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Design and Characterization of Valsartan Gastro retentive Floating Raft Gel Using Natural–Synthetic Polymer Combinations for Enhanced Bioavailability

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Abstract This research aimed to develop and assess gastro retentive floating raft gels containing valsartan by utilizing a blend of natural and synthetic polymers to improve stomach retention time and oral bioavailability. Six formulations (VR1–VR6) were created using sodium alginate, gellan gum, HPMC K15M, calcium carbonate, and sodium bicarbonate to facilitate in-situ gelation, buoyancy, and prolonged drug release. FTIR analysis verified the lack of drug–polymer incompatibility. All formulations demonstrated satisfactory clarity, consistent appearance, and compatibility with gastric pH. Elevated polymer concentration led to enhanced viscosity, gel strength, and regulated medication release. The raft gels exhibited swift floating (lag time 28–42 seconds) and maintained buoyancy for more than 12 hours. The drug content varied between 97.54% and 99.12%. In vitro release demonstrated sustained delivery for up to 8 hours, with VR3 exhibiting best efficacy. The release kinetics adhered to first-order and Higuchi models, exhibiting non-Fickian diffusion. Accelerated stability experiments of VR3 validated the formulation's stability. The optimised raft gel presents a promising gastro retentive method for enhancing valsartan therapy.

Keywords: Valsartan, Gastro retentive Floating Raft Gel, Natural polymers.

INTRODUCTION

The introduction of novel chemical entities into the pharmaceutical industry is crucial, but drug delivery technologies are just as vital, since they enable the efficient use of current drugs and the fruitful creation of new drug candidates.[1] The term "sustained release preparation" is now usually reserved for oral formulations whose mechanism of prolonged action depends on one or more of the gastrointestinal tract's environmental factors, such as pH, gastric motility, enzymes, etc., although the two terms were formerly used interchangeably. In contrast, what is commonly referred to as a controlled release dosage form are drug that are compatible with all methods of administration and whose mechanism of extended action is intrinsic to and entirely dictated by the delivery system. Therefore, this section provides the most cutting-edge solutions available today, with a precisely controlled drug release profile that is frequently able to be directed to a specific location or organ in the body.[2]

The inability to contain the dose form in the intended area of the gastrointestinal tract is a challenge when creating controlled release systems for improved absorption and enhanced bioavailability. Long-term stomach retention is possible with gastric retention medication delivery devices. These systems are crucial for medications like antacids and some antibiotics that are broken down in the intestine. The primary goal of creating these system is to improve the stability of the drug during stomach transit. One type of formulation is gastric emptying, which is an extremely variable process. The ability to prolong and control the emptying time is a useful feature for dosage forms that stay in the stomach longer than traditional dosage forms.[3] Additionally, GRDF will significantly enhance gastric pharmacotherapy by facilitating local drug release that results in high, sustained drug concentrations at the gastric mucosa. Drugs with so-called absorption windows will be carried by GRDF. The absorption of these compounds is site-specific, occurring most frequently in the small intestine's proximal region.[4]

The term "floating drug delivery system" (FDDS) refers to a type of drug delivery system that is able to float in the stomach for an extended length of time due to its bulk density being lower than that of the gastric fluid. The drug is released at a controlled rate from the system as it floats on the stomach contents. The stomach's residual system is gradually emptied when the drug is released. As a result, the GRT goes up and the variability in plasma drug concentrations is better managed. There are two main types of floating systems: effervescent and non-effervescent.[5] Raft-forming systems are a subset of gastro retentive drug delivery systems (GRDDS) intended to extend gastric retention by creating a gel or "raft" above the stomach contents. These systems are generally supplied orally as liquids or suspensions that, following interaction with gastric fluid, undergo in situ gelation, resulting in a thick, cohesive gel that remains atop the stomach contents. The raft serves as a barrier, prolonging the retention of the drug in the gastric region, therefore enhancing absorption for medications with limited absorption windows or those that exhibit greater solubility in acidic conditions. Reviews of GRDDS highlight raft-forming systems in conjunction with floating, mucoadhesive, swelling/expanding, and high-density systems as essential methodologies.[6]

Valsartan is an orally administered, non-peptide angiotensin II type 1 (AT_1) receptor antagonist (ARB) extensively utilized in the treatment of hypertension and associated cardiovascular conditions. It achieves its therapeutic action by competitively blocking the binding of angiotensin II to the AT_1 receptor, hence diminishing vasoconstriction, aldosterone secretion, sympathetic activation, and the consequent elevation of blood pressure. Preclinical and clinical research have shown that valsartan exhibits strong selectivity for AT_1 receptors with minimal affinity for AT_2 receptors, enhancing its advantageous side-effect profile relative to non-selective medicines. Valsartan exhibits a high plasma protein binding affinity (~95%).[7]

To the best of our knowledge, no previous research has documented the creation of a gastro retentive floating raft gel of valsartan using a combination of natural and synthetic polymers. The current work is unique in that it integrates sodium alginate with gellan gum/HPMC K15M to achieve sustained drug release, prolonged gastric retention, and rapid raft formation, thereby providing a new patient-centric approach to improve valsartan bioavailability and therapeutic performance.

MATERIALS AND METHODS:

Chemicals:

Valsartan is obtained as Gift sample from UniChem laboratories Ltd., Mumbai. Sodium alginate and HPMC K15M purchased from Global Exports Private Ltd., Mumbai. Gellan gum and Sodium citrate are purchased from Merck Life Science, India. Sodium bicarbonate and Calcium carbonate obtained from S.D. Fine-Chemical Ltd, Mumbai. All the used reagents and chemicals were of analytical grade.

Calibration of VST

To a 100 millilitre volumetric flask, 100 milligrammes of carefully weighed VST are introduced. The volume was raised to 100 ml using a stock solution of 1 mg/ml of 6.8 pH phosphate buffer. The stock solution was diluted to obtain solutions with concentrations of 2-10 µg/ml using 6.8 pH phosphate buffer. A UV-VIS spectrophotometer (EI 1372, Electronics India,

Pune, India) phosphate buffer blank 6.8 pH was used to quantify these solution's absorbance using a standard graph at wavelength 250 nm.

Formulation Design[8]:

The valsartan gastro retentive floating raft gels (VR1–VR6) were methodically formulated with a blend of natural and synthetic polymers to provide maximum gel strength, buoyancy, and prolonged drug release. Each 10 mL formulation comprised 80 mg of micronized valsartan, with varying polymer concentrations to examine their effects on gelation behaviour and drug release kinetics. The formulations VR1–VR3 utilized sodium alginate (120–180 mg) as the principal gel-forming polymer, complemented by HPMC K15M (20–40 mg) to increase viscosity, extend floating duration, and regulate drug release. Conversely, VR4–VR6 were formulated using gellan gum (20–30 mg) as the alternative natural polymer to enhance in-situ gelation via cation-induced crosslinking. The development of rafts and buoyancy were enabled by sodium bicarbonate (100–140 mg) as the gas-generating agent and calcium carbonate (50–100 mg), which both released Ca^{2+} ions to crosslink alginate/gellan and enhanced flotation. Sodium citrate (20 mg) was used into all formulations to inhibit premature gelation during preparation by briefly chelating free calcium ions. Purified water was utilized to get a final volume of 10 mL. The factorial change of polymer type and concentration facilitated the creation of raft gels exhibiting varying viscosity, gel strength, buoyancy, and regulated valsartan release, which are appropriate for greater stomach retention and improved bioavailability.

Table 1: Formulation table of Valsartan raft gel.

Ingredient (mg / 10 mL)	VR1	VR2	VR3	VR4	VR5	VR6
Valsartan	80	80	80	80	80	80
Sodium alginate	120	150	180	120	150	180
HPMC K15M	20	30	40	–	–	–
Gellan gum	–	–	–	20	25	30
Sodium bicarbonate	100	120	140	100	120	140
Calcium carbonate	50	75	100	50	75	100
Sodium citrate	20	20	20	20	20	20
Purified water q.s. to 10mL	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Preparation of VST raft gel

Valsartan gastro retentive floating raft gels were formulated with optimal mixtures of natural and synthetic polymers through a controlled thermal dispersion method. Precisely measured amounts of sodium alginate, HPMC K15M or gellan gum (according to the formulation), and sodium citrate were incrementally introduced into purified water heated to 70–80 °C while continuously stirring to guarantee thorough hydration and prevent clumping. The polymeric solution was permitted to cool to approximately 40 °C, after which micronized Valsartan was uniformly integrated using high-speed stirring to provide a homogeneous drug dispersion. Gas-forming agents, sodium bicarbonate and calcium carbonate, were included last with gentle agitation to avert early CO_2 release. The final volume was calibrated to 10 mL using purified water, and the generated gels were preserved in airtight amber containers to avert moisture absorption and ensure stability. The formulations were permitted to equilibrate for 24 hours prior to further assessment to guarantee complete swelling and internal gel structuring.

Drug - Polymer Compatibility Studies

Fourier Transform Infrared (FT-IR) Spectroscopy:

Using the ATR FTIR spectrometer (Shimadzu FTIR-8400S, Japan) drug's FT-IR spectra were recorded. When using the diffuse reflectance technique, the mid-IR 4000-400 cm-1

spectral region was covered. The sample was placed in sample holder made from Zinc Selenide. The position and relative strength of the absorption maximums in the spectrum produced with the substance under examination match those in the reference spectrum. To create a transparent raft gel, the mixture was taken and compressed in a hydraulic press at a pressure of 10 tons. The particle was scanned in an infrared spectrophotometer between 4000-400 cm-1. Following the light route, the raft gel was placed, the spectrum was recorded twice, and the characteristic peaks associated with the functional groups were determined. Consequently, an investigation was conducted in the current work utilizing an infrared spectrophotometer to determine whether VST and excipients could potentially interact chemically.

Evaluation parameters:

For raft gel formulations, various quality control tests were carried out.

Different Performed in vitro examinations are:

Physical appearance

The formulations were visually assessed for homogeneity, color, clarity, grittiness, and the presence of particle matter.

Surface pH

The pH of a 10% w/v raft gel dispersion in distilled water was measured using a calibrated digital pH meter. An average of three measurements per formulation made[9].

Rheological Studies

Viscosity was determined using a Brookfield viscometer (Spindle No. 64) at rotational speeds of 10, 20, and 50 rpm. Flow behaviour index (n) and consistency index (K) were calculated using the Power Law Equation:

$$\tau = K \cdot \gamma^n$$

Where,

τ = shear stress and

γ = shear rate.

In Vitro Gelation Analysis

Gelation was evaluated by introducing 10 mL of simulated stomach fluid (0.1 N HCl) to 1 mL of the formulation in a beaker and monitoring the gel's development and stability. The gelation time and length were documented.

Floating Behavior Floating Lag Time (FLT)

Duration necessary for the formulation to ascend to the surface following contact with 0.1 N HCl.

Total Floating Duration (TFD)

Time for which the formed gel remained buoyant.

Sodium bicarbonate + HCl reaction produced CO_2 enabling buoyancy:

$$\mathrm{NaHCO_3 + HCl \rightarrow NaCl + H_2O + CO_2 \uparrow}$$

Uniformity of drug content

This is determined by any conventional pharmacopoeia API assay technique. Content consistency is determined by examining API content in each strip. 85–115% is the maximum content homogeneity[10].

$$\text{Drug content} = \frac{\text{sample absorbance}}{\text{standard absorbance}} \times \frac{\text{standard dilution}}{\text{sample dilution}} \times \frac{\%\text{purity of drug} \times \text{Avg.wt}}{100}$$

$$\%\ \text{Drug content} = \frac{\text{Drug content} \times 100}{\text{Label claim}}$$

In vitro **Dissolution test[11]**

An **in-vitro dissolution study** of the formulated raft gels was performed using a USP type II (paddle) dissolution apparatus (EI-1916, Electronics India, Pune, India). The formulations were placed in 500 mL of pH 6.8 phosphate buffer maintained at 37 ± 0.5 °C and agitated at 50 rpm. Samples (5 mL) were withdrawn at predetermined intervals (2–20 min), replaced with fresh medium, and analysed at 250 nm using a UV–Visible spectrophotometer (EI-1372). Drug release was calculated from the calibration curve and expressed as percentage release. All studies were conducted in six replicates, and mean values were reported.

Release Kinetics[12]

Utilising the results of the in-vitro diffusion study, the order and mechanism of drug release kinetics of VST gummies were examined. Plotting of the kinetic models included the zero

order, first order, and Higuchi equations; the release was calculated using the Korsmeyer-Peppas equations.

Stability Studies

The term "drug stability" refers to a formulation's ability to maintain its physical, chemical, therapeutic, and toxicological parameters within a given container. When a medication's chemical or biological activity does not drop below a predetermined level of labeled potency within a set amount of time beginning from the date of production and preparation packaging, and if its physical properties have not changed significantly or negatively, the medication is considered stable. The International Conference on Harmonization (ICH) published "stability testing of New Drug Substance and Products" (QIA) Guidelines, which specify the stability test requirements for drug registration applications in the USA, Japan, and the EU. ICH specifies the length of the research and the storage requirements.

Procedure:

The designated formulations were tagged and placed in strip packing within a cardboard box. After that, they were kept at room temperature, 40°C/75% RH. Maintained for three months and assessed, in accordance with ICH Guidelines, for their outward look, medication content, and drug release at predetermined intervals[13].

RESULTS & DISCUSSION

Calibration of VST

Combine 50 mg of VST in 100 ml of water to get the stock solution. To make 100 millilitres, 10 millilitres of the stock solution were removed and diluted with water. Using several concentrations (2–10 µg/ml) and the appropriate stock solution dilution, a calibration curve was produced. The absorbance was obtained at 250 nm. The curve that results from calibrating VST in a pH 6.8 phosphate buffer is shown in Figure 1.

Drug excipient Compatibility Studies

FTIR spectroscopy was used to determine the drug excipient compatibility, and the graphs were displayed figure 2 to 4. To find out if there is any interaction between the excipients and VST, the physical mixture was put through FTIR analysis. The lack of a drug-carrier chemical interaction is confirmed by the absence of any drug-characteristic peak appearance or disappearance. Drug polymer and other excepient's physical mixtures all had their Fourier transform infrared spectra recorded and examined for chemical interactions. All samples, which were pure VST, underwent FTIR analysis to determine the presence of the pure API in the mixtures and to describe it.

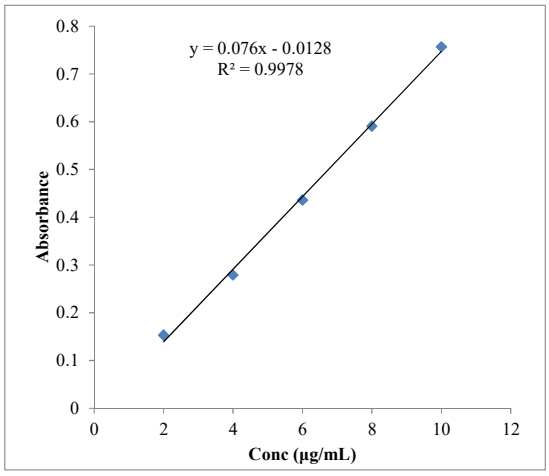

Fig 1: VST standard calibration curve in phosphate buffer with a pH of 6.8

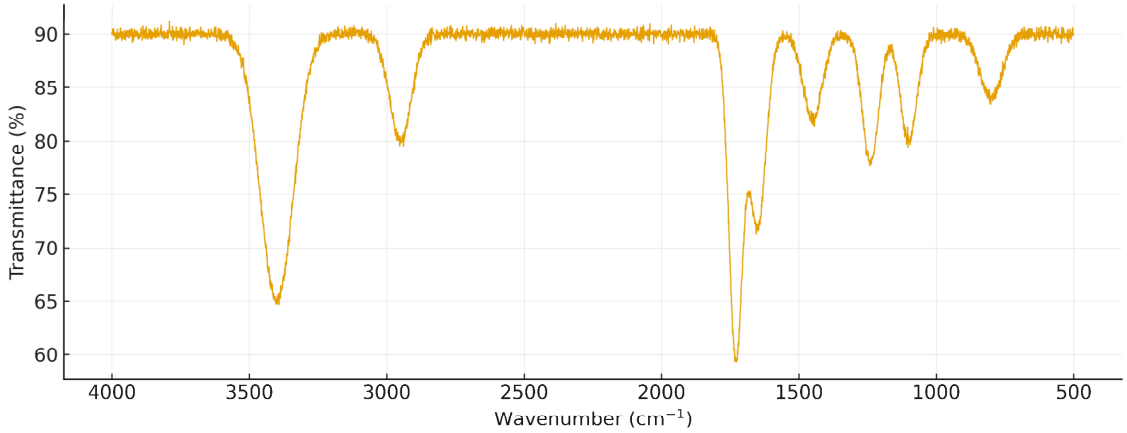

Fig 2: FTIR Spectral analysis of pure VST.

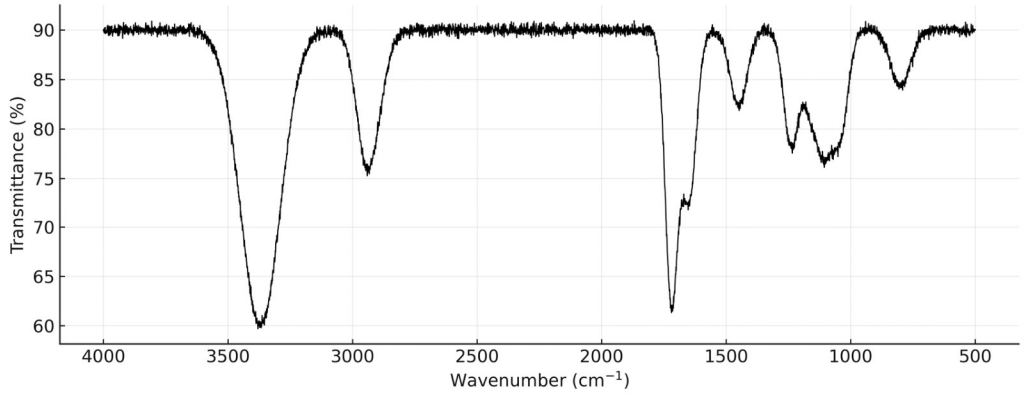

Fig 3: FTIR Spectral analysis of VST + Sodium alginate + HPMC K15M

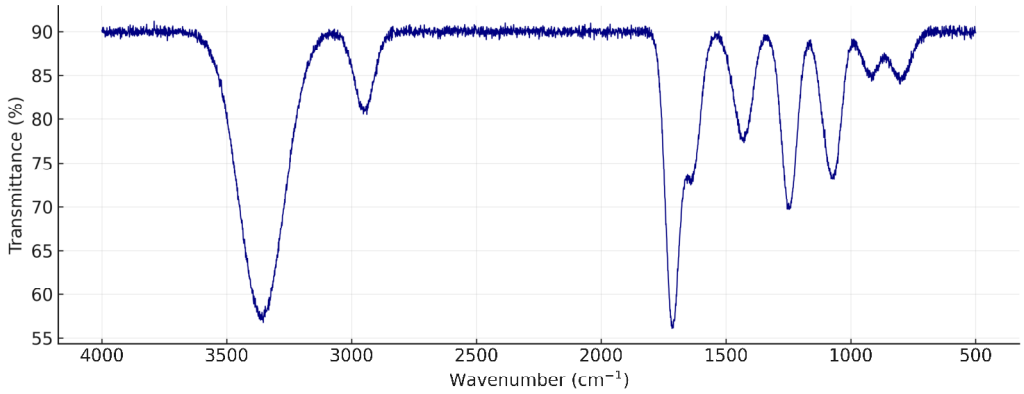

Fig 4: FTIR Spectral analysis of VST + Sodium alginate + Gellan gum

The acquired FTIR spectra are overlapped in the figure 2-4. The FTIR spectrum of pure valsartan exhibited its characteristic functional peaks, including a broad O–H stretching band near 3400 cm^{-1}, pronounced N–H stretching around 3300 cm^{-1}, C–H stretching between 2950–2850 cm^{-1}, a robust C=O stretching peak at approximately 1730–1700 cm^{-1}, and distinct aromatic C=C and C–N vibrations within the range of 1600–1000 cm^{-1}, thereby confirming the integrity of VST's chemical structure. In the spectra of Valsartan + Sodium alginate + HPMC

K15M, all principal valsartan peaks were maintained, exhibiting only modest shifts and slight intensity variations in the O–H and C=O bands, signifying physical mixing and hydrogen-bond interactions without any chemical incompatibility. The spectra of Valsartan combined with Sodium alginate and Gellan gum exhibited retention of Valsartan's distinctive peaks, accompanied by slight expansion in the O–H region and small peak shifts in polysaccharide-associated areas about 1000–1200 cm^{-1}, indicative of polymer–drug interactions. No additional peaks or loss of primary valsartan peaks were detected in either polymer blend, indicating a lack of chemical interaction and demonstrating favourable compatibility of valsartan with both natural and synthetic polymers utilized in the raft gel formulations.

In-vitro Evaluation Results for Valsartan Raft Gels:

Surface pH:

The results are shown in table 2. All formulations demonstrated surface pH within the appropriate physiological range (6.75–6.84), ensuring compatibility with stomach conditions. VR1 (6.82 ± 0.12), VR2 (6.78 ± 0.14), and VR4 (6.84 ± 0.13) exhibited marginally elevated pH levels, while VR3 and VR6 recorded pH values of 6.75 ± 0.11 and 6.76 ± 0.12, respectively, signifying no potential for stomach irritation.

Table 2: Findings of pH, viscosity, gelation time, floating lag time, and total floating time of Valsartan raft gel.

Batch	Appearance	Surface pH	Viscosity (cP)	Gel Strength (g)
VR1	Smooth, uniform	6.82 ± 0.12	1850 ± 52	28.5 ± 1.1
VR2	Smooth, thick	6.78 ± 0.14	2130 ± 65	32.8 ± 1.4
VR3	Smooth, viscous	6.75 ± 0.11	2485 ± 78	38.4 ± 1.6
VR4	Smooth	6.84 ± 0.13	1924 ± 58	30.6 ± 1.2
VR5	Smooth, thick	6.79 ± 0.15	2282 ± 71	35.2 ± 1.3
VR6	Highly viscous	6.76 ± 0.12	2610 ± 82	41.5 ± 1.7

Viscosity

Viscosity rose in direct correlation with polymer concentration. VR3 (2485 ± 78 cP) and VR6 (2610 ± 82 cP) exhibited the greatest viscosity attributable to elevated concentrations of HPMC K15M and gellan gum. The lower polymer batches VR1 (1850 ± 52 cP) and VR4 (1924 ± 58 cP) yielded moderately viscous systems appropriate for syringe ability.

Gel Strength

Gel strength measurements varied from 28.5 ± 1.1 g (VR1) to 41.5 ± 1.7 g (VR6), demonstrating robust raft forming capability. Elevated quantities of calcium carbonate and polymer in VR3 (38.4 ± 1.6 g) and VR6 (41.5 ± 1.7 g) markedly enhanced cross-linking, resulting in firmer and more stable rafts.

Floating lag time

The formulations exhibited swift buoyancy, with floating lag durations ranging from 28 to 42 seconds. VR6 (28 ± 2 sec) and VR3 (30 ± 2 sec) demonstrated the shortest durations due to optimal interaction between sodium bicarbonate and polymer, while VR1 exhibited the longest lag time (42 ± 3 sec) attributable to reduced gas-forming capacity.

Total Floating Time

All formulations demonstrated sustained floating for over 12 hours, validating the effective development of a raft essential for stomach retention.

Drug Content Uniformity:

The drug loading was consistent across all batches, ranging from 97.54% to 99.12%. VR3 (99.12 ± 1.86%) and VR6 (99.02 ± 1.92%) exhibited the greatest consistency, owing to superior solubilisation and distribution inside polymeric matrix.

Table 3: Findings of Floating Lag Time, Total Floating Duration and Drug Content of VST raft gel.

Batch	Floating Lag Time (sec)	Total Floating Duration (h)	Drug Content (%)
VR1	42 ± 3	12.5 ± 0.36	97.85 ± 2.10
VR2	35 ± 2	14.0 ± 0.53	98.24 ± 1.94
VR3	30 ± 2	16.0 ± 0.58	99.12 ± 1.86
VR4	39 ± 3	12.0 ± 0.39	97.54 ± 2.18
VR5	33 ± 2	14.5 ± 0.52	98.05 ± 2.05
VR6	28 ± 2	15.5 ± 0.70	99.02 ± 1.92

In-vitro dissolution:

In-vitro dissolution investigations were conducted in 900 mL of phosphate buffer at pH 6.8 and a temperature of 37 ± 0.5°C utilizing the paddle method. Cumulative drug release statistics for 8 hrs are displayed in figure 5.

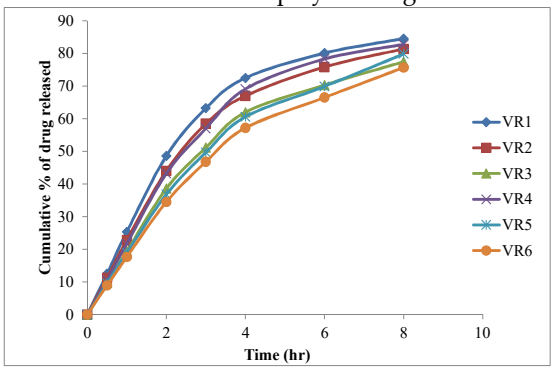

Fig 5: In-vitro dissolution studies of VST formulations.

All batches exhibited an initial moderate release, subsequently followed by a steady release for up to 8 hours. VR1 and VR4 had rapid release rates (about 84.5% and 82.7% at 8 hours), while VR2 and VR5 exhibited intermediate release profiles. In contrast, VR3 and VR6 displayed the slowest release rates (77.4% and 75.7% at 8 hours), correlating with their elevated polymeric matrix density. These profiles correspond with the objectives for a gastro retentive raft system, wherein polymer composition influences the release rate; VR3 was chosen as optimal due to its equilibrium of gel strength, viscosity, buoyancy, and sustained-release characteristics.

Application of Release Rate Kinetics to Dissolution Data:

The kinetics of drug release were investigated using a range of models. The drug release rate mechanism of the dose form kinetics was examined by fitting a variety of release models, such as first-order, zero-order, higuchi, and Korsmeyer-Peppas, to the collected data. The kinetics results were displayed in figures 6-9.

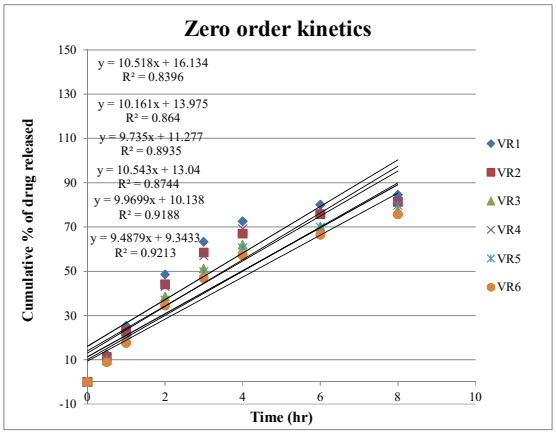

Fig 6: Zero order release kinetics graph of VST formulations.

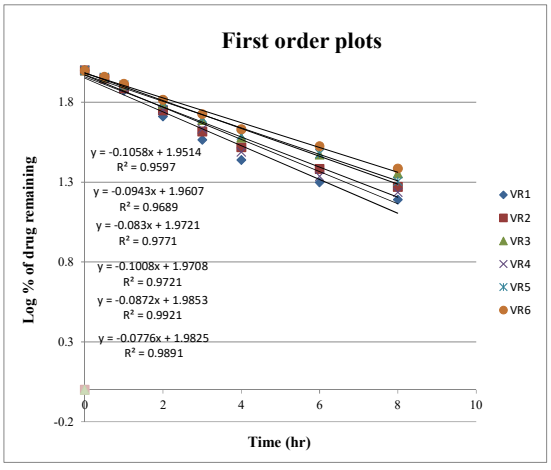

Fig 7: First order release kinetics graph of VST formulations.

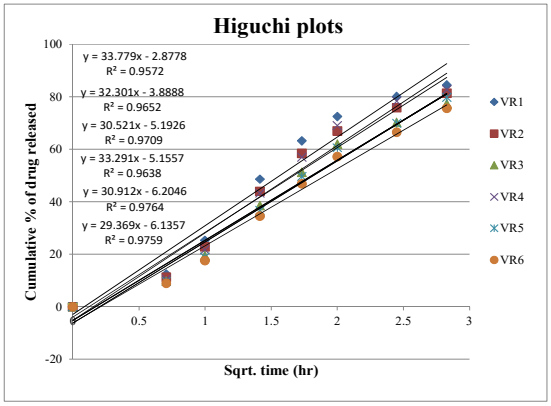

Fig 8: Higuchi release kinetics graph of VST formulations.

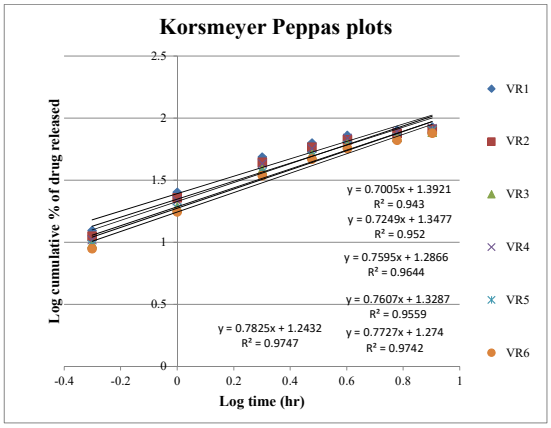

Fig 9: Korsmeyer-Peppas graph of VST formulations.

The drug release kinetics are summarized in Fig. 6 to 9. The kinetic study of valsartan raft gels (VR1–VR6) demonstrated that all formulations primarily adhered to first-order kinetics, with high R^2 values between 0.9597 and 0.9921, signifying concentration-dependent release. The Higuchi model correlations (R^2 = 0.9572–0.9764) validated diffusion-controlled drug transport inside the hydrated polymeric matrix. The Korsmeyer–Peppas model demonstrated n-values ranging from 0.7005 to 0.7825, indicating non-Fickian (anomalous) release, influenced by both polymer relaxation and diffusion mechanisms. Among all batches, VR5 and VR6 had the greatest first-order and Peppas R^2 values (up to 0.9921 and 0.9747), indicating a more regulated and prolonged release profile attributable to elevated polymer concentrations.

Selection of the best formulation

Following a comparative assessment of rheological and functional characteristics (viscosity, gel strength, floating behavior, drug content, and release), VR3 (Sodium alginate 180 mg + HPMC K15M 40 mg per 10 mL) was identified as the optimal formulation. VR3 achieves an ideal equilibrium between gel strength (38.4 ± 1.6 g) and controllable viscosity (2485 ± 78 cP), demonstrates swift buoyancy (floating lag = 30 s) and prolonged release (77.42% at 8 h), while preserving elevated drug content (99.12 ± 1.86%). In comparison to the highly viscous gellan-rich batch (VR6), which exhibited marginally superior gel strength but significantly higher viscosity and the slowest release, VR3 provides enhanced process ability, potentially improved gastric retention with favourable gel matrix integrity, and the requisite controlled release profile conducive to increased bioavailability.

Stability Studies:

Accelerated stability investigations of the optimised formulation (VR3) were performed in accordance with ICH recommendations at 40 ± 2 °C and 75 ± 5% relative humidity for a duration of 3 months. VR3 exhibited no notable alterations in appearance, pH, viscosity, gel strength, buoyancy, drug content, or dissolution profile during a period of 90 days. The formulation exhibited steady raft formation, prolonged floating for over 12 hours, and constant drug release, hence affirming its superior physical and chemical stability.

CONCLUSION

The research effectively created gastro retentive floating raft gels containing valsartan by utilising mixtures of natural and synthetic polymers to improve stomach retention and prolong medication release. All formulations exhibited excellent physicochemical stability, buoyancy, and consistent drug content. VR3 exhibited superior gel strength, extended floating duration (>12 h), and regulated drug release over 8 hours, according to diffusion-controlled kinetics. The results validate that the optimised raft gel system is an effective method to enhance valsartan bioavailability and therapeutic efficacy in hypertension treatment.

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