Abstract

In this study, investigation of an oral stomach specific, floating pulsatile device to achieve time and/or site specific release of drugs, based on chronopharmaceutical consideration. The rational of this study is to design and evaluate an oral site-specific, floating pulsatile drug delivery system containing atenolol and diclofenac sodium. A floating pulsatile compress coated tablet, multiparticulate coated pellet and floating pulsatile capsule with eroding plug dosage form, taken at bed time with a programmed start of drug release early in morning hours.

The atenolol tablets were prepared by direct compressed method with different polymer and atenolol calcium alginate bead by by ionotropic gelation method with different erodible polymer. Diclofenac sodium multiparticulate pellet was prepared by extrusion–spheronisation with different filler. Floating pulsatile dosage form were evaluated for particle size and morphology with SEM, FTIR, in vitro buoyancy time, in vitro release lag time and in vitro drug release. The ratio of HPMC K4M and HPMC E5 and the coating level was optimized using $3^2$ full factorial designs. Factors studied in design were percentage of HPMC K4M in combination with HPMC E5 and the effect of coating level on In vitro drug release. Tablet prepared (Batch AD) HPMC K4M and E5 in 20:80 ratio with 225 mg of outer coating material give suitable result. In vitro release lag time was 390 min and % drug release 57.40 % after 7 hr. Diclofenac sodium pellet were prepared with microcrystallline cellulose and superdisintegrating agent. This pellet were enteric coated with different grade of Eudragit and buoyancy layer containing different ratio of HPMC K100M and sodium bicarbonate, batch BL 8 were prepared with 60 : 40% respectively. The study showed that, lag time prior to drug release was highly affected by the coating level. The dissolution data reveled that the level of coating and the ratio of polymers are very important to achieve a optimum formulation. The basic design consists of an insoluble hard gelatin capsule body, filled with calcium alginate bead of atenolol with buoyancy material and sealed with a hydrogel plug. The buoyancy material was give site / time specific drug release.

The in vitro, drug release studies were carried out using 0.1 N HCL pH 1.2 as media for 6 hr. At the end of 6th hr the drug release in the range of 100.26 ± 1.53 to 44.64 ± 0.24 and from the obtained results; CP9 was selected as an optimized formulation for designing pulsatile device. Different exipient or hydrogel polymers (lactose, dicalcium phosphate, microcrystalline cellulose and HPMC) were used as plugs in different ratios, to maintain a suitable lag period.
Summary

Over the past two decades there has been a growing appreciation on the importance of circadian rhythms on GIT physiology and on disease states, together with the realization of the significance of time-of-day of the administration on resultant pharmacodynamics and pharmacokinetics parameters. The significance of these day-light variations has not been over looked from the drug-delivery perspective and pharmaceutical scientists have displayed considerable ingenuity in the development of time delayed drug delivery system to address emerging chronotherapeutic formulation.

A floating pulsatile compress coated tablet, multiparticulate coated pellet and floating pulsatile capsule with eroding plug dosage form, taken at bed time with a programmed start of drug release early in morning hours, can prevent a sharp increase in the incidence of essential hypertension and rheumatoid arthritis, during the early morning hours (essential hypertension), a time when the risk of essential hypertension is the greatest and rheumatoid arthritis, during early morning and evening time, a time when the risk of inflammation in joint.

Design, development and characterization of time controlled floating pulsatile tablets

Designed with various compositions of hydroxypropyl methyl cellulose and effervescent agent like sodium bicarbonate and citric acid. The physicodynamic properties of tablets such as thickness, hardness, Friability, content uniformity, buoyancy time, total floating time, Lag time (i.e. time for drug release start) and % drug release.

*In vitro* release lag time of the formulation is a function of the polymer nature and viscosity. Results of the *In vitro* release lag time show that the formulation with HPMC K4M and E5 ratio 25:75 and 275mg of coating has higher lag time 420 min than the formulation with HPMC K4M and E5 ratio 15:85 and 225mg of coating has 240 min. The in vitro release lag time of formulation with the combination of the HPMC K4M and E5 ratio 20:80 and 225mg of coating material was found to be 360 sec.

The formulation containing hydroxypropyl methyl cellulose K4M and HPMC E5 in percentage weight ratio of 20: 80 at 225mg coating material was in the optimum zone and has the potential for time-controlled pulsatile delivery of atenolol.
Formulation and evaluation of time controlling multiparticulate floating pulsatile pellets

In the present study, the core containing diclofenac sodium (100mg) were prepared by extrusion/spheronization and then coated sequentially with an inner enteric coating layer containing Eudragit® NE 30D, Eudragit® RL100 and RS100 with % weight gain (10%w/w, 20%w/w and 30%w/w) and an outer effervescent layer consisted of HPMC K100M and sodium bicarbonate (60:40). From result conclude that batches prepared by using 80% (w/w) HPMC K100M was more drug release retard and incomplete drug release, after 7 hr only 80% drug release. For chronopharmaceutic drug release set as predetermine lag, then complete drug was done but batches prepared with 80% HMPC K100M drug release time required up to 10 hr. When batches prepared with batches 60% HMPC K100M, 40% sodium bicarbonate and 20% weight gain of drug release within 8 hr, it’s suitable for cardiac rhythm.

Formulation and evaluation of time controlling floating pulsatile capsule with erodible plug

An inner filled bead prepared with sodium alginate and calcium chloride in 1:1 ratio and drug incorporated 2 gm atenolol which was expected to release the after a lag time of six hr. The solubility studies of empty gelatine capsule bodies, which where crosslinked with formaldehyde treatment, revealed that they are intact for 24 hrs, and hence suitable for colon targeting.

The drug releases lag time of dosage form mainly controlled by using plug material like MCC, lactose, dicalcium phosphate and HPMC E50 in different concentration and different ratio, but batch CP9 containing plug lactose and HPMC E 50 in 50:50 ratio which give better lag time of drug release. Optimization enabled formulation of atenolol capsule coated with combination of hydrophilic and hydrophobic polymer with the desired release profile.

On the basis of, buoyancy lag time, drug content, IR-study, in vitro drug release lag time, in vitro release studies and in vivo studies, CP9 was selected as an optimized formulation for designing pulsatile device.