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Technical Note: Using Biorelevant Media with Different Types of Orally Administered Formulations

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One of the most important aims of formulation development for a poorly soluble new chemical entity (NCE) or active pharmaceutical ingredient (API) is to enhance bioavailability. For orally administered compounds, this can be broadly assessed by knowing the solubility and the permeability of a compound. The Biopharmaceutical Classification System (BCS) proposed by Amidon et.al in 1995 (*1*) uses these two parameters to classify an NCE. If a compound is to be administered orally, the solubility in small intestinal fluids is particularly important because most compounds are absorbed in this region of the gastrointestinal tract. Therefore, information on how a formulation potentially enhances performance can be assessed by testing its solubility or dissolution rate in biorelevant media (*2–4*). The use of biorelevant media such as Fed State Simulated Intestinal Fluid (FeSSIF) and Fasted State Simulated Intestinal Fluid (FaSSIF) is particularly important for poorly water-soluble compounds because they simulate the solubilizing environment of mixed micelles. They comprise a bile salt and lecithin, which are responsible for the emulsification and absorption of dietary fats in humans and animals. This note reviews how biorelevant media can be used to assess the performance of different formulations for poorly water-soluble compounds.

SOLID DISPERSIONS

Solid dispersions can be an interesting formulation approach (*5*) to increase the solubility of an API. This is typically achieved by embedding the amorphous form into a water soluble polymer matrix to stabilize it. Amorphous formulations are also referred to as "solid dispersions," "solid solutions," or "high energy solutions." A solid dispersion can be produced by hot-melt extrusion or spray-drying. Upon hydration of the solid dispersion, the amorphous particles of the poorly soluble compound dissolve, and a supersaturated solution is typically formed that is transiently stabilized by polymers. Supersaturation is encouraged because of the lower energy required for dissolution of the amorphous form compared to the crystalline drug. Dissolution testing in biorelevant media can be helpful in ranking the performance of such solid dispersions (*6*). Additionally, these media are also helpful to check the physical stability of these formulations (i.e., to examine if the drug crystallizes).

NANOSUSPENSIONS

Another approach to increase the dissolution rate of a poorly water-soluble compound is to make a nanoparticle formulation from it. They can be produced by "constructive" processes (e.g., precipitation) or "destructive" processes such as pearl milling. An ultra-fine particle size leads to a higher surface area of the API, which may result in a higher dissolution rate. To establish the effect of a finer particle size for a specific API, the dissolution rate can be determined in FaSSIF or FeSSIF. Also, to gain an insight into a potential food effect, the dissolution rates in FaSSIF and FeSSIF medium can be compared (*7*).

LIPID-BASED FORMULATIONS

Lipid-based formulations are another option for increasing the solubility of a poorly water-soluble compound. The surface area of the resulting oil droplets can significantly influence the digestive process, and therefore, the use of biorelevant media simulating micellization is of importance (*8*). Additionally, the digested lipid from the formulation, such as monoglycerides and fatty acids, may also have an impact on the solubility (*9*). Therefore, biorelevant media containing mixed micelles from taurocholate and phosphatidylcholine comprising monoglycerides and fatty acids may yield more detailed information about the pharmacodynamic process in the intestine regarding lipolysis of lipids used for formulation (*10*).

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diss-17-02-07.indd 46 2010-6-4 14:08:14

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diss-17-02-07.indd 47 2010-6-4 14:08:15