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Development of a discriminative biphasic *in vitro* dissolution test and correlation with *in vivo* pharmacokinetic studies for differently formulated racecadotril granules

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ABSTRACT

The purpose of this study was to discriminate the release behavior from three differently formulated racecadotril (BCS II) granules and to establish an *in vitro-in vivo* correlation. Three granule formulations of the lipophilic drug were prepared with equivalent composition but prepared with different manufacturing processes (dry granulation, wet granulation with or without binder). *In vitro* release of the three granules was investigated using a biphasic dissolution system (phosphate buffer pH 6.8 and octanol) and compared to the conventional single phase USP II dissolution test performed under sink and non-sink conditions. *In vivo* studies with each granule formulation were performed in rats. Interestingly, the granule formulations exhibited pronouncedly different behavior in the different dissolution systems depending on different wetting and dissolution conditions. Single phase USP II dissolution tests lacked discrimination. In contrast, remarkable discrimination between the granule formulations was observed in the octanol phase of biphasic dissolution system with a rank order of release from granules prepared by wet granulation with binder > wet granulation without binder > dry granulation. This release order correlated well with the wettability of these granules. An excellent correlation was also established between *in vitro* release in the octanol phase of the biphasic test and *in vivo* data (R^2 = 0.999). Compared to conventional dissolution methods, the biphasic method provides great potential to discriminate between only minor formulation and process changes within the same dosage form for poorly soluble drugs.

1. Introduction

Establishing a correlation between *in vitro* dissolution profiles and *in vivo* pharmacokinetics has great interest and benefits in pharmaceutical research [1,2]. It is highly desirable that the *in vivo* performance of candidate formulations could be predicted based on *in vitro* release data. However, the predictive power of dissolution tests is often poor [3,4]. Ideally, changes in dissolution *in vivo* should be reflected by the corresponding *in vitro* release. A suitable dissolution test as a surrogate for *in vivo* absorption is highly attractive in the early stage of formulation development to reduce the high costs of animal and clinical studies.

Since conventional dissolution tests have limitations to address this need due to the lack of biorelevance [5], more physiologically relevant dissolution methods have been developed to predict *in vivo* performance. Examples are artificial stomach-duodenum models [6,7], physical stress models [8,9], dissolution-permeation models [10,11] and digestion model [12,13]. In particular, biphasic dissolution tests could be suitable for BCS II drugs due to poor aqueous solubility. Sink conditions can be maintained in dissolution tests by means of surfactants, a large volume of dissolution medium or cosolvents, but they have no physiological relevance [14]. Biphasic dissolution tests consist of immiscible aqueous and organic phases, which can maintain sink conditions due to a continuous partitioning into organic phase. The drug initially dissolves in the aqueous medium and the organic phase mimics gastrointestinal (GI) membrane that continuously removes the dissolved drug from the lower aqueous phase. Thus, the dissolution-partition process between two phases is analogous to drug dissolution and absorption from GI membrane. A two-phase system was firstly proposed to maintain sink conditions in 1961 [15]. Unfortunately, not much interest has been observed with this test.

Previous studies have reported the development of biphasic dissolution systems [16–18] and their correlation to *in vivo* absorption for different dosage forms, including immediate release [19], modified

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release [18], lipid [20] and amorphous formulations [21]. The biphasic dissolution model ideally also enables the evaluation of various formulation factors such as dose strength [22], excipient effects [19,21], drug precipitation [18,23] and particle size [24] on the *in vivo* performance of poorly soluble drugs. Shi et al. applied a biphasic system combining USP 4 and USP 2 methods to discriminate three celecoxib formulations (a Celebrex® capsule, a drug solution containing surfactant and a self-emulsifying drug delivery system) and to obtain a rank-order relationship between the amount of drug in the organic phase and *in vivo* pharmacokinetic parameters [19]. The different release kinetics observed in the biphasic model were attributed to the effect of surfactant within the formulations on the free drug concentration. In another study, three fenofibrate formulations (pure API capsule, micronized formulation and self-emulsifying lipid-based formulation) were discriminated by a biphasic dissolution test, whereas single phase dissolution tests (sink, non-sink and biorelevant) were not suitable [25]. However, there is still a lack in studies to discriminate between minor formulation and process changes within the same dosage forms.

Tablets are the most popular oral dosage forms. They are preferably prepared by direct compression, however, dry and wet granulation are also widely used to improve the physical properties (particle size, wettability, density, porosity, mechanical strength, flowability and compactability) of the drug: excipient blend and the tablets. Drug release rates are greatly influenced by different formulation compositions and manufacturing processes. Zhang et al. reported that different matrix tablets were prepared by dry blending, wet granulation, partial melt granulation, and melt granulation. Different dissolution profiles were obtained due to the formation of different matrix structures [26]. Juang and Storey investigated the effects of compositional and processing differences on drug dissolution from controlled release gel extrusion module tablets [27]. Tablets prepared by wet granulation released faster than those prepared by direct compression due to different swelling properties. Liu et al. used two viscosity grades of hydroxypropyl methylcellulose (HPMC, 50 and 4000 cP) in varying ratios with water to prepare diclofenac sodium matrix tablets by a wet granulation method [28]. The larger amount of high viscosity grade HPMC resulted in a slower release rate, which was in agreement with *in vivo* investigation. The aforementioned cases showed that differences of different granule formulations induced by composition and process variables could be reflected in the conventional dissolution tests. However, the release from granule formulations prepared by dry and wet granulation investigated in our study could not be discriminated by the conventional dissolution tests. Therefore, the objective was to develop a biphasic dissolution system and to evaluate its potential to discriminate three granules of racecadotril (model BCS II drug) with only minor differences induced by manufacturing variables and to compare the results to conventional dissolution tests under sink and non-sink conditions. A further objective was to establish an *in vitro-in vivo* correlation (IVIVC) based on *in vivo* data obtained from studies in rats.

2. Materials and methods

2.1. Materials

Racecadotril (Allphamed Pharbil Arzneimittel GmbH, Göttingen, Germany), thiorphan (Santa Cruz Biotechnology, CA, USA), pregelatinized maize starch (Lycatab PGS, Roquette, Lestrem, France), lactose (Granulac® 200, Meggle AG, Wasserburg, Germany), 1-octanol (Sigma Aldrich Chemie GmbH, Steinheim, Germany), acetonitrile (HPLC-grade, Honeywell/Burdick & Jackson, Muskegon, USA), sodium phosphate monobasic monohydrate (Merck KGaA, Darmstadt, Germany), sodium hydroxide, sodium lauryl sulfate (SLS) (Carl Roth GmbH & Co., Karlsruhe, Germany). All other reagents used were of analytical grade.

2.2. Granule formulations

Three granule formulations of racecadotril with the same quantitative composition were prepared by different manufacturing techniques. 10 g drug powder was passed through a 250 μm sieve and physically mixed with 8 g pregelatinized starch and 4 g lactose.

2.2.1. Dry granulation

Powder blends were compressed into tablet slugs to a hardness of 40 ± 10 N using a single punch tablet press EK0 (Korsch Pressen GmbH, Berlin, Germany). The slugs were crushed in a dry granulator (Erweka TG 2S attached to an Erweka AR 400 motor, Erweka GmbH, Frankfurt, Germany) to obtain granules using an 800 μm mesh sieve.

2.2.2. Wet granulation

Drug and diluents (lactose and pregelatinized starch) were mixed for 5 min in a mixer torque rheometer (Caleva Ltd., Dorset, UK) and granulated with 6.4 g water or 8.1% (w/w) Lycatab PGS binder solution. The wet mass was forced through a 1 mm sieve and then dried overnight at 50 °C. The dried granules were passed through an 800 μm mesh sieve.

2.3. Determination of drug content

50 mg granules were dispersed in 100 mL 80% (v/v) methanol aqueous solution. The samples were sonicated for 30 min, then placed in a shaker overnight. The solution was filtered through a 0.22 μm membrane filter and drug amount was determined by UV spectrometer at 232 nm (Agilent 8453, Agilent Technologies GmbH, Waldbronn, Germany). Each formulation was analyzed in triplicate.

2.4. Solubility measurements

20 mg racecadotril was added to 10 mL aqueous media (50 mM phosphate buffer pH 6.8 with or without 0.75% w/v SLS and phosphate buffer pH 6.8 saturated with octanol), and 1 g racecadotril was added to 10 mL 1-octanol. The solubility test was performed at 37 °C and 80 rpm for 48 h using a horizontal shaker (GFL® 3033, GFL Gesellschaft für Labortechnik, Burgwedel, Germany) (n = 3). Saturated solutions were filtered through a 0.22 μm membrane filter. The drug concentration was measured by UV spectrophotometry at 232 nm (Agilent 8453, Agilent Technologies GmbH, Waldbronn, Germany).

2.5. Conventional dissolution test

Racecadotril release from three granule formulations was determined in an USP II apparatus (900 mL 50 mM phosphate buffer pH 6.8 containing 0.75% w/v SLS [29], 75 rpm, 37 °C, sink conditions, n = 3) (VK 7010, Vankel Technology Group, Cary, USA). Samples were taken at 30, 60, 90, 120, 150, 180, 210 and 240 min and detected using UV-spectrophotometer at 232 nm.

2.6. Single phase dissolution test under non-sink conditions

Single phase dissolution tests were carried out using the USP rotating paddle method (500 mL 50 mM phosphate buffer pH 6.8, 75 rpm, 37 °C, non-sink conditions, n = 3) (VK 7010, Vankel Technology Group, Cary, USA). Samples were collected at 30, 60, 90, 120, 150, 180, 210 and 240 min and used for UV assaying.

2.7. Biphasic dissolution test

Racecadotril granules were placed in a hollow plastic cylindrical holder (2.0 cm × 1.2 cm) and wrapped with one-layer gauze to avoid granule floating (Fig. 1A). This device was tied to a magnetic stirrer. The biphasic test was performed in 250 mL glass beakers with 100 mL