////Title: Sugar Monoesters as Absorption Enhancers for Orally-Delivered Large Pharmaceuticals

////Stand-first:

The lining of the gut acts naturally as a protective barrier to harmful or oversized materials. Many orally-administered drugs consisting of macromolecules or peptides are difficult to deliver because of their poor permeability across the intestine resulting in failure to reach the bloodstream. Patient preference would be to take these types of medicines orally rather than the currently available delivery route of injections. Professor David J. Brayden, at University College Dublin, is dedicated to enhancing the oral delivery of peptides and other macromolecules. His team and collaborators are conducting cutting edge research on the effects of specific sugar-based monoesters as intestinal permeation enhancers.

////Body text:

Despite extensive research proving their safety and effectiveness, many drugs, especially peptides, can prove difficult to deliver by the oral route using tablets or capsules. One of the challenges they can pose to pharmaceutical scientists is their poor permeability across the intestine and failure to reach the bloodstream. The reason behind the poor permeability of peptides is that the lining of the gut acts naturally as a protective barrier to harmful or oversized materials. Undigested peptides are too bulky and too soluble to move across this barrier, unlike other digested nutrients that are processed in the gastrointestinal tract.

Researchers in the drug delivery field have focussed on three main strategies for the efficient oral delivery of peptides: formulating drugs so that the active principle is coupled to intestine permeability enhancers, using nanoparticles as carriers of peptides, or completely by-passing the gut wall with intestinal microneedles devices.

The most clinically advanced oral formulations for peptides are those that incorporate the use of permeability enhancers. Although there is still debate in the scientific community about their mechanism of action, it is widely accepted that some intestinal permeability enhancers work in part by opening the epithelial tight junctions of the intestine while others act on the epithelium directly to perturb it.

Despite the efforts of many researchers, the latest approved permeability enhancing formulations have yielded disappointing results. The bioavailability of these oral formulations (that is, the proportion of the drug reaching systemic circulation) is only around 1%, indicating the need for improved approaches. While this value is suitable for two recently approved oral peptide products, semaglutide and octreotide [sema-gloo-tide and oct-tray-o-tide], those two peptides are unique in that they are potent, have stability, and can be synthesised relatively cheaply compared to standard peptides.

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Professor David J. Brayden, at University College Dublin, Ireland, is dedicated to finding ways to enhance the oral delivery of peptides and macromolecules. The Brayden laboratory aims to conduct

a systematic assessment of permeability enhancers, which will yield more efficacious and safe candidates for oral peptide and macromolecule formulations.

Professor Brayden and his Dublin team, along with his collaborators from Italy and the UK, recently published an article in which they argue that most studies have examined blends of sugar esters rather than specific sugar monoesters as epithelial permeation enhancers. There are manufacturing advantages in using the monoester versions.

Sugar esters are molecules made from the conjugation of medium chain fatty acids with a hydroxyl group present in disaccharide [dai-sak-a-ride], sugars. If every molecule of the permeability enhancer has just one hydroxyl [hi-drok-sel] group of atoms bonded to a single fatty acid chain, then it will be a monoester, rather than a mixture of di- or tri-substituted compounds.

With this in mind, the team investigated how changing the sugar portion affected the permeation enhancing properties of three monoesters of the medium chain fatty acid, lauric acid, referred to for simplicity as C_{12} (See-twelve) The three monoesters investigated were C_{12}-sucrose, C_{12}-lactose and C_{12}-trehalose [tre-ha-lose].

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The researchers conducted their studies in colonic tissue epithelial segments isolated from rats and mounted in Ussing-[Us-ing] type diffusion chambers. The tissue is separated on each side by physiological buffers mimicking the food side of the gut on one side, and blood on the other. The colon tissue was exposed to solutions of the three C_{12}-monoesters and electrophysiology measurements were conducted to assess tissue functionality.

The permeability of the sugar, mannitol, across colonic tissue from the food side to the blood side was also measured following exposure to the three esters. Like most peptides, mannitol is normally poorly permeable across colonic epithelia, so it is a good benchmark test for a permeation enhancer.

The studies were also accompanied by an evaluation of the toxic effects of the three monoesters on cultured intestinal cells. Finally, the researchers compared the effects of increasing concentrations of the esters on rat colonic mucosal tissue by analysing tissue slides under a light microscope.

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The structural differences in the three disaccharides [dai-sak-a-rides], in conjugation with C_{12}, induced subtle differences in the capacity for permeation enhancement. All three sugar esters increased the permeability of mannitol across the isolated intestinal mucosae without damaging tissue at selected concentrations. The toxic effects and the impairment of tissue functionality only occurred at the highest concentrations tested. In the colonic tissue model, the permeation arose from the opening of tight junctions and this occurred at concentrations that were well below those that caused tissue damage.

The researchers propose that C_{12} is likely to be liberated at the tissue by intestinal tissue esterases [es-ter-ases], enzymes that target esters by breaking the hydroxyl/fatty acid bond. The enzymatic action allows the salt of lauric acid to exert its established permeation enhancer effects as a membrane-fluidising surfactant and tight junction opener. However, C_{12} is not normally used as a permeation

enhancer because it is too insoluble despite being very efficacious (Eff-ic-ash-us). The solubility of C_{12} attached to a sugar to form an ester is more suitable than C_{12} itself for liquid-filled formulations because of the better overall solubility of the esters. The presence of different sugars in the ester structure will still allow the enzymatic liberation of C_{12} in the gut for the permeation-enhancing effect of C_{12} to be seen.

In the present study, C_{12}-sucrose and C_{12}-lactose increased the permeability of mannitol across colonic tissue with similar potency and efficacy, whereas C_{12}-trehalose was not quite as potent or efficacious. However, C_{12}-trehalose did not damage tissue to the same extent as the other two esters.

Since the toxic effects of the three esters only appeared at high concentrations in the cell and tissue studies, the researchers concluded that all three compounds can be considered as safe and efficacious permeation enhancers and can therefore be included in oral formulations of macromolecules for further testing.

Finally, the researchers note that not only are sugar monoesters at least as effective than other competing permeating enhancers at improving the intestinal absorption of poorly permeable molecules, they are also highly biodegradable and biocompatible and have a low potential for toxicity. Some blended versions have a documented history of safe use in humans as food additives, while the pure versions used by the team here can be made with simple green, sustainable chemistry to yield pure products.

This SciPod is a summary of the paper 'Permeability-enhancing effects of three laurate-disaccharide monoesters across isolated rat intestinal mucosae', published with Open Access for readers in the International Journal of Pharmaceutics. https://doi.org/10.1016/j.ijpharm.2021.120593

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