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# DESIGN AND EVALUATION OF VALSARTAN GASTRORETENTIVE SUSTAINED RELEASED TABLETS

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**ABSTRACT**

Valsartan, an angiotensin-receptor blocker (ARB) widely prescribed in variety of cardiac conditions like hypertension, diabetic nephropathy and heart failure. The biological half-life is 3-6 hours and the maximum absorption is at initial part of gastro intestinal tract. In the present study Valsartan floating tablets were prepared by wet granulation method using non effervescence technique. The tablets were formulated using IPA as granulating fluid with binder PVP-k30 and employing polymers like HPMC K15M, HPMC K100M and EC. The prepared floating tablets were evaluated for various physicochemical parameters. The in-vitro drug release pattern of Valsartan floating tablets was fitted to different kinetic models which showed highest regression for zero order kinetics with Higuchi mechanism. Out of all formulations the one prepared with EC in granulation fluid and combination of different grades of HPMC was optimized (VF11) based on desired sustained release time (12hrs) followed by acceptable swelling and floating properties. The effect of $P^H$ on swelling index and floating properties of optimized formulation (VF11) were also investigated, and the study revealed that there are no significant changes on swelling index and floating properties.

**Keywords:** Valsartan, Non-effervescent, Gastroretentive drug delivery, wet granulation, HPMC, EC, PVP-k30, sustained release

## INTRODUCTION

Development of oral controlled release systems has been a challenge to formulation scientists because of their inability to restrain and localize the system in the targeted area of the gastrointestinal tract. Controlled release preparations using alternative routes have been formulated but the oral route still remains preferable. Amongst the various approaches to target the drug to the stomach or proximal region of small intestine, high density systems have a technical difficulty in formulating a dosage form having a density in the range of 2.4–2.8 g/cm$^3$, swelling systems require an optimum balance between the rate of swelling and rate of erosion of the polymer to avoid unwanted side effects and bio/mucoadhesive systems which can be dislodged from its site of adhesion, may not provide the optimum benefits.

When the drug is formulated with a gel forming polymer such as semi synthetic derivatives of cellulose, it swells in the gastric fluid with a bulk density less than one. It then remains buoyant and floats on the gastric fluid, prolonging gastric residence time (GRT). This floating dosage form is well known as a hydro dynamically balanced system (HBS) [(1,2,3).] It has been suggested for the following instances that an active material can be formulated as an HBS to enhance bioavailability: (1) having a dissolution and/or stability problem in the small intestinal fluids, (2) being locally effective in the stomach, (3) being absorbed only in the stomach

and/or upper part of the intestine (4). Floating tablets, capsules, beads, microspheres and chambers have been reported in literature (5). Floating systems can be developed by two approaches. First is the effervescent system which needs a gas generating agent that may alkalinize the microenvironment of the stomach and whose buoyancy would be dependent on the gas generating agent unlike the second which is a non-effervescent approach [4,5].

Valsartan, $C_{24}H_{29}N_5O_3$,is an anti hypertensive drug, which is an angiotensin -receptor blocker (ARB). It selectively inhibits the binding of angiotensin II to AT1 which effectively inhibits the AT1 -mediated vasoconstrictive and aldosterone - secreting effects of angiotensin II and results in a decrease in vascular resistance and blood pressure. Valsartan is selective for AT1 and has virtually no affinity for AT2. Inhibition of aldosterone secretion may inhibit sodium and water reabsorption in the kidneys while decreasing potassium excretion [6,7]. Valsartan has poor water solubility, low bioavailability (approximately 20-25%), and shorter half-life (nearly 6 hours).It shows good absorption in stomach. Since Valsartan has low bioavailability and shorter half-life, developing a sustained release system can maintain the plasma drug concentration in therapeutic window and increase the therapeutic efficacy of drug. Therefore the present work has been proposed.

## METHODOLOGY

**Materials:** Valsartan was obtained as a gift sample from MSN Pharma Ltd. Hyderabad, India. HPMC K15M, HPMC K100M and Ethyl Cellulose (EC) were received as gift samples from Colorcon, India. Other materials and solvents used were of analytical grade. All the studies were carried out using double distilled water.

**Preparation of Floating Tablets:** Formulations fulfilling minimum requirement are shown in Table I. For each formulation Valsartan, MCC, HPMC K15 and/or K100 were manually blended homogeneously with a mortar. The mixture was wetted using either isopropyl alcohol (IPA) or alcoholic solution of PVP K-30 or EC, passed through a 10 mesh screen, and dried in a hot air oven at 40°C overnight. The 20/40 fraction granules were collected and blended with talc. The homogeneous blend was then compressed into tablets on a single-punch tablet press equipped with 12.5 mm diameter flat punches. The tablet hardness was in the range 6-8 kg/cm$^2$ on a Monsanto tablet hardness tester.

***In Vitro* Buoyancy Studies:** The *in vitro* buoyancy was determined by FLT as per the method [8]. The tablets were placed in a 100-ml glass beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT). The total floating duration was also determined.

***In vitro* Drug Release:** The dissolution test was carried out using USP XXIII dissolution testing apparatus II (paddle method). The test was performed at a paddle speed of 50 rpm using 900 ml of 0.1 N HCl as the dissolution medium, at 37 ± 0.5°C. An aliquot of 5 ml of the sample solution was withdrawn at 0,1, 2, 4, 6, 8, 10, and 12h interval; and the absorbance was measured by using UV-visible spectrophotometer at 250 nm after appropriate dilution[9].

**Effect of pH on Floating Behavior:** Floating behavior of the optimized formulation was studied at various pH conditions. One hundred milliliters of Acidic buffer pH 1.2, Acetate buffer pH 4.0 and Phosphate buffer pH 6.0 [10].

**Effect of pH on Drug Release:** Drug release profile of the optimized formulation VF11 was studied at various dissolution media like Acidic buffer pH 1.2, Acetate buffer pH 4.0 and Phosphate buffer pH 6.0.

**Determination of Swelling Behavior:** The swelling behavior of tablets was determined in fallowing pH 1.2, pH4.0 and pH6.0 solutions at room temperature. The percent increase in diameter and thickness of the tablets were calculated and plotted against time to assess the swelling behavior. The swelling indices were calculated by the following equations: [11]

Swelling index= Final weight – initial weight/ Final weight x 100

## RESULTS AND DISCUSSION

***In Vitro* Drug Release:** The performance of floating formulations has been investigated.The drug release of Valsartan from VF1 was found to be 98.5±0.23% at end of 2$^{nd}$hour. VF2 was found to be 90.5±0.07% at end of 2$^{nd}$ hour, which was not satisfactory due to burst release and also tablet integrity was not maintained.

The drug release of Valsartan from VF3 was found to be 98.5±0.98% at end of 4hr , VF4 was found to

be 93.5±0.05% at end of 4hr, which was not satisfactory and showed less integrity**.**

The batches VF5 - VF8 containing higher concentration of polymers (HPMC K 100M and K15M) prepared by incorporating the PVP-K30 (3.65%) as binder improved the integrity of tablets. The formulations VF5-VF6 initially showed burst effect and released 98.5% and 96.5% at the end of 8hrs respectively.

The formulations VF7, VF8 were prepared by increasing the concentration of binder PVP-K30 (5.5%) in granulation fluid. Integrity of the tablets was improved but not sufficient to decrease initial burst effect.

The formulations (VF9, VF10 and VF11) were tried with Ethyl Cellulose (EC) as secondary retardant in granulation fluid. Formulation VF10 showed better control on initial burst effect than VF9 but exhibited incomplete release which might be due to high viscosity of HPMC K-100M.

The formulation VF11 was made with the combination of HPMC K-15M: HPMC K-100M in the ratio 1:1 using IPA solution of EC as a binder and drug release was found to be 99.89% at the end of 12hrs with better drug release pattern. Thus VF11 was optimized formulation as shown in Fig.1.

**Effect of pH on Drug Release:** The optimized formulation was subjected to study the effect of change in pH of dissolution medium. It was observed that there was no significant change in the drug released pattern as shown in Fig.2.

**Effect of pH on *In vitro* Buoyancy:** The optimized formulation was subjected to study the effect of change in pH on floating behavior. From the results shown in Table II, it was concluded that the variations in pH due to change in the gastric contents might not affect the FLT and FT of the tablets.

**Determination of Swelling Behavior:** Tablets composed of hydrophilic polymeric matrices build a gel layer around the tablet core when they come in contact with water. This gel layer governs the drug release as well as ensures floating [13,14]. The optimized formulation was subjected to study the effect of change in pH of dissolution medium. It was observed that there was no significant change in the drug released pattern as shown in Table III. It was observed that type of medium did not affect the swelling behavior of optimized tablets.

**Optimization formulation released kinetics:** Based on the results of optimized formulation (VF11) containing HPMC K15 M 200 mg, HPMC K100 M 200 mg as primary polymers and EC 20 mg as the retardant was devised as the optimized formula. Modeling of The optimized formulation drug released was plotted according to Zero, order, first order, Higuchi's and Koresmeyer-peppas graphically (Fig.3, 4, 5, 6) and the regression coefficient values were studied as shown in Table IV. Based upon $R^2$value the VF11 formulation follow zero order released and Higuchi's best fit diffusion mechanism.

## CONCLUSION

The study was aimed at preparation of gastroretentive tablets of Valsartan. The non-effervescent-based floating approach was selected. The hydrophilic matrix containing HPMC K15M and HPMC K100M alone and in combination could not control the drug release pattern. Incorporation of hydrophobic polymer EC in granulation fluid showed good drug release pattern. It was concluded that stable sustained release floating gastroretentive tablets of valsartan with slight increase in FLT and FT greater than 12 h and desired drug release pattern could be successfully prepared.

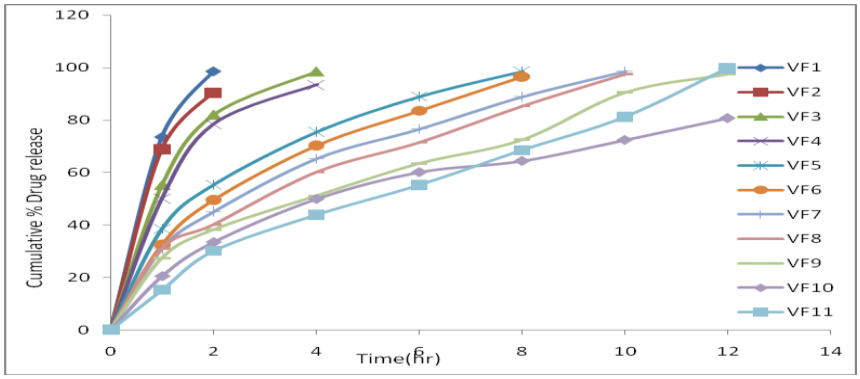


**Fig. 1 *in vitro* drug release profiles of floating formulations of Valsartan**

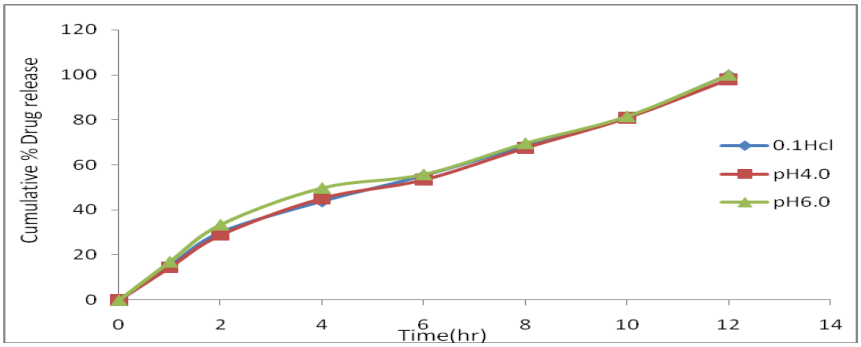


**Fig.2 Effect of pH on in-vitro dissolution profile of VF11**

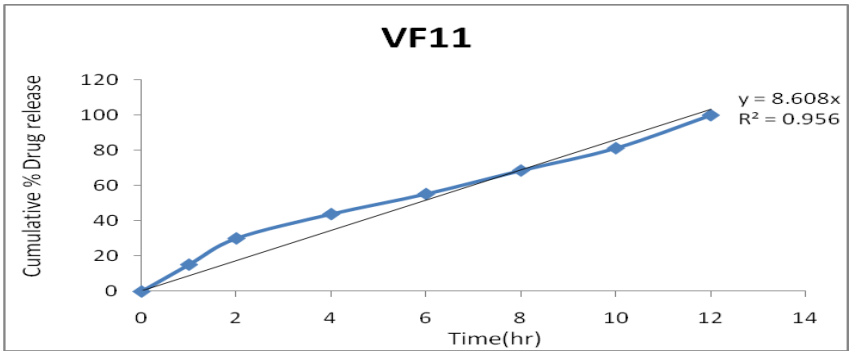


**Fig.3 Zero order release kinetics of VF-11formulation**

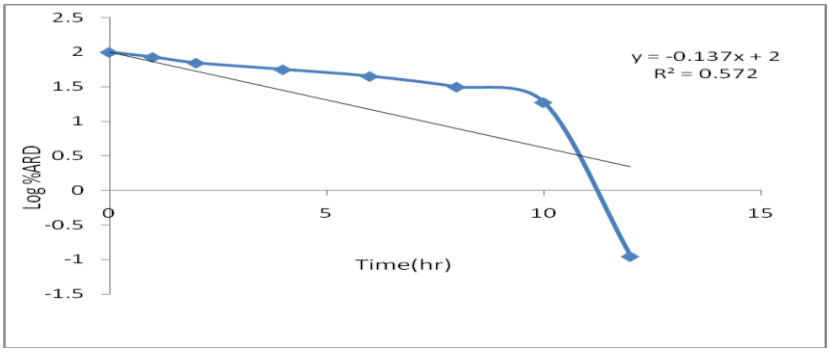


**Fig.4. First order release kinetics of VF-11 formulation**

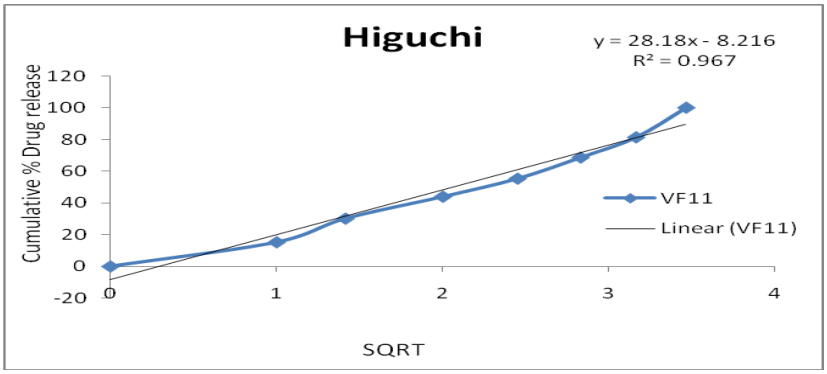


**Fig.5. Higuchi release mechanism of VF-11 formulation**

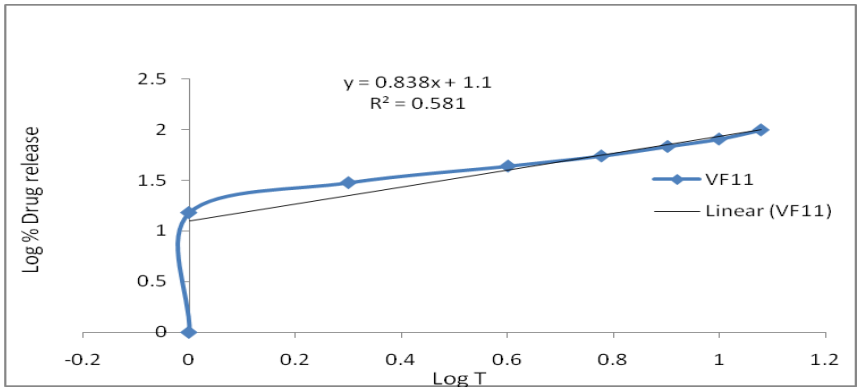


**Fig.6.Korsmeyer and Peppas release mechanism of VF-11formulation**

**Table I Composition of Valsartan Floating Tablets**

| S. No | Ingredients (mg) | Formulation Code | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | VF1 | VF2 | VF3 | VF4 | VF5 | VF6 | VF7 | VF8 | VF9 | VF10 | VF11 |
| 1 | VALN | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| 2 | HPMC K 15M | 200 | -- | 400 | -- | 400 | -- | 400 | -- | 400 | -- | 200 |
| 3 | HPMC K 100M | -- | 200 | -- | 400 | -- | 400 | | 400 | -- | 400 | 200 |
| 4 | PVP K-30 | -- | -- | -- | -- | 20 | 20 | 30 | 30 | -- | -- -- | -- |
| 5 | Ethyl cellulose | -- | -- | -- | -- | -- | -- | -- | -- | 20 | 20 | 20 |
| 6 | Microcrystalline cellulose | 293.5 | 293.5 | 93.5 | 93.5 | 73.5 | 73.5 | 63.5 | 63.5 | 73.5 | 73.5 | 73.5 |
| 7 | IPA | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S |
| 8 | SLS | 5.5 | 5.5 | 5.5 | 5.5 | 5.5 | 5.5 | 5.5 | 5.5 | 5.5 | 5.5 | 5.5 |
| 9 | Talc | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 |
| 10 | **Total weight** | **550** | **550** | **550** | **550** | **550** | **550** | **550** | **550** | **550** | **550** | **550** |

**Table II Effect of pH and on Floating Behavior of VF11**

| S.No | Medium | FLT(Sec) | FT(Hr) |
|---|---|---|---|
| 1 | 0.1N Hcl | 36 | 12 |
| 2 | Acid Phthalate Buffer pH4.0 | 52 | 12 |
| 3 | Phosphate buffer pH 6.0 | 59 | 12 |

**Table III Swelling index profile of optimized formulation (VF11)**

| SWELLING INDEX | | | | |
|---|---|---|---|---|
| S. No | Time (hr) | 0.1NHcl | pH 4.0 | pH6.0 |
| 1 | 1 | 103.0 | 105.0 | 104.7 |
| 4 | 6 | 102.3 | 100.2 | 100.1 |
| 5 | 8 | 99.9 | 98.99 | 99.5 |
| 6 | 10 | 95.7 | 93.79 | 94.6 |
| 7 | 12 | 95.4 | 95.24 | 94.9 |

**Table IV. Release kinetics data of optimized formulation VF11**

| | $R^2$ values | | | | n values |
|---|---|---|---|---|---|
| **Formulations** | **Zero order** | **First order** | **Higuchi** | **Korsmeyer-peppas** | **Korsmeyer-peppas** |
| VF-11 | 0.9560 | 0.5720 | 0.9670 | 0.5810 | 0.838 |

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