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Original Research Paper

Preparation and evaluation of tamsulosin hydrochloride sustained-release pellets modified by two-layered membrane techniques

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ABSTRACT

The aim of the present study was to develop tamsulosin hydrochloride sustained-release pellets using two-layered membrane techniques. Centrifugal granulator and fluidized-bed coater were employed to prepare drug-loaded pellets and to employ two-layered membrane coating respectively. The prepared pellets were evaluated for physicochemical characterization, subjected to differential scanning calorimetry (DSC) and *in vitro* release of different pH. Different release models and scanning electron microscopy (SEM) were utilized to analyze the release mechanism of Harnual® and home-made pellets. By comparing the dissolution profiles, the ratio and coating weight gain of Eudragit® NE30D and Eudragit® L30D55 which constitute the inside membrane were identified as 18:1 and 10%–11%. The coating amount of outside membrane containing Eudragit® L30D55 was determined to be 0.8%. The similarity factors (f_2) of home-made capsule and commercially available product (Harnual®) were above 50 in different dissolution media. DSC studies confirmed that drug and excipients had good compatibility and SEM photographs showed the similarities and differences of coating surface between Harnual® and self-made pellets before and after dissolution. According to Ritger-Peppas model, the two dosage form had different release mechanism.

1. Introduction

Tamsulosin hydrochloride (TSH), as a model drug, is a highly selective α_{1A}-adrenoreceptor antagonist. It has been developed to treat lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUPS/BPH) [1]. It is reported that TSH is absorbed rapidly and completely in intestinal and eliminated slowly after oral administration, which may bring many adverse effects. Therefore TSH is a perfect candidate drug for modified-release dosage form to modulate the release rate of drug and the absorption in GIT [2].

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Pellets, as carrier of active ingredient, have been applied extensively in sustained-release (SR) formulations. Compared with conventional single-unit drug delivery system, pellets are believed to represent many bio-pharmaceutical advantages. For example, pellets can homogeneously distribute in gastrointestinal (GIT), increase the contact area between drug and GIT, decrease local drug concentration and irritation, and provide stable plasma profiles and high bioavailability. In addition, pellets are more reproducible and repeatable because of its small unit, especially in the stomach [3].

The release homogeneity of commercial product Harnual® was not good because of the particle size distribution of its pellets. To overcome the defect, we employed a different preparation craft to prepare uniform drug-loaded pellets and we gained a formulation with nice release homogeneity. The self-made TSH sustained-release (SR) pellets consist of uniform blank pellets, the layer of drug-loading and two-layered coating membranes. So far, there are many approaches to make SR formulations [4–8]. In our study, centrifugal granulator was employed to prepare blank pellets and drug-loading pellets while fluidized-bed coater was used for coating. Considering the lower toxicity and less environmental concern, aqueous polymeric dispersions were chosen as coating materials. In general, through varying the type or weight gain of coating material, we could achieve the desired release profile. However, one single type aqueous polymer dispersion is not enough to produce a wonderful drug release behavior sometimes. Binary blends of polymers were proposed to make up the defect. This technique can not only provide broad range of drug release patterns, but also improve film thermo-sensitivity [9]. Eudragit® NE30D and Eudragit® L30D55 were utilized as the inside coating material to achieve a particular pH-sensitive release [10,11]. Eudragit® L30D55, as the enteric coating material, can prohibit drug release in the simulated gastric fluid and easily be dissolved in the intestinal environment as pore-forming agents, which is also the reason for selecting Eudragit® L30D55 as the outside coating polymer [3]. The model of TSH SR pellets is depicted as Fig. 1.

2. Materials and methods

2.1. Materials

TSH (99.8% purity) was purchased from Zhejiang Jinhua pharmaceutical Co., Ltd (Zhejiang, China), Microcrystalline cellulose (MCC) (Avicel PH101) was purchased from Huzhou Zhanwang Pharmaceutical Co., Ltd, (Huzhou, China), HPMC was a gift from Shanhe Pharmaceutical Co., Ltd, (Anhui, China), methacrylic acid copolymers (Eudragit® NE30D and Eudragit® L30D55) were kindly provided by Degussa (Esson, Germany), No. 3 hard gelatin capsules were purchased from Suzhou Capsule Co. (Suzhou, China), Commercially available controlled-release TSH capsule (Harnal, 0.2 mg/capsule, Yamanouchi Pharmaceutical Co. Ltd., Japan) was chosen for comparison. All organic solvents were of high-performance liquid chromatography (HPLC) grade. All other chemicals were of analytical grade.

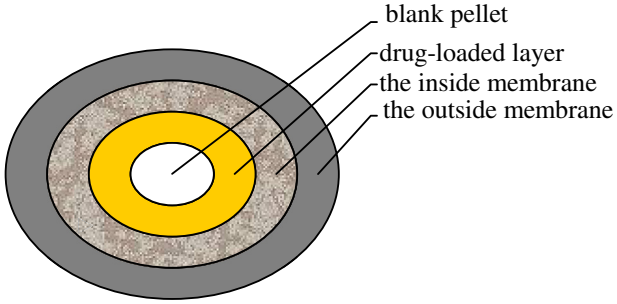

Fig. 1 – The model of TSH SR pellet.

2.2. Methods

2.2.1. Drug-excipient interaction studies

Differential scanning calorimetry (DSC) was used to investigate the possibility of drug-excipient interaction. Pure drug, the mixture of excipients and drug-excipient mixtures were separately sealed in aluminum cells at a heating rate of 10 °C/min in a nitrogen atmosphere over a temperature range of 30–300 °C. Alumina was utilized as the reference standard.

2.2.2. The preparation of blank pellets

Centrifugal granulator was chosen to prepare blank pellets and subsequent drug spraying. The particle size distribution of blank pellets is 0.3–0.4 mm. Pelletization by centrifugal granulator is an advanced technique. Being a multivariable process, it is of great significance to know and control the process variables and status. Rotational speed of plate, the ratio of spray rate of binding solution and rotating rate of powder feeder and grounding time were found to be critical parameters affecting the characteristics of pellets. Table 1 denotes the optimized process parameters.

400 g microcrystal cellulose (MCC) was loaded into the chamber of centrifugal granulator, then moistened with purified water. Adding MCC via a hopper to the above wet mass after 10 min wetting. In the process, we must keep all the parameters constant. The pellets need to be granulated for another 4 min even though the particle size distribution meets our requirement. The final products were discharged from the chamber and half-dry in the room temperature. Then, the pellets were placed into oven of 60 °C for 2 h. Finally, sieving the pellets through 40–50 mesh screen.

Table 1 – The optimized parameters of centrifugal granulator for the preparation of blank pellets.

Processing parameter	Value
Rotational speed of plate	200 r/min
Blower rate	10 × 14 L/min
Air flow rate	10 L/min
Spray air pressure	0.6 MPa
Spray rate of binding solution[a]	3–5 g/min
Rotating rate of powder feeder[b]	0–15 r/min
Inlet temperature (°C)	30
Outlet temperature (°C)	20

[a] The spray rate was 5 g/min for the first 15 min, and subsequently 3 g/min until the end.
[b] The rotating rate of powder feeder was 0 r/min for the first 15 min, and subsequently 15 r/min until the end.