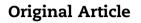
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## Triple-component nanocomposite films prepared using a casting method: Its potential in drug delivery



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#### ABSTRACT

The purpose of this study was to fabricate a triple-component nanocomposite system consisting of chitosan, polyethylene glycol (PEG), and drug for assessing the application of chitosan-PEG nanocomposites in drug delivery and also to assess the effect of different molecular weights of PEG on nanocomposite characteristics. The casting/solvent evaporation method was used to prepare chitosan-PEG nanocomposite films incorporating piroxicam-β-cyclodextrin. In order to characterize the morphology and structure of nanocomposites, X-ray diffraction technique, scanning electron microscopy, thermogravimetric analysis, and Fourier transmission infrared spectroscopy were used. Drug content uniformity test, swelling studies, water content, erosion studies, dissolution studies, and anti-inflammatory activity were also performed. The permeation studies across rat skin were also performed on nanocomposite films using Franz diffusion cell. The release behavior of films was found to be sensitive to pH and ionic strength of release medium. The maximum swelling ratio and water content was found in HCl buffer pH 1.2 as compared to acetate buffer of pH 4.5 and phosphate buffer pH 7.4. The release rate constants obtained from kinetic modeling and flux values of ex vivo permeation studies showed that release of piroxicam-β-cyclodextrin increased with an increase in concentration of PEG. The formulation F10 containing 75% concentration of PEG showed the highest swelling ratio  $(3.42 \pm 0.02)$  in HCl buffer pH 1.2, water content  $(47.89 \pm 1.53\%)$  in HCl buffer pH 1.2, maximum cumulative drug permeation through rat skin (2405.15  $\pm$  10.97  $\mu$ g/cm<sup>2</sup>) in phosphate buffer pH 7.4, and in vitro drug release ( $35.51 \pm 0.26\%$ ) in sequential pH change mediums, and showed a significantly (p < 0.0001) higher anti-inflammatory effect (0.4 cm). It can be concluded from the results that film composition had a particular impact on drug release properties. The different molecular weights of PEG have a strong influence on

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swelling, drug release, and permeation rate. The developed films can act as successful drug delivery approach for localized drug delivery through the skin.

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#### 1. Introduction

Modified drug delivery system (MDDS) means release of drug from a drug delivery system that is modified in some way [1]. MDDS includes transdermal drug delivery system, controlled or sustained released dosage form and delayed released dosage form. MDDSs are preferable to conventional drug delivery systems because of certain advantages such as improved patient compliance and comforts owing to reduced dosing frequencies, more efficient drug therapy to patients, and more uniform drug therapeutic levels [2].

Nanocomposites are composed of either multiple nanoscale substances or a single entity of nanoscale material that is incorporated into the bulk material. These nanocomposites may come in different combinations, i.e., two hard nanomaterials, two soft nanomaterials, or a combination of hard and soft nanomaterial [3]. Based on the nature of the matrix, the nanocomposites have been categorized as metal, ceramic, and polymer matrix nanocomposites [4]. Among all, polymer matrix-based nanocomposites have been formulated by different techniques including sol-gel reaction, solvent casting, extrusion, and dispersion of clays into the polymer matrices [5]. Solvent casting is mainly a manufacturing process where a filler and a solubilized polymer matrix are mixed together by creating agitation through the use of mechanical stirrer. This mixing is followed by casting and solvent removal via evaporation or any other drying methods [6].

Biodegradable polymers are used as biomaterials in numerous techniques, particularly in tissue engineering, gene therapy, wound healing, and controlled drug delivery systems. These biodegradable polymers are important in such a way that the implanted foreign materials vanish from the body as a result of their degradation. Examples of the most commonly used biodegradable polymers in biomedical applications are polylactic acid, polyethylene glycol (PEG), polyglycolic acid, poly-ɛ-caprolactone, poly-3-hydroxybutyrate, copolymers of polyglycolide, chitosan, alginate, and soy protein [7]. PEG is a biodegradable polymer with excellent properties such as biocompatibility and safety. It is used in combination with other polymers to formulate controlled release drugs [8]. The second most abundant polysaccharide in nature is chitosan, the cationic (1-4)-2-amino-2-deoxy- $\beta$ -Dglucan. Chitosan of different quality grades can be produced from chitin. Chitosan has great importance because of its biodegradability, biocompatibility, and nontoxicity [9].

Organic polymer matrixes and nanoscale-organophilic clay fillers make up a group of amalgam materials, i.e., polymer-clay nanocomposites [10]. In order to improve the blend properties, it has been suggested that nanoclays can improve the compatibility of immiscible polymers [11]. Sepiolite  $[Si_{12}O_{30}Mg_8(OH)_4(OH_2)_4 \cdot 8H_2O]$  is a fibrous hydrated magnesium silicate. Its structure is related to montmorillonite comprising octahedral layers of magnesium oxide/hydroxide inserted between two tetrahedral silica layers. The only difference between montmorillonite and sepiolite is the lack of continuous octahedral sheets [12]. Previously, it was used as filler for the formulation of polymer–clay nanocomposites [13].

Transportation of drug molecules through the skin undergoes two processes: drug penetration through the stratum corneum followed by drug diffusion into deeper tissues. The rate and extent of drug transportation depends on hydrogen bonding, size, ionic strength, log *P* (the partition coefficient of a molecule between an aqueous and lipophilic phases, usually octanol and water), and physicochemical properties [14].

Piroxicam- $\beta$ -cyclodextrin belongs to the class of nonsteroidal anti-inflammatory drugs (NSAIDs). This drug has many pharmacological roles, but the most important are its analgesic and antipyretic functions. At present, this drug is available in tablet and capsule dosage forms and is thus administered orally. However, prolonged oral administration of these dosage forms may result in many life-threatening effects including epigastric pain, heartburn, gastrointestinal bleeding, aplastic anemia, renal damage, hematuria, purpura, pemphigus vulgaris, and anaphylactic shock [15]. The rare adverse effects of piroxicam- $\beta$ -cyclodextrin include bladder dysfunction, erythema multiforme (Stevens-Johnson syndrome), alopecia, toxic epidermal necrolysis or Lyell's syndrome, stomatitis, agranulocytosis, and nail growth problems [16]. These side effects can be eliminated by delivering this transdermally drug through skin.

In order to overcome these side effects, we report a new formulation of piroxicam- $\beta$ -cyclodextrin as nanocomposite films. These nanocomposite films can produce controlled release therapeutic effect with negligible side effects. Such type of formulations with minimal side effects may play an important role for the pharmaceutical industry. The purpose of this study was to assess the applications of chitosan–PEG nanocomposites in drug delivery and also to assess the applications of different molecular weights of PEG in drug delivery in the form of nanocomposites with chitosan.

#### 2. Methods

#### 2.1. Materials

Chitosan was purchased from Sigma-Aldrich (USA). Its den-Q3 sity ranges from 0.15 g/cm<sup>3</sup> to 0.3 g/cm<sup>3</sup>. PEG in three different molecular weights (750, 2000, and 5000) was purchased from

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