A Novel Bilayer Gastro-Retentive Tablet of Ondansetron and Ginger Extract: Optimization, In-Vitro Evaluation, and Drug Release Kinetics

Tambe Sujit Tukaram[1]*, Kaliyaperumal Saravana[2],

[1,2]Department of Research, Bhagwant University, Ajmer, Rajasthan, India

[1]tambesujit05@gmail.com,

[2]kalyansar_mith@yahoo.co.in

***Abstract*- The present study focuses on the development of a gastro-retentive bilayer tablet combining Ondansetron hydrochloride and standardized ginger extract to enhance therapeutic effectiveness in chemotherapy-induced nausea and vomiting (CINV), radiotherapy-induced nausea and vomiting (RINV), and postoperative nausea and vomiting (PONV). Ondansetron, a BCS Class II drug with pH-dependent solubility and a short elimination half-life, requires sustained gastric residence to improve its oral bioavailability. Ginger extract, containing 75 mg GAE/tablet, offers complementary antiemetic activity and is incorporated as an immediate-release layer to provide rapid onset of action. A bilayer tablet system was formulated using sodium bicarbonate as a gas-generating agent and Hydroxypropyl Cellulose (HPC) and Ethyl Cellulose (EC) as polymeric components for floating and sustained-release characteristics. Nine formulations (F1–F9) were prepared with varying polymer concentrations, and evaluated for physicochemical parameters, buoyancy behavior, drug content, and in-vitro drug release. All formulations complied with pharmacopoeial limits for hardness, friability, disintegration time, and weight variation. The floating lag time ranged from 9.25 to 10.25 minutes for bilayer tablets, and total floating time extended up to 24 hours, particularly in formulations with higher HPC content. In-vitro release data showed that the ginger layer released > 93% of phenolic content within 40 minutes, while Ondansetron release was sustained for 24 hours in selected batches. Formulation F6 exhibited optimal buoyancy and sustained-release performance, achieving 97.8% Ondansetron release at 24 hours. Kinetic modeling demonstrated that the Hixson–Crowell model provided the best fit (R^2 = 0.9933), indicating erosion-controlled release. The Korsmeyer–Peppas diffusional exponent (n = 1.0945) confirmed Super Case II transport, signifying a mechanism governed by polymer relaxation, swelling, and erosion rather than simple diffusion. Overall, a gastro-retentive bilayer tablet combining immediate-release ginger extract with a floating sustained-release layer of Ondansetron was successfully developed. The optimized formulation offers the potential for improved patient compliance, enhanced gastric retention, and once-daily dosing for the effective management of nausea and vomiting.**

Keywords: Ginger extract, bilayer, buoyancy time, sustained release, gastric retention

INTRODUCTION

The systemic availability of orally ingested drug moiety is of great concern as far as the gastrointestinal transit time is considered. The drugs having short half life require the suitable approach for sustaining the drug release and minimizing dosing frequency. Ondansetron is the drug of interest used in CINV, RINV, or PONV. It is a weakly basic drug belonging to BCS Class II, having solubility 23.3 g/L in stomach below pH 1.2. Its intestinal solubility is poor, around 0.036 g/L above pH 6.8. The recommended oral dose is 8 mg thrice a day [13,12]. The gastro-retentive approach has been used to sustain the drug release and once-a-day formulation has been developed [3,4].

Moreover, the antiemetic activity of ginger extract is well established with animal studies by S.S. Sharma et al. in cisplatin-induced emesis. Its effect is primarily attributed to bioactive compounds like gingerols and shogaols, which antagonize serotonin (5-HT3)

and cholinergic (M3) receptors and enhance gastrointestinal motility resulting in reduced nausea and vomiting in various contexts such as chemotherapy, surgery, pregnancy, and acute gastroenteritis [2,14,1].

The effectiveness of ginger as a component of antiemetic regimens has been well established. Studies report that using both agents together decreases the incidence and severity of PONV compared to ondansetron alone. Ginger offers a natural, safe, and cost-effective addition to conventional pharmacotherapy, making it particularly useful where cost and safety are important [1,2,5].

The combination of ginger and ondansetron in tablet formulation and use of gastro-retentive approach for the same will help the sustained drug release, as ondansetron has a short half-life [3,4,6]. The present study aims to formulate a bilayer tablet with one layer floating over 24 hours to sustain the release of ondansetron and the other layer showing conventional release of ginger extract. The effective treatment option for CINV, RINV, and PONV can be achieved through the present approach. The ginger extract layer is optimized separately for its disintegration and then compressed with the ondansetron layer. The ondansetron floating layer is formulated with gas forming agent sodium bicarbonate and polymers like HPC and EC used for gas entrapment and drug release retardants. The effect of concentration of HPC and EC is related to the buoyancy and drug release rate from the floating layer [3,4,5].

MATERIALS AND METHODS

Materials: Ondansetron hydrochloride is obtained as a gift sample from Hetero Drugs Private Ltd (Hyderabad). Hydroxy Propyl Cellulose, Ethyl cellulose and Sodium bicarbonate are purchased from A.G. Traders. The ginger extract is purchased from Hiya India Ltd (New Delhi).

Standardized Ginger extract: The ethyl acetate extract of ginger roots contains highest phenolic contents and standardized extract having Total Phenolic Contents 250mg GAE/g of extract is used for the formulation.

Preparation of gingers extracts granules: The granules of standardized ginger extract are prepared for the immediate release layer. The amount of ginger extract taken is 300mg which is equivalent to 75mg GAE/Tablet. Starch is used as disintegrant and lactose as a diluent. The granules are prepared by wet granulation method using ethanol as a solvent. Water is avoided because this layer will be in immediate contact with sodium bicarbonate which a gas is forming agent used in floating layer. The flow properties of granules are evaluated and reported.

Method of Preparation of Bilayer tablet: Total six batches of bilayer tablets are prepared containing varying concentrations of excipients, with one floating layer and other immediate release layer. The floating layer is prepared using gas forming agent sodium bicarbonate. It generates gas in contact with gastric acid and the gas is entrapped in polymer matrix of Hydroxy Propyl cellulose and ethyl cellulose resulting in reduced density of formulation layer (<1 g/cc) which tends to float the layer over a longer time.

Ondansetron Hydrochloride, Hydroxy Propyl Cellulose, Ethyl Cellulose and Lactose are taken as per formulation table and mixed thoroughly. The weighed amount of this powdered mixture (260mg) is filled manually in die cavity and subjected for compression to form a primary layer. The weighed amount of ginger extract granules (350mg) are filled manually over the primary layer and subjected for the compression. The thickness and hardness are adjusted on trial and error basis during compression.

TABLE I: Formulation of Bilayer tablet

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Formulation of Floating Layer (Weights in mg)									
Ondansetron Hydrochloride	27	27	27	27	27	27	27	27	27
Hydroxy Propyl Cellulose	80	90	100	80	90	100	80	90	100
Ethyl Cellulose	50	50	50	40	40	40	30	30	30
Sodium Bicarbonate	70	70	70	70	70	70	70	70	70
Lactose	28	18	8	38	28	18	48	38	28
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Formulation of Immediate Release Layer (Weights in mg)									
Standardized Ginger Extract	300	300	300	300	300	300	300	300	300
Starch	15	15	15	15	15	15	15	15	15
Lactose	30	30	30	30	30	30	30	30	30
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Total (mg)	**610**	**610**	**610**	**610**	**610**	**610**	**610**	**610**	**610**

In-Vitro Characterization of Tablets:

Disintegration Time of Immediate Release layer: Disintegration time of the immediate layer (Ginger extract layer) is determined using Disintegration Test Apparatus IP. Test is performed for 6 tablets and DT is recorded.

Tablet Hardness: Tablet hardness is determined using Pfizer Hardness tester for 20 tablets and Mean hardness with standard deviation is reported.

Thickness: Thickness of 20 tablets is measured using Vernier Calliper and mean is expressed in mm with standard deviation.

Friability Test: The test is performed to determine resistance of tablet to abrasion or shock during handling, packaging, and transportation. It is performed on Roche Friabilator. 15 Tablets are weighed and put in Roche Friabilator which is operated at 25 rpm for 04 minutes. The tablets are weighed again and percent weight loss is determined and expressed as percent friability.

Weight Variation Test: 20 tablets are weighed individually and average tablet weight is determined. The individual tablet weight is compared with average tablet weight and percent deviation is determined. As per Indian Pharmacopoeia, for tablets having Avg weight more than 300mg, NMT 02 tablets show 5% deviation from average weight and not a single tablet shows more than 10% deviation from average weight.

Floating Lag Time: The time required for tablet to come out to the surface is called Floating lag time (FLT). It is determined for 10 tablets in 10 separate beakers containing 200ml, 0.1N HCl kept at 37.0 ^{0}C. The time for all 10 tablets to come out at the surface is recorded and expressed as mean in minutes with standard deviation.

Buoyancy Time (Total Floating Time): It is time for which the tablet remains buoyant on the surface. It is studied along the in-vitro drug release study in type II dissolution test apparatus. Total floating time of 06 tablets is determined and expressed as mean with standard deviation for each batch.

Drug Content: To determine Ginger content, 10 tablets are crushed and powder equivalent to 300mg of standardized ginger extract is weighed and dissolved in 100 ml of water. 1 ml of this solution is diluted to 10ml with water and again 1 ml to 10ml (Dilution factor 100). The absorbance is then measured at 760nm wavelength. The Total Phenolic Content is then determined from Gallic acid calibration curve and expressed as mg GAE/Tablet. 75mg GAE/Tablet is considered as 100% content for calculation.

To determine Ondansetron content, 10 tablets are crushed and powder equivalent to 27mg of Ondansetron hydrochloride is weighed and dissolved in 100 ml of water. Diluted 5 ml of this solution to 100ml with water and absorbance was measured at 310nm wavelength. The percent drug content is determined from calibration curve of Ondansetron hydrochloride.

In-vitro Drug Release Study: The drug release study is done using USP type II (Paddle Method) apparatus. 900 ml 0.1N HCl (pH 1.2) is used as a dissolution medium. The paddle is rotated at 100rpm and temperature is set at 37 ^{0}C. Initially 5ml samples are withdrawn at 10 minutes intervals for first 1 hour, diluted to 50ml with water and absorbance is measured at 760nm. The TPC is estimated using Gallic Acid calibration curve. TPC at each time interval is expressed as percent release of ginger extract. The TPC of 75mg GAE/tablet is considered for calculation of percent release of ginger extract. To determine Ondansetron HCl release, 5ml samples are withdrawn 2 hourly and absorbance is measured at 310nm. The percent drug release is determined using calibration curve of Ondansetron HCl. 27mg/tablet is considered for calculation of percent drug release.

Selection of Optimized batch: The optimized batch is selected from the buoyancy time and drug release behavior of the formulation. The drug release and buoyancy of about 24 hours is expected for the formulation. The optimized batch is further subjected to different kinetic models.

Kinetic Models for Drug Release: The drug release data of the optimized formulation is subjected to different kinetic models such that Zero order model, First order model, Higuchi model and Hixon-Crowell Model. The best fitted model for optimized batch is selected from R^2 values of their concerned graphs.

Drug Release Mechanism: Korsemeyer-Peppas model is applied to the drug release data of an optimized batch and the diffusional exponent n is determined graphically. The value of diffusional exponent n, predicts the probable mechanism of dug release.

RESULT AND DISCUSSION

Disintegration Time of Immediate Release layer: Disintegration time for all formulations is as per Table II, and found to be within limits (Not More Than 15 Minutes), prescribed by Indian Pharmacopoeia.

Tablet Hardness: Tablet hardness for all formulated batches is set on trial and error basis during compression and found to have values as per Table II, which are within acceptable limits.

Thickness: Thickness of 20 tablets is measured using Vernier Calliper and mean is expressed in mm with standard deviation as mentioned in Table II.

Friability Test: The calculated percent friability for all batches is within acceptable limits (<1%) as mentioned in Table II.

Table II: DT, Hardness, Thickness and Friability Test

Batch	Disintegration Time (Minutes)	Hardness (Kg) Mean with SD#	Thickness (mm) Mean with SD#	Friability (%)*
F1	5.0	5.35, 0.7280	5.33, 0.6352	0.5447
F2	4.5	5.85, 0.8236	5.26, 0.7381	0.2193
F3	4.0	4.95, 0.6983	5.18, 0.6821	0.7650
F4	5.0	5.45, 0.8665	5.17, 0.7314	0.5470
F5	5.5	4.95, 0.3562	5.24, 0.3962	0.4367
F6	4.0	4.85, 0.6582	5.36, 0.6428	0.3293
F7	5.5	5.35, 0.8146	5.26, 0.7542	0.4381
F8	5.0	4.65, 0.7213	5.31, 0.8631	0.2193
F9	5.0	5.15, 0.7356	5.21, 0.8235	0.6557
# Number of tablets tested = 20				
* Number of tablets tested = 15				

Weight Variation Test: Individual weight of 20 tablets is compared with average weight and percent deviation is mentioned in Table III. As per Indian Pharmacopoeia, for tablets having Avg weight more than 300mg, NMT 02 tablets show 5% deviation from average weight and not a single tablet shows more than 10% deviation from average weight. NMT 02 tablets show 5% deviation from avg weight and not a single tablet shows more than 10% deviation from average weight. Hence Tablets pass the weight variation test as per I.P.

TABLE III: Weight Variation Test

Tablet No	Individual Tablet Weight	Average Tablet Weight	% Deviation
1	610	610	0.00
2	620	610	1.64
3	630	610	3.28
4	590	610	-3.28
5	630	610	3.28
6	610	610	0.00
7	620	610	1.64
8	590	610	-3.28
9	600	610	-1.64

10	610	610	0.00
11	630	610	3.28
12	640	610	4.92
13	570	610	-6.56
14	600	610	-1.64
15	610	610	0.00
16	620	610	1.64
17	570	610	-6.56
18	620	610	1.64
19	630	610	3.28
20	600	610	-1.64

Floating Lag Time: The floating lag time is for all formulated batches is mentioned is Table IV. As mentioned in table, with the presence of ginger layer, the lag time of floating layer is slightly extended. It may be attributed to the increased tablet density due to presence of ginger layer.

Buoyancy Time (Total Floating Time): The Buoyance time for all batches is mentioned in Table IV and if compared, it can be observed that buoyancy extended to smaller extent with increasing concentration of Hydroxy Propyl Cellulose. It may be attributed to its enhanced gas entrapment efficiency at higher concentrations.

TABLE IV: Floating Lag Time and Total Floating Time

Batch	**Floating Lag Time of Floating Layer alone (Minutes) Mean with SD#**	**Floating Lag Time of Bilayer Tablet (Minutes) Mean with SD#**	**Total Floating Time (Hours) Mean with SD***
F1	06.55, 1.0862	09.25, 1.2288	22.00, 0.8185
F2	07.25, 1.2413	09.55, 0.8775	22.83, 0.6856
F3	05.50, 0.7251	09.50, 1.2042	24.08, 0.6083
F4	06.90, 1.1759	09.85, 1.0247	21.83, 0.6856
F5	07.35, 0.7542	09.90, 1.2410	23.00, 0.6481
F6	06.30, 1.1376	10.00, 1.118	24.17, 0.4690
F7	06.50, 0.9632	09.95, 0.7550	21.37, 0.7874
F8	05.80, 1.1134	09.60, 0.8000	22.08, 0.6708
F9	06.30, 0.7154	10.25, 0.7483	23.17, 0.4690
# Number of tablets tested = 10			
*Number of tablets tested = 06			

Drug Content: The drug content with respect to Ondansetron HCl in percent is mentioned in Table V along with standard deviations. For determination of Ginger content, Total Phenolic Contents are determined and percent content is calculated by taking 75mg GAE/Tablet as 100%.

TABLE V: Drug Content

Batch	Ondansetron content with SD*	Ginger content with SD*
F1	99.07%, 1.1296	98.90%, 0.8432
F2	99.50%, 1.2194	99.50%, 1.3587
F3	98.97%, 0.9960	101.20%, 0.9617
F4	99.51%, 1.7003	100.70%, 1.2643
F5	99.38%, 1.8893	99.70%, 1.4162
F6	99.32%, 0.9755	99.50%, 0.8358
F7	98.28%, 0.9442	98.80%, 1.3516
F8	98.59%, 2.2439	100.50%, 0.8712
F9	99.45%, 1.8768	101.00%, 1.1429

***In-vitro Drug Release Study*:** The *In-Vitro* drug release study revealed that the immediate-release layer gives around 93% release of ginger extract in 40 minutes, calculated on the basis of TPC expressed as mg GAE/Tablet. It complies with IP limits of dissolution study.

The percent drug release with time for ondansetron is mentioned in Table VI for all formulated batches. The concentration of ethyl cellulose alters the drug release rate. The lower concentration shows comparatively faster drug release rate. At higher concentrations, ethyl cellulose is found to retard the drug release rate. Formulations F4, F5 and F6 show desired drug release in about 24 hours. Conclusively the ethyl cellulose serves as drug release retardant and its concentration shall be optimized to get desired release rate.

TABLE VI: *In-vitro* drug release of Ondansetron

Time (Hours)	% Drug Release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	19.65	17.50	15.50	20.50	23.65	25.54	28.65	23.56	24.80
4	33.24	30.56	29.15	35.42	38.40	42.50	48.65	42.08	43.65
6	43.82	42.01	40.80	45.69	48.69	53.65	65.20	56.72	58.05
8	52.88	50.26	49.05	54.65	57.03	62.53	78.00	67.25	69.35
10	60.12	58.02	55.55	62.56	65.45	70.52	87.62	75.80	77.95

12	66.02	63.59	61.17	68.45	71.65	76.32	92.56	82.50	84.50
14	70.02	68.55	65.70	74.05	77.35	82.03	97.35	87.25	90.50
16	74.23	72.54	69.56	77.63	80.86	86.01	98.87	91.02	94.90
18	77.98	76.51	72.21	80.98	84.50	89.52	99.84	93.24	97.80
20	81.02	79.23	74.01	84.20	87.69	92.20	-	95.20	98.90
22	83.57	81.50	75.03	86.30	90.20	95.60	-	-	-
24	86.23	83.10	76.01	88.90	93.40	97.80	-	-	-

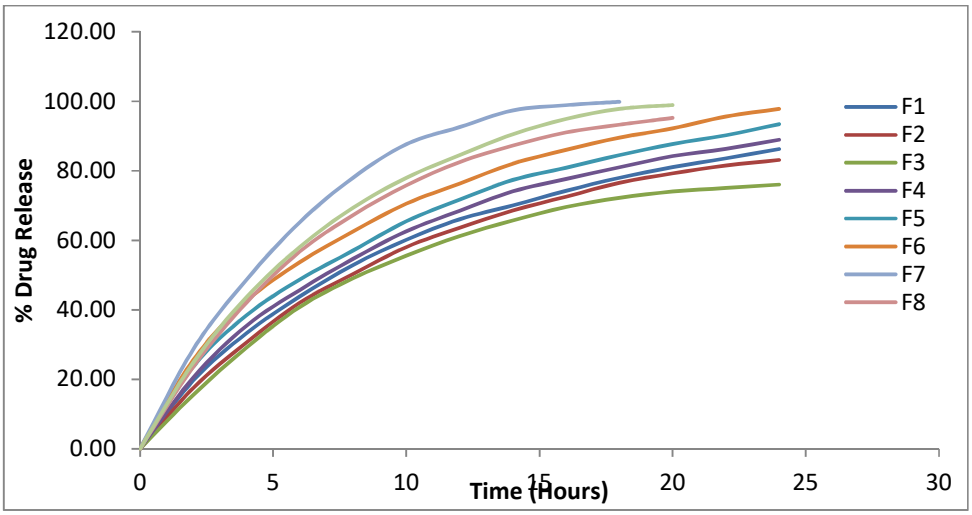

Fig. 1: Comparative Drug Release Profile

Selection of Optimized batch: On the basis of buoyancy characteristics batches F3 and F6 showed buoyancy time more than 24 hours which is desired for sustaining the drug release by increasing gastric residence time of drug. The *In-Vitro* drug release study reveals the formulation F6 being appropriately showing around 98 % drug release, till 24 hours. So from the buoyancy behavior and drug release kinetics, formulation F6 is promising and can be selected as an optimized batch.

Kinetic Models for Drug Release:

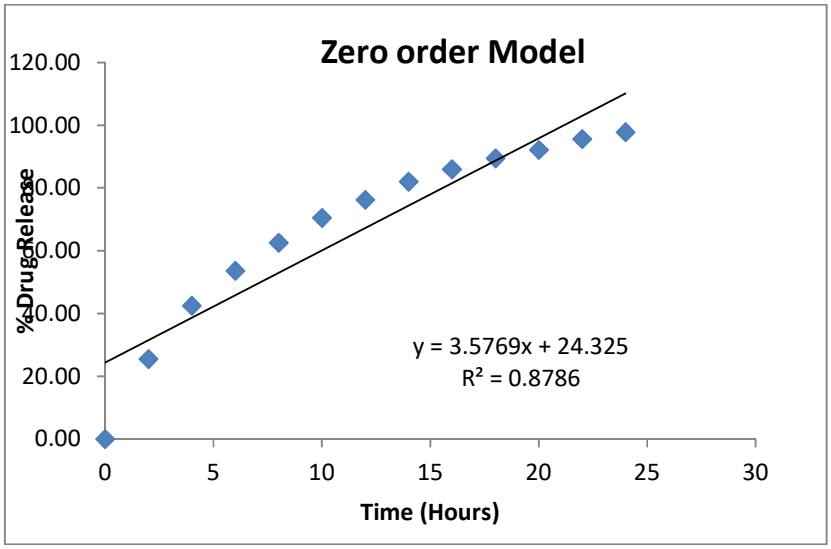

Fig. 2: Zero Order Model

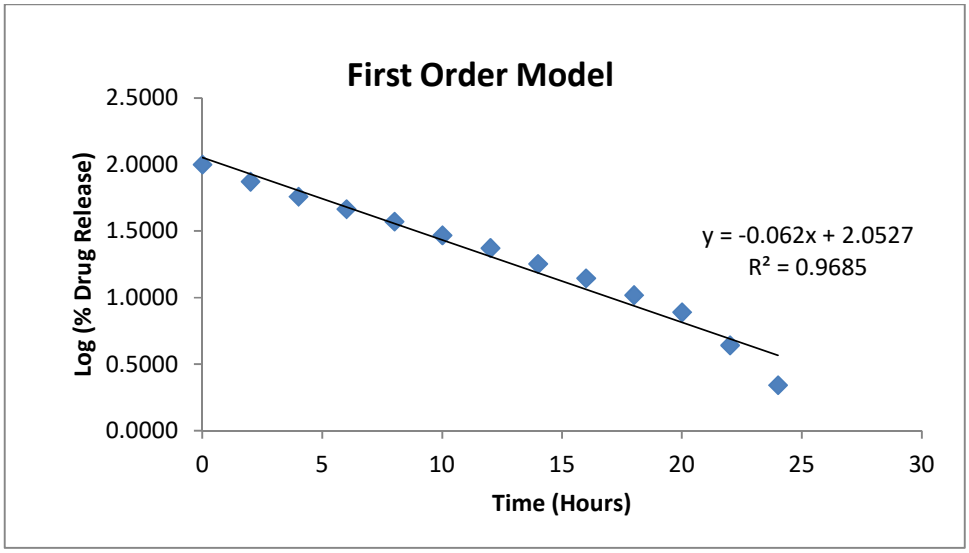

Fig. 3: First Order Model

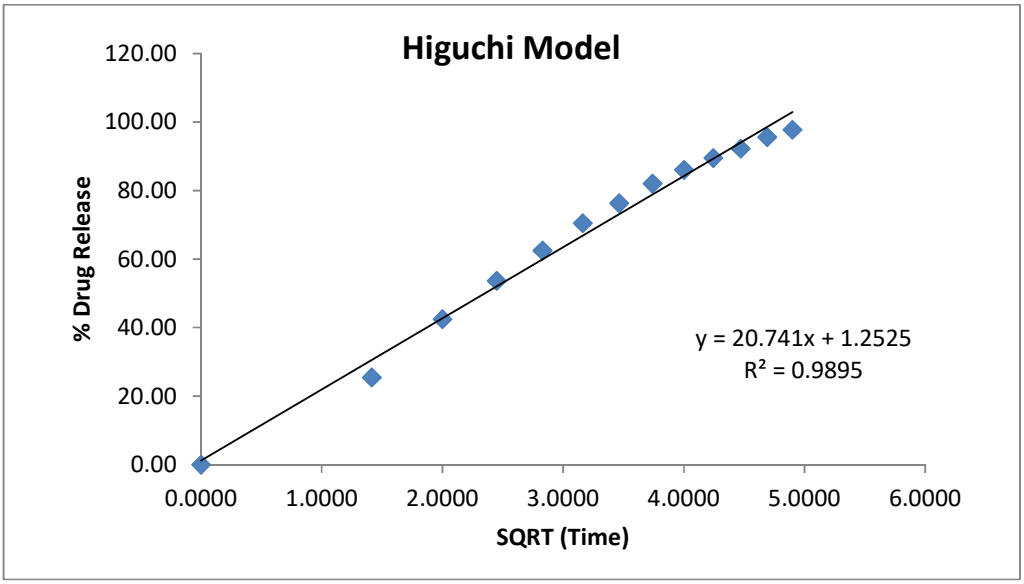

Fig. 4: Higuchi Model

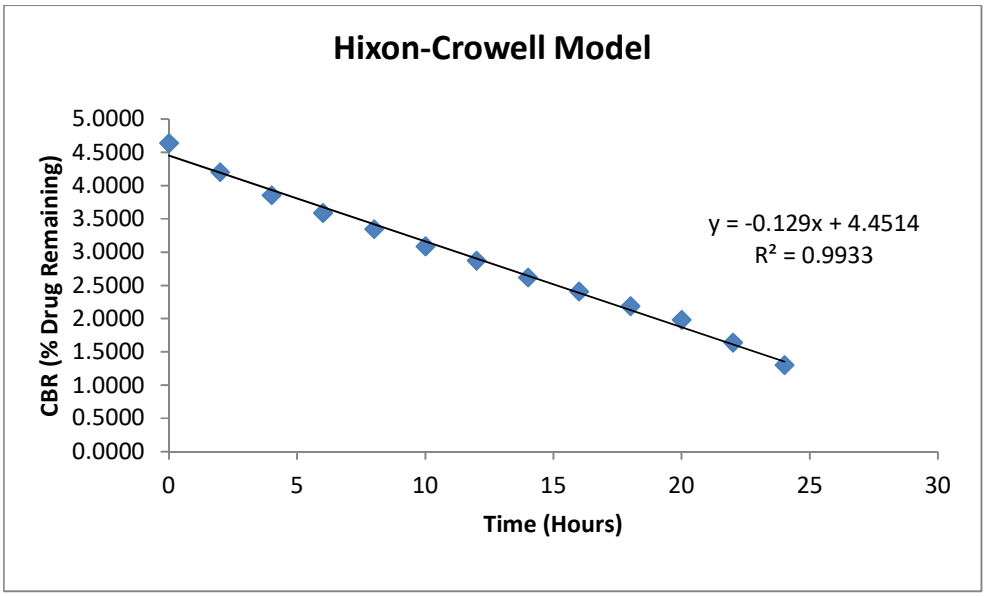

Fig. 5: Hixon-Crowell Model

The graphs for above models are plotted and the R^2 values are reported in Table 7. The Hixon Crowell model shows highest R^2 value hence can be considered as a 'Best Fitted Model'. It implies that the drug release takes place by erosion of polymer matrix.

TABLE VII: R^2 Values for Kinetic Models

Drug Release Kinetic Model	R^2 value
Zero order model	0.8786
First Order Model	0.9685
Higuchi Model	0.9895
Hixon-Crowell Model	0.9933

Drug Release Mechanism: Korsemeyer-Peppas model is applied to the drug release data of formulation F6 and the diffusional exponent n was found to be 1.0945. The drug release mechanism is Super Case II transport as per Table 8. It indicates the drug release is dominated by **polymer relaxation, swelling, and erosion**, rather than simple diffusion.

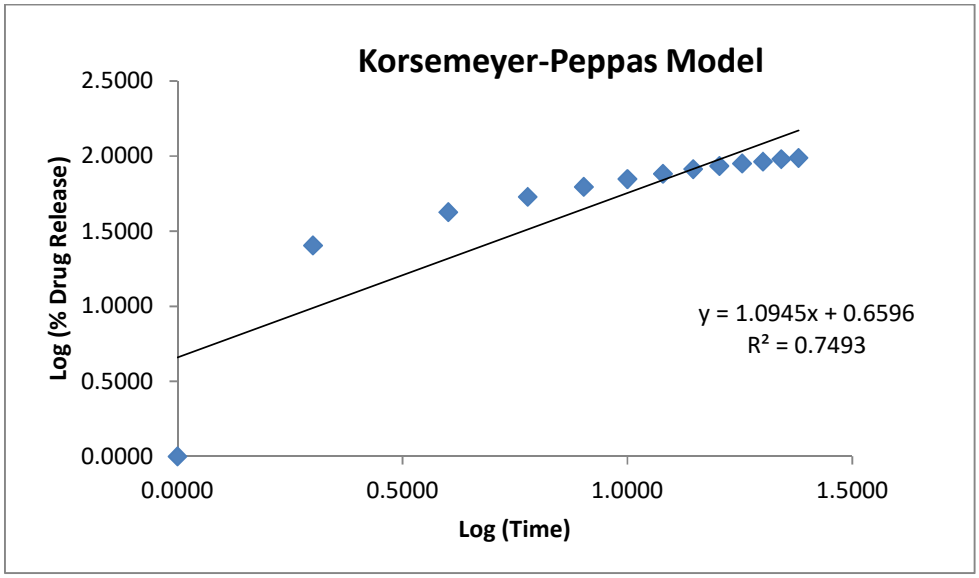

Fig. 6: Korsemeyer-Peppas Model

TABLE VIII: Drug Release Mechanism and Diffusional Exponent

Diffusional Exponent (n)	Release Mechanism
$n \leq 0.45$	Fickian Diffusion
$0.45 < n < 0.89$	Non-Fickian Diffusion
$n = 0.89$	Case II transport
$n > 0.89$	Super case II transport

CONCLUSION

The present study successfully developed a gastro-retentive bilayer tablet comprising an immediate-release layer of standardized ginger extract and a floating sustained-release layer of Ondansetron hydrochloride to enhance therapeutic management of CINV, RINV and PONV. The optimized formulation (F6), prepared using sodium bicarbonate as a gas-generating agent and Hydroxypropyl Cellulose with Ethyl Cellulose as matrix-forming polymers, demonstrated excellent buoyancy behavior with more than 24 hours of total floating time. All physicochemical evaluations complied with pharmacopoeial specifications, confirming the robustness and uniformity of the bilayer system.

The ginger extract layer achieved rapid disintegration and more than 93% release within 40 minutes, ensuring prompt onset of antiemetic activity. In contrast, Ondansetron release was effectively sustained for up to 24 hours, thereby supporting the objective of reducing dosing frequency. Drug-release kinetics revealed that the Hixson–Crowell model best described the release profile, indicating surface erosion-controlled release. Additionally, the Korsemeyer–Peppas diffusional exponent (n = 1.0945) confirmed a **Super Case II transport mechanism**, demonstrating that polymer relaxation, swelling and erosion played a dominant role in drug release.

Overall, the study establishes that the bilayer gastro-retentive system combining Ondansetron and ginger extract is a promising approach for providing both immediate and sustained antiemetic effects. This formulation has the potential to improve patient compliance, enhance gastric retention, and deliver more effective once-daily management of nausea and vomiting. Further in-vivo studies are recommended to validate its clinical applicability.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Mr. Sujit Tukaram Tambe has contributed in the selection of excipients, formulation and evaluation of the aforementioned project work. Being a supervisor Dr. Kaliyaperumal. Saravanan has guided the whole research work and the research work is conducted as per his suggestions and solutions.

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