

## Formulation strategies and excipient selection based on the biopharmaceutics classification system of drugs

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### Abstract

The Biopharmaceutical Classification System is an Essential and Helpful tool for getting the Waivers for *In vivo*-bioequivalence research. It is also Useful in the process of New drug Candidate For Formulation. As per the BCS classification system, classes I, II, III, and IV are classified as solubility and permeability factors Class I refers to High solubility- High permeability, class II refers to Low solubility- High permeability, class III refers to High solubility- Low permeability and class IV refers to low solubility- low permeability For BCS class I drugs, Conventional dosage Forms are suitable, like Immediate-release Tablet, Class II Formulation strategies Focus on Reduction of Particle Size where it includes Salt forms to Solid dispersion. Where Niosomes, Nano-emulsion are the preferred for class III drugs, Class IV drugs are considered to be challenging class as a drug having low solubility and low permeability. Lipid-based drug delivery system, Self-Emulsifying drug delivery system Preferred. The present review is focused on Study of different suitable Excipient Selection criteria for all four categories, which Mentioned, could help find the collective data on BCS, where Different Excipient Criteria are used in Formulations

**Keywords:** Biopharmaceutical classification system, bioavailability, solubility, permeability, bioequivalence, excipients, formulation strategy

### Introduction

For drugs with a systemic effect, route of administration where a substance is taken through the mouth <sup>[1]</sup> BCS concept improves insight into the relationship between drug release from a The process of drug release from a drug and assimilation In this regard, the rate-determining step is critical. Each BCS class has a specific rate-determining step and various methods for its modification, allowing the formulator to pick and optimise a dosage form for the drug substance belonging to that class of BCS. The BCS has also been included in several regulatory guidance documents <sup>[2, 3]</sup> The article highlights give a basic idea about the formulation strategies and selections of the excipients according to the drug profile; However, due to a lack of understanding of the core physical chemistry underlying these techniques, formulation development Remains methods of Experimentation.

**Table 1:** Definition Part s of solvents required for one part of solute (in ml) <sup>[4, 5]</sup>

Extremely soluble	< 1
Easily soluble	1 – 10
Soluble	10 – 30
Sparingly soluble	30 – 100
It is slightly soluble.	100 – 1000
Extremely slightly soluble	1000 - 10,000
Insoluble	> 10,000

### Purpose of the BCS Guidance <sup>[6]</sup>

Extends the applicability of the BCS regulations and suggests drug classification techniques.

Explains how we can obtain a waiver to conduct *In vivo* rate, extent, and resemblance of bioavailability on two drug formulations studies using BCS methodology.

### Formulation strategies and Excipient selection criteria BCS class I

Immediate-release dosage the drug dissolves faster by first kinetic profile. The plasma concentration of the drug starts decreasing according to its pharmacokinetic profile <sup>[9]</sup>

#### 1. Immediate dosage formulation strategies

Conventional Techniques for Preparing Immediate Release Tablets: Several technologies are available for the production of immediate-release tablets. Molding, lyophilization or freeze-drying, direct compression, spray drying, and sublimation are the most common preparation methods: Pneumatic Dry Granulation (PDG), Freeze Granulation Technology (FGT), Diffusion system, dissolution system, methods using ion exchange, methods using osmotic pressure, PH independent formulations, altered density formulation

#### 2. Excipient selection criteria for immediate dosage

Because drug dissolution is crucial for body absorption, formulators no longer select disintegrants based on the quickest disintegration time because we must also evaluate the impact of the super disintegrant on dissolve. Furthermore, the ionic character of both the API and the super disintegrants must be considered. Croscarmellose sodium and sodium starch glycolate, for example, can interact with cationic APIs to postpone dissolution. Non-ionic super disintegrants are so favoured. When interacting with cationic APIs, the effect is also taken into account <sup>[10]</sup>

#### 3. Modified solid dosage form

Dosage forms can be tailored to alter the drug's release over time or after the dosage form reaches the desired site. <sup>[9]</sup> Formulation strategies are matrix, reservoirs, degradable material, erodible material, osmotic pump, and hydrogels.

#### 4. Excipient selection criteria for modified solid dosage forms

**Molecular weight:** In general, increasing the molecular weight slows the release profile.

**pH dependency:** Formulators can choose where in the GI tract release will occur by using release-controlling polymers that dissolve at specific pHs at varying rates.

**Processability:** Melting point, flowability, and compactability must all be considered because they may have an impact on processing; particle size analysis provides hints <sup>[11]</sup>

#### 5. Requirement of polymer Choice

Specific properties must be evidenced by the polymer chosen as a promising therapeutic carrier. With a specific molecular weight and a confined distribution, the polymer must be soluble and simple to synthesis. It should include drug attachment or release sites to allow for drug-polymer interactions. The polymer should be biologically appropriate, which implies it should not be toxic, antigenic, or otherwise provocative. It should be biodegradable or eradicated from the organism once its function has been accomplished <sup>[12]</sup>

#### Formulation strategies and Excipient Selection Criteria BCS class II

##### 1. Salt form

In a liquid medium, the salt part is separated into different entities (i.e., the ionised drug and the counterion). Its solubility is determined by the solvent's solvation energy. <sup>[13]</sup>

##### 2. Excipient selection criteria in Salt form

Depending on the expected pharmaceutical profile, aqueous solubility is evaluated at various pH levels. The degree of long-range order in a material, which has a strong influence on its properties. Low moisture content (moisture content vs. water uptake) leads to sustained performance. Ideal chemical and solid-state stability under accelerated conditions (i.e., minimal chemical degradation or solid-state alterations at 40 °C and 75 percent relative humidity). Polymorphism is characterised by a small number of polymorphs or a lack of variety. The ease with which a composition, modification, or formulation can be developed <sup>[14]</sup>

**3. Micronization:** The increased API dissolving rate increases the particle surface area in contact with the dissolution in medium,

##### 4. Co – Micronization- Excipient's selection criteria for Co- Micronization physiochemical properties of the excipient

**Melting point:** low melting point excipient may issue (material agglomeration- product properties /processing jamming)

**Mechanical properties:** (determined by nanoindentation), blend homogeneity before co – micronization density – particles with higher porosity.

**Chemical compatibility:** with API, toxicity (surfactants) - dependent on the API /Excipient ratio selected. Surfactant, binders, diluents etc <sup>[15]</sup>

#### Newer and Novel Techniques

**1. Lipid Drug Delivery System:** As "real liquid dispersions for self (micro) emulsification, lipid-based delivery systems (LBDS) were found. And have been utilized efficiently to create poorly soluble lipophilic compounds with log P > 2.

##### 1.1 Excipient Selection Criteria in Lipid based Drug Delivery System

In oral preparations, digestible food-grade oils are used as the oil phase. In lymphatic absorption, long-chain oils are preferred. Medium-chain oils emulsified efficiently. The choice of surfactant is decided by the HLB values; surfactants with high molecular weight and low CMC values are preferred; do not undergo ionization when being dissolved in water. Are preferred owing to reduced toxicity and choice of LBDDS. Because of the wide spectrum of HLB, surfactants-polysorbates have been widely used. In an aqueous solution, surfactants including polar and nonpolar entities can self-assemble into aggregates <sup>[16, 17]</sup>.

##### Self Dispersing Lipid Formulation (SDLF)

The drug is integrated into the SDLFs, which comprise oil and a surfactant combination. Occurs Self-emulsification <sup>[18]</sup>

**1. Excipient selection Criteria in Self Dispersing lipid formulation** MCT oils with various degrees of saturation were utilized, as well as hydrolysed oils and a vast range of non-ionic surfactants <sup>[19-21]</sup>. In the formulation, lipophilic surfactants played the function of hydrophilic oils <sup>[19]</sup>. The self-dispersing system employs a non-ionic surfactant design <sup>[19, 20, 22, 23]</sup>. Instantaneous formation of O/W, combine high HLB with a hydrophilicity surfactant <sup>[24, 25]</sup>. The hydrophilic surfactant drug is dissolved in the lipid basis by organic solvents <sup>[19]</sup>

**Solid Dispersion System:** A solid dispersion is a type of solid product that appears to contain two aspects, typically a soluble matrix and a water - insoluble drug. The matrix could be crystal or noncrystalline. In nature The drug could be distributed molecularly, as noncrystalline (clusters), or crystalline particles <sup>[26, 27]</sup>.

##### 1. Excipient criteria for polymeric Transit in a solid dispersion system

Due to the surfactant properties of polymers, partitioning the drug with in miscelle any aid in increasing solubility and low load solid dispersions. The polymer is usually existing in a much greater proportionate the nanocrystalline state and immediately following phase separation greatly undermine physical stability glass substance to heat, fusion <sup>[28, 29]</sup> A elevated glass transition temperature (T<sub>g</sub>) is required for the polymer to remain fixed at room temperature, reducing the possibility of Johri-Goldstein (JG) relaxations <sup>[30, 31]</sup> Constructing an amorphous solid dispersion. The polymer used must be capable of producing good glasses with a wide range of compounds <sup>[32]</sup>. A polymer with high phase solubility with the drug is required to create a single-phase nanocrystalline system <sup>[30, 33-35]</sup>.

Safety	Inert Gras
Preparation	Melting methods thermally stable, Thermoplastic, sustainably grown liquid solvent soluble in methods
Liberation	Solubilizing and stabilising properties that are water soluble [36]
Strength	Elevated Tg, brittleness, hydrogen donor and acceptor [37, 38]

### Nanosuspension

Nanosuspensions are spherical particles of nanoparticles drug particles stabilised by surfactants that are submicron in size [39].

#### 1. Excipient selection criteria in Nanosuspension

The choice of stabiliser (s) is critical for nanosuspension activity and stabilization; APIs with elevated log P and elevated thermodynamic properties values have a better chance of producing a steady nanosuspension via both steric and electrostatic stabilisation [40].

### Formulation strategies and selection of excipients BCS class III

#### Potential Absorption Barriers

Tight Junctions, Capillary wall, Mucous and Apical cell membrane, Basal cell membrane Permeation enhancers such as SLS, polysorbate 20 and 80, sorbitan laurate, and glyceryl monolaurate can be used [41] Sodium deoxycholate, Sodium glycocholate, Sodium fusidate, and other bile salts Oleic acid, Caprylic acid, Lauric acid, and other fatty acids and derivative Chelators include substances such as sodium EDTA, citric acid, salicylates, and others. Cyclodextrins and derivatives, for example, are inclusion complexes. Chitosan, Polycarbophil, and other mucoadhesive polymers

### Niosomes

Niosomes are micron - sized fibrillar structures ranging in size from 10 to 1000nm. Surfactants that are non-immunogenic, bioresorbable, and good biocompatibility make up the niosome [42].

#### Excipient selection criteria in Niosomes Surfactant

An rise in surfactant HLB causes an rise in the average size of niosomes due to a reduction in surface free energy with a rise in surfactant hydrophobic nature. A decrease in surfactant Hydrophilic - lipophilic balance from 8.6 to 1.7 reduces loading capacity, and an HLB value of 8.6 results in the maximum loading capacity.

#### Nature of encapsulated drug

The encapsulated drug's physical-chemical properties have a significant impact on the charge and high stiffness of the niosomal membrane.

#### Hydration Temperature

The temperature of hydration impacts the size and form of the niosome.

### Cholesterol Levels

The incorporation of cholesterol improves niosome entrapment effectiveness and hydrodynamic diameter. Cholesterol has two effects: The bond arrange of liquid state bilayers is increased.

The bond arrange of gel state bilayers is reduced. When the concentration of cholesterol increases, the stiffness of the bilayers increases and the rate of encapsulated material release decreases

### Charge

Appearance of the charge Cause an raise Interlamellar distance between Consecutive Bilayer in multilamellar vesicle framework membrane total entrapped volume

### Resistance to Osmotic Stress

Introduction of isotonic environment reduces vesicular size and shape. In isotonic solution, inhibitor of removing liquid from vesicles outcomes in a gradual initial launch followed by a quicker release due to mechanical softening of micelles framework under osmotic adjustment [43-45].

**Nano emulsions:** Nano emulsions are nano particulate systems with sizes ranging from 10 to 1,000 nm that act as transporter for drug molecules. These transporters are solid spheres with a nanocrystalline, lipid soluble, and negatively charged surface [46]

#### 1. Excipient Selection criteria in Nano Emulsion

Oils used in the preparatory work of Nano emulsions include Captex 355, Captex 8000, and others. The drug's solubility in the oil phase is an important criterion for oil choice Hydrophilic drugs – water-in-oil nano emulsion. Lipophilic drugs solubilized in the oil-in emulsion [42, 47] Synthesized medium chain derivatives with surfactant properties (as amphiphilic compounds) are gradually and effectively replacing traditional fatty acids chain length 6-12 carbon atom [48, 49] Non-ionic, zwitterionic, cationic, and anionic surfactants can be used to stabilise Nano emulsions. Surfactants such as Capryol 90, Gelucire 44/14, 50/13, and Cremophor RH 40 may be used [50, 51].

### Formulation strategies and selection of excipients BCS class IV

#### 1. Lipid-based drug delivery systems (LBDDS)

The rate and extent of absorption of a drug are determined by the balance between its solubility in the aquatic environment of the digestive lumen and its permeability across the lipid soluble membrane of enterocytes [53].

### Conclusion

The strategies of the drug is done out with principal objectiveness enhancing their bioavailability. BCS class I, II, III and IV Exhibit formulation for the scientist to optimum therapeutic potential. A clear idea about the physicochemical properties and the limitation of lead challenging to the excipient's criteria blend with the formulation development. It's essential to perform pharma economics studies, values added new novel drugs for the various treatments.

BCS CLAASS I	BCS Class II
IR Dosage forms, Modified solid dosage form Examples Ketoprofen, Naproxen	Micronization / co- micronization Salt forms Lipid drug delivery system Self-Dispersing Lipid Formulation (SDLF) Solid dispersion system, PH modification Example phenytoin, Danazol, Ketoconazole
BCS Class III	BCS Class IV
Permeation enhancers Example: Acyclovir, Alendronate, Captopril	Combination of BCS class II and III Example: Chlorthalidone, Furosemide

## Abbreviations

Short form	Long Form
BA/BE	Bioavailability and Bioequivalence
PDG	Pneumatic Dry Granulation
FGT	Freeze Granulation Technology
SDLF	Self-Dispersing Lipid Formulation
HLB	Hydrophile-Lipophile-balance
LBDS	Lipid-Based delivery systems

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