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FORMULATION AND EVALUATION OF FLOATING PULSATILE DRUG DELIVERY FOR CHRONOTHERAPY OF HYPERTENSION

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Abstract

The purpose of this work was to develop a dosage form of an cardiovascular drug for pulsatile release intended for chronopharmacotherapy. Nifedipine was selected as the model drug for the study. Floating beads of calcium pectinate were thought to deliver the drug in intestine after the required lag time. The beads were prepared by ionotropic crosslinking method using acidified calcium chloride as crosslinking agent. Various process parameters like drug: polymer ratio, amount of sodium bicarbonate, concentration of calcium chloride, concentration of acetic acid were optimized to get the required lag time and release. The beads provided expected two-phase release pattern with initial lag time of 6hrs during floating in acidic medium followed by rapid pulse release in phosphate buffer. This approach suggested the use of hollow calcium pectinate beads as promising chronotherapeutic drug delivery system for site and time-specific release of Anti- rheumatoid drugs acting as per chronotherapy of the disease, thus increasing therapeutic effectiveness by improving patient compliance.

INTRODUCTION

Natural biodegradable polysaccharides like pectin, guargum, chitosan, carrageenans, sodium alginate and gellangum used in controlled drug delivery [1–3]. Multiparticulate systems obtained by ionotropic crosslinking of these polymers used to develop floating drug delivery. Various approaches to induce buoyancy in crosslinked beads, some of which include freeze-drying, entrapment of gas or gas forming agents, use of volatile oils or fixed oils, have been used [4–5]. These approaches are complicated, as they require specific equipment and handling techniques with limited acceptance. The oil containing beads have limitations of coalescence of oil droplets yielding beads of wider particle size distribution, volatilization or leaching of oil [6]. Comparatively, the floating dosage forms containing sodium bicarbonate as buoyancy imparting agent are simple to produce which have been already attempted [7,8]. Their floating property is based on the evolution of carbon dioxide when in contact with acidic environment followed by the ability of polymer gel to entrap in which decreases their density below one. On the other hand, violent gas generation, disintegration of dosage form, burst release, dose dumping and alkaline microenvironment [9] is limitations of these dosage forms. Chronopharmacotherapy of diseases (cardiovascular diseases, arthritis, asthma, cancer, hypercholesterolemia, duodenal ulcer, neurological disorders and diabetes) that show circadian rhythms in their pathophysiology and treatment of such diseases require pulsatile drug delivery systems, by which drug is released rapidly and completely as a pulse after a lag time [10-11].

To follow this principle one must have to design the dosage form such that it can be given at the convenient time, e.g., bedtime for the above-mentioned diseases with the drug release in the morning. Therefore, to develop dosage form for chronopharmacotherapy the desired drug release should be time-specific as well as site-specific also. [12]

The purpose of the present study was to produce hollow/porous-floating beads of pectin by a process of evolution of carbon dioxide during crosslinking in acidic environment. Nifedipine was used as model

drug. The obtained beads were evaluated for drug content, size analysis, porosity, mechanical strength, in vitro and in vivo floating properties and in vitro drug release.

MATERIALS AND METHODS

Materials:

Material Nifedipine was received from (Torrent pharmaceutical limited, Ahmadabad, india) Low methoxy pectin. (Central drug house, New delhi, India) Other materials used in the study were calcium chloride dihydrate (Central drug house, New delhi, India), sodium bicarbonate (central drug house, new delhi India), aceticacid, glacial (100%) (India).

Method:

Preparation of beads

Calcium pectinate beads containing nifedipine as active pharmaceutical ingredient were prepared by ionotropic gelation method. Initially, the required quantity of pectin was accurately weighed and dissolved in 10 ml of distilled water using mechanical stirrer. To this solution drug and sodium bicarbonate were added. The above solution was mixed thoroughly by means of mechanical stirrer. Then the solution was sonicated for about 30 min to remove air bubbles. After sonication, the solution was kept aside for 30 min. The resultant solution was dropped via a 23-gauge syringe needle (0.65 mm internal diameter) into 80 ml of calcium chloride (CaCl2) solution acidified with glacial acetic acid. Beads formed washed with distilled water, filtered and dried at room temperature for 24 hrs. Initial formulations (A1 to A6) were prepared with varying concentrations of pectin and calcium chloride solutions. Depending on the physical properties, drug entrapment and percentage yield of the beads obtained the amount of the polymer and calcium chloride was fixed. Further formulations (A7 to A12) were prepared varying the amounts of Sodium bicarbonate and acetic acid. The composition of formulations A1 to A6 and A7 to A12 are indicated in tables 3.1 and 3.2 respectively.

CHARACTERIZATION

Drug content

20 mg beads of each batch were placed in100 ml phosphate buffer, pH 7.4, and mechanically agitated on shaker (Steelmet Industries, Pune, India) at 200 rpm for 24 h.

The resultant dispersions were filtered and analyzed at 231.2 nm using UV spectrophotometer (JASCO-V500, Kyoto, Japan)

The encapsulation efficiency was determined by the following formula:

Encapsulation efficiency (%) = AQ/TQ

Where, AQ is the actual drug content of beads and TQ is the theoretical quantity of drug present in beads.

Infrared spectroscopy

The infrared spectra of nifedipine, calcium pectinate beads (without drug, sodium bicarbonate and aceticacid) and drug-loaded porous calcium pectinate beads were recorded on FTIR (JASCO-FTIR 5300).

Micromeritic studies: Calcium pectinate beads were characterized for their micromeritic properties such as particle size and shape.

a. **Particle size and shape:** The surface morphology and internal structure of the products were observed.

b. **Scanning electron microscopy:** The surface morphology and internal structure of the products were observed by scanning electron microscopy using JEOL JSM-T scanning electron microscope (Japan). Dry calcium pectinate beads were placed on an electron microscope brass stub and coated with gold in an ion sputter. Pictures of the microspheres were taken by random scanning of the stub.

***In-vitro* buoyancy studies:** *In-vitro* buoyancy studies were done using dissolution test apparatus USP type II (rotating paddle). 50 calcium pectinate beads of nifedipine were taken and added to the dissolution flask containing 0.1 N HCl as medium (900 ml). Temperature was maintained at 37 ºC ± 0.5 ºC for 8h. Paddle maintained at 50 rpm. The floating and the settled portion of beads recovered separately. Buoyancy percentage was calculated as the ratio of the number of beads that remained floating and the total number of beads taken.

***In-vitro* drug release studies:** *In-vitro* drug release was studied using dissolution test apparatus USP type II method (rotating paddle method). The drug loaded calcium pectinate beads equivalent to 20mg of nifedipine were filled in empty gelatin

capsules. These capsules were introduced into dissolution flasks containing 900ml of 0.1N HCl. The temperature was maintained at 37±0.5 ºC and paddle rotating speed at 50rpm. 1ml of aliquot was withdrawn at regular predetermined intervals and sink conditions maintained throughout the study by replacing equal volume of fresh dissolution medium. After 6 h, dissolution medium replaced with pH 7.4 Phosphate buffer and dissolution study carried out. The samples diluted to 10 ml with pH 7.4 phosphate buffer and analyzed spectrophotometrically at 231.2nm using pH 7.4 Phosphate buffer as blank. All the analysis carried out in triplicate.

RESULTS AND DISCUSSION

Polysaccharides have been widely used as pharmaceutical excipient for their biocompatible, biodegradable, inexpensive and non-toxic nature. They form multiparticulate system by simple ionotropic gelation, which can be formulated to provide various desired drug release patterns. Pectin,heterogeneous anionic polysaccharides with an ability to produce water-insoluble complexes with drug, has been used in oral novel drug delivery systems. In stomach pectin swelling but undergoes rapid gel relaxation/swelling in alkaline environment. [12, 13,14.]

Drug content

The drug entrapment efficiency was determined and the results were listed in Table 3.4. The values of drug entrapment efficiency were found between 23.92 and 83.79 As the polymer concentration was increased the entrapment efficiency was also increased.

Infrared spectroscopy

Particle size analysis:

Particle size distribution of microspheres was determined by optical microscope fitted with an ocular micrometer and stage micrometer. The particle sizes of the microspheres were found between167.4±2.2 µm & 350.3±3.5 µm.

SEM studies:

Surface morphology of the microspheres was investigated with a scanning electron microscope. Different magnifications were used while taking these photomicrographs. Particles surface of all formulations was rough surface but spherical and discrete.

***In vitro* Drug Release Studies**

In vitro release study of nifedipine beads were performed in pH progression medium (pH 1.2 to pH 7.4) at 37ºC ± 0.5ºC. The *in vitro* release profile obtained was shown below.

CONCLUSION

The main objective of the present study was to provide site specific, time specific release of the drug and also increase patient compliance. Drug nifedipine was selected as model drug for the current study. Polymer pectin was selected for the preparation of floating calcium pectinate beads (to be loaded with nifedipine). The initial trials of formulated beads were evaluated for parameters like size, shape, % yield and % drug entrapment to optimize the formulation. Acetic acid, SBC are employed in formulation of calcium pectinate beads to aid the floating concentrations of $CaCl_2$ and acetic acid were varied to achieve best results which were evaluated for release lag time, *in-vitro* drug release. Formulation A11 was found to be the optimized and ideal formulation exhibited 83.79% drug entrapment, 79% buoyancy, 6 hrs lag time with 7.31% drug release. The SEM photographs show the sphericity, porosity and hollow nature of the prepared beads. The I.R spectra of prepared beads show no major variations in the peaks of the drug indicating that the drug remained intact in the beads. Thus the formulated calcium pectinate beads were successful in achieving pulsatile release in which lag time of 6 hrs followed by a burst effect of the drug was found. It was concluded that these floating beads can play an important role in increasing therapeutic efficiency by increasing patient compliance by not only site specificity and time specificity that allows the bed time administration of the drug. From the present study, it can be concluded that the prepared floating calcium pectinate beads prepared by ionotropic crosslinking method provided the ideal release lag time and burst release that is site specific and time specific, which is an important criteria for chronotherapeutic drug delivery.

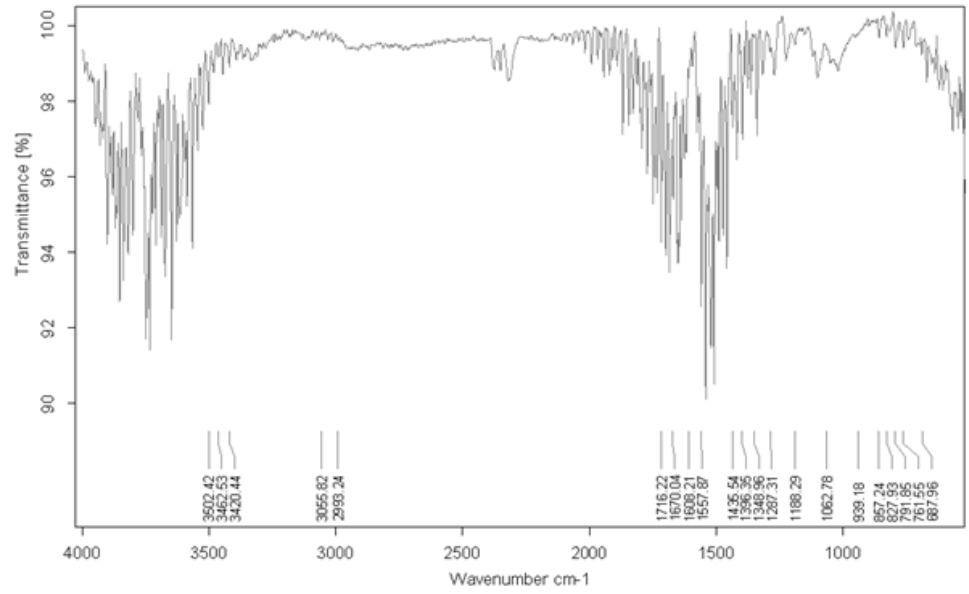


Fig 1: IR Spectra of pure drug

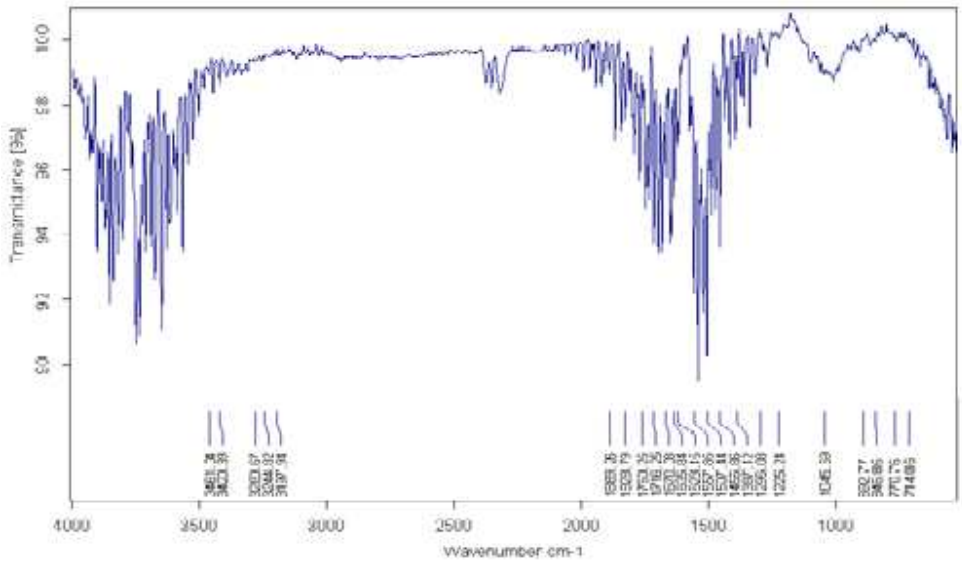


Fig 2: IR spectroscopy of pectin

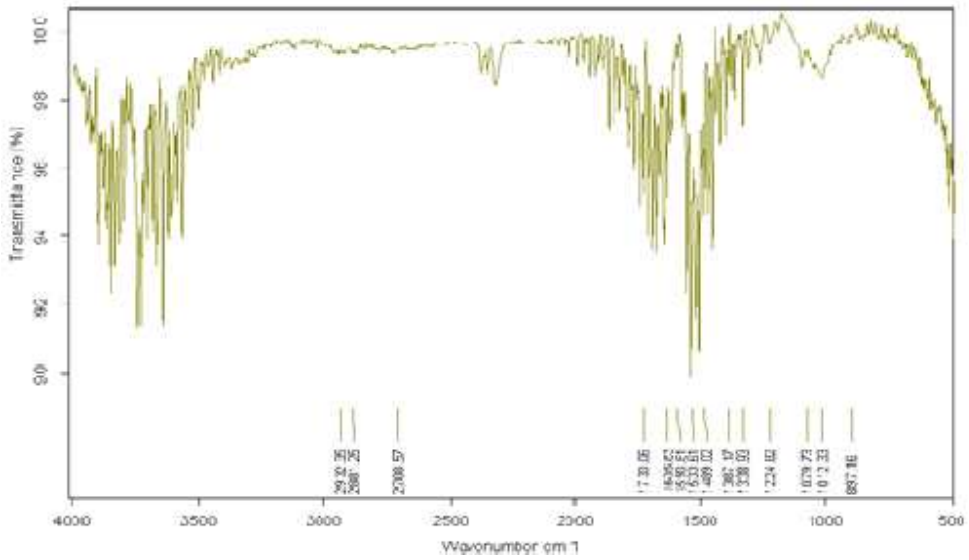
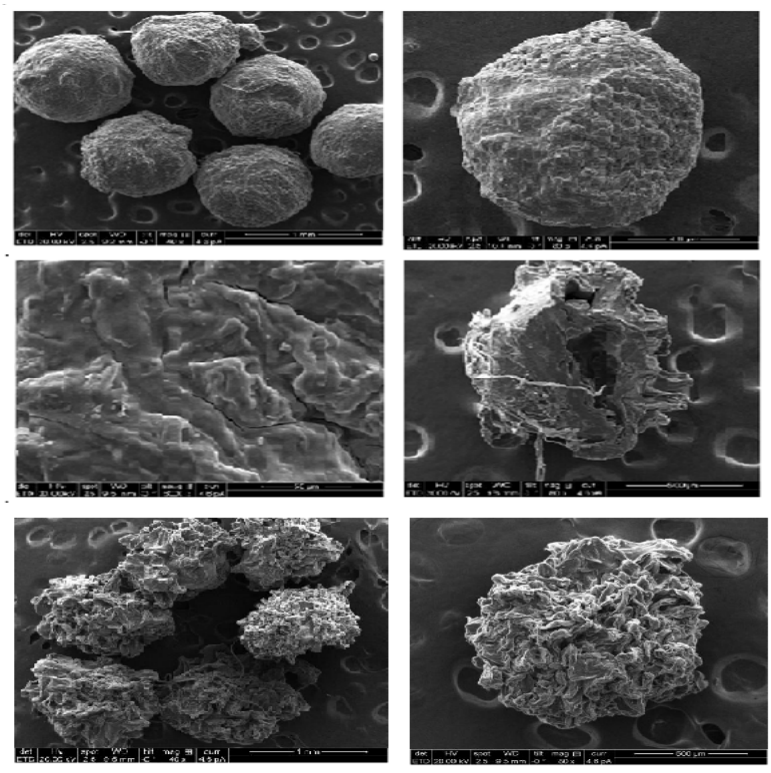


Fig 3: IR spectroscopy of pure drug and polymer

Fig 4: Scanning electron microphotographs of calcium pectinate beads of Nifedipine (A 11)



***In-vitro* drug release profiles of the formulations A7 to A12**

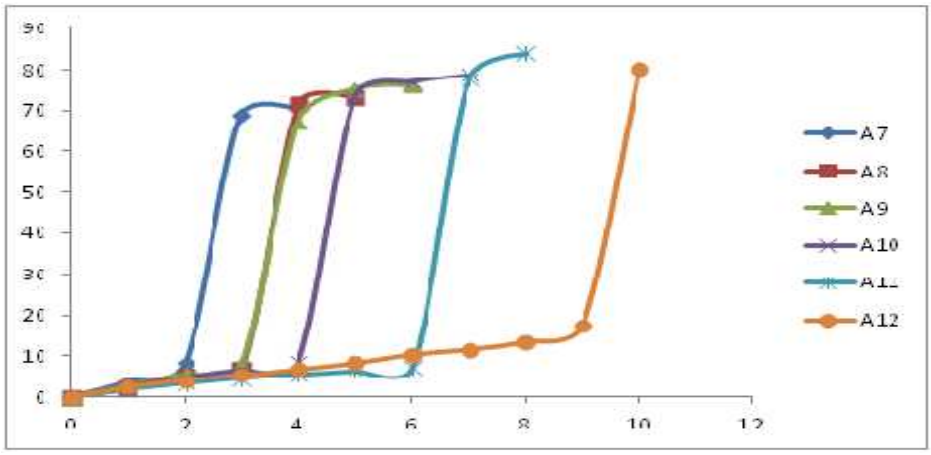


Table.1: Composition of formulations A1 to A6

INGREDIENTS	A1	A2	A3	A4	A5	A6
Nifedipine (mg)	20	20	20	20	20	20
Pectin (mg)	300	300	300	350	400	450
Calcium Chloride % w/v of distilled water	2	4	6	4	4	4

Table 2: Composition of formulations A7 to A12

INGREDIENTS	FORMULATIONS					
	A7	A8	A9	A10	A11	A12
Nifedipine (mg)	20	20	20	20	20	20
Pectin (mg)	400	400	400	400	400	400
Acetic acid % v/v of CaCl2 solution	2.5	2.5	2.5	5	5	5
Sodium bicarbonate (mg)	75	100	125	75	100	125
Calcium Chloride % w/v of distilled water	4	4	4	4	4	4

Table 3: Entrapment Efficiency

Formulation	Entrapment Efficiency (%)	Formulation	Entrapment
F1	23.92	F7	53.92
F2	31.76	F8	61.17
F3	29.41	F9	57.25
F4	38.62	F10	64.11
F5	45.68	F11	72.54
F6	42.90	F12	67.84

Table 4: Paricle size analysis

Formulation	Particle Size (µm)	Formulation	Particle Size (µm)
A1	167.4±2.2	A7	288.4±2.5
A2	190.1±4.9	A8	304.6±3.1
A3	233.5±3.8	A9	291.1±4.2
A4	278.8±3.2	A10	311.8±3.8
A5	313.7±3.2	A11	334.3±4.3
A6	350.3±3.5	A12	288.4±2.5

Table 5: *In vitro* Drug Release

Time (h)	% CR					
	A7	A8	A9	A10	A11	A12
1	3.64	2.05	2.7	2.37	1.85	2.31
2	8.31	5.3	5.84	4.95	3.32	4.1
3	68.80	7.12	7.95	6.72	4.50	5.42
4	70.55	71.46	67.05	8.43	5.58	6.85
5	-	73.20	74.97	73.21	6.46	8.36
6	-	-	75.87	76.72	7.31	10.4
7	-	-	-	78.52	77.62	11.56
8	-	-	-	-	83.79	13.41
9	-	-	-	-	-	17.54
10	-	-	-	-	-	81.13

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