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Biopharmaceutic Profiling of Salts to Improve Absorption of Poorly Soluble Basic Drugs

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ABSTRACT

AZD1175 and AZD2207 are 2 highly lipophilic compounds with a significant risk of not achieving therapeutic plasma concentrations due to solubility-limited absorption. The compounds have the same molecular weight and minimal structural differences. The aim of the present work was to investigate whether salts could be applied to improve the intestinal absorption, and the subsequent *in vivo* exposure. Drug solubilities, dissolution rates, and degree of supersaturation and precipitation were determined in biorelevant media. Dog studies were performed, in the absence and presence of a precipitation inhibitor (hydroxypropyl methylcellulose). Finally, a human phase I study was performed. For AZD1175, there was a good agreement between dissolution rates, *in vivo* exposure in dog, and the obtained exposure in human with the selected hemi-1,5-naphthalenedisulfonate of the compound. For AZD2207, the picture was more complex. The same counter ion was selected for the study in man. In addition, the chloride salt of AZD2207 showed promising data in the presence of a precipitation inhibitor *in vitro* and in dog that, however, could not be repeated in man. The differences in observations between the 2 compounds could be attributed to the difference in solubility and to the degree of supersaturation in the gastric environment rather than in the intestine.

Introduction

Oral delivery is the most convenient and widely used route of administration of drugs. However, the gastrointestinal (GI) tract may constitute a significant barrier against oral absorption of drugs, where the interplay of the physicochemical and biopharmaceutical properties of a drug (e.g., lipophilicity, ionizability, intestinal permeability, and solubility), formulation factors, and physiological factors (transit time, regional GI pH, water content and composition of intestinal fluids, local expression of transporter proteins and prandial state) determine the rate and extent of absorption.[1-3] One of the main biopharmaceutical and formulation development–related challenges during recent years has been the increased number of poorly water soluble drugs, that is, Biopharmaceutics Classification System class II and IV compounds according to the Biopharmaceutics classification system,[4-6] which in turn is associated with an increased risk of low extent of absorption and bioavailability, regional and particle size–dependent absorption, significant food effects, and dose-dependent (less than linear) pharmacokinetics.

Several formulation strategies may be applied to improve the rate and extent of absorption of poorly soluble drugs. For poorly soluble drugs with dissolution-limited absorption, particle size reduction, either by micronization or nanosizing, is a well-established approach to increase the dissolution rate and hence the rate and extent of absorption.[7,8] The major strategy to overcome solubility-limited absorption is to increase the apparent concentration of drug in the GI lumen through supersaturation.[9-11] The aim is to improve the absorption by increasing the amount dissolved in the GI tract. Supersaturation may be achieved using a number of different formulation approaches such as an amorphous form of the compound,[12-16] a less stable crystalline form,[17,18] crystalline salts,[11,19,20] formulating with cosolvents,[21] adsorption-based formulations,[22] cocrystals,[23,24] and lipid-based formulations.[25-28] However, in generating supersaturation, the drug in solution is thermodynamically unstable, generating a driving force for precipitation in the GI tract. There are some reports available regarding formulation strategies that can be applied to inhibit *in vivo* precipitation.[29-33]

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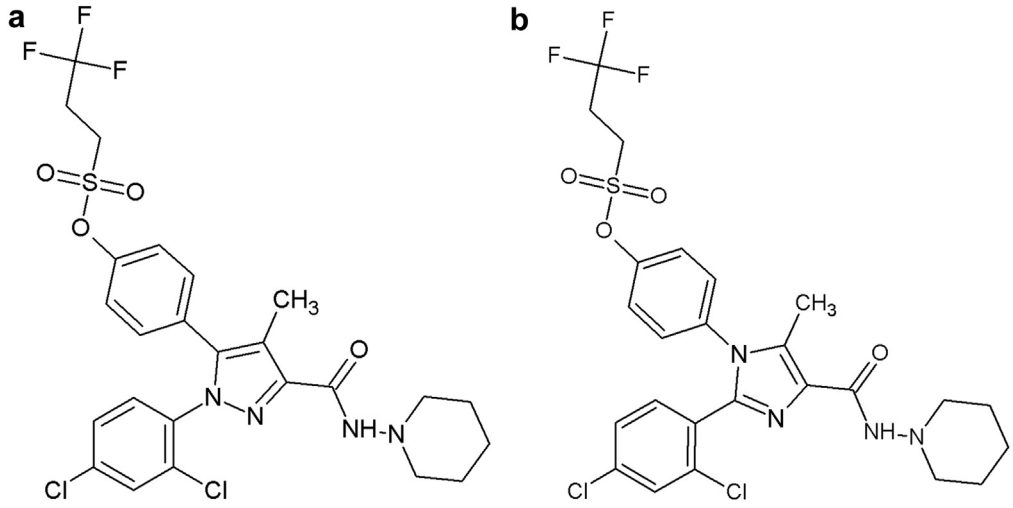

Figure 1. Molecular structure of (a) AZD1175 and (b) AZD2207.

The cannabinoid receptor 1 antagonists AZD1175 and AZD2207 are highly lipophilic weak bases with low pH-dependent solubility and high intestinal permeability in the Caco-2 model (Fig. 1 and Table 1). During the candidate drug selection process, it was predicted that administration of an oral formulation containing the base form of either of the candidates would result in incomplete absorption in the therapeutic dose range due to solubility-limited absorption in humans. The purpose with this study was to investigate whether salts could be applied to improve the intestinal absorption of AZD1175 and AZD2207 in humans and to investigate the underlying mechanisms driving the *in vivo* performance of different salts. Finally, a formulation approach to inhibit *in vivo* precipitation to improve absorption of salts was also evaluated.

Materials and Methods

The structure and physicochemical properties of AZD1175 and AZD2207 (AstraZeneca R&D Gothenburg) are shown in Figure 1 and Table 1, respectively. The free base form and the 3 salts, hemi-1,5-naphthalenedisulfonate (EQ), chloride (HCl), and hydrogen sulfate (H_2SO_4), of AZD1175 and AZD2207 were supplied by AstraZeneca R&D Gothenburg.

Chemicals

All excipients and solvents were of analytical grade and were purchased from Sigma. Sodium taurocholate was obtained from Biosynth AG and lecithin (Lipoid E PC) from Lipoid. Internally approved excipients were used for formulation manufacturing.

Table 1
Physicochemical Properties of AZD1175 and AZD2207

Property	AZD1175	AZD2207
Mw (g/mol)	605.5	605.5
pKa	2.4-3.2	2.8-3.3
LogP	6.1	5.6
Intrinsic solubility (μg/mL)	0.05	2
FaSSIF solubility (μg/mL)	7	11
Caco-2 Papp pH 6.5/7.4 ($\times 10^{-6}$ cm/s)	60[a]	92[a]

[a] The recoveries of the compounds were low in the experiments, 17% and 36% for AZD1175 and AZD2207, respectively, which results in an underestimation of the true permeability. The high permeability marker metoprolol has a permeability of 13×10^{-6} cm/s in the assay.

Solubility Experiments

The solubility of the free base form of AZD1175 and AZD2207 was determined in water, 0.1 M HCl pH 1 and in phosphate buffer pH 3, 5, and 8 after 24 h and pH-solubility profiles were constructed according to the Henderson-Hasselbalch equation. In addition, the solubility in Fasted State Simulated Intestinal Fluid (FaSSIF[34]) was determined after 24 h. The solubility experiments were performed at 37°C. An excess of substance was added to each media (n = 3) and placed in a thermomixer (Eppendorf AG) at 1000 rpm.[35] Samples were withdrawn and centrifuged (Rotina 46R; Hettich labinstrument AB) at 10,000 rpm for 15 min at 37°C. The supernatant was transferred to vials for analysis of drug content. The solid material from the solubility experiments was analyzed with X-ray powder diffraction (XRPD).

Intrinsic Dissolution Rate Experiments

The dissolution rate of AZD1175 and AZD2207 free base forms and their salts was studied in 0.1 M HCl and FaSSIF, using a rotating disc method (USP28; scaled down in size, with a disc diameter of 3 mm in comparison to the pharmacopoeial method). The discs were compacted in a tablet press (Kilian D-50735 SP300; Kilian & Co GmbH). The speed of rotation was set to 1000 rpm and the temperature of the dissolution media was maintained at 37°C. Each experiment ran for 30 min, and during this time sink condition was maintained. The dissolution rate was determined by linear regression from the initial linear phase in the amount dissolved versus time profile.

pH-shift Dissolution Experiments

The dissolution and precipitation behavior of AZD2207 EQ and HCl salts as well as 2 different tablets of the HCl salt (Table 2) was studied under biorelevant conditions using a pH-shift method similar to a previously reported scaled-down method.[21] Tablets or powder with an amount of AZD2207 equivalent to 40 mg free base were added to a solution of 200 mL water and 50 mL 0.1 M HCl with a final pH of 2.2 to mimic the human gastric environment. Samples were withdrawn at 5, 10, 15, and 30 min. After 30 min, 80 mL of concentrated FaSSIF (cFaSSIF, Table 3) was added and the pH was raised to a final pH of 6.5 to mimic the human intestinal environment. Additional samples were withdrawn at 40, 50, 75, 90, and