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Formulation and Optimization of Sustained Release Tablets of Rosuvastatin Using HPMC K4M, HPMC K100M and Carrageenan

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Abstract : The objective of the present study was to develop once daily sustained release tablets of Rosuvastatin (40mg) by using HPMC K4M, HPMC K100M and natural gum like carrageenan. Various ratios of drug and polymer like 1:1, 1:2 and combination were selected for the study. The drug- excipient mixture was subjected to physico chemical studies, in vitro drug release, and kinetic studies. The physicochemical properties of tablets were found to be within limits. The in vitro release of Rosuvastatin tablets was studied in 900ml of 0.1N HCl for 2 h at 37±0.5°C at 50 rpm, and then release studies were conducted in pH 6.8 phosphate buffer for 20 h. The optimized formulation F10 contain HPMC K4M (20mg) , HPMC K100M (20mg) shows drug release up to 99.4% in 20h and follows first order release with non Fickian diffusion mechanism.

Key words : Matrix tablets, Rosuvastatin, sustained release, HPMC K4M, HPMC K100M, carrageenan.

Introduction

Retention of drug delivery systems in the stomach prolongs overall gastrointestinal transit time improving oral bioavailability of the drugs that are having site specific absorption from the stomach or parts of small intestine. Therefore different approaches have been proposed to retain the dosage form in the stomach including bioadhesive systems, swelling, and expanding systems and delayed gastric emptying devices to achieve gastric residence time for sustained drug release[1].Sustained release dosage form is defined as well characterized and reproducible dosage form, which is designed to control drug release profile at a specified rate to achieve desired drug concentration either in blood plasma or at target site[2].

While selecting a drug candidate for sustained release system we must be careful. Drugs having characteristics like which are not effectively absorbed in the lower intestine, those having short biological half-lives,those for whom large dose is required, those with low therapeutic indices those for which no clear advantage of sustained release system,those with extensive first pass metabolism, candidates with low solubility and/or active absorption are not suitable for sustained release systems[3].

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The most employed method to modulate the sustained drug release is to include it in a matrix system. Because of their flexibility, hydrophilic polymer matrix systems are widely used in oral controlled drug delivery to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance[4].

Rosuvastatin is the newest member of the statin class of lipid lowering compounds, which inhibit HMG-CoA reductase and reduce cholesterol synthesis[5]prescribed extensively for cholesterol lowering in the primary and secondary prevention of cardiovascular disease.

In the present work sustained-release (SR) matrix tablets of Rosuvastatin were prepared by using different polymers like HPMC K4M, HPMC K100M and natural gum like carrageenan. Out of different granulation technologies[6,7,8,9] direct compression[10,11,12]technique was used to prepare the SR tablets. The compressed tablets were evaluated to study theeffect of nature of the polymer and also the drug to polymer ratio on the rate of drug release profile from the tablet formulations including relevant kinetic profiles.

Materials and Method

Materials

Rosuvastatin was purchased from YarroChem Products, Mumbai. Hydroxypropyl Methyl Cellulose (HPMC) K4M and HPMC K100M were obtained from Orchid Health Care, Chennai. Microcrystalline cellulose (MCC) was obtained from Moly Chemicals Ltd., Mumbai. Carragenanwas obtained from HiMedia Laboratories, Mumbai. All other reagents and solvents used were of analytical grade.

Construction of standard graph of Rosuvastatin

Accurately weighed amount of 100 mg of rosuvastatin was transferred into a 100 ml volumetric flask. Methanol was added to dissolve the drug and the primary stock solution was made by adding 100 ml of methanol. So the rosuvastatin stock solution concentration was 1 mg/ml. From the primary stock solution a 10 ml was transferred in to another volumetric flask and made up to 100 ml with 6.8 pH phosphate buffer and labeled as secondary stock solution. From this secondary stock 0.2, 0.4, 0.6, 0.8 and 1ml was taken separately and made up to 10 ml with 6.8 pH phosphate buffer. The absorbance was measured at 252 nm using a UV spectrophotometer (Systronic, Hyderabad, India).

Fourier transforminfrared spectroscopy (FTIR) studies

FTIR studies were performed on drug and the optimized formulation using Shimadzu FTIR (Shimadzu Corp., India). The samples were analyzed between wave numbers 4000 and 400 cm^{-1}.

Preparation of Rosuvastatin matrix tablets

Using various polymers like HPMC K4M, HPMC K100 and carrageenan tablets were prepared along with other additives. A total number of 12 formulations were prepared and evaluated. All the matrix tablets, each containing 40 mg of rosuvastatin, were prepared by direct compression method and also to study the effect of various ratios of different types of polymers on the drug release. MCC followed by rosuvastatin were passed through # 80 mesh and blended properly in a double lined poly bag for 5 min. The remaining excipients (details were given in table 1) were passed through # 80 mesh and added to the double lined poly bag for thorough mixing by blending one after another. The tablet powder was compressed into tablets on a 16- station tablet punching machine (M/s Cadmach machineries Pvt. Ltd., Ahmedabad) to a hardness of 5- 6 kg/cm^2using 9 mm flat punches. In each case 100 tablets were compressed.

In formulations prepared, the release retardants included were hydroxyl propylmethylcellulose (HPMC K4M, HPMC K100) and Carrageenan. Microcrystalline cellulose (MCC) was used as diluent. Magnesium stearate (2% w/w) and talc (4% w/w) were used as lubricants. Compositions of different formulations were given in table 1.

Table 1.Composition of matrix tablets

Ingredient	Formulation Code											
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Rosuvastatin	40	40	40	40	40	40	40	40	40	40	40	40
HPMC K4M	30	-	-	40	-	-	50	-	-	30	-	30
HPMC K100M	-	30	-	-	40	-	-	50	-	30	30	-
Carrageenan	-	-	30	-	-	40	-	-	50		30	30
MCC	124	124	124	114	114	114	104	104	104	94	94	94
Talc	4	4	4	4	4	4	4	4	4	4	4	4
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2
Total weight (mg)	200	200	200	200	200	200	200	200	200	200	200	200

Evaluation of precompression blend

Angle of repose

The angle of repose of precompression blend was determined by the funnel-method. The accurately weighed blend was taken in a funnel. The height of the funnel was adjusted in such a manner that the tip of the funnel just touched the apex of the heap of the powder blend. The powder blend was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone measured and angle of repose was calculated using the following equation.

$\tan \theta = h/r$

where, h and r are the height and radius of the powder cone, θ is the angle of repose.

Determination of bulk density and tapped density

An accurately weighed quantity of the granules/ powder (W) was carefully poured into the graduated cylinder and volume (V_0) was measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP). The density apparatus was set for 500 tabs and after that the volume (V_f) was measured and continued operation till the two consecutive readings were equal (Lachman et al., 1987).The bulk density and the tapped density were calculated using the following formulae.

Bulk density = $W/V_{0;}$ Tapped density = W/V_f

where, W= Weight of the powder; V_0 = Initial volume; V_f = final volume

Compressibility index (Carr'sindex)

Carr's index (CI) is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is (Lachman et. al., 1987).

CI = (TD-BD) x 100/TD; where, TD is the tapped density and BD is the bulk density

Hausner'sratio

It is the ratio of tapped density and bulk density. Hausner found that this ratio was related to inter particle friction and, as such, could be used to predict powder flow properties (Lachman et al., 1987). Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index.

Hausner's Ratio= Tapped density/ Bulk density

Evaluation of matrix tablets

Thickness

Twenty tablets from the representative sample were randomly taken and individual tablet thickness was measured by using Vernier caliper. Average thickness and standarddeviation values were calculated.

Hardness

Tablet hardness was measured by using Monsanto hardness tester. From each batch six tablets were measured for the hardness and average of six values was noted along with standard deviations.

Friability test

From each batch, ten tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator). Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were then taken after 100 rotations, deducted and reweighed. The friability was calculated as the percentage weight loss.

$$\% \text{ Friability} = (W_1 - W_2) \times 100/W_1$$

Where, W_1= Initial weight of the 20 tablets; W_2 = Final weight of the 20 tablets after testing.

Weight variation test

To study weight variation individual weights (W_I) of 20 tablets from each formulation were noted using electronic balance. Their average weight (W_A) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated.

$$\% \text{ weight variation} = (W_A - W_I) \times 100/ W_A$$

As the total tablet weight was 100 mg, according to IP 1996, out of twenty tablets ±10 % variation can be allowed for not more than two tablets. According to USP 2004, ±10% weight variation can be allowed for not more than two tablets out of twenty tablets.

Drug content estimation

The drug content of the matrix tablets was determined according to in-house standards and it meets the requirements if the amount of the active ingredient in each of the 3 tested tablets lies within the range of 90% to 110% of the standard amount. Three tablets were weighed and taken into a mortar and crushed into fine powder. An accurately weighed portion of the powder equivalent to average weight of three tablets of rosuvastatin was transferred to a 100 ml volumetric flask containing 6.8 pH Phosphate buffer solution and the volume was made up to the mark. From this 10ml was taken and shaken by mechanical means using centrifuge at 3000rpm for 30min. Then it was filtered through Whatman filter paper. From this resulted solution 1 ml was taken, diluted to 10 ml with 6.8 pH Phosphate buffer solution and absorbance was measured against blank at 252 nm.

*In vitro*drug release characteristics

Drug release was assessed by using dissolution test apparatus USP type II (paddle method). The in vitro release of rosuvastatin tablets was studied in 900 ml of 0.1N HCl for 2 h at 37±0.5°C at 50 rpm, and then release studies were conducted in pH 6.8 phosphate buffer for 20 h. Aliquot (5ml) was withdrawn at specific time intervals and replaced with the same volume of prewarmed (37°C ± 0.5°C) fresh dissolution medium. The absorbance values were analyzed by UV-visible spectrophotometer at 252 nm. All the experiments were conducted in triplicates (n=3).

Kinetic analysis of dissolution data

To analyze the in vitrorelease data various kinetic models were used to describe the release kinetics. The zero order rate equation (Eq. 1) describes the systems where the drug release rate is independent of its

concentration (Hadjiioannou*et al*., 1993). The first order equation (Eq. 2) describes the release from system where release rate is concentration dependent (Bourne, 2002). Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion equation (Eq. 3). The Hixson-Crowell cube root law equation (Eq. 4) describes the release from systems where there is a change in surface area and diameter of particles or tablets (Hixson and Crowell, 1931).

$$C = K_0 t \quad (1)$$

where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$LogC = LogC_0 - K_1 t / 2.303 \quad (2)$$

where, C_0 is the initial concentration of drug and K_1 is first order constant.

$$Q = K_H t^{1/2} \quad (3)$$

where, K_H is the constant reflecting the design variables of the system.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC} t \quad (4)$$

where, $Q_t$is the amount of drug remained in time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for Hixson-Crowell rate equation.

Mechanism of drug release

Korsmeyer*et al* (1983) derived a simple relationship which described drug release from a polymeric system equation (Eq. 5). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model.

$$M_t / M_\infty = Kt^n \quad (5)$$

where $M_t / M\infty$ is fraction of drug released at time t, K is the release rate constant incorporating structural and geometric characteristics of the tablet, and n is the release exponent. The n value is used to characterize different release mechanisms. A plot of log cumulative % drug release vs. log time was made. Slope of the line was 'n'. The 'n' value is used to characterize different release mechanisms as given in table4, for the cylindrical shaped matrices.Case-II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release (Peppas, 1985).

Table 4. Kinetic analysis of data from F1-F12 formulations

Formulation code	Higuchi (r^2) value	Korsemeyer Peppa's		Zero order (r^2) value	First order (r^2) value
		(r^2) value	'n' value		
F1	0.969	0.992	0.861	0.935	0.748
F2	0.961	0.990	0.846	0.947	0.869
F3	0.983	0.990	0.760	0.962	0.550
F4	0.986	0.979	0.583	0.965	0.848
F5	0.992	0.993	0.582	0.965	0.629
F6	0.979	0.984	0.700	0.966	0.759
F7	0.974	0.984	0.799	0.947	0.800
F8	0.990	0.994	0.579	0.949	0.637
F9	0.991	0.994	0.609	0.955	0.796
F10	0.994	0.995	0.658	0.967	0.830
F11	0.986	0.994	0.707	0.961	0.785
F12	0.981	0.992	0.759	0.958	0.887

Results and Discussions

Calibration curve of Rosuvastatin in 0.1 N HCl and pH 6.8 phosphate buffer

Standard graph of rosuvastatin was constructed using 6.8 pH phosphate buffer. Various concentrations 2 to 10 µg/ml were prepared. The absorbance of prepared concentrations was measured at 252nm (using pH 6.8 phosphate buffer as diluent) by adjusting to zero with blank sample. A graph was plotted by taking concentration on x-axis and absorbance on y-axis and best fit line was drawn and regression value and equation was calculated and represented in figure 1.

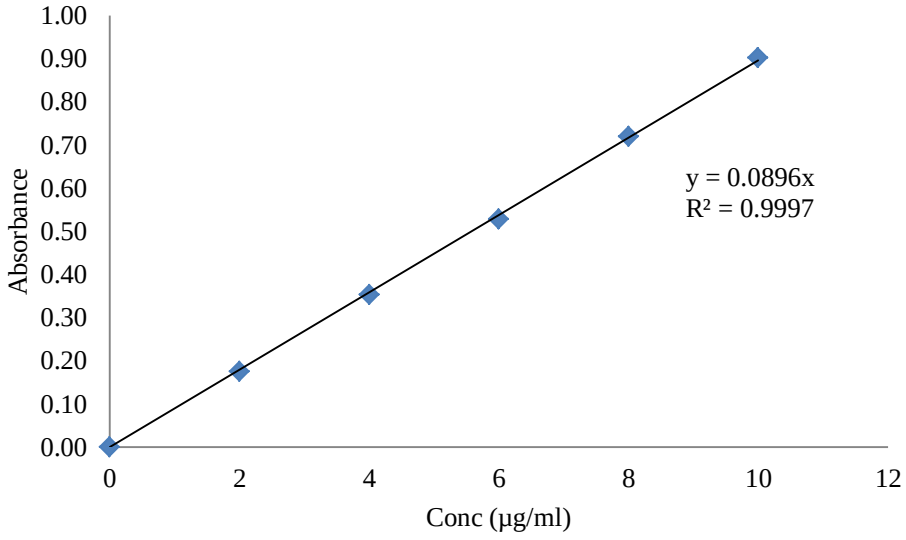

Figure 1.Calibration curve of rosuvastatin in 6.8 pH phosphate buffer

Drug-polymer interaction/ compatibility study using FTIR

FTIR studies were performed on drug and the optimized formulation using shimadzhu FTIR. The samples were analyzed between wave numbers 4000 and 400 cm-¹. Rosuvastatin pure drug is found to be stable and no interactions were identified in the formulation. The FTIR spectra's were given in figure 2, 3.

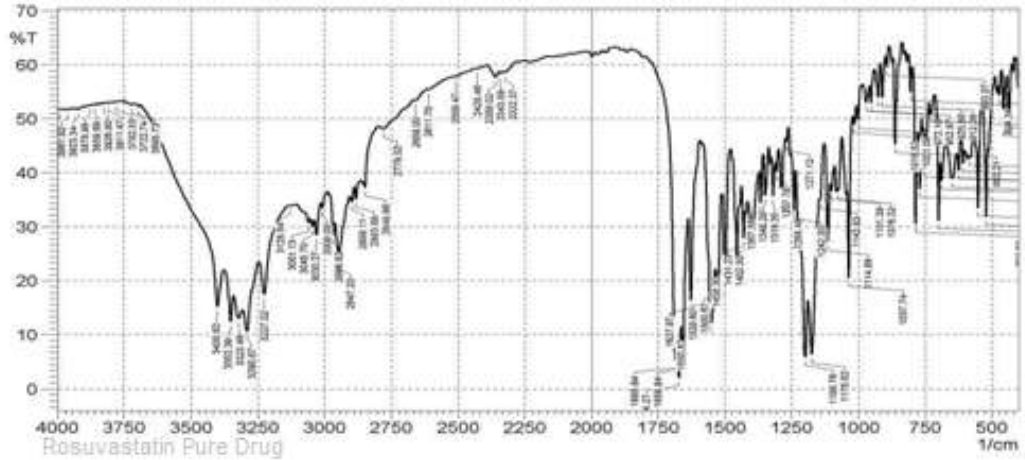

Figure 2. FTIR spectral analysis of Rosuvastatin

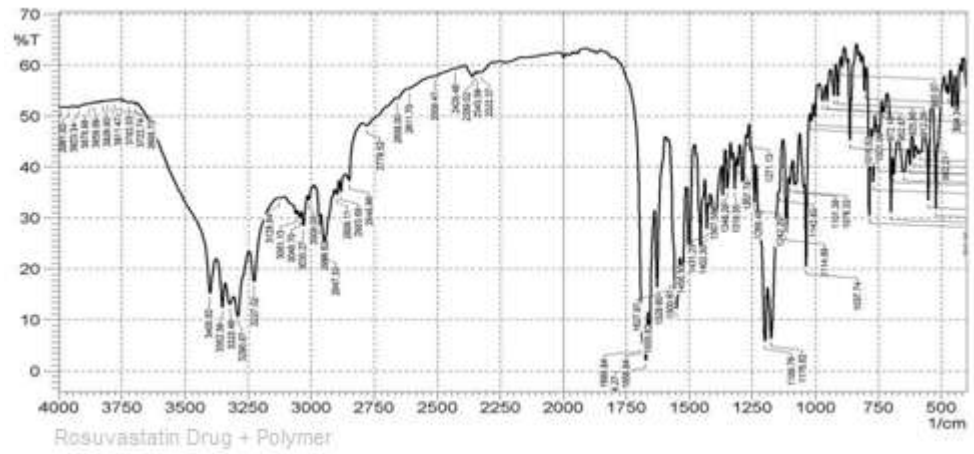

Figure3.FTIR spectral analysis of physical mixture of drug and polymer

Pre compression parameters

Before preparation of the SR tablets of rosuvastatin, the powder mass was evaluated for flow properties. All the prepared formulations showed good flow properties and the parameters were given in table 2. Bulk density and tapped density were found in the range 0.50-0.56 g/cc and 0.62-0.69 g/cc respectively. The value of Hausner's ratio was in between 1.18-1.34 indicating that all batches of powder blends were having good compressibility. Values of angle of repose (θ) was found in the range of 19.65- 21.80 showing that blend of powder mass was good flowing.

Table2. Pre compression parameter values

Formulation code	Bulk density	Tapped density	Carr's index	Hausner's ratio	Angle of repose
F1	0.55	0.65	15.38	1.18	19.45
F2	0.54	0.62	12.90	1.14	19.65
F3	0.56	0.64	12.50	1.14	21.35
F4	0.54	0.65	16.92	1.16	20.69
F5	0.50	0.67	16.37	1.34	20.82
F6	0.52	0.66	17.18	1.20	20.72
F7	0.51	0.67	18.88	1.31	20.89
F8	0.52	0.69	17.63	1.32	20.78
F9	0.56	0.68	17.64	1.21	20.61
F10	0.54	0.63	14.28	1.26	19.30
F11	0.51	0.62	17.74	1.21	21.62
F12	0.52	0.63	17.46	1.21	21.80

Table 3. Post compression parameter values

Formulation code	Thickness (mm)	Weight variation(mg)	Friability (%)	Hardness	%Drug content
F1	2.41±0.07	200.65±4.16	0.16	5.4±0.15	96.19±1.14
F2	2.45±0.07	199.67±5.17	0.18	5.5±0.14	99.69±0.80
F3	2.43±0.05	198.89±3.21	0.17	5.3±0.07	99.77±2.47
F4	2.35±0.04	201.05±6.24	0.25	5.6±0.11	100.38±1.87
F5	2.54±0.07	199.12±5.23	0.22	5.3±0.15	99.38±1.22
F6	2.60±0.09	196.46±4.78	0.32	6.0±0.14	98.51±1.37
F7	2.63±0.06	198.99±1.24	0.48	5.6±0.04	99.49±1.17
F8	2.72±0.23	199.76±2.35	0.25	5.5±0.12	98.17±1.20

F9	2.46±0.022	199.13±1.24	0.42	5.0±0.033	99.38±1.17
F10	2.62±0.04	198.45±3.21	0.02	5.5±0.14	98.30±1.22
F11	2.54±0.07	199.78±4.16	0.12	6.0±0.17	99.41±0.80
F12	2.20±0.05	199.56±5.23	0.14	5.5±0.11	98.63±1.14

Values are given as mean ± S.D,n=3

Post compression parameters

The average weight in all the 12 formulations was found to be 196.46 mg to 201.05mg. In all 12 formulations no tablets were outside the ±10%of tablet weight in weight variation test. The thickness varies between 2.20 to 2.72mm. In all formulations tablet thickness of all formulations was within ±5% of standard value. Friability values were less than 1% in all cases. Hardness of all the tablets was maintained at 5 to 6 kg/cm^2 for all the formulations. The results of the weight variation, hardness, thickness, friability, and drug content of the tablets are given in table 3.

Drug content

The rosuvastatin tablets were tested for drug content by UV method. Assay was performed and percent drug content of all the tablets were found to be between 96.2% and 100.38% of rosuvastatin, which was within the acceptable limits and the results were shown in table 3.

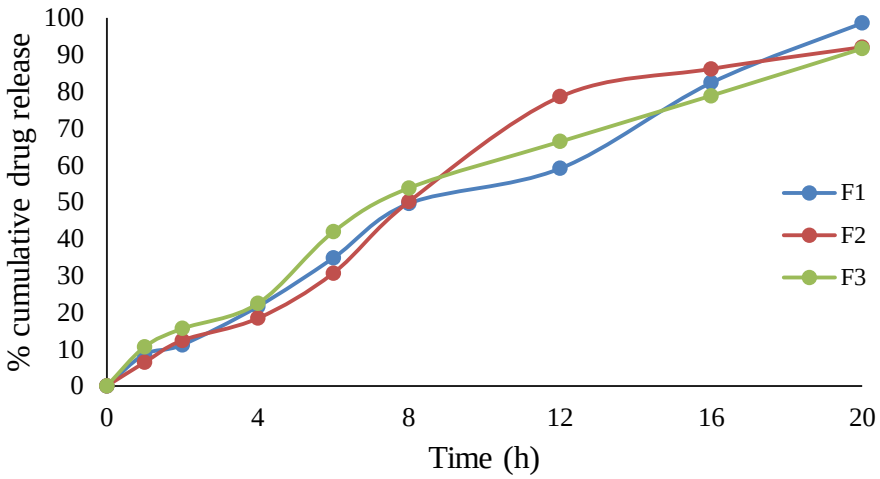

Figure4.Percentage cumulative drugrelease invitro release data of sustained release tablets of Rosuvastatin from F1 – F3 formulations

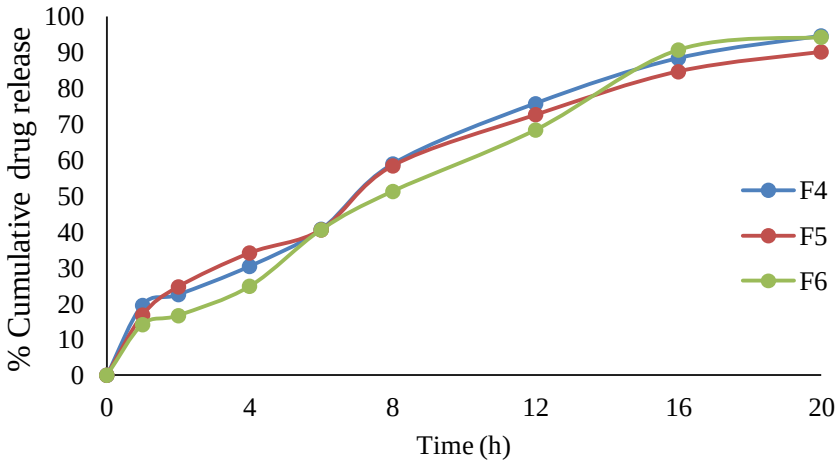

Figure 5.Percentage cumulative drug release invitro release data of sustained release tablets of Rosuvastatin from F4 – F6 formulations

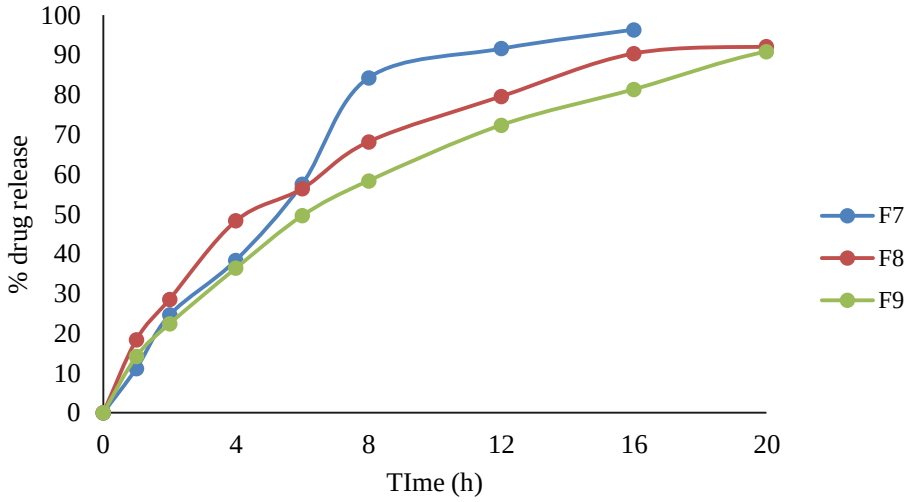

Figure 6.Percentage cumulative drug release invitro release data of sustained release tablets of Rosuvastatin from F7 – F9 formulations

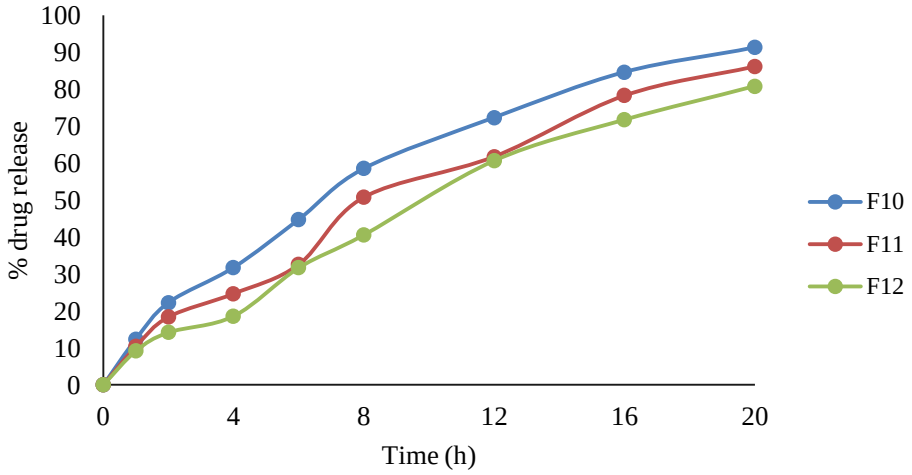

Figure 7.Percentage cumulative drug release invitro release data of sustained release tablets of Rosuvastatin from F10 – F12 formulations

In vitro dissolution and drug release kinetics

The dissolution rate was found to be increased linearly with the increase in concentration of polymer. The release rate kinetic data for all the formulations were shown in table 4.As shown in figures 4- 7 the drug release data was best explained by zero order equation where they showed the highest linearity (r^2= 0.967), followed by Higuchi's equation (r^2= 0.994).As the drug release was best fitted in zero order kinetics and indicatedthat the rate of drug release was concentration independent. Higuchi's kinetics explains how the drug diffuses at a comparatively slower rate as the distance for diffusion increases. The log cumulative percent drug release vs log time graphs for the Korsmeyer- Peppas equation indicated a good linearity (r^2= 0.995) and were shown in figure 8c. The diffusion exponent "n" was between 0.45-0.89, which indicated that the diffusion mechanism follows non-Fickian and further indicates that the drug release was controlled by more than one process.From the kinetic analysis data formulation 10 (F10) was selected as optimized formulation. The optimized formulation consists of HPMC K4M (30 mg) and HPMC K100M (30 mg) as release modifiers. From the dissolution profiles and dissolution kinetics F10 tablet formulation with a combination of HPMC K4M and HPMC K100M was found to be better with a drug release of 99.4%by the end of 20 h.

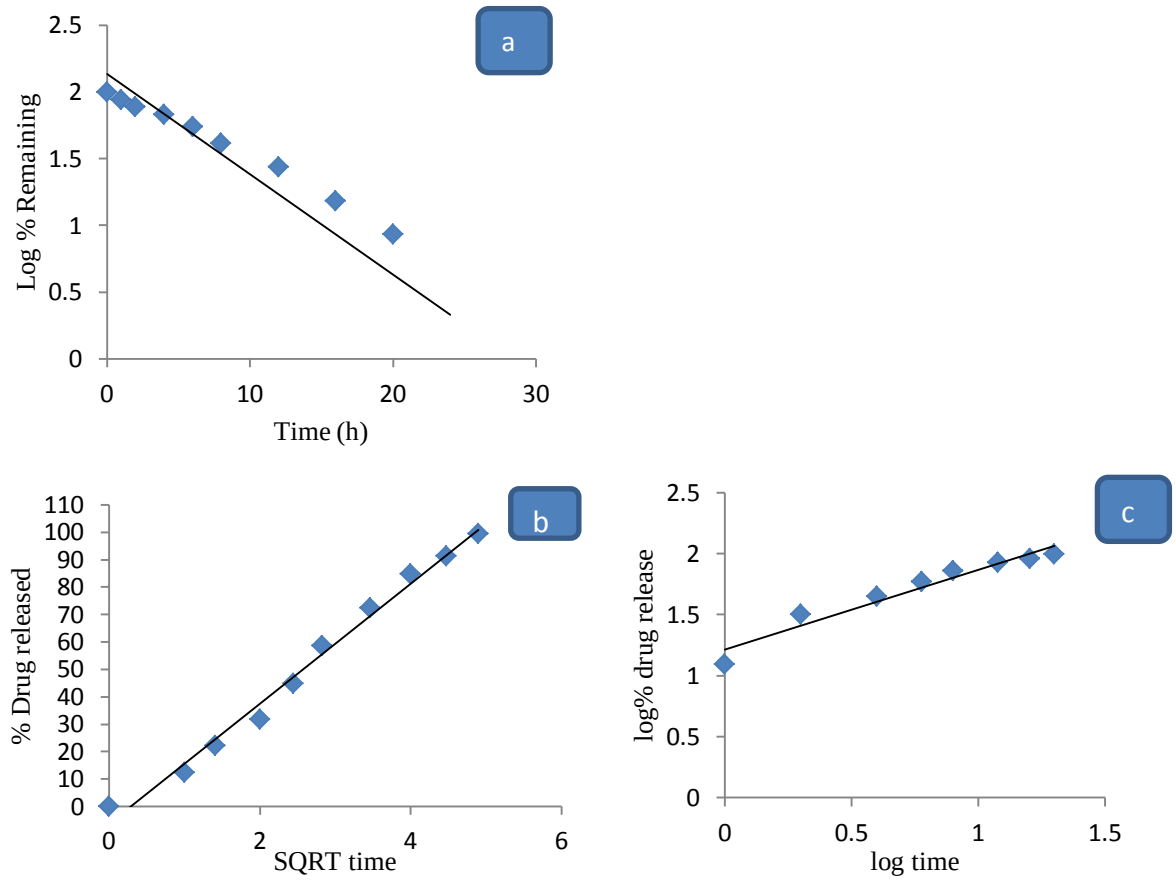

Figure 8.Optimized formulation (F10) a) First order graph; b) Higuchi plot; c) Korsemeyer Peppa's plot

Conclusion

The prepared sustained release rosuvastatin tablets were meeting all the physico chemical parameters. The sustained release rosuvastatin tablets can be prepared by using HPMC K4M and HPMC K100M in 1:1 ratio. The optimized formulation had shown a drug release up to 99.4% in 20 h and follows first order release with non- Fickian diffusion mechanism.

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