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Predicting the Oral Absorption of Poorly Soluble Drugs

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This work is dedicated to

Kurt Schanz

Acknowledgements

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List of Abbreviations

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a	time parameter (Weibull kinetics)
A	surface area of a membrane
ABC	ATP-binding cassette
ACE	angiotensin converting enzyme
A_{drug}	surface area of the drug
A_t	amount of drug absorbed at time t
ATP	adenosine triphosphate
AUC	area under the curve
b	shape parameter (Weibull kinetics)
BCS	Biopharmaceutics Classification Scheme
BDDCS	Biopharmaceutics Drug Disposition Classification Scheme
Caco 2	human epithelial colorectal adenocarcinoma cells
c_b	concentration of drug molecules in the bulk volume
c_{in}	drug concentration entering an (intestinal) compartment/drug concentration at basal side of gut wall
c_{max}	maximum (plasma) concentration
c_n	steady state concentration of dissolved drug
c_{out}	drug concentration leaving an (intestinal) compartment/drug concentration at apical side of gut wall
c_s	saturation solubility of the drug in a given medium
c_t	concentration at time t
CYP	cytochrome P 450
δ	thickness of diffusion layer
D_{drug}	diffusion coefficient of the drug
DGM	dynamic gastric model
DHP	dihydropyridine
E	erosion front
e.g.	*exempli gratia* (for example)
EMA	European Medicines Agency
Eq.	equation
ER	extended release
F	diffusion front
FaSSCoF	Fasted State Simulated Colonic Fluid
FaSSGF	Fasted State Simulated Gastric Fluid
FaSSIF (v2)	Fasted State Simulated Intestinal Fluid (version 2)
FDA	United States Food and Drug Administration

FeSSCoF	Fed State Simulated Colonic Fluid
FeSSGF	Fed State Simulated Gastric Fluid
FeSSIF (v2)	Fed State Simulated Intestinal Fluid (version 2)
Fig.	figure
HBD	hydrogen bond donor
HIF	human intestinal fluids
HIV	Human Immunodeficiency Virus
HT-29	strain of mucus-producing human colonic cells
i.e.	*id est* (this is; which means)
IND	investigational new drugs
IR	immediate release
IVISIVC	*In Vitro – In Silico – In Vivo* Correlations
J	net production rate of clusters per unit time and volume (nucleation theory)
J_d	drug flux in a polymer matrix
k, k_0	(dissolution rate) constant
k_{cg}	crystal growth rate constant
L	length/thickness of membrane
(L)ADME	(liberation), absorption, distribution, metabolism, and excretion
LLC-PK1	Lewis lung-carcinoma porcine kidney cells
MDCK II	Madin-Darby canine kidney cells
MDR	multi drug resistance
M	mass of drug per unit volume (Higuchi equation)
M_{max}	maximum amount of drug in solution
MMC	myoelectric migrating motor complex
M_r	molecular weight
M_t	amount of drug released or in solution at time t
N	number of undissolved particles
N_A	Avogadro's constant
n.a.	not applicable/not available
NDA	new drug application
NIDDM	non insulin-dependent diabetes mellitus
OATP	organic anion-transporting protein
P	precipitation
PAMPA	Parallel Artificial Membrane Permeability Assay
P_{app}	apparent permeability
PBPK	physiologically-based pharmacokinetic

PD	pharmacodynamic/-s
P_{eff}	effective permeability
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
φ	constant proportional to the diffusion of molecules per unit surface area (nucleation theory)
PK	pharmacokinetic/-s
PPAR α	peroxisome proliferator-activated receptor α
PSA	polar surface area
P_t	amount of precipitated drug at time t
QbD	Quality by Design
Q_{out}	perfusion flow rate
R, R_c	radius (of a cluster)
ρ_d	drug density
rpm	revolutions per minute
S	solubility
SAP	surface activity profiling
SDS	sodium dodecyl sulphate
S_{eff}	effective small intestinal surface area
SGF_{sp}	Simulated Gastric Fluid *sine* pepsin
SIF_{sp}	Simulated Intestinal Fluid *sine* pancreatin
STELLA®	Structural Thinking, Experimental Learning Laboratory with Animation
SUPAC	scale up and post-approval changes
S_w	whole surface area in the small intestine
T_{lag}	time until a process starts
t_{max}	time to reach the maximum (plasma) concentration
TNO	Nederlandse Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek
USP	United States Pharmacopoeia
UWL	unstirred water layer
V_a	available liquid volume in the small intestine
V_d	volume of distribution
v_d^+	fraction of drug volume at the erosion front
v_{ds}	fraction of drug volume at the diffusion front
V_w	whole liquid volume in the small intestine
Z	Zeldovich factor (nucleation theory)

This thesis is based on the following publications:

1) Juenemann D, Jantratid E, Wagner C, Reppas C, Vertzoni M, and Dressman JB. Biorelevant *in Vitro* Dissolution Testing of Products Containing Micronized or Nanosized Fenofibrate with a View to Predicting Plasma Profiles. Eur J Pharm Biopharm 77 (2011): 257 – 264

2) Wagner C, Jantratid E, Kesisoglou F, Vertzoni M, Reppas C, and Dressman JB. Predicting the Oral Absorption of a Poorly Soluble, Poorly Permeable Weak Base Using Biorelevant Dissolution and Transfer Model Tests Coupled with a Physiologically Based Pharmacokinetic Model. Eur J Pharm Biopharm 82 (2012): 127 – 138

3) Wagner C, Thelen K, Willmann S, Selen A, and Dressman JB. Utilizing *in Vitro* and PBPK Tools to Link ADME Characteristics to Plasma Profiles: Case Example Nifedipine Immediate Release Formulation. J Pharm Sci 102 (2013): 3205 – 3219

4) Wagner C and Dressman JB. *In Vitro – in Silico* Tools to Predict Pharmacokinetics of Poorly Soluble Drug Compounds. Chapter 12 in: Predictive ADMET: Integrated Approaches in Drug Discovery and Development (Editors: Jianling Wang and Laszlo Urban). John Wiley & Sons, Inc, Hoboken, NJ, USA (*Article in press*)

1. Introduction

The oral administration of a drug is the most frequent and convenient route of administration, and formulation researchers normally strive to formulate drugs so that they can be administered orally. Exceptions to this general rule occur when the site of action is accessible (e.g. creams and ointments for local treatment of skin conditions) or when the drug cannot be absorbed from the gastrointestinal tract (e.g. proteins like insulin). In most cases, orally administered drugs are intended to act systemically, so they have to be absorbed during their passage through the gastrointestinal tract. There are only a few drugs which are administered orally and are intended to act locally, e.g. some antacids like calcium carbonate or sucralfate, drugs used for pancreatic enzyme replacement therapy, and anti-inflammatory drugs which are used for the therapy of Crohn's disease and ulcerative colitis [1].

For a drug to be absorbed from the gastrointestinal tract into the systemic circulation, it has to be released from its formulation, dissolve within a reasonable time span (corresponding to the drug's passage through the regions in which it can be absorbed, e.g. in the small intestine and/or the colon), cross the gut wall, and enter into systemic circulation. If an orally administered drug does not dissolve within a reasonable time span, it cannot be completely absorbed and thus may not reach its target in sufficient quantities to exert its action. After reaching the blood stream, the drug is distributed in the body, and a certain fraction – depending on the distribution pattern– reaches the site of action. Parallel to drug absorption and distribution, elimination of the drug from the body starts. In most cases, the drug is metabolized in the liver, but there is also the possibility that the drug is metabolized in other organs, e.g. in the small intestine or in the lungs. After being metabolized, the drug is excreted, and the most important route of drug excretion is via the urine (renally). Other routes of excretion include e.g. pulmonary or biliary excretion or excretion via the sweat [1].

Scientifically speaking, the aforementioned processes can be described with the term "*pharmacokinetics*" (from the Greek φάρμακον [*pharmakon*; drug] and κινητικός [*kinetikos*; in motion]), and this term thus describes the process of absorption, distribution, metabolism, and elimination of all kinds of drugs (small or large molecules) and nutrients which are administered to living organisms. These processes are commonly referred to as "ADME" characteristics. By contrast, the term *"pharmacodynamics"* describes the (pharmacological) effect of the drug on the organism. It is thus reasonable that pharmacokinetics and pharmacodynamics must be linked together in order to describe the mutual relationship between drug and organism.

In earlier times, active compounds were often discovered either by coincidence (e.g. the discovery of penicillin by Alexander Fleming) or empirically developed from “natural” structures, e.g. acetylsalicylic acid (which is derived from salicin, an ingredient in willow bark), antihypertensives like β-blocking agents (which are structurally related to adrenaline), angiotensin-converting enzyme inhibitors (which are derived from the poison of *Bothrops jararaca*, a South-American lance-head viper), and some anti-cancer drugs such as paclitaxel (which is derived from taxol, an alkaloid from the Pacific yew) [1, 2].

More recently, combinatorial chemistry has gained importance in drug discovery. In this approach, a large number of potential drug candidates are synthesized and subsequently screened for their affinity to a potential target, e.g. a receptor, within a short time-frame (so-called high-throughput screening). However, selection of potential drug candidates using this approach is based on *in vitro* pharmacology (e.g. receptor affinity). In many cases, lipophilicity is important to the interaction, and where this is the case, the selected candidates will often tend to have poor aqueous solubility [2-4]. The prediction of liberation, absorption, distribution, metabolism, and excretion (LADME) properties for these poorly soluble drug compounds is often more challenging than for highly soluble compounds, since various physiological factors such as (variations in) gastric emptying rates, small intestinal residence times, first pass metabolism, gastrointestinal fluid volumes, concentrations of natural surfactants, and/or the effective surface area at the site of absorption can all impact the pharmacokinetic profile after oral ingestion. As a consequence of this paradigm shift in oral drug development, the prediction of the intralumenal solubility and dissolution behavior of poorly soluble drug compounds and their consequences for oral drug absorption has gained importance in recent years.

1.1. Classification of Poorly Soluble Drugs

1.1.1. The Biopharmaceutics Classification Scheme (BCS)

The first approach to systematically classify drugs in terms of their biopharmaceutical characteristics was introduced by Gordon Amidon and colleagues in 1995, and the BCS addresses the interplay between the drug’s solubility and permeability characteristics [5]. According to their solubility and permeability characteristics, drugs can be classified into four groups (Fig. 1-1.).