“Clinical Investigation of Valsartan Sustained-Release Matrix Tablets: Formulation Design and Performance Evaluation”

(Original Research Article)

ABSTRACT

The primary objective of this main study is to develop and assess the sustained-release matrix tablets containing Valsartan, an angiotensin II receptor type 1 antagonist. The powder mixtures underwent a thorough examination of pre-compression parameters and observed angle of repose, bulk density, tapped density, and Carr’s index, all of which exhibited satisfactory results. Following compression, the tablets were subjected to post-compression evaluations, including weight variation, thickness, hardness, friability, drug content, in-vitro dissolution, and stability studies. In-vitro dissolution investigations are conducted over 24 hours, employing 0.1 N HCL for the initial 2 hours and pH 6.8 phosphate buffer for the subsequent 24 hours. Notably, formulations F4 and F7 demonstrated promising dissolution profiles, effectively controlling the release of the drug. These formulations, enriched with higher concentrations of chitosan and sodium alginate in addition to other polymers, successfully sustained the drug release for the entire 24-hour duration. The compatibility of the drug, polymers, and other excipients was meticulously assessed using FT-IR Spectroscopy, affirming the harmonious interaction among these components. Further analysis involved fitting the release data to various mathematical models, including Zero-order, First-order, Higuchi equation, and Korsmeyer-Peppas model, to ascertain the kinetics and mechanisms governing drug release. Results indicated that the drug release adhered to first-order kinetics, with a non-Fickian mechanism prevailing. Stability studies conducted for 3 months provided reassurance regarding the stability of the selected formulations (F4 and F7), bolstering confidence in their potential for sustained release of Valsartan.

Keywords: Carbopol 934P, Chitosan, sodium, Zero-Order, First Order, Angiotensin.

INTRODUCTION

Oral drug delivery is widely preferred due to its ease of administration, patient compliance, and formulation flexibility. The market predominantly offers oral drug delivery systems, accounting for approximately 50% of available drug delivery options. This route of administration has historically been dominant, owing to its convenience, lack of sterility concerns, and minimal risk of tissue damage at the administration site[(1)].

Most oral pharmaceutical products are immediate-release formulations, designed for rapid drug release and absorption. However, these conventional dosage forms have limitations:

1. **Frequent Administration**: Drugs with short half-lives necessitate frequent dosing, increasing the likelihood of missed doses and compromising patient compliance.
2. **Peak-Valley Plasma Concentration Profiles**: Immediate-release formulations often yield fluctuating drug levels in the bloodstream, making it challenging to achieve steady-state conditions.
3. **Risk of Adverse Effects**: Fluctuating drug levels can trigger adverse effects, particularly for medications with narrow therapeutic windows, leading to potential overmedication-related complications[(2,3)]

To address these drawbacks, significant advancements are made in the development of controlled drug delivery systems. These innovations aim to revolutionize medication methods and offer several therapeutic advantages, including enhanced patient adherence, reduced dosing frequency, and minimized risk of adverse effects.

Design and formulation of oral sustained release drug delivery system: [(4, 5)]

The oral route of drug administration is favored due to its adaptability in dosage form design and patient adherence. However, it's essential to consider the diverse pH environments encountered during gastrointestinal transit, along with factors such as gastrointestinal motility and enzymatic activity, which can impact drug performance and dosage form integrity.

Many sustained-release systems rely on dissolution, diffusion, or a combination thereof to achieve prolonged drug release in the gastrointestinal tract. Ideally, sustained-release delivery devices should exhibit zero-order drug release kinetics, resulting in a plasma concentration-time profile akin to the intravenous constant rate infusion.

Sustained release formulations aim to provide medication over an extended period, offering temporal, spatial, or combined therapeutic control. While true zero-order release is often unattainable, sustained-release systems typically employ slow first-order release kinetics to mimic this idea. Repeat action tablets represent an alternative sustained-release approach, containing multiple doses released at intervals. In contrast, delayed-release systems, such as enteric-coated tablets, may not sustain drug release but serve to delay release until a specific site in the gastrointestinal tract is reached.

A well-designed sustained-release dosage form maintains therapeutic drug concentrations in the bloodstream throughout the dosing interval, reducing peak concentration ratios and ensuring steady drug levels for improved efficacy and patient comfort.

ADVANTAGES OF SUSTAIN RELEASE DOSAGE FORMS [(6,7)]

1. Minimization of dosing frequency.
2. Mitigation of adverse effects.
3. Consistent and controlled drug release throughout the duration of treatment.
4. Enhancement of patient adherence and cooperation.

DISADVANTAGES OF SUSTAINED RELEASE DRUG DELIVERY [8,9]

1. Elevated expenses associated with treatment.
2. Risks of toxicity stemming from dose dumping.
3. Challenges in establishing reliable and consistent in vitro-in vivo correlations.
4. Heightened susceptibility to first-pass metabolism and clearance.
5. Requirement for supplementary patient education and counselling efforts.

Matrix tablets [10]: A straightforward method for producing controlled-release dosage forms entails directly compressing a mixture of the drug, retardant material, and appropriate additives to create a tablet where the drug is encapsulated within a matrix of the retardant. Alternatively, the drug and retardant blend can undergo granulation before compression to form the desired dosage form.

Matrix tablets represent a category of controlled drug delivery systems designed to release medication continuously through a combination of dissolution and diffusion mechanisms. These tablets effectively regulate the release of drugs with varying solubility properties by dispersing the drug within swellable hydrophilic substances or embedding them in an insoluble matrix composed of rigid non-swellable hydrophobic materials or plastic materials.

A straightforward method for manufacturing sustained-release dosage forms involves directly compressing a mixing of drugs, releasing the retardant material, and additives to create a tablet where the drug is encased within a matrix of the released retardant. Alternatively, the drug and release retardant blend may undergo granulation before compression, offering another approach to formulating these controlled-release tablets.

ADVANTAGES OF MATRIX TABLET [11,12]:

- Highly adaptable, efficient, and cost-effective.
  • Capable of releasing high molecular weight compounds.
  • Sustained-release formulations can uphold the therapeutic levels for extended durations.
  • By avoiding abrupt spikes in blood concentration, sustained-release formulations can enhance patient adherence and minimize toxicity through gradual drug absorption.

DISADVANTAGES OF MATRIX TABLET:

After drug release, it is imperative to eliminate the residual matrix from the system.

Cost of preparation can be a significant drawback, often proving to be prohibitive. Release rates may be influenced by factors like food intake and gastrointestinal transit rates, impacting the predictability and consistency of drug delivery.

Matrix tablets are generally classified as various types [13, 14]:

a) Hydrophilic Matrix Tablet
b) Fat-wax Matrix Tablet
c) Plastic Matrix Tablet (Hydrophobic matrices)
d) Biodegradable Matrices
e) Mineral Matrices

HYPERTENSION [15,16]

High blood pressure stands as a main independent risk factor for cardiovascular ailments and strokes, contributing directly to approximately 5.8% of total fatalities. It is among the prevalent complex disorders, afflicting 15–20% of the adult population in Western societies. This condition is categorized into primary (essential) and secondary hypertension, with the former characterizing elevated blood pressure without identifiable pathology. Essential hypertension constitutes the

majority, accounting for about 90–95% of cases, while secondary hypertension, attributed to underlying conditions like pheochromocytoma or renal diseases, comprises the remaining 5%.

Hypertension, interchangeably known as high blood pressure (HTN or HPN), manifests as a persistent elevation of blood pressure levels. In common parlance, the term "hypertension" typically denotes arterial hypertension, although it can encompass elevated blood pressure in any vessel, including pulmonary or portal hypertension. Clinically, hypertension often refers to an increase in systolic arterial blood pressure. While not classified as a disease per se, hypertension represents a clinical finding with significant health implications.

Factors responsible for Hypertension is mainly three:-

1) Genetic factors
2) Racial factors
3) Risk factors modifying the course

METHODOLOGY [17,18,19]:

Table 1. Formulation development of valsartan by direct compression

FORMULA CODE	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)
Valsartan	80	80	80	80	80	80	**80**
Carbopol	100	100	100	100	100	100	**100**
Chitosan	--	5	10	15	--	--	**--**
Sodium alginate	--	--	--	--	5	10	**15**
PVP K 30	5	5	5	5	5	5	**5**
Magnesium Stearate	3	3	3	3	3	3	**3**
Talc	2	2	2	2	2	2	**2**
Micro crystalline cellulose QS to	**250**	**250**	**250**	**250**	**250**	**250**	**250**

PRE-FORMULATION STUDIES [20,21]

Analytical Method in the Determination of Valsartan.

The UV spectrophotometric method is developed by using the Shimadzu 1800 spectrophotometer for the analysis of the drug.

Preparation of 6.8 pH phosphate buffer solution[22,23]:

A 0.2M potassium dihydrogen phosphate solution was prepared by transferring 50 ml from the stock solution into a 200 ml volumetric flask. Subsequently, 22.4 ml of a 0.2M sodium hydroxide solution, sourced from its respective stock solution, was added to the flask. Distilled water was then employed to achieve the final volume.

Determination of λ_{max}[24,25]

A 1% w/v solution of Valsartan was meticulously prepared in 0.1 N NaOH, following which it was subjected to UV spectroscopic analysis using a double-beam spectrophotometer (Shimandzu-1800). The scanning range extended from 200 to 400 nm, with 0.1 N NaOH serving as the blank solution. Through this process, the maximum absorbance wavelength (λmax) of the Valsartan compound was determined to be 249 nm.

Standard Curve for Valsartan [26,27]

To prepare the first stock solution of Valsartan, precisely 100 mg of the compound is weighed and solubilised in 100 ml of 0.1 N NaOH. From this solution, a 10 ml aliquot was withdrawn and

made up to 100 ml with the same solvent to obtain the second stock solution. Subsequently, specific volumes of the second stock solution were further diluted with 0.1 N NaOH to achieve concentrations of 5µg, 10µg, 15µg, 20µg, 25µg, and 30µg of Valsartan per ml of the final solution.

The absorbance of these diluted solutions was then measured using a UV spectrophotometer at 249 nm, with 0.1 N NaOH serving as the blank. A graphical representation of absorbance versus concentration was plotted to determine the relationship between the two variables.

Compatibility study using FT-IR: [28,29]

The development of a reliable and efficient solid dosage form hinges on the meticulous selection of excipients. These excipients play a crucial role in facilitating administration, ensuring consistent drug release, enhancing bioavailability, and safeguarding the drug from degradation.

Infrared spectroscopy, carried out using advanced instrumentation such as the Thermo Nicolet FTIR, provides valuable insights into the interaction between the drug and excipients. Spectral analysis conducted in the region spanning from 4000 to 400 cm-1 enables the observation of any shifts in peaks within the drug spectrum when in physical contact with various excipients.

Through IR spectral studies, alterations or shifts in the characteristic peaks of the drug within the spectrum of the physical mixture can be discerned. These shifts serve as indicators of potential interactions between the drug and excipients, shedding light on the compatibility and suitability of the formulation components. Such observations are instrumental in guiding formulation optimization efforts, ensuring the development of stable and effective solid dosage forms with desirable properties and performance characteristics.

Procedure: A measured quantity of medication (3 mg) was combined with 100 mg of potassium bromide, which had been meticulously dried at temperatures ranging from 40 to 50 degrees Celsius. The resultant mixture was meticulously compressed under a formidable 10-ton pressure using a hydraulic press, thereby fashioning a distinctively transparent pellet. Subsequently, this pellet underwent comprehensive scanning via an infrared (IR) spectrophotometer to discern its spectral characteristics. This meticulous process was replicated for all pertinent excipients utilized in the formulation.

EVALUATION OF PRE-FORMULATION PARAMETERS [30,31,45]

1. Melting Point:
2. Angle of Repose
3. Bulk Density
4. Tapped Density
5. Carr’s Compressibility Index (Ci)
6. Hauser’s Ratio

POST-COMPRESSION EVALUATION PARAMETERS [32,33,44]

Evaluation of Valsartan sustained release matrix tablets:

Tablets are subjected to various evaluation parameters which include drug content uniformity, weight variation, tablet hardness, friability, and thickness, and *in-vitro* drug release with different media.

1. Weight variation
2. Tablet hardness
3. Friability
4. Tablet thickness

5. Drug content uniformity
6. *In-vitro* dissolution studies

Mathematical modelling of drug release profile [33,3,43]

a) Zero order kinetics
b) First order Kinetics
c) Higuchi's model
d) Korsmeyer equation/ Peppa's model

Stability studies: [35,36,42]

The stability of a drug is characterized by its capacity to maintain its defined physical, chemical, therapeutic, and toxicological attributes within a predetermined formulation under specific conditions. The primary objective set for the stability testing is to furnish empirical data elucidating how the quality of a drug formulation evolves, subject to diverse environmental factors such as temperature, humidity, and light exposure. Through this investigative process, insights into recommended storage conditions, re-test periods, and shelf-life determination for the drug can be methodically established, ensuring its efficacy and safety throughout its intended lifespan.

Reasons for stability studies [37,41]

1. This commitment from the manufacturer guarantees that patients will consistently receive a standardized dosage throughout the entirety of the drug's shelf life.
2. Regulatory bodies, such as the Drug Control Administration, mandate that manufacturers undertake comprehensive stability studies to ensure the sustained integrity of a drug's identity, potency, purity, and overall quality over an extended duration under normal storage conditions.
3. Stability testing serves as a critical safeguard against the potential introduction of unstable products into the market. Both physical and chemical degradation of a drug can lead to product instability, underscoring the importance of rigorous testing protocols to maintain product efficacy and safety.

Storage conditions [38,39,40]**:** The chosen formulations underwent a rigorous three-month stability assessment in accordance with the guidelines outlined by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). These formulations were carefully enclosed within wide-mouth glass bottles, securely sealed, and further shielded by aluminum foil packaging to minimize external influences. Throughout the duration of the study, stability evaluations were conducted under two distinct environmental conditions: 25°C with 60% relative humidity (RH), and 40°C with 75% RH, representing conditions simulating normal storage environments. This meticulous approach ensured a comprehensive assessment of the formulations' stability and viability over the specified timeframe, enabling thorough insights into their shelf-life and performance under varying climatic conditions.

RESULTS AND DISCUSSION

Determination of λ_{max} of Valsartan

The λ_{max} of the Valsartan is found to be at 249 nm in 0.1 N NaOH.

Calibration curve observed for Valsartan

The absorption characteristics of Valsartan were analyzed using a UV spectrophotometer, with measurements taken at a wavelength of 249 nm, utilizing 0.1 N NaOH as the blank reference. The resulting absorbance values were meticulously recorded and tabulated. Subsequently, a graphical representation was constructed by plotting the absorbance against varying concentrations of Valsartan. This graphical depiction facilitated the visualization of the relationship between

absorbance and concentration, providing valuable insights into the compound's optical properties and concentration-dependent behavior.

Table 2. Spectrophotometric data for the estimation of Valsartan in 0.1 N NaOH

SL. No.	Concentration (µg/ml)	Absorbance at 249 nm				
		Trail-1	Trail-2	Trail-3	Average	S.D.
1	0	0	0	0	0	0
2	5	0.0124	0.0152	0.0150	0.00951	0.00307
3	10	0.0223	0.0221	0.0218	0.0188	0.0089
4	15	0.0258	0.0259	0.0257	0.0257	0.00076
5	20	0.0321	0.0332	0.0328	0.0361	0.00350
6	25	0.0368	0.0377	0.0377	0.04173	0.00421
7	30	0.0431	0.0432	0.0433	0.0532	0.00411

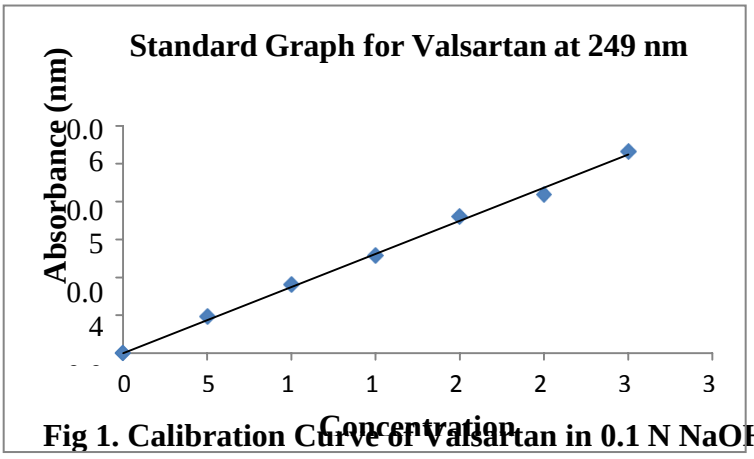

Fig 1. Calibration Curve of Valsartan in 0.1 N NaOH

Compatibility studies using FT-IR

Infra-red spectrum of drug, polymers and mixture of both were determined by KBr disks method. Samples were prepared in KBr disks by means of a hydrostatic press at 5 tons pressure for 5 min. All the characteristic peaks of Valsartan were present in the spectrum of drug and polymer mixture, indicating compatibility between drug and polymer. From the results, it was concluded that there was no interference of the functional group as the principle peaks of the Valsartan were found to be unaltered in the drug- polymer physical mixtures, indicating that they were compatible chemically. The spectrum confirmed that there is no significant change in the chemical integrity of the drug.

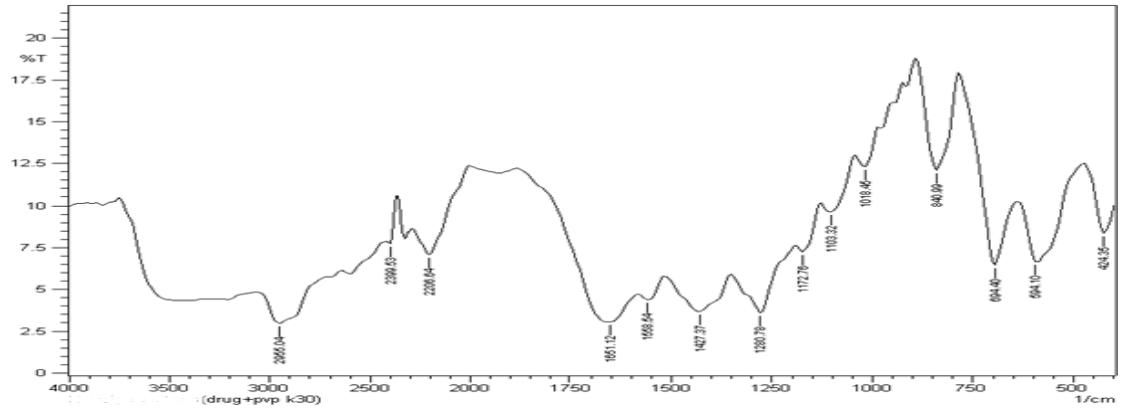

Fig 2. FT- IR Spectrum of Pure Drug Valsartan

FORMULATION DESIGN:

The primary objective of this research endeavours was to develop sustained-release matrix tablets of Valsartan employing chitosan, aimed at enhancing its therapeutic effectiveness while mitigating adverse effects through reduced dosing frequency. To achieve this goal, a series of nine formulations were meticulously prepared, incorporating various polymers including chitosan, sodium alginate, Carbopol, microcrystalline cellulose (MCC), and PVP K30, in varying ratios.

Both pre-compression and post-compression assessments were conducted on the powder mixture before and after compression, respectively. These evaluations were crucial in gauging the physical and mechanical properties of the formulations, ensuring optimal tablet characteristics such as uniformity, hardness, friability, and dissolution behaviour. Through systematic analysis at each stage of formulation development, the aim was to ascertain the suitability of the selected polymers and their combinations in achieving the desired sustained-release profile of Valsartan, ultimately enhancing its therapeutic efficacy and patient compliance.

Evaluation Parameters:

Powder blended characteristics of the matrix tablet formulation of Valsartan Evaluation

Table 3. Evaluation parameters of pre-formulation characteristics of powder blend

Formulations Number	Bulk Density (gm/cc)	Tapped Density (gm/cc)	Carr's Index (%)	Hausner'sRatio	The angle of Repose (θ)
F1	0.3715±0.0012	0.4102±0.0026	7.28±0.658	1.176±0.0077	29.72 0.42
F2	0.3802±0.0004	0.4121±0.0027	7.57±0.513	1.052± 0.0061	25.32 0.62
F3	0.3842±0.0016	0.4122±0.006	7.42±0.761	1.058±0.0089	28.41 0.36
F4	0.377±0.0021	0.4271±0.0038	13.79±0.387	1.072±0.0052	27.49 0.54
F5	0.356±0.0018	0.4601±0.0025	17.32±0.795	1.225±0.012	31.35 0.14
F6	0.3811±0.0046	0.4881±0.0066	18.43±0.121	1.26±0.0021	28.27 0.44
F7	0.3851±0.0082	0.4385±0.134	10.89±0.031	1.122±0.0022	27.28±0.43

Table 4. **Post-compression parameters results**

Formulation	Diameter (mm)± SD	Thickness (mm)± SD	Weight variation(mg)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	7.81±0.013	3.8±0.08	250.79±0.16	7.7±0.05	0.64±0.009	98.27±0.045
F2	7.82±0.004	4.1±0.03	253.89±0.65	7.7±0.02	0.54±0.007	100.32±0.039
F3	7.86±0.008	4.3±0.04	251.14±0.56	8.3±0.09	0.59±0.033	98.56±0.09
F4	7.83±0.024	3.8±0.09	249.82±0.14	6.6±0.05	0.73±0.017	99.69±0.088
F5	8.02±0.016	4.1±0.05	250.84±0.33	6.9±0.09	0.667±0.08	99.39±0.059
F6	7.96±0.012	3.9±0.08	248.93±0.46	7.5±0.05	0.715±0.05	98.99±0.075
F7	7.98±0.017	4.2±0.03	252.65±0.62	6.5±0.04	0.449±0.01	101.65±0.07

Discussion about the physical parameters such as

Thickness of tablets

The mean thickness measurements across all formulations fell within a narrow range of 3.8 to 4.2 mm, demonstrating consistency and adherence to the permissible deviation limit of 5% from the

standard value. Similarly, the crown diameter of the tablets for each formulation was observed to be within the range of 7.8 to 8.0 mm. These findings underscore the meticulous attention to detail in the manufacturing process, ensuring uniformity in tablet dimensions across the various formulations. Such precise control over tablet dimensions is crucial for dosage accuracy, ease of handling, and overall product quality, thereby affirming the robustness of the formulation development methodology employed in this study.

Hardness

Tablet hardness serves as a pivotal metric for assessing a tablet's resilience against potential issues such as capping, abrasion, or breakage during storage, transportation, and handling prior to administration. Across all formulations, the average hardness values were consistently measured within the range of 6.0 to 8.0 kg/cm². This uniformity in hardness underscores the robust structural integrity of the tablets, ensuring they possess favorable handling characteristics across all batches. Maintaining optimal tablet hardness is imperative for safeguarding against potential damage or deterioration, thereby preserving the efficacy and integrity of the formulated product throughout its lifecycle.

Friability

Across the spectrum of formulations examined, the average percentage friability fell within a satisfactory range of 0.447% to 0.72%, comfortably aligning with the stringent pharmacopeial threshold of less than 1%. Notably, the formulation denoted as F4 exhibited the maximum observed friability at 0.72%, while the lowest friability of 0.447% was recorded for formulation F7. These findings affirm the robustness of the tablet formulations, demonstrating their resilience to mechanical stress and confirming their suitability for storage, transportation, and handling without compromising their structural integrity.

Weight variation test:

The weight variation analysis conducted across all formulations revealed consistent results, with weights ranging from 249.92 to 253.88 mg. Notably, all formulations adhered to the stringent pharmacopeial limits, showcasing % weight variation well within the acceptable threshold of less than 5%. Furthermore, the uniformity in tablet weights was evident, as indicated by low standard deviation values across the board. This stringent adherence to weight variation specifications underscores the precision and reliability of the tablet manufacturing process, ensuring consistent dosing accuracy and quality assurance in pharmaceutical production.

Drug content:

The percentage amount of drug content of formulation F1 to F7 is found that between 98.25%w/w and 101.63%w/w. It will comply with all official specifications.

***In-vitro* drug release study:**

In the present investigation, Carbopol was designated as the polymer of choice and was combined with two of the compounds chitosan and sodium alginate to ascertain their potential for sustained release of Valsartan. The in-vitro release profiles of Valsartan from the matrix tablets were primarily influenced by several factors including the dissolution medium, concentrations of chitosan and sodium alginate, as well as the overall polymer concentrations.

The release behaviour of Valsartan was found to be intricately linked to the swelling characteristics of the tablets, whereby higher degrees of tablet swelling corresponded to diminished drug release. The in-vitro release study commenced in 0.1 N HCl for the initial two hours, followed by a transition to phosphate buffer (pH 6.8) for the subsequent 24-hour period.

Notably, a substantial portion of Valsartan was released within the first 6-7 hours across all formulations. Specifically, formulations containing chitosan-Carbopol released approximately 10.29% to 18.34% of the drug, while sodium alginate-Carbopol formulations released 16.90% to 21.91%. Tablets solely comprised of the release-retardant polymer exhibited a release of approximately 25.12%.

Distinct release patterns were observed among formulations, with certain formulations achieving complete drug release within 12 to 20 hours, falling short of the desired 24-hour release period. This discrepancy was attributed to the reduced ionic interaction between crosslinking agents and negatively charged polymers at pH 6.8, resulting in the formation of a loosely structured network with increased porous surface area, facilitating greater dissolution media penetration.

However, formulations F4 and F7, characterized by higher concentrations of chitosan and sodium alginate respectively, in combination with Carbopol gum, demonstrated prolonged release profiles, reaching the desired 24-hour release duration. This extended release behavior was attributed to the formation of self-assembled polyelectrolyte complex films on the surface of the crosslinking agent-polymer system.

Furthermore, swelling studies corroborated these findings, indicating that formulations containing higher concentrations of cross-linking agents exhibited increased swelling capacity, consequently prolonging drug release to the desired 24-hour timeframe. Overall, these results underscore the intricate interplay between polymer composition, swelling behavior, and release kinetics in achieving sustained release formulations of Valsartan.

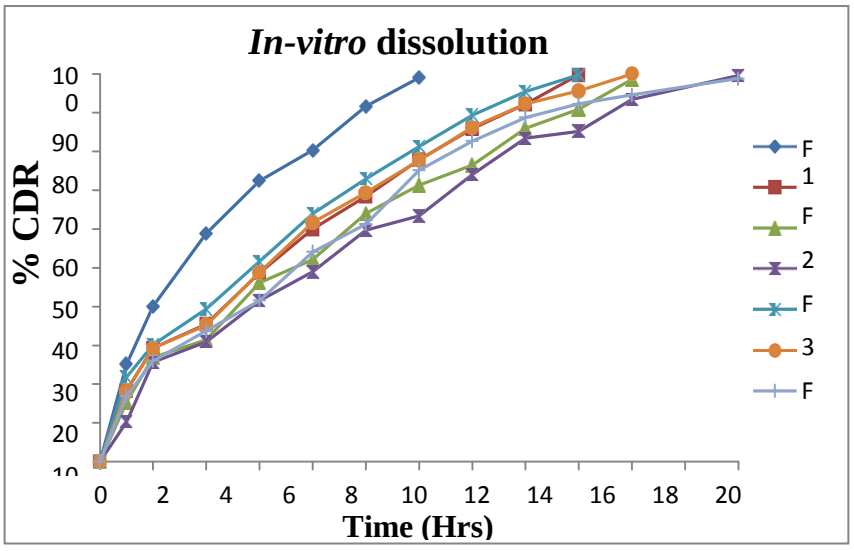

Fig 3. In-vitro dissolution

Table 5. **The comparative dissolution profile of formulations F_1 to F_7**

Time (Hrs)	Cumulative Percentage Drug Release						
	F_1	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**
0	0	0	0	0	0	0	0

1	25.12±0.09	18.34±0.43	15.386±0.33	10.29±0.55	21.91±0.54	18.25±0.32	16.90±0.85
2	40.02±0.12	29.24±0.21	26.905±0.45	25.64±0.62	30.92±0.43	29.25±0.22	25.99±0.42
4	58.82±0.14	35.45±0.33	31.465±0.21	30.94±0.53	39.33±0.54	35.20±0.64	33.71±0.79
6	72.41±0.14	48.71±0.2	46.137±0.13	41.54±0.45	51.64±0.51	48.82±0.73	41.55±0.54
8	80.03±0.28	59.99±0.54	52.186±0.43	48.96±0.38	63.93±0.65	61.73±0.85	54.08±0.64
10	91.61±0.34	68.41±0.55	63.97±0.42	59.68±0.42	72.96±0.72	69.40±0.88	61.27±0.53
12	99.07±0.12	77.09±0.22	71.33±0.54	63.38±0.38	81.23±0.42	77.73±0.95	75.14±0.43
14	--	85.86±0.26	76.50±0.65	74.11±0.43	89.37±0.45	86.24±0.76	82.67±0.48
16	--	92.15±0.33	85.96±0.66	83.39±0.14	95.39±0.62	92.28±0.87	88.75±0.48
18	--	99.71±0.42	90.88±0.59	85.21±0.11	99.77±0.11	95.62±0.73	92.23±0.48
20	--	--	98.54±0.43	93.39±0.14	--	99.99±0.61	94.54±0.48
24	--	--	--	99.54±0.11	--	--	98.78±0.48

***In-vitro* drug release profile sustain release Valsartan matrix tablets**

Table 6. Release exponent values and the release rate constant values of various formulations

Batch	**Zero order**	**First order**	**Higuchi's plots**	**Korsmeyer-Peppas plots**		**Best fitModel**	**Drug release mechanism**
	R^2	**R^2**	**R^2**	**R^2**	**N**		
F_1	0.9292	0.983	0.9117	0.915	0.596	First order	Non-Fickian
F_2	0.968	0.973	0.8945	0.914	0.593	First order	Non-Fickian
F_3	0.915	0.985	0.9216	0.898	0.6072	First order	Non-Fickian
F_4	0.944	0.977	0.8927	0.893	0.579	First order	Non-Fickian
F_5	0.943	0.990	0.9583	0.909	0.489	First order	Non-Fickian
F_6	0.899	0.957	0.9024	0.928	0.7912	First order	Non-Fickian
F_7	0.897	0.988	0.9259	0.939	0.4839	First order	Non-Fickian

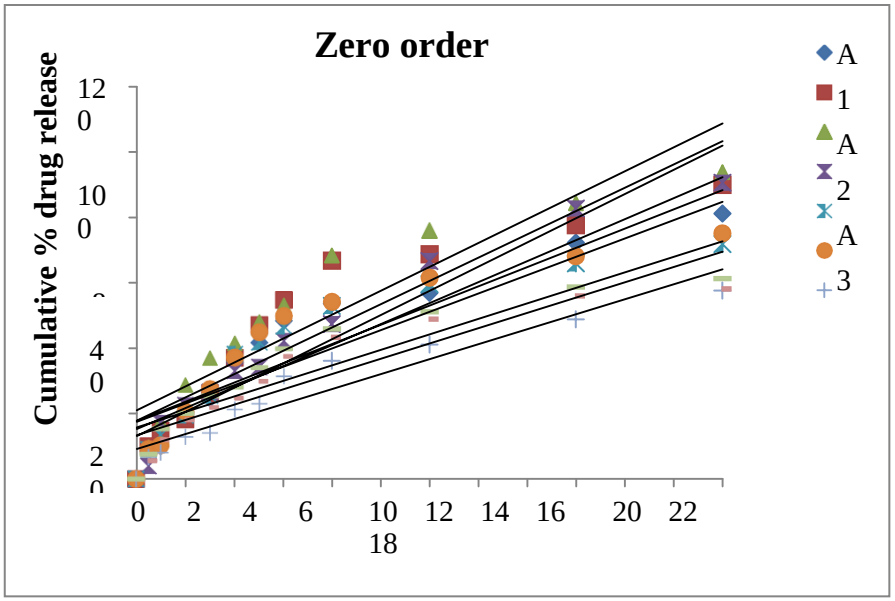

Fig 4. Comparative Zero Order release profile of formulations F_1 to F_7

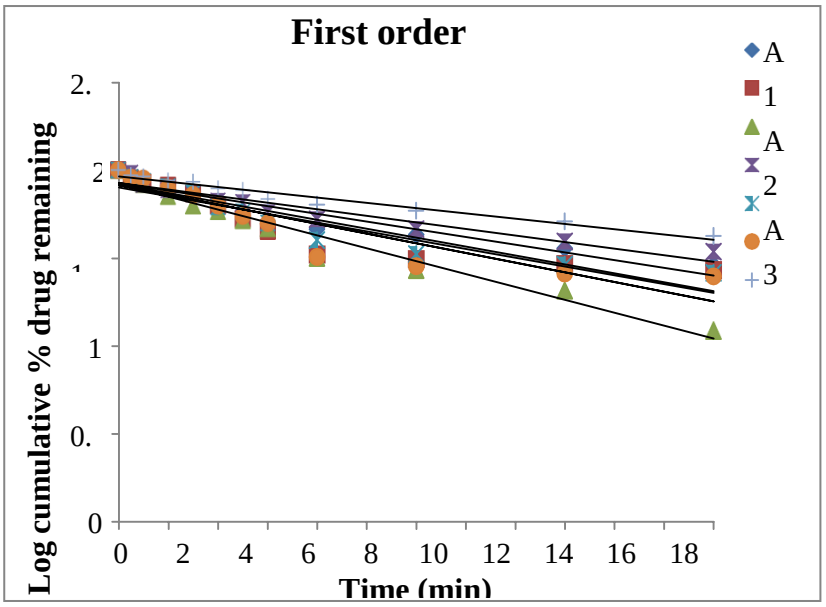

Fig 5. Comparative First Order release profile of formulations F_1 to F_7

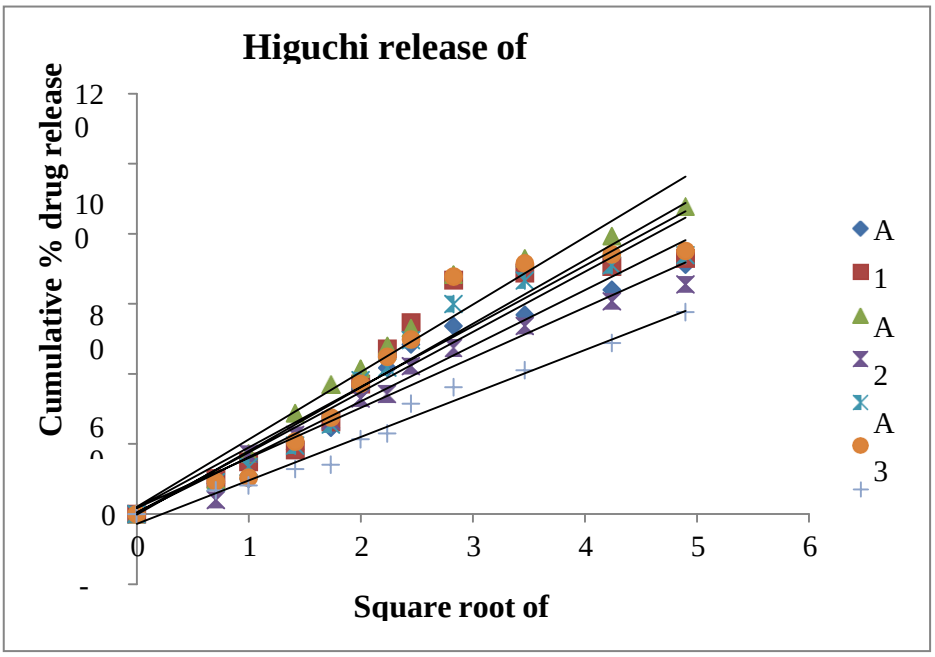

Fig 6. Comparative Higuchi release profile of formulations F_1 to F_7

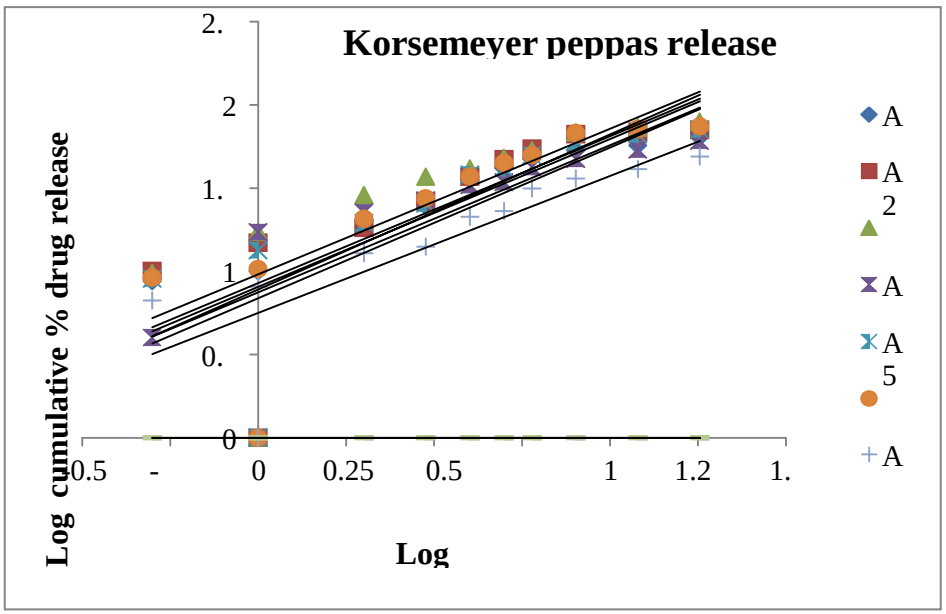

Fig 7. Comparative Korsemeyer Peppas release profile of formulations F_1 to F_7

Stability studies:

Following the in-vitro drug release analysis, formulations F4 and F7 emerged as the most promising candidates for further evaluation through three-month stability studies. These studies were conducted at two different storage conditions: 25ºC/60% RH and 45ºC/75% RH, as per the prescribed method outlined in section four.

During the stability assessment, the selected formulations underwent rigorous evaluation for key parameters including physical appearance, hardness, friability, drug content, and in-vitro drug release profiles. Encouragingly, the results demonstrated no significant alterations in any of these parameters throughout the entire study duration.

Throughout the three-month stability studies, both formulations exhibited remarkable stability, with no discernible changes in physical appearance, tablet hardness, or friability. Moreover, the drug content remained consistent, ensuring the formulations' potency remained intact. Importantly, the in-vitro drug release profiles also remained consistent, indicating sustained release characteristics were maintained throughout the study.

Crucially, no evidence of significant drug degradation was observed throughout the stability testing period, affirming the physical and chemical stability of the prepared formulations. These findings underscore the robustness and reliability of formulations F4 and F7, suggesting their suitability for further development and potential therapeutic application.

Table 7. Results of stability studies for formulation F_4 stored at 25ºC/60% and45ºC/75% RH

Storage period	Stored at 25ºC/60% RH				Stored at 40ºC/75% RH			
	Formulation F_4				Formulation F_4			
	Hardness Kg/cm^2	% friability	%Drug content	% CDR	Hardness Kg/cm^2	% friability	% Drug content	% CDR
Initial	8.1±0.09	0.59±0.11	99.69±0.31	99.6±0.41	8.2±0.073	0.59±0.22	99.5±0.32	99.6±0.2
After-1 month	7.8±0.13	0.62±0.31	98.82±0.12	99.4±0.41	7.8±0.096	0.63±0.13	98.8±0.22	99.2±0.5
After-2 month	7.9±0.47	0.67±0.21	97.98±0.22	98.8±0.41	7.6±0.08	0.65±0.32	97.3±0.32	98.5±0.4
After-3 month	7.7±0.14	0.63±0.11	97.77±0.31	98.2±0.41	7.6±0.08	0.67±0.12	97.9±0.4	97.7±0.4

Table 8. Results of stability studies for formulation F_7 stored at 25ºC/60% and45ºC/75% RH

Storage period	Stored at 25ºC/60% RH				Stored at 40ºC/75% RH			
	Formulation F_7				Formulation F_7			
	Hardness Kg/cm^2	% friability	% Drug content	% CDR	Hardness Kg/cm^2	% friability	Drug content	% CDR
Initial	6.5±0.08	0.55±0.23	101.5±0.31	98.5±0.51	6.7±0.08	0.55±0.31	96.7±0.34	98.8±0.52

After-1 month	6.6±0.18	0.56±0.32	99.5±0.13	98.7±0.52	6.5±0.12	0.56±0.12	96.6±0.31	98.6±0.53
After-2 months	6.2±0.23	0.62±0.42	99.5±0.22	98.3±0.54	6.3±0.25	0.58±0.12	96.3±0.32	97.9±0.23

CONCLUSION

The present study aimed to explore methods for sustaining the release of Valsartan from matrix tablets through the utilization of various concentrations of cross-linking agents and polymers. Key conclusions drawn from the obtained results are as follows:

- Pre-formulation studies encompassing angle of repose, bulk density, tapped density, Hausner's ratio, and Carr's index revealed that all formulations adhered to standard limits, ensuring consistency in powder characteristics.
- Fourier-transform infrared (FTIR) studies indicated the absence of any chemical interactions between the drug and excipients employed in the formulations, affirming the compatibility of the components.
- Post-compression evaluations, including weight variation, thickness, hardness, friability, and drug content assessments, exhibited satisfactory outcomes across all formulation batches.
- In-vitro drug release studies conducted in simulated gastric and intestinal fluids over 24 hours demonstrated that formulations containing higher concentrations of chitosan (e.g., F4) and sodium alginate (e.g., F7) sustained drug release effectively, achieving release percentages of 99.54% and 98.78% respectively.
- Analysis of drug release kinetics revealed adherence to first-order kinetics, suggesting a non-Fickian mechanism governing drug release.
- Stability studies affirmed the stability of the tablet formulations throughout the duration of the study, indicating robustness and reliability.
- Overall, the findings underscored the pivotal role of polymers and cross-linking agents in formulating sustained-release matrix tablets of Valsartan. Notably, formulations with elevated concentrations of these components exhibited reduced drug release rates, while demonstrating comparable diffusion and erosion kinetics.

In essence, this study illuminates promising strategies for enhancing the sustained release of Valsartan, offering valuable insights into the formulation parameters crucial for optimizing drug delivery and therapeutic efficacy.

SUMMARY

Valsartan, an angiotensin II receptor antagonist, plays a crucial role in managing conditions like hypertension, congestive heart failure, and post-heart attack complications by regulating blood pressure and reducing aldosterone activation. Its short half-life necessitates frequent administration, making sustained-release formulations desirable. To address this need, sustain-release matrix tablets of Valsartan were developed using Carbopol 934P and cross-linking agents alongside other excipients. Compatibility studies via FT-IR confirmed the absence of interactions between the drug and excipients. Pre-compression assessments, including flow and compressibility properties, demonstrated favourable characteristics. Post-compression evaluations encompassing weight variation, hardness, thickness, friability, and drug content confirmed compliance with official specifications. Notably, tablets exhibited hardness and thickness within the desired range of 6.0 to 8.0 kg/cm² and 7.8 to 8.0 mm respectively.

In-vitro dissolution studies revealed sustained drug release, with formulations F4 and F7 achieving release percentages of 99.54% and 98.78% respectively over 24 hours. Mechanistic analysis indicated first-order release kinetics with a non-Fickian mechanism. Stability studies over three months confirmed the physicochemical stability of the formulations, with no significant alterations observed in hardness, friability, drug content, or in-vitro drug release profiles. In summary, the development of stable matrix tablet formulations of Valsartan for sustained release represents a significant advancement in the management of hypertension, offering improved therapeutic efficacy and patient compliance.

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