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Development, optimization, and characterization of vitamin C-fortified oleogel-based chewable gels and a novel nondestructive analysis method for the vitamin C assay

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Abstract

Chewable gels represent an excellent alternative to oral dosage forms, such as tablets and capsules, owing to their appealing appearance, easy swallowing, and attractive colors. Given the inherent instability of vitamin C, particularly within chewable gels, it is imperative to enhance its stability and mitigate its degradation during processing and storage. Oleogel, systems prepared through an environmentally friendly and pollution-free method, exhibit a three-dimensional network structure that eliminates oxygen, alleviates oxidation, and enhances vitamin C stability. This study focused on optimizing vitamin C-fortified oleogel-based chewable gels using Plackett–Burman and D-Optimal design methodologies to maximize vitamin C stability while maintaining favorable mechanical properties. The optimal formulation, Opt-C, was achieved by crystallizing the gel at -18 °C, incorporating 2.5 g of distilled monoglyceride (DMG), and maintaining an oleogel-to-chewable gel ratio of 10%. Opt-C was comprehensively characterized using differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FT-IR), and its stability was rigorously assessed. Furthermore, a nondestructive assay method for vitamin C determination in chewable gels was developed employing near-infrared spectroscopy (NIR) and chemometric techniques. Storage studies demonstrated that Opt-C retained 85% of its vitamin C content during accelerated tests over ten weeks, surpassing the 69% retention observed in the control chewable gel. Opt-C exhibited a slower release of vitamin C in simulated digestive fluids; however, this release profile did not adversely impact the overall availability of vitamin C. Ultimately, the developed multivariate model successfully predicts vitamin C concentration: root mean square error of calibration (RMSEC): 0.284, R^2_{cal}: 0.9906; RMSE cross-validation (RMSECV): 0.501, R^2_{val}: 0.9722; RMSE prediction (RMSEP): 0.670, R^2_{pred}: 0.9154. This innovative approach enhances the stability of water-soluble vitamins in chewable gels.

Keywords Chewable gel, Vitamin C, Stability, Oleogel, Design of experiment, Chemometrics, Gummy

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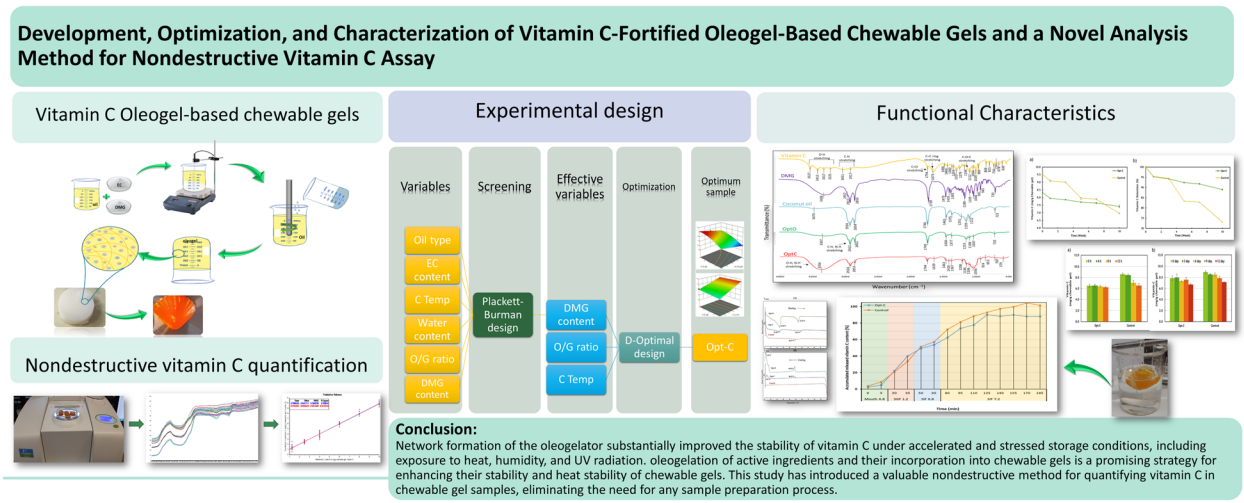
Graphical Abstract



Introduction/Background

Vitamin C (L-ascorbic acid), a water-soluble vitamin, can maintain average growth and improve iron absorption from the gut. Under physiological conditions, vitamin C is a powerful reducing agent that efficiently quenches potentially harmful free radicals produced by normal metabolic reactions. (Arrigoni & De Tullio 2002). However, most animals can synthesize substantial amounts of vitamin C endogenously, while humans have lost this ability due to a series of inactivating mutations (Li & Schellhorn 2007; Nishikimi et al. 1994). Chewable gels are also recognized as "gummies" in the confectionery and food industries, although that term is not used in official article titles (USP46-NF41 2023b). Chewable gels comprise sugars, gelling agents, colorants, flavorings, and active ingredients such as vitamins, minerals, and phytochemicals, which are molded into a shape (Mutlu et al. 2018). Its application has extended widely within the food and pharmaceutical industry as an innovative drug and supplement delivery system. They are particularly appealing to children and some adults due to their confectionery, taste and appearance (Čižauskaitė et al. 2019).

The gummy market is predicted to reach $5.8 billion in the United States by 2029 (Transparency Market Research. 2019). Chewable gels' higher viscosity than liquid formulations also provides further advantages in masking flavors, improving taste, and preventing drug particle sedimentation (Doolaanea & Bahari 2017). The first medicinal oral jelly dosage form developed in Japan was alendronate oral jelly. Furthermore, acyclovir, calcium gluconate, donepezil hydrochloride, amlodipine, tadalafil, and sildenafil are also available as jelly products in the Japanese market (Imai 2013). Moreover, numerous studies have explored medicated jellies, including carbamazepine (Mawazi et al. 2019), salbutamol sulfate (Begum et al. 2018), and vitamin C (Ibrahim et al. 2017; Yan et al. 2021).

Vitamin C is susceptible to oxidation under light, heat, humidity, oxygen exposure, and deviation from the optimal pH (Abbas et al. 2012). To address this issue, manufacturers often add excess quantities of vitamin C before production, leading to inconsistencies between the actual and labeled amounts throughout the product's shelf life (Andrews 2018; Andrews et al. 2017; Binns et al. 2018). It is recommended that manufacturers consider reducing the shelf life of chewable gels instead of relying on overages. Additionally, efforts should be focused on developing stabilization strategies to extend shelf life (Davydova 2018).

Vitamin C has been encapsulated using various techniques (Caritá et al. 2020), including spray chilling (Matos-Jr et al. 2015), spray drying (Abbas et al. 2012; Yan et al. 2021), melt extrusion of glassy carbohydrates (Chang et al. 2010), liposomes (Amiri et al. 2019; Maione-Silva et al. 2019), fluidized bed coating (Knezevic et al. 1998), and microfluidics (Comunian et al. 2014). The choice of encapsulation method should consider a wide range of factors, such as the encapsulating material, production and storage conditions, food matrix, and cost considerations (Abbas et al. 2012). Oleogels are three-dimensional structures with plastic properties and

mechanical resistance that are formed by adding small amounts of oleogelator (1–10%) to a suitable oil (above 90%) (Pehlivanoglu et al. 2017; Thakur et al. 2022). The solvent-free, environmentally friendly nature of oleogel preparation makes it widely used in foods due to its unique structure and functional properties, both in academic research and in the public, for its health and nutritional benefits (Co & Marangoni 2012; Pehlivanoğlu et al. 2018; Singh et al. 2017). Furthermore, oleogels can be easily incorporated into foods, including cakes and chocolate (Li & Liu 2019; Tabibiazar et al. 2020). Moreover, oleogels have found extensive applications in delivering micronutrients, attracting significant attention in the nutraceutical, pharmaceutical, and food industries over the last decade. Food oleogels are increasingly used to deliver micronutrients because the gel structure can be a physical barrier to these nutrients (Siraj et al. 2015; Zhao et al. 2022). Oleogel-based micronutrient delivery systems offer advantages such as higher loading capacity of micronutrients, improved dispersion in food, extended shelf life of encapsulated micronutrients, and reduced irritation of some micronutrients in the stomach, making them a focus of research in recent years (Zhao et al. 2022).

With the development of different oleogels, there has been an increased emphasis on incorporating hydrophilic compounds into oleogel systems in addition to lipophilic compounds (Masotta et al. 2019). Hydrophilic compounds are incorporated due to the water-soluble nature of most food-grade materials and may not readily disperse in hydrophobic solutions such as oil. Furthermore, these hydrophilic compounds are readily available and cost effective. Oleogels also have the potential to enhance the taste, aroma, and nutritional value of certain ingredients (Wang et al. 2020).

In general, there are four main groups of oleogelators used to prepare oleogels: crystalline elements such as fatty acids and monoglycerides; low-molecular-weight compounds; polymeric compounds such as ethyl cellulose (EC) and methylcellulose (MC); and inorganic materials (Meng et al. 2018). Among polymeric gelators, EC is generally recognized as safe (GRAS) by the United States Food and Drug Administration (US-FDA) (Gonçalves et al. 2022) and is a highly effective oleogelator. During oleogelation, when the EC-oil mixture reaches the glass transition temperature (Tg) of EC, amorphous regions are formed from some crystalline regions, resulting in exposed ethoxy groups that dissolve into the oil. As the oil temperature decreases, the soluble polymeric networks transform from an elastic state to an inflexible and plastic state, forming a pseudocoral polymer network with numerous cavities, similar to the structure of polymeric hydrogels. Current research suggests that creating the semicrystalline structure of oleogels is facilitated by the formation of intermolecular and intramolecular hydrogen bonds, effectively trapping liquid oil within interwoven polymeric networks (Fu et al. 2020; Gómez-Estaca et al. 2019; Gravelle et al. 2012, 2013).

In producing oleogels, nonpolar solvents such as oils often use commercial monoacylglycerols (MAGs) as emulsifiers (Lupi et al. 2018). MAGs can create a continuous network from lamellar structures and reverse micelles in oleogel production (López-Martínez et al. 2014; Miao & Lin 2019). MAGs are nontoxic, readily available, and cost effective. However, oleogels made solely from MAGs are generally weak and sensitive to production conditions (Pakseresht & Mazaheri Tehrani 2022). On the other hand, oleogels made from combinations of different oleogelators can achieve the desired properties by adjusting the oleogelator content and leveraging synergistic interactions between them (Doan et al. 2018). The self-assembly attributes of MAGs have also been explored in various studies, focusing on their physical interactions with other oleogelators (Pakseresht & Mazaheri Tehrani 2022). A study by (Lopez-Martínez et al. 2015) investigated the effect of EC on the polymorphic transition of MAGs, concluding that EC enhances the gel strength, stability, and oil binding capacity (OBC) of MAGs. Based on a literature review, it is hypothesized that a two-component oleogelation with EC and distilled monoglycerides (DMG) may yield the desired characteristics for chewable gels. Various processing factors were optimized for the first time to achieve the best combination. To our knowledge, no study encapsulates vitamin C in an oleogel for chewable gels.

Furthermore, nondestructive vibrational spectroscopy methods such as near infrared (NIR) and Fourier transmitted IR (FT-IR) methods have rapidly gained popularity due to the demand for in-process analyses in the pharmaceutical and food industries. The nondestructive and noninvasive nature of vibrational spectroscopy methods makes them powerful tools in these industries (Roggo et al. 2007). The versatility and speed of these methods contribute to improved process knowledge, enhanced process control, and improved product quality (Rahman et al. 2010; Räsänen & Sandler 2007). Chemometrics, a method introduced by chemistry researchers in the early 1970s, involves multivariate data analysis using computer techniques. Chemometric techniques allow for optimization, identification of potential outlier data, and multivariate calibration (Georgouli et al. 2020).

In this study, Plackett–Burman and D-Optimal designs were employed to determine the optimal ratio of oleogelators, oil type, crystallization temperature, and the ratio of oleogel to chewable gel, taking into account textural behavior and vitamin C retention. A release study of the optimal

formulation was conducted in simulated mouth, gastric, and intestinal fluids to evaluate the ability of the oleogel network to facilitate the release of the active ingredient from the chewable gel. The stability of vitamin C in the optimal formulation was assessed under different conditions, such as ultraviolet (UV) light, humidity, and accelerated conditions. Additionally, various methods, including FT-IR spectroscopy, differential scanning calorimetry (DSC), and NIR spectroscopy, were employed to characterize and develop a nondestructive method for quantifying vitamin C in chewable gels.

Materials and methods

Chemicals and reagents

Citric acid, *L*-ascorbic acid (vitamin C), sodium hydroxide, metaphosphoric acid, methanol, sodium citrate dehydrate, EC (46 cp), hexane, and saccharose were purchased from Sigma Aldrich (St. Louis, MO, USA). Coconut oil, *β*-carotene, and DMG were kindly donated by Sarang Tejarat International (Tehran, Iran) and Savola Behshar Company (Tehran, Iran), respectively. The orange flavor was purchased from Givaudan (Dubendorf, Switzerland). High maltose Corn syrup and sorbitol were purchased from Golshahd Grain Processing Refinery Company (Mashhad, Iran). The 220–250 Bloom beef gelatin was kindly gifted from Masterfoode Company (Tehran, Iran), and almond oil was purchased from a local drugstore.

Experimental designs and statistical analysis

Screening

The Plackett–Burman design was utilized in this study to screen for significant variables (Table 1). It is probable to study up to 7 factors in 8 runs, 11 in 12 runs, or even up to 99 in 100 runs (Plackett & Burman 1946). The effect of factor X_i is calculated using Eq. (1):

$$\text{Estimate of effect Xi} = \sum \overline{Y}(+1) - \sum \overline{Y}(-1) \quad (1)$$

Where $\overline{Y}$ is the average response of all the experiments. After the effect of Xi was estimated for all factors, the values were plotted using a half-normal plot. Utilizing the fitness of these plots, the significance of an effect was discriminated. Non-significant effects do not have deviations from a straight line through the origin, unlike the significant factors that deviate from this line (Fahmy et al. 2012). Every factor was established at high (+1) and low (-1) levels.

The factors selected for this study were oil type (O_T), DMG content (D_C), EC content (E_C), crystallization temperature (T_C), water content (W_C), and weight ratio of oleogel to chewable gel (O/G_C). The Plackett–Burman design method was investigated using Design Expert 12.0.3.0 software (Stat-Ease, Inc., USA). Six given factors were screened in 18 runs with three replications of the center points (Table 2). The significance of variables evaluated on three responses: cohesiveness, springiness, and vitamin C stability in chewable gels.

Optimization (D-optimal)

For maximization, as multiresponse optimization, the stability and mechanical behavior, springiness, and cohesiveness, and vitamin C retention in chewable gels, in the optimum formulation of chewable gel, the influential variables were investigated and optimized. Thus, the vitamin C chewable gel was modified by replacing the oleogel containing vitamin C instead of directly adding vitamin C to the chewable gels. A D-optimal design, as a versatile method in experimental design approaches, was used for this purpose. D-optimal experimental design is a statistical method used to optimize the efficiency and precision of experiments (Smucker et al. 2018). After recognition of the significant variables (independent variables) in the screening step as D_C (1 to 3 g), O/G_P (10% to 30%), T_C (-18, 3.5, and 25 °C), and O_T as a categorical variable (almond oil or coconut oil), a D-optimal Design was

Table 1 Plackett–Burman design for six factors

Coded factors	Variables	Level (+1)	Level (-1)
X1 (O_T)	Oil type (categorical)	Almond oil	Coconut oil
X2 (D_C)	DMG content (numerical)	1 g	3 g
X3 (E_C)	EC content (numerical)	0.5 g	1.5 g
X4 (O/G_C)[a]	Oleogel/chewable gel % (numerical)	10% (5 g oleogel/45 g chewable gel)	30% (15 g Oleogel/35 g chewable gel)
X5 (T_C)	Crystallization temperature (numerical)	-18 °C	25 °C
X6 (W_C)	Water content (numerical)	1 g	3 g

O_T oil type, D_C distilled monoglyceride content, E_C ethylcellulose content, O/G_C weight ratio of oleogel to chewable gel, T_C crystallization temperature, W_C water content

[a] O/G_C%: 30%: 15 g of Oleogel was added to 35 chewable gel; 20%: 10 g of Oleogel was added to 40 g chewable gel; 10%: 5 g of Oleogel was added to 45 g chewable gel

Table 2 Screening of potential variables by Placket-Burman design

Run	A: O_T	B: D_C (g)	C: E_C (g)	D: O/G_C[a]	E: T_C (°C)	F: W_C (g)
1	Almond oil	3	0.5	30	25	3
2	Coconut oil	3	1.5	10	25	3
3	Almond oil	1	1.5	30	-18	3
4	Coconut oil	3	0.5	30	25	1
5	Coconut oil	1	1.5	10	25	3
6	Coconut oil	1	0.5	30	-18	3
7	Almond oil	1	0.5	10	25	1
8	Almond oil	3	0.5	10	-18	3
9	Almond oil	3	1.5	10	-18	1
10	Coconut oil	3	1.5	30	-18	1
11	Almond oil	1	1.5	30	25	1
12	Coconut oil	1	0.5	10	-18	1
13	Coconut oil	2	1	20	3.5	2
14	Almond oil	2	1	20	3.5	2
15	Coconut oil	2	1	20	3.5	2
16	Almond oil	2	1	20	3.5	2
17	Coconut oil	2	1	20	3.5	2
18	Almond oil	2	1	20	3.5	2

O_T oil type, D_C distilled monoglyceride content, E_C ethylcellulose content, O/G_C weight ratio of oleogel to chewable gel, T_C crystallization temperature, W_C water content

[a] O/G_C%: 30%: 15 g of Oleogel was added to 35 chewable gel; 20%: 10 g of Oleogel was added to 40 g chewable gel; 10%: 5 g of Oleogel was added to 45 g chewable gel

developed and pruned. Table 3 details the additional 24 experiments proposed in the D-Optimal section.

Preparation of the vitamin C-fortified oleogel

Figure 1 illustrates the process involved in preparing the vitamin C-fortified oleogel. The quantities of ingredients employed were based on the experimental design outlined in Table 2 and Table 3. EC was incorporated into oil (either coconut oil or almond oil) as a mixture. The mixture was heated to 140 °C and stirred in a salt bath at 1000 rpm/min for approximately 15 min until it ultimately became transparent. Subsequently, the sample temperature was reduced to 90 °C, and DMG was added and stirred for 2 min. Vitamin C was dissolved in water and gradually added to the oil mixture under homogenization (at 6000 rpm/min) for 1 min. The oleogel was then crystallized at a predefined temperature based on Table 1. The vitamin C-fortified oleogels were then stored at 5 °C for subsequent evaluation.

Preparation of vitamin C chewable gel

Chewable gel preparation was based on a previous publication with certain modifications (Yan et al. 2021). The composition of the ingredients was derived from the designs outlined in Tables 2 and 3. The gelatin was hydrated with the addition of water and left at ambient temperature (22 ± 2 °C) for 30 min. The gelatin was then melted in a water bath at 60 °C. The sugar mixture consisted of high maltose corn syrup, sucrose, sorbitol, and water heated to 118 °C. After achieving a Brix measurement of 88–90° to assess the solid content, the mixture was cooled to 100 °C, added to the melted gelatin, and stirred for 4 min to obtain a homogeneous mixture (at 500 rpm/min). Subsequently, 50% (w/w) citric acid, the color (β-carotene), and the flavor were added, and the mixture was remixed for 3 min. Finally, oleogel-fortified vitamin C was introduced into the prepared chewable gel mixture at 55 °C and mixed to achieve homogeneity. The resulting mixture was then transferred to silicone molds and left at ambient temperature for 48 h. Subsequently, the chewable gels were relocated to glass bottles and stored at 5 °C for further evaluation. Fig. 2 Schematic representation of the procedure.

HPLC analysis

The quantification of vitamin C was investigated using a high-performance liquid chromatography system (HPLC, Agilent 1260, Infinity II, Japan) equipped with a quaternary pump system and an ultraviolet detector. A C_{18} analytical chromatography column (100 mm × 4 mm, inner diameter, 5 µm; Eurospher, Dr. Ing. H. Knauer GmbH., Berlin), as previously described by Wang, X. et al. with some modifications (Wang et al. 2020). The mobile phase was set to flow at a 0.3 mL/min rate. A 20 µL sample was

Table 3 The D-Optimal design was applied to a vitamin C chewable gel formulation

Run No	Processing parameters				Response Variables		
	D_C (g)	O/G_C[b]	T_C (°C)	O_T	Cohesiveness	Springiness	5-week Vitamin C retention[c]
19	2	20	3.5	Almond oil	0.924	0.931	82
20	3	22.5	25	Almond oil	0.929	0.921	75
21	1.5	25	3.5	Coconut oil	0.913	0.920	84
22	2.24	12.4	25	Almond oil	0.943	0.973	73
23	3	10	25	Coconut oil	0.949	0.998	81
24	1	30	25	Almond oil	0.888	0.877	68
25	3	10	-18	Almond oil	0.952	0.992	96
26	2.18	30	25	Coconut oil	0.875	0.904	70
27	1	19.9	25	Coconut oil	0.910	0.934	75
28	1.76	27.5237	-18	Almond oil	0.900	0.914	94
29	1	10	25	Almond oil	0.935	0.993	72
30	1	30	-18	Coconut oil	0.905	0.910	90
31	1	10	-18	Coconut oil	0.958	0.981	95
32	2	10	3.5	Coconut oil	0.944	0.991	86
33	3	19.6812	-18	Coconut oil	0.929	0.950	92
34	3	19.6812	-18	Coconut oil	0.929	0.950	91
35	3	30	3.5	Coconut oil	0.871	0.910	81
36	1	30	25	Almond oil	0.880	0.879	70
37	2.5	30	3.5	Almond oil	0.889	0.898	83
38	1	17.4	-18	Almond oil	0.903	0.970	95
39	1	30	-18	Coconut oil	0.898	0.899	91
40	3	10	25	Coconut oil	0.938	0.996	82
41	3	10	-18	Almond oil	0.950	0.992	97
42	3	30	-18	Almond oil	0.889	0.879	93
O	2.36	10	-18	Coconut oil	0.957	0.997	95.39
O	3	10	-18	Almond oil	0.952	0.988	96.28
E	2.36	10	-18	Coconut oil	0.959 ± 0.015[a]	0.995 ± 0.003[a]	96.74 ± 1.77[a]
E	3	10	-18	Almond oil	0.942 ± 0.018[a]	0.991 ± 0.004[a]	96.70 ± 2.30[a]

D_C distilled monoglyceride concentration, O/G_P Percentage of oleogel/chewable gel, T_C crystallization temperature, O_T oil type, *O* optimized conditions, *E* sample prepared at optimum condition

[a] Data represent the mean values ± SD ($n = 3$) of three independent experiments

[b] O/G_C%: 30%: 15 g of Oleogel was added to 35 chewable gel; 20%: 10 g of Oleogel was added to 40 g chewable gel; 10%: 5 g of Oleogel was added to 45 g chewable gel

[c] Vitamin C retention: percentage of vitamin C retention after 5 weeks at room temperature

injected into the column at 25 ± 1 °C, and chromatographic data were recorded at a wavelength of 245 nm for vitamin C quantification. A standard vitamin C solution was prepared with 12.5, 25, 50, 60, 80, 100, and 120 µg/mL vitamin C. The obtained response was utilized to construct a univariate linear regression equation derived from the calibration curve ($R^2 = 0.9986$). Due to the instability of vitamin C, a fresh standard solution was prepared each time and analyzed via sample analysis.

The extraction of vitamin C from the chewable gels was performed by adding 1 ± 0.01 g of gummy to a mixture of 5 mL of n-hexane and 5 mL of the mobile phase, consisting of a 0.03 wt% metaphosphoric acid solution and methanol (50/50, v/v). The mixture was sonicated at 40 °C for 15 min at 40 kHz (Backer Ultrasonic, Iran) until the chewable gel was dissolved. Subsequently, the mixture was vortexed for 1 min to obtain a homogenous solution. The solution was centrifuged (Biofuge 28 RS, Heraeus Sepatech, Netherlands) for 10 min at 6000 × g and 25 °C. The supernatant was combined with 5 mL of fresh mobile phase and vortexed for 1 min. This mixture was again centrifuged for 10 min at 6000 × g and 25 °C.

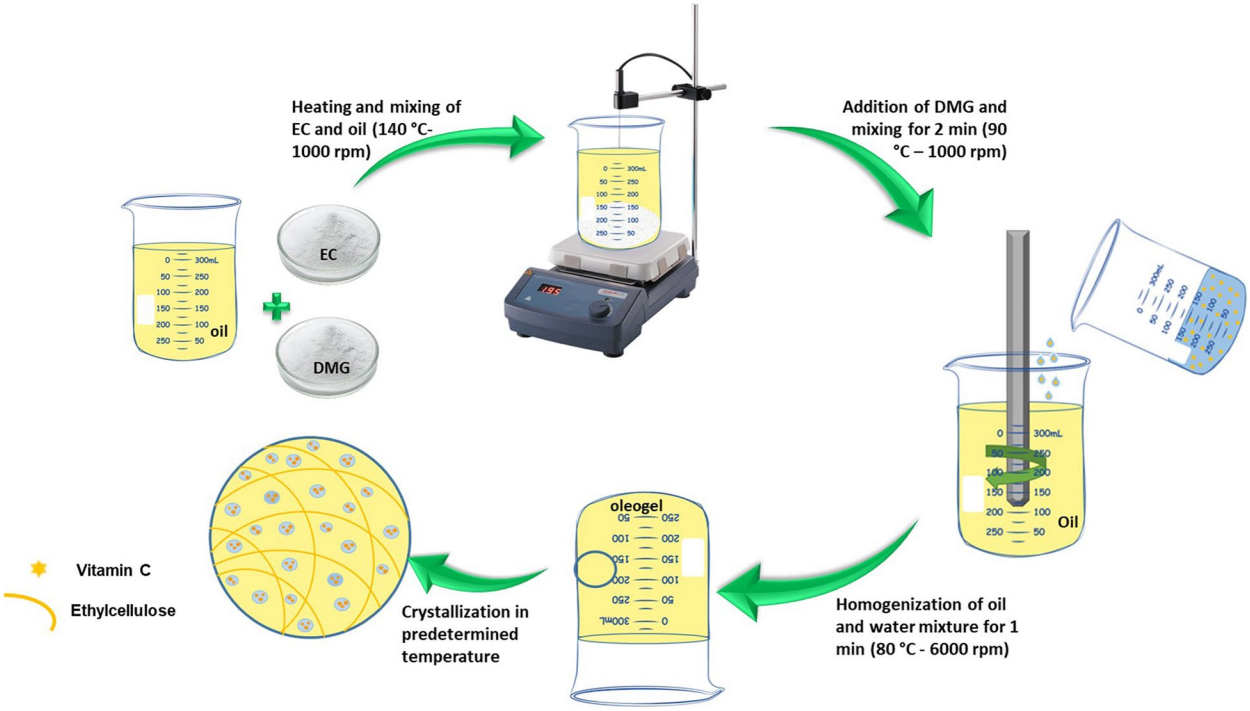


Fig. 1 Schematic representation of the vitamin C-loaded oleogel

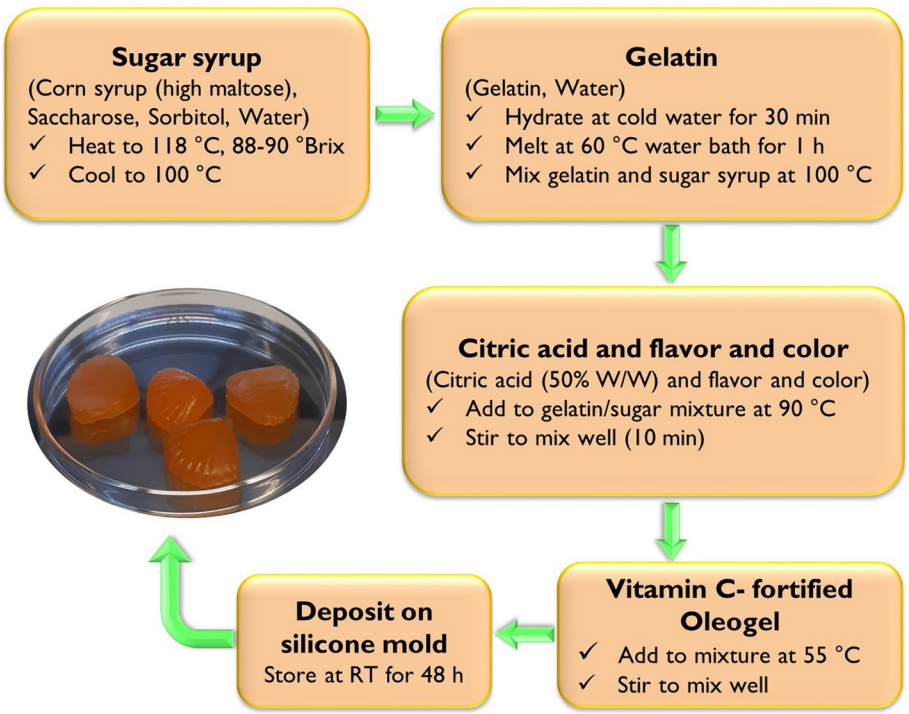


Fig. 2 Schematic representation of gummy preparation

The two separated mobile phases were mixed and centrifuged for 5 min at 6000 × g and 25 °C. Finally, 2 mL of the obtained sample was diluted with the mobile phase to bring the vitamin C concentration within the range of the calibration curve. Subsequently, 1 mL of the final solution was filtered through a PVDF membrane (0.45 µm) into an amber glass vial for HPLC analysis.

To assess method repeatability according to the international conference for harmonization (ICH) guidelines, five concentrations of vitamin C dissolved in the mobile phase were each injected five times, and the relative standard deviation (RSD) for each concentration was less than 2%. Furthermore, to investigate the accuracy of the extraction method as per ICH standards, recovery was calculated at three levels after extracting vitamin C from chewable gel samples (ICH 2023). The data are available in the supplementary S1.

Texture Profile Analysis (TPA)

The cohesiveness and springiness of the chewable gels were evaluated through TPA using a TA. XT plus C Texture Analyzer (Stable Micro Systems, Surrey, UK) equipped with a flat cylindrical aluminum probe (40 mm diameter). Samples with a height of 50 mm were prepared and stored in glass bottles. The probe applied a fixed speed of 5 mm/s and a deformation of 3.5 mm to achieve 70% strain at a controlled room temperature of 24 ± 2 °C. The recorded textural parameters included (1) springiness, which denotes the elastic recovery immediately after the compressive force is released, and (2) cohesiveness, representing the resistance of internal bonds within the specimen and is determined as the proportion of penetration forces.

Optimization and validation of the models

The parameters of the constructed models were calculated using multiple linear regression analysis based on the least-squares method, and their statistical significance was assessed through analysis of variance (ANOVA). The selection of the best-fitting models was determined by evaluating statistical parameters, including the coefficient of determination (R^2), R^2_{adj}, R^2_{pred}, lack-of-fit, and regression data (p value). Model terms with $p > 0.1$ were deemed nonsignificant and excluded from constructing the reduced models, while terms with $p < 0.05$ were considered statistically significant (Mirani & Goli 2021).

In cases involving multiple response variables, desirability function (DF) analysis was employed as a well-known method for optimizing variables. The DF analysis converts responses into a DF score, where values range from $0 < d < 1$, with desirability being 1 when the response variable reaches its predetermined target value. The optimization objectives included maximizing vitamin C stability (+ + + + + importance) and cohesiveness and springiness (+ + + importance). This approach allowed for the adjustment of the oleogel and chewable gel production parameters within the analyzed range. The optimum conditions obtained from the DF solutions were executed in independent additional runs and applied to validate the fitted models (E samples in Table 3). The resulting optimal samples were designated as the optimum coconut oil-based oleogel (Opt-O), an optimum chewable gel containing the optimum oleogel (Opt-C), and vitamin C dissolved in water and added directly to the chewable gel (control).

Characterization of the vitamin C oleogel and chewable gel

FT-IR

A Fourier transform infrared (FT-IR) spectrometer (PerkinElmer, Spectrum Two™, DTGS, Llantrisant, UK) was utilized to record the infrared spectra of the samples. After the reduction of the background scan, the samples were subjected to FT-IR analysis at a scanning range of 4000–450 cm^{-1} for vitamin C, EC, DMG, coconut oil, Opt-O, and Opt-C. The percentage of transmittance was employed as a response with an average of 128 scans and a resolution of 4 cm^{-1}.

Thermal properties

The thermal attributes (melting points) of the Opt-O, Opt-C, and control specimens were compared to those of an empty aluminum pan by differential scanning calorimetry (Mettler Toledo, DSC823e, Switzerland) as described in previous literature (Yang et al. 2017), with some modifications. A total of 7–14 mg of specimen was put on an aluminum pan and warmed from 0 °C to 100 °C at a rate of 5 °C min^{-1}, followed by cooling at the same rate from 100 °C to 0 °C.

Evaluation of the impact of temperature, UV light, and humidity on the stability of vitamin C in chewable gels

The effect of accelerated storage conditions on the preservation of vitamin C in chewable gels was investigated using methods outlined in prior literature (Yan et al. 2021). The Opt-C and control samples were placed in 100 mL sealed amber glass containers and stored at 33 °C for 10 weeks. Sampling was conducted at six distinct time points—0, 1, 3, 5, 7, and 10 weeks—followed by an analysis of vitamin C content via HPLC.

Chewable gels were retained in a beaker and subjected to an environment with 75% relative humidity (RH) at 40 °C for 12 days to assess the influence of elevated temperature and humidity on vitamin C retention. The desired RH was achieved through the utilization of a saturated NaCl solution. Sampling intervals were

established at 0, 3, 6, 9, and 12 days for subsequent HPLC analysis.

The effect of UV light on the degradation of vitamin C content was scrutinized. To accomplish this, 5 mm slices of chewable gels were positioned 10 cm below a UVLS-25 EL Series UV lamp (230 V, 50–60 Hz, 0.16 A, and 8 W, UVP, Upland, CA, USA) for 12 h at a wavelength of 254 nm. Throughout this investigation, sampling occurred at 0, 4, 8, and 12 h of UV exposure. These samples underwent analysis using the HPLC technique to determine vitamin C retention.

Release study of the chewable gel and accumulated release of vitamin C

To perform a release study of Opt-C and the control chewable gel, 3 g of sample was placed in a filtration bag and submerged in different pH buffers. Briefly, the samples were first immersed in a beaker (pH 6.8) containing 3.47 g of KH_2PO_4 and 8.77 g of Na_2HPO_4 up to 250 mL in Milli-Q water for 5 min. The filtration bag and sample were subsequently transferred to a second beaker containing 40 mL of simulated gastric fluid consisting of 0.5 g of NaCl, 1.75 mL of 37% w/w HCl, and up to 250 mL of Milli-Q water (SGF, pH: 1.2) without enzymes (USP46-NF41 2023a). Finally, the sample was relocated to third and fourth beakers containing buffers with pH values of 6.8 and 7.2 composed of 1.7 g of KH_2PO_4, 0.39 g of NaOH and up to 250 mL of Milli-Q water. Except for the first beaker, which was sampled after 5 min, the remaining samples were sampled every 15 to 150 min. All the samples were kept at 37 °C and stirred (Fig. 3). At each sampling time, 2 mL of medium was withdrawn to maintain the sync conditions, after which the medium was replaced with 2 mL of fresh, suitable medium. To improve the stability of vitamin C at pH 6.8 and 7.2, the withdrawn samples were also immediately diluted with 2 mL SGF immediately. Vitamin C standards solution with concentration 5–150 µg/mL was prepared in specific buffer media to be able to determine vitamin C concentration based on calibration curves of vitamin C at pH: 1.2 ($Y = 247.37\ X + 1401.9$, $R^2 = 0.999$) or pH: 6.8 ($Y = 298.03\ X — 1909.3$, $R^2 = 0.998$) and pH: 7.2 ($Y = 286.8\ X + 448.62$, $R^2 = 0.998$).

The percentage of cumulative vitamin C released from the Opt-C and control chewable gels was calculated based on previous methods (Yan et al. 2021). In more detail, the first amounts of vitamin C at every time point were calculated, but in contrast to the method of Yan et al., after every beaker was changed, the released fraction of vitamin C was removed.

Furthermore, dissolution tests of the chewable gels, Opt-C, and control samples were conducted based on the USP monograph for ascorbic acid chewable gels, disintegration and dissolution test (USP46-NF41 2023a). The USP expert committee suggested enhancing the stability of chewable gels (Davydova 2018). However, industries should consider not affecting the release of active ingredients. Consequently, the dissolution of both samples was evaluated by Eq. (2).

$$R = (r_u/r_s) \times (C_s \times V/L) \times 100 \tag{2}$$

Where r_u and r_s are the peak areas of vitamin C from the sample and standard solution, respectively. C_s is the concentration of vitamin C standard solution; V is the volume of medium, 900 mL; and L is the labeled amount of

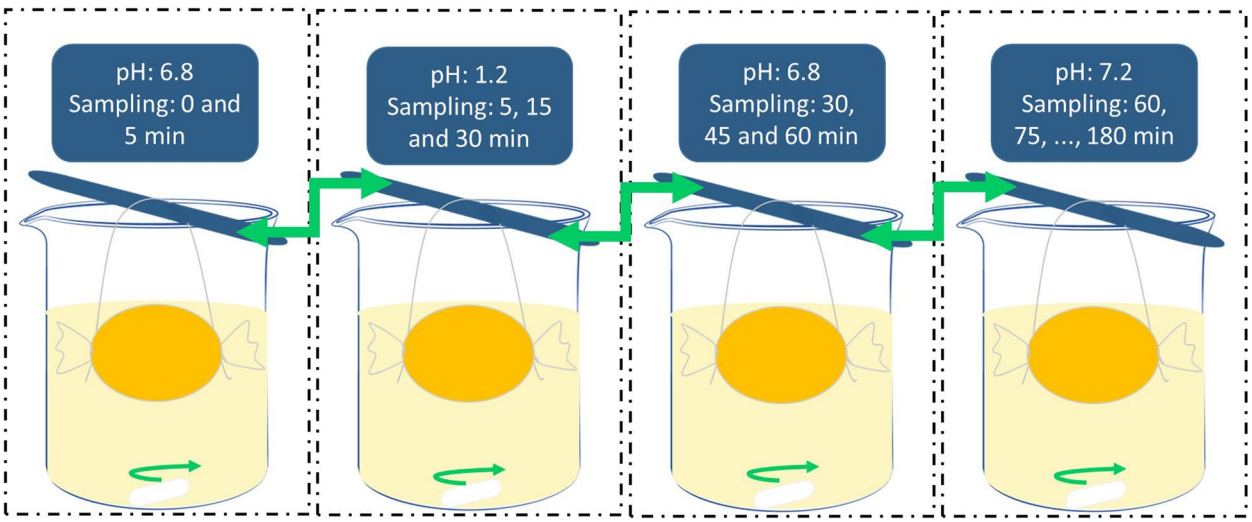


Fig. 3 Schematic representation of the release study of Opt-C and the control chewable gel in different pH buffers

vitamin C. As a result, *R* should not be less than 75% of this equation.

Nondestructive determination of vitamin C in chewable gels

In the NIR spectrum, distinctive bands of each element typically overlap with others, often degrading the precise identification of specific elements. Previous studies have employed NIR spectroscopy to quantify vitamin C at various concentrations in samples using stepwise multiple linear regression (SMLR) and partial least squares (PLS) regression methods (Yang et al. 2002). This study employed a PerkinElmer NIR instrument equipped with a prealigned tungsten halogen source and a temperature-stabilized InGa detector for spectrum acquisition. Spectroscopic analysis was conducted on samples containing varying amounts of vitamin C (1.25, 2.5, 4, 6, 8, and 10 mg/g of chewable gel), with at least five samples for each concentration.

Spectroscopy was performed on the samples directly without sample preparation steps. To mitigate the influence of the coating layer on the chewable gels, cross-sections of the samples were subjected to spectrometry and placed directly on plates. Measurements were conducted in reflectance mode, covering the spectral range from 9150 to 4000 cm^{-1}, with 64 scans and a spectral resolution of 8 cm^{-1}. Before the spectra were collected, sufficient time was allocated for device warm-up, resulting in improved reproducibility of the results. Additionally, a background spectrum was recorded to eliminate background noise.

In this study, 41 samples were prepared in the laboratory to create the calibration model, and 9 samples were used for the prediction set. The prediction set was ensured to be located in the inner region of the created space by the calibration dataset to create an optimal calibration model. This means that the calibration dataset covered the range observed in the prediction set. The measured variables were the dependent vector $y_{n\times c}$ and the independent matrix $X_{n\times m}$, where n is the number of samples in the calcination dataset, c is the number of chemical components, and m is the number of wavenumbers. The model was created using the amounts of vitamin C added to the samples as a y vector and their NIR spectra as an X matrix. The quality and validity of the developed model were evaluated using independent samples. The performance of the final model was evaluated by several metrics, including the correlation coefficient of calibration (R^2_{cal}), the correlation coefficient of validation (R^2_{val}), the root mean square error of calibration (RMSEC) and the root mean square error of prediction (RMSEP). The ratio of prediction to deviation (RPD) was also considered.

With respect to NIR spectroscopy, multivariate analysis of data preprocessing methods can be performed to create an optimal model (Rinnan et al. 2009). These methods aim to increase the quality of spectral data and improve the accuracy of the analysis (Grassi & Alamprese 2018). Standard preprocessing techniques include baseline correction to remove the baseline offset from the spectrum, which can be caused by factors such as scattering; smoothing techniques, such as the moving average or the Savitzky–Golay filter, which are used to reduce noise and fluctuations in the spectra; and multiplicative scatter correction (MSC) transformation, as a correction for the scattering effects due to changes in particle size or sample density. It involves dividing each spectrum by a reference spectrum to remove the scattering component. Standard normal variable (SNV) transformation includes a normalization technique that adjusts the spectra to have a mean and variance of zero. This approach helps eliminate unwanted changes in intensity caused by factors such as sample thickness or particle size (Rinnan et al. 2009).

The relationship between the vitamin C concentration and the NIR spectra of the prepared samples was evaluated using the PLS regression model Eq. (3). This model was used to investigate the relationships between the entire NIR spectra (independent variables) and the concentration of vitamin C in the chewable gels (response variables).

$$y = y_0 + a_1x_1 + a_2x_2 + \cdots + a_nx_m + \varepsilon \tag{3}$$

Where $\boldsymbol{y}_0$ is the intercept, y is the vector of response, X is the n by m (n number of samples and m = 5150 wavenumbers) matrix of predictor variables, and ε is considered to be noise from the model, which possesses dimensions similar to those of the Y matrix. Validation of the PLS model was performed by a full cross-validation method. The best R^2, RMSEC, and RMSECV values were obtained with the model with acceptable statistical quality. The data were analyzed using UNSCRAMBLER X 10.4 for Windows.

Results and discussion

Regression modeling and effect analysis

Variable screening aims to identify significant factors from a vast list of potential variables by conducting fewer experiments. In this study, we employed the Plackett–Burman design to discern the factors influencing the six potential variables in conjunction with five dummy variables, resulting in twelve experiments. Additionally, we conducted three replications of the center point for each categorical factor. Dummy variables, which are not assigned any specific effect, serve to estimate the variance of an effect (experimental error). The O/G_C ratio emerged

as a significant variable across all responses, along with the DMG content for cohesiveness and T_C for the 5-week vitamin C retention assessment.

In the subsequent phase, the levels of the significant variables were optimized using the D-optimal design. The properties of the chewable gels obtained based on the response parameters are presented in Table 3. Table 4 displays the coefficients and ANOVA results for the models. ANOVA and regression analysis were employed to assess the influence of parameter terms and the goodness of fit of the obtained models. The R^2 and adequate precision (AP) were used to evaluate the fitness of the models. The statistical significance of the parameters was determined through ANOVA to ascertain whether the model was significant ($p < 0.05$) or not ($p > 0.05$). The detailed statistical data, including p values, F values of the ANOVA models, and corresponding regression coefficients, can be found in supplementary data S2. Notably, it was established from the ANOVA tables that cohesiveness, springiness, and 5-week vitamin C retention models were significantly affected, all exhibiting p values < 0.0001. Furthermore, the R^2 values for all the response models exceeded 0.96, indicating that the obtained models were highly suitable for the optimization study. Additionally, the AP for all response models exceeded 24.

Cohesiveness

Cohesiveness refers to how well the chewable gel withstands a second deformation compared to its resistance during the initial deformation (Johnson 2015). The aim of producing chewable gels and gummies is to maximize this value, aiming for a value of up to 1 (Mahat et al. 2020). This value signifies the sample network's resistance during the second bite following the initial bite. The cohesiveness values of the chewable gels ranged from 0.871 to 0.957. The model describing the relationship between the factors and cohesiveness is expressed in Eq. (4), with R^2 and R^2_{adj} equal to 96.92% and 94.85%, respectively. An AP value of 24.41 indicates a satisfactory signal, and the obtained model can guide the experimental design space.

$$\begin{aligned}\text{Cohesiveness} &= 0.9174 + 0.0041 \times D_C - 0.0291 \\ &\times O/G_C - 0.0048 \times D_C \times O/G_C \\ &+ 0.0071 \times D_C \times O_T \\ &+ 0.0028 \times O/G_C \times O_T \\ &+ 0.0075 \times CT \times O_T \end{aligned} \tag{4}$$

The O/G_C and $C_T \times O_T$ were identified as highly significant variables ($p < 0.0001$) influencing the cohesiveness of the chewable gels (additional information is available in S2).

The influence of these factors on cohesiveness is illustrated in Fig. 4a. It is expected that increasing the content of DMG enhances the cohesiveness of the sample due to the greater number of crystals in the oil (Thakur et al. 2022; Zhao et al. 2020), thus improving the resistance of chewable gels during the second bite following the initial bite. However, the concentration of the oleogel relative to the chewable gel (O/G_C ratio) appeared to be more influential than the DMG concentration, and cohesiveness was maximized at a lower O/G_C ratio. Adding more than 15% of the chewable gel reduces the strength of the chewable gel network, leading to an inability to maintain its structure after the first bite and during the second bite.

Springiness

Springiness is defined as how well a chewable gel physically springs back after it has been deformed throughout the first deformation (compression) and is allowed to wait for the predetermined time between compressions (or bites) (Johnson 2015). According to Mahat

Table 4 Analysis of variance for the chewable gel models

Response	Fitted model	Source of variation	df	Sum of squares	Mean squares	F Value	*p* value	R^2
Cohesiveness	Modified 2FI model	Regression	6	0.0152	0.0025	71.66	< 0.0001	0.96
		Residual	17	0.0006	0.0000			
		Total	23	0.0158				
Springiness	Reduced quadratic model	Regression	8	0.0575	0.0072	91.98	< 0.0001	0.98
		Residual	15	0.0012	0.0001			
		Total	23	0.0587				
5-week Vitamin C retention[a]	Reduced 2FI model	Regression	6	2051.53	341.92	186.10	< 0.0001	0.98
		Residual	17	31.23	1.84			
		Total	23	2082.76				

2FI 2 factor interactions, *df* degree of freedom

[a] Vitamin C retention: percentage of vitamin C retention after 5 weeks at room temperature

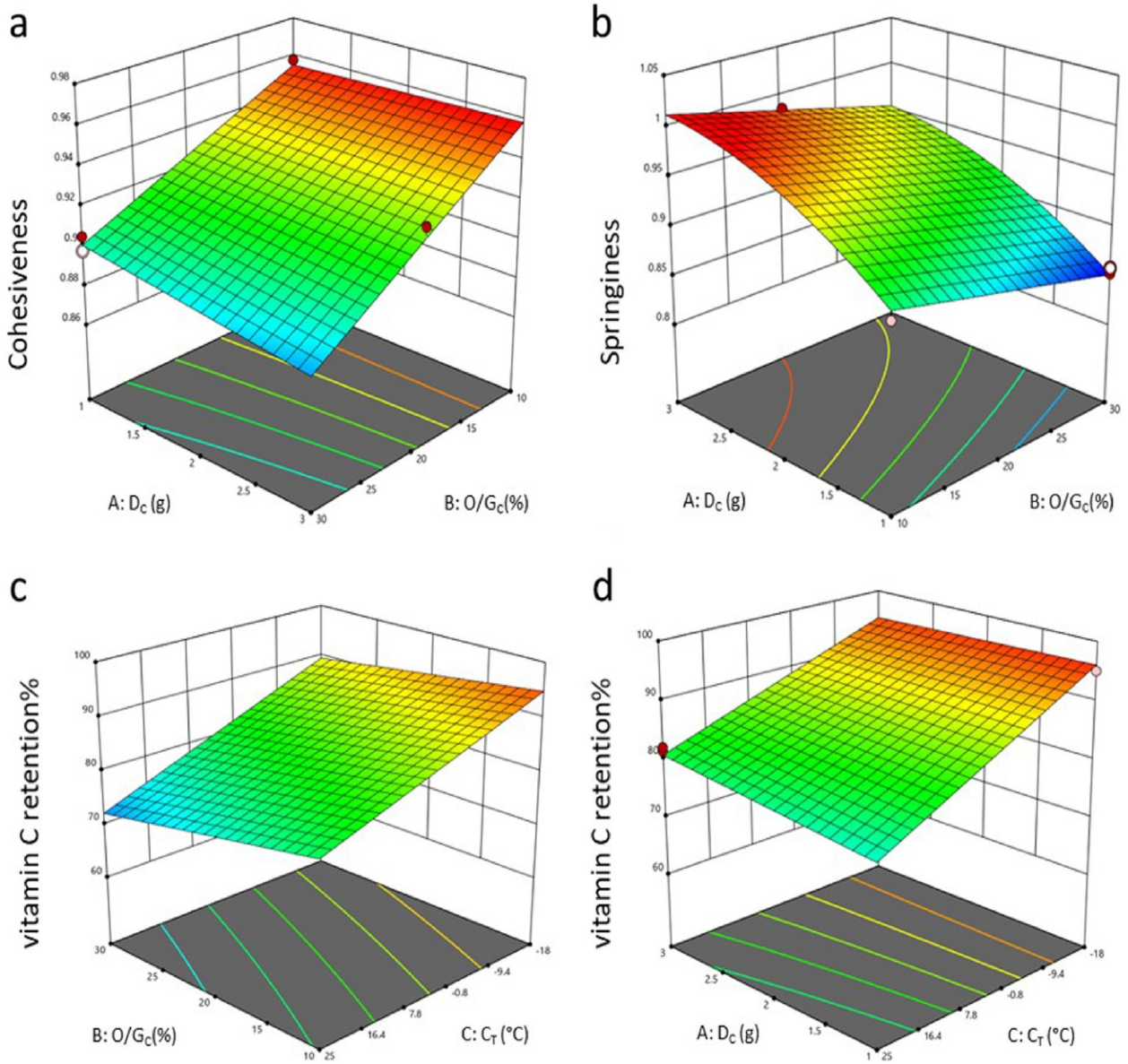


Fig. 4 **a** Effect of O/G_C and D_C on cohesiveness, **b** Effect of O/G_C and D_C on springiness, **c** Effect of O/G_C and C_T on vitamin C retention, *d* Effect of D_C and C_T on vitamin C retention

et al., the authors revealed that the desired chewable gels should have high cohesiveness and springiness values (Mahat et al. 2020). The springiness values of the chewable gels ranged from 0.852 to 0.996. The model that describes the correlation between factors and springiness is given in Eq. (5), with R^2 and R^2_{adj} equal to 98.00% and 96.94%, respectively. An AP value of 26.69 indicates an adequate signal, and the obtained model can be employed to direct the design space of the experiment.

$$\begin{aligned}\text{Springiness} &= 0.9441 + 0.0274 \times D_C - 0.0441 \\ &\times O/G_C - 0.0138 \times D_C \times C_T - 0.0098 \times D_C \\ &\times O_T - 0.0096 \times O/G_C \times C_T - 0.0055 \times O/GC \times O_T\end{aligned} \quad (5)$$

D_C and O/G_C and $D_C \times C_T$ were the most significant variables ($p < 0.0001$) for determining the springiness of the chewable gels. (More information is available in S2).

The effect of significant variables on springiness is shown in Fig. 4b. Adding oleogels, which have plastic properties, reduces the elasticity and ability of the

chewable gel to return to its previous shape. However, it was concluded that by maintaining D_C at concentrations between 2.5 and 3 g, adding up to a 20% oleogel-to-chewable ratio could be tolerated without decreasing the springiness value (0.98). However, for low levels of D_C, even in O/G_C, approximately 10% of the patients did not show springiness greater than 0.95.

Vitamin C retention after 5 weeks

The most crucial objective of the present study was to improve vitamin C retention in chewable gel samples and preserve good mechanical properties, as evaluated in two previous studies. For this purpose, vitamin C content was calculated based on the vitamin C content in the chewable gels at time 0 (VC_0). Then, the chewable gel samples were stored at room temperature in a glass container for 5 weeks (VC); after that, the vitamin C content of the samples was assayed via HPLC analysis. The percentage of vitamin C retention was calculated by Eq. (6):

$$\%\text{Vitamin C retention} = \frac{VC}{VC_0} \times 100 \tag{6}$$

The vitamin C retention values of the chewable gels ranged from 68 to 97. The model demonstrating the correlation between factors and vitamin C retention is given in Eq. (7), with R^2 and R^2_{adj} equal to 98.50% and 97.97%, respectively. An AP value of 37.26 shows an adequate signal, and the obtained model can be employed to direct the design space of the experiment.

$$\begin{aligned}\text{Vitamin C retention} = {} & 83.95 + 0.7687 \times \text{Dc} - 2.35 \\ & \times \text{O/Gc} - 9.91 \times C_T + 1.30 \times \text{Dc} \\ & \times C_T + 0.8835 \times \text{O/Gc} \times O_T - 1.50 \\ & \times C_T \times O_T\end{aligned} \tag{7}$$

C_T and O/G_C were significant variables ($p < 0.0001$) for determining vitamin C retention in chewable gels (More information is available in S2).

It was expected that C_T affect vitamin C retention. Wang et al. observed that with increasing C_T, the vitamin C concentration in oleogels produced from -18 °C to 5 °C decreased gradually (Wang et al. 2020). In the present study, as shown in Fig. 4c, d, the oleogels that were crystallized at a low level of C_T (-18 °C) had the maximum vitamin C retention. Moreover, the C_T was more critical than the O/G_C ratio, as vitamin C retention was near the minimum level in all ranges of the O/GC ratio if CT was high (25 °C).

Multiresponse optimization and model validation

The purpose of the present optimization study was to evaluate the effect of independent variables on vitamin C retention improvement of oleogel and chewable gel production process. For this purpose, D_C, O/G_C, C_T, and O_T were set in the range, and all the responses were maximized. In detail, cohesiveness and springiness with (+++) importance and vitamin C retention with (+++++) importance resulted in 11 possibilities with a desirability value of greater than 0.9. The solution with the best desirability of 0.970 for coconut oil was obtained under the following conditions: $D_C = 2.36$ g, $O/G_C = 10\%$, $C_T = -18$ °C, and O_T = coconut oil. Moreover, for almond oil, the point with the highest desirability was the twelfth solution, for which the desirability was 0.951, under the following conditions: $D_C = 3$ g, $O/G_C = 10\%$, $C_T = -18$ °C, and O_T = almond oil. Chewable samples under optimum conditions were prepared in triplicate to examine the model validity. The cohesiveness observed in the optimum samples was 0.959 for coconut oil and 0.942 for almond oil, respectively. These values are 100.2% and 98.9% of the value predicted by the model. The same is true for springiness, for which the observed values are 0.995 for coconut oil and 0.991 for almond oil, which are 99.7% and 100.3%, respectively, of the values predicted by the model.

Moreover, for the last one, the 5-week retention of vitamin C in the coconut oil was 96.74%, whereas that in the almond oil was 96.70%. These values are 101.4% and 100.4% of the values predicted by the coconut and almond oil models, respectively. The acceptable agreement between the observed values from the optimum samples and the values predicted by the model approves the statistical significance of the models. Furthermore, the agreement indicates the adequate precision of the equation for predicting the optimum parameters within the space of levels selected for the variables.

Characterization of the optimized vitamin C chewable gel

FT-IR

To evaluate the probable alterations in functional groups in Oleogel and the chewable gel, FT-IR spectra of vitamin C, DMG, coconut oil, Opt-O, and Opt-C are shown in Fig. 5. According to the literature for vitamin C spectra (Sk & Yue 2014; Yang et al. 2002), the peaks at 3527–3221 cm^{-1} and 3031–2917 cm^{-1} are assigned to O–H and C–H group stretching, respectively. C=O and C–C(=O)–O stretching can be observed at 1754 and 1279 cm^{-1}, respectively, and the peak at 1673 cm^{-1} corresponds to C=C bonds. The 1194 and 1112 cm^{-1} peaks fit in the C–O–C stretching. Vitamin C and C–OH bending can be observed at 1317, 1066, and 1026 cm^{-1}. The peaks at 821, 756, 719, 678, 621, and 1460 cm^{-1} belong to C–H bending, while the peaks corresponding to C–H and O–H bending can be found at 989 cm^{-1}. Ultimately, C–C peaks can be detected at 868 cm^{-1}.

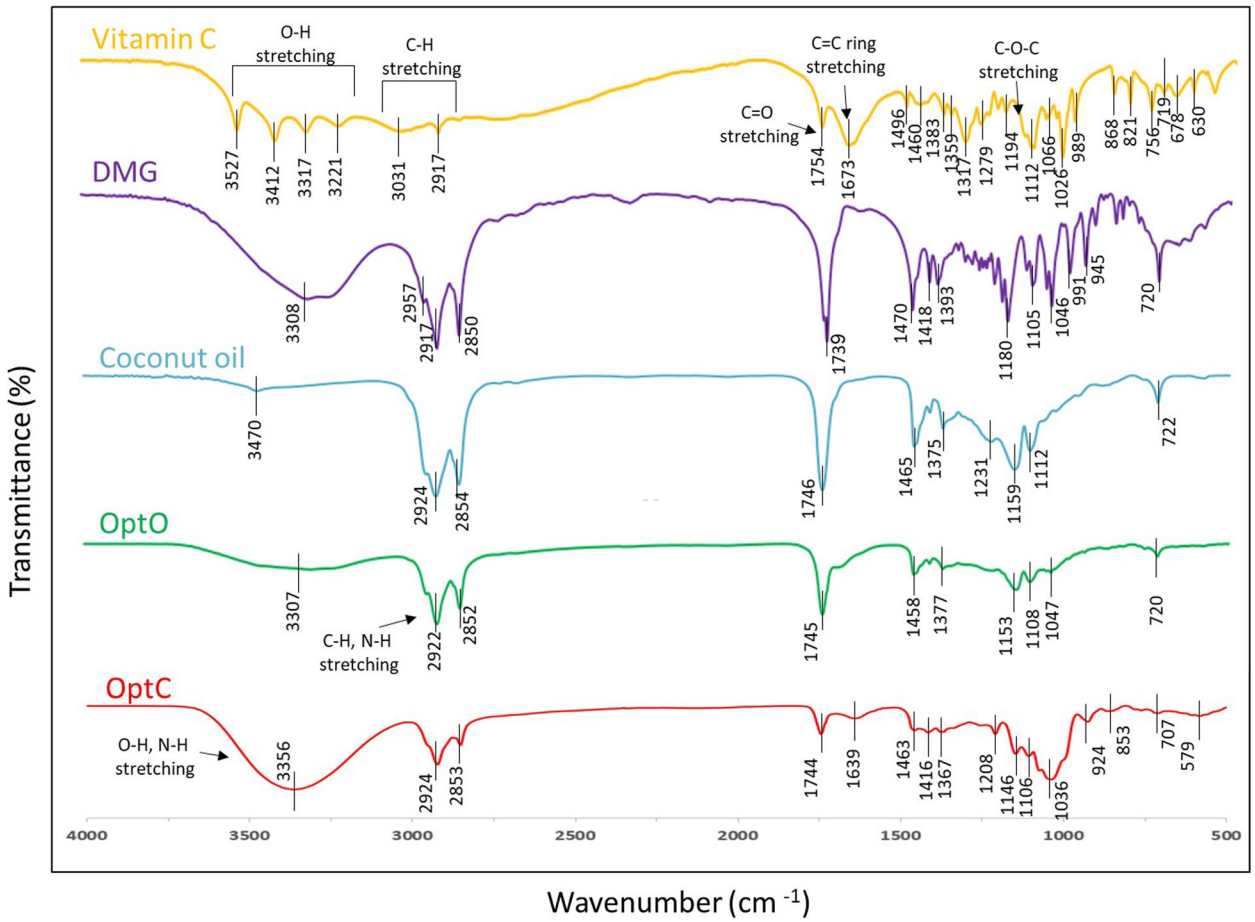


Fig. 5 FT-IR spectra of vitamin C, DMG, coconut oil, Opt-O and Opt-C

In a previous study of coconut oil, no peak was observed at approximately 3008 and 1654 cm^{-1} (Rohman 2017). The unsaturated double bonds (=CH; *cis*) and -C=C-(*cis*)) have peaks at 3008 and 1654 cm^{-1}, respectively. These peaks are indicative of an unsaturation degree of fatty acids. Because coconut oil comprises vast levels of saturated fatty acids (lauric acid; 50%), it is predictable that no peak was observed at 3008 and 1654 cm^{-1}. As references confirm (Dingcong et al. 2023), C-H and C=O group stretching peaks are observed at 2924 and 2854 cm^{-1} and 1746 cm^{-1}, respectively.

The DMG FT-IR spectra exhibited an indicative peak corresponding to the vibration of hydrogen bond bending between carboxylic acids at 945 cm^{-1}, and the C=O stretch was observed around 1739 cm^{-1} (Pakseresht et al. 2023; Rosen-Kligvasser & Davidovich-Pinhas 2021). The peak intensity was more significant for DMG than for Opt-O and diminished in the chewable gel (Opt-C), demonstrating the enfeebling of the intermolecular hydrogen bonds. Opt-O and DMG detected a broad doublet peak between 3000 and 3500 cm^{-1}, which correlated with the 2-OH and 3-OH absorption bands (Lupi et al. 2016).

Whereas the crystalline system and needle-like crystals were related to these groups and connected to hydrogen bonds (Lupi et al. 2016), it seems that the mentioned crystals were constructed in the oleogel system of the Opt-O sample. This result was confirmed by thermal analysis. As mentioned in a previous study, the peak corresponding to CH_2 bending at 720 cm^{-1} matched the structure of polymorph crystals (Rosen-Kligvasser & Davidovich-Pinhas 2021). In addition, stretching vibration peaks of C-O available at the ester group and symmetric and asymmetric bending vibration peaks of C-H were observed at 1047, 1108, 1153 cm^{-1}, 1377 cm^{-1}, and 1458 cm^{-1}, respectively.

The Opt-C represents a characteristic absorption at 3356 cm^{-1}, which fits the stretching of the N–H and O–H groups. Water molecules may be responsible for this peak formation. In addition, the observed peaks at 2924 and 2853 cm^{-1} belong to the O–H stretching of carboxylic acids and NH_3^+ stretching vibrations of free amino acids,

which are present in chewable gel structures. Moreover, chewable gels contain sucrose and high maltose corn syrup; consequently, we can anticipate observing sugar-related peaks from 1500 to 750 cm^{-1}. The peaks at 1146, 1106, and 1036 cm^{-1} are due to C–O and C–C stretching vibrations of the carbohydrate structure in the sucrose content. The peak at 924 cm^{-1} can be related to the vibrations of the glycosidic links of sucrose. The absorption at 1416 cm^{-1} can be recognized as the O–H stretching/bending vibrations of the bending mode of CH_2 and CH_3 groups in carbohydrates and proteins, and the abovementioned absorption peaks were observed in previous studies (Anjos et al. 2015; Cebi et al. 2019). Finally, the peak at 853 cm^{-1} fits the C–C peak in the chewable gels, and the spectral properties belonging to the presence of gelatin were observed as a significant peak (amide I) at 1639 cm^{-1}. The decreased intensities of the peaks at 2924, 2853, and 1744 can be because of the possible hydrogen bonding between the chewable gel and the oleogel (Guerin et al. 2016; Salama & Hashim 2022). This possible hydrogen bonding can enhance physical interactions, increasing the stability of the oleogel and vitamin C trapped in Opt-C. Additionally, as a result of the enhanced preservation of vitamin C in the oleogel and subsequently in Opt-C, it is anticipated that vitamin C would be more stable in Opt-C.

Thermal properties

Since Opt-O is designed for chewable gels, evaluating the melting profiles of these gels is essential for evaluating the heat resistance of the products. Figure 6 shows the DSC thermographs of Opt-O, Opt-C, and C. Opt-O exhibited a single peak at approximately 23.98 °C, which comes at a similar temperature, 23.48 °C for the Opt-C samples refer to the glass transition temperatures, whereas the control sample did not show any such peak. In addition, another peak at approximately 53 °C represents the melting temperature of Opt-O, and a broad peak occurs at approximately 58 °C for Opt-C; this peak is approximately 48 °C for the control. Adding the oleogel to the chewable gel increased the peak melting temperature of the Opt-C sample from 48.97 °C to 53.95 °C. It was observed that the melting temperature was increased by adding the oleogel to the Opt-C sample.

Vitamin C stability in chewable gel

The vitamin C retention of the Opt-C and control chewable gels under accelerated storage conditions (10 weeks, 33 °C) is shown in Fig. 7 A, B. In the first week, for both samples, vitamin C was slightly reduced (5%), followed by slight reductions in Opt-C of 9% and 11% after 7 and 10 weeks, respectively. On the other hand, significant decreases of 17% and 23% were observed in the control chewable gel sample. The slight decrease in vitamin C concentration in the control during the first 3 weeks may be attributed to the physical hindrance afforded by the formation of hydrogen bonds between the chewable gel ingredients and vitamin C. Nevertheless, the alterations in shape and textural changes in the samples lowered the protective oxygen barrier and heat availability. The reduction was significantly greater in the control treatment. DSC thermograph data demonstrated that the control was more prone to heat exposure than was Opt-C. Adding an oleogel could further improve the thermal texture resistance of the ensued chewable gel to the physical barrier obtained from oleogelator network formation.

The amount of vitamin C in the chewable gel control and Opt-C samples exposed to UV light (254 nm) for 12 h is presented in Fig. 8A. A slight reduction in vitamin C in the Opt-C chewable gel was observed, with a 5% reduction after 12 h. Then again, control's higher vitamin C content was reduced after 12 h (24% reduction). However, it was stable during the first 4 h (2% reduction). As stated, the physical barrier prepared by hydrogen bond formation is critical for preserving vitamin C. In addition, the stability of vitamin C in the Opt-C and control samples was evaluated against humidity and heat at 40 °C and 75% RH for 12 days (Fig. 8B). Under these conditions, a reduction in vitamin C was predictable in both samples. Nevertheless, the improved heat resistance of Opt-C is apparent: a 15% reduction in Opt-C versus a 20% reduction in C.

Release study of chewable gel

To assess the vitamin C release profile in various pH buffers, we employed a pH of 6.8 to simulate mouth conditions, a pH of 1.2 to SGF, a pH of 6.8 for upper intestinal fluid simulation, and a pH of 7.2 to simulate lower intestinal fluid conditions. We immersed 3 g of Opt-C and control chewable gel samples in 40 mL of predetermined buffer solution for scheduled sampling. All the solutions were maintained at 37 °C, akin to human body temperature. Fig. 9 illustrates that vitamin C release commences promptly upon immersion in the first buffer solution, with the control sample exhibiting a faster release rate. Subsequently, when introduced into SGF, the acidic conditions escalate vitamin C release from both the control and Opt-C samples. After 50 min, approximately 50% of both samples had been released, with no discernible difference between the Opt-C and control samples. Continued immersion of the samples in a filtration bag at pH 7.2 resulted in dissolution of the chewable gel and subsequent release of vitamin C, with both samples releasing approximately 90% after 125 min. The Opt-C sample reached a steady state with a 90% release, after which the rate of vitamin C reduction

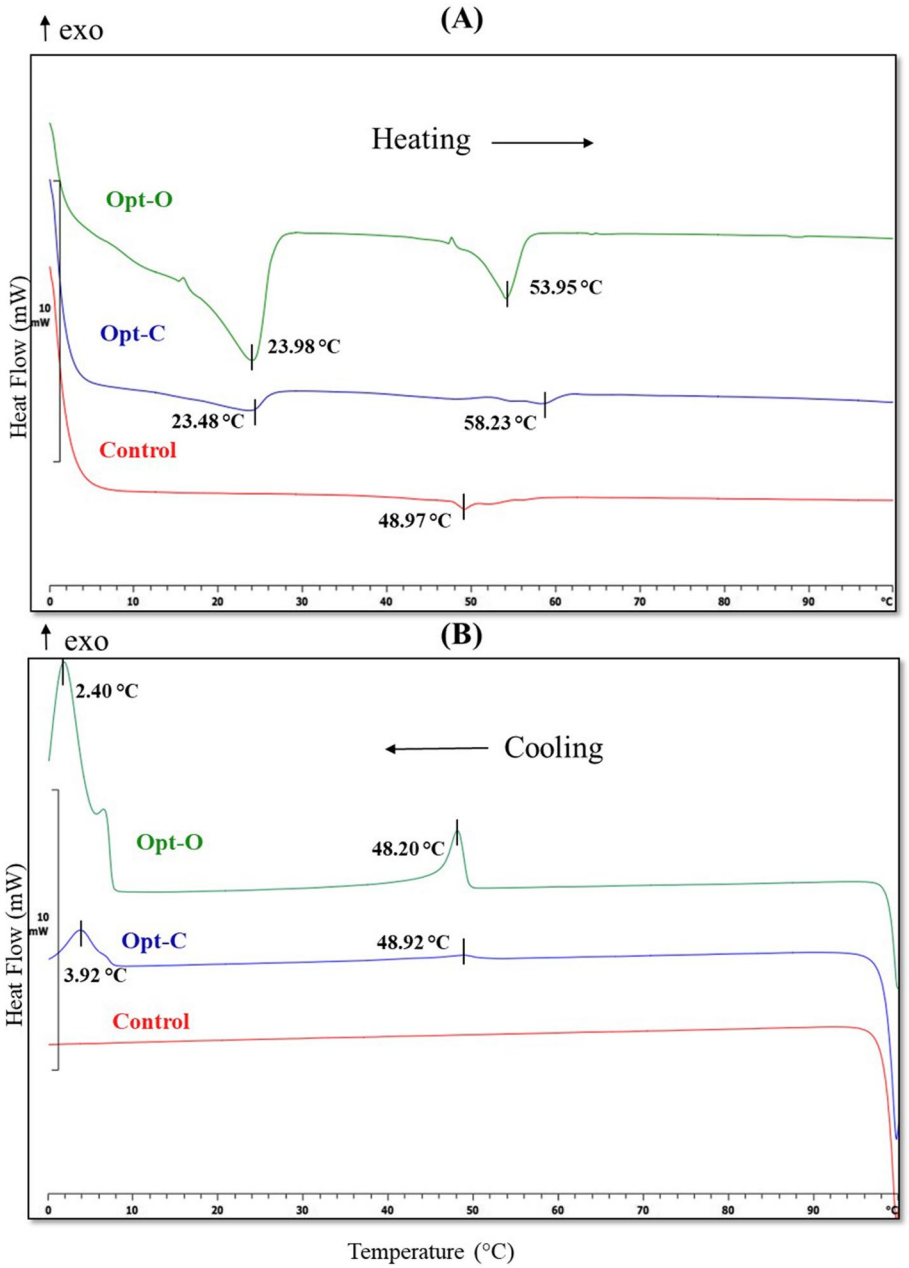


Fig. 6 DSC thermographs of Opt-O, Opt-C, and the control during the heating (**A**) cycle at + 5 °C/min and the cooling (**B**) cycle at 5 °C/min. Opt-O: optimum oleogel; Opt-C: optimum chewable gel; **C** chewable gel without an oleogel

was gradual. This phenomenon may be attributed to the instability and degradation of vitamin C.

In general, the cumulative release increases until it reaches a steady state, provided that the analyte is soluble in the solution and remains stable in the release medium. However, this was not the case in our study, as the vitamin C content in the specimens was determined by replacing the beaker. The reduction in vitamin C release from Opt-C over time (beyond 2 h) can be ascribed to the decomposition of vitamin C at pH 7.2 and the presence of oxygen in the solution. Additionally, the calculated vitamin C release accounts for both the cumulative release and degradation of vitamin C post-release. If the degradation rate surpasses the release rate indicates a decrease in the cumulative release.

Furthermore, a dissolution test of chewable gels, including Opt-C and control samples, was conducted

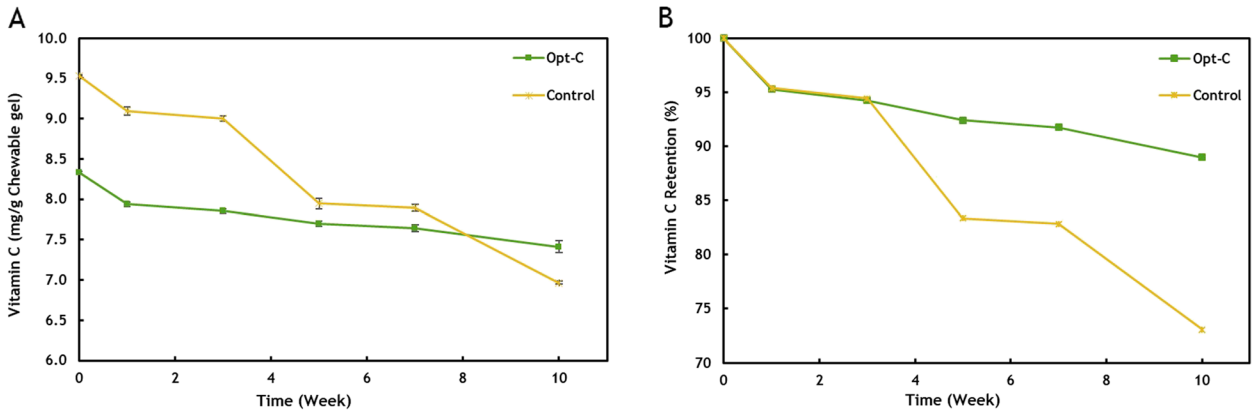


Fig. 7 Vitamin C content (**A**) and percentage reduction (**B**) in the accelerated stability study during 10 weeks at 33 °C. Data represent the mean values ± SD of three independent estimations

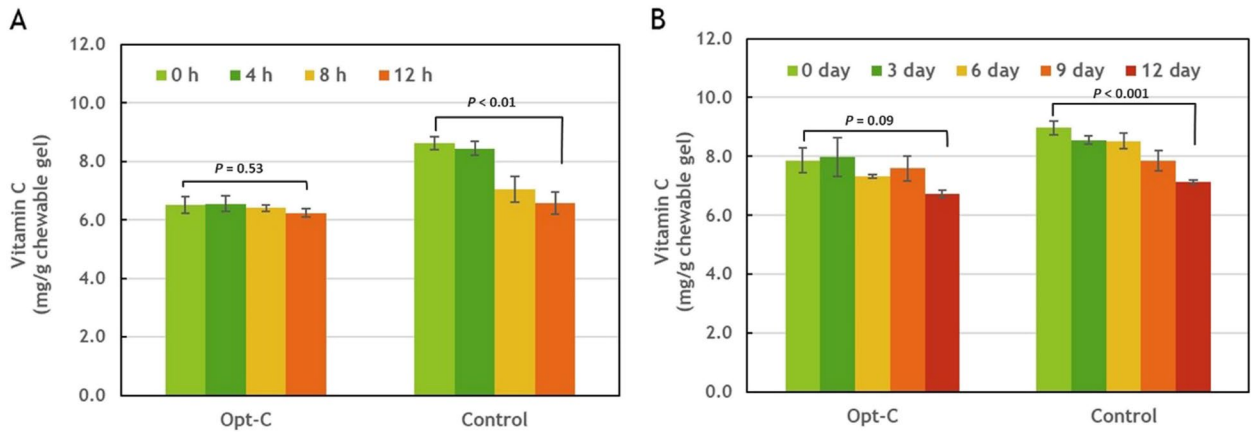


Fig. 8 Vitamin C stability in a chewable gel (**A**) exposed to UV radiation (254 nm) for 12 h and (**B**) treated at 40 °C-75% RH for 12 days. Data represent the mean values ± SD of three independent estimations. Statistical analysis was performed using one-way ANOVA, followed by Holm-Sidak multiple comparisons test where appropriate. Difference were considered significant when $P \leq 0.05$

following the USP monograph for ascorbic acid chewable gels; disintegration and dissolution tests were performed in 0.1 N HCl using 900 mL in apparatus 2, with a paddle rotation rate of 75 rpm for 15 min (USP46-NF41 2023a). With this method, the release percentages of Opt-C and the control were 97.2% and 103.3%, respectively. This outcome aligns with the release profiles of the samples, indicating that the prepared optimal formulation does not impede the release of vitamin C from the chewable gel.

Nondestructive determination of vitamin C in chewable gels

Figure 10A shows the NIR spectra of Opt-C chewable samples with varying vitamin C contents. This study employed several data processing methods and their combinations (Table 5). The best model for predicting vitamin C concentration was established using the MSC preprocessing technique and PLS regression. Fig. 10B shows the NIR spectra for the calibration dataset after MSC preprocessing. The choice of preprocessing technique depends on the specific characteristics of the samples and the desired analytical objectives.

The resulting model demonstrated exceptional performance, as evidenced by the high values of R^2_{cal}, R^2_{val}, R^2_{pred}, RMSEC, RMSECV, RMSEP, RER, and RPD, which were 0.991, 0.972, 0.915, 0.284, 0.501, 0.670, 9.0220, and 3.3552, respectively. These results indicate that NIR spectroscopy can be reliably utilized for predicting vitamin C levels in chewable gel samples. The use of various sources indicates that different RPD values reflect the model's predictive capability. A higher RPD signifies superior performance in calibration modeling, suggesting minimal deviation between the predicted and reference values (Zhao et al. 2015). Conversely, a lower RPD indicates poorer performance and a greater deviation between the

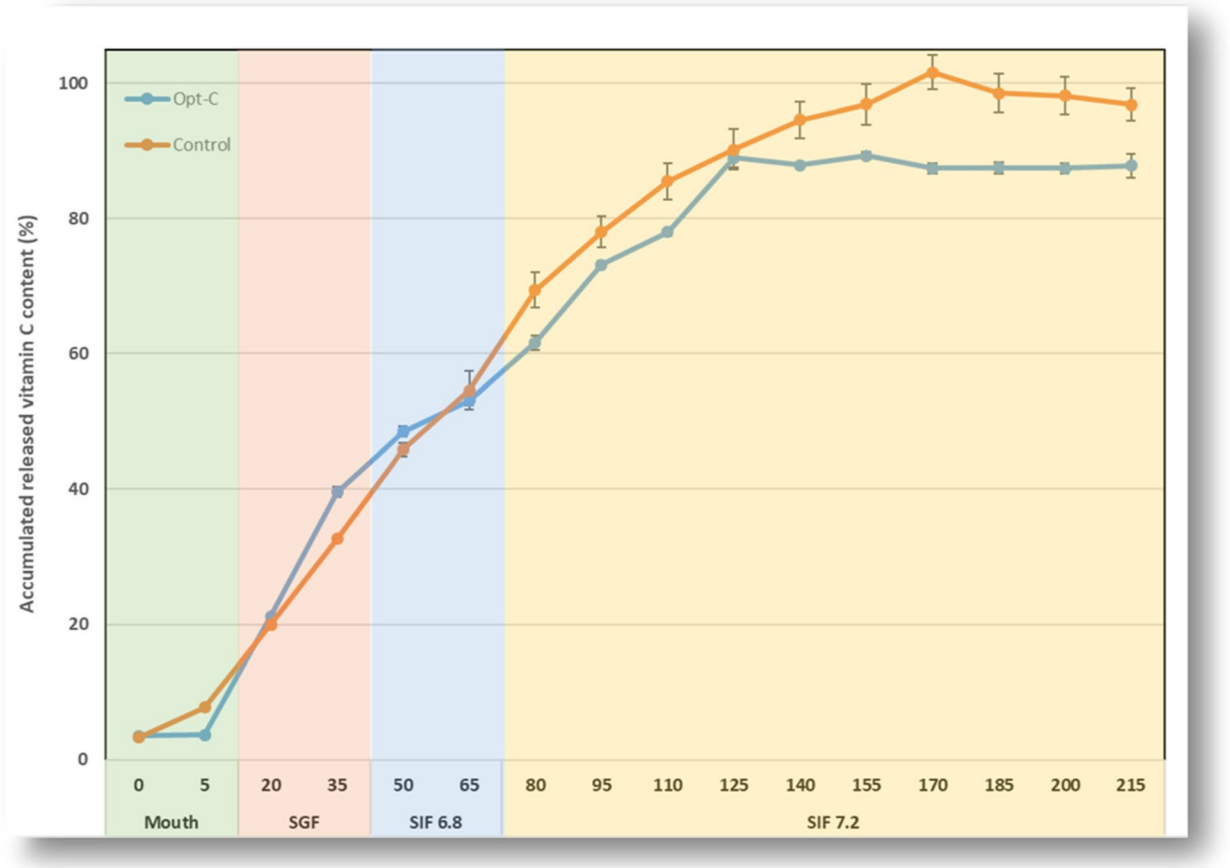


Fig. 9 Vitamin C release from Opt-C and control samples in different simulated fluids at 37 °C. Data represent the mean values ± SD of three independent estimations

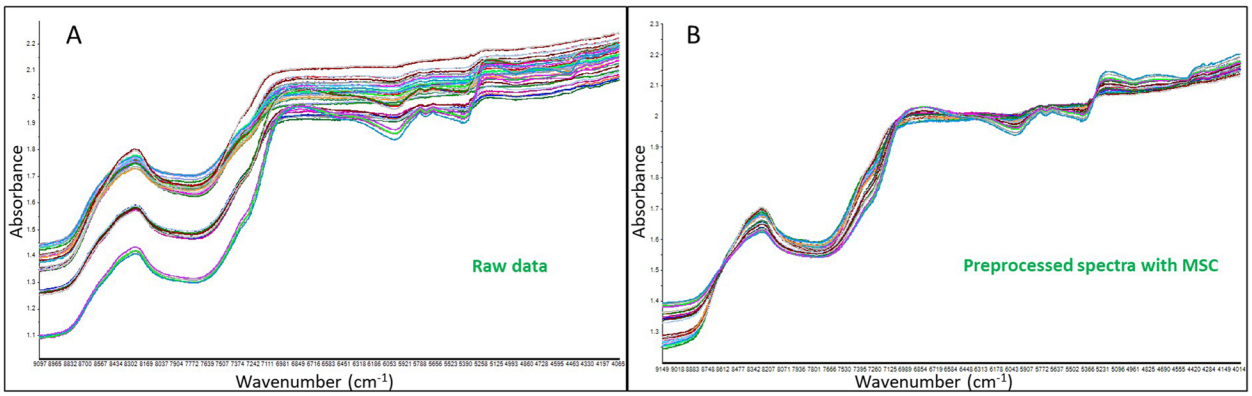


Fig. 10 Nondestructive quantification of vitamin C in chewable gels. **A** Raw NIR spectra of the samples. **B** Preprocessed MSC data

predicted and reference values. According to the literature in this field, an RPD value of 2.5 or higher indicates exceptional accuracy in prediction (De Bleye et al. 2012). The findings of this study demonstrated excellent performance in predicting vitamin C levels in chewable gels.

Conclusions

This study employed an innovative technique to enhance the stability of active ingredients within chewable gels. Specifically, we investigated the stability of vitamin C in an optimized oleogel-based chewable gel

Table 5 Different data preprocessing methods follow the PLS algorithm

Data preprocessing		Calibration		Full cross-validation	
	No. factors	**RMSEC**	R^2_{cal}	**RMSECV**	R^2_{val}
Raw spectra	6	0.4138	0.9801	0.5386	0.9679
Detrend (remove nonlinear trends)	6	0.3188	0.9882	0.5141	0.9708
SNV	5	0.5350	0.9668	0.6800	0.9489
MSC (Optimal data processing method)	**7**	**0.2840**	**0.9906**	**0.5013**	**0.9722**
Derivative-SG	2	0.4233	0.9792	0.7553	0.9370
SNV-Detrend	6	0.3347	0.9870	0.5295	0.9690
MSC-Detrend	6	0.3291	0.9874	0.5235	0.9697
Spectroscopic	5	0.4436	0.9771	0.5581	0.9656

SNV Standard normal variable, *MSC* multiplicative scatter correction, *SG* Savitzky–Golay

known as Opt-C compared to a conventional formulation denoted as C. Our results demonstrated that the network formation of the oleogelator substantially improved the stability of vitamin C under accelerated and stressed storage conditions, including exposure to heat, humidity, and UV radiation. These findings were corroborated through thermal analysis, in which Opt-C exhibited superior heat resistance compared to the control sample.

Furthermore, our release study involving Opt-C and control samples revealed no impediment to releasing the active ingredient due to oleogel formation and the oleogelator network. Thus, the oleogelation of active ingredients and their incorporation into chewable gels is a promising strategy for enhancing chewable gel stability and heat stability. This study introduced a valuable nondestructive method for quantifying vitamin C in chewable gel samples, eliminating the need for any sample preparation process.

Abbreviations

EC	Ethylcellulose
MC	Methylcellulose
GRAS	Generally recognized as safe
US-FDA	United States Food and Drug Administration
Tg	Glass transition temperature
MAGs	Monoacylglycerols
OBC	Oil binding capacity
DMG	Distilled monoglyceride
NIR	Near-infrared spectroscopy
FT-IR	Fourier transform infrared spectroscopy
DSC	Differential scanning calorimetry
HPLC	High-performance liquid chromatography system
ICH	International conference for harmonization
RSD	Relative standard deviation
TPA	Texture profile analysis
ANOVA	Analysis of variance
R^2	Coefficient of determination
DF	Desirability function
OPT-O	Optimum coconut oil-based oleogel
OPT-C	Optimum chewable gel containing the optimum oleogel
RH	Relative humidity
UV	Ultraviolet
SGF	Simulated gastric fluid
SMLR	Stepwise multiple linear regression
RMSEC	Root mean square error of calibration
RMSEP	Root mean square error of prediction
RPD	Ratio of prediction to deviation

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions
RS performed investigation, data curation, and major contributor in writing the manuscript. FAD wrote and edited the manuscript. MRK was major methodologist of the study. MA performed formal analysis. ZT wrote and edited the manuscript. JBG supervised and reviewed the manuscript. NS analyzed and visualized data. MH performed conceptualization, funding acquisition, and supervision. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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