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Bio-relevant Dissolution Media Development

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Generic pharmaceutical industry is a most important part of health care system, which provides affordable care to Americans. Generic drugs are same in strength, administration route, dosage form, safety and efficacy as brand drugs. The only thing in which generic drugs are not same as brand drugs is cost, in fact the generic pharmaceutical association states that consumers who are able to replace all their brand name drugs with generics can save up to 30% to as much as 80% on their daily drug costs [1]. Generic drugs are cheaper than brand drugs because it does not require multi stage clinical trials and lengthy formulation development. Generic drug must be bioequivalent with brand drug (should have same amount of absorption in blood as brand drug). Several unsuccessful bio studies may increase the cost of drug development and in the case of first to file status filling, ANDA (Abbreviated New Drug Application) applicant may lose the race. Development of bioequivalent formulation is a vary clanging task for formulator and being an analytical scientist it is our responsibility to develop a dissolution media which can show correlation between *in vitro* and *in vivo* release profile of generic and brand drug.

Dissolution test is essential for all solid oral doses form and it is used in all phases of development for product release and stability testing. In the case of lipophilic drugs dissolution release can be rate-limiting step in the *in vivo* absorption process and hence the dissolution medium is a critical component of the test that can cause problems [2,3]. The most challenging step is to correlating *in vitro* drug release to *in vivo* drug profile (IVIVC). Food effect on drug release and bioavailability of drug can be predicted by Bio relevant dissolution testing. *In vitro* dissolution in Bio relevant media simulates conditions of GI tract. Based upon food affect bio relevant dissolution media separated into two categories i.e., Fasted state and Fed state. Dr. Jennifer Dressman has developed Bio-relevant gastrointestinal media that simulate the fasted and fed state [4].

The preparation procedure for the Bio-relevant media is mention [4].

Fasted State Simulated Intestinal Fluid (FaSSIF) (Table 1).

Preparation of blank FaSSIF

Dissolve 1.74 g of sodium hydroxide pellets, 19.77 g of sodium dihydrogen phosphate monohydrate or 17.19 g of sodium dihydrogen phosphate anhydrous and 30.93 g of sodium chloride in 5 L of purified water. Adjust the pH to exactly pH 6.5 using 1 N Sodium hydroxide solution or 1 N Hydrochloric acid solution.

Preparation of FaSSIF

Dissolve 3.3 g sodium taurocholate was dissolved in approximately 500 mL of the blank FaSSIF. Then 11.8 mL of a Methylene chloride solution containing 100 mg/mL lecithin was added. This produced an emulsion (i.e., the resulting product was turbid). The Methylene chloride was then evaporated under vacuum using a Rotavap at a temperature of about 40°C. About 10 min at 500 mbar followed by 30 min at about 50 mbar led to complete removal of the methylene chloride. The result was a clear, micellar solution having no perceptible odor of Methylene chloride. After cooling to room temperature, the volume was brought to 2 L with blank FaSSIF.

Fed State Simulated Intestinal Fluid (FeSSIF) (Table 2).

Preparation of blank FeSSIF

Dissolve 20.2 g of sodium hydroxide pellets, 43.25 g of glacial acetic acid and 59.37 g of sodium chloride in 5 L of purified water. Adjust the pH to exactly pH 5.0 using 1 N Sodium hydroxide solution or 1 N Hydrochloric acid solution.

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 min 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 1 L.

In pharmaceutical industries Dr. Dressman bio-relevant media is widely used but this media also has some limitation and cannot

Reagents	Quantity
Sodium taurocholate (µM)	3 mM
Lecithin (µM)	0.75 mM
Sodium Hydroxide (Pellets)	0.174 g
Sodium dihydrogenphosphate monohydrate	1.977 g
Sodium Chloride	3.093 g
Water	500 mL
Media has a pH of 6.50 and an osmolality of about 270 mOsmol /kg.	

Table 1: Composition of fasted-state simulated gastric fluid (FaSSIF).

Reagents	Quantity
Sodium taurocholate (µM)	15 mM
Lecithin (µM)	3.75 mM
Sodium Hydroxide (Pellets)	4.04 g
Glacial acetic acid	8.65 g
Sodium Chloride	11.874 g
Water	1000 mL
Media has a pH of 5.00 and an osmolality of about 6700 mOsmol/kg.	

Table 2: Composition of fed state simulated intestinal fluid (FaSSIF).

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show *in vivo-in vitro* correlation (IVIVC) for all class of drugs. Drugs, which has very limited solubility and needed higher concentration of surfactant to dissolve, will not show IVIVC in Dr. Dressman's bio-relevant media. In that case analytical scientist should develop bio-relevant dissolution media and conditions by considering following,

1. Location of drug released from drug product.
2. Total time to release drug completely from drug product.
3. Chemical composition of fluids in which drug is released.

Another approach to develop a bio-relevant dissolution media also widely used by generic industry in the case of first unsuccessful bioequivalence study. This procedure is called reverse bio-relevancy. In this dissolution development scientist develops media and parameters for failed pilot/pivotal batch and brand batch which was used in clinical dosing and target to match bioequivalence study (*in vivo*) data. Finalized condition can be applied on further development batches, which will help formulator to decide next bioequivalence study batch.

The development of bio-relevant dissolution media is very important in generic pharmaceutical industry. Developing bio-relevant dissolution media not only provide information on drug behaviour in human body but also helps formulation scientist to early stage developments and later stage modification of formulation.

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