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Developing dissolution testing methodologies for extended-release oral dosage forms with supersaturating properties. Case example: Solid dispersion matrix of indomethacin

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ABSTRACT

The objective of this study was to develop an *in vitro* dissolution test method with discrimination ability for an extended-release solid dispersion matrix of a lipophilic drug using the United States Pharmacopeia (USP) Apparatus 4, flow-through cell apparatus. In the open-loop configuration, the sink condition was maintained by manipulating the flow rate of the dissolution medium. To evaluate the testing conditions, the drug release mechanism from an extended-release solid dispersion matrix containing hydrophobic and hydrophilic polymers was investigated. As the hydroxypropyl methylcellulose (HPMC) maintained concentrations of indomethacin higher than the solubility in a dissolution medium, the release of HPMC into the dissolution medium was also quantified using size-exclusion chromatography. We concluded that the USP Apparatus 4 is suitable for application to an *in vitro* dissolution method for orally administered extended-release solid dispersion matrix formulations containing poorly water-soluble drugs.

1. Introduction

In vitro dissolution tests play an important role in the pharmaceutical industry (FDA Guidance for Industry, 1997; Zhang and Lu, 2004; Brown et al., 2011). It is used as quality control tools to ensure consistent product quality for oral dosage forms and it may serve as an *in vitro* surrogate for intraluminal performance (Dressman et al., 1998; Galia et al., 1998; Klein, 2010; FDA Guidance for Industry, 2000; McGilveray, 1996).

In vitro drug release behaviors from solid oral dosage forms are usually evaluated using a compendial basket or paddle dissolution apparatus; the United States Pharmacopeia (USP) Apparatus 1 or 2 (USP 37-NF 32, 2014). However, when testing poorly water-soluble pharmaceutical compounds, maintaining sink conditions, *i.e.*, drug concentration three times lower than the equilibrium solubility (USP 37-NF 32, 2014), is difficult in the 1 L beaker. Sink conditions increase the discriminatory power of the test and are in line with the expected luminal conditions for lipophilic, poorly water-soluble drugs. Further, for quality control testing, a non-biorelevant medium or inclusion of surfactants such as polysorbate 80 (tween 80) or sodium lauryl sulfate (SLS) in the medium might be required for poorly water-soluble drugs to achieve 100% drug release (Shah et al., 1989, 1995). However, as the use of surfactant might diminish the discriminative ability of drug release due to increased drug solubility, the prediction of the biopharmaceutical character of certain products may be difficult. In addition, when high doses of lipophilic active pharmaceutical ingredients are employed, *e.g.*, in extended-release dosage forms, the development of discriminatory dissolution tests becomes challenging.

Other types of compendial dissolution apparatuses have therefore been proposed for the *in vitro* dissolution testing of oral dosage forms containing poorly water-soluble drugs (Brown et al., 2011; Nicolaides et al., 2000, 2001; Fotaki and Reppas, 2005; Fotaki et al., 2009; Jantratid et al., 2009; Kostewicz et al., 2002; Garbacz and Klein, 2012). Of these apparatuses, the flow-through cell

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apparatus, the USP Apparatus 4 (USP 37-NF 32, 2014), has drawn substantial attention in the pharmaceutical industry, as it enables the continuous supply of fresh medium in the open-loop configuration or the application of a sufficient volume of medium to maintain sink conditions in closed-loop configuration. This apparatus has been applied to the evaluation of extended-release hydrogel matrix tablets containing water-soluble drugs for the elucidation of drug release mechanisms, primarily through observations using imaging techniques (Fyfe et al., 2000; Kulinowski et al., 2008; Nott, 2010). However, only a few dissolution studies using the USP Apparatus 4 have been conducted on extended-release oral dosage forms containing poorly water-soluble drugs (Fotaki et al., 2009; Jantratid et al., 2009). In these studies, the discriminative ability was not considered, as the emphasis was on the prediction of luminal performance. The USP Apparatus 4 also offers other unique characteristics such as a variety of flow-cells, easy medium replacement and easy modification of medium flow rate. These characteristics facilitate the development of *in vitro–in vivo* correlation (IVIVC) for extended-release products, particularly for active pharmaceutical ingredients with characteristics of high permeability (Fotaki et al., 2009; Fang et al., 2010).

Here, as a case example, an appropriate *in vitro* dissolution test using the USP Apparatus 4 for an extended drug release matrix containing a poorly water-soluble drug was designed based on the release mechanism. The extended-release matrix consisted of a solid dispersion of hydrophobic ethyl cellulose (EC) and hydrophilic hydroxypropyl methylcellulose (HPMC) and indomethacin, which is a poorly water-soluble drug with weakly acidic characteristics (pK_a, 4.5 (Budavari, 1996) and log *P*, 4.27 (Hansch et al., 1995)). Ohara et al. (2005) studied a drug release mechanism of the EC matrix using the USP Apparatus 2 and reported that the drug release followed a diffusional mechanism whose constants of dissolution rate depended on medium pH. In some cases, however, the volumetric constraint of 1 L made maintenance of the sink condition difficult during the tests. Further, they also reported that hydrophobic interaction between indomethacin and the EC matrix affected their results (Ohara et al., 2005). In the present investigation, the USP Apparatus 4 was applied for the EC matrix to precisely evaluate the drug release behavior and the mechanism, as the open-loop configuration not only enables maintenance of the sink condition but also minimizes the potential interaction between released drug molecules and the matrix. Further, Ozeki et al. (1995) utilized the USP Apparatus 2 and reported that the behavior of water-soluble polymer during the dissolution test has a key role in the drug release mechanism from a solid dispersion prepared with water-soluble and water-insoluble polymers. Therefore, to comprehensively investigate and determine the unique release mechanism of a drug with low solubility from the EC matrix under sink conditions, we implemented the USP Apparatus 4 in the open-loop configuration, and assessed the release behavior of hydrophilic HPMC from the matrix using size-exclusion chromatography (SEC), which is the most common technique for obtaining information on the molecular mass distribution of polymers (Kuga, 1981; Laguna et al., 2001; Tajiri et al., 2010).

2. Materials and methods

2.1. Materials

Gamma-crystalline indomethacin with a particle size of approximately 180 μm or less was purchased from Wako Chemicals (Osaka, Japan). HPMC (TC-5E) with a mean viscosity of 3 mPa s was obtained from Shinetsu Chemical Industries (Tokyo, Japan), EC (ETHOCEL STD 10FP) was purchased from Dow Chemical Company (MI, USA). All other chemicals used were of reagent grade.

2.2. Preparation of extended-release solid dispersion matrix

Solid dispersions consisting of indomethacin, EC and HPMC (1:1:1, weight ratio) were prepared by the solvent evaporation method (Chiou and Riegelman, 1971), as follows: indomethacin (5 g), EC (5 g) and HPMC (5 g) were dissolved in a mixture of ethanol and dichloromethane (1:1) of 200 mL, and the solvents were then evaporated under reduced pressure using a rotary evaporator at 30 °C. Solid dispersion was dried for 3 nights under vacuum at 40 °C, and then milled and sieved with 3 particle size fractions (75–150 μm, 150–250 μm and 250–355 μm). After drying in a desiccator, solid dispersions were used for the studies below.

2.3. X-ray powder diffraction

X-ray diffraction (XRD) patterns of γ-indomethacin crystal and the EC solid dispersion matrix described in Section 2.2 were collected using an X-ray powder diffraction system (RINT-TTR III; Rigaku, Tokyo, Japan). Radiation was generated by Cu K at 50 kV and 300 mA. The instrument was operated in continuous scan mode with a scanning speed of 2° min^{-1}.

2.4. Infrared spectroscopy

Infrared (IR) spectra of each raw material and the EC solid dispersion matrix were measured at a wavenumber resolution of 4 cm^{-1} with 64 scans using a Fourier transform-IR spectrometer (NICOLET 6700; Thermo Fisher Scientific, MA, USA) equipped with a diamond-attenuated total reflection (ATR) accessory and a deuterated triglycine sulfate detector.

2.5. Supersaturation and sustainability study

The solubility of indomethacin in distilled water and in 0.1 and 0.5 mg mL^{-1} HPMC solutions was determined at 37 ± 0.5 °C using the USP Apparatus 2 (NTR-6100; Toyama, Osaka, Japan). The paddle rotation speed was 200 rpm. An excess of active ingredient, equivalent to approximately 100 mg of indomethacin, as a γ-crystalline powder, an indomethacin solution in ethanol (10 mg mL^{-1}), and EC solid dispersion matrix described in Section 2.2 were added to 500 mL of water, and 0.1 and 0.5 mg mL^{-1} HPMC solutions. A 10 mL aliquot of each medium was taken at 1, 2, 3, 6, 24 and 48 h and passed through a 0.2 μm membrane filter (DISMIC-25HP; ADVANTEC, Tokyo, Japan) with the first 5 mL being discarded. Following the addition of an equal volume of ethanol, the drug concentration of each fraction was measured using ultraviolet–visible (UV–vis) spectroscopy (UV-2400PC; Shimadzu, Kyoto, Japan) at 265 nm (Ohara et al., 2005) in confirmation of the linearity, precision, accuracy and limit of quantification of the UV–vis method. The concentration of indomethacin after 48 h was used to determine the solubility of the drug. Measurements were conducted in triplicate, and results are presented as the mean ± standard deviation (SD).

2.6. Dissolution studies of the EC solid dispersion matrix with the USP Apparatus 4

In vitro drug release properties of the EC matrix particles with particle size fraction of 75–150 μm were evaluated using a flow-through cell apparatus (CE7 Smart; SOTAX, Zürich, Switzerland) with a ceramic piston pump (CP 7-35; SOTAX, Zürich, Switzerland) at a medium flow rate of 4, 12, 16 and 24 mL min^{-1} in the open-loop configuration with large flow-cells of 22.6 mm i.d. Further, these