

Development and *In vitro* Evaluation of Rosuvastatin Tablets by Floating Drug Delivery System

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Abstract

Aim: Rosuvastatin has been the most widely used antihyperlipidemic drug. The present investigation concerns with the development and evaluation of single unit gastro-retentive drug delivery system of the hyperlipidemic drug to increase the gastric residence time and to prolong the drug release. **Materials and Methods:** The floating tablet of rosuvastatin was developed using gas-forming agents such as sodium bicarbonate and citric acid and gel-forming agents such as hydroxypropyl methylcellulose (HPMC) E50 and carbopol 934 with different drugs to polymer ratio by direct compression method. The prepared tablets were evaluated for their physical characteristics, namely, hardness, friability, drug content, buoyancy, buoyancy lag time, and swelling index. Further, tablets were studied for *in vitro* drug release characteristics for 12 h. **Results and Discussion:** From the *in vitro* release studies, the formulation F3 (2:1 ratio) showed 96.31% drug release at the end of 12 h and exhibited optimum floating lag time. A decrease in release rate of the drug was observed on increasing polymer ratio and also by increasing viscosity grades of the polymer (HPMC). Drug release from floating tablets was sustained over 12 h with buoyant properties. Based on the release kinetics, all formulations best fitted the Higuchi, first-order model, and non-Fickian as the mechanism of drug release. **Conclusion:** The overall result indicated that the formulation F3 containing HPMC E50 and carbopol 934 is fulfilling the needs of the gastro-retentive floating tablets of the antihyperlipidemic drug.

Key words: Carbopol 934, floating lag time, gastro-retentive drug delivery system, hydroxypropyl methylcellulose E50, rosuvastatin, swelling index

INTRODUCTION

In a country like India with an increase in population, the demand for health-care services is also increasing. With changing lifestyles and so-called “fast culture,” good health is almost deprived part. With the upgradation of lifestyle, the concepts and severity of illness, diseases, and disorders are also changing. The major challenge faced by health-care professionals in this view is that of gradation of the available drug delivery systems.^[1] The ultimate goal of any drug delivery system is effective disease/disorder management, minimum side effects, and greater patient compliance in a cost-effective manner. The drug therapeutic indices could be maximized while indices of adverse reactions or side effects could be minimized by regulating the drug release in the body in a well-defined, controlled manner. This would eliminate the haphazard and uncontrolled blood plasma

profiles of drugs usually associated with conventional dosage forms.^[2]

Controlled release dosage forms have been extensively used to improve therapy with several important drugs. However, the development processes are faced with several physiological difficulties such as the inability to restrain and localize the system within the desired region of the gastrointestinal tract and the highly variable nature of the gastric emptying process.^[3] This variability may

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lead to unpredictable bioavailability and time to achieve peak plasma level. On the other hand, incorporation of the drug in controlled release gastro-retentive forms which can remain in the gastric region for several hours would significantly prolong the gastric residence time of drugs and improve bioavailability, reduce drug waste, and enhance the solubility of drugs that are less soluble in high pH environment. Gastro retention would also facilitate local drug delivery to the stomach and proximal small intestine. Thus, gastro retention could help to provide greater availability of new products and consequently improved therapeutic activity and substantial benefits to patients.^[4]

Statins are a group of anti-hyperlipidemic drugs which regards as the treatment of choice because of their proven efficacy, the most common and best-selling group due to short gastric residence time represents the major challenge in developing controlled release oral drug delivery systems as well as improving bioavailability. Therefore, numerous approaches have been proposed to maintain the dosage form as long as in the stomach to be absorbed.^[5]

Rosuvastatin is the newest member of the statin class of lipid-lowering compounds, which inhibit HMG-CoA reductase and reduce cholesterol synthesis. The clinical program was designed to show that rosuvastatin is effective at:

- lowering total and LDL-cholesterol in patients with familial and nonfamilial hypercholesterolemia (Fredrickson Type IIA and IIB)
- lowering total and LDL-cholesterol levels in patients with heterozygous familial hypercholesterolemia
- lowering total and LDL-cholesterol levels in patients with homozygous familial hypercholesterolemia as an adjunct to other treatment modalities (e.g., LDL apheresis) or if such treatments were unavailable
- lowering triglycerides in patients with Fredrickson Type IIB and IV dyslipidaemia as an adjunct to diet.^[6]

Various works have been reported on gastro-retentive drug delivery system (GRDDS) employing statins to overcome the problems associated with oral administration. With an aim to improve the absorption and oral bioavailability, we took an attempt to formulate floating drug delivery systems using rosuvastatin as the drug candidate employing hydroxypropyl methylcellulose (HPMC) and carbopol 934.

MATERIALS AND METHODS^[7]

Materials

Rosuvastatin was obtained as a gift samples from Yarrow Chem Products, Mumbai, India. Sodium citrate was procured from S.D Chemical, Mumbai. All other ingredients used were of analytical grade.

Pre-compression parameters

Bulk density

Apparent bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder were determined.

Tapped density

The measuring cylinder containing a known mass of powder blend was tapped for a fixed number of times as per USP apparatus - II. The minimum volume occupied by the powder after tapping was measured.

Tapped density = Weight/tapped volume

Compressibility index

Compressibility index is calculated as follows. The value below 15% indicates a powder with good flow characteristics, whereas above 25% indicates poor flowability

Tapped density = Bulk density/Tapped density*100

Hausner's ratio

It is an indirect index of ease of powder flow, and it is calculated as follows. Hausner's ratio <1.25 indicates good flow properties, whereas >1.5 indicates poor flowability.

Tapped density/Bulk density

Angle of repose

The angle of repose was determined using funnel method. The blend was poured through a funnel that can rise vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured, and angle of repose was calculated as follows.

$$\theta = \tan^{-1}(h/r)$$

Preparation of floating tablets

Floating tablets containing rosuvastatin were prepared by direct compression technique using varying concentrations of polymers with sodium bicarbonate, citric acid, and dicalcium phosphate. All the ingredients were accurately weighed and passed through different mesh sieves (#40) accordingly. Then, all other ingredients were blended uniformly in a glass mortar. After sufficient mixing of the drug as well as other components, tablets were compressed using rotary tablet machine. The weights of the tablets were kept constant for all formulation [Table 1].^[1]

Evaluation test for tablets

The prepared tablets were evaluated for the following parameters:

Table 1: Formulation design of rosuvastatin gastro-retentive tablets

Ingredients	F1	F2	F3
Rosuvastatin	5	5	5
HPMC E50	15	10	20
Carbopol 934	15	20	10
Sodium bicarbonate	20	20	20
Citric acid	5	5	5
Dicalcium phosphate	15	15	15
Lactose	30	30	30
Total weight	100	100	100

HPMC: Hydroxypropyl methylcellulose

Weight variation test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance and the test was performed according to the official method.^[8]

Hardness and friability

For each formulation, the hardness and friability of 6 tablets were determined using the Monsanto hardness tester (Cadmach, Ahmedabad, India) and the Roche friabilator (Campbell Electronics, Mumbai, India) respectively.^[9]

Drug content

The drug content in each formulation was determined by triturating 20 tablets, and powder equivalent to average weight was added in 100 ml of 0.1 N hydrochloric acid, followed by stirring for 30 min. The solution was filtered through a 0.45µm membrane filter, diluted suitably, and the absorbance of resultant solution was measured HPLC.^[2,10]

In vitro buoyancy

The *in vitro* buoyancy was determined by floating lag time, per the method described by Rosa *et al.* The tablets were placed in a 100 ml beaker containing 0.1 N hydrochloric acid. The time required for the tablet to rise to the surface of time, the dosage form constantly remained on the surface of medium, was determined as the total floating time.^[7]

Determination of swelling index

Floating matrix tablet was introduced into basket-type dissolution apparatus containing 900 mL of 0.1 N HCl (pH 1.2 at 37°C) at 50 rpm. The tablets were removed at definite time intervals, and swollen weight of each tablet was determined. Swelling (%) was calculated.^[11]

In vitro drug release

The release rate of rosuvastatin from floating tablets was determined using dissolution testing apparatus 2 (paddle method). The dissolution test was performed using 900 ml of

0.1 N hydrochloric acid at $37 \pm 0.5^\circ\text{C}$ and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at regular intervals, and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45 µm membrane filter and diluted to a suitably, and resultant solution was measured ultraviolet. Cumulative percentage drug release was calculated using an equation obtained from a standard curve.^[2]

Stability studies

Whenever a new formulation is developed, it is mandatory to check the stability. Hence, to confirm the stability, the optimized formulation (F3) was subjected to stability studies at $25^\circ\text{C} \pm 2^\circ\text{C}/60\% \text{ RH}$ and $40^\circ\text{C} \pm 2^\circ\text{C}/75\% \text{ RH}$ for the period of 3 months which was seen.

RESULTS AND DISCUSSIONS

The prepared tablets were evaluated for the various pre-compression parameters as explained earlier. The bulk density was found in the range of 0.334-0.383 G/CC, and the tapped density was found to be in the range of 0.444-0.517 G/CC. Using the above two density data, the Carr's compressibility index was calculated, the compressibility index was found to be in the range of 8.4-11.5%, and the compressibility and flowability data indicated good flow properties for all the blended formulation. The better flow property of all powder blends was also evident from the angle of repose. The angle of repose was a range of 25.02-28°. Angle of repose below 30° indicates good flow property. In the present study, all powder blends showed good flow property. The results are shown in Table 2.

Post-compression evaluation parameters

Weight variation

The formulations were evaluated for their uniformity of weight according to the procedure, and they show that maximum weight of 105 mg in F2 and the minimum weight of 103 mg in F1 and F3 formulations were observed. The maximum allowed percentage weight variation for tablets 100 mg by Indian pharmacopoeia is 7.5%, and no formulations were exceeded the limit. Thus, all the formulations were found to be complying with the given standards, and the results are shown in Table 3.

Hardness

All the tablet formulations were evaluated for their hardness as per procedure, and all the formulations have an average hardness in the range 4.1 ± 0.11 to $4.7 \pm 0.15 \text{ kg/cm}^2$ which was found to be acceptable, and the results are shown in Table 3.

Table 2: Pre-formulation parameters

Formulation	Bulk density (g/cm ³)	Tap density (g/cm ³)	% Carr's index	Hausner's ratio	Angle of repose (è)
F1	0.334	0.444	8.4	0.65	26
F2	0.383	0.517	10.2	0.69	28
F3	0.367	0.506	11.5	0.75	25.02

Table 3: Post-compression parameters

Formulation	Hardness (kg/cm ²)	Friability (%)	Weight variation (mg)	Drug content (%)
F1	4.1±0.19	1.21	103±1%	67.4±1.8
F2	4.7±0.15	1.18	105±2%	71.2±2.3
F3	4.6±0.21	1.12	103±1%	75.4±1.3

Friability

The gastro-retentive tablets were evaluated for their percentage friability as per the standards, and the average percentage friability for all the formulations was found be 1.21-1.12%, which is observed to be within the limit, and the results showed that tablet possesses enough resistance to withstand the mechanical shock and abrasion during handling and transportation, and the results are tabulated in Table 3.

Drug content

The formulations were evaluated for their uniformity of drug content according to the procedure to determine the amount of drug in all the formulation. The percentage of drug was found to be in the range of 67.40-75.5% w/w. The maximum drug content of 75.5% w/w for F3 and the minimum of 67.40% w/w for F1 formulations were observed. The results are tabulated in Table 3.

All the formulations showed values within the prescribed limits for tests such as hardness, friability, and weight variation which indicate that the prepared tablets are of standard quality.

Buoyancy lag time and total floating time

The formulation was evaluated for their buoyancy test and total floating time according to the procedure, and they show maximum buoyancy time of 134.4 s and <10 h of total floating time for F2 formulation and minimum of 55.6 s and >12 h of floating time for F3 formulation, and it was observed that buoyancy time was increased on increasing the concentration of release retardant polymer. The results were tabulated in Table 4.

Swelling index

Swelling study was performed on all the batches. The formulation F2 shown highest percentage of 136% and the minimum of 114.3%. The results of swelling index are given

Table 4: Buoyancy lag time, total floating time of all formulations

Formulation	Buoyancy lag time (s)	Total floating time (h)	Swelling index (%)
F1	89.7	<8	114.3
F2	134.4	<10	136
F3	55.6	>12	120

in Table 4. From the results, it was concluded that swelling increases as the time passes because the polymer gradually absorbs water due to the hydrophilicity of polymer.

In vitro release profile

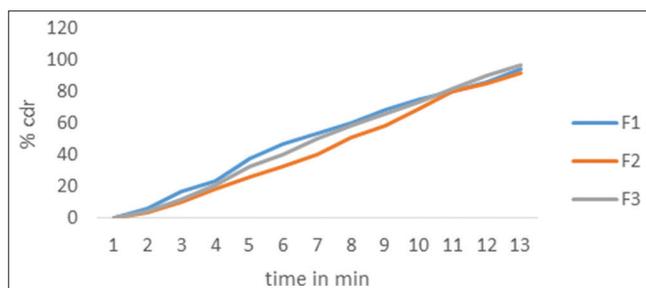
The drug release pattern was studied for all formulations for 12 h using paddle-type dissolution apparatus in both stimulated gastric fluid pH (1.2). The percentage cumulative drug release profile from formulation F1 to F3 was found to be in the range of 91.8-96.31%, respectively. In this, the maximum release was found to be 96.31% from F3 formulation and minimum release of 91.852% in F2 formulation. From the above studies, it was concluded that the formulation F3 containing HPMC E50 and carbopol (2:1) has shown maximum release when compared to other formulations. The results are shown in Figure 1.

Drug release kinetics

The result of *in vitro* release data was fitted to various kinetic models and results showed that drug release followed first-order kinetics, as the values for the first order (0.997-0.305) are higher in comparison to zero order (0.91-0.683) and Higuchi model (0.669-0.990). The release exponent value (*n*) for the formulation F1 was 0.468 and it follows non-Fickian diffusion mechanism, the formulation F2 was 0.994 and it follows super Case II, and the formulation F3 was 0.440 and it follows Fickian diffusion mechanism data is shown in Table 5.

Table 5: Drug release kinetics

Formulation code	Zero order	First order	Higuchi	Korsmeyer–Peppas model	
	R^2	R^2	R^2	R^2	n
F1	0.986	0.305	0.821	0.652	0.468
F2	0.688	0.997	0.990	0.33	0.994
F3	0.91	0.413	0.699	0.626	0.440

Figure 1: *In vitro* release study

CONCLUSION

The present study was conducted to develop a GRDDS of rosuvastatin using HPMC E50 and carbopol 934 of different polymer ratios. Out of the three different formulations, the formulation F3 was found to be an optimized formulation that has showed an excellent buoyant ability and a suitable drug release pattern. This could be advantageous in terms of increased bioavailability of rosuvastatin. The developed GRDDS provides advantages of ease of preparation and sustained drug release for 12 h.

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