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Research Article

**FORMULATION AND EVALUATION OF METFORMIN HYDROCHLORIDE BEADS BY IONOTROPIC GELATION TECHNIQUE**  
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**ABSTRACT**  
The purpose of the present investigation was to incorporate Metformin hydrochloride into beads giving sustained release of metformin and optimize best cross linking agent amongst calcium and aluminium. Formulation was prepared by ionotropic external gelation technique using Ca+2 and Al+3 ions. The prepared beads were characterized for Entrapment efficiency, Scanning electron microscopy, Swelling kinetics, Release behavior of beads by Kinetics modeling. Ca+2 cross linked beads showed sustained release of drug for about 8 hr while Al+3 cross linked beads shown sustained release of drug about 10 hrs. The entrapment efficiency was also lesser in case of Ca+2 cross linked beads. The alginate beads swelled and eventually disintegrated in phosphate buffer (pH 6.8). The results revealed that aluminium is better cross linking agent than calcium indicating that valence affects cross linking. In nutshell, by proper choice of cross linking agent metformin hydrochloride can be incorporated into beads giving sustained release action.

**KEY WORDS:** Metformin hydrochloride, Alginate beads, Ionotropic gelation.

**INTRODUCTION**  
Despite many advances in the development of oral hypoglycemic agents, an ideal drug for treating Type 2 diabetes is still a distant reality. Today, physicians can choose from among a variety of medications targeting numerous facets of disease, but each drug class poses some problems. The age-old molecules such as sulfonylureas and biguanides are still considered drugs of choice because of their well-studied mode of action, safety, better tolerability and ideal pharmacodynamic effects. Until we find an ideal drug for Type 2 diabetes, there is much scope and interest for pharmaceutical companies to modify the pharmacokinetics of older molecules in order to better suit larger sections of patients.

Metformin hydrochloride is an oral antihyperglycemic drug used in the management of Type-II diabetes. Metformin hydrochloride (N, N-dimethylimidodicarbonimidic diamide hydrochloride) is a biguanide and still today a widely used anti-hyperglycemic agent. Metformin hydrochloride is a highly hydrophilic drug with plasma half life 1.74 ± 0.20 hr⁻¹. Its oral bioavailability is only 52 ± 5 %. Conventional oral dosage forms need to be administered three to four times and therefore produce fluctuations in drug peak plasma level, it is recognized that many patients can benefit from drugs intended for chronic administration by maintaining plasma levels within a safe and effective range. An effort was therefore made to develop simple and effective sustained release beads of metformin to overcome limitations of its pharmacokinetics and thereby improving patient compliance. Also effect of various cross linking agents on release of drug was studied for selecting better cross linking agent².

**MATERIALS AND METHODS**  
**Materials**  
Metformin hydrochloride was a generous gift sample from USV Pvt. Ltd., Daman. Sodium Alginate was purchased from Central Drug House, Delhi, Calcium Chloride was purchased from S.D. Fine Chemicals, and Mumbai and Aluminium sulphate was purchased from Qualigens Pvt. Mumbai. All other chemical and solvents used were of analytical grade.

**Methods**  
**Preparation of sustained release beads of Metformin hydrochloride¹**  
The beads were prepared by method reported by Das MK³. The beads were prepared by ionotropic external gelation technique using the formulation as shown in table 1. The alginate solution comprising 6% w/v sodium alginate was prepared initially dissolving the polymer in de-ionized water using gentle heat and magnetic stirring. On complete solution, an accurately weighed quantity of Metformin hydrochloride was added to the solution to afford the homogeneous dispersion. The sodium alginate-drug dispersion (10 ml) was added drop wise via a 20-gauge needle fitted with 10 ml syringe into a 20 ml of 20 % solution of gelling agents [CaCl₂, Al₂(SO₄)₃ for Ca⁺² and Al⁺³ respectively]. The formed alginate beads were further kept in the solution of gelling agents for an additional 1 hr. on expiration of this period the solution of gelling agents were decanted and the beads were dried at 80 °C for 2 hr.

**Characterization of Beads**

**Drug Entrapment Efficiency**  
The drug entrapment efficiency was measured indirectly by measuring the nonencapsulated drug in the gelling agent solution. After preparation of beads the gelling solution was filtered through 0.45 mm membrane filter. The drug was quantified spectrophotometrically at 234 nm after appropriate dilution with the phosphate buffer of pH 6.8. Drug Entrapment Efficiency (DEE) was calculated according to the formula

\[ \text{% DEE} = \left[ \frac{\text{Amount of added drug} - \text{amount of nonencapsulated drug}}{\text{amount of added drug}} \right] \times 100 \]

**Morphology Characterization**  
The morphology and appearance of beads were examined by Table Top Microscope. Prior to examination the samples were placed on adhesive tape.

**Particle size**  
Particle size of dried beads was measured with micrometer for 100 beads and size range is shown in results.

**Swelling degree determination²**  
For estimation of swelling index beads were suspended into 0.1 N Hydrochloric acid and Phosphate buffer pH 6.8. The
swelling degree of equilibrium (SDs) of beads was calculated by formula:

\[
SDs = \left( W_e - W_0 \right) / W_0
\]

where, \( W_e \) is equilibrium weight of the beads in buffer and \( W_0 \) is the absolutely dried weight of beads.

**Release profile of Metformin hydrochloride**

The dissolution studies were performed in a fully calibrated six station dissolution test apparatus (37±0.5 °C, 50 rpm) using the USP rotating paddle dissolution rate apparatus. The dissolution parameters [beads equivalent to 50mg drug; 500 ml of USP phosphate buffer (pH 6.8)] were maintained for both type of beads. 2ml of aliquot were withdrawn at specific interval and after suitable dilution assayed by SHIMAZDU UV-VIS 1601 at 234 nm.

**Kinetic modeling**

In order to investigate the release mechanism the release data were fitted to the following power law expression:

\[
M/M_0 = Kt^n
\]

Where, \( M_0 \) and \( M_t \) is amount of drug released at time \( t \) and the overall amount released, \( K \) is the release rate constant and \( n \) is the release exponent indicative of release mechanism. The values of \( n \) was calculated from the slope of the plot of log \( (M_t / M_0) Vs \) Log \( (t) \) for interpretation of the result. The release data were further analyzed using the different kinetic models. Fitness of the various kinetic models was assessed by the determining the correlation of coefficient.

**RESULTS AND DISCUSSION**

**Drug Entrapment Efficiency**

Drug entrapment efficiency was found to be 25 % for Ca\(^{2+}\) cross linked beads where as for Al\(^{3+}\) cross linked bead it was found to be 37 %. The reason for low entrapment efficiency may be high solubility of drug. Increase in entrapment efficiency, in both cases, was found with increase in polymer concentration because formation of more complex gel network of alginate. It was low in case of Ca\(^{2+}\) cross linked because of its porous surface which ensures the diffusion of drug out of beads at the time of curing.

**Morphology Characterization**

Morphology of alginate beads prepared was found to be discrete and spherical in shape. The SEM photomicrographs of the dried alginate beads are shown in Figure 1 and 2. It is clearly seen that surface of plain alginites beads is a spherical with minor ridges of shrinkage (Figure 1). Increase in concentration of polymer produced more spherical surface. The photo after loading the drug as shown in figure 2 shows the entrapment of drug as white dots which are clearly seen.

**Particle size**

Prepared bead were lies in the range of 1.33-1.67 mm (for Ca\(^{2+}\) cross linked beads) and 1.47-1.73 mm (for Al\(^{3+}\) cross linked beads). Size of beads increases as increase in concentration of polymer because of increase the entrapment of drug in beads.

**Swelling Degree Determination**

In 0.1 N Hydrochloric acid

Overall swelling of Ca\(^{2+}\) cross linked beads was found lesser than that was of Al\(^{3+}\) cross linked beads. The reason for that may be poor matrix of Ca-alginate which produces larger pores than Al-alginate matrix structure which leads to leakage of drug from the matrix when kept in the solution for longer time. This phenomenon was confirmed by the result of the Swelling behavior of the beads. As shown in table 2, in first 15 minutes Ca\(^{2+}\) cross linked beads show more swelling than Al\(^{3+}\) cross linked beads. Afterward it decreases, may be because of leakage of drug from the matrix structure. In case of Al\(^{3+}\) cross linked beads the matrix structure is so complex that it retards the solution which got penetrated in side of matrix and hence retards the movement of drug across the matrix structure in to the swelling solution.

**In Phosphate Buffer (pH 6.8)**

In case of phosphate buffer Ca\(^{2+}\) cross linked beads again showed the less swelling than Al\(^{3+}\) in same manners. The reason for that remains same as in 0.1 N Hydrochloric acid. Swelling index for Ca\(^{2+}\) cross linked beads: 4.9075 and swelling index for Al\(^{3+}\) cross linked beads: 5.235

**Release Profile of Metformin Hydrochloride**

The release profile of beads is shown in Figure 5. In case of Ca\(^{2+}\)-alginate beads, rapid removal of Ca\(^{2+}\) as calcium phosphate from the beads due to ion exchange process with the Na\(^+\) of phosphate buffer medium and thus and leading to greater water uptake and rapid release. In case of Al\(^{3+}\)-alginate beads the delay was due to the ability of Al\(^{3+}\) to form three-dimensional bonding structure with the sodium alginate inside the beads. The dimensional bonding results in an extended cross linking through the whole beads, producing hard alginate beads with less water uptake and thus leading to slow removal of Al\(^{3+}\) due to ion exchange process with the Na\(^+\) in the phosphate buffer. As a result, the swelling of the beads are delayed leading to slow disintegration.

**Kinetic Modeling**

The in vitro dissolution data were analyzed by different kinetic models in order to find out the n value, which describe the drug release mechanism. The values of the coefficient of correlation (R\(^2\)) obtained for the respective models are listed in Table 3. The best fit model with the highest correlation coefficient was shown in power law expression. The value of n for the release of metformin hydrochloride from the alginate beads is 1.1985 and 1.118 for both Ca-alginate and Al-alginate cross linked beads respectively, indicating that the drug release from the beads followed super case-II transport mechanism control by swelling and relaxation of polymer chains.

**CONCLUSION**

It can be concluded from above investigation that the proper selection of formulation condition is very important to achieve high encapsulation efficiency to control the release of metformin hydrochloride from alginate beads. The alginate beads swelled and eventually disintegrate in the phosphate buffer of pH 6.8. Consequently, 100 % of Metformin hydrochloride was released in the dissolution medium. Therefore, more formulation studied is needed to design the best controlled release formulation.

**REFERENCES**


### TABLE 1: FORMULATION OF DRUG LOADED ALGINATE BEADS

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Metformin HCl (% w/v)</th>
<th>Sodium alginate (% w/v)</th>
<th>Gelling agent (20% w/v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>6</td>
<td>CaCl₂</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>6</td>
<td>Al₂(SO₄)₃</td>
</tr>
</tbody>
</table>

### TABLE 2: INTERPRETATION OF DRUG RELEASE MECHANISM

<table>
<thead>
<tr>
<th>Release exponent (n)</th>
<th>Drug release mechanism</th>
<th>Rate as a function of time</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>Fickian diffusion</td>
<td>tⁿ/²</td>
</tr>
<tr>
<td>0.5&lt; n &lt; 1.0</td>
<td>Anomalous transport</td>
<td>tⁿ⁻¹</td>
</tr>
<tr>
<td>1.0</td>
<td>Case-II transport</td>
<td>Zero order release</td>
</tr>
<tr>
<td>&gt; 1.0</td>
<td>Super Case-II transport</td>
<td>tⁿ⁺²</td>
</tr>
</tbody>
</table>

### TABLE 3: KINETIC VALUES OBTAINED FROM DIFFERENT PLOTS OF MODELS

<table>
<thead>
<tr>
<th>Alginate beads</th>
<th>Zero order (R²)</th>
<th>First order (R²)</th>
<th>Higuchi’s (R²)</th>
<th>Power law expression (R²)</th>
<th>Hixon crowell’s (R²)</th>
<th>n value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al⁺⁺ Cross linked beads</td>
<td>0.960</td>
<td>0.997</td>
<td>0.9792</td>
<td>0.9998</td>
<td>0.9814</td>
<td>1.195</td>
</tr>
<tr>
<td>Ca⁺⁺ Cross linked beads</td>
<td>0.9579</td>
<td>0.9996</td>
<td>0.9877</td>
<td>0.9998</td>
<td>0.9765</td>
<td>1.118</td>
</tr>
</tbody>
</table>

Fig 1: Alginate blank bead (10X)
Fig 2: Drug loaded Alginate bead (10X)
Swelling behavior in 0.1 N HCl

Swelling behavior in PBS (pH 6.8)

Release profile of Metformin Hydrochloride

Fig 3: Swelling behavior in 0.1 N HCl

Fig 4: Swelling behavior in PBS (pH 6.8)

Fig. 5: Release profile of Metformin Hydrochloride

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