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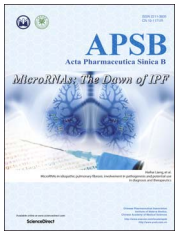

REVIEW

Understanding *peroral* absorption: Regulatory aspects and contemporary approaches to tackling solubility and permeability hurdles

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Abbreviations: ABC, ATP-binding cassette; AP, absorption potential; API, active pharmaceutical ingredient; ATP, adenosine triphosphate; AZT, azidothymidine; BA/BE, bioavailability/bioequivalence; BCRP, breast cancer resistance protein; BCS, biopharmaceutical classification system; BDDS, biopharmaceutical drug disposition system; BSP, bromosulfophthalein; CD, cyclodextrin; CDER, Centre for Drug Evaluation and Research; CNT, concentrative nucleoside transporter; CNT, Na^+-dependent concentrative transporter; CYP, cytochrome P450; D:S, dose:solubility; E217G, estradiol 17β-glucuronide; EMEA, European Medicines Agency; ENT, equilibrative nucleoside transporter; FaSSIF, fasted state simulated intestinal fluid; FATP, fatty acid transporter protein; FDA, U. S. Food and Drug Administration; FeSSIF, fed state simulated intestinal fluid; FIP, International Pharmaceutical Federation; GIS, gastrointestinal simulator; GIT, gastrointestinal tract; GITA, gastrointestinal transit and absorption; GLUT, sodium-independent facilitated diffusion transporter; GRAS, generally recognized as safe; HIV, human immunodeficiency disease; HPC-SL, LBDDS, lipid based drug delivery system; HUGO, Human Genome Organization; ICH, International Council of Harmonization; IDR, intrinsic dissolution rate; IR, immediate release; ISBT, sodium dependent bile salt transporter; MCT, monocarboxylate transporter; MPP, 1-methyl-4-phenylpyridinium; MRP, multidrug resistance associated protein; NLC, nanostructured lipid carrier; NME, new molecular entity; NTCP, sodium-dependent taurocholate co-transporting polypeptide; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cationic transporter; OCTN, organic cationic/carnitine transporter; OMM, ordered mesoporous material; PAH, *p*-aminohippurate; PAMPA, parallel artificial membrane permeability assay; P_{app}, apparent permeability; P_{eff}, effective permeability; PEG, polyethylene glycol; PEI, polyethyleneimine; PEPT, peptide transporter; PGA, polyglycolic acid; P-gp, P-glycoprotein; PLA, poly(lactic acid); PLGA, poly-D,L-lactide-*co*-glycoside; PMAT, plasma membrane monoamine transport; pMMA, polymethyl methacrylate; PSA, polar surface area; Psi, porous silicon; PVDF, polyvinylidene difluoride; RFC, reduced folate transporter; SDS, sodium dodecyl sulphate; SGLT, sodium dependent secondary active transporter; SIF, simulated intestinal fluid; SLC, solute carrier; SLCO, solute carrier organic anion; SLN, solid lipid nanoparticles; SMVT, sodium dependent multivitamin transporter; SPIP, single pass intestinal perfusion; SUPAC, scale-up and post approval changes; SVCT, sodium-dependent vitamin C transporter; TEOS, tetraethylortho silicate; UWL, unstirred water layer; VDAD, volume to dissolve applied dose; vit. E TPGS, vitamin E tocopherol polyethylene glycol succinate; WHO, World Health Organization

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KEY WORDS

BCS;
Solubility;
Permeability;
Formulation strategies;
Factors affecting absorption

Abstract Oral drug absorption is a process influenced by the physicochemical and biopharmaceutical properties of the drug and its inter-relationship with the gastrointestinal tract. Drug solubility, dissolution and permeability across intestinal barrier are the key parameters controlling absorption. This review provides an overview of the factors that affect drug absorption and the classification of a drug on the basis of solubility and permeability. The biopharmaceutical classification system (BCS) was introduced in early 90's and is a regulatory tool used to predict bioavailability problems associated with a new entity, thereby helping in the development of a drug product. Strategies to combat solubility and permeability issues are also discussed.

1. Introduction

Peroral administration is the predominantly acceptable route of drug administration owing to its benefits such as self administration with minimal discomfort to patients, which improves patient compliance, makes it cost effective and provides flexibility in design of dosage form[1]. There are various factors which control of absorption through the oral route and thus affect the bioavailability of a drug. FDA defines bioavailability as "the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action". A prior knowledge of biopharmaceutical optimization and *in vivo* availability of drug were first only on focused disintegration time while ignoring fundamental factors like dissolution. Researchers tried to mimic the biological conditions like gut pH, food content and peristalsis for precisely predicting *in vivo* performance. In the years 1960–1970, several studies were carried out which demonstrated the effect of dissolution, formulation parameters [excipients, slight change in concentration of active pharmaceutical ingredient (API), dosage form, etc.] and food on bioavailability. Bioavailability concerns and quality control consideration further initiated the need for an official dissolution test. The first dissolution test apparatus, basket stirred flask type (USP apparatus I) was introduced in 1970 and subsequently paddle type (USP Apparatus II) in 1978[2]. *In vitro* tests have been successful in predicting *in vivo* performance of dosage forms. Despite the complexity of the factors, progress has been made to improve the performance of dosage forms *in vivo*. Some of the prominent research carried out in this field is listed chronologically in Table 1[3-12].

This article reviews the drug absorption process which depends upon drug properties, such as solubility and permeability, physiological factors like pH, regional permeability differences, food effects and formulation factors. Combinatorial chemistry and high throughput screening has led to the development of lead drug compounds having higher molecular weight, poor wetting properties and high lipophilicity, thus placing 40% of lead candidates into Biopharmaceutical Classification System (BCS) class II and class IV. Better understanding of the various factors during the lead optimization phase can help to reduce the cost of development. The other approach to address poor solubility and permeability issues is to modify the drug by using different formulation approaches. This review provides insight on fundamentals of BCS and a literature database of formulation strategies used to manage solubility and permeability problems. These approaches can help in shifting the lead candidate to a better class of BCS.

2. Movement of drug through the gastrointestinal tract

Fig. 1 shows the journey of a drug through the gastrointestinal (GI) tract. The GI tract is a complex system; the first organ which a drug encounters is the stomach, which contains many digestive enzymes, has an acidic environment (pH 1.5–3.5) and very few drugs are absorbed through stomach. The small intestine (duodenum, jejunum, and ileum) is the major site for drug absorption. Dosage form disintegration and dissolution, degradation, binding in the intestinal lumen, intestinal permeation and intestinal and hepatic metabolism controls the pharmacological activity and transition of a drug in the GI tract[13,14]. Also, these processes in the GI tract are interlinked and controlled by various factors like physicochemical, physiological and the type of dosage form (tablet, capsule, solution, suspension, emulsion, and gel)[15,16]. Physicochemical factors include pK_a, solubility, stability, diffusivity, lipophilicity, polar and nonpolar surface area, the presence of hydrogen bonding functionalities, particle size, and crystal form,

Table 1 Evolution of BCS.

Year	Prominent research	Ref.
1897	Noyes-Whitneys first experiment on dissolution	3
1904	Nernst-Brunner diffusion layer concept	4
1931	Hixon-Crowell model	5
1950	Official disintegration test in USP	6
1951	Danckwert's theory	7
1961	Higuchi's interfacial barrier model	8
1970	Dissolution apparatus I (Basket type)	9
1978	Dissolution Apparatus II (Paddle type)	9
1981	FIP guidelines for dissolution of solid dosage form	10
1985	General chapter on "drug release" in USP	9
1991	USP dissolution apparatus III "reciprocating cylinder type"	9
1995	USP dissolution apparatus IV "flow through cell"	9
1995	Amidon Gordan introduced BCS	11
2000	FDA introduced BCS guidelines	12

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