Fabrication & Characterization of Dual Cross Linked Pulsatile Beads of Diacerin Using Natural Gum

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FABRICATION & CHARACTERIZATION OF DUAL CROSS LINKED PULSATILE BEADS OF DIACEREIN USING NATURAL GUM

ABSTRACT

In the present study, pulsatile dual cross linked beads were prepared by ionotropic gelation method. Diacerein dual crossed linked beads were prepared by dropping dispersed phase of diacerein (DCN), Moringa olifera gum and sodium alginate into dispersed phase of different concentration of calcium chloride solution followed by 5% & 10% Aluminum chloride solution and 2% sodium Tripolyphosphate (TPP) solution. In vitro release studies showed lag time of 3-7 hrs before the release of diacerein from the formulated beads, which were found to be intact for 5 hrs. Thus, formulated dual cross linked beads when administered at morning time may release the drug when needed most for chronotherapeutics of osteoarthritis in chronic patients.

Keywords: Diacerein, Moringa olifera gum, pulsatile microbeads, TPP, Osteoarthritis

INTRODUCTION

Osteoarthritis is a degenerative disease of the joints and is the commonest of all joint diseases, affecting nearly everyone at least to some degree by age 70. The weight bearing joints of the hip, knee, back, toes and fingers are mostly affected. Osteoarthritis (OA) is a chronic disease that affects up to 80% of population over 65 years of age. A recent study indicates that knee OA is likely to become fourth most common cause of disability in women and eighth most common cause in men. Recent estimates suggest that total costs for arthritis, including OA may exceed 2% of the US gross domestic product. Due to longevity of working careers and the prevalence of OA in middle age persons, OA may cause a significant burden in lost time at work and early retirement. OA is characterized by loss of articular cartilage and bony over growth seen mostly in elderly persons. The initial bland progression of OA may become clinically relevant as inflammation brought about by increasing deposition cartilaginous debris.

Diacerein is anti-inflammatory, analgesic and antipyretic drug recently found useful in treatment of osteoarthritis. It also significantly reduces severity of pathological changes of OA compared to placebo and increases the expression of transforming growth factor (TGF)-beta 1 and TGF beta 2 with potential cartilage repairing properties.

Sodium alginate (SA) is a sodium salt of alginic acid, naturally occurring, nontoxic polysaccharide found in green algae. It is made of two molecules of uronic acid α-L-glucoronic, one β-D mannuronic acid and homopolymeric blocks with alternating sequence. Alginate is found as an mixed salt of various cations such as Al³⁺, Mg²⁺, Sr²⁺, Ba²⁺, Na⁺.

Moringa olifera is a small genus of quick growing tree distributed in India. Moringa olifera is one of the best known and most widely distributed and naturalized species of a monogeneric family moringaceae. When the gum mucilage is mixed with water a protective soothing preparation results, which when applied externally will protect lesion or ulcer, contamination, infection, sepsis. It has capability to protect the active drug from stomach & small intestine so it can be used in colon specific drug delivery.

The objective of present investigation was to prepare dual cross linked pulsatile beads contains diacerein as a model drug and employing simple technique (ie ionotropic gelation) using sodium alginate & Moringa olifera gum.

MATERIALS & METHOD

Materials

*Moringa olifera* gum was isolated and characterized in our laboratory. Diacerein was supplied as a gift sample from Taj Pharmaceuticals, Mumbai. All other chemicals used were of analytical grade. Double distilled water was used throughout the experiment.

METHOD

Preparation of Ca²⁺ single cross linked beads

Pre weighed amount of sodium alginate & *Moringa olifera* gum were completely dissolved in distilled water. Diacerein was added in above solution and stirred for few minutes using a mechanical stirrer to achieve uniform mixing. Then whole dispersion was dropped into CaCl₂ solution using insulin syringe and then cross linked for 10-15 min for further gelation of alginate: *Moringa olifera* gum beads. Following cross linking for pre-determined time the cross linked beads were separated by filtration & was washed thrice with 50 mL double distilled water.
Preparation of dual cross linked beads
The Ca\textsuperscript{2+} cross linked beads (M6, M7, M8) were directly dipped into 50mL solution of aluminum chloride (5%, 10%), TPP (2%) for 10-15 min then the dual cross linked beads were separated by filtration, washed trice with 50mL double distilled water and finally dried at 37\textdegree C ± 2 till constant weighed. The formulation batches of single and dual cross linked beads are shown in Table I.

In vitro characterization of fabricated beads Drug content: \textsuperscript{14,15}
For determining drug content weighed amount (50 mg) of each formulation of drug loaded dual cross beads individually placed in 100mL phosphate buffer 6.8pH & 1.2 pH. It was then mechanically stirrer vigorously for 12hrs. These solutions were then filtered through whatman\textsuperscript{s} filter paper (diameter 0.45 mm) and subjected to analysis by a UV spectrophotometer (1650, shimadzu, japan) at 259 nm.

Scanning electron microscopy (SEM)
The surface topography was studied using. The formulated dual beads were coated with palladium for 5 min. The morphological examination of beads surface was performed at 10 KVat approximate magnifications using a Scanning electron microscope.

In vitro drug release studies
In vitro drug release was performed in a USP dissolution apparatus with paddle speed of 50 rpm. Studies were conducted in 900 mL (0.1 N HCl) pH 1.2 for 2 hrs & pH 6.8 for remaining hrs at 37 ±0.5 \textdegree C at the end of 2 hrs, pH 1.2 was replaced with pH 6.8 for next 10 hrs. At regular time interval, an aliquot was removed & replenished fresh pre warmed medium. The aliquot was assayed for diacerein content using UV spectrophotometer at 259 nm.

RESULTS & DISCUSSION

FTIR spectra
FTIR spectra of diacerein, Moringa olifera gum and physical show peak 1680, 1450 of C=O, C-O stretch of COOH respectively. It shows C-H stretch of aromatic at 30450.60 were as C-O stretch of ester at 1028. It showed C=C stretch of aromatic at 1593. It also showed peak at C=O stretch of ester at 1766. FTIR spectra of drug Moringa gum & formulation has been compared. It showed that there is no interaction between them hence they are compatible.

DSC ANALYSIS
DSC thermogram of diacerein showed a sharp endothermic peak at 253.56\textdegree C.Drug melting peak is also present in physical mixture of sodium alginate & Moringa olifera gum. Physical mixture of sodium alginate & Moringa olifera gum & Moringa olifera gum showed peak at respectively. It indicates that there is no interaction between drug & polymers.

Scanning electron microscopy
Surface morphology of beads studied by SEM; showed that beads are rigid with cracks. Beads were observed to be spherical in shape from the SEM images.

In vitro drug release studies
Drug release study of dual cross linked beads of diacerein was carried out using USP dissolution apparatus II (basket type) at 50 rpm & temperature of 37.0 ±0.5 \textdegree C shown in Fig. 1. Drug release of dual cross linked pulsatile beads was performed in pH 1.2 for 2 hrs & pH 6.8 for remaining hrs. It was observed that drug release from beads was observed after complete swelling. It was observed that swelling of beads was rapid after a desired lag time. All batches of single cross linked beads (M1–M5) showed the lag time of 3- 4 hrs before complete drug

Table I: Formulation of batches

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<tr>
<th><em>Dispersion phase</em></th>
<th><em>Dispersion media</em></th>
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<tr>
<td><strong>Batches</strong></td>
<td><em>Sod. Alginate (mg)</em></td>
</tr>
<tr>
<td>M1</td>
<td>450</td>
</tr>
<tr>
<td>M2</td>
<td>500</td>
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<tr>
<td>M3</td>
<td>450</td>
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<td>M4</td>
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release from beads. Batches M2 & M5 showed rapid & fast drug release as compared to other batches (M1, M3, M4). Dual cross linked beads (M6, M7, M8) showed more lag time as compared to single cross linked beads. They showed lag time of 4 - 6 hrs. as compared to single cross linked beads. Batch M8 showed maximum 7 hrs as compared to AlCl₃ dual cross linked beads.

CONCLUSION

Dual cross linked pulsatile beads of diacerein were obtained by ionotropic gelation method. Beads were evaluated for in vitro drug release studies average particle size, entrapment efficiency, swelling study etc. In case of dual cross linked beads a lag time of 4 - 7 hrs was obtained, which was necessary for treatment of osteoarthritis when it is worst in late afternoon in chronic patients. Dual cross linked beads may be a promising approach for the development of pulsatile drug delivery for osteoarthritis.

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REFERENCES