Original Article

Design and Characterization of Sustained Release *in situ* Gastric Floating Gel of Ropinirole Hydrochloride

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ABSTRACT

Background: This *in situ* solution which on gelation floats in the gastric region is suitable for sustaining the release of the drug. In the present research work, Ropinirole Hydrochloride which is an Anti-parkinson agent, used to formulate an *in situ* gel for prolonged action. **Materials and Methods:** Sodium alginate is a natural polymer used to form the gel matrix, calcium carbonate plays a dual role i.e. the source of CO_2 entrapped in the matrix for floatation of gel and source of Ca^{2+} ion for sol to gel transition, HPMC K100M as the release retard polymer was investigated. The mechanism for the floatation of the gel was pH induced ion gelation. For the formulated *in situ* solution different evaluation parameters were used. **Results and Discussion:** On the basis of the outcomes pale colored, viscous solution of uniform consistency was obtained, the drug content was found to be >87%, the viscosities were in the acceptable range suitable for swallowing, pH was found to be in the range of 7.35-7.87 which was compatible for oral ingestion. Design Expert 12 software was used to derive the results of interaction and responses on the basis of concentration of polymer and statistical analysis. F5 (0.75mg SA and 0.5mg HPMC) the optimized formulation showed a slow drug release of 96.10% up to 12 h. The best fit model for the drug release was Korsmeyer Peppas model which explained drug release on imbibition of water from surrounding by polymer matrix. **Conclusion:** The *in situ* gel prepared can ultimately provide prolonged release, enhance the bioavailability of the drug and increase the patient compliance due to development of a once in a day dosage form in comparison to multi dose of tablets therefore, can be considered as promising dosage form for increased therapeutic action.

Key words: *In situ* gel, pH induced ion gelation, Sodium Alginate, $CaCO_3$, Gastro Retentive, Ropinirole Hydrochloride.

INTRODUCTION

Oral sustained release drug delivery has received an increasing attention in the pharmaceutical field because of its certain advantages over other dosage forms which includes easier administration of dose, improved patient compliance, formulation flexibility and cost effectiveness.[1] Floating drug delivery system provides adequate buoyancy to float over the gastric contents because of its low density. It remains buoyant for an extended period without affecting the gastric emptying rate.[2] Oral liquid dosage as an *in situ* solution can be the most suitable means adopted for any drug delivery to the systemic circulation. The *in situ* solution undergoes gelation on coming into contact with the digestive fluid in the stomach.[3,4] The drug in the gel matrix steadily diffuses at the desired rate while it floats on the gastric contents. The remnant of the gel is emptied from the gastric region after release of the drug. Various triggers that induce gelation of solution include pH, ions and temperature.[5,6]

Ropinirole Hydrochloride (RH) is a non-ergoline dopamine drug which has an agonist action which enhances the level of chemical messenger dopamine in the brain. Due to its high specificity it generates full intrinsic activity at D2 and D3 receptor

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subtypes and therefore is useful for the treatment of Parkinson's disease.[7] This drug is often used for the treatment of moderate to severe Restless Leg Syndrome (RLS) which causes an impulsive movement of legs and an uncomfortable sensation to the patient.[8] RLS which is a common condition in patients suffering from Parkinson's disease. Medications like Ropinirole helps in overcoming the unpleasant feeling and also combat the problem temporarily. The biological half-life of RH is only 5 h and its bioavailability is about 55%. Conventionally, the drug is available as a tablet which is given 3 times a day with a dose of 0.25 – 5 mg for the therapeutic effect. The frequency of this dosage promotes the formulation of once a day *in situ* gel to overcome the problem of multiple administrations and reduced patient compliance.[9]

Also, formulation of a prolonged release dosage form using RH can enhance the bioavailability of the drug up to 100% in comparison to multi dose tablets of RH, which shows a low bioavailability of 50-55%. Once in a day can also prevent the fluctuations in the plasma drug concentration.The patients suffering from Parkinson's are generally unable to swallow the tablets due to decreased muscle functions and dryness of the mouth. However, it would be easier for them to partake dosage in liquid form. Every dose of 10 ml *in situ* will contain 2 mg of drug which will be administered to the patient, to overcome the problem of patient incompliance due to multiple administrations.[9]

RH is prepared in the form of *in situ* floating gel for the retention of the drug in the gastric area for a prolonged period of time i.e. short transit time of the tablet while *in situ* gel is a sustained release formulation to be taken once a day for effective action. As RH is a highly water soluble drug it is prone to the problem of dose dumping, which can be overcome by preparing sustained release *in situ* gel of the drug. Also, the fluctuations in plasma drug concentration can be controlled by formulating an *in situ* gel. This also helps in enhancing the local action of the drug to the gastric region as the drug RH is actively adsorbed in the stomach region.[9,10]

MATERIALS AND METHODS

Materials

Ropinirole Hydrochloride was a generous gift sample obtained from Neuland Laboratories Ltd. Hyderabad, India. Sodium Alginate was obtained from S D Fine-Chem Ltd, Mumbai, India. HPMC K100M was procured from Otto Chemie Pvt. Ltd. and Calcium Carbonate was procured from Priya Research Labs, Bangalore, India. All the chemicals and materials were of analytical or pharmaceutical grade.

Method of Preparation of *in situ* Polymeric Solutions

100 ml distilled water was stirred on the magnetic stirrer followed by addition of 250 mg of tri-sodium citrate. Then weighed quantity of sodium alginate was added slowly as the solution reached 70°C followed by the addition of HPMC K100M which acts as a release retard. The solution is stirred till a clear solution is obtained; the temperature is maintained to 70°C. The clear solution is taken and cooled to 40°C followed by addition of calcium carbonate after cooling with continuous stirring to provide a uniform solution. To this Ropinirole Hydrochloride is added and finally 180 mg of methyl paraben is added as a preservative in the solution. The solution is stirred continuously till a uniform solution is obtained. The quantities of Sodium alginate and HPMC K100M are varied from 500-750 mg and 400-600 mg respectively. Table 1 represents composition of formulations prepared and the schematic representation for preparation *in situ* polymer solution and its evaluation is depicted in Figure 1.[11,12]

Table 1: Composition of Formulation of Ropinirole HCl *in situ* Solutions.

Ingredients	Formulations (w/v)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ropinirole Hydrochloride (mg)	20	20	20	20	20	20	20	20	20
Sodium Alginate (mg)	500	500	500	750	750	750	1000	1000	1000
HPMC K100M (mg)	400	500	600	400	500	600	400	500	600
Calcium Carbonate (mg)	1000	1000	1000	1000	1000	1000	1000	1000	1000
Tri-Sodium Citrate (mg)	250	250	250	250	250	250	250	250	250
Methyl Paraben (mg)	180	180	180	180	180	180	180	180	180
Distilled Water (upto 100 ml)	100	100	100	100	100	100	100	100	100

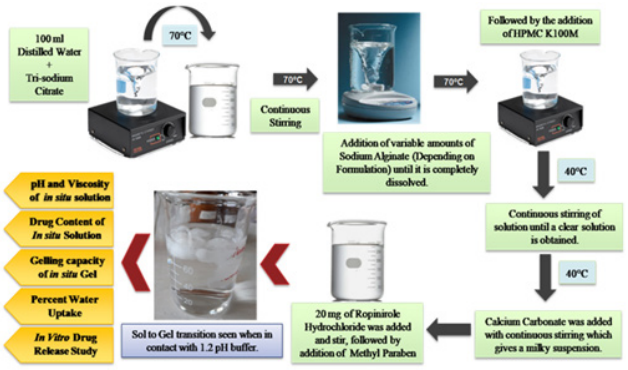

Figure 1: Schematic Representation for Preparation *in situ* Polymer Solution and Its Evaluation.

Experimental Designing of the Formulations

The experimental designs of the formulations were done using Design Expert 12 Software. Based on full factorial design 3^2, that is two factors having 3 levels each, 9 runs were obtained. Responses were taken accordingly, which were drug release in the 1st h, % drug release in 8 h and viscosity of the formulations. On the basis of the results of the interactions and effects obtained in the software, the optimized gel was obtained.[12]

Evaluation methods of *in situ* solution

Compatibility study by FT-IR and Differential Scanning Calorimetry (DSC)

The FTIR Spectrum for the pure drug and the excipients were obtained using FT-IR Spectrophotometer Shimadzu Japan and the compatibility of the drug and excipients was checked using DSC 60 apparatus Shimadzu, Japan at KLE College of Pharmacy, Belagavi.

Physical Appearance of the *in situ* solution

The formulations prepared were observed physically for their appearance, colour and odour.

pH and Drug Content of the Formulations

The pH of the formulations was measured using calibrated digital pH meter. The drug content of the formulations was obtained by dissolving the required quantity of the solutions equivalent to dose of the drug (2mg) into 20 ml of 1.2 pH buffer. The gel formed along with the 20 ml of buffer was shaken using propeller for 15 mins, till all the gel was completely dispersed. The absorbance was taken using UV spectrophotometer, to calculate the drug content.[12,13]

In vitro Gelling Capacity

The gelling capacity of the formulations was measured using test tube method. About 1 ml of formulated gel was transferred to test tubes containing 5 ml of 1.2 H buffer (similar to gastric fluid) with 5% Sodium Lauryl Sulphate (SLS) respectively. As the solution comes in contact with the buffer, sol to gel transition occurs thereby system becomes buoyant and floats. The floating, gelling capacity and floating duration is evaluated.[14]

Viscosity Assessment

The viscosity of the solutions were measured using Brookfield viscometer (Model CAP 2000+) using spindle number 1, using 60 µl of sample at 100 rpm. All the readings were taken in triplicate with each of the sample for 30 sec each.

In vitro Buoyancy Study

The floating duration was determined by assessing the time taken for the 10 ml solution (equivalent to 2 mg of drug) to float over the gastric fluid (Floating Lag Time) and the duration of time for which the gel floats.[15]

Density of the Gel

The densities of the formulations were measured by calculating the mass and volume of the gels formed for each of the formulation. The polymeric solution converted to form stiff gel when it contacts acidic buffer. For the gels, the mass was recorded using weighing balance; gel transferred to measuring cylinder and the volume was noted.

Water Uptake Test

Into 20 ml of 0.1N HCl, 10 ml of *in situ* solution was transferred for sol to gel transition. The excess buffer was removed through sieving. Later the stiff formed gel was weighed using the electronic weighing balance. The initial weight was noted. Further, the gel obtained was put in 10 ml distilled water for 1 h and weighed again.[15] The continuous process of replacing the water after every hour along with weighing of the gel was continued till 6 h. The final weight of the swollen gel was reported.

In vitro Drug Release

The drug release study from the *in situ* gel was done using USP Type II Dissolution Apparatus. 10 ml of *in situ* solution was taken equivalent to 2 mg of the dose of RH. The 10 ml solution was put in the dissolution basket using measuring cylinder containing 900 ml of 1.2 pH buffer (simulated gastric fluid) and 5% Sodium Lauryl Sulphate. The temperature was set at 37°C and rpm at 50. The drug release was studied upto 12 h. 5 ml sample was withdrawn at every hour and the content was determined by measuring absorption at 249 nm using UV spectrophotometer.[16]

Study of Drug Release Kinetics

The data which was obtained after performing the *in vitro* drug release study was plotted in various mathematical models which predict the release kinetics for the *in situ* gel. The release kinetics for different models like First order, zero order model, Higuchi model, Hixon Crowel and Korsmeyer Peppas model were examined. The data for mechanism of release was obtained using PCP Disso V3 Software (Version 3, Bharati Vidyapeeth Poona). The best fit model was selected on the basis of the r^2 value obtained. The graphs for the release kinetics were prepared for the optimized formulation using Microsoft Excel and the linearity was observed.

Stability Study

The optimized formulation was contained in a glass bottle of 100 ml capacity and kept in the stability chamber. The stability of the *in situ* solution was monitored at the accelerated conditions for the required period as per the guidelines specified by the ICH. In the present study the sample was kept in the Humidity control chamber at 25±2°C / 60% ±5% RH and was withdrawn on the 7th, 15th and 30th day of the stability chamber.[17]

RESULTS AND DISCUSSION

FT-IR Spectroscopy

The spectrum showed important functional peaks for Ropinirole HCl were observed for groups C-N 1242.16, C=O 1724.36, C-N 2881.62, N-H 3234.20 cm^{-1} and similar peaks were observed for physical mixture indicative of no physical and chemical interactions i.e., no influence of the polymer on the API. Results observed can be seen in Figure 2a and 2b.

DSC Study

As per the DSC carried out, a sharp endothermic peak appears at a temperature of 247.01°C. In the physical mixture the endothermic peak for the drug was recorded at 244.34°C alongside a peak of HPMC K100M at a temperature of 166.8°C. The peaks represented that there was compatibility among the drug and excipients as Figure 3a and 3b.

Physical Appearance

The *in situ* solutions prepared were white to pale yellow and creamy in appearance when prepared. The physicochemical properties of the solution were not altered on autoclaving. Thus the solutions can be categorized under Newtonian fluids. It showed slow flow ability due to solutions viscous nature and a calcite smell obtained because of presence of calcium carbonate in the solution. On conversion of the *in situ* solution into gel the visual appearance of the gel was white in color with a good consistency.

pH and Drug Content

pH determination is considered as a very important parameter for the orally administered dosage form as it shouldn't affect the solubility and stability of the liquid and must be compatible for drinking. The pH was found in the range of 7.66-7.86 which was optimal for oral administration of dosage form. Secondly, the drug content was found to be in the range of 1.741-1.862 mg/10 ml which explained that most of the drug was uniformly distributed in the entire liquid formulation and there was no drug loss during formulation of *in situ* solution. The results are shown in Table 2.

In vitro Gelling Capacity

For the gelling capacity it was shown that all the formulations showed that the polymeric solution converted to a stiff floating gel as soon as it comes

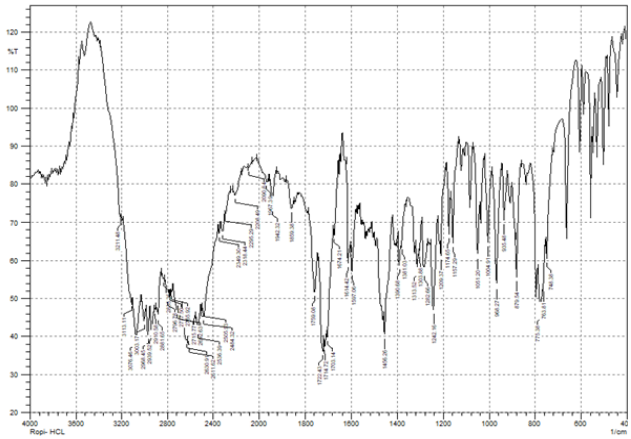

Figure 2a: FTIR Spectrum of Pure API (Ropinirole HCl).

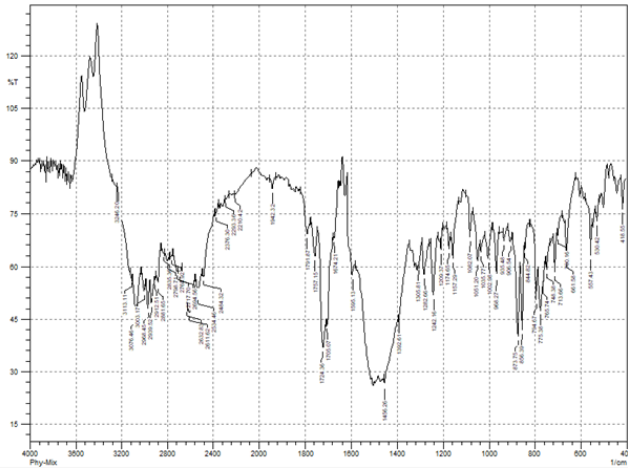

Figure 2b: FTIR Spectrum of Physical Mixture.

in contact with the gastric simulated fluid (0.1 N HCl Buffer). Also, the gel remained floating for more than 12 h i.e. for prolonged period of time due to the presence of calcium carbonate which is the source of carbon dioxide gas which gives buoyancy to the gel as shown in Figure 4.

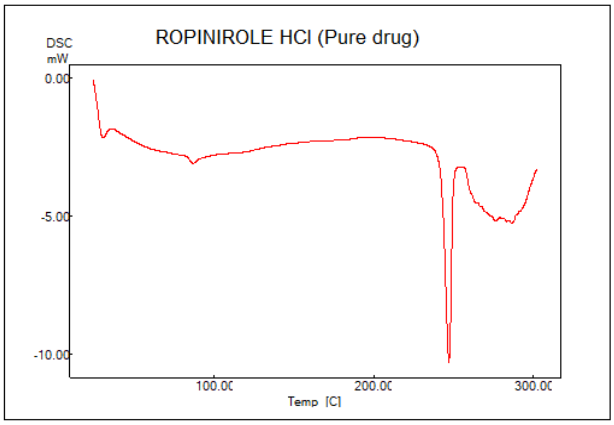

Figure 3a: DSC Spectrum of pure drug of Ropinirole HCl.

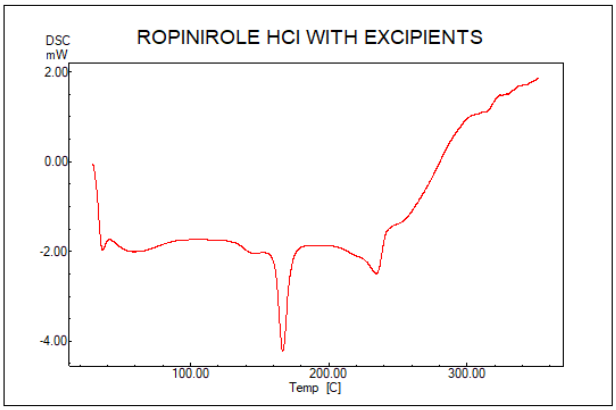

Figure 3b: DSC Spectrum of Physical Mixture of Ropinirole HCl along with HPMC K100M.

Viscosity

The polymeric solutions showed a marked increase in the viscosity i.e., change in the rheological properties was seen with the increase in the concentration of HPMC K100M. The viscosity of solution was found to increase with proportional increase in the concentration of HPMC and sodium alginate, also the flowability was affected which is depicted in Figure 5.

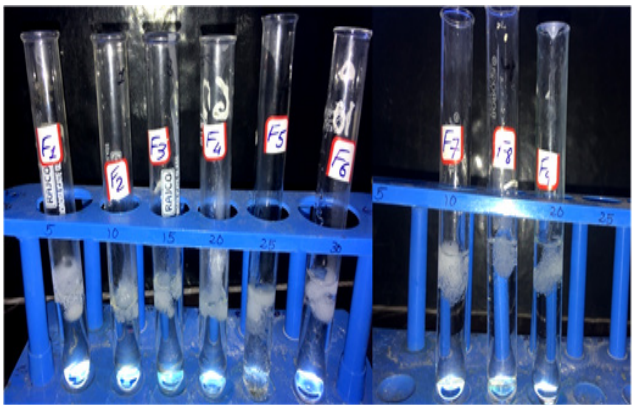

Figure 4: *In vitro* gelling capacity of formulations F1 to F9.

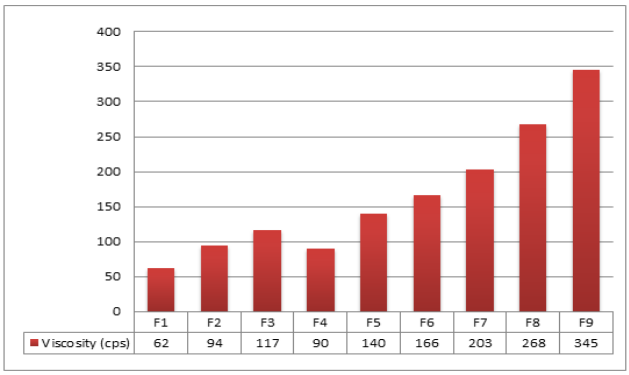

Figure 5: Viscosity of formulated *in situ* solutions of Ropinirole HCl.

Table 2: Evaluation of Formulated *in situ* solutions of Ropinirole HCl.

S No.	Formulation Code	pH	Drug Content	Buoyancy Test	Gel Density (gm/cm^3)	Water Uptake (%)
1	F1	7.68 ±0.037	1.809 ±0.030	> 15 hr	0.671± 0.12	22.442
2	F2	7.78 ±0.020	1.851 ±0.035	> 15 hr	0.684± 0.19	26.49
3	F3	7.76 ±0.015	1.810 ±0.076	> 15 hr	0.699± 0.08	28.92
4	F4	7.83 ±0.005	1.814 ±0.064	> 15 hr	0.748± 0.05	31.48
5	F5	7.66 ±0.026	1.775 ±0.012	> 15 hr	0.754± 0.11	34.573
6	F6	7.73 ±0.010	1.744 ±0.094	> 15 hr	0.771± 0.04	36.60
7	F7	7.72 ±0.005	1.862 ±0.055	> 15 hr	0.832± 0.20	39.841
8	F8	7.81 ±0.057	1.790 ±0.022	> 15 hr	0.857± 0.15	43.388
9	F9	7.84 ±0.011	1.784±0.076	> 15 hr	0.868± 0.17	46.41

Buoyancy Study

The floating duration for all the formulations was found to be more than 15 h. All the formulations contained 1000 mg of $CaCO_3$ each, which was responsible for the floatation of the gel mass. It was concluded that 1 g of calcium carbonate was able to float the gel mass of all formulations having different densities due to various concentrations of polymers as indicated by the floating duration checked in 900 ml of simulated gastric fluid with 5% SLS in the dissolution basket at 37± 0.5°C.

Gel Density

For the formulations to float in the gastric region the density of the *in situ* gel should be less than 1.004 g/cm^3. The densities of all prepared gel formulations were found to be less than 1 g/cm^3. Thus, they were seen to be floating for a prolonged period of time. It was observed that the densities of the formulations were increasing gradually with the increase in the polymer concentration. There was increase in the weight of the gel due to more water absorption. The results are given in Table 2.

Water Uptake

The release of the drug from the matrix is based on imbibing of water and further diffusion of drug from the gel. At the end of 6 h it was found that the highest water uptake of 46.41% was observed for formulation F9 as it contains the highest concentration of both the polymers i.e. 1 g sodium alginate and 0.6 g of HPMC K100M which expands as it absorbs water and vice versa in case of F1 formulation which absorbed the least amount of water i.e. 22.44 % due to lowest concentration of the polymers which is tabulated in Table 2.

In vitro Drug Release

The effect of polymer concentration on the *in vitro* drug release was found to be influenced to a great extent. The polymer concentration was variable for all the 9 formulations, thus the response of the independent factor was shown. Sodium alginate is the gel forming polymer in the *in situ* gel, through the gel matrix the drug gradually diffuses out as the water enters the matrix. Also HPMC acts as the swelling agent which retards the drug release to a large extent. All the formulations showed more than 80% drug release for the dissolution studies, excluding F3, F6 and F9 formulation which consisted of highest concentration of HPMC which showed high swelling property leading to a retarded drug release. F9 gave the lowest drug release after 12 h due to highest concentration of both sodium alginate and HPMC. While, F1 showed more than 90% drug release within 8 h due to lowest concentration of both the polymers. Out of all the formulations F5, F6 showed the required slow drug release up to 12 h as depicted in Figure 6a and Figure 6b.

Release Kinetic Study Data

The results which were obtained by the *in vitro* drug release study were plotted in various mathematical models. The R^2 values were obtained which in turn gave the results about the best fit model for the release of the drug. According to the results obtained the best fit model found was Korsmeyer Peppas Model. This model explains the slow drug release from the polymeric matrix. The drug slowly diffuses out of the matrix as the buffer enters in the system. Based on the data obtained graph was plotted for the selected formula which is the optimized formula (F5) as tabulated in Table 3.

Statistical Analysis

The statistical analysis was carried out using Design Expert 12 software. The results for the various responses selected were put in the software. The results

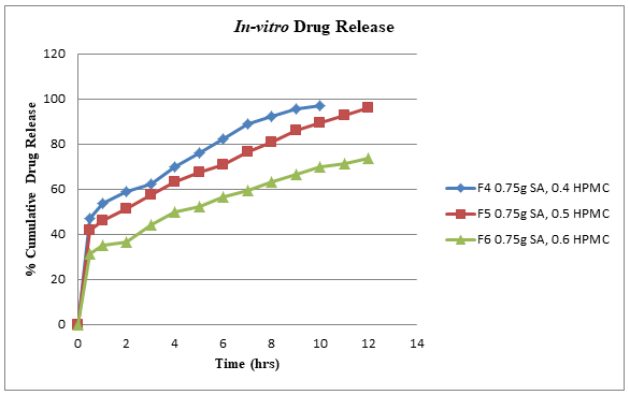

Figure 6 (a): *In vitro* drug release profile for formulated *in situ* gels of Ropinirole HCl F4, F5 and F6.

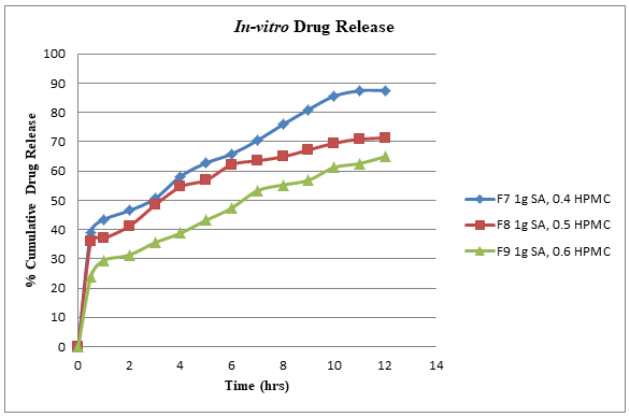

Figure 6 (b): *In vitro* drug release profile for formulated *in situ* gels of Ropinirole HCl F7, F8 and F9.

were obtained, showing that HPMC K100M retards the release of the drug more as compared to sodium alginate. Quadratic model was used to run the design, which gave the probable values i.e., *P*-value, *F*-value which explained the significance of the results. The *P*-value for all the dependent variables should be < 0.05, thus there is a significant difference in the values. The P-value obtained explained that the terms obtained in the model were significant. "Adeq. Presicion" value was more than 4 which explained the models were desirable. The response surface plots obtained for the responses explained that the increase in the concentration of sodium alginate and HPMC was significantly retarding the release of drug at various interval of time i.e. 1 h and 8 h and the viscosity was found to increase with the respect to concentration of polymers as Figure 7.

Optimization of the Formulation

A manual optimization was carried out on the basis of the results obtained by the evaluation parameters of the formulations. F5 was found to be the optimized formulation as the drug was found to be released up to 12 h as per the requirement. The optimization was carried out by setting constraints. The constraints were set according to the required limits for all the independent variables which are the concentration of sodium alginate, HPMC K100M and viscosity of the formulation. An overlay plot was obtained based on the inputs, the optimum values of the independent variables were obtained by adding flag to the center of the plot, which comprised of 771.51 mg of sodium alginate and 437.32 mg of HPMC K100M. The optimized formulation (OP5) generated using DX software was evaluated for drug content, viscosity, drug release and pH respectively. The results obtained using software was compared practically obtained F5 formulation and it was concluded that there was no significant difference between both the formulations.

Stability Studies

The samples were withdrawn at 7th, 15th and 30th day and evaluation of the sample was carried out. There were no changes observed regarding change in color and odour of the solution. Negligible variation was observed in terms of pH, drug content and viscosity. The drug release of the F5 formulation was increased by 1%. Thus, we can conclude that there were no significant stability issues in the solution; it was edible and stable for administration as shown in Table 4.

Table 3: Release Kinetics of Formulated *in situ* gels of Ropinirole HCl.

Batches	Zero Order	First Order	Higuchi Matrix	Korsmeyer Peppas		Hixon Crowell	Best Fit Model
	R^2	R^2	R^2	R^2	N	R^2	
F1	0.7528	0.9530	0.9633	0.9771	0.2821	0.9611	Peppas
F2	0.4828	0.9711	0.9455	0.9979	0.2806	0.9523	Peppas
F3	0.5079	0.9644	0.9504	0.9798	0.2840	0.9286	Peppas
F4	0.6547	0.9491	0.9681	0.9783	0.3080	0.9614	Peppas
F5	0.5361	0.9539	0.9547	0.9822	0.2896	0.9419	Peppas
F6	0.4374	0.8760	0.9425	0.9836	0.2764	0.9833	Peppas
F7	0.6272	0.9742	0.9613	0.9742	0.2900	0.9207	Peppas
F8	0.5975	0.9683	0.9623	0.9713	0.3036	0.9153	Peppas
F9	0.5318	0.8516	0.9585	0.9957	0.3073	0.9882	Peppas

Table 4: Stability Studies for optimized formulation F5 *in situ* solution.

Formulation Code	Colour			Drug content (mg/10ml)		
F5 (Optimized Formulation)	0 day	15th day	30th day	0 day	15th day	30th day
	No change	No change	No change	1.775	1.775	1.773
	Viscosity (cps)			pH		
	0 day	15th day	30th day	0 day	15th day	30th day
	140.7	139.1	138.4	7.66	7.65	7.61

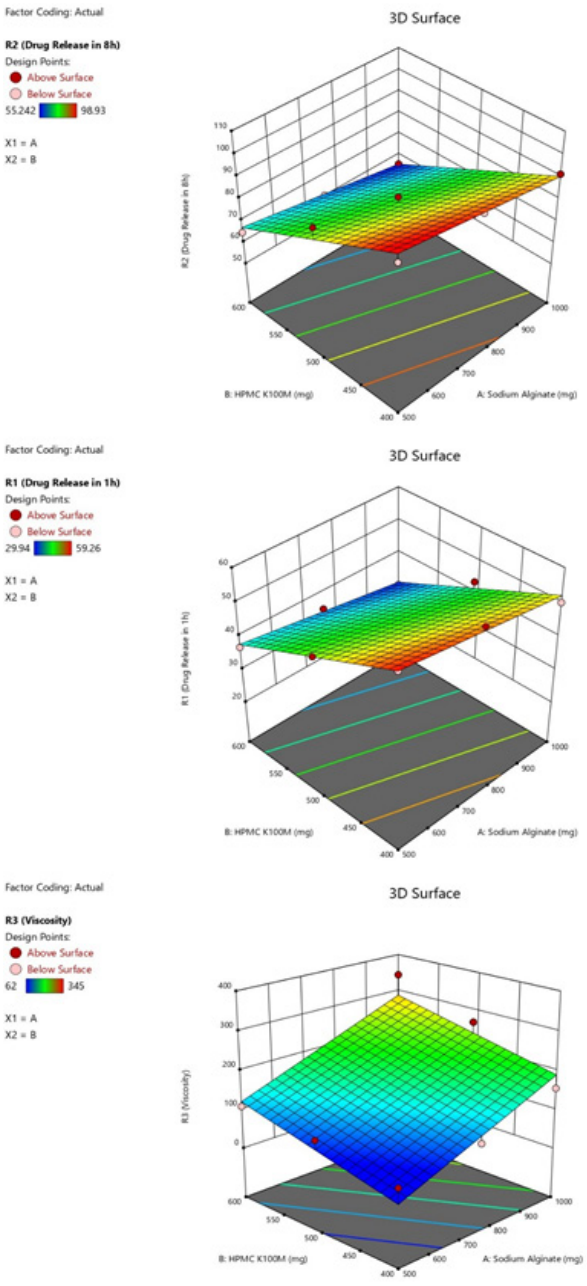

Figure 7: 3D graph representing the influence of HMPC K100M and Sodium alginate on the drug release at 1st h, 8th h and influence on Viscosity of solutions.

CONCLUSION

In this research work it was demonstrated that, as the concentration of the polymers were increased the drug release was decreasing with respect to their properties. Furthermore, F5 formulation consisting of 750 mg of SA and 500 mg of HPMC was selected as the optimized formulation due to its highest drug release of 96.10% up to 12 h. The statistical analysis carried out using Design Expert 12 Software explained that the results obtained on carrying out the evaluations were significant. In a nutshell, the prepared gastric floating *in situ* gel gave sustained release action upto 12 h, which could ultimately enhance the bioavailability of the drug and increase the patient compliance due to development of a once in a day dosage form in comparison to multidose of tablets.

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CONFLICT OF INTEREST

There was no kind of conflicts of interest regarding the publication of this research work.

ABBREVIATIONS

RH: Ropinirole Hydrochloride; **RLS:** Restless Leg Syndrome; **CDR:** Cumulative Drug Release.

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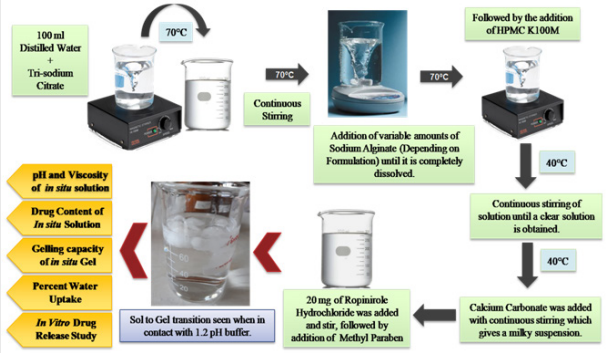
PICTORIAL ABSTRACT



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SUMMARY

- On getting a successful compatibility results for the drug and the polymers, the dosage form was developed using different concentration of sodium alginate as the gelling agent and HPMC K100M as the viscosity enhancing polymer which retards the release of the drug.
- The best suitable combination of both the polymers was selected, based on the results of the evaluation parameters and the statistical analysis (optimization) using Design Expert 12 (DX12) software.
- F5 was found to be the optimized formulation as per the results of the evaluations carried out. The max drug release was found in case of F5 i.e. for 12 h upto 96%.
- All the formulations were evaluated on the basis of the variables set and the responses to it based on the DX12 software.
- The dependent variables were the varying concentration of polymer sodium alginate from lower to higher (500 to 1000 mg) and HPMC K100M (400 to 600 mg). Depending upon the variables the responses were % drug release for 1st hour, % drug release for 8th hour and viscosity of the solutions (F1 to F9).
- The stability study for the optimized formulation was carried out and it was found out that there was no colour changes seen on visual analysis of the gel over a time period of 0, 15 and 30 days. Moreover, there was little or no variation in the drug content, viscosity and pH of the formulated *in situ* solution after 0, 15 and 30 days of stability analysis.

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