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A comprehensive study of glucose transfer in the human small intestine using an *in vitro* intestinal digestion system (i-IDS) based on a dialysis membrane process

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ABSTRACT

Human digestion is a complex process that involves several phenomena: chemical and enzymatic reactions, absorption, hydrodynamic processes, and mass transfer. The most accurate way to determine the bioavailability of different nutrients is through human studies. However, there are ethical, economic, and technical reasons that restrict their application. Aiming at contributing with a new experimental prototype and phenomenological model to study nutrient absorption in the human small intestine, an *in vitro* intestinal digestion system (i-IDS), based on a hollow fiber dialysis membrane process, was constructed and tested under different operational conditions of feed flow/dialysate flow ratio. This dialysis membrane process here presented, allowed to simulate and extrapolate results of the process of glucose transfer in the human small intestine, where the glucose mass transfer reached around 90% at times ranging between 25 and 40 min. The mathematical model was validated with respect to the experimental results, obtaining a good agreement (root mean square error, %RMS, between 3% and 19%) among them. Overall permeabilities for the experimental conditions ranged between 3.85×10^{-6} and 4.86×10^{-6} m^3/s. The experimental results of glucose absorption were extrapolated to those found in the human small intestine using a phenomenological model, where a good agreement among results of glucose absorption was found in human studies. This first experimental and phenomenological approach allows to acquire a better knowledge of the complex mass transfer processes found in human small intestine for nutrient absorption.

1. Introduction

1.1. In vitro systems to simulate human digestion

Human digestion is a complex process wherein several chemical, enzymatic, and mechanical phenomena occur. The gastrointestinal tract (GIT) can be viewed as a versatile multi-compartment reactor that operates on a variable solid/liquid feed but delivers more or less standardized products [1]. Human studies are the most accurate way of determining the bioavailability of different foods, but there are ethical, economic and technical reasons that restrict their application [2–4]. Despite these limitations, several *in vitro* digestion systems have been developed to predict the *in vivo* behavior of foods during digestion and absorption.

The construction of *in vitro* digestion systems is challenging because of the complex biochemical and mechanical phenomena present in the GIT. The use of realistic digestion systems is a key feature to generate *in vitro* results comparable to *in vivo* data [5]. To date, most of the studies have focused on fabricating gastric models [2,6–10], but few models have been developed to simulate the small intestine or other parts of the GIT [11]. However, intestinal absorption is critical in determining bioavailability, because what is exclusively absorbed can be then used by the human body. Simple artificial or biological membrane systems or assays based on biological cell monolayers (*e.g.* Caco-2 cells) [12,13] have been used to simulate the *in vitro* absorption. According to Marze [5], a limitation of most *in vitro* intestinal models is the difficulty to

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Nomenclature

1	Subscript of the equipment input conditions.
2	Subscript of the equipment output conditions
φ	Packing fraction of the module ($\varphi = n[d_{out}/D_s]^2$)
ΔC_g	Concentration difference between the bulk of the feed and dialysate phases (kg/m^3)
ΔP	Transmembrane pressure (Pa)
ε	Porosity of the fibers
ρ_{water}	Water density (kg/m^3)
τ	Tortuosity of the fibers
μ_{water}	Water viscosity (kg/ms)
A_T	Total area of mass transfer (m^2)
C_g^0	Initial glucose concentration (kg/m^3)
C_g^F	Concentration of glucose in the bulk of the feed solution (kg/m^3)
C_g^D	Concentration of glucose in the bulk of the dialysate solution (kg/m^3)
CL	Characteristic length (*e.g.* internal diameter for the membrane lumen side and equivalent diameter for the shell side). The characteristic length of the shell side is defined by the equivalent or hydraulic diameter as d_h (4∗[flow surface area]/[wetted perimeter])
$D_{glucose\text{-}water}$	Diffusion coefficient of glucose in water (m^2/s)
D_s	Shell inside diameter (m)
d_{in}	Inside diameter of the fibers (m)
d_{mL}	Mean logarithmic diameter of fibers defined as $(d_{out}\text{-}d_{in})/ln(d_{out}/d_{in})$ (m)
d_{out}	Outer diameter of the fibers (m)
e	Fibers thickness (m)
J_g	Total flux of glucose in the dialysis membrane process (kg/m^{2}s)
J_D	Flux of glucose transferred by diffusive effect (kg/s m^2)
J_C	Flux of glucose transferred by convective effect (kg/s m^2)
J_{water}	Water flux promoted by the TMP present in the system (m^3/s m^2)
K	Overall mass transfer coefficient (m/s)
K_{UF}	Ultrafiltration coefficient reported by suppliers of dialysis membrane modules (m^3/Pa s)
k_i	The local mass transfer coefficient for the lumen (k_L) or shell side (k_S), (m/s)
k_L	Local mass transfer coefficient in the boundary layer of the feed solution circulating in the membrane lumen side (m/s)
k_m	Local mass transfer coefficient through the liquid that fills the membrane pores (m/s)
k_S	Local mass transfer coefficient in the boundary layer of the dialysate solution circulating in the membrane shell side (m/s)
L	Fibers length (m)
N_g	Overall glucose transferred through the membrane (kg/s)
N_g^D	Glucose transferred by diffusive effect (kg/s)
N_g^C	Glucose transferred by convective effect (kg/s)
n	The total number of fibers
P	Overall permeability (m^3/s)
Re_i	Reynolds number of the lumen (Re_L) or shell side (Re_S)
Re_L	Reynolds number of the membrane lumen side
Re_S	Reynolds number of the membrane shell side
RMS	Root mean square error (%)
Sc	Schmidt number of the aqueous phases (in this work both phases were similar to water, therefore Sc had the same value)
Sh_i	Sherwood number of the lumen (Sh_L) or shell side (Sh_S)
Sh_L	Sherwood number of the membrane lumen side
Sh_S	Sherwood number of the membrane shell side
t	time (s)
V_F	Volume of the feed tank (m^3)
v_i	Flow velocity of the solution circulating through the lumen or shell side (m/s)

separate the used enzymes from their digestion products, because it is known that the hydrolytic products generated in the GIT tend to inhibit further enzymatic hydrolysis. Hence, the use of semi-permeable membranes, acting as selective barrier, is valuable for this kind of *in vitro* intestinal systems.

Few models of the small intestine based on membrane systems have been developed. Tharakan et al. [11] fabricated an *in vitro* small intestine model (SIM) to study glucose absorption. The small intestine was simulated using an inner semi-permeable dialysis membrane and an outer flexible tube to reproduce peristalsis and segmentation motion; but no attempt was made to simulate relevant biological phenomena (*e.g.,* intestinal pH and fluids, and body temperature). An improvement of the SIM was done by the same research group [14]. The Dynamic Duodenum (DDuo) model incorporated simulated intestinal secretions and points of pressure to reproduce segmentations and peristaltic movements. Recently, Wright and co-workers [15] developed the Human Duodenal Model (HDM) which mimics the sigmoidal shape of this first section of the small intestine, simulating the peristaltic motion by means of pneumatic movement, allowing to estimate nutrient absorption using a membrane dialysis. Other systems that simulate the coupled gastric and intestinal digestion are the *in vitro* dynamic TNO gastrointestinal model (TIM-1) [7], and the new Engineered Stomach and Small Intestine (ESIN) model [4]. Both systems use a dialysis hollow fiber membrane to simulate the passive absorption of water and digestion products in the small intestine; whereas the SimuGIT model uses a tubular ceramic microfiltration membrane for the *in vitro* absorption [16]. Although these last systems possess comparative advantages (*e.g.,* dynamic multi-compartmental computer-controlled models) respect to other systems, they do not shed any new light on the complex transfer processes found in absorption phenomena in the small intestine.

To provide a better understanding of the intestinal absorption phenomena, some mathematical models have been developed, where permeation of artificial membranes, as well as biological cell layers, are mainly related to passive diffusion processes [12,13]. Moser et al. [17] developed a mathematical model for the absorption/desorption process of lipophilic organic pollutants. This model assumes that the transfer across the wall of the digestive tract can be modeled as a diffusive process. Tharakan et al. [11] and Gouseti et al. [14], using an *in vitro* mechanical small intestinal model, studied the mass transfer phenomena occurring in the lumen and their potential effect on the concentration of species available for absorption. Their results suggest that nutrient absorption is controlled by mass transfer phenomena, with motion and viscosity of lumen having a strong effect on increasing and decreasing the mass transfer coefficient, respectively.

Starch is the main source of carbohydrates and energy from foods. *In vitro* starch hydrolysis has been widely studied because it can be associated with the glycemic response (GR), an indicator of postprandial glucose response for starch-based foods [18]. Several works have compared the *in vitro* starch digestion with *in vivo* blood-glucose indicators, such as GR, trying to find correlations between the fate of starch during digestion and the generation and absorption of glucose in the GIT, but discrepancies have been reported [18–22]. *In vitro* models do not resemble the physiology of the GIT, so that differences in digestion protocols can account for the lack of correlations between *in vitro* and *in vivo* tests. Argyri et al. [23] proposed a simulated