Research Article

International Journal of Indigenous Herbs and Drugs
Content Available at www.saap.org.in ISSN: 2456-7345

DEVELOPMENT AND EVALUATION OF FLOATING BEADS OF BACLOFEN AS A GASTRORETENTIVE DOSAGE FORM

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Article Info
Article History
Received on: 04-08-2023
Revised on: 15-09-2023
Accepted on: 22-09-2023

Abstract

Gastro retentive delivery systems are designed to be retained in the stomach for a prolonged time and release their active ingredients and thereby enable sustained and prolonged input of the drug to the upper part of the gastrointestinal (GI) tract. The goal of any drug delivery system is to provide a therapeutic amount of drug to proper site in the body to achieve promptly and then maintain a desired drug concentration. Baclofen is a gamma-aminobutyric acid (GABA) agonist used as a skeletal muscle relaxant used for the relief of painful and uncomfortable muscle spasms caused by a variety of conditions. Twelve different formulation of Baclofen floating beads were successfully developed using emulsion solvent diffusion method. The beads had good yield and showed high, drug entrapment efficiency. The flow properties of beads were within the acceptable range and therefore would be easily filled into capsules.
Study concludes successfully delivery of Baclofen by the means of floating beads.
Keywords: Gastro retentive delivery systems, floating beads, Baclofen.

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DOI: https://doi.org/10.46956/ijihd.v8i5.488

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Introduction

Conventional drug delivery system achieves as well as maintains the drug concentration within the therapeutically effective range needed for treatment, only when taken several times a day [1]. 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 systemic circulation for a long time [2-5]. The goal of any drug delivery system is to provide a therapeutic amount of drug to proper site in the body to achieve promptly and then maintain a desired drug concentration. Recent development in technology has provided viable dosage alternatives that can be administered via different routes of administration [6-8].

Various routes that are used include oral, topical, nasal, rectal, vaginal and ocular, etc. but out of these routes oral route of drug delivery is considered as the most favoured and practiced way of delivery, due to following reasons, ease of administration, ease of production, low cost [9,10]. Baclofen is administered for the relief of signs and symptoms of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and associated pain and clonus, in addition to muscular rigidity [11]. Baclofen has a bioavailability of 70% to 85% and is therefore rapidly absorbed through the gastrointestinal tract following oral administration. Peak plasma concentrations are generally observed 2 to 3 hours after ingestion. The absorption is dose-dependent and increases with higher doses [12]. Baclofen is rapidly and extensively absorbed and eliminated. The half-life of the drug is ~2.5 to 4 hrs in plasma. Baclofen has absorption window in upper Gastrointestinal (G.I.) tract. Baclofen is difficult to formulate in to sustained release dosage forms because on arrival to colon its absorption is diminished or non-existent [13].

In the present investigation efforts were made to formulate floating beads of Baclofen to improve the absorption of Baclofen in stomach, to prepare spherical floating beads, to study sustained effect of floating beads, to study the effect of different polymers on buoyancy and % drug release.

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Material and Methods

Baclofen was received as the gift sample from Solarium Pharmaceuticals, New Delhi. Sodium Hydroxide pellets, Sodium lauryl sulfate, Ethanol, Pectin were obtained from Shweta Scientific, Lucknow. Other used chemicals were of analytical grade.

Development of floating beads of Baclofen by emulsion solvent diffusion method

Sodium alginate and solutions of other ingredients of different concentrations were prepared by dissolving required amount of alginate (Table 11) in 100 ml of distilled water under gentle agitation. Baclofen and calcium carbonate (as gas forming agent) were dispersed in

alginate solution under constant stirring for uniform mixing. The resultant dispersion was dropped through a syringe needle into 100 ml of 15% (w/v) calcium chloride solution containing 10% (v/v) acetic acid at room temperature. For 10 min the beads formed were allowed to remain in the stirred solution. The beads were filtered and subsequently oven-dried at 50ºC for 4 hours [8, 9].

Evaluation Parameters of Floating Beads of Baclofen

Measurement of particle size

The particle size was measured by microscopic technique. In this method suspension of floating beads were prepared using castor oil. A drop of suspension was mounted on a slide and observed under optical microscope about 600 particles were measured with the help of the eye piece micrometer. The floating beads were uniformly spread on a slide. The particle size of the beads was measured, along the longest axis and the shortest axis (cross shaped measurement). Average of these three readings was given as mean diameter of particles. The particle size was calculated by multiplying the number of division of the ocular disc occupied by the particle with calibration factor. All the beads in a field were counted [10].

Determination of Percentage yield

The prepared beads were collected and weighed. The measured weight was divided by the total amount of all non-volatile components, which were used for the preparation of the beads [11].

$$\text{Percentage yield} = \frac{\text{Actual weight of products}}{\text{Weight of drug and excipients}} \text{x} 100$$

Measurement of bulk density

Bulk density is determined by pouring pre-sieved floating beads into a graduated cylinder via a large funnel and measure the volume and weight. This volume is bulk volume and it includes true volume of the powder and the void space among the floating beads [12].

$$\text{Bulk density} = \frac{\text{Mass of microbeads}}{\text{Bulk volume}}$$

Measurement of tapped density

In this method floating beads were transferred to a measuring cylinder and tapped for 100 times. After tapping volume of floating beads was visually examined. The ratio of mass of floating beads to volume of floating beads after tapping gives tapped density floating beads [13].

$$\text{Tapped density} = \frac{\text{Mass of microbeads}}{\text{Volume after tapping}}$$

Determination of Carr's (compressibility) index

This parameter was calculated from bulk density (the ratio of weighed quantity of microbeads to its volume), DP, and tapped density as follows [14].

$$\text{Compressibility index} = \frac{(\text{DT} - \text{DP})}{\text{DTx}100}$$

Determination of Hausner, s ratio

Hausner, s ratio of floating beads was determined by comparing tapped density to bulk density using the equation [15].

$$\text{Hausner, s ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Values less than 1.25 indicate good flow (= 20% Carr), whereas greater than 1.25 indicates poor flow (= 33% Carr).

Results and discussion

Table 1: Composition of Alginate Beads of Baclofen.

Batch code	Amount of Baclofen (mg)	Pectin (mg)	Sodium alginate (%)	Calcium chloride (%)	CaCO3 (gm)	Coconut oil
AB 1	270	540	1	4	2	2
AB 2	270	540	2	4	2	2
AB 3	270	540	3	4	2	2
AB 4	270	540	1	4	2	2
AB 5	270	540	2	5	5	5
AB 6	270	540	3	5	5	5
AB 7	270	540	1	5	5	5
AB 8	270	540	2	5	5	5
AB 9	270	540	3	6	10	10
AB 10	270	540	1	6	10	10
AB 11	270	540	2	6	10	10
AB 12	270	540	3	6	10	10

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Table 2: Micromeritic properties of Baclofen loaded floating alginate gel beads.

Batch code	Particle size (µm)	Angle of repose	Bulk density (g/cm2)*	Tapped density (g/cm2)*	Carr's compressibility index (%)*	Hausner's ratio
AB1	1155.42±0.06	13.25±0.13	0.471±0.08	0.521±0.02	9.88±0.06	1.11
AB2	1187.31±0.04	14.63±0.08	0.453±0.03	0.533±0.06	9.64±0.08	1.10
AB3	1176.38±0.02	13.58±0.04	0.432±0.09	0.487±0.09	10.53±0.09	1.13
AB4	1174.34±0.07	15.52±0.01	0.465±0.43	0.535±0.05	9.72±0.08	1.10
AB5	1167.24±0.02	17.38±0.06	0.457±0.45	0.487±0.03	10.16±0.07	1.11
AB6	1152.51±0.08	14.61±0.01	0.466±0.04	0.516±0.08	9.98±0.07	1.10
AB7	1186.47±0.02	21.48±0.09	0.476±0.07	0.542±0.06	8.54±0.02	1.09
AB8	1175.31±0.08	16.43±0.08	0.488±0.11	0.628±0.09	8.11±0.08	1.08
AB9	1179.46±0.08	18.48±0.08	0.414±0.12	0.464±0.03	10.21±0.07	1.12
AB10	1134.22±0.02	19.66±0.07	0.453±0.12	0.532±0.06	11.45±0.02	1.12
AB11	1148.64±0.08	18.35±0.12	0.472±0.18	0.542±0.08	9.42±0.08	1.10
AB12	1183.68±0.09	18.57±0.14	0.436±0.09	0.486±0.06	10.41±0.08	1.11

Table 3: Characteristics of Alginate Beads of Baclofen.

Batch code	Percentage yield (%)	% Buoyancy	Swelling index (%)	% Drug content	DEE (%)
AB1	93.61±0.14	89.31	1380.4±0.07	92.52±0.37	54.64
AB2	93.15±0.15	86.57	1402.4±0.08	91.81±0.42	55.62
AB3	96.48±0.16	91.52	1377.2±0.07	89.44±0.09	55.24
AB4	97.14±0.19	93.82	1411±0.06	97.82±0.05	56.42
AB5	94.46±0.31	94.82	1382±0.02	98.02±0.11	56.39
AB6	96.57±0.28	91.37	1397.4±0.04	96.53±0.17	60.37
AB7	96.51±0.36	86.15	1371.2±0.09	88.54±0.46	39.21
AB8	95.44±0.13	88.17	1395±0.08	97.34±0.78	42.58
AB9	92.32±0.23	91.48	1374.4±0.03	95.56±0.09	45.36
AB10	90.28±0.41	92.58	1400.8±0.01	99.01±0.08	45.38
AB11	92.18±0.18	94.39	1377.4±0.04	97.32±0.14	53.25
AB12	91.42±0.17	95.48	1404.4±0.04	96.41±0.26	51.48

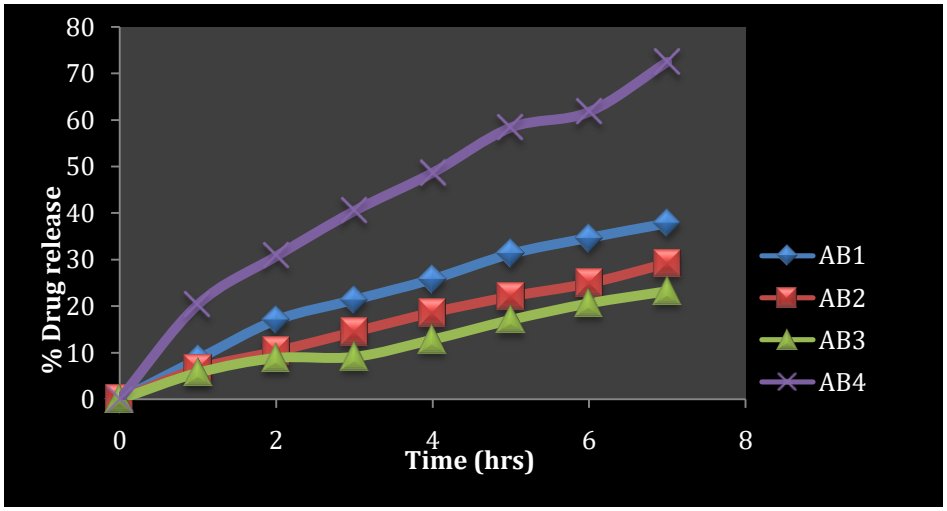

Figure 1: Percentage of Baclofen released from alginate beads of batch AB1-AB4

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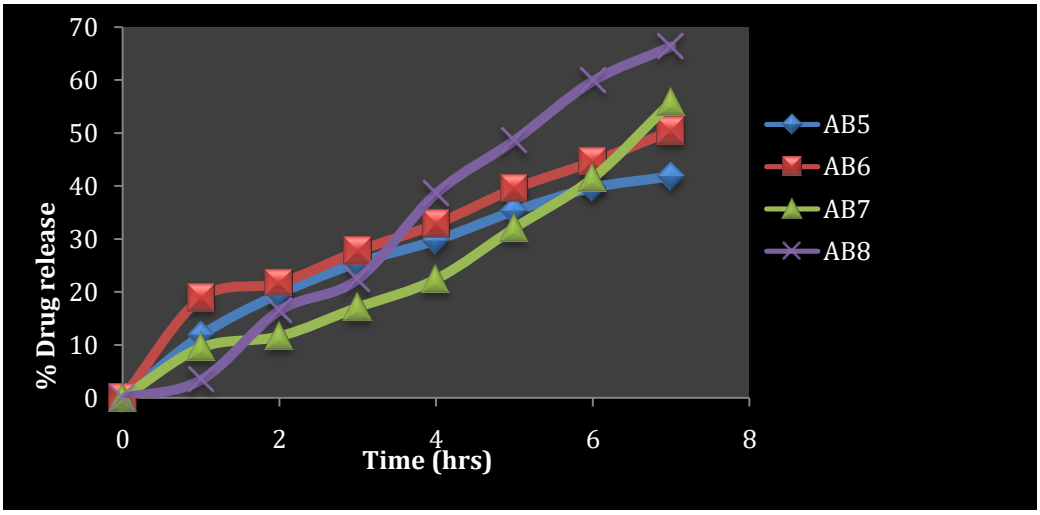

Figure 2: Percentage of Baclofen released from alginate beads of batch AB5-AB8.

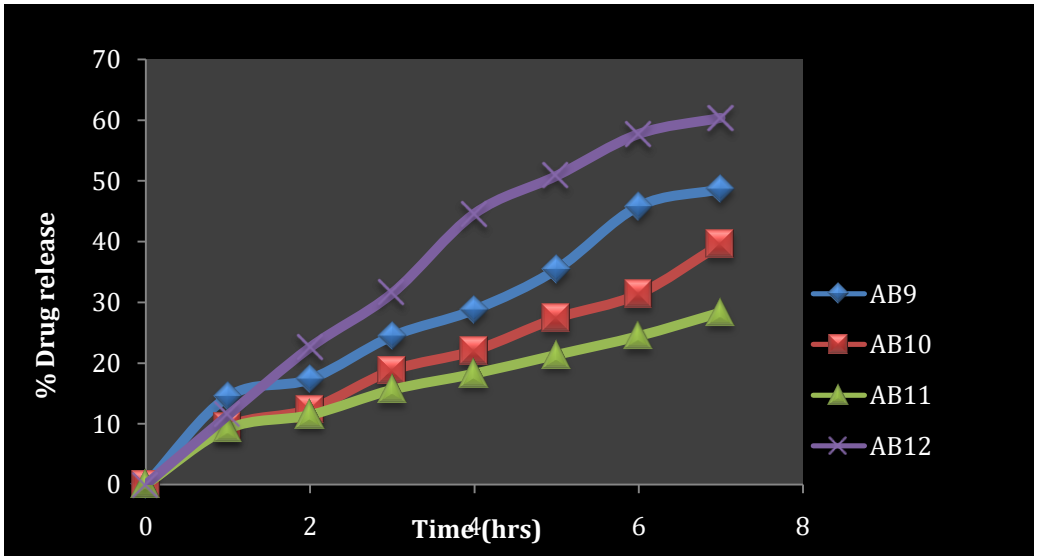

Figure 3: Percentage of Baclofen released from alginate beads of batch AB9-AB12.

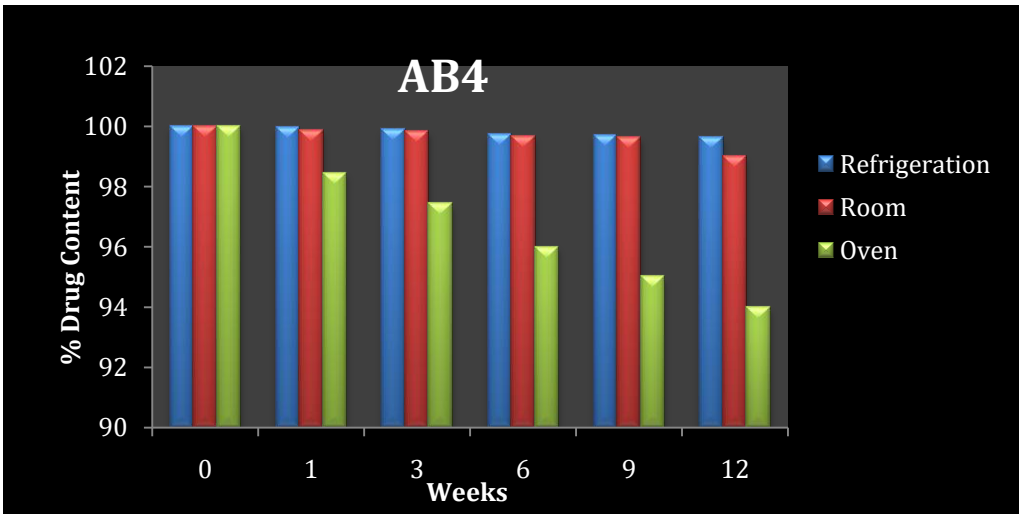

Figure 13: Stability studies of alginate beads of Baclofen of batch AB4 at different temperature.

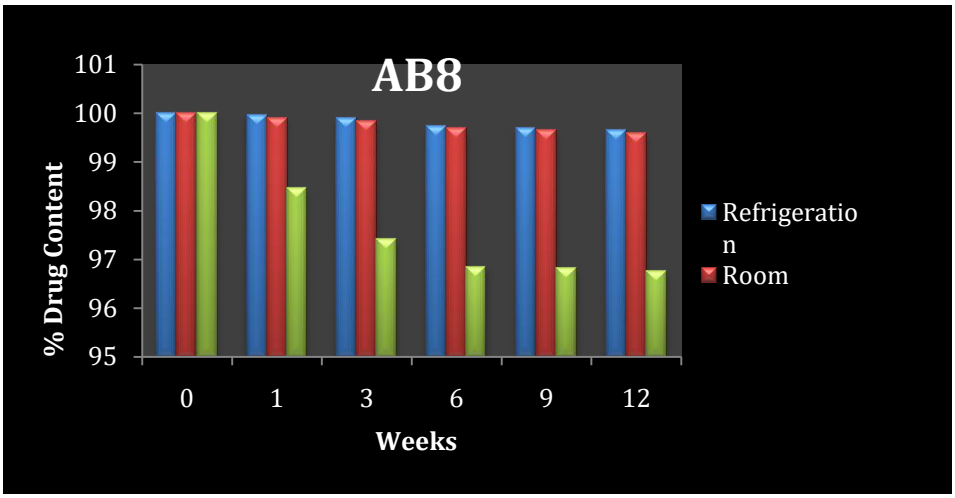

Figure 14: Stability studies of alginate beads of Baclofen of batch AB8 at different temperature.

Total 12 floating beads formulations of Baclofen were prepared by using different ingredients i.e. Pectin, Sodium alginate, Calcium chloride, CaCO3 and Coconut oil in different ratio by emulsion solvent diffusion method. The mean particle diameter of the floating beads was between 1134.22±0.02-1183.68±0.09µm. As the polymer concentration increases, the particle size also increases. Increase in particle size diameter was also due to increase in the concentration of calcium carbonate as gas forming agent. As the amount of calcium chloride was increased, more crosslinking structure was observed that lead to a decrease in particle size9.

The result of bulk density (g/cm3) ranged from 0.414±0.12 to 0.488±0.11. Bulk density of different formulations of beads was found to be much less than the density of the gastric fluid (1.004 g/ml) and 0.1 N HCl, pH 1.20 (0.997 g/ml). The low density of beads increased the porosity and indicates good packing capacity of beads. Being less in density, the beads were expected to float immediately with less or no floating lag time.

The higher amount of effervescent agent caused faster and higher CO2 generation. This may be attributed to a decrease in the bulk density. The tapped density of floating beads of all formulation was found to be in the range of 0.464±0.03 to 0.628±0.09g/cm3. Therefore, it was expected to be suitable for formulation of floating beads as they were having less density than 0.1 N HCl, pH 1.20. Values of tapped density also have shown good packability of beads.

The flow properties of all the formulations were found out by measuring the angle of repose and compressibility index. A higher Hausner,s ratio indicates greater cohesion between particles while a high Carr index is indicative of the tendency to form bridges12.

The values of angle of repose were between of 13.25±0.13 to 21.48±0.09 which are within the normal acceptable range of 20 to 40. The porous floating beads thus showed reasonably good flow potential, indicating good flow characteristics of the floating beads. This also implies that the floating beads are non-aggregated.

Carr's compressibility index of floating beads of all twelve formulations ranged from 9.42±0.08 to 11.45±0.02 % indicating excellent compressibility of beads. Therefore, floating beads shown good packability inside the capsules with ease of filling the beads.

Hausner's Ratio for all eight formulations was in the range of 1.08 to 1.12 (<1.25) indicating good flow properties of floating beads108.

The percentage entrapment efficiency of the floating beads was between 39.21-60.37%. Encapsulation efficiency was found to be increased with the increase in the concentration of gelatin solution (calcium chloride) due to crosslinking structure. DEE of some formulation was low due to high porosity (CaCO3) because of leakage of the drug.

Such data may be due to low solubility of Baclofen in water which facilitates the diffusion of a part of entrapped drug to surrounding medium during preparation of floating beads. The percentage yield of the floating beads was between 86.57 to 95.4886.57 to 95.48%.

The purpose of preparing floating beads was to extend the gastric residence time of a drug. The floating ability test was carried out to investigate the floatability of the prepared floating beads. The mean percentage buoyancy of the floating beads was between 86.57 to 95.48 %. *In-vitro* buoyancy studies reveal that in spite of stirring the dissolution medium for more than 12 hrs formulations were still continued to float without any apparent gelation, thus indicating that floating beads exhibit excellent buoyancies which can be attributed to the pores and cavities present in them. In general with increase in

the amount of polymers there is an increase in the buoyancy percentage. The increase in the buoyancy percentage may be attributed to air which caused swelling because of increased amount of the polymers present. The good buoyancy behavior of the floating beads may be attributed to the hollow nature of the floating beads. *In vitro* buoyancy study shown that incorporation of high concentration of calcium carbonate helped in floating properties when it comes in contact with aqueous fluid, produce carbon dioxide gas which reduces the density of dosage form due to the entrapment of CO2 gas in hydrophilic matrices10.

In the present study drug release was studied using a modified USP XXIV dissolution apparatus type I (basket) at 100 rpm in distilled water and 0.1 mol/L HCL (pH 1.2) as dissolution fluids (900ml) maintained at 37±10C. The minimum cumulative percent drug release after 7 hrs of the Baclofen floating beads 24.344±0.82% was shown by batch AB3 and the maximum release 74.51±0.09% was shown by the floating beads of batch AB4. Release profile shown initial burst release up to 1 h due to the surface associated drug, followed by a sustained release phase as the entrapped drug slowly diffused into the dissolution medium. There was the sustained release of drug at a constant rate.

The *in vitro* drug release studies revealed that the formulation having less concentration of CaCl2 made the swollen beads, which ensured floating and slow diffusion of Baclofen from floating beads, for example. Sodium alginate itself released in a slow manner and has main role in entrapment of drug due to which it also lead information of sustained release floating beads. The response variables of different formulations were calculated from *in vitro* dissolution profiles to characterize the drug release rate from the floating beads19. The results obtained in the *in-vitro* drug release studies were plotted in three models i.e. first order kinetic model, and Korsemeyer, s and Peppas release model.

The kinetic treatment of the drug release data was used as an indicator for the release mechanism from matrix delivery systems. In this study, the in vitro drug release data were fitted to four commonly employed release kinetic models, namely zero-order, first-order, and Higuchi and Peppas models to analyze drug release mechanism from the polymeric system.

The highest regression coefficient (r2) value was obtained for Korsmeyer– Peppas (0.9981) followed by Higuchi model (0.9830), by, zero-order (0.9646), and first-order (0.9574) model. It indicates diffusion to be the predominant mechanism of drug release from floating beads16.

Accelerated stability studies for 12 weeks revealed that the floating obeads formulations were stable at up to 450C. The results showed that floating beads formulation was quite stable at refrigeration and room temperatures as not much leakage of drug was found at these temperatures. Therefore, the selected floating beads formulations can be stored at either refrigeration or room temperature.

Stability studies performed on selected formulations (AB4 and AB8) revealed that the microspheres kept at room temperature (~25°C) and 40°-75% RH showed the maximum stability. The values of drug content and *in-vitro* studies were close to that of the initial data with only slight variations suggesting that it has an acceptable shelf life. It should be stored in a cool, dry place.

Conclusion

Twelve Baclofen floating beads formulations were successfully developed by using different ingredients like calcium carbonate, sodium alginate. All floating beads formulations were found to be transparent and were free from presence of particles. The stability study of the optimized formulation showed satisfactory characteristics without being drastically influenced. On basis of drug content, in-*vitro* release and stability studies, it can be concluded that formulation of batch AB4 was an optimum formulation.

Funding

None

Conflict Of Interest Statement

No conflict of interest.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgements

None

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