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Synthesis and characterization of modified starch/polybutadiene as novel transdermal drug delivery system

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ABSTRACT

Transdermal drug delivery systems are topically administered medicaments in the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate. It works very simply in which drug is applied inside the patch and it is worn on skin for long period of time. Polymer matrix, drug, permeation enhancers are the main components of transdermal drug delivery systems. The objective of the present study was to develop the modified starch and 1,4-cis polybutadiene nanoparticles as novel polymer matrix system. We have been studied the properties of a novel transdermal drug delivery system with clonidine as drug model.

1. Introduction

Transdermal drug delivery systems are topically administered medicaments in the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate [1]. A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative route for administering medication. These devices allow for pharmaceuticals to be delivered across the skin barrier [2]. In theory, transdermal patches work very simply. A drug is applied in a relatively high dosage to the inside of a patch, which is worn on the skin for an extended period of time. Through a diffusion process, the drug enters the bloodstream directly through the skin [3]. Since, there is high concentration on the pacth and low concentration in the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow [4]. This approach to drug delivery offers many advantages over traditional methods. Transdermal drug delivery enables the avoidance of gastrointestinal absorption, with its associated pitfalls of enzymatic and pH associated deactivation [5]. This method also allows for reduced pharmacological dosaging due to the shortened metabolization pathway of the transdermal route versus the gastrointestinal pathway [6,7]. The patch also permits constant dosing rather than the peaks and valleys in medication level associated with orally administered medications. Multi-day therapy with a single application, rapid notification of medication in the event of emergency, as well as the capacity to terminate drug effects rapidly via patch removal [8]. The drug that requires high blood levels cannot be administered and may even cause irritation or sensitization of the skin. The adhesive may not adhere well to all types of skin and may be uncomfortable to wear. High cost of the product is also a major drawback for wide acceptance of this product [9]. The release of the medicament from the vehicle, penetration through the skin barrier and activation of the pharmacological response are the properties of transdermal delivery [10,11]. Knowledge of skin permeation kinetics is vital to the successful development of transdermal therapeutic systems. Transdermal permeation of a drug involves the several steps. These steps are included sorption by stratum corneum, penetration of drug through epidermis, uptake of the drug by the capillary network in the dermal papillary layer. This permeation can be possible only if the drug possesses certain physiochemical properties [12]. The drug should have a molecular weight less than approximately 1000 Da. The drug should have affinity for both lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conductive to successful drug delivery via the skin. The drug should have low melting point. Along with these properties the drug should be potent, having short half life and be non-irritating [13]. These are the physicochemical properties of transdermal drug delivery systems. Transdermal clonidine comes as patch to apply to the skin. It is usually applied to the skin

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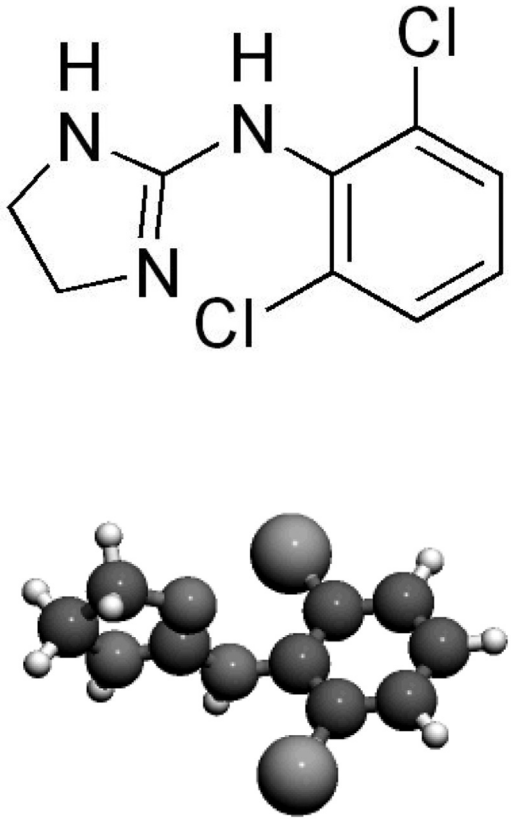


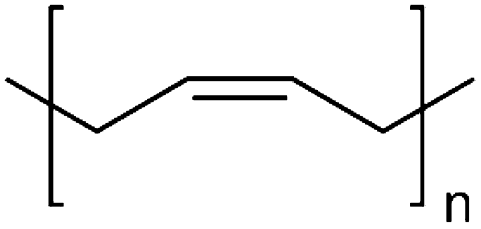
Scheme 1. The chemical structure of clonidine.

every 7 days. If the clonidine patch loosens while wearing, apply the adhesive cover that comes with patch. The adhesive cover will help to keep the clonidine patch on until it is time for the patch to be replaced (Scheme 1).

There are four major transdermal systems:

(1) *Single-layer Drug-in-Adhesive* – The Single-layer Drug-in-Adhesive system is characterized by the inclusion of the drug directly within the skin-contacting adhesive. In this transdermal system design, the adhesive not only serves to affix the system to the skin, but also serves as the formulation foundation, containing the drug and all the excipients under a single backing film.
(2) *Multi-layer Drug-in-Adhesive* – The Multi-layer Drug-in-Adhesive is similar to the Single-layer Drug-in-Adhesive in that the drug is incorporated directly into the adhesive.
(3) *Drug Reservoir-in-Adhesive* – The reservoir transdermal system design is characterized by the inclusion of a liquid compartment containing a drug solution or suspension separated from the release liner by a semi-permeable membrane and adhesive.
(4) *Drug Matrix-in-Adhesive* – The matrix system design is characterized by the inclusion of a semisolid matrix containing a drug solution or suspension which is in direct contact with the release liner [15–18].

In this research, the modified starch (CMS) and hyperbranched 1,4-cis polybutadiene (1,4-PBD) (Scheme 2) as novel polymer-matrix nanoparticles (PMPs) have been used for transdermal drug delivery systems. Also, the physicochemical properties and permeation enhancers of PMPs have been examined [14].



Scheme 2. The chemical structure of 1,4-cis polybutadiene.

2. Materials and methods

2.1. Materials

The cornstarch was purchased from Merck Co., Germany. 1,4-PBD was prepared from our previous research project and Clonidine drug (molecular weight 230 Da) or Catapres-TTS (Trade name) was purchased from Sigma Chemical Co. All other solvents and materials were of analytical grade. Deionized water (Milli-Q water) was used in the preparation of buffers and standard solutions. All other chemicals and reagents used in this study were of analytical grade. Sodium hydroxide and chloroacetic acid were used as received.

2.2. Instruments

Melting points were obtained on a Mel-Temp melting point apparatus. Analytical TLCs were run on commercial Merck plates coated with silica gel GF250 (0.25 mm thick). The amount of released drug was determined on a Philips PU 8620 UV spectrophotometer at the absorption maximum of the free drug in aqueous alkali, using a 1 cm quartz cell. The nanoparticle samples were obtained by Freeze dryer Model FD-10 (Pishtaz Engineering Company). The samples were examined to determine the mean diameter and size distribution. The powder morphology nanoparticles in the form of pellets (to measure grain size) was investigated using Philips XL-30 E SEM scanning electron microscope (SEM) at 30 kv (max.). The samples were prepared by physical vapor disposition method. The gold layer thickness was about 100 Å at these samples. Mooney viscometer, Shimadzu SMV-201, was used for Mooney viscosity characterization and measurements.

2.3. Preparation of carboxymethylstarch (CMS)

Firstly, the 0.5 g corn starch and 120 mL 2-propanol were placed in a 500 ml vessel and stirred fro 2 h. The 5 g sodium hydroxide was added and reacted for 1 h at 78–80 °C. After that, the 10 g chloroacetic acid was added to the vessel and stirred for another 2 h at 50 °C. The product was filtered and washed several times with ethanol, then dried under vacuum. The resulting CMS was crushed in a mortar [degree of substitution (DS) = 0.49].

2.4. Preparation of CMS–1,4-PBD nanoparticles with clonidine

Nanoparticles (50 mg) and clonidine (10 mg) were dispersed with stirring in 25 mL deionized water. After approximately 180 min, the sample was sprayed into a liquid nitrogen bath cooled down to 77 K, resulting in frozen droplets. These frozen droplets were then put into the chamber of the freeze-dryer. In the freeze drying process, the products are dried by a sublimation of the water component in an iced solution.