Formulation And Evaluation Of Pulsatile Drug Delivery System Of Atorvastatin Using Press Coating Technique

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ABSTRACT: The objective of present investigation is to formulate and evaluate press coated tablet for pulsatile drug delivery system of Atorvastatin, which can be taken at bed time (10pm) and capable of releasing the drug between night and early morning hours after predetermined time delay (4 hr), when free cholesterol levels are more prevalent, can prevent various heart diseases like atherosclerosis, stroke, angina and myocardial infarction. The rationale of this study is to achieve sequential release of Atorvastatin that suits the biological requirement (circadian rhythm) of hypercholesterolemia. The press coated tablets containing Atorvastatin have been made by incorporating crosspovidone by direct compression method with an outer coating of different ratios of Xanthun gum and guar gum. The disintegration time and percentage drug release was analysed for all prepared tablets from each formulation. Drug excipients compatibility has been studied by FT-IR spectroscopic studies. The formulated tablets were evaluated by stability, friability, drug content uniformity tests. Result of *in-vitro* dissolution study of the formulated tablet was suggested that, the release of drug from pulsatile unit match with the chronobiological requirement of disease.

KEY WORDS: Pulsatile drug delivery system, hypercholesterolemia, circadian rhythm, Atorvastatin.

INTRODUCTION:

Oral drug delivery has been known for decades has the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of different dosage forms.[1] Time controlled oral drug delivery systems offer several advantages over immediate-release dosage forms, including the minimization of fluctuations in drug concentrations in the plasma and at the site of action over prolonged periods of time, resulting in optimized therapeutic concentrations and reduced side effects; a reduction of the total dose administered (while providing similar therapeutic effects); and a reduction of the administration frequency leading to improved patient compliance.[2]

In the field of modified release, there has been a growing interest in time specific oral delivery which generally refers to preprogrammed release of drug following administration, to achieve improved therapeutic efficacy. These systems constitute a relatively new class of devices, the importance of which is specially connected with recent advances in Chronopharmacology.[3]

Cholesterol is essential for the formation of cell membranes and the manufacture of several hormones, but it is not required from the diet because the liver produces all the cholesterol the body needs. Hyperlipidemia is a family of disorders that are characterized by abnormally high levels of lipids (fats) in the blood. Therefore, a suitable drug delivery system for the supply of drug in appropriate intervals of time and in accordance with the level of is very important.

Pulsatile drug delivery system

Pulsatile drug delivery systems have gained attention in present days because of their multiple applications compared to other conventional dosage forms. These systems have a defined mechanism of delivering the drug rapidly and completely after a "lag time," i.e., a period of "no drug release." These delivery systems are designed in such a way that they deliver the drug at right time, at the right site of action and in right amount for constant drug release over a prolonged period of time which are basically time controlled drug delivery systems in which the system controls the lag time independent of environmental factors like pH, enzymes, gastrointestinal motility, etc. Pulsatile delivery systems are characterized by a programmed drug release, as constant blood levels of a drug may not always be desirable. These systems are beneficial for drugs having high first-pass effect.[3]

Atorvastatin is in a group of drugs called HMG CoA reductase inhibitors, or "statins." Atorvastatin reduces levels of "bad" cholesterol (low-density lipoprotein, or LDL) and triglycerides in the blood, while increasing levels of "good" cholesterol (high-density lipoprotein, or HDL). Atorvastatin undergoes high intestinal clearance and first-pass metabolism, which is the main cause for low systemic availability. So in present study Atorvastatin has been found to be suitable drug candidate for the development of pulsatile drug delivery system.

MATERIALS AND METHODS:

Materials

Atorvastatin calcium was procured from Hetero drug Limited. Vishakhapatnam, guar gum was gifted by Himalaya drug company Bangalore. All other chemicals and reagents used were of analytical grade.

Methods

Formulation of core tablets

The Core tablets of Atorvastatin calcium (10 mg/tab) were formulated in nine different formulations i.e. F1 to F9 by incorporating different quantities of super-disintegrating polymers and other excipients. All ingredients were weighed accurately as given in table 1. and passed through sieve no 80. All the ingedients except Magnesium Stearate were transferred into the mortar and mixed thoroughly for 5 minutes by triturating with the help of pestle. Magnesium Stearate was added and dry blended by tumbling method

for 10 minutes. Tableting machine was set for 150 mg compressed into a flat tablet using 8mm die and punch by direct compression method in single head rotatory tablet compression machine.

Formulation of press coated pulsatile release tablets

The optimized core tablets were press-coated with different compositions of hydrophilic polymers (Xanthun gum and Guar gum) as given in table 2. The accurately weighed coating material for each formulation were bleded for 5 minutes. During coating procedure, initially half the quantity(150mg) of coating polymer is placed in the die cavity(10mm), and then the core tablet is carefully positioned manually at the center of die cavity. The remaining 150mg of the polymer is filled into the die, and the content was compressed.

Name of the Ingredients	Quantity (mg/ tablet)								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Atorvastatin calcium	10	10	10	10	10	10	10	10	10
Crospovidone	7.5	11.25	15	-	-	-	-	-	-
Croscarmellose Sodium	-	-	-	7.5	11.25	15	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	7.5	11.25	15
MCC	126.2	122.72	118.7	126.2	122.72	118.7	126.2	122.72	118.7
Magnesium Stearate	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3
Total Weight (mg)	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**

Table 1: Formulation table

CHARACTERIZATION OF DRUG:

Evaluation studies

The prepared pulsatile tablets of Atorvastatin calcium from each formulation were analysed for hardness, thickness, friability, distingration time and drug content uniformity tests.

Hardness test

The hardness of prepared tablets of atorvasatin calcium was measured by Pfizer hardness tester.

Thickness

The thickness of each single tablet was measured using Vernier Caliper, which provides the information about variation between individual tablet.

Friability

This test is used to measure the strength of tablet. It is measured by using Roche friabilator.

$$\mathbf{F} = \frac{\boldsymbol{W}(initial) - \boldsymbol{W}\ (final)}{\boldsymbol{W}\ (initial)} \times 100\ \%$$

% friability of the tablets less than 1% is considered acceptable.

Uniformity of Content:

The content of active ingredient in each of 5 core tablets from each formulation taken at random was determined using the analytical method to find out whether the individual contents are within limits set with reference to the average content of the sample.

***In-vitro* Disintegration test:**

Disintegration test for core tablets was carried by placing one tablet in each tube of the basket and disc was dropped on tablet. The disintegrating apparatus was operated using simulated intestinal fluid (Phosphate buffer pH 6.8) maintained at 37±0.5^{0}C as the immersion liquid. The assembly was raised and lowered between 30 cycles per minute. The time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded. The experiment was carried out in triplicate for each formulations of core tablet.

***In-vitro* drug release studies of core tablets:**

Drug release studies of 6 core tablets from each formulation were carried out using a USP dissolution rate test apparatus (Apparatus II, 50 rpm, 37±0.5°C) for 60 minutes in Phosphate buffer pH 6.8(500 ml). The samples were withdrawn at time intervals 5, 10, 20, 30, 40, 50 and 60 minutes and directly analyzed for Atorvastatin calcium content using UV spectrophotometer at 246 nm. Suitable volume of the dissolution media was added after each sample withdrawal to compensate loss.

***In-vitro* drug release studies of press-coated tablets:**

Drug release studies of 6 press-coated tablets from each formulation were carried out using a USP dissolution test apparatus (Apparatus I, 50 rpm, 37 °C) for 2 hr in simulated gastric fluid (0.1 N HCl, 500 ml) as the average gastric emptying time is about 2 hr. Then the dissolution medium was replaced with simulated intestinal fluid (pH 6.8 phosphate buffer, 500 ml) and tested for drug release up to complete drug release. The samples were withdrawn at time intervals of 60 minutes and directly analyzed for Atorvastatin calcium content using UV spectrophotometer at 246 nm. Suitable volume of the dissolution media was added after each sample withdrawal to compensate loss.

Table 2: Composition of outer shell coating materials.

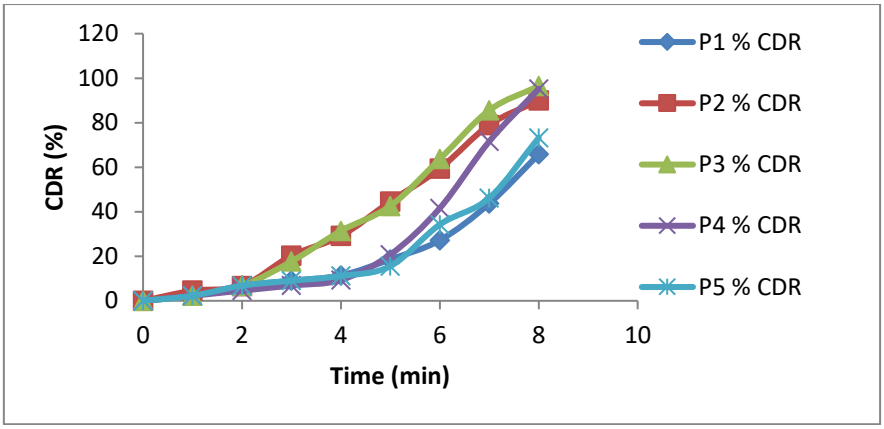
Name of Ingredients	Quantity (mg./ tablet)				
	P1	P2	P3	P4	P5
Xanthun gum	300	-	150	225	75
Guar gum	-	300	150	75	225
Total Weight(mg.)	300	300	300	300	300

Table 3. Evaluation of formulated core tablets.

Code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation (mg)	Drug content (%)	Cumulative % drug release
F1	3±0.0	4.0±0.130	0.55±0.01	150.61±1.6	97.14±1.33	89.66±0.57
F2	3±0.0	4.0±0.103	0.45±0.01	150.82±1.1	96.24±1.39	96.4±0.52
F3	3±0.0	4.0±0.123	0.54±0.01	151.30±1.2	96.00±1.41	97.42±0.05
F4	3±0.0	5.0±0.181	0.74±0.01	149.93±2.3	96.11±1.78	90.33±0.49
F5	3±0.0	5.0±0.130	0.56±0.00	150.48±2.7	95.00±0.27	91.13±0.11
F6	3±0.0	5.0±0.194	0.44±0.00	149.21±2.6	97.75±0.79	89.46±0.37
F7	3±0.0	4.0±0.136	0.57±0.01	150.6±1.40	95.99±1.63	86.33±0.5
F8	3±0.0	5.0±0.178	0.69±0.07	148.48±2.1	96.71±1.58	92.36±0.55
F9	3±0.0	5.0±0.083	0.74±0.02	151.04±2.1	95.53±0.50	86.43±0.45

Table 4. Evaluation of formulated press-coated tablets.

Formula code	Wt. variation(mg)	Hardness(kg/ cm^2)	Thickness(mm)	Cumulative % drug release
P1	449.9±0.75	7.5 ± 1.13	4.0 ± 0.0	65.8±0.41
P2	449.8±0.5	7.5 ± 1.42	4.0 ± 0.0	90±0.1
P3	450.2±0.1	8.0 ± 1.12	4.0 ± 0.0	96.5±0.3
P4	450.0±0.23	8.0 ± 1.06	4.0 ± 0.0	95.2±0.25
P5	449.9±0.20	7.5 ± 1.12	4.0 ± 0.0	73.26±0.15



Graph 1: Dissolution profile of press-coated pulsatile tablets P1-P5

All the formulated press-coated tablets (P1 to P5) passed the weight variation test, i.e., the average percentage weight variation was found to be within the prescribed Pharmacopoeial limits of ±5%.The thickness in 4.0 ± 0.0 mm and hardness in 7.5 ± 1.12 to 8.0 ± 1.12 kg/cm^2 as reported in (**table 4**) and the tablets possess good mechanical strength with sufficient hardness. The cumulative percentage drug released from each core tablet formulation was studied at different time intervals. The dissolution profile for press-coated tablets from batch P1 to P5 is shown in (**table 4 and graph 1**).Coated tablets from formulation P4 shown maximum drug release after 6 hrs hence it is selected as best formulation.

RESULTS AND DISCUSSION:

The pulsatile tablets of Atorvastatin were formulated using direct compression technique. The prepared tablets were analysed for physical characteristics such as hardness, friability, weight variation all these parameters were well within specified standards.

The drug-excipients interaction study by FTIR reveals that characteristic peaks of the drug and polymers/excipients used at their respective wave numbers with no major shifts indicating compatibility of drug with the used excipients. It shows that there was no significant change in the chemical integrity of the drug. There was no significant difference in the stability study of Atorvastatin press-coated tablets before or after 3 months of storage; there was no significant changes in either physical properties of the drug or dissolution profile.

CONCLUSION:

The immediate drug releasing core tablets were formulated and press-coated for intentionally delaying the drug release from therapeutic point of view in inhibiting synthesis of Cholesterol, where maximum synthesis are observed in the early morning. The formulated pulsatile-release dosage form of Atorvastatin may be taken at bed time with maximum drug release in early morning hours, inhibit the enzyme HMG Co-A reductase, which is responsible for Cholesterol synthesis during early morning hrs (4am to 6am). Such drug delivery system offers improved therapeutic efficacy and have better patient compliance.

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