Design and Description of Gastro spongy Drops of Anti-Hypertensive Mediator

1Name of 1st Dr. Vikram Panchal
[1]Designation of 1st Assistant Professor
[1]Name of Department of 1st Faculty of Science
[1]Name of organization of 1st Gokul Global University, Sidhpur, Patan, Gujarat – India

Abstract : Extended release gastroretentive beads of amlodipine besylate was prepared by an ionotropic external gelation method in ratios of 1:0.5, 1:1, 1:1.5, 1:2, 1:2.5, 1:3, 1:3.5, 1:4, 1:4.5 using.

diameter in the range of 3.21 – 4.74 mm. The drug loading efficiency, around 24.63±0.04 %, 98.51±0.001 % entrapment efficiency and good floating characteristics comprising short onset (around 5 minutes) and the long duration of buoyancy (more than 7 hours). of the beads with swelling Index 176±0.33.

Keywords: Gastroretentive, beads, amlodipine besylate, ionotropic gelation, swelling index.

INTRODUCTION

Classification of Different Modes of Gastric Retention

Floating drug delivery systems (FDDS)

FDDS are invented to retain the drug in the stomach as presented in Figure and applicable for drugs with poor solubility and low stability in intestinal fluids. a prolonged period of time. (Mirmeera NG. et al., 2017)

Superporous hydrogel systems

MATERIALS & EQUIPMENTS

1 Amlodipine besylate Kopalle Pharma Chemicals Pvt. Ltd. CAS No. [9005-38-3] 2 Sodium alginate Ozone International, Mumbai Batch No: AB-50220520 3 Calcium chloride OXFORD lab Fine Chem LLP 4 Calcium carbonate Samar Chemicals

1 Mechanical stirrer Remi Elctrotechnik Limited 2 UV spectrophotometer UV-1800 Shimadzu Spectrophotometer 3 Optical microscope Samar Optik 4 FT-IR Spectrophotometer Alpha II E-ATR (OPUS Version 8.5), Lab India Analytical Instruments Pvt.Ltd. 5 Magnetic stirrer HICON Magnetic Stirrer 6 Dissolution apparatus ELECTROLAB Tablet Dissolution tester 7 Hot Air Oven HICON Hot Air Oven

EXPERIMENTAL WORK

SOLUBILITY PROFILE: Determination of solubility profile of amlodipine besylate. The solubility profile of the selected drug (Amlodipine besylate) was determined.

Preparation of stock solution: 20 mg of Amlodipine besylate was accurately weighed and dissolved in 10 ml of methanol in 10 ml volumetric flask and the volume was made up to the mark using methanol, to make (2000 µg/ml) standard stock solution (I).

Preparation of sample solution: 1 ml stock solution (I) was taken in another 100 ml volumetric flask and further dilute in 100 ml of methanol to make (20 µg/ml) standard stock solution (II), then final concentrations were prepared 02, 04, 06, 08, 10, 12, 14, 16, 18 and 20µg/ml with 0.1N HCL.

Fourier transform Infra-red (FTIR) spectroscopy Study I.R. spectroscopy can be used to investigate and predict any physiochemical interactions between difference components in a formulation and therefore it can be applied to the selection of suitable chemically compatible excipients. The aim of the present study was to find out the possible interaction between selected polymer and the drug Amlodipine besylate and also identify the compatibility between the drug and polymer.

A small amount of triturated sample was taken into a pellet marker and was compressed at 10 kg/cm2 using hydraulic press. The pellet was kept in a sample holder and scanned from 4000 cm-1 in Alpha II E-ATR (OPUS Version 8.5) FT-IR spectrophotometer. Samples were prepared for pure polymer, pure drug, physical mixture of drug and polymer and drug loaded microparticles. The spectra obtained for these samples were compared and interpreted for the shifting of major functional peaks and disappearance of functional peaks if any.

Formulation of Amlodipine Besylate Floating Gastroretentive Beads Sodium alginate solutions of different concentrations were prepared by dissolving required amount of alginate (Table) in 100 ml of deionized water under gentle agitation. Amlodipine Besylate and calcium carbonate (as gas forming agent) were dispersed in alginate solution under constant stirring for uniform mixing. The dispersion was sonicated for 30 minutes to remove any air bubbles.

Production Yield

The prepared beads were collected and weighed. Percentage yield was obtained by dividing measured weight of floating beads by the total weight of drug and the polymer. Percentage yield = (Weight of Beads/Weight of Polymer + drug) x 100

The fixed funnel free standing cone method was used to determine angle of repose. Beads were passed through fixed funnel to make a heap of the predetermined height.

The angle of repose of the beads was determined by fixed funnel free standing cone method using the following formula. Θ = tan−1 h/ r where "h" is height between the lower tip of funnel and the base of heap of beads, and "r" is radius of the base of heap formed. Relationship between angle of repose (Θ) and flow ability is represented in Table No

Angle of repose (Θ)	Flow ability
<20	Excellent
20-30	Good
30-40	Passable
>40	Very poor

Relationship between Flow properties and Angle of Repose

Bulk density and tapped density: To calculate the bulk density and tapped density, the beads were weighed, and transferred to a measuring cylinder. The volume occupied by beads was noted as bulk volume and the cylinder were tapped until the constant volume was achieved, and this was noted as tapped volume. The values of bulk density and tapped density were calculated by using following equations: Bulk density = weight of powder/ volume of the packing Tapped density = weight of powder/ volume of the packing

Compressibility Index: Carr's compressibility index were determined from the value of bulk density and tapped density using following formulae. Car's compressibility index = {(tapped density − bulk density)/ bulk density}x 100

Determination of Swelling Index Beads were studied for swelling characteristics. Samples from drug-loaded beads were taken, weighed and placed in the wire basket of USP dissolution apparatus-I. The basket containing beads was put in a beaker containing 100 mL of 0.01 N HCl maintained at 37 ◦C. Then the swelling Index was calculated as per the following formula: Swelling Index = weight of wet beads/ weight of dried bead x 100

RESULT

Color and Appearance

Amlodipine besylate is an almost white powder.

Melting Point determination

The melting point for Amlodipine besylate was found to be 200-202°C which complies with the reported literature.

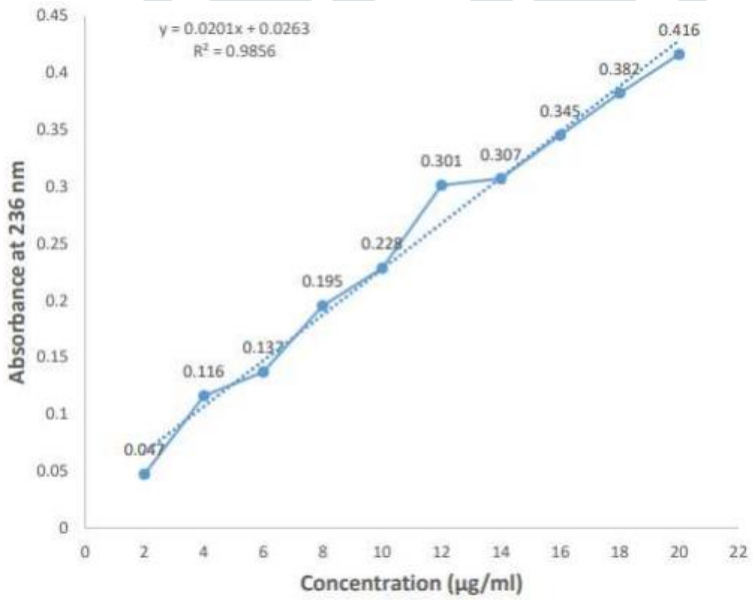
Solubility determination

Solvent	Solubility
Water	Slightly soluble
Methanol	Freely soluble
0.1 N HCL	Soluble

Sr. No.	Absorption Ranges(cm^{-1})	Observed Peaks (cm^{-1})	Type of Vibration
1	600-800	712.47	C-Cl Stretch
2	1300-800	875.24	C—C Stretch
3	1300-1000	1203.69	C-O Stretch
4	1470-1430	1430.28	N-H Bend
5	1675-1600	1671.79	C-C=C Symmetric Stretch
6	1755-1650	1794.16	C=O Stretch

FTIR spectra of Physical Mixture

Standard Calibration Curve of Amlodipine Besylate in 0.1N HCL Buffer



DISCUSSION

The principle objective of this research study was to formulate and characterize Gastroretentive Beads of Anti- Hypertensive Agent (Amlodipine besylate) using sodium alginate polymer. To achieve the above

objective, sodium alginate was found to be suitable polymer due to its biocompatibility, good stability, and ease of fabrication. The drug was received from Kopalle Pharma Chemicals Pvt. Ltd. Batch No: AB-50220520.

Manufacturing Date: May-2017. Expiry Date: Apr-2024. With certificate that complies tests result. The prepared Gastroretentive Beads were evaluated for percentage yield, Micromeritic properties such as Angle of repose, Bulk density, tapped density, compressibility index, Hausner's ratio, particle size, Morphology analysis, swelling index (%), Drug content (%), Drug Entrapment efficiency (%), Buoyancy studies, in-vitro drug release and finally stability studies.

FT-IR study was carried out to see whether there is any incompatibility between drug and polymer and also to know whether there is complete physical adsorption of drug on to the polymer matrix without any mutual interaction. The results obtained from the IR studies are shown in Fig. Amlodipine showed prominent peaks. The same peaks were also observed in the physical mixture of drug & polymer and drug loaded Gastroretentive Beads.

After interpretation through the spectra, it was confirmed that there was no major shifting of functional peaks between the spectra of drug, polymer, physical mixture of drug and polymer and drug loaded Beads. The Drug excipients interaction was studied using (FT-IR) Fourier transformed infrared spectroscopy. The characteristic peaks of the drug (Fig.) were observed at wave numbers 613.93cm-1, 753.53cm-1, 1300.96cm-1, 1492.46 cm-1, 1672.60 cm-1 in the functional group region of the pure drug spectrum. These characteristic peaks in the spectrum correspond to 712.47cm-1, 1203.69 cm-1, 1671.79 cm-1, 1794.16 -1 for stretching vibration of functional groups (C- Cl, C-O, C-C=C Symmetric Stretch, C=O).

These characteristic peaks also appear in the spectrum of amlodipine beads formulation at the same range of wave numbers indicating that there was no interaction between the drug and formulation excipients. Percentage yield of all formulations varies from F1 to F9 which are shown in fig. and indicates that F9 shows highest percentage yield of 77.2%.

Angle of repose value of all the formulations were in the range of 17.02±0.24 to 35.36±0.82, which shows free flow nature of the prepared beads, the results were shown in Table No. It has been stated that, bulk density values less than 1.2 gm/cm3 indicate good glow and values greater than 1.5 gm/cm3 indicate poor flow characteristic. It is seen from Table No. that the bulk density values are less than 1.2 gm/cm3 indicating good flow characteristics of the beads.

The Carr's index of all the formulations was less than 20, i.e from 5.66±0.09 to 17.91±0.03, which indicates good flow properties and compressibility. Hausner's ratio was ranging from 1.06±0.01 to 1.21±0.01 i.e., all the preparation showed that they had good flow properties. The improvement in flow properties suggests that the beads can be easily handled during processing.

The results were shown in Table No. In the study of Partical size, keeping drug ratio constant and varied polymer ratio as the polymer concentration increases, viscosity increases, which influences the interaction between disperse phase and dispersion medium and affects the size concentration, there was increase in relative viscosity so as resulted in an increase in mean particle size. The particle size of drug loaded batches, ranges from 3.21±0.48 mm to 4.74±0.51 mm.

The surface morphology it was performed on the prepared Amlodipine besylate beads to access their surface and morphological characteristics as shown in Fig. indicate that beads were spherical and discrete. The swelling index for all F1 to F9 formulations are ranges from 161±0.30 to 196±0.35%. Loading efficiency of drug loaded batches are found to be 19.65±0.08 % to 24.63±0.04%.

The drug loading efficiency of all formulations were shown in fig. which indicates that the highest drug loading was found to be F9 as 24.63±0.04%. A decrease in drug entrapment was observed after that point due to saturation capacity of the polymer. The entrapment efficiency of drug loaded batches, ranges from 78.61±0.001 to 98.51±0.001. The maximum drug entrapped in the F9 formulation, 98.51±0.001%. In the study of Buoyancy, the values range from 86.00% to 96.00%.

Cumulative percentage release of amlodipine besylate loaded Beads carried out in 1.2 pH HCl upto 7, hours. The release rate was decreased by increasing the polymer concentration and particle size. The rapid release was obtained in formulation F1 due to low concentration of polymer and size of the particle results in higher contact of dissolution medium due to increased surface area. Drug release from all the formulations was slow and sustained over 7 hours. By the end of 7 hours the polymer/drug F6 showed better sustained release pattern and found to be most suitable among all the other formulations.

Because the more the amount of alginate, more would be the cross-linking between sodium alginate and calcium chloride; hence more drug would remain entrapped and decrease the release. CaCO3 is present as an insoluble dispersion in neutral pH aqueous alginate solution. After studying the drug release kinetics, it was observed that the F6 formulation follow First order kinetics (Table No.).

In-vitro release profiles of all the formulations have been shown in Fig. Stability studies of formulated Amlodipine beads was done 40°C±2°C at 75% RH ± 5 % for 01-03 months. Evaluating for month one and two, founded that there is no significant changes in appearance, solubility, colour, particle size, swelling index, in-vitro drug release. Decided to do in-vivo studies in future.

SUMMARY AND CONCLUSION

Floating amlodipine besylate beads using polymer sodium alginate was developed by ionotropic gelation technique using CaCl2 as cross-linking agent and it was found to be a suitable Amlodipine besylate was the prototype of Calcium Chanel blocker used in the treatment of cardiovascular system especially hypertension.

Amlodipine besylate possess the mean half-life of 30-35 hours and 97.5% of circulating amlodipine is bound to plasma proteins, Hence, it was chosen as the good candidate for the Controlled release gastroretentive beads in order to improve the bioavailability and prolong period of drug released.

On comparing the major criteria in evaluation such as percentage yield, drug content, entrapment efficiency and In-Vitro drug released profile, the formulation F6 was selected as the best formulation, as it showed a good Controlled drug release pattern up to 07 hrs. Stability studies of formulated Amlodipine beads was done at 40°C±2°C at 75% RH ± 5 % for a period of three months.

Then beads were withdrawn at the intervals of one month and in evaluation founded that there is no significant changes in appearance, solubility, colour, particle size, swelling index, in-vitro drug release. Decided to do in-vivo studies in future.

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