Original Article

Polymeric implants of diclofenac for site specific and prolonged drug delivery for use in orthopedic or arthritic patients.

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Running Title: Polymeric implants of diclofenac

Received: 07 November, 2016; Revised: 11 December, 2016 Accepted: 30 December, 2016

Available online at http://www.thescientificpub.com http://dx.doi.org/10.19046/abp.v03i06.04

Abstract

In the present study, diclofenac loaded implants were prepared for prolonged and site specific drug delivery in orthopedics and other related areas. The polymeric biodegradable implants of diclofenac were prepared using sodium alginate and gelatin by solvent evaporation method. The prepared implants were characterized for various physico-chemical parameters (like visual appearance, thickness, weight variation, drug content, formaldehyde test) and in-vitro drug release (in franz diffusion cell). The surfaces of prepared implants were smooth and shiny with yellow colour. Drug content was found to be 98.56 ± 1.98 and 97.99 ± 1.60 % for formulation F1 and F2, respectively. Both formulations of implant were free from free formaldehyde. In the in vitro drug release study the drug release across the membrane was 95.11 ± 2.26 and 91.66 ± 2.08 % at the end of 24 h. The implants prepared with gelatin and sodium alginate in 3:1 ratio was concluded to be the better formulation. The study concluded that the biodegradable implants of diclofenac might be effective in orthopedics for getting prolonged drug release.

Keywords: Diclofenac, implant, in vitro release, orthopedic implant, gelatin, alginate.

Introduction

Among the various drug delivery systems rate controlled implantable drug delivery systems entered in to the therapeutics with silicone implants in 1964 [1]. Developing orthopedic implant is an art as well as the science for the diagnosis and treatment of various orthopedic disorders or diseases [2, 3]. The implant is an advanced drug delivery system, which delivers the drug in the microenvironment of the target site for prolonged period of time with the least possible dosage [4]. Due to site specific drug delivery with small doses the systemic side effects of the drugs are minimized with improved efficiency of drug delivery, [5].

The implants may be mechanical/metalllic/electronic devices (like pacemakers, infusion pumps etc.) or the polymer based systems [6]. A polymeric implant is used to replace/enhance/support a biological structure that is either missing/existing or damaged. Provide prolonged drug delivery and improving patient compliance with the therapy is another important area of application.

The polymeric implant may be biodegradable or non-biodegradable on the basis of polymeric nature. Biodegradable implant prepared with poly glycolic acid (PGA), poly l-lactic acid (PLLA), poly lactic co polymer and other biodegradable polymers have been investigated for treating osteoarthritis and rheumatoid arthritis. Biodegradable implantable drug delivery systems have been designed to release the drug of choice at the target site for an extended period of time [7, 8]. Non-biodegradable subdivided into matrix system or reservoir system polymer matrix system. The drug is dispersed.
homogeneously inside the matrix material. Drug diffusion slowly through the matrix and provide sustained release of drug from the delivery system. Reservoir type system consist of a compact drug core surrounding by a permeable non-degradable membrane whose thickness and permeability properties can control the diffusion of drug in the body. There are many type of implantable pump system such as infusion pump, peristaltic pump, osmotic pump, positive displacement pumps. Depending on the site of administration, the shape and size of the implant may vary. The implant may be pin, rod, cube, film, sponge or tablet shaped [6-9].

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) of the phenyl acetic acid class with anti-inflammatory, analgesic, and antipyretic properties. Diclofenac inhibit cyclooxygenase-2 (COX2) enzyme with greater potency than it does cyclooxygenase-1 (COX1). The main side effect of diclofenac is gastric ulceration and bleeding and renal adverse effect [10, 11].

The present study dealt with preparation and characterization of the implants of diclofenac. The implants were prepared using gelatin and sodium alginate by solvent evaporation method.

Materials and Methods

Materials

Diclofenac sodium was obtained as a gift sample from Sharon bio medication Ltd, selauqi Dehradun Uttarakhand, India. All other chemicals were of analytical grade.

Preparation of orthopedic implants of diclofenac sodium

Two formulations of implants were prepared using gelatin and sodium alginate (Table 1). Weighed quantity of gelatin was sprinkled on the surface of water in a beaker and stirred (200 rpm on magnetic stirrer) to avoid formulation of lumps and allowed to hydrate for 30 min. Sodium alginate was added in hydrated gelatin. Glycerin was added as plasticizing agent with continuous stirring for one hour. In other beaker diclofenac was dissolved in a minimum quantity of methanol and added to the gelatin and sodium alginate solution. After homogenous mixing, the solution was poured in a glass Petridis and kept in ice bath for 1 hour. Then it was allowed to set by placing in a refrigerator for 3 days followed by hardening with formaldehyde. After that the implants were dried at room temperature for 3 days. For hardening the implants were kept into the intimate contact of formaldehyde vapors in a glass desiccator (containing 50 ml of 37 % v/v formaldehyde) for 2 days. Then after taking out the implants were air dried for 3 days. After drying the implants were cut into number of pieces of rectangular shape. The pieces of implant were sealed in a polyethylene foils.

Characterization of implants

Measurement of implant thickness

The thickness of implant from every batch was measured with the help of screw gauge (n=6) and was subjected for analysis four samples were taken for study from each batch.

Weight variations of implant

Weight variation was determined by individual weighing and weighing together the 20 implants of one formulation. Weight variation (as per USP using the formulae % WV = Total weight of twenty implants—sum of individual weight of twenty implants/Total weight of twenty implants×100).

Drug content

One implant of diclofenac sodium of each formulation were weighed and dissolve in 100ml menthol in a beaker. The solution was stirred on magnetic stirrer (5MLH, Remi equipment, India) for 4 hours. After 4 hour 1ml sample was withdrawn, filtered, diluted and then analysed spectrophotometrically (Double beam UV - Vis spectrophotometer, AU-2701, Systronics Ltd. India) 285nm.

Test for free formaldehyde

Formaldehyde is toxic in nature. It is used to harden the implants. The implants were subjected to pharmacopoeia test for free formaldehyde. During the test the colour of 1ml of 1 in 10 dilution of implant preparation was compared with the colour of 1ml of standard formaldehyde solution.

In vitro release study

In vitro drug release study was performed in modified Franz diffusion cell using 25ml pH 7.4 phosphate buffer as dissolution medium in 37±1°C for 24 hour. The rat abdominal skin was placed between the donor and receptor compartment. The samples (1 ml) were withdrawn at the different time intervals up to 10 h and replaced with the same volume of fresh prewarmed medium to maintain the constant volume during the study. Each sample was diluted suitably and analysed spectrophotometrically (Double beam UV - Vis spectrophotometer, AU-2701, Systronics Ltd. India) 285 nm.
Drug release kinetic study

The drug release data obtained for both the formulations was analyzed by using various mathematical drug release kinetic models such as zero order, first order, Higuchi and korsmeyer peppas model. Zero order in vitro dissolution data was fitted into zero order kinetic model and a zero order release graph was developed by plotting percent cumulative drug release data on (y-axis) vs. time on (x axis). First order in vitro dissolution data obtained for each formulation was fitted to the first order kinetic model and a first order release curve was developed by plotting log % drug remaining (y-axis) vs. time (x-axis). Higuchi release kinetic it describes the release of drug from insoluble matrix. Higuchi plot was obtained by plotting the percent cumulative drug release on (y-axis) against the square root of time on (x-axis). Korsmeyer –peppas release curve was developed by plotting the Log percent cumulative drug release (y-axis) vs. Log time (x-axis). The n value (slope) of the korsmeyer -peppas curve indicated the mechanism of drug release.

Statistical Analysis

Data were expressed as mean values and standard deviation (± S.D). Drug release study data was convoluted and fitted in predefined drug release models to analyze the kinetics and mechanism of drug release.

Results

Diclofenac sodium implant were prepared using gelatin and sodium alginate in different ratio (3:1) or (1:3). Diclofenac sodium implants showed satisfactory results for weight variation, thickness and drug content. The physical appearance of F1 formulation was smooth and shiny with light yellow colour. On the other hand, F2 formulation was rough with reddish yellow color (Figure 1). The thickness of implant was measured by screw gauge and the thickness of F1 and F2 formulation was found to be 10.2 ± 0.08 mm and 11.05 ± 0.03 mm respectively. The total weight variation was found to be 85.80 ± 1.30 and 84.62± 1.45 mg for formulation F1 and F2, respectively (Table 2).

Drug content was found to be 98.56 ± 1.98 and 97.99 ± 1.60 for formu

<table>
<thead>
<tr>
<th>Implant Formulation</th>
<th>F1</th>
<th>F2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug (Diclofenac sodium)</td>
<td>1gm</td>
<td>1gm</td>
</tr>
<tr>
<td>Polymer (Gelatin &amp; Sodium alginate)</td>
<td>3:1</td>
<td>1:3</td>
</tr>
<tr>
<td>Glycerin (Plasticizer)</td>
<td>1ml</td>
<td>1ml</td>
</tr>
<tr>
<td>Distilled water</td>
<td>50ml</td>
<td>50ml</td>
</tr>
</tbody>
</table>

Table 2: Evaluation of diclofenac implants

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Hardness* (mm±SD)</th>
<th>Weight variation* (mg ± SD)</th>
<th>Drug content* (% ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1 (3:1)</td>
<td>10.2±0.08</td>
<td>85.80±1.30</td>
<td>98.56±1.98</td>
</tr>
<tr>
<td>F2 (1:3)</td>
<td>11.05±0.03</td>
<td>84.62±1.45</td>
<td>97.99±1.60</td>
</tr>
</tbody>
</table>

* n = 6

Table 3: Pharmacokinetic modeling of drug release from implants

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Zero order (R² value)</th>
<th>First order (R² value)</th>
<th>Higuchi model (R² value)</th>
<th>Korsmeyer peppas model (R² value)</th>
<th>N value</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.8205</td>
<td>0.8173</td>
<td>0.8447</td>
<td>0.8041</td>
<td>0.643</td>
</tr>
<tr>
<td>F2</td>
<td>0.8674</td>
<td>0.823</td>
<td>0.8203</td>
<td>0.8616</td>
<td>0.556</td>
</tr>
</tbody>
</table>
Figure 1: Circular cast of prepared implants of diclofenac

Figure 2: In vitro drug release study of diclofenac implants in pH 7.4 phosphate buffer; (Zero order release profile)

Figure 3: First order release profile
Discussion

The implant formulation F1 and F2 were solid matrix of gelatin and alginate. The ratio of alginate and gelatin played the role in bringing the variation in physicochemical properties. Firstly, in visual inspection F1 was smooth and shiny because high gelatin concentration. The formulation F1 prepared using 3% gelatin and 1% sodium alginate showed the highest drug content and the formulation F2 prepared with 1% gelatin and 3% sodium alginate showed the lowest drug content value. It was also found that higher the gelatin concentration used for formulation of implants higher is the drug content. The results were well supported with previous studies [12-15].

The in vitro drug release study also showed significant difference in the drug release from both the formulations. Formulation F1 prepared using (3:1) gelatin and sodium alginate showed highest percent cumulative drug release while the formulation F2 prepared (1:3) gelatin and sodium alginate showed lowest release at the end of 24 h. The n value obtained from the korsmeyer–peppas kinetic model or curve is known as the release exponent and it indicates the mechanism of drug release [16-18]. The value of n for implants formulation was between 0.45 to 0.89 and this indicated that the release mechanism was Anomalous transport mechanism. F1 formulation was better than as compared to F2 formulation.
The diffusion and degradation were the primarily explained mechanisms of drug release from biodegradable polymeric systems earlier but now a day’s combination of both diffusion- and degradation-controlled mechanism have also been studied and elaborated. The combination of diffusion and degradation is the most common mechanism of drug release from implants [19-22]. When degradation or erosion rate of a polymer carrier is more than the diffusion rate of a drug, the degradation-controlled mechanism took place. The tremendous release of drug ensures the degradation of polymer that can be seen in release profile in the form of sigmoidal curve. Surface-degrading approach and bulk-degrading approach are the two subcategories of the degradation-controlled mechanism [23, 24]. Further studies are needed to be performed in animals followed by the clinical study to validate the effectiveness of the prepared implants.

Conclusion

It is concluded that the diclofenac implants prepared from gelatin and sodium alginate in 3:1 (F1) and 1:3 (F2) might be used for the prolonged therapeutic action in orthopedics. The study concluded that the use of natural polymer might be a more potential and safer alternative approach than using synthetic polymer for developing drug implants. Biodegradable polymers and the implants prepared from them may be the answer for the next generation therapeutics for providing better treatment with improved effectiveness, prolonged duration of action and improved patient compliance.

Financial Assistance

None Declared

Conflict of interest

The authors declare that there is no conflict of interest to reveal.

References


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