Lampyrid 2023: Volume 13, 742-757
ISSN: 2041-4900
https://lampyridjournal.com

Formulation and Characterization of Enteric Coated Tablets of Zingiber Officinale Extract for Antimigraine Activity.

Prachi Shrimant Farande[1*], Dr. Vaibhav Ravindra Vaidya[2], Mohit Ashok Mahajan[3], Abhishek Ashok Galgate[4], Shrutika Janardan Bhagde[5], Rohit Shashikant Jadhav[6]

[1*] Student at Department of Pharmaceutics, Dr. D. Y. Patil College of Pharmacy, Akurdi, Dr. D. Y. Patil Educational Complex, Pune 411044, Maharashtra, India.
2 Faculty at Department of Pharmaceutics, Dr. D. Y. Patil College of Pharmacy, Akurdi, Dr. D. Y. Patil Educational Complex, Pune 411044, Maharashtra, India.
3 Student at Department of Pharmaceutics, Dr. D. Y. Patil College of Pharmacy, Akurdi, Dr. D. Y. Patil Educational Complex, Pune 411044, Maharashtra, India.
4 Student at Department of Pharmaceutics, Dr. D. Y. Patil College of Pharmacy, Akurdi, Dr. D. Y. Patil Educational Complex, Pune 411044, Maharashtra, India.
5 Student at Department of Pharmaceutics, Dr. D. Y. Patil College of Pharmacy, Akurdi, Dr. D. Y. Patil Educational Complex, Pune 411044, Maharashtra, India.
6 Student at Department of Pharmaceutics, Dr. D. Y. Patil College of Pharmacy, Akurdi, Dr. D. Y. Patil Educational Complex, Pune 411044, Maharashtra, India.

Author contribution:
Conceptualization: [Prachi Shrimant Farande and Dr. Vaibhav Ravindra Vaidya]; Methodology: [Mohit Ashok Mahajan]; Formal analysis and investigation: [Abhishek Ashok Galgate and Rohit Shashikant Jadhav]; Writing - original draft preparation: [Shrutika Janardan Bhagde and Prachi Shrimant Farande]; Writing - review and editing: [Prachi Shrimant Farande]; Funding acquisition: [N/A]; Resources: [Dr. Vaibhav Vaidya]; Supervision: [Prachi Shrimant Farande and Dr. Vaibhav Ravindra Vaidya]

Conflict of interest:
The authors have no conflicts of interest regarding this investigation

Acknowledgments:
The author is grateful to Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune, India for providing facility to carried out this study
Ethicas Approval: N/A
NO FUNDING WAS RECEIVED FOR CONDUCTING THIS STUDY.
THE AUTHORS HAVE NO RELEVANT FINANCIAL OR NON-FINANCIAL INTERESTS TO DISCLOSE

Lampyrid 2023: Volume 13, 742-757
ISSN: 2041-4900
https://lampyridjournal.com

*Corresponding author:
Department of Pharmaceutics,
Dr. D. Y. Patil College of Pharmacy, Akurdi,
Dr. D. Y. Patil Educational Complex, Pune 411044, Maharashtra, India.
E-mail address: prachifarande25@gmail.com
Contact No. 9822254776

Abstract:
Purpose-For the purpose of treating the aura phase of migraines, an enteric-coated zingiber officinale (Ginger) extract tablet formulation, and evaluation was attempted in the current study.
Methods-To achieve this goal, core ginger extract tablets were prepared by using the direct compression method. Based on results of factors drug release and disintegration time from design of experiment software, optimization of batch was done. Optimized batch used for formulation and evaluation of enteric coated tablet by dipping method. Eudragit L 100, PEG, and acetone was used for the coating of the tablet. Drug release and disintegration time for the first 2 Hr in 0.1 N HCL and then 1 Hr in 6.8 pH phosphate buffer were performed for the prepared coating tablet.
Result-All Prepared tablets are evaluated for their pre-compression and post-compression characters. Optimized formulation shows no drug release at first 2 hrs in gastric fluid and shows 86.78% drug release in pH 6.8.
Conclusion- Ginger Extract is an acid sensitive medication and it is protected by enteric coating to give better therapeutic results.

Keywords: Anti-Migraine; Enteric Coating; Tablet; Zingiber Officinalae; Edgragit L 100

Introduction :

A chronic, episodic primary headache called migraine is assumed to be a neurovascular pain syndrome that involves the trigeminovascular system and altered central neuronal processing. Symptoms may be severe in intensity and normally continue for 4-72 hours[1]. symptoms of migraine are head movements, nausea, vomiting, photophobia, phonophobia, etc[2]. Pain is constantly unilateral, palpitating in form, worsens with exertion, and is constantly accompanied by autonomic symptoms. The pathophysiology of migraine is allowed to be hold by both hereditary and environmental factors. According to the trigeminal nerve vascular theory, trigeminal nerve stimulation results in the release of vasoactive peptides, which aids in blood vessel dilating and dura mater neurogenic inflammation. Nitric Oxide (NO), substance P, Endothelin (ET), and Calcitonin

Gene-Related Peptide (CGRP) has been the most frequently reported among the released chemicals[3].

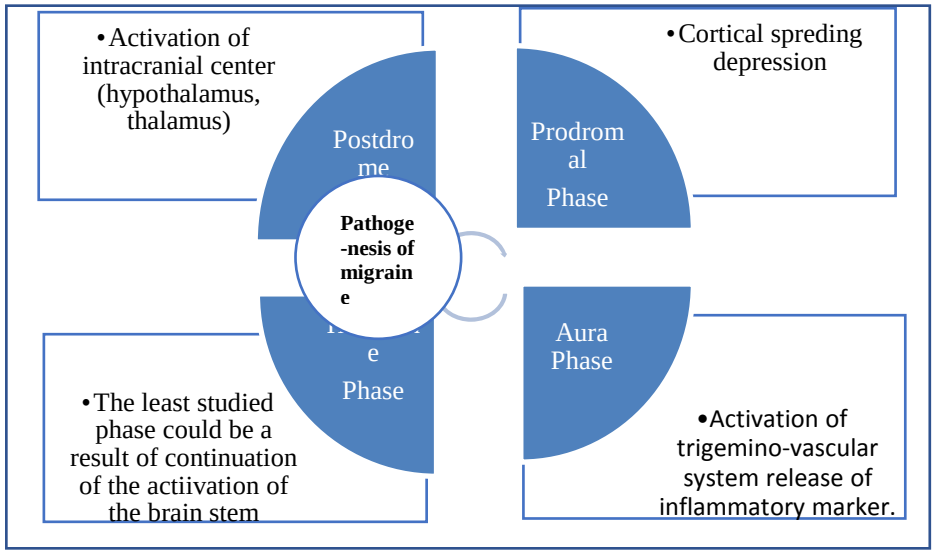


Figure 1.Pathogenesis of migraine[4].

A plant called ginger (zingiber officinale) produces a pungent spice known as a rhizome. Ginger is a plant that is extensively available and has a long history of operation in traditional drug. Ginger has numerous chemical components. These include terpenes, polysaccharides, lipids, organic acids, and phenolic chemicals such as 6- shagol, 6-gingerol, 8- gingerol, 10-gingerol, paradol, zingeron zingiberene, phellandrene, etc. Among these, 6-shagol, 6-gingerol, and 10-dehydrogingerdione may be significant for antimigraine activity. Ginger has anti-inflammatory, antioxidant anticarcinogenic, and antinausea properties also[5].
Ginger leads to vasoconstriction by inhibiting NO which results in the relief of migraine pain[6]. Ergotamine and dihydroergotamine have anti-migraine properties because they bind to the $5HT_1$ and $5HT_2$ receptors and prevent the ventral spinal cord's release of potassium-stimulated substance P. It has also been demonstrated that antihistaminic specifics, similar as the combination of cimetidine chlorpheniramine, are helpful in treating spontaneous migraine[7]. Ginger has antihistaminic and antioxidant properties. Histamine is released due to arachnoid acid and its free radicals[8]. It combines the release of prostaglandin, leukotriene, and histamine, which are the two fundamental mechanisms in inflammatory pain-related disorders. As this process cannot be replicated by either arachidonic acid (without conversion) or by the byproducts of the arachidonic acid cascade, it is stopped by reduced Glutathione (GSH), d-mannito1, lipoxygenase, and cyclooxygenase pathway inhibitors. The antihistaminic effects of ginger may be due to its capacity to prevent the production of free radicals from substances like arachidonic acid and others that are known to cause the release of histamine. Other studies discovered that ginger significantly reduces prostaglandin production[9].

According to one study, ginger powder reduced migraine intensity after two hours just as well as the medication sumatriptan. Compared to sumatriptan, ginger powder exhibited fewer adverse effects. In another study, ginger was put up against a placebo (fake tablet) or an IV medication. A 400 mg dose of ginger extract or placebo was administered to each patient along with an IV dose of the anti-inflammatory medication ketoprofen. At 1, 1.5, and 2 hours following treatment, those who took ginger reported reduced pain and fewer migraine symptoms[10].

Due to low bioavailability of ginger, it's nutritional and therapeutic uses in nutraceuticals or fortified food items are restricted. Gingerols and derivatives are lipid-soluble compounds and therefore it would be expected good absorption by passive diffusion across the intestinal epithelium. However, prior to absorption, they must reach brush border cells, due to their chemical structure, they present a low solubility in water[11].

A tried-and-true method to drug release in the small intestine by restricting release in the small intestine is to apply an enteric coating to a solid dosage form. Carboxylic group-containing polymer and pH-dependent polymers are having the ability to ionise in the higher pH environment of the small intestine and these do not ionise in the low pH environment of the stomach hence these are widely used enteric coating material, allowing the coating to dissolve and the medication to be released from polymers in a controlled manner[12]. To protect the drug core from the acidic environments of the stomach, a number of polymers are available. These polymers dissolve in the colon and release the core for immediate action since they are soluble at higher pH levels. Several artificial polymers, such as polymethacrylates (Eudragits), cellulose acetate phthalate (CAP), and hydroxy propyl methyl cellulose phthalate (HPMCP), are among these polymers.[13].

Materials And Methods:

Materials

Ginger extract was a gift sample from Kisaliya herbal PVT. limited, other excipients such as Microcrystalline cellulose, Crosscarmellose, Lactose, and Magnesium stearate are gift samples from Neeta Chemicals, Pune

Preparation of formulation

Ginger extract tablets of total weight 450 mg were prepared by direct compression method with 400 mg of ginger extract and other 50 mg excipients using a rotary tablet compression machine.

Table 1. Composition of zingiber officinale extract tablet

Composition	F1	F2	F3	F4	F5	F6	F7	F8	F9
Zingeber officinale extract	400	400	400	400	400	400	400	400	400

(mg)									
Microcrystalline cellulose (mg)	110	100	110	120	95.85	120	110	124.14	100
Crosscarmellose sodium (mg)	15	20	7.928	10	15	20	22.07	15	10
Lactose (mg)	20	25	27.072	15	34.12	5	12.93	5.86	35
Mg stearate (mg)	5	5	5	5	5	5	5	5	5

Coating of compressed zingiber officinale extract tablet

To make the enteric coating solution the simple solution approach was used. It was made using Acetone as the solvent, 4% of Eudragit L 100 as an enteric polymer, and 1.5% of PEG as a plasticizer. A coating solution was created by adding diethyl phthalate and combining it with the remaining solvent mixture to make up the volume. This mixture was then mechanically agitated continuously for one hour at a speed of 1000 rpm[14].

Table 2. Composition of the coating solution

Constituent	Quantity (%)
Eudragit L 100	4
PEG	1.5
Acetone	59.4
Diethyl phthalate	Q.s.

Enteric coating of Ginger extract compressed tablets was done by dipping method. Desired tablet coating continued the dipping and weight gain was achieved. The coated tablets were studied for their weight variation, thickness, uniformity of drug content, and in vitro dissolution study.

Evaluation of compressed tablet

a) Drug-excipient compatibility

spectra of pure drug and drug samples with excipients were recorded using an FTIR spectrophotometer (shimadzu, japan). The samples were dispersed in Kbr and compressed into discs/pellets by application of pressure. The sample was placed in the light path for recording the IR spectra. Zingiber officinale extract compatibility with excipients was studied by FTIR[15].

b) HPTLC analysis

HPTLC was used to qualification of pure drug sample. Sample preparation was done by weighed 100 mg of extract sample, dissolved in 10 ml of methanol, sonicated for 30 mins, centrifuged at 10000 rpm for 15 mins and the

supernatant was filtered and used for spotting. The solvent system used for spotting was hexane: ether 4:6 v/v for 20 min saturation time[16].

c) Bulk density

Bulk density was calculated as the mass (m) of the sample poured into a 50 ml graduated cylinder divided by the volume (v) of powder[17].

Bulk density was calculated as:

$$\text{Bulk density} = \frac{\text{mass (m)}}{\text{volume (v)}}$$

d) Tapped density

Electro lab's density tester, which comprises a graduated cylinder mounted on a mechanical tapping mechanism, was used to measure the tap density. A carefully measured (m) sample of powder was put into the cylinder. After observing the initial volume, the cylinder was mechanically tapped 100 times and the volume was recorded as the final tapped volume (v)[17].

The following formula is used to compute tapped density:

$$\text{Tapped density} = \frac{\text{mass (m)}}{\text{volume (v)}}$$

e) Compressibility index and Hausner ratio

Both the compressibility index and hausner's ratio were determined by using bulk density and the tapped density of a powder [15].

$$\text{Compressibility index} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100$$

Hausner ratio is determined by the ratio of tapped density to the bulk density[18].

$$\text{Hausner ratio} = \frac{\text{tapped density}}{\text{bulk density}}$$

f) Angle of repose

The flow characteristics of solids have been described in terms of the angle of repose. An aspect of inter particulate friction or resistance to particle movement is called the angle of repose[15].

This maximum angle is the highest that the surface of the powder or granule pile can be inclined away from the horizontal plane. Over the platform, a funnel was mounted at a height of about 2 cm. Till the powder cone formed, the loose powder was slowly moved along the funnel's wall. By taking measurements of the powder cone's height and heap's radius, you may determine the angle of repose.

$$\Theta = \tan^{-1}\frac{h}{r}$$

Where, θ = angle of repose, h = height, r = radius.

Post-compression parameters of core and coated prepared tablets were evaluated for various parameters.

g) Weight variation

Ten tablets were randomly selected and the average weight was determined. Then individual tablets were weighed and the percent deviation from the average was calculated[18].

h) Thickness

The thickness in millimetres (mm) was measured individually for 10 pre-weighed tablets by using a micrometer screw gauge. The average thickness and standard deviation were reported[18].

i) Hardness

A tablet hardness tester (Monsanto hardness tester) was used to measure it. Three tablets from Each formulation were tested at random, and the average reading was recorded.

j) Friability

The friability of the tablets was determined using a Roche Friabiltor (electro-lab, India). This device consists of a plastic chamber that is set to revolve around 25 rpm for 4 min dropping the tablets at a distance of 6 inches with each revolution. Pre weighed sample (w_0) of 20 tablets was placed in the friability and was subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed (w)[18].

The formula below yields the friability (f%).

$$\text{friability (\%f)} = 1 - \frac{W0}{W} \times 100$$

Where W_0 = Initial weight of the tablets before the test

W = Final weight of the tablets after the test.

k) Disintegration time

The USP disintegration tester (electro-lab, Bangalore, India) was used to conduct the disintegration test for the enteric-coated tablets. Each tube of the device was filled with six enteric-coated tablets, and the disintegration test was initially run at pH 1.2 for two hours without the discs. The identical tablets were tested for disintegration in a solution containing pH 6.8 phosphate buffer mixed with discs after two hours. Throughout the test, the water bath's temperature was held constant at 37 5°c. The pills' breakdown time was measured in minutes[19].

l) Determination of drug content

The average weight of 20 tablets was determined after a random selection of them. A glass mortar was used to grind up the tablets. In a volumetric flask, 5 mg of powder was measured and dissolved in 100 ml of phosphate buffer with a pH of 6.8. At 281 nm, this solution's absorbance was measured compared to a control. The standard curve was used to calculate the percentage assay[20].

m) Dissolution study

Using the USP dissolving testing apparatus-1 (basket method), the release rate of the Ginger extract was calculated. The dissolution medium consisted of 900 ml of 0.1N HCL for two hours and 1 hour of 6.8 pH phosphate buffer. The temperature was kept at 37°c with a 50rpm stirring rate while the tablet was kept in a basket. After a predetermined amount of time, the sample was removed and replaced with new dissolving media. As a dissolving medium, the core tablets utilized 900 ml of 6.8 pH phosphate buffer. The samples were filtered, and a UV spectrophotometer was used to measure the absorbance of these solutions at about 281 nm using

buffer as the blank and acid stage media as the blank. Plotting the medication release percentage versus time allowed to determine the release profile [15].

Result and discussion:

Fourier Transform Infrared

From the figure 2 & 3 it was observed that the following characteristic peaks at 1080.14 (C-H stretching), 3387.10 (O-H stretching), 1510.30 (C=C stretching), 2868.15, 2995.45 (C-H stretching) are present in both pure drug and in formulations, indicating no chemical reaction between pure drug and formulation[21]

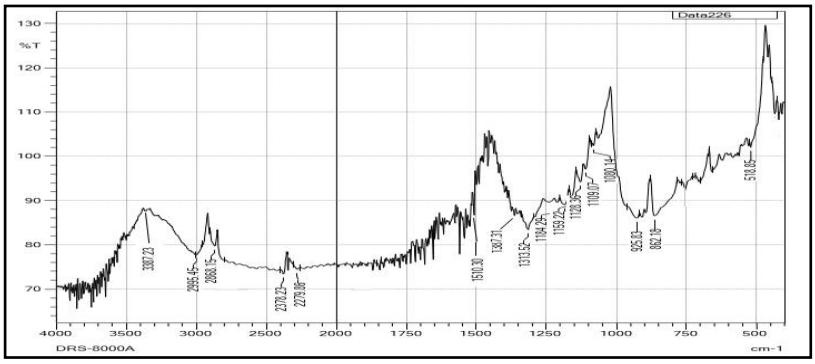


Figure 2. FTIR spectra for the pure drug.

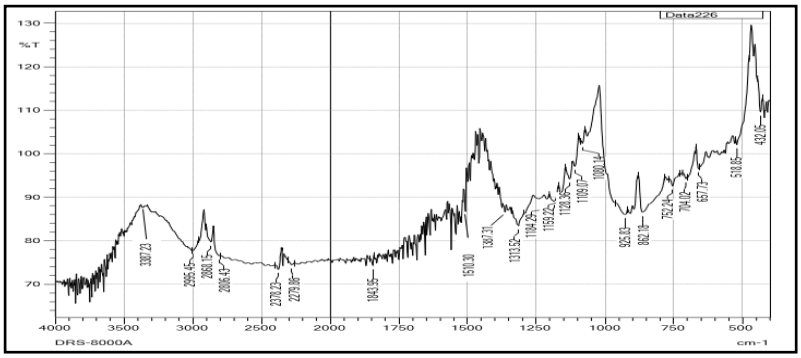


Figure 3. FTTIR spectra for formulation.

High performance thin layer chromatography

The peak is observed at UV 254 and also UV 366 nm at rf = 0.41. The peak was

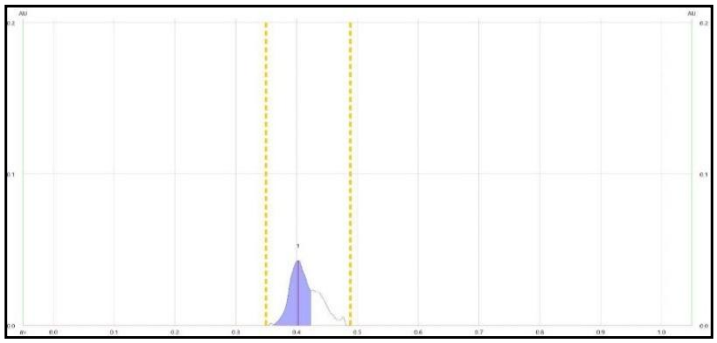


figure 4. HPTLC Chromatogram of the pure drug.

scanned at 254 nm and the densitogram was recorded. On derivatization, no extra bands were visible.

Pre-compression parameter of ginger extract powder

The prepared ginger extract powder blend was evaluated by the angle of repose, bulk density, tapped density, hausner's ratio, and compressibility index as given in table.

Table 3. Pre-compression parameter of ginger extract powder

Formulation Code	Parameter				
	Bulk density	Tapped density	Carr's index	Hausner's ratio	Angle of repose
F1	0.368 ±0.03	0.386± 0.04	7.04±0.09	1.065±0.04	29.31±0.26
F2	0.316 ±0.05	0.328±0.03	6.74±0.014	1.061±0.05	28.20±0.14
F3	0.307 ±0.04	0.319±0.05	6.13±0.013	1.056±0.02	27.13±0.34
F4	0.319 ±0.04	0.336±0.04	6.49±0.014	1.070±0.06	27.18±0.26
F5	0.307 ±0.03	0.331±0.03	8.31±0.17	1.089±0.08	26.78±0.18
F6	0.379 ±0.06	0.401±0.04	10.36±0.20	1.113±0.07	26.79±0.24
F7	0.359 ±0.04	0.398±0.03	6.94±0.13	1.065±0.03	29.52±0.14
F8	0.294 ±0.05	0.324±0.04	7.53±0.07	1.084±0.03	27.95±0.15
F9	0.357 ±0.04	0.397±0.03	5.36±0.13	1.05±0.08	27.13±0.26

Post compression parameter of ginger extract

The prepared ginger extract tablets were evaluated by the thickness, hardness, friability, weigh variation, and drug content as given in table

Table 4. Post compression parameter of ginger extract

Formulation Code	Thickness	Hardness	Friability	Weight Variation	Drug content
F1	4.38±0.4	4.5±0.27	0.32±0.08	445.29±2.6	99.87%
F2	4.63±0.32	4±0.24	0.28±0.06	444.23±4.4	98.63%
F3	4.98±0.61	3.5±0.21	0.34±0.12	439.57±11.1	98.96%
F4	4.72±0.5	4.5±0.31	0.30±0.28	442.54±8.6	99.53%
F5	4.61±0.98	4±0.25	0.36±0.08	445.33±3.4	98.93%
F6	4.62±0.7	4.5±0.32	0.26±0.07	445.66±2.4	99.31%
F7	4.82±0.36	4±.30	0.32±0.06	446.01±2.5	99.78%
F8	4.58±0.44	4±0.29	0.31±0.14	446.66±2.6	98.64%
F9	4.42±0.13	4.5±0.33	0.38±0.08	446.24±2.8	98.34%

In vitro drug release studies of core tablets:

The release rate of the ginger extract was determined using USP dissolution testing apparatus-1 (basket method). The dissolution medium was 900 ml 0.1N HCL for 1hrs. The tablet was kept in the basket and the temperature was maintained at 37±0.5 °c with a stirring rate was 50 rpm. After a specific time, interval sample was withdrawn and replaced with fresh dissolution media for core tablets 900 ml of 6.8 pH phosphate buffer was used as dissolution media. The samples were filtered and the absorbance of these solutions was measured at about 281 nm, using acid stage media as blank and at 281 nm using buffer as blank using a UV spectrophotometer. The percentage of drug release was plotted against time to determine the release profile. The formulation which shows the most satisfactory result is f1, where the drug released a maximum of 84.05% in 1 hrs. Remaining were respectively, released started and reached maximum, f2 at 83.75%, f3 at

81.04% f4 at 79.78% f5 at 83.82%, f6 at 83.96%, f7 at 81.6%, f8 at 79.78%, f9 at 83.50% in 1hrs. The cumulative percentage releases of zingiber officinale extract from the tablets were shown in table 3. And figure 6-7.

Table 5. % drug release of formulated batches.

	% Drug release								
Time	**Formulation batches**								
(min)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
5	5.014	4.821429	4.371429	3.278571	3.535714	2.057143	2.764286	5.785714	5.592857
10	12.792	12.27857	11.57143	11.89286	9.707143	7.392857	8.935714	14.27143	13.24286
20	22.564	22.05	21.72857	22.43571	19.28571	15.68571	17.61429	25.07143	22.37143
30	34.585	34.45714	32.59286	35.16429	31.05	28.41429	30.08571	36.83571	33.87857
40	48.278	48.21429	44.87143	49.05	46.86429	44.03571	45.70714	49.88571	47.7
50	65.185	64.86429	58.56429	63.25714	64.02857	60.55714	63.12857	63.96429	64.47857
60	84.05	83.75	81.04	79.78	83.82	83.96	81.6	79.78	83.50714

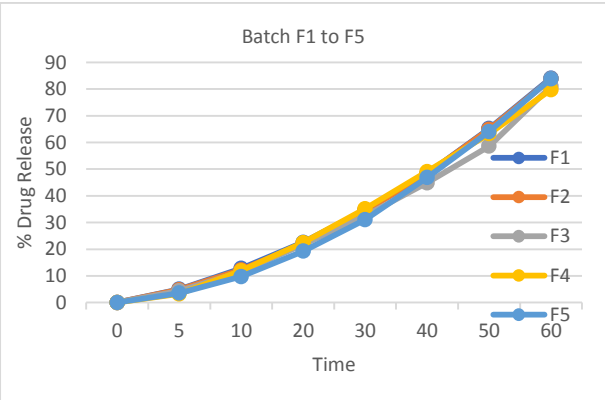


Figure 5. % Drug release of batch f1 to f5

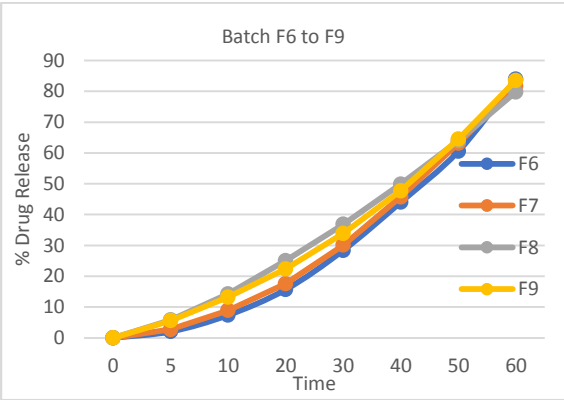


Figure 6. % Drug release of batch f6 to f9

DOE specification

DOE was used to assess the impact of factors on tablet disintegration and medication release. Using response surface design, variables were optimized.

However, it was discovered that factors had no appreciable impact on the effectiveness of tablet drug release.

To investigate the impact of formulation and processing parameters on the drug release and tablet disintegration time, a total of 9 tests were conducted.

Since a linear function of the independent variables provides a good fit to the responses collected for this investigation, the function's first-order polynomial was employed to approximate it [22].

$Y = \beta_0 + \beta_1 x_1 + \beta_2 x_2$

The values of response surface y_1 (% drug release) and y_2 (disintegration time) range from 79.18% to 84.05 % and 37min to 53 min respectively.

Anova was applied to determine the significance and magnitude of the effects of the main variable and their interaction. The regression model obtained was used to generate the counterplots for independent factors.

Y_1 (% drug release) = -18.89+1.94*a + 0.41*b

Y_2 (disintegration time) = +40+0.3964*a- 6.82*b

A positive sign in the above equation represents synergistic effects and a negative sign indicates antagonistic effects. A positive sign of the y_1 equation shows an increase in % drug release with an increase in conc. Of super disintegrant. The negative sign of the y_2 equation shows a decrease in disintegration time with an increase in superdisinitgrant concentration.

The relationship between the dependent and independent variables was further evaluated by using contour plots

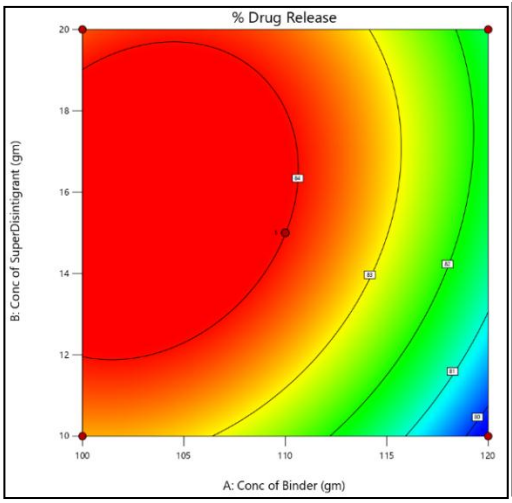


Figure 7. Counter plot for % Drug release.

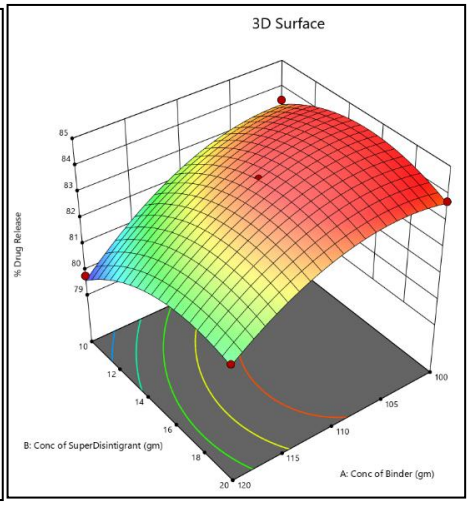
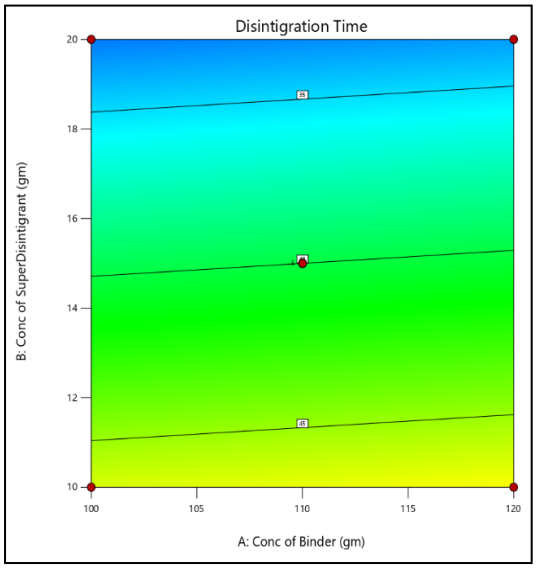


Figure 8. 3D surface graph for the % Drug release.

Figure 8 shows the effects of factors a & b on response y_1, it was observed that % the drug release of formulation increases with a high concentration of super disintegrant and a low concentration of binder.



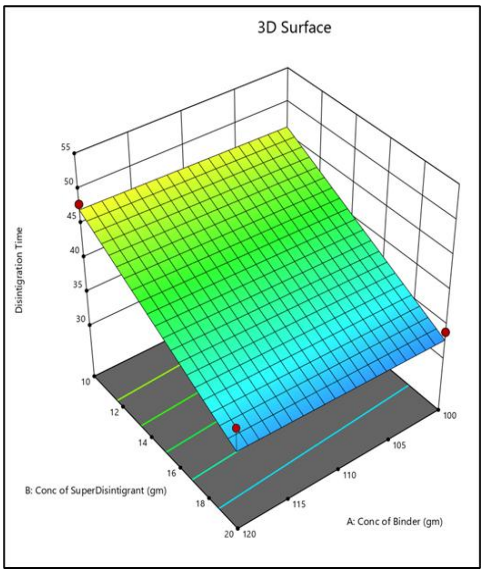


Figure 9. Counter plot for Disintegration time. **Figure 10. 3D surface graph for disintegration time.**

The figure 10 shows the effects of factors a & b on response y_2, it was observed that the disintegration time of formulation decreases with a high concentration of super disintegrant and a low concentration of binder.

Evaluation of enteric-coated tablet

Table 6. Evaluation of enteric-coated tablet

Enteric coated tablet	Thickness	Hardness	Friability	Weight variation	Disintegration Time in phosphate buffer	Drug content
	5.12±0.62	5±0.32	0.35±0.06	445.29±2.6	53 min	89.53%

In vitro drug release studies coated tablets:

Using the USP dissolving testing apparatus-1 (basket method), the release rate of the ginger extract from coated tablet was calculated. 900 ml of 0.1N HCL for two hours and 1 hour of 6.8 pH phosphate buffer, this dissolution medium was used to study drug release. The temperature was maintained at 37° C with a 50rpm stirring rate while the tablet was kept in a basket. The samples were filtered, and a UV spectrophotometer was used to measure the absorbance of these solutions at about 281 nm using buffer as the blank and acid stage media as the blank. To determine the drug release profile, percentage of drug release was plotted against time. Prepared coated tablet shows drug release 86.78 % at 180 min. İn intestinal pH and no drug release in gastric fluid.

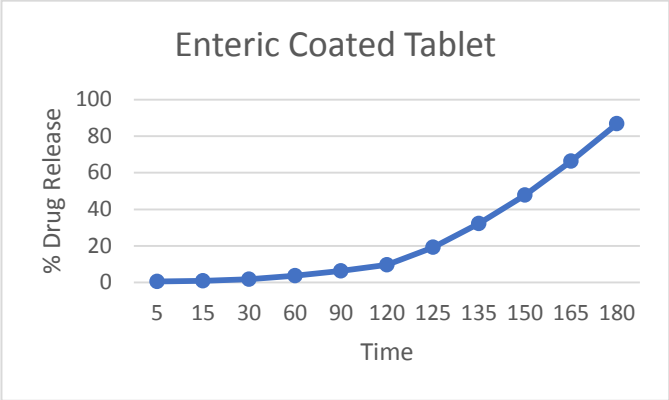


Figure 11. % drug release of enteric-coated tablet.

Conclusion:

Ginger extract is an acid-sensitive medication that breaks down in the stomach's acidic pH. Enteric coating of the medication was tried in an effort to restrict the release in the stomach and speed up release in the intestine. The f1 formulation of the core tablet was chosen among the other formulations because it had a better medication release and disintegration time. This improved formulation was utilized to make tablets with enteric coating. By using the dipping approach, an enteric coated delayed release formulation was effectively created, giving no drug release after 1 hour in 0.1 N HCL and drug release after 1 hour in pH 6.8 phosphate buffer. According to FTIR characterization of the drug and excipients it was observed that there was no interaction between the drug and the polymer.

References:

[1] Manack AN, Buse DC, Lipton RB. Chronic migraine: epidemiology and disease burden. Current pain and headache reports. 2011 Feb;15:70-8.doi:10.1007/s11916-010-0157-z

[2] Goadsby, P. Pathophysiology of migraine. Annals of ındian academy of neurology 2012;15(5): 15 Eadie MJ. The pathogenesis of migraine–17th to early 20th century understandings. Journal of clinical neuroscience. 2005 May 1;12(4):383-8.doi:10.4103/0972-2327.99993

[3] Sun J, Li H, Sun J, Liu H, Chen J, Wang C. Chemical composition and antimigraine activity of essential oil of Angelicae dahuricae radix. Journal of medicinal food. 2017 Aug 1;20(8):797-803. doi:10.1089/jmf.2016.3898

[4] Khan J, Al Asoom Lı, Al Sunni A, Rafique N, Latif R, Al Saif S, Almandil Nb, Almohazey D, Abdulazeez S, Borgio Jf. Genetics, pathophysiology, diagnosis, treatment, management, and prevention of migraine. Biomed pharmacother. 2021 March; 1(139):111557.doi:10.1016/j.biopha.2021.111557

[5] Bode, A.; Dong, Z. The amazing and mighty ginger. Oxidative stress and disease herbal medicine. 2011:131–156.doi:10.1201/b10787-8

[6] Nievergelt A, Huonker P, Schoop R, Altmann KH, Gertsch J. Identification of serotonin 5-HT1A receptor partial agonists in ginger. Bioorganic & medicinal chemistry. 2010 May 1;18(9):3345-51.doi:10.1016/j.bmc.2010.02.062
[7] Nanda RN, Arthur GP, Johnson RH, Lambie DG. Cimetidine in the prophylaxis of migraine. Acta Neurologica Scandinavica. 1980 Aug;62(2):90-5.doi:10.1111/j.1600-0404.1980.tb03008.x
[8] Mannaioni PF, Giannella E, Palmerani B, Pistelli A, Gambassi F, Bani-Sacchi T, Bianchi S, Masini E. Plenary lecture Free radicals as endogenous histamine releasers. Agents and actions. 1988 May;23:129-42.doi:10.1007/bf02142522
[9] Mustafa T, Srivastava KC. Ginger (Zingiber officinale) in migraine headache. Journal of Ethnopharmacology. 1990 Jul 1;29(3):267-73.doi:10.1016/0378-8741(90)90037-t
[10] Martins LB, Rodrigues AM, Rodrigues DF, Dos Santos LC, Teixeira AL, Ferreira AV. Double-blind placebo-controlled randomized clinical trial of ginger (Zingiber officinale Rosc.) addition in migraine acute treatment. Cephalalgia. 2019 Jan;39(1):68-76.doi:10.1177/0333102418776016.
[11] Arcusa R, Villaño D, Marhuenda J, Cano M, Cerdà B, Zafrilla P. Potential role of ginger (Zingiber officinale Roscoe) in the prevention of neurodegenerative diseases. Frontiers in Nutrition. 2022:374.doi:10.3389/fnut.2022.809621
[12] Catteau D, Barthelemy C, Deveaux M, Robert H, Trublin F, Marchandise X, Van Drunen H. Contribution of scintigraphy to verify the reliability of different preparation processes for enteric coated capsules. European journal of drug metabolism and pharmacokinetics. 1994 Jun;19:91-8.doi:10.1007/bf03188829
[13] Bushra R, Shoaib MH, Aslam N, Mehmood ZA, Hashmat D. Enteric coating of ibuprofen tablets (200 mg) using an aqueous dispersion system. Brazilian journal of pharmaceutical sciences. 2010;46:99-107.doi:10.1590/s1984-82502010000100011
[14] Marvola M, Nykänen P, Rautio S, Isonen N, Autere AM. Enteric polymers as binders and coating materials in multiple-unit site-specific drug delivery systems. European journal of pharmaceutical sciences. 1999 Feb 1;7(3):259-67.doi:10.1016/S0928-0987(98)00032-3
[15] Prasanthi D, Prashanti S, Meghana G. Formulation and evaluation of press coated tablets of lansoprazole. International Journal of Applied Pharmaceutics. 2019 May;11(4). doi:10.22159/ijap.2019v11i4.32617
[16] Mian SS, Upadhayay S, Naqvi SN. Physicochemical Analysis of Ginger (Zingiber officinale Rosc.) Rhizome along with its TLC, HPLC and HPTLC Profile. Pharmaceutical Methods. 2019 Jan 1;10(1).doi:10.5530/phm.2019.1.6
[17] Shervington A, Tayyem R. Arginine. Profiles of drug substances, excipients and related methodology. 2001;27:1-32.doi:10.1016/s1075-6280(01)27003-7
[18] Prajapati ST, Patel PB, Patel CN. Formulation and evaluation of sublingual tablets containing Sumatriptan succinate. International journal of

pharmaceutical investigation. 2012 Jul;2(3):162.doi:10.4103%2f2230-973x.104400

[19] Pan XM, Li J, Gan R, Hu XN. Preparation and in vitro evaluation of enteric-coated tablets of rosiglitazone sodium. Saudi Pharmaceutical Journal. 2015 Oct 1;23(5):581-6.doi:10.1016/j.jsps.2015.02.018

[20] Enayatifard R, Saeedi M, Akbari J, Tabatabaee YH. Effect of hydroxypropyl methylcellulose and ethyl cellulose content on release profile and kinetics of diltiazem HCl from matrices. Tropical Journal of Pharmaceutical Research. 2009;8(5).doi:10.4314/tjpr.v8i5.48086

[21] Raval MK, Ramani RV, Sheth NR. Formulation and evaluation of sustained release enteric-coated pellets of budesonide for intestinal delivery. International journal of pharmaceutical investigation. 2013 Oct;3(4):203.doi:10.4103%2f2230-973x.121294

[22] Kilor VA, Sapkal NP, Awari JG, Shewale BD. Development and characterization of enteric-coated immediate-release pellets of aceclofenac by extrusion/spheronization technique using κ-carrageenan as a pelletizing agent. AAPS PharmSciTech. 2010 Mar;11:336-43.doi:10.1208%2fs12249-010-9389-9