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Research paper

Time-dependent effects on small intestinal transport by absorption-modifying excipients

D. Dahlgren[a], C. Roos[a], A. Lundqvist[b], C. Tannergren[b], M. Sjöblom[c], E. Sjögren[a], H. Lennernäs[a,*]

[a] Department of Pharmacy, Uppsala University, Uppsala, Sweden
[b] AstraZeneca R&D, Gothenburg, Sweden
[c] Department of Neuroscience, Division of Physiology, Uppsala University, Uppsala, Sweden

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ABSTRACT

The relevance of the rat single-pass intestinal perfusion model for investigating *in vivo* time-dependent effects of absorption-modifying excipients (AMEs) is not fully established. Therefore, the dynamic effect and recovery of the intestinal mucosa was evaluated based on the lumen-to-blood flux (J_{abs}) of six model compounds, and the blood-to-lumen clearance of ^{51}Cr-EDTA (CL_{Cr}), during and after 15- and 60-min mucosal exposure of the AMEs, sodium dodecyl sulfate (SDS) and chitosan, in separate experiments. The contribution of enteric neurons on the effect of SDS and chitosan was also evaluated by luminal coadministration of the nicotinic receptor antagonist, mecamylamine. The increases in J_{abs} and CL_{Cr} (maximum and total) during the perfusion experiments were dependent on exposure time (15 and 60 min), and the concentration of SDS, but not chitosan. The increases in J_{abs} and CL_{Cr} following the 15-min intestinal exposure of both SDS and chitosan were greater than those reported from an *in vivo* rat intraintestinal bolus model. However, the effect in the bolus model could be predicted from the increase of J_{abs} at the end of the 15-min exposure period, where a six-fold increase in J_{abs} was required for a corresponding effect in the *in vivo* bolus model. This illustrates that a rapid and robust effect of the AME is crucial to increase the *in vivo* intestinal absorption rate before the yet unabsorbed drug in lumen has been transported distally in the intestine. Further, the recovery of the intestinal mucosa was complete following 15-min exposures of SDS and chitosan, but it only recovered 50% after the 60-min intestinal exposures. Our study also showed that the luminal exposure of AMEs affected the absorptive model drug transport more than the excretion of ^{51}Cr-EDTA, as J_{abs} for the drugs was more sensitive than CL_{Cr} at detecting dynamic mucosal AME effects, such as response rate and recovery. Finally, there appears to be no nicotinergic neural contribution to the absorption-enhancing effect of SDS and chitosan, as luminal administration of 0.1 mM mecamylamine had no effect.

1. Introduction

Absorption-modifying pharmaceutical excipients (AMEs) may increase intestinal drug absorption by reducing the mucosal barrier integrity of the intestinal epithelial cell layer. An AME may increase paracellular permeability by interacting directly with the tight junction proteins, or indirectly by affecting the physiological regulation of paracellular permeability. Alternatively, an AME can affect the integrity of the intestinal epithelial cell membrane, thereby increasing transcellular transport. The bioequivalence an oral drug product containing an AME may consequently be affected if the rate and/or fraction dose absorbed (f_{abs}) of a drug is increased [1]. Conversely, AMEs may be used in oral drug delivery systems (DDS) to increase the f_{abs} of drugs with low intestinal permeability, such as BCS class III and IV drugs, and pharmaceutical peptides. Oral DDS with an AME designed to increase intestinal drug absorption require that the onset of their effects are rapid. This is to enable drug absorption in the area with the reduced barrier integrity before the drug translocates to uncompromised intestinal areas [2]. AME effects should also be rapidly reversible. This is to avoid, for instance, invasion of bacteria and other harmful luminal constituents into the mucosa. At the same time, exaggerated mucosal epithelial effects must be avoided because they may disturb the homeostasis of the epithelium, which is normally under strict physiological regulation by neural and paracrine signaling and by inflammatory factors. These physiological effectors regulate paracellular permeability and respond to luminal conditions, such as osmolarity and

Abbreviations: AME, absorption-modifying excipient; BCS, Biopharmaceutical Classification System; CL_{Cr}, clearance of ^{51}Cr-EDTA; J_{abs}, absorptive model compound flux; SDS, sodium dodecyl sulfate

* Corresponding author at: Department of Pharmacy, Uppsala University, Box 580, SE-751 23 Uppsala, Sweden.
E-mail address: hans.lennernas@farmaci.uu.se (H. Lennernäs).

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Table 1
Physicochemical properties, BCS (Biopharmaceutics Classification System) classification, and human jejunal effective permeability (P_{eff}) historically determined with intestinal perfusion, of the four model drugs [43,44].

Substance (BCS class)	MM (g/mol)	pK_a	PSA	HBA/HBD	Log P	Log $D_{7.4}$	Log $D_{6.5}$	P_{eff} ($\times 10^{-4}$ cm/s)
Acyclovir (III)	225.2	$2.19^a/9.25^a$	117	7/3	−1.8	−1.8	n/a	No data
Atenolol (III)	266	9.6^b	88.1	4/4	0.18	−2.0	< −2.0	0.2
Enalaprilat (III)	348	$3.17^b/7.84^a$	102.1	6/3	−0.13	−1.0	−1.0	0.2
Metoprolol (I)	267	9.6^b	57.8	4/2	2.07	0.0	−0.5	1.3
Ketoprofen (II)	254	3.89^a	54.2	3/1	3.37	0.1	0.8	8.7
Phenol Red (n/a)	354	7.9^a	92	5/2	3.02	n/a	n/a	No data

[a]acid, [b]base, HBA/HBD – hydrogen bond acceptor/donor, Log $D_{7.4/6.5}$ – n-octanol–water partition coefficient at pH 7.4/6.5, Log P – n-octanol–water coefficient, MM – molar mass, pKa – dissociation constant, PSA – polar surface area.

pH, and are also affected by neural inhibitors and various enteroendocrine mechanisms [3,4].

Preclinical *in vivo* evaluations of permeability effects are commonly performed in the rat single-pass intestinal perfusion (SPIP) model, and/or in oral *in vivo* pharmacokinetic studies in rat, pig, and dog [2,5,6]. However, these models do not generally take into account the time dependence of AMEs with different mechanism(s) of action. These factors are important for both the pharmacodynamics (such as onset, efficacy, duration) and the safety of DDSs containing an AME. Hence, these are key regulatory issues for any advanced oral formulation. Slow onset of an AME may result in inadequate mucosal drug permeation, while a long effect duration may increases the risk of unwanted side effects due to unspecific absorption of potentially toxic antigens and xenobiotics. An increased understanding of the kinetics of these processes is expected to support in the development of novel oral drug delivery systems, by addressing transit effects, secretion, spreading and interactions with luminal constituents.

In a previous evaluation of intestinal permeation enhancement in a rat SPIP model, both chitosan (cationic polysaccharide) and SDS (anionic surfactant) increased the intestinal blood-to-lumen transport of the mucosal barrier marker, ^{51}Cr-EDTA, and intestinal absorption four low-permeation model compounds (acyclovir, atenolol, enalaprilat, phenol red) [7]. Based on previous rat SPIP and in vitro cell monolayer studies, SDS is assumed to increase the transcellular lipoidal diffusion by increasing the cell membrane fluidity, while chitosan is assumed to increases paracellular diffusion by interacting with tight junction proteins [8,9]. These effects were further evaluated in the rat and dog intraintestinal bolus models [5]. The bolus GI model takes into account dynamic, *in vivo* relevant aspects—such as intestinal transit, spreading and dilution—that affect the contact time and concentration of AME at the intestinal mucosa [10,11]. The effect of both SDS and chitosan were consequently lower in the bolus study than in the SPIP study at comparable concentrations [5,7]. Intraintestinal bolus administration is more predictive than the SPIP model for the clinical usefulness of an AME-containing drug product. However, the SPIP model is useful for evaluation of the *in vivo* mechanisms of an AME, as it allows for detailed investigations of the dynamic, time-dependent effect of the AME on the epithelial membrane.

The main objective in the present study was to evaluate the dynamic, time dependent effect of mucosal exposure time of two AMEs (SDS and chitosan) on intestinal permeability of seven model compounds with various passive transport mechanisms (^{51}Cr-EDTA, acyclovir, atenolol, enalaprilat, ketoprofen, metoprolol, and phenol red). The effect of AME on the mucosa was evaluated after a 15- and 60-min intestinal exposure in the SPIP model, respectively. The 15-min luminal exposure period is physiologically relevant, on the basis of intestinal water secretion, content and distribution, and small intestinal transit time [12–14]. The mucosal effect and recovery time after a 60-min intestinal exposure was tested to evaluate the severity of the reduced barrier integrity. The longer exposure time was selected to account for the potentially longer *in vivo* exposures caused by mucoadhesive formulation strategies, or with enteral drug/nutrient administration to some patient groups [15–17]. The second objective of the study was to evaluate the mechanism of action of the *in vivo* absorption-promoting effects of chitosan and SDS. The impact of a neurally mediated, physiologically regulated mechanism was investigated by adding mecamylamine, a nicotinic receptor antagonist, to the perfusate.

2. Materials and methods

2.1. Active pharmaceutical ingredients, pharmaceutical excipients and other chemicals

Six model compounds were selected: acyclovir, atenolol, enalaprilat, ketoprofen, metoprolol, and phenol red. These model compounds belong to classes I, II, and III according to the biopharmaceutics classification system (BCS) [18]. BCS class and physicochemical properties are summarized in Table 1. The two AMEs were SDS and chitosan. Atenolol and metoprolol tartrate were provided by AstraZeneca AB (Mölndal, Sweden). Acyclovir, enalaprilat, ketoprofen, phenol red, sodium dodecyl sulfate (SDS), bovine albumin, mecamylamine hydrochloride, and inactin were purchased from Sigma-Aldrich (St. Louis, US). Sodium phosphate dibasic dihydrate ($Na_2HPO_4 \cdot 2H_2O$), potassium dihydrogen phosphate (KH_2PO_4), sodium hydroxide (NaOH), and sodium chloride (NaCl) were purchased from Merck KGaA (Darmstadt, Germany). ^{51}Chromium-labeled ethylenediaminetetraacetate (^{51}Cr-EDTA) was purchased from PerkinElmer Life Sciences (Boston, MA). Chitosan hydrochloride (molecular mass 40–300 kDa, degree of acetylation 8.8%) was purchased from Kraeber & Co GmbH (Ellerbek, Germany).

2.2. Study perfusion solutions

Eight isotonic (290 mOsm) perfusion phosphate buffer (8 mM) solutions at pH 6.5 were prepared, all containing a 50 μM cassette-dose of the six model compounds. There was one control solution and seven test solutions. The test solutions in the evaluation of time-dependent effects contained one of the following AMEs: SDS 1 mg/mL (3.5 mM), SDS 5 mg/mL (17.3 mM), chitosan 1 mg/mL, and chitosan 5 mg/mL. The AME doses (concentrations) are previously evaluated and corresponds to an oral dose of 0.2 and 1.0 g administered with 250 mL water [7]. The mechanistic evaluation contained the control solution, and the two high-dose (5 mg/mL) SDS and chitosan solutions in the perfusate. These were tested together with luminal addition of the nicotinic receptor antagonist, mecamylamine (0.1 mM), in the perfusate. This was to evaluate the contribution of local, enteric nerve activity to the basal intestinal permeability determined with the control solution, and the AME-induced changes in intestinal permeability. This is important as it has been reported that the time to effect and recovery time is shown to be substantially faster for neural membrane effects, compared to mucosal injury [19]. Luminal mecamylamine at 0.1 mM is effective in the rat SPIP model without causing adverse systemic events [20].

The preparation procedure of the perfusion buffer solutions (100 mL) is earlier described by Dahlgren et al. [7]. All solutions had a

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