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Preparation and Evaluation of Anti-Emetic Ginger Orodispersible Tablets from Standardized Extract using Phenolic Profile Effects

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Abstract – Ginger (*Zingiber officinale* Roscoe) is widely utilized in Thailand's healthcare system to alleviate motion sickness-induced nausea and vomiting. Its anti-emetic properties are attributed to various phenolic constituents, primarily gingerols and shogaols, which can vary due to processing and environmental factors. Tracking these compounds is quite complex. Therefore, this study aims to scientifically verify a practical quantitative approach for assessing active constituents, in terms of phenolic profiles, using ginger orodispersible tablets (ODTs) from standardized extracts as the target. The standardized ginger extract, quantified in 6-gingerol via validated HPLC, was combined with the superdisintegrant, sodium starch glycolate, using the wet granulation technique to prepare the ODTs. The optimized formulation met Pharmacopoeia standards, exhibiting desirable characteristics that can be used as a sample prototype for assessing the total phenolic content (TPC) using the modified Folin-Ciocalteu (F-C) assay. Determining the phenolic profiles in both the standardized ginger extracts and the tablets proved effective, facilitating the accurate quantification of total active constituents. This was particularly useful for handling multiple samples during dissolution tests. This study contributes to frontier knowledge on the phenolic profiles in standardized ginger extracts and theirs ODTs, which play an important role in interpreting the amounts of active constituents in the ODTs for their antiemetic properties.

Keywords – *Zingiber officinale* Roscoe, Standardized ginger extract, Ginger orodispersible tablets, Total phenolic content, HPLC

Introduction

Ginger (*Zingiber officinale* Roscoe, Zingiberaceae) has been widely used as a spice, dietary supplement, and potential remedy for various ailments related to inflammation, metabolic syndrome, and digestive disorders.[1–2] The bioactive compounds in fresh ginger rhizomes are typically categorized into volatile and non-volatile pungent components. The volatile constituents consist of terpene compounds, while the pungent principles are primarily composed of phenolic compounds, including gingerols, shogaols, and related derivatives.[1] Among these phenolic constituents, 6-gingerol emerges as the most abundant and noteworthy bioactive compound.[1,3–4]

Previous clinical studies support the efficacy and safety of ginger in managing nausea and vomiting during pregnancy, motion sickness, post-operation, and chemotherapy.[3–5] In Thailand, ginger plays significant role in primary health care and is highly valued for its medicinal properties. The Food and Drug Administration encourages the utilization of ginger rhizomes for medicinal purposes within healthcare facilities. Additionally, the Thai Herbal Pharmacopoeia and Thailand National List of Essential Medicines (NLEM) promote the use of ginger rhizomes for the treating indigestion and alleviating nausea and vomiting associated with motion sickness and chemotherapy.[6] Ginger preparations are generally available in conventional tablet and capsule forms. However, these solid dosage forms can pose challenges for certain patient groups, particularly children, the elderly, and individuals with swallowing difficulties, as well as for users while travelling. To enhance user compliance and convenience in product administration, ODTs, which dissolve rapidly in the mouth in less than three minutes without the need for chewing or water,[7] were chosen as the dosage form for this study. Additionally, the effects of different ingredient concentrations in the formulations and the quality control of the resulting formulations were preliminary studied.

Multiple pieces of evidence support the anti-emetic properties

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and motion sickness prevention of ginger, attributed to its various inherent phenolic compounds such as gingerols (including structural analogs like 6-, 8-, 10-, and 12-gingerol), shogaols, gingerdiol, and other phenolic constituents.[1,3,8–9] Certain conditions, such as thermal processing and prolonged storage, can transform gingerols into shogaols.[9] Monitoring each of these compounds is quite complicated. Therefore, evaluating the total phenolic content in ginger extract and ODTs could provide more accurate and comprehensive insights than focusing solely on the 6-gingerol content. Due to insufficient information on this aspect, the present study proposes evaluating the phenolic profiles in the standardized extract, alongside assessing the drug content during the quality control of the optimized ginger ODT formulation derived from the standardized extract.

Experimental

Plant materials – Ginger rhizomes were acquired from a local producer in Chachoengsao, a province in the east of Thailand, in August 2022. The plant samples were identified by Associate Prof. Dr. Ratana Indranupakorn, then dried at 45ºC, and ground into coarse powders.

Preparation of standardized ginger extract – An accurately weighed amount of ginger powder was extracted with ethanol (1:5 w/v) by maceration and concentrated in vacuo at 45ºC. The extract was standardized in 6-gingerol using the developed HPLC method and determined for TPC using the modified F-C assay.

HPLC analysis – The identification and determination of 6-gingerol in ginger extract was performed using a Finnigan modular LC system (P4000 dual pump equipped with a Rheodyne 7725i injector, 20 μL loop, and UV6000 photodiode array detector). The separation was achieved using an ACE® C18 column (250 × 4.6 mm, 10 μm, Advanced Chromatography Technologies Limited, Scotland), detected at 280 nm at room temperature. The mobile phase consisted of acetonitrile (A) and water (B). The optimized gradient condition was set as follows: The % A was linearly increased from 40% to 50% in 2 min, then to 90% in 7 min, finally to 100% in 11 min and kept there for 5 min. The total gradient run time was 25 min. A standard curve was generated using solutions of standard 6-gingerol (Chendu Biopurify Phytochemicals Ltd, China) in methanol ranging from 1.5 to 100 μg/mL. The concentration of 6-gingerol in the extract was then calculated using the standard curve equation ($y = 47782x + 85455$; $r^2 = 0.9985$; where y represents the peak area and x represents the solution concentration).

Validation of the HPLC method – The developed analytical method for 6-gingerol was validated in terms of system suitability, linearity, accuracy, precision, and specificity, in compliance with USP guidelines.[10]

Total phenolic content determination – The TPC of the samples was determined using the modified F-C colorimetric assay, as described by Kupina et al. with slight modifications.[11] In brief, the extract was dissolved in ethanol to a concentration of 400 μg/mL. Subsequently, 1 mL of the extract was mixed with 8 mL of F-C reagent (Merck KGaA, Germany), previously diluted with water at a ratio of 1:15 v/v, and thoroughly mixed. The mixture was then incubated in the dark for 60 min at room temperature. Then, 8 mL of 7% Na_2CO_3 was added, and the incubation continued in darkness for an additional hour. Absorbance was measured at 765 nm. A standard curve using a 20–60 μg/mL gallic acid solution (Fluka, Switzerland) was generated. The TPC in extracts was then calculated using the provided standard curve equation ($y = 0.0089x + 0.0148$; $r^2 = 0.9921$; where y represents the absorbance and x represents the solution concentration). Results were expressed as milligrams of gallic acid equivalent (GAE) per gram of dried extract. Each TPC analysis was done in triplicate.

Preparation of standardized ginger ODTs – Based on the clinical trial, which demonstrated that an oral dose of ginger extract containing 8 mg of 6-gingerols effectively reduced motion sickness,[4] ginger ODTs containing approximately 2–3 mg of 6-gingerol were prepared. The recommended dosage for reducing motion sickness is of 3-4 tablets. SSG (Onimax Co., Ltd, Thailand) was used as a superdisintegrant for the ODTs at concentrations ranging from 4% to 10% w/w of dried powder. Various standardized ginger ODT formulations (Table 1) were subsequently prepared using the wet granulation. Initially, standardized ginger extract, mannitol, microcrystalline cellulose (Avicel PH101), citric acid, aspartame, and sodium chloride were thoroughly blended using the geometric dilution method. Subsequently, the blend was granulated using a PVP-K30 solution in alcohol (as required) as the granulating fluid, and wet mass was screened using sieve No.10. The resulting wet granules were dried at 50ºC for 4 hours and then screened using a No.12 sieve to obtain discrete granules. These dried granules were further mixed with SSG, magnesium stearate, and talcum.

The resulting granules from each formula were evaluated for the precompression parameters to study their flow properties before being compressed into 300–500 mg tablets using a single punch tableting machine with concave punch 10 mm in diameter. Evaluation of the standardized ginger ODTs was conducted using the post-compression in-process control testing, according to the standard methods outlined in the Pharmacopoeia.

Precompression studies – The flowability of granules in all

Table 1. Composition of different formulas (F1–F6) of prepared ginger ODTs (data in mg)

Ingredients	F1	F2	F3	F4	F5	F6
Standardized ginger extract	20	20	20	25	25	25
PVP-K30	5	15	15	9	9	15
Mannitol	407.5	387.5	377.5	216.5	105.25	59.55
Avicel PH101	-	-	-	-	105.25	138.95
Citric acid	25	25	25	15	15	15
Aspartame	7.5	7.5	7.5	4.5	4.5	4.5
NaCl	-	-	-	3	3	3
SSG	20	30	40	18	24	30
Magnesium stearate	5	5	5	3	3	3
Talcum	10	10	10	6	6	6
Total	500	500	500	300	300	300

formulation batches was assessed through various parameters including angle of repose, bulk density, tapped density, and compressibility index (CI), following the procedures outlined in the USP.[10] Three determinations were carried out for each parameter.

Evaluation of standardized ginger ODTs – The resulting ginger ODTs of various formulations were randomly selected and assessed for their physical appearance and organoleptic characteristics by authors and co-workers. Selected formulations were tested for physical properties including hardness, thickness, weight variation, friability, *in vitro* disintegration time, *in vitro* dissolution study, and TPC.

Hardness assessment of standardized ginger ODTs utilized an Erweka TBH20 hardness tester (Germany), with the crushing strength of ten randomly chosen tablets reported as mean hardness ± standard deviation (SD) in kiloponds (kp). The acceptable range is 2–4 kp.[12] Tablet thickness was measured using a Teclock SM-112 thickness gauge (Japan), with data reported as mean ± SD across ten tablets from each formulation. The USP weight variation test involved twenty tablets weighed individually on an electronic balance (Sartorius, Germany), comparing individual weights to average values and deviations. Friability assessment employed tablets weighing 6.5 g from each formulation, dedusted and rotated at 25 rpm for 4 min in a Labindia FT1020S friabilator (India), with post-dedusting reweighing to calculate percentage (%) of weight loss; a friability below 1% was considered acceptable.[10]

The *in vitro* disintegration time of standardized ginger ODTs was determined using a modified method.[12–13] Tablets were placed in a petri dish with water, and the time taken for complete disintegration into fine particles was recorded. The average of six determinations was calculated. Additionally, wetting time, which corresponds to the time taken for the tablet to disintegrate when kept motionless on the tongue, was measured by placing a tablet on folded paper in a petri dish containing water. The time for complete wetting of the tablet was measured in seconds.[12,14]

The i*n vitro* dissolution studies of ginger ODTs were conducted using USP apparatus type II (Electrolab EDT-08Lx, India) at 75 rpm in phosphate buffer (pH 6.8)[15] at 37ºC. Samples were withdrawn at intervals, replaced with fresh dissolution fluid, and analyzed for TPC using F-C reagent. The concentration of phenolic compounds in withdrawn samples was determined using a standard curve prepared with gallic acid in phosphate buffer (pH 6.8), ranging from 10 to 60 μg/mL (y=0.0087x+0.0059; r^2=0.9972; where y represents the absorbance and x represents the solution concentration). Results were expressed as mg of GAE per gram of dried extract. Each TPC analysis was performed in triplicate.

The drug content of standardized ginger ODTs was determined by sonicating a weighed tablet powder in ethanol for 30 min, followed by dilution and assessment to TPC using the F-C assay. Additionally, the HPLC technique was used to analyze the phytochemical profile, including 6-gingerol and its dehydration product, 6-shogaol, in the ginger ODTs extract. The amount of 6-gingerol was calculated using a standard curve, as described previously, while 6-shogaol quantity was determined through linear regression between standard 6-shogaol concentration and peak area (y=57381x–66730; r^2=0.9979; where y represents the peak area and x represents the solution concentration).

Short-term stability of TPC – A preliminary stability study was conducted on both standardized ginger extract and the promising ginger ODT formulation (formulation 6). Based on our unpublished preliminary research, it was observed that the 6-gingerol in ginger extract remained stable when stored in a

freezer. Samples were stored in amber glass bottles under two conditions: room temperature (27°C ± 2°C) and in a freezer (−20°C ± 5°C, Haier HFC568C, China) for a short period of 4 months. Chemical stability, measured in terms of TPC, was then evaluated.

Statistical analysis – The data were expressed as the mean value ± SD. Statistical differences among the sample groups were assessed using a two-tailed independent samples *t*-test at a significance level of 5% ($p < 0.05$).

Results and Discussion

The optimal conditions for the simultaneous quantitative determination of the main component, 6-gingerol, in ginger extract were developed. All components, including 6-gingerol, were eluted within 25 minutes, with satisfactory resolution observed at 7.96 minutes (Fig. 1). Identification of the 6-gingerol peak relied on comparing its retention time and photodiode array spectra with those of the standard. Compared to previous reports, the developed HPLC method for quantifying 6-gingerol is relatively simple and fast.[16,17]

To validate the developed HPLC method for determining 6-gingerol content, it was evaluated following USP guidelines, covering specificity, linearity, intra-day and inter-day precision, and accuracy (Table 2).[10] Specificity was confirmed by peak purity analysis at various points using UV spectra from a diode array detector, showing homogeneity of spectra for both sample and standard peaks. The method exhibited linearity over the range of 1.5–100 μg/mL, demonstrating a high correlation between the peak area and six different concentrations (six replicates for each concentration level), with a correlation coefficient (r^2) of 0.9985. Intra-day precision was assessed by analyzing 63.7 μg/mL of 6-gingerol solutions six times within one day, and inter-day precision was evaluated in triplicate on three different days, both demonstrating %RSD lower than 2%. Accuracy was evaluated by spiking known amounts of the standard at three concentration levels (80%, 100%, 120%), with mean recoveries indicating good accuracy of the method. These results confirm the accuracy and reproducibility of the proposed HPLC method for determining 6-gingerol in ginger extract and dosage form.

Table 2. Method validation data of the proposed HPLC method

Validation Parameters	6-gingerol
Linearity range (μg/mL)	1.5–100
Regression equation[a]	$y = 47782x + 85455$
Correlation coefficient (r^2)	0.9985
Intra-day precision (%RSD)	0.69
Inter-day precision (%RSD)	1.98
%Recovery (mean ± SD, %RSD)	102.66 ± 1.19, 1.16

[a]x represents the solution concentration of 6-gingerol, y represents the peak area.

The ginger extract was prepared via maceration in ethanol, chosen for its reported effectiveness in extracting total phenolics compared to other methods.[18] The resulting extract appeared as a yellowish-brown viscous liquid, yielding 7.52% based on the dried ginger extract. Subsequently, the extract was standardized using a validated HPLC method with 6-gingerol as a reference

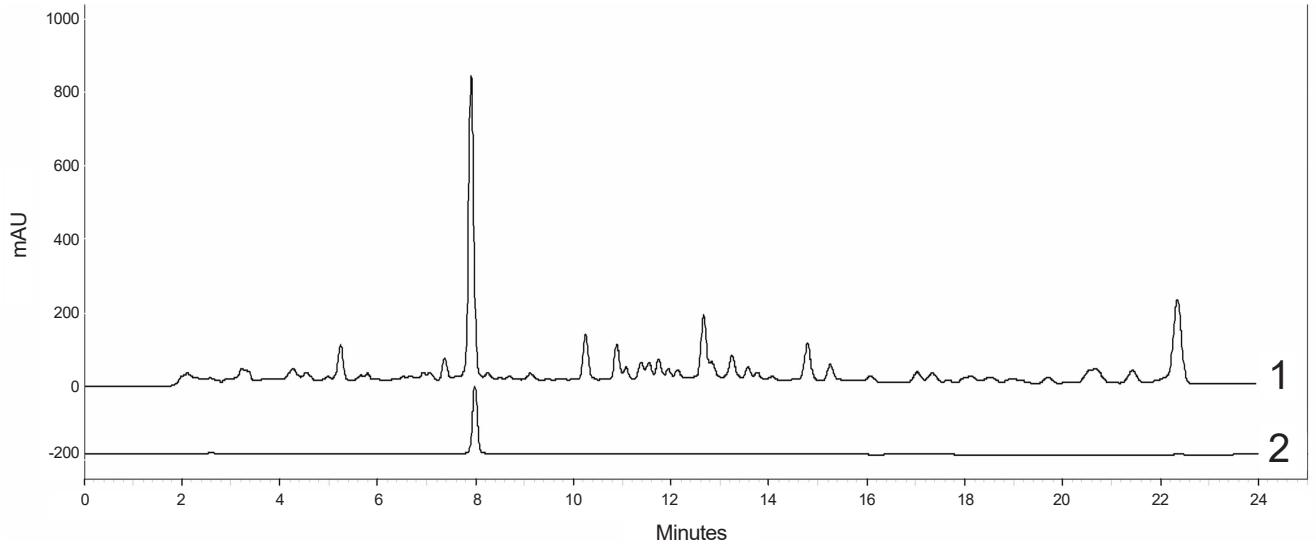

Fig. 1. HPLC chromatograms of the 6-gingerol (1) in standardized ginger extract (upper chromatogram) and the 6-gingerol reference standard (2) (lower chromatogram).

standard. The 6-gingerol concentration was calculated based on the linear calibration function, considering the dilution factor. The F-C assay revealed a TPC of 135.47 ± 0.2463 mg GAE/g extract, higher than the concentration of gingerol, the predominant phenolic compound, at 111.10 ± 1.1400 mg/g extract (Fig. 1). This suggests the presence of other phenolic compounds contributing to the overall phenolic content. The F-C assay correlated well with HPLC analysis of gingerol in the extract.

Previous studies have reported the TPC of ginger extracts obtained through conventional rotary shaker extraction in 50% ethanol to be 6.5044 ± 0.2732 mg GAE/g extract.[19] In our study, the TPC of the ethanol extract by maceration was higher, at 135.47 ± 0.2463 mg GAE/g extract. Similarly, Puengphian et al. (2008) reported a TPC of 126.04 ± 0.72 mg GAE/g extract for extracts obtained using the green, supercritical-carbon dioxide extraction method at 230 bar and 40ºC.[20] Several studies have asserted that the variety of phenolic contents resulted from processing and extraction processes.[1]

Based on previous studies showing the effectiveness of an 8 mg dose of 6-gingerols in ginger extract for reducing motion sickness symptoms,[4] this study aimed to formulate standardized ginger extract into ODTs using wet granulation.

To optimize disintegration time, various ratios of SSG and binder (PVP K-30) were tested, with the ratio yielding the optimal disintegration time and hardness selected. Excipients commonly used in oral dosage forms, including mannitol, microcrystalline cellulose (Avicel PH 101), magnesium stearate, and talcum, were incorporated as diluent, lubricant, and anti-adherent agents. Mannitol was chosen for its cold sensation and pleasant aftertaste, while magnesium stearate provided low-cost lubrication. To enhance palatability and mask the hot taste, citric acid, aspartame, and sodium chloride were added. Six formulations of the ODTs containing standardized ginger extract were developed to study the effects of excipient type and concentration on achieving optimal formulation characteristics, as detailed in Table 1.

In pre-compression evaluation, powders showed good appearance and similar flowability across all six formulas of ginger powder. The angle of repose ranged consistently from 33º to 35º, indicating good flow characteristics, while compressibility fell within the range of 9–10, suggesting excellent compressibility in all formulations. These findings demonstrate that standardized ginger granules exhibit favorable flow quality, facilitating subsequent compression studies.

In a preliminary study, the optimized concentration of binder (PVP K-30) combined with superdisintegrant (SSG) on disintegration time was investigated. The Center for Drug Evaluation and Research (CDER) at The US Food and Drug Administration recommends, in its Guidance for Industry on ODTs, a maximum total weight of 500 mg for tablets to ensure patient safety and compliance.[21] Tablets (500 mg) in formulations 1-3 were prepared with different ratios of SSG and concentrations of PVP K-30 (4:1, 6:3, 8:3, respectively). However, standardized ginger ODTs from formulations 1-3 showed significant variations in tablet physical properties such as hardness and friability, impacting mechanical strength.

There is no specific test for evaluating the disintegration time of ODTs in the USP and the Ph. Eur. The disintegration medium of 900 mL of water and the oscillating apparatus used in USP <701> disintegration cannot replicate the conditions found in the human body.[10] Therefore, the disintegration time for standardized ginger ODTs was evaluated using a modified method. Disintegration time of standardized ginger ODTs was assessed, revealing a decrease with increased SSG concentration. SSG acts as a superdisintegrant by absorbing water and swelling within the tablet matrix, facilitating faster disintegration. However, formulation 3, with a higher SSG to PVP K-30 ratio (8:3), showed disintegration beyond 3 min, indicating a need for increased SSG to achieve desired characteristics in ginger ODTs.

Tablet size and hardness significantly influence disintegration time, with ODTs typically compressed at lower forces than conventional tablets, resulting in weaker mechanical strength. Smaller tablet sizes are preferable to enhance disintegration time, aiming for less than 3 minutes per Ph. Eur. guidelines.[13] Formulations 4-6 were prepared as 300 mg tablets, maintaining excipient ratios but adjusting mannitol in formulation 4 to match the original. Avicel PH 101, a multifunctional excipient, was added to formulations 5-6 to aid disintegration and compressibility. Avicel PH 101's wicking action promotes rapid wetting, enhancing granule and tablet disintegration. Varying ratios of mannitol and Avicel PH 101 were explored in formulations 5-6. Standardized ginger ODTs with acceptable hardness and improved disintegration times (120 sec in formulation 4, 94 sec in 5, and 48 sec in 6) were achieved with the reduction to 300 mg, addition of Avicel PH 101, and increased SSG. This size is convenient for administration to both children and elderly patients.

Based on the results for disintegration time of less than 1 minute, formulation 6 was selected as the optimal formulation to prepare the standardized ODTs and subjected to quality control tests, as shown in Table 3. The percent weight variation remained within the acceptable range that none of the tablet weight deviated outside weight variation limit of ±7.5%, and TPC exhibited consistent levels at 3.3225 ± 0.08 GAE/tablet. Analysis changes in the bioactive profile during tablet manufacturing, with

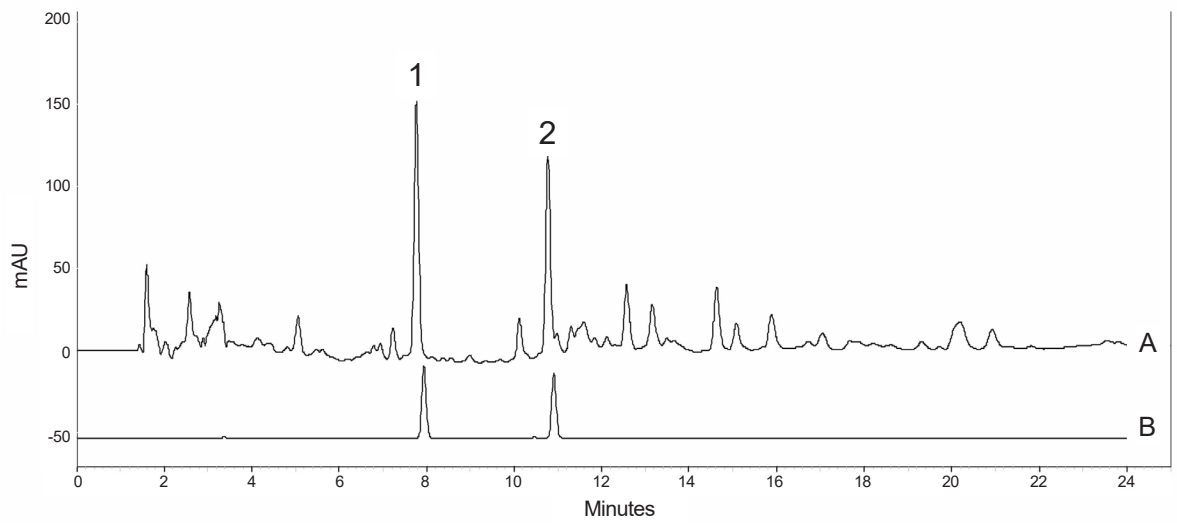

Fig. 2. HPLC chromatogram of the standardized ginger ODTs extract (upper chromatogram, A) overlaid with the chromatogram of standard mixtures, 6-gingerol (1) and 6-shogaol (2) (lower chromatogram, B).

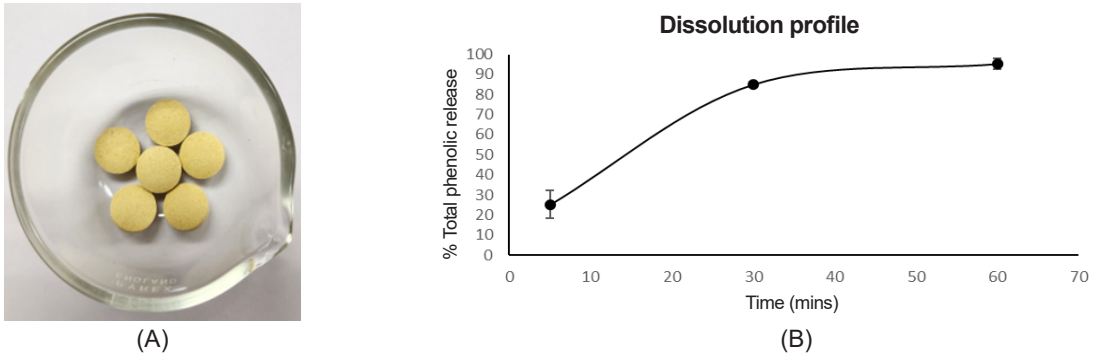

Fig. 3. Appearance of the standardized ginger ODTs (A) and in vitro release profile of total phenolics from the standardized ginger ODTs (B).

Table 3. Physical properties obtained from granules and standardized ginger ODTs (formulation 6).

Evaluation parameters	Physical properties
Granules	
Angle of repose	35.12 (Good)[a]
%Compressibility	9.48 (excellent)[a]
Standardized ginger ODTs	
Appearance	Yellowish-brown color with smooth surface, round in shape
Taste and mouthfeel	pungent taste, accompanied by a subtle heat sensation
Weight variation	Passed (not more than 7.5%)[a]
Hardness (kg)	2.37 ± 0.22[b]
Thickness (mm)	4.61 ± 0.02[b]
Friability (%)	0.15[a]
Disintegration time (sec)	48 ± 1.07[b]
Wetting time (sec)	39 ± 1.53[b]
Total phenolic content (GAE/tablet)	3.3225 + 0.08[b]

[a] as per USP[10]; [b] data are expressed as mean ± SD

Table 4. The TPCs of standardized ginger extracts and standardized ginger ODTs at different storage conditions

Sample	Storage temperature	TPC at different storage time	
		0 days	4 months
Standardized ginger extracts	−20°C	135.48 ± 0.54[a]	133.73 ± 0.67[a]
	RT	135.48 ± 0.54[a]	123.36 ± 1.49[b]
Standardized ginger ODTs	−20°C	3.3225 ± 0.08[a]	3.2565 ± 0.19[a]
	RT	3.3225 ± 0.08[a]	3.0576 ± 0.14[b]

[a,b] means ± SD in the same row with different letters is significantly different ($p < 0.05$)

a decrease in 6-gingerol and an increase in 6-shogaol content (Fig. 2). This indicates a relationship between constituent content and the likelihood of the transformation of gingerols to shogaols. The results of this study are consistent with previous findings.[1,22] Interestingly, the overall content of gingerol and shogaol, known for reducing motion sickness, remained similar before and after tablet production, 2.7773 mg/tablet and 2.6633 mg/tablet, respectively. The F-C assay correlated well with HPLC analysis of gingerol and shogaol in the tablets.

Moreover, they demonstrated satisfactory hardness. The friability of the standardized ginger ODTs was less than 1%, aligning with the criteria stipulated in the USP.[10] The tablets demonstrated low disintegration and wetting times (under 1 minute), affirming the appropriateness of the ODT formulation. According to the Ph. Eur., ODTs should disintegrate within 3 minutes.[7] *In vitro* dissolution studies indicated that over 85% of the TPC in ODTs was released within 30 minutes, meeting the criteria outlined by the US Food and Drug Administration.[7] The rapid release of total phenolics could be attributed to the efficient breakdown of particles facilitated by the action of superdisintegrants (Fig. 3).

Preliminary chemical stability studies were conducted on standardized ginger extract and standardized ginger ODTs (formulation 6), assessing the TPC under both −20°C and room temperature conditions (Table 4).

The TPC of standardized ginger extract stored at −20°C for 4 months remained stable, suggesting no degradation of phenolic components. Conversely, at room temperature, a significant 8.94% decline occurred over the same period, aligning with prior findings indicating gradual degradation of TPC with storage, particularly at higher temperatures.[1]

Similar storage conditions were applied to ginger ODTs. At −20°C, no significant change was observed after 4 months, confirming stability and compatibility between the chemical compositions in the extract and the excipients used in tablet formulation. However, at room temperature, a notable 7.97% decrease occurred, highlighting the importance of proper storage to maintain efficacy of ginger formulations. Further research on long-term stability is warranted.

In conclusion, the developed HPLC method in this study effectively separates, identifies, and quantifies the major phenolic compound, 6-gingerol, in standardized ginger extract, making it suitable for routine phenolic analysis. Formulating standardized ginger ODTs using the wet granulation method with 10% SSG and Avicel PH101 resulted in fast disintegration times and good mechanical properties, meeting Pharmacopeial requirements. This study demonstrates the feasibility of formulating standardized *Zingiber officinale* extract into anti-emetic ODTs with desirable characteristics, serving as a prototype for assessing TPC. Additionally, TPC evaluation proves useful in quality control due to its convenient and time-saving benefits, especially when handling multiple samples, compared to individual quantification of pharmacologically active components. This approach facilitates further scientific investigation.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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