Development And Evaluation Of Gastroretentive Floating Tablet Of Rosuvastatin

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Abstract: Gastroretentive floating matrix tablets of the antihyperlipidemic drug Rosuvastatin were successfully prepared using hydrophilic polymers like HPMC K4M and Carbapol. From the Preformulation studies for drug excipients compatibility it was observed that there was no compatibility problem with the excipients used in the study. The Formulated tablets gave satisfactory results for various physicochemical evaluation studies like Weight variation, Floating lag time, Content uniformity, Total floating time, Mucoadhesion time, mucoadhesive strength and in vitro drug release and shows a floating time of around 12 hrs.

Keywords: Gastroretentive dosage form, antihyperlipidemic drug, Rosuvastatin, Mucoadhesion.

1. Introduction

Oral route is the most preferable and convenient route for drug administration to any other route of drug administration. Therefore formulation scientists have been focusing on controlled release oral drug delivery systems for last few decades. But the various difficulties are associated in designing the controlled delivery systems for better absorption and enhanced bioavailability. The most significant difficulty is the inability to confine the dosage forms in the desired area of gastrointestinal tract. In case conventional oral delivery systems the dosage forms passes through the stomach and small intestine within very short period of time where the most absorption take place in less than 12 hours. So, the main aim is to prolong the time for drug administration from the small intestine. Oral dosage forms have to stay inside the stomach or upper intestine for desired period of time so that entire drug can be released from the dosage forms. Therefore effective attempts have been made to developed oral sustained release dosage forms for last few decades because of their several significant advantages. Gastro retentive systems confine the dosage forms for several hours inside the stomach and considerably prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It is also beneficial for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. The controlled gastric retention solid dosage forms have been developed by means of various mechanisms such as of mucoadhesion, **[1]** flotation, [2] sedimentation, [3] expansion,[4] modified shape systems, **[5]** or by the simultaneous administration of pharmacological agents **[6]** that delay gastric emptying. Among the above different techniques Floating drug delivery systems (FDDS) [7] are novel drug delivery systems. Where the solid dosage forms remain buoyant condition on the gastric fluid and release the drug slowly and gastric residence time can be enhanced significantly. This is a very simple but highly innovative concept. Moreover it has several advantages over other gastro retentive drug delivery systems [8]. To develop floating tablet of Rosuvastatin in order to achieve an extended retention in upper part of GIT for desired time period. It should deliver the entity directly to the site of action (stomach), and retain it therefore prolonged periods of time, thus, minimizing or eliminating side effects and improving bioavailability. To carry out the physical parameter testing like hardness, thickness, diameter, friability, weight variation, content uniformity of the prepared tablets. To carry out floating lag time and total floating time, in-vitro drug release studies and release kinetics studies.

2. Materials:

Rosuvastatin(Gifted sample from Glenmark Pharm, India), HPMC, Carbopol, Sodium bicarbonate, MCC, Citric acid and other chemicals used are of analytical grade.

3 Methodology of the experiment:

3.1. Preformulation study:

Preformulation testing is the first step in the rational development of dosage forms of drug substances. It can be defined as an investigation of physical and chemical properties of a drug substances alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms that can be mass produced [8].

3.1.1. Solubility Profile:

About 10 mg of Rosuvastatin was taken and solubility was studied in different solvents.

3.1.2. Melting Point Determination:

Melting point of drug sample was determined using melting point apparatus by filling the drug sample in three separate capillaries. The capillaries were inserted in chamber. The chamber was gradually heated. The temperature at which the rosuvastatin melted was noted. The process was repeated 3 times.

3.1.3. Standard plot of rosuvastatinin methanol:
Different concentration of rosuvastatin: 4, 8, 12, 16, 20, 24, 28, 32, 36, 40 mcg/ml were prepared in mthanol and absorbances were determined.

3.1.4. Solution stability of drug in methanol:
The solution stability of drug was assessed in methanol for 12 hours at 37 ± 5 ºC to predict their stability in the solvent [9].

3.2. FORMULATION DEVELOPMENT:
In order to optimize the ratio of HPMC K4M & carbopol for matrix system used in extended release tablet formulation, different batches were prepared by trial and error method. Among those batches the following ratio of polymer, drugs & other additives were added to prepare 500mg final weight.

Table No.2: *Different formulations and the ingredients*

Components	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)
Drug	10	10	10	10
HPMC K4M	125	100	150	200
Carbopol	140	190	115	90
$NaHCO_3$	50	50	50	50
Citric acid	25	25	25	25
MCC	135	135	135	135
Mg-Stearate	5	5	5	5
talc	10	10	10	10
Total weight of Tablet:	500	500	500	500

3.2.1. Determination of bulk density and tapped density:
About 5 gms of formulation powder blend was weighed and different parameters like, bulk density, tapped density, Hausner ratio and carr index were calculated.

3.2.2. Preparation of tablet formulation of the above mentioned batches:
At first all ingredients (HPMC K4M, carbopol, Rosuvastatin, MCC, $NaHCO_3$, citric acid) were mixed by geometric dilution. Then the mixture was passed through 16 mesh and subsequently followed by 24 mesh sieve. The sieved mixture was weighed for 500mg and punched in tablet punching machine to prepare tablets [10].

3.3. EVALUATION OF FORMULATIONS:
Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations [11].

3.3.1. Hardness Testing:
The resistance of tablet for shipping or breakage, under conditions of storage, transportation and handling, before usage, depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester.

3.3.2. Thickness testing of formulated tablets:
Thickness of tablets was important for uniformity of tablet size. Thickness was measured using Vernier Calipers on 3 randomly selected samples.

3.3.3. Weight Variation Test of final formulation:
The USP weight variation test is run by weighing 20 tablets individually, calculating the average weight & comparing the individuals tablet weight to the average. The tablets meets the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

3.3.4. Content Uniformity Test of final formulation:
To assure uniform potency for tablets a content uniformity test is applied. In this test 30tablets are randomly selected for the sample and at least 10 of them are assayed individually. Nine of the 10 tablets must contain not less than 85% or more than 115% of the labeled drug content. The tenth tablet may not contain less than 75% or more than125 % of the labeled content. If this condition is not meet, the tablets remaining from the30 must be assayed individually and none may fall outside of the 85% to 115% range.

3.3.5. Friability Test:
Friability is the measure of tablet strength. Roche friabilator was used for testing the friability using the following procedure. Friability was done as per USP specification. According to USP conventional compressed tablets that lose weight less than 0.5% –1.0% of their actual weight are generally considered acceptable.

$$\%\text{Friability} = \frac{(\text{Initial wt. of tablets} - \text{Final wt. of tablets}) \times 100}{\text{Initial wt. of tablets}}$$

3.3.6. Buoyancy / Floating Test:
The time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT). The lag time was carried out in beaker containing 250 ml of 0.1N HCl (pH 1.2) as a testing medium maintained at 37°C.

3.4. DISSOLUTION STUDY [12]**:**
Apparatus: Dissolution test apparatus (USP XXIII)
Method: USP type 2 apparatus (paddle)
Dissolution medium: 0.1N HCl + 0.5% SLS
Volume of DM: 900 ml
Temperature: 37 + 0.5° C
Speed: 50 rpm

Procedure:
The tablet was placed inside the dissolution vessel. 10 ml of sample were withdrawn at time intervals of 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12hr.The volume of dissolution fluid adjusted to 900 ml by replacing 10ml of dissolution medium after every sample. Each sample was analyzed at 245nm using double beam UV and Visible Spectrophotometer against reagent blank. The drug concentration was calculated using standard calibration curve.

3.5. MECHANISM OF DRUG RELEASE:
Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted

into zero-order, first order, Higuchi [13], Hixon-Crowell model and Korsmeyer-Peppas release model [14].

Zero order release rate kinetics: -
To study the zero–order release kinetics the release rate data are fitted to the following equation.

F= Ko.t

Where 'F' is the drug release, 'K' is the release rate constant and 't' is the release time. The plot of % drug release versus time is linear.

First order release rate kinetics:
The release rate date are fitted to the following equation

Log (100-F) = kt

A plot of log % drug release versus time is linear.

Higuchi release model:
To study the Higuchi release kinetics, the release rate data were fitted to the following equation,

F = k t1/2

Where 'k' is the Higuchi constant. In Higuchi model, a plot of % drug released versus square root of time is linear.

Korsmeyer and Peppas release model:
The release rate data were fitted to the following equation,

Mt /M = K.tn

Log (Mt /M) =Log K + n Logt

Where, Mt /M is the fraction of drug released,
'K' is the release constant,
't' is the release time.
'n' is diffusion exponent, if n is equal to 0.89, the release is zero order. If n is equal to 0.45 the release is best explained by Fickian diffusion, and if 0.45 < n< 0.89 then the release is through anomalous diffusion or nonfickian diffusion (swellable & cylinder Matrix). In this model, a plot of log (Mt/M) versus log (time) is linear.

4. RESULT:

4.1. EVALUATION OF DRUG:

Melting point:
Melting point of Rosuvastatin was found to be in the range 154° C, which complied with Indian Pharmacopoeia standards, indicating purity of the drug sample.

Standard calibration curve of Rosuvastatin:
The λ max of rosuvastatin in methanol solution was found to be 244nm, and the peak was shown in fig 1.

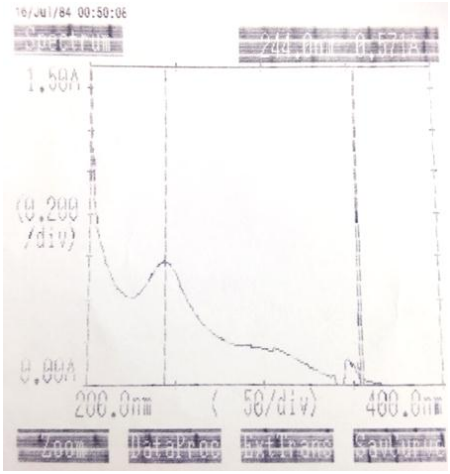

Figure 1: *Absorbance peak of Rosuvastatin at 244 nm.*

Graph of absorbance Vs concentration was plotted (λ max 244nm) and found to be linear over the range of 10 to 100µg/ml obtained indicating its compliance with beer's and lamberts' law.

Study of micromeritic properties:
The powder mixtures of all the formulations were tested by various studies including, bulk density (ranging from 0.36 to 0.44 gm/ml), tapped density (ranging from 0.42to 0.47 gm/ml), Carr's index (ranging from 1.52 to 23.73%) and Hausner's ratio (ranging from 1.02 to 1.33) in table no 5,6,7.8. All the results showed moderate flow property.

Table No 9: *Mean value of Micromeritic properties.*

Micromeritic properties	Mean ±SD			
	F1	F2	F3	F4
Bulk Density	0.38±0.01	0.44±0.02	0.39±0.05	0.36±0.03
Tap Density	0.42±0.02	0.45±0.01	0.46±0.01	0.47±0.03
Hausner's Ratio	1.11±0.05	1.02±0.03	1.19±0.18	1.33±0.17
Carr's Index	9.51±44	1.52±2.63	14.56±11.93	23.73±10.79

4.2. Physicochemical characterization of the prepared tablets:
The results of physicochemical characterizations are given in table no 7-12. The thickness of formulations from F1 to F4 was measured by digital thickness tester and was found to be between 4.12± 0.2 to 5.00 mm. The hardness of formulations from F1 to F4 was measured by Monsanto tester and was found to be between 5 and 6.5 Kg/cm^2. The friability of all the formulations was measured by Roche friabilator and was found to be in the range of 0.45 to 0.61%. The weight variation for different formulations was found to be ranging in between 98.61% - 100.97%, showing satisfactory results as per Indian pharmacopoeia (IP) limit. The content uniformity of all the formulations was between 97.83% - 100.17% and found to be within the limit (100±2 %). The evaluated properties showed good enough results for further studies.

Table no 9: *Weight Variation Test of final formulation*

Observation	Batch Code (Mean ±SD)			
	F1	F2	F3	F4
Hardness (kg/ Cm^2)	5.33±0.12	5.97±0.07	5.65±0.1	5.92±0.11
Thickness	5.35±0.11	4.19±0.06	4.67±0.21	4.83±0.10
Friability Test	0.80±0.20	0.53±0.11	1.07±0.11	0.73±0.23

Table no 10: *Content Uniformity Test of final formulation*

Codes of final formulation	Percentage of content uniformity
F1	99.2
F2	100.06
F3	98.66
F4	99.93

4.3. DETERMINATION OF FLOATING CHARACTERISTICS:

Studies to determine the Floating lag time and duration of floating of various formulations were carried out and the results indicated that floating lag time which was observed for all the tablets was within 0-1 minute after immersion into gastric media and duration of floating was around 12 hrs. hours for all batches. The effect of hardness on buoyancy lag time was studied and results indicated that with increasing the hardness lag time also increased.

Table No 14: *Duration of floating of various formulations.*

Observation	Duration of floating (hours)			
	Batch Code			
	F1	F2	F3	F4
Mean ±SD	12.05±0.46	14.31±0.17	12.33±0.08	13.39±0.17

Figure 7: *Picture showing floating behavior of the prepared tablet (After floating)*

4.4. COMPARISON OF IN-VITRO DRUG RELEASE STUDY

The in vitro dissolution study shows that the floating tablets are capable of drug release over a period of 13 hours. The study shows that the floating tablets absorbed water and got swollen. Initially a barrier gel layer forms around the tablet and the interior of the tablet remains dry. The drug diffuses through this barrier gel layer gradually erodes with time and release the drug. The floating lag time (FLT) is inversely proportional to the concentration NaHCO3 but the optimum floatability is obtained in the specified range of concentration of NaHCO3. Beside that Magnesium stearate which was used as lubricant in tablet formulation have also no effect on drug release profile. The dissolution data are treated and analyzed to understand the kinetic and mechanism of the drug release from the floating matrix tablet. The treated data are fitted into various kinetic models and R^2 value are evaluated. The analysis shows that the drug release from the floating matrix followed Higuchi release kinetics more preferably. As the "n" (release exponent) values of Krosmeyer- Pappes model of most of the formulation batch are in the range of 0.56 – 0.68. So, the release mechanism is non-fickian or anomalous transport leading to gradual erosion of matrix and to some extent Case- II transport mechanism. Comparing between Zero order and First order release pattern, Most of the formulation showed Zero order release than First order. So, release of drug from the formulation is not concentration dependent, which is a principle criterion of an extended release dosage form.

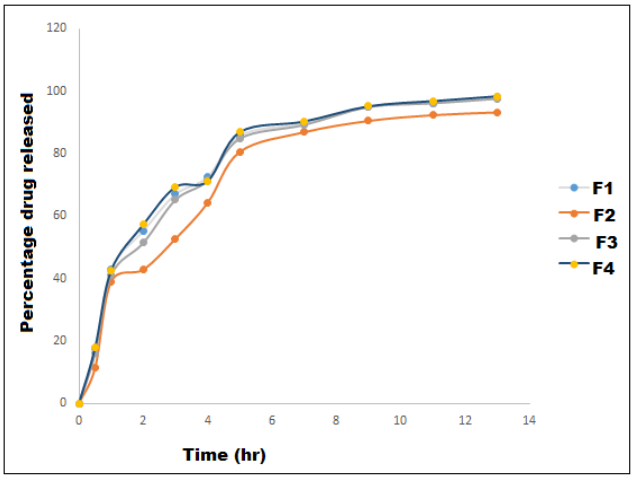

Figure 6: *In Vitro Drug Release Profile of all formulations*

5. CONCLUSION:

The main aim of the present work was to minimize the liver extraction ratio by controlling the release of drug from the prepared dosage form. Thus gastroretentive dosage form was formulated to achieve the above aim. These systems proved to give better efficacy by minimizing extraction ratio. Thus from the data obtained, it can be concluded that: Gastroretentive dosage form of an antihyperlipidemic drug rosuvastatin formulated as an approach to increase gastric residence time and thereby minimizing hepatic extraction ratio. Among the polymers used to improve the gastric residence, cellulose polymers HPMC K_4M showed better control over drug release, and Carbopol showed good control on mucoadhesive strength. The Formulated tablets gave satisfactory results for various physicochemical evaluation like Weight variation, Floating lag time, Content uniformity, Total floating time, Mucoadhesion time, mucoadhesive strength and in vitro drug release. Formulated gastroretentive dosage form best fitted to Korsmeyerpeppas and Zero-order model rate kinetics.

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