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Development and evaluation of sodium alginate-based ketorolac tromethamine floating beads for sustained drug delivery system

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Abstract
The study aimed the preparation of floating beads of sodium alginate by using ionotropic gelation method, which is used to prepare sodium alginate floating beads of Ketorolac tromethamine. The influence of various formulation factors such as *In vitro* drug release, entrapment efficiency, and drug content and floating properties was investigated. The entrapment efficiency were found in range of 60-100 the particle size were found in range of 500-600mm this suggest the ionotropic gelation method was successful in producing sodium alginate floating beads of Ketorolac tromethamine.

Keywords: sodium alginate, calcium carbonate, Ketorolac, tromethamine, ionotropic gelation technique

Introduction
A drug delivery system release the drug in the particular body compartment at the controlled rate required for a specific treatment. Now a day's most available drug delivery system use bio-degradable, biocompatible and natural bio-polymer and are capable of rate controlled drug release efforts is being solid dosage form researchers developed various sustained and controlled release form by entrapped the drug natural polymer and forming a gel. The floating beads have been employed to make a sustained release of the drug in the stomach and to decrease the dose of the drug and hence overcome it's side effect. The common benefits of the floating beads were it is easy preparation, without the need of a high temperature and high percentage of the drug entrapment. Gastric residence time is an important parameter for different dosage forms and the prolongation and control of this time, epically for a longer period of time result in better absorption and enhances bioavailability.

The floating drug delivery systems are low density, matrix type system designed by the addition of some polymers such as cellulose derivatives, polysaccharides, carbopol and chitosan and different effervescent component like sodium bicarbonate, calcium carbonate, citric acid or tartaric acid.

Alginate beads have been designed in the present study as vehicle for drug delivery system. Alginate is a hydrophilic polymer, stable in acidic media and easily depredated in alkaline media. These properties have enabled widespread use of alginate beads in gastro-retentive dosage forms for sustained release of drug. Ketorolac tromethamine is a potent non-steroidal anti-inflammatory drug with biological half-life ranged from 4 to 6 hours and it is mainly absorbed in the proximal part of small intestine. KT is 800 times more potent than aspirin and produces strongly analgesic and moderate anti-inflammatory activity.

The main principle of floating beads can be applied to decrease the irritant effect of KT on the stomach by avoiding the direct contact with the gastric mucosa and obtaining a low dosage for prolonged periods. The aim of the present work is to prepare KT in different floating calcium alginate beads to control the drug release using calcium carbonate as a gas forming agent. The influence of hydroxypropyl cellulose, sodium carboxymethyl cellulose, methyl cellulose and pectin as hydrophilic co-polymer

Advantage
1. The floating bead loaded with the antibiotics is useful for the oral administered for the treatments of gastric and intestinal diseases.
2. The floating beads can be applied to decrease the irritant effect
3. It is an increased the gastric residence time and better control of the variability in the plasma drug concentration.
4. Piperine was fabricated into alginate beads using sodium alginates.

Disadvantage
1. It is always higher in cost.

Method of preparations-
Floating beads can be prepared by the following method-
1. Ionotropic gelation technique
2. Cross-linking
3. Extrusion congealing method

Following these some methods shows many a disadvantage-
- Easy and mild, inexpensive preparation techniques.
- No organic solvent or high shear force to be used.
- These method would be use for broad categories of drug such as macromolecules, protein, others.
- Stable

Steps involved in the preparation of floating beads
1. Ionotropic Gelation Technique
Weigh accurately all the materials including the drug used, sodium alginate and calcium chloride. Distilled water is added to the weighed quantity of sodium alginate to make mucilage pest and allowed to heat for 5-10 minutes in a Hot plate. After that, distilled water is also added to the weighed

quantity of calcium chloride to make a solution. The mucilage past of sodium alginate is then stirred in a magnetic stirrer at a suitable speed for several minutes. Then the drug and calcium carbonate is dispersed in the mucilage pest of sodium alginate and stirred at suitable speed in the magnetic stirrer. The floating beads are formed by dropping the mucilage pest in a calcium chloride solution in it through a glass syringe with the help of a needle. Then the solutions are allowed for few hrs. and then filtered & washed thoroughly with the distilled water, and dried at room temperature subsequently for few hours.

2. Cross-linking

The cross-linking polymer solutions of the different concentration were prepared by dissolving in water under slow agitation. The drug was added in the polymer solution under constant stirring for 2 minutes for uniform distribution throughout the solution. Finally, drug and polymer solution was extruded drop wise through a 1.2 mm diameter needle into stirred calcium chloride solution at room temperature and then floating beads were formed and beads were allowed to remain in the stirred solution for 10 min curing time. Then the floating beads were filtered and washed with distilled water and beads dried at room temperature.

3. Extrusion congealing method

The stock solution of KT was prepared by dissolving the drug in 5 ml of water. The KT solution then was added to 95 ml sodium alginate solution containing some co-polymer such as pectin, sodium carboxymethyl cellulose, methyl cellulose. Calcium carbonate was added to sodium alginate solution in a ratio of 1:1 and the mixture dropped using syringe needle into 100 ml of calcium chloride solution (1%w/v) which contains glacial acetic acid(10%v/v). Then the beads formed in the solution were stirred for 10 min to improve its hardness. After that the beads were collected and washed with distilled water, then dried for 48 h.

Objective

1. To optimize sodium alginate concentration for formulating floating beads.
2. To formulate Ketorolac tromethamine floating beads.
3. To evaluate the Ketorolac tromethamine floating beads for different parameter.
   (Particle size, Entrapment Efficiency, Drug content, % drug release)

Literature review

1. Patil P. *et al.* (2012) [12] have formulated Ionotropic gelation method to achieve a pharmaceutical product with desired characteristics. Ionitropic gelation is based on the ability of polyelectrolyte's counter ions to cross link to form hydro gels. Naturally occurring polysaccharides use as biopolymers has been increased in the novel areas such as hydro gel sustained release formulation, thus providing an ecofriendly pharmaceutical product development process. This review focused on recent developments of multiple-unit floating drug delivery system approaches based on Ionotropic gelation method, polymer used and factors affecting on method of ionotropic gelation
2. Patel G. *et al.* (2012) have formulated Micro-pellets of verapamil hydrochloride by ionotropic gelation technique using sodium alginate, hydroxy propyl methyl cellulose and hydroxy propyl cellulose. Prepared micro-pellets were evaluated for flow behavior, drug entrapment efficiency, *In vitro* dissolution and stability studies, including scanning electron microscopy and optical microscopy. Of the nine formulations prepared and evaluated formulations F3, F6 and F9 were found to show satisfactory result. The release of the drug from the micro-pellets was found to be following Non-Fickian diffusion, drug diffusion coefficient and correlation coefficient were also assessed using various mathematical models. From the study it was concluded that, prolonged release Verapamil hydrochloride micro-pellets can be achieved with success using ionotropic gelation technique.
3. Ghosh S. *et al.*(2010) [16] have formulated the micro-beads were prepared by an industrially feasible micro orifice ionotropic gelation method using glutinous rice starch from Assam Bora rice, and sodium alginate backbone with different cross-linking agent. The micro-beads fabricated through several preformulation trials were evaluated in reference to drug release, drug excipients compatibility and mucoadhesive potential. The effect of various formulation and processing parameters was studied by scanning electron photomicrographs taken before and after dissolution. Photomicrographs provides information about the surface texture, size, mechanistic properties, suitability of drying condition and mechanism of drug release from the prepared micro device.
4. Kohli K. *et al.* (2015) have formulated of alginate beads loaded with ranitidine hydrochloride by employed ionotropic gelation technique. The beads were prepared by varying the formulation and processing parameter such as concentration of calcium chloride solution and curing on drug entrapment efficiency was investigated. It was observed that the encapsulation efficiency of hydrophilic drug. Moreover, it was also found that curing time influenced the leaching of hydrophilic drug.
5. Rajeshwar V. *et al.* (2016) have formulated and evaluate alginate micro-beads of Propranolol hydrochloride by using ionotropic gelation technique. The prepared micro-beads were evaluated for various parameters like particle size, entrapment efficiency, surface area, *In vitro* drug release, X-Ray diffraction analysis, etc. It was found that all formulations showed improve flow behavior as compare to pure drug, it was observed that on increasing the polymer concentration of formulations the entrapment efficiency and particle size were increased. The surface morphology study by SEM indicated that micro-beads were spherical with rough outer surface. There was no interaction between the drug and the polymer, as studies by FTIR study. Therefore, it can be concluded that Propranolol Hydrochloride loaded algino-chitosan micro-beads can be formulated for sustained drug delivery of Propranolol Hydrochloride.
6. Mandal S. *et al.* (2010) have formulated the objective of this study was to develop a sustained release form of Trimetazidine dihydrochloride (TMZ) using a natural polymeric carrier prepared in a completely aqueous environment TMZ was entrapped in calcium alginate beads prepared with sodium alginate micro-beads. The drug was incorporated either into preformed calcium alginate gel beads (sequential method) or incorporated

simultaneously during the gelation stage (simultaneous method). The beads were evaluated for particle size and surface morphology using optical microscopy and SEM, respectively. Beads produced by the sequential method had higher drug entrapment. Drug entrapment in the sequential method was higher with increased CaCl2 and polymer concentration but lower with increased drug concentration were increased and also rose to a certain extent with increase in CaCl2 concentration, where further increase resulted in lower drug loading. FTIR studies showed that the crystalline drug changed to an amorphous state after formulation. Release characteristics of the TMZ loaded calcium alginate beads were studied in enzyme-free simulated gastric and intestinal fluid.

Drug profile
Drug name: Ketorolac tromethamine
Structure:

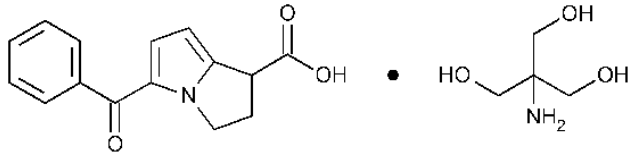


Fig 1

Solubility: Highly soluble in water, 25mg/mL
Molecular formula: $C_{15}H_{13}NO_3$
pH: 6.5-8.5
Melting point: 165-167° C
pka: 3.5
Indication: Acute pain in adult patient. Also as an anti-inflammatory, analgesic, antipyretic.
Pharmacodynamic: Ketorolac is traditional non steroidal anti-inflammatory drug (NSAID) widely used for its analgesic, anti-inflammatory & anti-pyretic.
Mechanism of action: The primary mechanism of action responcible for ketorolac anti- inflammatory, anti- pyretic, analgesic effect is the inhibitory of prostaglandin Synthesis by competitive blocking of the enzyme cyclooxygenase.
Volume of distribution: 0.1-0.3 L/kg
Protein binding: >99%
Route of elimination: The route of elimination of ketorolac and its metabolites is renal. About 92% of a given dose is found in the urine, approximately 40% as metabolites and 60% as unchanged ketorolac.

Materials and Methods
Materials: All material obtained from given chart.

Table 1

Sr No	Chemicals	Mfg
1	Ketorolac tromethamine	FDC. LTD. Mumbai
2	Sodium alginate	SD Lab Fine Chem. Industries Mumbai
3	Calcium chloride	Lab. Chem. Mumbai
4	Calcium carbonate	Lab. Chem. Mumbai

Methods
Preparation of KT floating beads
Stock solution of Ketorolac tromethamine was prepared by dissolving 100 mg in 5 ml of water. The Ketorolac tromethamine solution then was added to 95 ml sodium alginate solution, (1% w/v) (1 gm of sodium alginate is dissolved in 95 ml water with heating) cool the solution. The sodium alginate and calcium chloride are taken in 1:1 ratio.
Then dispersed the calcium carbonate in sodium alginate solution.
The calcium chloride solution prepared by taking 1 gm(1% w/v) $cacl_2$ in 100 ml of distilled water which contains glacial acetic acid (10% v/v) The mixture is dropped using 5 ml syringe needle into the $cacl_2$ solution Then the beads formed in the solution were stirred for 10 min to improve its hardness. After that the beads were collected and washed with distilled water, then dried for few hours. The different formulations of Ketorolac tromethamine are presented in Table 2.

Table 2: Formulation table (processing parameter) Formulation table

Formulation Code	Sodium alginate (mg)	Calcium carbonate (mg)	Ketorolac tromethamine (mg)	Cross-linking Agent (% w/v)	Stirring speed (rpm)	Curing time(h)
F1	1000	750	100	1%	500	1
F2	1500	750	100	1%	500	1
F3	2000	750	100	1%	500	1

Characterisation of beads
Particle size
Average particle size of beads was determined using optical microscope fitted with calibrated ocular & stage micrometer & particle size distribution was calculated 50 particles in five different fields were examined.

Percentage yield
Determination of percentage yield, drug loaded (DL) encapsulation efficiency of the prepared beads. Percentage yield for the formulated beads was calculated from the following equation

Yield% = Weight of the beads/weight of drug + polymer weight x100

Floating time & buoyant time
Specified weight (50 mg) of floated beads was placed in a beaker containing 100 ml of buffer 1.2 pH and shacked at 50 rpm in a water bath 37 ± 0.5 °C. The time taken by beads to float on the surface was determined (lag time).
The layer of the floated beads was removed and the layer at the bottom was separated by filtration. The upper and the lower layers were dried at 40 °C until constant weight. Buoyant time was calculated by the Following equation:

(%) floating = weight of floated beads (Wf) /weight of floated beads (Wf) +weight of settled beads (Ws) x100

Entrapment efficiency
Twenty-five milligrams were weighed of the KT prepared

beads and were dissolved In 50 ml of buffer pH 1.2 centrifuged, filtered and then the filtrate was analyzed at 322 nm using a UV/visible spectrophotometer the experiment was carried out in triplicate and drug loading was calculated from the following equation

Drug loading = Weight of drug in beads/Total weight of beads X 100

Percentage encapsulation efficiency was calculated using the

Following formula

The encapsulation efficiency was determined from the following Equation= actual amount of drug (AQ)/theoretical amount of drug (TQ) x100

% Drug content

Determination of drug content the 30 mg of drug containing beads are triturated & Dissolved in 100 ml (PBS 6.8) solution. Filter this solution & measure the absorbance determines using spectrophotometrically at 323 nm.
Percentage of drug content = (Actual drug content of bead / Theoretical drug Content) x100

Drug Release study

The drug release behavior of the floating beads was evaluated in the phosphate buffer with the PH value 6.8. The basket method (USP type I dissolution test apparatus) was used to conduct the dissolution tests and each experiment was performed in triplicate. The basket position set from the bottom of the flask and the speed was adjusted to 50 rpm. The *In vitro* dissolution studies were carried out in 900 ml of phosphate buffer maintained at 37 ± 0.5° C. Floating beads containing 30 mg of the drug were employed in each case. Aliquots of 5 ml were withdrawn And immediately replaced with 5 ml of dissolution medium to maintain a constant Volume of 900 ml. The sample were taken at the following time intervals: 0, 1, 2, 3, 4, 5, 6 h respectively. The sample were filtered through a Whatman filter paper and the absorbance was determined at 323 nm, UV-VIS Spectrophotometer against an appropriate buffer as a blank.

Result and discussions

Calibration curve of ketorolac tromethamine

Standard curve of ketorolac tromethamine is carried out in water because the KT is highly soluble in water at 323 nm was plotted using various concentration against the absorbance values found at respective concentration. The standard curve of KT was found to linear range 2- 12 ug/ml, which means that the present drug sample was obeying beer- lamberts range and coefficient of correlation was found to be 0.997. The observation of calibration curve are shown in table 3, the plot of calibration curve shows in figure 2 and the statistical parameter from the calibration curve are mentioned in the table.

Observation for standard curve of Ketorolac tromethamine

Table 3: Calibration Curve

Concentration	Absorbance
1	0.053
2	0.136
3	0.176
4	0.241
5	0.306
6	0.363
7	0.415
8	0.472
9	0.545
10	0.605

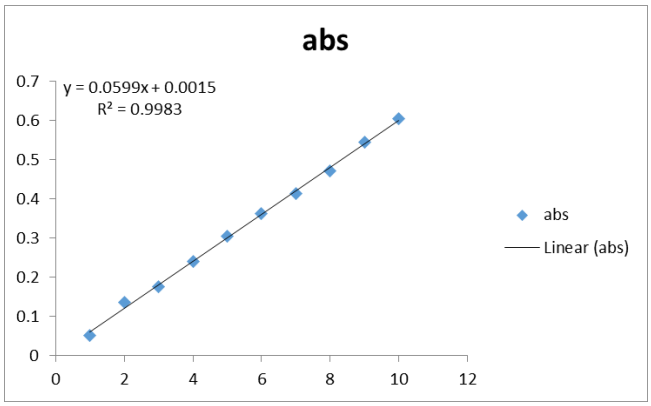


Fig 2: Calibration curve of KT

Particle size determination

The results of particle size of all formulations are depicted in table 4. All formulations of sodium alginate floating beads showed the particle size between 500 to 600 mm. The higher particle size was obtained with formulation F3 i.e. 573 mm. The result also suggest that increasing concentration of sodium alginate in formulation does not affect on particle size.

Table 4: Particle size determination

Formulation code	Particle size(mm)
F1	541.38
F2	536.62
F3	573.5

% Entrapment efficiency

The% drug loading of various beads was ranged from 68% to 119.72% for F1 and F3, respectively, while the % encapsulation was 68.0% for (F1) and 119.72% for (F3). Results indicated that the drug loading and drug content were increase for beads composed of sodium entrapment efficiency alginate (F1) to (F3).
The result demonstrated that effect on % entrapment efficiency with increasing concentration of sodium alginate. The % entrapment efficiency study suggest that the higher particle leads to maximum % drug content entrapment

efficiency of some of formulation of floating beads in formulation F2 & F3 produced higher capacity of drug to drug release in floating beads due to higher particle size.

Table 5: % Entrapment efficiency

Formulation code	% Entrapment efficiency
F1	68.84
F2	98.1
F3	119.72

%Drug content

The % drug content of entire formulation of sodium alginate based floating beads of Ketorolac tromethamine was showed in table 6. All the formulation of floating beads produced the optimum drug content in the range of 16.9-44%. The minimum drug content (%) was obtained for formulations F1. The higher percent drug content was found to be in formulation (F3) i.e. 44%

Table 6: % Drug content

Formulation code	% Drug content
F1	16.9
F2	30
F3	44

Floating lag time & buoyant time

The results showed that all prepared beads had lag time from 72 to 240 s and also from 62.31% to 80% of beads remained floated for 6 h.

Table 7: %Floating

Formulation code	Floating lag time(S)	% Floating after (6h)
F1	72	76.19
F2	160	80.15
F3	240	62.31

In vitro dissolution study

The *In vitro* drug release of Ketorolac tromethamine from sodium alginate based floating beads was carried out in USP dissolution apparatus type –I (basket type).

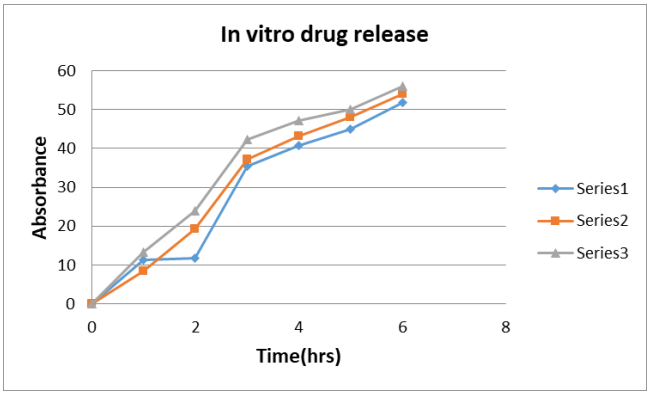
The results of *In vitro* release study are presented in table 8 and fig 3. The drug from floating beads showed maximum in formulation F3 i.e.56.1 at 6 hrs.

The minimum drug release was obtained in formulation F2 i.e. 8.4%.

This is due to general rule, such as smaller size of floating beads provide large surface area for higher drug release.

Table 8: *In vitro* drug release study

Time (hrs)	F1	F2	F3
0	0	0	0
1	11.25	8.4	13.2
2	11.73	19.2	24
3	35.33	37.2	42.3
4	40.7	43.2	47.1
5	45	48	50.1
6	51.9	54	56.1



(F1-Series1, F2-Series2, F3-Series3)

Fig 3: *In vitro* drug release study

Conclusion

In the present study floating beads of Ketorolac tromethamine were formulated to achieve sustained release of the drug. The sodium alginate beads showed better loading and floating characteristics and the release studies revealed that the beads exhibited sustained drug release. The ionotropic gelation can be used in producing Ketorolac tromethamine sodium alginate floating beads. The formulation variable, drug loading, polymer concentration, cross – linking agent, stirring speed and curing time influenced the mean particle size, entrapment efficiency drug content and *In vitro* drug release characteristics of the prepared floating beads. Results obtained from ionotropic gelation method showed a good agreement with those obtained from the hot plate method and revealed the sustained analgesic effect of the drug for more than 6 h.

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