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Density-dependent gastroretentive microparticles motion in human gastric emptying studied using computer simulation

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ABSTRACT

Density-dependent gastroretentive drug delivery systems have been used to prolong the gastric retention time of drugs since the 1960s. The design of density-dependent gastroretentive dosage forms, however, usually focuses on specific parameters rather than combines with the fluid dynamics of dosage form in the gastric emptying. Therefore, the purpose of the present study was to develop a 2-D model of multiple-phase flows for the simulation of gastric emptying and gastroretentive microparticles motion, and the influence of microparticle density, microparticle viscosity, and gastric juice viscosity on the gastric retention were studied. The recirculating flows, formed in the gastric emptying, could mix the conventional-density microparticles and transport them to the pylorus. However, the low-density microparticles remained floating on the surface of gastric juice, while the high-density microparticles could sink and deposit in the bottom of the stomach. The remaining integral area of microparticles was higher than 90% after 18.33 min of simulation when the density of microparticles was lower than 550 kg/m^3 or higher than 2500 kg/m^3, which was higher compared to conventional-density microparticles (67.05%). These results are in good agreement with experimental data previously reported. In addition, the viscosity of microparticle and gastric juice also influenced the remaining integral area of gastroretentive microparticles. This study shows that the multiple-phase computational fluid dynamics models could provide detailed insights into the fluid dynamics of density-dependent gastroretentive microparticles in gastric emptying, which offers a powerful tool to further understand the mechanism of gastric retention for gastroretentive dosage forms and study the influence of different parameters on their ability for gastric retention.

1. Introduction

Prolonging the gastric retention time of the oral dosage forms can supply a high localized drug concentration in the upper gastrointestinal tract (Bardonnet et al., 2006; Hao et al., 2014b), and numerous gastroretentive drug delivery systems based on different mechanisms have been developed over the past decades, including floating (Prajapati et al., 2013; Whitehead et al., 1998), sinking (Hao et al., 2014a), swelling (Chen et al., 2000; Klausner et al., 2003), mucoadhesive (Dhaliwal et al., 2008), and so on. Among them, density-dependent (floating and sinking) gastroretentive drug delivery systems have been developed since the 1960s (Davis, 1968), which could remain in the stomach for a long time due to the density difference between the carriers and gastric juice (Sharma and Pawar, 2006; Streubel et al., 2003). There have been already a few density-dependent dosage forms in the market so far (Chen et al., 2013; He et al., 2012; Lees, 1987). However, the design of density-dependent gastroretentive system only focuses on specific parameters, such as density and drug release speed, rather than combines with the fluid dynamics of dosage form in the gastric emptying.

The stomach, from a mechanic prospective, is a mixer, a grinder, a storehouse, and a pump that can control the movement and release of liquid and semisolid chyme into duodenum (Meyer et al., 1994; Pal et al., 2007, 2004). Meanwhile, gastric emptying is the main resistance for the gastric retention of drugs after oral administration (Heading et al., 1973; Pohle and Domschke, 2003). So it is essential to understand how the drugs move in the gastric emptying, which is useful for the design of gastroretentive dosage forms.

The gastric motility has been studied and used to explain the human digestion process (GILJA et al., 2005; Hunt and Spurrell, 1951; Schwizer et al., 1992). The *in vivo* characterization of stomach motility can be observed using the magnetic resonance imaging (MRI) and ultrasonography (Holt et al., 1980; Schwizer et al.,

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1994), but it is difficult to reproduce the geometry and motility due to the complex nature of human stomach (Xue et al., 2012). And predicting the gastric flow and mixing using *in vitro* experimental system also seems to be difficult to achieve (Ferrua and Singh, 2010). Therefore, the dynamics of gastric contents in digestion have been studied by the numerical models in recent years. Pal et al. simulated the gastric flow and mixing using the lattice-Boltzmann method, and the two dimensions (2D) stomach geometry model was built based on the *in vivo* anatomical data from MRI (Pal et al., 2004). The previous simulation found that antral contraction waves (ACWs) were central to gastric mixing, and a gastric emptying "Magenstrasse" was discovered that could transfer liquid gastric contents from the distal end of the fundus directly to the intestines (Pal et al., 2007). In addition, Singh et al. developed a 3D model of the shape and motility pattern of the stomach wall in digestion, and the flow field with different viscosities of gastric contents within stomach was predicted using the computational fluid dynamics (CFD) (Ferrua and Singh, 2010; Kozu et al., 2010). The fluid dynamics of gastric contents in digestion can be predicted through the above numerical models, but a model of single-phase flow was used to describe the gastric flow and mixing in the previous simulations, i.e. presuming that the stomach was filled with liquid. Moreover, the gravitational effect is often neglected in the most of numerical modeling studies (Imai et al., 2013). For density-dependent gastroretentive dosage forms, gravity is regarded as one of critical factors to affect their behaviors, such as floating on the liquid surface or sinking to the bottom of the stomach (Bardonnet et al., 2006).

The purpose of the present study was to develop a 2D model of air–liquid two-phase flow for the simulation of gastric emptying, and a three-phase model (air–liquid–liquid) for the motion of density-dependent gastroretentive microparticles in gastric emptying was described. The effects of different microparticles densities, microparticles viscosities and gastric juice viscosities on the gastric retention of microparticles were studied, and the remaining integral area of microparticles within the computational domain after simulation was used to describe their ability for gastric retention.

2. Mathematical model

2.1. Simulation of gastric emptying

The present computational model was carried out using the FLUENT CFD code based on the volume of fluid (VOF) technique, and the air and gastric juice were chosen as the continuous phase and discrete phase, respectively.

2.1.1. Geometry and mesh

There was no unique geometry model for the human stomach, because the size and shape of stomach are different for individuals, and the alteration in the shape of the stomach is also affected in different positions of the body. However, a realistic geometry model of the human stomach was built by James G. Brasseur according to the physiological data (Pal et al., 2004), and the established 2D model has the same qualitative behavior as the corresponding 3D, due to its axisymmetric peristaltic transport.

Therefore, we built the 2D geometry stomach model using the physiological data from the literature (Fig. 1A and B) (Pal et al., 2004). The regular-peristaltic antral contraction waves (ACWs), which were initiated every 20 s at 14.4 cm from the pylorus, would contribute to the gastric emptying. The width (λ) and propagation value of the ACWs were 1.8 cm and 0.25 cm/s, and the relative occlusion of the ACW (antral diameter ratio of under the wave to without the wave, ε/D) decreased from 1.0 to 0.6 in the first 17.5 s at 10 cm from the pylorus, and then it remained constant for 0.6 in the next 16 s. The occlusion diameter ratio decreased linearly to 0.1 at the pylorus for final 24 s (Ferrua and Singh, 2010; Pal et al., 2004; Singh, 2007). In the present study, the boundary of computational domain was fixed according to an instantaneous state of the gastric peristalsis, which contained three ACWs simultaneously at 3 cm, 8 cm, and 13 cm from the pylorus. The pylorus diameter was assumed to be 1.2 mm.

Because of the complex boundary of stomach model established, the quad/pave element was used for face meshing with 0.05 spacing, and the final meshes contained 64,124 nodes, 63,469 cells, and 126,284 faces (Fig. 1C and D).

2.1.2. Boundary and initial conditions

The inlet boundary was located at the position of the cardia, and a pressure-inlet boundary condition was used (Fig. 1C). In the investigation, the pressure at the inlet boundary was set as atmospheric pressure, which was consistent with the physiological condition. While, the boundary pylorus was the outlet boundary, and the velocity-inlet condition (minus direction) was used. A constant gastric emptying rate (0.3 mm/s) was selected in the present simulation, so as to ensure that the volume of fluid output was similar to physiological condition. Furthermore, a stationary wall was used in the present simulation. A no-slip boundary condition was considered at the solid wall, and the wall shear stress was also assumed negligible.

In the air–water two-phase simulation, line AB would be the air–liquid interface (Fig. 1E), and the integral area of liquid-phase accounted for 56% of the total computational domain. The gastric juice was assumed a Newtonian fluid with a density of 1000 kg/cm^3 and a viscosity of 1 cp.

2.1.3. Governing equations

Gastric juice was assumed as a laminar and incompressible fluid in the present simulation, and the governing equations consisted of the conversation of mass (continuity equation) and the mass (Reynolds-averaged N–S equations), which were given in Eqs. (1) and (2):

$$\frac{\partial \varphi}{\partial t} + u \cdot div\varphi = 0 \tag{1}$$

$$\frac{\partial}{\partial t}(\rho u) + div(\rho u) = -grad(p) + div[\mu grad(u)] + \rho g \tag{2}$$

where t is the time, u is the velocity, p is the pressure, ρ is the density, μ is the kinematic viscosity, and g is the acceleration due to gravity.

2.1.4. Solution procedure

The set of governing equations were solved using the FLUENT commercial code for 110,000 iterations, subjecting to the given boundary condition. The unsteady solver and second order implicit formulation options were chosen, and the gravitational acceleration was set Y direction to -9.81 m/s^2. A time step size of 0.01 s was used in the simulation of gastric emptying, and this iteration was adequate to achieve convergence for the majority of time steps. Additionally, the convergence criterion of 1×10^{-5} was set for each scaled residual component, and the pressure–velocity coupling was obtained by phase-coupled SIMPLE algorithm. In the present simulation, the CFD simulation was carried out on a desktop computer with Inter i7-3770 CPU @ 3.40 GHz and 15.7 GB of RAM.

2.2. Simulation of microparticles motions in the stomach

The simulation of microparticles motions in the stomach was carried out using the VOF model with three phases (air–liquid–liquid), and a circle with 0.5 cm diameter was chosen as the microparticles-phase, which was located in the air-phase