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Formulation and Evaluation of Stomach Specific *in-situ* Gel of Urapidil Hydrochloride

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Abstract

The present work deals with the stomach specific floating oral *in-situ* gel of urapidil hydrochloride by using sodium alginate as a gelling polymer and HPMC K15M as a release retardant polymer. Urapidil hydrochloride stomach specific *in-situ* gels were prepared by ionic gelation method using different concentrations of sodium alginate and matrix forming polymers. $CaCO_3$ was used as CO_2 gas as well as Ca^{++} generating agent for ionic gelation and floating. Formulation (F9) was considered to be the optimized formulation based on sustained drug release up to 10 hours and having higher viscosity, swelling index and drug content when compared to other developed formulations. Mechanism of drug release studies of optimized formulation showed zero order following non-fickian type drug release. Floating oral *in-situ* gelling system of urapidil hydrochloride was formulated using sodium alginate as a gelling Polymer, which sustained the drug release of 98.86% for 12 h with controlled release kinetics, while the floating lag time was 45seconds.

Keywords

Oral *in-situ* gel, gastro retentive, urapidil hydrochloride, HPMC, sodium alginate.

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INTRODUCTION

Gastro retentive dosage forms are drug delivery systems which remain in the stomach for an extended period of time and allow both spatial and time control of drug liberation. Basically, gastro retentive system retains in the stomach for a number of hours and continuously release the incorporated drug at a controlled rate to preferred absorption sites in the upper intestinal tract [1]. The retention of oral dosage forms in the upper GIT causes prolonged contact time of drug with the GI mucosa, leading to higher bioavailability and hence therapeutic efficacy, with reduced dose size and time intervals for drug administration the patient compliance is improved. The need for gastro retentive dosage forms has led to extensive efforts in both academia and industry towards the development of such drug delivery systems [2, 3].

In-situ gel forming polymeric formulations are drug delivery systems that are in sol or suspension form before administration into the body. Once administered, it undergoes gelation *in-situ* to form a gel. *In-situ* gel forming systems have been widely investigated as vehicles for sustained drug delivery [4]. Formulation of *in-situ* gel system involves the use of gelling agent which can form a stable sol/suspension system contain the dispersed drug and other excipients. The gelling of this sol/suspension system will be achieved in gastric environment, triggered by ionic complexation due to change in pH [5]. The formulation adopted is a gellan gum or sodium alginate solution containing calcium

chloride and sodium citrate, which complexes with free calcium ions and releases them in the acidic environment of stomach [6].

Urapidil hydrochloride is selective post synaptic α_1 adrenoreceptor antagonist with strong vasodilating properties and investigated for the treatment of hypertension during pre-eclampsia. It is rapidly absorbed and has an average bioavailability of about 78%. It is assumed to have first pass metabolism. It has shorter half-life of about 3.1 hrs, frequent dosing is required in order to reach the therapeutic drug concentration levels in blood [7]. So, the novel system was developed to optimize the dosage regimen without compromising the therapeutic effect of drug. In the present work, gastro retentive floating oral *in-situ* gel was developed using synthetic and natural polymers to offer a simple and practical approach of increased gastric residence time as well as to provide a sustained release dosage form.

Here, urapidil hydrochloride urapidil hydrochloride is selected as drug candidate. It fulfils the following characteristics which indicate its suitability for development into oral floating *in situ* gel drug delivery system. It has high acid solubility; therefore, it can be incorporated in to the aqueous *in-situ* formulation which upon contact with gastric fluids gets converted into gel by which sustained release is obtained.

MATERIALS AND METHODS

Materials:

Urapidil hydrochloride was a gift sample from Yarrow chemicals, Mumbai, India. Sodium alginate and sodium citrate were procured from Sigma Chemicals Ltd, New Delhi. India. HPMC K15M was a gift sample from Colorcon Asia Pvt. Limited, Goa, India. Calcium carbonate procured from SD fine chemicals, Mumbai**,** India. All ingredients and reagents used were of analytical grade.

Methods:

Method of preparation of *in-situ* gelling solution:

A measured quantity of sodium alginate (SA) required to make a **0.5%, 0.75%, and 1 %** (w/v) solution was dissolved separately in distilled water containing 0.2% of sodium citrate at 60°C using heating magnetic stirrer. Low level of cations present in the solution is sufficient to hold the molecular chains together and inhibit hydration. After cooling to below 40°C, appropriate amounts of polymer (HPMC K15M), methyl and propyl paraben (9:1), drug and gas generating agent (calcium carbonate) were dissolved/dispersed uniformly in sodium alginate solution with continuous stirring until a uniform dispersion was obtained. The mixture was allowed to cool at room temperature. Finally, the volume was adjusted to 100% with distilled water and mixed well to get final preparation. The prepared *in situ* gel formulation was stored in amber colored bottles until further use. Floating *in situ* gel formulations of urapidil hydrochloride were prepared using trial compositions given in Table 1.

Identification of drug by FTIR:

The Infrared spectroscopy of the sample was carried out to ascertain identity of the drug. A pellet of approximately 1mm thickness of drug and excipient was prepared by compressing 3-5mg of the drug with 100-150mg of potassium bromide in KBr press. The pellet was mounted in IR compartment and scanned in the wave number range of 4000–400cm^{-1} using FTIR [8].

Evaluation parameters:

***In-vitro* floating study:**

The *in-vitro* floating study was carried out by introducing 10 mL of formulation into a beaker containing 100 mL of 0.1N HCl (pH 1.2) at 37°C without much disturbance. The time taken by the formulation to emerge on the medium surface (floating lag time) and the time of formulation to float constantly on surface of the dissolution medium (duration of floating) were recorded.

Viscosity measurement of *in-situ* gelling system:

Viscosity of the *in-situ* gelling solution was determined using Brookfield viscometer (Programmable DV-III Rheometer). The sample volume of 2 mL was sheared at a rate of 20 rpm/ min using spindle number 40 at room temperature. Viscosity measurement for each sample was done in triplicate, each measurement took approximately 30 seconds.

***In vitro* gelation study:**

To evaluate the formulations for their *in-vitro* gelling capacity, accurately measured 10 mL of formulation was added to 100 mL of 0.1N hydrochloric acid (HCl, pH 1.2) at 37°C in a beaker with mild agitation to avoid breaking of formed gel. The *in vitro* gelling capacity was graded in three categories on the basis of stiffness of formed gel, gelation time and time period for which they formed gel remains as such.

(+) Gels after few minutes, dispersed rapidly, (++) Gelation immediate remains for extended period (+++).

Determination of drug content:

Accurately, 10 mL of *in-situ* gel from all the batches was taken and to this 50-70 mL of 0.1 N HCl was added and sonicated for 30 min. Finally, volume was adjusted to 100 mL. Complete dispersion of contents was ensured visually, and the dispersion was filtered using whatsman filter paper. From this solution, 10

mL of sample was taken and diluted to 100 mL with 0.1 N HCl. Urapidil hydrochloride was quantified at maximum absorbance wavelength (268 nm) using UV-Visible Spectrophotometer [9].

Swelling index:

A gel of 100mg was weighed accurately (W1). It was kept in a petri dish and 50ml of 0.1 N HCl was added. The petri dish was kept aside for 12 hrs. The weight of swollen matrix gel (W2) was measured and swelling index was calculated using following formula:

$$\text{Swelling Index} = \frac{W2-W1}{W1} \times 100$$

Where, W_1=initial weight of gel (100mg), W_2 = Weight of swollen matrix after16 hrs

Density:

Density of the floating oral *in-situ* gel was determined by using water displacement method. To (10 ml) *in-situ* solution, 20 mL of 0.1 N HCl (pH 1.2) was added to convert the solution into gel. Excess of HCl was drained off and the gel so formed was weighed. The gel was then transferred to a 50 mL measuring cylinder and allowed to settle at the base. Distilled water was added up to 50 mL mark of measuring cylinder. Volume of water in the presence of gel was noted. From the difference in the volumes of water with and without gel, the volume of gel was obtained i.e., amount of water displaced by the gel was calculated [10].

***In vitro* drug release study:**

The release rate of urapidil hydrochloride from *in-situ* gel was determined using USP type II dissolution testing apparatus at 50 rpm. This speed was slow enough to avoid the breaking of formed gel. Mild agitation conditions which were believed to exist *in vivo* were maintained. 10 mL of gelling solution was added into the 900 mL of 0.1 N HCl dissolution medium, and temperature was maintained at 37± 0.5 ^{0}C. From this dissolution medium, 5 mL of the sample solution was withdrawn at different time intervals and replenished to maintain sink condition. The samples were filtered through whatsman filter paper and drug was estimated spectrophotometrically at 268 nm using double beam UV-Visible spectrophotometer [11].

Modelling of Dissolution Profiles:

In the present study, data of the *in vitro* release were fitted to different equations and kinetic models for optimized formulation to explain the release kinetics of urapidil hydrochloride from the floating *in-situ* gel.

Based on the highest regression values for correlation coefficients for formulations, the best fit model was predicted [12, 13].

Stability study:

Prepared *in-situ* gel formulation of urapidil hydrochloride was stored in a amber colored glass containers (well stoppered) for three months and the stability of the *in-situ* gel formulation of urapidil hydrochloride was monitored up to 3 months at controlled temperature (40 ±2^{0}C) and controlled humidity (75±2% RH) conditions. Periodically (initial, 1, 2 and 3 months) samples were removed and evaluated for pH, viscosity, drug content and *in vitro* release [14, 15].

RESULTS AND DISCUSSIONS

FTIR studies:

Drug excipients interaction study by FTIR was carried out as per standard procedure. FTIR studies were carried out for pure drug and optimized formulation. FTIR spectrum of pure urapidil hydrochloride and optimized formulation (F9) was shown in Figure 1. Characteristic peaks were not affected and prominently observed in FTIR spectra. This indicates that there is no interaction between urapidil hydrochloride and polymers, and the drug was compatible with the formulation components.

In situ gel of formulation were characterized for various evaluation parameter such as colour, visual observation of viscosity, pH, gel capacity, lag time, floating duration time, % drug content and dissolution. The result of characterization of preliminary batches (F1 to F12) was show in Table 2

Effect of sodium alginate and its concentrations:

In-vitro release profile of different concentrations of sodium alginate solutions loaded with 1.15g of urapidil hydrochloride are shown in Table 2, the results showed rapid release from alginate solutions at concentration1%, with almost 100% of the drug released within 12hrs. In acidic medium, sodium alginate converts rapidly to insoluble alginic acid, which swells upon hydration.

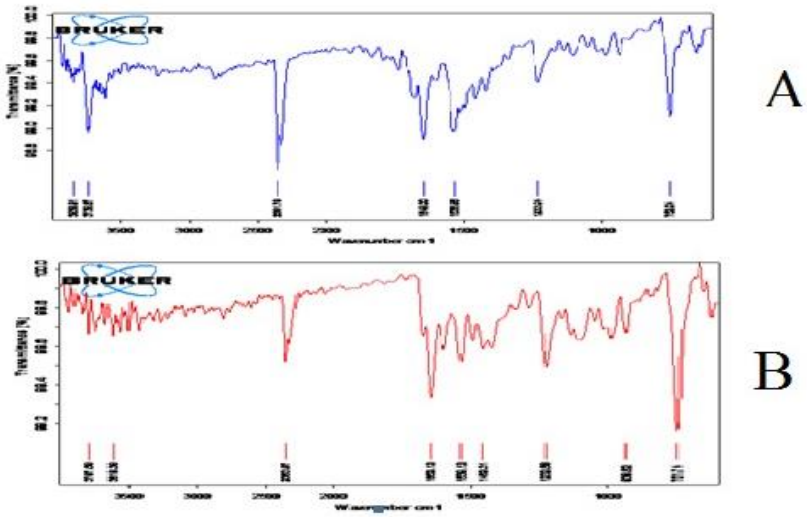


Figure 1: FT-IR spectrum A) Pure drug B) Optimized formulation (F9)

Table 1: Composition of preliminary batches (F1 to F12) (n=3)

S. No.	Drug (g)	Sodium alginate (g)	Xanthan gum (g)	HPMC K15M (g)	Carbopol 971P (g)	Calcium carbonate (g)	Sodium citrate (g)
F1	1.15	0.5	-	-	-	1	0.20
F2	1.15	0.75	-	-	-	1	0.20
F3	1.15	1.0	-	-	-	1	0.20
F4	1.15	1.0	0.25	-	-	1	0.20
F5	1.15	1.0	0.5	-	-	1	0.20
F6	1.15	1.0	0.75	-	-	1	0.20
F7	1.15	1.0	-	0.25	-	1	0.20
F8	1.15	1.0	-	0.5	-	1	0.20
F9	1.15	1.0	-	0.75	-	1	0.20
F10	1.15	1.0	-	-	0.25	1	0.20
F11	1.15	1.0	-	-	0.5	1	0.20
F12	1.15	1.0	-	-	0.75	1	0.20

Table 2: Evaluation parameters of preliminary batches (F1 to F12) (mean ± SD, n=3)

S. No.	Colour	Visual observation of viscosity	pH	Gel capacity	Lag time (sec)	Floating duration (h)	Drug content (%)	Dissolution (%CR of 12hr)
F1	Off white	No viscous	7.0±0.03	++	58±2.6	< 6	98.6 ± 0.85	84.28 (2hrs)
F2	Off white	No viscous	7.2±0.02	+	75±1.57	< 8	97.8 ± 0.95	92.63 (4hrs)
F3	Off white	Very less viscous; pourable	7.0±0.03	++	56±2.03	>12	98.3 ± 0.75	96.45 (5hrs)
F4	Off white	Very less viscous; pourable	7.1±0.05	++	54±2.08	>12	98.6 ± 0.85	95.64 (6 hrs)
F5	Off white	Very less viscous; pourable	7.3±0.01	++	53±1.65	>12	96.8 ± 0.88	97.76 (8 hrs)
F6	Off white	Very less viscous; pourable	7.2±0.02	++	52±1.25	>12	98.2 ± 0.40	96.37 (10hrs)
F7	Off white	Very less viscous; pourable	7.1±0.01	+++	48±1.37	>12	97.5 ± 0.87	97.64 (7 hrs)

F8	Off white	less viscous; pourable	7.3±0.02	+++	43±2.08	>12	97.5 ± 0.47	96.48 (9 hrs)
F9	Off white	less viscous; pourable	7.0±0.04	+++	**45±1.36**	>12	99.26±0.52	98.86 (12hrs)
F10	Off white hazy solution	More viscous; non pourable	7.36±0.032	+++	10min	>12	97.5 ± 0.95	62.64 (12hr)
F11	Off white hazy solution	More viscous; non pourable	7.21±0.015	+++	4 min	>12	98 ± 0.62	58.36 (12hr)
F12	Off white hazy solution	More viscous; non pourable	7.33±0.05	+++	3min	>12	98.6 ± 0.85	49.87 (12hr)

Table 3: Compositions of formulations (F1-F9) (n=3)

Formulations	Drug (g)	Sodium alginate (g)	HPMC K15M (g)	Sodium citrate (g)	Calcium carbonate (g)	Preservatives
F1	1.15	0.5	0.25	0.20	1	(9:1)
F2	1.15	0.5	0.25	0.20	1	(9:1)
F3	1.15	0.5	0.25	0.20	1	(9:1)
F4	1.15	0.75	0.5	0.20	1	(9:1)
F5	1.15	0.75	0.5	0.20	1	(9:1)
F6	1.15	0.75	0.5	0.20	1	(9:1)
F7	1.15	1	0.75	0.20	1	(9:1)
F8	1.15	1	0.75	0.20	1	(9:1)
F9	1.15	1	0.75	0.20	1	(9:1)

Table 4: Evaluation parameter of formulation batches (F1-F9) (mean ± SD, n=3)

Evaluation Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Colour	Off white	Off white	Off white	Off white	Off white	Off white	Off white	Off white	Off white
pH	7.0±0.03	7.2±0.02	7.0±0.03	7.1±0.05	7.3±0.01	7.2±0.02	7.1±0.01	7.3±0.02	7.0±0.04
Viscosity (cp)	253.3	234.5	328.3	184.6	318.6	346.3	324	386.2	425
Gelling time (sec)	31	35	33	31	26	25	28	27	35
Gel capacity	++	+	++	++	++	++	+++	+++	+++
Lag time (sec)	58±2.6	75±1.57	56±2.03	54±2.08	53±1.65	52±1.25	48±1.37	43±2.08	45±1.36
Floating duration	>4	<6	>6	>8	>8	>8	>12	>12	>12
Swelling index (%)	43.3±0.90	30.3±1.15	55.5±1.85	34.5±2.8	48.03±1.0	63.4±0.8	59.1±0.6	65.3±1.0	77.6±0.8
Density (gm/cc)	0.55±0.3	0.51±0.04	0.58±0.01	0.61±0.04	0.62±0.05	0.60±0.01	0.66±0.03	0.65±0.01	0.64±0.02
Drug content (%)	98.6±0.85	97.8±0.95	98.3±0.755	98.6±0.85	96.8±0.88	98±0.4	97.5±0.47	97.5±0.8	99.2±0.43

Effect of combination polymer:

In this study three different polymers like natural (xanthan gum), and synthetic like hydrophilic (HPMC K15M), hydrophobic (carbopol 971P) in three different concentration (0.25, 0.5, 0.75) were used to determine the best suitable polymer combination to

sustain the release of drug shown in Table 3. Among all formulations (F1 to F9), formulation F9 (0.75% HPMC K15M+1% sodium alginate) showed better release of 98.86% up to 12hrs. HPMC acts as a release retardant and viscosity enhancing agent. So, HPMC was selected for further studies. It was observed that the formulations containing combination of polymers showed more retardation in drug release at same concentration compared to sodium alginate alone. This indicates that Combination of polymers are more efficient in formulating the sustained release dosage form.

pH of *in-situ* gelling solutions:

The pH value of all prepared *in-situ* gel formulations (F1-F9) were found in range 7.0 to 7.3 and is shown in Table 4 and given in Figure 2.The pH values of all prepared formulations were within the limit of neutral pH. This indicates formulations can be used without any irritation in the oral cavity [16].

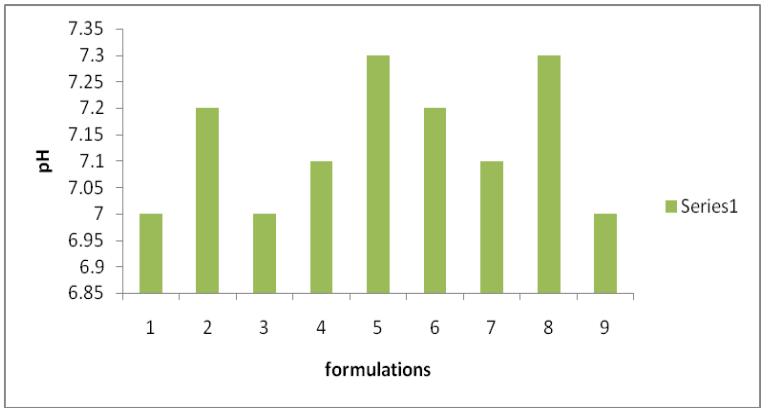


Figure 2: pH measurement of urapidil hydrochloride floating oral *in-situ* gels of F1-F9

Viscosity of *in-situ* gelling solutions:

The formulation should have an optimum viscosity that will allow ease of administration and swallowing as a liquid and produces satisfactory gel strength for use as a delivery vehicle [17]. Viscosity results of formulations F1 to F9 were mentioned in Table 4. The optimized formulation (F9) viscosity was found to be 425cp is given in Figure 3. The solutions showed a marked increase in viscosity with increasing concentration of HPMC K15M and sodium alginate.

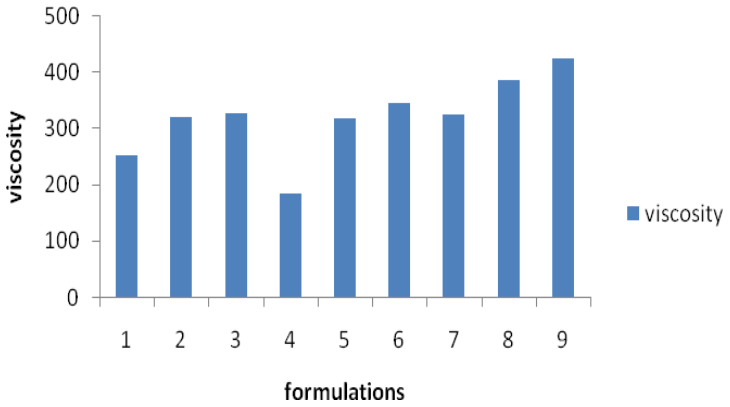


Figure 3: Viscosity of urapidil hydrochloride floating oral *in-situ* gels of F1-F9

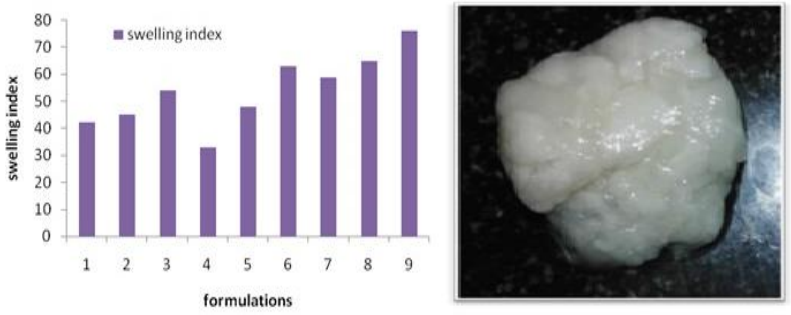
***In vitro* buoyancy studies of *in-situ* gelling solution:**

The buoyancy of the prepared formulations was performed in 0.1 N HCl (pH 1.2). Results of *in-vitro* buoyancy time of formulations F1 to F9 were described in Table 4. Formulations containing calcium carbonate demonstrated excellent floating ability, while formulations without this agent settled to bottom of the medium. The buoyancy time for all formulations as found in the range of 43 sec to 75 sec. The optimized formulation (F9) buoyancy time was 45±1.36 seconds [18, 19].

Swelling index:

The swelling index of the prepared formulations was performed in 0.1N HCL (pH 1.2). Results of swelling index of formulation F1 to F9 were described in Table 4. The higher water uptake was found for formulation F9 which contained 1% sodium alginate and maximum amount of HPMC K15M. It was

observed that the swelling indices were increased with increase in polymer concentration. Formulation F9 containing a high percentage of polymer shows the maximum swelling i.e. 77.6% at 12 hrs is given in Figure 4 [2].



(A) **(B)**

Figure 4: A) Swelling index of urapiidl hydrochloride floating oral *in-situ* gels of F1-F9 B) Swelling index of optimized formulation (F9)

***In-vitro* gelation study:**

In vitro gelation of the prepared formulations was performed in 0.1N HCL (pH 1.2). Results of *in vitro* gelation of formulation F1 to F12 were described in Table 2. The *in-situ* formed gel should preserve its integrity without dissolving or eroding for prolonged period to facilitate sustained release of drugs locally. F1, F3, F4, F5 and F6 formulations formed gel immediately and remained for few hours (+ +). Formulations F7, F8, F9, F10, F11 and F12 formed gel immediately and remained for extended period (+++). Formulation F2 formed gel after few minutes and is dispersed rapidly (+) [21].

Drug content:

Results of drug content of formulation F1 to F12 and F1 to F9 were described in Table 2 and 4 respectively. The solutions showed percentage drug content from 96.86% to 99.26 %.

***In vitro* drug release studies:**

In-vitro dissolution studies of all the formulations of urapidil hydrochloride floating oral *in-situ* gels were carried out in 0.1 N HCl and percentage drug release was calculated [23]. Dissolution profile of formulations F1 to F9 is shown in Fig 5. The effect of polymer concentration on *in vitro* drug release from *in-situ* gels F1, F2, F3 and F4 formulations showed maximum drug release at 4^{th}, 6^{th} and 8^{th} hrs respectively. F5, F6, F7 and F8 formulations showed maximum release at 8^{th} and 10^{th} hrs. F9 formulation extended release for 12hrs and showed drug release of 98.86%. A significant decrease in the rate and extent of drug release was observed with increase in the polymer concentration.

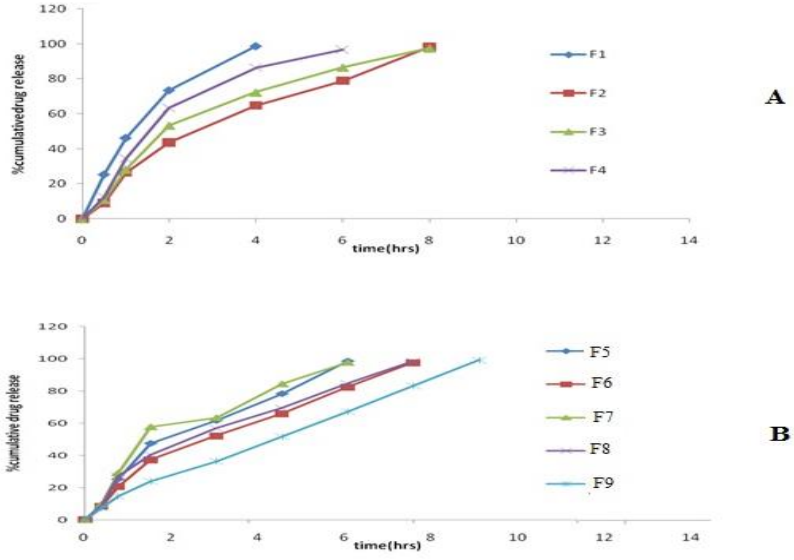


Figure 5: A) *In vitro* release profile of urapidil hydrochloride from formulations (F1-F4)
B) *In vitro* release profile of urapidil hydrochloride from formulations (F5-F9)

Kinetics of drug release:

The dissolution data of optimized formulation F9 so obtained was fitted to various kinetic models like zero order, first order, Higuchi, Korsmeyer-Peppas models. The release of drug from the *in-situ* gel followed zero with a (R^2) value of 0.996. The correlation coefficient (R^2), for different kinetic models were tabulated in Table 5 [24].

Table 5: Mechanism of drug release from optimized formulation (F9)

Formulation Code	R^2value				Best fit model
	Zero order	First order	Higuchi	Peppas	
F9	**0.996**	0.728	0.958	0.713	**Zero order**

Table 6: Stability studies of optimized formulation (F9) (mean ± SD, n=3)

Evaluation parameters	Time period for sampling			
	Initial	1month	2 months	3 months
pH	7.0± 0.04	6.9± 0.06	6.8± 0.03	**6.6± 0.04**
Viscosity (cp)	425	427	426	**428**
In-vitro gelling capacity	+++	+++	+++	**+++**
In-vitro buoyancy (sec)	45± 1.52	47± 1.46	50± 1.63	**48± 1.42**
Total floating time (hr)	>12	>12	>12	**>12**
Drug content (%)	99.2±0.43	98.32±0.67	97.56±0.84	**96.43±0.64**

Stability study of optimized formulation:

The stability studies conducted for optimized formulation (F9) revealed that, there is slightly reduction in pH, drug release, drug content and slight increase in buoyancy time and viscosity. The F9 formulation and it's *in vitro* gelling was shown in Figure 6. No significant changes were observed on total floating time and *in vitro* gelling capacity parameters over period of 3-months of stability study under controlled environment conditions (40±2^{0}C and 75±5%RH). The formulation was found to be stable for 3 months. The results are shown in Table 6 [25].

Figure 6: A) Oral *in-situ* formulation of F9 B) Formation of *in-situ* gel

CONCLUSION

It was concluded that floating oral *in situ* gel formulation (F9) containing sodium alginate and HPMC K15M showed good viscosity and good stability. *In situ* gel remained in stomach for prolong time up to 12 hours and released drug in sustained manner. *In situ* gel will be promising pharmaceutical formulation for development of gastro-retentive drug delivery system for urapidil hydrochloride. *In-Vitro* release rate studies showed that the drug release was maximum i.e., 98.6% from formulation F9 (Containing 1% w/v of sodium alginate + 0.75% of HPMC K15M) overall F9 formulation was found to be an excellent *in-situ* gel based on sustained release, viscosity, gel capacity and buoyancy

REFERENCES

1. Kumar S., Shashi K. and Bharat P., Sustained release drug delivery system: A Review. International Journal of Institutional Pharmacy and Life Sciences, 2(3):356-376, (2012)
2. Sonia D., Thakur G.S., Ashish Kumar R., Surbhi S. and Sandeep A., Gastroretentive: a controlled release drug delivery system. Asian J Pharm Clin Res, 4(1):5-13, (2011)
3. Dongare P.S., Darekar A.B., Gondkar S.B. and Saudagar R.B., Floating drug delivery system: A Better

approach. International Journal of Pharmacy and Biological Science, 3(4):72-85, (2013)
4. Vadgama N. and Baladaniya M., Gastro retentive *in situ* gel formulation an overview. International Bulletin of Drug Research**,** 3(5):69-82, (2013)
5. Rathod H., Vishnu P. and Modasia M., *In situ* gel as a novel approach of gastroretentive drug delivery. International Journal of Pharmacy and Life Sciences, 1(8): 440-447, (2010)
6. Manisha W., Sandip Prasad T., Amit R. and Trilochan S., New insights into gastroretentive floating drug delivery systems. World Journal of Pharmacy and Pharmaceutical Sciences, 3(1):252-270, (2013)
7. Manfrid E., Investigations on the mode of action of a new antihypertensive drug, urapidil, in the isolated rat vas deferens. European Journal of Pharmacology, 59(1-2):1-9, (1979)
8. Mishra B. and Rajinikanth P.S., floating *in situ* gelling system for stomach site-specific delivery of Clarithromycin to eradicate H. pylori. Journal of Controlled Release, 125:33-41, (2008)
9. Dasharath M.P., Divyesh K.P. and Chhagan N.P., Formulation and Evaluation of Floating Oral *In-Situ* Gelling System of Amoxicillin. International Scholarly Research Network Pharmaceutics,1-8. (2011)
10. Rajalakshmi R., Sireesha A., Subhash K.V., Pavani Venkata P., Mahesh K. and Lokeshwara Naidu K., Development and Evaluation of a Novel Floating *In-situ* Gelling System of Levofloxacin Hemihydrate. International Journal of Innovative Pharmaceutical Research,2(1):102-108, (2011)
11. Deepak C., Pratibha P., Gaurav J. and Sheorey R.V., Formulation and evaluation of oral floatable *in-situ* gel of Diltiazem HCl. International Journal of Novel Drug Delivery Technology, 2(1):264-270, (2012)
12. Korsmeyer R., Gurny R., Doelker E., Buri P. and Peppas N., Mechanisms of solute release from porous hydrophilic polymers. Int. J. Pharm, 15:25-35, (1983)
13. Higuchi T., Rate of release of medicaments from ointment bases containing drugs in suspensions. J. Pharm. Sci, 50:874-875, (1961)
14. Rishad R., Chhagan N.P., Dashrath M.P. and Nurudin P.J., Development of a Novel Floating *In-situ* Gelling System for Stomach Specific Drug Delivery of the Narrow Absorption Window Drug Baclofen. Iranian Journal of Pharmaceutical Research, 9(4): 359-368, (2010)
15. Sanket C., Dron M., Ravi P., Jay P., Rahul D. and Sunita C., Formulation & Evaluation of Floatable *In-situ* Gel for Stomach specific Drug Delivery of Ofloxacin. American Journal of Advanced Drug Delivery, 1(3):285-299, (2013)
16. Parekh K.S. and Shah K.V., Formulation development and evaluation of oral *in-situ* floating gel of Domperidone. An International Journal of Pharmaceutical Sciences, 4(3): 228-246, (2013)
17. Vora V. and Biswajit B., Formulation and characterization of novel floating *in-situ* gelling system for controlled delivery of Ramipril. International Journal of Drug Delivery, 5(1):43-55, (2013)
18. Aakash S.P. and Manoj S., Formulation and Evaluation of Floating Stomach Specific *In-Situ* Gel of Nizatidine. International Journal of Pharmaceutical & Biological Archives, 5(1):115-123, (2014)
19. Monica R.P. and Swapnil U.S., Controlled Release Ion Sensitive Floating Oral *in situ* Gel of a Prokinetic Drug using Gellan Gum. Indian Journal of Pharmaceutical Education and Research*,* 49(2):158-167, (2015)
20. Sivannarayana T., Murthy S.N., John Noble D.K., Prakash K. and Rajendra A., Formulation and evaluation of floating oral *in-situ* gel of Moxifloxacin HCl. Indo American Journal of Pharmaceutical Research*,* 3(10):8211-8220, (2013)
21. Wataru K., Miyazaki S. and Attwood D., Oral sustained delivery of Ambroxol from *in-situ* gelling pectin formulation. International Journal of Pharmaceutics, 271, 233-240, (2004)
22. Vijayasankar G.R., Naveen Kumar J.S., Suresh A.G. and Packialakshmi M., Formulation and evaluation of Captopril gastroretentive floating drug delivery system. Int. J. Pharm & Ind. Res*,* 01(01):11-16, (2011)
23. Jadhav S.L. and Banerjee S.K., Formulation and evaluation of floating *in situ* gel of Nizatidine. International Journal of Research in Pharmaceutical Sciences, 4(2):250-255, (2013)
24. Rajinikanth P.S., Balasubramaniam J. and Mishra B., Development and evaluation of a novel floating *in situ* gelling system of Amoxicillin for eradication of Helicobacter pylori. Int J Pharm, 335(1-2):114-122, (2007)
25. Wamorkar V., Varma M.M. and Manjunath S.Y., Formulation and evaluation of stomach specific *in-situ* gel of Metoclopramide using natural, biodegradable polymers. International Journal of Research in Pharmaceutical and Biomedical Sciences, 2(1),193-201, (2011)