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Review

Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability

Prakash Khadka [a,1], *Jieun Ro* [a,1], *Hyeongmin Kim* [a], *Iksoo Kim* [a], *Jeong Tae Kim* [a], *Hyunil Kim* [a], *Jae Min Cho* [a], *Gyiae Yun* [b], *Jaehwi Lee* [a,*]

[a] *College of Pharmacy, Chung-Ang University, Seoul 156-756, Republic of Korea*

[b] *Department of Food Science and Technology, Chung-Ang University, Anseong 456-756, Republic of Korea*

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ABSTRACT

Pharmaceutical particle technology is employed to improve poor aqueous solubility of drug compounds that limits *in vivo* bioavailability owing to their low dissolution rate in the gastrointestinal fluids following oral administration. The particle technology involves several approaches from the conventional size reduction processes to the newer, novel particle technologies that modify the solubility properties of the drugs and produce solid, powdered form of the drugs that are readily soluble in water and can be easily formulated into various dosage forms. This review highlights the solid particle technologies available for improving solubility, dissolution and bioavailability of drugs with poor aqueous solubility.

1. Background

1.1. *Drug solubility and bioavailability*

It has been well explained that solubility, dissolution and gastrointestinal permeability are fundamental parameters that control rate and extent of drug absorption and its bioavailability [1]. The water solubility of a drug is a fundamental property that plays an important role in the absorption of the drug after oral administration. It also governs the possibility of parenteral administration of a drug and is useful in manipulating and testing of drug properties during the drug design and development process. The drug solubility is an equilibrium measure but also the dissolution rate at which the solid drug or drug from the dosage form passes into solution is critically important when the dissolution time is limited [2]. Although the oral bioavailability of a drug depends

* *Corresponding author*. College of Pharmacy, Chung-Ang University, 84 Heuksuk-ro, Dongjak-gu, Seoul 156-756, Republic of Korea. Tel.: +82 2 820 5606, +82 10 9872 3384 (mobile); fax: +82 2 816 7338.
E-mail address: jaehwi@cau.ac.kr (J. Lee).

[1] These two authors equally contributed to this work.

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on aqueous solubility, drug permeability, dissolution rate, first-pass metabolism and susceptibility to efflux mechanisms, aqueous solubility and drug permeability are also important parameters attributed to oral bioavailability [3]. In drug discovery, the number of insoluble drug candidates has increased in recent years, with almost 70% of new drug candidates showing poor water solubility [4]. For these drug candidates, poor aqueous solubility and poor dissolution in the GI fluids is a limiting factor to the *in vivo* bioavailability after oral administration. Therefore, *in vitro* dissolution has been recognized as an important element in drug development and thus increasing the dissolution rate of poorly soluble drugs and enhancing their bioavailability is an important challenge to pharmaceutical scientists [5,6].

1.2. *Biopharmaceutics classification system*

Biopharmaceutics classification system (BCS) is a scientific classification of a drug substance based on its aqueous solubility and intestinal permeability that correlates *in vitro* dissolution and *in vivo* bioavailability of drug products (Table 1) [1,7]. When combined with *in vitro* dissolution characteristics of the drug product, BCS takes into account two major factors: solubility and intestinal permeability, which govern the rate and extent of oral drug absorption from solid dosage forms and ultimately, its bioavailability [8]. Due to this reason, BCS is the fundamental tool in the drug development especially in the development of oral drug products.

The food and drug administration (FDA) criterion for solubility classification of a drug in BCS is based on the highest dose strength in an immediate release (IR) oral product [8]. A drug is considered highly soluble when the highest strength is soluble in 250 ml (this volume is derived from typical bioequivalence study protocols) or less of aqueous media over the pH range of 1.0–7.5; otherwise the drug substance is considered poorly soluble. On the other hand, the permeability classification is based directly on the extent of intestinal absorption of a drug substance in humans or indirectly on the measurements of the rate of the mass transfer across the human intestinal membrane, or in animals, or *in vivo* models [7,8]. A drug substance is considered highly permeable when the extent of intestinal absorption is determined to be 90% or higher based on mass-balance or in comparison to an intravenous reference dose.

The bioavailability of BCS class II drugs is likely to be dissolution rate limited. But due to their high permeability, the BCS class II drugs have been on focus for solubility enhancement researches in the recent times and several formulation approaches for this class of compounds has been developed [9,10,11]. In case of class III drugs, the bioavailability is permeability-rate limited, but dissolution is likely to occur rapidly. Thus for class III drugs, formulating IR solid dosage forms with absorption enhancers can be a viable formulation option to improve their permeability [4]. But in case of BCS class IV compounds, the bioavailability is limited by both dissolution as well as intestinal permeability. Because of low membrane permeability, BCS class IV drugs are often poor candidates for drug development since solubility and dissolution enhancement alone might not help improve their bioavailability. However, these classes of compounds cannot be ignored just because of their permeability issues. Therefore the current approaches being used for BCS class II drugs, together with absorption enhancers, can be applied to formulate class IV compounds [4]. Another formulation development approach for class IV compounds is the selection of a better drug candidate with more appropriate physiochemical properties during the lead optimization phase [12,13].

1.3. *Science of pharmaceutical powders*

From one of the oldest professions of mankind, powder technology has now transformed itself from an art into a science with its principal applicability in food, chemical and pharmaceutical industries [14]. Not only the active drug substance, but also most of the pharmaceutical excipients are available in the powder form which makes the science of powder technology an inevitable discipline in pharmaceutical industry and pharmaceutics. Apart from the basic conventional processes like grinding, mixing and formulating, pharmaceutical manufacturing processes involve modification of powder and particle properties to create a novel drug formulation, with enhanced solubility and dissolution properties. Pharmaceutical powder technology deals with the examining of materials, formulations, additives and processes on achieving the desired properties or performance of the particles or composites [15]. Particle properties of active drug substances or excipients play an important role in the dosage form fabrication and performance. Pharmaceutical powder technology also deals with areas of surface engineering usually explored through the applications of surface chemistry and surface morphology. Overall, the properties like particle shape, size, adhesiveness, morphology, roughness, wettability, density, surface chemistry, plasticity, hardness, brittleness and hygroscopicity are important for successful dosage form design and development. Ultimately, these strategies are implemented to produce a drug product that is readily soluble in the GI tract because incomplete dissolution in the GI tract can severely restrict their oral bioavailability drug compounds [16].

Table 1 – Biopharmaceutics Classification System (BCS) with characteristics of drugs.

BCS class	Solubility	Permeability	Absorption pattern	Examples
I	High	High	Well absorbed	*Metoprolol, Diltiazem, Propranolol*
II	Low	High	Well absorbed	*Phenytoin, Nifedipine, Danazol*
III	High	Low	Variable	*Cimetidine, Acyclovir, Captopril*
IV	Low	Low	Poorly absorbed	*Hydrochlorothiazide, Taxol, Furosemide*