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Short communication

Influence of *in vitro* dissolution test conditions on drug precipitation behavior: Aripiprazole example

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Introduction

Aripiprazole is a weakly basic drug with pronounced pH-dependent solubility, exhibiting high solubility in acidic conditions and decreased solubility at higher pH (Krstevska et al., 2025). During gastrointestinal (GI) transit, this may result in drug's supersaturation and precipitation, potentially affecting its oral bioavailability (BA).

Biopredictive *in vitro* dissolution methods for orally administered weakly basic drugs should adequately capture the interplay between dissolution and precipitation phenomena. However, literature reports have shown that drug precipitation behavior is highly dependent on the applied *in vitro* dissolution methodology (Patel et al., 2019; Dwyer et al., 2019).

Hence, the aim of this study was to evaluate the precipitation behavior of aripiprazole from immediate release (IR) tablets using two different *in vitro* dissolution test setups.

Materials and Methods

Dynamic two-vessel glass-bead flow-through system

Dissolution experiments of Abilify 15 mg and 30 mg IR tablets (Otsuka, Netherlands) were performed using a dynamic two-vessel, glass-bead flow-through system (University of Ljubljana, Faculty of Pharmacy), simulating gastric-to-intestinal transfer. A detailed description of the apparatus is provided in Bogataj et al. (2015). The gastric vessel contained 40 mL of 0.01 M HCl pH 2.0, glass beads (25 g) and a magnetic bar, stirring the content at 50 rpm, while the intestinal vessel was pre-filled with 40 mL of medium with pH 5.4, which is a 1:1 (v/v) mixture of 0.01 M HCl pH 2.0 with Japanese Pharmacopeia (JP) acetate buffer pH 5.5. The sample was transferred from the gastric to intestinal vessel and subsequently to the collection cylinder at flow rate of 1.25 mL/min. To maintain constant medium volumes in each vessel, fresh medium was supplied throughout the experiment duration (1 h). Only the samples collected in the cylinder were analyzed.

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Three-stage, pH shift in vitro dissolution setup

Additional experiments of Abilify 15 mg and 30 mg IR tablets were conducted in a single compartment, three-stage pH-shift dissolution method using a paddle apparatus operating at 50 rpm. Tablets were initially introduced into 250 mL of 0.01 M HCl pH 2.0. After 15 min, 250 mL of JP acetate buffer pH 5.5 was added, resulting in a total volume of 500 mL and final medium pH of 5.4. A third stage was initiated after 30 min by adding 450 mL of JP acetate buffer pH 4.0. The experiment continued for 6 h. The third stage was included to evaluate potential precipitate redissolution; however, only the first hour was considered in this study.

Data analysis

Dissolved aripiprazole concentrations were quantified using the previously described HPLC method (Krstevska et al., 2025). Precipitation kinetic (in terms of precipitation time (t_{prec})) was evaluated using a first-order precipitation model.

Results and discussion

In the dynamic glass-bead flow-through system, maximum dissolved concentrations (C_{max}) were reached at 30 min, followed by a gradual decline in drug concentration. C_{max} increased with dose (0.04 to 0.06 mg/mL for the 15 mg and 30 mg IR tablet strengths, respectively). Additionally, a more pronounced decline in drug concentration was observed at the higher dose, indicating dose-dependent precipitation. Under these conditions t_{prec} of 47 min and 30 min were obtained for the 15 mg and 30 mg IR tablet strengths, respectively.

In the three-stage pH-shift setup, higher initial drug concentrations were observed compared to the dynamic system, particularly for the 30 mg tablet strength. This is likely due to more extensive drug dissolution during the first stage, facilitated by the larger medium volume and prolonged time for dissolution prior to pH change. Following pH shift to 5.4, a more rapid decline in dissolved drug concentration occurred compared to the dynamic system. While t_{prec} was similar for the 15 mg tablet strength (45 min), a substantially shorter t_{prec} was observed for the 30 mg tablet strength (16 min).

Despite identical pH conditions and medium composition, the dissolution setup influenced the extent and rate of aripiprazole precipitation. The faster precipitation observed in the pH-shift method for the 30 mg tablet strength is likely related to the higher dissolved drug concentrations achieved during the first stage prior to exposure to intestinal medium. In contrast, in the dynamic glass-bead flow-through system, dissolution and transfer between compartments occur simultaneously under continuous flow conditions, better reflecting GI physiological conditions and resulting in a more gradual decline in the dissolved drug concentrations.

Conclusion

This work demonstrated that precipitation time for a given compound may vary substantially depending on the *in vitro* methodology. To better reflect *in vivo* precipitation that might occur during GI transit of an orally administered drug, it is essential that *in vitro* dissolution setups closely mimic physiological conditions.

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