European Journal of Pharmaceutical Sciences 67 (2015) 12–20

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

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

Concomitant intake of alcohol may increase the absorption of poorly soluble drugs

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ARTICLE INFO

Article history:
Received 15 August 2014
Accepted 23 October 2014
Available online 31 October 2014

Chemical compounds:
Cinnarizine (PubChem CID: 1547484)
Dipyridamole (PubChem CID: 3108)
Felodipine (PubChem CID: 3333)
Griseofulvin (PubChem CID: 441140)
Indomethacin (PubChem CID: 3715)
Indoprofen (PubChem CID: 3718)
Progesterone (PubChem CID: 5994)
Terfenadine (PubChem CID: 5405)
Tolfenamic acid (PubChem CID: 610479)

Keywords:
Solubility
Biorelevant dissolution
Poorly soluble compounds
Ethanol
Molecular properties
Absorption modeling

ABSTRACT

Ethanol can increase the solubility of poorly soluble and hence present a higher drug concentration in the gastrointestinal tract. This may produce a faster and more effective absorption resulting in variable and/or high drug plasma concentrations, both of which can lead to adverse drug reactions. In this work we therefore studied the solubility and absorption effects of nine diverse compounds when ethanol was present. The apparent solubility was measured using the μDiss Profiler Plus (pION, MA) in four media representing gastric conditions with and without ethanol. The solubility results were combined with in-house data on solubility in intestinal fluids (with and without ethanol) and pharmacokinetic parameters extracted from the literature and used as input in compartmental absorption simulations using the software GI-Sim. Apparent solubility increased more than 7-fold for non-ionized compounds in simulated gastric fluid containing 20% ethanol. Compounds with weak base functions (cinnarizine, dipyridamole and terfenadine) were completely ionized at the studied gastric pH and their solubility was therefore unaffected by ethanol. Compounds with low solubility in intestinal media and a pronounced solubility increase due to ethanol in the upper gastric compartments showed an increased absorption in the simulations. The rate of absorption of the acidic compounds indomethacin and indoprofen was slightly increased but the extent of absorption was unaffected as the complete doses were readily absorbed even without ethanol. This was likely due to a high apparent solubility in the intestinal compartment where the weak acids are ionized. The absorption of the studied non-ionizable compounds increased when ethanol was present in the gastric and intestinal media. These results indicate that concomitant intake of alcohol may significantly increase the solubility and hence, the plasma concentration for non-ionizable, lipophilic compounds with the potential of adverse drug reactions to occur.

1. Introduction

Poor hydration as a consequence of high lipophilicity is the main cause of the low aqueous solubility of modern drugs. *In vivo*, solubility in the gastrointestinal tract is mainly a result of the pH-gradient and presence of naturally available lipids. The stomach has a low pH with a reported range of 1.7–3.3 (median of 2.5) and low concentrations of lipids. In contrast, in the small intestine, where most of the absorption occurs, the pH increases to 6.5–7.7 (median 6.9) with a bile salt and phospholipid concentration of 2.52 mM and 0.19 mM, respectively (Bergström et al., 2014). The dissolution rate and apparent solubility (S_{app}) of ionizable drugs are dependent on their charge as a function of their dissociation constant (pKa) and the pH of the gastrointestinal milieu. This relationship is described with the Henderson–Hasselbalch equation (Hasselbalch, 1916) and results in bases carrying a positive charge in the stomach whereas acidic functions are neutral. When emptied into the small intestine, the bases become less charged whereas the acidic compounds typically become negatively charged. These changes in ionization make classical acidic drugs with a pKa < 5.5 significantly more soluble in the small intestine compared to the stomach. For weak bases with a pKa < 6, an increased solubility is achieved in the gastric compartment compared to the intestinal one and the compounds are at risk for precipitating when emptied from the stomach (Carlert et al., 2010; Psachoulias et al., 2011). In early drug development platforms, surrogates for gastrointestinal fluids (e.g., fasted state simulated gastric and intestinal fluids, FaSSGF and FaSSIF, respectively) are used to mimic the dissolution in the gastrointestinal compartments (Galia et al., 1998; Vertzoni et al., 2005).

Ethanol can act as a cosolvent and increase the S_{app} in gastrointestinal fluids. This may therefore affect the absorption of poorly

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http://dx.doi.org/10.1016/j.ejps.2014.10.017
0928-0987/

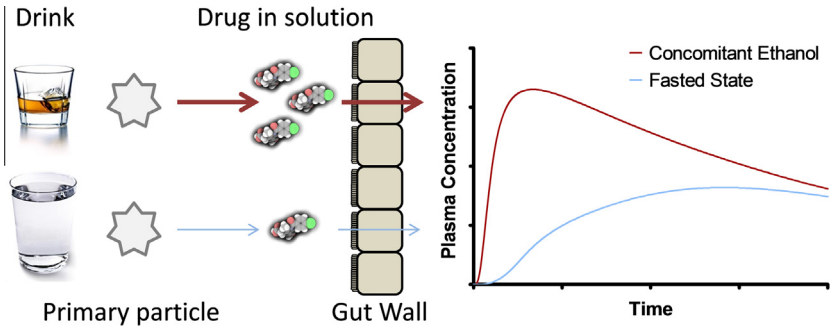

Fig. 1. Potential effect of concomitant ethanol intake on solubility and subsequent absorption. Ethanol in gastrointestinal media can increase the solubility of lipophilic compounds. As a result, the higher concentration gradient drives their absorption.

soluble drugs. Common modified release formulations carrying high doses of drugs have been shown to disintegrate prematurely and unload the complete dose in the small intestine in response to ethanol intake (Fadda et al., 2008; Walden et al., 2007). This phenomenon is referred to as dose dumping and can lead to increased and potentially hazardous plasma concentrations and adverse side effects of drugs with narrow therapeutic window (Lennernäs, 2009). A well-known example of this phenomenon is hydromorphone for which one formulation was withdrawn from the market in 2005 after reports of ethanol-induced, dose-dumping-related, adverse drug reactions (ADR). The withdrawn product was a capsule with an extended release formulation consisting of hotmelt extruded granules of the drug, ammonio methacrylate copolymer type b and ethylcellulose. The latter has been shown to be sensitive to ethanol in dissolution tests (Fadda et al., 2008). Following this observation the FDA composed a number of substance specific guidelines (e.g., bupropion hydrochloride, morphine sulfate and trospium chloride) to test for ethanol sensitivity of modified release formulations. In these guidelines dissolution behavior should be assessed for 2 h with 0%, 5%, 20% and 40% *v*/*v* ethanol in an acidic medium reflecting the gastric milieu (Anand et al., 2011).

We hypothesized that immediate release formulations of drugs with low solubility in gastrointestinal fluids may, in a similar fashion as extended release formulations during dose-dumping, show increased absorption in response to alcohol intake. This hypothesis is based on the large drug load of such compounds which is not dissolved during gastrointestinal transit under normal fasted conditions. If the presence of ethanol in gastrointestinal fluids increases the dissolution rate and/or the S_{app} of a compound, it may also affect the absorption profile of that drug (Fig. 1). Indeed, in a previous study investigating 22 compounds in FaSSIF, we found that non-ionizable compounds and weak acids in particular were at a high risk for obtaining significantly different dissolution profiles when administered with ethanol. However, ethanol is rapidly absorbed in the intestinal tract and the impact on absorption was not revealed in the previous study. For instance, it has been shown that if ethanol is co-administered with water, the ethanol disappears from the gastric compartment within 30 min and half of the dose is emptied into the duodenum within 5 min (Levitt et al., 1997). Other studies have shown that although the absorption of ethanol from the small intestine is fast, it is not instantaneous, and elevated levels of ethanol have been found in the upper small intestine up to 30 min after intake (Halsted et al., 1973). It is clear that if ethanol is taken together with food it is diluted and the ethanol absorption is delayed. Human *in vivo* studies of drug ethanol sensitivity would require a combination of high drug doses with ethanol intake and are not ethically feasible. In this study we therefore employed *in vitro* solubility measurements and *in silico* absorption simulations to identify compounds potentially sensitive to concomitant ethanol intake.

2. Materials and methods

2.1. Data set

Nine model compounds were included in this study on the basis of their lipophilicity, aqueous solubility (with focus on poorly soluble compounds), and results from a previous study of ethanol sensitivity in FaSSIF (Fig. 2) (Fagerberg et al., 2012). The data set included three acidic compounds (indomethacin, indoprofen and tolfenamic acid), three non-ionizable compounds (felodipine, griseofulvin and progesterone), and three weak bases (cinnarizine, dipyridamole and terfenadine); these compounds were selected to cover both charged and non-ionizable compounds with a diversity in physicochemical properties (Table 1). Only compounds available in their free form were included to exclude effects from salt formation. ADMET Predictor (Simulations Plus, CA) was used to calculate lipophilicity expressed as log*P* and log$D_{pH2.5}$, and the total effective permeability (P_{eff}) for the nine compounds. Diffusivity in water was calculated according to the Stoke–Einstein's equation on the basis of the molecular volume estimated using ACD/Chemsketch 12.0 (Advanced Chemical Development Inc, Canada). Pharmacokinetic parameters were gathered from the literature. All input data used in the computational simulations are summarized in Table 2.

2.2. Dissolution media preparation

The composition of FaSSGF was a modification of the gastric medium described by Vertzoni et al. (2005). No pepsin was included and the pH was increased from the suggested 1.6 to 2.5. The latter was done to reflect recent findings regarding the pH of human gastric-fluid aspirates (Kalantzi et al., 2006; Pedersen et al., 2013) and to avoid unnecessary wear on the stainless-steel fiber-optic dip probes used for concentration determination.

A NaCl solution with pH 2.5 ($NaCl_{pH2.5}$) was prepared by dissolving 2 g NaCl in 0.9 L MilliQ water, after which the pH was adjusted to 2.5 by the addition of HCl before adjusting the final volume to 1 L. The resulting $NaCl_{pH2.5}$ was sterile-filtered and stored at 8 °C. $NaCl_{pH2.5}$ with 20% ethanol ($NaCl_{pH2.520\%Ethanol}$) was prepared in the same fashion except that 2.5 g NaCl was used and 20% (*v*/*v*) ethanol was added to the 1 L volume (final volume 1.2 L). The corresponding biorelevant dissolution media (BDM), i.e. FaSSGF and $FaSSGF_{20\%Ethanol}$, were prepared by dissolving 6 mg SIF powder in 100 mL of each NaCl solutions.

2.3. Solubility determination

Apparent solubility was determined in the four different media using a three-channel μDiss Profiler Plus (pION, MA) described