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Original Article

FORMULATION AND OPTIMIZATION OF BUOYANT *IN SITU* GELLING SYSTEM OF VALSARTAN USING NATURAL POLYMER

S. PRASANTHI[1], M. VIDYAVATHI[*2]

[1]Department of Pharmaceutics, Annamacharya College of Pharmacy, New Boyanapalli, Rajampet 516126, A. P, India, [2]Institute of Pharmaceutical Technology, Sri Padmavati Mahila Visvavidyalayam, Tirupathi 517502. A. P., India
Email: prasanthiram84@gmail.com

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ABSTRACT

Objective: Currently natural polymers have wide spread importance in fabrication of controlled drug delivery systems. Hence in this study *ocimum basilicum* mucilage, (OBM) a natural polymer used to know its effect as polymer alone and in combination with HPMC K15M and Guargum in oral *in situ* floating gel of Valsartan using 3 full level factorial design.

Methods: FTIR studies conducted to know major drug polymer interactions. OBM, HPMC K15M and Guargum were chosen as three independent variables and examined at 3 levels for *in vitro* buoyancy (Y_1) and drug release at 10 h (Y_2) as responses. By using mathematical model approach formulation variables were quantitatively evaluated, and optimized formulation (VFIG) subjected for *in vitro* buoyancy, density, pH, *in vitro* drug release, drug content, gelling capacity and drug release kinetics. In addition VFIG studied for *In vivo* buoyancy and release kinetics.

Results: FTIR studies revealed that excipients were compatible with drug. ANOVA results shown that independent variables have significant effect ($p<0.05$) on both the responses. Observed responses of optimized formulation (3 % OBM, 0.88 % HPMC and 1.25 % Guar gum) were in good agreement with the experimental values. Results of all *in vitro* evaluations lies within the limits and drug release kinetics followed non-fickian diffusion mechanism. *In vivo* buoyancy study in rabbit evidenced floatation for>8 h and *in vivo* pharmacokinetic study exhibited increased bioavailability of optimized formulation.

Conclusion: Prepared VFIG with optimized concentrations of OBM, HPMC K15M and Guargum exploiting as a promising dosage form for enhanced gastric delivery.

Keywords: Valsartan, Natural polymers, OBM, *In situ* floating gel, Buoyancy studies, 3 Level full factorial design

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INTRODUCTION

As the oral route account for ease of self-administration and other advantages, most manufacturers prefer to formulate a drug in suitable dosage form for oral delivery. These reasons now attributed for the development of oral drug delivery systems. Drugs which have primary absorption in the stomach region require gastric residence for longer times. Such drugs, if formulated in oral conventional dosage forms fail to reside the drug in gastric region. Hence gastro retentive drug delivery systems have been developed by many approaches [1]. Raft forming system is one of the commonly used approaches for gastric retention of drugs with primary absorption in the stomach region [2].

Valsartan is an angiotensin-II receptor (which is a potent vasoconstrictor), type I antagonist, especially used in hypertension, congestive heart failure and heart attack. Angiotensin-II binding at AT-I receptor is blocked by this drug results in vasodilation which in turn lowers blood pressure [3]. This is a weak acidic drug has absorption window in the acidic environment of stomach [4]. It is rapidly absorbed orally but unfortunately its bioavailability is 23 %. Hence number of formulations in the form of solid dispersions [5], β-cyclodextrin complexes [6], microcapsules [7] etc., have been fabricated by many researchers in order to overcome its low bioavaiability and low solubility. But no attempt has been made to address the retention of valsartan at it's absorption window. So in the present study an attempt was made to develop an *in situ* gel dosage form to increase the bioavailability of drug by taking the advantage of its primary absorption in the stomach region.

Recently there is a trend in the use of natural polymers in tailoring of drug delivery systems due to added advantages [8]. Hence in this study *ocimum basilicum* mucilage (OBM) was selected which is an anionic polysaccharide obtained from seeds of *ocimum basilicum* linn., comprised of glucomannan (43 %) as major fraction and glucan (2.3 %) as minor fraction [9, 10]. It's thickening and stabilizing properties have been attributed to offer potential application in this formulation and first time this study conducted to explore it as gelling polymer. *In situ* solutions undergo phase transition to gel, due to variation in physiochemical properties like change in pH, temperature, ion activation etc., [11]. Main principle involved in this formulation is pH induced ionic gelation. Sodium citrate complexes with free $Ca^{2+}$and maintains the fluidity of *in situ* gel until it reaches the stomach. Once the formulation reaches the stomach, in the presence of acidic environment Ca^{2+}get releases and triggers the gelation of OBM. Effervescent agent helps the formulation to float on the gastric contents for extended period [12].

Statistical experimental design involves study of effect of independent variables on dependent variables with least number of experiments and reduces the time required for developmental work [13-16]. OBM elicit gelation in gastric pH and it's combination with HPMC K15M and guargum postulates durg release retarding power and excellent buoyant properties. The present study aimed at optimization of OBM as gelling polymer alone and in combination with HPMC K15M and guar gum using 3^3 factorial design.

MATERIALS AND METHODS

Materials

Valsartan was obtained as a gift sample from Dr. Reddy's labs, Hyderabad, India. *Ocimum basilicum* seeds were purchased from local market Rajampet, A. P, India. Their species was authenticated by Mrs. N. Uma, Botanist from Government degree college, Rajampet A. P. India. HPMC K15 M was obtained from Vijaya chemicals pvt. Ltd, Pune, India. Calcium carbonate was obtained from Thermo fisher scientific Pvt. Ltd Mumbai; India. Guar gum was obtained from

Genuine chemicals co., Mumbai, India. Sodium citrate, Sodium bicarbonate were procured from Universal laboratories pvt. Ltd Mumbai, India. All other chemicals used were of pharmaceutical or analytical grade.

Methods

Extraction of *Ocimum basilicum* seed mucilage

Mucilage extraction from *ocimum basilicum* seeds was carried out by a modified method of Razavi *et al.* [17] where100 g of cleaned *ocimum* seeds were subjected for soaking in distilled water (at 35 °c for 12 h) seed ratio of 10:1 and blended at 1500 rpm for 15 min to scrap the gum layer off the seed surface. Blended mass allowed to squeeze with the aid of 8 folds of muslin cloth to extract the mucilage. The filtrate was precipitated in the equal amount of the acetone. The precipitated mucilage was separated, dried, milled, packed and kept in dry condition.

FTIR studies

FTIR studies were conducted to know the compatibility between drug and excipients. In this studies pure valsartan, pure OBM and its mixture with HPMC K15M and guargum were grounded thoroughly with IR grade KBr, then compressed in a hydraulic press at a pressure of 10,000 psig, to get a disc. Each disc was scanned over a range of 400-4500 cm^{-1} using FTIR instrument (FTIR-1600, Shimadzu, Japan). The characteristic peaks were observed and recorded.

Formulation of *in situ* gel

Solutions of OBM, guargum, HPMC K15M, were made individually and in combination by the use of deionized water containing 0.05 %w/v of sodium citrate and calcium chloride, using magnetic stirrer with constant stirring. These polymer solutions were heated to 60 °C then allowed to reduce temperatures to 40 °C. Sodium bi carbonate (0.75 %w/v) and valsartan were added and stirring was continued to get an uniform dispersion. Finally sodium benzoate (0.1 % w/v) and sucrose (10 %w/v) were added and volume was made up to 100 ml [18].

Experimental design

A three-level, three-factorial (3^3) design chosen for present experimentation using a software DESIGN EXPERT® version 8.0.7.1. Independent variables selected were the concentration of HPMC K15M (*A*), Guar gum (*B*), and OBM (*C*). Low (-1), medium (0), and high settings (+1) were the coded factorial levels for three independent variables [19,20]. Chosen dependent variables for investigation were floating lag time (*in vitro* buoyancy) (Y_1), and drug release at 10 h (Y_2). A total of 27 experimental runs were conducted as shown in table 1 to optimize and analyze the interaction of each level on parameters of formulations. Multiple factorial regression analysis (quadratic model) was carried out to measure the effect of three variables on response (Y_i).

$$Y_i = b_0 + b_1A + b_2B + b_3C + b_4AB + b_5AC + b_6BC + b_7A^2 + b_8B^2 + b_9C^2 \quad (1)$$

Where Y_i-Dependent variable,

b_0- Arithmetic mean response of 27 combinations;

b_1, b_2, b_3 b_4 b_5 b_6 b_7 b_8 b_9-Regression coefficients

A, B and C (Main effects) were the average results of changing one factor at a time from its low to high levels by keeping other two constant. AB, AC and BC (Interaction terms) show, how the response changes when two factors are simultaneously changed. A^2, B^2 and C^2 (Polynomial terms) were used to investigate nonlinearity.

The significance of three factors and their interactions were evaluated with analysis of variance (ANOVA) and F statistics and t-values were also calculated [21]. 3D response surface plots given visualized observation of how the response parameters affected by independent variables. Desirability approach was employed to locate the optimal settings of the formulation variables to obtain desired response.

Table 1: 3^3 full factorial design of valsartan floating *in situ* gel

Coded values	Actual values		
	HPMC K15M (%) A	Guar gum (%) B	OBM (%) C
High (+1)	1.50	1.25	3.0
Medium (0)	0.75	0.63	1.75
Low (-1)	0	0	0.5

Evaluation of formulations

Total 27 formulations were evaluated for following two parameters.

Floating lag time studies for *in vitro* buoyancy

Floating lag time was measured in *in vitro* buoyancy test. USP Type II dissolution test apparatus containing 500 ml of simulated gastric fluid (pH-1.2), with paddle rotation of 50 rpm and 37±0.5 °C temperature were selected for this study. Petri plate (diameter 2 inch) containing *in situ* gelling solution (10 ml) was placed on the surface of the medium and plunged in to the medium with the moving paddle. The time required for the gelled mass to reach surface of the dissolution medium as floating lag time (Y_1) was noted. This was measured for each formulation in triplicate [22-24].

***In vitro* drug release studies**

USP type II (paddle type) apparatus was used to know the drug release by providing 50 rpm in 900 ml of simulated gastric fluid (pH 1.2),at 37±0.5 °C temperature. Ten milliliters of in situ gel containing valsartan was transferred to dissolution medium, at predefined time intervals, 1 ml of aliquot was collected, filtered through a 0.45 µm membrane filter, suitably diluted and analyzed at 250 nm by UV spectrophotometer (UV-1800, Shimadzu, Japan). Withdrawn test sample replenished with fresh dissolution medium. All studies were run for a period of 10 h in triplicate [25-27] and the amount of drug dissolved at 10^{th} h (Y_2) was noted for all 27 formulations.

Preparation of optimized formulation

Based on the results of above 2 responses of 27 formulations, the optimized concentration for A, B and C were obtained in desirability approach using software DESIGN EXPERT® version 8.0.7.1. Optimized valsartan floating *in situ* gel (VFIG) was prepared using optimized concentrations of HPMC K15M, guar gum and OBM and evaluated for the responses ($Y_1$and Y_2). The values obtained were compared with those predicted by the mathematical model generated, in addition VFIG was also evaluated for pH, density, viscosity, drug content, *in vitro* gelling capacity, *in vivo* buoyancy and *in vivo* pharmacokinetic studies**.**

Characterization of optimized floating *in situ* gel

pH

Determination of pH for VFIG was carried out by electrometric method by taking adequate volume in a 50 ml beaker using standardized digital pH meter at room temperature.

***In vitro* gelling capacity**

Five milliliters of the gelation solution (simulated gastric fluid, pH 1.2) was taken into a 15 ml test tube maintained 37±1 °C temperature and formulation (1 ml) was added slowly to (surface of

the fluid) the test tube. A stiff gel like structure was formed immediately after formulation comes in contact with gelation solution. The gelling capacity of solution was graded based on the stiffness of formed gel and time period for which the gel retained its rigidity into following three categories [28]. 1. (+) Gels after five min, dispersed within 8 h; 2. (++) Gels within 60 sec. and retains gel structure for 12 h.; 3. (+++) Gels immediately and retains gel structure for more than 12 h.

Density

Water displacement method was used to determine the density of the gel formulation. In this study 20 ml of simulated gastric fluid (pH 1.2) was added to 10 ml of *in situ* solution, to form a gel. So formed gel was weighed after decantation of excess of gastric fluid. The gel was allowed to settle at the base in a 50 ml measuring cylinder. Distilled water was added up to 50 ml marking of measuring cylinder. In presence of gel the volume of water was noted. Amount of water displaced by the gel was calculated from the difference in the volumes of water with and without gel [29].

Determination of viscosity

Brook field viscometer (DV-ELV) was utilized for viscosity measurement of optimized formulation. The sample aliquot of 50 ml was sheared with speed of spindle 100 rpm at physiological temperature (37 °C). Three replicates were carried out [30].

Drug content

Ten milliliters of the formulation was added to 900 ml of simulated gastric fluid and stirred for 1 h on a magnetic stirrer. The solution was filtered, suitably diluted with simulated gastric fluid and the drug concentration was determined by using a UV-visible spectrophotometer (UV-1800 Shimadzu, Kyoto, Japan) at 250 nm against a suitable blank solution [31].

***In vivo* floating studies in rabbit**

After getting approval from Institutional Ethics Committee, Sri Padmavathi Women's University (SPMVV), Tirupati, Andhra Pradesh, India (1677/PO/Re/S/2012/CPCSEA/11), the study was employed using 2.5 kg healthy rabbit which was housed three days and fasted for 12 h prior to the study but water allowed. An *in situ* gel prepared by employing $BaSo_4$ as X-ray opaque material (to enable visibility) in place of drug was made to swallow using stomach sonde needle and X-ray photographs of rabbit abdomen were taken at pre identified time intervals of 0,0.5,2 and 8 h [32].

***In vivo* pharmacokinetic studies**

Rabbits with weight of 2.5±0.5 kg were selected for the study with 24 h fasting just before the start of the experiment. Twelve such male rabbits were randomly divided into two groups. Using stomach sonde needle, VFIG and valsartan drug suspension were administered first and second groups respectively at a dose of 03 mg/kg body weight of rabbit. At appropriate time intervals 0.5 ml blood samples were collected through ear vein into heparinized tubes. With maintenance of 5,000 rpm for 10 min using a high-speed centrifuging machine, blood samples were centrifuged and resulting samples were stored at −18 °C until analyzed by HPLC [18].

Treatment of plasma samples

An aliquot of 100 µl plasma sample was taken into a RIA® vial, 10 µl of 100 µg/ml amilodipine (ISTD (internal standard)) was added, mixed and vortexed for 20 sec. A 100 µl of 1.5 %v/v HCl was added to this mixture, mixed for 30 sec and 2 ml of ethyl acetate was added. Samples were extracted for 4 min and centrifuged at 3200 rpm for 4 min. Supernatant 1.6 ml was transferred to evaporation tubes and dried gently under nitrogen gas at 50C for 12 min and reconstituted with 500 µl of mobile phase and 20 µl was injected onto an analytical column to perform the analysis [33].

HPLC analysis

Chromatographic separation was performed at a flow rate of 1.0 ml/min, at a wavelength of 272 nm, using an inertsil ODS-3, C18, (4.6×250 mm, 5.0 µm) column. The column temperature was maintained at 35 °C. The mobile phase was water: acetonitrile: glacial acetic acid (500:500:01). Representative chromatogram has been shown in fig. 5.

With aid of kinetica software various pharmacokinetic parameters like-maximum plasma concentration (C_{max}), time to reach maximum concentration (T_{max}), area under the plasma concentration-time curve ($AUC_{0\to t}$ and $AUC_{0\to\infty}$), elimination half-life ($t_{1/2}$), mean residence time (MRT) and elimination rate constant (K_{el}) etc, were determined.

RESULTS AND DISCUSSION

FTIR studies

FTIR spectrum of valsartan (fig. 1(a)) exhibited characteristic peaks at 3286 cm^{-1}(N–H functional group), 3059 cm^{-1} (Saturated C–H group stretching), 2962 cm^{-1} (Unsaturated C–H group stretching), 1728 cm^{-1} (carboxyl carbonyl),1600 cm^{-1} (amide carbonyl group). The peak at 1469 cm^{-1} indicated the presence of C=C aromatic group. In the FTIR of OBM (fig. 1[b]) occurrance of peak at the 2958 cm^{-1} signified C-H stretching of alkyl group. The observed characteristic peak at 3429 cm^{-1} owing to OH stretching of alcohol (or water absorbent). Peaks at 1060 cm^{-1} and at 952 cm^{-1} were also detected in the present study for N-H primary amide and C-H aromatic bond respectively. Appearance of characteristic peaks in the physical mixture (fig. 1(c), pure valsartan and polymer OBM indicated the absence of incompatibility between drug and polymers.

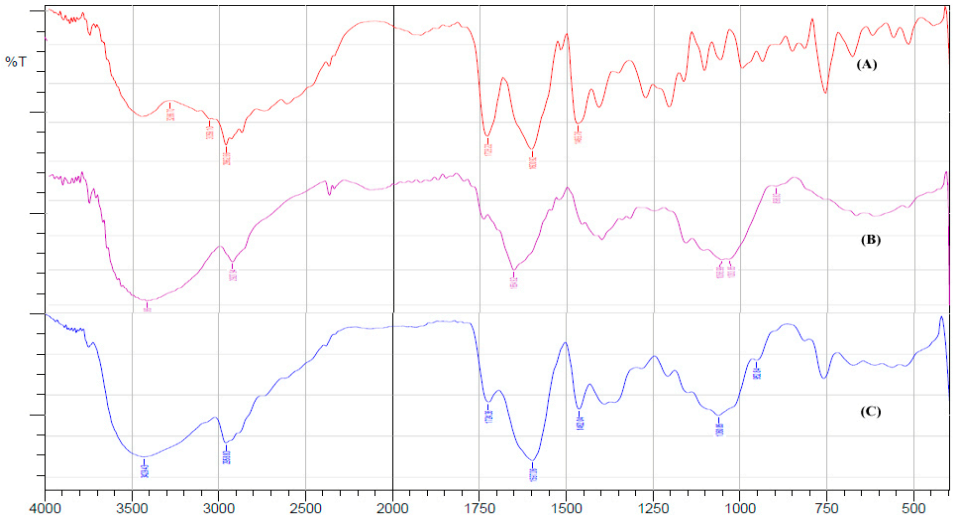


Fig. 1: FTIR spectrum of (A) Valsartan (B) OBM (C) valsartan+polymer mixture

In vitro buoyancy test

Measurement of floating lag time (Y1) was carried out for all 27 runs. For response (Y1) a quadratic model was suggested by software on application of factorial design. The Model F-value of 62.00 implied that model was significant. There was only a 0.01% chance that a large "Model F-Value" could occur due to noise. Values of "Prob>F" less than 0.0500 indicated model terms were significant. In this case A, B, C, AB, A2, C2 were considered as significant model terms due to their P values. P values lesser than 0.1000 indicated, the model terms were significant. The quadratic equation for Y1 was shown in equation (2).

$$Y_1 = +31.69 - 21.33 * A - 4.83 * B - 4.22 * C + 12.17 * A * B + 3.17 * A * C - 0.75 * B * C + 57.61 * A^2 + 2.44 * B^2 + 11.27 * C^2 \quad (2)$$

Equation (2) prooved that floating lag time decreases with an increase in amount of factor A,factor B and factor C. This was due to high swelling property of the polymers. Similar result was found in gastro retentive matrix tablets of ziprasidone hydrochloride containig HPMC K4M by Sateesha *et al.* [34]. Combined effect of A* B and A* C were positive but B* C was negative on floating lag time which was exhibited by contour plot and 3D response surface plots (fig. 2).

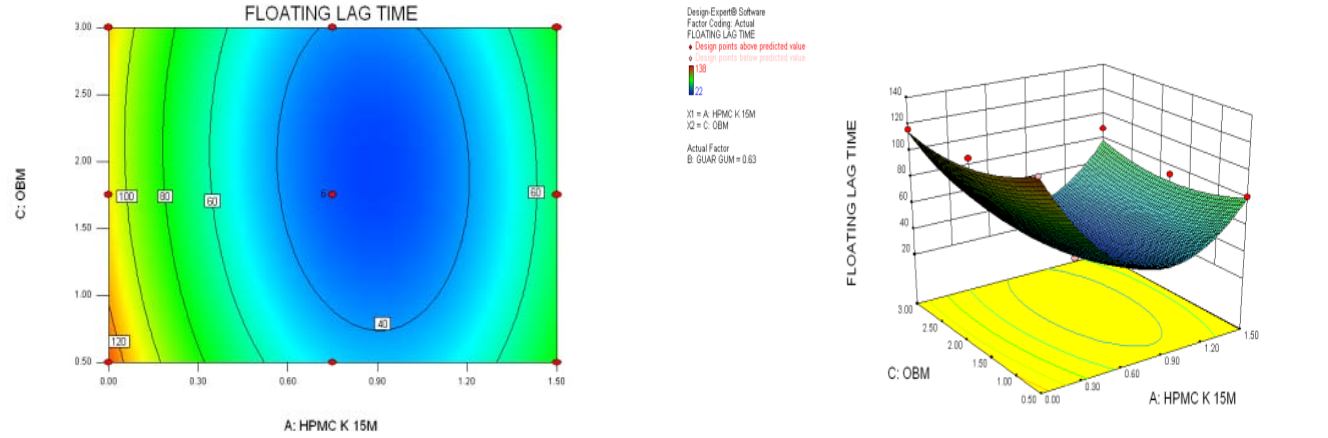
In vitro drug release at 10 h, Q_{10} (Y_2)

Measurement of drug release at 10 h (Y_2) was carried out for all 32 runs. For this response (Y_2) a quadratic model was suggested by software on application of factorial design. The Model F-value of 395.51 implied that the model was significant. Values of "Prob>F" less than 0.0500. indicated that the model terms were significant. In this case A, B, C, AB, BC, C2 were significant model terms. The equation for response Y_2 was shown in equation (3).

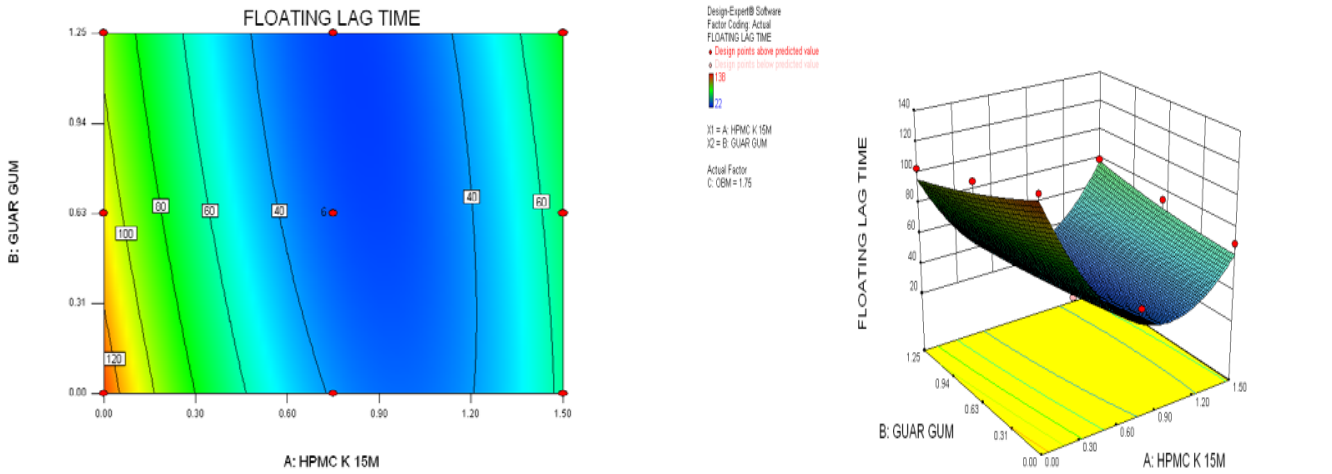
$$Y_2 = +79.90 - 3.71 * A - 2.86 * B - 11.25 * C - 0.81 * A * B - 0.28 * A * C + 0.67 * B * C + 0.22 * A^2 + 0.44 * B^2 + 1.86 * C^2 \quad (3)$$

Equation (3) prooved that drug release rate appeared to decrease with an increase in amounts of factors A, B, and C. This is in agreement with the literature provided by Rajani *et al.* [35]. The combined effect of A*B, A*C are negative but B*C is positive on drug release at 10 h was exhibited by contour plot and 3D response surface plots (fig. 3).

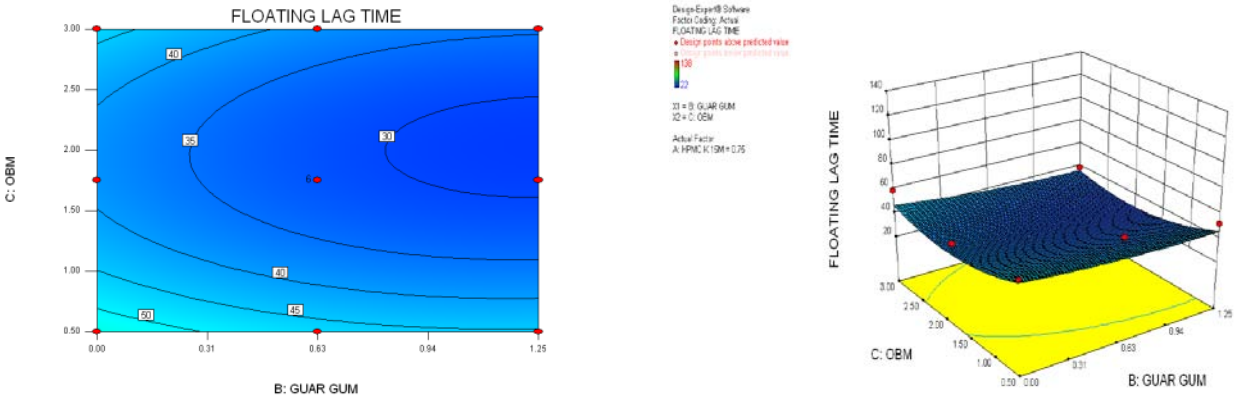
A numerical optimization technique using the desirability approach with Design Expert software was employed to develop optimized formulation with the desired responses. Constraints were set for minimizing floating lag time and drug release at 10 h to locate the optimum setting of independent variables. Optimized *in situ* gel formula was arrived by the software which comprised of 3 %w/v of OBM, 0.88 %w/v of HPMC K15M and 1.25 %w/v of Guar gum. The optimized formulation (VFIG) was evaluated for percentage drug release at 10 h, and floating lag time, which were in good correlation with the predicted values as shown in table 2 with desirability of 0.923. The optimized formulation was further evaluated for parameters like pH, drug content, *in vitro* gelling capacity, viscosity, density, *in vitro* drug release kinetics, *in vivo* buoyancy studies and *in vivo* pharmacokinetics and results were shown in table 3.



(a)

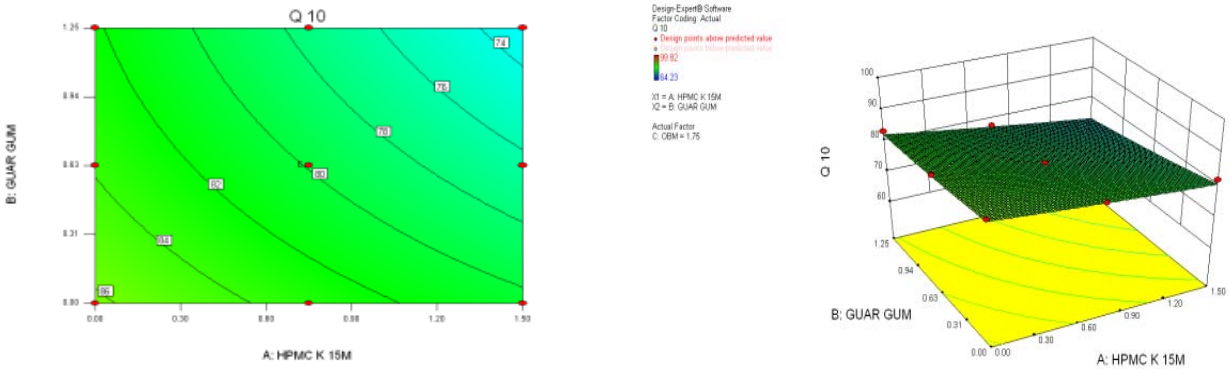


(b)

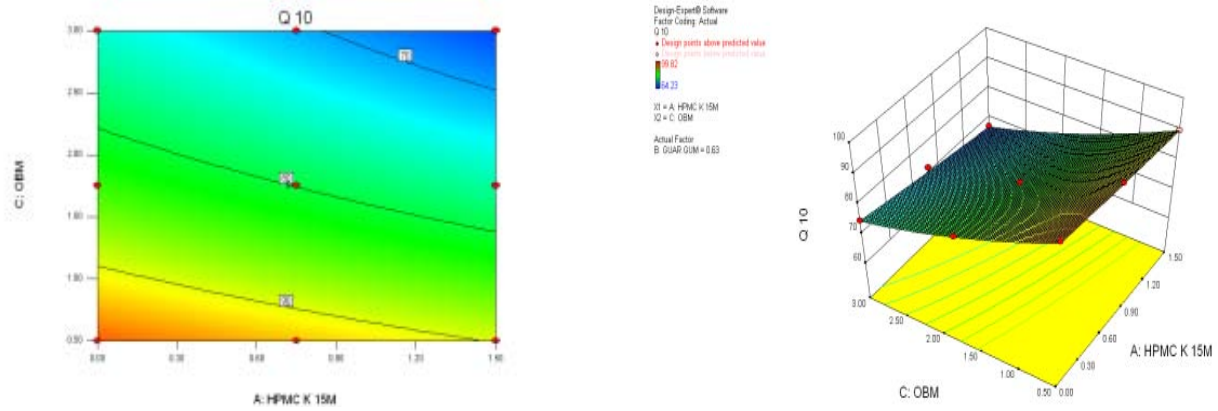


(c)

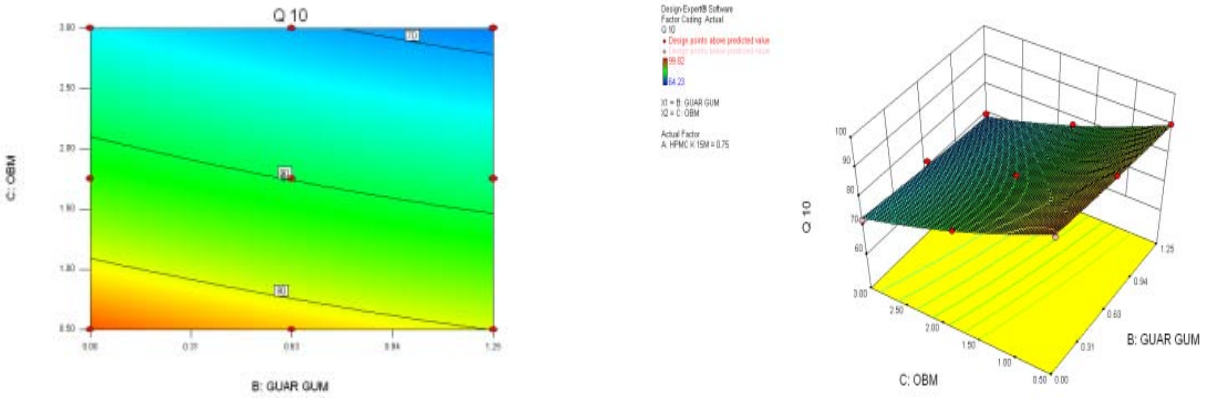
Fig. 2: Counter plots and response surface plots for (a) effect of A*C, (b) effect of A*B, (c) effect of B*C on Floating lag time (Y_1)



(a)



(b)



(c)

Fig. 3: Counter plots and response surface plots for (a) effect of A*B, (b) effect of A*C, (c) effect of B*C on drug release at 10 h (Y_2)

Table 2: Comparison between predicted and experimental values for VFIG

Parameter	Predicted values	Experimental Values
1. Floating lag time (secs)Y_1	36.3024	36.0021±0.24
2. Drug release at10h(Q_{10})Y_2	67.9226	66.9678±0.2

Each value represents the mean±standard deviation (n=3)

Evaluation of optimized formulation

pH and density

VFIG was found to have pH of 6.5 and it was within the acceptable range. It is worthy to note that floating systems must possess density lesser than gastric contents (~1.004 gm/cm^3). The measured density of VFIG was 0.869 gm/cm^3 (table 3). This less density could contribute to the floatability of VFIG.

Viscosity and drug content

Optimized formulation was shown viscosity of 339.5±0.76 cps, (table 3) which is suitable for retaining it's gel structure and it was considered to be attributed by optimized concentrations of HPMC K15M and Guargum which was evidenced by counter plots. Significance of viscosity built up in formulations by HPMC K15M and guargum was evidenced by Nanjwade *et al.* [36] and Alexander *et al.* [37] in their individual studies. Insignificant loss of drug during the formulation was evidenced by the result of percent drug content of formulation and it was found to be 99.57±0.86 (table 3).

***In vitro* gelling capacity**

Optimized formulation after administration turned out in gel form by formation of 3D-network by complexation with Ca^{2+}ions and hydrogen bonding with water as a result of consequences of aggregation of the double helical segments this gelling capacity of OBM is evidenced by Yadav *et al.* in their study [38]. The ascribed grade for gelling capacity of the formulation was (+++), indicating immediate gelation on contact with acidic environment and retains gel structure for more than 12 h. The rigidity of the gel has been citing as a primary factor for controlled release of the formulation since the drug molecules have to infiltrate through the complex network of polymer chains to reach the physiological environment.

Table 3: Results of different parameters of VFIG

S. No.	Parameter	Values
1.	Floating lag time (Sec.)	36.0021±0.24
2.	Q_{10} (%)	66.9678±0.2
3.	Density (gm/cm^3)	0.869±0.1
4.	Viscosity (cps)	339.5±0.76
5.	Drug content (%)	99.57±0.86
6.	*In vitro* gelling capacity	+++
Drug release kinetics		
7.	Zero order (R^2)	0.964
8.	Higuchi (R^2)	0.963
9.	Hixson crowell (R^2)	0.981
10.	Korsmeyer peppas (R^2)	0.991
11.	Korsmeyer peppas (n)	0.819

(+++)-Gels immediately and retains gel structure for more than 12 h, Each value represents the mean±standard deviation (n=3)

Kinetic modeling of dissolution data

Optimized formulation (VFIG) drug release data fitted to kinetic modeling. Regression coefficient values evidenced that dissolution data was well fitted to zero order, first order, Higuchi model, Korsmeyer peppas and Hixon–crowell model (table 3). But highest value of regression coefficient (R^2 = 0.991) found for Peppas indicated the best fit model the 'n' value of Peppas was 0.819. This provided the information of formulation follows non-Fickian release or anomalous diffusion mechanism. This findings confirmed that drug exhibited chain relaxation as well as diffusion mechanisms.

Formulation containing OBM when comes in contact with simulated gastric fluid, calcium chloride brokendown and released free ca^{2+}ions that induced gelation due to dimeric association of OBM. Similar dimeric association of OBM with Ca^{2+}ions was supported by Razavi *et al.* [39] in their study. As polymer (OBM) being anionic readily cross links with free ca^{2+}ions [9]. In addition HPMC K15M and guargum used in the formulation, slowed down the valsartan release and improved residence time of the formulation. Abraham *et al.* [40] reported drug release retardant potential of guargum in their study and Deng *et al.* [41] proved drug release retarding efficiency of HPMC K15M.

***In vivo* buoyancy studies**

X-ray studies were performed on rabbit to check the floating ability of VFIG after oral administration (oral feeding tube was served for administration). The X-ray radiographic images on abdomen were taken at i) Empty stomach, ii) after 0.5 h of feeding of gel iii) after 2 h iv) after 8 h. These studies, confirmed that VFIG floated in stomach immediately after administration and continued for nearly 8 h without any disturbance as shown in fig. 4. It has been speculated that in addition to firm gel formation, floating also a prerequisite for this formulation.

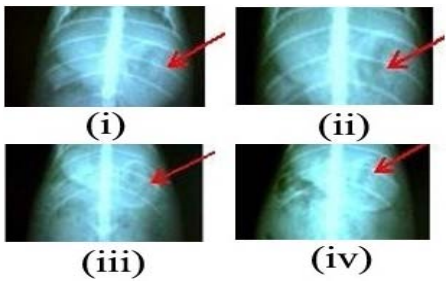
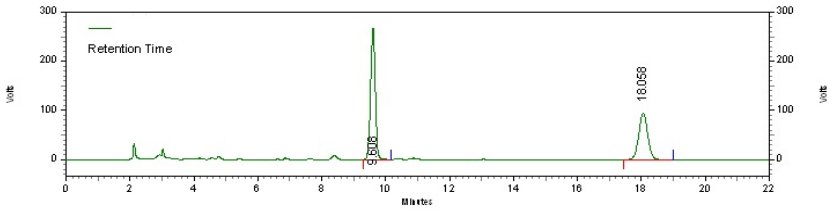


Fig. 4: X-ray radiograms showing presence of VFIG in gastric region of rabbit at i) 0 h, ii) 0.5 h,iii) 2 h, iv) 8 h respectively

***In vivo* pharmacokinetic studies**

Pharmacokinetic parameters derived from plasma concentration time profile and HPLC chromatogram of valsartan and ISTD were presented in table 4, fig. 5 and 6. Mean pharmacokinetic values

obtained after plasma analysis of plain drug suspension (standard) and VFIG (test) were as follows: $C_{max,}$ 0.4246 and 0.483 µg/ml; $T_{max,}$ 1 and 12 h; $AUC_{0\text{-}12,}$ 0.5630 and 5.998 h. µg/ml respectively. In VFIG hike in T_{max}, elevation in $AUC_{0\text{-}12}$ implied extended release and improved bioavailability of the drug. Although standard formulation reached peak plasma in 1 h, gradually decreased within 2 h, but VFIG attained a peak at 12 h and decreased gradually, this prolonged plasma concentrations relied on the synergistic effect of polymers. Further, significant increase in AUMC, MRT and $t_{1/2}$ with VFIG proven the controlled release of valsartan from *in situ* gel. This significant differences between pharmacokinetic parameters made this VFIG the best formulation.



Detector A (272 nm)

Peak Name#	Retention Time	Area
Valsartan	9.6	1988283
Amlodipine	18	215225

Fig. 5: HPLC Chromatogram of valsartan and ISTD (Amlodipine)

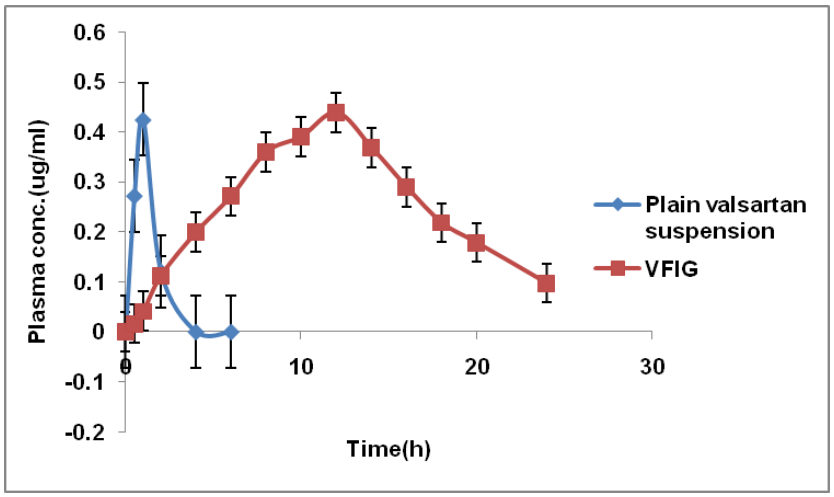


Fig. 6: Plasma concentration time profile of plain valsartan suspension and VFIG (n=6, mean±SD)

Table 4: Pharmacokinetic parameters of VFIG (test) and plain drug suspension (Reference) (n=6, mean±SD)

Pharmacokinetic parameters	VFIG (Test)	Plain drug suspension (Reference)
C_{max} (µg/ml)	0.438±0.42	0.4246±0.12
T_{max} (h)	12±0.04	1±0.005
AUC (µg*h/ml)	5.9987±1.45	0.5630±0.04
AUMC (µg*h ^{2}/ml)	72.006±0.003	0.6548±0.01
MRT (h)	12.0036±2.54	1.16292±0.06
$T_{1/2}$ (h)	5.1266±0.68	0.6369±0.55
Cl (1/h)	0.4466±0.88	4.6496±0.33
V_d (l)	3.3037±1.45	4.2725±0.56

CONCLUSION

In this study an improved *in situ* gel was formed by pH induced and ionic activation mechanism, in the combination of OBM, Guar gum and HPMC K15M with desirable characteristic features in acidic environment. By application of 3^3 full level factorial design, it was found that the concentration of OBM, HPMC K15M and Guar gum significantly affected the dependent variables like floating lag time (Y_1) and percent drug released at 10 h (Y_2). From findings of the factorial design it was concluded that natural polymer OBM exhibited better drug release in combination with two polymers when compared to alone, and Korsmeyer-Peppas model provided information on drug release from gel structure and indicated diffusion-controlled release. Nonetheless the present work aimed to combine OBM, Guar gum and HPMC K15M, seems to possess sufficient viscosity, increased bioavailability as the gel being present in high amounts at optimized concentrations of polymers. This property could contribute increased diffusion length so that drug release was retarded. This floating oral *in situ* gel predominantly beneficial for pediatric and geriatric patients and reducing dose frequency.

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CONTRIBUTION OF AUTHORS

Conception and design of work: Prof. M. Vidyavathi

Data collection and analysis: Mrs. S. Prasanthi

Data interpretation: Prof. M. Vidyavathi

Drafting of the article: Mrs. S. Prasanthi

Critical revision of article: Prof. M. Vidyavathi and Mrs. S. Prasanthi

Final approval of the article to publish: Prof. M. Vidyavathi and Mrs. S. Prasanthi

CONFLICT OF INTERESTS

The authors report no conflict of interest, financial or otherwise

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