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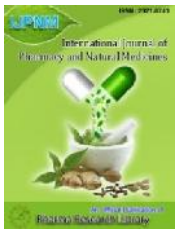

Research Article **Open Access**

Formulation and Evaluation of Chitosan Based Hydrogel Beads for Controlled Release of Ketorolac Tromethamine

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A B S T R A C T

The present work deals with the formulation and evaluation of particulate drug delivery systems for the controlled release of ketorolac. The main objective of any drug therapy is to achieve a desire concentration of drug in blood or tissue, which is therapeutically effective and non toxic for an extended period of time. Oral controlled release multi-particulate dosage forms such as beads, pellets and micro particles are becoming more popular than single unit dosage forms. These systems tend to spread uniformly throughout the gastro-intestinal tract -GIT. In this present investigation Ketorolac tromethamine was formulated into controlled release micro beads with three different polymers (Sodium alginate, HPMC, Eudragit RSPO) each at two different ratios. The beads were prepared by ionotropic cross linking method, using TPP as cross linking agent and the prepared beads were evaluated for surface morphology, bead size, entrapment efficiency, fourier transform infrared spectroscopy, differential scanning calorimetric, dynamic swelling, in vitro drug release, stability studies. Out of all the polymers used beads made of sodium alginate at higher ratio showed significant results than other polymers used. Micro beads prepared using sodium alginate showed better entrapment efficiency, swelling index and improved in-vitro drug release compared to other two polymers used.

Keywords: Multiparticulate system, Controlled delivery, Ketorolac tromethamine, Beads.

A R T I C L E I N F O

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1. Introduction

The ideal dosage regimen is one in which an acceptable therapeutic concentration of the drug is immediately attained at the site of action and is maintained constant for the desired duration of treatment. Conventional dosage form systems aim for an effective concentration. However, these dosage systems have the disadvantages of frequent dosage administration and varying half life. The dosing interval may not be appropriate for the biological half life of the drug. This will result in large peaks in the blood level [17]. For example, drugs with short half lives require frequent dosing to sustain constant therapeutic levels [1-3]. Ketorolac tromethamine is a non steroidal anti inflammatory drug (NSAID) that exhibits analgesic activity mediated by peripheral effects. It inhibits the synthesis of prostaglandins through inhibition of the cyclo-oxygenase enzyme system. The drug is having an oral daily dose of 10-20 mg, with bioavailability of less than 5%, and plasma half life of about 3-6 hours. Hence, there is a need for ketorolac to be formulated in the form of controlled release system [4].

2. Materials and Methods

Ketorolac Tromethamine- Bright Labs, Chitosan- Mahtani Chitosan Pvt. Ltd, Sodium alginate- Finar chemical Ltd., Ahmedabad, Eudragit RSPO- Dr. Reddys, HydroxyPropyl methyl cellulose, Calcium chloride, Glacial acetic acid-SD Fine-Chem. Pvt., Mumbai, India(5,10).

Preparation of Chitosan Based Hydrogel Beads:

The beads were prepared by the. Ionotropic cross linking method. Thus, the complexation mechanism is an ionotropic cross linking or interpolymer complex. The drug, ketorolac (10 mg) was dissolved in and dispersed in 10 ml of 1.5 % glacial acetic acid. Chitosan with another polymer such as sodium alginate was dispersed in the above dispersion of ketorolac tromethamine with low heat. A micro tip attached to a syringe was used to deliver the dispersion drop wise into 50 ml of 1% TPP solution (adjusted at a pH of approximate 6-6.5) with magnetic stirring at room temperature. The beads were allowed to cure for 20 minutes in the solution. They were then, separated by filtration and allowed to dry at 35^0C temperature overnight [7, 17].

Formulation of Hydrogel Beads:

Table 1: Formulation chart for the preparation of beads

Code	F1	F2	F3	F4	F5	F6
Drug(mg)	10	10	10	10	10	10
Chitosan(mg)	300	300	300	300	300	300
HPMC(mg)	300	200	-	-	-	-
Sod. Alginate(mg)	-	-	300	200	-	-
Eudragit RSPO (mg)	-	-	-	-	300	200
TPP(ml)	50	50	50	50	50	50
Curing Time(min)	20	20	20	20	20	20

4.9. Evaluation of Beads:

The prepared beads were evaluated by the following parameters:

Estimation of drug entrapment efficiency:

A known amount of micro beads (20 mg) were added to 20 ml USP phosphate buffer of pH 7.4 for complete swelling at 37^{o}C. The beads were crushed in a glass mortar with pestle, the solution was than for 2 h to extract the drug completely and centrifuged to remove polymeric debris. The clear supernatant solution was analyzed for drug content using UV-visible spectrophotometer at 323 nm [6,8,9].

Dynamic swelling index:

The dynamic swelling behavior of the micro beads was studied by mass measurement. The 50 mg of beads were incubated with 25 ml phosphate buffer solution pH 7.4 at 37^{o}C. The beads were taken out at different time intervals and blotted carefully without pressing hard to remove the excess surface liquid. The swollen beads were weighed using the electronic microbalance.

In-vitro **release kinetics:** Zero order kinetics, first order kinetics, Korsmeyer-Peppas model, Higuchi model.

Stability studies:

In the present study, stability studies were carried out at 40^{o}C/75% RH for about 3 months as per ICH guidelines for the selected formulation. The selected formulation was then analyzed for physical evaluation and percentage drug content [7, 11, 15].

Characterization of Microbeads

Differential Scanning Calorimetric Analysis:

The samples were heated from 0-300^{o}C at a heating rate of 10^{o}C/min under argon atmosphere using a micro calorimeter ((DSC S110 6300) and then thermo grams were obtained **[12, 15,16]**.

3. Results and Discussion

Drug-Excipient Compatibility Study by FTIR:

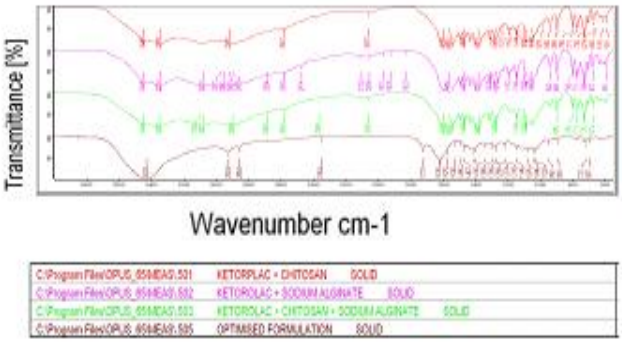

Figure 1: Interpretation of FTIR Spectra

Compatibility studies were performed using FTIR spectrophotometer. The IR spectrum of pure ketorolac tromethamine drug and physical mixture of drug chitosan, sodium alginate were studies. Based on the results, it was concluded that there is no chemical interaction between drug and the excipients used and thus it can be safely used in the formulations.

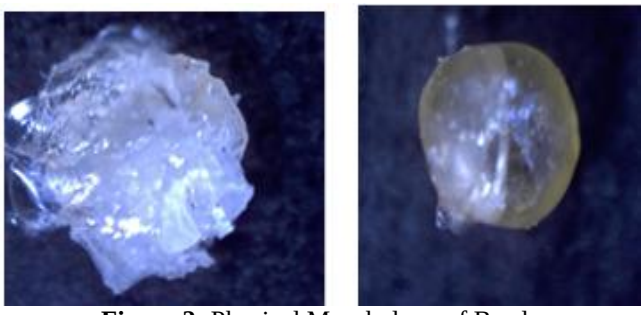

Figure 2: Physical Morphology of Bead

A sponge like internal structure was seen. The pores of the beads containing drug were observed in the beads. The above mentioned figures show the presence of the gel structure during the process. The beads were observed to be spherical to oval and the surface was found to be smooth. From the images, we can see that the drug is dispersed and entrapped within the pores of the beads.

Average Bead Size:

Table 2: Chart Showing Bead Size

Formulation	Average bead size (µm)
F1	1010±3.14
F2	1015±2.31
F3	1025±3.34
F4	1047±1.58
F5	1056±1.27
F6	1036±1.36

Values are mean ± SD, n=3

The size of micro beads was determined using digital micrometer and was found to be in the range of 1010-1056µm.By increasing the polymer concentration in the beads, an increase in size of the beads was observed.

Entrapment Efficiency:

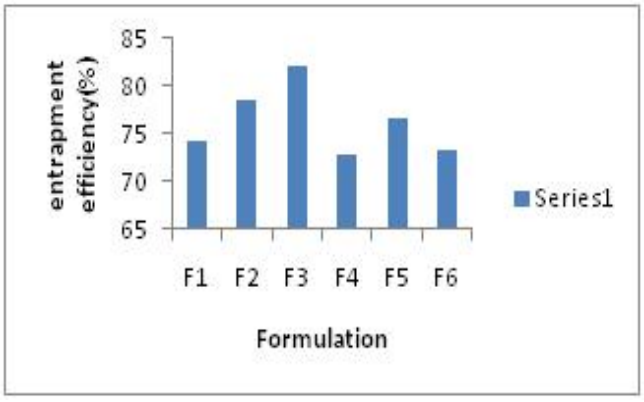

Figure 3: Chart Showing Drug Entrapment Efficiency of Various Formulations

The drug entrapment efficiency from the hydrogel beads was obtained using UV spectrophotometer. The filtrate obtained after bead collection on the filter medium and diluting with phosphate buffer 7.4 was analyzed using a UV-Visible spectrophotometer and the absorbance value of the solution was noted from the UV spectrophotometer. This value was then compared using the calibration curve. The calibration curve was first obtained by scanning the wavelength at maximum absorbance. This occurred at about 323 nm. The concentration of the drug was known at this wavelength. The drug entrapment efficiency was found to be in the range of 74.31% to 82.25%. The results indicate that the DEE of the micro beads prepared with lower concentration of polymer was lowest as compared to those prepared with higher concentration of polymer. Among all the formulations, F3 was found to have maximum entrapment efficiency compared to all other formulations.

Swelling Ratio: The swelling rate was found to be different basing on the ratio of chitosan and polymer used. Due to polymer-polymer interactions and solvent-polymer interactions a mixed phase is observed where a hydrogel gains its maximum of hydrophilicity and swells. From the study it was observed that the rate of swelling more for F3 formulation.

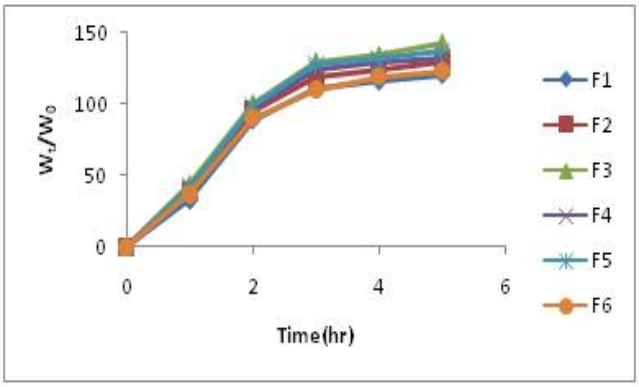

Figure 4: Graph Showing the Swelling Index of Various Formulations

***In-Vitro* Drug Release Study:**

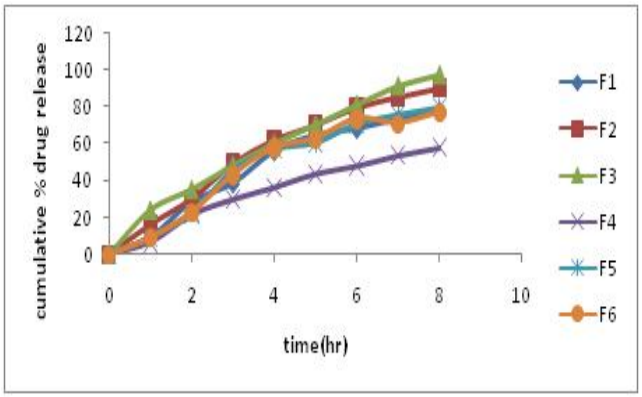

Figure 5: Dissolution Profile of Chitosan Beads Formulations

The in vitro drug release study was performed using dissolution rate test apparatus and 0.1 N HCl (pH 1.2) and phosphate buffer (pH 7.4).The results indicate that the beads were capable of releasing drug up to 8 hours. The 78.12, 90.09, 97.18 57.9, 79.98% and 76.98% of drug was released from the beads F1, F2, F3 and F4, F5 and F6 respectively at the end of 8th hour.

Drug Release Kinetics:

The release data were fitted according to zero order, first order release, Higuchi's equation and Korsemeyer's and Hixon crowel equation and the mechanism of drug release was calculated according to Peppas equation. The values of *n* depend upon the cross-link density and polymer concentration; the *n* values increase with increase in cross-link density and polymer concentration. The calculated *n* values suggest that the mechanism of drug release followed non-Fickian transport. This non-Fickian transport of drug may be due to relaxation of the polymer chains in dissolution medium. On comparing the dissolution profile of formulation F3, and values of drug release kinetics, the best fit model and the drug release by F3 follows zero order kinetics with peppas model and non-Fickian or anomalous diffusion.

Differential Scanning Calorimetry (DSC):

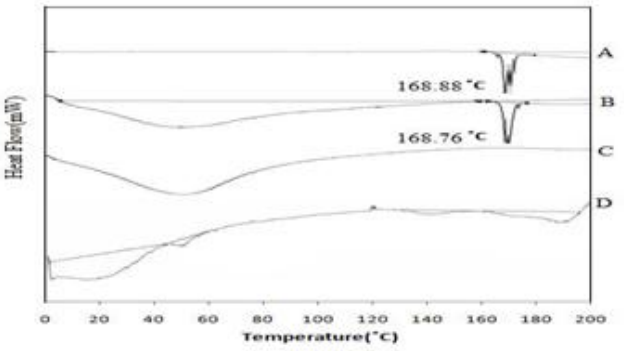

Figure 6: Differential Scanning Calorimetry

Thermograms: The DSC trace of drug showed a sharp endothermic peak at 168.88°C, its melting point. The physical mixture of drug and blank microspheres showed the same thermal behavior 168.76°C as the individual component, indicating that there was no interaction between the drug and the polymer in the solid state. The absence of endothermic peak of the drug at 168.88°C in the DSC of the drugloaded microspheres suggests that the drug existed in an amorphous or disordered crystalline phase as a molecular dispersion in polymeric matrix.

Surface Morphology:

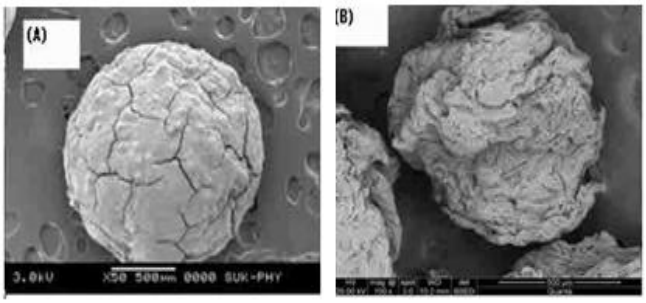

Figure 7: Scanning Electron Microscopic Photographs of Groups of Drug Loaded Chitosan Based Hydrogel Beads. A) SEM Photographs in 0.1N HCL B) SEM Photographs in 7.4 pH PB.

Surface morphology by SEM revealed that the best formulation beads are very spherical with a soft surface. On considering some important parameters like bead size (1025µm), Swelling Index (142.4), Entrapment efficiency (82.21%) and in-vitro drug release study (97.18% for about 8hr); F3 was selected as the best formulation.

Stability Studies:

Table 3: Results of Stability Studies

Number of days	Entrapment efficiency
0	82.25 ± +0.45
15	82.20 ± 0.43
30	83.6 ± 0.36
45	81.0 ± 0.39
90	82.4 ± 0.42

Values are mean ± SD, n=3

The selected formulation was subjected to stability studies and the formulation was evaluated for physical appearance and percentage drug content. The results indicated that at elevated temperature and freezing temperature there was no change in the physical appearance of the beads but insignificant alteration in entrapment efficiency of the hydrogel bead system was found.

Table 4: *In-vitro* Release Kinetics Data

Formulations	Zero order R^2	First order R^2	Higuchi model R^2	Peppas model R^2	Hixson model R^2	n
F1	0.9750	0.9432	0.9901	0.9692	0.8889	0.54
F2	0.9552	0.9928	0.9903	0.9818	0.8858	0.57
F3	0.9938	0.9901	0.9919	0.9958	0.9634	0.60
F4	0.9584	0.9909	0.9941	0.9473	0.8469	0.66
F5	0.9102	0.9833	0.9663	0.9474	0.8190	0.53
F6	0.928	0.968	0.978	0.8345	0.7363	0.46

4. Conclusion

Chitosan-based polymeric hydrogel beads have a wide range of applications and may be used to solve numerous biomedical problems. Chitosan and its derivatives can be easily obtained as beads and also digested by lysozymal enzymes in the digestive tract. Therefore, chitosan and its derivatives can be utilized as a delivery system for a number of drugs, vaccines, hormones, and anti cancer agents to release them in a controlled manner. This concept of chitosan-based polymeric hydrogel bead systems and macro molecular drug formulations is expected to be useful for enhancement of efficacy and minimization of toxic side effects. From the studies reviewed, it is concluded that chitosan and its derivatives as polymeric hydrogel bead

systems are promising materials for controlled drug delivery.

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