

Dissolution Media Simulating Fasted and Fed States

Margareth Marques

United States Pharmacopeia

Rockville, MD

email: mrm@usp.org

When dissolution testing is used to forecast the in vivo performance of a drug, it is critical that the in vitro test mimic the conditions in vivo as closely as possible. A team of researchers, led by Dr. Jennifer Dressman of the J. W. Goethe University, Germany, has developed biorelevant gastrointestinal media that simulate the fasted and fed states. These media have been used to examine the solubility and dissolution characteristics of several classes of drugs including poorly soluble weak bases and lipophilic drugs to assist in predicting in vivo absorption behavior (1).

Biorelevant in vitro dissolution testing is useful for qualitative forecasting of formulation and food effects on the dissolution and availability of orally administered drugs. It has been observed that biorelevant media can provide a more accurate simulation of pharmacokinetic profiles than simulated gastric fluid or simulated intestinal fluid.

The use of biorelevant media can have a great impact on the pharmacokinetic studies performed to optimize dosing conditions and product formulation. In addition, biorelevant dissolution testing could be used to assess bioequivalence of post-approval formulation changes in certain kinds of drugs (2–5).

The formulation and preparation instructions for the biorelevant media developed by Dr. Dressman's group are detailed below.

Fasted State Simulated Intestinal Fluid (FaSSIF)

Sodium taurocholate	3mM
Lecithin	0.75 mM
NaOH (pellets)	0.174 g
NaH ₂ PO ₄ ·H ₂ O	1.977 g
NaCl	3.093 g
Purified water qs.	500 mL

Media has a pH of 6.50 and an osmolality of about 270 mOsmol/kg.

Preparation of blank FaSSIF

Dissolve 1.74 g of NaOH (pellets), 19.77 g of NaH₂PO₄·H₂O or 17.19 g of anhydrous NaH₂PO₄, and 30.93 g of NaCl in 5 L of purified water. Adjust the pH to exactly 6.5 using 1 N NaOH or 1 N HCl.

Preparation of FaSSIF

Dissolve 3.3 g of sodium taurocholate in 500 mL blank FaSSIF. Add 11.8 mL of a solution containing 100 mg/mL lecithin in methylene chloride, forming an emulsion. The methylene chloride is eliminated under vacuum at about 40°C. Draw a vacuum for fifteen minutes at 250 mbar, followed by 15 minutes at 100 mbar. This results in a clear, micellar solution, having no perceptible odor of methylene chloride. After cooling to room temperature, adjust the volume to 2 L with blank FaSSIF.

For dissolution tests a volume of 500 mL is recommended.

Fed State Simulated Intestinal Fluid (FeSSIF)

Sodium taurocholate	15 mM
Lecithin	3.75 mM
NaOH (pellets)	4.04 g
Glacial Acetic Acid	8.65 g
NaCl	11.874 g
Purified water qs.	1000 mL

Media has a pH of 5.00 and an osmolality of about 670 mOsmol/kg.

Preparation of blank FeSSIF

Dissolve 20.2 g of NaOH (pellets), 43.25 g of glacial acetic acid, and 59.37 g of NaCl in 5 L of purified water. Adjust the pH to exactly 5.0 using 1 N NaOH or 1 N HCl.

Preparation of FeSSIF

Dissolve 16.5 g of sodium taurocholate in 500 mL of blank FeSSIF. Add 59.08 mL of a solution containing 100 mg/mL lecithin in methylene chloride, forming an emulsion. The methylene chloride is eliminated under vacuum at about 40°C. Draw a vacuum for fifteen minutes at 250 mbar, followed by 15 minutes at 100 mbar. This results in a clear to slightly hazy, micellar solution having no perceptible odor of methylene chloride. After cooling to room temperature, adjust the volume to 2 L with blank FeSSIF.

The recommended volume for simulating conditions in the upper small intestine after a meal is one liter.

References

1. Kostwicz, E. S., Brauns, U., Becker, R., Dressman, J. B. – Forecasting the oral absorption behavior of poorly soluble weak bases using solubility and dissolution studies in biorelevant media. *Pharm. Res.*, 19(3): 345–349, 2002.
2. Dressman, J. B., Reppas, C. – In vitro-in vivo correlations for lipophilic, poorly water-soluble drugs. *B. T. Gattefosse*, 93: 91–100, 2000.
3. Nicolaidis, E., Symillides, M., Dressman, J. B., Reppas, C. – Biorelevant dissolution testing to predict the plasma profile of lipophilic drugs after oral administration. *Pharm. Res.*, 18(3): 380–388, 2001.
4. Horter, D., Dressman, J. B. – Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract. *Adv. Drug Del. Rev.*, 46: 75–87, 2001.
5. Lobenberg, R., Kramer, J., Shah, V. P., Amidon, G. L., Dressman, J. B. – Dissolution testing as a prognostic tool for oral drug absorption: Dissolution behavior of glibenclamide. *Pharm. Res.*, 17: 439–444, 2000.