Biorelevant dissolution models to assess precipitation of weak base drug

Viviane Annisa¹, Teuku Nanda Saifullah Sulaiman², Agung Endro Nugroho*³

¹Faculty of Pharmacy, Universitas Gadjah Mada, Sekip Utara, Yogyakarta-55281, Indonesia
²Departement of Pharmaceutics, Faculty of Pharmacy, Universitas Gadjah Mada, Sekip Utara, Yogyakarta-55281, Indonesia
³Departement of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada, Sekip Utara, Yogyakarta-55281, Indonesia

The impact of precipitation can affect the amount of drug absorbed, thereby affecting the amount of drug in the systemic body. The precipitation process is preceded by a supersaturation phase, caused by decreased drug solubility in the gastrointestinal tract. This precipitation occurs for weak base drugs with low solubility. When the drug entering the small intestine, the solubility of weak base drugs decrease, then occurs supersaturation, which leads to precipitation, so that drug precipitation is one of a challenge for the pharmaceutical industry in drug development. Precipitation testing of water-soluble weak base drugs can be carried out by the pH shift method to describe the gastrointestinal pH gradient from gastric to small intestine. This pH change can cause supersaturation and then trigger precipitation, especially for weak base drugs. The methods that can used to assess precipitation drug is modification of the USP dissolution which are two compartment and multi compartment model. The choice of dissolution medium play an important role in the test results. The use of bio relevant medium can produce closer in vitro and in vivo correlations than the use of buffers. Generally, the medium used to simulate the weakly condition in the small intestine is FaSSIF (Fasted State Simulated Intestinal Fluid) or FeSSIF (Fed State Stimulate Intestinal Fluid) medium. The medium used to simulate the acidic condition in the stomach is FaSSGF (Fasted state simulated gastric fluid) or FeSSGF (Fed state simulated gastric fluid) medium.

INTRODUCTION

Gastrointestinal pH plays an important role in the solubility of ionized drugs. The solubility of drugs with weak bases and weak acids depends on the gastrointestinal pH. Weak acid drugs easier dissolved in base pH, while weak base drugs easier dissolved in acidic pH. In weak base drugs, although the solubility is high at the pH of gastric acid, only a few drugs are absorbed in the stomach because the drug is mostly absorbed in the small intestine due to a wider intestinal surface area. This plays an important role in the amount of drug absorbed so that it affects the bio availability of the drug (Kostewicz et al,
Drug precipitation is one of the dominant factors causing decreased drug bioavailability. It is necessary to carry out tests to predict drug precipitation in the gastrointestinal tract. Generally, testing method of drug precipitation is carried out using dissolution methods (Dai, 2010; Rubbens et al., 2016). When designing in vitro tests for supersaturation evaluation, it is necessary to attention about the various test conditions because they can play a significant role in the results of supersaturation testing. Media that are usually used such as buffers do not represent the pH of the stomach or intestines because they are not biorelevant with the gastrointestinal composition, such as osmolarity, ionic strength, buffer capacity, viscosity, bile and pancreatic secretion, and facial tension. Media that biorelevant with stomach is FaSSGF (Fasted state simulated gastric fluid) or FeSSGF (Fed state simulated gastric fluid) media, while biorelevant with intestinal is FaSSIF (Fasted State Simulated Intestinal Fluid) or FeSSIF (Fed State Stimulate Intestinal Fluid) media (Klein, 2010).

**Supersaturation of Weak Base Drugs**

Supersaturation is a thermodynamically unstable state in the presence of an increase in the concentration of free drug in solution above the saturation solubility value (Kaur et al., 2018). Supersaturation can be occur by co-solvents in liquid preparations, meta stable form in solid form such as salt or amorphous form, and decreased solubility of weak bases caused by a shift in pH when the drug from the stomach enters the small intestine (Carlert et al., 2014). Several techniques can be used to create supersaturation conditions, there are removing solvents, dissolving the meta stable solid phase, changing temperatures, changing pH, and adding solvents to reduce solubility (Warren et al., 2010). Supersaturation that occurs in the gastrointestinal tract can be explained in 2 cases. The first case is supersaturation occurs in weak drugs which ionize in an acidic environment, then when it enters the small intestine occurring the pH shift to higher pH so that the degree of ionization and equilibrium solubility have decreased.

The second case is supersaturation occurs by losing of drug solubilization capacity (Warren et al., 2010). The presence of food can contribute to increase significantly in solubility as long as the drug is in the gastrointestinal tract. The concentration of bile components containing bile salts and lecithin will increase when food is present. Solubility is increased through micellar solubilization or increased wetness of the intestinal contents (Kostewicz et al., 2004). Weak base drug interactions with drugs that inhibit gastric acid secretion, such as Proton Pump Inhibitor (PPI) drugs, H2 antagonists, and antacids can decrease the solubility of weak base drugs (Kambayashi and Dressman, 2019).

An increase in gastric acid pH can decrease drug solubility, the strength of force absorption, and intestinal supersaturation (Rubens et al., 2016). Super-saturated drug preparations are effective for increasing the absorption of oral drugs with poor solubility. However, the supersaturation phase is thermodynamically unstable so that the drug has the potential to undergo precipitation as a result of changes in physiological conditions (Kataoka et al., 2019). A higher degree of supersaturation has a greater risk of precipitation. The degree of supersaturation is defined as the ratio between the activity of the drug dissolved in the supersaturated solution compared to the activity of the drug in the saturated solution of the thermodynamically stable form (Blaabjerg et al., 2018).

Several strategies can be used to inhibit precipitation by selecting excipients that inhibit precipitation, such as dissolved polymers (for example: HPMC, PVA, PVP, Eudragit) surfactants (for example: Tween, SDS, Span) or cyclodextrin derivatives (Taupitz et al., 2013). Saturated drug formulas such as salt form or amorphous solid dispersions are suitable for amorphous or polymorphic precipitated drugs because they increase solubility so that absorption is also increased. For drugs that are crystalline precipitated from the super saturation phase, a controlled release formulation is an appropriate strategy to increase drug absorption by keeping the small intestine concentration below the nucleation critical concentration. The use of watersoluble polymers can form a super saturation phase which can also inhibit precipitation (Kataoka et al., 2004). If the weak base drugs with poor solubility go into intestine, their solubility will decrease drastically and then undergo supersaturation. Supersaturation can potentially lead to precipitation (Kambayashi and Dressman, 2019). Drug precipitation is the result of nucleation and crystal growth as a thermodynamically undesirable phase when supersaturated. The separation process usually referred to as crystallization is divided into 2 stages, including the nucleation stage and the crystal growth stage. In the first stage, the molecules of the solute particles accumulate then configure to small nuclei bodies in the solution. Aggregation of nuclei bodies causes their size to be larger than the critical size, then initiation of crystal growth (Kumar and Sureshkumar, 2020; Singh et al., 2019).
An understanding of the small bowel supersaturation and precipitation of weak base drugs is important for predicting the pharmacokinetic profile of the drug (Kaur et al., 2020).

**Drug Precipitation**

Drug precipitation is formed from nucleation and crystal growth as a thermodynamically undesirable supersaturated phase. The separation process usually referred to crystallization, is divided into 2 stages, which are the nucleation stage and the crystal growth stage. The first stage is the molecules of the solute particles accumulate and form small nuclei bodies in the solution. Aggregation of the nuclei body causes its size to be larger than the critical size, then initiation of crystal growth occurs. The second stage is crystal growth, the molecules are periodically organized to form a crystal skeleton (Kumar and Sureshkumar, 2020; Singh et al., 2019). The two stages occur simultaneously which are influenced by physical conditions. The rate and mechanism of crystallization are determined by the solubility of the solute, degree of supersaturation, speed of supersaturation, diffusivity, temperature, and reactivity of the nucleation surface (Warren et al., 2010).

Precipitation can be caused by a drastic change in pH, dilution of the drug preparation in body fluids, or digestion of the solubilized excipient in the formulation. The molecular structure of active substance has tendency to crystallize of the drug. The crowded drug structures with many rotating bonds are usually slow to crystallize, whereas rigid structures are usually quick to crystallize (Raina et al., 2015). The precipitates form as a crystalline or amorphous material. The precipitation mechanism in crystalline and amorphous materials is generally the same, the difference is only in the natural packaging of the solid material that is formed (Warren et al., 2010). Drug precipitation can reduce the drug concentration in the aqueous phase thereby reducing the amount of drug that will be absorbed into the systemic circulation. The reduced amount of absorption will decrease the AUC of the drug as well as the efficacy of the drug (Dai, 2010). Kinetics of precipitation have a various result depending on the physiological conditions and physical and chemical properties of the drug.

Physiological conditions, such as gastric acid pH, time of residence in the stomach, gastric emptying time, pancreatic secretion, bile secretion, gastrointestinal transfer, hydrodynamics, presence or absence of food in the gastrointestinal tract, while the chemical-physical properties of drugs, such as pKa, solubility, molecular structure, velocity dissolution, and disintegration (Bevernage et al., 2013; Hens et al., 2016). Drug precipitation from supersaturated solutions can be accelerated by increasing degree of supersaturation, increasing solubility, decreasing temperature, decreasing solution viscosity, and decreasing interface stress. If the rate of precipitation is slow during the drug absorption process, there is no precipitation (Warren et al., 2010).

**Biorelevant Medium**

The choice of dissolution media plays an important role in the test results. Media that are usually used such as buffers do not represent the pH of the stomach or intestines because they are not biorele-
vant with the gastrointestinal composition, such as osmolarity, ionic strength, buffer capacity, viscosity, bile and pancreatic secretion, and facial tension. The use of this biorelevant medium resulted in closer in vitro and in vivo correlations than the use of buffers (Klein, 2010).

**SIF (Simulated Intestinal Fluid) Media**

Generally, the media used for simulating base conditions in the small intestine is FaSSIF (Fasted State Simulated Intestinal Fluid) or FeSSIF (Fed State Stimulate Intestinal Fluid) media. Table 1. FaSSIF was developed to stimulate fasting conditions in the proximal small intestine. This medium contains leticin as a representation of bile salts and phospholipids which facilitate to wet solids as well as the solubilization of lipophilic drugs into the mixed micelle. Sodium taurocholate is chosen as the representation of bile salts because cholic acid is one of the bile salts in human bile. The phosphate buffer serves to avoid instability in the pH value. NaCl functions to achieve conditions close to iso-osmolar (Dressman and Reppas, 2000; Klein, 2010).

The presence of food causes hydrodynamic changes and intraluminal volume. After the entry of solids, the pH of the chyme decreases slowly after food is entered so that a decrease in facial tension in the media is caused by the presence of pepsin like physiological conditions (Jantratid et al., 2008). FeSSIF does not contain lipolysis products so together with bile it increases solubility of poor soluble drugs. Data in humans shows that the pH in the upper small intestine decreases slowly after food is entered so that a review is needed to obtain better predictions of in vivo data (Jantratid et al., 2008).

**SGF (Simulated Gastric Fluid) Media**

The use of simulated gastric fluid is FaSSGF (Fed state simulated gastric fluid) or FeSSGF (Fed state simulated gastric fluid) media. Table 2. FaSSGF contains pepsin and a small amount of bile salts and leticin. This medium is more suitable for physiological conditions because the decrease in facial tension in the media is caused by the presence of pepsin like physiological conditions (Jantratid et al., 2008). The use of FaSSGF is highly recommended for in vitro dissolution testing. However, this volume does not represent the volume of stomach acid in the fasted state. The volume in the stomach is estimated to be 200-300 ml, but it is difficult to obtain reproducible results on dissolution tests using the standard USP apparatus with too little volume. Therefore, it is advisable to use a “mini paddle” for volumes less than 300 ml (Klein, 2010).

The condition of the stomach containing food is very dependent on the composition of the food being digested. The ideal medium that represents the condition of the stomach at a mealtime should be similar to the nutritional and physical chemical properties of food. There are two alternative media that approach the condition of the stomach when eating, namely milk containing 3.5% fat and Ensure Plus. Both media have physical and chemical properties similar to the food standards recommended by the American HHS-FDA for the study of the effect of food on the bioavailability-bioequivalence test (Jantratid et al., 2008). Ensure Plus is closer to the chemical properties of FDA breakfast standards, whereas milk is more suitable for simulating a low-fat breakfast. However, both media still have drawbacks related to pH or pepsin (Klein, 2010).

**Modification of Dissolution Methods**

Precipitation testing on water-soluble weak base drugs can be carried out by the pH shift method to describe the gastrointestinal pH gradient from gastric pH to small intestine pH. This process of pH changes that can cause super saturation and trigger precipitation, especially for immediate reaction weak base drugs. The pH shift method can test the supersaturation potential of ionized drugs. The shift in pH can decrease the solubility of ionized drugs according to the acidic or base properties of the drug. Acidic drugs are more soluble at base pH, while base drugs will dissolve more in acidic pH. Compared to the solvent square method, this method is more biorelevant for weak base drugs that are transferred from the stomach to the small intestine. Then there is supersaturation due to decreased solubility of weak base drugs. The pH shifting can be performed with one compartment or multiple compartments (Bevernage et al., 2013). Modifications of the USP dissolution method have been carried out to obtain results that are close to physiological conditions. This modification can be a two-compartment or a multi-compartment model.

**Two compartment model**

The two compartment method is designed to simulate the condition of the stomach and small intestine. This method uses USP II apparatus based on pH shift with 2 compartments, which are the donor com-
Figure 2: Multi Compartments Model. (1) Gastric Compartment (2) Intestine Compartment (3) Absorption Compartment (4) Reservoir Compartment.

Table 1: Composition of FaSSIF and FeSSIF.

| Composition       | FaSSIF       | FeSSIF       |
|-------------------|--------------|--------------|
| Sodium Taurocholate | 3000 μM      | 15000 μM    |
| Lecithin          | 750 μM       | 3750 μM     |
| NaH2PO4           | 3.438 g      | -           |
| Acetate acid      | -            | 8.65 g      |
| NaCl              | 6.186 g      | 11.874 g    |
| NaOH pellet       | -            | 4.04 g      |
| Deionisation water| ad 11        | ad 11       |
| NaOH              | qs ad pH 6.5 | -           |
| pH                | 6.5          | 5           |
| Osmolality        | 270 mOsmol/kg| 670 mOsmol/kg|
| Buffer capacity   | 12 mEq/pH/L  | 72 mEq/pH/L |
| Ionic strength    | 0.200 mol/L  | 0.304 mol/L |
| Surface tension   | 54 mN/m      | 48 mN/m     |

The multi-compartment model is designed as closely as possible to the gastrointestinal tract, there are 4 compartments, which are the gastric, small intestine, absorption/sink, and reservoir compartment Figure 2. The multi-compartment model is more advantageous than the single compartment. The multi-compartment method not only can evaluate drug precipitation directly, but also can estimate...
Table 2: Composition of FaSGF and FeSGF.

| Composition                  | FaSSGF       | FeSSGF       |
|------------------------------|--------------|--------------|
| Sodium Taurocholate          | 80 µM        | -            |
| Lecithin                     | 20 µM        | -            |
| Pepsin                       | 0.1 mg/ml    | -            |
| NaCl                         | 34.2 mM      | 237.02 mM    |
| Acetate acid                 | -            | 17.12 mM     |
| Acetate sodium               | -            | 29.75 mM     |
| Milk/acetate buffer          | -            | 1:1          |
| Deionisation water           | ad 11        | -            |
| HCl                          | qs ad pH 1.6 | qs ad Ph 5.0 |
| pH                           | 1.6          | 5.0          |
| Osmolality                   | 120.7±2.5 mOsmol/kg | 400 mOsmol/kg |
| Buffer capacity              | -            | 25 mEq/pH/L  |
| Ionic strength               | 1.6±0.1 mol/L| 5.0±0.1 mol/L|
| Surface tension              | 42.6 mN/m    | -            |

the precipitation potential to diagnose whether the precipitation contributes to bioavailability. This method also obtains results that are closer to in vivo simulations and more efficient than conventional dissolution methods (Dai, 2010). The dissolution test of a formula that has the potential to be supersaturated and precipitated can use the USP I or II apparatus method. The dissolution method of USP I or II has been widely used for the study of dissolution or precipitation of oral drugs under different parameter conditions, such as dissolution medium, dissolution volume, stirring rate, and hydrodynamics (Dai, 2010). There are many advantages of using the USP apparatus, namely that it provides robust results, is easy to operate, and is widely available (Klein, 2010).

It should be noted that several factors contribute to dissolution and absorption. These factors include: physical and chemical properties of drugs, bio pharmaceuticals, and physiological conditions. In order to develop a model that has a good correlation between in vitro and in vivo, it is important to consider these factors. Physical and chemical factors affect the dissolution of drugs including solubility, environmental pH, salt form, and particle size. Bio pharmaceutical factors are represented from the permeability of the drug, the non-ionized form of the drug is easier to permeate than the ionized form. Partition coefficient value (Log P) which has good permeability is between 0 and 3. Physiological conditions that need to be considered is the pH in the gastrointestinal tract. A pH gradient from a low pH in the stomach (1 to 2) to a high pH in the intestinal (5 to 8) can change the solubility, dissolution, stability, and permeability of the drug entering. Apart from pH, other physiological factors are gastric emptying time and existence of food (Lu et al., 2011).

Case Study

Dipyridamole

Kambayashi, 2016 (Kambayashi et al., 2016) tested dipyridamole precipitation in FaSSIF-V2 with a 2-stage dumping setup. The dipyridamole precipitation profile was faster at higher dipyridamole concentrations. The result shows that the predicted total and dissolved drug concentration curves have similar results to the in vivo profile so that the test method could be used to predict drug precipitation in the small intestine, particularly for early development. Kambayashi, 2019 (Kambayashi and Dressman, 2019) conducted another dissolution test of dipyridamol (Persantine tablets) used the same method. Persantine tablet dissolved in FaSSGF about 80% for 30 minutes, whereas in FaSSIF-V2 only 9% dissolved after 1 hour.

The dipyridamol precipitation test (2x Persantine 25 mg tablets) in various acidic pH was carried out by Gu, 2005 (Gu et al., 2005) used a multi compartment method with a peristaltic pump transfer system. The dissolution rate of dipyridamole is higher at pH 1.2 than at pH 2.0. Dipyridamol was easier to dissolve at a more acidic stomach pH. Dipyridamol was dissolved at both pH for 25 minutes. The rate of drug transfer from the stomach compartment to the intestine was slower at pH 2.0, whereas the amount of drug transferred to the absorption compartment at pH 1.2 and 2.0 was almost the same. An experiment was also conducted on stomach acid with a pH of 5.9 using famotidine to increase the pH of stomach acid. The test results of the multi compartment
method showed exceeds the estimate result than in vivo test, but was still closer than the conventional dissolution method.

**Ketoconazole**

The ketoconazole precipitation test (Nizoral 200 mg tablets) was carried out by Ruff, 2017 (Ruff et al., 2017) in FaSSGF-V2 and FaSSIF-V2 media used the mini vessel method and USP II Apparatus with a peristaltic pump transfer system. In FaSSGF-V2 medium more than 80% dissolved after 20 minutes and completely dissolved after 45 minutes, whereas in FaSSIF-V2 media only 2% of the drug was dissolved. Ketoconazole at a higher concentration results in a faster precipitation rate. If it compared with dipyridamole, ketoconazole had a higher degree of supersaturation (the ratio of initial solute concentration to saturation solubility) is higher. This was probably due to the pKa value of ketoconazole (pKa 2.9) which was lower than dipyridamole (pKa 5.7-6.4) so that it had a greater potential to change into a non-ionized form and then its solubility decreased at neutral pH (Kambayashi et al., 2016).

**Cinnarizine**

The precipitation test for cinnarizine tablets used Cinnarizine 30 mg, Arlevert 20 mg (Cinnarizine / Dimenhidrinat) and Stugeron 25 mg (Cinnarizine) tablets was carried out by Berlin, 2014 (Berlin et al., 2014) with a peristaltic pump transfer system. In FaSSGF media pH 1.6, Arlevert tablets were dissolved for 15 minutes, while Stugeron tablets were dissolved for 30 minutes. In FaSSIF-V2 media both tablets were slowly dissolved, releasing only 5.6% and still continued to reach the solubility value after 240 minutes. Arlevert tablets released as much as 47% in FeSSGF media after 240 minutes, whereas cinnarizine tablets 30 mg were significantly slower to release only 27% in 240 minutes. In FeSSIF-V2 medium, both Arlevert and Cinnarizine 30 mg tablets had greater dissolution than in FeSSGF media. Cinnarizine tablets have a lower percentage dissolution value than Artlevart.

The cinnarizine precipitation test (cinnarizine tablets 25 mg and 50 mg) with various acidic pH was carried out by (Gu et al., 2005) multi compartment method with peristaltic pump transfer system. The dissolution rate of cinnarizine is higher at pH 2.0 than at pH 5.0. Cinnarizine dissolved faster at a more acidic stomach pH. Cinnarizine was completely dissolved at pH 2.0 for 30 minutes. When compared the dissolution profile between the multi compartment method and the conventional dissolution test method there were differences. The dissolved concentration at pH 2.0 used the multi compartment method was 4.6x higher, whereas with the conventional dissolution method it was 57x higher. The results of the dissolution used the multi compartment method were closer to the in vivo data. Therefore, the multi compartment method was more accurate to estimate cinnarizine concentrations with different gastric pH. This could be due to the multi-compartment simulation method closer to the actual physiological conditions, where the volume of media in the gastric compartment has decreased into the intestinal compartment, while the volume in conventional dissolution was constant or unchanged.

**CONCLUSIONS**

The dissolution test of a formula that has the potential to precipitate can use a modified USP II apparatus method. The dissolution method has been widely used for the study of dissolution or precipitation of oral drugs under different parameter conditions, such as dissolution media, dissolution volume, stirring rate, and hydrodynamics. There are many advantages of using the USP apparatus, that it provides robust results, is easy to operate, and is widely available. The use of bio relevant media resulted in closer in vitro and in vivo correlations than the use of buffers. The bio relevant medium for the stomach is FaSSGF / FeSSSGF, while the bio relevant medium for the intestine is FeSSIF / FeSSIF.

**ACKNOWLEDGEMENT**

The authors acknowledge the receipt of financial support from the State Ministry of Research and Technology under PMDSU program (a scholarship sponsor).

**Funding Support**

The authors declare that they have no funding support for this study.

**Conflict of Interest**

The authors declare that they have no conflict of interest for this study.

**REFERENCES**

Berlin, M., Przyklenk, K.-H., Richtberg, A. 2014. Prediction of oral absorption of cinnarizine - A highly supersaturating poorly soluble weak base with borderline permeability. European Journal of Pharmaceutics and Biopharmaceutics, 88(3):795-806.

Bevernage, J., Brouwers, J., Brewster, M. E. 2013. Evaluation of gastrointestinal drug supersatura-
tion and precipitation: Strategies and issues. *International Journal of Pharmaceutics*, 453(1):25–35.

Blaabjerg, L., Grohganz, H., Lindenberg, E., et al. 2018. The Influence of Polymers on the Supersaturation Potential of Poor and Good Glass Formers. *Pharmaceutics*, 10(4):164–164.

Carlert, S., Lennerås, H., Abrahamsson, B. 2014. Evaluation of the use of Classical Nucleation Theory for predicting intestinal crystalline precipitation of two weakly basic BSC class II drugs. *European Journal of Pharmaceutical Sciences*, 53:17–27.

Dai, W.-G. 2010. In vitro methods to assess drug precipitation. *International Journal of Pharmaceutics*, 393(1-2):1–16.

Dressman, J. B., Reppas, C. 2000. In vitro–in vivo correlations for lipophilic, poorly water-soluble drugs. *European Journal of Pharmaceutical Sciences*, 11(2):S73–S80.

Gu, C.-H., Rao, D., Gandhi, R. B., et al. 2005. Using a novel multicompartiment dissolution system to predict the effect of gastric pH on the oral absorption of weak bases with poor intrinsic solubility. *Journal of Pharmaceutical Sciences*, 94(1):199–208.

Hens, B., Brouwers, J., Corsetti, M., Augustijns, P. 2016. Supersaturation and Precipitation of Posaconazole Upon Entry in the Upper Small Intestine in Humans. *Journal of Pharmaceutical Sciences*, 105(9):2677–2684.

Jantratid, E., Janssen, N., Reppas, C., Dressman, J. B. 2008. Dissolution media simulating conditions in the proximal human gastrointestinal tract. *Pharmaceutical Research*, 25(7):1663–1676.

Kambayashi, A., Dressman, J. B. 2019. Predicting the changes in oral absorption of weak base drugs under elevated gastric pH using an in vitro-in silico-in vivo approach. *Journal of Pharmaceutical Sciences*, 108(1):584–591.

Kambayashi, A., Yasuji, T., Dressman, J. B. 2016. Prediction of the precipitation profiles of weak base drugs in the small intestine using a simplified transfer model coupled with insilico modeling. *European Journal of Pharmaceutics and Biopharmaceutics*, 103:95–103.

Katoaoka, M., Takeyama, S., Minami, K., et al. 2019. In vitro assessment of supersaturation/precipitation and biological membrane permeation of poorly water-soluble drugs. *Journal of Pharmaceutical Sciences*, 108(8):2580–2587.

Kaur, N., Narang, A., Bansal, A. K. 2018. Use of biorelevant dissolution and PBPK modeling to predict oral drug absorption. *European Journal of Pharmaceutics and Biopharmaceutics*, 129:222–246.

Kaur, N., Thakur, P. S., Shete, G., et al. 2020. Understanding the Oral Absorption of Irbesartan Using Biorelevant Dissolution Testing and PBPK Modeling. *AAPS PharmSciTech*, 21(3):102–102.

Klein, S. 2010. The Use of Biorelevant Dissolution Media to Forecast the In Vivo Performance of a Drug. *The AAPS Journal*, 12(3):397–406.

Kostewicz, E. S., Wunderlich, M., Brauns, U. 2004. Predicting the precipitation of poorly soluble weak bases upon entry in the small intestine. *Journal of Pharmacy and Pharmacology*, 56(1):43–51.

Kumar, R. S., Sureshkumar, R. 2020. A Review on Precipitation inhibitors in supersaturable self emulsifying drug delivery system. *International Journal of Research in Pharmaceutical Sciences*, 11(2):2481–2488.

Lu, Y., Kim, S., Park, K. 2011. In vitro-in vivo correlation: Perspectives on model development. *International Journal of Pharmaceutics*, 418(1):142–148.

Raina, S. A., Ererdenbrugh, B. V., Alonzo, D. E., et al. 2015. Trends in the Precipitation and Crystallization Behavior of Supersaturated Aqueous Solutions of Poorly Water-Soluble Drugs Assessed Using Synchrotron Radiation. *Journal of Pharmaceutical Sciences*, 104(6):1981–1992.

Rubbens, J., Brouwers, J., Tack, J., et al. 2016. Gastrointestinal dissolution, supersaturation and precipitation of the weak base indinavir in healthy volunteers. *European Journal of Pharmaceutics and Biopharmaceutics*, 109:122–129.

Ruff, A., Fiolka, T., Kostewicz, E. S. 2017. Prediction of Ketoconazole absorption using an updated in vitro transfer model coupled to physiologically based pharmacokinetic modelling. *European Journal of Pharmaceutical Sciences*, 100:42–55.

Singh, D., Singh, M., Tharmatt, A., et al. 2019. Polymeric precipitation inhibitor as an effective trigger to convert supersaturated into supersaturable state in vivo. *Therapeutic Delivery*, 10(9):599–608.

Taupitz, T., Dressman, J. B., Klein, S. 2013. In Vitro Tools for Evaluating Novel Dosage Forms of Poorly Soluble, Weakly Basic Drugs: Case Example Ketoconazole. *Journal of Pharmaceutical Sciences*, 102(10):3645–3652.

Warren, D. B., Benamer, H., Porter, C. J., et al. 2010. Using polymeric precipitation inhibitors to improve the absorption of poorly water-soluble drugs. *Journal of Drug Targeting*, 18(10):704–731.