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Development and Evaluation of Valsartan Sustained Release Matrix Tablets

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ABSTRACT

Objective: *The primary goal of the current study was to create and assess valsartan, an angiotensin II receptor type 1 antagonist, sustain release matrix tablets. Formulations with sustained release give the medication either systemically or locally at a predefined rate for a set amount of time.*
Methods: *Using a mixture of different release retardant polymers and chitosan and sodium alginate concentrations, a direct compression approach was used to prepare the matrix tablet. Different pre-compression and post-compression parameters were applied to the powder mixes.*
Results: *The results of 24-hour in-vitro dissolution experiments using pH 6.8 phosphate buffer for 24 hours and 0.1 N HCL for the first two hours reveal that formulations F4 and F7 had good solubility profiles in comparison to other formulations. To assess the kinetics and drug release, the release data was fitted to a number of mathematical models, including the Korsmeyer-Peppas model, the Higuchi equation, the Zero-order, and the First-order models. The mechanism was discovered to be non-Fickian, and the drug release followed first order.*
Conclusion: *In summary, the drug release was sustained for a whole day in a formulation that included release retardant polymers and higher concentrations of chitosan and sodium alginate.*

Keywords: *Valsartan, Carbopol 934P, Chitosan, sodium alginate, sustain release matrix tablet.*

INTRODUCTION

The best way to give pharmaceuticals is orally since it is the most convenient method because it is also the most flexible in terms of formulation, patient compliance, and convenience of administration. Oral medication delivery methods make up the majority of drug delivery systems on the market.[1]

However, it's likely that around 80% of all medications that have a systemic effect are taken orally. Due to its many benefits, including painless drug administration and self-administration, the oral route is among the most practical methods for delivering medication. Tablets are a popular solid dosage form that offer several potential benefits. They are unit dose form, have the best combined properties of chemical, mechanical, and microbiological

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stability, and are the least expensive of all oral dosage forms. They also have the least amount of variability in their content and are the easiest to package and ship. [1-2]

Release retardant polymers are used in the formulation of matrix tablets, an oral medication, to extend the duration of action. When compared to alternative prolonged release dosage forms, matrix tablets have a number of benefits, including being simple to make, adaptable, efficient, affordable, and able to release substances with a high molecular weight.[3] In order to make matrix tablets, a medication and carrier material are typically blended and then compressed. Tablets with a hydrophilic matrix are frequently employed to deliver medications under control. The outer surface of these tablets swells upon contact with water or bodily fluids due to chain relaxation and polymer hydration, creating a hydrogel cover around the dry core. It is widely acknowledged that the gel layer acts as a diffusional barrier to impede the absorption of water and, consequently, the release of drugs.[4]

An independent important risk factor for stroke and cardiovascular disease is high blood pressure; in fact, hypertension is directly responsible for 5.8% of all deaths. All things considered, hypertension is one of the five chronic illnesses (together with psychological disorders, diabetes, heart disease, and asthma) that account for half of the health system's spending.[5]

Angiotensin II receptor antagonist valsartan is commonly used to treat heart failure and hypertension in patients with left ventricular dysfunction after myocardial infarction. It also lowers cardiovascular mortality in these patients. Patients with hypertension can reduce their blood pressure with valsartan, a strong and extremely specific type I antagonist.[6] The current study set out to create and assess the antihypertensive medication matrix tablets that included valsartan as the active ingredient.

MATERIALS AND METHODS

Materials

The supplier of valsartan was PM Pharmaceutical Pvt. Ltd, Hyderabad, India. Sodium alginate, chitosan, and carbopol 934P were purchased from S.D. Fine Chemical in Mumbai, India. Analytical grade substances were employed in all other cases.

Preparation of Valsartan Matrix release Tablets

By using different concentrations of chitosan and sodium alginate as cross-linking agents, carbopol 934 P as release retardant polymers, magnesium stearate as lubricant, talc as a glidant, and microcrystalline cellulose as filler, sustain release matrix tablets of Valsartan were prepared by the direct compression method. Each formulation has 80 milligrams of pure medication in it. Accurate weight measurements of the medicine and excipients were made, and each was passed through sieve number 60 in isolation. After transferring the sieved powder materials to a mortar using the geometrical dilution method, they were thoroughly mixed for ten to fifteen minutes. Finally, lubricant and glidant were added, and the mixture was further mixed for three to five minutes.

Prior to compressing the powder mixes, the hardness was modified. A single punch tablet machine (Lab Press, India) with 8mm flat surface punches and a compression force of 6–8 kg/cm3 was used to compress the powder mixtures into 250 mg tablets. Table 1 lists the contents of the Valsartan sustain release matrix tablets. [7]

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Table 1: Formulae for the Preparation of Lamivudine Microspheres

Name of Ingredients	Quantity of Ingredients per each tablet (mg)						
	F1	F2	F3	F4	F5	F6	F7
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
MCC	60	55	50	45	55	50	45
Total Weight	250	250	250	250	250	250	250

Evaluation Tests for prepared Formulations

Hardness

It was carried out with the help of Monsanto Tablet Hardness Tester. [8]

Friability/ Durability

Twenty tablets were weighed and noted as W0 cumulatively (Initial weight). The pills were then dedusted with a Roche Friabilator for 4 minutes at a speed of 25 rpm, and weighed again recorded as (W). The following equation was used to obtain the percentage of friability (%Friability ≤1).

$$\text{Friability (\%)} = (W0 - W) / W0 \times 100$$

In-vitro Dissolution Study

The USP-II (Paddle) dissolving equipment (Lab India) was used for the in-vitro dissolution investigations, and it was rotated at 50 rpm. For the first two hours, 0.1 N HCL was the dissolution medium employed; for the next twenty-two hours, 6.8 pH phosphate buffer was used. The dissolving medium's temperature was kept at 37±0.5oC. At certain intervals, a 5 ml was removed, and the same volume of fresh medium was added. Using pH 6.8 phosphate buffer as a blank, the extracted samples were diluted with pH 6.8, filtered, and examined at 249 nm using a UV spectrophotometer. The percentage cumulative release of the drug was computed, and the same information was fitted to kinetic modeling. [9-10]

RESULTS AND DISCUSSION

The produced tablets were assessed for drug content, hardness, friability, and weight variation. Table 2 displayed post-compression study results. The range of 3.8-4.2 mm was found to be the average thickness for all formulations, falling within the permitted deviation limit of 5% of the standard value. One of the most important metrics for assessing a tablet's resistance to capping, abrasion, or breakage during handling, storage, and transit prior to administration is its hardness. The average hardness of each formulation ranges from 6- 8 kg/cm2. This guarantees that every formulation batch has good handling qualities. The Roche friabilator was used to assess the produced tablets' friability. All of the formulations' average

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percentage friability was determined to be within the pharmacopoeial range, ranging from 0.447% to 0.72%. Because the powder material flowed freely, uniform die fill with permitted fluctuation in accordance with IP specifications resulted in tablets with uniform weights. All formulations showed weight variations between 249.92 and 253.88 mg. For formulations F1 through F7, the percentage of drug content was found to range between 98.25% and 101.61% w/w.

Table 2: Post-Compression Parameters

Formulation	Diameter (mm)± SD	Thickness (mm)± SD	Weight variation (mg)	Hardness (kg/cm2)	Friability (%)	Drug content (%)
F1	7.82±0.012	3.9±0.09	250.89±0.12	7.3±0.04	0.61±0.007	98.25±0.044
F2	7.80±0.002	4.0±0.02	253.88±0.60	7.8±0.03	0.52±0.005	100.31±0.037
F3	7.85±0.007	4.2±0.01	251.12±0.52	8.0±0.07	0.58±0.031	98.54±0.07
F4	7.84±0.022	3.9±0.07	249.81±0.13	6.5±0.04	0.72±0.016	99.67±0.087
F5	8.0±0.015	4.0±0.04	250.80±0.32	6.8±0.08	0.665±0.09	99.37±0.058
F6	7.94±0.010	3.8±0.09	248.92±0.44	7.1±0.03	0.714±0.01	98.97±0.073
F7	7.97±0.016	4.1±0.01	252.61±0.60	6.0±0.05	0.447±0.00	101.61±0.08

The *in-vitro* release profile for chitosan-carbopol and sodium alginate-carbopol based Valsartan sustain released matrix tablets are illustrated in Figure 1. The concentration of chitosan, sodium alginate, polymers, and dissolving media had the greatest effects on the in-vitro release of valsartan from matrix tablet formulations. The swelling behaviour of the tablets affects the in-vitro release of Valsartan from produced matrix tablets; the more the tablet swells, the less medication is released *In-vitro*.

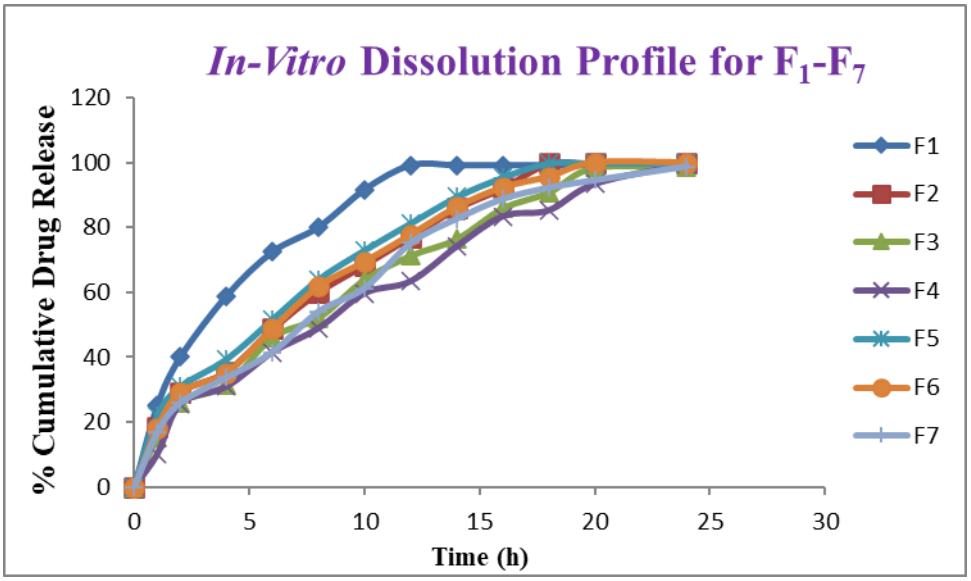

Figure 1: Comparative *In-vitro* Dissolution Profiles for Lamivudine Microspheres

Since Formulation F1 doesn't include a crosslinking agent, nearly all of the medications were released after 12 hours. Formulations F2, F3, F5, and F7, which had reduced sodium alginate and chitosan concentrations, demonstrated nearly complete drug release in 16 hours, 20 hours, 16 hours, and 18 hours, respectively. Because the maximum amount of medicine was

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released before the desired period of time, i.e., 24 hours, these formulations were therefore regarded as poor formulations.

At this pH of 6.8, the ionic interaction between negatively charged polymers and crosslinking agents was significantly reduced, forming a loose network with an increased porous surface that permits a large portion of the dissolving media. The release of Valsartan is prolonged to 24 hours in Formulations F4 and F7, which have the highest concentrations of chitosan and sodium alginate, respectively, along with carbopol gum. This may be because a self-assembled poly electrolyte complexes film forms on the surface of the cross-linking agent-polymer based system. The data from the dissolution study was well fitted to kinetic models to ascertain drug release characteristics. The same was present in Table 3.

Table 3: Kinetic parameters

Formulation code	Zero order	First order	Higuchi	Korsmeyer- Peppas	
	R	R	R	R	n
F1	0.9293	0.982	0.9116	0.912	0.597
F2	0.969	0.974	0.8944	0.915	0.594
F3	0.916	0.984	0.9217	0.899	0.6077
F4	0.946	0.978	0.8926	0.892	0.577
F5	0.944	0.992	0.9581	0.902	0.488
F6	0.895	0.958	0.9022	0.929	0.7911
F7	0.896	0.981	0.9258	0.938	0.4838

CONCLUSION

Sodium alginate, chitosan, and carbopol were used as release retardant polymers and crosslinking agents to successfully produce sustain release matrix tablets of the anti-hypertensive drug Valsartan in the current investigation. Pre-compression evaluation results indicated that the medication and excipients were compatible, and the powder mixture had good to acceptable flow qualities, resulting in tablets with consistent weight, thickness, and hardness. For the treatment of hypertension, formulations F4 and F7, which have higher concentrations of chitosan and sodium alginate, respectively, and release retardant polymers, demonstrated the desired percentage of drug release at the end of 24 hours. This could increase patient compliance by lowering dosage and frequency of administration.

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