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Formulation and evaluation of floating pulsatile beads of diltiazem hydrochloride

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ABSTRACT

The objective of developing floating pulsatile beads of diltiazemHClwas to overcomecomplications faced during morninghypertension. All the current sustained release formulation have a shortcoming of inability to maintain high blood levels for that long period with high disease intensity. This may lead to leaving the patient unprotected against the worse events of morning hyper tension. Thus, a smart drug delivery that is administrated before sleep and maintains high blood levels in the morning, during which maximum intensity of the disease occurs and this could be very much beneficial for proper management of morninghypertension.The reason behind selecting diltiazemHCl is its efficiency to control heart rate in early morning. The pulsatile alginate beads were developed by ionotropic gelation technique using polymers sodium alginate, Na CMC, HPMC and sodium bi carbonate as effervescent agent.Scanning electron microscopy revealed that the microspheres were spherical and had smooth surfaces. The prepared beads were studied for drug entrapment efficiency, swelling index and dissolution studies. From the results formulation F6 was selected as best formulation.

Keywords: Floating pulsatile beads, DiltiazemHCl, Morning hypertension, Ionotropic gelation technique, Sodium alginate.

1. INTRODUCTION

The main principle involved in the pulsatile drug delivery [1-3] system is release of drug as a pulse after a lag time. Pulsatile drug delivery systems are gaining a lot of interest as they deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increase in patient compliance. These systems are designed according to circadian rhythms [4] of the body. A number of common diseases are affected by chronobiology. Such diseases include angina [5], rheumatoid arthritis, allergic rhinitis [6], hypertension [7] and cancer [8]. Hypertension may be the most common disease with the largest circadian variation. In cardiac patients the heart rate, capillary resistance and vascular reactivity are high in early morning [9-14] and decreased during day time, so the mortality rate is high in the early morning.

The reason behind developing floating pulsatile delivery of diltiazemHCl is it is well absorbed from the gastrointestinal tract and its potency to control increased heart rate in early morning. The absolute bioavailability of an oral dose of diltiazen HCl [15] (compared to intravenous administration) is approximately 40%. The plasma elimination half-life [16-17] of diltiazemHCl is approximately 3.0 - 4.5 h. Therapeutic blood levels of diltiazemHCl appear to be in the range of 40 - 200 ng/ml. There is a departure from linearity when dose strengths are increased; the half-life is slightly increased with dose. DiltiazemHCl produces its antihypertensive effect primarily by relaxation of vascular smooth muscle and the resultant decrease in peripheral vascular resistance. The magnitude of blood pressure reduction is related to the degree of hypertension, thus hypertensive individuals experience an antihypertensive effect, whereas there is only a modest fall in blood pressure in normotensives.

2. MATERIALS AND METHODS

2.1. Materials

Diltiazem hydrochloride drug was obtained as a gift sample from NatcoPharma., Hyderabad, India. Polymers HPMC, CMC were procured from Yarrow Chem. Products, Mumbai, India. Pectin and sodium alginate were purchased from Himedia lab. Sodium bicarbonate and calcium chloride were procured from Reachem Laboratory Chemicals Pvt. Ltd., Chennai, India. All the chemicals were of analytical grade.

2.2. Preparation of microbeads

Thefloating microbeads were prepared by ionotropic gelation method. Drug and the polymers mentioned in the table1, except cacl2 and acetic acid were taken in beaker and allow to dissolve completely in 30 ml of water using magnetic stirrer. The stirring is continued until clear dispersion was formed, then this dispersion was dropped via 23# needle in to 50ml calcium chloride (CaCl2) solution containing 8ml of acetic acid.

2.3. Evaluation of gastro retentive floating micro beads

2.3.1. Optimization of acetic acid concentration

Optimized concentration of acetic acid is selected from various concentrations including 2%, 4%, 6%, and 8% of acetic acid from the floating efficiency. The floating efficiency of various batches was studied from total floating time and floating lag time.

2.3.2. Optimization of $CaCl_2$ concentration

The optimized concentration of $CaCl_2$ was selected from 2%, 3%, 4%, and 5% concentrations of calcium chloride solutions by estimating micro encapsulation efficiency. Micro encapsulation efficiency was calculated by estimating percentage of drug content and this was compared with theoretical percentage drug content.

Micro encapsulation efficiency = (estimated percent drug content/ theoretical percent drug content) x 100

2.3.3. Surface topography

The surface topography and structures were determined using scanning electron microscope (SEM, JEOL JSM – 6701 F, Japan) operated with an acceleration voltage of 20k.v, Contact angle meter, Atomic force microscopy (AFM), Contact profiliometer.

2.3.4. Buoyancy / Floating Test

The time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

2.3.5. Swelling Study

The swelling behavior of a dosage form was measured by studying its weight gain or water untake the dimensional changes could be measured in terms of the increase in tablet diameter and/or thickness over time. Water uptake wasmeasured in terms of percent weight gain, as given by the equation.

$WU = (Wt – W0)/W0 \times 100$

Wt= Weight of dosage form at time t.

W0= Initial weight of dosage form

Table-1: Formulation of floating beads

Formulation	Pioglitazone (gm.)	NaHCO3 (gm.)	Na alginate (gm.)	Pectin (gm.)	HPMC (gm.)	CMC (gm.)
FP1	1	1	1	1	-	-
FP2	1	1	1.5	1.5	-	-
FP3	1	1	2	2	-	-
FH4	1	1	1	-	1	-
FH5	1	1	1.5	-	1.5	-
FH6	1	1	2	-	2	-
FC1	1	1	1	-	-	1
FC2	1	1	1.5	-	-	1.5
FC3	1	1	2	-	-	2

2.3.6. Determination of drug content

1 gm. of beads were powdered and dissolved in 100 ml of 0.1 N HCl and this was analyzedspectrophotometrically and studied for drug content by comparing with calibration curve.

2.3.7. In vitro Drug release study

The drug release profiles of all batches of microbeads were carried out in buffer of pH1.2. The dissolution process was carried out by using USP XIII rotating basket apparatus. Basket rotated at a constant speed at 50rpm and maintained temperature 370C.The 900ml of the dissolution medium of pH1.2. At scheduled time intervals, the sample (5ml) was withdrawn and replaced with same volume of fresh medium. The withdraw sample were filtered through a 0.45µm membrane filter and after appropriate dilution, and then estimated for drug concentration 269nm spectrphotometrically. Finally, corresponding drug content in the samples was calculated from the calibration curve pioglitazone to determine the drug release pattern.

3. RESULTS AND DISCUSSION

3.1. Optimization of acetic acid

The microbeads prepared with sodium alginate were studied in various concentrations of acetic acid. At 8ml of 2%, 4% acetic acid in $CaCl_2$solution beads does not show buoyancy and at 6%, 8% acetic acid in $CaCl_2$ solution beads show good floating property with lag time. At 8ml concentration of 10% acetic acid in $CaCl_2$ solution beads show good floating property with negligible floating lag time. Therefore 8 ml concentration of acetic acid is used for further formulations.

3.2. Optimization of $CaCl_2$ concentration

Different batches of sodium alginate formulations were prepared using 2%, 3%, 4%,5% concentrations of $CaCl_2$. The drug entrapment efficiency of formulations prepared using 2%, 3%, 4% and 5% concentrations of $CaCl_2$ were 88%,74%, 65% and 72% respectively and were shown in table 2. So 3% $CaCl_2$ was used for other formulations.

Table-2: Optimization of $CaCl_2$

% of CaCl2	% Drug Entrapment
2	88
3	74
4	65
5	72

3.3. Surface topography

SEM photographs of best formulation FC3 were showed in figure 1. The images implying that the microspheres were spherical and had smooth surfaces.

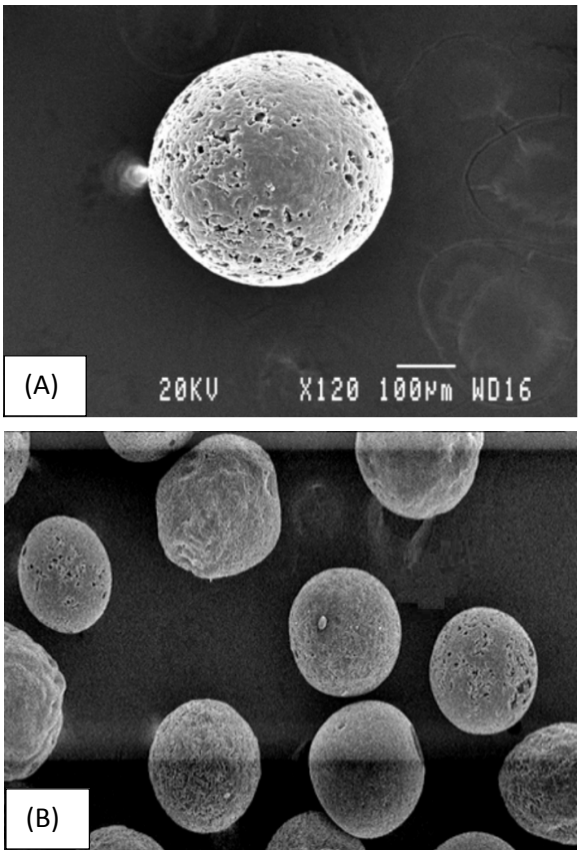

Figure-1: SEM (Scanning Electron Microscopy) Photographs of alginate beads (A) Single (B) Group

3.4. Buoyancy / Floating Test

The formulations were studied for floating lag time and total floating time in 0.1N HCl. All the formulations show no or negligible floating lag time and the total floating time is more for formulations prepared with sodium alginate, Na CMC. The total floating time of formulations prepared with Na CMC, FC1, FC2, FC3 are 26hrs, 28hrs, and 24hrs respectively.

3.5. Swelling Study

The prepared microbeads gets in contact with water the soluble hydrophilic layer stars to swell by absorbing the liquid thereby creates a gel layer which acts as barrier preventing the liquid from reaching the drug contents. Swelling index values of microbeads increases still the burst release takes place, there after the values are fallen. From the results the swelling index is more for formulation FC3 prepared with core:coat ratio of 2:2. Formulation FP1 prepared with pectin showed least swelling index of 33% and formulation FC3 prepared with Na CMC showed maximum swelling index of 106%. The swelling index of all formulations was showed in figure 2.

The floating time, micro encapsulation efficiency, swelling index and mean diameter of all formulations were shown in table3.

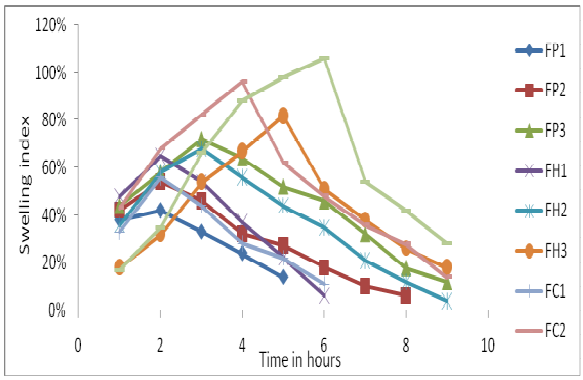

Fig-2: Swelling index graph of all formulations

3.6. Drug content estimation

The Drug content in formulations was in the range of 77.4 to 97.6 and was expressed in table3. The drug content is more for formulation FH2 prepared with HPMC, least for FP3 batch prepared with pectin.

Table-3: Characterization of beads

Table-3: Characterization of beads

Formulation	Drug content	Floating time	Floating lag time
FP1	87.4	24hrs	0
FP2	92.3	22hrs	0
FP3	77.4	18hrs	0
FH1	86.5	26hrs	0
FH2	92.6	24hrs	0
FH3	84.5	16hrs	0
FC1	88.4	26hrs	0
FC2	90.4	28hrs	0
FC3	83.5	24hrs	0

3.7. In vitro Drug release study

The dissolution profile of all formulations were studied and shown in figure 3. From the figure it is evident that the formulation with CMC, FC1 showed lag time of 2 hours, formulation FC2 showed a lag time of 4 hours and the formulationFC3 showed a lag time of 6 hrs. On other hand formulations with pectin have prolonged lag time than the formulations with Na CMC. The formulations FP1, FP2, FP3 showed a lag time of 2 hours, 2 hours, 3 hours lag time respectively and the formulations prepared with HPMC showed a lag time of 2hours, 3hours, 5 hours for FH1,FH2, FH3 respectively. Time required to release 90% of drug is called T90 and is showed in Figure 4. Formulations FP1, FP2, FP3 prepared with pectin had T90 of 4.4hrs, 6.5hrs, and 10hrs respectively. The formulations FH1, FH2, FH3 prepared with HPMC had T90 of 4.5hrs, 8.4hrs, 12hrs respectively, the batches prepared with Na CMC namely FC1, FC2, FC3 showed T90 of 4.3hrs, 8.1hrs, 12.2hrs respectively and the values are graphically represented in figure 4.

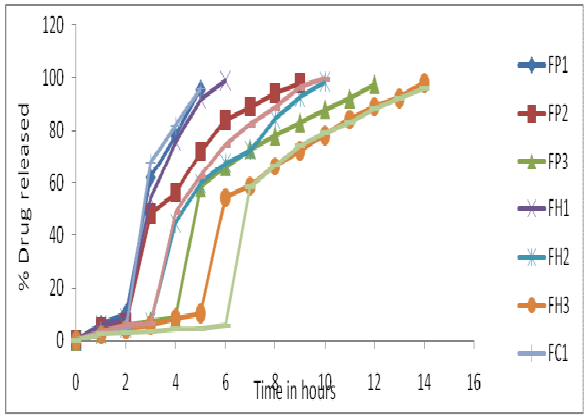

Figure -3: Dissolution profiles of formulations

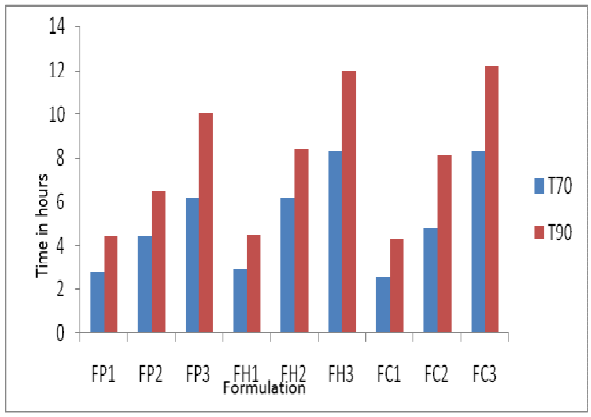

Figure - 4: T70 and T90 of formulations

4. CONCLUSION

From the results it is impeding that formulation FC3 prepared with sodium carboxy methyl cellulose and sodium alginate and drug in the ratio of 2:2:1 showed maximum lag time of 6 hours and T90 of 12.2 hours. So it is selected as best formulation to release drug at desired time to control morning hypertension since such dosage is enough to release drug in early morning 3am to 8am when taken at bed. Morning hypertension is the one of main cause for deaths in cardiac patients, so in order to reduce the mortality in cardiac patients a desired dosage form such as pulsatile beads is required to control heart rate and vascular resistance in early morning. The reason for selecting diltiazemHCl is recent studies reveals that calcium antagonists such as diltiazemHCl, clinidipine have been used in specific treatment of morning hypertension because they have an inhibitory effect on increasing heart rate.

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