Research Article

Preparation of Alginate Gel Beads Containing Metformin Hydrochloride Using Emulsion-Gelation Method

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Abstract

A new emulsion gelation method was used to prepare gel beads for a highly water-soluble drug metformin hydrochloride using sodium alginate as the polymer. The gel beads containing oil was prepared by gently mixing or homogenizing oil and water phase containing sodium alginate which was then extruded into calcium chloride solution to produce gel beads. The effects of factors like type of oil and percentage of oil on the morphology and release characteristics were investigated. A variety of oils were used to study the effect on the sustaining property of the formed beads. The oil entrapped calcium alginate gel beads showed good sustained release. Scanning electron photomicrographs demonstrated minute oil globules on the beads and also through the inner surface of the beads. The beads also showed floating behavior depending on the type of the oil that have been used for the preparation.

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Introduction

Metformin hydrochloride is an antidiabetic drug used to treat non-insulin dependent diabetes mellitus (NIDDM-Type II diabetes), alone or in combination with other hypoglycemic agents. This drug in monotherapy is used, as an adjunct to diet to lower blood glucose in patients whose hyperglycemia cannot be satisfactorily managed on diet alone\(^1\). The recommended dosing schedule for the drug involves dose escalation with each dose given with meals. This allows metformin to be better tolerated, as gastrointestinal symptoms usually associated with therapy may be minimized. It has been reported in the physician desk reference electronic library release 2000 that food decreases the extent and slightly delays the absorption of Metformin.

In the present investigation, an extended and controlled release composition and formulation of metformin hydrochloride capable of providing detectable blood levels over 10 hr was formulated using expandable, gelling, swellable hydrocolloid polymer along with the variety of oils. The polymer used was sodium alginate, which is an inexpensive, nontoxic product extracted from kelp. Sodium alginate has been used as thickening and gelling agent. Additionally it also reduces interfacial tension between an oil and water phase and is efficient for preparation of emulsion. Alginate is a linear co-polymer composed of two monomeric units. D-mannuronic acid and L-guluronic acid. These monomers occur in the alginate molecule as regions made up exclusively of one unit or the other, referred to as M-blocks or G-blocks, or as regions in which the monomers approximate an

![Figure 1: Comparative release profile of gel beads](image-url)
alternating sequence. The calcium reactivity of
alginate is a consequence of the particular
molecular geometries of each of these regions \(^2\).
Sodium alginate is capable of forming rigid gels
by the action of calcium ion or multivalent
cations. Although it is relatively easy to describe
alginate in terms of M and G units but the
detailed molecular compositions of alginates in
terms of block lengths and block distributions are
much more difficult to determine.

The use of oil entrapped calcium pectinate
beads has been used in various ways for
sustained release of drugs or for the targeting
drugs to colon\(^3\). Theophylline tablets composed
of mineral oil entrapped agar for the controlled
release have been reported\(^4\). Calcium alginate
emulsion beads for extended release
formulations have not been tested. The effects of
factor like type of oil, percentage of oil on the
prepared beads were investigated.

**Materials and Methods**

Sodium alginate was obtained from CDH, New
Delhi, and Metformin hydrochloride was donated
by Sun Pharmaceuticals, Baroda. Light mineral
oil, castor oil, vegetable oil and mentha oil were
of standard pharmaceutical grade and all other
chemicals used were of analytical grade.

**Preparation of gel beads**

Conventional alginate beads were prepared by
ionotropic gelation method. Sodium alginate was
dissolved in 50 ml of water with gentle agitation.
Drug (1g) was added and mixed thoroughly. This
was then extruded into 5% calcium chloride
solution with gentle agitation at 37°C. The
formed beads were allowed to stand for 5 min in
the solution, separated and then filtered, and
dried overnight at room temperature.

The oil entrapped calcium alginate beads were
prepared by emulsion gelation method. Polymer
was dissolved in water with stirring. Selected oils
(5ml) were added to polymer solution. 1g of the
drug was added. The homogenized or non-
homogenized mixture was extruded into 5%
calcium chloride solution with gentle agitation at
room temperature. The formed beads were
allowed to stand for 5 min in the solution,
separated by filtration, and dried at room
temperature.

**Size distribution and size analysis**

Gel beads were separated into different size
fractions by sieving for 10 min using a
mechanical shaker containing standard sieves
having as per Indian pharmacopoeia. The
particle size distribution was determined and
mean particle size of gel beads was calculated
by the formula

\[
\text{Mean particle size} = \frac{\sum (\text{Mean particle size of the fraction} \times \text{weight fraction})}{\sum (\text{Weight fraction})}
\]

**Study of morphology of gel beads**

The mean diameter of 50 dried beads and
morphological examination of dried beads were
performed using optical microscopy.

**Scanning electron microscopy (SEM)**

The samples for the SEM analysis were
prepared by sprinkling the gel beads on one side
of the double adhesive stub. The stub was then
coated with fine gold dust. The gel beads were
then observed with the scanning electron
microscope (Leica Electron Optics, Cambridge,
USA) at 15kv.

**Measurement of floating property**

For the evaluation of floating property,
approximately 100 beads were counted and
pasted to one side of the glass slide secured to
the USP disintegration apparatus. The apparatus
was run for 5 hrs and at predetermined interval
(30 min), the slide was taken out and the number
of beads still adhering to the slide was counted.

**In vitro release studies**

The in vitro release studies of the drug
incorporated gel beads were carried out at 37±
5°C and at 100 rpm using phosphate buffer pH
7.4 (200 ml) in sink conditions using a Diffusion cell. Accurately weighed samples of gel beads were added to the donor cell and at pre-set intervals; 5ml of aliquots are withdrawn and replaced by an equal volume of fresh dissolution medium. The aliquots were analyzed spectrophotometrically at 233 nm after proper dilution if required.

Results and Discussion

The formation of gel beads of calcium alginate using various oils is a simple and rapid process. The incorporation of oil into the drug-alginate solution was done with and without homogenization. Without homogenization, oil started being separated out and uneven sized beads were formed. On increasing the homogenization time, the size of the beads formed decreased and size uniformity was obtained. The concentration of drug and polymer throughout the study was kept constant but type of oil utilized was altered.

The beads prepared using castor oil and vegetable oil were off white in color, owing to original color of oil phase and those prepared using mentha oil were light brown in color.

The mean diameter of conventional calcium alginate beads was 780 to 900 µm whereas that of the oil entrapped formulations ranged from 840 µ to 1.1 mm. The results show that the amount of oil affected the morphology of beads. An increase in concentration of oil caused increase in size and sphericity of the beads, which could be due to their density and volatility. The higher the density of the oil used, the larger was the size and better the spherical nature. As the density of oil decreased the volatility increased. When the beads were dried, the higher volatile oil evaporated quickly leading to uneven sphere production and also greater loss of original size of the beads.

As seen from the increase in size of the beads, it was evident that alginate shows emulsifying property by its surface-active ability to reduce the interfacial tension between an oil and water phase. During the homogenization process fine dispersion of oil and water phase was obtained. When this emulsion was extruded in calcium chloride solution, the gel was formed by the action of calcium on negatively charged groups of alginate. The prepared beads were analyzed by optical microscopy and Scanning electron microscopy for their surface and size analysis. Sponge like internal structure was seen with a few crystals of drug on the surface. Oil filled pores were visible on the surface with size ranging from 0.5 to 49 µm (Figure 2). The uneven size of the pores could be due to the coalescence of the oil droplets during the gelling process. The release profile indicates that the sustaining action was more pronounced with liquid paraffin followed by groundnut oil> castor oil> mentha oil> conventional alginate beads. As compared to conventional (no oil) beads, the release of the drug was sustained sufficiently for more than 8hrs in simulated gastric juice (without pepsin).

Figure 2: Alginate beads showing presence of oil filled pores on the surface of gel beads (a) and alginate gel bead showing drug particle on the surface (b)

An additional property of buoyancy was observed for the oil-entrapped beads, which was due to incorporation of oil having density less than water. The lower the density of the oil, the lesser was the amount of the oil required to give it a buoyant nature.

The effect of addition of oil in the formulation created an additional barrier. The model chosen drug Metformin hydrochloride is a very high water-soluble drug. Formulation of an extended release dosage form for such a highly water-
soluble drug with high dose is difficult and causes increase in bulk. The pores of the beads containing oil limited the release of drug. This could be attributed to an additional diffusion layer to the release of the drug. The SEM picture shows the presence of oil droplets throughout the alginate matrix. The initial burst effect seen was due to some amount of the drug, which might have been dragged to the surface during the processing. When calcium ions are added to a sodium alginate solution, alignment of the G-blocks occurs; and the calcium ions are bound between the two chains like eggs in an egg box. Thus the calcium reactivity of algins is the result of calcium-induced dimeric association of the G-block regions. Depending on the amount of calcium present in the system, these inter-chain associations can be either temporary or permanent. With low levels of calcium, temporary associations are obtained, giving rise to highly viscous, thixotropic solutions. At higher calcium levels, precipitation or gelation results from permanent associations of the chains.

When a drug is incorporated in a hydrophilic matrix, it swells upon ingestion and the gel layer forms on the surface. This gel layer fills the interstices. Dissolution rate of soluble drugs is controlled by both diffusion through the gel layer and by matrix erosion as seen from the release kinetics values (Table1). The data show that the release mechanism is chiefly by zero order kinetics. The release of cationic drugs is more retarded than anionic drugs, which could be due to the electrostatic interaction between the negative charge of the ionized carboxyl group in alginate chain and positive charge of the cationic drug\(^7\). Metformin is a cationic drug, thus its release could be retarded by an interaction with alginate. By the use of alginate and employing oil entrapment technique, even a highly water-soluble drug can be retarded in the stomach.

**Conclusion**

A new sustained release system of oil entrapped calcium alginate beads were designed and prepared by an emulsion gelation method and it’s morphological and release characteristics were studied. The prepared beads were easy to prepare and the mean diameter of beads increased with increase in the amount of the oil phase. The pore size of oil-entrapped beads was affected by concentration of the oil. The beads showed excellent sustaining properties as compared to the conventional beads. Thus, oil entrapment technique can become a useful tool for the development of multiparticulate system even for a highly water-soluble drug like metformin hydrochloride.

**Acknowledgement**

The authors want to thank Dr. S R Jakhar for carrying out the scanning electron microscopy of the formulations.

**References**


| Table1: Release kinetic equation values of the prepared formulations |
|-------------------------------|----------------|----------------|
| **Type of Oil**               | **Zero order R^2 value** | **First order R^2 value** | **Higuchi R^2 value** |
| Plain                         | 0.991          | 1              | 0.9273               |
| Mentha Oil                    | 0.9923         | 0.8403         | 0.9414               |
| Castor Oil                    | 0.9912         | 0.9905         | 0.9593               |
| Groundnut Oil                 | 0.9392         | 0.9764         | 0.9939               |
| Liquid Paraffin               | 0.9954         | 0.9890         | 0.9295               |