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FORMULATION AND EVALUATION OF GASTRO RETENTIVE FLOATING TABLET OF ROSUVASTATIN

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ABSTRACT

The aim of the present study was to develop a Gastro retentive floating tablets (GRFT) of Rosvastatin was developed by direct compression method, by using drug with different polymer ratio like HPMC E50, HPMC K15M, HPMC 5cps. The formulation were evaluated for their physical characteristics, viz., hardness, friability, drug content and floating properties. Further the tablets were studied for in vitro drug release characteristics for 12 h. The tablets exhibited controlled and prolonged drug release, with optimum hardness, consistent uniformity in weight and low friability. The formulation with F_2 showed 99% drug release at the end of 12 h and exhibited optimum floating lag time. A decrease in release rate of the drug was observed by increasing viscosity grades of the polymer (HPMC). Drug release from effervescent floating matrix tablets was sustained over 12 h with buoyant properties. FTIR study revealed that there is no drug excipients interaction. Based on the release kinetics, all formulations best fitted the Higuchi, first-order model and non-Fickian as the mechanism of drug release.

KEYWORDS: Rosvastatin, Direct compression, HPMC E50, HPMC K15M, HPMC 5cps.

INTRADUCTION

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 of this group. 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.[1]

From these approaches development of bioadhesive systems, swelling and expanding systems, floating systems and delayed gastric emptying devices. Floating drug delivery systems are designed to prolong the gastric residence time after oral administration, at specific site and controlling the drug release. The prospective advantages of this idea include the reduction of drug-related side effects due to controlled therapeutic blood levels instead of fluctuating blood levels and improved patient compliance due to reduced frequency of dosing. Therefore, it is clear that formulation of novel floating drug delivery system facing both the identification of technologies and formulation excipients to optimize both the floating behaviour and drug release pattern.[2]

The control of placement of a Drug Delivery Systems (DDS) in a specific region of the GIT offers advantages for a variety of important drugs characterized by a narrow absorption window in the GIT or drugs with a stability problem.[3] These considerations have led to development of a unique oral controlled release dosage form with gastro retentive properties. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GIT is to control the Gastric Residence Time (GRT), i.e. Gastro Retentive Dosage Form (GRDF).

Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs.[4] Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment.

Such retention systems (i.e. GRDDS) are important for the drugs that are degraded in intestine or for drugs like antacids or certain enzymes that should act locally in the stomach. Gastric retention may increase solubility for the drugs which are poorly soluble in intestine due to alkaline pH before they are emptied, resulting in improved bioavailability.[5]

These systems also offer advantages in improving GIT absorption of a drug with narrow absorption windows as well as for controlling release of those drugs which are having site-specific absorption limitations.

These systems are useful in case of those drugs which are best absorbed in stomach. From the formulation and technological point of view, floating drug delivery system (FDDS) is considerably easy and logical

approach in development of GRDFs. Therefore, this review article focuses on the current technological development in FDDS with special emphasis on the principal mechanism of floatation and advantages to achieve gastric retention and its potential for oral controlled drug delivery.[6]

Floating systems or hydro dynamically balanced systems, are low density systems that have sufficiently 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 and a better control of the fluctuations in plasma drug concentrations. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hallow micro spheres.[7]

Floating drug delivery systems are designed to prolong the study of the dosage form in the gastro intestinal tract and aid in enhancing the absorption. Such systems are best suited for drug having a better solubility in acidic environment and also having specific site of absorption in upper part of the small intestine.[8] To remain in the stomach for a prolonged period of time the dosage form must have a bulk density of less than 1. It should stay in the stomach, maintain its structural integrity, and release drug constantly from the dosage form. It is widely known that gastric residence time (GRT) is one of the important factors affecting the drug bioavailability of pharmaceutical dosage forms.[9]

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., LDLapheresis) or if such treatments were unavailable
− lowering triglycerides in patients with Fredrickson Type IIB and IV dyslipidemia as an adjunct to diet

Rosuvastatin was studied at single daily oral doses of 1, 2.5, 5, 10, 20, 40 and 80 mg. The sponsor proposes a starting dose of 5 mg daily with a dose range of 10 mg to 40 mg once daily for patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Type IIA and IIB). In heterozygous or homozygous familial hypercholesterolemia the starting dose is 20mg with severe hypercholesterolemia (LDL-cholesterol >190mg/dl).[10]

In conclusion, statins have been associated with liver transaminases elevations but rarely hepatitis and liver failure. Rosuvastatin, like other statins, shows a dose-related increase in liver transaminases. The incidence of multiple transaminase elevations is similar at 80 mg of rosuvastatin to that seen at the highest approved doses of other statins. Liver function monitoring, as currently recommended for all members of the statin drug class, is also recommended for patients receiving treatment with rosuvastatin.10% of rosuvastatin is metabolized by the P450 2C9 enzyme system.[11]

In the present investigation using rosvastatin as the model drug with a hydrophilic cellulose derivative HPMC. Investigations were performed to observe the effect of polymer content upon the floating lag time of the tablets. The impact of polymer loading upon the release rate, mean dissolution time and release mechanism were also evaluated with the help of various mathematical models.

MATERIALS AND METHODS

MATERIALS

Rosvastatin from HPMC E50, HPMC K15M, HPMC5cps were obtained from Colorcon Asia Private Limited (India) and all excipients were of USP/NF grades and all other chemicals used were of analytical grades.

Pre-Compression Parameters

The various Pre-compression parameters like Angle of repose, Bulk density, Tapped density, compressibility index, Hausner's ratio and Carr's index were studied.

Preparation of effervescent tablets

Floating tablets containing Rosvastatin were prepared by direct compression technique using varying concentrations of different grades 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 glass mortar. After sufficient mixing of 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: formulation

Ingredients	F1	F2	F3
Rosvastatin	5	5	5
HPMC E50		25	
HPMC K15M	25		
HPMC 5cps			25
Sodium bicarbonate	20	20	20
Citric acid	5	5	5
Dicalcium phosphate	15	15	15
Lactose	30	30	30
Total weight	100	100	100

EVALUATION TEST FOR TABLETS

The prepared tablets were evaluated for the following parameters:

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.

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.

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

In vitro buoyancy
The in vitro buoyancy was determined by floating lag time, per the method described by Rosa et al.[20] The tablets were placed in a 100 ml beaker containing 0.1N 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.

Determination of swelling index
Floating matrix tablet was introduced into basket type dissolution apparatus containing 900mL of 0.1N HCl (pH 1.2 at 370C) at 100rpm. The tablets were removed at definite time intervals and swollen weight of each tablet was determined. Swelling (%) was calculated.

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 900ml of 0.1N hydrochloric acid, at 37± 0.5^0c and 50 rpm. A sample 10ml of the solution was withdrawn from the dissolution appartous at regular intervals and the samples were replaced with the fresh dissolution medium. The samples were filtered through 0.45i membrane filter and diluted to a suitably resultant solution was pre formulation parameters data were presented in the Table and all the obtained values are well with in the limit.

Stability studies
Stability studies were conducted for the optimized formulation F_2. To assess their stability with respect to drug content after storing at 40°C/75% RH for 3 months was seen.

RESULTS AND DISCUSSIONS
For each type of formulation the active pharmaceutical ingredients and excipients was formulated and evaluated for various pre-compression parameter as explained earlier. The Bulk density was found in the range of 0.317 to 0.357 G/CC and the tapped density was found to be in the range of 0.370 to 0.444 G/CC. Using the above two density data, the Carr's compressibility index were calculated, the compressibility index was found to be in the range of 7.14 to 10.34% the compressibility and flow ability data indicated good flow properties for all the blended formulation. The better flow property of all powder blends was also evident from angle of repose. The angle of repose was range of 24.28 to 25^0. Angle of repose below 30º indicates good flow property. In the present study all powder blends showed good flow property. The results are shown in the Table (2).

Table 2: Pre formulation parameters

Formulation	Bulk density (g/cm3)	Tap density (g/cm3)	% Carr's Index	Hausner's ratio	Angle of repose (è)
F1	0.317	0.370	7.14	0.582	25
F2	0.344	0.434	10.34	0.631	25.12
F3	0.357	0.444	9.82	0.622	24.28

Post- Compression evaluation parameters
Weight Variation
The formulations were evaluated for their uniformity of weight according to the procedure and they show maximum weight of 104 mg in F2 and the minimum weight of 103 mg in F1 & 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 4.2 ± 0.11 Kg/cm^2 and 4.3±0.15 Kg/cm^2.which was found to be acceptable and the results are shown in the Table 3.

Friability
The Gastro retentive tablets were evaluated for their percentage friability as per the standards the average percentage friability for all the formulations were found be 1.26% to 1.12%, which is observed to be within the

limit as per the standard and the results were tabulated in the 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 63.40 to 74.5% w/w. The maximum drug content of 74.5% w/w for F2 and the minimum of 63.40% w/w for F1 formulations was observed. The results are tabulated in the table 3.

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

Table 3: Post compression parameters.

Formulation	Hardness (Kg/cm2)	Friability (%)	Weight Variation (mg)	Drug content (%)
F1	4.3 ± 0.15	1.14	103 ±2%	63.4 ± 3.1%
F2	4.2 ± 0.11	1.12	104 ±2%	74.5 ± 1.4 %
F3	4.3 ± 0.31	1.26	103 ±1%	73.2 ± 2.1%

Buoyancy Lag Time & Total floating time

The formulation were evaluated for their buoyancy test & total floating time according to the procedure and they show maximum buoyancy time of 123.6 sec and <10h of total floating time for F1 formulation and minimum of 68.4 sec and >12h of floating time for F2 formulation and the results were tabulated in the table 4.

Figure 1

Figure 2

Swelling Index

Swelling study was performed on all the batches for 8 hr. The formulation F2 shown highest percent of 236% and the minimum of 104.5%. The results of swelling index are given in Table 4. From the results it was concluded that swelling increases as the time passes because the polymer gradually absorb water due to hydrophilicity of polymer.

Table 4: Buoyancy Lag Time, Total Floating Time of all formulations

Formulation	Buoyancy Lag Time (Sec)	Total Floating Time (h)	Swelling Index (%)
F1	123.6	<10	104.5
F2	68.4	>12	110.6
F3	258	<8	236

In-vitro release profile

The drug release pattern was studied for all formulations for 12 hours by 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 92.9% to 99.28% respectively. In this the maximum release was found to be 99.89% from F3 formulation and minimum release of 56.55% in F3 formulation. From the above studies it was concluded that the formulation F2 containing HPMC E50 has shown maximum release when compared to other formulation. The results are shown in Figure1.

Table 5: In-vitro release profile

Time (hr)	Cumulative drug release (%)		
	F_1	F_2	F_3
0	0	0	0
1	5.76	35.47	6.65
2	9.79	43.63	8.9
3	13.8	49.12	10.25
4	18.7	57.35	12.92
5	22.28	63.09	15.59
6	25.85	69.23	17.83
7	29.86	72.84	21.39
8	33.43	79.32	24.96
9	39.99	81.22	32.33
10	46.55	89.01	40.84
11	53.54	94.54	53.05
12	60.26	99.89	56.55

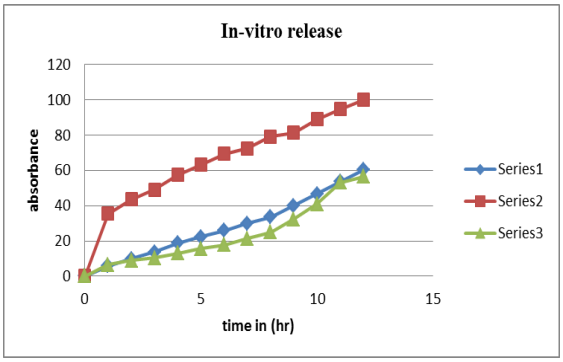

Figure 4: in-vitro release study.

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 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 fallows non fickian diffusion mechanism, the formulation F2 was 0.994 and it fallows super case II and the formulation F3 was 0.440 and it fallows fickian diffusion mechanism data is shown in Table 6.

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

CONCLUSION

The present study was conducted to develop an effervescent floating drug delivery system using three grades of HPMC polymer, in different concentrations. Optimized formulation F2 showed an excellent buoyant ability and a suitable drug release pattern. This could be advantageous in terms of increased bioavailability of Rosvastatin. The developed gastro retentive drug delivery system provides advantages of ease of preparation and sustained drug release for 12 hours.

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