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Review

The effects of excipients on transporter mediated absorption

Jonathan Goole[a,b,*], David J. Lindley[a], Wyatt Roth[a], Stephen M. Carl[a], Karim Amighi[b], Jean-Michel Kauffmann[b], Gregory T. Knipp[a]

[a] Department of Industrial and Physical Pharmacy, College of Pharmacy, Nursing and Health Sciences, Purdue University, West Lafayette, IN, USA
[b] Department of Pharmaceutical Sciences, Université Libre de Bruxelles, Brussels, Belgium

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ABSTRACT

Traditionally most pharmaceutical excipients used for peroral dosage forms have been considered to be inert, although they have been known to play an important role in governing the release of the active pharmaceutical ingredient (API) required for the desired therapeutic effect. Of considerable interest is the emerging data demonstrating that many of these "inert" excipients may produce subtle changes that could directly or indirectly alter the activity of membrane-spanning proteins such as transporters. In this way, excipients could be altering the overall ADMET properties of an incorporated drug thereby affecting its intended therapeutic efficacy and/or enhancing adverse side effects. Therefore, given this recent evidence, it seems necessary to review what has been reported in the literature on interactions of excipients with human physiological entities, particularly transporters. As of today, safety/toxicity evaluations are typically based on the appearance of gross morphological changes rather than the effects on a cellular level, the ability of excipients in modifying the pharmacological activity of an active drug could lead to toxicity evaluation in routine for each additive used in oral formulations.

Further knowledge on this subject will enable formulators to make more rational decisions in dosage form design and will help answer the question of whether certain excipients should be considered active pharmaceutical components of formulations.

Contents

Abbreviations: ABC, ATP-binding cassette transporters; ADMET, absorption, distribution, metabolism, excretion, and toxicity; ACE, angiotensin-converting enzyme; AIDS, acquired immune deficiency syndrome; AMP, adenosine mono-phosphate; AP, apical; API, active pharmaceutical ingredient; ATP, adenosine tri-phosphate; BBB, blood–brain barrier; BBMEC, bovine brain microvessel endothelial cells; BCECF, 2′-7′-bis′(carboxyethyl)-5-(6′)-carboxyfluorescein; BCRP, breast cancer resistance protein; BL, basolateral; Caco-2, epithelial human Caucasian colon adenocarcinoma; CERT, ceramide transfer protein; CHO, Chinese hamster ovary; CMC, critical micellar concentration; CsA, cyclosporin A; CYP, Cytochrome P450; DM-β-CD, dimethyl-β-cyclodextrin; DNA, deoxyribonucleic acid; DPPC, dipalmitoyl phosphatidylcholine; DPPE, dipalmitoyl phosphatidylethanolamine; DRM, detergent-resistant membrane; EDTA, ethylenediaminetetraacetic acid; FASSIF, fasted state simulated intestinal fluid; FM, flippase model; GIT, gastrointestinal tract; HBSS, Hank's balanced salt solution; HDL, high density lipoprotein; HVC, hydrophobic vacuum cleaner; LPS, lipopolysaccharide; LTC_4, leukotriene C; MCT, monocarboxylate transporters; MDCK, Madin-Darby Canine Kidney; MDR, multidrug resistance; MRP, multidrug resitance-associated protein; NaTC, sodium taurocholate; NSAID, non-steroidal anti-inflammatory drug; P-gp, P-glycoprotein; Panc-1, pancreatic adenocarcinoma cell line; PEG, polyethylene glycol; PEPT, peptide transporter; PKC, protein kinase C; RT-PCR, reverse transcription-polymerase chain reaction; SM, sphingomyelin; ™, Traded Mark; URL, uniform resource locator.

* Corresponding author at: Laboratoire de Pharmacie Galénique et Biopharmacie, Université Libre de Bruxelles, Campus de la Plaine, CP 207, Boulevard du Triomphe, 1050 Brussels, Belgium. Tel.: +32 2 650 5252; fax: +32 2 650 5269.
E-mail address: jonathan.goole@ulb.ac.be (J. Goole).

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1. Introduction

Pharmacokinetics and pharmacodynamics (PK/PD) are processes that encompass drug absorption, distribution, metabolism, excretion, and response (ADMET). Absorption is the rate and extent at which drugs reach the systemic circulation from the site of administration. Distribution is the process of reversible transfer of a drug to and from the site of measurement, usually the blood or plasma (Rowland and Tozer, 1989). Metabolism involves all the biochemical processes that result in a chemical change to the drug compound including both the metabolism in the gut wall, the liver, and the blood circulation. Excretion is the process in which the drug is eliminated from the systemic circulation into bile, urine, feces, sweat, and air (Rowland and Tozer, 1989). Collectively, these parameters (ADMET) significantly affect the overall bioavailability of selected compounds in target populations.

As it can be seen in Fig. 1, dissolution rate, solubility and permeability are the three primary factors that influence drug absorption following oral administration (Amidon et al., 1995). If the rate of dissolution is the rate-limiting step in drug absorption, any factor affecting the dissolution rate will have an impact on bioavailability (Tong, 2008). This rate is mainly influenced by the solubility of the drug, which depends on its physicochemical properties (Amidon et al., 1995).

On the other hand, the dosage form components also play an important role in the dissolution rate of a particular drug. In addition to the API, excipients or "inert" materials are added to formulations to aid in further processing of the materials into its final dosage form and to achieve an optimum absorption and therapeutic effect (Badawy et al., 2006). Most of "inert" materials commonly used in the design of oral dosage forms are assumed to not influence API absorption. However it has been reported recently that they can have an effect on specific transporters located in the GIT.

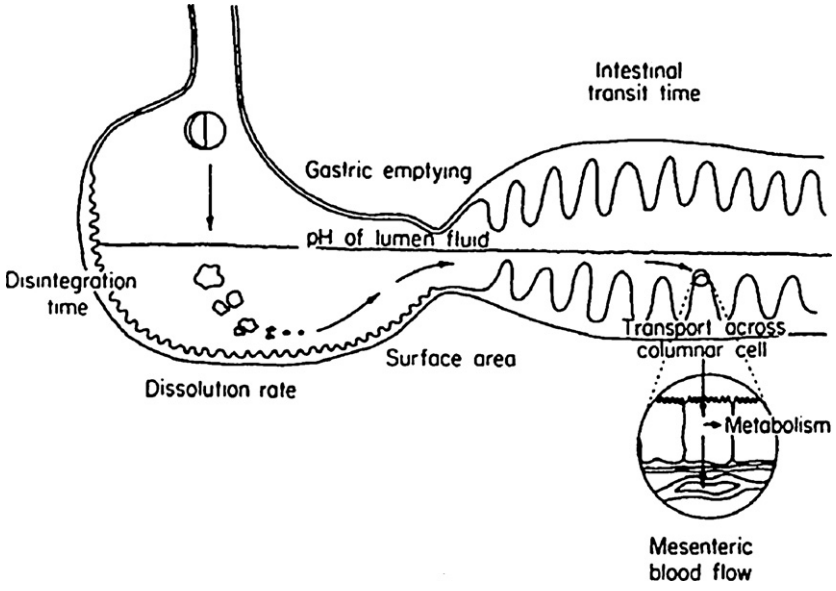

Fig. 1. Factors affecting the rate of absorption of drug from the gastrointestinal tract.