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Original Article

Excipient-drug pharmacokinetic interactions: Effect of disintegrants on efflux across excised pig intestinal tissues

Q8 *Werner Gerber, Josias H. Hamman**, *Johan D. Steyn*

Centre of Excellence for Pharmaceutical Sciences, North-West University, Private Bag X6001, Potchefstroom, 2520, South Africa

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ABSTRACT

Pharmaceutical excipients were designed originally to be pharmacologically inert. However, certain excipients were found to have altering effects on drug pharmacodynamics and/or pharmacokinetics. Pharmacokinetic interactions may be caused by modulation of efflux transporter proteins, intercellular tight junctions and/or metabolic enzyme amongst others. In this study, five disintegrants from different chemical classes were evaluated for P-glycoprotein (P-gp) related inhibition and tight junction modulation effects. Bi-directional transport studies of the model compound, Rhodamine 123 (R123) were conducted in the absence (control group) and presence (experimental groups) of four concentrations of each selected disintegrant across excised pig jejunum tissue. The results showed that some of the selected disintegrants (e.g. Ac-di-sol® and Kollidon® CL-M) increased R123 absorptive transport due to inhibition of P-gp related efflux, while another disintegrant (e.g. sodium alginate) changed R123 transport due to inhibition of P-gp in conjunction with a transient opening of the tight junctions in a concentration dependent way. It may be concluded that the co-application of some disintegrants to the intestinal epithelium may lead to pharmacokinetic interactions with drugs that are susceptible to P-gp related efflux. However, the clinical significance of these *in vitro* permeation findings should be confirmed by means of *in vivo* studies.

Q2 1. Introduction

The oral delivery route is the most preferred route for drug administration. The safety, ease of administration and flexible dosage form design include some of the advantages that contribute to its popularity [1,2]. Essentially, all oral dosage forms contain excipients, which can be defined as the ingredients other than the active pharmaceutical ingredient(s) that comprise a completed dosage form [3,4]. Disintegrants are included in some immediate release solid oral dosage

* *Corresponding author*. Fax: +27 18 299 2248.
E-mail address: sias.hamman@nwu.ac.zatel (J.H. Hamman).

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forms (e.g. tablets) to mediate breakup of the drug delivery system into smaller units, which leads to a larger surface area with increased dissolution, absorption and bioavailability [5,6]. Although most pharmaceutical excipients in solid oral dosage forms have been considered inert, it has been observed that certain excipients can increase membrane permeability of drug molecules or decrease absorption by means of different mechanisms [6,7].

Pharmacokinetic interactions occur when one compound alters the pharmacokinetics (i.e. the absorption, distribution, metabolism and/or excretion) of another compound [8]. Pharmacokinetic interactions may be caused by different mechanisms of action. It has, for example, been demonstrated that metabolic enzymes such as cytochrome P450 as well as active efflux transporters such as P-gp can be modulated (i.e. inhibition, induction or activation) by certain compounds to alter the pharmacokinetics of co-administered drugs [6,7,9]. Efflux transport by members of the ATP-binding cassette (ABC) transporter proteins is responsible for decreasing absorption of substrates from the gastro-intestinal tract after oral administration by actively transporting the molecules back into the lumen from the epithelial cells. This active efflux transport may result in a reduced bioavailability of orally administered drugs that are substrates of these efflux proteins [10,11]. Intentional or unintentional inhibition of P-gp related efflux of a drug in the epithelium of the gastro-intestinal tract would result in the increased uptake of a drug that is a substrate of this efflux transporter when co-administered with the efflux inhibitor [12]. Certain pharmaceutical excipients have shown the ability to inhibit P-gp related efflux and/or modulate tight junctions and thereby enhance the absorption of certain drugs across the intestinal epithelium as well as change the *in vivo* pharmacokinetic profiles of some drugs [6,7,13,14].

R123 is a known P-gp substrate that has been used as model compound in previous studies to investigate the modulating effect of selected chemicals (e.g. Brijs) on absorptive and secretory transport across Caco-2 cell monolayers as well as intestinal absorption in rats [2]. R123 has also been used as a representative P-gp substrate in an *in situ* closed loop study in rats to investigate the effect of sodium nitroprusside on absorption and excretion in the ileum [15].

2. Materials and methods

2.1. Materials

R123, Krebs–Ringer bicarbonate (KRB) buffer and sodium alginate (batch number MKBN7680V) were purchased from Sigma–Aldrich (Johannesburg, South Africa). Croscarmellose sodium (Ac-di-sol®, batch number T017C) and microcrystalline cellulose (Avicel® PH-200, batch number M939C) were purchased from FMC Corporation (Cork, Ireland). Sodium starch glycolate (Explotab®, batch number SSGP0601) was purchased from Mirren (PTY) LTD and crospovidone (Kollidon® CL-M, batch number 91416136W0) was purchased from BASF (Ludwigshafen, Germany). Costar® 96-well plates (lot number 07914036) were purchased from The Scientific Group (Randburg, South Africa). Pig intestinal tissue was collected at a local abattoir in Potchefstroom, South Africa. The chemical structures of the selected disintegrants are shown in Fig. 1.

2.2. Preparation of pig intestinal tissue for ex vivo transport studies

Before every transport experiment, a piece of approximately 20 cm of pig proximal jejunum was collected from an abattoir (Potchefstroom, South Africa) directly after slaughter of the animal. Jejunum tissue was obtained from Landrace pigs, which forms part of the domestic pig family (*Sus scrofa domesticus*), that are bred on farms in South African and routinely slaughtered for meat production. All animals used were designated for slaughter by the abattoir on behalf of independent providers. Feeder pigs ranging from approximately 4 to 6 months were selected as far as possible for tissue sample collection. After excision of this intestinal segment, it was rinsed and submerged in freshly prepared, ice-cold KRB buffer. On arrival at the laboratory, the intestinal segment was pulled over a glass tube and the serosal layer was stripped off via blunt dissection. The jejunum tissue was cut along the mesenteric border and the resulting sheet of tissue was spread open onto filter paper. The intestinal tissue sheet was cut into smaller segments, which were mounted between the half-cells of six Sweetana-Grass diffusion chambers. Peyer's patches were avoided when selecting jejunal tissue pieces suitable for mounting between the half-cells of the diffusion apparatus [1,14].

3. Bi-directional transport studies

3.1. Preparation of solutions

All the selected disintegrants were evaluated for transport effects at four different concentrations based on the recommended minimum and maximum quantities to be incorporated into tablet formulations [16–20] as well as taking into account that a tablet (e.g. 200 mg as a typical example) is commonly taken with 100 ml (scenario 1) to 200 ml (scenario 2) of fluid [7]. The mass of each selected disintegrant that was used to prepare 50 ml of each test solution/suspension for the transport studies are given in Table 1.

R123 was used as model compound and was completely dissolved in KRB to a final concentration of 5 μM in the bi-directional transport studies, since it is a fluorescence marker that is also a substrate of the P-gp efflux transporter [2,15,21,22]. For the transport experiments in the apical-to-basolateral (absorptive) direction, the R123 and required amount of disintegrant was mixed and placed in the apical chamber, while KRB was placed in the basolateral chamber. For the transport studies in the basolateral-to-apical (secretory) direction, two separate solutions were applied to the different half cells of each diffusion chamber. A clear solution of R123 (5 μM) in KRB buffer was inserted in the basolateral side, while a solution/suspension of each disintegrant in KRB buffer was placed in the apical side.

The rationale behind the application of two different solutions to the chambers for the transport studies in the basolateral-to-apical direction as described above, was to

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