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Evaluation Parameters and In-Vitro Studies of Floating Beads of Analgesic Drug

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ABSTRACT

The objective of this present investigation was to develop gastro-retentive floating sustained release alginate beads of Diclofenac sodium by the ionotropic gelation method. The floating beads were prepared by dispersing Diclofenac sodium together with CaCO3 (as gas forming agent) into a solution of sodium alginate and HPMC. The resulting solution was then extruded through a 22 gauge syringe needle into 100 ml cross-linking solution containing calcium chloride (1% w/v) plus acetic acid (10% v/v). Prepared beads were evaluated for their micromeritic characteristics, particle size, in-vitro dissolution studies, encapsulation efficiency, buoyancy test and FT-IR spectroscopy. The drug entrapment efficiency was increased with the increment of polymer ratio. All of the formulations (F1 to F5) floated immediately or with a very short lag time and remained floating upto 12 hours. Rough and porous surface was observed in microscopic studies and many large hollow pores or multiple small hollow pockets were observed in case of cross-sectional microscopic studies of beads. *In vitro* dissolution studies were performed for twelve hours into 900 ml 0.1N HCl (pH 1.2) using USP Apparatus II (paddle type) maintained at a temperature of 37ºC and stirred at a speed of 50 rpm. The dissolution study revealed that, after eleven hours the percent of drug release for five formulations were 76.7% (F1), 73.5%% (F2),72.2% (F3), 70.56% (F4), and 69.1 %(F5) and all of the formulations followed zero order and Higuchi model.

Keywords: Floating drug delivery system, Floating beads, Gastro-retentive, Diclofenac sodium, Bouyancy.

INTRODUCTION

The oral route of drug administration is the most popular convenient and commonly used route for the administration of therapeutic drugs because of its cost efficiency and improved advantages such as ease of administration that leads to good patient compliance. The effectiveness of oral drug administration depends on various factors such as gastric emptying time, gastrointestinal transit time of dosage form and the release of drug from the dosage form.(1)

The drugs having short half lives are easily absorbed from GIT and eliminated quickly from systemic circulation. Thus the frequent dosing is required to achieve bioavailability and thereby therapeutic activity. Thus there is a need to develop oral sustained drug delivery system to reside in GIT and release the drug slowly for a long period of time.(2)

The bioavailability of drug from its dosage form is influenced by various factors. One of which is gastric residence time.(3) The gastric emptying process from the stomach to small intestine generally lasts from a few minutes to 1-2 hr.

This variability leads to an unpredictable bioavailability of an orally administered dosage form.

Floating drug delivery system is a specialized gastro-retentive novel drug delivery system also called as hydro dynamically balanced systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying time for a prolonged period of time. [4]

Advantages of floating drug delivery system are:

- **I**mproved drug delivery and ease of administration
- Control in the amount of drug to be delivered
- Local action on stomach with minimization of mucosal irritation
- Convenient equipment for manufacturing
- Target/site specific drug delivery.

Disadvantages of floating drug delivery system

- Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be assured
- Drugs that cause irritation and lesion to gastric mucosa are not good to be formulated as floating drug delivery
- High variability in gastric emptying time due to its all or non-emptying process
- Gastric emptying of floating forms in supine subjects may occur at random and becomes highly dependent on the diameter and size.

Diclofenac sodium, an acid insoluble NSAID, and Analgesic was used as model drug. This drug requires multiple dosing due to its short biological half life and it may lead to fluctuation in the plasma drug concentration and may also fail to release the drug at the desired amount which often results in poor patient compliance and inefficient therapy.

The main objective of this present investigation was to develop gastro-retentive sustained release alginate beads of Diclofenac sodium by the ionotropic gelation method, in order to minimize gastric mucosal irritation caused by the release of Diclofenac sodium by other systems.

Further the characterization and evaluation of prepared floating beads.

In this work, the floating drug delivery system employed calcium carbonate (CaCO3) as a gas forming agent dispersed in an alginate matrix. Hydroxyproplyethyl cellulose (HPMC) is used as binder.

Alginate is a polysaccharide which contains varying amounts of 1,4'-linked β-D-mannuronic acid, α-L-glucoronic acid residues. As biocompatible and biodegradable biopolymer, it forms a bio-adhesive and stable gel with divalent cations such as Ca2+, Sr2+, and Ba2+.8 These properties have enabled wide spread use of sustained release of drugs. Alginate beads are stable in acidic media and easily depredated in alkaline media.

During formation of the floating drug beads, carbonate react with acetic acid to produce carbon dioxide.

The evolving gas permeates through the alginate leaving gas bubbles or pores. [2]

Thus, in this study, an attempt has been made to prepare controlled release sodium alginate beads containing Diclofenac sodium using calcium carbonate (CaCO3) as gas forming agent.

The obtained beads were evaluated for encapsulation efficiency, infrared spectroscopy, and dissolution study.[2]

MATERIALS AND METHOD

Materials

Diclofenac sodium was obtained as a gift sample from Lupine Pharmaceuticals, Nagpur, Sodium alginate, calcium carbonate; calcium chloride, HPMC, and acetic acid were purchased from s.d. fine chemicals, Mumbai. All other reagents used were of analytical grade [2]

METHODS

Preparations of floating alginate beads

Sodium alginate and HPMC dispersions of different concentrations were prepared by mixing required amount of alginate in 100 ml of deionized water under gentle agitation. Diclofenac sodium and calcium carbonate (as gas forming agent) were dispersed inalginate dispersion under constant stirring for uniform mixing.

The dispersion was sonicated for 30 minutes to remove any air bubbles. The resultant dispersion was dropped through a 22 gauge syringe needle into 100 ml of 1% (w/v) calcium chloride solution containing 10% (v/v) acetic acid at room temperature. Then the beads formed were allowed to remain in the stirred solution for 10 min.

The beads were filtered and subsequently air dried to constant weight. [3&2]

EVALUATION PARAMETERS

Micromeritic characterization of prepared beads

Bulk density:-

The bulk density is defined as the weight per unit volume of dry products. The bulk density is used to check the uniformity of bulk chemicals. It is determine by following method, take 10gm of beads was placed in 100ml graduated cylinder of bulk density apparatus. The cylinder was fixed to the apparatus and the timer knob is set for 100 tapping. The final volume was noted calculated bulk density. The formula is given as below.[9]

Bulk density = Mass of sample / Bulk volume of sample

Tapped density:-

The tapped density is defined as the ratio of mass powder to the tap volume , the tapped volume is defined as it is volume occupied by the same mass of powder after a standard tapping apparatus, the tapped density determine by using equation,
Tapped density =mass of sample/ tapped volume of sample

Angle of repose:-

The good flow properties are critical for development of any pharmaceuticals capsule containing beads and powder formulation. It is measured by using fixed funnel method. The beads or powder allowing to fall from specific height through funnel on to a sheet of paper to form a heap.

Considering approximately 90 percent of powder sample a circle is drawn. The radius of the circle is measured in cm and substituted in given equation.

The procedure is followed for measuring angle of repose, a glass funnel is held in place with a clamp on a ring support over a glass plate. The glass plate is placed on micro lab jack.

The weigh 5 gm of sample using balance , the sample was taken on a funnel by closing the orifice of funnel by the thumb, after that remove thumb , the lab jack is adjusted so as lower the plate and maintain about 6.4 mm gap between the bottom of funnel stem and the top of powder pile. The height of the pile (h) and the radius (r) of base are measured with ruler.

Using the formula the angle of repose is measured,

Angle of repose=tan`(h/r)

Carr`s Index:-

It is specified by using tapped density and fluff density (poured density), the lowest Carr`s index of any sample such as 5-15% having excellent flow. That means the Carr`s index explain the flowing property by using given formula, [9]
Carr`s index– **{**(Tapped density-Fluff density)/Tapped density}×100

Percentage yield:-

The alginate beads were evaluated for percentage yield. The yield was calculated as per equation.

Percentage yield = (Practical yield/ Theoretical yield)×100

Particle size analysis:-

The prepared beads were analyzed by optical microscopy for their surface structure and size analysis. The surface of the prepared beads was observed under microscope for its morphological characteristics. The size of the beads was determined using a calibrated using Stage micrometer and Eyepiece micrometer.

Determination of drug entrapment efficiency:-

50 mg of floating beads from each formulation were weighed and crushed in a mortar and pastel and the crushed material was dissolved in 100 ml of phosphate buffer at pH 7.4. This solution was mechanically agitated on shaker at 200 rpm for 2h. The resultant dispersions were filtered and analyzed at 276 nm using UV Spectrophotometer (Shimadzu). The encapsulation efficiency was determined by the following formula.

Entrapment efficiency = (AQ/TQ) X 100

Where AQ is the actual drug content of beads and TQis the theoretical quantity of drug present in beads.[2]

Floating Behaviour (Buoyancy Test):-

The prepared beads were studied for buoyancy and floating time using USP Apparatus II (Paddle type). Floating alginate beads (100 mg) were spread over the surface of USP XII paddle type dissolution apparatus using 0.1 N HCl (pH 1.2) as dissolution medium. The medium was agitated with a paddle rotating at 100 rpm for 12 h. The temperature was maintained at 37°C. After 12 hours, the layer of buoyant alginate beads was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in a desiccators until constant weight was achieved. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles.

Buoyancy (%) =Wf (Wf + Ws) X 100

Where, Wf and Ws are the weights of the floated and settled alginate beads, respectively. All the determinations were made in triplicate

Floating Lag Time:-

Ina beaker 100ml of 0.01M HCL was taken and 100mg of alginate beads were dropped in beaker. The stopwatch was started and the time duration was noted till the beads reached the top of the fluid in the beaker. [3]

Ft-Ir Study:-

Drug polymer interactions were studied by FT-IR spectroscopy. The infrared spectra of Diclofenac sodium and drug loaded beads were recorded on FT-IR (Shimadzu FTIR 8400S). The samples were prepared on KBr press and the spectra were recorded over the wave number range of 4,000 to 400 cm^{-1}. [2]

In-Vitro Dissolution Studies:-

In-vitro dissolution studies of the beads were performed for all the formulations using USP apparatus II (Paddle type). An accurately weighed floating alginate beads were taken into 900 ml 0.1N HCL buffer (pH 1.2). The temperature was maintained at 37ºC and stirred at a speed of 50rpm. At 30 minutes time intervals, a 10-ml aliquot of the sample was withdrawn and the volume was replaced with an equivalent amount of plain dissolution medium kept at 37ºC. The collected samples were filtered and analyzed at 276 nm using UV- visible spectrophotometer against 0.1N HCL buffer (pH 1.2) taken as blank.[2]

Accelerated Stability Studies:-

Stability studies were performed according to ICH guidelines. The formulation was stored in room temperature at 25 ± 1°, in incubator at 37 ± 1°, and at 60± 1° for a period of 12 weeks. The samples were analyzed for drug content every two weeks by spectrophotometer at 270nm and compatibility of drug with excipients was determined by infrared spectroscopy. [3]

RESULTS AND DISCCUSION

Floating beads of Diclofenac sodium were prepared by the ionotropic gelation method using HPMC and sodium alginate. The prepared beads were then subjected to various evaluation parameters. The micromeritic characteristics of the beads

were determined such angle of repose, bulk density, tapped density particle size, particle structure and Carr's Index to ascertain the flow properties of beads. The micromeritic properties were found to be satisfactory and summarized in table Percentage yield of all formulation was determined individually and it was found to be above 50% w/w. Among all the formulations F4 showed best percentage yield as compared to other formulations.

Particle Size Analysis:-

The prepared beads were analyzed by optical microscopy for their surface structure and size analysis. The surface of the prepared beads was observed under microscope for its morphological characteristics. It was found that the beads were spherical to elliptical in shape. The surface of most of the beads was found to be smooth but small number of beads showed slightly rough surface within the batch. The beads were prepared using different ratios of sodium alginate and HPMC to study the effect of polymer concentration on the drug release of beads and to obtain sustained release. The size of the beads was determined using calibrated stage micrometer and eyepiece micrometer. The particle size was calculated using following equation.

The mean particle size was found to be in the range of 588.8 ± 7.8µm to 678± 9.0µm. This showed the difference of about 90µm in particle size between different batches. This might have happened due to increase in polymer concentration, variation in the extrudability, fluctuations in temperature etc. To minimize these variations the beads may be subjected to size separation to obtain uniformity in size for large scale preparation.

Determination of drug entrapment efficiency:-

The drug entrapment efficiency was found to be good ranging from 75% to 81%. In case of formulation-F1, the percentage of encapsulation was 75%, where the drug to alginate ratio was 1:2. But, this was increased in F2 to F5where entrapment efficiency was 78.8% to 80%. The drug entrapment efficiency was increased with the increment of drug to polymer ratio.

Floating behavior:-

The floating test was performed to investigate the floatability of the prepared beads. The beads floated for prolonged time over the surface of the dissolution medium. Good in vitro percentage buoyancy was observed for all the beads formulations. Buoyancy percentage of the beads was in the range 68.9± 0.7(F3) to 84.8±0.7 (F5). F5 formulation shows the best floating ability 84.8±0.7 (F5) as compared with other formulations.

Floating lag time:-

The floating lag time of all the formulations were measured. All the formulations could float to the top in less than 1 minute.

FT-IR study:-

FT-IR spectra of sodium alginate showed the bands around 3443, 1632, 1415 and 1039cm−1, indicating the stretching ofO−H, COO− (asymmetric), COO− (symmetric) and C−O−C, respectively. FT-IR spectra of formulation 4 showed the characteristic absorption band of diclofenac sodium at 1505 cm−1which indicated that diclofenac sodium was successfully entrapped into the sodium alginate matrices and a remarkable shift to lower wave number of COO− (asymmetric) and C−O−C stretching peaks of sodium alginate with a decrease in intensity of COO− (asymmetric) stretching peaks. It can be described that amino groups of diclofenac could protonate in sodium alginate dispersion and then interacted with carboxyl and ether groups of alginate before cross-linking process and after cross linking calcium ion form ionic bond and a partial covalent bond with carboxyl groups and ether groups of alginate respectively.

In-vitrorelease kinetics:-

After eleven hours thepercent of drug release for five formulations were76.7% (F1), 73.5% (F2), 72.2% (F3), 70.56%(F4) and69.1% (F5). The decrease in drug release was due to simultaneous increase inalginate amount. Because the more the amount of alginate, more would be the cross-linking between sodium alginate and calcium chloride; thus more drug would remain entrapped and decrease the release. Inthe absence of gas-forming agent the release rate was very slow. CaCO3 is present as an insoluble dispersion in neutral pH aqueous alginate solution. However in acidic media, the CaCO3 becomes water soluble. The drug which is dispersed in hydrophilic matrix is mainly released by zero order kinetics as the

hydrophilic polymer absorbs dissolution medium and swell. Thus a gel layer is formed on the surface and gradually fills the internal spaces. Dissolution rate of drug is thus controlled both by diffusion through the gel layer and by matrix erosion. After studying the drug release kinetics, it was observed that all the formulation follow both zero order and Higuchi release kinetic.

Accelerated stability studies:

The accelerated stability studies were performed according to ICH guidelines for 12 weeks and the results were found to be stable.

CONCLUSION

The gastro-retentive floating beads of analgesic drug i.e. Diclofenac sodium were formulated. That having good floating property, with retaining the long time in stomach and provide long period time of action with minimizing adverse drug reaction, like mucosal irritation. Also floating system shows the local action on the stomach. According to in vitro studies of formulated Diclofenac sodium beads were concluded that the floating lag time, buoyancy are better improve their action. And also have in vitro release kinetics of formulation are prolonged.

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