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Development of pectin nanoparticles through mechanical homogenization for dissolution enhancement of itraconazole

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ABSTRACT

A simple method to fabricate itraconazole (ITZ)-loaded pectin nanoparticles prepared from nanoemulsion templates is described in this study. Nanoemulsions containing ITZ were prepared by a mechanical homogenization using pectin as emulsifier. After freeze-drying, the morphology, crystallinity state, thermal properties, drug dissolution and stability of the obtained pectin nanoparticles were characterized. The results demonstrated that the morphology of freeze-dried products was different, depending on the type of internal phase; the nanoparticles prepared from chloroform-based nanoemulsions were completely dried and provided a fragile characteristic. The pectin nanoparticles also demonstrated good properties in terms of redispersibility, thermal properties, drug crystallinity and dissolution. The ITZ-loaded pectin nanoparticles showed high percentage of drug dissolved (about 60–80% within 2 h), and maintained their good dissolution properties even after 1-year storage. The results suggested that freeze-dried pectin nanoparticles prepared from nanoemulsions could be used as an effective carrier for enhancement of ITZ dissolution.

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1. Introduction

Pectin is a natural polysaccharide structurally composed by large amounts of poly-D-galacturonic acid bonded via α -1,4-glycosidic linkage. According to its degree of methyl esterification, pectin can be classified as high methoxyl (HM) pectin or low methoxyl (LM) pectin, which yields some differences in its properties [1,2]. Pectin has commonly been used as a gelling agent, a thickening agent and a colloidal stabilizer in the food industry [3]. Its applications in the pharmaceutical industry are increased in the last decade (e.g. [4-6]). The presence of surface-active molecules in pectin offers the emulsification properties [7]. In addition, pectin is known to be biocompatible and to exhibit very low toxicity, which are mandatory prerequisites for drug delivery application. In the previous study [8], the nanoemulsions containing a poorly water-soluble drug were prepared by using pectin as a polymeric emulsifier. The influences of type of internal phase, type and concentration of pectin on the droplet size, morphology, and zeta potential of the pectin-based emulsions have been examined. Pectin with high DE offers good emulsion properties because of its high amount of hydrophobic molecules.

Itraconazole (ITZ) is a poorly water-soluble antifungal drug having a broad spectrum of activity against a variety of pathogens causing opportunistic infection in HIV-infected patients [9]. ITZ is a weak basic drug ($pK_a = 3.7$) which is virtually ionized at low pH, having extremely low water solubility (about 1 ng/mL at neutral pH and about 4-6 μ g/mL at pH 1) [10]. Over the last decade, a large number of publications dealt with drug delivery strategies for poorly water-soluble and lipophilic drugs, including solid dispersions and nanoparticulate based formulations [11]. However, the major disadvantages of solid dispersion are related to their instability (e.g., physical instability/re-crystallization risks of solid dispersion with the potential of deteriorating drug release and bioavailability). Thus, polymeric nanoparticles have been extensively studied as particulate carriers in the pharmaceutical fields because they show promise as drug delivery systems as a result of their subcellular size and enhanced intestinal absorption of poorly water-soluble drugs [11]. In addition, nanoparticles are described to permeate epithelia more easily than microparticles and provide a controlled release of the encapsulated drugs.

In general, high-pressure homogenization (e.g., microfluidizer) has been used for preparation of nanoparticles according to its advantages of supplying the available energy in a short time and having homogenous flow, which is suitable for the preparation of nanoemulsions [12]. The disadvantage of this method, however, is that about 50-100 passages through the microfluidizer are generally required to result in nano-sized particles [13,14]. Alternatively, other types of homogenizers such as mechanical or ultrasonic homogenizers could be used to reduce processing time and increase batch size [13]. Rotor-stator generator type homogenizer is one type of mechanical homogenizer, which is the most economical and the easiest to operate as well as maintain. This homogenizer consists of a rotor that turns within a stationary stator. As the blades rotate, materials are continuously drawn into one end of the mixing head and expelled at high velocity through the openings of the stator. The differential speed and close tolerance between the

rotor and stator generate high levels of hydraulic shear, promoting fast mixing and producing small droplets in emulsions [13,15].

The aim of this study was to develop pectin nanoparticles containing a poorly water-soluble drug, ITZ, from nanoemulsion templates. A rotor-stator generator type of homogenizer was used to prepare nanoemulsion templates to avoid high-pressure conditions. The effects of homogenization speed, type of internal (oil) phase, type of pectin on the properties of the nanoemulsion templates were also examined. The obtained nanoemulsions were then freeze-dried in order to get the solid nanoparticles. The dried nanoparticles were characterized to investigate the drug properties, including morphology, crystallinity state, thermal properties and dissolution. The stability of nanoparticles in various conditions was also studied.

2. Materials and methods

2.1. Materials

The pectins used in this study were a gift from Herbstreith & Fox KG (Germany), namely, LM pectin (referred to as LMP) with a degree of esterification of 38, amidated LM pectin (referred to as ALMP) with a degree of esterification of 29 and degree of amidation of 20, and HM pectin (referred to as HMP) with degree of esterification of 70. The molecular weight of LMP, ALMP and HMP was 70, 150 and 200 kDa, respectively. Caprylic/capric triglyceride (Miglyol® 812) was a gift from Sasol GmbH (Germany) and referred to as CCT. ITZ was from Nosch Labs Private (India). Chloroform was supplied by Carl Roth GmbH (Germany). Deionized water was used as aqueous phase in all preparations. The simulated gastric fluid (SGF) used in this study was prepared based on USP guideline. Briefly, 7 mL of hydrochloric acid and 2 g of sodium chloride were dissolved in distilled water before adjusting the solution volume to 1 L; the pH of SGF was adjusted to 1.20 ± 0.05 . All other chemicals used in this study were of pharmaceutical grade and used as received without further purification.

2.2. Preparation of pectin nanoparticles containing ITZ from nanoemulsion templates by mechanical homogenizer

Oil-in-water or chloroform-in-water emulsions were prepared by using mechanical homogenization. ITZ was dissolved in oil phase (either CCT or chloroform) at different concentrations depending on its solubility (i.e., 0.003% (w/w) in CCT or 3% (w/w) in chloroform) [8]. Twenty grams of CCT or chloroform were mixed with pectin solution (80 g) using a rotor-stator type of mechanical homogenizer (Ultra-Turrax® T50 Basic, IKA, Germany). The pectin (HMP) concentration investigated was 0.5, 1, 1.2 and 3% (w/w). The effect of homogenizing speed on droplet size of emulsions using 3% (w/w) HMP was also determined at varying speeds of 8000, 9500, 13,500, 20,500, and 24,000 rpm. The homogenization was operated for 20 min, in an ice-bath at the controlled temperature of -10°C to avoid overheating.

Consequently, the suitable conditions were chosen for further experiments. Three types of pectin, i.e., LMP, ALMP and HMP,

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