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Formulation design and *in-vitro* evaluation of simvastatin pulsatile drug delivery system

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ABSTRACT

Theaimofthestudy wasto prepare Simvastatin pulsatile tablets to release the drug at predetermined time after a lag period, so that drug from the formulation will be released according physiological need of the body for the effective treatment of peptic ulcer .The approach of the present study was to make a comparative evaluation among concentration of these polymers and to assess the effect of physico-chemical nature of the active ingredients on the drug release profile. The λ max of Simvastatin in 7.2 pH Phosphate buffer was scanned and found to have the maximum absorbance at 247 nm. Standard graph of Simvastatin in 7.2 pH phosphate buffer was plotted. The Bulk density and tapped density of the Controlled release tablets were found to be 0.39-0.56 and 0.44 to 0.69 respectively. The angle of repose values obtained for the Controlled release tablets ranged from 18.17 to 25.98 This indicates good flow property of the powder blend. The compressibility index values for the Simvastatin Pulsatile tablets ranged from 12.24 to 20.0 This indicates the powder blend have good flow property. The cars index values for the Simvastatin Pulsatile tablets ranged from 1.057 to 1.26 This indicates the powder blend have good flow property. *In vitro* drug release profiles for all Simvastatin Pulsatile tablets were carried out by using 7.2 pH phosphate buffer as dissolution medium for about 24 hrs. From the above results it was found that the release of drug from F12 formulation with Eudragit RLPO gave the better release than other Simvastatin Pulsatile tablets.

Keyword: Simvastatin, Pulsatile tablets, 7.2 pH Phosphate buffer

INTRODUCTION

Controlled drug delivery systems have acquired very important role in pharmaceutical Research and Development (R&D) business. Such systems offer control over the release of drug and grant a new lease on life to a drug molecule in terms of patentability. These dosage forms offer many advantages over the conventional drug delivery systems; such advantages include nearly constant drug level at the site of action, prevention of peak-valley fluctuations, reduction in dose of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance. The oral controlled-release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time, thereby ensuring sustained therapeutic action [1].

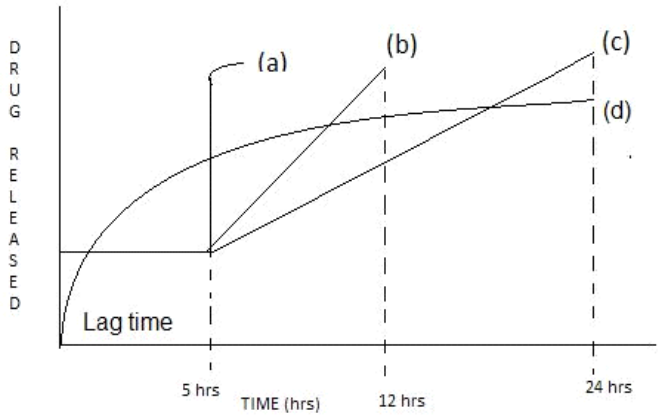


Fig. 1: Schematic representation of different drug delivery systems where (a) = sigmoidal release after lag time, (b)= delayed release after lag time, (c) = sustained release after lag time, (d) = ex**tended release without lag time**

Recent studies have revealed that diseases have a predictable cyclic rhythm and that the timing of medication regimens can improve the outcome of a desired effect. This condition demands release of drug as a "pulse" after a time lag and such system has to be designed in a way that complete and rapid drug release should follow the lag time. Such systems are known as pulsatile drug delivery systems (PDDS), time controlled systems, or sigmoidal release systems (Fig 1). PDDS have been developed in close connection with emerging chronotherapeutic views. In this respect, it is well established that the symptoms of many pathologies, as well as the pharmacokinetic and pharmacodynamic profiles of most drugs, are subject to circadian variation patterns [2]. As far as widespread chronic pathologies with night or early morning symptoms are concerned, such as cardiovascular disease (CVD), bronchial asthma and rheumatoid arthritis, remarkable efficacy, tolerability and compliance benefits could arise from modified release medications [3]. In addition to being potentially suitable for chronotherapy, pulsatile release is also exploited to target proximal as well as distal colonic regions via the oral route. Colon delivery is being extensively investigated as it may yield improved topical inflammatory bowel disease (IBD) treatments and is even suggested as one means of enhancing the poor oral bioavailability of peptides, proteins, oligonucleotides and nucleic acids. For the purpose of time-controlled colon targeting, delayed-release systems have to be presented in an enteric-coated configuration so that the high intra - and inter-subject variability in gastric residence may be overcome, and provide, following stomach emptying, a lag phase roughly corresponding to fairly reproducible small intestinal transit time [4]. The maximal production occurs early in the morning, i.e. 12 h after the last meal. Studies with HMG CoA reductase inhibitors have suggested that evening dosing was more effective than morning dosing [5]. The chronotherapy of asthma has been extensively studied. The role of circadian rhythms in the pathogenesis and treatment of asthma indicates that airway resistance increases progressively at night in asthmatic patients Circadian changes are seen in normal lung function, which reaches a low point in the early morning hours. As broncho constriction and exacerbation of symptoms vary in a circadian fashion, asthma is well suited for chronotherapy. Chronotherapies have been studied for asthma with oral corticosteroids, theophylline, and B2-agonists [6]. Human and animal studies suggest that chemotherapy may be more effective and less toxic if cancer drugs are administered at carefully selected times that take advantage of tumor cell cycles while less toxic to normal tissue .The blood flow to tumors was threefold greater during each daily activity phase of the circadian cycle than during the daily rest phase. The chronotherapy concept offers further promise for improving current cancer-treatment options, as well as for optimizing the development of new anticancer or supportive agents [7]. All of these conditions demand a time-programmed therapeutic scheme releasing the correct amount of dose of the drug at

the appropriate time. This requirement is usually fulfilled by PDDS [8]. Diverse directions of circadian changes in lipid fractions in patients and normal subjects may contribute to alteration in the rhythmicity of other metabolisms and in the blood coagulation system, thus leading to various complications. a circadian rhythm occurs during hepatic cholesterol synthesis [9, 10]. The pulsatile delivery provided by the aforementioned devices in this invention may be for therapeutic purpose, nutritional purpose, preventive purpose, and a wide variety of situations in general [11]. Simvastatin is a prodrug in which the 6-membered lactone ring of simvastatin is hydrolyzed *in vivo* to generate the beta, delta-dihydroxy acid, an active metabolite structurally similar to HMG-CoA (hydroxy methyl glutaryl CoA). Once hydrolyzed, simvastatin competes with HMG-CoA for HMG-CoA reductase, a hepatic microsomal enzyme. Interference with the activity of this enzyme reduces the quantity of mevalonic acid, a precursor of cholestrol [12, 13]

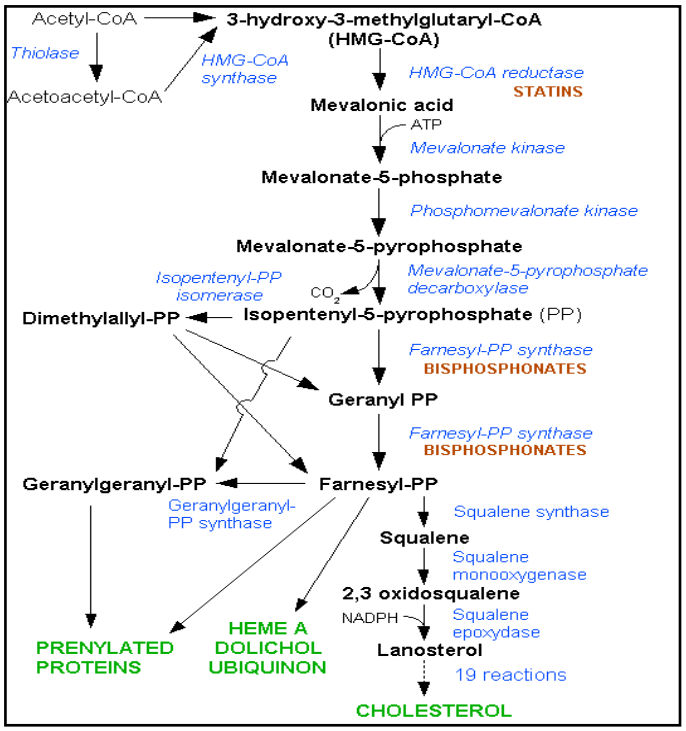


Fig.2: Mechanism of Action of Simvastatin

MATERIALS AND METHOD

Material selection

Simvastatin obtained as gift sample from Aurobindo Pharmaceuticals, Hyderabad. Eudragit RLPO, Eudragit RSPO, PVP K 30, Talc, HPMC 50 cps purchased from SD fine Chemicals Ltd., Mumbai, Formaldehyde purchased from Hi pure chemicals Magnesium stearate purchased from Ranbaxy pharmaceuticals, Delhi.

Method

All the formulations were prepared by direct compression. The compression of different formulations is given in Table. The tablets were prepared as per the procedure given below and aim is to prolong the release of Simvastatin.

Procedure

Simvastatin and all other ingredients were individually passed through sieve no. 60. All the ingredients were mixed thoroughly by triturating up to 15 min. The powder mixture was lubricated with talc. The tablets were prepared by using direct compression method and Punched in 6mm Punch Preparation of Hydrogels Plug: All the chemicals were weighed and were mixed in ascending order according to their weights and were punched in 6 mm punch with hardness 3.01. The capsule bodies were exposed to formaldehyde (15%) and for 6 hrs and were then utilized for theformulation.

Table 1: Formulation of Simvastatin Core tablets

Formulation code/Chemicals	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)	F10 (mg)	F11 (mg)	F12 (mg)
Simvastatin	40	40	40	40	40	40	40	40	40	40	40	40
Eudragit RSPO	5	10	15	20	25	30	-	-	-	-	-	-
Eudragit RLPO	-	-	-	-	-	-	5	10	15	20	25	30
Avicel pH 101	47.9	42.9	37.9	32.9	27.9	22.9	47.9	42.9	37.9	32.9	27.9	22.9
Sodium CMC	20	20	20	20	20	20	20	20	20	20	20	20
PVP K 30	5	5	5	5	5	5	5	5	5	5	5	5
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Total	120	120	120	120	120	120	120	120	120	120	120	120

Table 2: Formulation Table for Hydrogel plug

Chemicals	Quantity(mg)
HPMC 50 Cps	93.8
PVP K 30	5
Magnesium stearate	0.6
Talc	0.6

RESULTS

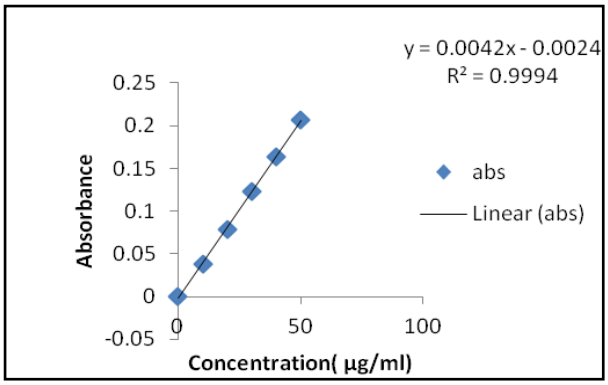
Standard Calibration Curve of Simvastatin in 7.2 ph Phosphate buffer

Standard graph of Simvastatin in pH 7.2 phosphate buffer showed linearity in the concentration range of 10-50 µg with correlation coefficient of 0.999. Table 3 gives data of the standard graph and Fig. 3 shows the standard graph in pH 7.2 phosphate buffer.

Table 3: calibration curve of Simvastatin in pH 7.2 ph phosphate buffer

S.NO	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.072
3	20	0.151
4	30	0.221
5	40	0.294
6	50	0.38

Fig. 3: Standard Calibration Curve of Simvastatin in 7.2 pH Phosphate buffer



Fourier transforms infrared spectroscopy (FT-IR) studies

Drug excipients compatibility study

To study the compatibility of drug with various polymers, IR Spectra of drug, polymer and the physical mixture of drug and polymers were taken. The IR Spectra of the drug and polymer combinations were compared with the spectra of pure drug and physical mixture of drug and polymer. The results were satisfactory with their characteristic absorption bands, the principle peaks obtained for the combinations were similar to that of the pure drug. The IR Spectra of drug-sodium alginate did not show much changes. The possibility of interaction was ruled out as there was no major shift in absorption bands of the drug and physical mixture, shows that there is no appearance

or disappearance of peaks. It is therefore, expected that the drug and polymer are compatible and free from chemical interactions. The detailed comparison of characteristic peaks of drug, polymers and their combination with drug are reported in table and spectra of pure drug, drug and sodium alginate physical mixture and spectra of optimized formulation are given in fig no 4 and 5.

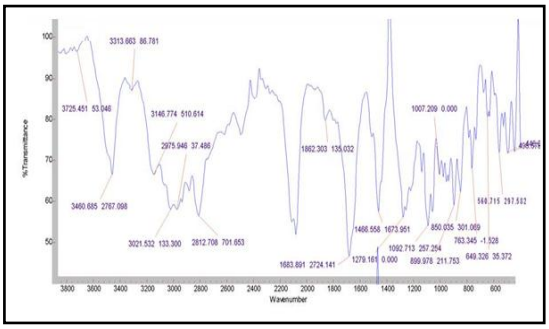


Fig.4: FT-IR spectra of Simvastatin

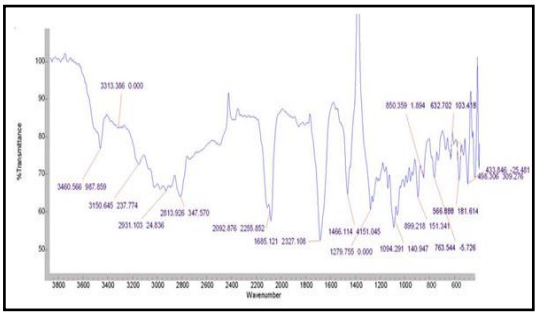


Fig.5: FT-IR spectra of Optimized formulation

Bulk density

About 30 g powder blend was introduced into a dry 100 mL cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.

Tapped density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provided a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute. The cylinder was tapped 500 times initially followed by an additional tap of 750 times until difference between succeeding measurement was less than 2 % and then tapped volume, Vf was measured, to the nearest graduated unit.

Carr's compressibility index

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is a measure of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed.

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose (θ). It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle θ, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured.

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Table 4: Pre-compression parameters

Formulation code	Bulk Density (g/cc)	Tapped density (g/cc)	Hausner's ratio	Carr's index (%)	Angle of Repose
F1	0.5	0.625	1.25	20	18.17
F2	0.52	0.55	1.057	15.45	19.24
F3	0.45	0.55	1.22	18.18	20.42
F4	0.5	0.62	1.24	19.35	22.34
F5	0.46	0.55	1.195	16.36	23.56
F6	0.56	0.69	1.23	18.84	20.24
F7	0.53	0.59	1.113	12.01	19.17
F8	0.52	0.62	1.192	16.12	18.24
F9	0.53	0.62	1.26	19.85	22.26
F10	0.43	0.49	1.14	12.24	24.57
F11	0.41	0.47	1.14	12.76	24.32
F12	0.39	0.44	1.12	11.36	25.98

Tablet thickness

The thickness in millimeters (mm) was measured individually for 10 pre weighed tablets by using a Mitutoyo Digital Vernier Caliperse. The average thickness and standard deviation were reported.

Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of five tablets was determined using Monsanto hardness tester and the average is calculated and presented with standard deviation.

Friability

It is a measure of mechanical strength of tablets. Roche friabilator (Electrolab, Mumbai, India) was used to determine the friability by following procedure. Preweighed tablets (20 tablets) were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were reweighed; loss in the weight of tablet is the measure of friability and is expressed in percentage as:

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

Where: W_1 = Initial weight of 20 tablets, W_2 = Weight of the 20 tablets after testing

Weight variation test

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity. The percent deviation was calculated using the following formula:

% Deviation = (Individual weight – Average weight / Average weight) × 100

Determination of Drug Content

Standard solution

100 mg of pure drug was weighed accurately and dissolved in 5 ml of distilled water. A sufficient quantity of Phosphate buffer pH 7.2 was added to produce 100 ml and mixed well. From this 1 ml taken and Phosphate buffer pH 7.2 was added to produce 100 ml.

Sample solution

Ten tablets with pre determined weight from each batch were taken and crushed in a mortar and weight equivalent to one average tablet was taken, transferred to a 250 ml volumetric flask and 7.2 pH Phosphate buffer was added. The volume was then made up to the mark with 7.2 pH phosphate buffer. The solution was filtered and the filtrate was sufficiently diluted and the absorbance was recorded against the blank at 238 nm. The total content of Simvastatin in the solution was

calculated using the absorbance of a standard solution. The Drug content was determined by the formula:

$$\text{Drug content} = \frac{\text{Amount in test}}{\text{Amount in standard}} \times 100$$

The tablet passes the requirements if the amount of the active ingredient in each of the 10 tested tablets lies within the range of 85% to 115% of the stated amount.

In-vitro Dissolution Studies

In vitro dissolution of Simvastatin tablets was studied in USP XXIII dissolution apparatus (Electro lab) employing a paddlestirrerat100 rpm. 900ml of Phosphate buffer of pH 7.2 was used as dissolution medium. The temperature of the dissolution medium was previously warmed to 37±0.5ºC and was maintained throughout the experiment. One tablet was used in each test.5mlof the sample of dissolution medium was withdrawn by means of a syringe fitted with prefilter, at known intervals of time (1hour).

The sample was analyzed for drug release by measuring the absorbance at 247 nm using UV-visible spectrophotometer after suitable dilutions. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The study was conducted in triplicate.

Table 5: Post compression parameter

Formulation code/Parameter	Weight variation	Hardness (kg/cm^2)	Friability (%)	Content uniformity
F1	Passes	3.00	0.12	99.92
F2	Passes	3.01	0.15	98.3
F3	Passes	3.02	0.14	100.01
F4	Passes	3.00	0.19	98.5
F5	Passes	3.03	0.19	98.9
F6	Passes	3.02	0.10	100.02
F7	Passes	3.01	0.11	98.6
F8	Passes	3.03	0.14	100.01
F9	Passes	3.01	0.12	99.2
F10	Passes	3.03	0.12	99.46
F11	Passes	3.0	0.12	98.36
F12	Passes	3.0	0.12	99.73

Table 6: *Invitro* Drug release studies

Formulation code/Parameter	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)	F8 (%)	F9 (%)	F10 (%)	F11 (%)	F12 (%)
1 hr	0	0	0	0	0	0	0	0	0	0	0	0
2 hr	0	0	0	0	0	0	0	0	0	0	0	0
3 hrs	0	0	0	0	0	0	0	0	0	0	0	0
4 hr	52	49	42	36	34	31	47	46	43	38	34	26
6 hr	63	61	56	44	45	43	58	58	54	44	47	38
8 hr	75	71	62	52	60	54	76	70	69	57	55	48
10 hr	98	87	79	68	73	66	94	89	84	62	63	56
12 hr	-	97	86	76	79	75	98	91	91	71	69	62
14 hr	-	-	98	85	86	81	-	98	94	88	76	68
16 hr	-	-	-	98	92	88	-		98	91	83	74
18 hr	-	-	-	-	98	92	-		-	97	89	77
20 hr	-	-	-	-	-	96	-		-	-	92	84
22 hr	-	-	-	-	-	98	-		-	-	98	89
24 hr	-	-	-	-	-		-		-	-	-	96

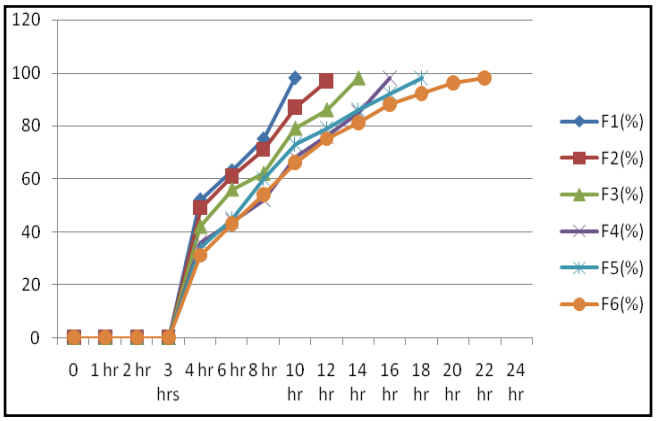

Fig.6: Invitro dissolution study of F1-F6

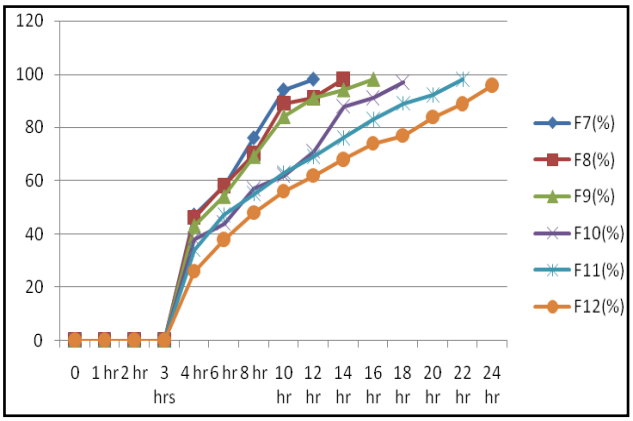

Fig.7: Invitro dissolution study of F7-F12

CONCLUSION

Simvastatin pulsatile tablets will be prepared to release the drug at predetermined time after a lag period, so that drug from the formulation will be released according physiological need of the body for the effective treatment of peptic ulcer. The approach of the present study was to make a comparative evaluation among concentration of these polymers and to assess the effect of physico-chemical nature of the active ingredients on the drug release profile. The angle of repose, compressibility index and sieve analysis results shown that the formulation is suitable for direct compression. This study have been showed that Simvastatin could be used in Controlled release drug delivery system by formulating it has Controlled drug delivery system, provides extended duration of action in therapeutic range without reaching toxic levels as in the case of conventional dosage forms. These dosage forms have the ability to reduce the dosing frequency and as it is a pulsatile formulation a lag period of 3 hrs is observed due to the hydrogel plug. The technique employed in the preparation of matrix system i.e. direct compression, is highly practical and economical from the industry point of view. The sustainability of the drug with Eudragit RLPO at a concentration of 30 mg was found to show good sustainability when compared to the marketed formulation, as it showed 96% drug release for 24 hrs. Success of the *In vitro* drug release studies recommends the product for further *In vivo* studies, it may improve patient compliance.

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