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Preparation and evaluation of duloxetine hydrochloride enteric-coated pellets with different enteric polymers

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ABSTRACT

The main purpose of the present study was to prepare duloxetine hydrochloride (DXH) enteric-coated pellets using different enteric polymers. Three layers (drug-loaded layer, barrier layer, and enteric-coated layer) were applied to the inert core pellets, successively. The optimal formulation was manufactured by employing suspension layering method in fluidized bed processor (FBP) with varieties of enteric polymers like Aqoat® AS-LF, Eudragit® L30D55 and HPMCP-HP55. The prepared pellets were measured for physical characterization and the *in vitro* dissolution profile. Scanning electron microscopy (SEM) was conducted to observe the morphology of pellets, and different kinetic models were applied to analyze the release mechanism of Cymbalta® and home-made pellets. The coating weight gain of enteric-coated layer containing Eudragit® L30D55, Aqoat® AS-LF and HP-55 were determined to be 35%, 26% and 24%, respectively. The similarity factors (f_2) of self-made capsules with above polymers and commercially available capsules (Cymbalta®) were above 50 in the dissolution medium of pH 6.8 phosphate buffer solution (PBS). SEM figures showed the smooth surfaces of self-prepared pellets using Eudragit® L30D55 and Aqoat® AS-LF, whereas rough surface was found in the HP-55 pellets at day 0, and an impurity was appearing in the condition of 40 °C/75% relative humidity for 1 month. In conclusion, the pellets prepared by utilizing Eudragit® L30D55 and Aqoat® AS-LF were the optimal preparations based on the dissolution profile and stability.

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1. Introduction

Duloxetine is a selective serotonin norepinephrine reuptake inhibitor (SNRIs) currently known as a safe and effective antidepressant. It is usually in the form of hydrochloride. Duloxetine hydrochloride (DXH) enteric-coated capsule under the name Cymbalta® has been approved for marketing by the FDA. Cymbalta® is indicated in the United States for the treatment of major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathic pain, and fibromyalgia [1].

Pellets, multi-part dosage forms, have both pharmaceutical and therapeutic advantages. Their pharmaceutical benefits including the flexibility in development and design enable the administration of incompatible bioactive compounds owing to the low surface-area-to-volume ratio compared with granules and powders. Therapeutic advantages involve enhancement of bioavailability, decrease of irritation and alteration of mechanism of drug release in the gastrointestinal tract (GIT) when administered orally. Consequently, pellets acting as a substrate of drug are able to be coated with large amounts of drugs and excipients.

Owing to the lability of DXH at pH value less than 2.5, enteric polymers should be applied to prevent acid degradation of DXH in the stomach and provide for rapid drug-release in the small intestine. In this study, several enteric polymers have been employed, such as Eudragit® L30D55, hydroxyl propyl methyl cellulose acetate succinate (HPMCAS) and hydroxyl propyl methyl cellulose phthalate (HPMCP). Eudragit® L30D55 is an anionic copolymer of methacrylic acid and ethyl acrylate, and the ratio of carboxyl to ester group is 1:1. The backbone structures of HPMCAS and HPMCP are all water-soluble polymers, HPMC. HPMCP contains a carboxybenzoyl (phthalyl) group, which can define the solubility of HPMCP, while HPMCAS includes acetyl and succinyl groups, and its solubility is determined by their ratio. The polymers have very low solubility in water due to their hydrophobic nature, when their carboxyl groups are in undissociated form. The structure state of polymer shifts to the formation of the ionized form with increasing water solubility as the pH rises. Thus, the pH can be controlled by adjusting the phthalyl content to make HPMCP soluble. HP-55 and HP-50 are dissolved at a pH around 5.5 and 5.0, respectively. In the same way, HPMCAS-LF (Aqoat® AS-LF) with 8% acetyl and 15% succinyl can be soluble at a pH around 5.5. HP-55 and HPMCAS-LF are selected, because Cymbalta® has been proven to release the drug from pH 5.5 PBS. If the described polymers are employed, we should pay attention to their stability with duloxetine. It is the residual free acids group present in HPMCAS or HPMCP that has been found to react with DXH, and the reactions form succinamide or phthalamide impurities accelerated by humidity and heat [2]. Thus, the barrier layer is an indispensable part of pellets to separate the drug from polymers and improve the stability of preparation.

The aim of the present study is to (a) prepare duloxetine hydrochloride enteric-coated pellets using several enteric polymers; (b) evaluate the effect of the type of enteric polymer, coating weight, pH of enteric polymers and curing conditions on gastric stability and *in vitro* dissolution; and (c) investigate the drug stability by accelerated test.

2. Materials and methods

2.1. Materials

Duloxetine hydrochloride was purchased from Shanghai Wonder Pharmaceutical Co. Ltd. (Shanghai, China). Sucrose-starch nonpareils were from Hangzhou Gaocheng Biotech & Health Co. Ltd. (Hangzhou, China). Hydroxy-propyl methylcellulose E5 (HPMC-E5) was kindly provided by Shanhe Pharmaceutical Co. Ltd. (Anhui, China), and methacrylic acid copolymer (Eudragit® L30D55) was from Evonik (Germany). The polymers of hydroxyl propyl methyl cellulose acetate succinate-LF (Aqoat® AS-LF) and hydroxyl propyl methyl cellulose phthalate (HPMCP) were obtained from Shin-Etsu Chemical Co. Ltd. (Japan) and Samsung Fine Chemicals Co. Ltd. (Korea). No.3 hard gelatin capsule shells were from Suzhou Capsule Co. Ltd. (Suzhou, China). Commercially available duloxetine delayed-release capsules (Cymbalta®, 30 mg/capsule, Eli Lilly and Company, USA) were chosen for comparison. All organic solvents used in HPLC were of high-performance liquid chromatography (HPLC) grade. All other ingredients were of analytical grade.

2.2. Methods

2.2.1. Preparation of pellets

Duloxetine hydrochloride delayed-release pellets were composed of four parts, namely nonpareils (sugar spheres), drug layer, barrier layer and enteric-coated layer successively. All the layers were prepared in a fluidized bed processor (Table 1) by the suspension layer method. Drug layer could also be manufactured by a centrifugal granulator (Table 2).

HPMC-E5 was applied both as binder and as barrier polymer because of its low molecular weight (MW) and its application

Table 1 – Various process parameters of three layers in fluidized bed processor.

S. No.	Parameters	Drug layer	Barrier layer	Enteric-coated layer
1	Inlet temperature (°C)	55–60	50–55	45–50/55–60
2	Outlet temperature (°C)	50–55	45–50	40–45/50–55
3	Product temperature (°C)	40–45	38–40	35–40/40–45
4	Atomization (Bar)	1.0–1.5	1.5–2.0	1.5–2.0
5	Air flow (m^3/h)[a]	50–55	45–50	50–55
6	Spray rate (g/min)[a]	5–7	4–6	4–7

[a] Adjusted according to the experimental conditions in the process of drug-loading or coating.