ISSN: 2277- 7695
CODEN Code: PIHNBQ
ZDB-Number: 2663038-2
IC Journal No: 7725

ISSN 2277-7695

Vol. 1 No. 7 2012
Online Available at www.thepharmajournal.com

THE PHARMA INNOVATION

Formulation and Evaluation of Pulsatile Drug Delivery System of Rosuvastatin Calcium Using Different Swelling Polymers

BK Garg[1*], G. Gnanarajan[1], P. Kothiyal[1]

1. Division of Pharmaceutical sciences, Shri Guru Ram Rai Institute of Technology & Science, Division Of Pharmaceutical Sciences, Patel Nagar, Dehradun (Uttrakhand)

The objective of this study was to develop and evaluate a pulsatile drug delivery system consisting of cores coated with two layers of swelling and rupturable coatings was prepared and evaluated as pulsatile drug delivery system. Cores containing Rosuvastatin calcium as model drug were prepared by direct compression of different ratios of spray-dried lactose and microcrystalline cellulose and were then coated sequentially with an inner swelling layer containing a superdisintegrant (croscarmellose sodium) and an outer rupturable layer of ethylcellulose. The effect of level of swelling layer was investigated. Rupture and dissolution tests were performed using the USP XXIV paddle method at 50 rpm in 0.1 N HCl. The lag time of the pulsatile release tablets decreased with increasing levels of swelling layer. Increasing levels of the ethylcellulose coating retarded the water uptake and thus prolonged the lag time.

Keyword: Rosuvastatin calcium, PDDS, Polymer coated tablet..

INTRODUCTION: Oral control drug delivery offers a number of advantages over conventional immediate release preparations. These systems are designed to deliver the drug at controlled and predetermined rate thus maintaining their therapeutic effective concentration in systemic circulation for prolonged periods.

Corresponding Author's Contact information:
Bhuvnesh Garg*
Division of Pharmaceutical sciences, Shri Guru Ram Rai Institute of Technology & Science, Patel Nagar, Dehradun, Uttrakhand, India
E-mail: bhuvnesh.grg89@gmail.com

On the other hand, for certain therapies a pulsatile drug release pattern, where the drug is released after well-defined lag time [1]. However, pulsatile delivery is desirable for drugs acting locally or having an absorption window in the gastro-intestinal tract or for drugs with an extensive first pass metabolism, e.g. β-blockers or for drugs, which develop biological tolerance, where the constant presence of the drug at the site of action diminishes the therapeutic effect, or for drugs with special pharmacokinetic features designed according to the circadian rhythm of human [2–3].

Pulsatile drug delivery systems are generally classified into time-controlled and site-specific delivery systems. The release from the first group is primarily controlled by the system, while the release from the second group is primarily controlled by the biological environment in the gastro-intestinal tract such as pH or enzymes. Most pulsatile drug delivery systems are reservoir devices covered with a barrier coating [4–6]. The barrier can dissolve, erode or rupture [7–9] during/after a certain lag time, after which the drug is released rapidly from the inner reservoir core. The rupturing of the barriers are induced by an expanding core upon water penetration through the barrier coating. The expansion can be caused by effervescent excipients [10] or swelling agents [10–13].

This study focused on the development of pulsatile release tablets as a peroral, time-controlled, single-unit dosage form. The proposed system consists of a core tablet coated with two layers, an inner swelling layer and an outer rupturable coating. The swelling layer is composed of croscarmellose sodium, a super-disintegrant and polyvinyl pyrrolidone (PVP) as a binder, while the rupturable coating is an ethylcellulose film.

3. MATERIALS AND METHODS

3.1 MATERIALS:-

Rosuvastatin calcium was gifted by Ranbaxy Pvt. Ltd. Ponta sahib(HP).Microcrystalline cellulose & HPMC K 100M was donated by Akums pharmaceutical Ltd. Haridwar. Citric acid, potassium di hydrogen phosphate and ammonium carbonate were purchased from Ltd. Dorset, UK. Tri ethyl citrate was gifted by Themis medicare ltd. haridwar, india

3.2 METHODS:-

3.2.1 PREPARATION OF ROSUVASTATIN CALCIUM TABLETS

Tablets were prepared containing 14% by weight, Rosuvastatin calcium, 55% by weight lactose, 30% by weight microcrystalline cellulose, 1% by weight, magnesium stearate. Tablets were prepared by direct compression method and were produced using a single punch tableting machine. A 8-mm punch and die set were used to obtain tablets of mass 150 mg (containing 20 mg of drug) and crushing strength of 80 N. The friability of the tablets was measured as per USP specifications and found to be less than 0.05%.

3.2.2 PREPARATION OF SPRAYING DISPERSION FOR COATING INNER COATING DISPERSION (SWELLING LAYER)

Croscarmellose sodium (Ac-Di-Sol) was layered onto the core tablets using PVP (KollidonR 90F) as a binder (Ac-Di-Sol R: KollidonR 90F, 6:1 w/w). KollidonR 90F was dissolved in 96% v/v ethanol by stirring overnight until a clear solution was obtained. Ac-Di- Sol R was dispersed into the KollidonR 90F solution and agitated for at least 30 min to obtain a homogeneous dispersion prior to coating. The coating dispersion was then layered onto the core tablets in a Pan-coater to obtain appropriate swelling layer levels.

OUTERMOST COATING DISPERSION (RUPTURABLE LAYER)

These tablets were then coated with an ethanolic ethylcellulose solution, using dibutyl sebacate as a plasticizer. The coating solution was prepared by dissolving ethylcellulose in 96% v/v ethanol (3.5% w/w solution) and was stirred overnight to obtain a clear solution. The plasticizer (5% w/w based on polymer solids) was added into the polymer solution and the solution was further agitated for at least 30 min prior to coating to obtain a homogeneous solution. If required, magnesium stearate was dispersed into the polymer solution (ethylcellulose: magnesium stearate, 90:10 w/w). The homogeneous dispersion was gently stirred throughout the coating process.

3.2.3-COATING OF TABLET

For the inner coat, the tablets were coated by Pan coating apparatus, and in-process samples were taken to check if the target polymer weight gain was achieved. Coating was continued until complete polymer weight gain was achieved.

After the coating, the tablets kept a side for 10 min after which they were cured at 40 ◦C for 24 h. For the middle coat, the cured tablets coated with the inner layer were further coated in the Pan coating apparatus. Again, in-process samples were taken to check for the target weight gain. After the coating, the tablets kept a side for 10 min there after they were cured in an oven for 24h at 40◦C. The double-layer coated cured tablets were then taken for the final enteric coating, and after the coating, the tablets were dried by gentle fluidization in the Pan coating apparatus for 15 min and then, cured for 24 h at 40 ◦C. The processing parameter show in.

TABLE -1: PROCESSING PARAMETER USED FOR COATING[4]

S.NO	Parameter	Set at value
1	Bed temperature	30-40 ◦C
2	Suspension spray rate(gm/min)	5-7
3	Suspension spray time (min)	45-55
4	Spray nozzle (mm)	1
5	Spray pressure (kg/cm^2)	4
6	Pan speed(rpm)	20
7	Drying in equipment(min)	10

Table-3: WORKING FORMULA: F1 – F6

S.No	INGREDIENTS	QUANTITY
1	Rosuvastatin calcium	20
2	Spray dried lactose	83
3	Microcrystalline cellulose	45
4	Magnesium stearate	2
5	Mean wt. of tablet	150

*Formula for 150 mg single tablet, and all weight taken in mg

Table-4: THE ABOVE QUANTITIES ARE EXPRESSED IN TERMS OF MG PER TABLET

Polymers	F1	F2	F3	F4	F5	F6
Croscarmellose	7%	-	-	9%	-	-
Sodium Starch glycolate	-	7%	-	-	9%	-
HPMC K100M	-	-	7%	-	-	9%
Ethylcellulose	3.5 %	3.5 %	3.5 %	3.5 %	3.5 %	3.5 %

4. STUDY OF DIFFERENT PARAMETERS

4.1-DRUG CONTENT:

Five tablets were powdered in a mortar. Weighed accurately the quantity equivalent to 20 mg of Rosuvastatin calcium and transferred to a 100ml volumetric flask containing few ml of methanol and mixed well, made up the volume up to 100ml with methanol. Pipette out 1.0 ml from the stock solution into another 10 ml volumetric flask and made up the volume with methanol. From the above solution withdraw the aliquots of 1.0 ml, 2.0 ml and 3.0 ml (as per Beer's range 10 to 30 µg/ml) and the volume was made up to 10 ml with methanol. The absorbance was measured at 245 nm using methanol as blank.

4.2-*IN-VITRO* RELEASE STUDIES:

The *in-vitro* dissolution profile of the designed formulations was carried out using USP type I apparatus under conditions specified (Temp 37± 0.5°C, at 100 rpm).As artificial gastric fluid, 0.1N HCl (pH 1.2) was used. The artificial intestinal fluid was prepared phosphate buffer (pH 6.8).

4.3-Water uptake studies

The water uptake studies were carried out on the coated tablet, i.e. tablets with the inner hydrophobic layer and the outer drug release-triggering layer. The coated tablets were

accurately weighed and immersed in the artificial colonic medium (pH 5.4) in USP apparatus I, with the stirring speed at 100 rpm. The conditions for the water uptake studies were kept the same as for the dissolution study. At predetermined time intervals, the tablets were removed from the release medium, washed twice with distilled water in order to remove the buffer solution from the surface of the tablets and then blotted with lint free tissue paper. The weight of the tablets was recorded before and after drying to constant weight in an oven at 50 ◦C.

The water uptake was calculated as follows:

$$\text{Water uptake} = \frac{W(t) - W(d)}{W(d)}$$

Where W (t) is the weight of the wet tablets removed at time *t* and W (d) is the weight of the tablets after drying at time *t*. The water uptake data are represented tablet[10, 11].

5- RESULTS & DISCUSSION:

5.1 COMPATIBILITY STUDIES

In order to investigate the possible interactions between Rosvastatin calcium and distinct polymers and/or diluents, FT-IR studies were carried out. FT-IR results proved that the drug was found to be compatible with excipients as wave numbers are almost similar for pure drug and also drug excipients mixture.

5.2 Evaluation of pre-compression parameters:

Based on the results of pre-compression tests, formulation showed angle of repose 36.5^0 indicating a good flow property and Carr's index is 20.92, indicating compressibility of the Blend is fairly passable (Table 5)

Table 5: PRE-COMPRESSION PARAMETERS OF BLEND POWDER

PARAMETERS	MEAN READINGS
Bulk Density	0.65
Tapped Density	0.84
Carr' index	20.92
Hausner ratio	1.34
Angle of repose	36.5^0

5.3 EVALUATION OF POST-COMPRESSION PARAMETERS:

The tablets of different formulations were subjected to various evaluation tests, such as thickness, uniformity of weight, hardness, friability, and drug content and the result are shown in Table 7. All the formulations showed uniform thickness. The thickness and hardness of the tablets were in the range of 3.19 ± 0.01 to 3.22 ± 0.01 mm and 7.66 ± 0.40 to 8.33 ± 0.40 kg/cm2 respectively. The percentage friability was found to be less than 1% indicating that the friability is within the prescribed limits. In weight variation test, the average percentage deviation of all tablet formulations was found to be within the limit, and hence they met the test as per official requirements and were found to contain 96.7±1 to 98.2±1 mg of the labelled amount of Rosuvastatin calcium indicating uniformity of drug content.

5.4- WATER UPTAKE STUDIES OF COATED TABLET

Core tablets were coated with two different levels of Swelling polymer & rupturable polymer by spray coating. The % water uptake capacity of tablets was determined in the containers filled with 100 ml of pH 1.2 buffer. Formulations. F1 & F4 were coated with same (croscarmellose sodium) inner polymeric coating (7% and 9%). Tablet coated with 7% coating showed 17.89% water uptake after 4 hour. Tablet coated with 9% coating showed 17.59% water uptake

after 6 hour. So increasing outer coating decreased % water uptake capacity and increased Lag-time. Another formulation pair like F2 & F4, F3 & F6 also showed same type of water uptake phenomena.

Table 6: Post-compression parameters of Formulations (F1-F6)

Parameters	**Core tablet**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Weight variation(mg)	148.4±0.5	153.8±0.5	152.9±0.5	153.4±0.5	153.5±0.5	153.1±0.5	153.2±0.5
Friability	0.89%	0.65%	0.76%	0.79%	0.83%	0.67%	0.76%
Hardness(Kg/cm^2)	4.2	5.1	5.2	4.9	4.7	5.0	5.3
Content uniformity(%)	97.8±1	97.8±1	97.6±1	97.9±1	98.2±1	97.2±1	96.7±1
Disintegration time(Sec)	11	673	545	483	528	529	465

Table 7: Thickness of coated tablets:

Formulation No.	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Thickness (mm)	7.2±0.2	7.7±0.2	7.6±0.2	7.3±0.2	7.6±0.2	7.3±0.2

Table 8: Effect of Outer Polymer Concentration on % Water Uptake

TIME(hrs)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
1	5.9	4.42	4.76	5.67	3.58	3.51
2	9.32	7.28	8.22	7.58	6.42	5.42
3	15.76	9.47	11.35	9.46	8.56	6.55
4	17.79	13.73	14.11	12.48	11.89	9.33
5	17.82	17.28	17.51	14.54	15.71	13.39
6	17.84	17.38	17.82	17.59	17.51	15.98
7	17.89	17.41	17.62	17.96	17.67	18.14

Fig 1: % WATER UPTAKE GRAPH OF FORMULATION F1& F4

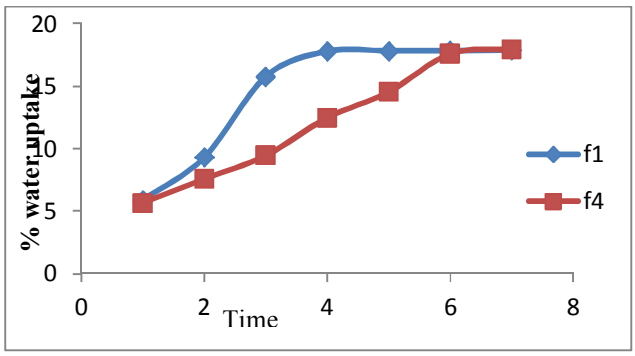


Fig 2: % WATER UPTAKE GRAPH OF FORMULATION F2 & F5

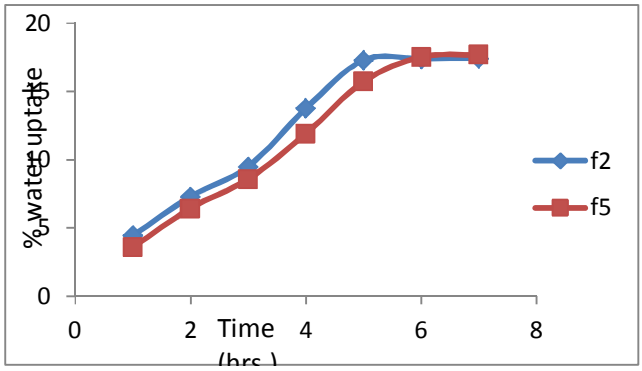
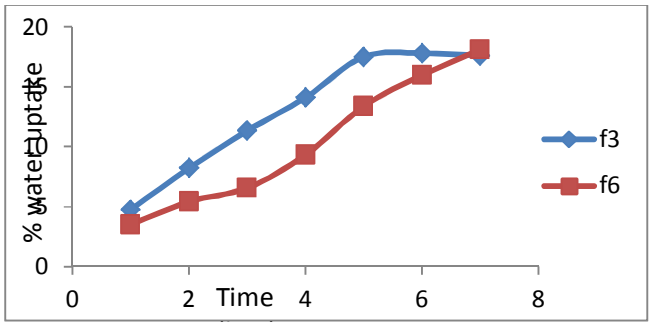


Fig 3: % WATER UPTAKE GRAPH OF FORMULATION F3 & F6



5.5- *IN-VITRO* RELEASE STUDIES:

All the Six formulations prepared coated tablets of RC were subjected to *in-vitro* release studies. These studies were carried out using USP dissolution apparatus type-II, and pH 1.2 buffer and pH 6.8 phosphate buffer as dissolution media.

In-vitro release profiles of pulsatile device during 10 hrs studies were found to have very good sustaining efficacy. During dissolution studies, it was observed that, the enteric coat of the Ethyl cellulose was intact for 2 hours in pH 1.2 buffer, but dissolved in intestinal pH, form pores through these pores water penetrates inside the membrane and came in contact with Swellable layer which swells which resulted in building up of pressure inside the core and helped in early rupturing of outer coating layer in pH 6.8 buffers.With all the formulations, there was neligible drug release in pH 1.2, thus indicating the efficiency of EC for enteric coating.

In case of formulation F1 & F4 which has 7% & 9% respectively of croscarmellose sodium, the cumulative percentage drug release was found to be 39.23% and 42.45% respectively at the end of 5 hrs., because high pressure was created inside in F4 due to swelling of high amount swellable polymer to rupture the outer coating. So F4 is having highest cumulative percentage drug release. This shows that increase in amount in swelling layer the lag time of formulation is decrease. The same pattern of release phenomena was shown by other two pairs F2 & F5, F3 & F6.

Fig 4: Cumulative percentage drug release of coated formulation F1, F2 & F3

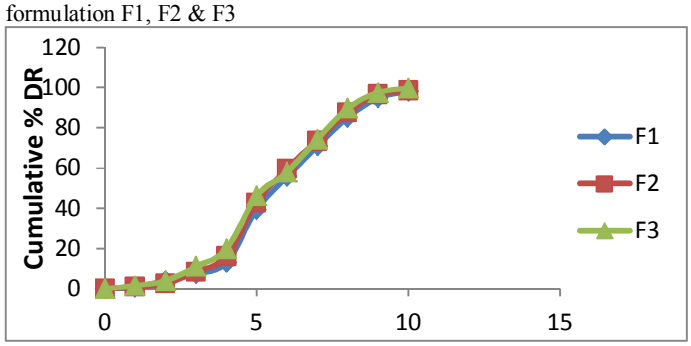
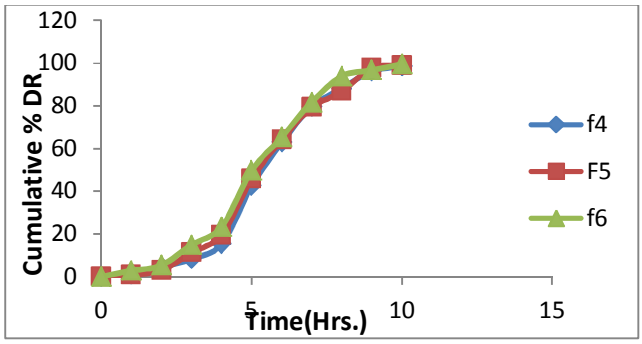


Fig 5: Cumulative percentage drug release of coated formulation F4, F5 & F6



5.6 RUPTURE TEST:

The Rupture test on coated tablets was carried out using USP paddle apparatus. Here all other Parameters were same as In-Vitro Dissolution Method. The time at which the outer coating layer starts to rupture is called as lag time. This was determined by Rupture test.

Table 9: Rupture test of all formulations

Formulation No.	F1	F2	F3	F4	F5	F6
Rupture time (hrs)	4.24	5:38	4:58	4:11	5:08	4:45

6.1 CONCLUSION:

The pulsatile release tablets with a swelling layer and rupturable ethylcellulose coating were developed. The system released the drug rapidly after a certain lag time due to the rupture of the ethylcellulose film. The lag time of the system could be modified by level of swelling layer and rupturable coating. Croscarmellose sodium swelling layer polymer gives better rupture of outer coating & Increases in amount of swelling coating concentration reduce the rupture time.

REFERENCE:

1. Geest S, Koker J, Demeester J, De Smedt S, Hennink WE. Pulsed in vitro release and in vivo behavior of exploding microcapsules. J. Control. Release 2009;135:268–73.
2. N. Rouge, P. Buri, E. Doelker, Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery, Int. J. Pharm. 136 (1996) 117– 139.
3. R.K. Chang, X. Guo, B.A. Burside, R.A. Couch, E.M. Rudnic, Formulation approaches for oral pulsatile drug delivery, Am. Pharm. Rev. 2 (1) (1999) 6 – 13.
4. Kro¨gel, R. Bodmeier, Evaluation of an enzyme-containing capsular shaped pulsatile drug delivery system, Pharm. Res. 16 (9) (1999) 1424– 1429.
5. Kro¨gel, R. Bodmeier, Pulsatile drug release from an insoluble capsule body controlled by an erodible plug, Pharm. Res. 15 (3) (1998) 474– 481.
6. Kro¨gel, R. Bodmeier, Floating or pulsatile drug delivery systems based on coated effervescent cores, Int. J. Pharm. 187 (1999) 175– 184.
7. A. Gazzaniga, P. Iamartino, G. Maffione, M.E. Sangalli, Oral delayed-release system for colonic specific delivery, Int. J. Pharm. 108 (1994) 77– 83.
8. M.E. Sangalli, A. Maroni, L. Zema, C. Busetti, F. Giordano, A. Gazzaniga, In vitro and in vivo evaluation of an oral system for time and/or site-specific drug delivery, J. Control. Release 73 (2001) 103– 110.
9. P.W.S. Heng, L.W. Chan, S.H. Chew, Mechanism of pellet coat rupture and its effect on drug release, Chem. Pharm. Bull. 47 (7) (1999) 939–943.
10. T. Hata, Y. Shimazaki, A. Kagayama, S. Tamura, S. Ueda, Development of a novel drug release system, time-controlled explosion system (TES). V. Animal pharmacodynamic study and human bioavailability study, Int. J. Pharm. 110 (1994) 1– 7.
11. A. Gazzaniga, M.E. Sangalli, F. Giordano, Oral ChronotopicR drug delivery systems: achievement of time and/or site specificity, Eur. J. Pharm. Biopharm. 40 (1994) 246–250.
12. [25] T.Y. Fan, S.L. Wei, W.W. Yan, D.B. Chen, J. Li, An investigation of pulsatile release tablets with ethylcellulose and Eudragit L as film coating materials and cross-linked polyvinylpyrrolidone in the core tablets, J. Control. Release 77 (2001) 245–251.
13. R. Morita, R. Honda, Y. Takahashi, Development of oral controlled release preparations, a PVA swelling controlled release system (SCRS) I. Design of SCRS and its release controlling factor, J. Control. Release 63 (2000) 297– 304.