

## FORMULATION AND EVALUATION OF ORAL SUSTAINED *IN SITU* GELLING SYSTEM OF ROXATIDINE

Mohammed Gulzar Ahmed\*, Chirag Kapoor and Sanjana Adinarayana

Yenepoya Pharmacy College &  
Research Centre, Yenepoya  
University, Deralakatte 575018  
India

Submitted:06-05-2017

Revised:17-06-2017

Accepted:22-07-2017

\*Corresponding author  
Mohammed Gulzar Ahmed

Email:  
mohammedgulzar1@gmail.com

### ABSTRACT

Gel dosage forms are successfully used as drug delivery systems to control drug release and protect the medicaments from a hostile environment. The main objective of this present work is to formulate and evaluate *in situ* gels of roxatidine for the treatment of peptic ulcer. This system utilizes polymers that exhibit sol-to-gel phase transition due to change in specific physico-chemical parameters. In the present work *in situ* gels have been developed by using gellan gum and sodium alginate based on the concept of ion activated systems. Sol-to-gel transformation occurred in the presence of monovalent/divalent cations. Formulations were evaluated for clarity, drug content, *in vitro* gelling capacity, determination of pH, *in situ* release study, viscosity, gel strength, *ex vivo* gelation and stability study. All the results found to be satisfactory. The experimental part showed that viscosity of sols and gel strength was increased with increase in the concentration of polymers, also drug release gets sustaining. The formulations were therapeutically efficacious, sterile and provided sustained release of the drug over a period of time. These results demonstrated that the developed system is an alternative to conventional drug delivery systems and can improve patient compliance.

**Key words:** *In situ* gels, roxatidine, peptic ulcer, *in vitro*, viscosity

### INTRODUCTION

Over the past 30 years greater attention has been focused on the development of controlled and sustained drug delivery systems. The goal in designing these systems is to reduce the frequency of dosing or to increase the effectiveness of the drug by localization at the site of the action. Amongst the extensive research has been carried in designing of polymeric drug delivery systems, the development of *in situ* gel systems has received considerable attention over the past few years. These systems are capable of releasing the drug in a sustained manner maintaining relatively constant plasma profiles and they are liquid at room temperature but undergo gelation when in contact with body fluids or change in pH. This is a characteristic property of temperature dependent, pH dependent and cation induced gelation. *In situ* gel forming drug delivery is a type of mucoadhesive drug delivery system. In contrast to very strong gels, they can be easily applied or used in liquid form to the site of

drug absorption, where, they swell to form a strong gel that is capable of prolonging the residence time of the active substance. Both natural and synthetic polymers can be used for the production of *in situ* gels (Patel *et al.*, 2012; Pallavi *et al.*, 2016).

A peptic ulcer is a lesion in the mucosa of the stomach or duodenum in which acid and pepsin play a major role, the term is often used to encompass any gastric or duodenal ulceration. Peptic ulcers constitute a major problem in hyperacidity patients, which is due to inflammation of the stomach or duodenal mucosal lining of the GIT.

Roxatidine, a competitive histamine H<sub>2</sub>-receptor antagonist, is used to treat gastrointestinal disorders such as gastric or duodenal ulcers, gastro esophageal reflux disease, and pathological hyper secretory conditions. Local availability of H<sub>2</sub>-antagonists in the stomach has a greater clinical significance especially in the treatment of peptic ulcers (Tripathi *et al.*, 2013, Ramana *et al.*, 2016).

In the present work, *in situ* gelling liquid formulation for sustained delivery of roxatidine is done because roxatidine is available in the market as tablets, capsules and in injection form. The formulation is prepared by using gellan gum and sodium alginate (different concentration), sodium citrate and calcium carbonate (source of cations) and roxatidine for the treatment of peptic ulcer disease.

## MATERIALS AND METHODS

### Materials and reagents

Roxatidine acetate HCl was obtained from Win-Win chemical Co. Limited, China. Gellan gum was provided by Hi Media laboratories Ltd, Mumbai and sodium alginate was obtained from S.D. Fine-Chem limited, Mumbai. All the other materials used were of analytical grade.

### Preparation of *in situ* gelling systems

Polymer solutions (gellan gum and sodium alginate) of various concentrations were prepared by adding to deionised water containing 0.17% w/v sodium citrate and heated to 90°C while stirring. After cooling to below 40°C appropriate amounts of calcium chloride (0.05% w/v), drug solution (roxatidine) and preservative (benzyl alcohol) were added to the polymer solution. Make up the volume up to 20mL with water. The mixture was stirred by using a magnetic stirrer to ensure thorough mixing (Table I) (Harish *et al.*, 2009; Divyesh *et al.*, 2016).

### Evaluation of gels

#### FT-IR Absorption Spectrum

FT-IR spectroscopy was carried out to check the compatibility between drug and polymer. The FT-IR spectra of the drug with polymers were compared with the standard FT-IR spectrum of the pure drug (Roshan *et al.*, 2015).

#### Clarity test

The clarity of formulated solutions was determined by visual inspection under black and white background. Black particles can be identified under white background and white particles can be identified under black background (Nirmal *et al.*, 2010).

### pH measurement

The pH was measured in each of the solutions of sodium alginate and gellan gum based *in situ* solutions, using a calibrated digital pH meter at 27°C. The measurements of pH of each data were in triplicate (Hareesh *et al.*, 2012).

### Measurement of viscosity of sols

Viscosity determinations for the prepared formulations were carried out on a Brook-field digital viscometer using spindle No 4. The viscosity of *in situ* gelling solutions was measured at different angular velocities at a temperature of 37°C. A typical run comprised changing of the angular velocity from 0.0 to 100 rpm. The averages of three readings were used to calculate the viscosity (Hareesh *et al.*, 2012).

### Gelling capacity study

The gelling capacity was determined by placing a drop of the system in a vial containing 2mL of 0.1N HCl (pH 1.2) freshly prepared and equilibrated at 37°C and visually assessing the gel formation and noting the time for gelation and the time taken for the gel formed to dissolve. Different grades were allotted as per the gel integrity, weight and rate of formation of a gel with respect to time (Patel *et al.*, 2012).

### Spreadability

To determine the Spreadability of the gel, approximately 1g of the gel was placed at the center of the glass plate (20×20cm). This glass plate was covered with another glass plate of the same size. Next, the weight of 1000g was carefully applied on the upper side of the plate; as a result, the gel was spread out in between the plates. After one minute, the weight was removed and the diameter of the spread area (cm) was measured. This determination was carried out in triplicate (Patel *et al.*, 2012).

### Determination of gel strength

The method by which the properties of the polymeric system may be conveniently determined is texture profile analysis. A TA-XT2 Texture analyzer is used. The experiment was done by placing the gels in standard Beaker below an aluminum probe of 7.6cm at room temperature. The instrument was set to the

Table I Formulation of *in situ* gel of roxatidine with various polymers at different concentrations.

Formulation code	G <sub>1</sub>	G <sub>2</sub>	G <sub>3</sub>	G <sub>4</sub>	S <sub>1</sub>	S <sub>2</sub>	S <sub>3</sub>	S <sub>4</sub>	S <sub>5</sub>
Gellan gum (% w/v)	0.1	0.2	0.3	0.4	-	-	-	-	-
Sodium alginate (% w/v)	-	-	-	-	0.2	0.4	0.6	0.8	1.0
Sodium citrate (% w/v)	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17
Calcium chloride(% w/v)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Preservative (1.0% m/m)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Roxatidine(mg)	300	300	300	300	300	300	300	300	300
Water	Qs	Qs	qs	qs	qs	Qs	qs	qs	qs

‘gelling strength test’ mode with a test-speed of 1.0mm/s. An acquisition rate of 50 points per seconds and a trigger force of 5g were selected. The force required to penetrate the gel was measured as gel strength in terms of grams (Hareesh *et al.*, 2012).

**Determination of drug content**

Accurately 5mL of the suspension was taken in a volumetric flask, dissolved in a small quantity of 0.1N HCl. After the solutions were completely dissolved the volume were made up to 100mL with 0.1N HCl. From this solution 1mL was taken and diluted to 10mL respectively and then drug content was determined by measuring the absorbance at 275nm by UV spectrophotometer (Patel *et al.*, 2012).

**In situ release studies**

Drug release studies from the *in-situ* gel were carried out by using a cellophane membrane. Apparatus was designed as per the literature; a glass tube had a length of 10.5cm and a diameter of 2.1cm. The lower base was tied with cellophane membrane and added a known quantity of *in situ* gel and this was placed in a beaker containing 100mL of phosphate buffer pH 1.2 as diffusion medium which is maintained at 37°C with 50rpm. Samples (5mL) were withdrawn at different time intervals from the reservoir till the gel was completely eroded (3h).The cumulative percent drug release was determined by spectrophotometric method (Hareesh *et al.*, 2012).

**Ex vivo gelation study**

*Ex vivo* gelation study was performed to check *in situ* gel formation in mice. Animals

(24h fasted mice) were divided in to two groups each contain 6 animals. Group -1: served as control and Group -2: served as treated.

In group-1 animal was sacrificed and stomach was removed, cut along with the greater curvature. In group-2 *in situ* gel formulation was administered orally and after the 3h animal was sacrificed. Stomach was removed outside and cut along the greater curvature to observe weather gel forms or not (Patel *et al.*, 2012).

**Stability study**

Prepared *in situ* gel formulation of roxatidine was stored in glass containers (well stoppered) to perform short-term stability studies for two months. Stability of the *in situ* gel formulation of roxatidine was monitored at room temperature (25±1°C). Periodically samples were removed and evaluated for pH, viscosity, drug content and *in vitro* release (Patel *et al.*, 2012).

**RESULTS AND DISCUSSIONS**

**FT-IR Spectrum**

All the characteristic peaks of roxatidine were present in the spectrum of drug and polymer mixture, indicating compatibility between drug and polymers. The spectrum confirmed that there is no significant change in chemical integrity of the drug.

**Clarity test**

Clarity test for the prepared formulations has done by visual inspection under black and white background. There was no evidence of contamination, the entire formulations pass clarity test (Table II).

Table II. Characteristics of various *in situ* gel formulations

Formulation code	Clarity test	pH	Spreadability g.cm/s	Drug content (%)	Gelling capacity
G1	Passes	7.1	12± 0.13	94.96±0.002	+
G2	Passes	6.9	09±0.03	95.65±0.013	++
G3	Passes	6.8	11±0.15	98.08±0.045	+++
G4	Passes	6.7	13±0.02	92.26±0.056	+++
S1	Passes	7.2	07±0.03	96.66±0.086	+
S2	Passes	7.1	12±0.01	95.14±0.074	+
S3	Passes	6.9	17±0.03	94.10±0.045	++
S4	Passes	6.8	12±0.16	92.29±0.046	+++
S5	Passes	6.6	12±0.14	91.49±0.089	+++

+ -Good, ++ - average, +++ -excellent

Table III. Release exponent values and rate constant values for different formulations.

Formulation code	Kinetic models				
	Zero order	First order	Higuchi	Korsmeyer <i>et al.</i>	
	R <sup>2</sup>	R <sup>2</sup>	R <sup>2</sup>	N	R <sup>2</sup>
<b>G1</b>	0.912	0.902	0.975	0.290	0.951
<b>G2</b>	0.934	0.923	0.988	0.451	0.939
<b>G3</b>	0.919	0.907	0.978	0.493	0.944
<b>G4</b>	0.923	0.911	0.976	0.893	0.950
<b>S1</b>	0.914	0.903	0.971	0.281	0.951
<b>S2</b>	0.920	0.909	0.959	0.330	0.923
<b>S3</b>	0.939	0.925	0.965	0.390	0.914
<b>S4</b>	0.924	0.915	0.974	0.431	0.922
<b>S5</b>	0.959	0.945	0.993	0.499	0.945

### Determination of pH

The pH of *in situ* gels was determined using a calibrated pH meter. The readings were taken for average of 3 samples (Table II). Aqueous gellan gum and sodium alginate sols exhibited pH values in the range of 6.6 to 7.2 at 27°C.

### Viscosity of the *in situ* sols

The viscosity of *in situ* sols was determined by Brookfield viscometer (Table III). Among all formulations, S1 (sodium alginate 0.2%) shows least viscosity (8.56 Pa·s) and G4 was more (15.98 Pa·s). The formulations S2 and G2 were nearly same (10.54 and 11.00 Pa·s respectively). This says the increase in polymer concentration causes an increase in viscosity of the sols.

### *In vitro* gelling capacity

It was found that the gel intensity was increased when the concentration of polymers

was increased. Experimental part (Table II) have shown that the formulation G3, G4, S4, S5 were satisfactory to cause gelation.

### Gel strength

The gel strength of *in situ* gels was determined by A TA-XT2 Texture analyzer (Table 2). Among all formulations, S1 (Sodium alginate 0.2%) shows least gel strength (2.4 g/s) and G4 was more (7.9 g/s). This says the increase in polymer concentration causes an increase in gel strength.

### Drug content

Accurately 5mL of the suspension was taken in a volumetric flask, dissolved in a small quantity of 0.1N HCL. After the solutions were completely dissolved the volume were made up to 100mL with 0.1N HCL. From this solution 1mL was taken and diluted to 10mL respectively and then drug content was measured at 275nm

Table IV. Stability study

Time Period for sampling	pH	Viscosity (Pa.s)	Drug content (%)	% Drug release at 180 min.
Initial	6.7	15.98	92.26± 0.056	76.35± 0.087
After 1Month	6.7	15.99	92.24± 0.058	74.68± 0.063
After 2Month	6.7	16.01	92.22± 0.032	73.43± 0.048

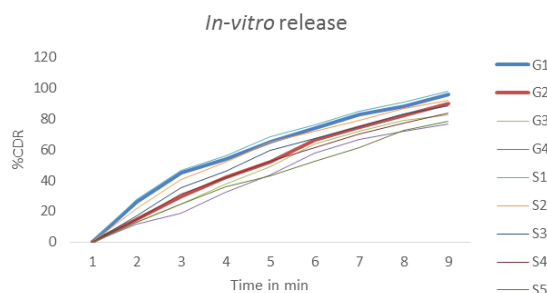


Figure 1. Comparative drug release profile of the formulations (G1, G2, G3, G4, S1, S2, S3, S4 and S5)

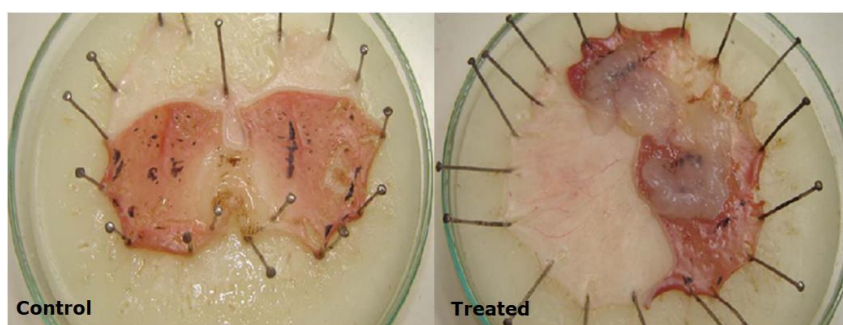


Figure 2. *Ex vivo* study in mice.

by UV spectrophotometer. Drug content of all formulations was found between 91.49 to 98.08 % W/W (Table II). Further it was observed that the drug content values didn't obtain 100%, this may be due to the embedment of the drug in the polymer, hence not came in solution.

#### **In situ release studies**

All the prepared formulation was subjected to *in situ* release studies by using phosphate buffer of pH 1.2 in the diffusion medium for 180min. The formulations from G1-G4 containing a gellangum concentration of (0.1-0.4% W/V) showed the drug released up to 91.56% and the formulation containing sodium alginate as a polymer of concentration (0.2-1.0%W/V) has shown a maximum release of 97.38%. Among the nine formulations the formulation S1 containing (0.2%w/v) of

sodium alginate has shown the of drug released in a sustained manner up to the end 180min when compared to other formulation.

#### **Release kinetics**

The examination of the correlation coefficient 'r' indicated that the drug release followed diffusion controlled mechanism from the *in situ* gels (Table III), as the values of 'r' for first order (ranged from 0.902 to 0.945) found to be less in comparison to zero order (ranged from 0.912 to 0.959) and Higuchi's square root of time (ranged from 0.959 to 0.993). It was understood to be predominant zero order release pattern. Further, to understand the drug release mechanism, the data were fitted into Peppas exponential model  $M^t/M^\infty = Kt^n$ , where  $M^t/M^\infty$  is the fraction of drug released after time 't' and 'K' is kinetic constant and 'n' is

release exponent which characterizes the drug transport mechanism. The values 'n' was in the range of 0.281 to 0.893. The formulations G1, S1, S2, S3 and S4 were following fickian release mechanism ('n' values are less than 0.45), G2, G3 and S5 are indicating non-fickian release mechanism ('n' values are between 0.45-0.89) and G4 is following super II release ('n' values are more than 0.89).

#### **Ex vivo gelation study**

Results of *ex vivo* gelation study showed that when the group 2 animals are sacrificed after 3h the gel formed in the stomach was observed. It was observed that formed gel remained on a mucosal layer of the stomach to release the drug in a controlled manner (Figure 1 and 2).

#### **Stability study**

Short term stability study of *in situ* gel of roxatidine was carried out for 2 months at normal room temperature and humidity condition (Table IV).

#### **CONCLUSION**

In the present study *in situ* gel of roxatidine were prepared by using gellangum and sodium alginate of different concentration from (0.1-0.4% W/V) and (0.2-1.0% W/V) as the gel base. All the prepared formulation was evaluated in order to determine the suitability for the formulation. And all the prepared formulation provides intimate contact between the drug and the absorbing tissue which may result in high drug concentration in the local area. Based upon obtained results it can be concluded that prepared formulation is suitable for the treatment of peptic ulcer. Out of this nine-different formulation the formulation containing 0.2% W/V of sodium alginate is considered as an optimized formulation based on the evaluation parameter. The formulation S1 containing (0.2% W/V) has shown gelation time within 4min and pH of 1.2 which is suitable for the treatment of peptic ulcer. The *in vitro* release of 97.38% of drug release up to an end of 180min which provides a controlled manner of drug release and prolong the residency time. Thus, it can be concluded that the prepared formulation gives a better patient

compliance with increased bioavailability which is suitable for the treatment of peptic ulcer.

#### **ACKNOWLEDGEMENTS**

Authors were grateful to the Principal and Department of Pharmaceutics, Sri Adichunchanagiri College of Pharmacy, B.G Nagara for providing necessary facilities to carry out this research work.

#### **REFERENCES**

- Divyesh HS., Hitesh DD., Pragna S., Alkesh KB., 2016. Formulation development and evaluation of a gastroretentive *In situ* oral gel of cefuroxime axetil. *J Yun Pharm*. 8(4):324-329.
- Hareesh BK., Gulzar MA., Narayana CR., 2012. Development and evaluation of *in situ* gels of Moxifloxacin for the treatment of Periodontitis. *Indonesian J Pharm*. 23(3):141-146.
- Harish NM., Prabhu P., Charyulu RN., Gulzar MA., Subrahmanyam EVS., 2009. Formulation and evaluation of *in situ* gels containing clotrimazole for oral candidiasis. *Int J Pharm Sci*. 10(8):421-27. <http://home.intekom.com/pharm/hmr/roxit.html>
- Pallavi C., Pratibha., Gnanrajan G., Preethi K., 2016. *In situ* gel: A review. *Ind J Pharm Biol Res*. 4(2): 11-19
- Patel NA., Mahesh KS., Ravi K., Senthil A., Viral GP., 2012. Development and evaluation of oral gastro-retentive *in situ* gel of famotidine. *Indo-Global Res J Pharm Sci*. 2(1):238-43.
- Ramana BV., Jalalu SS., Swapna C., *et al.*, 2016. Design and development of floating *in situ* gel of pantoprazole. *Scholar Res Lib*. 8(8): 239-249.
- Roshan RM., Vaishali G., Gupta S., 2015. Novel study in sustained release drug delivery system: A Review. *Int J Pharm Med Res*. 3(2): 204-215.
- Tripathi KD., 2013. Drugs for peptic ulcer in essentials of medical pharmacology. 7th edn. New Delhi: *Jaypee Brothers Medical Publishers*. 585-91.