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Design of mucoadhesive hydropilic beads entrapped with ketoprofen for delivery into small intestine

R Sivakumar*, NN Rajendran, N Narayanan[a]

Swamy Vivekanandha College of Pharmacy, Elayampalayam -637 205 (T.N.) India
[a]Madras Medical College, Chennai - 600 003 (T.N.) INDIA

ABSTRACT

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The purpose of this study was to develop and evaluate pH dependent multiparticles of ketoprofen loaded mucoadhesive beads to target the small intestine. The hydrogel beads were prepared by inotropic gelation method using sodium alginate, pectin and xanthan gum as polymers. The prepared gel beads were coated with 1 % chitosan. The obtained beads were filled into hard gelatin capsules and enteric coated with Eudragit L100. The beads were evaluated for particle size, morphology, encapsulation efficiency, *in vitro* release, and mucoadhesion. The size of microbeads ranged from 1mm to 2mm and the encapsulation of ketoprofen beads was between 60 to 70%. The *release* of ketoprofen from the gel beads at pH 6.8 was initially fast followed by a slower and more controlled release. The drug release from the beads was found to follow case II transport mechanism (n>0.85) and was independent of time, which corresponds with zero-order kinetics.

Keywords: Ketoprofen, inotropic gelation method, mucoadhesion, small intestine

Corresponding author

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INTRODUCTION

Among modified- release oral dosageforms, increasing interest has currently turned to achieve time specific (delayed, pulsatile) and site specific delivery of drugs[1]. Delivery of drugs to small intestine has assumed significance as one of the site-specific drug delivery systems for drugs which are primarily absorbed in the small intestine that meet with improved bioavailability. Along with many applications in local and systemic delivery of drugs the small intestine would also be advantageous when a delay in drug absorption is desirable from a therapeutic point of view as for the treatment of diseases that have peak symptoms in the early morning and that exhibit circadian rhythm, angina, and rheumatoid arthritis [1,2].

Ketoprofen is widely used anti-inflammatory and analgesic drug. It is used for treatment of muscular skeleton pains of all types of trauma, rheumatoid arthritis, ankolysing spondylitis, acute gout and other pains. The biological half life of drug is about 2-3 h and so requires frequent dosing to maintain the therapeutic effect. Moreover the drug shows better absorption in the small intestine [3,4]. So a controlled and intestine site specific delivery of ketoprofen is beneficial to effectively control the diseases. Of the many approaches, multiparticulate drug delivery is selected in the present study for its known advantages that due to their small size, enable drugs disperse freely in the gastro-intestinal tract which maximizes absorption, minimizes side effects and reduces the inter and intra patient variability.

The microbeads of ketoprofen were prepared by ionotropic gelation method using sodium alginate, pectin and xanthan gum as polymers and zinc chloride as cross linking agent. In the presence of divalent ions (Zn^{2+}), an elastic gel is formed due to ionic interaction between the divalent ions and glucuronic blocks of the polymers. The microbeads were coated with 1% chitosan to increase mucoadhesion of the microbeads for increasing the residence time of the beads in the site and to target the small intestine. The microbeads were enteric coated with Eudragit L100 which dissolves freely in intestinal fluid and releases the microbeads.

The aim of the work was to prepare and evaluate mucoadhesieve controlled release beads using novel polymeric composition to target the small intestine.

EXPERIMENTAL

Materials

Ketoprofen USP was procured from BEC chemicals Mumbai,India.Sodium alginate, Pectin, Xanthan gum and Calcium chloride were obtained from SD Fine Chemicals Mumbai, India. Chitosan (MW 150 kDa) was obtained from Central Fisheries Laboratory,Cochin India. Eudragit L100 was obtained from Loba Chemie Pvt Ltd Mumbai, India. All other materials and solvent used of analytical grade.

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Methods

Preparation of drug loaded beads

The beads of Ketoprofen were prepared by the inotropic gelation method [5,6]. All polymeric solutions (1% w/v each of sodium alginate, pectin and xanthan gum) were prepared by dissolving polymers in de-ionized water to get the viscosity of 45 centipoises. Weighed quantity of ketoprofen was dispersed into aqueous polymeric solution. The resultant solution was introduced drop wise using a syringe kept at a distance of 3cm and at an average rate of 2ml/min, using a nozzle of 0.3mm inner diameter, into a gently agitated solutions of 7.5 % Zinc chloride for 1 h at ambient temperature. The gel beads were separated by filtration, rinsed with distilled water and dried at 40^0C for 30 min. The gelled beads were coated by membrane forming step where the beads were suspended in a solution of chitosan (1 % w/v in acetic acid) for 1 minute at room temperature. The micro beads were allowed to harden for 24 h in a dessicater and filled into the hard gelatin capsules. All the batches were prepared with composition as shown in Table 1.

Coating of capsules

The coating solution was prepared by dissolving 10 g of Eudragit L100 in 100 ml isopropyl alcohol. PEG 200 and titanium dioxide were added and mixed with methanol and methelene chloride solution. The volume of coating solution was adjusted to 100 ml using isopropyl alcohol. Micro beads equivalent to 50 mg of ketoprofen were filled into hard gelatin capsules and coated with the enteric coating solution using dipping and drying technique. At each stage the pellets were kept in an hot air oven for 30 minutes at 45^0C.The capsules were weighed and the weight gain limited to (8 %w/w) indicating completion of enteric coating.

Evaluation Studies

Micromeritics Study, shape and surface morphology [7,8]

Particle size analysis was carried out by using Malvern master sizer. The SEM analysis of microbeads was done sing Jeol Jsm S 300 Scanning electron microscope.

Drug content determination [9]

The amount of ketoprofen present in the microbeads was determined by a hot extraction method [13]. Accurately weighed 50 mg of ketoprofen loaded microbeads were extracted with phosphate buffer (pH.6.8) for 1h by refluxing at 100˚C. It was then cooled to room temperature and filtered. Suitable dilution of the filtrate was prepared and estimated for ketoprofen content at 256 nm by spectrophotometer (Shimadzu UV 1601) against a standard ketoprofen solution exposed to the same extractive condition (Table 2).

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Degree of Swelling [10]

Swelling was measured as a function of pH. The degree of swelling was measured gravimetrically by weighing the particles prior to and after swelling. The dried microbeads were first weighed and then immersed in the phosphate buffer pH 6.8 until equilibrium was reached. Subsequently, they were removed from the buffer solution, carefully blotted with a tissue paper and then they were re-weighed. The degree of swelling (Swelling index) was calculated using the following formula

$$\text{Swelling Index} = W2 - W1 \times 100 / W1$$

Where W1 and W2 are the weight of dry beads and swollen beads respectively.

Drug loading and Encapsulation efficiency [11]

100 mg of accurately weighed microspheres were crushed in a glass mortar-pestle and the powered microspheres were suspended in 25 ml of phosphate buffer (6.8) for 12 h at room temperature to release the entrapped drug. After 12 h the solution was filtered using micro pore filter and the filtrate was diluted and analyzed for the ketoprofen content using UV spectrophotometer at 256 nm wave length. The amount of ketoprofen present in the microspheres were determined using a calibration curve. The drug loading and entrapment efficiency were determined for all batches using Equation (1) and (2), respectively.

Drug Loading % (Actual Drug Content)

$$\text{Drug Loading} = \frac{\text{Weight of ketoprofen in microbeads}}{\text{Microbeads sample weight}} \times 100$$

Encapsulation efficiency % (EE)

$$EE = \frac{\text{Actual weight of ketoprofen in beads}}{\text{Theoretical weight of ketoprofen in beads}} \times 100$$

Test for Mucoadhesion [12, 13]

Mucoadhesieve properties of the Ketoprofen multiparticles were evaluated using everted sac technique. The animal study protocols have been approved by the International Animal Ethical Committees (IACC meeting proposal, Ref No: 14/243, Dated 26.2.2008, Madras Medical College, Chennai-3).Un fasted rats(400g,male) are sacrificed and intestinal tissue was exercised and flushed with 10 ml of ice cold phosphate buffered saline, pH 7.2 containing 200mg /dl glucose(PBSG). 6 cm segments of jejunum were everted using a stainless steel rod and lightly washed with PBSG to remove the contents. Ligatures were placed at both ends of the segment and the sac was filled with 1-1.5 ml of PBSG. Tissue was maintained at 4 C prior to incubation. The sac was introduced into a 15 ml tube containing

60 mg of bioadhesieve multiparticles and 5 ml of PBSG. The sacs were introduced into a 15 ml glass tube containing 60 mg of microspheres and 5 ml of PBSG. The sacs were incubated at 37 C and agitated end - over - end. After 30 min the sacs were removed, and the solution of PBSG and unbound microparticles was centrifuged for 30 min. The supernatant fluid was discarded. The sedimented particles were washed three times with 5ml of distilled water and centrifuged for 30 minutes. The multiparticles were dried by lyophilization for 24 h . The weight of the bound particles was determined by subtraction of the tarred weight of the tube and lyophilized particles. The results are expressed as percent binding (Table 2).

***In- vitro* release studies [14-17]**

The in vitro drug release studies of ketoprofen carried out using USP dissolution apparatus type1 (Basket type) at 50 rpm at 37˚C ±0.50˚C using 0.1 N Hcl for 2 h and phosphate buffer (pH 6.8) for 10 h . From each batch 50 mg of ketoprofen multiparticles containing enteric capsules were taken and subjected to dissolution studies. 5 ml of dissolution medium was withdrawn at every 1 hr and the medium was replaced with equal quantity of fresh dissolution medium. The sample withdrawn was suitably diluted and ketoprofen content was analyzed spectrophotometer at 256nm.(Fig.1)The experimental results were fitted to the exponential equation proposed by the Ritger and peppas.

RESULTS AND DISCUSSIONS

Chemical reaction between sodium alginate / pectin / xanthan gum and zinc chloride to form zinc alginate or pectinate was utilized for micropellets of ketoprofen. In this case xanthan gum were used to regulate the drug release pattern. The acceptable range for angle of repose is between 20° to 30°. In all cases microbeads are characterized by a nearly spherical in shape with rough surface. As previously found in other studies one can observe that the presence of drug generally results in an increase of particle size, this behavior can be possibly related to a corresponding increase in the precursor of droplet size [14] . The loading capacity ranged from ~50 % to ~ 69 %. The drug entrapment efficiency of all the formulations was in the range of 60 % to 70 % as shown in Table 2. The drug entrapment efficiency of microbeads increasing with increase in concentration of polymers. The higher entrapment efficiency of ketoprofen may be related to its lower aqueous solubility. The drug showed poor drug leakage to the external aqueous medium. The ketoprofen release profile from microbeads is characterized by an initial phase of rapid drug release followed by a more gradual release. The initial burst effect can be attributed to the release of drug encapsulated near the microbeads surface and is clearly related to the drug loading in the microbeads. higher drug release can be justified by the smaller mean sizes of beads..The ability of polymeric matrix to absorb enough water is an important factor in the form of the gel layer, which controls the drug release. From the analysis of swelling data, it was possible to conclude that the polymers under investigation accept water at different rates. The microbeads did not show any drug release during the initial 2 h in the acidic medium due to enteric coating. But once the pH was changed to 6.8 drug release started. The prepared gel beads (D1, D2, D3, D4,D5 ,D6) having a coat of 1% chitosan at the end of the 14 h the drug release was found to be 90.13±1.43,87.50±1.92,80±1.63,78.80 ±2.33,77.90±1.56,75.60.±1.22. The r values of zero order plot were between 0.975 to 0.987 and first order plot between 0.915 to 0,968.The r values indicate all these formulations

followed zero order kinetics. The release mechanism of each drug in all the formulations was initially characterized in terms of the different exponent, n. The entire exponent values lie between 0.908 and 1.246.In the geometry of the formulations, these n values signify a non-fickian or anomalous mechanism (case 11 transport) of drug release. In the anomalous process of drug, diffusion through the hydrated layer of the polymeric matrix and polymeric chain relaxation /erosion are both involved. The contribution of these two mechanisms to the overall release is considered to be addictive. The bio/mucoadhesion test for all the formulations were performed by everted sac technique. The percent bioadhesion for D1 – D6 was increased from 42.2±3.6 to 57.3±4.1.It indicate increase in polymer concentration, the percent bio adhesion increases.

Table 1: Composition of Ketoprofen Beads

S. No	Composition	1:1 (g)	1:2 (g)	1:3 (g)	1:4 (g)	1:5 (g)	1:6 (g)
1	Ketoprofen	1.00	1.00	1.00	1.00	1.00	1.00
2	Sodium alginate	0.70	1.40	2.10	2.80	3.50	4.20
3	Pectin	0.20	0.40	0.60	0.80	10.00	12.00
5	Xanthan Gum	0.10	0.20	0.30	0.40	0.50	0.60

Table 2: Physico-chemical characterization of ketoprofen beads

Code	Drug: Polymer	Particle size (mm)	Loading Capacity (%)	Entrapment Efficiency (%)	Swelling (%)	Bio adhesion (%)
D1	1:1	1.60±0.4	50.32±6.4	60.21±7.9	09±1	42.2 ±3.6
D2	1:2	1.64±0.3	53.14±6.9	63.14±4.3	13±2	50.4±4.7
D3	1:3	1.68±0.2	57.36±5.3	67.36±8.2	19±2	51.0±2.9
D4	1:4	1.73±0.3	61.81±6.1	71.81±5.3	22±3	54.3.±4.3
D5	1:5	1.75±0.2	65.47±5.0	75.47±3.8	32±4	56.4±5.6
D6	1:6	1.81±0.3	69.68±9.3	79.68±6.5	35±3	57.3±4.1

CONCLUSION

The study revealed that the multiparticulate enteric beads prepared with combination of sodium alginate, pectin and xanthan gum with chitosan coating can be suitable for mucoadhesive controlled release of ketoprofen to target the small intestine

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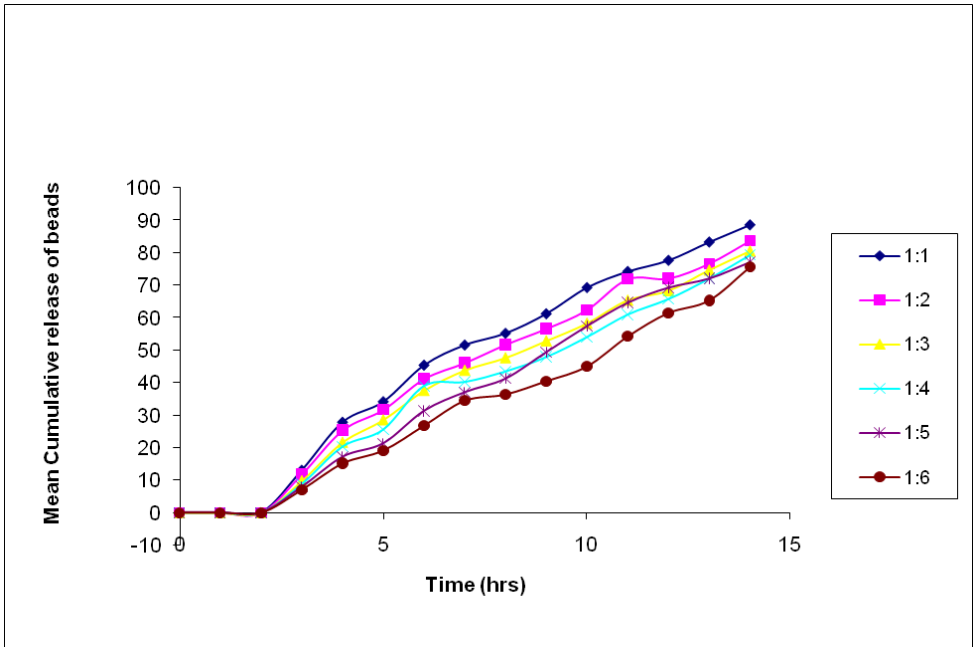
Fig 1



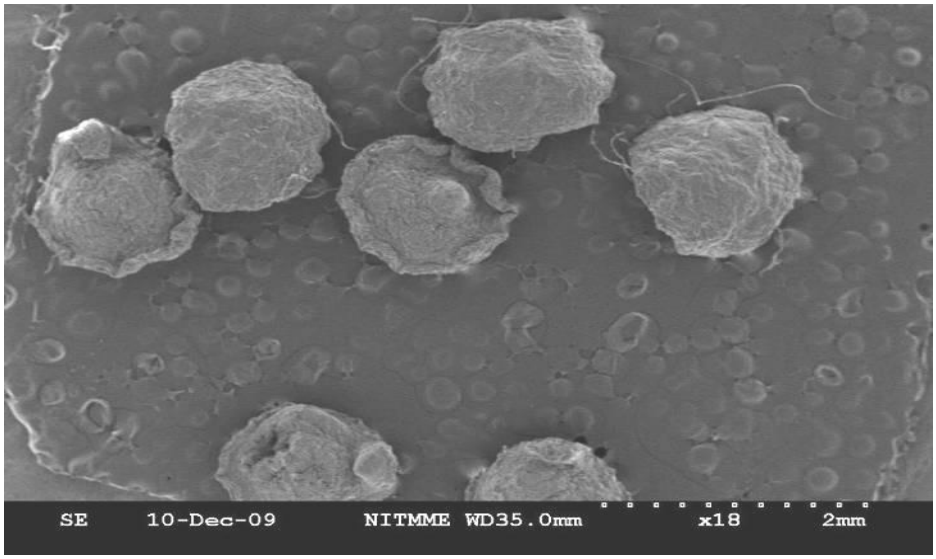


Fig.2. SEM Photograph of dry beads

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