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Research Article

DESIGN OF PULSINCAP DRUG DELIVERY SYSTEM CONTAINING MICROSPHERES OF ROSUVASTATIN CALCIUM

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Abstract

The objective of the study was to prepare and evaluate pulsincap drug delivery system containing extended release microspheres of rosuvastatin calcium which is an inhibitor of HMG-CoA reductase enzyme. The basic design consists of an insoluble hard gelatin capsule body, filled with microspheres and sealed with a hydrogel plug which was formulated using HPMC K4M (93.8mg) and PVP K 30 (4mg) to maintain a suitable lag time. Nine formulations of microspheres were prepared by solvent evaporation method using polymers such as HPMC K4M, HPMC K15M, HPMC K100M. They were characterized for micrometric properties like particle size, morphology by SEM, flow properties such as bulk density, tapped density, compressibility index and hausner's ratio and also for drug content, percentage yield, entrapment efficiency and in-vitro drug release studies. The particle size was found to be in the range of 127.3±0.31 (F1) to 198.4µm±0.14 (F4). The microspheres were smooth and elegant in appearance, showed no visible cracks as confirmed by SEM analysis. The percentage yield was found to be in the range of 72.2% (F1) to 86.94% (F9). Drug loading percentage was found to be in the range of 57.34% (F1) to 65.39%±0.5 (F9). Drug entrapment efficiency was found to be in the range of 85.17±0.17 (F8) to 94.14±0.36 (F9).The formulation F9 was selected as an ideal formulation based on all the parameters and the *in vitro* release profile which shows an extended drug release of 99±0.01% at the end of 24hours in phosphate buffer of pH7.2 with the lag time of about 6hrs in 0.1N HCl (2hrs) and in pH 6.8 Phosphate buffer (4hrs). The release kinetic studies revealed that formulation F9 follows Korsemeyer peppas model.

Keywords: Rosuvastatin calcium microspheres, Pulsincap drug delivery system, Solvent evaporation method, Hydroxy Propyl Methyl Cellulose(K4M, K15M, K100M)

Introduction[1-4]

Modified drug delivery systems are known to provide a zero order or first order release in which the drug is released at a substantially steady rate per unit of time. There are certain cases for which constant release pattern i.e. a zero-order release is not suitable and that needs release of a drug after a lag time which are called as delayed release preparations. The delayed release is achieved by the incorporation of a special coat, such as enteric coating, or other time barriers such as the formaldehyde treatment of soft and hard gelatin capsules. The goal of is to prevent side effects related to the drug release in the stomach, protect the drug from degradation in the highly acidic pH of the gastric fluid.

Pulsatile drug delivery system is time delayed or site-specific drug delivery, which provides spatial and temporal delivery to improve patient compliance. These systems are designed according to the circadian rhythm of the body. Circadian rhythm implies approximately a day, major periodic components of biological rhythms are found around 24 hours (circadian) and 30 days (circamensual) and one year (circannual). Chronotherapeutics refers to a treatment method in which drug availability is timed to match rhythms of disease in order to maximize therapeutic effects and minimize side effects. It is based on the observation that there is an interdependent relationship between the peak-to rhythmic activity in disease symptoms. The

best approach to increase the efficiency of pharmacotherapy is to release drugs at times at which the symptoms of the disease aer high and thus achieving more effective treatment with less dose.

Rosuvastatin calcium is an antilipidaemic agent comes under the class of medications called statins which reduces plasma cholesterol levels and prevent cardiovascular disease. The mechanism of action of rosuvastatin calcium is that it competitively inhibits hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase. HMG-CoA reducuase catalyzes the conversion of HMG-CoA to mevalonic acid, the rate-limiting step in cholesterol biosynthesis. Rosuvastatin calcium acts primarily in the liver. Decreased hepatic cholesterol concentrations stimulate the upregulation of hepatic low density lipoprotein (LDL) receptors which increases hepatic uptake of LDL. Rosuvastatin calcium also inhibits hepatic synthesis of very low density lipoprotein (VLDL). The overall effect is a decrease in plasma LDL and VLDL. The biological half life of Rosuvastatin calcium is 19hrs. It is a BCS class II drug which has a problem of low bioavailability (absolute bioavailability 20%) so it is required to improve dissolution of rosuvastatin calcium by formulating it as microspheres which increase the specific surface area. The site specific delivery of the drug to colon is achieved by encapsulating them in a pulsincap drug delivery system.

Materials and Methods

Rosuvastatin Calcium was obtained as gift sample from Hetero Drugs Pvt. Ltd, Hyderabad and HPMC K 4M, HPMC K 15M, HPMC K 100M were obtained from SD Fine chemicals limited, Mumbai

Prepration of Microspheres:[17]

Rosuvastatin calcium microspheres were prepared by solvent evaporation method. Firstly, polymer was dissolved in methanol. Drug was dissolved in methanol separately and then was added to the above solution. The polymer drug solution so obtained was injected into heavy and light liquid paraffin (1:1) containing 0.5ml of span 80 at a stirring speed (1000–1500 rpm) of mechanical stirrer for about 30 minutes. Glutaraldehyde was added to the system for hardening the microspheres and to accelerate settling. Microspheres were separated by decantation following filtration through a whatmann filter paper (No. 41). Microspheres were then washed with *n*-hexane and then with water and the washed microspheres were dried in an oven maintained at 37°C for 24 h. Dried microspheres were stored at room temperature.

Table 1: Composition of Rosuvastatin calcium microspheres(F1-F9)

S.NO.	INGREDIENTS	BATCHES OF MICROSPHERES								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	**Rosuvastatin Calcium (ratio)**	1	1	1	1	1	1	1	1	1
2	**HPMC K4M (ratio)**	1	1.5	2	-	-	-	-	-	-
3	**HPMC K15M (ratio)**	-	-	-	1	1.5	2	-	-	-
4	**HPMC K100M (ratio)**	-	-	-	-	-	-	1	1.5	2
5	**Light Liquid Paraffin (ml)**	100	100	100	100	100	100	100	100	100
6	**Span 80 (ml)**	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
7	**Heavy Liquid Paraffin (ml)**	100	100	100	100	100	100	100	100	100

Preparation of Hydrogel plug[17]

Direct compression method was used to prepare the tablets of hydrogel plugs. The plug ingredients HPMC K4M (93.8mg) and PVP K 30 (5mg) were mixed for 10 minutes. Magnesium stearate (1%) and Talc was added to the previous mixture and further blended for 5 minutes and compressed using single punch tablet machine (CADMACH). The diameter of the tablet plug was 7mm and the weight was varied between 100-110mg.

Preparation of impermeable/insoluble capsule body

The body and the cap of the hard gelatin capsules (size 0) were separated. Capsule bodies was exposed to formaldehyde vapors for six hours at room temperature and dried at 50^0C for 12 hours in hot air oven. Afterwards the capsule body and the untreated soluble cap were stored in desiccators for further use and volume was measured which is called initial bulk volume. Bulk density is expressed in gm/cc and is given by,

$$D_b = M / V_o$$

Where, D_b = Bulk density (gm/cc)
M is the mass of microspheres (g)
V_o is the bulk volume of microspheres (cc)

Tapped density (D_t)

10g of powder was introduced into a clean, dry 100ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and tapped volume was read. It is expressed in gm/cc and is given by,

$$D_t = M / V_t$$

Where, D_t is the tapped density (gm/cc)
M is the mass of microspheres(g)
V_t is the tapped volume of microspheres (cc)

Compressibility index

The compressibility of the microspheres was determined by the Carr's compressibility index.

$$\text{Carr's index (\%)} = [(D_b - D_t) \times 100]/D_t$$

Angle of repose (θ)

It is defined as the maximum angle possible between the surface of pile of the microspheres and the horizontal plane.

The angle of repose was then calculated using the formula,

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

where, θ= angle of repose of microspheres
h = height of pile, r = radius of the base of the pile.

Evaluation of Microspheres

Particle Size

Particle size of rosuvastatin calcium microspheres was determined by optical microscopy. The stage micrometer is replaced with slide containing microspheres and the size of each particle was measured in terms of eye piece divisions. Mean particle size was calculated by measuring 200 particles with the help of a calibrated ocular micrometer.[7]

Percentage Yield

The total amount of microspheres obtained were weighed and evaluated for percentage yield[7].

$$\text{Percentage yield} = \frac{\text{actual yield}}{\text{theoretical yield}} \times 100$$

Drug loading

The dried microspheres were crushed in mortar with pestle and the homogenous solution with 10ml of pH 7.2 phosphate buffer and was sonicated for 2min at 60MHz of frequency. About 20ml of methanol was added to precipitate the polymers and the drug concentrations were analyzed by UV– Visible spectrophometer at λmax value of 242nm.

Percentage drug entrapment efficiency

It was calculated by taking 50mg of microspheres. The drug was extracted from microspheres by digesting for 24hrs with 10ml of pH 7.2 phosphate buffer by shaking on mechanical shakers for 24 hours. After that the solution was filtered and the filtrate was analyzed for drug content as mentioned above. The drug entrapment efficiency was calculated by using the following formula

$$\text{Entrapment efficiency} = \frac{\text{Actual drug content in microspheres}}{\text{Theoretical drug content in microspheres}} \times 100$$

Scanning electron microscopy (SEM)

The surface morphology and structure of microspheres were visualized by scanning electron microscopy (SEM). The samples were prepared by lightly sprinkling the microspheres powder on a double side adhesive tape which already stucked to aluminum stubs. The stubs were then placed into fine coat ion sputter for gold coating. After gold coating the samples were randomly scanned for particle size and surface morphology.

***In- vitro* drug release studies**

In- vitro drug release studies was carried out in USP basket type dissolution test apparatus. Volume of dissolution medium was 900ml and bath temperature was maintained at $(37\pm1)^0$C throughout the study. The speed was maintained to 50rpm. First 900ml of buffer pH 1.2 was used as dissolution medium up to 2 hours. There after the dissolution medium was replaced by phosphate buffer (pH 6.8) for 4hrs and the dissolution test was continued in pH 7.2 Phosphate buffer medium**.** At an interval of 1hr, 5 ml of sample was withdrawn with replacement of 5ml fresh medium and analyzed for drug content by UV-Visible

spectrophotometer at 242nm. All the studies were conducted in triplicate.

Kinetics of *In-vitro* drug release

In-vitro drug released data was subjected to *in- vitro* kinetic models such as zero order, first order, Higuchi and Korsemeyer- Peppas. The regression value nearer to 1 indicates the best fit model. The regression values are mentioned in table 5

Results and Discussion

Preformulation studies

Drug excipent compatability studies were performed by force degradation and fourier transform infrared spectroscopy. Results obtained showed that drug and excipients were compatible with each other. FTIR spectra was represented in figure 1-4

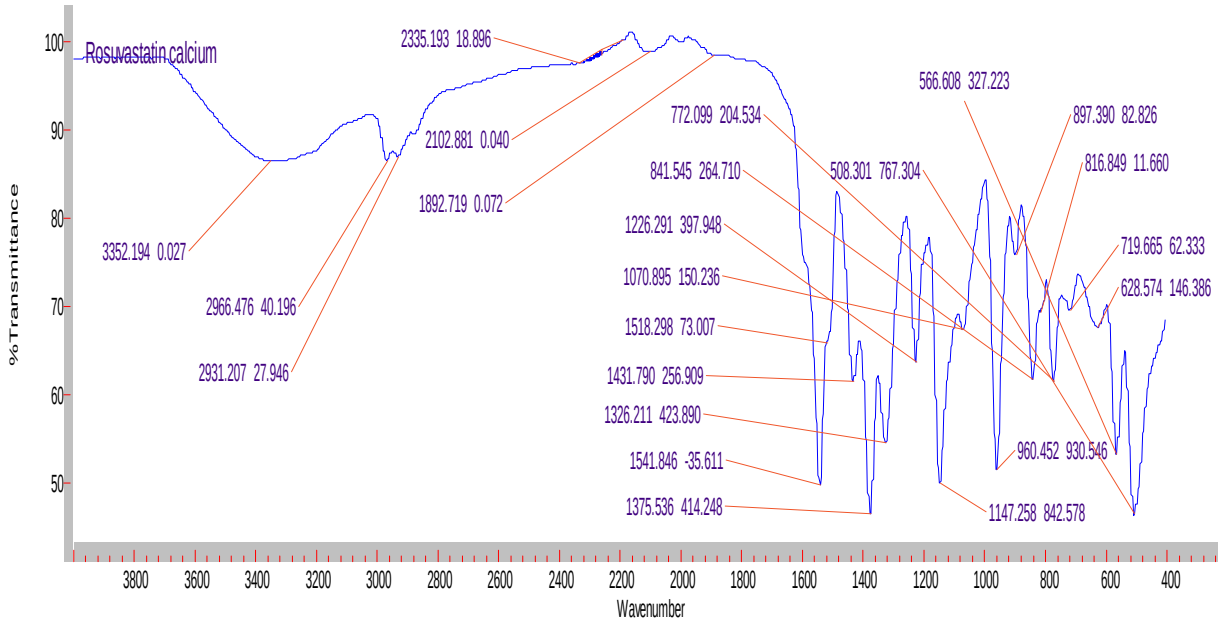

Fig.1: FT-IR Spectra of Rosuvastatin calcium

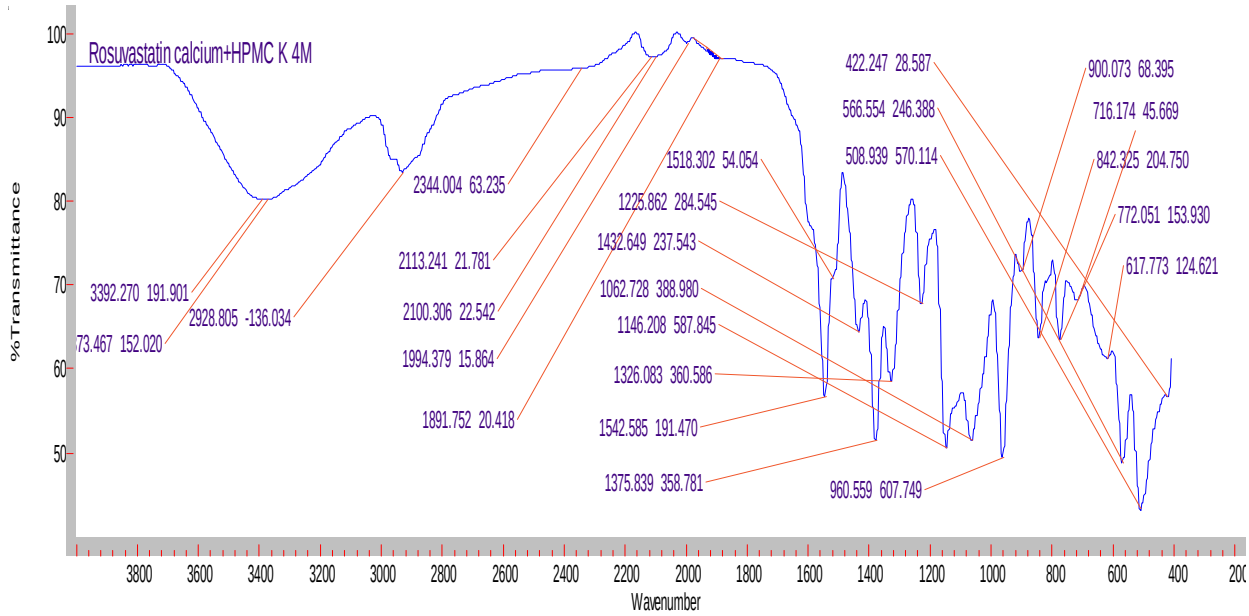

Fig.2: FT-IR Spectra of Rosuvastatin calcium + HPMC K 4M

Fig. 3: FT-IR Spectra of Rosuvastatin calcium + HPMC K 15M

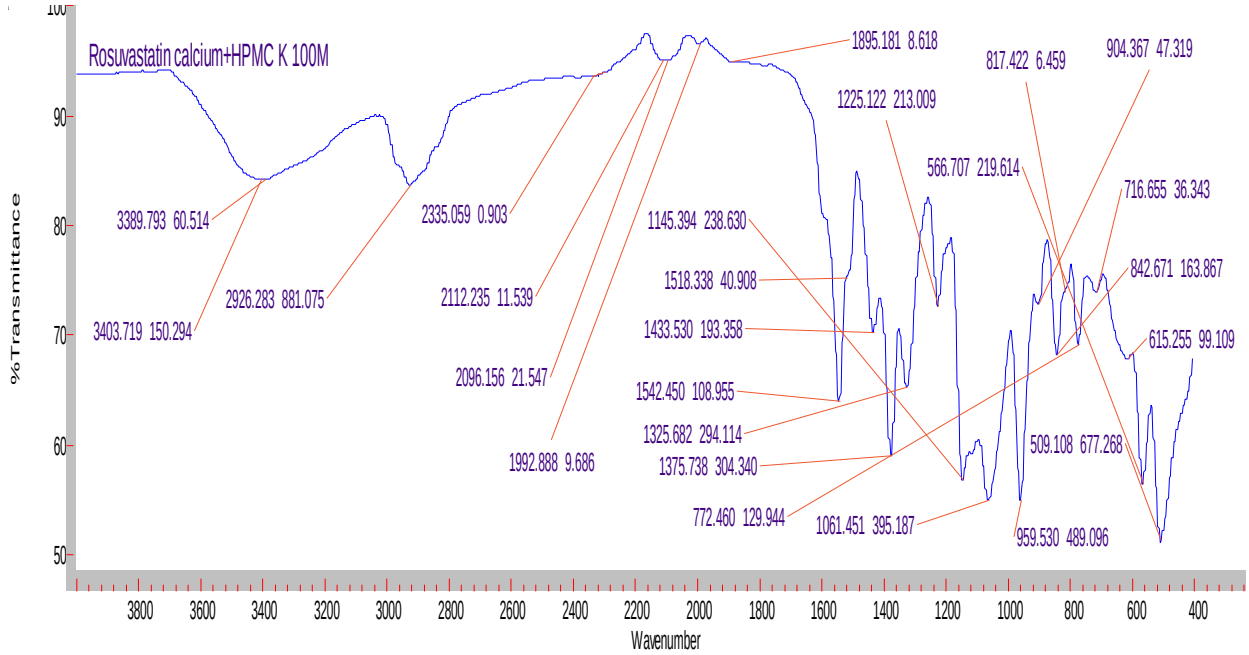

Fig. 4: FT-IR Spectra of Rosuvastatin calcium + HPMC K 100M

Evaluation of flow properties:

The microspheres of nine formulations were evaluated for Bulk density, tapped density, compressibility index, angle of repose. The results are mentioned in (Table 2).

Table 2: Characteristics of Rosuvastatin calcium microspheres

Formulation code	Bulk Density	Tapped Density	% Compressibility Index	Hausner's Ratio	Angle of Repose
F1	0.46±0.004	0.54±0.001	14.46±0.12	1.16±0.002	27°01'±0.34
F2	0.46±0.003	0.56±0.001	16.39±0.21	1.19±0.001	36°62'±0.12
F3	0.47±0.001	0.58±0002	18.43±0.13	1.22±0.002	31°33'±0.16
F4	0.48±0.002	0.63±0.002	24.61±0.22	1.32±0.001	35°61'±0.21
F5	0.48±0.002	0.63±0.002	23.72±0.15	1.25±0.003	28°64'±0.12
F6	0.48±0.003	0.56±0.003	24.61±0.22	1.16±0.004	27°17'±0.16
F7	0.68±0.001	0.86±0.003	20.81±0.25	1.26±0.007	26°34'±0.34
F8	0.70±0.003	0.84±0.004	17.55±0.29	1.21±0.005	39°42'±0.42
F9	0.67±0.002	0.84±0.001	20.52±0.17	1.25±0.001	28°91'±0.31

n=3

Bulk density and tapped density of the microspheres were found to be 0.46±0.004 gm/cm^3-0.70±0.003 gm/cm^3 and 0.54±0.001 gm/cm^3 to 0.86±0.003 gm/cm^3 respectively. The results obtained for percentage compressibility for all the formulations lies within the range of index 14.46±0.12 to 24.61±0.22.

The results obtained for hausner's ratio for all the formulations lies within the range of index 1.16±0.002 to1.32±0.001. The angle of repose values obtained for the formulations ranged from 26°34'±0.34 to 39°42'±0.42. The values obtained lies within the acceptable range. This indicates good flow property of the microspheres.

Table 3. Characterization of prepared rosuvastatin calcium microspheres

Formulation code/ingredients	Particle Size(µm)	Percentage Yield	Percentage Drug Content(mg)	Percentage Drug Entrapment
F1	127.3±0.31	72.20±0.15	57.34±0.2	85.68±0.41
F2	154.4±0.24	86.57±0.23	59.72±0.23	87.54±0.41
F3	172.8±0.41	78.68±0.56	62.89±0.19	88.63±0.41
F4	198.4±0.14	78.24±0.47	63.77±0.26	91.42±0.32
F5	192.5±0.46	72.47±0.31	58.24±0.22	89.41±0.21
F6	178.4±0.22	86.19±0.25	64.57±0.1	87.34±0.14
F7	182.6±0.38	84.36±0.23	63.51±0.4	83.78±0.26
F8	187.3±0.18	79.64±0.16	58.34±0.48	85.17±0.17
F9	184.3±0.29	86.94±0.12	65.39±0.5	94.14±0.36

Discussion on Results:

The particle size was found to be in the range of 127.3±0.31 (F1) to 198.4µm±0.14 (F4).The percentage yield of microspheres were found to be in the range of 72.2 (F1) to 86.94 (F9)

Drug loading percentage was found to be in the range of 57.34 (F1) to 65.39±0.5 (F9). Maximum drug loading was shown by F9 where as miminum by F1. Drug entrapment efficiency was found to be in the range of 85.17±0.17 (F8) to 94.14±0.36 (F9). Maximum drug entrapment efficiency was shown by F9 whereas minimum percentage drug entrapment efficiency by F8 as shown in Table 3.

***In-vitro* dissolution studies**

Table 4. *In- vitro %* drug release profile of Rosuvastatin calcium microspheres (F1-F9)

Formulation code/Parameter (hr)	Cumulative % Drug Release								
	F1(%)	F2(%)	F3(%)	F4(%)	F5(%)	F6(%)	F7(%)	F8(%)	F9(%)
In 0.1N HCl									
1 hr	0	0	0	0	0	0	0	0	0
2 hr	0	0	0	0	0	0	0	0	0
In pH 6.8 Phosphate Buffer									
4hr	0	0	0	0	0	0	0	0	0
6hr	0	0	0	0	0	0	0	0	0
In pH 7.2 Phosphate Buffer									
8 hr	44±0.03	39±0.01	36±0.02	34±0.05	32±0.05	33±0.02	28±0.03	26±0.03	24±0.02
10 hr	56±0.05	45±0.06	43±0.01	52±0.01	44±0.04	39±0.05	44±0.01	36±0.03	33±0.04
12 hr	68±0.02	58±0.04	59±0.04	66±0.03	57±0.03	45±0.02	52±0.02	45±0.02	41±0.05
14 hr	82±0.02	63±0,02	62±0.04	77±0.01	62±0.01	63±0.04	68±0.03	53±0.04	58±0.07
16 hr	92±0.01	72±0.01	79±0.07	82±0.02	81±0.02	73±0.06	79±0.04	68±0.02	63±0.07
18hr	98±0.03	87±0.04	86±0.07	98±0.05	97±0.01	84±0.01	89±0.05	72±0.01	74±0.05
20 hr	-	96±0.05	97±0.02	-	-	98±0.03	97±0.01	84±0.02	83±0.04
22 hr	-	-		-	-	-	-	98±0.04	93±0.03
24hr	-	-	-	-	-	-	-	-	99±0.01

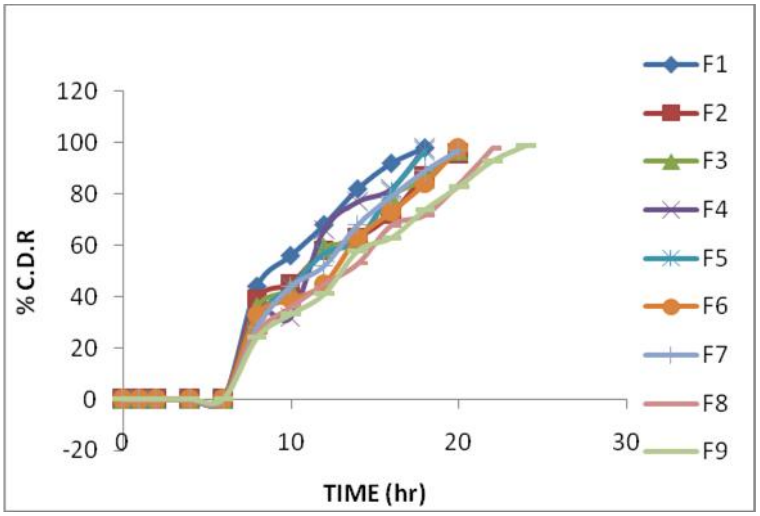

Fig.5 *In-vitro* dissolution profile of F1 to F9 formulations.

Table 5. *In vitro* drug release kinetics of F1 to F9 formulations

Formulation code	Release kinetics regression values			
	Zero Order	First Order	Korsemeyer peppas model	Higuchi model
F1	0.973	0.935	0.995	0.995
F2	0.989	0.978	0.950	0.985
F3	0.983	0.974	0.946	0.949
F4	0.930	0.848	0.986	0.981
F5	0.969	0.908	0.987	0.983
F6	0.993	0.969	0.949	0.969
F7	0.917	0.797	0.984	0.982
F8	0.997	0.959	0.965	0.971
F9	0.992	0.946	0.999	0.992

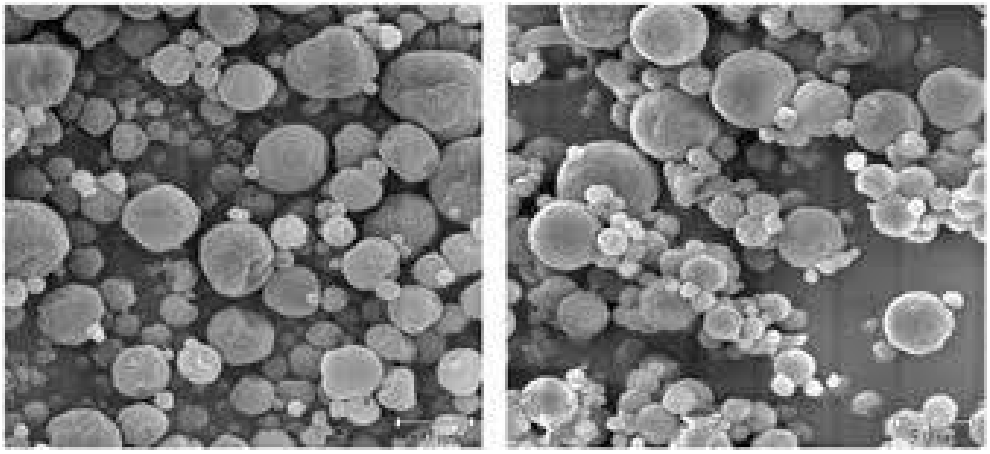

Fig.6 Scanning electron microscopy of optimized formulation(F9)

Conclusion

The microspheres of rosuvastatin calcium were prepared by solvent evaporation method using various grades of HPMC(K4M, K15M&K100M). From the dissolution data it is evident that F9 formulation with Drug and HPMC K 100M in the concentration of 1:2 gave the better sustained release for 24hrs than other Microspheres.The kinetic data revealed that korsemeyer peppas is the best fit model which indicates that the mechanism of drug release of microspheres is diffusion.

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References

1. Sharma GS, Srikanth MV, Uhumwangho MU, Phani Kumar KS and Ramana Murthy KV, Recent Trends In Pulsatile Drug Delivery Systems - A Review. International Journal Of Drug Delivery, 2010; 2: 200-212
2. Chein, Y.W., Oral Drug Delivery and Delivery Systems, International Novel Drug Delivery Systems, Vol 50, Marcel Decker Inc, Newyork, 1992; 50: 139 – 177.
3. Control Release Dosage Forms by Y.W.Chein. Edition no. 1 page no 35-60
4. Gothaskar, AV, Joshi AM, Joshi, NH, 2004. Pulsatile Drug Delivery System—A Review. Drug Del. Technol.

5. V.Kamalakkanan et al, KSG Arul Kumaran / Formulation and Evaluation of Time Delayed Capsule Device for chronopharmaceutical drug delivery system of Diltiazem Hydrochloride- Research Journal of Pharmaceutical, Biological and Chemical sciences, 2014; 5(1); 0975-8585
6. S.Kishore Kumar / Enhancement of Dissolution Rate and Formulation development of rosuvastatin calcium solid dispersion tablets employing starch phosphate as carrier, International Journal of Pharmacy Research and Science, 2014,02(2), 164-170. ISN:2348-082
7. Satyabrata Bhanja, P. Rushikesh, K. Lakshmi Deepthi, V. Neelima / Formulation, development and evaluation of rosuvastatin calium immediate release tablets, American Journal of Pharmacy and Health Research 2014;2(1) ISSN: 2321-3647
8. Bheemeswara Rao K, Prasanna Kumar Desu, Sudhakar Babu AMS1, Venkateswar rao P / Formulation and Evaluation of Rosuvastatin Immediate Release Tablets, Singapore Journal of Pharmaceutical Research, 2014; 1(1):12-18
9. Sayantan Mukhopadhyay, Reetika Pant and Laxmi Goswami/Formulation and evaluation of pulsatile drug delivery system for sequential release of Atorvastatin. International Journal of Pharmaceutical and Chemical Sciences Vol. 3 (2) Apr-Jun 2014
10. Ehsan, Ali mohammed Dr. Shaimaa N, Abd al hammid/ Formulation and evaluation of Rosuvastatin orodispersible tablets, International journal of pharmacy and pharmaceutical sciences, vol. 5, suppl. 2, 2013
11. Brahmaiah B, Sasikanth K, Sreekanth Nama, Siva Sankara Kumar GV, Krishna Chaitanya G., Formulation and evaluation of extended release mucoadhesive microspheres of rosuvastatin/ International Journal of Biological & Pharmaceutical Research. 2013; 4(4): 271-281.
12. P. Rohini/ Formulation and evaluation of orally disintegrating tablets of rosuvastatin. Global Journal of Pharmacology 7 (3): 249-257, 2013
13. J. Kapure, V. V Pande and P. K. Deshmukh / Dissolution enhancement of rosuvastatin calcium by liquisolid compact technique, Journal of Pharmaceutics, 2013, 1-9
14. Nayana D. Patil, Manoj M. Bari, Shashikant D. Barhat[1], Shaikh Moh. Subhani, Sanjay T. Lamne / Formulation development and *In vitro* evaluation of simvastatin pellets as a Pulsatile drug delivery system. Indo American Journal of Pharmaceutical Research 2013; 3(6); 4430-4443
15. Vidyadhara, A. Ramu, N. Devanna, Ch. Anusha and J. Keerthi, Formulation and evaluation of rosuvastatin fast dissolving tablets, Asian Journal of Chemistry; Vol. 25, No. 10 (2013), 5340-5346
16. M. Sukanya and V. Sai Kishore, Design and development of chronopharmaceutical drug delivery of simvastatin, Journal of Chemical and Pharmaceutical Research, 2012, 4(6):3195-3200
17. Amish V. Panchal, Markand Mehta, Viral H. Shah, Umesh Upadhyay., Formulation and *in-vitro* evaluation of mucoadhesive bilayered buccal tablets of rosuvastatin calcium, IJPSR, 2012; Vol. 3(8): 2733-2740
18. D. Krishnarajan N. Senthil Kumar, G. Jeyabalan., Design and evaluation of bioadhesive tablets of rosuvastatin calcium, International Journal of Biological & Pharmaceutical Research, 2012; 3(4): 624-630
19. J. Dwivedi and O.P.Mahatma., Formulation & evaluation of Sustained Release Formulation of rosuvastatin calcium, Asian Journal Of Biochemical & Pharmaceutical Research Issue 3 (Vol. 1) 2011 ISSN: 2231-2560
20. D. Hitesh, Jayvadan P. Chronpharmaceutics, Pulsatile drug delivery system as current trend. Asian Journal of Pharmaceutical sciences 2010;5(5):207-30.
21. Alexander, N. Bhoyar, M. Sharma / Important Aspects And Fundamentals Of Chronotherapeutic Drug Delivery System For Optimizing Therapeutic Effect. A Review. American Journal Of Pharmtech Research. 2012;2(2):755-91.
22. G. Rasve, G. Borade, S. Deshmukh, et al/ Pulsatile drug delivery system: current scenario. International journal of pharma and Bioscience. 2011;2(3). Epub 332
23. Lachman L, Liberman H and Kanig J. (2000). The Theory and Practice of Industrial Pharmacy, 3, 293-345.
24. Ansel H, Allen L and Popovich N. (2004). Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, 8, 227-259. M.E. Aulton, Pharmaceutics: The Science of Dosage Form Design, Churchill Livingstone, P. 310 (2002).