectra indicate that all the characteristic peaks of gingerol and the functional group peaks of the excipients are retained without significant shifts or the appearance of new peaks. This retention demonstrates that the components do not chemically react but interact physically through hydrogen bonding or van der Waals forces. These observations confirm the chemical compatibility of gingerol with the excipients, ensuring the stability and integrity of the formulation.

The gingerol powder sample was subjected to a scanning procedure spanning the range of 200–400 nm to identify its maximum wavelength. In methanol, the UV spectrum (Fig. 2b) revealed a distinct peak at 282 nm. The presence of gingerol was confirmed through both FTIR and UV studies, and the results were consistent with previously reported values.[46]

3.2. Evaluation of ginger oleoresin-enriched marshmallow candy

3.2.1. Physiochemical characterization

The consistency of the initial sugar syrup's °Brix measurement, averaging 69.65 ± 1.05 across all batches, stems from the deliberate balance of sugar (32% w/w) and corn syrup (31% w/w) in each formulation. This careful composition ensures a stable and uniform °Brix level throughout the production process. Furthermore, the moisture content analysis (Table 3) revealed a range between 20.14% and 22.78%, corresponding to water activity levels of 0.625–0.776. This finding is consistent with the typical water activity values observed in marshmallow-type products, which generally fall between 0.60 and 0.75, further validating our results. Interestingly, hydrocolloids such as acacia and agar, despite being present, did not notably affect water activity or moisture content. These findings suggest that these compounds serve dual functions as both gelling agents and auxiliary stabilizers without disrupting these crucial parameters.[62] These findings also align with those of previous studies, which highlighted the influence of sugar type and quantity on water activity dynamics.[40,62] Notably, the combination of inverted sugar and sucrose, which was maintained at a consistent 1:1 ratio across all batches, had a synergistic effect on reducing water activity. This synergy highlights the importance of sugar selection and

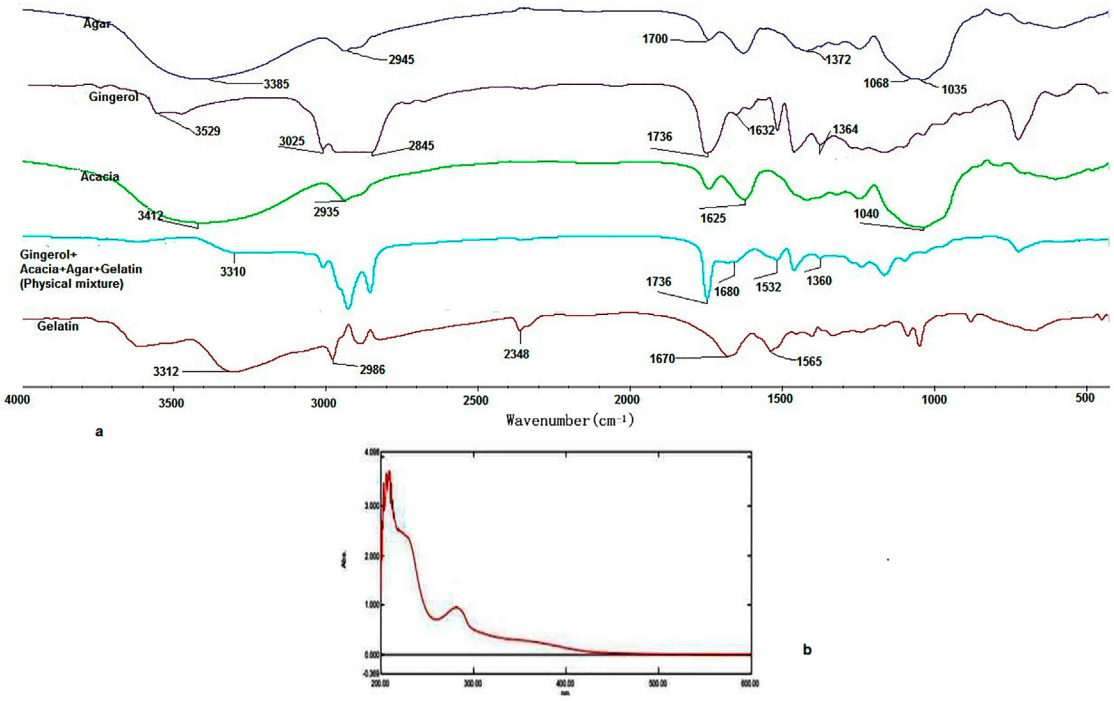

Fig. 2. a) FTIR spectra of Agar, Gingerol, Acacia, Physical mixture and Gelatin; b) UV spectrum of gingerol powder extract in methanol.

Table 3
Results for water activity, moisture content, weight variation, thickness and diameter (mean ± SD, n = 3).

Formulation batches	Moisture content (%)	Water activity (a_w)	Weight variation (%)	Thickness (cm)	Diameter (cm)
F1	21.22 ± 0.25	0.641 ± 0.012	2.25 ± 0.012	0.50 ± 0.0001	2.50 ± 0.0012
F2	21.95 ± 0.75	0.698 ± 0.018	3.25 ± 0.005	0.55 ± 0.0050	2.75 ± 0.0018
F3	22.52 ± 1.11	0.752 ± 0.038	3.06 ± 0.023	0.58 ± 0.0250	2.95 ± 0.0250
F4	20.14 ± 0.62	0.625 ± 0.009	2.15 ± 0.015	0.60 ± 0.0560	3.00 ± 0.0500
F5	21.45 ± 1.15	0.668 ± 0.014	2.75 ± 0.031	0.62 ± 0.0850	2.68 ± 0.0350
F6	22.78 ± 0.45	0.776 ± 0.046	3.57 ± 0.035	0.65 ± 0.0450	2.55 ± 0.0016
F7	21.48 ± 1.05	0.691 ± 0.021	2.58 ± 0.018	0.63 ± 0.0590	2.82 ± 0.0350
F8	20.54 ± 0.58	0.639 ± 0.004	2.35 ± 0.001	0.56 ± 0.0015	2.60 ± 0.0026
F9	21.77 ± 1.30	0.678 ± 0.011	3.15 ± 0.028	0.52 ± 0.0018	2.85 ± 0.0420
F10	21.26 ± 0.28	0.661 ± 0.032	2.72 ± 0.009	0.62 ± 0.0005	2.69 ± 0.0014
F11	21.34 ± 0.65	0.665 ± 0.025	2.78 ± 0.005	0.62 ± 0.0320	2.68 ± 0.0220

proportion in achieving the desired product characteristics.

3.2.2. *Weight variation, thickness, diameter, and gingerol content*

To ensure that consumers receive the intended dosage of the active ingredient with each serving, it is crucial to maintain uniformity in the weight of each ginger marshmallow candy. This consistency helps guarantee therapeutic effects and prevents under- or overdosing. Table 3 presents the data for weight variation, which was found to be within a ±5% deviation limit. Additionally, the thickness and diameter of the candies were reliably within 0.50–0.65 cm and 2.5–3.0 cm, respectively. The gingerol content in all batches ranged between 98.57% and 99.75%.

3.2.3. *Texture profile test*

Textural properties are among the main quality parameters of confectionery products. As shown in Table 4, the hardness, springiness, and cohesiveness values of the marshmallow samples varied between 30 and 70 N, 0.38 and 0.56, and 2.4 and 3.4, respectively. In the formulation of marshmallow candies, achieving a soft and chewy texture is critical. Our study investigated the effects of varying concentrations of agar and acacia while maintaining a constant gelatin concentration of 6% w/w. Increasing the acacia concentration from 0.5% to 2.5% significantly decreased the hardness of the marshmallow. The formulations with 2.5% acacia (F7, F8, and F9) presented the lowest hardness (30–36 N), making them the softest and chewiest. These findings indicate that acacia plays a dominant role in disrupting the gel network, resulting in a softer texture. At a low acacia concentration (0.5%), increasing the amount of agar from 2.5% to 4.5% reduced the hardness, but this trend was less pronounced at higher acacia concentrations. When the percentage of acacia was 2.5%, varying the agar concentration (2.5%–4.5%) had a minimal effect on hardness, maintaining a soft texture. With a fixed gelatin concentration, the role of agar in hardness reduction is evident at low acacia levels, likely due to hydrogen bonding and physical entanglement. Acacia, which is negatively charged, interacts with gelatin through electrostatic interactions, weakening the gel network. The interaction between neutral agar and negatively charged acacia primarily involves physical entanglement and hydrogen bonding, contributing to the overall gel structure. The optimal formulations for soft and chewy marshmallows are F7 (2.5% acacia, 2.5% agar) and F8 (2.5% acacia, 3.5% agar) because they have the lowest hardness values. A high acacia concentration (2.5%) consistently results in a desirable soft texture, indicating its significant role in gel disruption. The agar concentration can be adjusted within the range of 2.5%–4.5% without significantly affecting the softness when the acacia concentration is high. By focusing on these formulations, the desired soft and chewy texture for marshmallow candies is possible. In terms of springiness and cohesiveness, higher acacia concentrations (2.5%) consistently increase springiness, resulting in a light and airy texture, while maintaining cohesiveness within a desirable range for a stable and pleasant mouthfeel. Low acacia concentrations (0.5%) result in lower springiness and varying cohesiveness, with higher agar levels enhancing cohesiveness. Moderate acacia concentrations (1.5%) are balanced, with increased springiness and variable cohesiveness. Gelatin, acacia, and agar collectively enhance the formulation of gingerol-enriched marshmallow candies by contributing distinct and synergistic properties. Gelatin provides gelation and elasticity, while acacia stabilizes and disperses gingerol uniformly, and agar ensures firmness and water retention. Together, these hydrocolloids improve the structural, textural, and functional attributes of the marshmallow matrix, supporting the bioactive retention and controlled release of gingerol. Coacervation between gelatin and polysaccharides further enhances these properties, creating complexes that strengthen the product's stability and texture.[41] The optimal formulations for achieving soft and chewy marshmallow candies are F7 (2.5% acacia, 2.5% agar), F8 (2.5% acacia, 3.5% agar), and F9 (2.5% acacia, 4.5% agar), as they exhibit the best balance of high springiness and acceptable cohesiveness.

Table 4
Results for texture analysis and disintegration time (mean ± SD, n = 3).

Formulation batch	Hardness (N)	Springiness	Cohesiveness	Disintegration time (s)
F1	70 ± 1.15	0.38 ± 0.002	3.40 ± 0.01	261 ± 1.15
F2	56 ± 0.75	0.41 ± 0.004	3.28 ± 0.05	248 ± 1.10
F3	48 ± 1.10	0.43 ± 0.008	2.98 ± 0.03	228 ± 0.58
F4	46 ± 0.50	0.47 ± 0.006	2.85 ± 0.06	201 ± 0.75
F5	42 ± 0.25	0.52 ± 0.012	2.65 ± 0.02	197 ± 1.25
F6	36 ± 0.50	0.53 ± 0.011	2.48 ± 0.04	192 ± 0.45
F7	30 ± 0.45	0.52 ± 0.009	2.40 ± 0.01	182 ± 0.55
F8	34 ± 1.15	0.53 ± 0.014	2.54 ± 0.11	186 ± 0.35
F9	36 ± 0.85	0.56 ± 0.016	2.52 ± 0.13	188 ± 1.11
F10	43 ± 1.25	0.51 ± 0.007	2.75 ± 0.07	199 ± 0.65
F11	41 ± 0.35	0.52 ± 0.005	2.72 ± 0.08	198 ± 1.12

3.2.4. *Disintegration time*

The disintegration time results shown in Table 4 clearly indicate that increasing the acacia concentration significantly impacts both disintegration time and texture. Low acacia levels (0.5%) resulted in longer disintegration times (228–261 s), suggesting a denser texture. Moderate acacia levels (1.5%) led to shorter disintegration times (192–201 s), improving texture. High acacia levels (2.5%) produced the shortest disintegration times (182–188 s), indicating the softest texture. The agar concentration had a less pronounced effect: at low acacia levels, increasing the amount of agar slightly reduced the disintegration time, whereas at moderate acacia levels, it further reduced the disintegration time and enhanced the texture. At high acacia levels, the agar concentration minimally impacts disintegration, maintaining softness. These findings demonstrate that texture properties significantly influence disintegration time. Interactions between gelatin and polysaccharides like acacia and agar promote the formation of a cohesive network, contributing to predictable dissolution behavior in aqueous environments.[58] This network is beneficial for formulations that require stability during storage while ensuring rapid disintegration when consumed. The optimal formulations F7 (2.5% acacia, 2.5% agar), F8 (2.5% acacia, 3.5% agar), and F9 (2.5% acacia, 4.5% agar) offer the best balance of light, airy texture and rapid disintegration. These formulations ensure faster

disintegration of medicated marshmallows, thereby enhancing the timely release and efficacy of the active ingredient of *Zingiber officinale*. Thus, the disintegration test results align with the texture profile of the candies, confirming the consistency of the findings.

3.2.5. *In vitro dissolution*

The dissolution time results for ginger-loaded marshmallow candies are shown in Fig. 3 indicate that higher acacia concentrations significantly enhance ginger release, which is correlated with improved texture and shorter disintegration times. Formulations with low acacia (0.5%)—F1, F2, and F3—had lower dissolution rates (72%–82%), longer disintegration times (228–261 s), and denser textures. Moderate acacia levels (1.5%) in formulations F4, F5, F6, F10, and F11 resulted in moderate dissolution rates (86%–90%), shorter disintegration times (192–201 s), and improved texture. High acacia levels (2.5%) in formulations F7, F8, and F9 resulted in the highest dissolution rates (90%–98%), the shortest disintegration times (182–188 s), and the softest textures. The agar concentration had a minimal effect on dissolution rates at low acacia levels but improved dissolution at moderate acacia levels. At high acacia levels, the agar concentration had little effect, maintaining high ginger release efficiency. The optimal formulations for achieving the best balance of texture, rapid disintegration, and efficient gingerol release are F7 (2.5% acacia, 2.5% agar), F8 (2.5% acacia, 3.5% agar), and F9 (2.5% acacia, 4.5% agar).These properties ensure a light, airy texture and effective release of active ingredients such as *Zingiber officinale*, making them ideal for medicated marshmallows. Release kinetics analysis confirmed that all formulations followed a first-order release model, indicative of concentration-dependent release. Formulations F7, F8, and F9, containing high acacia levels (2.5%), exhibited the highest R^2 values and release rate constants (Table 5), suggesting erosion-dominated release mechanisms. Additionally, the Korsmeyer-Peppas equation revealed an N value ranging from 0.8080 to 0.9472, indicating anomalous (non-Fickian) transport, driven by a combination of diffusion and polymer relaxation rather than diffusion alone. These findings align with prior research, demonstrating that networks formed by gelatin-acacia[63] and gelatin-agar[64] effectively regulate active compound diffusion. The cohesiveness of these networks contributes to consistent texture, disintegration time, and dissolution results, making these formulations ideal for medicated marshmallows delivering *Zingiber officinale*.

3.2.6. *Multiple regression analysis of factorial batches*

To identify the optimized batch, multiple regression analysis was conducted to study the effects of independent formulation variables—acacia and agar concentrations—on the dependent responses: hardness (Y_1), disintegration time (Y_2), dissolution time (Y_3), springiness (Y_4), and cohesiveness (Y_5). This analysis aimed to quantify the relationships and interactions between these variables and the texture and performance attributes of *Zingiber officinale*-loaded marshmallow candies.

All the responses analyzed were found to follow a quadratic model. Table 6 details the results of the ANOVA for all the responses, and the RSM plots are depicted in Fig. 4. The following equations were obtained for the dependent responses: hardness (Equation (2)), disintegration time (Equation (3)), drug release (Equation (4)), springiness (Equation (5)), and cohesiveness (Equation (6)).

$$Y_1 = 41.58 - 12.33A - 4.33 + 7AB + 4.05A^2 + 0.0526B^2 \quad \text{Equation 2}$$

$$Y_2 = 198.16 - 30.17A - 6B + 9.75AB + 18.61A^2 - 1.89B^2 \quad \text{Equation 3}$$

$$Y_3 = 88.17 + 8.33A + 1\,B - 4.5AB - 2.42A^2 - 0.4211B^2 \quad \text{Equation 4}$$

$$Y_4 = 0.5126 + 0.065A + 0.025B - 0.0025AB - 0.0366A^2 - 0.0066B^2 \quad \text{Equation 5}$$

$$Y_5 = 2.72 - 0.367A - 0.1117B + 0.135AB + 0.1801A^2 - 0.0639B^2 \quad \text{Equation 6}$$

These findings highlight that increasing the concentrations of acacia and agar decreased hardness, disintegration time, and cohesiveness, with a more pronounced negative effect from acacia. Conversely, the interaction between agar and acacia increased hardness, disintegration time, and cohesiveness, indicating a positive impact. For drug release and springiness, higher concentrations of acacia and agar positively increased their values. However, the interaction between agar and acacia negatively affects drug release and springiness, reducing their values.

To identify the optimized batch, constraints were applied to the dependent responses: minimizing hardness, disintegration time, and cohesiveness while maximizing drug release and springiness. The predicted and observed results are shown in Table 7, and the contour plot for the responses is depicted in Fig. 5a. Consequently, F7 was identified as the optimized batch, exhibiting a desirability of 0.924. The design space was thus navigated, as shown in Fig. 5b.

3.2.7. *Stability studies*

The optimized batch F7 was subjected to a three-month stability

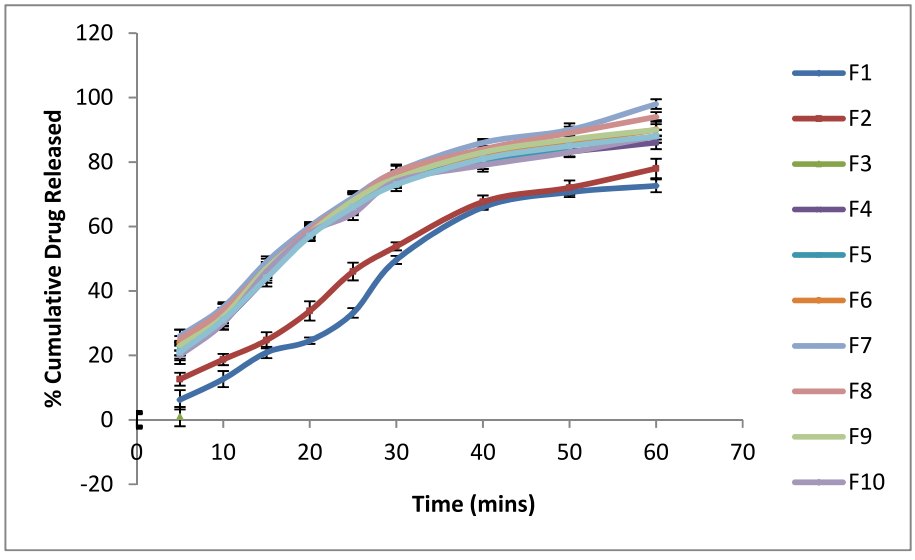

Fig. 3. Cumulative release of gingerol from marshmallow candies.

Table 5
In vitro drug release kinetics.

Formulation Batch	R^2 value					Best Fit model	Korsemeyer peppas equation	
	Zero order	First order	Matrix	Peppas	Hixson Crowell		k	N
F1	0.9780	0.998	0.9767	0.9876	0.9876	**First order**	5.09	0.8134
F2	0.9198	0.9854	0.9673	0.9526	0.9710		5.29	0.8434
F3	0.9205	0.9852	0.9659	0.9509	0.9710		5.09	0.8564
F4	0.9215	0.9935	0.9567	0.9618	0.9636		6.05	0.8080
F5	0.9190	0.9930	0.9520	0.9513	0.9615		5.64	0.9037
F6	0.9479	0.9885	0.9567	0.9686	0.9834		6.27	0.9156
F7	0.9757	0.9922	0.9801	0.9610	0.9835		7.40	0.9472
F8	0.9239	0.9935	0.9785	0.9665	0.9794		7.19	0.9145
F9	0.9256	0.9819	0.9796	0.9504	0.9736		6.86	0.9287
F10	0.9194	0.9940	0.9530	0.9523	0.9625		5.68	0.9047
F11	0.9188	0.9928	0.9518	0.9511	0.9612		5.62	0.9027

Table 6
ANOVA results for the central composite design batches studied for various dependent responses.

	R^2 value	F value	*P* value
Model for hardness (Y_1)	0.9912	113.15	<0.0001
A-conc of acacia		407.70	<0.0001
B-conc of agar		50.33	0.0009
AB		87.55	0.0002
A^2		18.59	0.0076
B^2		0.0031	0.9575
Model for disintegration time (Y_2)	0.9984	621.97	<0.0001
A-conc of acacia		2440.06	<0.0001
B-conc of agar		96.53	0.0002
AB		169.93	<0.0001
A^2		391.88	<0.0001
B^2		4.06	0.09
Model for Drug release (Y_3)	0.9924	129.84	<0.0001
A-conc of acacia		518.56	<0.0001
B-conc of agar		7.47	0.041
AB		100.81	0.0002
A^2		18.48	0.0077
B^2		0.56	0.4883
Model for springiness (Y_4)	0.9867	74.09	0.0001
A-conc of acacia		282.49	<0.0001
B-conc of agar		41.79	0.0013
AB		0.28	0.6202
A^2		37.77	0.0017
B^2		1.22	0.3139
Model for cohesiveness (Y_5)	0.9787	46.00	0.0004
A-conc of acacia		178.95	<0.0001
B-conc of agar		16.57	0.0096
AB		16.14	0.0101
A^2		18.19	0.0080
B^2		2.29	0.1903

Note: "conc" means "concentration".

study. The quality attributes of the gingerol-loaded marshmallow candies were evaluated before and after the study. Visual inspections revealed no changes in color, odor, or mold growth, maintaining their original form. Key parameters such as hardness, disintegration time, water activity, active content, springiness, cohesiveness, and drug release remained stable, with no significant changes ($P > 0.05$, 0.8182) compared with the initial state (Table 8). These findings confirm that the batch meets the stability standards and that the storage conditions had no significant effect on the product's quality attributes.

4. Discussion

The development of ginger oleoresin-enriched marshmallow candies as a pediatric nutraceutical addresses a significant challenge in drug delivery systems for managing CINV in children. Marshmallows, as a delivery format, align with World Health Organization (WHO) recommendations for flexible solid oral dosage forms, which are ideal for pediatric populations due to their ease of swallowing, stability, and cost-effectiveness.[5] Their soft texture, palatability, and potential for customization make them a promising alternative to traditional formulations, particularly for children undergoing chemotherapy. Gingerol, the active compound in ginger, has been widely studied for its antiemetic properties. Clinical trials confirm gingerol's efficacy in reducing nausea and vomiting in pediatric patients.[6,21] These studies underline its potential as a natural, safe, and effective therapeutic agent, making it an excellent candidate for incorporation into child-friendly delivery systems. The marshmallow matrix in this study integrates hydrocolloids—acacia, agar, and gelatin—known for their multifunctional roles in texture, stabilization, and controlled release. Acacia, in particular, has been extensively studied for its emulsifying properties, as highlighted by Rai et al.[35] In their work, ginger oleoresin was stabilized by emulsification with acacia and encapsulated in a sucrose matrix, facilitating improved bioavailability and controlled release. Similarly, in this study, acacia ensures the uniform dispersion and stabilization of gingerol within the marshmallow matrix while contributing to its structural integrity and sensory quality. Saira et al.[44] developed marshmallows enriched with *Apis mellifera* honey and *Lactobacillus rhamnosus*. These studies emphasize that honey treatments exhibited higher levels of total antioxidant activity and total phenolic compounds, which enhance bioactive delivery while maintaining a desirable texture and mouthfeel. Santoso et al. [65] developed marshmallows with added kinang (betel chew) extract, which exhibited antibacterial and antioxidant activity, as well as caries inhibition. Milea et al.[66] incorporated anthocyanins from sweet cherry skins in marshmallows, resulting in increased anthocyanin content and antioxidant activity over time. Moreover, Bakshi et al. reported an improvement in antibacterial, antioxidant, and anticancer activity of berberine by incorporating it into gellan-acacia gum[67] and tragacanth-acacia gum[68] nanocomplexes, demonstrating the role of acacia in enhancing the stability and controlled release of bioactive compounds. In another study acacia and whey protein were used by Ahad et al.[69] to stabilize ginger oleoresin powder. Using a central composite design, the study systematically optimized the formulation, resulting in an optimal marshmallow matrix (F7) with favorable water activity, texture, and drug release characteristics. These findings align with the optimization strategies reported in previous studies.[70,71] The marshmallow matrix demonstrated first-order release kinetics with high dissolution efficiency, validating its effectiveness as a bioactive delivery system. This work bridges traditional applications of hydrocolloids in food systems with innovative delivery strategies tailored for pediatric populations. By integrating gingerol into a palatable and functional marshmallow matrix, the study addresses challenges in taste masking, ease of administration, and patient compliance. The soft, airy texture of marshmallows not only aligns with pediatric preferences but also facilitates effective drug delivery without compromising therapeutic efficacy. This study demonstrates that gingerol-enriched marshmallows provide a novel, stable, and palatable delivery system for pediatric nutraceuticals. By utilizing acacia's emulsifying and stabilizing properties along with other hydrocolloids, the research highlights the marshmallow matrix's effectiveness in addressing CINV. This approach offers a child-friendly,

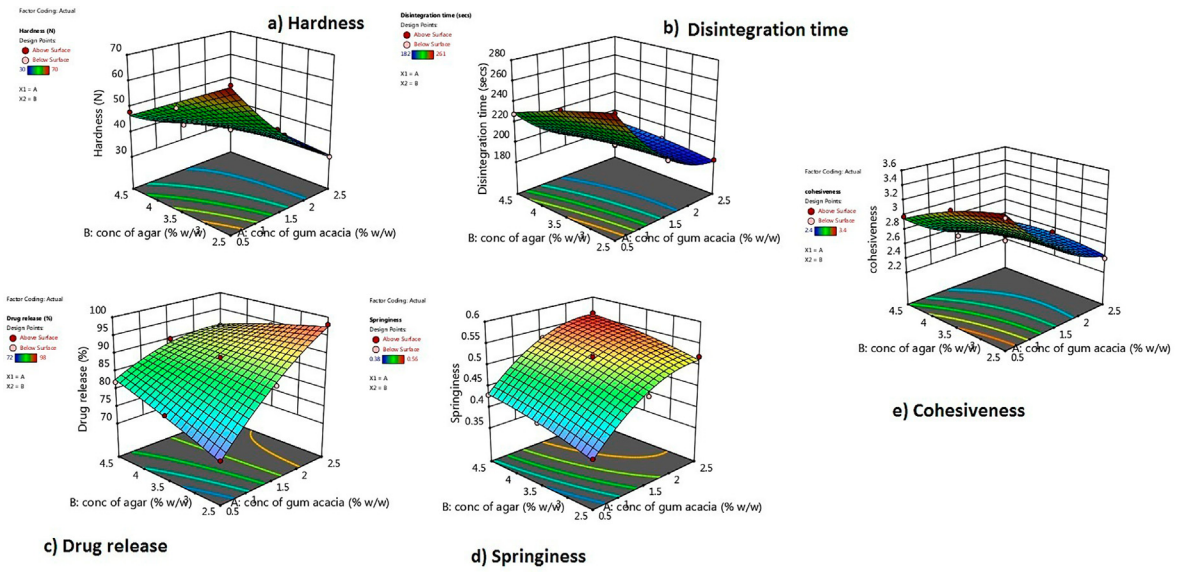

Fig. 4. Response surface plots for the dependent responses: a) hardness, b) disintegration time, c) drug release, d) springiness and e) cohesiveness.

Table 7
Predicted and observed results for the optimized batch (F7).

Response	Predicted	Observed
Hardness	30.68 N	30 N
Disintegration time	180.95 s	182 s
Drug release	97.35%	98%
Springiness	0.51	0.52
Cohesiveness	2.44	2.4

accessible solution, with potential for wider applications in pediatric drug delivery and nutraceuticals.

5. Conclusion

Marshmallow candies enriched with gingerol, the active constituent of *Zingiber officinale*, were developed using a central composite experimental design to optimize their antiemetic properties for pediatric use. The influence of acacia concentration was critical in determining textural properties, disintegration time, water activity, and gingerol release. The optimized formulation, batch F7, demonstrated ideal characteristics with balanced water activity (0.691), favorable texture (hardness 30 N, springiness 0.52, cohesiveness 2.4), rapid disintegration (182 s), and efficient gingerol release (98.27%). These properties were attributed to its composition of 2.5% acacia and 2.5% agar, which provided a light, airy texture and effective drug delivery, following a first-order release mechanism. Stability studies confirmed the retention of quality attributes over three months. This formulation aligns with the study's goal of developing a gingerol-enriched marshmallow candy as a nutraceutical for managing pediatric CINV. Its palatable and child-friendly format enhances treatment adherence while showing potential for managing

Table 8
Results of the stability studies (mean ± SD, n = 3).

Test parameter	Initial	After three months' storage
Hardness	30 ± 0.45 N	32 ± 0.75 N
Cohesiveness	2.40 ± 0.01	0.25 ± 0.00
Springiness	0.52 ± 0.009	0.51 ± 0.003
Drug Content	98.87% ± 0.25%	97.87% ± 0.75%
Water activity	0.691 ± 0.021	0.698 ± 0.004
Disintegration time	182 ± 0.55 s	184 ± 1.11 s
Drug release	98.27% ± 2.15%	97.55% ± 1.25%

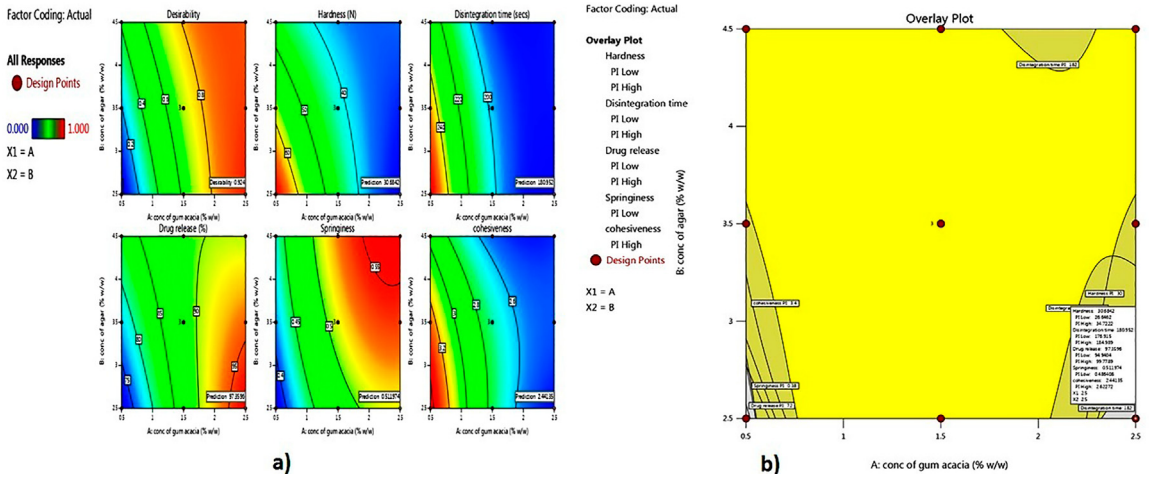

Fig. 5. a) Contour plots for the predicted optimized batch F7 for dependent responses; b) Identified design space for the central composite experimental design (highlighted in yellow).

other emesis-related conditions such as motion sickness, thereby improving overall patient comfort and quality of life.

CRediT authorship contribution statement

Marzooka Kazi-Chishti: Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Data curation. **Umme Jasvi Kulsum:** Methodology, Investigation, Formal analysis, Data curation. **Mohamed Hassan Dehghan:** Writing – review & editing, Visualization, Supervision, Project administration, Conceptualization. **Mohd Nazimuddin Chishti:** Writing – review & editing, Visualization, Software, Conceptualization. **Kazi Bilal:** Writing – review & editing, Visualization, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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