**Bulletin of Environment, Pharmacology and Life Sciences**
Bull. Env. Pharmacol. Life Sci., Vol 10 [9] August 2021 : 89-94

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

**ORIGINAL ARTICLE** **OPEN ACCESS**

# Development and Characterization of Rosuvastatin SMEDDS Loaded in situ gel for gastric Retention

**Chatlapelli Kishore* 1 Bhaskar Reddy K 2 Suggala Venkata Satyanarayana [3]**
*1.Research Scholar, Jawaharlal Nehru Technological University, Anantapur, Ananthapuramu-515002, Andhra
Pradesh, India.
2. Department of Pharmaceutics, Sri Venkateswara college of pharmacy, Centre for Pharmaceutical Nanotechnology, RVS Nagar, Tirupati road, Chittoor-517127, Andhra Pradesh, India.
3. Department of Chemical Engineering, Jawaharlal Nehru Technological University Anantapur, Ananthapuramu-
515002, Andhra Pradesh, India.
Corresponding Author: Name: Bhaskar Reddy K, E Mail: bhaskurra@gmail.com.

**ABSTRACT**

*Rosuvastatin used in treatment of hyperlipidemia. It has very short biological half life and it undergoes extensive first pass metabolism. The aim of present work is formulation and characterization of Gastroretentive In situ gel based system of Rosuvastatin. Different polymers like gellan gum, sodium alginate and HPMC were screened at different concentration to arrive at optimized formulation. Formulations were screened based on in vitro gelling time and behavior and drug release. All the batches were evaluated for pH, viscosity, floating lag time and total floating time, water uptake The optimized batch (F8) followed the release as per Korsemeyer-Peppas model and drug release from the formulation can be best explained by the Higuchi model due to highest R-square value among all the models. Release kinetics study showed that the diffusion mechanism is anomalous and model which was followed by Higuchi model. Thus, In-situ gelling system of Rosuvastatin was successfully developed by ionic cross linking method that could form gel instantaneously when in contact with gastric fluid and remains in stomach for more than 12 h.*

***KEYWORDS:*** *Rosuvastatin, Gastroretentive, In situ gel.*

Received 11.06.2021 Revised 01.08.2021 Accepted 22.08.2021

## INTRODUCTION

Recent scientific and patent literature reveals increased interest in novel dosage forms that can be retained in the stomach for a prolonged and predictable period of time. One of the most feasible approaches is to control the gastric residence time using gastro retentive dosage forms (GRDDS) that can provide newer therapeutic options. GRDDS can improve controlled delivery of drugs by continuously releasing the drug for a prolonged period of time before it reaches its absorption site, thus ensuring its optimal bioavailability [1, 2]. Now a days *insitu* gel drug delivery has become the standard in modern Pharmaceutical design this interest has been sparked by the advantages shown by *in situ* forming polymeric delivery systems such as ease of administration and reduced frequency of administration, improved patient compliance and comfort. The system basically utilizes polymers which undergo transformation from solution to gel like consistency due to change in their physicochemical Properties.

The formation of gels depends on factors like temperature modulation, pH change, presence of ions and ultra violet irradiation, from which the drug gets released in a sustained and controlled manner. Various biodegradable polymers that are used for the formulation of in situ gels include gellan gum, alginic acid, xyloglucan, pectin, chitosan, poly (DLlactic acid), poly (DL-lactide-co-glycolide) and poly-caprolactone etc[1]. Gastro-retentive *in situ* gel forming system have provided a suitable way of providing the controlled drug delivery within stomach where an environment specific gel forming solution, on conversion to gel, floats on the surface of the gastric fluids. This low density gel formation not only provide the much desired gastro retention to prolong the contact time, but also produce the continuous and slow drug release.

Rosuvastatin is a crystalline compound and is practically insoluble in water and hence poorly absorbed from the GI tract with a oral bioavailability of 5% [3, 4]. It is a potent and specific inhibitor of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG CoA) reductase [5, 6], which catalyzes the reduction of HMG CoA to mevalonate. Thus, Rosuvastatin arrests a key step for cholesterol biosynthesis in the liver and is widely used in the treatment of hypercholesterolemia and dyslipidemia as an adjunct to diet. After oral administration, Rosuvastatin is metabolized to its β-dihydroxy acid form (Rosuvastatin acid) by the cytochrome-3A system in the liver, where it inhibits the rate-limiting step in cholesterol biosynthesis. Being a BCS Class II drug, it often shows dissolution rate-limited oral absorption and high variability in pharmacological effects. Therefore, improvement in its solubility and dissolution rate may lead to enhancement in bioavailability [7, 8]. Rosuvastatin has a narrow absorption window and mainly absorbed from proximal areas of GIT. The gastroretentive drug delivery system can be retained in the stomacth and assist in improving the oral sustained delivery of drugs that have absorption window in a particular region of the GIT. This system will help continuously releasing the system before it reaches absorption window, thus ensuring optimal bioavailability. Hence to improve the oral bioavailability of Rosuvastatin best choice will be combination of solubility enhancement and gastroretention [9-11].

## MATERIAL AND METHODS

In situ gel forming Polymer (i.e. Gellan gum/sodium alginate/HPMC K 15M/HPMC K100M) solution of different concentration was prepared in deionized water containing sodium citrate using magnetic stirrer. Polymeric solution was heated at 60°C to form uniform dispersion of polymer with stirring on magnetic stirrer. After cooling below 30°C Rosuvastatin was incorporated in above mixture. Solution of gas forming agent was separately made in minimum quantity of deioniszd water with continuous stirring, aspartame as sweetening was incorporated in this solution. gas forming agent containing solution was added to the polymeric solution. The resulting in situ gel solution was finally stored in amber colored narrow mouth bottles until further use [12].

Gellan gum is used as main in situ gel forming polymer. Different concentrations were selected to observe the in situ gel forming ability and retarding potential of Gellan gum on drug release which will help to decide the quantity and need of any other polymer

**Table 1: Composition of Rosuvastatin stomach specific *insitu* gel**

| Ingredients (mg) | B1 | B2 | B3 | B4 | B5 | B6 | B7 | B8 |
|---|---|---|---|---|---|---|---|---|
| Rosuvastatin | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Sodium citrate | 125 | 125 | 125 | 125 | 125 | 125 | 125 | 125 |
| Gellan gum | 200 | 250 | 300 | 100 | 150 | 100 | 150 | 200 |
| Sodium alginate | -- | -- | -- | 100 | 150 | -- | -- | -- |
| HPMC K100M | -- | -- | -- | -- | -- | 100 | 150 | 150 |
| Calcium carbonate | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| Aspartame | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. |
| Distilled water (q.s. to 50ml) | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. |

### Physical appearance, pH measurement and gel strength:

All the prepared in situ gel solutions of were checked for their clarity and time required for their gel formation. The pH of the prepared formulations was measured by digital pH meter.

### Measurement of viscosity:

Viscosity of the dispersion was determined using a Brookfield digital viscometer. The samples (200 mL) were sheared at a rate of 100 rpm/min using spindle number 2 at room temperature. Viscosity measurement for each sample was done in triplicate, with each measurement taking approximately 30 seconds.

### Determination of Density (wt/mL):

For the purpose of density measurement, calibration of density bottle was carried out as per I.P. It was done with boiled/ cooled water at 25°C. Density of water at 25°C is 0.99602 as per I.P. standard. From weight and density of water capacity of pycnometer was calculated. wt/ml was determined by dividing the weight in gm suspension by capacity expressed in ml of the pycnometer at 25°C.

**Water uptake:**

In the present study a simple method has been adopted to determine the water uptake by the gel. The *in situ* gel formed in 40 mL of 0.1N HCl (pH 1.2) was used for this study. The gel was separated from the buffer solution and blotted out with tissue paper; all the formulations were done in the same way and weighed. It is considered as an initial weight of the gel. To this gel 10mL of distilled water was added. After 30 minutes decanted the water and reweighed the gel. It was considered as final weight of the gel. Following formula was used to calculate water uptake [13, 14].

$$\%\text{water uptake} = \frac{\text{Final wt} - \text{Initial wt}}{\text{Initial wt}} \times 100$$

***In vitro* floating study:**

Determination of floating lag time and duration of floating was determined by visual inspection method using dissolution test apparatus (paddle type) containing 900 ml of 0.1N HCl at room temperature.

**Drug content**

Accurately weighed *In situ* gel equivalent to 10mg of Rosuvastatin was placed in 50mL volumetric flask and volume was made up with methanol, followed by sonication in bath sonicator for 15-20min to extract and solublize the Rosuvastatin. The methonolic extract was filtered through whatman filter paper and concentration was determined by inhouse developed and validated stability indicating HPLC method using Zorbax Eclipse® XDB- C18 column using acetonitrile : phosphate buffer pH 3.2(9:1) as mobile phase. Experiment was performed in triplicate.

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

The dissolution studies were performed in triplicate using a type II (paddle method) dissolution apparatus. The dissolution medium used was 900 ml of 0.1 N HCl (pH 1.2), maintained at 37ºC. The stirring rate was adjusted to 50 rpm. This speed was believed to simulate the *in vivo* existing mild agitation and was slow enough to avoid the breaking of gelled formulation. At predetermined time intervals, 10 mL samples were withdrawn and replaced by fresh dissolution medium, filtered through whatman filter paper, diluted, and assayed at maximum absorbance at 243 nm using UV-Visible Spectrophotometer .

**Release kinetic study:**

Drug release data of the optimized batch was fitted into different release kinetic model like Zero-order, First-order, Higuchi, Hixson-Crowell and Korsemeyer-Peppas. Results of release kinetic study are shown in the Table 3.

The best fitted model was selected on the basis of relatively high R-square values.

**Stability studies:**

The batch was selected as the final optimized batch with desired properties, this batch was selected for accelerated stability studies according to the ICH guideline. The accelerated stability studies were carried out by keeping the optimized batch at 40°C/75%RH for 6 Month. The selected formulations were packed in amber-colored glass bottles, which were tightly secured and capped. At predetermined intervals samples were evaluated for their physical appearance, drug content, drug release, and drug excipients compatibility at specified intervals of time (before and after stability period).

***In vivo* gastroretention study:**

Placebo formulation containing barium sulphate as radio opaque agent was used to determine the behavior in upper GI tract in the fed state. In the study, total 3 New Zealand rabbits were used. Rabbits were kept overnight in fasting conditions. Insitu gel containing barium sulphate were administered to each rabbit orally followed by 15mL of drinking water and food as required. X-ray images were taken at 0, 6 and 12hours time interval.

**RESULT AND DISCUSSION**

Initial batches (B1, B2, B3) taken with gellan gum as the insitu gelling agent showed the burst release and sustained effect only till 4 hr. Next set of batch (B4, B5) was taken with a combination on gellan gum and sodium alginate as the in situ gelling agent in various proportions. With incorporation of sodium alginate drug release was sustained up to 8 hrs still problem of burst release was observed (approximately 49% in 1 hr). Next set of batches (B6, B7, B8) were prepared by using gellan gum and HPMC K100M as the polymers. With HPMC K100M burst effect was minimized with sustained effect up to 9hrs. The reason for reduction in burst effect and improvement in sustained release can be because higher viscosity of HPMC K100M. With all the polymers it was observed that at lower concentration of polymer, no gelling was observed and at higher concentrations very stiff gel was obtained. Hence concentration of in situ gelling polymer should be optimum to get proper gelling. Parameters like pH, viscosity, floating lag time and total

floating time, water uptake of all the formulations were in the acceptable range. Assay of all the formulation was in the range of 90-95%. Considering the sustained effect B8 was selected as the final batch for further evaluation.

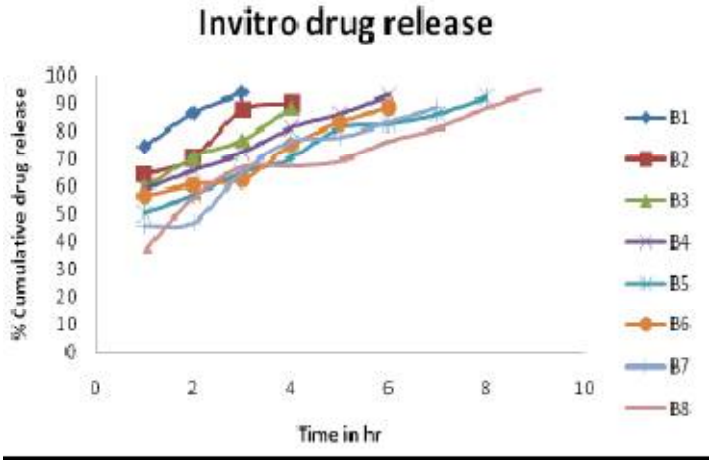



**Figure 1: Cumulative drug release of test batches**

**Table 2: Evaluation of Rosuvastatin stomach specific *insitu* gel**

| Parameters | B1 | B2 | B3 | B4 | B5 | B6 | B7 | B8 |
|---|---|---|---|---|---|---|---|---|
| **Sol to gel formation** | **low gel strength after addition of 0.1N HCl** | **optimum gel strength after addition of 0.1N HCl** | **Gel before addition of 0.1N HCl** | **low gel strength after addition of 0.1N HCl** | **optimum gel strength after addition of 0.1N HCl** | **low gel strength after addition of 0.1N HCl** | **optimum gel strength after addition of 0.1N HCl** | **optimum gel strength after addition of 0.1N HCl** |
| pH of formulation | 7.3±0.21 | 7.0±0.24 | 7.2±0.22 | 7.1±0.21 | 7.5±0.21 | 7.2±0.23 | 7.5±0.21 | 7.3±0.19 |
| Viscosity (cps) | 224±1.14 | 214±1.19 | 265±1.27 | 180±1.16 | 224±1.18 | 184±1.15 | 205±1.19 | 240±1.17 |
| Density (wt/ml) | 0.9867±0.11 | 0.9932±0.09 | 0.9912±0.1 | 0.9856±0.09 | 0.8919±0.08 | 0.9618±0.08 | 0.9545±0.09 | 0.9489±0.09 |
| Floating lag time | 1-2min | 1-2min | 1-2min | 1-2min | 1-2min | 1-2min | 1-2min | 1-2min |
| Duration of floating | >12hr | >12hr | >12hr | >12hr | >12hr | >12hr | >12hr | >12hr |
| Assay | 94.85±0.16 | 92.56±0.19 | 94.87±0.20 | 93.23±0.16 | 94.36±0.18 | 90.58±0.17 | 94.28±0.16 | 94.5±0.16 |

**Figure 2: Sol to gel conversion of optimized batch**

## Release kinetic study:

Drug release data of the optimized batch was fitted into different release kinetic model like Zero-order, First-order, Higuchi, Hixson-Crowell and Korsemeyer-Peppas. Results of release kinetic study are shown in the Table 2.

The best fitted model was selected on the basis of relatively high R-square values. It has diffusion exponent (n) values between 0.5 to 0.85 which indicates that it follows non- Fickian diffusion (Anomalous diffusion). The optimized batch followed the release as per Korsemeyer-Peppas model and drug release from the formulation can be best explained by the Higuchi model due to highest R-square value among all the models.

**Table 3: Results of kinetic model fitting**

| Batch code | R-Square | | | | | | |
|---|---|---|---|---|---|---|---|
| | Higuchi | Zero Order | Korsemeyer-Peppas | | | Hixon Crowell | First Order |
| | | | R Square | n | K | | |
| B8 | 0.9982 | 0.9943 | 0.9988 | 0.5318 | 0.2854 | 0.994 | 0.9290 |

n=Release Exponent, k-kinetic constant.

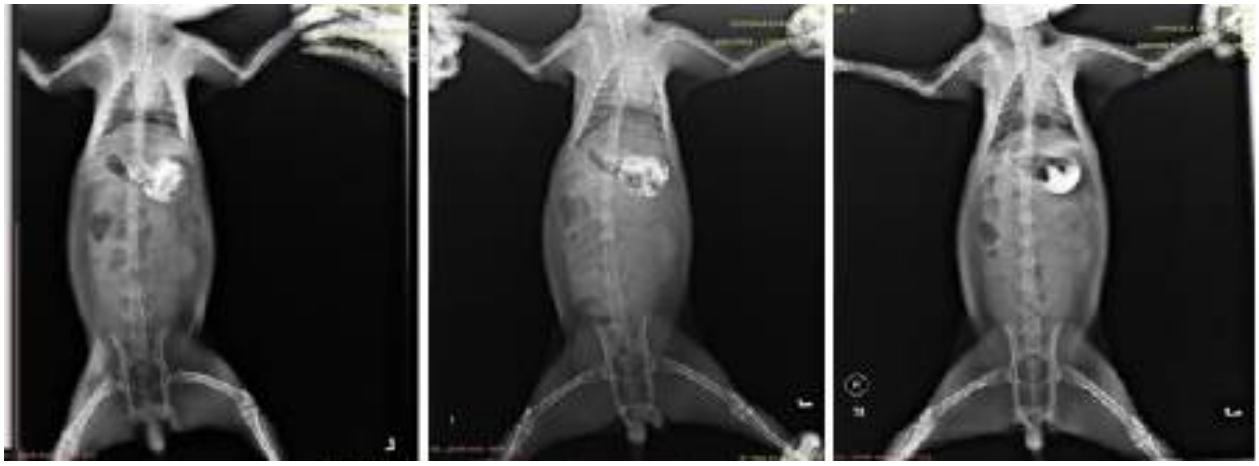
**Stability study:**

Physical characteristics and Dissolution remained unchanged after 6 months of accelerated conditions suggesting that insitu gel of Rosuvastatin is stable confirming stability of developed formulation.

***In vivo* gastroretention Study:**

Insitu gel floated immediately after administration with a floating lag time of approximately 1 to 2 minutes, from the x-ray images it is confirmed that the formulation remained in the stomach for up to 12hrs.

| Parameter | Initial | 1Month | 2Month | 3Month | 4Month | 5Month | 6Month |
|---|---|---|---|---|---|---|---|
| pH of formulation | 7.3±0.21 | 7.3±0.21 | 7.4±0.19 | 7.3±0.20 | 7.3±0.22 | 7.2±0.21 | 7.3±0.24 |
| Viscosity(cps) | 240±1.14 | 256±1.14 | 258±1.16 | 250±1.18 | 254±1.14 | 258±1.14 | 257±1.14 |
| Floating lag time | 1-2 min | 1-2 min | 1-2 min | 1-2 min | 1-2 min | 1-2 min | 1-2 min |
| Duration of floating | >12hr | >12hr | >12hr | >12hr | >12hr | >12hr | >12hr |
| Assay | 94.50 | 94 | 94.2 | 94.1 | 94 | 94 | 94.1 |
| % dug released at the end of 8 hrs | 93.01±0.16 | 92.89±0.18 | 92.54±0.14 | 93.13±0.16 | 92.8±0.16 | 93.07±0.16 | 92.76±0.16 |



**5 min after administration** **6hrs after administration** **12 hrs after administration3**

**Figure 3: X-ray images after administration**

**CONCLUSION**

Based on the results obtained it is concluded that dug release from *insitu gel* can be modulated by using different polymers and its proportion. From the results obtained batch B8 was selected as optimized batch, it contains Sodium alginate 125mg, gellan gum 200mg and HPMC K100M 150mg. Release kinetics study showed that the diffusion mechanism is anomalous and model which was followed by Higuchi model. Thus, *In-situ* gelling system of Rosuvastatin was successfully developed by ionic cross linking method that could form gel instantaneously when in contact with gastric fluid and remains in stomach for more than 12 h.

**ACKNOWLEDGMENT**

Further, the authors thank Department of Science and Technology (DST), New Delhi for providing support under FIST Program of DST (SR/FST/College-280 dated 18.11.2015)''

**CONFLICT OF INTEREST**

Nil.

## REFERENCES


1. Shashi Kiran Mishra et.al., (2008). Formulation and evaluation of oil entrapped gastroretentive floating gel beads of loratadine, Acta Pharm. 58, 187–197.
2. Modasiya, M.K., B.G. Prajapati, V.M. Patel and J.K. Patel, (2010). Sodium alginate based in situ gelling system of famotidine: preparation and in-vivo characterizations. E-Journal of Science and Technology, 5(1): 27-42.
3. Kang, B. K.; Lee, J. S.; Chon, S. K.; Jeong, S. Y.; Yuk, S. H.; Khang, G.; Lee, B. H.; Cho, S. H. (2004). Development of self microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of Rosuvastatin in beagle dogs. *Int. J. Pharm*. *274* (1–2), 65–73.
4. Ambike, A. A.; Mahadik, K. R.; Paradkar, A. (2005). Spray-Dried Amorphous Solid Dispersions of Rosuvastatin, a Low Tg Drug; In Vitro and In Vivo Evaluations. *Pharm. Res*. *22* (6), 990–998.
5. Cheng, H.; Sutton, S. C.; Pipikin, J. D.; Zentner, G. M.; Rogers, J. D.; Schwartz, J. I.; Mitchel, Y. B.; Grasing, K.; Schwartz, M. S.; Amin, R. D.; Liu, L.; Ebel, D. L.; Coulter, A.; Engle, K.; McClelland, G. A.; Lui, C. Y.; Rork, G. S. (1993). Evaluation of sustained/controlled-release dosage forms of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor in dogs and humans. *Pharm. Res*. *10* (11), 683–1687.
6. McClelland, C. A.; Stubbs, R. J.; Fix, J. A.; Pogany, S. A.; Zentner, G.M.(1991). Enhancement of 3-hydroxy-3-methylglutaryl-coenzyme A (HMGCoA) reductase inhibitor efficacy through administration of a controlled-porosity osmotic pump dosage form. *Pharm. Res*. *8* (7), 873–876.
7. Dixit, R. P.; Nagarsenker, M. S. (2007). In vitro and in vivo advantage of celecoxib surface solid dispersion and dosage form development. *Ind. J. Pharm. Sci*. *69* (3), 370–377.
8. Monica Rao, Yogesh Mandage, Kaushik Thanki, Sucheta Bhise, (2010). Dissolution improvement of Rosuvastatin by surface solid dispersion technology, Dissolution technology, 27-34.
9. Arora S.; Ali J.; Ahuja A.; Khar RK.; Baboota S. (2005). Floating Drug Delivery System: A review. AAPS Pharm. Sci. Tech., 6(3);85-90
10. Jaimini, M.; Rana A.C.; Tanwar, Y.S. (2007).Formulation and evaluation of famotidine floating tablets, Current Druf Delivery., 4,51-56
11. Swati Jagdale, Prasad Kurhe, Bhanudas Kuchekar, Aniruddha Chabukswar, (2013). Application of Design of Experiments to Optimizing novel Gastro retentive Drug Delivery of Rosuvastatin. Curr Drug Deliv ;10(5):527-41.doi: 10.2174/1567201811310050004.
12. Jyotsana R Madan, Bhushan R Adokar, and Kamal Dua, Development and evaluation of *in situ* gel of pregabalin, Int J Pharm Investig. 2015 Oct-Dec; 5(4): 226–233.
13. Vyas, J.; Ghedia, T.; Gajjar, V. (2011). Review on novel in-situ polymeric drug delivery system. *Int. J. Pharm. Res. Dev.* 3(5), 53–59.
14. Tang, J.; Tung, M.; Zeng, Y. (1997). Gelling properties of gellan solutions containing monovalent and divalent cations. *J. Food Sci.* 62(4), 688–712.



## CITATION OF THIS ARTICLE

C Kishore, Bhaskar Reddy K, S V Satyanarayana . Development and Characterization of Rosuvastatin SMEDDS Loaded in situ gel for gastric Retention. Bull. Env.Pharmacol. Life Sci., Vol10[9] August 2021 : 89-94