DESIGN AND EVALUATION OF GASTRO RETENTIVE FLOATING DRUG DELIVERY SYSTEM OF VALSARTAN

Abdul Hasan Sathali. A*, Yuganya. B., Nisha.N
Department of Pharmaceutics, College of Pharmacy, Madurai Medical College,
Madurai- 625 020, Tamil Nadu, India
E-mail: abdulhasan@hotmail.com

Abstract: The aim of the present work is to develop a gastro retentive floating dosage form of valsartan because of its narrow absorption window in the upper gastrointestinal tract (GIT). Hydrophilic (Hydroxypropylmethylcellulose K100M, K15M, K4M and methylcellulose) and hydrophobic polymer (ethyl cellulose) were used to prepare non-effervescent floating drug delivery system. The formulations were evaluated for physiochemical parameters such as hardness, friability, weight variation, swelling studies, *in vitro* buoyancy studies and *invitro* release studies. The viscosity of the polymer had a major influence on swelling process and matrix integrity. All the tablets have shown floating duration for more than 12hrs. *In vitro* release studies showed the formulation F5 had sustained the drug release (67.1%) for 12 hours. All the formulations followed zero order kinetics and Non-fickian diffusion mechanism. Fourier transform infrared (FT-IR) and Differential scanning colorimetry (DSC) studies revealed no interaction between the drug and polymers. Scanning electron microscopy (SEM) studies showed intact surface without any perforations, channels or troughs. *In vivo x-ray* studies of the selected formulation showed gastric residence of 12 hours. The results of the present study clearly indicate the feasibility to develop valsartan in the form of floating drug delivery system to prolong gastric retention time and controlled drug release.

Keywords: Gastro retentive floating tablets, Non- effervescent, Swelling index, *in vivo* x- ray studies, Release kinetics.

1. INTRODUCTION

Oral drug administration still remains the preferred route of choice for delivery of drugs into systemic circulation. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the GIT and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the GIT. These drug delivery systems suffer from mainly two adversities: the short gastric retention time (GRT) and unpredictable short gastric emptying time (GET), which can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine) leading to diminished efficacy of administered dose. To formulate a site-specific orally administered controlled release dosage form, it is desirable to achieve a prolong gastric residence time by the drug delivery. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment. Also prolonged GRT in the stomach could be advantageous for local action in the upper part of the small intestine (e.g. treatment of peptic ulcer, etc) [1].

Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper GIT for local or systemic effects. Gastro retentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time of drugs. Over the last few decades, several gastro retentive drug delivery approaches being designed and developed, including: High density (sinking) systems that is retained in the bottom of the stomach, Low density (floating) systems that causes buoyancy in gastric fluid, mucoadhesive systems that causes bioadhesion to stomach mucosa, unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach, super porous hydrogel systems, magnetic systems etc [2,3].

Valsartan is a potent orally active non peptide tetrazole derivative and selectively inhibits (ACE

Inhibitor) angiotensin II receptor type 1 which causes reduction in blood pressure and it's widely prescribed for treatment of hypertension. Since the drug is prefentially absorbed in the upper GIT (narrow absorption window), the drug displays oral bioavailability problems as given in conventional dosage forms[4]. To overcome these problems, different approaches have been proposed to retain dosage form in the stomach. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GIT is to control the gastric residence time (ie. Gastroretentive dosage form). This dosage form can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the GIT, thus ensuring optimal bioavailability.

The objective of the present study was to develop a floatable dosage forms of valsartan were prepared by non-effervescent technique using two different polymers hydrophilic and hydrophobic polymers are designed to prolong the gastric residence time and to enhance the drug bioavailability. The main aim of the work was to evaluate the effect of both hydrophilic and hydrophobic polymer on in vitro drug release, floating behavior, and in vivo x-ray studies.

2. MATERIAL AND METHODS

2.1. Materials

Valsartan, Hydroxypropylmethylcellulose (HPMC) K100M, K4M, K15M, methylcellulose and ethyl cellulose were obtained as gift samples from Dr. Reddys Lab. Pvt. Ltd., Hyderabad; and lactose, talc and magnesium stearate were procured from Central Drug House, New Delhi. All other solvents and reagents used were of analytical grade.

2.2. Drug-polymer interaction studies

2.2.1. Fourier transform infrared spectroscopy (FTIR) studies

The possibility of drug-excipients interactions were further investigated by FT-IR. The FT-IR graph of pure drug and combination of drug with Excipients are recorded. The analysis was performed by using FT-IR Spectrometer (Shimadzu, Japan). The scanning range was 450-4000 cm-1 and the resolution is 4cm-1. Samples were prepared in KBr pellets [5].

2.2.2. Differential scanning calorimetry (DSC) Studies

DSC was performed using DSC Q200 Thermal Analyzer. The instrument is calibrated with indium standard. Accurately weighed (it varies from 3mg-5mg). Samples were placed in an open type ceramic sample pans5. Thermo grams were obtained by heating the sample at a constant heating rate of 100 C/minute. A dry purge of Argon gas (25ml/min) is used for all runs. Samples were heated from 37°C -400°C [6].

2.3. Preparation of valsartan floating tablets

The tablet excipients and polymers were chosen after comprehensive drug-polymers interaction studies. The floating tablets of valsartan were prepared by direct compression method. Accurately weighed quantities of drug, polymers and lactose were manually blended homogenously in a mortar; the powder blend was passed through sieve no.22, and adequately lubricated with talc and magnesium stearate. It was then compressed into10mm biconvex tablets by using a single punch tablet machine. The composition of formulations was given in Table 1.

2.4. Evaluation of floating tablets

2.4.1. Physical properties

The powder blends of all the formulations were evaluated for angle of repose, bulk density, tapped bulk density, compressibility index, Hausner's ratio and drug content. Similarly the prepared floating tablets were evaluated for hardness, thickness, diameter, friability, drug content, and weight variation.

2.4.2. In vitro buoyancy studies

The in vitro buoyancy was determined by measuring floating lag time and duration of buoyancy. The tablets were placed in a beaker containing 100ml of 0.1N Hcl maintained at 37°C. The time required for the tablet to rise to the surface was determined as floating lag time and the time period up to which the tablet remained floating was termed as total floating time or buoyancy time [7].

2.4.3. Swelling studies

Swelling is a vital factor to ensure buoyancy and dissolution of floating matrix tablet. The swelling of polymers can be measured by their ability to absorb water and swell[8]. Tablets were weighed and placed in a beaker containing 200ml of 0.1N Hcl at room temperature. After each hour the tablet was removed from the beaker, blotted with filter paper to remove excess of water and weighed again upto 12 hours[9]. Water uptake is measured in terms of percent weight gain, as given by the equation

Swelling index (%) = Final weight – initial weight / initial weight x 100 (1)

2.4.4. In vitro release studies

In vitro release studies were performed in USP type II paddle apparatus for 12 hours. The tablets were placed in the dissolution medium of 900ml 0.1N hydrochloric acid

TABLE 1: Composition of valsartan floating tablets

Formulation codes	Ingredients (mg/tablet)								
	Valsartan	HPMC K100M	HPMC K4M	HPMC K15M	MC	EC	Lactose	Talc (1%)	Magnesium stearate (1%)
F1	40	200	-	-	-	-	5	2.5	2.5
F2	40	187.5	-	-	-	12.5	5	2.5	2.5
F3	40	175	-	-	-	25	5	2.5	2.5
F4	40	162.5	-	-	-	37.5	5	2.5	2.5
F5	40	150	-	-	-	50	5	2.5	2.5
F6	40	-	200	-	-	-	5	2.5	2.5
F7	40	-	187.5	-	-	12.5	5	2.5	2.5
F8	40	-	175	-	-	25	5	2.5	2.5
F9	40	-	162.5	-	-	37.5	5	2.5	2.5
F10	40	-	150	-	-	50	5	2.5	2.5
F11	40	-	-	200	-	-	5	2.5	2.5
F12	40	-	-	187.5	-	12.5	5	2.5	2.5
F13	40	-	-	175	-	25	5	2.5	2.5
F14	40	-	-	162.5	-	37.5	5	2.5	2.5
F15	40	-	-	150	-	50	5	2.5	2.5
F16	40	-	-	-	187.5	-	5	17.5	2.5
F17	40	-	-	-	175	12.5	5	17.5	2.5
F18	40	-	-	-	162.5	25	5	17.5	2.5
F19	40	-	-	-	150	37.5	5	17.5	2.5
F20	40	-	-	-	137.5	50	5	17.5	2.5

Each tablet weight is 250mg

in the dissolution apparatus. The paddle is rotated at 50 rpm maintained at 37 ± 5°C[10]. Samples (5ml) were withdrawn at every 15 minutes intervals for the first hour and every 30 minutes intervals for the next 11hours. The same volume of buffer solution was replaced into the dissolution medium. The withdrawn samples were filtered and diluted to a suitable concentration with 0.1N hydrochloric acid. Samples were analyzed at 204 nm using UV spectrophotometer (Shimadzu, Japan)[11]. The studies were done in triplicate.

2.4.5. In vitro drug release kinetics studies

The in vitro release profiles obtained from the floating tablets were fit to zero order, first order, Higuchi, Hixson Crowell, Korsemeyer & Peppas model kinetics, to find out the mechanism of drug release[12,13].

Zero Order	Qt = Q0 + K0.	(2)
First Order	log C = log C0 + K1 t/2.303	(3)
Hixson-Crowell	W01/3 - Wt1/3 = Kht	(4)
Higuchi	Qt = K2t1/2	(5)
Korsmeyer - Peppas	Qt / Qσ = Kp.tn	(6)

where Qt, Q0 and Qσ are the amounts of drug dissolved initially, at time t and at time σ, (in most cases, Qo = 0), C0 and C are the concentrations of drug initially and at time t, Wt and W0 are the amounts of drug in the pharmaceutical dosage form initially and at time t, K0, K1, K2, Kh, Kp refer to the rate constants obtained from the linear curves of the respective models.

2.4.6. Comparison of selected formulation with marketed formulation

The release of the selected formulation was compared with the marketed formulation.

2.4.7. Assay of valsartan by HPLC method

Quantitative determination of valsartan was performed by HPLC (Int L-C-GC Agilent Model). Fifteen tablets were taken and crushed to powder with mortar and pestle[14]. Exact amount of powder (average weight) were taken and diluted with methanol upto 50ml in a volumetric flask. After sonication for 15mts, solution was filtered through 0.45µm filter paper. The total amount of drugs within the tablets are analyzed after appropriate dilution of test solution by using the HPLC method as described below against the reference solution of valsartan pure powder prepared in the same procedure [15,16]. The column is made up of stainless steel (25cmx4.6mm) and packed with octadecylsilane bonded to porous silica (5µm particle size). The mobile phase consists a mixture of 50 volumes of water, 50 volumes of acetonitrile and 0.1 volumes of glacial acetic acid (50:50:0.1). The injection volume is 10µl, flow rate 1ml per minute and detected using UV at 273nm.

2.4.8. Scanning electron microscopy

The scanning electron microscopy (SEM) image of the tablet has been used to examine surface topography, texture and morphology of fractured surface are compared to hypothesize the mechanism of drug release and floating. The surface of the tablets is studied by SEM. The preparation of the samples are accomplished by placing the intact tablets before and after 12 hours dissolution, by drying them to remove water content and placing these tablets on specimen holder. The samples were coated with a gold-palladium target using a Novatec vaccum evaporator for 15minutes[17]. SEM images were obtained at an acceleration voltage of 8 to 10KV. Study of the morphology of the particles using SEM is done, which provides information about the 3-D structure of the particles with the resolution power up to 50 A. Imaging is done at a magnification of 200µm and pressure of 0.98 torr [18].

2.4.9. In vivo x – ray studies

The in vivo studies approved by Institutional animal ethical committee reference No. 14024/E1/4/2011 were performed on a healthy male albino rabbit weighing 2-2.5 kg. The animal is fasted overnight but allowed to take water ad libitum[19]. Then 30 ml of 5 % dextrose solution is given immediately before administering the tablets by using stomach tube (No. 12 French catheter) and 20ml syringes. The tablets were made opaque by incorporating barium sulphate (BaSO4) instead of drug. The rabbit was exposed to X-ray imaging in the abdominal region, and photographs were taken at 0, 2, 4, 6, 8, 10 & 12 hrs after administration of tablet. At hourly intervals 30 ml of 5 % dextrose solution was given to maintain optimum fluid level in the stomach [20]. The gastric residence time was observed.

3. RESULTS AND DISCUSSION

3.1. Drug-polymer interaction studies

3.1.1. Fourier transform infrared spectroscopy (FTIR) studies

FT-IR spectrum showed that the drug had characteristic peaks of N-H Stretching (VF 3443.05 cm-1), C-H Stretching in Alkane (VF 2964.69cm-1), C=O Stretching (VF 1730.21cm-1), Ar C=C Stretching (VF 1600.97 cm-1), Isopropyl Stretch (VF 1469.81cm-1), CH3 Bending (VF 1410.01 cm-1), C-N Stretching (VF 1274.99 cm-1), C-C Stretching (VF 1205.55 cm-1), p-substituted benzene (VF 852.56 cm-1), thus indicating the identity and purity of the drug. All the major bands

present in the spectrum of the pure drug are clearly observed in the spectrum of polymers with negligible changes in their position. This study clearly suggests that the pure drug remains in its normal form and hence there was no interaction between the drug and polymer. The results are shown in the Figure 1.

3.1.2. Differential Scanning Calorimetry (DSC) Studies

The DSC thermograms of pure drug and the different polymers showed that an endothermic peak corresponding to the melting point of pure drug was prominent in all the drug polymer mixture, which suggested clearly that there was no interaction between the drug and the polymers and the drug was existed in its unchanged form as shown in the Figure 2.

3.2. Evaluation of floating tablets

3.2.1. Physical properties

The floating matrix tablets of valsartan were prepared by direct compression technique using HPMC (K4M, K15M, and K100M), MC, EC, lactose, along with magnesium stearate and talc. The Powder blend of all the formulations were found to possess good flow property which was indicated by angle of repose 27º.08' to 30º.26', bulk density 0.250 g/ml to 0.367 g/ml, tapped density 0.290 g/ml to 0.480 g/ml, Hausner's ratio 1.16 to 1.25 and percentage compressibility index 14% to 25.03%, as shown in the Table 2. The formulated tablets were white color, biconvex and round shaped without any scoring on any sides. All the tablets were elegant in appearance. Hardness of all the formulations were found to be in the range of 3.5 – 4 Kg/cm2, thickness 3.5 – 4 mm, diameter 10 mm, friability less than 1% and weight variation within the acceptable limits as per I.P. The percentage drug content of all the formulations was found to be within the limits of 90% to 110%. The results of the physical characteristics of floating tablets are shown in Table 3.

3.2.2. In vitro buoyancy studies

Among the twenty formulations, the formulations F1 – F15 (containing various grades of HPMC (HPMC K100M, HPMC K4M and HPMC K15M) alone and it is combined with ethyl cellulose) floated immediately. The formulation F16 (containing methylcellulose alone) had a lag time of 10minutes. The formulations F17 – F20 (containing the combination of methylcellulose and ethyl cellulose) had a lag time of 3 – 10 minutes. All the formulations remained buoyant upto 24hours (as indicated in Table 3 and Figure 3). With reference to buoyancy studies results it can be concluded that the batch containing HPMC polymers alone and its combination with ethyl cellulose showed good floating lag time when compared to batch containing methylcellulose polymers alone and its combination with ethyl cellulose. The buoyancy of the tablet varies from polymer to polymer which is governed by both the swelling of the hydrocolloid upon contact with the dissolution fluid and the presence of voids in the centre of the tablet[21].

3.2.3. Swelling studies

Swelling of tablets is a direct indication of amount of water uptake by the tablets. The percentage swelling index of all the formulations is shown in Figure 4. The formulations (F1, F6, F11 and F16) containing hydrophilic polymers formed a gel layer around the tablet when they contact with water. This is due to the penetration of solvent into the free spaces between macromolecular chains of polymer and so the dimension of the polymer molecule was increased (swelling) due to polymer relaxation caused by stress of the penetrated solvent[21,9].

The formulations (F2-F5, F7-F9, F12-F15 and F17-F20) contain the combination of hydrophilic and hydrophobic polymers having less swelling index than that of the formulations containing hydrophilic polymers alone. This could be due to the less permeability of water into the hydrophobic polymer, which minimized the swelling of the matrix tablets. The formulation with HPMC K100M showed higher swelling index compared to other formulations due to high viscosity and high water retention property of HPMC K100M. The swelling index of the tablets increases with an increase in the polymer viscosity grades[22,23].

3.2.4. In vitro release studies

3.2.4.1. Effect of hydrophilic polymers on invitro drug release studies

The invitro release studies of formulations (F1, F6, F11 and F16) containing hydrophilic polymers showed drug release at 75.3%, 85.6%, 80.6%, & 90.3% in 12hours respectively (Table 3 and Figure 5). From above the results, the formulation F1 showed more retardant effect than the other formulations F6, F11, F16. This was due to the high viscosity of the polymer (HPMC K100M) than the others. The high viscosity grades induce the formation of strong viscous gel layer when they come in contact with aqueous media that slowed down the rate of diffusion of medium into the tablet, which may results in the retardation or decreases the drug release[17,21,23,24].

3.2.4.2. Effect of combination of hydrophilic and hydrophobic polymers on in vitro drug release studies

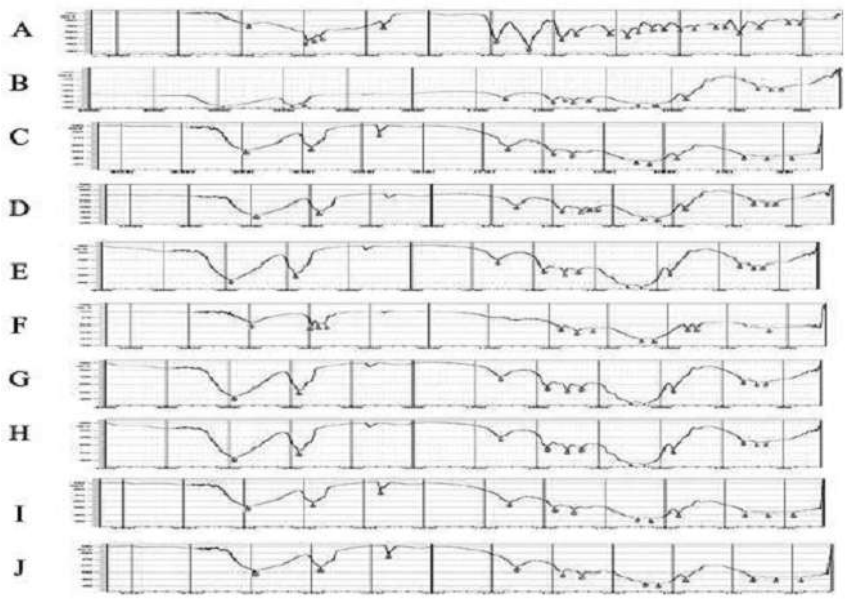


FIGURE 1: FTIR spectra of drug and excipients (A) valsartan (B) MC (C) HPMCK4M (D) HPMCK15M (E) HPMCK100M (F) EC (G) valsartan, HPMCK100M and EC (H) valsartan, HPMCK4M and EC (I) valsartan, HPMCK15M and EC (J) valsartan, MC and EC.

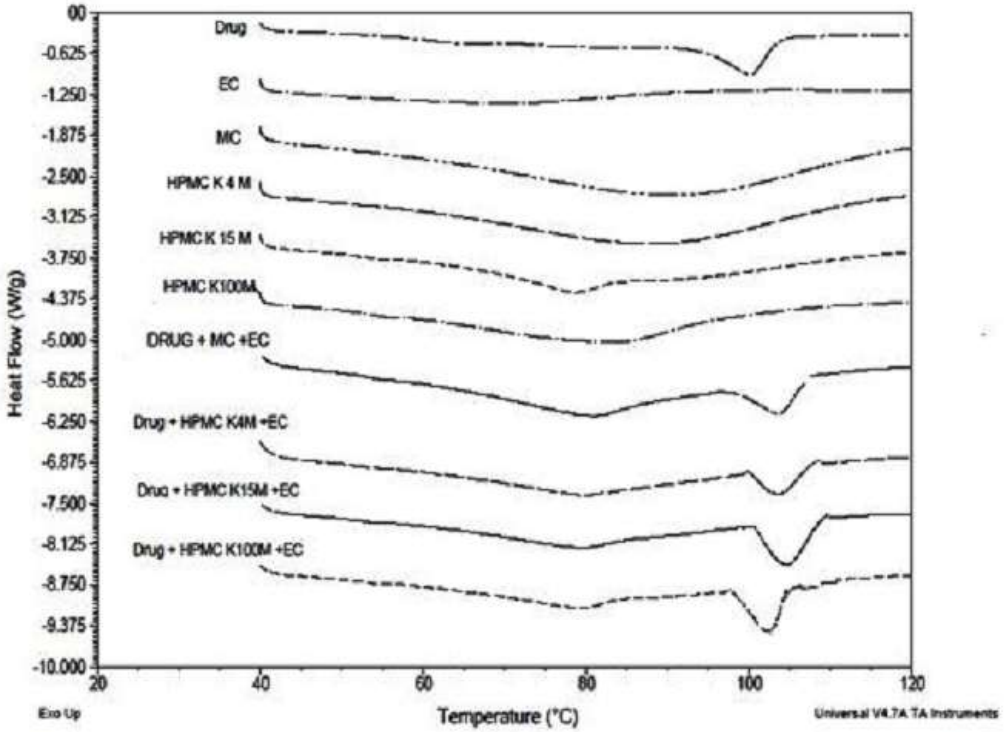


FIGURE 2: DSC thermograms of drug (valsartan) and excipients

TABLE 2: Physical parameters of valsartan floating tablets

Formulation codes	Angle of Repose (θ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hausner's Ratio	Drug Content (%)
F1	30º.13'	0.312	0.367	14.98	1.17	99.68
F2	29º.19'	0.297	0.390	23.8	1.21	99.79
F3	28º.17'	0.265	0.320	17.03	1.20	99.47
F4	29º.93'	0.290	0.390	25.0	1.24	99.37
F5	28º.09'	0.297	0.378	21.42	1.25	99.58
F6	28º.60'	0.277	0.367	24.46	1.22	99.58
F7	28º.53'	0.250	0.290	14	1.16	99.68
F8	28º.15'	0.265	0.357	24.9	1.24	99.26
F9	28º.03'	0.255	0.337	24.48	1.22	99.16
F10	27º.99'	0.347	0.446	22.19	1.18	99.16
F11	27º.08'	0.357	0.480	25.03	1.24	99.26
F12	29º.53'	0.367	0.480	23.5	1.20	99.26
F13	28º.24'	0.357	0.462	22.7	1.24	99.16
F14	29º.54'	0.312	0.416	24.98	1.20	99.16
F15	30º.26'	0.320	0.416	23.06	1.19	99.05
F16	28º.50'	0.297	0.357	16	1.19	98.95
F17	28º.34'	0.296	0.416	20.6	1.20	98.84
F18	28º.35'	0.284	0.357	20.4	1.25	98.63
F19	28º.17'	0.337	0.415	18.9	1.23	98.68
F20	28º.24'	0.271	0.357	23.91	1.21	98.32

TABLE 3: Physical parameters of valsartan floating tablets

Formulation codes	Hardness (kg/cm^2)	Thickness (mm) ± SD*	Diameter (mm) ± SD*	Friability (%)	Weight variation (mg) ± SD*	Drug Content (%) ± SD*	Floating lag time (min)	Buoyancy time (h)	Drug release($t^{1/2}$) (%) ± SD*
F1	3	4	10	0.13	249.54	99.79	Immediately	>24hrs	75.3 ± 0.16
F2	4	4	10	0.25	249.17	99.58	Immediately	>24hrs	74.5 ± 0.36
F3	4	4	10	0.27	248.09	99.37	Immediately	>24hrs	73.3 ± 0.70
F4	4	4	10	0.22	247.00	99.47	Immediately	>24hrs	71.3 ± 0.53
F5	4	4	10	0.28	249.03	99.79	Immediately	>24hrs	67.1 ± 0.80
F6	4	3.9	10	0.23	246.91	99.47	Immediately	>24hrs	85.6 ± 0.68
F7	4	3.9	10	0.38	247.64	99.47	Immediately	>24hrs	84.0 ± 0.30
F8	4	3.9	10	0.21	247.80	99.37	Immediately	>24hrs	83.6 ± 1.51
F9	4	3.9	10	0.36	246.71	99.79	Immediately	>24hrs	82.5 ± 3.22
F10	4	3.9	10	0.30	244.25	99.58	Immediately	>24hrs	81.3 ± 0.36
F11	4	3.9	10	0.27	247.99	99.79	Immediately	>24hrs	80.6 ± 0.59
F12	4	3.9	10	0.35	247.76	99.89	Immediately	>24hrs	79.6 ± 0.75
F13	3.5	3.9	10	0.43	246.50	99.58	Immediately	>24hrs	78.6 ± 0.59
F14	4	3.9	10	0.28	246.58	99.37	Immediately	>24hrs	77.7 ± 0.68
F15	4	3.9	10	0.23	247.54	99.37	Immediately	>24hrs	76.6 ± 0.98
F16	3	3.5	10	0.32	245.64	99.27	10 mts	>24hrs	90.3 ± 0.65
F17	3.5	3.5	10	0.29	247.73	99.35	3 mts 20sec	>24hrs	89.7 ±0.30
F18	3.5	3.9	10	0.50	248.18	99.79	10mts 15sec	>24hrs	88.0 ± 0.71
F19	4	3.9	10	0.25	248.74	99.16	15mts	>24hrs	87.8 ± 0.36
F20	3.5	3.9	10	0.30	248.08	98.63	8mts 10sec	>24hrs	86.7 ± 1.24

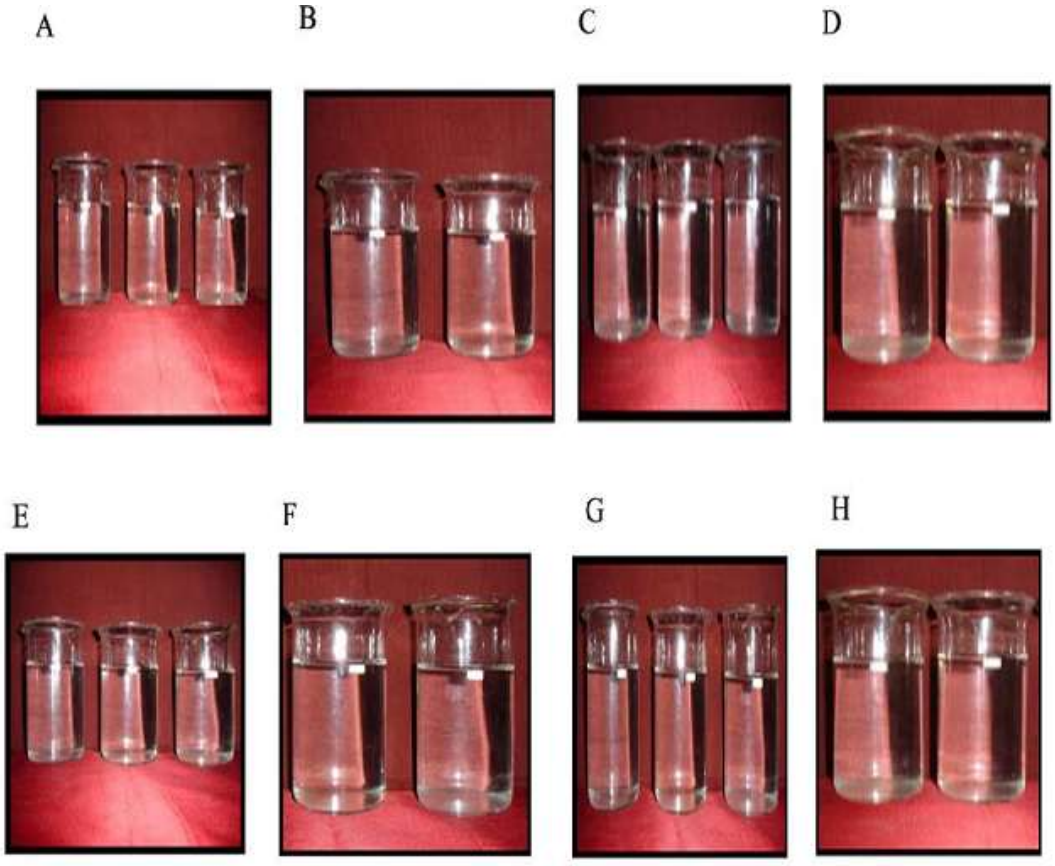


FIGURE 3: *Invitro* buoyancy studies of valsartan floating tablet (A) F1 to F3 (B) F4 to F5 (C) F6 to F8 (D) F9 to F10 (E) F11 to F13 (F) F14 to F15 (G) F16 to F18 (H) F19 to F20.

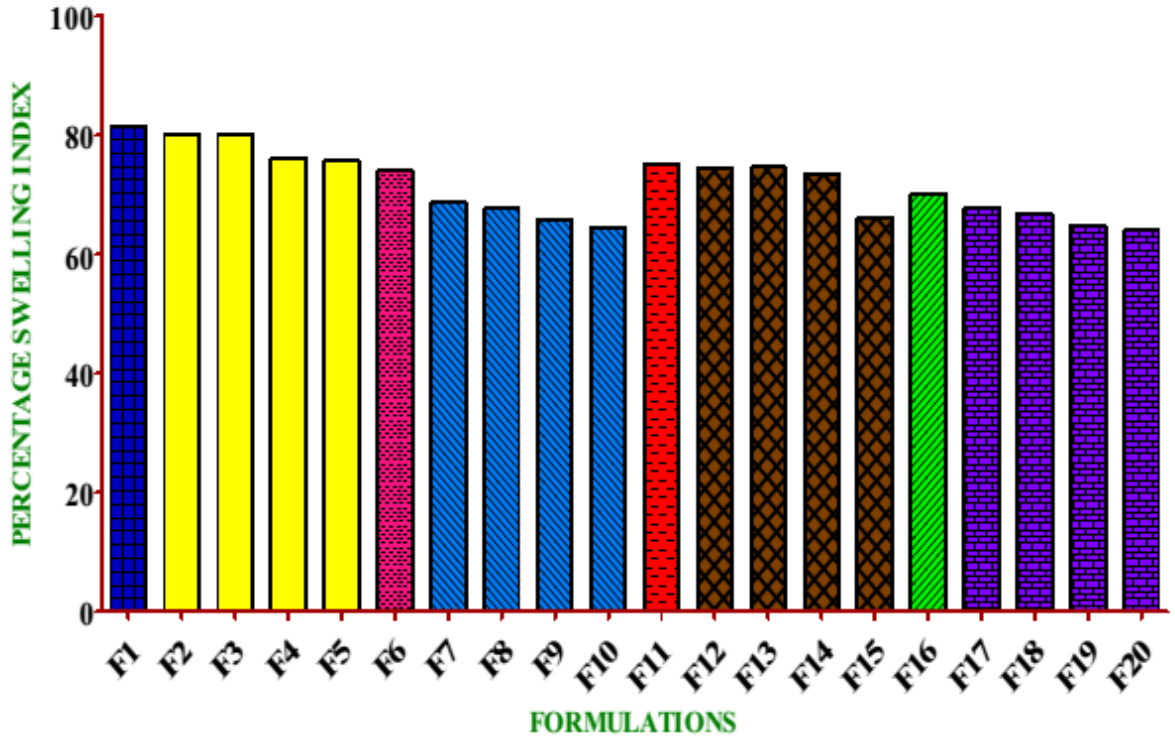
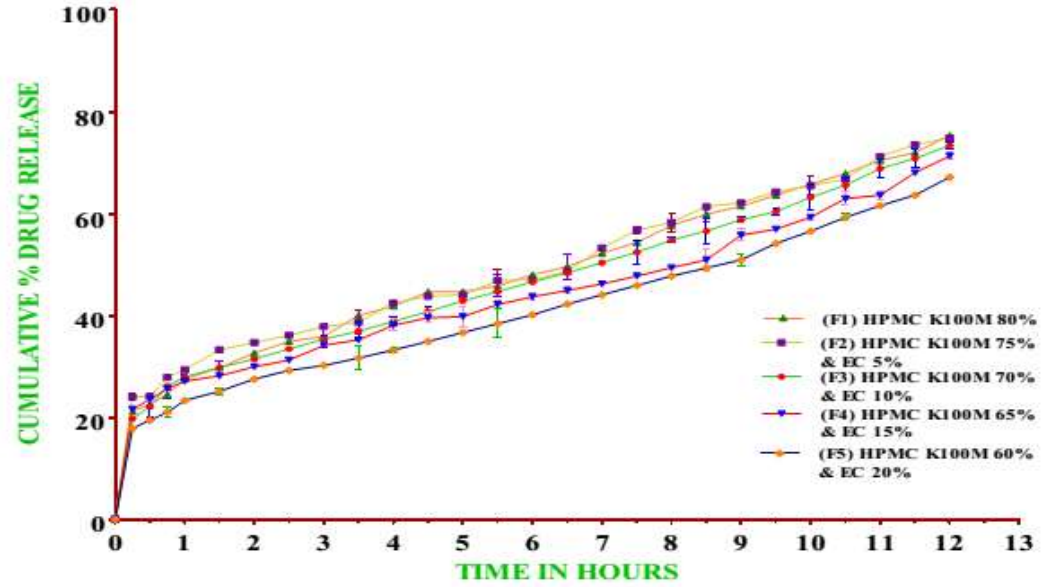
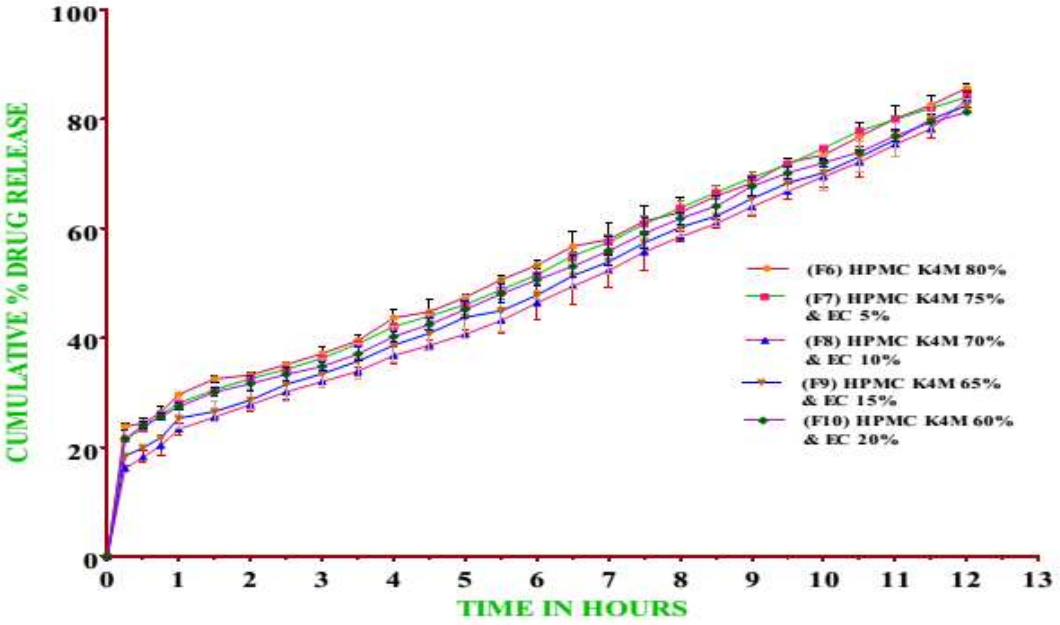


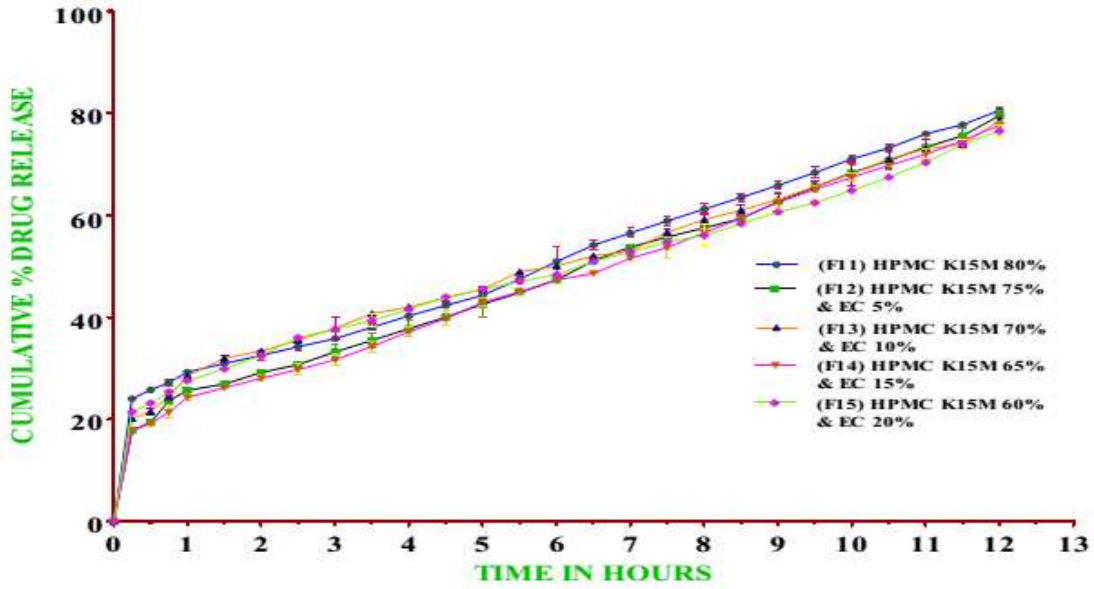
FIGURE 4: Percentage swelling index of formulations (F1 to F20)


CUMULATIVE % DRUG RELEASE
TIME IN HOURS
(F1) HPMC K100M 80%
(F2) HPMC K100M 75% & EC 5%
(F3) HPMC K100M 70% & EC 10%
(F4) HPMC K100M 65% & EC 15%
(F5) HPMC K100M 60% & EC 20%

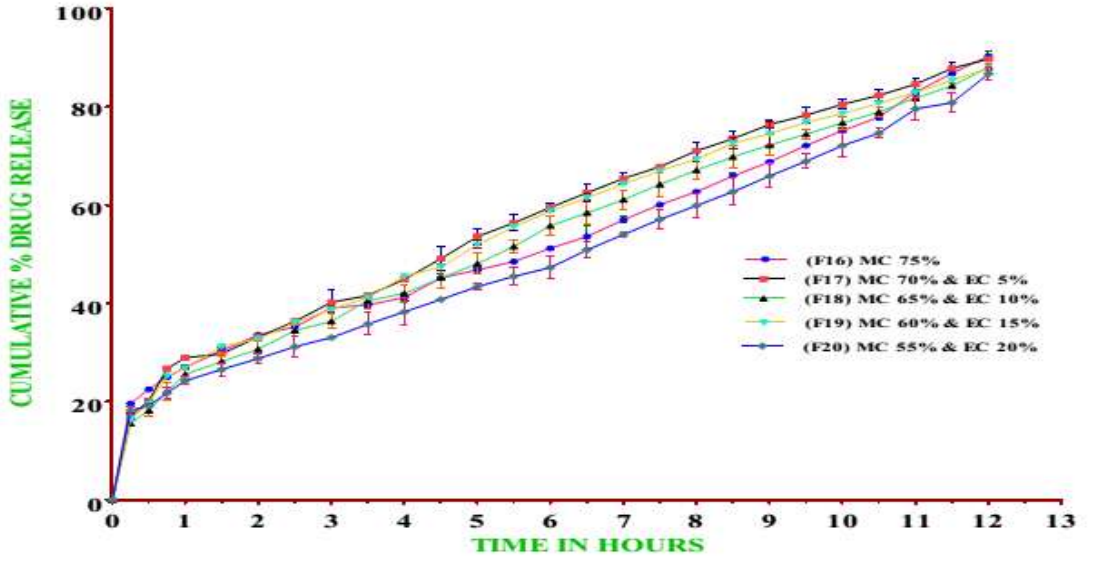
(A)


CUMULATIVE % DRUG RELEASE
TIME IN HOURS
(F6) HPMC K4M 80%
(F7) HPMC K4M 75% & EC 5%
(F8) HPMC K4M 70% & EC 10%
(F9) HPMC K4M 65% & EC 15%
(F10) HPMC K4M 60% & EC 20%

(B)



(C)



(D)

FIGURE 5: *Invitro* buoyancy studies of valsartan floating tablet (A) HPMC K100M and EC (F1 to F5) (B) HPMC K4M and EC (F6 to F10) (C) HPMC K15M and EC (F11 to F15) (D) MC and EC (F16 to F20).

To increase the release retardation of the drug, the formulations were prepared by a combination of both hydrophilic and hydrophobic polymers. The cumulative % drug release of formulations containing F2, F7, F12 and F17 showed 74.5%, 84%, 79.6% and 89.7% in 12 hours respectively (Table 3 and Figure 5). The cumulative % drug release of formulations containing F3, F8, F13, F18 showed 73.3%, 83.6%, 78.6% and 88% in 12 hours respectively (Table 3 and Figure 5). The cumulative % drug release of formulations containing F4, F9, F14 and F19 showed 71.3%, 82.5%, 77.7% and 87.8% in 12 hours respectively (Table 3 and Figure 5). The cumulative % drug release of formulations containing F5, F10, F15 and F20 showed 67.1%, 81.3%, 76.6% and 86.7% in 12 hours respectively (Table 3 and Figure 5). From above the results, it was observed that the drug release was slower for formulations containing F2 – F5, F7 – F10, F12 – F15, F17 – F20 due to the decreased concentration of hydrophilic polymer and increased concentration of hydrophobic polymer. Ethyl cellulose is hydrophobic in nature, which restricts the penetration of dissolution medium inside the matrix and also restricts the formation of gel layer around the matrix. So that, the drug release from the hydrophobic matrix decreased as compared to the hydrophilic polymers. Among all the twenty formulations, F5 was selected as a best formulation which had the better retardant effect (67.1% in 12 hours). Hence, it was concluded that the floating matrix tablets prepared with the combination of hydrophilic and hydrophobic polymers showed better controlled drug release than that of hydrophilic polymers alone[22,25].

3.2.5. In vitro drug release kinetics studies

The mechanism of drug release for the above formulations was determined by finding the r2 value for each kinetic model viz. zero-order, first-order, Higuchi, Hixson Crowell and Korsmeyer–Peppas corresponding to the release data of each formulation. For most of the formulations the r2 value of zero order and Korsmeyer–Peppas model is very near to one than the r2 values of other kinetic models. Thus, it can be said that the drug release follows zero order and Korsmeyer–Peppas model mechanism. The 'n' values of Korsmeyer–Peppas model for the best formulation were in the range of 0.45–0.85. Therefore, the most probable mechanism of release was non-Fickian diffusion or anomalous diffusion (both diffusion and swelling)[21,24,26]. All the values are shown in Table 4.

3.2.6. Comparison of selected formulation with marketed formulation

The promising formulation (F5) as found by evaluation studies was compared with marketed product (Conventional tablet - Valent 40mg). The cumulative % drug release of the best formulation was found to be 67.1% in 12hours when compared to the marketed product whose cumulative % drug release was 101% in 1hour. Thus the formulation F5 showed controlled release profile than the marketed conventional tablet. The results are shown in the Figure 6.

3.2.7. Assay of valsartan by HPLC method

The percentage of valsartan content from the best formulation (F5) was determined by High performance liquid chromatography (HPLC) method and was found to be 100.573% (40.229mg of Valsartan). Hence, the percentage drug content of the best formulation complies with official specifications as per U.S.P (Limits: 90% - 110%). The same result was obtained by UV spectrometry while analyze the best formulation (F5). The results are shown in the Figure 7.

3.2.8. Scanning electron microscopy

The Surface topography, texture and morphology of fractured surface of best formulation were evaluated by using SEM. The SEM images of the optimized formulation (F5) were taken before and after dissolution. The SEM images of the tablet showed intact surface without any perforations, channels or troughs. After dissolution the solvent front enters the matrix and moves slowly toward the centre of the tablet. The drug diffuses out of the matrix after it comes in contact with dissolution medium. The SEM images of the formulation showed a network in the swollen polymer through which the drug diffused to the surrounding medium[18]. Hence, it was concluded that the drug was released from matrix by diffusion mechanism. The results are shown in the Figure 8.

3.2.9. In vivo x-ray studies

The in vivo floating behavior of the optimized formulation (F5) was assessed by x-ray image studies in rabbits. Gastric radiography was done in the abdominal region at periodic time intervals using the x-ray machine. The tablet was clearly seen in the GIT at different positions on the upper part of stomach confirmed its in vivo floating behavior. Gastric residence time was found to be more than 12 hours. Thus it was evident that the formulation could be retained in the gastric region to ensure complete release of drug. The x-ray photographs are shown in Figure 9.

TABLE 4: Drug release kinetics studies of valsartan floating tablets

Formulation codes	Zero order		First order		Higuchi		Korsmeyer Peppas		Hixson Crowell		Release mechanism
	r^2	K_0 (h^{-1})	r^2	K_1 (h^{-1})	r^2	K_H ($h^{-1/2}$)	r^2	n	r^2	K_{HC} ($h^{-1/3}$)	
F1	0.977	2.382	0.954	-0.038	0.979	18.01	0.973	0.459	0.936	-0.107	Non-Fickian
F2	0.969	2.325	0.941	-0.037	0.981	17.25	0.959	0.524	0.949	-0.104	Non-Fickian
F3	0.969	4.490	0.943	-0.036	0.983	17.18	0.964	0.451	0.944	-0.101	Non-Fickian
F4	0.945	4.113	0.930	-0.031	0.963	15.48	0.936	0.497	0.906	-0.089	Non-Fickian
F5	0.993	3.855	0.965	-0.029	0.992	15.77	0.949	0.452	0.927	-0.087	Non-Fickian
F6	0.963	5.524	0.942	-0.054	0.972	21.31	0.956	0.470	0.921	-0.142	Non-Fickian
F7	0.967	5.613	0.953	-0.054	0.977	21.73	0.959	0.483	0.924	-0.144	Non-Fickian
F8	0.979	5.618	0.935	-0.050	0.966	22.01	0.948	0.453	0.938	-0.137	Non-Fickian
F9	0.976	5.566	0.948	-0.050	0.974	21.73	0.954	0.518	0.932	-0.137	Non-Fickian
F10	0.965	5.381	0.961	-0.049	0.980	20.77	0.953	0.573	0.914	-0.133	Non-Fickian
F11	0.959	5.138	0.955	-0.047	0.978	19.61	0.947	0.541	0.894	-0.126	Non-Fickian
F12	0.970	5.249	0.960	-0.045	0.980	20.44	0.959	0.464	0.939	-0.118	Non-Fickian
F13	0.970	4.995	0.953	-0.043	0.986	19.38	0.976	0.475	0.976	-0.122	Non-Fickian
F14	0.973	5.219	0.967	-0.044	0.984	20.37	0.960	0.471	0.937	-0.122	Non-Fickian
F15	0.966	4.632	0.941	-0.038	0.982	17.76	0.966	0.484	0.971	-0.107	Non-Fickian
F16	0.966	5.820	0.887	-0.061	0.949	22.60	0.942	0.462	0.941	-0.156	Non-Fickian
F17	0.970	6.306	0.967	-0.069	0.989	25.04	0.981	0.520	0.982	-0.173	Non-Fickian
F18	0.976	6.178	0.961	-0.062	0.983	24.54	0.976	0.537	0.980	-0.079	Non-Fickian
F19	0.976	6.164	0.966	-0.064	0.986	24.47	0.980	0.515	0.975	-0.165	Non-Fickian
F20	0.978	5.772	0.919	-0.054	0.958	22.57	0.952	0.539	0.947	-0.146	Non-Fickian

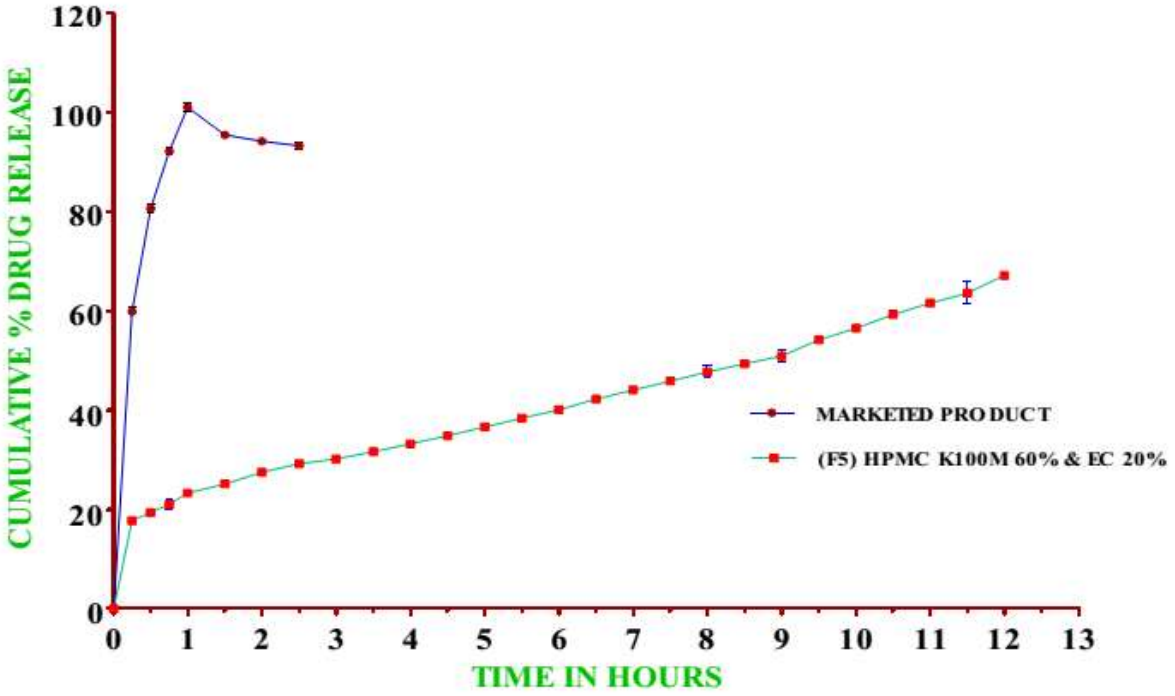
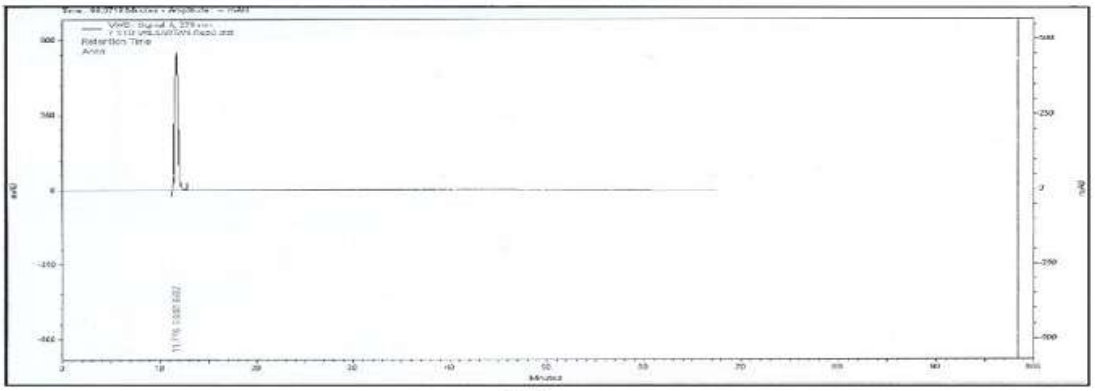
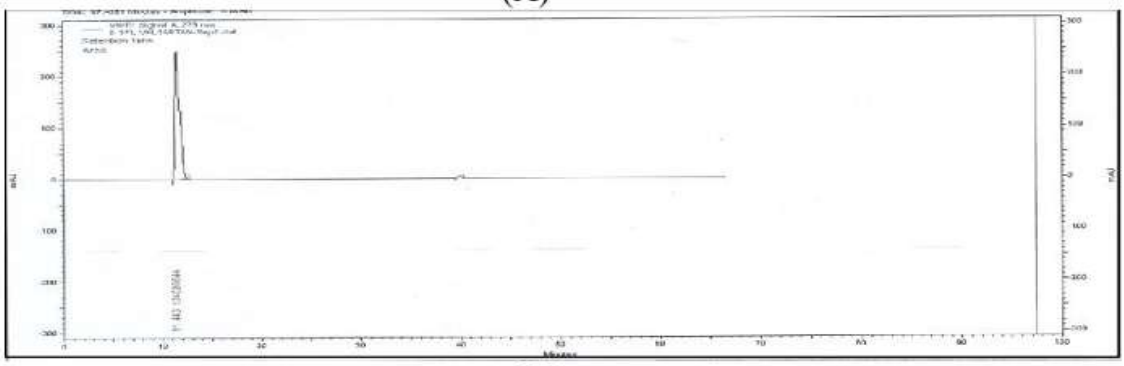


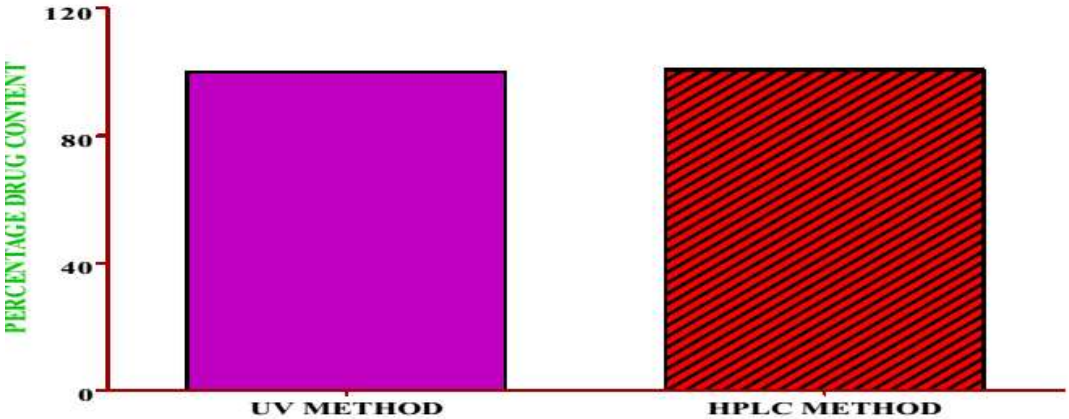
FIGURE 6: *Invitro* drug release profile of optimized formulation compared with marketed product.



(A)

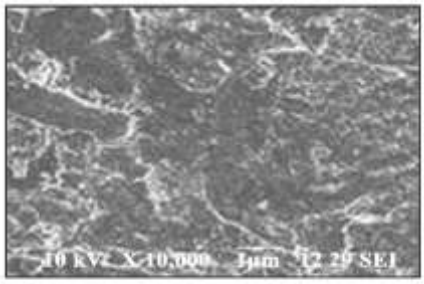


(B)

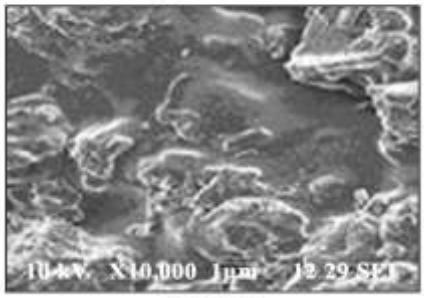


(C)

FIGURE 7: HPLC analysis of valsartan floating tablet (A) retention time area of standard valsartan (B) retention time area of sample valsartan (optimized formulation) (C) comparison of percentage drug content of optimized formulation by UV and HPLC method.



(A) BEFORE



(B) AFTER

FIGURE 8: Scanning electron microscopy images of optimized formulation (A) before dissolution (B) after dissolution.

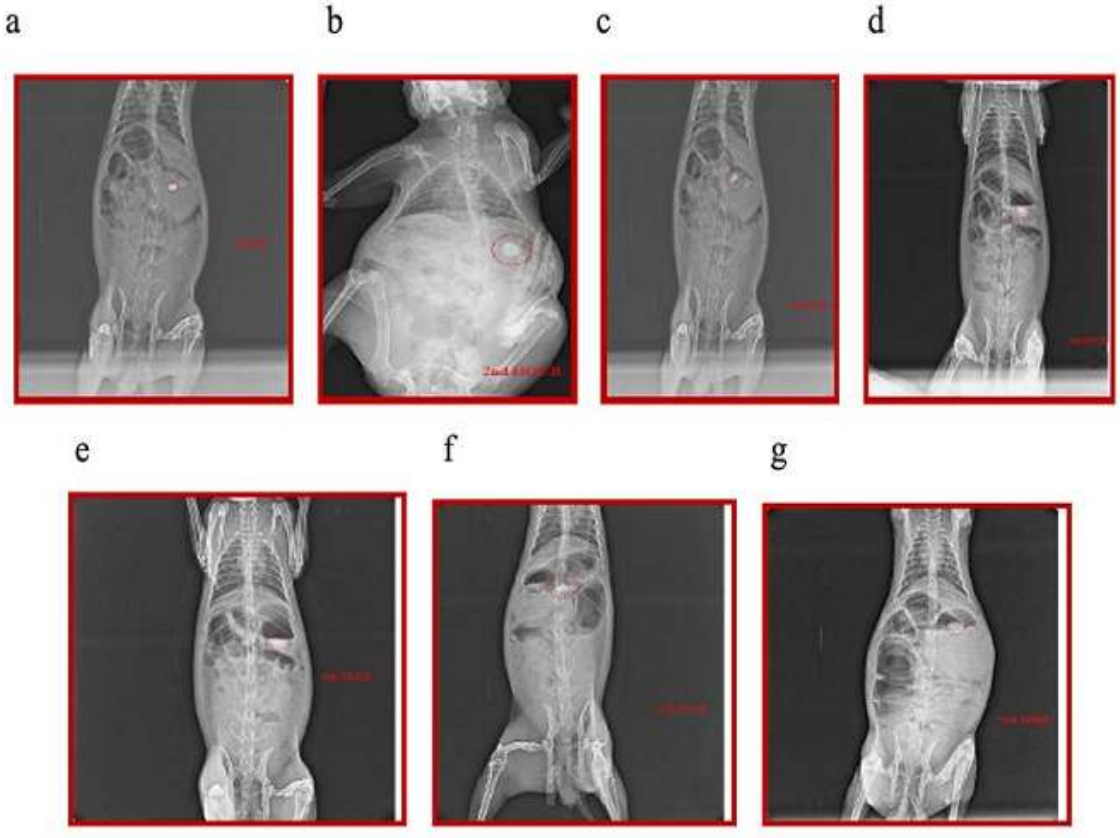


FIGURE 9: X-ray photographs of valsartan floating tablet of optimized formulation in a rabbit (a) 0h (b) 2h (c) 4h (d) 6h (e) 8h (f) 10 h (g) 12 h.

4. CONCLUSIONS

The results of the present study clearly indicate the feasibility to develop valsartan in the form of floating drug delivery system with prolongation of gastric retention time and controlled drug release. The future studies may be extended to reveal the pharmacokinetic parameters related to bioavailability and clinical trial investigations, which may prove that this type of the formulation can be administered safely for the treatment of hypertension with improved therapeutic efficacy.

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