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ORIGINAL ARTICLE

Design and Evaluation of Gasrtoretentive Drug delivery film system of Rosuvastatin

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ABSTRACT
Rosuvastatin is a BCS class II drug (poor solubility, good permeability) with low bioavailability (less than 5%). The aim of the present study was divided in to two phases, first phase was to develop self-emulsifying drug delivery system of Rosuvastatin to improve solubility and dissolution rate of Rosuvastatin and second phase was formulation and characterization of Gastroretentive floating film delivery system of Rosuvastatin. Different film forming polymers based on ability to float and film forming ability were screened at different concentration to arrive at optimized formulation with a combination of HPMC K4M: ethyl cellulose (1:1) is considered for further development. All the batches were evaluated for Thickness of film, Folding endurance, % Moisture content, Tensile strength, Unfolding study, In vitro Drug release study, Release kinetic study, 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.
Keywords: *Rosuvstatin, Floating Film, Factorial Design, Release Kinetics.*

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INTRODUCTION

Most of the orally administered dosage forms have several physiological limitations, such as GI transit time, incomplete drug absorption due to incomplete release of drug from the devices and too short residence time of the dosage forms in the absorption region of GI tract. To overcome these limitations many attempts have been made by scientists by designing various drug delivery systems. Among these systems, Floating drug delivery systems (FDDS) is one of the approaches which remain buoyant due to their lower density that that of the GI and intestinal fluids.[1,2] Prolonged gastro retention of the therapeutic moiety may offer numerous advantages, including improvement of bioavailability, therapeutic efficiency and possible reduction of dose.[3,4,5] It has been reported that prolonged local availability of antibacterial agents may augment their effectiveness in treating H. Pylori infections.[6]
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%. It is a potent and specific inhibitor of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG CoA) reductase, which catalyzes the reduction of HMG CoA to mevalonate. Thus, Rosuvastatin inhibits a key step for cholesterol biogenesis in the liver and is used in the treatment of dyslipidemia and hypercholesterolemia in addition to diet. After oral administration cytochrome-3A system in liver metabolizes Rosuvastatin to N-desmethyl Rosuvastatin it inhibits the rate-limiting step in cholesterol biogenesis. Being a BCS Class II drug (poor solubility and good permeability) it displays high variability in pharmacological effect because of dissolution rate limited oral absorption.

Rosuvastatin has a narrow absorption window and mainly absorbed from proximal areas of GIT. The Gastro retentive drug delivery system can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have absorption window in particular region of the GIT. These systems 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.

MATERIAL AND METHODS

Materials

Rosuvastatin was obtained as a gift sample from Dr. Reddy Lab, Hyderabad. Other excipients like Methyl cellulose K15M, Ethyl cellulose, HPMC K4M, Xanthan gum and other reagents used were of analytical grade.

Method

Gastro retentive floating Films were formulated by solvent casting technique given by Darandale Sharad and Vavia Pradeep [7]. Polymer was soaked in solvent system (water: Isopropyl alcohol 1:1) containing PEG 400 as the plasticizer for30 min. Dispersion was homogenized with high speed homogenizer to exclude lumps if any and to get smooth dispersion. SMEDDS was incorporated in the dispersion and film was casted in the fabricated mold (dimension 5 cm X 6.7 cm) and allowed to set firmly set and dry at room temperature for 24 hours. Combinations of various hydrophilic and hydrophobic polymers were screened on the basis of nature of film formed and floating ability. Floating film was further optimized by applying 2^2factorial designs.

SMEDDS Loaded Floating Film

Table 1. Screening of film forming polymer

Batch	Polymer	Ratio
F1	Methyl cellulose K15M : Ethyl cellulose	1:1
F2	Methyl cellulose K100M : Ethyl cellulose	1:1
F3	HPMC K4M : Ethyl cellulose	1:1
F4	Xanthan gum : Ethyl cellulose	1:1
F5	Xanthan gum : Pullulan : Ethyl cellulose	0.5:0.5:1
F6	Pullulan : Ethyl cellulose	1:1

Optimization of Floating Film using Full Factorial design

2^2 full Factorial design was constructed where the amount of HPMC K4M (Y1) and amount of ethyl cellulose (Y2) were independent variables and time required for 90% release of Rosuvastatin (DRR 90%) was dependent variables [8]. Two levels (low and high) for each factor were selected as shown in Table 3.12. All the other formulation ingredients like drug concentration Rosuvastatin (10 mg), PEG 400 and solvent system (IPA: water) were kept invariant throughout the study for all 4 formulation batches of Films. Films were pleated and filled in hard gelatin capsules of size 0.

Table 2. Optimization of Floating Film

Ingredients	F7	F8	F9	F10
SMEDDS (mg)	300	300	300	300
HPMC K4M (mg)	100.0 (-)	150.0 (+)	100.0 (-)	150.0 (+)
Ethyl cellulose (mg)	100.0 (-)	150.0 (+)	150.0 (+)	100.0 (-)
PEG400 (ml)	1	1	1	1
Solvent system (ml) (IPA:Water)	q.s. to 15	q.s. to 15	q.s. to 15	q.s. to 15

Characterization of Floating Film

Thickness of film

Thickness of the film was measured at three different place on the patch using a micrometer and mean value is calculated. [9]

Folding endurance

It is calculated by number of times the film could be folded at the same place without breaking/cracking. This was accomplished by repeatedly folding film at the same place till it cracked completely. The observation was carried out in triplicate. ipc-tm-650 test methods [7].

% Moisture content

The films were placed in a desiccators containing activated silica after weighing (F0) and it was maintained at room temperature for 24 hours. Observation was made by weighing the individual film till constant in weight (Fu) and % moisture content was determined [10] as,

% Moisture content = Fu-F0/Fu X100

Tensile strength

Tensile strength of films free of physical defects was determined in triplicate using Lemi Coat tester. Rectangular samples of film (30 mm X 5 mm) were subjected to analysis. The films were carefully placed between the two vertical grips of the tester and the movable grip then driven upward at 5 mm/ min until the film ruptured. From the recorded load-extension profile, the tensile strength was calculated.

Assay

Floating film loaded with Rosuvastatin SMEDDS was placed in 50 mL volumetric flask and volume was made up with methanol, followed by sonication in bath sonicator for 15-20 min to extract and solubilize the Rosuvastatin. The methonolic extract was filtered through whatman filter paper and concentration was determined by in house developed and validated HPLC method using Zorbax Eclipse® XDB- C18 column using acetonitrile : phosphate buffer pH 3.2 (9:1) as mobile phase[11]. Experiment was performed in triplicate.

Uniformity of content

10 individual dosage units were taken and assay procedure is performed on individual dosage unit as mentioned in procedure for assay [11].

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 0.1 N HCl at room temperature [12].

Unfolding study

The unfolding study of the floating film was carried out in USP Type-I dissolution apparatus. The capsule was placed in the basket and it was on immersed into the 900 ml of 0.1 N HCL the capsules dissolve and then the unfolding of the inner film was observed [13].

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 rotation was adjusted to 50 rpm. 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 239 nm using UV- Visible Spectrophotometer [14] .

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

Stability study

The optimized batch of floating film were tested for accelerated stability at 40ºC/75% RH for a period of six months and real time stability at 30 ºC/65% RH for a period of twelve months. All the films were packed in ALU- PVC-PVC-ALU type strip package. The films were evaluated for their physical characteristics, *in vitro* drug release and content of active ingredient, floating time at the end of 15, 30, 60, 90, 120, 150, 180, 240, 360 days of storage period. These conditions for stability studies were selected as per ICH Q1A (R2). As per these guidelines, India lies in zone III & IV, thus these temperature and humidity conditions were selected [15-17].

RESULTS AND DISCUSSION

Screening of film forming polymer

Various polymers were screened based on ability to float and film forming ability. Combination of methyl cellulose K15M: ethyl cellulose (1;1) and methyl cellulose K15M: ethyl cellulose (1:1) produced floating film, but it disintegrated in 4 hr and 5hr respectively. Film formulated using HPMC K4M: ethyl cellulose (1:1) produced good film with floating ability upto 12hr. Combinations of xanthan gum: ethyl cellulose (1:1), xanthan gum: pullulan: ethyl cellulose 0.5:0.5:1 and pullulan: ethyl cellulose (1:1) do not show good film forming ability. Hence combination of HPMC K4M: ethyl cellulose (1:1) is considered for further development.

Optimization of Film Floating using Full Factorial design

Full Factorial Two-Square design was utilized to understand critical factors in the film formulation that may be influencing time required for more than 90% drug release (DRR 90%). Values of the responses for prepared formulations F7 toF10 are seen in table. Each of the readings was performed in triplicate and the average taken. ANNOVA and regression analysis performed on the data points and the probability value was found to be significant (i.e., *p<0.05) for Y1 and Y2 on response of DRR 90%. The line of fit for

optimized release parameters with confidence interval of 95% for the predicted value (fit) for Film formulations was as follows;

$$DRR\ 90\% = (-3.5) + 0.070*Y1 + 0.080*Y2 - 4.00000E^{-04}*Y1*Y2$$

Table 3. DR 90% of optimization batches of SMEDDS loaded floating film

Batch	F7	F8	F9	F10
Time required to release more than 90% of the drug (hr) – DR 90%	7.5	10.0	9.50	9.0

The values found were further constructed into contour plots to depict effect of Y1 and Y2 on DRR 90% .

e further constructed into contour plots to depict effect of Y1 and Y2 on DRR 90% .

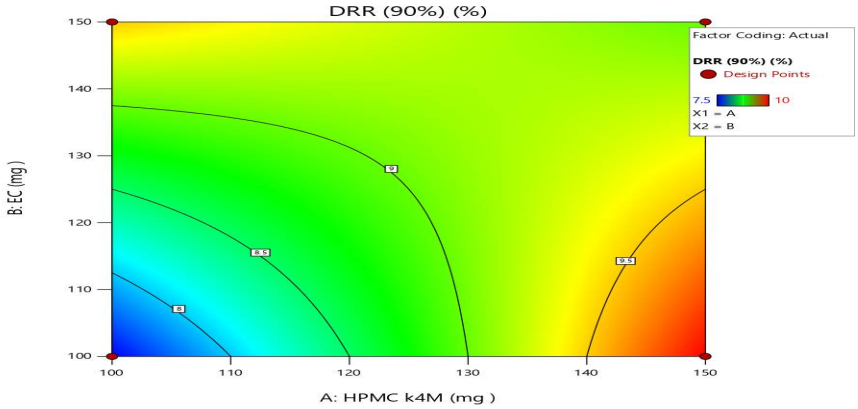

Fig. 1. Contour plot of Effect of concentration of HPMC K4M and concentration of ethyl cellulose on time required for 90% drug release

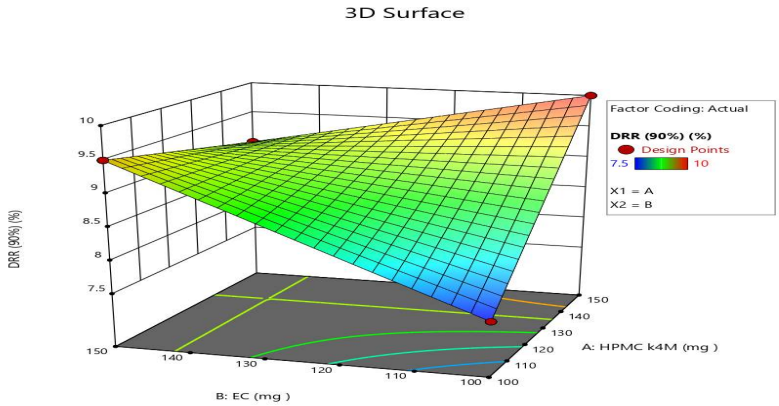

Fig 2. Surface response curve of Effect of concentration of HPMC K4M and concentration of ethyl cellulose on time required for 90% drug release

Surface response curves were constructed as shown in figure 2, which defines design space for optimized response of DRR 90% with varying ranges of Y1 and Y2.

Characterization of Floating Film

Table 4. Characterization of floating film

Batch	F7	F8	F9	F10
Thickness of film (mm)	1.4 ± 0.23	1.54± 0.65	1.53 ±0.66	1.47 ±0.4
Folding endurance	167.9 ± 6.3	290.0 ± 3.3	236.8 ± 11.2	205.3 ±8.5
Percentage ofmoisture content	1.01± 0.22	1.01 ± 0.09	1.01± 0.09	1.01± 0.13
Percentage moisture absorption	1.13 ± 0.03	1.13 ± 0.07	1.13 ± 0.09	1.13 ± 0.05
Tensile strength (mPa)	8.4 ± 2.1	15.2 ± 3.3	13.9 ± 4.1	10 ± 2.9
Assay	96.6 ± 0.02 %	99.8 ± 0.01%	95± 0.1%	97.1± 0.2%
Content uniformity	95.8 ± 0.1	98.9±0.4	96± 0.5	98.5 ± 0.4
Floating lag time (min)	25 ± 0.05	18 ± 0.1	16 ± 0.2	17.5 ± 0.3
Total floating time (hr)	≥12	≥ 12	≥ 12	≥ 12

* All result expressed are mean ± SD, n=3.

Tensile strength of film varies from 8.4-15.2m Pa. Increase in polymer weight/ratio shows a significant increase in the tensile strength. The data indicates that as the concentration of polymer increases thickness increases. Thickness is directly proportional to tensile strength. In other words as thickness increases tensile strength also increases. The moisture content of the prepared formulations was low, which could help the formulations remain stable and reduce brittleness during long term storage. The moisture uptake of the formulations was also low, which could protect the formulations from microbial contamination and reduce bulkiness. Low moisture content ensures stability and prevents the formation of dried and brittle films. The moisture uptake of the formulations indicates that in high humid environment, the patches take up very little moisture (1-2%). This may favors the stability as well as compatibility with high humid conditions of the formulations.

Unfolding study

Optimized batch of capsule has good unfolding characteristic. For dissolution of out capsule shell it took almost 10-15 mins and simultaneously unfolding of film also started. Within 5 minutes of dissolution of the capsule film unfolds and takes a planar structure.

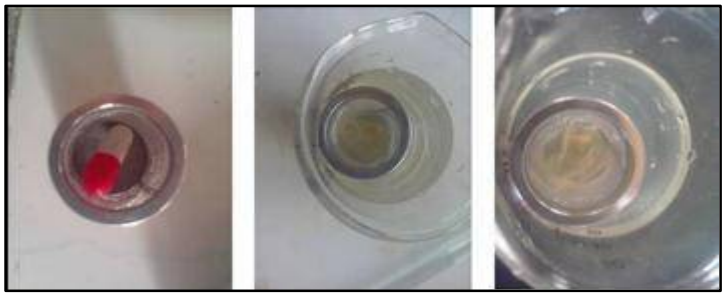

Fig. 3. Unfolding behaviour of floating film

In vitro Drug release study

Table 5. Dissolution profile of various batches of floating film

Time in hrs	% cumulative release			
	F7	F8	F9	F10
1	6.89 ± 0.06	3.51 ± 0.03	4.38 ± 0.01	1.99 ± 0.05
2	15.54 ± 0.1	8.74 ± 0.04	9.65 ± 0.05	6.89 ±0.08
3	27.63 ± 0.017	15.96 ± 0.08	17.76 ± 0.02	13.98 ± 0.1
4	41.82 ± 0.015	27.63 ± 0.07	35.99 ± 0.043	25.21 ± 0.04
5	63.64 ± 0.45	39.03 ± 0.05	49.88 ± 0.21	35.82 ± 0.037
6	72.88 ± 0.045	50.76 ± 0.22	65.44 ± 0.03	48.12 ± 0.035
7	85.91± 0.26	60.9 ± 0.36	81.01 ± 0.07	58.95 ± 0.032
8	96.79 ± 0.095	74.76 ± 0.07	92.65 ± 0.09	72.89 ± 0.07
9	--	85.53 ± 0.11	96.88 ± 0.1	85.11 ± 0.02
10	--	98.43 ± 0.02	--	94.24 ± 0.01

All result expressed are mean ± SEM, n=6

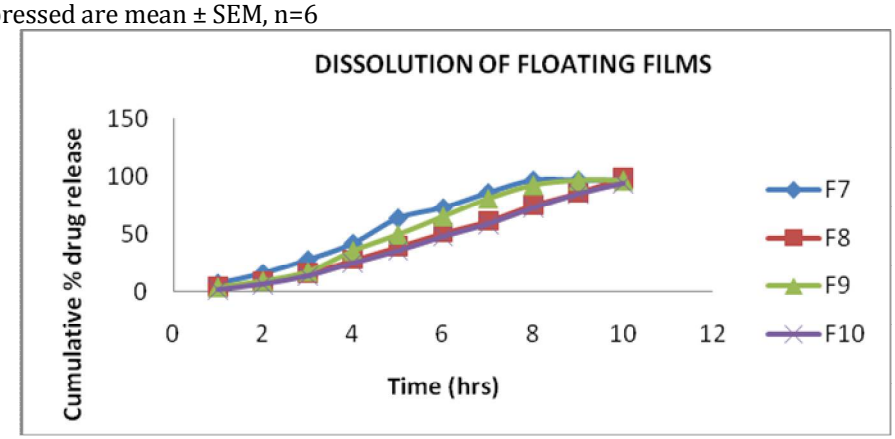

Fig. 4. Dissolution profile of Floating film

Release kinetic study

From mathematical modeling data, it is seen that the R^2 for the optimized formulation F8 follows Zero order. It had a regression coefficient of 0.9624. Thus the release mechanism of release for the optimized formulation is independent of concentration and constant drug release from a drug delivery system and drug level in the blood remains constant throughout the delivery.

Table 6. Mathematical Modeling of Kinetic Release of optimized batch of floating film

Batch Code	R^2			
	Zero order	First order	Higuchi	Korsemeyer Peppas
F8 (Optimized Formulation)	0.9624	0.9256	0.7836	0.8838

Stability study

Table 7 Stability study of SMEDDS loaded floating film

Parameters	Storage condition	0 day	15 days	30 days	60 days	90 days	120 days	150 days	180 days	240 days	360 days
Physical appearance	40 ºC/ 75% RH	+++	+++	+++	+++	+++	+++	+++	+++	--	--
	30 ºC/ 65% RH	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
Folding endurance	40 ºC/ 75% RH	6.7±0.02	6.7 ±0.71	6.7 ±0.31	6.7±0.43	6.7±0.40	6.6 ±0.23	6.6 ±0.15	6.6±0.36	--	--
	30 ºC/ 65% RH	6.7± 0.20	6.7 ± 0.45	6.7 ± 0.32	6.7±0.41	6.7±0.39	6.6±0.18	6.6 ±0.19	6.6±0.16	6.6 ±0.11	6.6 ± 0.15
Assay (%)	40 ºC/ 75% RH	99.93±0.01	99.92±0.05	99.83±0.1	99.94±0.02	99.94±0.07	99.93±0.06	99.93±0.2	99.92±0.03	--	--
	30 ºC/ 65% RH	99.93±0.04	99.92±0.01	99.89±0.04	99.90±0.1	99.87± 0.02	99.92±0.04	99.88±0.03	99.89±0.01	99.85±0.03	99.83±0.02
Content uniformity	40 ºC/ 75% RH	98.65±0.1	98.6±0.2	98.63±0.8	98.47±0.2	98.45±0.13	98.4±0.14	98.3±0.18	98.32±0.5	--	--
	30 ºC/ 65% RH	98.6± 0.1	98.6± 0.1	98.6± 0.1	98.4± 0.3	98.40± 0.1	98.3 ±0.1	98.3±0.1	98.3 ±0.2	98.3± 0.3	98.3 ±0.2
Tensile strength (%w/w)	40 ºC/ 75% RH	15.4±0.1	15.1±0.1	15.3±0.2	15.1±0.1	15.2±0.2	15.2±0.2	15.2±0.1	15.1±0.1	--	--
	30 ºC/ 65% RH	15.4±0.1	15.0± .2	15.3±0.1	15.3±0.2	15.2± 0.5	15.1± 0.4	15.0± 0.5	15.0± 0.6	14.9± 0.3	14.9± 0.4
Average Floating lag time (sec)	40 ºC/ 75% RH	390±5.77	390± 2.88	375± 2.30	380± 0.57	390± 2.51	380±5.77	400±2.88	420±2.30	--	--
	30 ºC/ 65% RH	390±5.77	390±2.88	395±2.88	375±1.15	400±5.77	388±4.04	410±2.51	400±2.88	420±4.04	420±2.88
Total floating time (hrs)	40 ºC/ 75% RH	≥12	≥ 12	≥ 12	≥ 12	≥ 12	≥12	≥12	≥ 12	--	--
	30 ºC/ 65% RH	≥ 12	≥12	≥ 12	≥12	≥12	≥12	≥ 12	≥12	≥12	≥ 12

All values are expressed as mean ± SD, n=3

Table 8. Dissolution profile of SMEDDS loaded floating film during stability study at 40ºC/75%RH

Time in hr	% Cumulative Release							
	0 day	15 days	30 days	60 days	90 days	120days	150days	180days
1 hr	3.42± 0.01	3.42± 0.02	3.41± 0.05	3.41± 0.08	3.40± 0.04	3.39± 0.01	3.38± 0.01	3.38± 0.12
2 hrs	9.1±0.2	9.1± 0.22	9.1± 0.03	9.0± 0.2	9.0± 0.05	8.91± 0.03	8.89± 0.03	8.84± 0.12
3 hrs	16.7± 0.03	16.75±0.23	16.71±0.04	15.91±0.07	15.89±0.01	15.82±0.16	15.79±0.01	15.76±0.04
4 hrs	27.97±0.4	27.95±0.07	27.90±0.03	27.88±0.04	27.86±0.23	27.85±0.18	27.81±0.03	27.79±0.1
5 hrs	40.12±0.07	40.13± 0.03	40.01± 0.2	39.98 ± 0.03	39.94± 0.05	39.93± 0.01	39.90± 0.05	39.87±0.5
6 hrs	51.15±0.03	51.13±0.06	51.09±0.04	51.02±0.07	50.99±0.04	50.89±0.67	50.82±0.03	50.76±0.05
7 hrs	61.2± 0.01	61.2± 0.03	61.15±0.06	61.10±0.2	61.01±0.13	60.99±0.05	60.91±0.25	60.85±0.07
8hrs	74.98±0.34	74.92±0.05	74.89±0.07	74.84±0.05	74.80±0.04	74.76±0.01	74.73±0.08	74.71±0.04
9 hrs	85.85±0.06	85.85±0.1	85.81±0.06	85.75±0.04	85.71±0.03	85.68±0.04	85.61±0.05	85.58±0.04
10 hrs	98.71±0.01	98.69±0.02	98.61±0.02	98.57±0.11	98.51±0.11	98.49±0.02	98.45±0.06	98.41±0.01
All values are expressed as mean ± SEM, n=6								

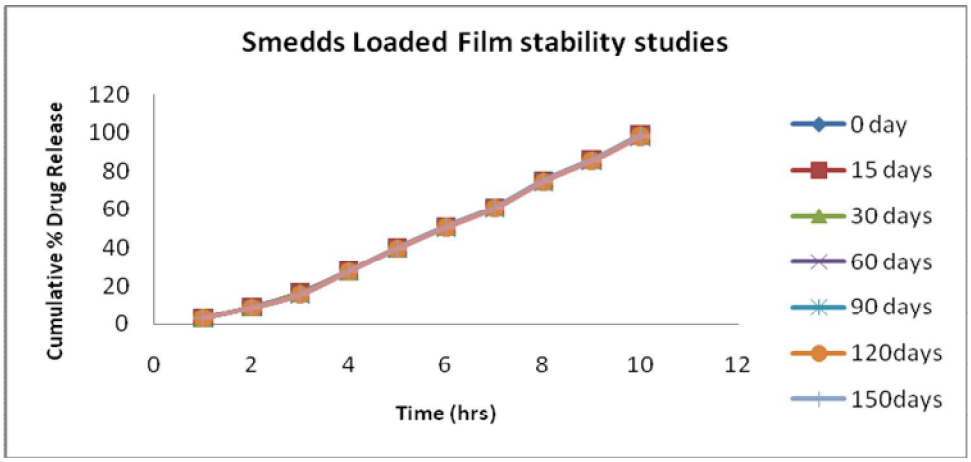

Fig. 5. Dissolution profile of stability batches at 45 ^{0}C/75%RH

Table 9. Dissolution profile of SMEDDS loaded floating film during stability study at 30 ºC/65% RH

Time in hr	% Cumulative Release									
	0 day	15 days	30 days	60 days	90 days	120 days	150 days	180 days	240 days	360 days
1 hr	3.42±0.04	3.4±0.01	3.41±0.04	3.40±0.1	3.40±0.03	3.39±0.06	3.38±0.05	3.36±0.04	3.35±0.09	3.31±0.05
2 hrs	9.1±0.01	9.0 ± 0.02	8.89±0.01	8.88±0.06	8.86±0.05	8.85±0.03	8.85±0.07	8.84±0.05	8.84±0.01	8.79±0.02
3 hrs	16.76±0.07	16.74±0.2	16.72±0.04	16.71±0.01	16.70±0.02	16.0±0.02	15.91±0.03	15.88±0.01	15.81±0.02	15.78±0.06
4 hrs	27.97±0.01	27.96±0.03	27.95±0.02	27.91±0.06	27.89±0.05	27.86±0.04	27.85±0.07	27.83±0.05	27.82±0.06	27.79±0.03
5 hrs	40.12±0.03	40.12±0.1	40.10±0.06	40.09±0.2	40.07±0.01	40.04±0.03	40.03±0.2	40.01±0.04	39.90±0.1	39.86±0.07
6 hrs	51.15±0.04	51.14±0.01	51.14±0.08	51.13±0.05	51.10±0.3	51.06±0.06	50.91±0.2	50.87±0.7	50.84±0.06	50.76±0.03
7 hrs	61.2±0.08	61.2±0.04	61.1±0.01	61.06±0.03	61.01±0.01	60.96±0.08	60.93±0.06	60.90±0.3	60.88±0.1	60.85±0.02
8hrs	74.98±0.52	74.98±0.04	74.97±0.07	74.93±0.05	74.89±0.01	74.85±0.03	74.83±0.02	74.81±0.1	74.79±0.03	74.77±0.6
9 hrs	85.85±0.01	85.85±0.05	85.84±0.03	85.81±0.4	85.77±0.03	85.73±0.02	85.69±0.05	85.65±0.03	85.62±0.04	85.59±0.07
10 hrs	98.71±0.1	98.71±0.05	98.72±0.2	98.69±0.05	98.65±0.3	98.61±0.1	98.58±0.3	98.53±0.2	98.51±0.01	98.45±0.03

All values are expressed as mean ± SEM, n=6

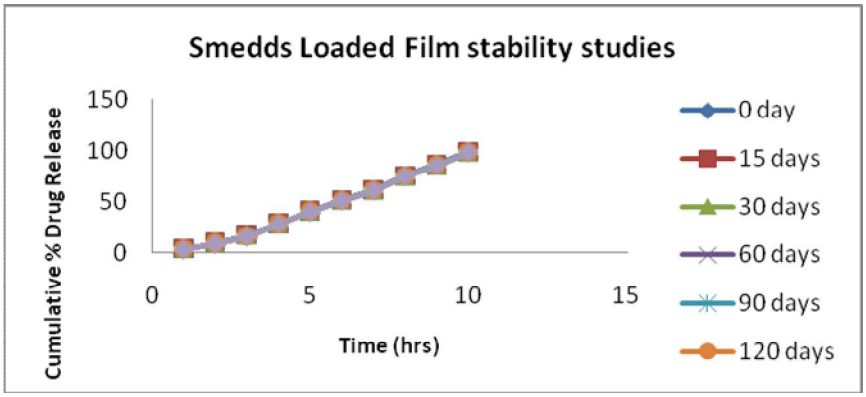

Fig. 6. Dissolution profile of stability batches at30°C/60% RH

Long term stability of floating film loaded with SMEDDS were evaluated at 40 °C/75 % RH for a period of 6 months and at 30 °C/65% RH for a period of 12 months. From the stability study data it was found that there was no significant change in the physical parameters and dissolution profile of drug. Thus, the formulation is found to be stable.

CONCLUSION

Rosuvastatin is a HMG COA reductase inhibitor widely used in the treatment of hypercholesterolemia and dyslipidemia as an adjunct to diet. It is a BCS class II drug and has absorption window in the upper duodenum, making it an ideal candidate to formulate as SMEDDS to improve solubility and dissolution rate and incorporating it in a Gastro retentive dosage form. It has a dose of 5-10 mg and short half- life of 3-4 hr

thereby justifying development of its sustained release dosage form. Thus Rosuvastatin is an ideal candidate to be formulated as a combined dug delivery which encompassed the advantages of sustained release Gastro retentive system loaded with SMEDDS Further Gastro retentive film was developed using combination of various hydrophilic and hydrophobic polymer. SMEDDS loaded Gastroretentive floating films were developed using solvent casting method. Developed films were characterized for parameters like folding endurance, tensile strength, floating lag time, total floating time, assay and dissolution study. F8 Optimized formulation was subjected to stability study at 40^0c/75% RH for 6 months and 30 ^{0}c/65% RH for 12 months. *In vivo* Gastro retention studies were carried out in rabbits and monitored by X-ray. Lipid lowering study was carried out on plain drug, SMEDDS and SMEDDS loaded film. Hence from this we can conclude that the developed floating films can be effective in treating the hyperlipidemia.

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CONFLICT OF INTEREST

Nil.

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