Original Article

Development and Optimization of Chamomile Extract Pastilles for Potential Oral Ulcer Treatment

Pooya Javaherchian [1], Mostafa Azimzadeh [2], Fereshteh Azimzadeh [3*]

[1] Department of Pharmacognosy, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[2] School of Dentistry, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[3] School of Pharmacy and Pharmaceutical Sciences, Islamic Azad University, Tehran Medical Sciences, Tehran, Iran

Article info:
Received: 18 January 2025
Revised: 26 February 2025
Accepted: 12 March 2025

[*] **Corresponding Author:**

Fereshteh Azimzadeh, School of Pharmacy and Pharmaceutical Sciences, Islamic Azad University, Tehran Medical Sciences, Tehran.
Email:Fereshte_a.farmacy@yahoo.com

ABSTRACT

Objectives: This study aimed to develop and optimize chamomile extract pastilles as a potential therapeutic option for oral ulcer treatment, focusing on masking chamomile's bitterness, ensuring stability, and achieving controlled release of active constituents to enhance patient compliance.

Methods: Chamomile (Matricaria chamomilla L.) extract was prepared via percolation using 80% ethanol. Pastilles were formulated with gelatin, xylitol, aspartame, citric acid, and flavoring agents (eucalyptus, lemon, raspberry, cola). Physical properties (smoothness, elasticity, color), sensory acceptability (rated by 10 volunteers), quercetin content (UV-Vis spectrophotometry), and dissolution profiles (in artificial saliva, pH 6.8) were assessed. Sensory scores were analyzed using one-way ANOVA with Tukey's post hoc tests ($p < 0.05$)..

Results: Formulations J1 and J2, incorporating citric acid, exhibited significantly higher sensory scores ($p < 0.0001$) than G1–G3, effectively masking bitterness. Quercetin content indicated 85–89% loading efficiency across formulations. Dissolution tests showed controlled release of chamomile extract from J2 pastilles compared to pure extract, with stable release over 60 minutes. Physical assessments confirmed smooth, cohesive pastilles with favorable elasticity.

Conclusion: Chamomile extract pastilles represent a promising formulation with potential for oral ulcer treatment, offering improved palatability and controlled release. Their natural composition and high acceptability suggest potential for pediatric and adult use, warranting further clinical trials to validate efficacy and long-term stability.

Keywords: Chamomile, Oral Ulcers, Pastilles, Herbal Therapeutics, Formulation

Use your device to scan and read the article online

Citation: Javaherchian P, Azimzadeh M, Azimzadeh F. Development and Optimization of Chamomile Extract Pastilles for Potential Oral Ulcer Treatment. Acta Biochimica Iranica. 2025;3(1):30-35.

https://doi.org/10.18502/abi.v3i1.19348

Introduction

Oral ulcers, commonly known as aphthous ulcers or canker sores, are painful lesions affecting the oral mucosa, with a prevalence of 20–50% in the general population and up to 9% in children (1, 2). These sores, typically appearing on the inner lip, cheek, tongue, or sublingual region, are more frequent in women, particularly during menstruation, and in pediatric populations (3). Their etiology is multifactorial, encompassing genetic predispositions, mechanical trauma (e.g., from vigorous tooth brushing or dental appliances), psychological stress, nutritional deficiencies (e.g., iron, vitamin B12, folic acid), immune dysregulation, and food hypersensitivities (e.g., dairy, gluten) (4, 5). While simple ulcers often resolve within 7–14 days, recurrent aphthous stomatitis (RAS) significantly impairs quality of life due to persistent pain, difficulty eating, and challenges in maintaining oral hygiene (6). In children, these lesions can lead to anxiety and reduced food intake, potentially exacerbating nutritional deficiencies (1).

Current treatments, such as topical corticosteroids, antimicrobial mouthwashes, and analgesics, provide symptomatic relief but are limited by side effects, variable efficacy, and poor acceptability, particularly in pediatric patients (7). Corticosteroids, while effective, may cause mucosal atrophy or systemic absorption, leading to adrenal suppression (6). Antimicrobial mouthwashes can disrupt the oral microbiome and cause taste disturbances, while analgesics offer temporary relief without addressing underlying inflammation (8). These limitations have spurred interest in herbal remedies, valued for their safety and natural origins.

Chamomile (*Matricaria chamomilla* L.), a member of the Compositae family, is a promising candidate due to its bioactive compounds, including flavonoids (e.g., apigenin, quercetin) and sesquiterpenes (e.g., bisabolol), which exhibit anti-inflammatory, analgesic, antioxidant, and immunomodulatory properties (9, 10). Apigenin inhibits pro-inflammatory cytokines, promoting wound healing, while bisabolol soothes mucosal tissues (11). Clinical studies have demonstrated chamomile's efficacy in reducing inflammation and pain in oral mucosal lesions, such as those caused by chemotherapy-induced mucositis or minor aphthous stomatitis (12). In Iran, chamomile mouthwashes are traditionally used for oral ulcers, but their bitterness reduces patient compliance, particularly among children (13).

The bitterness of chamomile extract poses a significant barrier to its clinical use, as taste sensitivity in children often leads to treatment refusal. Traditional formulations like mouthwashes and gels frequently fail to mask this bitterness and may not provide sustained delivery of active constituents, which is critical for effective ulcer treatment (14). Pastilles—semi-solid, suckable dosage forms that release active ingredients gradually—offer a promising solution. They combine ease of administration, high patient acceptability, and controlled release, making them ideal for pediatric and adult populations (15). By incorporating chamomile extract into a gelatin-based matrix with non-cariogenic sweeteners (e.g., xylitol, aspartame) and flavoring agents, pastilles can mask bitterness while ensuring stability and prolonged therapeutic action.

This study aimed to develop and optimize chamomile extract pastilles as a potential therapeutic option for oral ulcer treatment, addressing the limitations of existing formulations. The objectives were to: (1) formulate pastilles with acceptable physical and sensory properties, effectively masking chamomile's bitterness; (2) optimize the composition for stability and controlled release of active constituents; and (3) assess performance through physical, chemical, and dissolution testing. By creating a palatable, child-friendly delivery system, this research aims to lay the foundation for improved patient compliance and future clinical validation of chamomile pastilles for oral ulcer treatment.

Method and Materials

Materials

High-quality materials ensured consistency. Persian chamomile (*Matricaria chamomilla* L.) was sourced locally in Iran and authenticated (voucher specimen No. MC-2023-01, Herbarium of Iran University). Ethanol (80% v/v) was procured from Kimia-Zanjan Company, Iran. Gelatin, xylitol, and aspartame were obtained from Merck, Germany, as a gelling agent, a non-cariogenic sweetener, and an additional sweetener, respectively. Glycerin was provided by Dr. Mahbali, Iran University of Medical Sciences, Iran. Methylparaben and propylparaben were sourced from Hubei Aoks Bio-Tech Co., Ltd., China. Food-grade essences (eucalyptus, lemon, raspberry, cola) were supplied by Firmenich, Germany. Citric acid and ascorbic acid (Merck, Germany) were used for pH adjustment and antioxidant properties. Materials were stored at 25°C, 40% relative humidity, with deionized water as the solvent.

Chamomile Extraction

Chamomile extract was prepared using percolation. Ground chamomile (1 kg, particle size <1 mm) was macerated in 2 L of 80% ethanol for 72 hours at 25°C, collected at 10 mL/min, and repeated thrice over 10 days. The hydroalcoholic extract was evaporated under a fume hood for 14 days, yielding a concentrated extract.

Formulation and Preparation of Chamomile Pastilles

First, water and glycerin were placed in a water bath to dissolve the gelatin, then glycerin was added to achieve a uniform mixture. The remaining excipients, as listed in Table 1, were added to the mixture while the beaker containing the materials was still on the

Table 1. Composition of Chamomile Pastille Formulations

group name	H2O	Gly	GEL	Xyl	Asp	MP	PP	ChamEx	EucEO	LemEO	NaCl	CA	RaspEO	ColaEO
G1	1850	1850	700	250	10	9	1	310	20	0	0	0	0	0
G2	1915	1915	700	250	10	9	1	180	20	0	0	0	0	0
G3	1928	1928	700	250	10	9	1	154	20	0	0	0	0	0
J1	1822.5	1822.5	700	250	5	9	1	180	0	0	75	125	10	0
J2	1822.5	1822.5	700	250	5	9	1	180	0	0	75	125	0	10

All ingredients are reported in milligrams (mg). H2O: Water, Gly: Glycerin, Gel: Gelatin, Xyl: Xylitol, Asp: Aspartame, MP: Methylparaben, PP: Propylparaben, ChamEx: Chamomile Extract, EucEO: Eucalyptus Essential Oil, LemEO: Lemon Essential Oil, CA: Citric Acid, NaCl: Sodium Chloride, RaspEO: Raspberry Essential Oil, ColaEO: Cola Essential Oil.

Table 2. Composition of Artificial Saliva (pH 6.8) for Dissolution Testing.

Components	Quantity (m mol/ L)
KH_2PO_4	2.50
$Na_2 HPO_4$	2.40
$KHCO_3$	15.00
NaCl	10.00
$MgCl_2$	1.50
$CaCl_2$	1.50
Citric Acid	0.15
pH adjusted to 7.4 with NaOH or HCL	

Table 3. Quercetin Content in Chamomile Extract

(mg/ml) ChamEx concentration	OD	(µg/ml) Quercetin concentration
210	0.27	214.61

The table presents the measured quercetin concentration, serving as an indicator for standardizing the amount of chamomile extract incorporated into the pastille formulations. ChamEx: Chamomile Extract, OD: Optical Density.

water bath. The chamomile extract was then added to the resulting mixture, and finally, the essences were added after removing the beaker from the water bath. The mixture was poured into molds and kept at room temperature for some time. The components of this formulation series are listed in milligrams in Table 1.

Assessment of Physical Properties

Formulations were evaluated for surface smoothness, color uniformity, strength, and cohesiveness. Elasticity was assessed manually. Sensory evaluation involved a blinded panel of 10 healthy, non-smoking volunteers (5 male, 5 female, aged 18–40 years), rating taste on a 1–3 scale (1 = least favorable, 3 = most favorable).

Measurement of Quercetin Content in Each Formulation

Quercetin was quantified using UV-Vis spectrophotometry. Chamomile extract (2.1 g) was dissolved in 10 mL of methanol, and absorbance was measured at 415 nm against a quercetin standard curve (100-400 µg/mL). Pastilles were pulverized in 1 mL of methanol, filtered, and analyzed.

Dissolution Test

Release profiles were assessed by immersing a 5 g pastille (0.18 g extract) in 10 mL artificial saliva (pH 6.8) (Table 2) at 37°C on a shaker water bath (100 rpm). Aliquots (1 mL) were withdrawn at 10, 20, 30, and 60 minutes, filtered, and analyzed at 415 nm. A control used 0.18 g of extract in 10 mL of artificial saliva.

Statistical Analysis

Sensory scores were compared using one-way ANOVA with post-hoc Tukey tests ($p < 0.05$).

Results

Validation and Determination of Active Ingredient Content

Quercetin was selected as the marker compound to quantify chamomile extract content in the formulations. Using UV-Vis spectrophotometry at 415 nm, a standard curve (100–400 µg/mL) was established, revealing a quercetin content of 214.61 µg/mL in the chamomile extract at a concentration of 210 mg/mL (Table 3). Formulations G1, G2, G3, J1, and J2 were analyzed for quercetin content, with results ranging from 283.08 µg/mL (G3) to 539.23 µg/mL (G1), corresponding to chamomile extract concentrations of 138.49–263.81 mg/mL (Table 4). Loading efficiencies ranged from 85.10% (G1) to 89.93% (G3), indicating effective incorporation of the extract across all formulations.

Table 4. Quercetin Content and Loading Efficiency

Name	Absorption (at a wavelength of 415nm)	Quercetin concentration (µg/ml)	ChamEx concentration (mg/ml)	ChamEx (mg/ml)	Loading Efficiency (%)
G1	0.69	539.23	527.62	263.81	85.10
G2	0.41	324.62	317.63	158.81	88.23
G3	0.36	283.08	276.98	138.49	89.93
J1	0.42	326.92	319.89	159.94	88.86
J2	0.41	320.00	313.11	156.56	86.98

The table provides the absorbance values, calculated quercetin content, amount of chamomile extract (ChamEx), and percentage loading efficiency (85–89%) relative to the initial extract content. ChamEx: Chamomile Extract.

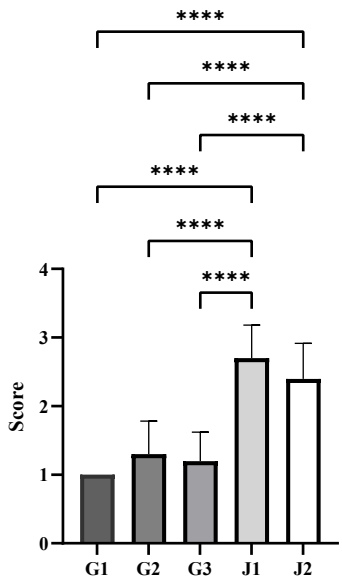

Figure 1. Sensory Evaluation Scores of Chamomile Pastille Formulations Data represent the mean sensory scores (± standard deviation) for taste and mouthfeel of formulations G1, G2, G3, J1, and J2, as evaluated by participants. (****p < 0.0001, one-way ANOVA with post-hoc Tukey tests).

Assessment of Physical Properties

Physical evaluations confirmed that all formulations (G1, G2, G3, J1, J2) exhibited smooth surfaces, uniform color, and adequate cohesiveness. Elasticity assessments revealed that G1 was overly elastic, likely due to higher chamomile extract content (310 mg), while J1 and J2 showed optimal elasticity. Sensory evaluation by a blinded panel of 10 volunteers rated taste and mouthfeel on a 1–3 scale. Formulations J1 and J2, incorporating citric acid (125 mg) and flavoring agents, achieved significantly higher mean scores (J1: 2.7 ± 0.48; J2: 2.4 ± 0.51) compared to G1 (1), G2 (1.3 ± 0.48), and G3 (1.2 ± 0.42) ($p < 0.0001$, one-way ANOVA with Tukey post hoc tests; Figure 1). No significant differences were observed between J1 and J2 ($p = 0.52$) or among G1, G2, and G3. Volunteers noted excessive bitterness in G1 and overly sweet profiles in G2 and G3, whereas J1 and J2 were described as palatable, with raspberry (J1) and cola (J2) flavors enhancing acceptability.

Quercetin Content

The absorbance of the prepared formulations is shown in Table 4. As indicated in Table 4, the amount and percentage of extract loading in each formulation are also provided at the end of the table. As seen in Table 1, approximately 1.022 µg of quercetin was observed per 1 mg of extract, resulting in a loading efficiency of 85% to 89% compared to the initial amount in all samples.

Dissolution Test

Dissolution profiles of formulation J2 and a control of pure chamomile extract were assessed in 10 mL artificial saliva (pH 6.8) at 37°C, with absorbance measured at 415 nm at 10, 20, 30, and 60 minutes. J2 exhibited a controlled release, with 38.1% of the extract released by 10 minutes and 97.7% by 60 minutes, compared to pure chamomile extract (0.18 g in 10 mL), which released 81.2% within 10 minutes (Figure 2). This sustained release profile confirms the gelatin matrix's ability to regulate active constituent delivery, critical for potential therapeutic applications.

Discussion

This study's formulation of chamomile extract

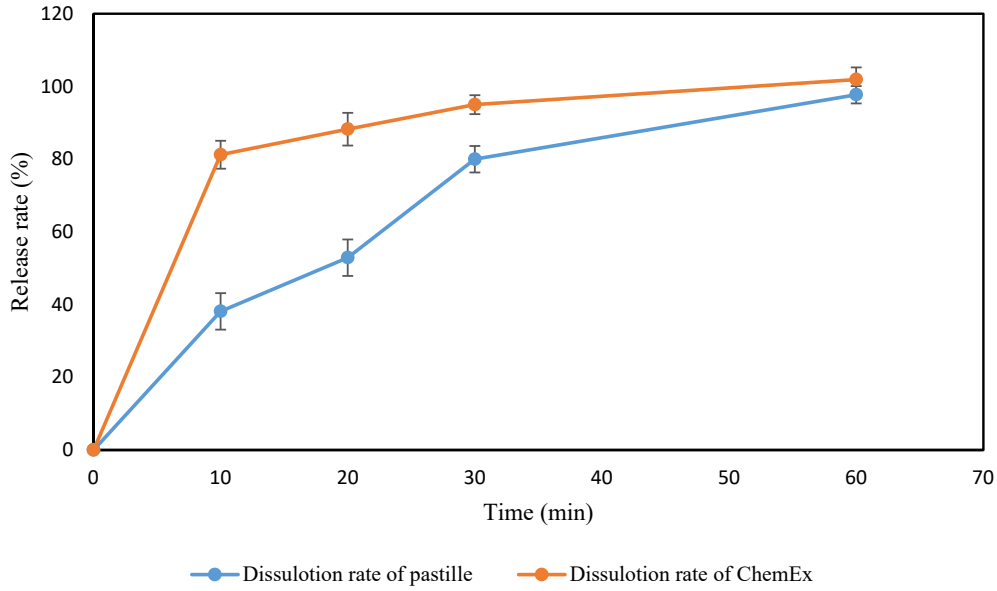

Figure 2. Dissolution Profiles of J2 Pastille and Pure Chamomile Extract Dissolution profiles depict the release rate of chamomile extract from formulation J2 compared to pure chamomile extract.

pastilles introduces an optimized delivery system with potential for oral ulcer treatment, prioritizing patient acceptability and therapeutic efficacy. Formulation challenges included gelatin incompatibility with ascorbic acid (16), causing elasticity issues. Citric acid resolved this while enhancing taste. Sensory assessments confirmed that formulations J1 and J2, incorporating citric acid and non-cariogenic sweeteners (xylitol, aspartame), effectively masked chamomile's bitterness, with J1 achieving a mean acceptability score (17). Palatability is a critical advantage, particularly for pediatric patients. Strickley emphasized taste masking as vital for oral pediatric formulations, a challenge this study overcame through excipient optimization (17). Stability was maintained with glycerin and parabens, mitigating microbial risks and ensuring physical integrity, aligning with stability principles outlined by Bajaj et al. (18). These features distinguish the pastilles from conventional therapies, offering a natural, patient-friendly alternative. Dissolution tests demonstrated controlled release of active constituents with high loading efficiencies, consistent with findings by Karas et al. on herbal oral dosage forms (19). The pastilles leverage chamomile's bioactive properties, supported by Seyyedi et al., who reported reduced pain and inflammation in oral mucositis using chamomile-based gels (20). This sustained delivery ensures prolonged mucosal contact, essential for effective ulcer healing. The pastilles align with increasing demand for herbal therapeutics, as Petronilho et al. noted in their review of chamomile's anti-inflammatory applications (21). This resonates with patient preferences for natural remedies, supported by Fidler et al., who highlighted chamomile's role in mucosal healing (22). However, clinical trials are necessary to validate efficacy against standard treatments, a priority echoed by El Mihyaoui et al. in their analysis of herbal product development (21). Compared to corticosteroid pastilles, chamomile pastilles offer a natural alternative with fewer side effects, consistent with chamomile's anti-inflammatory properties. A clinical trial by Pourgholami et al. found that chamomile in Orabase reduced ulcer size and pain in minor aphthous stomatitis, comparable to triamcinolone (12). Preclinical studies further support chamomile's role in reducing inflammation in oral mucositis (23). The high loading efficiency is comparable to other herbal pastilles (24). The sustained release aligns with controlled drug delivery principles, critical for ulcer treatment (25).

Conclusion

This study successfully developed and optimized chamomile extract pastilles with favorable physical, sensory, and release characteristics, offering a promising formulation for potential oral ulcer treatment. The use of non-cariogenic sweeteners and a gelatin matrix improved palatability and stability, addressing barriers to patient compliance. Future research should focus on clinical trials to validate efficacy, long-term stability studies, and potential combinations with other anti-inflammatory agents.

Acknowledgments

We sincerely thank the volunteers for their participation in this study. The research was conducted with approval from the Ethics Committee of Islamic

Azad University, Tehran Medical Sciences, ensuring compliance with rigorous ethical standards.

Author Contributions

FA: Conceptualization, Data Curation, Formal Analysis, Investigation, and Methodology, PJ: Formal analysis, writing original draft and review and editing, MA: writing, review and editing

Conflict of interests

The authors declare no conflict of interest.

Funding

This study was funded by Islamic Azad University.

References

1. Légeret C, Furlano R. Oral ulcers in children- a clinical narrative overview. Ital J Pediatr. 2021;47(1):144. https://doi.org/10.1186/s13052-021-01097-2
2. Scully C, Porter S. Oral mucosal disease: recurrent aphthous stomatitis. Br J Oral Maxillofac Surg. 2008;46(3):198-206. https://doi.org/10.1016/j.bjoms.2007.07.201
3. Natah SS, Konttinen YT, Enattah NS, Ashammakhi N, Sharkey KA, Häyrinen-Immonen R. Recurrent aphthous ulcers today: a review of the growing knowledge. Int J Oral Maxillofac Surg. 2004;33(3):221-34. https://doi.org/10.1006/ijom.2002.0446
4. Chavan M, Jain H, Diwan N, Khedkar S, Shete A, Durkar S. Recurrent aphthous stomatitis: a review. J Oral Pathol Med. 2012;41(8):577-83. https://doi.org/10.1111/j.1600-0714.2012.01134.x
5. Porter SR, Scully Cbe C. Aphthous ulcers (recurrent). BMJ Clin Evid. 2007;2007.
6. Al-Maweri SA, Alaizari N, Alharbi AA, Alotaibi SA, AlQuhal A, Almutairi BF, et al. Efficacy of curcumin for recurrent aphthous stomatitis: a systematic review. J Dermatolog Treat. 2022;33(3):1225-30. https://doi.org/10.1080/09546634.2020.1819529
7. Mehdipour M, Taghavi Zenouz A. Role of Corticosteroids in Oral Lesions. In: Magdeldin S, editor. State of the Art of Therapeutic Endocrinology. Rijeka: IntechOpen; 2012.
8. McKay DL, Blumberg JB. A review of the bioactivity and potential health benefits of chamomile tea (Matricaria recutita L.). Phytother Res. 2006;20(7):519-30. https://doi.org/10.1002/ptr.1900
9. Andishe Tadbir A, Pourshahidi S, Ebrahimi H, Hajipour Z, Memarzade MR, Shirazian S. The effect of Matricaria chamomilla (chamomile) extract in Orabase on minor aphthous stomatitis, a randomized clinical trial. Journal of Herbal Medicine. 2015;5(2):71-6. https://doi.org/https://doi.org/10.1016/j.hermed.2015.05.001
10. Srivastava JK, Shankar E, Gupta S. Chamomile: A herbal medicine of the past with bright future. Mol Med Rep. 2010;3(6):895-901. https://doi.org/10.3892/mmr.2010.377
11. Zargaran A, Borhani-Haghighi A, Faridi P, Daneshamouz S, Kordafshari G, Mohagheghzadeh A. Potential effect and mechanism of action of topical chamomile (Matricaria chammomila L.) oil on migraine headache: A medical hypothesis. Med Hypotheses. 2014;83(5):566-9. https://doi.org/10.1016/j.mehy.2014.08.023
12. Pourdeghatkar F, Motaghi M, Darbandi B, BagherSalimi A. The Effect of Chamomile Mouthwash on the Prevention of Oral Mucositis Caused by Chemotherapy in Children with Acute Lymphoblastic Leukemia. SSU. 2017;7(2):76-81.
13. Refaey MS, Abosalem EF, Yasser El-Basyouni R, Elsheriri SE, Elbehary SH, Fayed MAA. Exploring the therapeutic potential of medicinal plants and their active principles in dental care: A comprehensive review. Heliyon. 2024;10(18):e37641. https://doi.org/https://doi.org/10.1016/j.heliyon.2024.e37641
14. Sohail Arshad M, Zafar S, Yousef B, Alyassin Y, Ali R, AlAsiri A, et al. A review of emerging technologies enabling improved solid oral dosage form manufacturing and processing. Advanced Drug Delivery Reviews. 2021;178:113840. https://doi.org/https://doi.org/10.1016/j.addr.2021.113840
15. Lopez FL, Ernest TB, Tuleu C, Gul MO. Formulation approaches to pediatric oral drug delivery: benefits and limitations of current platforms. Expert Opin Drug Deliv. 2015;12(11):1727-40. https://doi.org/10.1517/17425247.2015.1060218
16. Rowe RC, Sheskey, P. J., & Quinn, M. E. Handbook of Pharmaceutical Excipients (6th ed.)(2009).
17. Strickley RG. Pediatric Oral Formulations: An Updated Review of Commercially Available Pediatric Oral Formulations Since 2007. J Pharm Sci. 2019;108(4):1335-65. https://doi.org/10.1016/j.xphs.2018.11.013
18. Sanjay Bajaj DS, Neha Sakhuja. Stability Testing of Pharmaceutical Products: ssue : 3. 129-38 p.
19. Maheswari KM, Devineni PK, Deekonda S, Shaik S, Uppala NP, Nalluri BN. Development and Evaluation of Mouth Dissolving Films of Amlodipine Besylate for Enhanced Therapeutic Efficacy. J Pharm (Cairo). 2014;2014:520949. https://doi.org/10.1155/2014/520949
20. Elhadad MA, El-Negoumy E, Taalab MR, Ibrahim RS, Elsaka RO. The effect of topical chamomile in the prevention of chemotherapy-induced oral mucositis: A randomized clinical trial. Oral Dis. 2022;28(1):164-72. https://doi.org/10.1111/odi.13749
21. El Mihyaoui A, Esteves da Silva JCG, Charfi S, Candela Castillo ME, Lamarti A, Arnao MB. Chamomile (Matricaria chamomilla L.): A Review of Ethnomedicinal Use, Phytochemistry and Pharmacological Uses. Life (Basel). 2022;12(4). https://doi.org/10.3390/life12040479
22. Dai YL, Li Y, Wang Q, Niu FJ, Li KW, Wang YY, et al. Chamomile: A Review of Its Traditional Uses, Chemical Constituents, Pharmacological Activities and Quality Control Studies. Molecules. 2022;28(1). https://doi.org/10.3390/molecules28010133
23. Curra M, Martins MA, Lauxen IS, Pellicioli AC, Sant'Ana Filho M, Pavesi VC, et al. Effect of topical chamomile on immunohistochemical levels of IL-1β and TNF-α in 5-fluorouracil-induced oral mucositis in hamsters. Cancer Chemother Pharmacol. 2013;71(2):293-9. https://doi.org/10.1007/s00280-012-2013-9
24. Beltrán O, Luna M, Valbuena Gregorio E, Valdez-Melchor R, Burruel Ibarra S, Quihui L, et al. Optimization of Carvacrol Nanoemulsion for the Incorporation in Pectin Membranes: Influence on Their Load Capacity, Microstructure and Antibacterial Properties. Mater Res. 2022;25. https://doi.org/10.1590/1980-5373-mr-2021-0534
25. Makadia HK, Siegel SJ. Poly Lactic-co-Glycolic Acid (PLGA) as Biodegradable Controlled Drug Delivery Carrier. Polymers [Internet]. 2011; 3(3):[1377-97 pp.].