Design, development, and *in-vitro* assessment of Gastroretentive effervescent floating tablets of valsartan using various polymers

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***Abstract*—Objective: To formulate buoyant valsartan tablets by direct compression technique by hydroxypropyl methylcellulose K4M, hydroxypropyl methylcellulose K100, and Xanthan gum polymers to avoid side effects related to stomach and to obtain the controlled release of the drug. Methods: In this study, 12 formulations were made using different polymers in different proportions by direct compression. For all the formulations post-compression studies were studied. Results: Pre-formulation studies, Fourier Transform Infrared Spectroscopy, drug content, *in-vitro* drug release, and kinetics of drug release showed acceptable values. Solubility, melting point, and Ultraviolet analysis of the drug were within the acceptable ranges. Conclusion: Fourier Transform Infrared Spectroscopy shows the spectra of the drug alone and the combination of polymers and valsartan drug showed that there are no interactions between them and that shows they are compatible with each other. Based on release kinetics data and graphical analysis. F3 formulation has a polymer-drug ratio of 1.5:1 and shows a better release of the drug. Drug release data fitted into zero order kinetics. Korsemeyer-Peppas plot has an 'n' value that was in the range of 0.47-0.77. Valsartan tablets formulated with hydroxypropyl methylcellulose K4M demonstrate a better release of the drug for 12 hours. Drug releases through Non-Fickian diffusion. It shows good buoyancy. From all the data it can be concluded that it is feasible to design controlled-release gastroretentive effervescent buoyant valsartan tablets using HPMC K4M.**

***Index Terms*—Blood pressure, Effervescent, Polymers, Valsartan.**

INTRODUCTION

The most popular and practical method of medicine delivery is oral administration. Despite significant drawbacks, the drug given orally is regarded as the best medication delivery route due to its ease of administration, high patience compliance rate and treatment at low cost. Frequent intake of drugs is necessary because medications with short half-lives and are rapidly removed from the systemic circulation. In order to address this issue, gastroretentive delivery systems for drugs have been developed which lower the frequency of doses by maintaining an effective plasma drug concentration over extended periods of time. Administering the medication in a regulated and repeatable way, also has the benefit of reducing variations in plasma drug concentration [1].

Because the gastroretentive drug delivery system was designed to stay in the stomach for a long time and release the medicine, it is possible to frequently and constantly inject drugs into the upper part of the GIT. Medications that are unstable in the intestinal environment or that function locally in the stomach that have an absorption window in the stomach or upper section of the small intestine or that have limited solubility at higher pH were changed to reside for a longer duration in the stomach[2].

A variety of techniques, such as floating drug delivery systems, raft systems, high-density and low-density systems, magnetic systems, super porous hydrogel, and bioadhesive/mucoadhesive systems, are being

employed to develop a superior gastroretentive drug delivery system. Floating drug delivery medications are the most popular. Floating medication delivery medications remained buoyant in the stomach for a longer amount of time because their bulk density was lower than that of the gastric fluid. As the medication delivery system floated on the contents of the stomach, the drug was delivered gradually. This aids in controlling the drug's plasma fluctuation and extending the stomach retention period [3].

Angiotensin receptor blockers like valsartan are frequently recommended for hypertension. The upper portion of the digestive system absorbs it. 23% was found to be the oral bioavailability of valsartan. For the efficient treatment of hypertension, an adult should take 80 mg of valsartan orally. The drug's short life of 3-6 hours leads to the controlled release formulation development. Frequent intake of doses is necessary because medications with short half-lives are absorbed in the gastrointestinal tract and rapidly removed from the systemic circulation. In order to solve this issue gastroretentive drug delivery methods were developed. Administering the medication orally to the stomach has the benefit of reducing variations in plasma drug concentration [4].

This is an attempt to develop and evaluate gastroretentive effervescent buoyant tablets that contain valsartan drug by different polymers such as hydroxypropyl methylcellulose K4M, hydroxypropyl methylcellulose K100, Xanthan gum with citric acid enhances floating and $NaHCO_3$ as a gas producing agent. Investigating how polymers affect the release of drugs and the sodium bicarbonate effect on buoyancy.

METHOD

A direct compression technique was used to create the valsartan effervescent floating tablets. Xanthan gum and HPMC were employed as drug-retarding polymers. The gas-generating agent utilized was sodium bicarbonate. A floating enhancer is a citric acid. The binder is polyvinyl pyrrolidine. Cellulose in microcrystalline form serves as a diluent. Talc is a glidant, and magnesium stearate is a lubricant. A 40-mesh sieve was used to pass the drug and excipients.

The required quantities of valsartan drug, HPMC K4M/HPMC K100/Xanthum gum, citric acid, sodium bicarbonate, pvp, microcrystalline cellulose, taken and homogenously in mortar and pestle for 15mins and again allowed to pass through sieve no-40 for the uniformity in the particle size later add magnesium stearate and talc for 5minutes and allowed to pass through sieve no-40. With constant compression force in the rotary tablet compression machine drug mixtures were directly compressed into tablets. Different formulations composition was given in the tables

Table 1- Formulation 1

Ingredients	Amount (mg)
Valsartan	80
HPMC K4M	40
HPMC K100	-
Xanthan gum	-
Sodium bicarbonate	50
Citric acid	10
PVP	15
Microcrystalline cellulose	135
Magnesium stearate	10
Talc	10
Total	350

Table 2- Formulation 2

Ingredients	Amount (mg)
Valsartan	80
HPMC K4M	80
HPMC K100	-
Xanthan gum	-
Sodium bicarbonate	50
Citric acid	10
PVP	15
Microcrystalline cellulose	95
Magnesium stearate	10
Talc	10
Total	350

Table 3- Formulation 3

Ingredients	Amount (mg)
Valsartan	80
HPMC K4M	120
HPMC K100	-
Xanthan gum	-
Sodium bicarbonate	50
Citric acid	10
PVP	15

Microcrystalline cellulose	55
Magnesium stearate	10
Talc	10
Total	350

Table 4- Formulation 4

Ingredient	Amount (mg)
Valsartan	80
HPMC K4M	160
HPMC K100	-
Xanthan gum	-
Sodium bicarbonate	50
Citric acid	10
PVP	15
Microcrystalline cellulose	15
Magnesium stearate	10
Talc	10
Total	350

Table 5- Formulation 5

Ingredient	Amount (mg)
Valsartan	80
HPMC K4M	
HPMC K100	40
Xanthan gum	
Sodium bicarbonate	50
Citric acid	10
PVP	15
Microcrystalline cellulose	135
Magnesium stearate	10
Talc	10
Total	350

Table 6- Formulation 6

Ingredient	Amount (mg)
Valsartan	80
HPMC K4M	-
HPMC K100	80
Xanthan gum	-
Sodium bicarbonate	50
Citric acid	10
PVP	15
Microcrystalline cellulose	95
Magnesium stearate	10
Talc	10
Total	350

Table 7- Formulation 7

Ingredient	Amount (mg)
Valsartan	80
HPMC K4M	
HPMC K100	120
Xanthan gum	
Sodium bicarbonate	50
Citric acid	10
PVP	15
Microcrystalline cellulose	55
Magnesium stearate	10
Talc	10
Total	350

Table 8- Formulation 8

Ingredient	Amount (mg)
Valsartan	80
HPMC K4M	-
HPMC K100	160
Xanthan gum	-
Sodium bicarbonate	50
Citric acid	10
PVP	15
Microcrystalline cellulose	15
Magnesium stearate	10
Talc	10
Total	350

Table 9- Formulation 9

Ingredient	Amount (mg)
Valsartan	80
HPMC K4M	-
HPMC K100	-
Xanthan gum	40
Sodium bicarbonate	50
Citric acid	10
PVP	15
Microcrystalline cellulose	135
Magnesium stearate	10
Talc	10
Total	350

Table 10- Formulation 10

Ingredient	Amount (mg)
Valsartan	80
HPMC K4M	-
HPMC K100	-

Xanthan gum	80
Sodium bicarbonate	50
Citric acid	10
PVP	15
Microcrystalline cellulose	95
Magnesium stearate	10
Talc	10
Total	350

Table 11- Formulation 11

Ingredient	Amount (mg)
Valsartan	80
HPMC K4M	-
HPMC K100	-
Xanthan gum	120
Sodium bicarbonate	50
Citric acid	10
PVP	15
Microcrystalline cellulose	55
Magnesium stearate	10
Talc	10
Total	350

Table 12- Formulation 12

Ingredient	Amount (mg)
Valsartan	80
HPMC K4M	-
HPMC K100	-
Xanthan gum	160
Sodium bicarbonate	50
Citric acid	10
PVP	15
Microcrystalline cellulose	15
Magnesium stearate	10
Talc	10
Total	350

Precompression parameters: Prior to compression, the powder blend flow characteristics

Angle of repose(θ): The angle of repose was determined using the fixed funnel method. It is the angle formed between a powder pile's surface and the horizontal plane when powders are free to flow through a funnel from a specific height. Additionally, the heap's height and radius were measured [5].

Tan θ= Powder cone's height/ Radius of the heap

Bulk density: Bulk density is defined as the ratio of powder mass to bulk volume. Initial bulk volume was measured after a graduated measuring cylinder was carefully filled with a carefully weighed quantity of powder using a funnel [6].

Bulk density= Powders mass/ Bulk volume

Tapped density: A 100ml measuring cylinder that had been cleaned and dried and 10g powder was filled. Following 100 tappings of the cylinder from a fixed height, the tapped volume was measured using the formula below [6].

Tapped density=Powder total mass/Final tapped volume of powder

Carr's index: The powder blend bulk and tapped densities one can assess the flowability of the powder [7].

[(Tapped density-Bulk density)x100 /Tapped density] = Carrs index

Hausner's ratio: Derived from the relation between the bulk density and the tapped density, which determines flow characteristics of powder blend [7].

Tapped density/ Bulk density=Hausner's ratio

Evaluation of post-compression specifications

Diameter and thickness: 10 tablets were randomly chosen from each formulation to test the thickness and diameter. A screw gauge was used, and the tablet's thickness and diameter were measured and expressed in mm [8].

Hardness: Hardness was measured by using a Monsanto hardness tester. From each formulation, 5 tablets were taken and the average was calculated. kg/cm^2 is the unit of hardness [9].

Weight variation: 20 tablets were weighed separately, using a digital weighting balance. Each tablet's weight was compared to the average weight. The following formula can be used to assess weight variation [10].

Weight variation= [(Tablet individual weight- Tablets average weight) x 100/Tablets average weight]

Friability: Tablet strength was measured by using a Roche Friabilator. A total of 10 tablets were weighed and put in the friability chamber. Rotational speed was 25 rotations per minute. After 100 rotations tablets were removed from the chamber (4 minutes) and the total number of intact tablets was weighed again. To calculate the percentage of weight loss, the tablets were reweighed. The % of weight loss should be less than 1%. Percentage friability can be calculated by following the formula [11].

[(Initial Weight-Final weight)x100/ Initial weight] = % Friability

Floatation test: 0.1N hydrochloric acid was added to a 250 ml beaker containing the tablets. A floating lag time calculation was made to determine how long it would take the tablet to rise to the surface and float, and the total floating time was determined by measuring how long the tablet stayed on the medium surface continuously [12],[13].

Drug content uniformity: 10 tablets from each batch were chosen randomly, powdered, and placed in 100ml of 0.1N hydrochloric acid (pH:1.2). Mixture was placed on the magnetic stirrer for 15 minutes before being filtered. Dilutions were done if necessary and absorbance was measured using a UV spectrophotometer at 250nm**.** This measured absorbance was used to calculate the drug content [8].

Swelling index: The tablet's swelling index was measured at room temperature by placing the tablet in a beaker containing 0.1N hydrochloric acid (pH 1.2). The tablets were placed in a 250ml buffer solution beaker. At certain intervals, the weight of the tablets after swelling was measured. The swelling index was calculated using the following formula [13],[14].

Swelling index= [(Weight after swelling-Tablet initial weight) x100/ Tablet initial weight]

Dissolution study: Investigations on in-vitro release were carried out using Dissolution Testing Apparatus II (Paddle type). At 37±0.5ºC and 50 rpm,900milli liter of 0.1N hydrochloric acid and 1% Sodium Lauryl Sulphate was used. 5ml of the sample was taken out at various intervals of 1,2,3,4,5,6,7,8,9,10,11, and 12 hours, and the fresh medium was replaced as the same amount that was withdrawn from the apparatus. If necessary, samples that were withdrawn were diluted. A UV spectrophotometer set to 250 nm was used to test the sample's absorbance. The cumulative percentage of drug release was calculated [15].

Kinetics of drug release: To determine the mechanism and kinetics of drug release, the results of the *in-vitro* drug release research of the formulations were fitted using a range of kinetics equations, such as zero order, first order, and Higuchi plots. To create a model that would better fit the formulation, drug release data was further examined using the Peppas equation. The linear curves derived from regression analysis of the above-mentioned plots were subjected to regression coefficient values [16].

RESULTS

Standard calibration curve

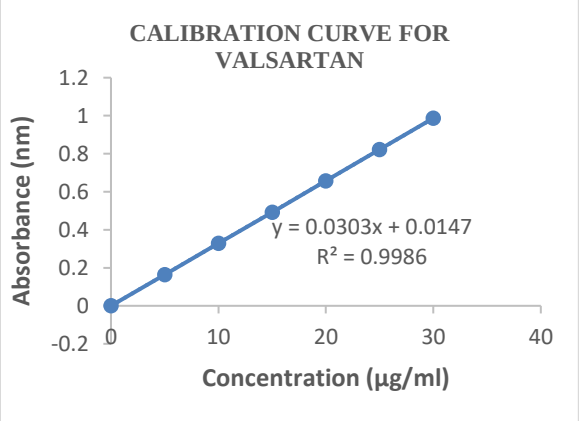

Figure 1- Standard calibration curve of valsartan

Interaction studies using FTIR: Compatibility between valsartan drug and polymers was studied

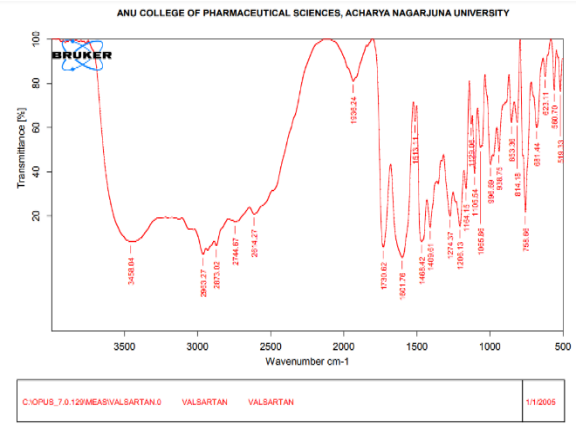

Figure 2-Pure drug (Valsartan) FT-IR spectrum

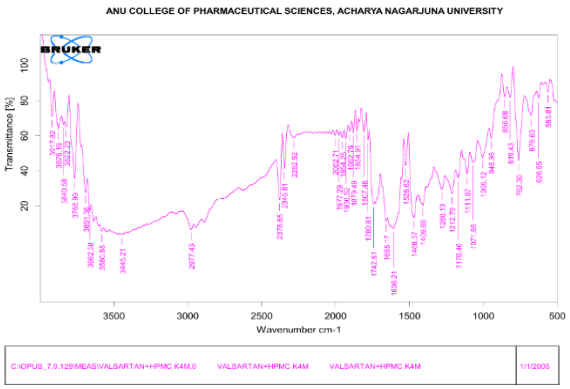

Figure 3-Valsartan+HPMC K4M FT-IR spectrum

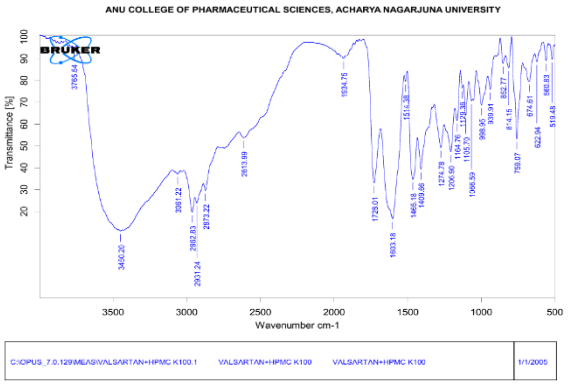

Figure 4-Valsartan+HPMC K100 FT-IR spectrum

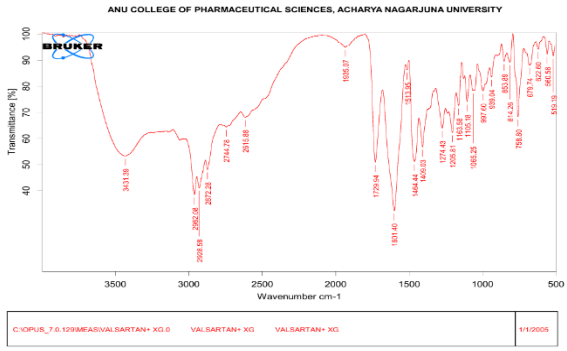

Figure 5-Valsartan+ Xanthum gum FT-IR spectrum

Precompression parameters:

Table 13(a)- Precompression parameters

Code of formulation	Angle of repose (θ)	Bulk density(g/ml)
F1	25.52	0.28
F2	26.80	0.30
F3	22.90	0.30
F4	26.54	0.31
F5	28.18	0.33
F6	26.02	0.29
F7	27.57	0.28
F8	26.92	0.30
F9	25.63	0.31
F10	26.80	0.33
F11	25.23	0.30
F12	25.78	0.31

Table 13(b)- Precompression parameters

Code of formulation	Tapped density (g/ml)	Carr's Index (%)	Hausner's ratio
F1	0.32	13.21	1.13
F2	0.34	10.50	1.11
F3	0.35	13.93	1.16
F4	0.35	13.03	1.15
F5	0.39	14.16	1.16
F6	0.33	12.96	1.14
F7	0.32	12.00	1.13
F8	0.35	13.33	1.13
F9	0.36	14.30	1.18
F10	0.37	10.63	1.11
F11	0.36	14.60	1.16
F12	0.35	12.33	1.13

Post-compression studies: Thickness, diameter, hardness, and weight variation studies were performed and the values obtained were given below

Table 14(a)- Post-compression studies

Code of formulation	**Thickness(mm)**	**Diameter (mm)**
F1	2.99	10.90
F2	2.82	10.88
F3	3.51	10.88
F4	3.52	10.88
F5	3.48	10.91
F6	3.49	10.90
F7	3.51	10.90
F8	3.50	10.89
F9	3.51	10.90
F10	3.48	10.89
F11	3.52	10.90
F12	3.51	10.91

Table 14(b)- Post-compression studies

Code of formulation	**Hardness (kg/cm^2)**	**Weight variation(mg)**
F1	3.95	349
F2	4.23	349
F3	4.46	349
F4	4.83	349
F5	4.33	348

F6	4.16	347
F7	4.83	347
F8	4.10	348
F9	4.06	348
F10	4.33	348
F11	4.93	349
F12	5.80	348

Table 14(c)- Post-compression studies

Code of formulation	Friability (%)	Floating lag time (sec)
F1	0.09	40
F2	0.24	51
F3	0.28	28
F4	0.28	76
F5	0.24	44
F6	0.24	24
F7	0.28	32
F8	0.47	55
F9	0.24	26
F10	0.03	43
F11	0.43	50
F12	0.48	121

Table 14(d)- Post-compression studies

Code of formulation	**Total floating time (hrs)**	**Drug content uniformity (%)**
F1	8	97.26
F2	10	98.74
F3	12	99.39
F4	>12	98.48
F5	8	99.39
F6	9	98.17
F7	11	96.96
F8	11	98.48
F9	9	97.87
F10	11	99.08
F11	>12	97.56
F12	>12	97.87

Dissolution(in-vitro) study: A graph was created using the results derived from the drug-dissolving studies to determine the percentage of medication release.

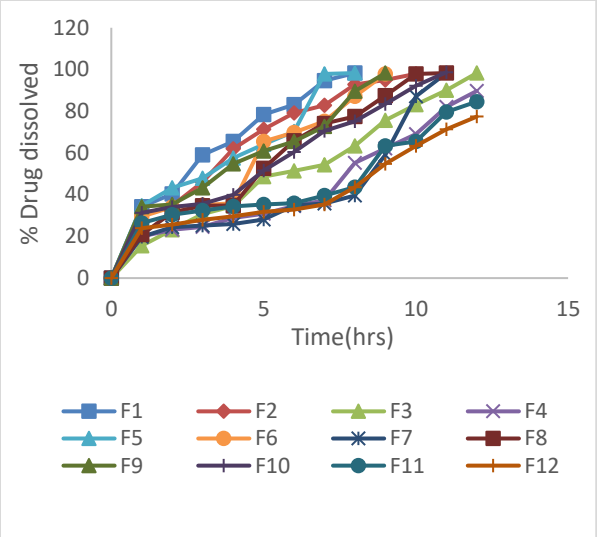

Figure 6-F1-F12 *in-vitro* %drug release profile of valsartan floating tablets

Swelling index: A swelling index was performed for every 1hr for 5hrs

Table 15: Swelling index

Code	**1hr**	**2hr**	**3hr**	**4hr**	**5hr**
F1	57.02	66.47	77.36	92.55	100.57
F2	69.54	85.28	110.89	134.50	146.11
F3	59.94	86.74	104.89	126.80	165.44
F4	45.80	65.61	77.36	91.97	138.36
F5	54.04	79.19	115.89	120.23	131.21
F6	49.46	78.44	94.54	98.85	106.89
F7	70.82	87.42	98.00	12.57	154.00
F8	74.63	93.94	104.61	115.63	125.07
F9	57.59	68.48	76.21	97.55	125.78
F10	65.33	74.85	85.42	101.71	114.80
F11	69.82	74.13	94.82	108.04	135.05
F12	67.04	78.51	92.55	105.73	118.33

Plots of zero-order:

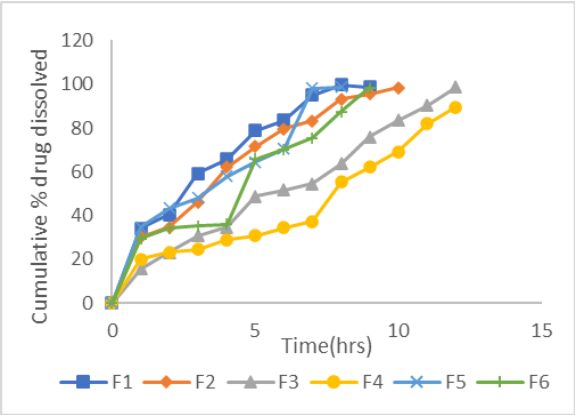

Figure 7. Zero-order kinetic data plot of F1-F6

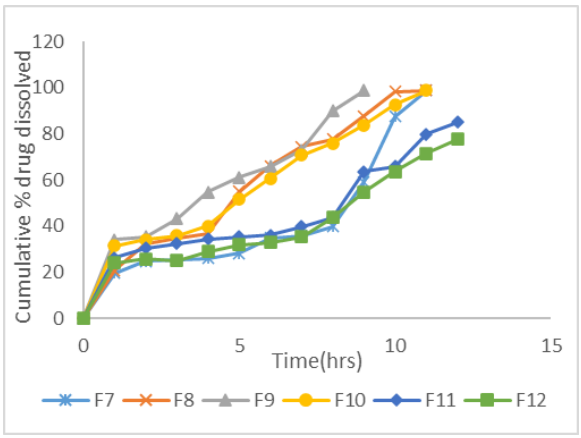

Figure 8. Zero-order kinetic data plot of F7-12

Plots of the first order:

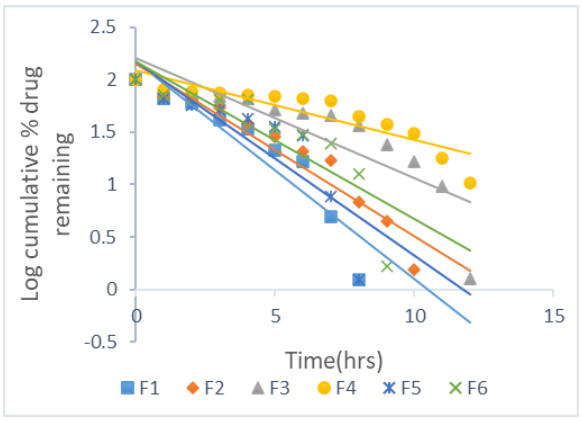

Figure 9-First-order kinetic plot of F1-F6

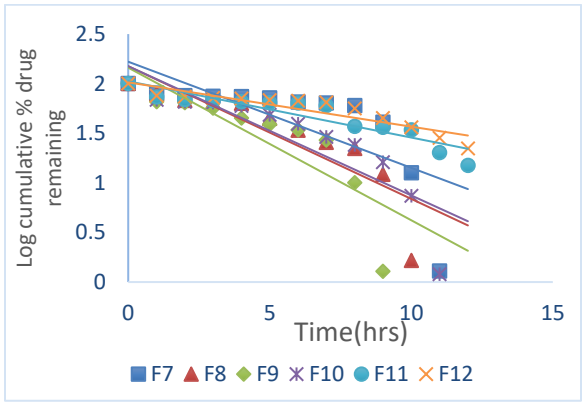

Figure 10-First-order kinetic plot of F7-F12

Higuchi Plots:

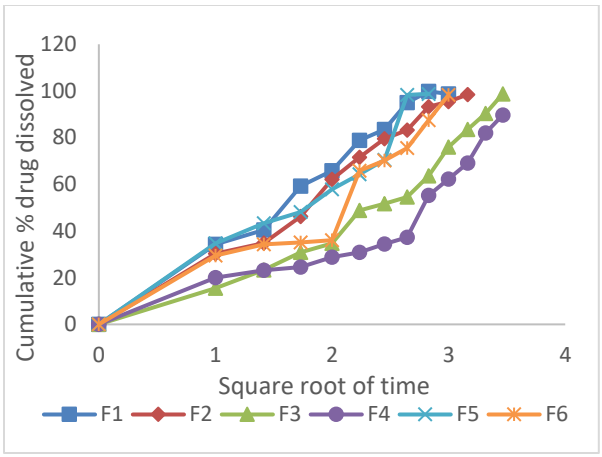

Figure 11-Higuchi release kinetic plot of F1-F6

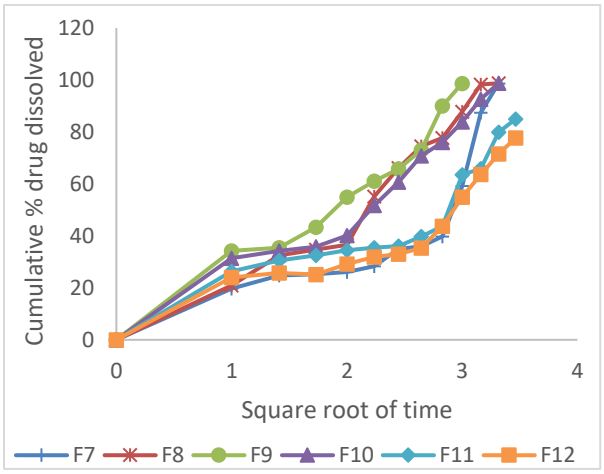

Figure 12-Higuchi release kinetic plot of F7-F12

Peppas Plots:

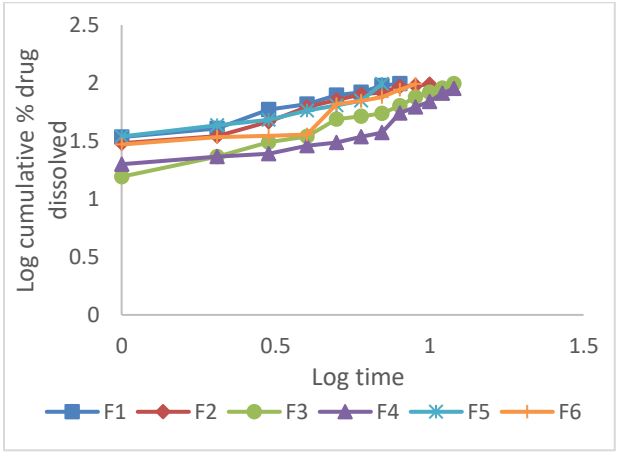

Figure 13-F1-F6 Korsmeyer Peppas kinetic plot

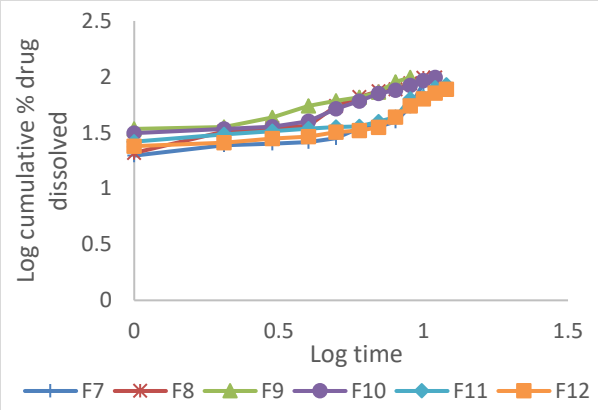

Figure 14-Korsmeyer Peppas kinetic plot of F7-F12

DISCUSSION

From FT-IR studies the combined spectrum contained all of Valsartan's distinctive peaks, which confirms the drug and the polymers do not interact thus indicating compatibility between them. A powder blend of all the formulations was subjected to determine the angle of repose. Formulation values were found to be between 22.90 to 28.18 which shows the good flow property. Bulk density values were 0.28 g/ml to 0.33 g/ml. Values of tapped density were 0.32 g/ml to 0.39 g/ml. Values compressibility index of the powder were between 10.63% to 14.60%. It shows good flow properties. Values of Hausner's ratio were 1.11 to 1.18. The combination of powder has good flow characteristics. The tablets of all the formulations were subjected to measure diameter and thickness by screw gauge. The range of thickness was 2.99 mm to 3.52 mm and the diameter ranges were between 10.88mm to 10.9mm. Tablets hardness was found to be 2.82 kg/cm^2 to 5.80 kg/cm^2. The tablets of all the formulations range from 347mg to 349mg. As per IP, the variation of weights of tablets is <5%. So, the tablets of all formulations pass the test. Friability values were 0.09% to 0.48%. The values were <1% which indicates they are within the pharmacopeial limits. The drug content of the tablets was found to be 96.96 % to 99.39% they were within the pharmacopeial limits of 85-100%. This reveals that the drug is uniformly dispersed in the formulation and confirms the homogenous mixing of the drug and polymer. The swelling was observed and at intervals of every 1hr, they were taken and weighed. Based on R^2 values of all the formulations it follows zero-order kinetics. It was determined that the drug's release follows Non-Fickian diffusion by looking at the values of the release exponent(n) from the Korsmeyer Peppas model. F3 was determined to be the optimal formulation, and it exhibits zero-order kinetics.

CONCLUSION

By continuously releasing the drug over a long length of time the idea of creating gastroretentive effervescent floating tablets containing valsartan provides an appropriate, useful method to produce a prolonged therapeutic effect. In this work, effervescent floating tablets of valsartan were successfully made using the direct compression method with different quantities of polymers such as hydroxypropyl methylcellulose K4M, hydroxypropyl methylcellulose K100, and Xanthum gum.

The preformulation investigations that satisfied the requirements, based on the experimental data above, included valsartans' melting point, solubility, and UV analysis.

The FTIR spectrum showed that valsartan and polymers did not interact with each other. Valsartan was compatible with every polymer that was used in the work.

Post-compression investigations were also conducted, and all study values were within the range, micrometric qualities demonstrate that all formulations had good flow properties

The study also demonstrated that as the polymer concentration raised, the amount of medication released was reduced. Valsartan floating tablets demonstrated a controlled and regulated release of medication *in vitro*. When compared to formulations using HPMC K100, Xanthum gum the formulation with HPMC K4M had a higher rate of valsartan release. F3 is therefore considered an optimized formulation that is taken into consideration for additional research

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