Research Article

Indian Journal of Science and Research

Patel K. & Chouksey R., Ind. J. Sci. Res. 2023, 3(1), 18-28

ISSN 2583 – 2913

FORMULATION AND EVALUATION OF VALSARTAN FLOATING BIOADHESIVE SYSTEM USING OPTIMIZED POLYMER BLENDS INDIA

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Abstract*:* Oral sustained release gastro retentive dosage forms offer several advantages for drugs having absorption from the upper gastrointestinal tract to improve the bioavailability of medications which have narrow absorption window. The aim of the study was to develop a floating bioadhesive drug delivery system exhibiting a unique combination of floatation and bioadhesion to prolong the residence in the stomach using Valsartan as a model drug. Prior to compression, polymeric blend(s) were evaluated for flow properties. The tablets were prepared by direct compression method using bioadhesive polymer like Carbopol 934P and hydrophilic polymers like HPMC K4M, HPMC K15M, and HPMC K100M. The prepared tablets were evaluated for physical characteristics, bioadhesive strength, buoyancy lag time, swelling index and *in vitro* drug release studies. The mean bioadhesive strength was found to be in the range of 16.2 to 52.1 gm. The optimized blend (F11) showed 92.3% drug releases after 24 hrs. Whilst, increase in concentration of carbopol 934P, bioadhesive strength and swelling index was increased with slow release. The n values of optimized formulations were found in the range of 0.631-0.719 indicating non-fickian anomalous type transport mechanism. The study aided in developing an ideal once-a-day gastro retentive floating drug delivery system with improved floating, swelling and bioadhesive characteristics with better bioavailability.

Key words: Valsartan, Carbopol 934P, Gastro Retentive Floating Bioadhesive Tablets, HPMC K4M, HPMC K15M, HPMC K100M, Polymer Blends**.**

Introduction*:* Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration with more patient compliance. These systems have progressed from immediate release to site specific delivery over a period.[1,2] An ideal drug delivery system should have two main properties that are, containing a single dose or less frequent dosing for the whole duration of treatment and the dosage form must release active drug directly at the site of action.[3-5] The recent developments of floating and bio-adhesive drug delivery systems (FBDDS) considering the role physiological environment and formulation variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems. Among the methods described, floating drug delivery and bio-adhesive drug delivery systems (DDS) are promising systems in gastro retention with few limitations, which has a great impact on the drug delivery to its intended site of administration. [6-11]

The major disadvantage of the floating system is a requirement of a sufficiently high level of fluids in the stomach for the system to float. The floating DDS are effective only when the fluid level in the stomach is sufficiently high. Nonetheless, as the stomach empties dosage form reaches to the pylorus, the buoyancy of the dosage form may be impeded. Thus, bio-adhesive DDS are suffering from the effect of mucous turnover. The mucous secreted by the mucosa lining of stomach wall may detach the dosage form from the wall of the stomach which get emptied from the stomach along with its contents. This limitation can be overcome by making the floating system eventually adhere to the mucous lining of the stomach wall. [12]

Thus, FBDDS offers the advantage of increased gastric residence time of drugs over normal floating DDS. The FBDDS can be formulated by incorporating bio-adhesive polymers to normal floating DDS.

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Published on Web 30/03/2023, www.ijsronline.org

Floating bio-adhesive systems can persist in the stomach for several hours and hence considerably extend the gastric residence time of therapeutics. Due to the extended gastric retention the delivery system enhances bioavailability. It has applications also for delivery of drug to the upper gastric tract. Floating and bio-adhesive delivery scaffold system helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. [13-15]

Several classes of medications collectively referred to as antihypertensive drugs for treating hypertension. Therapeutic agents within a particular class generally share similar pharmacologic mechanisms of action and in many cases have an affinity for similar cellular receptors. Valsartan is a beta-adrenergic blocking agent that blocks the effects of adrenergic drugs. [16]

Moreover, the site of absorption of Valsartan is in the stomach. Dosage forms that are retained in the stomach would increase the absorption, improve drug efficiency, and decrease dose requirements. Due to its high permeability in nature controlled drug delivery is required for prolonged gastric retention may offer numerous advantages including an increase in the extent of absorption, improved bioavailability, and therapeutic efficacy. [5] The objective of the present study is to develop a floating-bio-adhesive drug delivery system exhibiting a unique combination of floatation and bio-adhesion to prolong residence in the stomach using Valsartan as a model drug.

MATERIALS AND METHODS

Valsartan as a gift sample from Vapi Care Pharma Limited, Vapi, Gujarat; Hydroxypropyl methylcellulose K100M, hydroxypropyl methyl cellulose K15M, hydroxypropyl methyl cellulose K4M from Burgeon Pharmaceuticals, Chennai; Carbopol 934P, PVP K-30 from Triveni Chemicals, Vapi, Gujarat; Sodium bicarbonate, Magnesium stearate, talc from SD Fine Chemicals, Mumbai; Citric acid, Spray dried Lactose from Kawarlal and Co., Mumbai.

Preparation of floating bioadhesive tablets containing Valsartan

Floating bioadhesive tablets of Valsartan were prepared by employing various polymers like Carbopol 934P, HPMC K4M, HPMC K15M, and HPMC K100M in combination by direct compression method using compression machine. For the preparation of floating bio-adhesive tablets, all components were screened through sieve number 60 and mixed thoroughly in a mortar and pestle for 10 min. Magnesium stearate and talc were added to the above blend as flow promoters.

In all the formulations, the amount of Valsartan was kept constant at 50 mg. The polymers like Carbopol 934p, HPMC K4M, HPMC K15M, and HPMC K100M were used in different concentrations in combination. Total weight of the tablet was kept constant at 350 mg. The formulae of different floating bioadhesive tablets of Valsartan are given in Table 1.

Table 1: Composition of floating bioadhesive tablets of Valsartan

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Valsartan	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
HPMC K4M	70	60	50	40	30	-	-	-	-	-	-	-	-	-	-
HPMC K15M	-	-	-	-	-	70	60	50	40	30	-	-	-	-	-
HPMC K100M	-	-	-	-	-	-	-	-	-	-	70	60	50	40	30
Carbopol 934P	30	40	50	60	70	30	40	50	60	70	30	40	50	60	70
Citric acid	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5
Sodium bicarbonate	35	35	35	35	35	35	35	35	35	35	35	35	35	35	35
PVP K	30	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5
Magnesium stearate	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Talc	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Spray dried lactose	120	120	120	120	120	120	120	120	120	120	120	120	120	120	120

Preformulation studies of the optimized blends

The aforementioned polymeric blends were tested for the angle of repose, Hausner's ratio, Carr's index (% compressibility).

Evaluation of physical parameters

Hardness and friability

The hardness of prepared tablets was determined by using Monsanto hardness tester and measured in terms of kg/cm2. The friability test was performed to assess the effect of friction and shocks, which may often cause the tablet to chip, cap or break. Roche friabilator was used for testing the friability of prepared floating bioadhesive tablets. Ten tablets were accurately weighed and placed in the friabilator and operated for 100 revolutions. The tablets were de-dusted and reweighed and friability (F) was calculated.

Weight variation

The weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weights to the average. The percentage difference in the weight variation should be within the permissible limits (7.5%). The percent deviation was calculated.

Drug content

Six tablets from each batch were weighed and powdered. Powder equivalent to the average weight of the tablet was accurately weighed and transferred into a 100 ml volumetric flask and dissolved in a suitable quantity of phosphate buffered saline buffer (100 ml). A portion of the sample was filtered and analyzed by an ultraviolet (UV) spectrophotometer at 225 nm.

Buoyancy/floating test

The *in vitro* buoyancy was determined by floating lag time. The tablets were placed in a 100 ml 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. The duration of time the dosage form constantly remained on the surface of the medium was determined as the total floating time.

***In vitro* bioadhesive strength**

The test methods for determining muco-adhesion can be classified into two major categories: In vitro/ex vivo methods and in vivo methods. The most common methods are based on the measurement of either tensile or shear stress. In this study, an instrument was designed to evaluate the tensile force. This instrument consists of a modified physical balance. This method was used for determination of the in vitro bioadhesion strength. The balance was modified by replacement of one pan with the metal shaft 5 g heavier in weight than the pan. Fresh sheep mucosa obtained from local slaughterhouse was cut into pieces, washed with distilled water followed by 0.1 N HCl.

A piece of the mucosa was fixed in a petri dish with instant adhesive, which was filled with 0.1 N HCl so that it just touched the mucosal surface. The tablet was stuck to the lower side of a shaft with instant adhesive. The two sides of the balance were made equal before the study, by keeping 5 g weight on the right hand pan. A weight of 5 g was removed from the right hand pan, which lowered the shaft along with the tablet over the mucosa. The balance was kept in this position for 3 min contact time. The weight was added slowly to the right hand pan until the tablet detached from the mucosal surface. This detachment force gave the bioadhesion strength of the bioadhesive tablet in gram (total weight on right hand pan minus 5 g).

Selling studies

The extent of swelling was measured in terms of percentage weight gained by the tablet. One tablet from each formulation was weighed and kept in petri dish containing 15 ml of 0.1 N HCl. At the end of specified time intervals tablets were withdrawn from petri dish and excess buffer blotted with tissue paper and weighed. The percentage of weight gained by the tablet was calculated.

***In vitro* drug release studies**

The dissolution of the floating bioadhesive tablet was performed using USP type II XXIII dissolution apparatus (paddle method) using 900 ml of 0.1 N HCl with pH 1.2 as the dissolution medium to mimic stomach, which was maintained at 37°C and stirred at 50 rpm. Aliquots of 5 ml of samples were withdrawn with a bulb pipette at different time intervals and replaced with equal volume of 0.1 N HCl at each withdrawal, filtered it through Whatman filter paper number l. The samples were then analyzed using UV spectrophotometer at 225 nm and the cumulative amount of drug released at various time intervals was calculated.

Kinetic studies

To analyze the release mechanism, several release models were tested such as:

$$\text{Zero order: } Q_t = Q_o + K_{ot} \quad (1)$$

Where Q_t is the amount of drug released at time t, K_o is the apparent dissolution rate constant or zero order release constant and Q_o is the initial concentration of the

drug in the solution resulting from a burst effect; in this case the drug release runs as a constant rate.

First order: $\ln Q_t = \ln Q_o + K_1 t$ (2)

Where K_1 is the first order release constant; in this case, the drug released at each time is proportional to the residual drug inside the dosage form.

Higuchi: $Q_t = K_H \sqrt{t}$ (3)

Where Qt is the amount of drug released at time t and KH is the Higuchi release rate constant; this is, the most widely used model to describe drug release from pharmaceutical matrices.

Korsmeyer–Peppas: $Q_t/Q_\infty = K_k t^n e$ (4)

Where K_k is a constant incorporate in structural and geometric characteristic of the drug dosage form and n is the release exponent, indicative of the drug release mechanism.

The value of n for a tablet, n = 0.45 for Fickian (Case I) release, >0.45 but <0.89 for non-Fickian (anomalous) release and 0.89 for Case II (zero order) release and >0.89 for super case II type of release.

Case II transport generally refers to the dissolution of the polymeric matrix due to the relaxation of the polymer chain and anomalous transport (non-Fickian) refers to the summation of both diffusion and dissolution controlled release.

RESULTS AND DISCUSSION

Precompressional parameters

Precompression parameters of all formulations blend were conducted for angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio. Table 2 shows all the precompressional parameters of the prepared blends.

Table 2: Pre-compression properties of prepared blends (n = 3)

Batch	Bulk density	Tapped density	Angle of repose	Compressibility index	Hausners ratio
F1	0.453±0.13	0.53±0.02	27.3±0.5	14.40±0.26	1.16±0.01
F2	0.453±0.02	0.53±0.01	27.84±0.49	15.5±0.37	1.18±0.02
F3	0.50±0.05	0.56±0.02	29.17±0.18	13.31±0.19	1.13±0.04
F4	0.46±0.18	0.53±0.01	26.24±0.41	14.26±0.23	1.16±0.01
F5	0.48±0.11	0.56±0.02	28.31±0.92	14.29±0.16	1.16±0.02
F6	0.47±0.16	0.55±0.01	28.10±0.54	13.88±0.24	1.16±0.06
F7	0.49±0.06	0.57±0.01	25.57±0.89	13.43±0.15	1.15±0.05
F8	0.41±0.01	0.52±0.01	28.3±0.62	21.05±0.14	1.26±0.01
F9	0.41±0.02	0.51±0.02	24.11±0.43	20.69±0.16	1.25±0.02
F10	0.45±0.07	0.53±0.13	25.16±0.85	16.16±0.25	1.19±0.08
F11	0.43±0.12	0.53±0.16	25.16±0.54	18.58±0.34	1.22±0.04
F12	0.45±0.02	0.55±0.15	26.61±0.70	17.87±0.49	1.21±0.01
F13	0.50±0.14	0.57±0.02	28.14±0.22	13.28±0.27	1.15±0.02
F14	0.45±0.03	0.52±0.01	27.37±0.45	12.86±0.18	1.14±0.04
F15	0.45±0.12	0.52±0.02	28.32±0.64	14.47±0.52	1.16±0.01

Physical parameters of the prepared tablets

Table 3 shows post compressional parameters of the prepared tablets. The hardness of the tablets was found to be 5.0 ± 0.36-5.9 ± 0.33 kg/cm2 and friability was found to be below 1% indicating good mechanical resistance. The thickness of the tablets was found to be 3.10 ± 0.04-3.20 ± 0.05. The entire tablets passed weight variation test, as percentage weight variation was within the pharmacopeial limits that is, ±7.5%, mean percentage of drug content was found to be 98.5%.

Buoyancy lags time studies

All tablet formulations exhibited satisfactory floatation ability and remained buoyant for 10-24 h in the dissolution medium. The buoyancy lag time of tablets depends on the amount of sodium bicarbonate and citric acid involved in CO_2 formation and the concentration of polymers used. It was clearly observed that the reduction in the concentration of HPMC in each batch the floating lag time increased as well as floating duration decreased and also increase in the viscosity of HPMC polymers delayed the floating lag time and prolonged the drug release.

Table 3: Physical evaluation of floating bioadhesive tablets of Valsartan (n = 3)

Batch	Thickness (mm)	Hardness (kg/cm^2)	Weight variation	Friability (%)	Drug content (%)
F1	3.11±0.03	5.9±0.33	Passes	0.62±0.02	98.23±0.04
F2	3.12±0.01	5.7±0.25	Passes	0.74±0.03	97.12±0.05
F3	3.11±0.04	5.4±0.64	Passes	0.81±0.01	99.12±0.12
F4	3.10±0.06	5.2±0.30	Passes	0.88±0.03	97.54±0.09
F5	3.13±0.02	5.1±0.28	Passes	0.44±0.01	100.1±0.06
F6	3.11±0.01	5.8±0.35	Passes	0.52±0.04	97.36±0.07
F7	3.10±0.03	5.6±0.40	Passes	0.61±0.02	98.24±0.19
F8	3.20±0.05	5.4±0.46	Passes	0.68±0.01	99.45±0.21
F9	3.10±0.04	5.1±0.24	Passes	0.72±0.04	98.39±0.07
F10	3.11±0.01	5±0.36	Passes	0.29±0.01	99.56±0.06
F11	3.17±0.01	5.6±0.55	Passes	0.38±0.01	98.2±0.12
F12	3.12±0.04	5.5±0.64	Passes	0.69±0.03	99.38±0.09
F13	3.14±0.06	5.3±0.30	Passes	0.45±0.04	97.43±0.17
F14	3.11±0.02	5.2±0.28	Passes	0.51±0.01	98.21±0.06
F15	3.17±0.01	5.2±0.35	Passes	0.56±0.01	99.12±0.07

Swelling studies

The percentage water uptake of the formulations ranged from 70% to 142% [Table 4]. The formulation F15 shows maximum swelling index. It was observed that as we increase the concentration of Carbopol 934P and the viscosity of the hydrophilic polymers the water uptake capacity increased which results in an increase of swelling index. This may be because of the mobility of polymer chains was very dependent on the water content of the system.

Table 4: Physical properties of floating bioadhesive tablets of Valsartan (*n* = 3)

Batch number	Percentage swelling index	Floating lag time (min)	Total floating time (h)
F1	70±2.3	2.0±0.2	15±1.0
F2	79±1.8	2.4±0.4	14±1.5
F3	91±2.6	3.0±0.5	13±2.0
F4	101±2.5	3.5±1.0	12±1.5
F5	112±2.8	4.0±1.2	10±1.0
F6	76±3.5	2.2±0.5	24±3.0
F7	89±4.4	3.0±0.2	24±2.5
F8	96±3.0	3.6±0.8	23±1.5
F9	120±2.5	4.2±1.2	23±1.0
F10	137±1.5	5.0±1.5	21±2.0
F11	80±2.0	2.9±0.4	24±4.5
F12	87±2.5	3.4±0.6	24±4.0
F13	104±1.0	4.3±0.4	>24
F14	134±3.5	4.8±1.0	>24
F15	142±2.6	5.2±0.5	>24

***In vitro* bioadhesive study**

In vitro bioadhesion evaluation test was conducted for all formulations, the result showed in Figure 1. The mean bioadhesive strength values were found in a range of 16.2-52.1 g for the floating bioadhesive tablets F1 to F15. There was a gradual increase in the bioadhesion strength in each batch that is, from F1 to F5, F6 to F10, and F11 to F15.This was due to the increase in the concentration of bioadhesive polymer Carbopol 934P. Maximum bioadhesion strength was found for formulations F11-F15 and low bioadhesion strength was found for formulations F1-F5, this may be expected that as the viscosity of the hydrophilic polymer increases and concentration of Carbopol 934P increases the adhesive property also increases.

***In vitro* dissolution studies**

The dissolution rates of all floating bioadhesive tablets were studied by using USP type II apparatus (paddle type) in 0.1 N HCl. The release of Valsartan from floating bioadhesive tablets depends on the type and concentration of polymer. Batches F1, F2, F3, F4, and F5 are composed with HPMC K4M as a hydrophilic polymer and Carbopol 934P as bioadhesive polymer in increasing ratios of Carbopol 934P and decreasing ratios of HPMC K4M. The release profile depicted in Figures 2-4 shows that Carbopol 934P was helpful in retarding drug release. Batches from F6 to F10 were composed with HPMC K15M as hydrophilic polymer and Carbopol 934P as bioadhesive polymer in increasing ratios of

Carbopol 934P and decreasing ratios of HPMC K15M respectively showed slower drug release than HPMC K4M batches. This might be due to high viscosity of polymer HPMC K15M than HPMC K4M.

Batches from F11 to F15 were composed with HPMC K100M as hydrophilic polymer and Carbopol 934P as bioadhesive polymer in increasing ratios of Carbopol 934P and decreasing ratios of HPMC K100M, respectively, showed slower drug release than HPMC K4M and HPMC K15M batches. This might be due to high viscosity of polymer HPMC K100M than HPMC K4M and HPMC K15M.

Kinetic studies

To investigate the mechanism of drug release from floating bioadhesive tablets, various kinetics models such as zero order, first order, Higuchi's and Korsmeyer–Peppas equations were applied to the in vitro release data obtained from different formulations. The values of correlation-coefficient (r2) for all the formulations were high enough to evaluate the drug dissolution behavior. The value of release exponent (n) was found to be a function of polymer used and the physicochemical property of a drug molecule itself. It was evident that the formulation F11 followed first order process as the correlation coefficient (r^2) value was 0.988, respectively. This indicated that the dissolution rate of the drug was dependent on the concentration of dissolving species. Further, when the drug release data was put into Higuchi equation, good correlation coefficient (r^2) values 0.963-0.992 were obtained, indicating that the drug release was diffusion controlled [Figures 5-8].

The release data obtained were also put in Korsmeyer–Peppas model to find out n values, which describe the drug release mechanism; good correlation coefficient (r2) values 0.97-0.997 were obtained. The n values were in the range of 0.623-0.719 indicating non-Fickain anomalous type transport mechanism [Tables 5 and 6].

Table 5: Kinetic study of optimized floating bioadhesive tablets of Valsartan

F11

Time (h)	√ t	Log t	Cumulative release*		Cumulative retained	
			Percentage	Log percentage	Percentage	Log percentage
0	0	0	0	0	100	2.000
0.5	0.707	−0.301	10.62	1.026	89.38	1.951
1	1.000	0.000	14.65	1.166	85.35	1.931
2	1.414	0.301	19.98	1.301	80.02	1.903
3	1.732	0.477	23.04	1.362	76.96	1.886
4	2.000	0.602	29.7	1.473	70.3	1.847
5	2.236	0.699	36.54	1.563	63.46	1.803
6	2.449	0.778	42.46	1.628	57.54	1.760
7	2.646	0.845	49.37	1.693	50.63	1.704
8	2.828	0.903	54.21	1.734	45.79	1.661
9	3.000	0.954	60.72	1.783	39.28	1.594
10	3.162	1.000	68.4	1.835	31.6	1.500
11	3.317	1.041	71.3	1.853	28.7	1.458
12	3.464	1.079	76.3	1.883	23.7	1.375
14	3.742	1.146	80.3	1.905	19.7	1.294
16	4.000	1.204	84.6	1.927	15.4	1.188
18	4.243	1.255	88.9	1.949	11.1	1.045
20	4.472	1.301	90.3	1.956	9.7	0.987
24	4.899	1.380	92.3	1.965	7.7	0.886

Table 6: Kinetic study of floating bioadhesive tablets of Valsartan

Formulation Code	Zero order	First order	Higuchi	Korsmeyer–Peppas	
	r^2	r^2	r^2	r^2	n
F1	0.924	0.978	0.986	0.988	0.623
F2	0.955	0.950	0.988	0.997	0.646
F3	0.954	0.969	0.992	0.996	0.624
F4	0.982	0.937	0.971	0.995	0.647
F5	0.979	0.959	0.97	0.988	0.717
F6	0.974	0.887	0.979	0.996	0.704
F7	0.961	0.917	0.980	0.99	0.712
F8	0.920	0.982	0.979	0.985	0.687
F9	0.898	0.983	0.976	0.983	0.681
F10	0.877	0.971	0.968	0.977	0.712
F11	0.909	0.988	0.970	0.978	0.631
F12	0.898	0.983	0.965	0.976	0.663
F13	0.909	0.99	0.971	0.976	0.672
F14	0.912	0.985	0.966	0.973	0.691
F15	0.915	0.983	0.963	0.97	0.719

Conclusion

In this current work, an attempt was made to design floating bioadhesive drug delivery system of an antihypertensive drug. Floating-bioadhesive tablets of Valsartan that exhibit a unique combination of floatation and bioadhesion for prolonged residence in the stomach were prepared by direct compression technique using polymers such as HPMC K4M, HPMC K15M, HPMC K100M, and Carbopol 934P. From aforesaid results, it can be concluded that among all the formulations the formulations with HPMC K100M with Carbopol 934P showed controlled release. The F11 formulation showed a satisfactory dissolution profile, detachment stress and floating characteristics, which can increase the gastric residence time as well as bioavailability and better patient compliance.

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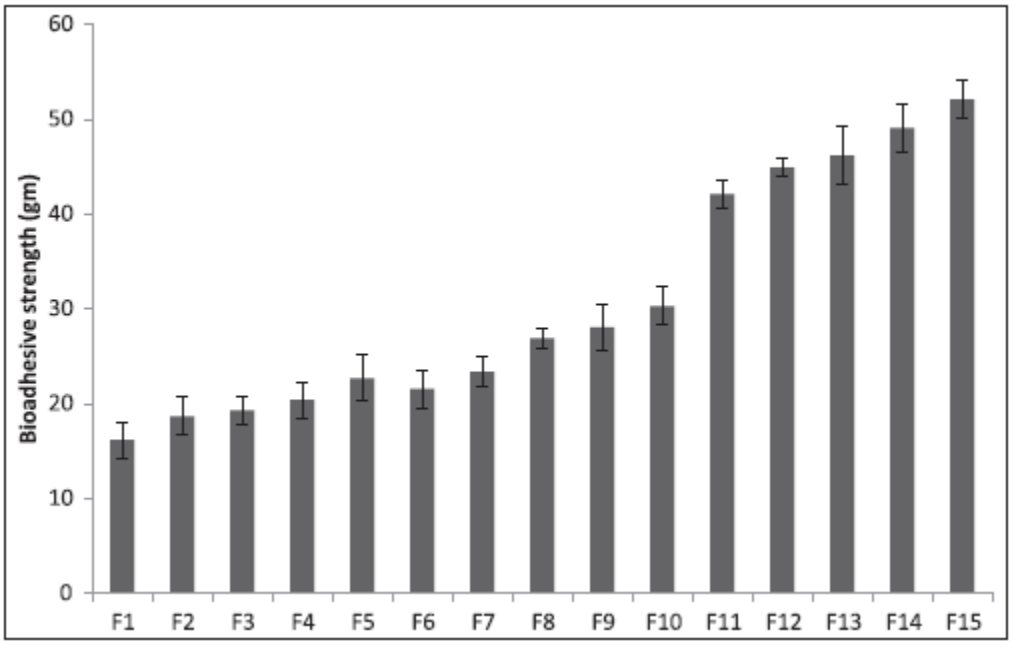

Figure 1: Bioadhesive strength of floating tablets of Valsartan using modified physical balance (n = 3)

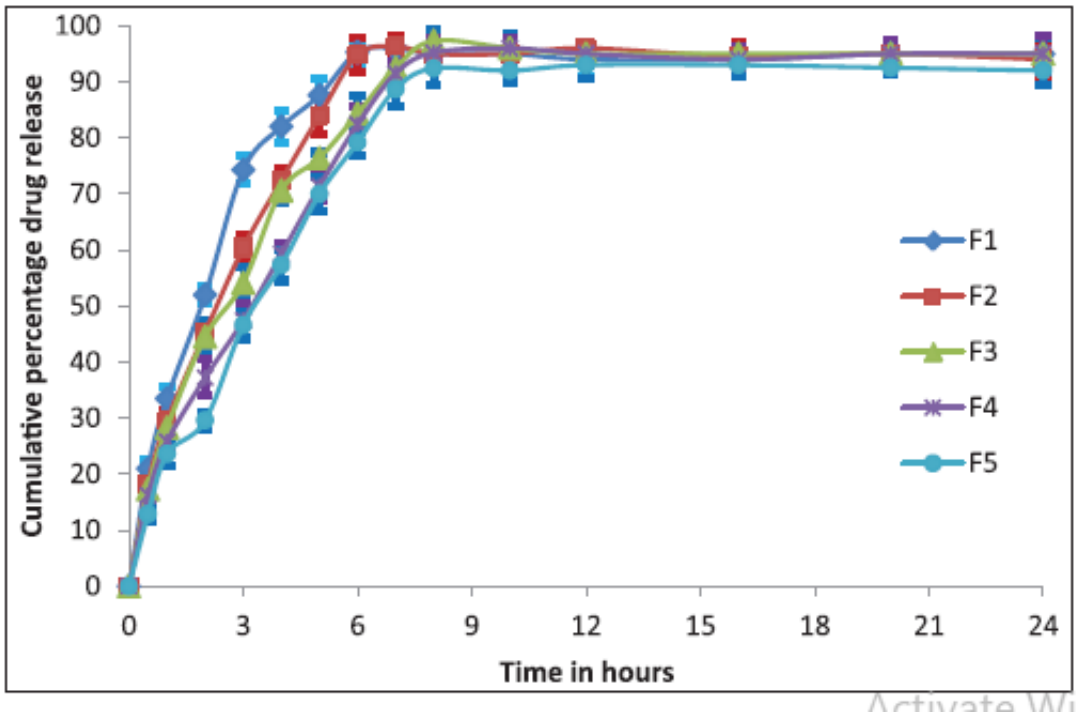

Figure 2: *In vitro* release profile of floating bioadhesive tablets of Valsartan

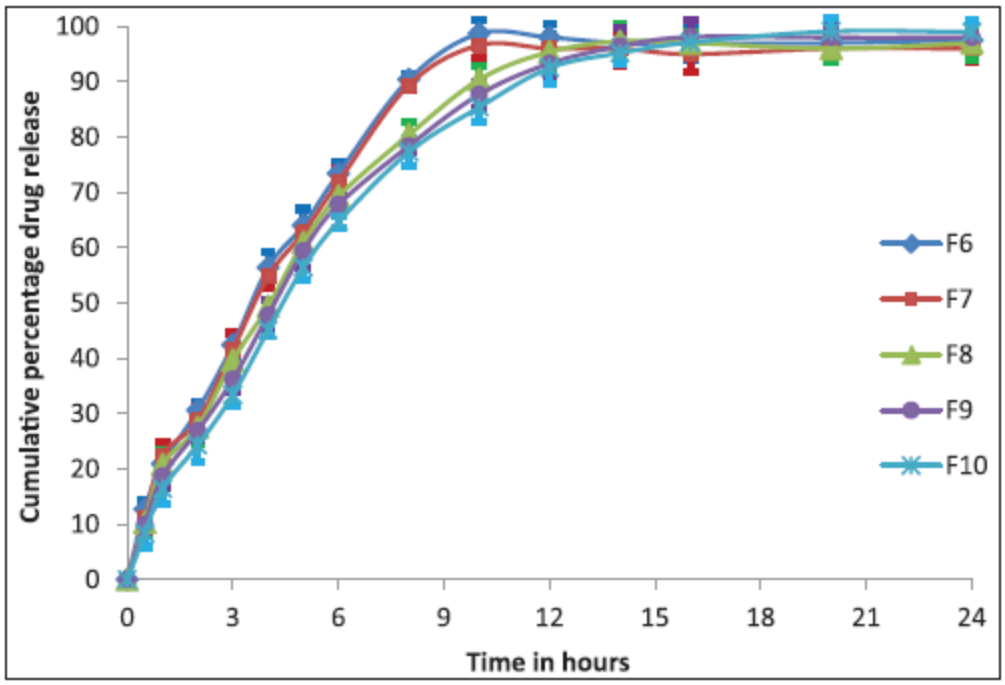

Figure 3: *In vitro* release profile of floating bioadhesive tablets of Valsartan

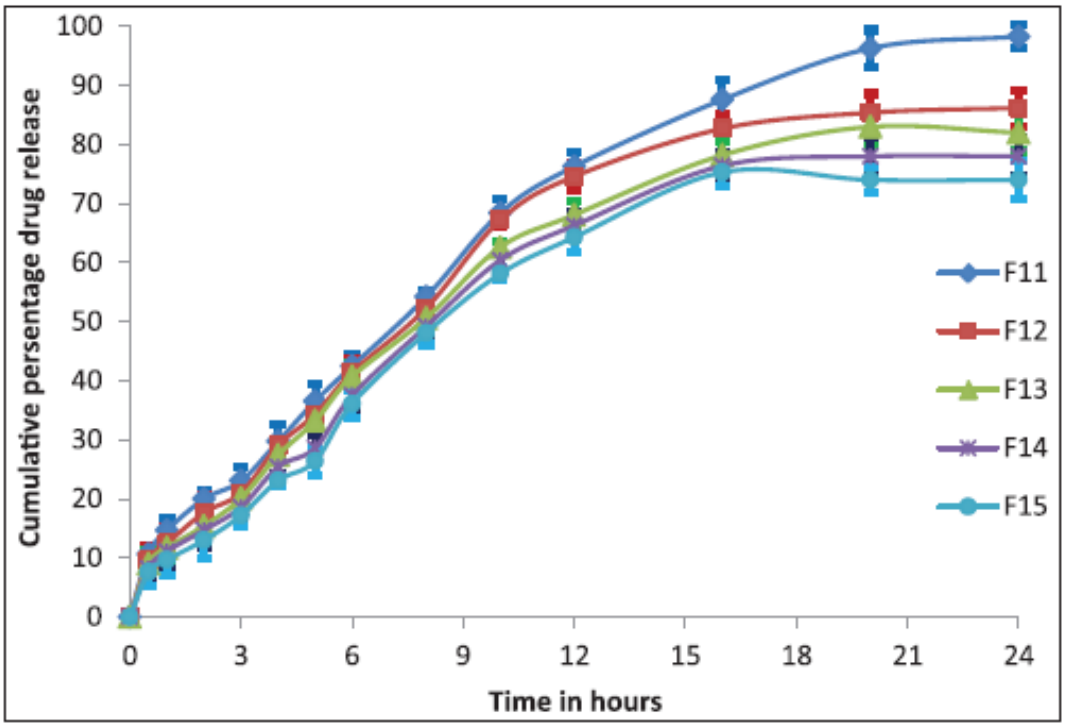

Figure 4: *In vitro* release profile of floating bioadhesive tablets of Valsartan

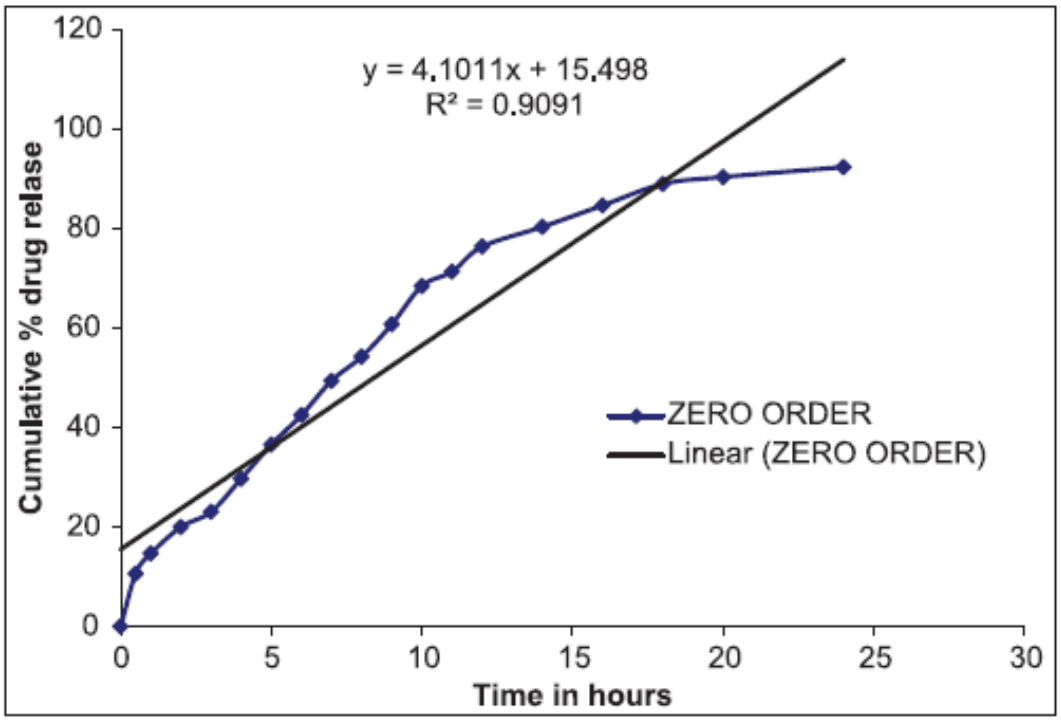

Figure 5: Zero order plot of optimized floating bioadhesive tablets of Valsartan

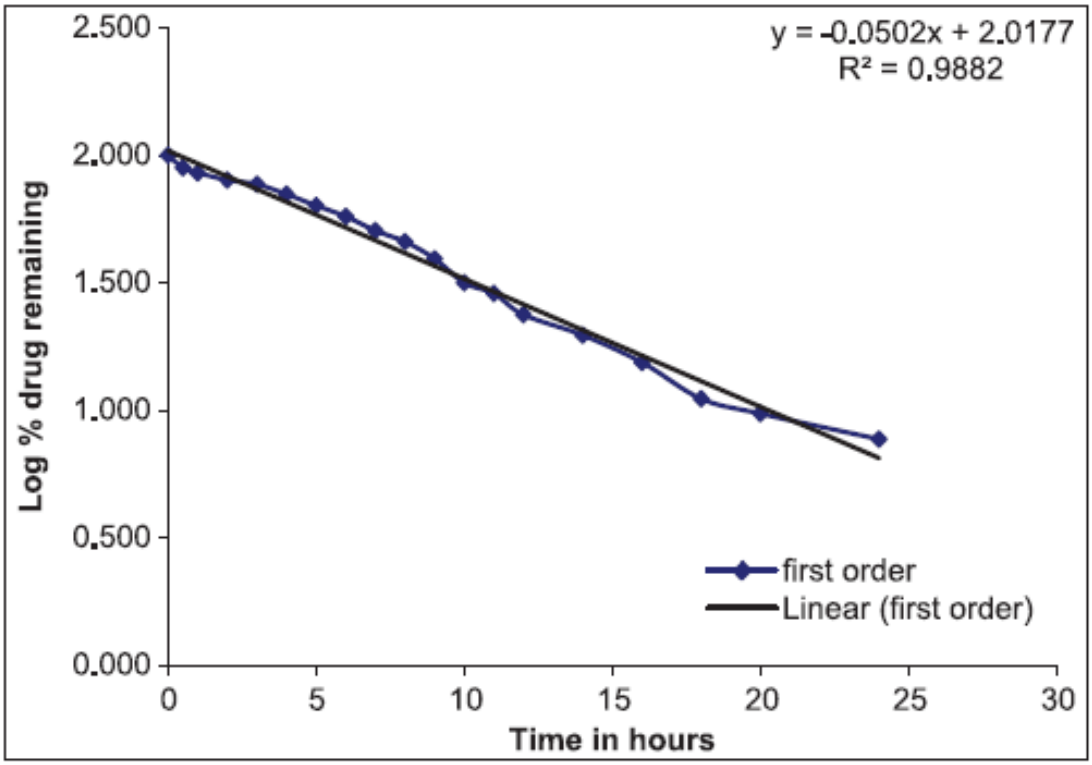

Figure 6: First order plot of optimized floating bioadhesive tablets of Valsartan

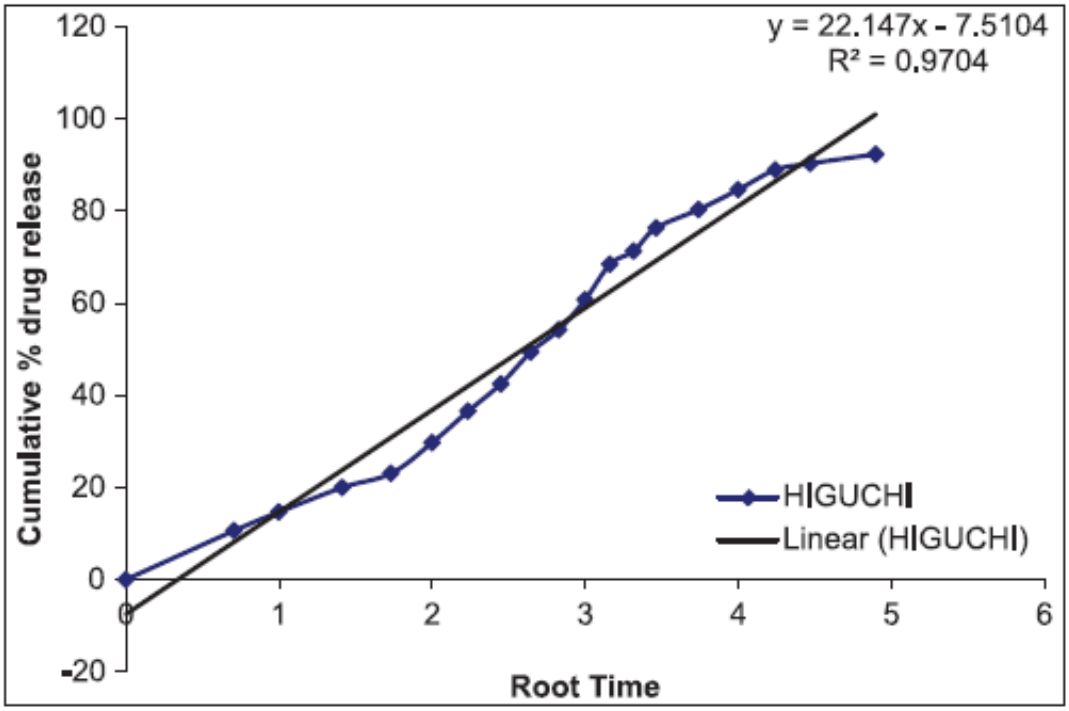

Figure 7: Higuchi plot of optimized floating bioadhesive tablets of Valsartan

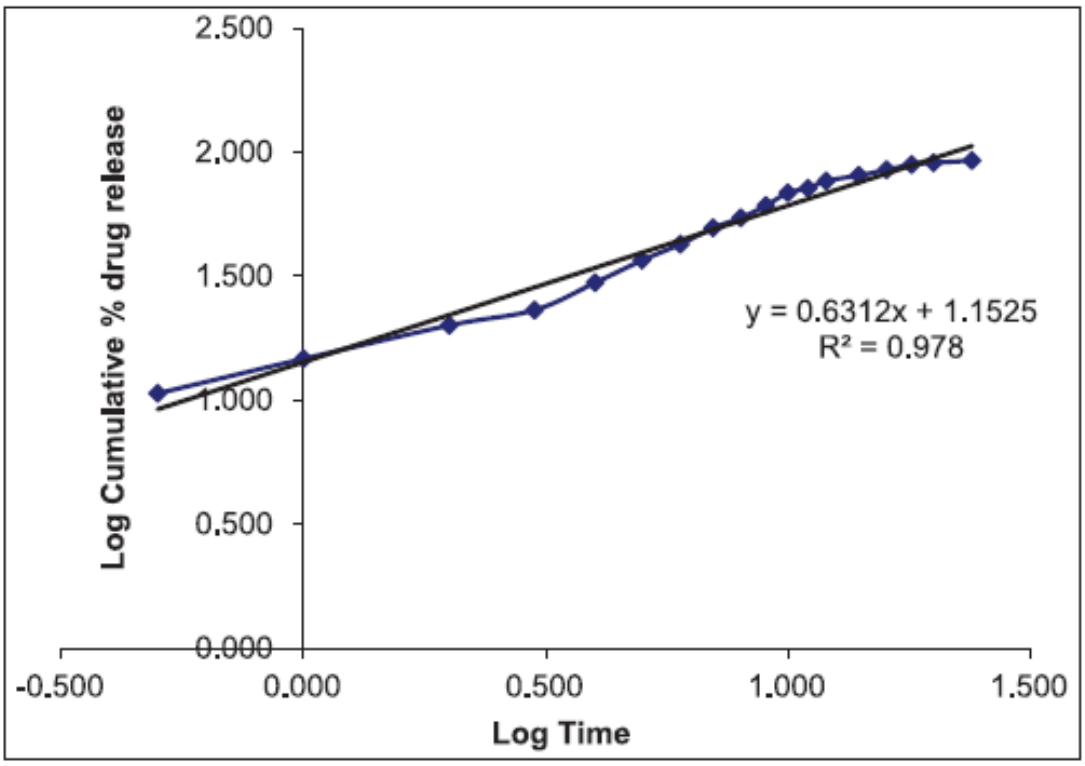

Figure 8: Korsmeyer–Peppas plot of optimized floating bioadhesive tablets of Valsartan