International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 8, Issue 3, 2016

Original Article

FORMULATION AND EVALUATION OF FLOATING BEADS OF DILTIAZEM HCL

*SHIVENDRA AGARWAL, FARAZ ZAMIL, LOKENDRA SINGH, AMIT SAXENA

Vivek College of Technical Education, Bijnor, 246701 (U. P) India
Email: agarwalshivacsr@gmail.com

Received: 10 Mar 2016, Revised and Accepted: 31 May 2016

ABSTRACT

Objective: Diltiazem, a benzothiazepine calcium channel blocker, is used alone or with an angiotensin-converting enzyme inhibitor, to treat hypertension, chronic stable angina pectoris, and Prinzmetal's variant angina. The elimination half-life of Diltiazem is 3 to 4.5 h. In the present research work multiple units floating drug delivery systems of Diltiazem Hydrochloride were prepared by using sodium alginate, mustard oil and olive oil.

Methods: The floating systems were prepared by using emulsion gelation technique to improve gastric retention. The prepared beads were evaluated for physical characterization floating lag time, total floating time, swelling index and *in vitro* drug release studies. The prepared beads were found to be spherical, free flowing and remain buoyant for 24 h with a short floating lag time.

Results: Percentage drug content of beads in the formulation F9 For olive oil and H8 for mustard oil was found to be in the range of 95.89 to 54.08%. Swelling properties of all formulation increased as the concentration of SCMC increased. The particle size increased as the amount of polymer was increased in each formulation.

Conclusion: Floating beads of Diltiazem HCL could prompt a potential sustained drug delivery over an extend period of time that can reduce dose frequency. It was also found that the cumulative drug release from all formulations was found to be between 94.93 to 100.042.

Keywords: Beads, Diltiazem HCL, Sodium alginate, Calcium chloride, Olive Oil

INTRODUCTION

Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation. Oral controlled release drug delivery has recently been of increasing interest in the pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance, and flexibility in formulation. Drugs that are easily absorbed from the gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. To avoid this limitation, the development of oral sustained controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT) [1].

These drug delivery systems suffer from mainly two adversities: the short gastric retention time (GRT) and unpredictable short gastric emptying time (GET), which can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine) leading to diminished efficacy of administered dose [2]. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drug solubility that is less soluble in a high pH environment [3]. The gastro retentive dosage form can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Diltiazem, a benzothiazepine calcium channel blocker, is used alone or with an angiotensin-converting enzyme inhibitor, to treat hypertension, chronic stable angina pectoris, and Prinzmetal's variant angina. Diltiazem is a non-dihydropyridine (DHP) member of the calcium channel blocker class, along with Verapamil. Diltiazem is similar to other peripheral vasodilators. The elimination half-life of Diltiazem is 3 to 4.5 h. Diltiazem is well absorbed from the gastrointestinal tract but undergoes substantial hepatic first-pass effect. Its Protein binding is up to70%-80%. Its melting point is up to 231^{o}c.

MATERIALS AND METHODS

Materials

Diltiazem HCl was obtained as Gift sample from Quality Pharma Pvt Ltd. Sodium alginates were obtained from Loba Chemie laboratory. Calcium chloride was obtained from Qualigens Fine Chemicals. Olive and mustered oil

Method

Emulsion gelation method was selected for the preparation oil entrapped beads. Emulsion gelation method is simpler than the ones used so far for the preparation of other floating dosage form. Diltiazem HCL loaded calcium alginate beads were prepared by the emulsion–gelation method [4]. In this method, the sodium alginate solution was prepared in water in different ratio. Oil in concentrations (10%, 12% and 14% w/w), was then added to the polymer solution to make mixtures. To ensure emulsion stabilization, the mixtures were homogenized at 10,000 rpm using a homogenizer for 10 min. Diltiazem HCl was then dispersed in the formed emulsion. The bubble-free emulsion was extruded; using a 23G syringe needle into 250 ml gently agitated (5%) calcium chloride solution at room temperature. The emulsion gel beads were allowed to stand in the solution for 20 min before being separated and washed with distilled water. The beads were air-dried at room temperature.

Evaluation

Study of homogeneity and uniformity of beads

To prepare uniform beads (i.e. of the same size and density), it is essential that synthesis conditions such as viscosity, the rate of falling of drops, stirring rate and distance between syringe and gelation medium, be maintained constant during the course of the formation of beads. Variation in any of these parameters during the bead formation process may result in the production of non-homogenous and non-uniform beads, affecting the overall results to an appreciable extent [5]. Also, process homogeneity was greatly influenced by emulsion homogenization which yields fine dispersion

of oil and water with size uniformity. Without homogenization, the oil might separate out from the solution and uneven sized beads were formed [6].

Scanning electron microscopy

The size of Beads was determined using a microscope (Olympus NWF 10x, Educational Scientific Stores, India) fitted with an ocular micrometer and stage micrometer. Scanning electron microscopy (SEM) (Leo 430, Leo Electron Microscopy Ltd, and Cambridge, England) was performed to characterize the surface of the formed Beads [5, 7].

Flow properties

The flow properties of Beads were characterized in terms of angle of repose, carr index and hausner ratio For determination of angle of repose (θ), the Beads were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The Beads were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. The tan-1 of the height of the pile/radius of its base gave the angle of repose. Beads were poured gently through a glass funnel into a graduated cylinder cut exactly to 10 ml mark.

Excess Beads were removed using a spatula and the weight of the cylinder with pellets required for filling the cylinder volume was calculated. The cylinder was then tapped from a height of 2.0 cm until the time when there was no more decrease in the volume. Bulk density (ρb) and tapped density (ρt) were calculated. Hausner ratio (HR) and carr index (IC) were calculated according to the two equations given below: [8]

$$HR = \rho t / \rho b$$

$$IC = (\rho t\% \ \rho b)/\rho t$$

Table 1: Composition of floating beads of diltiazem HCL

S. No.	Ingredients	Mass (mg)
1	Diltiazem hydrochloride	90
2	Sodium alginate	225-325
3	Oil	10-14%
4	Water	10 ml

Table 2: Formula of floating beads of diltiazem HCL (F1-F9)

Formulation	Diltiazem hydrochloride(mg)	Sodium alginate(mg)	Olive oil(ml)	Mustard oil(ml)	Water(ml)
F1	90	225	10	10	10
F2	90	275	10	10	10
F3	90	325	10	10	10
F4	90	225	12	12	10
F5	90	275	12	12	10
F6	90	325	12	12	10
F7	90	225	14	14	10
F8	90	275	14	14	10
F9	90	325	14	14	10

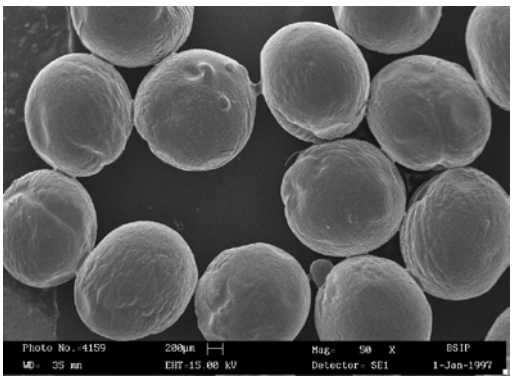

Fig. 1: Olive oil

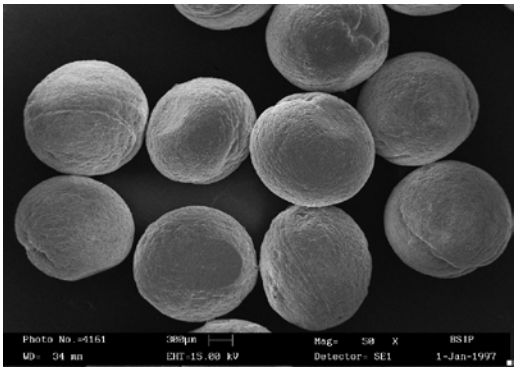

Fig. 2: Mustard oil

Floating lag time and total floating time determination

The time between the introduction of the beads into the medium and its rise to an upper one-third of the dissolution vessel is termed as floating lag time and the time for which the dosage form floats termed as the floating or flotation time. These tests are usually performed in 0.1N HCl maintained at 37°C in using USP dissolution apparatus [9].

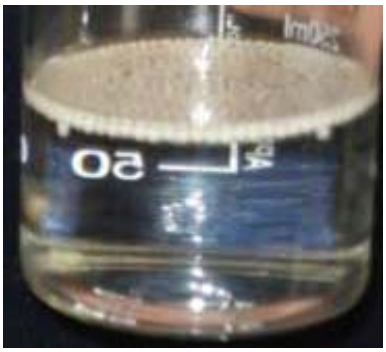

Fig. 3: Floating lag time and total floating time

***In vitro* (%) percent buoyancy**

Beads (90 mg) were spread over the surface of a USP XXIV dissolution apparatus type II filled with 900 ml of 0.1 N hydrochloric acid. The medium was agitated with a paddle rotating at 100 rpm for 11 h. The floating and the settled portions of Beads were recovered separately. The Beads were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the Beads that

remained floating and the total mass of the Beads Development and evaluation of floating Beads of diltiazem [10].

Drug content

Practical drug content was analyzed by using the following procedure, The beads equivalent to 90 mg of Diltiazem HCl were taken and dissolved in 100 ml of 0.1 N HCL. This solution was kept overnight for the complete dissolution of the drug from floating beads in 0.1N HCl. This solution was filtered and further diluted to make a conc. of 10 µg/ml. The absorbance of the solutions was measured at 237 nm using double beam UV-Visible spectro-photometer against 0.1N HCl solution as blank and calculated for the percentage of drug present in the sample [10].

Swelling studies

Weight gain or water uptake can be studied by considering the swelling behavior of Floating dosage form. The study is done by immersing the dosage form in 0.1N HCl at 37°C. The beads were periodically removed from the beaker, and the excess surface liquid was removed carefully using the paper. The swollen beads were then reweighed, and swelling index is measured in the terms of percent weight gain, as given by equation SU = (Wt–Wo) X 100/Wo In which Wt and Wo are the weights of the dosage form at time t and initially, respectively [11]

***In vitro* drug release studies**

The drug release was studied using a USP dissolution apparatus type I at 50 rpm in 0.1N hydrochloric acid as dissolution medium (900 ml) maintained at 37±0.5 °C. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus hourly, and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45 µ membrane filter and diluted to a suitable concentration with 0.1 N hydrochloric acid. The absorbance of these solutions was measured at 237 nm using a UV-Visible spectrophotometer, and Cumulative percentage drug release was calculated [6].

Mathematical models

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration. The first order Eq. (2) describes the release from a system where release rate is concentration dependent. Higuchi described the release of drugs from the insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets.

$$C = k_o t \quad (1)$$

Where, K_0 is zero-order rate constant expressed in units of concentration/time, and t is the time.

$$LogC = LogCo - kt/2.303 \quad (2)$$

Where, C0 is the initial concentration of drug and K is first order constant.

$$Q = Kt^{1/2} \quad (3)$$

Where, K is the constant reflecting the design variables of the system.

$$Q0^{1/3} - Qt^{1/3} = K_{HC}\, t \quad (4)$$

Where, Qt is the amount of drug released in time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for Hixson-Crowell rate equation. The following plots were made:

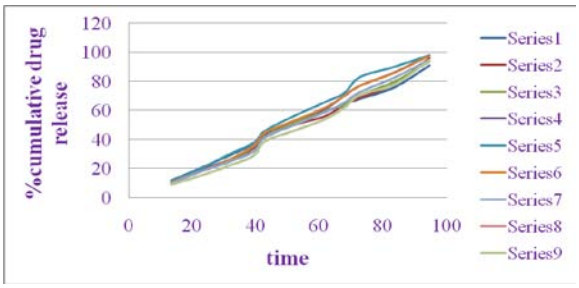

Fig. 4: Drug-release profile of floating beads of diltiazem HCL

Table 3: Kinetic data of various models for release study

Formulation no.	Zero order	First order	Higuchi model	Peppas model		Hixson model
				R	N	
F1	0.998	0.822	0.950	0.992	1.103	0.912
F2	0.987	0.840	0.945	0.996	1.065	0.925
F3	0.998	0.714	0.953	0.996	0.965	0.853
F4	0.996	0.811	0.943	0.994	1.002	0.912
F5	0.996	0.756	0.952	0.997	0.982	0.905
F6	0.998	0.810	0.941	0.992	1.044	0.922
F7	0.999	0.768	0.952	0.996	0.993	0.909
F8	0.994	0.801	0.963	0.998	0.971	0.915
F9	0.998	0.784	0.960	0.995	0.906	0.887

Physical evaluation

Table 4: Result of size of beads, oil leakage, shape and weight of 100 beads for olive oil

Formulation code	Sod. alginate	Olive oil	Size of the beads	Oil leakage	Shape	Wt of 100 beads
F1	-1	-1	96	YES	Spherical	154
F2	-1	0	100	No	Spherical	169
F3	-1	+1	93	No	Spherical	146
F4	0	-1	98	No	Spherical	155
F5	0	0	100	No	Spherical	160
F6	0	+1	100	YES	Spherical	173
F7	+1	-1	99	NO	Spherical	187
F8	+1	0	97	No	Spherical	220
F9	+1	+1	98	No	Spherical	212

Table 5: Result of size of beads, oil leakage, shape and weight of 100 beads for mustard oil

Formulation code	Sod. alginate	Mustard oil	Size of the beads	Oil leakage	shape	Wt of 100 beads
F1	-1	-1	82	No	spherical	154
F2	-1	0	85	Yes	spherical	169
F3	-1	+1	100	No	spherical	146
F4	0	-1	100	No	spherical	155
F5	0	0	84	No	spherical	160
F6	0	+1	98	No	spherical	173
F7	+1	-1	97	No	spherical	187
F8	+1	0	97	No	spherical	220
F9	+1	+1	99	NO	spherical	212

Table 6: Result of floating time, floating lag time, drug content and drug release for olive oil

Formulation code	Sod. alginate	Olive oil	Floating lag time (Sec)	Floating time (H)	(%) Drug content	(%) Drug release in 12 h
F1	-1	-1	30	24	44.92	99.708
F2	-1	0	20	24	62.50	95.920
F3	-1	+1	10	24	69.14	100.042
F4	0	-1	90	24	58.59	97.440
F5	0	0	50	24	51.95	97.861
F6	0	+1	35	24	52.73	96.828
F7	+1	-1	120	nf	46.09	94.939
F8	+1	0	40	24	56.25	97.767
F9	+1	+1	20	24	95.89	99.744

Table 7: Result of floating time, floating lag time, drug content and drug release for mustard oil

Formulation code	Sod. alginate	Mustard oil	Floating lag time	Floating time	(%) Drug content	(%) Drug release 12 h
F1	-1	-1	50	24	39.62	97.388
F2	-1	0	42	24	31.44	90.263
F3	-1	+1	30	24	37.42	91.300
F4	0	-1	45	24	40.09	99.809
F5	0	0	39	24	45.91	98.781
F6	0	+1	25	24	51.25	98.855
F7	+1	-1	41	24	44.65	99.828
F8	+1	0	37	24	54.08	98.140
F9	+1	+1	20	24	43.23	92.664

Table 8: Result of beads density, (%) buoyancy, swelling studies and flow property for olive oil

Formulation code	Sod. alginate	Olive oil	Beads density	percent buoyancy	Swelling studies	Flow property
F1	-1	-1	0.47	100	12.50	+
F2	-1	0	0.55	90	11.10	++
F3	-1	+1	0.58	100	10.00	++
F4	0	-1	0.43	90	22.21	++++
F5	0	0	0.50	100	20.00	++++
F6	0	+1	0.54	100	11.1	++
F7	+1	-1	0.51	nf	11.00	++++
F8	+1	0	0.56	100	11.05	++++
F9	+1	+1	0.57	100	9.09	++++

Table 9: Result of beads density, (%) buoyancy, swelling studies and flow property for mustard oil

Formulation code	Sod. alginate	Mustard oil	Beads density	percent buoyancy	Swelling studies	Flow property
F1	-1	-1	0.58	100	18.75	++++
F2	-1	0	0.72	100	13.33	++
F3	-1	+1	0.71	100	10.26	+++
F4	0	-1	0.56	100	11.11	++++
F5	0	0	0.63	90	09.52	++++
F6	0	+1	0.75	100	05.00	++++
F7	+1	-1	0.55	100	15.00	++++
F8	+1	0	0.56	100	10.26	++++
F9	+1	+1	0.54	100	09.52	+++

6.8.1 Zero-order release kinetics: Cumulative% drug release vs. time.

6.8.2 First order release kinetics: Log cumulative of % drug remaining vs. time.

6.8.3 Higuchi Model: Cumulative % drug release vs. square root of time.

6.8.4 Korsmeyer-Peppas Model: Log cumulative % drug release vs. log time.

6.8.5 Hixson-Crowell cube root Model: Cube root of drug % remaining in matrix vs. Time [12].

RESULTS AND DISCUSSION

Percentage drug content

Percentage drug content in the formulation F9 For olive oil and H8 for mustard oil was found to be in the range of 95.89 to 54.08%. It showed the uniform dispersion of the drug in the polymer system.

Particle size

The particle size of Diltiazem HCL beads as measured as 82 to 100 (µm). The particle size of the beads was affected by a factor such as preparation technique, polymer concentrations, needle size and stirring time. The mean particle size of Diltiazem HCL beads was in range value (table) depending upon the types of polymer used. The particle size increased as the amount of polymer was increased in each preparation.

Swelling studies

The amount of polymer directly affected the solvent transfer rate thus, as the polymer concentration increased the swelling index also increased. *In vitro* swelling studies were carried in 0.1NHCL at 37 °C and degree of swelling index for each were determined gravimetrically. Swelling index for all formulation increased as the concentration of polymer increased.

In vitro drug release studies

In vitro drug release from the floating beads of Diltiazem HCL (for mustard oil and olive oil) was found to be from 91.30 to 100.04%. Among all formulation, f3 was found to be the best formulation for olive oil as its release 100.04%, f7 was found to be the best formulation for mustard oil as its release 99.82% in a sustained manner with constant fashion over an extended period of time. The release study was further investigated for the kinetic studies. Various kinetic models were applied. *In vitro* drug release data fitted into various kinetic models suggest that the all formulations obey zero-order models from the *n* values obtained (table 2).

CONCLUSION

The best formulation of Diltiazem HCL floating beads for olive oil was found to be F-3 100.04% and for mustard oil was found to be F-7 99.82 %, drug release in 12 h.

It is noticeable that further formulation of Diltiazem HCL could prompt a potential sustained drug delivery over an extended period of time that can reduce dose frequency.

CONFLICT OF INTERESTS

Declare none

REFERENCES

1. Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery system. Expert Opin Drug Delivery 2006;3:217-33.
2. Iannucelli V, Coppi G, Bernabei MT, Camerorni R. Air compertment multiple-unit system for prolonged gastric residence Part-I. Formulation study. Int J Pharm Sci 1998;174:47-54.
3. Garg R, Gupta GD. Progress in controlled gastro retentive delivery systems. Trop J Pharm Res 2008;7:1055-66.
4. Ferna´ndez-Herva´s MJ, Holgado MA, Fini A, Fell JT. *In vitro* evaluation of alginate beads of a diclofenac salt. Int J Pharm Sci 1998;163:23–34.
5. Choudhury PK, Kar M. Preparation of alginate gel beads containing metformin hydrochloride using emulsion–gelation method. Tropical J Pharm Res 2005;4:489–93.
6. Clarke GM, Newton JM, Short MD. Comparative gastrointestinal transit of pellet systems of varying density. Int J Pharm Sci 1995;114:1-11.
7. British Pharmacopoeia. The controller of her majesty's stationary office, Council of Europe, London; 2001;1;1103.
8. Gaur RS, Gupta GD. A practical physical pharmacy. 9th edtn. CBS Publishers and Distributers PVT. LTD; 2011.
9. Indian Pharmacopoeia. The government of India, Ministry of Health and Family welfare, Controller of Publications, New Delhi; 1996. p. 634-5.
10. Goyal MK, Mehta SC. Preparation and evaluation of calcium silicate based floating beads of amoxicillin. J Appl Pharm Sci 2011;1:137-41.
11. Gergogiannis YS, Rekkas DM, Dallos PP, Chailis NH. Floating and swelling characteristics of various excipients used in controlled release technology. Drug Dev Ind Pharm 1993;19:1061-81.
12. Singhvi G, Singh M. Review *in vitro* drug release characterization models. Int J Pharm Studies Res 2011;2:77-84.