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Formulation and evaluation of Etodolac alginate beads prepared by ionotropic gelation for sustained release

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Abstract

Oral sustained release drug delivery system is getting greater attention due to its therapeutic advantages. Etodolac is a non-steroidal anti-inflammatory drug with potent analgesic and anti-arthritic properties. It has a short biological half life of 6.4 hours and is administered in a dose of 200-400 mg every 6-8 hours. In the present study, a suitable particulate system of Etodolac has been developed, by ionotropic gelation method for sustained release that would result in prolonged clinical efficacy, reduced frequency of administration and lesser side effects. Microbeads were prepared with and without using maize starch as polymer and were evaluated for particle size and size distribution analysis, flow properties, loose surface crystal study, entrapment efficiency, swelling ratio, percentage yield and drug content uniformity and in-vitro drug release. It was found that the particle size distribution of both formulations was varied within a narrow size range. Drug leaching (15.46 % ± 0.118) was more with presence of maize starch. Entrapment efficiency was retarded with the presence of maize starch. Swelling ratio (54.29 ± 0.151) suggested that maize starch incorporated microbeads swelled more to behave as a matrix for controlled drug delivery. Formation of highly viscous dispersion with the incorporation of polymer led to high percentage yield (51.48% ± 0.180). Drug release data was fitted into various kinetic models and indicated that the mechanism was according to Peppas model. The study revealed that the microbeads of Etodolac could be successfully prepared by ionotropic gelation technique with sustained release characteristics.

Keywords: Etodolac, Alginate beads, Maize starch, Ionotropic gelation, Sustained release.

Introduction

Safe and efficient oral sustained release drug delivery systems are formulated to release active ingredient gradually and predictably over a long period and is getting greater attention due to convenience and acceptance among patients. Sustained release is a sub classification of controlled release system which release drug over an extended period of time. Generally, hydrophilic polymer matrix is used for formulating sustained dosage forms. Various physicochemical and biological factors are also considered while formulating oral sustained drug delivery system.[1]

Gastric emptying of a drug is a complex process that makes *in vivo* performance of drug delivery systems uncertain; however, the floating or hydro dynamically controlled drug delivery systems namely, floating microspheres, micro beads, and microcapsules are useful in overcoming such uncertainty. Micro beads are small, solid and free flowing particulate carriers containing dispersed drug particles either in solution or crystalline form that allows a sustained release or multiple release profiles compared with the monolithic formulations. They release the active ingredients through a double mechanism: diffusion and/or biodegradation of the polymer. The cross-linked microbeads, depending on the biodegradability and biocompatibility, can be administered as long lasting medications. The use of coating substances which can dissolve either in different areas of the gastrointestinal tract (depending on pH and/or the enzymes present) or after a preset time (depending on the thickness) allows

coated microbeads to be used both in a space- and- time focussed manner.[2]

The present paper describes the preparation of microbeads of Etodolac by ionic gelation with and without maize starch as polymer, and studies various pre and pro evaluation parameters to obtain the required release rate of Etodolac microbeads.

Materials and Methods

Materials

Etodolac was a gift sample from Dr. Reddy's Laboratories, Hyderabad. Maize starch, Methanol AR, Sodium alginate AR, Calcium chloride AR, and Sodium hydroxide AR were USP/NF quality and were procured from Nice Chemicals, Cochin, Kerala. All other chemicals used throughout the study were of analytical grade.

Methods

Preparation of Etodolac alginate microbeads: Alginate microbeads, each containing 200 mg Etodolac were prepared by Ionotropic gelation method. The composition of various formulations of the microbeads with their codes is listed in Table 1. Formulation F_2 was prepared with maize starch, while F_1 was devoid of maize starch. Active ingredient Etodalac was added to slurries of 2.5% w/v sodium alginate. Both the slurries were separately dispersed thoroughly using mechanical stirrer for 15 minutes and taken in 10 ml hypodermic needle fitted with a 20 gauge needle. The mixtures were added drop wise to calcium chloride solution (3% w/v), and stirred at 200 rpm. The gelation time of 1 hour was allowed to complete the curing reaction and to produce spherical and rigid microbeads. The beads were collected by decantation, washed 3 times with distilled water and dried at 60^o C for 2 hours in a hot air oven.[3]

Table 1: Formulation details

Formulation code	Drug (mg)	Sodium alginate (% w/v)	Calcium chloride (% w/v)	Maize starch (mg)	Curing time (min)
F_1	200	2.5	3	nil	30
F_2	200	2.5	3	200	30

Physical characterisation: The particle sizes of the microbeads were determined using optical microscopy method. The microbeads were mounted in light liquid paraffin and the diameters of 100 particles were measured by means of an optical microscope with calibrated micrometers and the mean diameter was calculated.[4]

Loose surface crystal study (LSC) was conducted to estimate the amount of drug present on the surface of the microbeads. 100 mg of microbeads were suspended in 100 ml phosphate buffer (pH 6.8), simulating the dissolution media. The samples were shaken vigorously for 15min in a mechanical shaker. The amount of drug leached out from the surface was analyzed spectrophotometrically at 274 nm. Percentage of drug released with respect to entrapped drug in the sample was recorded.[5]

Entrapment efficiency was calculated to determine the ability of microbeads to entrap the drug: About 50 mg of accurately weighed drug loaded microbeads were crushed in a glass mortar and pestle and mixed with 100 ml phosphate buffer (pH 6.8) and kept for 24 hours. The solution was stirred on a magnetic stirrer for 15 min, filtered and 1ml of the filtrate was diluted using phosphate buffer (pH 6.8) and analysed spectrophotometrically at 274nm. The drug entrapment efficiency was calculated as per the following formula.[6]

$$\text{Entrapment efficiency (\%)} = \text{Actual drug content} / \text{Theoretical drug content} \times 100$$

The flow properties of microbeads were investigated by measuring the angle of repose of drug loaded microbeads using fixed base cone method. Microbeads were allowed to fall freely through a funnel fixed at 1cm above the horizontal flat surface until the apex of the conical pile just touches to the tip of the funnel. The height and diameter of the cone was measured and angle of repose was calculated using the formula:

$$\theta = \tan^{-1}(h/r)$$

where; h = cone height, r = radius of circular base formed by the microbeads on the ground.

The bulk and tapped densities were measured in a 10 ml graduated cylinder as a measure of packability of the microbeads. The sample contained in the measuring cylinder was tapped mechanically by means of constant velocity rotating cam. The initial bulk volume and final tapped volume were noted from which, their respective densities were calculated.[7]

Compressibility index or Carr's index value of microbeads were computed according to the following equation:

$$\text{Carr's index (\%)} = (\text{Tapped density} - \text{Bulk density}) / \text{Tapped density} \times 100$$

Hausner's ratio of microbeads was determined by comparing the tapped density to the bulk density using the equation: Hausner's ratio= Tapped density / Bulk density

Swelling properties of the drug loaded microbeads were determined at pH range 6.8. Thirty dried beads were placed in phosphate buffer (pH 6.8) and allowed to swell at 37^o C. After 2 hour interval, the equilibrium swollen beads were observed and measured by optical microscopy. Swelling ratio was determined from the following relation.[8]

$$\text{Swelling ratio} = (\text{Mean diameter at time t-initial diameter})/\text{Initial diameter of beads} \times 100$$

The percentage yield of micro beads has been calculated using following equation.[9]

$$\text{Percentage yield of microbeads} = \text{Total yield of microbeads}/\text{Total weight of polymer} \times 100$$

The *in-vitro* drug release behaviour of the microbeads was evaluated in phosphate buffer (pH 6.8). The basket method was used to conduct the dissolution tests. The basket position was set at 2.5 cm from the bottom of the flask and speed was adjusted to 75 rpm. The dissolution studies were carried out in 900 ml phosphate buffer maintained at 37 ± 0.5°C. Microbeads containing 200 mg of the drug were employed in each case. Aliquots of 5ml were withdrawn and immediately replaced the dissolution medium to maintain a constant volume of 900 ml. The samples were taken at the following intervals of 0.0, 0.1, 0.5, 1.0, 2.0, 3.0, 4.0 and 5.0 hours respectively. Stirring was continued for 5 hours and speed was increased to 200rpm for the last 15 minutes in order to estimate the 100 % release point. The samples were filtered and absorbance was determined at 274 nm using UV-Visible spectrophotometer against an appropriate buffer as a blank.[10]

Statistical analysis: Each experiment was carried out in triplicate and the results are mean ±SD.

Results and Discussion

Particle size and size distribution analysis: It was found that the particle size distribution of both formulations was varied within a narrow size range as shown in Table 2. But the mean particle sizes were different among these formulations. The results indicated that the proportional increase in the mean particle size of microbeads increased with the presence of sodium maize starch in the formulation. This could be attributed to the formation of large droplets during addition of polymer solution to the gelling agent.

Loose surface crystal study: The percentage of drug release was found to be more for the formulation containing maize starch as polymer F_2 (15.46 % ± 0.118) than F_1 (10.93 % ± 0.176) due to the less dense matrix structure.

Entrapment efficiency: The amount of drug entrapped was more in F_1 (36.08% ± 0.125) that does not contain maize starch when compared to F_2 (28.75% ± 0.291).This may be attributed to lesser number of binding sites of alginate for Ca^{2+} ions resulting in the formulation of a less compact gel membrane which, in turn, increases influx of Ca^{2+} ions leading to decrease in drug entrapment efficiency.

Flow properties: The results presented in Table 3 showed that F_2 which has the polymer incorporated is more freely flowing than F_1 which lack polymer. Thus, the microbeads if tabletted or encapsulated, requires less amount of lubricants and ensures low production cost leading to its feasibility for large scale production.

Swelling ratio and percentage yield of microbeads: The mean diameter of swelling beads to dried beads was found to be greater for formulation prepared by utilizing maize starch polymer F_2 (54.29 ± 0.151), compared to F_1 (58.27 ± 0.199) suggesting that maize starch microbeads may begin to swell more and behave as matrices for controlled release of incorporated drug. The percentage yield was found to be higher for the formulation prepared using maize starch polymer F_2 (51.48% ± 0.180) when compared to F_1 (45.17 ± 0.142 %). This could be due to the formation of high viscous polymer dispersion which is not lost during manufacturing process.[11]

The drug release behaviour: Both the formulations of microbeads was evaluated in phosphate buffer (pH 6.8). The release profiles of both the formulations are shown in Figure 1. The results indicate that release of drug from maize starch blended microbeads were found to be lower than that of microbeads that doesn't contain maize starch.[12]

The drug release kinetics is presented in Table 4 and follows a complex order drug release. The correlation co-efficient (r^2 value = 0.966) indicates that the release mechanism is diffusion and the n value of Peppas model (0.339) indicates that the mechanism of drug release follows Fickian diffusion. This suggests that drug release occurs mainly by diffusion through polymer matrix from a region of high concentration to lower concentration.

Table 2: Average mean diameter of the alginate beads

Contents	**F_1**	**F_2**
Length number mean diameter (µm)	412.00 ± 0.577	419.00 ± 0.548
Surface mean diameter (µm)	415.48 ± 0.122	422.29 ± 0.151
Volume mean diameter(µm)	418.96 ± 0.543	425.56 ±0.339
Surface-length mean diameter (µm)	418.99 ± 0.547	425.60 ± 0.868
Volume-surface mean diameter (µm)	426.01 ± 0.171	432.19 ± 0.467
Weight- moment mean diameter (µm)	432.97 ± 0.275	438.71 ± 0.208

Table 3: Values for different flow property parameters for F_1 and F_2

Properties	**F_1**	**F_2**
Angle of repose	27.82° ± 0.071	28.01° ± 0.112
Bulk density	0.43 ± 0.042(g/ml)	0.46 ± 0.055(g/ml)
Tapped density	0.58 ± 0.068(g/ml)	0.50 ± 0.103(g/ml)
Carr's index	24.58 ± 0.211 %	8.04 ± 0.140 %
Hausner"s ratio	1.33 ± 0.065	1.09 ± 0.117

Table 4: Release kinetic models

Formulation Code	**Correlation co-efficient (r^2 value)**			
	Zero order	First order	Peppas model	Higuchi model
F1	0.771	0.614	0.836	0.898
F2	0.847	0.654	0.966	0.941

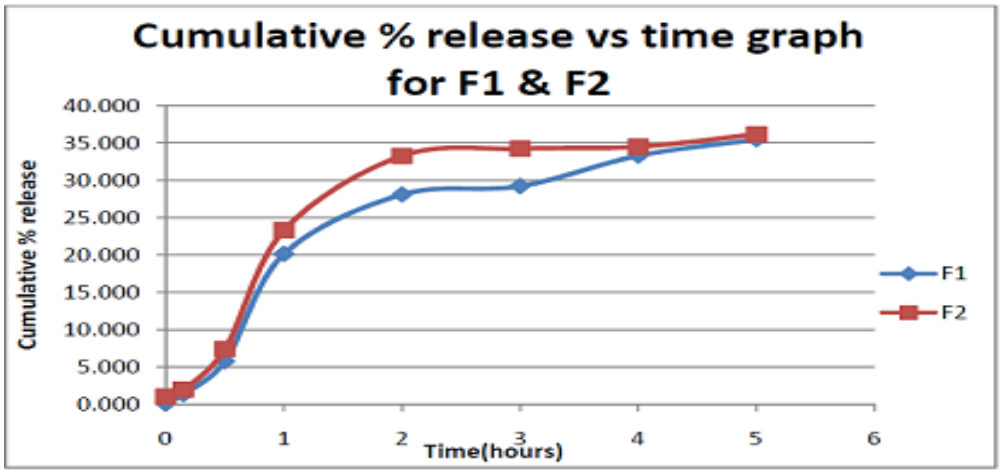

Figure 1: Cumulative percentage release *vs* time graph for F_1 and F_2

Conclusion

The present study revealed that ionotropic gelation technique can be successfully used for preparation of Etodolac microbeads. Selection of polymer is important to achieve more entrapment efficiency and to sustain the release of drug from beads. Maize starch blended microbeads showed more entrapment efficiency as well as more sustained release of drug. Also the formulation containing maize starch was found to be freer flowing. Therefore maize starch is comparatively better polymer of choice for Etodolac when compared to a formulation without maize starch. Maize starch can also be used for texture and clarity and also as a binder and excipient.

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