

Development and optimization of a yogurt-based nutraceutical lozenge: A quality by design approach

Desy NAWANGSARI^{1*}, Tri SUMARNI², Dina FEBRINA¹, Erza GENATRIKA³, Ayu PUJIANTI¹, Binar Asrining DHIANI³, Hery WINARSI⁴

1 University Harapan Bangsa, Faculty of Health, Universitas Harapan Bangsa, Pharmacy Study Program, Purwokerto, Indonesia

2 University Harapan Bangsa, Faculty of Health Diploma in Nursing Program, Purwokerto, Indonesia

3 University Muhammadiyah Purwokerto, Faculty of Pharmacy, Purwokerto, Indonesia

4 University Jenderal Soedirman, Faculty of Health, Department of Nutrition, Purwokerto, Indonesia

ABSTRACT

Yogurt is a functional food rich in probiotics and bioactive compounds but limited by short shelf life and storage constraints. This study aimed to develop a yogurt-based nutraceutical lozenge incorporating peanut sprout, ginger, and lemongrass using a Quality by Design (QbD) approach. A Simplex Lattice Design was applied to optimize Avicel PH 102 and Isomalt ratios for improved friability, hardness, and dissolution. The optimized formulation showed friability <1% and hardness between 4.67–7.33 kg, meeting pharmacopeial standards. Differential Scanning Calorimetry and X-ray Diffraction confirmed an amorphous structure, enhancing dissolution. Scanning Electron Microscopy revealed porous morphology for rapid disintegration, while Energy Dispersive Spectroscopy confirmed organic composition. QbD ensured a reproducible, stable, and pharmaceutically acceptable lozenge. This approach demonstrated the feasibility of transforming yogurt into a shelf-stable solid dosage form with

* Corresponding author: Desy NAWANGSARI

E-mail: desynawangsari@uhb.ac.id

ORCID:

Desy NAWANGSARI: 0000-0001-7782-070X

Tri SUMARNI: 0000-0002-4872-2147

Dina FEBRINA: 0009-0008-2991-7257

Erza GENATRIKA: 0000-0002-9206-0638

Ayu PUJIANTI: 0009-0000-9710-8517

Binar Asrining DHIANI: 0000-0003-1447-2597

Hery WINARSI: 0000-0002-4314-7614

(Received 25 Jul 2025, Accepted 6 Feb 2026)

© Medipol University Press / ISSN: 2636-8552

retained bioactivity. Future studies should address long-term stability, sensory properties, and *in vivo* pharmacokinetics to support commercial application.

Keywords: lozenges, optimization, quality by design, simplex lattice design, yogurt

INTRODUCTION

The increasing consumer interest in functional foods is attributed to their potential health benefits, including nutritional value and disease prevention properties¹. Yogurt-based products have become particularly popular due to their rich probiotic content, bioactive compounds, and essential nutrients like proteins, vitamins, and minerals that contribute to overall health². Research highlights yogurt's advantages for digestive health, immune function enhancement, and promoting a balanced gut microbiota². However, traditional yogurt products encounter several limitations such as a short shelf life, refrigeration requirements, and microbial instability, which can hinder widespread distribution and long-term storage³. To address these drawbacks, researchers are exploring alternative delivery systems, which include tablet, lozenge, and powder formulations of yogurt⁴. Lozenges, in particular, provide a solid oral dosage form that allows for controlled release of bioactive components, enhanced stability, and improved consumer compliance⁴. Recent advancements illustrate the effectiveness of lozenge formulations for delivering probiotics and vitamins, making them an appealing option for nutraceutical applications⁵. Moreover, their non-refrigeration requirement enhances product accessibility, extending shelf life more effectively than conventional yogurt products⁴.

Current research has investigated various hydrocolloid applications in yogurt to improve its structural stability; however, studies focused on yogurt-based solid dosage forms remain sparse⁶. Efforts in food engineering and formulation optimization have yielded functional yogurt products; nonetheless, most studies emphasize conventional yogurt textures rather than solid dosage forms⁴. Advances in personalized nutrition present opportunities for integrating functional additives into yogurts; however, the application of probiotics and bioactive compounds in lozenge forms has not been thoroughly explored⁷. Additionally, while mixture design approaches have been effective in other sectors, their application in optimizing yogurt-based lozenges is limited⁸. Hence, the present study proposes a systematic optimization approach to develop a yogurt-based functional lozenge using the Quality by Design (QbD) methodology, aiming for superior stability and consumer convenience^{4,9}.

The QbD approach has emerged as a powerful strategy for product development, enabling systematic formulation processes¹⁰. By employing statistical optimization methods, such as Simplex Lattice Design and Response Surface Methodology (RSM), QbD ensures formulations meet high standards of stability and reproducibility¹¹. Utilizing the QbD framework in yogurt-based lozenge formulation allows for precise control over significant formulation factors, including excipient selection, friability, hardness, and dissolution characteristics, culminating in an optimized product⁹.

This study's objectives include the development and optimization of a yogurt-based functional lozenge formulation through a QbD approach. Key aims comprise evaluating thermal stability, mechanical strength, and dissolution profiles of the lozenges to guarantee optimal performance; determining optimal ratios of essential excipients (such as Avicel PH 102, Isomalt, and stevia powder) via Simplex Lattice Design for enhanced integrity; and assessing the final formulation's physicochemical properties to ensure compliance with nutraceutical and pharmaceutical standards for long-term stability and consumer acceptance.

METHODOLOGY

Materials

Pharmaceutical-grade excipients, including Avicel PH 102, Isomalt, and stevia powder, were used in the formulation of YOCANSERAH, a yogurt-based lozenge incorporating peanut sprout, ginger, and lemongrass. All excipients were pharmaceutical grade and used as received without further purification. The instruments used included an analytical balance (Mettler Toledo), 8 and 12 mesh sieves (SS-200 Type Vibrating Circular Motions), a tablet compression machine (TDP 1.5, maximum pressure 15 kN, throughput 5000 pcs/h, power 550 W, power supply 220V/50Hz), an oven (Memmert), a moisture balance analyzer (Mark-i Thermo 163L), a stopwatch, a hardness tester (as 304p, 30 cm diameter, 4 cm), a friability tester (Bonnin), and a disintegration tester (Biostellar). Avicel PH 102 and Isomalt were selected due to their roles in enhancing the mechanical and sensory properties of lozenges.

Formulation and optimization

A Simplex Lattice Design (SLD) within Design-Expert 13 software was used for excipient optimization. This design was selected due to its ability to model nonlinear relationships between formulation components, allowing for precise optimization^{12,13}. The target parameters were hardness within the range of 4–10 kg to ensure mechanical stability while maintaining dissolution properties, and friability below 1% to meet pharmaceutical durability standards.

Preparation of lozenges

Lozenges were prepared using the wet granulation method. The excipients were mixed in a planetary mixer (Hobart N50, capacity: 5 liters, mixing speed: 60 rpm) for 10 minutes to ensure uniform distribution. A binder solution consisting of PVP K-30 or acacia gum was gradually added, followed by an additional 15 minutes of mixing at 60 rpm. The granules were then passed through an 8-mesh sieve and dried in a Memmert UFE 400 oven at 40°C for 6 hours. For compression, a single-punch tablet press (TDP 1.5, maximum pressure: 15 kN, throughput: 5000 pcs/h, power: 550 W) was used, maintaining an average tablet weight of 250 mg. Room conditions were controlled at a temperature of 22–25°C and relative humidity of 45–55% to prevent moisture-related issues during compression and ensure granule stability. Equipment was calibrated before use to maintain accuracy and consistency¹⁴.

Physicochemical characterization

The friability of the lozenges was measured using a friability tester, ensuring that the weight loss remained below 1% after 100 rotations. Hardness was determined using a hardness tester, with an acceptable range of 4–10 kg to ensure structural integrity. Disintegration time was evaluated using a disintegration tester in simulated gastric fluid to assess the breakdown of the lozenge under physiological conditions¹⁵. Weight variation was assessed by individually weighing twenty lozenges using a digital balance, followed by the calculation of the mean weight^{13,16}.

Statistical analysis

A numerical optimization approach was applied to determine the ideal excipient ratios, ensuring optimized friability and hardness properties¹⁷. Data analysis was performed using ANOVA, with significance set at $p < 0.05$. A quadratic model was used for prediction and validation of the experimental results, ensuring statistical reliability. This systematic Quality by Design (QbD) approach ensures the reproducibility and robustness of the formulation, providing a stable solid dosage form with enhanced bioactive compound retention and pharmaceutical acceptability¹⁸.

RESULTS and DISCUSSION

To the best of our knowledge, this is the first study to successfully develop and optimize yogurt-based functional lozenges using a Quality by Design (QbD) approach, providing a shelf-stable solid dosage form that retains the bioactive properties of yogurt and plant-derived ingredients. The formulation strategy

aimed to overcome the inherent stability challenges of yogurt by transforming it into a lozenge matrix while maintaining its functional bioactive compounds. The study demonstrated that Avicel PH 102 and Isomalt played a critical role in optimizing the mechanical properties, particularly in improving friability, hardness, and overall stability, ensuring compliance with pharmacopeial quality standards.

Avicel PH 102 and Isomalt are indeed crucial excipients in the formulation of pharmaceutical tablets, significantly enhancing their mechanical properties. Numerous studies have shown that Avicel PH 102 effectively improves tablet hardness and reduces friability, which in turn contributes to greater overall stability of the formed tablets^{19,20}. The importance of these attributes is underscored by the requirement that tablets must meet strict pharmacopeial quality standards, which necessitate both strength and minimal weight loss under handling conditions²¹. Furthermore, the compressibility characteristic of Avicel PH 102 is critical as it allows for robust tablet formation, particularly for applications involving direct compression, thereby simplifying the production process and ensuring product uniformity²². In the case of Isomalt, its role transcends mere bulk-forming properties; it serves as a stabilizing excipient contributing to the controlled release of active ingredients. Research indicates that Isomalt not only aids in stabilizing the formulation but also enhances the dissolution profile of contained bioactive compounds. Such a controlled release mechanism is vital for pharmaceuticals where a steady delivery of active ingredients is intended²³. This attribute ensures that the formulations are not only effective but also user-friendly, appealing to both patients and healthcare providers. The synergistic use of Avicel PH 102 and Isomalt provides a comprehensive solution for achieving optimal tablet characteristics that fulfill the rigorous safety and efficacy requirements mandated by pharmacopoeias. When employed together, these excipients establish a favorable mechanical environment for the active ingredients, thereby facilitating their retention during storage and administration. This characteristic is particularly important when looking at the long-term stability of lozenges and similar dosage forms, which are subject to environmental factors that can destabilize pharmaceutical compounds²⁴. Avicel PH 102 and Isomalt are indispensable in the context of modern pharmaceutical formulations. Their combined functionalities act to improve not just physical parameters such as hardness and friability, but also enhance the bioavailability of active ingredients through controlled release. This dual action ensures that final products meet the quality standards expected in current pharmaceutical practice.

Thermal analysis (DSC)

Differential Scanning Calorimetry (DSC) revealed two distinct thermal events, indicating significant phase transitions. The first endothermic peak at 150.26°C (onset: 148.83°C, endset: 151.68°C) with an enthalpy change of -14.01 mJ suggests moisture evaporation or melting of thermolabile components, likely involving protein-bound water. The second peak at 170.71°C (onset: 168.24°C, endset: 177.65°C, $\Delta H = -1.09$ mJ) is attributed to protein denaturation, particularly affecting casein, whey, or peanut sprout proteins. The minor heat flow values suggest limited structural disruptions, supporting the thermal stability of the lozenges under standard storage conditions (Figure 1).

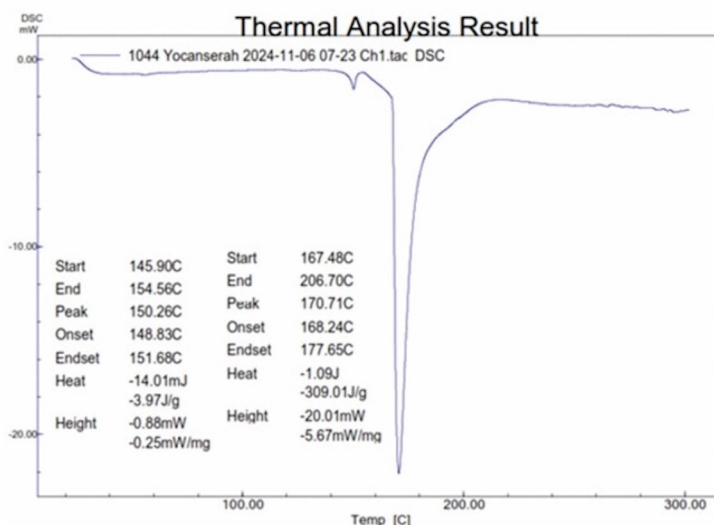


Figure 1. Differential scanning calorimetry (DSC) thermogram of YOCANSERAH

The thermal analysis using Differential Scanning Calorimetry (DSC) indicates that the lozenges maintain their structural integrity under typical storage conditions. The identified endothermic peaks at 150.26°C and 170.71°C are critical markers, signifying processes of controlled moisture evaporation and protein denaturation. These processes are essential in preventing degradation during storage, thus affording the product enhanced stability and longevity^{25,26}. Previous research has established that dehydration usually occurs below 160°C, aligning with our findings and underscoring the protective role of controlled temperatures in preserving bioactive compounds within formulations²⁷. The low enthalpy changes recorded (-14.01 mJ and -1.09 mJ) further indicate minimal structural disruption, which enhances the formulation's ability to withstand

temperature variations without significant degradation. This phenomenon is particularly important for products intended for long-term storage, as stability throughout the product's lifespan is crucial for maintaining both efficacy and safety²⁸. By demonstrating resilience against thermal stress, our formulation not only extends shelf life, but also suggests reliability in maintaining bioactive properties essential for therapeutic effectiveness. This is paramount, particularly given the increasing consumer demand for nutraceuticals and functional foods that promise bioactivity without compromising quality²⁹.

Crystallinity analysis (XRD)

X-ray Diffraction (XRD) analysis exhibited a broad peak around $2\theta = 20^\circ$, confirming an amorphous structure. The absence of sharp diffraction peaks suggests that the formulation lacks significant crystalline domains, which is beneficial for enhanced dissolution and bioavailability. The amorphous nature likely results from thermal processing and wet granulation, which disrupts crystalline arrangements in the raw materials. Since amorphous matrices often improve solubility and controlled release, these findings indicate potential advantages for bioactive compound delivery, particularly for phenolics from ginger and lemongrass (Figure 2).

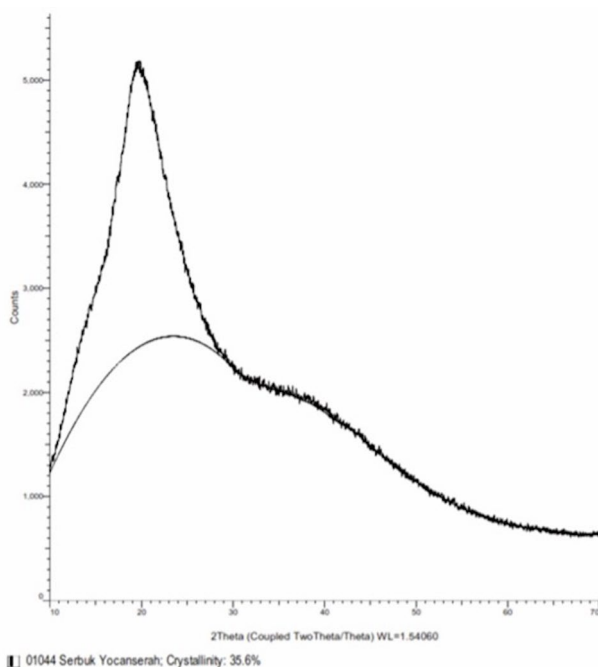


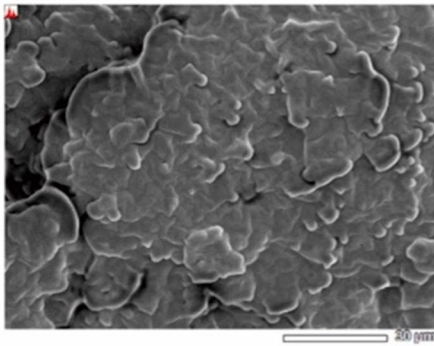
Figure 2. X-ray diffraction (XRD) pattern of YOCANSERAH

The X-ray diffraction (XRD) analysis has elucidated the amorphous nature of the lozenge formulation, indicated by the broad peak observed at $2\theta = 20^\circ$. This amorphous structure is particularly beneficial as it significantly enhances the dissolution properties, which directly facilitates the bioavailability of important functional components like phenolics derived from ginger and lemongrass. In comparison, crystalline structures are often characterized by lower solubility; thus, their presence can hinder the release and effectiveness of bioactive ingredients due to hindered dissolution properties. This aligns with the literature that discusses the impact of amorphous forms on solubility and bioavailability³⁰. The observed broad peak implying amorphous characteristics confirms that the formulation strategy effectively optimized solubility while keeping the active components readily bioavailable.

Morphological and elemental analysis (SEM-EDS)

Scanning Electron Microscopy (SEM) analysis at 2,000× magnification revealed an irregular, porous surface morphology, further supporting the amorphous nature confirmed by XRD. The observed porosity may enhance dissolution rates, which is crucial for optimizing bioavailability. The Energy Dispersive X-ray Spectroscopy (EDS) spectrum confirmed an organic composition dominated by carbon (52.09%) and oxygen (47.91%), aligning with the formulation's biopolymeric matrix. The thermal stability observed in DSC, combined with the porous structure, indicates a well-optimized formulation for nutraceutical applications (Figure 3).

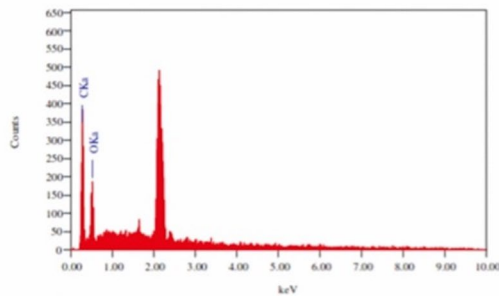
View000



JEDL 1/1

```

Title       : IMG1
-----
Instrument  : 6510(1A)
Volt       : 10.00 kV
Mag.       : x1,000
Date       : 2024/11/28
File1     : 1024 x 768
  
```



```

Acquisition Parameter
Instrument : 6510(1A)
Acc. Voltage : 10.0 kV
Probe Current : 1.00000 nA
PMA mode : F3
Real Time : 50.31 sec
Live Time : 50.00 sec
Dead Time : 0 %
Counting Rate : 693 cps
Energy Range : 0 - 20 keV
  
```

```

ZAF Method Standardless Quantitative Analysis
Fitting Coefficient : 0.5884
Element (keV) Mass% Sigma Atom% Compound Mass% Cation %
C K 0.277 52.15 0.62 59.22 52.0890
O K 0.525 47.85 1.38 40.78 47.9110
Total 100.00 100.00
  
```

Figure 3. Scanning electron microscopy (SEM) image and energy dispersive X-ray spectroscopy (EDS) spectrum of YOCANSERAH

Further insights into the lozenge's structure were provided by the morphological and structural analysis conducted via Scanning Electron Microscopy with Energy Dispersive X-ray Spectroscopy (SEM-EDS). At a magnification of 2,000 \times , the irregular and porous surface morphology was indicative of a formulation with high disintegration potential, thereby enhancing rapid dissolution when introduced into the oral cavity. These characteristics are especially advantageous for lozenge forms, which rely on quick release mechanisms for bioactive ingredients³¹. The Energy Dispersive X-ray Spectroscopy (EDS) analysis corroborated the structural integrity and composition of the lozenges, revealing carbon (approximately 52.09%) and oxygen (approximately 47.91%) as the dominant elements, consistent with the biopolymeric matrix of the formulation. This organic, biopolymer-based matrix not only contributes to stability but also significantly enhances dissolution, making the product suitable for both pharmaceutical and nutraceutical applications³².

The optimization of formulation parameters yielded specific proportions of Avicel PH 102 and Isomalt, with a composition of 42.5% and 12.5%, respectively, resulting in the lowest friability recorded at 0.07%. This low friability score indicates enhanced resistance to mechanical stress, which is crucial for maintaining tablet integrity during handling³³. The findings are in line with the well-established properties of microcrystalline cellulose (MCC), known for its superior binding and compaction abilities that significantly improve interparticle bonding and thereby increase tablet durability³⁴. The statistical analysis showed that variations in excipient concentrations had a significant impact on both friability ($p=0.001$) and hardness ($p=0.002$), with predictive accuracies for the models being high ($R^2=0.98$ for friability and $R^2=0.96$ for hardness), affirming the robustness of the optimization model employed³⁵.

Optimization of formulation parameters

A numerical optimization approach was employed to determine the ideal excipient ratios, focusing on friability and hardness as key mechanical properties. The simplex lattice design was used to systematically evaluate the interaction between Avicel PH 102 and Isomalt (Table 1).

Table 1. Mixture components of YOCANSERAH lozenges

Factor	Name	Min	Max	Coded Low	Coded High
A	Avicel PH 120	20	50	+0 ↔ 20	+1 ↔ 50
B	Isomalt	5	35	+0 ↔ 5	+1 ↔ 35

The formulation trials revealed variations in friability and hardness, as summarized in Table 2.

Table 2. Optimization responses of YOCANSERAH lozenges

Run	Avicel PH 102 (%)	Isomalt (%)	Friability (%)	Hardness (N)
1	50	5	0.19	7.33
2	27.5	27.5	0.69	5.33
3	35	20	0.50	6.67
4	35	20	0.48	6.33
5	50	5	0.13	6.67
6	42.5	12.5	0.07	7.00
7	20	35	0.23	4.67
8	20	35	0.13	5.00

Friability test

The friability test assessed the mechanical resilience of the lozenges under simulated handling conditions. According to pharmacopeial standards, friability values below 1% indicate sufficient mechanical stability. The values obtained ranged from 0.07% to 0.69%, with the lowest friability observed at 42.5% Avicel PH 102 and 12.5% Isomalt. This suggests that Avicel PH 102 plays a dominant role in reducing friability due to its microcrystalline cellulose structure, which enhances interparticle bonding. Statistical analysis (ANOVA, $p=0.001$) confirmed the significant influence of excipient composition on friability, with a quadratic model yielding a high correlation ($R^2=0.98$), supporting the predictive reliability of the optimization approach (Figure 4).

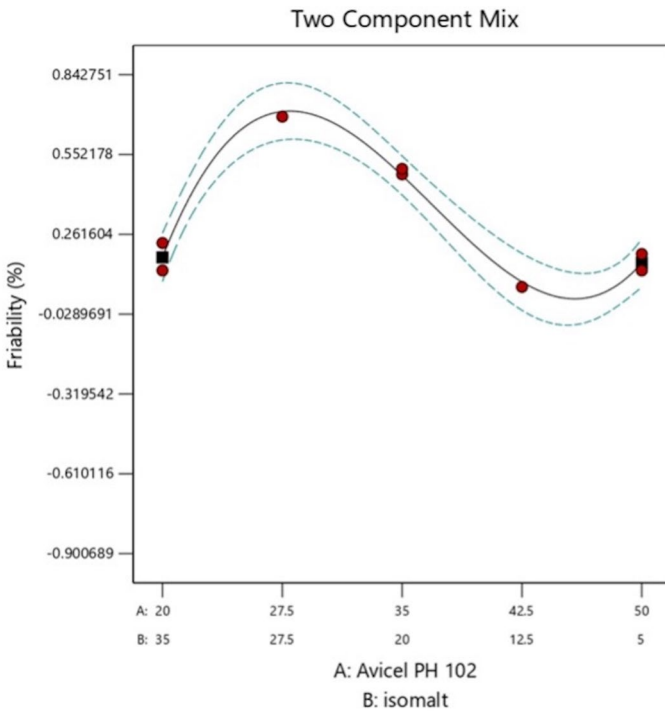


Figure 4. Graph of friability response

Hardness test

Hardness values ranged from 4.67 kg to 7.33 kg, which falls within the acceptable range of 4–10 kg for lozenges. The highest hardness value of 7.33 kg was achieved with 50% Avicel PH 102 and 5% Isomalt, whereas lower hardness values were observed at higher Isomalt concentrations. This highlights the role of Avicel PH 102 as a binder, enhancing compressive strength, while Isomalt primarily serves as a bulking and sweetening agent. ANOVA analysis ($p=0.002$) confirmed the significant effect of excipient composition on hardness, with a quadratic model ($R^2=0.96$) demonstrating high predictive accuracy provided in Table 3 (see also Figures 5 and 6).

Table 3. Observed values of YOCANSERAH lozenges

Responses	Observed Value	Avicel PH 102 (%)	Isomalt (%)
Organoleptic	White color, smooth and uniform surface	20	35
Friability (%)	0.14 ± 0.04		
Hardness (kg)	4.36 ± 0.12		
Tablet weight (mg)	251.3 ± 0.18		
Disintegration time (min)	13.21 ± 0.15		

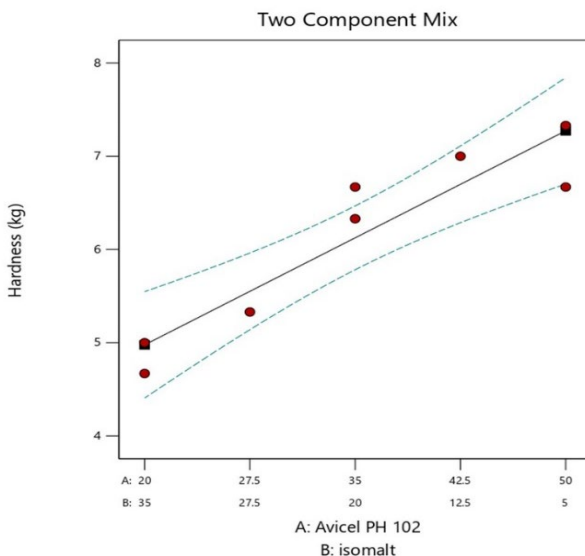


Figure 5. Response of YOCANSERAH lozenges hardness

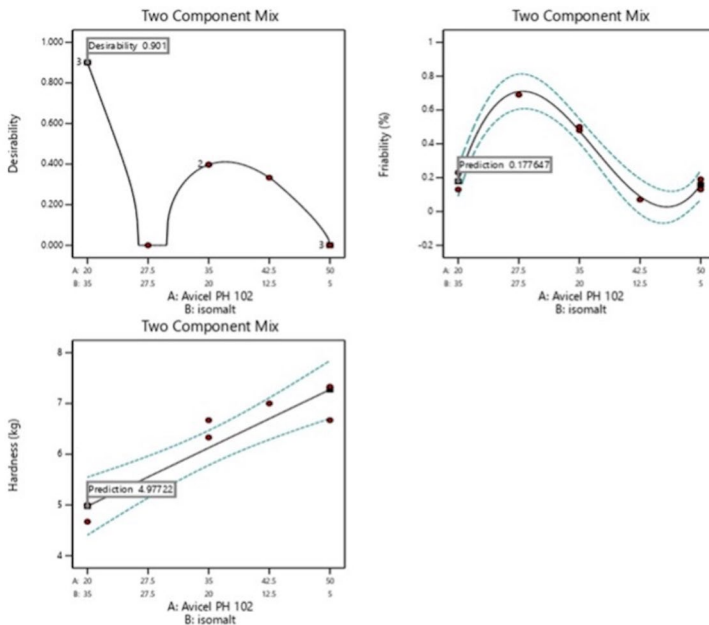


Figure 6. Response of desirability, friability (%), and hardness (kg) of two components

In evaluating the mechanical properties of the lozenges to ensure compliance with pharmacopeial standards, the friability was maintained below 1%, which is imperative for product integrity during both handling and storage. Hardness values were recorded in the range of 4.67 kg to 7.33 kg, well within the acceptable range for lozenges (4–10 kg), thus ensuring a balanced approach between mechanical strength and ease of dissolution³⁶. An inverse relationship was noted between Isomalt concentration and hardness. This is likely attributed to Isomalt's primary role as a bulking and sweetening agent, rather than that of a binding excipient^{37,38}. The incorporation of Isomalt may soften the formulation, which aligns with its known properties as a plasticizer that can influence the hardness of formulations while enhancing overall mouthfeel and palatability³⁹.

The successful development of these lozenges offers promising prospects in both pharmaceutical and nutraceutical applications. Solid dosage forms, such as lozenges, present distinct advantages over traditional yogurt, notably longer shelf life, enhanced portability, and simplicity in administration, while eliminating refrigeration needs. These characteristics are particularly valuable for consumers seeking convenient health solutions without compromising product efficacy or quality. The integration of bioactive ingredients like phenolics and proteins into a stable solid matrix further amplifies the potential for creating innovative functional

foods that can contribute to health and well-being^{38,40}. The implementation of the Quality by Design (QbD) approach in this formulation process has systematically optimized the critical process variables, effectively reducing formulation variability and enhancing overall product quality.

However, despite these advancements, certain limitations persist. The formulation was not intended to provide nutritional equivalence to a conventional serving of yogurt (150–200 mL), but rather to deliver a defined fraction of yogurt-derived solids and plant bioactives in a shelf-stable nutraceutical dosage form. Therefore, potential health benefits should be interpreted in relation to the dose delivered per lozenge rather than as a replacement for traditional yogurt consumption. Notably, the absence of *in vivo* pharmacokinetic evaluations is a significant drawback, as such assessments are essential to accurately determine the bioavailability and metabolic fate of the bioactive compounds after consumption. Additionally, the lack of consumer sensory testing leaves questions regarding taste acceptability and mouthfeel unresolved, which are critical factors in product acceptance and success in the marketplace. Future research should be directed towards bioactive quantification, dose-response evaluation, comprehensive long-term stability studies across various storage conditions, thorough sensory evaluations, and pharmacokinetic profiling to fully validate the commercial viability and effectiveness of these yogurt-based lozenges as a cutting-edge functional food product.

This study successfully developed and optimized yogurt-based functional lozenge using a Quality by Design (QbD) approach, demonstrating their potential as a stable, shelf-stable alternative to conventional yogurt products. The optimized formulation, containing Avicel PH 102 and Isomalt, exhibited desirable mechanical properties, with low friability, acceptable hardness, and an amorphous structure that enhances dissolution and bioavailability. Thermal and structural analyses confirmed the stability of bioactive compounds, while morphological assessments highlighted the porous nature of the lozenges, facilitating rapid disintegration. The systematic formulation optimization ensured compliance with pharmaceutical quality standards, making these lozenges a promising candidate for nutraceutical and functional food applications. While this study provides a strong foundation for future research, further investigation into long-term stability, consumer sensory evaluations, and pharmacokinetic profiling is necessary to validate their commercial feasibility and therapeutic potential.

STATEMENT OF ETHICS

This study does not require any ethical permission.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conceptualization, DN, TS; methodology, EG, DN, HW; investigation BAD, AP data curation, DN, TS, EG writing-original draft preparation, DN, EG writing-review and editing, TS, AP; supervision, TS, AP; funding acquisition, AP. All authors have read and agreed to the published version of the manuscript.

FUNDING SOURCES

This research was funded by a Grant from the Directorate of Research, Technology, and Community Service (DRTPM), Ministry of Education, Culture, Research, and Technology (Kemdikbudristek) Indonesia under contract number 061/E5/PG.02.00/PL.BATCH.2/2024. We are deeply grateful for the grant and the support provided.

ACKNOWLEDGMENTS

The authors would like to thank Directorate of Research, Technology, and Community Service (DRTPM), Ministry of Education, Culture, Research, and Technology (Kemdikbudristek) Indonesia, Universitas Harapan Bangsa, Universitas Muhammadiyah Purwokerto, and Universitas Jenderal Soedirman.

REFERENCES

1. Valencia-Avilés E, Martínez-Flores H-E, García-Pérez M, Meléndez-Herrera E, García-Pérez M-E. Investigation of the antibacterial activity and subacute toxicity of a *Quercus crassifolia* polyphenolic bark extract for its potential use in functional foods. *J Food Sci*, 2019;84(7):1692–1702. Doi: 10.1111/1750-3841.14652
2. Idaayath A, Jnaneshwar PR, Krishnaraj R, Ravi K. Evaluation and comparison of shear bond strength and adhesive remnant index score in brackets bonded with probiotics impregnated orthodontic adhesive and commercially available orthodontic adhesive — an *in vitro* study. *Int J Orthod Rehabil*, 2023;14(1):18–25. Doi: 10.56501/intjorthodrehabil.v14i1.696
3. Tanello AC, de Souza Silveira CD, Carasek E, Verruck S, Prudencio ES, Amboni R. Analysis of volatile compounds in probiotic yogurt during storage through solid-phase microextraction gas chromatography. *Asian J Adv Agric Res*, 2019;9(2):1–11. Doi: 10.9734/ajaar/2019/v9i229995
4. Mustafa MA, Mahmood A, Shahzad S, Kanwal N, Rasheed N, Mahmood M, et al. Formulation and *in vitro* characterization of metoclopramide lozenges by using the quality by design (QbD) approach. *Univers J Pharm Res*, 2024;9(3):8–15. Doi: 10.22270/ujpr.v9i3.1111
5. Palaiogiannis D, Athanasiadis V, Chatzimitakos T, Mantiniotou M, Bozinou E, Makris DP, et al. Extraction of bioactive compounds from *Cistus creticus* leaves and their use in the preparation of yogurt desserts. *Oxygen*, 2024;4(1):90–107. Doi: 10.3390/oxygen4010005
6. Zaman B. Adaptive CUSUM control charts for efficient monitoring of process dispersion. *Qual Reliab Eng Int*, 2022;38(5):2273–2302. Doi: 10.1002/qre.3075
7. Usen JE, Akpan SS, Ugbe TA, Ikpang IN, Uket JO, Obeten BO. Multivariate-based technique for solving multi-response surface optimization (MRSO) problems: the case of a maximization problem. *Asian J Probab Stat*, 2021;11(4):60–85. Doi: 10.9734/ajpas/2021/v11i430275
8. Laghari GF, Malik SA, Daraz A, Ullah A, Alkhalifah T, Aslam S. A numerical approach for solving nonlinear optimal control problems using the hybrid scheme of fitness dependent optimizer and Bernstein polynomials. *IEEE Access*, 2022;10:50298–50313. Doi: 10.1109/access.2022.3173285
9. Shehata TM, Elsewedy HS. Paclitaxel and myrrh oil combination therapy for enhancement of cytotoxicity against breast cancer; QbD approach. *Processes*, 2022;10(5):907–922. Doi: 10.3390/pr10050907
10. Gijo EV. Application of tools and techniques of quality by design in pharmaceutical process. *Int J Product Perform Manag*, 2021;71(7):2932–2950. Doi: 10.1108/ijppm-09-2020-0472
11. Yilmaz GR, Tuncay Tanrıverdi S, Aksu B, Yeğen G, Özer Ö. Preparation and *in vitro* characterization of Etofenamate emulgels using quality by design. *Sanat Tas Derg*, 2019;23(6):1033–1039. Doi: 10.35333/jrp.2019.67
12. Souiy Z, Amri Z, Sharif H, Souiy A, Cheraief I, Hamden K, et al. The use of D-optimal mixture design in optimizing formulation of a nutraceutical hard candy. *Int J Food Sci*, 2023;2023:1–12. Doi: 10.1155/2023/7510452
13. Wang W, Cheng Y, Tan G, Tao J. Analysis of aggregate morphological characteristics for viscoelastic properties of asphalt mixes using simplex lattice design. *Materials*, 2018;11(10):1908–1928. Doi: 10.3390/ma11101908
14. Khan MI, Abbas YM, Fares G. Simplex-lattice hydration prediction and microstructure verification of cementitious systems. *Materials*, 2019;12(3):490–511. Doi: 10.3390/ma12030490
15. Rahmani SIP, Zulkarnain AK. Optimization of HPMC and Na-CMC as gelling agents on physical properties and stability in sunflower seed oil gel formulation. *J Food Pharm Sci*, 2023;11(2):812–819. Doi: 10.22146/jfps.8227

16. Nawangsari D, Siregar T, Kusuma IY. *Piper betel* L. leaf extract lozenges for preventing dental caries for children. *J Herb Med*, 2025;52:101032–101040. Doi: 10.1016/j.hermed.2025.101032
17. Usman HN, Pratiwi L, Wijianto B. Cosmetic serum loaded Arabica coffee (*Coffea arabica*) extract: formulation and antioxidant study. *Maj Obat Tradi*, 2023;28(2):93–102. Doi: 10.22146/mot.83120
18. Setyowati EP, Puspitasari A, Afini DI, Nasution FH, Nafingah R. Influence of some extraction conditions factor on phenolic content and antioxidant activity of *Solanum Betaceum Cav*. *Maj Obat Tradis*, 2019;24(3):216–225. Doi: 10.22146/mot.51772
19. Caleja C, Barros L, António AL, Carochi M, Oliveira MBPP, Ferreira ICFR. Fortification of yogurts with different antioxidant preservatives: a comparative study between natural and synthetic additives. *Food Chem*, 2016;1(210):262–268. Doi: 10.1016/j.foodchem.2016.04.114
20. Fernández-Fernández AM, Dellacassa E, Nardin T, Larcher R, Ibañez C, Terán D, et al. Tannat grape skin: a feasible ingredient for the formulation of snacks with potential for reducing the risk of diabetes. *Nutrients*, 2022;14(3):419–439. Doi: 10.3390/nu14030419
21. Ye Y, Li P, Zhou J, He J, Cai J. The improvement of sensory and bioactive properties of yogurt with the introduction of tartary buckwheat. *Foods*, 2022;11(12):1774–1190. Doi: 10.3390/foods11121774
22. Sıçramaz H, Ayar A. Investigation of the effects of different processing methods on the selected nutritional properties of pumpkin and determining the appropriate process for pumpkin yogurt. *Food Sci Nutr*, 2023;11(11):6878–6887. Doi: 10.1002/fsn3.3580
23. Karaca OB, Saydam IB, Güven M. Physical, chemical, and sensory attributes of low-fat, full-fat, and fat-free probiotic set yogurts fortified with fiber-rich persimmon and apple powders. *J Food Process Preserv*, 2019;43(6):e13926–e13939. Doi: 10.1111/jfpp.13926
24. D'Addezio L, Mistura L, Sette S, Turrini A. Sociodemographic and lifestyle characteristics of yogurt consumers in Italy: results from the INRAN-SCAI 2005-06 survey. *Mediterr J Nutr Metab*, 2015;8(2):119–129. Doi: 10.3233/mnm-150043
25. Aanisah N, Sulistiawati S, Djabir YY, Asri RM, Sumarheni S, Chabib L, et al. Development of solid lipid nanoparticle-loaded polymeric hydrogels containing antioxidant and photoprotective bioactive compounds of safflower (*Carthamus tinctorius* L.) for improved skin delivery. *Langmuir*, 2023;39(5):1838–1851. Doi: 10.1021/acs.langmuir.2c02754
26. Na-Bangchang K, Teerachaisakul M, Pnunuch M, Kasemnitichok Y, Sangnarong N, Boonprasert K, et al. Antiproliferative and anti-inflammatory activities of Deprungsith formulation and its bioactive compounds against mild psoriasis and potential of metabolic herb-drug interactions. *J Evid-Based Integr Med*, 2023;28. Doi: 10.1177/2515690x231191101
27. Fărcaș AC, Socaci SA, Socaciu C, Maxim C, Tofană M. Development of novel added-value products, using brewers spent grain as ingredient. *Bull Univ Agric Sci Vet Med Cluj-Napoca Food Sci Technol*, 2019;76(1):80–84. Doi: 10.15835/buasvmcn-fst:2019.0011
28. Arribas C, Cabellos B, Cuadrado C, Guillamón E, Pedrosa MM. Bioactive compounds, antioxidant activity, and sensory analysis of rice-based extruded snacks-like fortified with bean and carob fruit flours. *Foods*, 2019;8(9):381–393. Doi: 10.3390/foods8090381
29. Martysiak-Żurowska D, Puta M, Rodzik A, Malinowska-Pańczyk E. The effect of lyophilization on selected biologically active components (vitamin c, catalase, lysozyme), total antioxidant capacity and lipid oxidation in human milk. *Zywnosc Nauka Technol JakoscFood Sci Technol Qual*, 2017;3(112):121–128. Doi: 10.15193/zntj/2017/112/203

30. Chrastina A, Welsh J, Borgström P, Baron VT. Propylene glycol caprylate-based nanoemulsion formulation of plumbagin: development and characterization of anticancer activity. *Biomed Res Int*, 2022;2022(1):1–9. Doi:10.1155/2022/3549061
31. Circioban D, Ledeti A, Ridichie A, Vlase T, Ledeti I, Bradu I-A, et al. Compatibility study of mirtazapine with several excipients used in pharmaceutical dosage forms employing thermal and non thermal methods. *J Therm Anal Calorim*, 2024;150(4):1–13. Doi: 10.1007/s10973-024-13181-w
32. Vangara KK, Yellepeddi VS. Excipients in pediatric formulations: biopharmaceutical and toxicological considerations. In: Narang A, Boddu S, editors. *Excipient applications in formulation design and drug delivery*. Cham: Springer; 2015. p. 497–519. Available from: https://doi.org/10.1007/978-3-319-20206-8_16. [Oct 3, 2025].
33. Domínguez-Robles J, Stewart SA, Rendl A, González Z, Donnelly RF, Larrañeta E. Lignin and cellulose blends as pharmaceutical excipient for tablet manufacturing via direct compression. *Biomolecules*, 2019;9(9):423–440. Doi: 10.3390/biom9090423
34. Han M, Jiang R-L, Ying X-Y, Gao J-Q. How should we think about pharmaceutical excipients in clinical pharmacy education? *Indian J Pharm Educ Res*, 2023;57(2):372–376. Doi: 10.5530/ijper.57.2.46
35. Shahbaz M, Tariq A, Majeed MI, Nawaz H, Rashid N, Shehnaz H, et al. Qualitative and quantitative analysis of azithromycin as solid dosage by raman spectroscopy. *ACS Omega*, 2023;8(39):36393–36400. Doi: 10.1021/acsomega.3c05245
36. Nadendla RR, Pinnamaneni P, Morla SP, Patchala A. Physico-chemical characterization of paliperidone palmitate and compatibility studies with its pharmaceutical excipients. *J Pharm Res Int*, 2021;33(5):85–91. Doi: 10.9734/jpri/2021/v33i531183
37. Ramos P. Compatibility studies of selected mucolytic drugs with excipients used in solid dosage forms: thermogravimetry analysis. *Farmacia*, 2021;69(3):585–594. Doi: 10.31925/farmacia.2021.3.22
38. Swain SS, Unnikrishnan L, Mohanty S, Nayak SK. Insight on to mechanical, thermal, long-term, hydrothermal, and chemical stability of PSf based membrane systems for separation of O₂/N₂. *Korean J Chem Eng*, 2021;39(3):785–797. Doi: 10.21203/rs.3.rs-269353/v1
39. Verma V, Peddapatla RVG, Crowley CM, Crean AM, Davern P, Hudson S, et al. Experimental study on the influence of excipients on the heterogeneous crystallization and dissolution properties of an active pharmaceutical ingredient. *Cryst Growth Des*, 2017;18(1):338–350. Doi: 10.1021/acs.cgd.7b01336
40. Kusuma IY, Matuz M, Bordás R, Haverinen JM, Bahar MA, Hajdu E, et al. Antibiotic use in elderly patients in ambulatory care: a comparison between Hungary and Sweden. *Front Pharmacol*, 2022;17(13):1042418. Doi: 10.3389/fphar.2022.1042418