

“FORMULATION AND EVALUATION OF ONDANSETRON BILAYER TABLET FOR BIMODAL RELEASE”

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ABSTRACT:

This study aimed to develop and evaluate an ondansetron bilayer tablet capable of providing both immediate and sustained drug release. The tablet consisted of two layers: an immediate-release layer and a sustained-release layer. The immediate-release layer was prepared using direct compression with different superdisintegrants, while the sustained-release layer was prepared by wet granulation using varying concentrations of HPMC K100M and ethyl cellulose. During the preformulation studies, ondansetron showed maximum absorbance at 310 nm. FTIR analysis indicated that the drug was compatible with all the selected excipients. Among the immediate-release formulations, IF1 produced the fastest drug release and was therefore selected for incorporation into the bilayer tablet. Among the sustained-release formulations, SF2 provided the most suitable controlled-release profile and was selected as the optimized formulation. The optimized bilayer tablet released approximately 34% of the drug within the first 20 minutes, followed by gradual and sustained release for up to 20 hours. The release profile of the bilayer tablet showed the best fit with the first-order kinetic model, with an R^2 value of 0.8456. The sustained-release formulation SF2 showed the best fit with the Higuchi model, with an R^2 value of 0.9894. The tablets maintained satisfactory physical properties during the two-month stability study. Only minor changes were observed in tablet weight, hardness, friability, thickness, and drug content. Overall, the developed ondansetron bilayer tablet demonstrated the potential to provide rapid initial drug release followed by prolonged drug delivery.

Keywords: Ondansetron, bilayer tablet, immediate release, sustained release, bimodal drug delivery, drug-release kinetics, stability study.

1. Introduction

Bilayer tablets combine an immediate-release layer and a sustained-release layer in a single pill. This design delivers a quick initial dose of the drug, followed by a slower, controlled release over many hours. As a result, patients can take fewer doses each day, which makes treatment more convenient and gives formulators greater flexibility in designing the dosage form^[1-3]. Recent progress in oral drug delivery has largely centered on creating smarter formulation approaches that give better control over how a drug is released, improve its therapeutic effectiveness, and make dosing more convenient for patients^[4].

Superdisintegrants such as croscarmellose sodium, crospovidone, and sodium starch glycolate are commonly used in immediate-release formulations because they help the tablet break apart quickly after administration^[5]. In sustained-release formulations, hydrophilic polymers such as HPMC K100M form a gel layer around the tablet. This gel layer controls drug diffusion and slows the release of the drug. Ethyl cellulose, a hydrophobic polymer, can further reduce the rate of drug release^[6,7]. The choice between direct compression and wet granulation depends on the specific formulation and the physical and chemical properties of the materials being used^[8-10].

Ondansetron is a selective 5-HT₃ receptor antagonist commonly used to prevent and treat nausea and vomiting associated with chemotherapy, radiotherapy, and surgical procedures^[11,12]. Developing a bilayer tablet containing ondansetron may provide rapid relief from nausea while maintaining drug levels over an extended period.

Therefore, the present study was designed to formulate and evaluate an ondansetron bilayer tablet capable of providing bimodal drug release. Different superdisintegrants were evaluated in the immediate-release layer, while different concentrations of HPMC K100M and ethyl cellulose were investigated in the sustained-release layer. The optimized formulations were then combined and evaluated for their physical properties, drug-release behavior, release kinetics, and short-term stability.

2. Materials and Methods

2.1 Materials

Ondansetron was obtained from Shilpa Medicare Ltd., India. Croscarmellose sodium was procured from Bangalore Fine Chem, Bengaluru, India, while crospovidone was supplied by Maple Biotech Pvt. Ltd., Pune, India. Sodium starch glycolate, hydroxypropyl methylcellulose (HPMC K100M), sodium lauryl sulfate, and lactose were obtained from Essel Fine Chem, Mumbai, India. Ethyl cellulose was purchased from Thomas Baker Chemicals Pvt. Ltd., Maharashtra, India. Polyvinylpyrrolidone K30 (PVP K30) was used as the binder. Microcrystalline cellulose (MCC) was obtained from Chemfield Cellulose Pvt. Ltd., Maharashtra, India. Magnesium stearate and talc were used as lubricant and glidant, respectively.

2.2 Equipment

The study utilized an electronic analytical balance (Essae, India), UV–Visible spectrophotometer (Shimadzu UV-1800, Japan), digital pH meter (Fisher Scientific, India), hot-air oven (Serve Well Instruments Pvt. Ltd., India), digital Vernier caliper (Mitutoyo, Japan), USP friabilator (Electrolab, India), rotary tablet compression machine (Rimek, Karnavati Engineering Ltd., India), Monsanto hardness tester (Ketan Engineering Ltd., India), tap density tester (Electrolab, India), and USP dissolution test apparatus I (basket) and II(paddle) (Electrolab, India).

2.3 Methods

2.3.1 Preformulation studies:

2.3.1.1 Determination of λ_{max} :

10mg of ondansetron was dissolved in methanol and diluted to 10 mL to obtain a stock solution (1000 $\mu\text{g/mL}$). The λ_{max} was found to be 310 nm when the solution was diluted to 10 $\mu\text{g/mL}$ and scanned from 200–400 nm using a UV–Visible spectrophotometer^[13].

2.3.1.2 Preparation of calibration curve:

A secondary stock solution (100 $\mu\text{g/mL}$) was obtained by diluting an ondansetron stock solution (1000 $\mu\text{g/mL}$) made in methanol. Working solutions of 2–16 $\mu\text{g/mL}$ were made using phosphate buffer (pH 6.8) and 0.1 N HCl. The absorbance of each solution was measured at 310 nm, and calibration curves were prepared by plotting concentration against absorbance^[13].

2.4 Drug-excipient compatibility study by FTIR:

Fourier-transform infrared spectroscopy was used to evaluate the compatibility of ondansetron with the selected excipients. The drug and drug–excipient mixtures were mixed with dry potassium bromide, compressed into pellets, and scanned using an FTIR spectrophotometer.

The resulting spectra were examined for changes in the characteristic absorption peaks of ondansetron^[14].

2.5 Preparation of Immediate-Release Tablets:

The immediate-release tablets were prepared using the direct-compression method. Ondansetron, lactose, microcrystalline cellulose, and the selected superdisintegrant were mixed for 20 minutes. Talc and magnesium stearate were then added, and the mixture was blended for an additional two minutes. The final blend was compressed into tablets weighing 100 mg each. Seven formulations, designated IF1 to IF7, were prepared using different types and concentrations of superdisintegrants^[15]. The composition of the IR tablet formulations is presented in **Table 1**.

Table No 1: Formulation of IR layer

Ingredients	Designed batch formulation in mg/tab						
	IF1	IF2	IF3	IF4	IF5	IF6	IF7
Ondansetron	8	8	8	8	8	8	8
Croscarmellose sodium	1	5	-	-	-	-	1
Sodium starch glycolate	-	-	2	8	-	-	-
Crosspovidone	-	-	-	-	2	5	-
Sodium lauryl sulphate	-	-	-	-	-	-	0.5
Avicel pH 102	70	70	70	70	70	70	70
Lactose	19.5	15.5	18.5	12.5	18.5	15.5	19
Magnesium Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Talc	1	1	1	1	1	1	1
Total weight (mg)	100	100	100	100	100	100	100

2.6 Preparation of sustained-release tablet

Sustained-release (SR) tablets were prepared by wet granulation. Ondansetron, HPMC K100M, ethyl cellulose, and microcrystalline cellulose were sieved and mixed uniformly. PVP K30 solution was added as a binder to form a wet mass, which was granulated, dried at 50°C, and resized. The dried granules were lubricated with magnesium stearate and talc and compressed into 150 mg tablets. Five formulations (SF1–SF5) containing different concentrations of HPMC K100M and ethyl cellulose were prepared^[16]. The composition of the SR tablet formulations is presented in **Table 2**.

Table No 2: Formulation of SR tablet

Ingredients	Designed batch formulation in mg/tab				
	SF1	SF2	SF3	SF4	SF5
Ondansetron	16	16	16	16	16
HPMC K 100M	30	45	60	30	60
Ethyl cellulose	15	30	45	45	15
PVPK 30	5	5	5	5	5
Microcrystalline cellulose	82.5	52.5	22.5	52.5	52.5
Magnesium stearate	0.5	0.5	0.5	0.5	0.5
Talc	1	1	1	1	1
Total weight (mg)	150	150	150	150	150

2.7 Preparation of bilayer tablets:

The optimized immediate-release and sustained-release formulations were combined to prepare the bilayer tablets. First, the sustained-release granules were placed in the die and lightly compressed. The immediate-release powder blend was then added, and the complete tablet was compressed. Each bilayer tablet contained 8 mg of ondansetron in the immediate-release layer and 16 mg in the sustained-release layer. The total tablet weight was 250 mg^[1]. The composition of the optimized bilayer tablet is presented in **Table 3**.

Table No 3: Formulation of bilayer tablet

Ingredients	Designed batch formulation in mg/tab	
	IR layer	SR layer
Ondansetron	8	16
Croscarmellose sodium	1	-
HPMC K 100	-	45
Ethyl Cellulose	-	30
PVPK 30	-	5
Avicel pH 102	69.5	-
Microcrystalline cellulose	-	52.5
Lactose	19.5	-
Amaranth	0.5	-
Magnesium Stearate	0.5	0.5
Talc	1	1
Total weight of the tablet (mg)	100	150
	250	

2.8 Evaluation of powder blend and granules^[11]:

The IR powder blends and SR granules were evaluated for pre-compression parameters to assess flowability and compressibility. Bulk density, tapped density, angle of repose, Carr's index, and Hausner's ratio were determined using standard pharmacopoeial methods to ensure uniform die filling and consistent tablet quality.

2.9 Evaluation of tablets^[11]

The IR, SR, and optimized bilayer tablets were evaluated for appearance, thickness, hardness, friability, weight variation, and drug content to assess their quality and physical properties.

2.10 Evaluation of Bilayer Tablet Integrity:

Layer integrity and flaws such cracking, chipping, capping, and layer separation were visually assessed in the optimized bilayer tablets. Additionally, their thickness, hardness, friability, weight fluctuation, and drug content were assessed.

2.11 In Vitro Dissolution Studies

The drug release of IR, SR, and optimized bilayer tablets was evaluated using a USP dissolution apparatus at $37 \pm 0.5^\circ\text{C}$. Samples were collected at predetermined time intervals and analyzed at 310 nm using a UV-Visible spectrophotometer and the respective calibration curves.

2.11.1 Dissolution Study of Immediate-Release Tablets

The IR tablets were evaluated using USP Apparatus II (paddle) in 0.1 N HCl at 100 rpm and 37°C . Samples were withdrawn at 5, 10, 15, 20, 25, 30, 45, and 60 minutes and analyzed at 310 nm. Cumulative drug release was calculated to compare the IR formulations.

2.11.2 Dissolution Study of Sustained-Release Tablet

The SR tablets were tested using USP Apparatus II (paddle) in phosphate buffer (pH 6.8) at 100 rpm and 37°C . Samples were taken out every 30 minutes, 1, 2, 4, 6, and 8 hours, then every 2 hours for the next 24 hours. Cumulative medication release was computed by analyzing ondansetron release at 310 nm.

2.11.3 Dissolution Study of Bilayer Tablets

The bilayer tablets were evaluated using USP Apparatus I at 100 rpm in a medium containing 0.1 N hydrochloric acid and phosphate buffer with a pH of 6.8. The study was continued for up to 24 hours to assess the initial rapid release followed by sustained drug release.

2.11.4 Drug Release Kinetic Analysis^[11]

To characterize the mechanism and kinetics of Ondansetron release from the optimized formulations, the dissolution data were fitted to different mathematical models, namely **zero-order**, **first-order**, **Higuchi**, and **Korsmeyer-Peppas models**.

2.12 Stability Study

The optimized bilayer tablets were evaluated for short-term stability over 2 months by comparing weight, hardness, friability, thickness, drug content, and in vitro drug-release profiles before and after storage.

3. Results

3.1 Preformulation Studies

3.1.1 Determination of λ_{max} and Calibration Curve

For quantitative study, ondansetron's highest absorption was found at 310 nm. The calibration curves prepared in 0.1 N hydrochloric acid and phosphate buffer with a pH of 6.8 showed good linearity. The R^2 values were 0.9968 in 0.1 N hydrochloric acid and 0.9955 in phosphate buffer. These results confirmed that the UV spectrophotometric method was suitable for estimating ondansetron concentration.

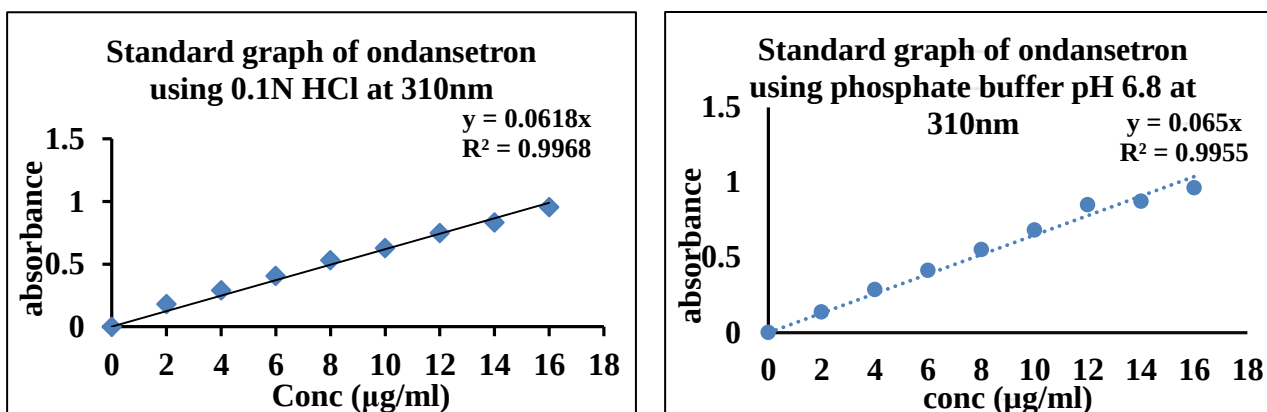


Fig No 1: Standard graph of ondansetron using 0.1N HCl and Standard graph of ondansetron using phosphate buffer pH 6.8

3.1.2 FTIR Compatibility Studies

The FTIR spectrum of pure ondansetron showed characteristic peaks at 3369.36, 2935.76, 1618.33, 1348.29, and 1130.33 cm^{-1} . The spectra of the optimized IR and SR formulations retained the principal drug peaks without significant shifts or new peaks, indicating no significant drug–excipient interactions and suggesting compatibility with the excipients used.

3.2 Pre-compression Properties:

The IR powder blends showed acceptable-to-passable flow properties, as indicated by their angle of repose, compressibility index, and Hausner's ratio (Table 4). The SR granules exhibited better flowability, with lower compressibility indices and Hausner's ratios, which may be attributed to the wet-granulation process (Table 5).

Table No 4: Pre-compression properties of IR powder blends

Formulation code	Bulk density(g/ml)	Tapped density(g/ml)	Angle of repose (θ)	Compressibility index (%)	Hausner's ratio
IF1	0.33	0.416	29.72°	20.67	1.26
IF2	0.322	0.4	30.45°	19.5	1.24
IF3	0.33	0.434	29.72°	23.96	1.315
IF4	0.312	0.4	29.72°	21.87	1.28
IF5	0.434	0.434	31.21°	25.8	1.347
IF6	0.384	0.384	29.72°	21.09	1.26
IF7	0.323	0.41	30.40°	19.5	1.25

Table No 5: Pre-compression properties of SR granules

Formulation code	Bulk density(g/ml)	Tapped density(g/ml)	Angle of repose (θ)	Compressibility index (%)	Hausner's ratio
SF1	0.45	0.493	28.85°	8.72	1.09
SF2	0.408	0.432	29.05°	5.48	1.05
SF3	0.434	0.462	27.89°	6.06	1.06
SF4	0.456	0.470	29.50°	2.97	1.03
SF5	0.49	0.506	28.72°	3.19	1.03

3.3 Post-compression Evaluation of IR Tablets

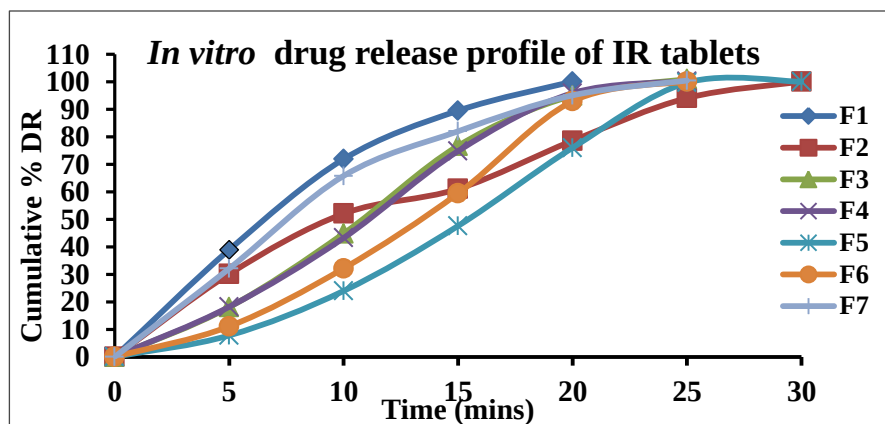
The IR formulations showed satisfactory post-compression characteristics, with **99.1–99.8% drug content** and disintegration times of **40–110 seconds**. IF1 and IF6 exhibited the fastest disintegration (**40 seconds**), indicating rapid tablet disintegration (**Table 6**).

Table No 6: Post-compression characteristics of IR formulations

Formulation code	Weight variation (mg)	Hardness (kg/cm ²)	Friability (%)	Thickness (mm)	Disintegration test (sec)	%drug content
IF1	99.5	8.5	0.196	1.93	40	99.1
IF2	99.6	8.4	0.198	1.94	70	99.8
IF3	99.5	8.2	0.379	1.96	110	99.5
IF4	99.7	8	0.196	1.95	110	99.7
IF5	99.8	8.4	0.2	1.96	75	99.2
IF6	99.6	8.5	0.195	1.95	40	99.3
IF7	99.8	8.6	0.197	1.95	70	99.8

3.4 *In vitro* Drug release from IR formulation:

Among the IR formulations, IF1 was selected as the optimized formulation due to its rapid drug release, reaching 38.924%, 71.904%, 89.513%, and 100.09% at 5, 10, 15, and 20 min, respectively (**Fig. 2**). Its rapid disintegration was attributed to croscarmellose sodium, supporting the desired immediate-release phase of the bilayer tablet.

**Fig No 2: *In vitro* dissolution profile of IR tablets**

3.5 Post-compression Evaluation of SR Tablets

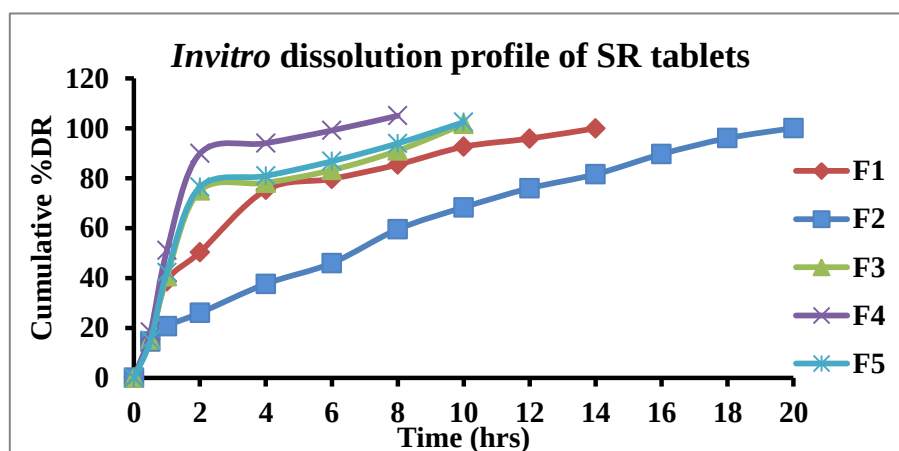
The SR formulations showed satisfactory post-compression characteristics, with 148–149.4 mg tablet weight, 6.0–6.8 kg/cm² hardness, low friability, and acceptable thickness. SF2 showed the lowest friability (0.129%) and drug content of 98.8%, indicating satisfactory tablet quality (**Table 7**).

Table No 7: Post-compression characteristics of SR formulations

Formulation code	Weight variation (mg)	Hardness (kg/cm ²)	Friability (%)	Thickness (mm)	%drug content
SF1	147.9	6	0.191	2.76	98.6
SF2	148.6	6.2	0.129	2.81	98.8
SF3	148.9	6.8	0.158	2.74	9.2
SF4	149.2	6.4	0.198	2.79	8.7
SF5	149.4	6.2	0.186	2.80	9.2

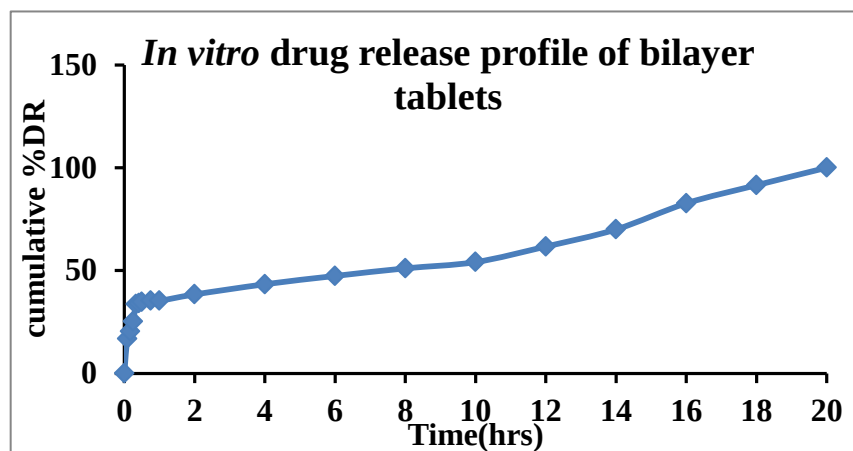
3.6 *InVitro* Drug Release from SR Formulations

Among the SR formulations, **SF2 was selected as the optimized formulation** based on its sustained drug-release profile, extending up to **20 h (Fig. 3)**. SF2 delivered a steady, controlled release of the drug, making it well suited for the sustained-release portion of the bilayer tablet.

**Fig No 3: *In vitro* dissolution profile of SR tablets**

3.7 *InVitro* Drug Release from bilayer tablet Formulations

The optimized bilayer tablet showed approximately 34% drug release within 20 min, followed by sustained release up to 20 h (Fig. 4), demonstrating the desired bimodal release profile.

Fig No 4: *In vitro* dissolution profile of bilayer tablets

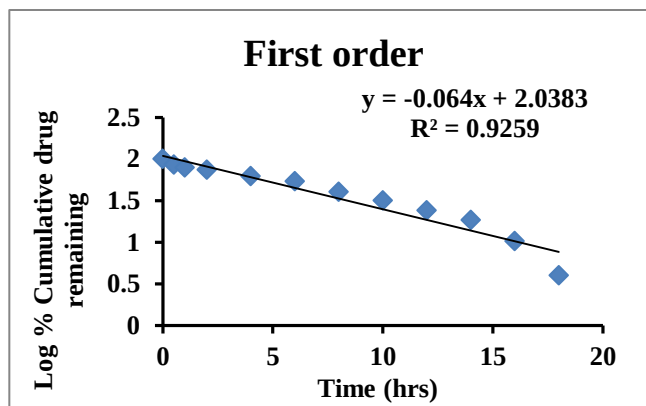
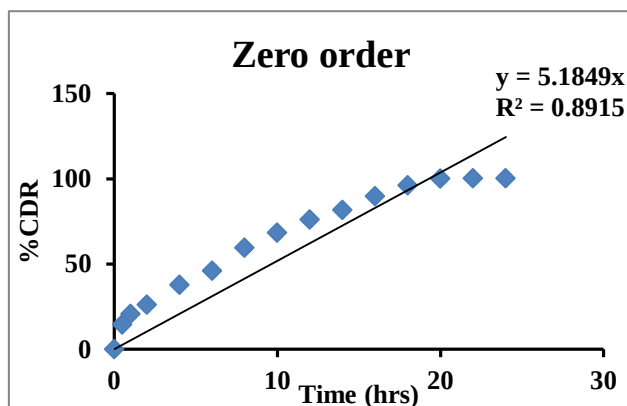
3.8 Drug release kinetics:

3.8.1 For SR optimized formulation (SF2) and for bilayer formulation:

The kinetic profiles of SF2 and the optimized bilayer tablet are shown in **table 8**. SF2 best fitted the Higuchi model ($R^2 = 0.9894$), while the bilayer tablet best fitted the First-order model ($R^2 = 0.8456$). The Korsmeyer–Peppas n values were 1.6486 for SF2 and 1.0836 for the bilayer tablet.

Table 8: Kinetic values obtained from *in-vitro* released data

Formulation code	Kinetic Models					Mechanism of Drug release
	Zero order plot	First order plot	Higuchi plot	Korsmeyer-Peppas		
	R ²	R ²	R ²	n	R ²	
Optimised SR formulation	0.8915	0.9259	0.9894	1.6486	0.57	Supercase II, swelling and erosion of matrix
Bilayer formulation	0.512	0.8456	0.838	1.0836	9.261	



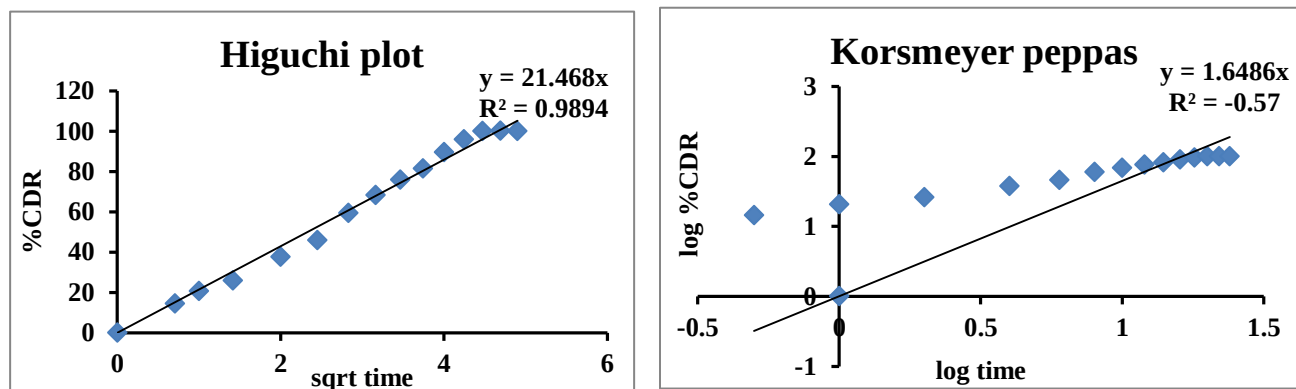


Fig No 5: Kinetics model of optimized SR formulation

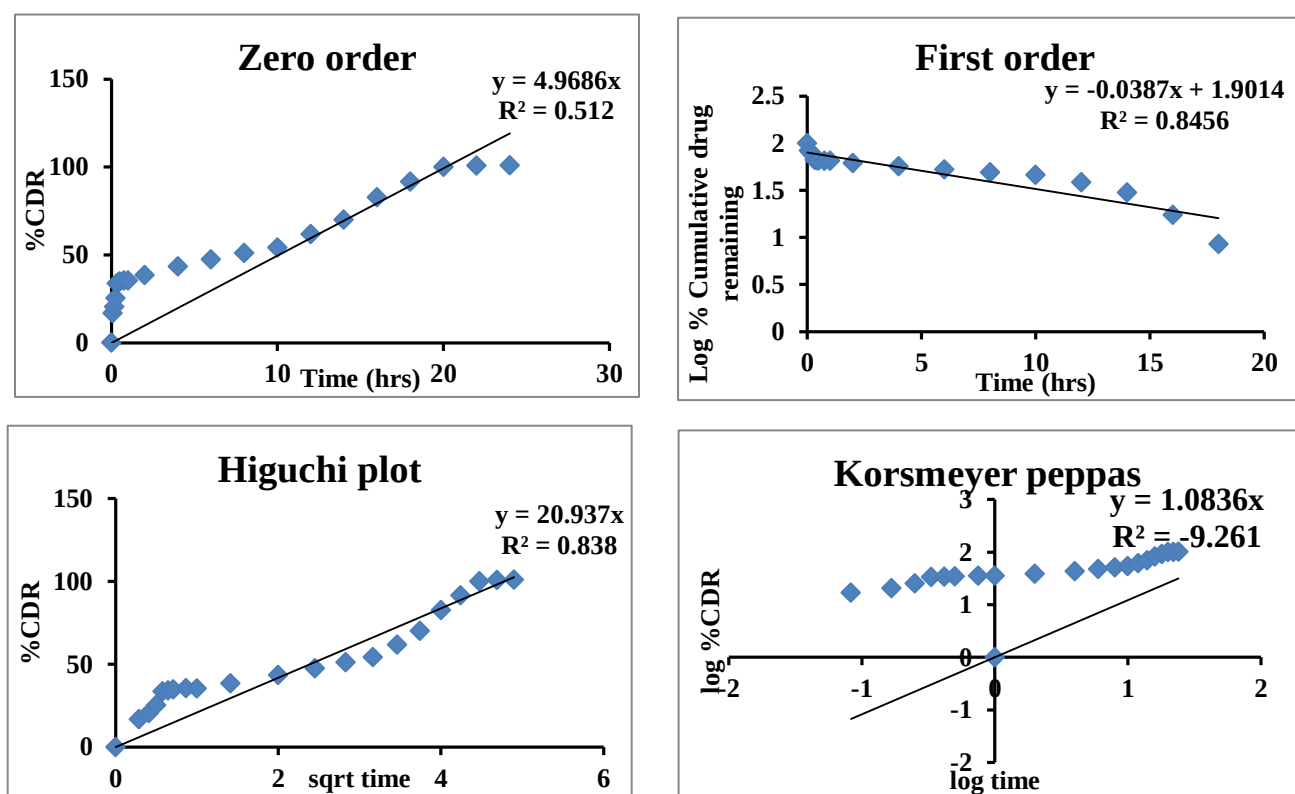


Fig No 6: Kinetics model of bilayer tablet

3.9 Stability studies:

The stability results of the optimized bilayer tablets after two months. Tablet weight, hardness, friability, and thickness remained nearly unchanged, while drug content decreased slightly from 98.6% to 98.0%. Drug release at 20 hours was 100.02% initially and 100.59% after storage Figure 7.

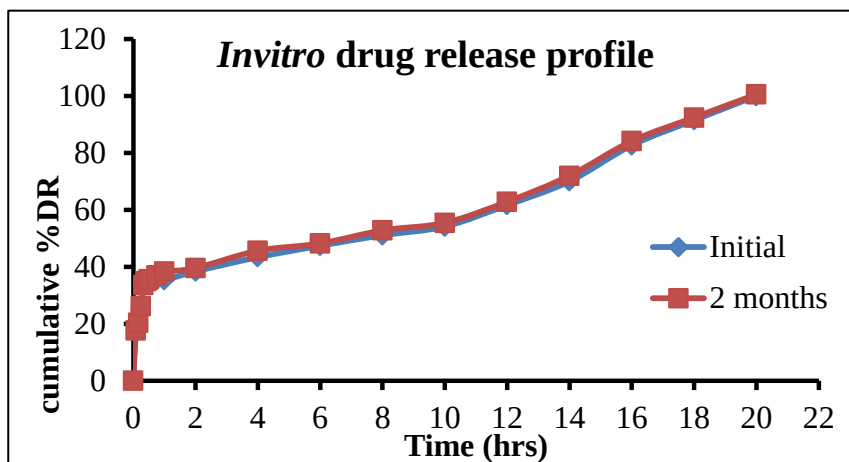


Fig No 7: Comparative *In-vitro* Drug Release Profile of Optimized Ondansetron Bilayer Tablets Before and After Stability Study

CONCLUSION:

The present study successfully developed and evaluated an Ondansetron bilayer tablet designed to provide bimodal drug release. The optimized immediate-release formulation, IF1, showed rapid drug release, reaching approximately 100% within 20 minutes, whereas the optimized sustained-release formulation, SF2, extended drug release for up to 20 hours. Combining these two optimized layers resulted in a bilayer tablet that released approximately 34% of the drug within the first 20 minutes, followed by a gradual and sustained release for up to 20 hours. The formulation showed satisfactory drug content, physical properties, layer integrity, release behavior, and short-term stability. The release kinetics indicated that SF2 followed a diffusion-controlled mechanism, while the bilayer tablet followed first-order release kinetics. Overall, the developed formulation demonstrated promise as a bimodal ondansetron delivery system capable of providing rapid initial relief followed by prolonged drug release.

Reference:

1. Abdul S, Poddar S, 2004. A flexible technology for modified release of drugs: multi layered tablets. *Journal of Controlled Release*. 97(3), Pages 393–405. doi:10.1016/S0168-3659(04)00186-5.
2. Akhtar M, Jamshaid M, Zaman M, et al, 2020. Bilayer tablets: A developing novel drug delivery system. *Journal of Drug Delivery Science and Technology*. 60, Pages 102079. doi:10.1016/j.jddst.2020.102079.
3. Gandhi B, Bhagwat A, Matkar S, et al, 2025. Formulation and Evaluation of Bilayer Tablets of Atenolol and Amlodipine for the Treatment of Hypertension. *Research Journal of Pharmacy and technology*. Pages 2037–42. doi:10.52711/0974-360X.2025.00291.
4. Alqahtani MS, Kazi M, Alsenaidy MA, et al, 2021. Advances in Oral Drug Delivery. *Front Pharmacol*. 12, Pages 618411. doi:10.3389/fphar.2021.618411.
5. Desai PM, Liew CV, Heng PWS, 2016. Review of Disintegrants and the Disintegration Phenomena. *Journal of Pharmaceutical Sciences*. 105(9), Pages 2545–55. doi:10.1016/j.xphs.2015.12.019.
6. Siepmann J, Peppas NA, 2000. Hydrophilic Matrices for Controlled Drug Delivery: An Improved Mathematical Model to Predict the Resulting Drug Release Kinetics (the “sequential Layer” Model). *Pharm Res*. 17(10), Pages 1290–8 <https://doi.org/10.1023/A:1026455822595>.
7. Siepmann J, Peppas NA, 2012. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). *Advanced Drug Delivery Reviews*. 64, Pages 163–74. doi:10.1016/j.addr.2012.09.028.
8. Parikh DM. *Handbook of pharmaceutical granulation technology*. 2016.
9. Zhao H, Shi C, Zhao L, et al, 2022. Influences of different microcrystalline cellulose (MCC) grades on tablet quality and compression behavior of MCC-lactose binary mixtures. *Journal of Drug Delivery Science and Technology*. 77, Pages 103893. doi:10.1016/j.jddst.2022.103893.
10. Kleinebudde P, 2022. Improving Process Understanding in Roll Compaction. *Journal of Pharmaceutical Sciences*. 111(2), Pages 552–8. doi:10.1016/j.xphs.2021.09.024.

11. Gan TJ, 2005. Selective serotonin 5-HT₃ receptor antagonists for postoperative nausea and vomiting: are they all the same? *CNS drugs*. 19(3), Pages 225–38. <https://doi.org/10.2165/00023210-200519030-00004>.
12. Hesketh PJ, 2008. Chemotherapy-Induced Nausea and Vomiting. *N Engl J Med*. 358(23), Pages 2482–94. doi:10.1056/NEJMr0706547.
13. Shirole PL, Sanap DP, Jadhav KR, 2024. Development and Validation of a UV Spectrophotometric Method for determination of Ondansetron hydrochloride in Bulk and Tablet Dosage Form. *Research Journal of Pharmacy and technology*. Pages 1061–4. doi:10.52711/0974-360X.2024.00165.
14. Tkachenko Y, Niedzielski P, 2022. FTIR as a Method for Qualitative Assessment of Solid Samples in Geochemical Research: A Review. *Molecules*. 27(24), Pages 8846. doi:10.3390/molecules27248846.
15. Rowe RC, Sheskey PJ, Quinn ME. *Handbook of pharmaceutical excipients*. 6th ed. London: Pharmaceutical press; 2009.
16. Chien Y. *Novel Drug Delivery Systems* [Internet]. 0 ed. CRC Press; 1991 [cited 2026 Sep 1]. doi:10.1201/9780367805456.