

Formulation, Development and Characterization of Floating Beads of Diltiazem Hydrochloride

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Available Online: 1st February, 2016

ABSTRACT

The main goal of any drug delivery system is to achieve desired concentration of the drug in blood or tissue, which is therapeutically effective and nontoxic for a prolonged period. Various attempts have been made to develop gastroretentive delivery systems such as high density system, swelling, floating system. The recent developments of FDDS including the physiological and formulation variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems, and their classification and formulation aspects are covered in detail. Gastric emptying is a complex process and makes in vivo performance of the drug delivery systems uncertain. In order to avoid this variability, efforts have been made to increase the retention time of the drug-delivery systems for more than 12 hours. The floating or hydrodynamically controlled drug delivery systems are useful in such application. Background of the research: Diltiazem HCL (DTZ), has short biological half life of 3-4 h, requires rather high frequency of administration. Due to repeated administration there may be chances of patient incompliance and toxicity problems. Objective: The objective of study was to develop sustained release alginate beads of DTZ for reduction in dosing frequency, high bioavailability & better patient compliance. Methodology: Five formulations prepared by using different drug to polymer ratios, were evaluated for relevant parameters and compared. Alginate beads were prepared by ionotropic external gelation technique using CaCl₂ as cross linking agent. Prepared beads were evaluated for % yield, entrapment efficiency, swelling index in 0.1N HCL, drug release study and SEM analysis. In order to improve %EE and drug release, LMP and sunflower oil were used as co-polymers along with sodium alginate.

Keywords: Floating, gastrointestinal, gastro retentive system, Entrapment Efficiency

INTRODUCTION

The oral route is considered as the most promising route of drug delivery. Effective oral drug delivery may depend upon the factors such as gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs^{1,2}. Floating multiparticulate are gastro-retentive drug delivery systems based on non-effervescent and effervescent approach. Beads are in strict sense, spherical empty particles without core. These Beads are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 1000 micrometer³. Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment⁴. It is a formulation of a drug with gel forming hydrocolloids meant to remain buoyant in the stomach contents. Drug dissolution and release from the dosage form retained in the stomach fluids occur at the pH of the stomach under fairly controlled conditions⁵.

Mechanism of floating systems

While the system is floating on the gastric contents the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach however, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to main submerged object. The object floats better if F is on the higher positive side (Fig. 1.3). This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations⁶. $F = F_{\text{buoyancy}} - F_{\text{gravity}} = (D_f - D_s) g v$
Where, F= total vertical force, D_f = fluid density, D_s = object density, v = volume and g = acceleration due to gravity⁷.

MATERIALS AND METHODS

Materials

The drug, chemicals and equipment were used in the

Table 1: List of Chemicals

S. No	Materials	Source
1.	Diltiazem Hydrochloride	A gift sample of Zydus Cadila
2.	Sodium Alginate	Central Drug Store [P] Ltd. (CDH)
3.	Low Methoxy Pectin(LMP)	Central Drug Store [P] Ltd. (CDH)
4.	Sodium Chloride	Central Drug Store [P] Ltd. (CDH)
5.	Calcium Chloride	Central Drug Store [P] Ltd. (CDH)
6.	Sunflower oil	Central Drug Store [P] Ltd. (CDH)

Table 2: List of Equipments

S. No	Equipments	Model/Company
1.	UV- Visible Spectrophotometer	Shima DZU UV-1700
2.	Electronic Balance	Citizen cy220
3.	Fourier Transform Infrared Radiation(FTIR)	Bruker alpha
4.	USP Dissolution apparatus	Electrolab TDTO 6L
5.	Optical Microscope	Olympus OIC
6.	Hot Air Oven	Roletx
7.	Sonicator	Citizen cy220
8.	Magnetic Stirrer	Instrument India

Table 3: The formulations for *Diltiazem* Hydrochloride are given

S. No	Formulation code	Drug (mg)	Sodium Alginate(%)	LMP (%)	Sunflower oil (ml)	Calcium Chloride(%)
1.	F1	100	2	3	2	5
2.	F2	100	3	3	2	5
3.	F3	100	2	3	5	5
4.	F4	100	3	3	5	5
5.	F5	100	4	3	10	5

Table 4: Characterization of Floating Beads

Formulation	Practical (%)	Yield	Particle size (mm)	Density (gcm-3)	Swelling (%)	Index	Entrapment Efficiency (%)
F1	67.43		1.241±0.012	0.964±0.24	0.78±0.28		46.42±0.24
F2	70.98		1.285±0.0.15	0.928±0.64	1.38±0.24		56.24±0.14
F3	80.54		1.468±0.016	0.892±0.78	0.75±0.17		72.82±0.56
F4	82.12		1.492±0.015	0.874±0.42	1.35±0.14		75.88±0.48
F5	88.92		1.638±0.032	0.718±0.24	1.82±0.06		86.45±0.38

Table 5. In Vitro Buoyancy of Beads.

Formulation code	Amount of Oil (ml)	Floating Time (min)	Floating Duration (Hrs)
F1	2	11	>12
F2	2	11	>12
F3	5	5	>12
F4	5	6	>12
F5	10	3	>12

present research work are given in Table 1 and Table 2. Drugs and chemicals were of analytical grade procured either as gift samples or purchased.

Chemicals

Equipments and Instruments

Preparation of simulated gastric fluid pH 1.2: 1000ml buffer solution with pH 1.2: 250 ml of 0.1 M HCl solution was taken in 1000ml beaker and 500ml 0.1M HCl solution were added into the 1000ml beaker. Adjust the pH 1.2 with adding distilled & demineralised water respectively. After

adjusting the pH of the buffer solution the buffer solution were taken into 1000ml volumetric flask⁸.

Determination of absorption maxima of Diltiazem Hydrochloride

Accurately weighed 10 mg of Diltiazem Hydrochloride hydrochloride is transferred in to 100 ml flask. The drug was then dissolved and diluted up to the mark with simulated gastric fluid pH 1.2 to get a concentration of 100 µg/ml of stock solution. From the stock solution aliquot of 2 ml was taken and diluted to 50 ml to get the concentration 4 µg/ml and scanned over the wavelength range of 400 nm to 200 nm against simulated gastric fluid pH 1.2 as blank using UV-Spectrophotometer (UV-1700, Shimadzu). The spectrum of absorbance versus wavelength was recorded using UV-Spectrophotometer and analysis for absorption maxima (λ_{max}) the wavelength at which highest absorbance was observed⁹.

Preparation of standard curve of Diltiazem Hydrochloride

100 mg of Diltiazem Hydrochloride was weighed accurately and dissolved 50ml simulated gastric fluid pH 1.2 in a 100 ml of volumetric flask and then volume was made to 100 ml. 10 ml of this solution was diluted to 100

Table 6: In Vitro release of drug from formulations in SGF (pH 1.2)

Time (h)	F1	F2	F3	F4	F5
0	0	0	0	0	0
1.	16.45	13.44	3.05	25.33	35.57
2.	27.34	21.62	4.89	36.73	45.07
3.	39.57	34.05	5.76	43.78	48.98
4.	46.077	38.95	6.37	50.64	52.44
5.	57.9	51.02	6.74	55.02	56.84
6.	67.96	62.57	7.69	60.22	60.39
7.	79.972	75.98	8.33	68.75	63.2
8.	90.58	83.85	9.93	75.38	67.3
9.	95.43	92.47	10.59	80.44	70.894
10.	98.5	100.134	11.04	87.38	72.549

ml with simulated gastric fluid pH 1.2 to obtain a stock solution of 100ug/ml. From this stock solution, aliquots of 1ml, 2ml, 3ml, 4ml.....10ml, 12 ml were transferred 10 ml volumetric flasks and volume was made up to 10 ml simulated gastric fluid pH 1.2. The absorbances of these solutions were measured at 240 nm against a blank simulated gastric fluid pH 1.2. The standard curve was plotted between concentration and absorbance. Formulation of floating beads of Diltiazem hydrochloride^{10,11}.

Preparation of floating beads of Diltiazem hydrochloride
Diltiazem hydrochloride, LMP, Sodium alginate were pass through sieve no 80 separately. Diltiazem Hydrochloride was dissolved in different proportions of sunflower (2, 5 and 10ml) LMP and sodium alginate in two different concentrations (2%, 3% and 4%) were dissolved in distilled water. To the above polymer solution was added and stirred to form a homogeneous emulsion. The drug loaded was extruded through a 23 G syringe in to calcium chloride solution (5% w/v) maintain under gentle agitation. The beads are allowed to remain in the same solution for 30 minutes to improve their mechanical strength. This solution was filtered and formed beads were allowed to dry over night at room temperature. Table 3 lists the formulation variables for different formulations of Diltiazem Hydrochloride loaded floating beads.

Evaluation of Diltiazem Hydrochloride Beads

Production Yield¹²

The obtained propranolol hydrochloride of each were collected and weighed to determine production yield (PY) using following equation.

$$PY (\%) = \left(\frac{\text{Practical mass (beads)}}{\text{Theoretical mass (polymer + drug)}} \right) \times 100$$

Partical size determination¹³

The diameter of gel beads of each formulation were collected and weighed using a dial thickness meter. Measurement for each sample was repeated 3 times. Mean diameter and standard deviation was recorded.

Determination of swelling index¹⁴

The swelling behavior of the beads was studied in SGF (pH 1.2). Approximately 100 mg of beads were taken in a dissolution basket and weighed; the basket along with the beads immersed in SGF. The weighed of the basket along with the beads is determined after 1 hour, and then every hour after that. The swelling index (SI) of each formulation was calculated using the following equation.

$$\%SI = \frac{W_2 - W_1}{W_1} \times 100$$

Where W1 is weight of dry beads and basket. W2 is weight of the swollen beads and basket.

Density measurements¹⁵

The mean weight and diameter of the beads were measured and used to mathematically calculate the densities of the spherical beads using the following equations:

$$D = M/V$$

$$V = \frac{4}{3} \pi r^3$$

Where D = Density of the beads. M = Weight of the beads.

V = Volume of the beads. r = Radius of the beads.

Determination of buoyancy of beads¹⁶

Floating properties of beads were evaluated using USP dissolution apparatus containing 500 ml SGF (pH 1.2). The temperature of the medium was maintained at 37± 0.50C. Fifty beads were placed in the media and the total floating time was observed by visual observation (n=3).

Drug content¹⁷

100 mg accurately weighed beads was crushed in a mortar and added to 100 ml simulated gastric fluid (pH 1.2) this was sonicated for complete dissolution. The mixture was kept overnight to elute complete drug from the polymer matrix. The mixture was filtered and analyzed spectrophotometrically at a wavelength of 240 nm. The drug content of each formulation was recorded as mg/100 mg gel beads.

Drug entrapment efficiency¹⁸

The percentage drug entrapment efficiency (%DEE) of each bed formulation was calculated using following equation.

$$DEE\% = \frac{\text{Actual Drug Content} \times 100}{\text{Theoretical Drug Content}}$$

Scanning Electron Microscopy

SEM may be used as qualitative tool for the analysis of drug substance and drug product in order to obtain information on the shape and surface structure of the material. SEM play an important role in the characterization of nanoscale and sub-micron particles. It has been used to determine surface topography, texture and to examine the morphology of factured or sectioned surfaces. The examination of the surface of polymeric drug delivery system can provide important information about the porosity and microstructure of the device.

In vitro drug release study²⁰

In vitro release characteristics of diltiazem hydrochloride floating gel beads were evaluated employing USP XXIII dissolution testing type I apparatus (basket). The

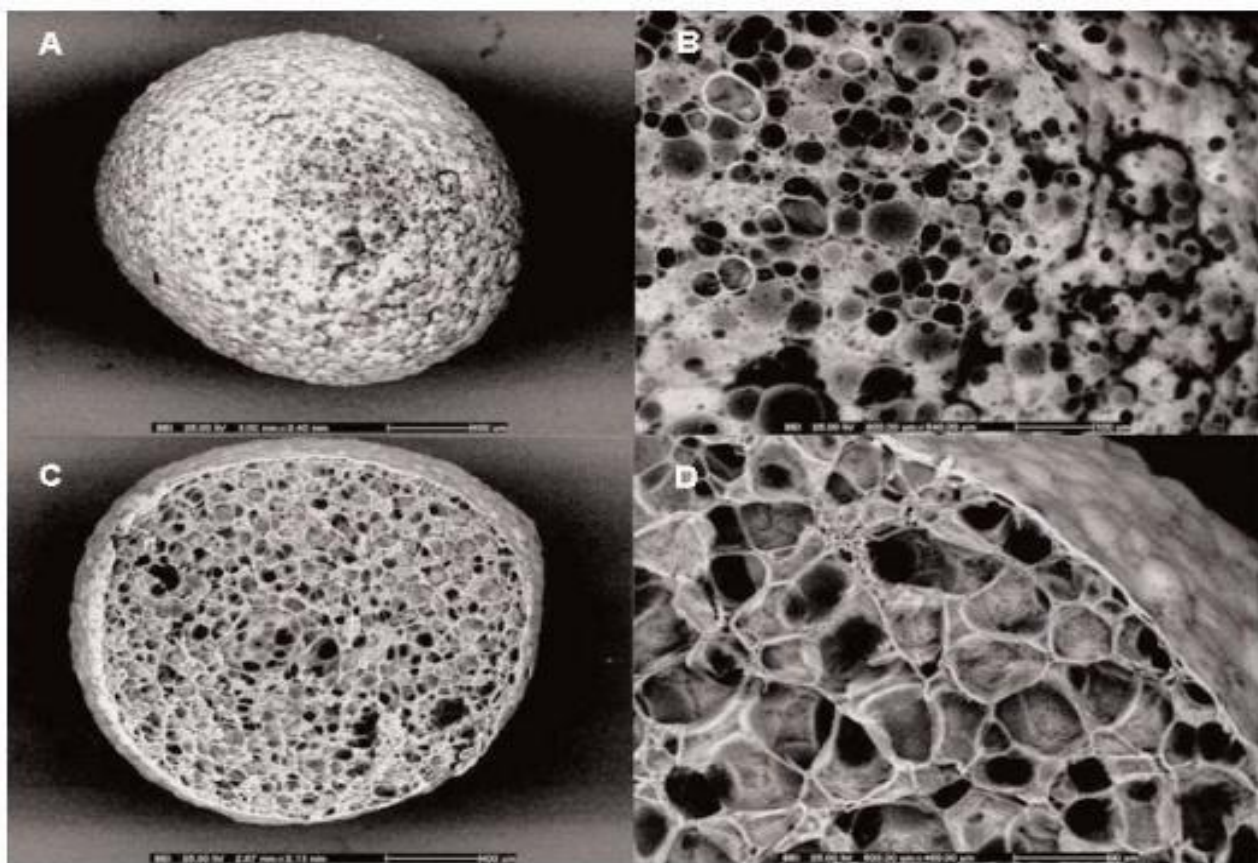
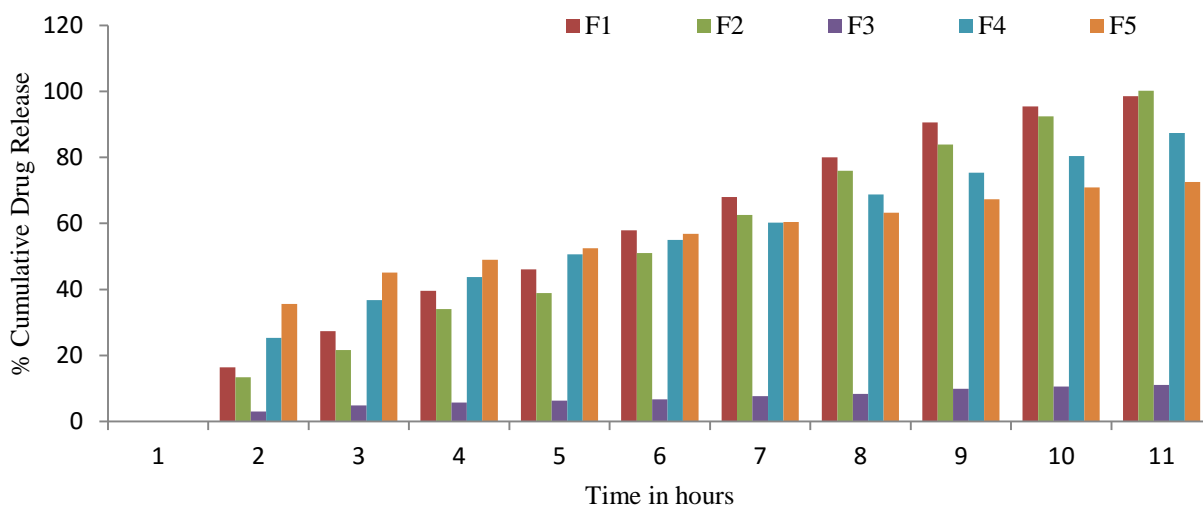


Figure 1: SEM of (A and B) external and (C and D) internal structure of optimized Formulation F5 In Vitro Release Profile



dissolution test was performed using 900 ml of SGF buffer as dissolution medium maintained at $37 \pm 0.5^\circ\text{C}$. The contents were stirred at 50 rpm. A 5 ml aliquot of the solution was withdrawn at predetermined time intervals for 10 h and fresh 5 ml dissolution media was replaced to maintain sink condition. The sample aliquots were analyzed spectrophotometrically at a wavelength of 240 nm.

The general conditions for in vitro dissolution studies are summarized below.

Dissolution Apparatus: USPXXIII Type I.
 Dissolution Media: Simulated Gastric Fluid pH 1.2
 Volume of the Media: 900 ml
 Sampling Volume: 5 ml
 Rotation speed: 50 rpm
 Temperature: $37 \pm 0.5^\circ\text{C}$

Determination of Buoyancy of Beads

The floating ability of prepared beads was evaluated using USP XXIII dissolution apparatus containing 500 ml of SGF (pH 1.2). All the formulations shows good buoyancy for more than 12 hours.

Scanning Electron Microscopy

Surface morphology of the prepared floating beads was examined by scanning electron microscopy (SEM). The beads were found spherical in shape. The scanning electron micrographs of external and internal surfaces of formulation is shown in Figure 1. The beads were spherical and the external surface was smooth with slightly rougher surface. Shrinkage is due to drying. The internal surface of the beads showed sponge-like nature with little droplets of entrapped oil which imparts buoyancy to the beads. In vitro release study of Diltiazem Hcl floating beads was carried out using USP rotating basket apparatus in simulated gastric fluid (pH 1.2) , for a period of 10 h. Amount of beads equivalent to 10 mg of Diltiazem Hcl were introduced in the basket which were rotated to 50 rpm in 900 ml of SGF, maintained at $37 \pm 0.50^\circ\text{C}$. Aliquots of 5 ml of the solution were withdrawn at predetermined time intervals and replaced by fresh dissolution medium. The withdrawn sample were analyzed for Diltiazem Hcl content spectro photo metrically at 240 nm. The drug release profiles were presented by plotting the amount of Diltiazem Hcl released against time. The cumulative drug release of formulations were calculated and noted in Table: 4. the beads exhibited a biphasic release profile as an initial rapid drug release phase (burst effect) which was followed by a sustained, gradually increase drug release phase after 1 h extending up to 10 hrs. Formulation F1 which contained least concentration of oil and polymer could not contain sustain Diltiazem release up to 10 h. It released complete drug at the 9 hrs. whereas formulations contain higher concentration of polymers and oil (F5) showed a sustain release profile at the end of 10 hrs.

SUMMARY AND CONCLUSION

Drug absorption from the gastrointestinal tract is highly variable process and hence prolong gastric retention of the dosage form is challenging task. Under such circumstances floating drug delivery proves to be a promising approach of gastric retention. A new sustained release system of oil entrapped beads were designed and prepared by an emulsion gelation method and evaluated for production yield, particle size, swelling index, density, buoyancy, drug content, drug entrapment efficiency, morphology and in vitro release characteristics. The results obtained and the conclusion drawn from the study are as follows: Diltiazem Hcl beads were efficiently prepared by emulsion-gelation method by virtue of high gelating and cross-linking property of alginate and pectin molecules. Total 5 formulations were prepared and characterized. The beads were spherical and their external surface was smooth with slightly rougher surface. The internal surface of the bead showed sponge-like nature with little droplets of entrapped oil which imparting buoyancy to the beads. Formulation F1 which contain least concentration of oil and polymer sustain the Diltiazem Hcl release up to 10 hrs. Complete drug release occur in 10 hrs whereas, formulations

containing higher concentration of oil and polymer (F5) showed a sustained release profile at the end of 10 hrs. From the studies performed it was concluded that the oil entrapped gastroretentive floating beads of Diltiazem Hcl showed excellent buoyancy and sustain drug release up to 10 hrs. Due to the retention of the formulation for longer time in stomach an enhancement in the bioavailability of the drug was observed by this method we can thus reduce the dosing frequency and improve patient compliance.

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