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Effects of polyvinylpyrrolidone both as a binder and pore-former on the release of sparingly water-soluble topiramate from ethylcellulose coated pellets

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ABSTRACT

Delivering sparingly water-soluble drugs from ethylcellulose (EC) coated pellets with a controlled-release pattern remains challenging. In the present study, hydrophilic polyvinylpyrrolidone (PVP) was used both as a binder and a pore-former in EC coated pellets to deliver sparingly water-soluble topiramate, and the key factors that influenced drug release were identified. When the binder PVP content in drug layers below 20% w/w was decreased, the physical state of topiramate changed from amorphous to crystalline, making much difference to drug solubility and dissolution rates while modifying the drug release profile from first-order to zero-order. In addition, without PVP in drug layering solution, drug layered particles were less sticky during layering process, thus leading to a shorter process and higher loading efficiency. Furthermore, PVP level as a pore-former in EC coating layers mainly governed drug release from the coated pellets with the sensitivity ranging from 23% to 29%. PVP leaching rate and water permeability from EC/PVP film increased with the PVP level, which was perfectly correlated with drug release rate. Additionally, drug release from this formulation was independent of pH of release media or of the paddle mixing speed, but inversely proportional to the osmolality of release media above the physiological range.

1. Introduction

Delivering sparingly water-soluble drugs for a controlled release from polymer coated pellets remains a huge challenge (Mehta et al., 2001). Drug release is affected by multiple factors, such as drug solubility, pore-former types and levels, coating thickness, and osmotic pressure gradient across the membrane (Verma and Garg, 2004). It is well-accepted that the primary mechanism controlling drug release from polymer coated formulations is diffusion of the dissolved drug from the systems (Sadeghi et al., 2003; Muschert et al., 2009a). As dissolved molecules alone can diffuse, the solubility or dissolution rate of drugs plays an important role in governing drug release of the coated pellets (Ragnarsson et al., 1992). Factors affecting the saturation solubility or dissolution rate of drugs in coated pellets, be they process or formulation variables, have positive effect on the release of coated pellets (Kawabata et al., 2011).

The drug layering process, identified as a critical step for coated pellets, directly impacts not only the smooth surface and loading efficiency of drug-loaded cores, but the coating efficiency and uniformity of outer polymeric coating and the reproducibility of drug release from obtained pellets (Iyer et al., 1993; Sinchaipanid et al., 2004; Baki et al., 2010). To improve loading efficiency and surface smoothness of drug-loaded cores, adding a suitable binder into drug layering solution is a conventional formulation strategy. However, the effect of the binder on drug stability, especially on physical stability, was largely ignored though their chemical interaction had been explained thoroughly. In fact, the presence of the binder in drug loading solution might influence physical properties (crystalline state, solubility, or dissolution rate) of sparingly water-soluble drugs during the loading process, thus governing the drug release pattern from coated pellets (Ho et al., 2009; Lee et al., 2011). Therefore, an extensive investigation focused on physical interactions between the binder and drug should also be carried out before production development to find out whether a

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particular sustained release formulation will provide the desired sustained release for sparingly water-soluble drugs.

Apart from the solubility or dissolution rate of drugs, the permeability of polymeric film coats is another important determinant of drug release of coated pellets (Zhang et al., 2007; Siepmann et al., 2007, 2008; Andersson et al., 2013). Ethylcellulose (EC) is the most widespread natural polymer for controlled release, which possesses a good film-forming property and stability under normal physiological or storage conditions but it shows poor permeability to most drugs (Bodmeier, 1997; Siepmann et al., 2007, 2008). In order to increase the permeability of EC film coats, water-soluble particles/materials as a pore-former are usually added to EC coating layers (Gunder et al., 1995). After administration of the dosage form, the pore-former dissolves and forms pores or channels in the coating, or makes the polymer coating micro-porous, inducing drug release (Bodmeier and Paeratakul, 1991). It is thus clear that the hydrophilicity and level of pore-formers in the EC coating layer mainly govern drug release profiles of EC coated pellets (Lin and Shiue, 2011).

Different pore-formers in the release-controlling membranes have been evaluated, including inorganic agents (Bodmeier and Paeratakul, 1991), water-soluble organic agents (Heckötter et al., 2011), and such water-soluble hydrophilic polymers as hydroxypropyl methylcellulose (HPMC) (Gunder et al., 1995), hydroxypropylcellulose (HPC) (Marucci et al., 2011), poly(vinyl alcohol)–poly(ethylene glycol) graft copolymer (PVA–PEG graft copolymer) (Siepmann et al., 2007), and polyvinylpyrrolidone (PVP) (Verma et al., 2003). Among those pore-formers, water-soluble hydrophilic polymers (HPMC and PVP) are most commonly used, thanks to their good solubility in organic solvents and their desirable compatibilities with polymeric coat materials (Andersson et al., 2013). More important, water-soluble polymers can also contribute to improving film formation and providing appropriate mechanical film coating stability when osmotically active pellet/capsule/tablet cores generate considerable hydrostatic pressure within the systems during drug release (Lecomte et al., 2005). However, those water-soluble polymers do not completely leach out from polymeric coatings, nor do they create well-defined porous structures, especially when the pore-former level is lower (Siepmann et al., 2008; Lin and Shiue, 2011). Given the influence of levels and formation state of pore-formers on drug release from coated pellets (Nesbitt et al., 1994), it is likely that the precise mechanism responsible for in vitro drug release patterns of pellets cannot be fully clarified in terms of aqueous solubility of pore-former alone. Therefore, further investigations are equally important (Sadeghi et al., 2003; Muschert et al., 2009a).

Topiramate (TPM) (Fig. 1), a sparingly water-soluble drug with solubility in water of 9.8 mg/ml at 25 °C, is commercially utilized in the treatment of partial seizures and generalized tonic-clonic seizures as well as migraine (Liang et al., 2012). Unfortunately, TPM exhibits a series of peripheral side effects and poor adherence to antiepileptic therapy due to its narrow therapeutic window and frequent doses (Mula et al., 2003). Despite its relatively long half-life of 21 h in vivo, TPM has never been prescribed as a single, daily-dose, in part due to its severe side-effects that often result in peak plasma levels of the drug when taken in high doses (Marino et al., 2012). Accordingly, there is a need for oral delivery of TPM in an extended-release manner, which reduces or eliminates the side effects associated with peaking and fluctuating plasma levels of the drug and is preferably administered in a once-daily regimen (Pellock et al., 2004; Lambrecht et al., 2011).

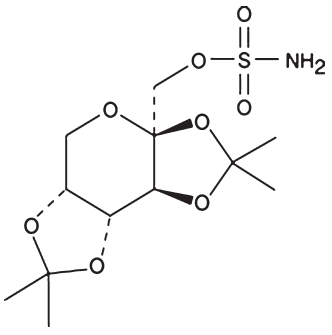

Fig. 1. Chemical structure of model drug topiramate.

In the present study, an intense hydrophilic PVP (K30) was used both as a binder and a pore-former to prepare EC-coated pellets to deliver sparingly water-soluble drug TPM for a controlled release without sigmoid release profiles, and its effects on the process of manufacture, drug physical states, and release patterns of such formulation were investigated.

2. Materials and methods

2.1. Materials

Topiramate (99.8% purity, Beijing Institute of Pharmacology and Toxicology, Beijing, China), nonpareils (600–710 μm, Hangzhou Gaocheng Biotech&Health, Co. Ltd., Hangzhou, China), ethylcellulose (EC, ethocel standard 20 premium, Colorcon Coating Technique Company, UK), polyvinyl pyrrolidone (PVP, Kollidon 30, BASF, Berlin, Germany), and ethanol (95%, Beijing Zhenyu Minsheng Pharmaceutical, Co. Ltd., Beijing, China) were used as received. All the other reagents were either of analytical or chromatographic grades.

2.2. Methods

2.2.1. Drug assay method

TPM solubility, its contents in drug-loaded cores or coated pellets, and in vitro release of coated pellets in the present study were determined using a validated high-performance liquid chromatography (HPLC) equipped with a Waters Model 410 differential refractometer, a Waters Model 600 pump and a Waters Model 2707 autosam-pler under the following conditions: Vensil XBP C_8 column (5 μm, 4.6 mm × 150 mm, Agela Technologies); column temperature, 35 °C; mobile phase, methanol–water (50/50, v/v); flow rate, 1.5 ml/min; injection volume, 200 μl.

2.2.2. Preparation and characterization of coated pellets

2.2.2.1. Preparation of drug-loaded cores. Drug-loaded cores (40% w/w drug loading) were prepared by layering an oversaturated topiramate solution of ethanol–water (7:3, v/v) onto nonpareils in a fluidized bed coater (GPCG-1, Glatt GmbH, Binzen, Germany) using bottom spray under the following conditions: inlet temperature 50 °C, product temperature 36–40 °C, outlet temperature 33–37 °C, air flow rate 30–50 m^3/h, nozzle diameter 0.8 mm, spray pressure 2.0 bar, and spray rate 10 ml/min. The drug and binder PVP of 0%, 10%, 15%, 20%, 25%, and 50% w/w of the drug, respectively, were dissolved in ethanol–water (7:3, v/v) before being layered onto 600 g nonpareils. During this process, the oversaturated layering drug solution was maintained at 40 °C to prevent drug recrystallization in the passageway. Finally, the drug-loaded cores were incubated at 45 °C for 10 min in the coating chamber and subsequently transferred out of the fluid-bed mesh screening (mesh 30/40).

The Drug loading efficiency (%) could be calculated as follows:

$$\text{Drug loading efficiency } (\%) = \left(\frac{\text{Ma}}{\text{Mt}}\right) \times 100 \quad (1)$$

where, Ma (The actual drug content, g/g) was determined by assaying the drug in cores using the above-mentioned HPLC. Mt