FORMULATION AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM CONTAINING BEADS OF ATORVASTATIN

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Abstract

Chronopharmceutics is the branch of pharmaceutics that develops the formulation that will release the bioactive agent at the rhythm that identically matches the biological requirement of a given disease therapy in real time. Atorvastatin is a member of the drug class known as statins. It is used for lowering cholesterol. It inhibits the rate determining enzyme located in hepatic tissue that produces mevalonate, a small molecule used in the synthesis of cholesterol and other mevalonate derivatives. The maximum release (cholesterol synthesis will occurred at night as compared to day) when we administered conventional dosage form of Atorvastatin , 40% of drug released before the requirement of the biological system , so to avoid the release of drug before requirement, we are formulating chronomodulated drug delivery system of Atorvastatin. Drug was entrapped in calcium alginate beads and further coated with release controlling polymer and filled in hard gelatin capsule shell. From the dissolution studies it was observed that enteric coating of CAP was intact for 2hr. in pH 1.2 buffer. On the basis of in-vitro release studies and other evaluation parameters formulation F2,F3 and F6 were selected as optimized formulation for designing pulsatile device.

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Introduction:

Controlled and targeted drug delivery have been dominating over the conventional dosage form since the last 30 years.[1] These systems have focused on constant, variable; sustain drug release targeting the therapeutic agent to a specific site[2]. However, there are certain diseases for which such release pattern is not appropriate. Such disease conditions which show the requirements for a time programmed therapeutic system, which is able to release drug after predetermined time delay and maintain constant drug level entire day[3-4]. To achieve this pattern of release of drug the concept of Chronopharmceutics has been introduced and it is seeking the attention[5-7]. Chronopharmceutics is the branch of pharmaceutics that develop the formulation that will release the bioactive agent at the rhythm that identically matches in real time the biological requirement of a given disease therapy[8-9]. Atorvastatin is a member of the drug class known as statins. It is used for lowering cholesterol. Atorvastatin inhibits the rate-determining enzyme located in hepatic tissue that produce mevalonate, a small molecule used in the synthesis of cholesterol and other mevalonate derivatives. This lower the amount of cholesterol produced which in turn lowers the total amount of LDL cholesterol. Atorvastatin is a competitive inhibitor of HMG-CoA reductase. It is very slightly soluble in distilled water[10-11].

Methodology:

Preparation and fabrication of Atorvastatin loaded pulsatile Capsule:

Preparation of beads of Atorvastatin:

Aqueous solution of sodium alginate was prepared by stirring at the speed of 500 rpm to form a homogeneous polymer solution. The drug sample (Atorvastatin) was dispersed in an appropriate proportion. Stirring was continued for one to two hours to allow complete dispersion. The dispersion was drop from a glass van syringe having 1 ml insulin syringe to the stirred calcium chloride water solution. The beads are collected followed by washing and drying at room temperature[12].

Coating of Beads:

Dip Coating:

Prepared beads were coated by using dip coating technique. In this method selected polymer dissolve in organic solvent like methanol, ethanol, acetone, at a concentration of 10% w/v. Beads were coated using coating pan. Coating procedure repeated until 10% overall weight gain observed[13].

Preparation of Capsule:

The encapsulation process consists of filling gelatine capsule with one or more beads populations using commercial capsule filling equipment. To manufacture capsule dosage form, the shell hopper is filled with empty capsule while one or both bead dosing hopper are filled with the test beads and the valve on hopper 1 is opened to deliver the amount of beads required to fill each capsule based on the potency of the beads[14].

Table 1: Formulation table

Ingredients	F1	F2	F3	F4	F5	F6
Drug	1	1	1	1	1	1
Sodium alginate	4	4	4	4	4	5
Sodium starch glycolate	4	4	4	4	4	4
Aluminium chloride	4%	4%	4%	4%	4%	4%
CAP	1%	1.5%	2%	2.5%	3%	1%
Acetone(ml)	100	100	100	100	100	100
Water (ml)	100	100	100	100	100	100

Evaluation of Formulation:

Bulk Density:

Bulk density is determined by pouring the beads into a graduated cylinder via a large funnel and measuring the weight and volume obtained by the beads without tapping and calculated using the following formula

Bulk Density= Weight of the Beads/ Bulk Volume of the Beads.

Tapped Density:

Tapped density is calculated by placing a graduated cylinder containing known mass of beads on a mechanical tapped apparatus, which is operated for a fixed number of taps till the powder bed volume has reached a minimum volume. Using the weight of the drug in the cylinder and minimum volume, the tapped density was calculated using the following formula.

Tapped Density=Weight of Beads/ Tapped Volume of Beads

Angle of Repose:

Weighed quantity of granules was passed through a funnel kept at a height of 2cm from the base. The powder is passed till it forms heap and touches the tip of funnel. The radius was measured and angle of repose was calculated using the following formula.

Tan θ = h/r

Where h = Height of the heap, R = Radius of the heap

Carr's Index:

Carr's Index was measured using the values of the bulk density and tapped density. The following equation is used to find the Carr's index

CI = (TD-BD)/TD*100

Where, TD= Tapped Density, BD= Bulk Density

Hausner's Ratio:

Hausner's ratio was determined by the ratio between the tapped density to that of the bulk density.

Hausner's ratio= TD/BD

Where, TD =Tapped Density, BD= Bulk Density

Drug Entrapment efficiency:

20 mg of micro beads were powdered and dispersed in methanol and kept for 24hrs. Then the resulting solution was stirred for 20min in Sonicator. Filtered the solution. The resulting solution was analyzed at 247nm using UV-visible spectrophotometer. Standard curve obtain will give the exact content of the drug entrapment.

Particle Size:

Particle size of Atorvastatin micro beads was determined by optical microscopy. The stage micrometer is replaced with slide containing micro beads 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[15].

Percentage Yield:

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

Percentage yield= Actual drug content/ Theoretical drug content X 100

Drug loading:

The dried micro bead 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 specified λmax.

Scanning electron microscopy (SEM):

The surface morphology and structure of micro beads 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 sucked to aluminium 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[16].

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±1)0C 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.

Kinetics of In-vitro drug release:

In-vitro kinetic release study involves the in-vitro medicament release data. It includes zero order, First order, Higuchi and Korsemeyer-Peppas model.

Result and Discussion

The physicochemical parameters of micro beads were performed. The results are mentioned in table.

Table no.2 : Characteristics of Atorvastatin micro beads:

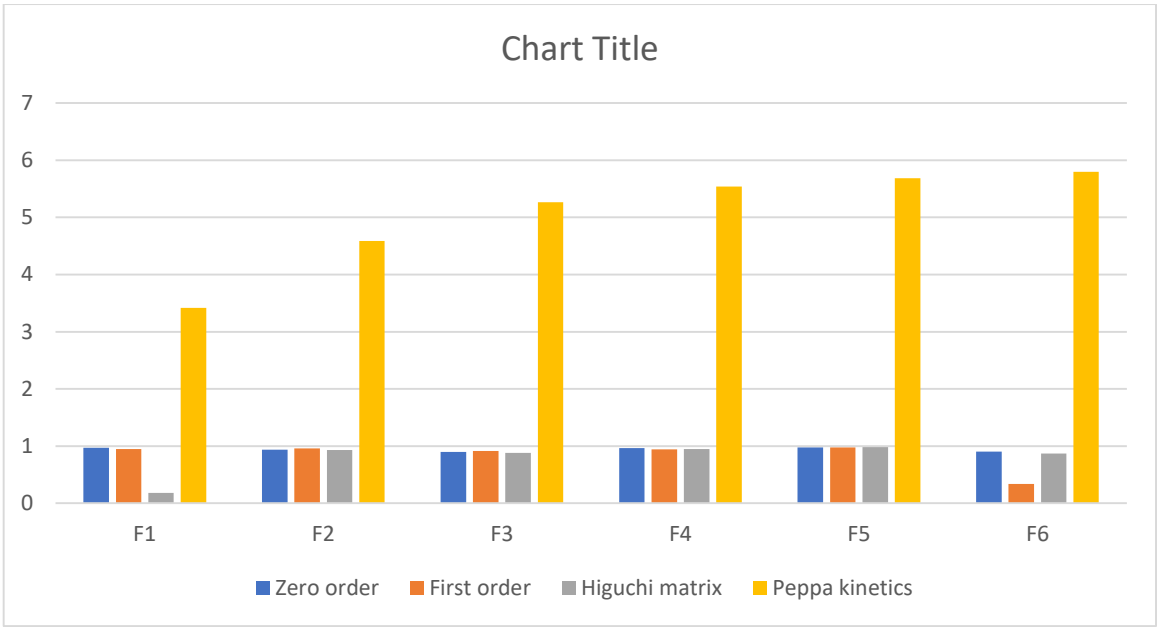
Formulation Code	Bulk Density	Tapped Density	Percentage Compressibility index	Hauser's Ratio	Angle of Repose
F1	0.44±0.004	0.49±0.01	10.20±0.12	1.11±0.002	27°01±0.34
F2	0.44±0.003	0.52±0.02	15.38±0.21	1.18±0.06	35°62±0.16
F3	0.45±0.002	0.55±0.02	18.18±0.22	1.22±0.003	28°64±0.12
F4	0.48±0.002	0.63±0.003	23.80±0.15	1.31±0.004	27°17±0.1
F5	0.68±0.003	0.84±0.03	19.04±0.29	1.23±0.005	39°42±0.32
F6	0.67±0.002	0.84±0.001	20.23±0.17	1.25±0.001	28°91±0.31

The values obtained lies within the acceptable range. This indicates good flow property of the micro beads.

Table no.3: Release Kinetic Study

The all formulations were evaluated for release kinetics:

Formulation Code	Zero Order	First Order	Higuchi matrix	Peppas Kinetic N-value	Best Fit Model
F1	0.969	0.948	0.178	3.416	Peppas Kinetic
F2	0.935	0.958	0.933	4.586	Peppas Kinetic
F3	0.896	0.913	0.878	5.267	Peppas Kinetic
F4	0.964	0.940	0.945	5.541	Peppas Kinetic
F5	0.977	0.978	0.979	5.685	Peppas Kinetic
F6	0.904	0.335	0.867	5.797	Peppas Kinetic



Graph: Release kinetic study

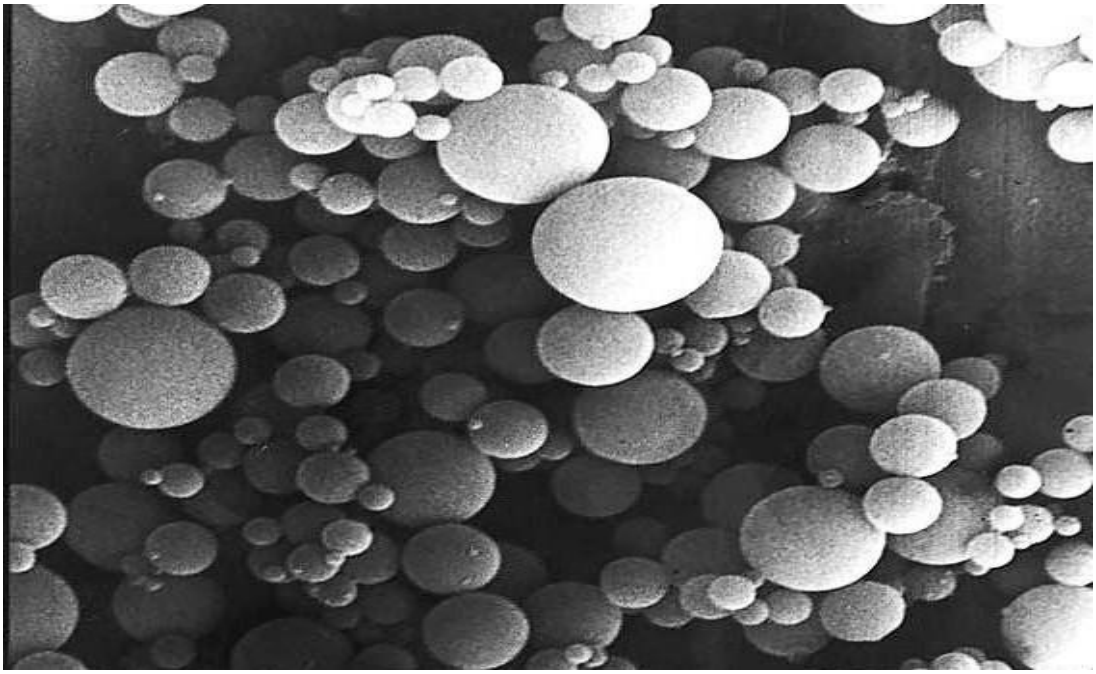


Figure No. 1: -SEM image of prepared microbeads of Atorvastatin

In the present study, an attempt was made to develop and evaluate pulsatile drug delivery system containing Atorvastatin as active ingredient for better treatment of hyperlipidemia. Pulsatile drug delivery of Atorvastatin could prevent unwanted systemic side effects and subsequently a lower dose of drug may be sufficient to prevent hyperlipidemia.

The main purpose of this current research project was to meet requirement of hyperlipidemia which required chronomodulated or time dependent drug delivery for effective treatment of disease. A satisfactory attempt was made to develop pulsatile system of Atorvastatin and evaluated it.

Conclusion:

The result which was obtained from experimental study it can be concluded that coating of CAP in different ratio was suitable as intermediate polymeric coating for the beads. Coating of CAP is suitable as outer most coating layer to retard the drug release in acidic media. Increase in amount of sodium alginate increase drug entrapment efficacy. From the dissolution studies it was observed that enteric coating of CAP was intact for 2hr. in pH 1.2 buffer. On the basis of in-vitro release studies and other evaluation parameters formulation F2, F3 and F6 were selected as optimized formulation for designing pulsatile device. Though several other study like stability, kinetic of drug release, in-vivo characteristics was required but from the above experimental result it was concluded that through this prepared pulsatile unit we can able to provide a sequential release of Atorvastatin and thus provide a better management of hyperlipidemia.

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