

# BIO-AVAILABILITY ENHANCEMENT OF POORLY WATER SOLUBLE DRUGS

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**Abstract** - Lipid-based drug delivery systems have shown great potentials in oral delivery of poorly water-soluble drugs, primarily for lipophilic drugs, with several successfully marketed products. Pre-dissolving drugs in lipids, surfactants, or mixtures of lipids and surfactants omits the dissolving/dissolution step, which is a potential rate limiting factor for oral absorption of poorly water-soluble drugs. Lipids not only vary in structures and physicochemical properties, but also in their digestibility and absorption pathway; therefore selection of lipid excipients and dosage form has a pronounced effect on the biopharmaceutical aspects of drug absorption and distribution both *in vitro* and *in vivo*. The aim of this review is to provide an overview of the different lipid-based dosage forms from a biopharmaceutical point of view and to describe effects of lipid dosage forms and lipid excipients on drug solubility, absorption and distribution.

**Key Words:** Lipid-based, Drug delivery, Absorption, Bio-availability, Permeability

## 1. INTRODUCTION

### 1.1 ORAL DRUG ADMINISTRATION

Oral drug administration is desirable due to good patient convenience and consequently better compliance. For absorption of drug from the gastrointestinal (GI) tract, a drug needs to be dissolved in the GI fluids. It is therefore a problem for the increasing number of poorly water-soluble drug candidates that do not dissolve in GI fluid and thereby obstructing absorption from GIT. Thus solubilisation of poorly water soluble drugs and in turn absorption from GIT

to enhance bioavailability is increasingly undertaken for development in the Pharmaceutical industry. However, it seems that a high permeability is maintained for most of these compounds, rendering them class II drugs in the Biopharmaceutics Classification System (BCS). Thus the solubility and/or dissolution rate in the GIT often is the limiting step for the absorption of these drugs. The interests in lipid-based drug delivery systems (LBDDS) have increased since past two decades as a function of identification of these Pharmaceutically difficult candidates, and increased even further after successful launch of lipid-based oral pharmaceutical product is adopted on large scale. One of the advantages of LBDDS is that drug molecules are pre-dissolved in lipid excipients, avoiding a potentially rate limiting dissolution step in the GI tract, thereby achieving an increased and consistent bioavailability. (1)

To develop LBDDS, several complex biological processes have to be taken into account, such as digestion of lipid excipients, formation of different colloid phases during lipid digestion, and transfer of the drug between these colloid phases. Several reviews of lipid based formulations are available; each focusing on different aspects of lipids in drug delivery and proposed a Lipid Formulations Classification System (LFCS) and categorised lipid-based formulations into four different types according to their compositions. (2-5)

### 1.2 BCS AND BDDCS CLASSIFICATION SYSTEM

BCS classification was introduced in 1995 for selected compound and were subjected to lipid base formulation for predicting the likelihood of *in-vitro* - *in-vivo* correlations for immediate release dosage forms. It was recognition for drug solubility/dissolution properties and gastrointestinal

permeability which are the fundamental parameters controlling the rate and extent of drug absorption. According to BCS, drug substances are classified as:

- 1) **Class I - High solubility high permeability**
- Class II - Low solubility high permeability**
- Class III - High solubility low permeability**
- Class IV - Low solubility low permeability**

The Food and Drug Administration (FDA) has set specifications regarding the solubility and permeability and boundaries to be used for this BCS classification.(6)

## 2. SOLUBILITY

A drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over a pH range of 1 to 7.5 (equilibrium solubility at 37°C).

## 3. PERMEABILITY

In the absence of evidence suggesting instability in the gastrointestinal tract, a drug substance is considered highly permeable when the extent of absorption in humans is determined to be 90% or more of an administered dose based on mass balance determination or in comparison to an intravenous reference dose (absolute bioavailability study). (7-10)

A typical representation of the BCS indicating the absorption of a class II drug can be markedly improved by attention to the formulation is mentioned in Figure 1. (11)

	High Solubility	Low Solubility
High Permeability	<b>Class 1</b> High Solubility High Permeability (Rapid Dissolution for Biowaiver)	<b>Class 2</b> Low Solubility High Permeability
Low Permeability	<b>Class 3</b> High Solubility Low Permeability	<b>Class 4</b> Low Solubility Low Permeability

Figure 1. A Typical Representation of the BCS Classification

Compounds with a low aqueous solubility, i.e. belonging to the BCS class II and IV, are frequently discussed in relation to LBDDS. Compounds may fall into BCS II and IV for different physical chemical reasons; therefore it can be helpful to identify the etiology of the poor solubility.

In 2005, Wu and Benet introduced the Bio pharmaceuticals Drug Disposition Classification System (BDDCS) as they recognized that there was a very strong correlation between the intestinal permeability rate and the extent of metabolism.

In proposing the BDDCS classification system, Wu and Benet substituted extensive and poor metabolism for high and low permeability in the BCS while utilising the same criteria as the FDA for high and low solubility. Using the BDDCS certain drugs were classified based on the extent of metabolism and solubility.

BDDCS is a means to predict the drug disposition characteristics of novel chemicals ("new molecular entities", NMEs) during the early stages of drug discovery and development. Recently, Benet and Larregieu reviewed the differences between BCS and BDDCS in terms of purpose and basis. The purpose of BCS is to facilitate biowaivers of *in-vivo* bioequivalence studies for drugs that exhibit no significant intestinal absorption problems. In contrast, the purpose of BDDCS is to predict the drug disposition of NMEs as well as potential drug-drug interactions for NMEs and drugs on the market with respect to the intestine and liver. BDDCS, using elimination criteria, may expand the number of class 1 drugs eligible for a waiver of *in-vivo* bioequivalence studies and provide predictability of drug disposition profiles for classes 2, 3 and 4 compounds. The Bio pharmaceuticals Drug Disposition Classification System (BDDCS) as proposed by Wu and Benet is depicted in Figure 2. (12)

	High Solubility	Low Solubility
Extensive Metabolism	<b>Class 1</b> High Solubility Extensive Metabolism	<b>Class 2</b> Low Solubility Extensive Metabolism
Poor Metabolism	<b>Class 3</b> High Solubility Poor Metabolism	<b>Class 4</b> Low Solubility Poor Metabolism

Figure 2. The Biopharmaceuticals Drug Disposition Classification System (BDDCS)

The therapeutic effectiveness of a drug depends upon the ability of the dosage form to deliver the medicament to its site of action at a rate and amount sufficient to elicit the desired pharmacological response. The attribute of the dosage form is referred to as physiologic availability, biologic availability or simply bioavailability. For most drugs, the pharmacologic response can be related directly to the plasma levels. Thus the term bioavailability is defined as the rate and extent (amount) of absorption of unchanged drug from its dosage form. It can also be defined as the rate and the extent to which the ingredients or active moiety is absorbed from the drug product and becomes available at the site of action. As per the definition of bioavailability, a drug with poor bioavailability is one with poor aqueous solubility, slow dissolution rate in biological fluids, poor stability of dissolved drug at physiological pH, poor permeation through bio membrane and extensive pre-systemic metabolism. (11,13-14)

In recent years drug bioavailability has become a subject of interest not only in drug development, but also in the early stages of drug discovery.

#### 4. METHODS FOR ENHANCEMENT OF BIOAVAILABILITY (6)

As far as the definition of bioavailability is concerned, a drug with poor bioavailability is the one with;

- A. Poor aqueous solubility and/ or slow dissolution rate in the biologic fluids.
- B. Poor stability of the dissolved drug at the physiologic pH.
- C. Inadequate partition coefficient and thus poor permeation through the bio-membrane.
- D. Extensive pre-systemic metabolism.

#### 5. THERE ARE THREE MAJOR APPROACHES TO OVERCOME THE BIOAVAILABILITY PROBLEMS

- A. **PHARMACEUTICS APPROACH:** Modification of formulation and manufacturing processes or to alter Physiochemical Properties of the Drug.
- B. **PHARMACOKINETIC APPROACH:** Pharmacokinetics of drug is altered by modifying its chemical structure.
- C. **BIOLOGICAL APPROACH :** The route of drug administration may be changed such as parenteral form instead of oral form. Rate dissolution and its solubility are very important factors in third approach. The second approach of chemical modification has number of drawbacks such as being very expensive, time consuming, requires repetition of chemical studies, risk of precipitation and adverse effects. Moreover, the new chemical entity may suffer from another pharmacokinetic disorder or bear the risk of precipitating adverse effects. So generally only pharmaceuticals approach is considered as most beneficial and effective.

The attempts, to optimise the formulation with manufacturing process or physiochemical properties of the drug, are mainly aimed to enhance dissolution rate as it is the major rate limiting step in the absorption of most drugs. There are several ways in which the dissolution rate of the drug can be enhanced. Some of the widely used methods, are aimed to increase the effective surface area of the drugs and are separated in present studies.

It is a consequence of the finding that most of the drug candidates that are failed in clinical trials because of problems with ADME (absorption, distribution, metabolism, excretion) and toxicology, rather than of efficacy.

Efforts are being directed in the pharmaceutical industry to improve success rates by considering the ADME and toxicology aspects in drug discovery from very early period. Therefore, it is not surprising that the numbers of publications on drug bioavailability has been increasing steadily. Thus, the approaches to improve drug solubility as well as drug permeability are the two main strategies in order to enhance the bioavailability of drugs. (6)

Presently the formulation of poorly water soluble compounds presented interesting challenge to formulation scientists in the pharmaceutical industry. It was observed that over 40% of new chemical entities discovered by the pharmaceutical industry are poorly soluble or lipophilic compounds, which lead to poor oral bioavailability, high intra and inter subject variability and lack of dose proportionality. (6,11)

Currently, number of technologies are available to deal with the poor solubility, dissolution rate and bioavailability of insoluble drugs. Various formulation strategies are reported in the literature which includes, incorporation of drug in oils, solid dispersions, emulsions, liposome, use of cyclodextrins, co precipitates, micronization, nanoparticles, permeation enhancers and lipid solutions as mentioned in Figure 3.

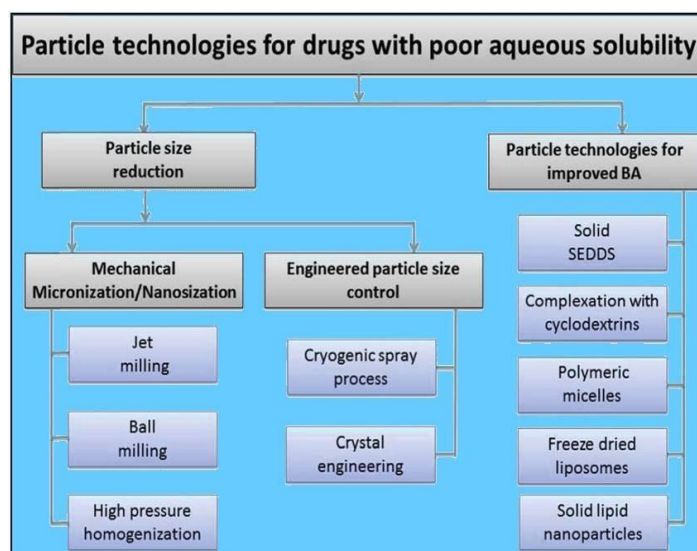


Figure 3. Pharmaceutical Particle Technologies for Improved Solubility, Dissolution and Bioavailability of Drugs (15)

## 6. CONCLUSION

LBDDS have great potentials for improving oral bioavailability of poorly water-soluble drugs, especially lipophilic drugs. Rational design of lipid-based formulations can be achieved by utilisation of DoE, which can also be used in prediction of optimised formulations. It is possible to target lymphatic transport of drugs by selection of lipid excipients containing long-chain fatty acids for lipophilic drugs with good solubility in lipids. Drug precipitation during dispersing of lipid-based formulations in the GI fluids may affect bioavailability, possibly depending on the polymorphic form of precipitated drugs. Supersaturated SNEDDS may be utilised improving bioavailabilities, but their stability should be carefully considered. The in vitro lipolysis model is a useful tool in characterisation of LBDDS and may be used for prediction of drug solubility in the GI fluids during dispersing and lipid digestion processes. However, a better understanding of the mechanisms behind the absorption of drugs from LBDDS, including the important parameters in the in vitro lipolysis, is needed in order to enable a rational optimisation of LBDDS with high and reproducible performance.

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## REFERENCES

1. Mua H, Holma R, Mullertz A. Lipid-based formulations for oral administration of poorly water-soluble drug. *International Journal of Pharmaceutics*. 2013; 453: 215–224.
2. Abrams LS, Weintraub HS, Patrick JE, McGuire JL. Comparative bioavailability of a lipophilic steroid. *J Pharm Sci*. 1978; 67: 1287–1290.
3. Amidon GL, Lennernas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification – the correlation of in-vitro drug product dissolution and in-vivo bioavailability. *Pharm Res*. 1995; 12: 413–420.
4. Armand M. Lipases and lipolysis in the human digestive tract: where do we stand? *Curr Opin Clin Nutr Metab Care*. 2007; 10: 156–164.
5. Basalious EB, Shawky N, Badr-Eldin SM. SNEDDS containing bioenhancers for improvement of dissolution and oral absorption of Lacidipine. I. Development and optimization. *Int J Pharm*. 2010; 391: 203–211.
6. Ahmed NA, Gamal S, Viviane F. Naggar, Bioavailability: A Pharmaceutical Review. *J Novel Drug Delivery Tech*. 2011;1(1):77-93.
7. Brahmanekar DM & Jaiswal SB. *Biopharmaceutics and Pharmacokinetics A Treatise*. 1st Edn, Vallabh Prakashan, 2006: 296- 297.
8. Sakaeda T, Okamura N, Nagata S, Yagami T, Horinouchi M. Molecular and pharmacokinetic properties of 222 commercially available oral drugs in humans. *Biol Pharm Bull*. 2001; 24: 935-940.
9. Vieth M, Siegel MG, Higgs RE, Watson IA, Robertson DH. Characteristic physical properties and structural fragments of marketed oral drugs. *J Med Chem*. 2004; 47: 224-232.
10. Etmayer P, Amidon GL, Clement B, Testa B. Lessons learned from marketed and investigational prodrugs. *J Med Chem*. 2004;47: 2393-2404.
11. Pouton CW. Formulation of poorly water-soluble drugs for oral administration: Physicochemical and physiological issues and the lipid formulation classification system. *Eur J Pharm Sci*. 2006; 2 (9):278–287.
12. Benet LZ, Broccatelli F and Oprea TI. BDDCS Applied to Over 900 Drugs. *AAPS J*. 2011; 13(4): 519–547.
13. Dressman JB, Reppas C. In vitro–in vivo correlations for lipophilic, poorly water-soluble drugs. *Eur J Pharm Sci*. 2000;112(2), S73–S80.
14. Embleton JK, Pouton CW. Structure and function of gastro-intestinal lipases. *Adv Drug Deliv*. 1997;25: 15–32.
15. Khadka P, Jieun Ro, Hyeongmin K et al. Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and Bioavailability. *Asian J of Pharma Sci*. 2014; 9:304-316.