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Formulation and Evaluation of Loratidine Hydrogel Beads

Preethi voorella* and K. Sudhamani

Department of Pharmaceutical Technology, Mallareddy Institute of Pharmaceutical sciences, JNTU Hyderabad, Telangana.

* Corresponding author: Preethi voorella, e-mail: preethi.voorella@gmail.com

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ABSTRACT

Loratadine is a derivative of azatadine and a second-generation histamine H1 receptor antagonist used in the treatment of allergic rhinitis and urticaria. The aim of the study was to formulate and compare wax incorporated alginate and pectinate beads for their in-vitro release, kinetics and gastric retention. An attempt was made to prepare beads of Loratidine by using sodium alginate and pectin polymers and also incorporating oil and waxes by ionotropic gelation method along with hot melt extrusion technique. In the present study twelve formulations were formulated by using sodium alginate and pectin polymers along with waxes in various proportions. The drug is delivered at controlled/sustained manner into GIT consequently to the systemic circulation. the prepared hydrogels were evaluated for particle size, flow properties, entrapment efficiency, swelling index, %yield and in-vitro drug release studies. From the various trials formulated the F3 formulation showed sustained drug release when compared with other trials. The optimized formulation follows zero order drug release with supercase II transport mechanism.

Keywords: Hydrogel beads, Ionic gelation, Pectin, Loratidine.

1. INTRODUCTION

The design of oral controlled DDS should be primarily aimed to achieve more predictable and increased bioavailability. Now a days most of the pharmaceutical scientists are involved in developing the ideal DDS. This ideal system should have advantage of single dose for the whole duration of treatment and it should deliver the active drug directly at the specific site. Controlled release implies the predictability and reproducibility to control the drug release, drug concentration in target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose [1]. However, this approach has several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the GIT due to variable gastric emptying and motility. Furthermore, the relatively brief GIT in humans which normally average 2-3 hrs through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose. Therefore, control of placement of a DDS in a specific region of the GI tract offers advantages for a variety of important drugs characterized by a narrow absorption window in the GIT or drugs with a stability problem [2].

2. MATERIALS AND METHODS

Loratidine was obtained as a gift sample from Cipla Pharmaceuticals Limited. Sodium alginate, pectin were purchased from Narmada chemicals, and other excipients were procured from spectrum pharma research solutions, Hyderabad.

2.1 Preparation of wax incorporated emulsion Hydro gel beads

Method used – hot melt extrusion along with ionotropic gelation method. Accurate quantity of polymer was dissolved in 50ml of distilled water and stirred to form dispersion. Drug was added to the above dispersion and again stirred for uniform distribution. Later, liquid paraffin was also added to the same and stirring was continued to get homogenous emulsion.

In another beaker, various amounts of waxes (viz. white bees wax, carnauba wax) were melted in water bath at 60–85°C, depending on the melting range of the waxes used. The molten wax was added to the homogenized emulsion mixture of polymer, oil and SA which was already heated to same temperature and stirred until a homogenous mixture was obtained. The hot melted mixture was extruded through a 23G syringe needle into calcium chloride solution (2% w/v). The beads were allowed to remain in the same solution for 30 min to improve their mechanical strength. The formed beads were separated, washed with water and allowed to dry at room temperature overnight.

2.2 Evaluation of formulations

2.2.1 Compatibility Studies

Compatibility with excipients was confirmed by FTIR studies. The pure drug and polymers were subjected to FTIR studies. In the present study, the potassium bromide disc (pellet) method was employed.

2.2.2 Preparation of Standard Calibration Curve of Loratidine in 6.8 pH buffer

10mg of Loratidine was accurately weighed and transferred into 10ml volumetric flask. It was dissolved and diluted to volume with 0.1N HCL to give stock solution containing 1000µg/ml.

The standard stock solution was then serially diluted with 6.8 phosphate buffer to get 5 to 30µg/ml of Loratidine. The absorbance of the solution were measured against 0.1N HCL as blank at 270nm using UV visible spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

2.3 Evaluation of flow properties of pure drug:

i. Angle of repose.
ii. Determination of Bulk Density and Tapped Density
iii. Hausner's Ratio
iv. Compressibility index (Carr's Index)

2.4 Evaluation of Loratidine Hydrogel Beads

2.4.1 Flow properties of pure drug

From the recorded observations it was found that Carr's index of model drug was 17.41 and Hausner's ratio was 1.21 indicating drug have fair compressibility index. Angle of repose was found to be 29 indicating drug has excellent flow properties.

2.4.2 Surface morphology (SEM)

Scanning electron microscopy has been used to determine particle size distribution, surface topography, texture, and to examine the morphology of fractured or sectioned surface. SEM is probably the most commonly used method for characterizing drug delivery systems, owing in large to simplicity of sample preparation and ease of operation. SEM studies were carried out by using JEOL JSM T-330A scanning microscope (Japan). Dry SS gel beads were placed on an electron microscope brass stub and coated with in an ion sputter. Picture of hydrogel beads were taken by random scanning of the stub.

2.4.3 Frequency distribution analysis

The diameter of a sample of gel beads of each formulation was determined using vernier caliper. In order to be able to define a frequency distribution or compare the characteristics of particles with many different diameters, the frequency distribution can be broken down into different size ranges, which can be presented in the form of a histogram. Histogram presents an interpretation of the frequency distribution and enables the percentage of particles having a given equivalent diameter to be determined.

2.4.4 Percentage yield

Percentage practical yield of beads was calculated to know about percentage yield or efficiency of any method, thus it helps in selection of appropriate method of production. Practical yield was calculated as the weight of beads recovered from each batch in relation to the sum of starting material.

The percentage yield of beads prepared was determined by using the formula.

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

2.4.5 Buoyancy behaviour

The time between the introduction of the FDDS into the medium and its buoyancy to the upper one third of the dissolution vessel (floating lag time) and the floating ability was determined using USP dissolution tester apparatus II (Paddle method). Fifty beads were put in the vessel and the paddles were rotated at 50 rpm in 900 ml 0.1 N HCl pH 1.2, maintained at 37±0.5 °C for 12 hours. The floating ability of the beads was measured by visual observation. The preparation was considered to have buoyancy, only when all beads floated on the test solution immediately or within a lag time which did not exceed 2 min.

2.4.6 Drug Content

To determine the drug content and encapsulation efficiency of the beads, 200 mg beads were crushed using a porcelain mortar and a pestle, and dispersed in suitable solvent (methanol). The dispersion was sonicated for 15 minutes and left overnight for 24 hrs, then the dispersion was filtered. A 1 ml sample was taken and diluted with suitable solvent (methanol), and drug content assayed using a UV-visible spectrophotometer at λmax of 270 nm.The drug content of each formulation was recorded as mg / 200 mg of gel beads.

2.4.7 Drug Entrapment Efficiency

The drug entrapment efficiency of prepared beads was determined by using the following equation:

EE (%) = Actual Drug Content/ Theoretical Drug Content X 100

2.5 *In vitro* dissolution studies

2.5.1 Procedure for In vitro dissolution study

The release rate of Loratidine Hydrogel beads was determined by employing USP XXIII apparatus II (paddle method). The dissolution test was performed using 900 ml 0.1N HCL, in 37 ±0.5°C at 50 rpm. Loratidine hydrogel beads equivalent to 10 mg of Loratidine was used for the study. At various time points (hourly) 5ml of the sample solution was withdrawn from the dissolution apparatus for upto 12 hrs, and the samples were replaced with fresh dissolution medium. The samples were filtered and the absorbance was determined at 270nm. Dissolution profiles of the formulations were analyzed by plotting cumulative percentage drug release versus time. The data obtained were also subjected to kinetic treatment to understand release mechanism.

2.6 Kinetics of drug release

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing zero order (Q v/s t), first order [Log(Q_0-Q) v/s t], Higuchi's square root of time (Q v/s $t^{1/2}$) and Korsemeyer Peppas double log plot (log Q v/s log t) respectively, where Q is the cumulative percentage of drug released at time t and (Q_0-Q) is the cumulative percentage of drug remaining after time t.

In short, the results obtained from *in vitro* release studies were plotted in four kinetics models of data treatment as follows.

- Cumulative percentage drug release Vs. Time (zero order rate kinetics)
- Log cumulative percentage drug retained Vs. Time (first order rate kinetics)
- Cumulative percentage drug release Vs. √T (Higuchi's classical diffusion equation)
- Log of cumulative percentage drug release Vs. log Time (Peppas exponential equation)

Table 1: Formulation design for Loratidine hydrogel beads using different ratios of drug, polymers and waxes

Ingredients	Formulations											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
DRUG	1	1	1	1	1	1	1	1	1	1	1	1
SA	1.5	1.5	1.5	1.5	1.5	1.5	-	-	-	-	-	-
LMP	-	-	-	-	-	-	2	2	2	2	2	2
WBW	1	2	3	-	-	-	1	2	3	-	-	-
CW	-	-	-	1	2	3	-	-	-	1	2	3

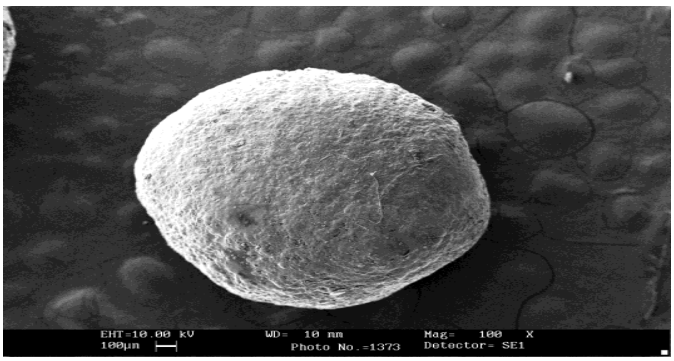

Figure 1: SEM

Table 2: Average size, Floating duration, Percentage Yield, Drug content (%), Entrapment Efficiency (%)

Formulation code	Average	sizeFloating	Percentage	Drug content	Entrapment
F1	1.5	12	83.67	54.09	89.79
F2	1.3	12	87.76	62.36	93.71
F3	1.1	12	95.65	80.24	94.02
F4	1.6	12	76.37	58.27	85.82
F5	1.4	12	77.79	42.58	87.88
F6	1.2	12	81.74	27.19	87.93
F7	1.7	12	82.13	24.86	89.59
F8	1.5	12	84.38	19.09	92.46
F9	1.3	12	88.19	14.58	93.58
F10	1.8	12	72.32	22.84	82.10
F11	1.7	12	76.48	18.36	85.75
F12	1.5	12	82.09	15.68	86.16

3. RESULTS AND DISCUSSION

3.1 Determination of Loratidine λ-max

Determination of Loratidine λ-max was done in 0.1N HCL for accurate quantitative assessment of drug dissolution rate. The Loratidine peak value is 270. The linearity was found to be in the range of 5-30 µg/ml in 0.1N HCL. The regression value was closer to 1 indicating the method obeyed Beer-lamberts' law. The solubility studies were conducted in various buffers we can say that 0.1N HCL has more solubility when compared to other buffer solutions.

3.2 FTIR Studies

It indicates that the drug was intact and has not reacted with the excipients used in the formulation and hence they are compatible. Hence, it can be concluded that the drug is in free-state and can release easily from the polymeric network in the free form.

3.3 Surface morphology (SEM)

The surface morphology of the Loratidine beads was studied by SEM. SEM photographs of the various formulations are shown in the Fig. 5.11 to 5.14. Surface smoothness was observed with beeswax incorporated Loratidine beads when compared to carnauba wax incorporated beads which was found to have a slightly rough surface.

3.4 Frequency distribution analysis

Average diameter of wax incorporated Hydro gel beads was found to be 1.1-1.8mm.

3.5 Buoyancy characteristics

The buoyancy time of the prepared hydrogel beads was found to be more than 12hrs.

3.6 Percentage yield

The percentage yield of the formulated hydrogel beads was found to be in the range of 72.32-95.65%. the highest percentage yield was found in the F3 formulation.

3.7 Drug Content

The drug content for the formulated hydrogel beads was found to be in the range of 14.58-80.24%. the highest percentage yield was found in the F3 formulation.

3.8 Drug Entrapment Efficiency

The drug entrapment efficiency for the formulated hydrogel beads was found to be in the range of 82.10-94.02%. the highest percentage yield was found in the F3 formulation.

3.9 *In-vitro* dissolution studies

The *in vitro* drug release studies for the formulated hydrogel beads differ for the different polymers used. The drug release profiles of the formulated hydrogel beads using sodium alginate with white bees wax with higher concentration shows sustained drug release up to 12hours than the other polymers. The *in vitro* dissolution data for best formulation f3 were fitted in different kinetic models i.e, zero order, first order, Higuchi and korsemeyer-peppas equation. Optimized formulation F3shows R^2 value 0.937. As its value nearer to the '1' it is conformed as it follows the First order release. The mechanism of drug release is further confirmed by the korsmeyer and peppas plot, if n = 0.45 it is called Case I or Fickian diffusion, 0.45 < n < 0.89 is for anomalous behavior or non-Fickian transport, n = 0.89 for case II transport and n > 0.89 for Super case II transport. The 'n' value is 0.108 for the optimised formulation (F3) i.e., n value was between 0.45 and 0.89 this indicates anomalous transport (fickian diffusion).

4. CONCLUSION

The concept of formulating wax incorporated gel beads containing Loratidine offers a suitable, practical approach to achieve a prolonged therapeutic effect by continuously releasing the medication over extended period of time. In present work, hydrogel beads of Loratidine were prepared successfully by hot extrusion along with ionotropic gelation method using different polymers and waxes. The hydrogel beads formulated with sodium alginate along with white bees wax shows sustained drug release up to 98.26% at the end of 12hrs, when compared with the other formulations. So F3 formulation is considered as the optimized formulation.

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