Development of novel chitosan based ketorolac implant controlled release formulation for subcutaneous drug delivery.

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Abstract

This present experiment deals with a formulation of novel drug delivery system of chitosan implants to modulate the release of ketorolac through the fabrication of subcutaneous implant. The implants were prepared by compression technique. The chemical stability and the characteristic features of surface morphology of the implants were confirmed by using FTIR and SEM. The thermodynamic behavior of the novel implants was investigated by using DSC/TGA. The loading capacity of Ketorolac into chitosan implants was also evaluated. The release kinetic parameters were studied in dissolution media of phosphate buffer solution (PBS). The results find that the final formulation maintains chemical stability of the drug. The morphological features of the implant confirmed uniform inclusion and distribution of ketorolac into the chitosan matrix with an evidence of porous structure. The drug release pattern of the Ketorolac exhibited controlled release behavior from chitosan implants up to 45 d governed mainly by drug diffusion mechanism. The formulated of novel implants have shown a great potential in the long term subcutaneous delivery of ketorolac.

Keywords: FTIR, SEM, Phosphate buffer solution, Drug.

Introduction

Ketorolac can be classified as model non-steroidal anti-inflammatory drugs (NSAIDs) that are highly effective for the treatment of symptomatic and non-symptomatic pain and inflammation. Compare to other conventional NSAIDS ketorolac is highly effective for management of different kind of pain and inflammation [1]. The mechanism of ketorolac is mainly involved in reduction of synthesis of prostaglandins and other inflammatory chemicals that are originated from the immune system. However, oral administration of ketorolac has many shortcomings including low patient compliance [2,3]. Preparations that reduce tolerability help patients with diseases of chronic pain such as terminal cancer and lethal autoimmune disease. In a previous study, implantable drug delivery system reduced the opioid reported toxicity to a large extent [4-6]. The present experimental study aimed at designing of novel ketorolac formulation in a specially designed subcutaneous biocompatible implant that can control the drug release for more than 45 days. Thorough literature investigation of subcutaneous implants reveals that the use of the long acting biodegradable polymer chitosan to design the formulation of ketorolac has not been executed before. Therefore, our investigation to design prolonged release dosage formulation in the form of subcutaneous implant will be useful for effective treatment and management of operative and non-operative pain.

Material and Methods

Material Ketorolac hydrochloride (>98% HPLC) was purchased from Sigma pharmaceuticals. Chitosan, PEG 6000, Tween 80, and glycerol were also purchased from Sigma-Aldrich (Germany). ALL other chemicals used for analysis were of high analytical grade and purchased from Sigma Co., US 2.2.

Compression technique

Required amount of Chitosan powder, glycerol or Tween 80 PEG 6000 as mentioned in Table 1 were heated at a temperature of 75°C on a water bath under stirring condition with a glass rod. The exact quantity of pure Ketorolac drug was dispersed uniformly when the entire mass is in semi melted condition. The solidified blend was kept in a refrigerator for more than 1 h. After the solidification of the mass, hard mass
was converted to fine powder and the entire fine mass passed through a sieve (aperture 0.45 mm). The fine granules were properly lubricated with talcum and compressed form 10 mm (flat) tablet shaped pellets. 7 different formulations were designed and formulated by using various quantity of glycerol or Tween 80 concentration [7].

<table>
<thead>
<tr>
<th>Table 1. Formulations of compressed and molded implants using erosion enhancers sample formulation</th>
<th>Ingredient (%)</th>
<th>Drug</th>
<th>GMS PEG 6000 Tween 80</th>
<th>Glycerol</th>
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<tr>
<td>C1</td>
<td>20</td>
<td>40</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>C2</td>
<td>20</td>
<td>42.5</td>
<td>37.5</td>
<td>2.5</td>
</tr>
<tr>
<td>C3</td>
<td>20</td>
<td>45</td>
<td>35</td>
<td>5</td>
</tr>
<tr>
<td>C4</td>
<td>20</td>
<td>47.5</td>
<td>32.5</td>
<td>7.5</td>
</tr>
<tr>
<td>C5</td>
<td>20</td>
<td>37.5</td>
<td>42.5</td>
<td>2.5</td>
</tr>
<tr>
<td>C6</td>
<td>20</td>
<td>35</td>
<td>45</td>
<td>0.05</td>
</tr>
<tr>
<td>C7</td>
<td>20</td>
<td>32.5</td>
<td>47.5</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Chemical integrity of the prepared implants FT-IR spectra

The compressed implant in the form of tablets were crushed into powder form and the chemical stability of the powder samples were analyzed by using a Perkin Elmer Spectrum 2000 FT-IR spectrometer, universal FTIR spectrum series at a resolution of 4 cm⁻¹ [8].

Thermodynamic behavior of the ketorolac-loaded implants

The thermal behavior of the compressed implants in the form of tablets was evaluated by using Differential Scanning Calorimeter (DSC) and thermal gravimetric analysis (TGA). The required quantity of the samples (100 ± 1 mg) was placed in platinum crucible with a specified heating range of 25-500°C with a heating rate of 10 C/min [9].

Morphological features of the ketorolac-loaded implants

The internal morphological features and surface area of the ketorolac loaded implants was investigated by using Scanning Electron Microscope (SEM). Samples were undergone the process of gold-sputter coating (SPI Module™ Sputter Coater, SPI Supplies, PA) for the purpose of rendering electrically conductivity to the samples before analysis [10].

In vitro drug release

Actual concentration of loaded ketorolac in prepared implants was estimated by grinding ketorolac-loaded implants and extracting ketorolac in DMSO by at a temperature of 40°C for more than 6 h. The final solution was then properly filtered and diluted with Phosphate buffer solution. The concentration of ketorolac was then estimated UV spectrophotometry. All measurements were performed in triplicate and the encapsulation efficiency and the percentage of loaded ketorolac was calculated. The in vitro drug release of ketorolac implant was calculated in PBS (pH 7.4; 37°C) at different time intervals using UV-vis spectrophotometer (Lambda 25 UV/Vis Spectrophotometer, PerkinElmer, MA, USA) at a wavelength of 271 nm.

Mathematical modeling of release kinetics

In order to evaluate the release mechanism of the ketorolac the percentage of drug release data were compared with the fundamental mathematical models of zero order, diffusion and using the Korsmeyer-Peppas equation.

Results

FT-IR spectrum of chitosan implants

Chemical integrity of the prepared implants evaluated by the FT-IR spectra of ketorolac-loaded implants are illustrated in Figure 1. A strong band in the region 3611 cm⁻¹ corresponds to N-H and O-H stretching, as well as the intramolecular hydrogen bonds. The absorption bands at around 2921 cm⁻¹ can be attributed to C-H symmetric and asymmetric stretching, respectively. These bands are characteristics of typical polysaccharides. First, the characteristic bands of the basic polymers were observed as follows; the main characteristic bands of chitosan were observed at 1652 cm⁻¹ corresponding to carbonyl stretching, bands at 1423 and 1112 cm⁻¹ indicating CAC and CAO stretching in chitosan.

In Figure 1, the FTIR spectrum of final chitosan-implant representing the chemical integrity of the ketorolac loaded in chitosan implants. It is clearly evident that the entire major characteristic peak which corresponds to
identify of both chitosan and ketorolac are clearly visible. So the chemical integrity and stability of the drug and polymer in the final form of chitosan implant are intact.

**Figure 2.** Characteristic features of thermal behavior of Chitosan implants.

**Thermodynamic behavior of the ketorolac-loaded implants**

The thermal behavior of ketorolac-loaded implants was determined by DSC as shown in Figure 2. The native carbohydrate polymer; chitosan showed one characteristic peak at 60°C corresponding to Tm of chitosan as early reported. Ketorolac exhibited a long and sharp characteristic endothermic peak at 163.04°C due to its phase transition system. The powder grinded from chitosan implant of Ketorolac shows characteristic peak at 158.90°C. It showed the slight change in characteristic peak may be due to fusion of excipient present in the physical mixture. From this result, it clears that there is no interaction in between Ketorolac and excipients.

**Morphology of the ketorolac-loaded implants**

The ketorolac-loaded implants morphology and ketorolac-free implants were investigated using SEM. Ketorolac-free implants exhibited amorphous smooth surfaces (Chitosan) (Figures 3 and 4), while ketorolac-loaded implants showed a porous structure based morphology and rough surfaces. The characteristics features of this implant were due to with increased concentrations of ketorolac embedded in the implant.

**Drug loading efficiency and in vitro drug release**

The entrapment efficiency values ranged from 98.00 ± 0.70% for all the formulation. The cumulative drug release (%CDR) profiles of ketorolac-loaded implants are presented in Figure 4. Ketorolac exhibited controlled release behavior from chitosan implants up to 1000 h. The formulation F5 shows a longer duration of time.

**In vitro drug release kinetics**

In vitro ketorolac release from ketorolac-loaded implants was fitted using different mathematical models and the kinetic parameters are listed in Table 2. It is evident from the release figure that the plots are curvilinear suggesting that the release process is not zero-order in nature. The release pattern is very close to Korsmeyer-peppas model.

**Table 2.** Drug release kinetics parameters based on various dissolution models.

<table>
<thead>
<tr>
<th>Formula code</th>
<th>Zero-order</th>
<th>Diffusion</th>
<th>Korsmeyer-peppas model</th>
<th>n value</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.722</td>
<td>0.912</td>
<td>0.934</td>
<td>0.343</td>
</tr>
<tr>
<td>F2</td>
<td>0.745</td>
<td>0.923</td>
<td>0.945</td>
<td>0.359</td>
</tr>
<tr>
<td>F3</td>
<td>0.789</td>
<td>0.912</td>
<td>0.958</td>
<td>0.365</td>
</tr>
</tbody>
</table>

**Figure 3.** Percentage cumulative drug release of various formulations at different time interval.

**Figure 4.** Scanning electron microscopy of: (a) Chitosan powder; (b) Chitosan drug implants.
the drug release up to 45 days. For successful management of subcutaneous implant dosage form may be an effective sustaining the drug for at least 45 d.

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References
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