European Journal of Pharmaceutical Sciences 57 (2014) 173–199

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Early pharmaceutical profiling to predict oral drug absorption: Current status and unmet needs

Christel A.S. Bergström [a,*], René Holm [b], Søren Astrup Jørgensen [c], Sara B.E. Andersson [a], Per Artursson [a], Stefania Beato [d], Anders Borde [e], Karl Box [f], Marcus Brewster [g], Jennifer Dressman [h], Kung-I. Feng [i], Gavin Halbert [j], Edmund Kostewicz [h], Mark McAllister [k], Uwe Muenster [l], Julian Thinnes [h], Robert Taylor [f], Anette Müllertz [c]

[a] Department of Pharmacy, Uppsala University, Biomedical Centre P.O. Box 580, SE-751 23 Uppsala, Sweden
[b] Biologics and Pharmaceutical Science, H. Lundbeck A/S, Ottiliavej 9, DK-2500 Valby, Denmark
[c] Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen, Universitetsparken 2, DK-2100 Copenhagen, Denmark
[d] Novartis Pharma AG, Novartis Campus, CH-4056 Basel, Switzerland
[e] Pharmaceutical Development, AstraZeneca R&D, Mölndal, Sweden
[f] Sirius Analytical Instruments Ltd., Riverside, Forest Row Business Park, Forest Row, East Sussex RH18 5DW, UK
[g] ChemPharm Development, Johnson & Johnson Pharmaceutical Research & Development, 2340 Beerse, Belgium
[h] Institute of Pharmaceutical Technology, Goethe Universität, 60438 Frankfurt/Main, Germany
[i] Basic Pharmaceutical Sciences, Merck Research Laboratories, Merck & Co., Inc., USA
[j] Strathclyde Institute for Pharmacy and Biomedical Sciences, Robertson Wing, University of Strathclyde, 161 Cathedral Street, Glasgow G4 0RE, Scotland, UK
[k] Drug Product Design, Pfizer PGRD, Sandwich, Kent CT13 9NJ, UK
[l] Material Science and Early Characterization, Bayer Pharma AG, Research Site Wuppertal-Aprath, Germany

ARTICLE INFO

Article history:
Received 3 June 2013
Received in revised form 17 October 2013
Accepted 27 October 2013
Available online 9 November 2013

Keywords:
Preformulation
Physicochemical properties
Pharmaceutical profiling
Biorelevant media
Intestinal fluid
Absorption

ABSTRACT

Preformulation measurements are used to estimate the fraction absorbed *in vivo* for orally administered compounds and thereby allow an early evaluation of the need for enabling formulations. As part of the Oral Biopharmaceutical Tools (OrBiTo) project, this review provides a summary of the pharmaceutical profiling methods available, with focus on *in silico* and *in vitro* models typically used to forecast active pharmaceutical ingredient's (APIs) *in vivo* performance after oral administration. An overview of the composition of human, animal and simulated gastrointestinal (GI) fluids is provided and state-of-the art methodologies to study API properties impacting on oral absorption are reviewed. Assays performed during early development, i.e. physicochemical characterization, dissolution profiles under physiological conditions, permeability assays and the impact of excipients on these properties are discussed in detail and future demands on pharmaceutical profiling are identified. It is expected that innovative computational and experimental methods that better describe molecular processes involved *in vivo* during dissolution and absorption of APIs will be developed in the OrBiTo. These methods will provide early insights into successful pathways (medicinal chemistry or formulation strategy) and are anticipated to increase the number of new APIs with good oral absorption being discovered.

1. Introduction

Large efforts are directed toward pharmaceutical profiling of active pharmaceutical ingredients (APIs) during the discovery and early development process. The aim of this profiling is to evaluate the potential of the API to display satisfactory biopharmaceutical properties. However, currently available methods are often not able to accurately predict *in vivo* API performance. The increased

Abbreviations: ADMET, absorption, distribution metabolism, elimination, toxicity; API, active pharmaceutical ingredient; BS, bilesalt; BS/PL, bile salt to phospholipid ratio; CMC, critical micellar concentration; DDI, drug–drug interaction; FaSSGF, fasted state simulated gastric fluid; FaSSIF, fasted state simulated intestinal fluid; FeSSGF, fed state simulated gastric fluid; FeSSIF, fed state simulated intestinal fluid; GI, gastrointestinal; HGF, human gastric fluid; HIF, human intestinal fluid; IVIVC, *in vitro–in vivo* correlation; IVIVR, *in vitro–in vivo* relationship; log*D*, logarithm of pH-dependent distribution of all species between octanol and water; log*P*, logarithm of partitioning between octanol and water of neutral species; lyso-PC, lyso-phosphatidylcholine; MO, mono-olein; OA, oleic acid; PBPK, physiology-based pharmacokinetics; PC, phosphatidylcholine; PEG4000, polyethyleneglycol 4000; pK_a, dissociation constant; PL, phospholipid; S, solubility; Tm, melting point.

* Corresponding author. Fax: +46 18 471 4223.
E-mail address: christel.bergstrom@farmaci.uu.se (C.A.S. Bergström).

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http://dx.doi.org/10.1016/j.ejps.2013.10.015

number of compounds profiled within the industrial research programs has led to the development of high throughput assays. In the early discovery stages when low amounts of API of limited purity is available, these provide physicochemical data allowing for categorization or binning of APIs into classes based on properties such as lipophilicity, solubility and permeability. During later discovery stages and at the phase of early development, when the compound library is significantly smaller, methods providing more accurately measured physicochemical properties are also used. In addition, the impact of factors such as components present in the gastrointestinal (GI) tract are investigated. In particular, solubilization effects obtained by colloidal lipid structures present in the GI fluid under fasted and fed conditions are explored. As part of the Oral Biopharmaceutical Tools (OrBiTo) project, this review provides a summary of the pharmaceutical profiling methods available, with focus on *in silico* and *in vitro* models typically used to forecast active pharmaceutical ingredient's (APIs) *in vivo* performance after oral administration. Here we provide a detailed review of the human and animal GI fluids under fasted and fed conditions (Section 2) and an update on the simulated intestinal fluids currently employed for *in vitro* dissolution studies (Section 3). Further, we provide a chapter on state-of-the-art methods for physicochemical and pharmaceutical profiling (Section 4), which are then set in an industrial context in Section 5. Finally, we analyse the gaps and challenges presently existing when using current *in vitro* methodologies to forecast the *in vivo* performance and the need for enabling formulations of APIs. It is expected that innovative *in silico* and *in vitro* methods that better describe molecular processes involved *in vivo* during dissolution and absorption of APIs will be developed in the framework of OrBiTo. We anticipate such models to early inform projects on successful pathways (molecular structure optimization and/or formulation strategies) to increase the number of APIs with good oral absorption being discovered.

2. Composition of GI fluids

The composition of the GI fluids has a large impact on the solubility and dissolution of poorly soluble API in the GI tract, and hence a large influence on the drug absorption. Gastric and intestinal fluids sampled from humans have been characterized in a number of studies, and this review summarizes the current knowledge with regard to pH, buffer capacity, osmolarity, surface tension and lipid concentration of GI fluids under fasted and fed conditions. It should be noted that the studies are varying in pre-dosing liquid and volume (if any), aspiration time, analytical methods and the composition of the ingested meal (for the fed state media). The focus of this review will be on data published on gastric, duodenal and jejunal composition. Although drug absorption takes place in the lower part of the gastrointestinal tract, the literature is sparse and will not be addressed further in this review (Hirtz, 1985).

The methods used for aspiration of gastric or intestinal fluids involve either intubation orally (Hernell et al., 1990; Lindahl et al., 1997; Carrière et al., 2000; Pedersen et al., 2000; Persson et al., 2005; Brouwers et al., 2006; Moreno et al., 2006; Kossena et al., 2007; Clarysse et al., 2009; AstraZeneca, data on file) or nasally (Armand et al., 1996; Kalantzi et al., 2006a, 2006b; Psachoulias et al., 2011; Vertzoni et al., 2012). After intubation, the position of the catheter is observed via fluoroscopy, or other suitable radiology methods (Dewar et al., 1982; Schindlbeck et al., 1987; Armand et al., 1996; Lindahl et al., 1997; Pedersen et al., 2000; Brouwers et al., 2006; Kalantzi et al., 2006a, 2006b; Moreno et al., 2006; Persson et al., 2006; Clarysse et al., 2009; Bevernage et al., 2011; Psachoulias et al., 2011). Intubation catheters vary in the method applied to collect GI fluid. Brouwers et al. (2006) used two double-lumen catheters to simultaneously aspirate fluid from the duodenum (Salem Sump Tube) and the proximal jejunum (Bowel Decompression Catheter), which prevented the creation of lower pressure in the intestine during aspiration. Kalantzi et al. (2006a) used a nasally intubated single lumen tube positioned in the stomach to aspirate gastric fluid and also for administration of meals prior to fed state sampling. Another more complex aspiration method utilizes a 175 cm long multichannel tube (Loc-I-Gut), which can be used to aspirate both gastric and intestinal fluid simultaneously (Hedeman et al., 1996; Lindahl et al., 1997; Pedersen et al., 2000; Holm et al., 2001a, 2001b; Nielsen et al., 2001b, 2001a; Zangenberg et al., 2001b, 2001a; Holm et al., 2002, 2003; Christensen et al., 2004; Karpf et al., 2004; Persson et al., 2005; Moreno et al., 2006; Kossena et al., 2007). The Loc-I-Gut tube has two latex balloons distally on the tube positioned 10 cm apart from each other. These balloons are inflated to prevent the tube from passing further down in the intestine after the targeted position has been reached, as determined fluoroscopically. It should be noted that introducing a catheter was found to cause duodenogastric reflux (Hoare et al., 1978). According to Nolan, there was also an increased risk of duodenogastric reflux upon rapid duodenal and jejunal intubation (Nolan, 1979). This suggested a potential problem with aspirated gastric fluid during simultaneous intestinal intubation by the Loc-I-Gut method. In addition to the different types of tubes, a Heidelberg Capsule has been administered orally to healthy volunteers to measure intestinal fluid pH (Dressman et al., 1990). The capsule is a battery-operated high frequency radio transmitter and a radio antenna signal receiver positioned around the waist of the volunteer records pH over time.

The protocols for aspiration in the fasted state conditions vary; some investigators administered liquid to the volunteers (Dewar et al., 1982; Persson et al., 2005; Brouwers et al., 2006; Kalantzi et al., 2006a, 2006b; Moreno et al., 2006; Clarysse et al., 2009; Bevernage et al., 2011, 2012b; Psachoulias et al., 2011), whereas others did not (Piper et al., 1965; Finholt and Solvang, 1968; Lindahl et al., 1997; Moreno et al., 2006; Persson et al., 2006; Pedersen et al., 2013). In some studies a solution of a non-absorbable marker (PEG4000) was administered to enable corrections for water absorption and/or secretion (Kalantzi et al., 2006a, 2006b; Persson et al., 2006). This can result in lower concentrations of salt and/or lipids measured in the fasted volunteers due to dilution by the marker. The emptying water from the stomach has been found to follow an exponential curve with a half-time of 8–15 min (Brener et al., 1983; Dressman, 1986; Armand et al., 1994), and hence, the effect of the dilution will be dependent on the sampling time-point post fluid administration. Another study examined gastric emptying with relation to the three different phases of the interdigestive migrating myoelectric complex (IMMC), where subjects received either 50 mL and 200 mL of water (Oberle et al., 1990). Overall the observed emptying half-life was fastest in phase I, and slowest in phase III. The emptying half-life was faster in all three phases for subjects receiving 200 mL of water. When 50 mL of water was administered the emptying half-life ranged from 9.0 ± 4.9 min (Phase I) up to 60.6 ± 21.0 (Phase III). For patients receiving 200 mL of water the emptying half-life ranged from 4.9 ± 2.1 to 22.8 ± 17.8 min.

Studies of GI fluid characteristics in the fed state vary with regard to the composition of the administered meal prior to sampling. Nutritional supplements such as Ensure Plus® (Kalantzi et al., 2006a, 2006b; Clarysse et al., 2009), Scandishake Mix (Clarysse et al., 2009), Shak Iso (Carriere et al., 1993) and Biosorbin MCT® (Schindlbeck et al., 1987) contain the same nutrients as a meal and are often used. However, in some studies homogenized meals were administered (Dewar et al., 1982; Hernell et al., 1990;