Formulation strategies to improve the permeability of BCS class III drugs: Special emphasis on 5 Fluorouracil

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Abstract

Nearly 60-70 % of the synthesized drug candidates are found to be poorly water-soluble and low permeable from the gastrointestinal tract (GIT). Owing to this, formulation scientists and researchers are adopting various strategies to enhance the solubility as well as absorption of these drugs. This review article focuses on the biopharmaceutical classification system (BCS) with special emphasis on BCS class III drugs, limitations of several conventional techniques and the benefits of employing newer approaches such as like self emulsifying drug delivery systems, microspheres, beads, nanoparticles, suppositories, and permeation enhancers. Along with this, the article also highlights on the various studies carried out by formulation scientists to solve the problems associated with BCS class drugs.

Keywords: BCS, 5 FU, Oral, solubility, permeability

1. Introduction

BCS classification (Biopharmaceutics Classification System) is classified into four main classes which categorized the drugs on major bioavailability parameters i.e., solubility, dissolution and permeability [1]. BCS classification is provided by USFDA and WHO which divides drugs into 4 different classes on the based upon their solubility as well as permeability in two levels i.e., high or low, shown in figure 1 below. It is a scientific structure to classify a drug or its substance based on its solubility in water and permeability across intestinal layers [2].

Examples of some drugs fall into different BCS classification are discussed below:

- Class I High solubility and High permeability (HSHP)

Examples of BCS Class I- Propranolol, Paracetamol and Chloroquine

- Class II- Low solubility and High permeability (LSHP)

Examples of BCS Class II- Ketoconazol, Phenytoin and Nefidipine

- Class III- High solubility and Low permeability (HSLP)

Examples of BCS Class III- Atenolol, Captopril, Ranitidine, Metformin, 5-FU

- Class IV- Low solubility and Low permeability (LSLP)

Examples of BCS Class IV- Ritonavir, Cyclosporin A and Furosemide

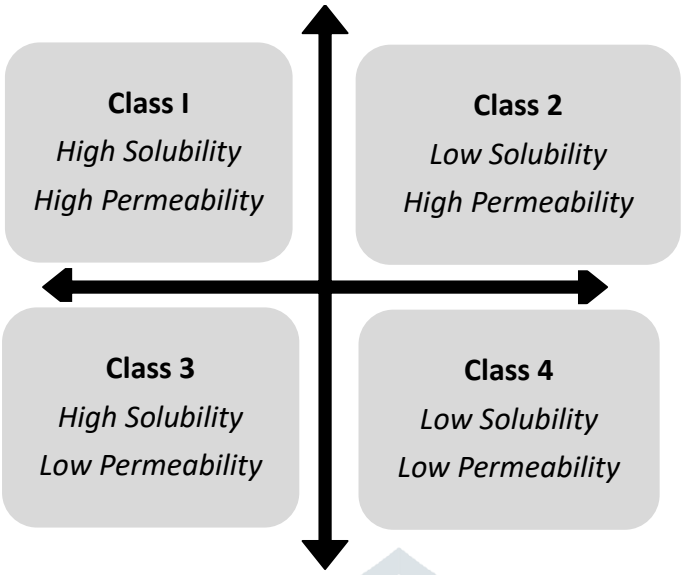


Figure 1: BCS Classification

2. BCS Class III Drug

Amongst all the classes of drugs, BCS Class III drugs are having high solubility and low permeability. A drug fall in this class is 5-Fluorouracil (5-FU).

2.1. 5-Fluorouracil

5-FU, an antimetabolite also acts as an anticancer drug used for the treatment of frequent types of malignancies particularly for colorectal cancer. Due to its antimetabolite activity it affects the working of cancer cells. It was discovered by Dushinsky R, Pleven E, Heidilberger C. After conducting many studies, they came to know that both uracil and 5- FU are greater settled into the tumor cells as a substrate as compared to other pyrimidine bases. Hence, the scientist synthesize 5-FU, in which at fifth position of hydrogen in uracil was fluorine substituted [3]. In combination with different chemotherapeutic agents it increases the survival rate in breast, head and neck cancers.

In one of the study, 5-FU alone shows limited therapeutic effect (response rate about 10–15%) in a highly developed colorectal cancer. From the past two decades, various treatment strategies are adopted to improve the permeability of 5-FU which will enhance its anticancer activity and overcome the resistance clinically. Hence forth 5-FU is considered as the potential drug candidate for treatment of colorectal cancer at both early-stage as well as advanced-stage [4].

.1.1. Mechanism of action (MOA) of 5-FU

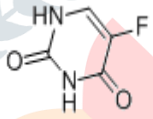
5- FU, a uracil analogue (having fluorine at C_5 position instead of hydrogen) swiftly invades into the cell by facilitated transport mechanism. Intracellularly 5-FU converts into various active metabolites such as

fluorodeoxyuridine triphosphate (FdUTP), fluorouridine triphosphate (FUTP), and fluorodeoxyuridine monophosphate (FdUMP) (Longley and Harkin 2003). These active metabolites cause interruption in RNA synthesis and action of thymidine synthtase [4,5]. After administration, 5-FU pursues different metabolic targets i.e., basically in the liver over 80% of the portion is inactivated by biotransformation, in urine 15-20% is eliminated and a little amount is remains accessible to exert its anti-cancer activity. Recent studies showed that the co-treatment of 5-FU with leucovorin and methotrexate increases its anticancer activity. Capecitabine, a prodrug of 5-FU, when orally administered gets converted into 5-FU and its active metabolites with the help of a key enzyme named thymidine phosphorylase (TP) [6].

2.1.2. Physicochemical Properties of 5-FU

The physicochemical properties are discussed below in Table 1 [7,8].

Table 1 Physicochemical properties of 5-FU

Chemical Name	5- Fluorouracil
IUPAC Name	5-fluoro-1,2,3,4-tetrahydropyrimidine-2,4-dione
Structure	
Molecular Formula	$C_4H_3FN_2O_2$
Synonyms	5-FU, Arumel, Efudex, Efurix, Fluril
Melting Point	282-286ºC
Boiling Point	190-200ºC
Molecular Weight	130.08 g/mol
Form	Powder
Color	White
Solubility	H_2O: 10mg/ml, clear 1M NH_4OH: soluble DMSO/ DMF: soluble Methanol: soluble
Storage temperature	0-5ºC
Sensitive	Air sensitive
Stability	Light sensitive, stable, incompatible with strong oxidizing agents and combustible.
Chemical property	Crystalline
Routes of administration	Intravenous injection, by infusion, topically applied as

	ointment and cream
Toxicity	Diarrhoea, Encephalopathy, Mucositis, Myelotoxicity, hand- foot syndrome, neurotoxicity
Mechanism of action	5-FU can act through inhibition of thymidylate synthase (TS) from its anabolites which includes fluorodeoxyuridine monophosphate (FdUMP). Conversion of dUMP to TMP is catalyzed by thymidylate synthase called as precursor of TPP, needed for synthesis of DNA.

3. Permeability improvements techniques

BCS class III categorized drugs as low permeability and high solubility drugs. Hence various formulation strategies such as delivery systems are also reported to improve the permeability issues of 5-FU. These delivery systems are nanoparticles, microsphere, lipoproteins, microbeads, film coated systems, co-crystallization, binding with metal, etc. Table 2 shows the delivery systems employed to enhance and permeability of 5-FU. Table 3 reports the delivery approaches used to enhance the permeability of other BCS class III drugs [9] and Table 4 discuss the formulation strategies which increase the permeability of class III BCS drugs [10]. These techniques are discussed in detail as follows:

3.1. Co-crystallization: Co-crystallization is introduced as a novel technique to increase the membrane permeability of 5-FU. Three formulations of 5-FU co-crystals such as 5-FU with 3- hydrobenzoic acid, 4-aminobenzoic acid as well as cinnamic acid prepared with a slurry technique as well as by liquid-assisted grinding process. Further permeability study was done by Franz diffusion cell. All prepared co-crystals provide better membrane permeability as compared to free drug [11]

3.2. Binding of 5-FU with metal: As per the results of biological assays, 5-FU shows antifungal and antibacterial activities against the gram-negative bacteria after its binding with gold nanoparticles through complexation. Moreover combination of 5-FU with metal gold forms a more effective complex than individual parts [12]

3.3. Ionic liquid-based microemulsion formulation: A novel formulation of 5-FU composed with ionic liquid-in-oil based microemulsion was prepared for dermal delivery *Ex vivo* mice skin permeation activity shows 4-fold, 2.3 fold and 1.6 fold enhancement in 5-FU permeation as compared to its solution, ointment and water-in-oil based microemulsion, respectively. Further, *in vivo* studies exhibited enhanced therapeutic efficacy and improved permeability of 5-FU for treatment of cancer [13]

3.4. Ethosomal gel formulation: For topical delivery of 5-FU in various skin malignancies, ethosome based gel formulation also known as ethogel was developed. For preparation of gel formulation, Carbopol

934P in different ratios such as 0.5, 0.75, 1.0 and 1.5% w/w are explored to optimize the consistency for topical use. Results shows that prepared 5-FU ethogel formulations exhibit better bioavailability as compared to marketed formulation [14].

Table 2: Delivery systems employed in the permeability improvement of 5-FU

Delivery system	Remarks	References
Nanoparticles	Nanoparticles has came as another strategy which enhances the drug permeability by exerting its site-specific drug delivery by avoiding the uptake by reticuloendothelial system and it has the capability to turn multidrug resistance	[15]
Microsphere	Solid-oil-hydrophilic oil based microsphere system prolonged the 5-FU release and increases its concentration in malignancy cells	[16]
Gellan gum microbeads	5-FU loaded calcium-zinc-gellan microbeads reduces the systemic toxicity by increasing the efficiency of encapsulation, controlled particle size and prolonged release of drug due to increased proportion of gellan gum and ethyl cellulose	[17]
Mixed film coated unit system	Strategy of this system is to focus on the colon malignant growth. Maximum release of drug is obtained by the polymers ethylcellulose and Eudragit S100 in the proximal segment of colon which avoid premature release of 5-FU because of its pH- dependent solubility and hydrophobicity	[18]
Lipoproteins	By incorporating 5-FU into supramolecular biovector, a synthetic nanocarrier, its pharmacokinetic behavior is improved and metastasis and tumor growth is controlled by cross-linking of polyguluronate units in alginate	[19]

	molecules with calcium ions	

Table 3: Delivery systems employed in the permeability improvement of BCS Class III drugs [9]

Drug	Delivery system	Conclusion
Doxorubicin	Double emulsion system	In this system drug is available in internal hydrophilic centre which act provide safe environment to drug and act as a storage cavity and from intestine these can get directly absorbed as oil droplets
Acyclovir	Niosomes	Niosomal dispersion has improved the oral bioavailability of acyclovir by more than 2-folds as compared to free drug solution because they are osmotically active and chemically stable
Pidotimod	Self-double emulsifying drug delivery system (SDEDDS)	*In vivo* study shows that time profiles of plasma concentration in mice shows increased absorption of pidotimod loaded SDEDDS loaded as compared to its plain solution
Doxorubicin	Nanoparticles	Nanoparticles control the release of doxorubicin in a pH dependent manner and enhance the efficacy of drug
Metformin	Liposomes	*In vivo* study performed on metformin-loaded liposomes coated with chitosan cross-linked with beta-glycerophosphate suggested that microcomplexes controlled the delivery of drugs and improve the oral bioavailability
Atenolol	Solid- lipid nanoparticles	*In vitro* permeability study suggested that drug- phosphotidylcholine solid dispersion increases percentage permeation as compared to pure drug and as the amount of phospholipid increases relative to that of drug, permeability of drug increases. This system has ability to enter through various anatomical boundaries, sustained release of their contents and their stability in nanometer size.

Table 4 Intestinal permeation enhancers for BCS class III drugs

Surfactants	• Ionic: Sodium lauryl sulphate, Sodium dodecylsulphate • Non ionic: Polysorbitate and Tween 80
Bilesalts and its derivatives	• Sodium glycolate • Sodium deoxycholate
Derivatives of fatty acids	• Caprylic acid • Lauric acid • Oleic acid
Chelating agents	• EDTA • Citric acid • Salicylates
Other enhancers	• Zonula occludens toxin • Polycarbophyl-cysteine conjugate

4. Current and evolving strategies to improve the permeability of BCS class III drugs

4.1. Prodrugs: Clinically, most of the prodrugs are utilized to enhance permeability of drug by enhancing its lipophilicity [20]

4.2. Cyclodextrins (solublizing excipients): Cyclodextrins can enhance the drug uptake and increase the drug delivery by enhancing the accessibility of drug molecules dissolved to membrane surface [21,22]

4.3. Electroporation: In this technique, skin permeation of drug is increased by the applying the pulses of high voltage (50-1000) for short duration of time. Bioavailability of drug increases due to the penetration of drug molecules through the pores formed by the pulses.

4.4. Magnetophoresis: In this enhancement method, penetration of drug molecule is facilitated with the help of magnetic field. Magnetoliposomes (magnetic lipososmes) are utilized as targeted approach and as a imaging biomarkers for diagnosis of cancer and other thermal cancer remedies [23]

4.5. Cyclopentadecalactone: It is also known as pentadecalactone and used as a permeation enhancer. It is used in Testim (a testosterone gel applied by transdermal route) which is a gel formulation containing ethanol and 8% pentadecalactone [24]

4.6. Hot-Melt Extrusion Technology: This method is performed to formulate mucoadhesive buccal tablets of Ondansetron hydrochloride, which avoid GI tract and first pass effect. In this drug delivery system, oleic acid is used as permeation enhancers. Permeation of oleic acid through the membrane causes disturbance in multilamellar shape and give rise to pathways which are open for permeation [25,26]

7. Conclusions

BCS is a scientific structure to classify drugs based on their solubility in water and permeability across the intestinal layers. 5-Fluorouracil is an anticancer drug which comes under BCS class III drugs (high solubility and low permeability) and used for the treatment of frequent types of malignancies particularly for colorectal cancer. It is an antimetabolite which stops cancer cells to work properly. 5-FU has wide range of properties which provide tremendous applications in various conditions like keratoacanthomas, Bowen's disease, skin lesions, stop growth of cancer cells, management of carcinoma of breast, rectum, colon, pancreas and stomach. But it has limited therapeutic effect due to its permeability issues as well as drug resistance which can be overcome with the role of novel drug delivery approaches such as nanoparticles, microsphere systems, lipoproteins, microemulsions, liposomes, etc which has led to increase its membrane permeability. Some intestinal permeation enhancers like surfactants, chelating agents, bile salts and its derivative, etc are also helps to enhance the bioavailability with poor permeability.

At the end, it was concluded that there is a need for all the pharmaceutical scientists, manufacturers and researchers to join hands and develop different formulations of BCS class III drugs with enhanced membrane permeability for the benefit of patients suffering from cancer.

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