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Original Article

CONTROLLED RELEASE FLOATING ORAL *IN SITU* GEL OF ITOPRIDE HYDROCHLORIDE USING PH SENSITIVE POLYMER

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ABSTRACT

Objective: *In situ* gels are suitable to overcome problems of immediate release and short gastrointestinal residence of liquids. These systems are liquids before administration and on contact with gastric contents are converted to gel. The present work deals with the formulation, evaluation and optimization of pH triggered floating oral *in situ* gel of Itopride hydrochloride by using sodium alginate as a gelling polymer and HPMC K100M as a release retardant polymer.

Methods: A 3^2 factorial designs was carried out and the effect of variation in concentrations of sodium alginate and calcium carbonate on percent drug release at 1 h, 6 h, gel strength and $T_{50\%}$ i. e. time required for the release 50 % of loaded drug was evaluated. The gels were studied for their viscosity, *in vitro* buoyancy and drug release, *in vitro* gelling capacity, density, gel strength.

Results: The results of a 3^2 full factorial design revealed that the concentration of sodium alginate and concentration of calcium carbonate significantly affected the dependent variables. A controlled release profile was observed for these formulations. The dissolution data were fitted to various kinetic models which indicated diffusion controlled release profile. *In vivo* studies revealed higher T_{max} of gel compared to plain drug which is suggestive of slower absorption. However, the $AUC_{0\text{-}12\ h}$ was found to be nearly 90% higher than plain drug. Thus, bioavailability was found to be increased with in situ gel of Itopride hydrochloride.

Conclusion: Floating oral *in situ* gelling system of amoxicillin can be formulated using sodium alginate as a gelling polymer to sustain the drug release for 12 h with diffusion controlled release kinetics.

Keywords: Gastro retentive drug delivery, Oral *in situ* gel, Sodium alginate, Calcium carbonate.

INTRODUCTION

Oral administration is a most convenient and preferred means of any drug delivery to the systemic circulation. Oral controlled release drug delivery has received increasing attention in the pharmaceutical field as it enables improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Floating drug delivery system is low density system that has sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate. After release of drug, the residual system is emptied from the stomach. This results in an increased gastric retention time and a better control of the fluctuations in plasma drug concentration *In situ* gel is a type of this system forming polymeric formulations is in sol form before administration in the body, but undergo gelation *in situ* to form a gel when in contact with physiological fluids. Various triggers to induce gelation include pH, ions and temperature [1, 2]. The gelling of this solution is to be achieved in gastric environment [3, 4, 5]. The present work deals with formulation, optimization and evaluation of pH triggered floating oral *in situ* gel in which sodium alginate has been used as a gelling polymer and HPMC K100M as a release retardant polymer for controlled release.

Itopride hydrochloride (ITO) is an oral prokinetic agent used in the treatment of gastric motility disorder. It activates the gastrointestinal motility through synergism of its dopamine D2 receptor antagonistic action and acetylcholine esterase-inhibitory action. In addition to these actions, ITO has an antiemetic action, which is based on its dopamine D2 -receptor antagonistic action. The short biological half-life (6 h), 60 % bioavailability and higher dosing frequency (50 mg t. i. d.) Makes ITO an ideal candidate for the controlled drug delivery [6, 7]. ITO is indicated in various digestive conditions such as heartburn, regurgitation, epigastric pain, and esophagitis. These conditions include gastro esophageal reflux disease, non ulcer dyspepsia, chronic gastritis and a very important complication seen in diabetics where in the gastric emptying is markedly reduced "i. e"; diabetic gastro paresis.

MATERIALS AND METHODS

Materials

Itopride Hydrochloride was obtained as a gift sample from Ami Life Sciences Pvt. Ltd. Baroda Gujarat, India. Sodium alginate was obtained from Vijay chemicals Pvt. Ltd, Pune, India. Calcium carbonate was obtained from Thermo Fisher Scientific Pvt. Ltd Mumbai; India. HPMC K100M was obtained from Vijay Chemicals Pvt. Ltd, Pune, India. All other materials and chemicals used were of either pharmaceutical or analytical grade.

Methods

Preparation of *in situ* gelling solutions

Sodium alginate (0.75-1% w/v) and sodium citrate (0.5% w/v) were dissolved in deionised water followed by addition of HPMC K100M (0.4% w/v) with stirring for 30 min. Calcium carbonate (0.5-1% w/v) was separately dissolved in deionised water. Both solutions were mixed and the drug was added and stirred till it was completely dissolved. The final volume was made up to 100 ml with deionised water [8].

Experimental design

Preliminary trials were conducted to identify the concentration of sodium alginate and calcium carbonate that formed *in situ* gels of desired strength and floating lag time. Based on this, a 3^2 simple full factorial design having 9 runs (SA1-SA9) (Table 1) were selected. Two independent variables, concentration of sodium alginate (X1) and calcium carbonate (X2) were selected at 3 levels and dependent variables were percent drug release at 1 h (Y1), at 6 h (Y2), gel strength (Y3) and $T_{50\ \%}$ (Y4) time required to release 50 % of loaded drug dose. The experimental data was analyzed statistically using

Design Expert Software V 9.1 and the main effects and interactions were calculated. The effect of independent variables on the response parameters was visualised using 3D response plots. Desirability approach was employed to locate the optimal settings of the formulation variables to obtain desired response. The optimized formulation was evaluated for the responses and the experimental values obtained were compared with those predicted by the mathematical model generated.

Table 1: Formulation combination as per the 3^2 full factorial design for pH sensitive floating oral *in situ* gel.

Ingredient	Formulations (Quantity in %w/v)								
	SA1	SA2	SA3	SA4	SA5	SA6	SA7	SA8	SA9
ITO	1	1	1	1	1	1	1	1	1
Sodium alginate	0.75	0.75	0.75	1	1	1	1.5	1.5	1.5
Coded level (X1)	-1	-1	-1	0	0	0	+1	+1	+1
Calcium carbonate	0.5	0.75	1	0.5	0.75	1	0.5	0.75	1
Coded level (X2)	-1	0	+1	-1	0	+1	-1	0	+1
HPMC k100M	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Sodium citrate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Deionised water(up to)	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml

Characterization of floating oral *in situ* gel

Physical appearance, pH and drug content

All the formulations were visually checked for their appearance and color. The pH of the *in situ* solution was measured using the standardized digital pH meter (Deluxe pH meter 101/EI) at room temperature by taking adequate volume in a 50 ml beaker [9]. For drug content *in situ* solution (equivalent to 100 mg of ITO) was taken in a volumetric flask. To this 50 ml of 0.1 N HCl was added and shaken on the mechanical shaker for 30 min. This was followed by sonication for 15 min for complete dispersion of contents and filtration using 0.45 µm membrane filter. From this solution, 10 ml of sample was withdrawn and diluted to 100 ml with 0.1 N HCl. Contents of ITO were determined spectrophotometrically at 248 nm using double beam UV-visible spectrophotometer (LABINDIA 3000+) [10].

***In vitro* gelling capacity**

The *in vitro* gelling capacity of the formulations was measured by placing 5 ml of the gelation solution in simulated gastric fluid (0.1N HCl, pH 1.2) in a 15 ml borosilicate glass test tube maintained at 37±1ºC temperature. The formulation (1 ml) was added slowly by placing the pipette at the surface of fluid in the test tube. As the solution comes in contact with gelation solution, it is immediately converted into a stiff gel like structure. The gelling capacity of solution was graded in three categories evaluated on the basis of stiffness of the formed gel and time period for which the gel retained its rigidity [11].

(+) Gels after five min, dispersed within 8 h

(++) Gels within 60 sec and retains gel structure for 12 h

(+++) Gels immediately and retains gel structure for more than 12 h.

***In vitro* buoyancy test**

In vitro buoyancy was characterized by floating lag time and total floating duration. This study was carried out using USP dissolution apparatus Type II using 500 ml of 0.1N HCl (pH-1.2) as the medium. The test was carried out at 50 rpm at 37±0.5°C. The *in situ* gelling solution (10 ml) was transferred to a petriplate (diameter 2") using a syringe. The plate was then 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 rise to the surface of the dissolution medium [floating lag time] and the duration of the time for which the gel constantly floated on the dissolution medium [floating duration] was noted for each formulation[12-14].

Density

Density of the floating oral *in situ* gel was determined by using water displacement method [15]. To (10 ml) *in situ* solution, 20 ml of 0.1 N HCl (pH 1.2) was added to convert the solution in to 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 marking 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.

Gel strength

An in house penetrometer was fabricated based on the method explained by Dettmar et al [16] to measure the gel strength. The apparatus was comprised a plastic measuring cylinder of 1.2 cm radius and a bore of 0.1 mm at its base. A needle, 2 cm in length was used to which a nylon thread was tied. Sol (15 ml) was taken in the cylinder with temporarily sealed bore followed by addition of 50 ml of 0.1 N HCl (pH 1.2) for gelation. After gelation, the HCl was drained off by opening bore seal leaving the gel mass in the measuring cylinder and the needle was rested on the surface of the gel. At the free end of the thread, pan was attached to which the weights were added. The gel strength was reported in terms of weight required to pass the needle probe through the gel mass[16]. The gel strength was calculated using this formula [17],

Gel strength = Mg/a - - - - - - - - - (1)

Where, M = weight at which needle passes through the formed gel mass. g = gravitational force, taken as 980 cm/s^2; a = Area of surfaces.

Viscosity determination

The viscosities of the solutions were determined by Brookfield viscometer (Model RVDV-II+P). The samples (10 ml) were shared at a rate of 100 rpm using S21 spindle at room temperature. Viscosity measurement for each sample was done in triplicate, with each measurement taking approximately 30s [18].

***In vitro* drug release**

The drug release study was carried out using USP type II paddle type apparatus at 37±0.5ºC and at 50 rpm using 900 ml of 0.1 N HCl (pH 1.2). *In situ* gel (10 ml) equivalent to 100 mg of ITO was used for the test. Sample solution (1 ml) was withdrawn at predetermined time intervals, filtered through a 0.45 µm membrane filters, diluted suitably and analyzed by UV spectrophotometric LABINDIA 3000+at 248 nm. Fresh dissolution medium was replaced immediately after withdrawal of the test sample to maintain sink condition. The dissolution studies were carried out for a period of 12 h [19, 20]. The dissolution data were analyzed by DD Solver™ software for mathematical modeling to predict the release kinetics [21, 22].

***In-vivo* pharmacokinetic studies**

Male Wistar rats, weighing 230–330 g, were fasted for 24 h with free access to water. The rats were divided into three groups of six rats each, viz., first group served as negative control, second group was administered pure ITO solution and third group was administered optimized formulation (10mg/kg of animal weight). The rats were anaesthetized with the help of ether, and the retro-orbital method was used to removal of blood samples. Blood samples were

withdrawn from the retro-orbital vein at intervals of 0, 1, 2, 4, 6, 8, 10, 12 h and analyzed by bioanalytical HPTLC method using a mixture of methanol- ammonium acetate (6:4, v/v) as mobile phase and detected at λ_{max} of 288 nm [23, 24]. A simple protein precipitation method was employed for extraction of the drug from human plasma using 10% perchloric acid. The protocol for the animal experiment was approved by the Animal Ethical Committee ref no. (AISSMS/IAEC/13-14/01-28).

RESULT AND DISCUSSION

Physical appearance, pH and drug content:

All the formulations were found to be milky white colored solution. The pH was observed in the acceptable range of 7-8. Drug content for the prepared formulations was observed with high drug loading which is more than 90% showing maximum drug entrapment. The drug content was found to be in the range of 90-95%.

In vitro gelling capacity

Alginate forms hydrogels by means of calcium, which positions in the interstices between G blocks (α-L gluronopyranosyl), leading to an ordered conformational structure called "egg-box" array [5]. The pre-requisites for *in situ* gelling system is gelling capacity which is defined in terms of speed and extent of gelation. The *in situ* gel should maintain its integrity without dissolving or eroding for prolonged periods to facilitate controlled release of drugs locally. From the results, it was observed that (SA1-SA3) batches which contain low amount of polymer and calcium carbonate form slimy gel mass within 5 min which dispersed rapidly. Batches (SA5-SA9) form gel within few seconds and remained in their gel state for more than 12 h without losing their integrity.

In vitro buoyancy test

The time taken by the formulation to emerge on the surface of the medium (floating lag time) and the time for which the formulation constantly floated on the dissolution medium surface (duration of floating) are shown in (Table 2). On contact with gastric environment, calcium carbonate effervesced, releasing carbon dioxide and calcium ions. Then, gelation and complexation by Ca^{+2} ions took place to provide a gel barrier at the surface of the formulation. The released carbon dioxide was entrapped in the gel network producing a buoyant preparation, which resulted in extended floating [25]. The floating properties of the formulation mainly depend on calcium carbonate, on increasing the calcium carbonate concentration, the floating lag time was reduced and the duration of floating was extended. The increasing amounts of Ca^{+2} and CO_2 resulted from the increase in calcium carbonate concentration, are responsible for the observed reduction in floating lag time and increasing duration of floating. The floating lag time is minimum for SA3 and highest for SA1. This is because SA3 contains highest concentration of calcium carbonate. Similar was the case with formulation SA6 & SA4 and SA9 & SA7 (Table 2). Increase in polymer concentration results in an increase in viscosity. Hence time taken by the sol to form a cohesive gel mass and to emerge on the surface of the medium was lowered.

Gel strength

Gel strength is indicative of tensile strength of the gelled mass. It signifies the ability of the gelled mass to withstand to the *in-vivo* peristaltic movements. The gel strength of the formulation is an important variable dependent on the concentration of the gelling agent as well as cation source. The high concentration of polymer and calcium carbonate resulted in gels with adequate gel strength indicating that they can withstand the shear forces likely to be encountered in the stomach. Formulations containing low amount of sodium alginate formed very weak slimy gel. But with increase in calcium carbonate content there was a marginal increase in gel strength. This was observed in case of SA1, SA2 & SA3 for which the gel strength was in the range of 19.83-53.96 gm/cm^{2}because it contains the increasing amount of the calcium carbonate. Similar pattern was observed in the batches [SA4-SA6] gel strength observed in the range of the 20.17-61.12 gm/cm^2 and [SA7-SA9] 21.36-69.24 gm/cm^2 (Table: 2). From this result it was revealed that the formulation having high gel strength can remained at high peristaltic movements.

Density

The prime requirement of the floating system is that it should have density lesser than gastric contents (~1.004 gm/cm^3). The density of all floating *in situ* gel formulations was observed less than that of the gastric content (Table 2). Density is an important parameter as far as the floating properties of the gastroretentive dosage form is concerned. The density of all the formulations was recorded and found to be lesser than the reported density of gastric fluids. All the formulations contain entrapped CO_2 and thus were found to have excellent buoyancy. The average densities of (SA1-SA9) formulations were found to be in the range of 0.670 to 0.862 gm/cm^3. Lowered the density of the formulation can floated over an extended period.

Viscosity

The rheological properties of the solutions are important in view of their proposed oral administration. The solutions showed a marked increase in viscosity with increasing concentration of polymer (Table 2). The solution showed a marked increase in viscosity with increasing concentration of sodium alginate and calcium carbonate and also due to the presence of HPMC K100M. The calcium carbonate content in the formulation simultaneously increased the viscosity since it was present in the formulation as insoluble dispersion, an increasing concentration of polymer thus contributing to increased viscosity. The order of viscosity of all formulations were SA9 > SA8 > SA7 > SA6 > SA5 > SA4 > SA3 > SA2 > SA1. The formulations showed a marked increase in viscosity with increasing concentration of sodium alginate, calcium carbonate and HPMC K100M. It was found to be in the range of 136.1-182.3 cps.

In-vitro drug release

The effect of polymer concentration on *in vitro* drug release from in situ gels is depicted in (fig. 1). A significant decrease in rate and extent of drug release was observed with the increase in polymer concentration, and is attributed to increase in the density of the polymer matrix and also increase in the diffusional path length which the drug molecules have to traverse. The release of the drug from these gels are characterized by an initial phase of high release (burst effect) followed by a slower release as the gelation proceeds. This bi-phasic pattern of release is a characteristic feature of matrix diffusion kinetics. Since the in situ gelling systems are aqueous in nature the matrix formed before the complete gelation cross-linking is already be in a hydrated state there by circumventing the rate limiting step of matrix hydration in the initial stages [26].

The dissolution profile of all the batches revealed that concentrations of sodium alginate, calcium carbonate and HPMC K100M have an important role in drug release pattern. *In vitro* drug release profile is depicted in (fig. 1). Among the 9 formulations evaluated, SA1 which contained the lowest proportion of sodium alginate and calcium carbonate showed burst release with > 90 % drug released in about 4 h though HPMC K100M was also present in the formulation. On the other hand formulations SA7, SA8 and SA9 which contained the highest proportion of sodium alginate, calcium carbonate with HPMC K100M displayed a gradual and sustained release over a period of 12 h.

Release kinetics

Mathematical modelling of the release profiles for the nine formulations revealed that dissolution followed Peppas model (r^2=0.9818-0.9955). The value of diffusion exponent 'n' for all factorial formulations was less than 0.45 (Table 3) indicating Fickian drug release which indicates the release of the drug from the matrix system.

Statistical Analysis

Analysis of experimental results was carried out by using Design Expert V 9.1 software. The quadratic model was suggested to run the design. F-values, P-value and model F-value for percent drug release at 1 h, 6 h, gel strength and $T_{50\%}$ were obtained from ANOVA. For all responses, the Model F-value implied that the quadratic model was

significant. The probability values (p≤ 0.05) indicated that all the model terms across all the responses were significant. Polynomial equations for responses Y1, Y2, Y3 and Y4 depict the relation between the factors and responses. The coefficients of various terms in the polynomial equations generated by the software give the nature and magnitude of the relationship between the variables and the responses (Table 4). The concentration of sodium alginate and calcium carbonate was found to significantly retard drug release at 1 h and 6 h. Both variables were found to have a direct influence on gel strength and $T_{50\%}$.

Table 2: Floating lag time, Floating duration, Gel strength, density and viscosity of pH triggered floating oral *in situ* gel (n=3).

Formulation code	*In vitro* gelling capacity	Floating lag time (s)	Floating duration (h)	Gel strength (gm/cm²)	Density (gm/cm^{-3})	Viscosity (Cps)
SA1	+	17±2.1	8	19.89±0.2	0.694±0.1	136.1±0.26
SA2	+	15±1.2	8	32.77±0.2	0.837±0.5	144.6±0.15
SA3	+	12±0.8	8	53.96±0.2	0.728±0.5	152.1±1.5
SA4	++	14±0.9	12	20.17±0.2	0.862±0.8	149.5±0.1
SA5	+++	12±1.5	12	33.62±0.2	0.759±0.5	158.2±0.20
SA6	+++	10±0.2	12	61.12±0.1	0.869±0.3	163.4±0.11
SA7	+++	10±1.6	>12	21.36±0.5	0.670±0.3	172.3±0.25
SA8	+++	08±2.3	>12	38.49±0.1	0.799±0.5	177.8±0.05
SA9	+++	07±1.2	>12	69.24±0.2	0.720±0.1	182.3±0.73

(+) Gels after five min, dispersed within 8 h, (++) Gels within 60 sec and retains gel structure for 12 h, (+++) Gels immediately and retains gel structure for more than 12 h.

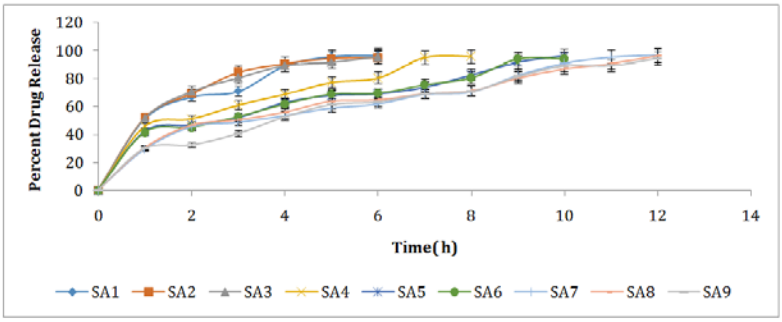

Fig. 1: *In vitro* drug release profiles for pH sensitive floating oral *in situ* gel of batches SA1-SA9

Table 3: The release kinetic data of pH sensitive floating oral *in situ* gel of ITO batches SA1-SA9.

Batches	Regression value					Parameter's for Peppas equation	
	Zero order	First order	Higuchi	Peppas	Hixon Crowell	n	K
SA1	0.7303	0.9698	0.9814	0.9916	0.9444	0.400	49.860
SA2	0.6760	0.9946	0.9767	0.9955	0.9684	0.367	54.109
SA3	0.5425	0.9906	0.9508	0.9945	0.9624	0.323	55.217
SA4	0.6802	0.9498	0.9786	0.9856	0.9278	0.428	40.116
SA5	0.6179	0.9144	0.9658	0.9818	0.8717	0.413	35.500
SA6	0.6269	0.9206	0.9717	0.9821	0.8795	0.418	35.013
SA7	0.7433	0.9370	0.9813	0.9818	0.9182	0.423	27.678
SA8	0.6455	0.9383	0.9829	0.9885	0.8990	0.442	30.936
SA9	0.8034	0.9693	0.9867	0.9891	0.9593	0.443	24.508

Table 4: Summary of results of regression analysis of pH triggered floating oral *in situ* gel for responses Y1, Y2, Y3 and Y4

		For percent drug release at 1 h			
Model	**Model F value**	**p value**	**R^2**	**Adeq. precision**	**Std. deviation**
Quadratic	44.62	0.0051	0.9867	15.564	1.80
$Y1 = 43.32 -10.88*X1 – 0.56*X2 – 3.92*X1*X2 - 2.40* X1^2 + 0.040*X2^2$					
For percent drug release at 6 h					
Quadratic	15.54	0.0235	0.9628	9.579	4.65
$Y2=72.21-16.67X1-1.79X2-0.59X1X2-6.45X1^2+1.62X2^2$					
For gel strength					
Quadratic	479.51	0.0001	0.9988	56.479	1.07
$Y3= 34.31+3.75X1+20.48X2+3.45X1X2+0.98X1^2+6.00X2^2$					
For $T_{50\%}$ -Time required for release of 50% of loaded drug dose					
Quadratic	16.56	0.0215	0.9650	10.506	0.34
$Y4= 2.03+1.23X1+0.14X2+0.18X1X2-0.018X1^2+0.11X2^2$					

The same is reflected in the 3D response surface plots which depict the relationship between the response and independent variable across a wider domain.(fig. 2, 3, 4 and 5).

Fig. 2: 3-D Response surface plot showing the influence of sodium alginate and calcium carbonate concentration on the percent drug release at 1 h.

Fig. 3: 3-D Response surface plot showing the influence of sodium alginate and calcium carbonate concentration on the percent drug release at 6 h.

Fig. 4: 3-D Response surface plot showing the influence of sodium alginate and calcium carbonate concentration on the gel strength

Optimized batch

A numerical optimization technique using the desirability approach using the Design Expert software was employed to develop optimum formulation with the desired responses. Constraints were set for minimizing drug release at 1 h, drug release at 6 h, gel strength and $T_{50\%}$ to locate the optimum setting of independent variables. Based on the input constraints the optimized *in situ* gel formula was generated by the software which comprised 1 % w/v sodium alginate and 1 % w/v of calcium carbonate and 0.4 %w/v HPMC K100M.

Fig. 5: 3-D Response surface plot showing the influence of sodium alginate and calcium carbonate concentration on $T_{50\%}$. time required to release 50% of loaded drug dose

The optimized formulation (S1) was evaluated for percentage drug release at 1 h, 6 h, gel strength and $T_{50\%}$. A low residual error was evident in the observed and predicted responses (0.48, 0.98, 0.93 and 0.15) with desirability of 0.999 for the optimized formulation. Drug release at 1 h, 6 h, gel strength and $T_{50\%}$ from optimized batch was found to be 28.96 %, 61.62 %, 68.03 gm/cm^{2}and 3.5 h. The optimized batch was evaluated further for parameters like pH, gel strength and density (Table 5).

In-vivo studies

In vivo studies were performed to quantify plasma concentration of ITO after oral administration of *in situ* gel formulation and pure ITO. The various pharmacokinetic parameters are presented in (Table 6).

The plasma concentration time profile of pure drug and formulation is represented in (fig. 6). Itopride Hydrochloride was available in plasma within an hour after its oral administration with C_{max} of 0.163 µg/ml. T_{max} for test formulation was found to be 6 h and C_{max} was found to be 0.179 µg/ml (Table no 6). The higher T_{max} of the test formulation suggests slower absorption. This delayed absorption of test preparation is due to the sustained release of the drug. This indicates control release of drug over 12 h. The total area under the curve of AUC $_{0\text{-}12\ h}$ was found to be 1.528, an increase in the 90% bioavailability of the formulation was observed than that of the plain drug. The elimination rate constant for ITO in the sodium alginate in *situ* gelling system was found to be 0.151/h which was 23% lower than that for pure drug. The relative bioavailability of ITO is 60% due to first-pass effect [27]. It is metabolized in liver by N-oxidation to inactive metabolites by the enzyme flavin-containing monooxygenase [28]. Thus we may infer that formulating ITO as a controlled release formulation using pH triggered *in situ* gelling system.

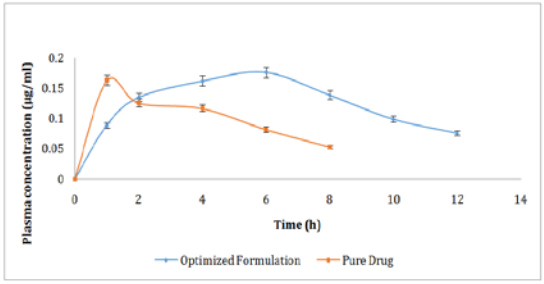

Fig. 6: *In vivo* drug release profile of optimum formulation and pure drug ITO of pH triggered floating oral *in situ* gel

Table 5: Evaluation of optimized formulation of pH sensitive floating oral *in situ* gel(n=3)

Optimized Formulation	Percent drug release at 1 h	Percent drug release at 6 h	$T_{50\%}$ (h)	pH	Gel strength (gm/cm^2)	Density (gm/cm^{-3})
S1	28.96	61.62	3.5	7.22±0.8	68.03±1.5	0.684±0.08

Table 6: Pharmacokinetic parameters for pH triggered floating oral *in situ* gel (n=3)

Parameters		Pure Drug	Optimized Formulation (S1)
C_{max}	µg/ml	0.163±0.06	0.179±0.08
T_{max}	H	1±0.68	6±1.02
AUC_{0-12}	h. µg/ml	0.80±0.5	1.528±0.9
K_{ele}	h^{-1}	0.198±0.09	0.151±0.08

CONCLUSION

Itopride hydrochloride was successfully formulated as a pH triggered floating oral *in situ* gelling system using sodium alginate as a natural polymer. The results of 3^2 full factorial designs revealed that the concentration of sodium alginate and concentration of calcium carbonate significantly affected on the dependent variables like percent drug release at 1 h, 6 h, gel strength and $T_{50\%}$. The optimized formulation provided controlled *in vitro* release of the drug over an extended period of 12 h. The drug release from gel structure follows a Korsemeyer-Peppas model, which indicates a diffusion-controlled release. The optimized formulation can be a competent alternative to conventional oral solid dosage form. Controlled release oral *in situ* gel of Itopride Hydrochloride was prepared successfully improving its bioavailability. The oral *in situ* gel improves patient compliance by reducing the frequency of the dosing.

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CONFLICT OF INTERESTS

Declared None

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