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In Silico Studies of Fluid Flow, Digestion of Food and Drug Dissolution in Human Stomach

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Abstract

This review article explores the significant role of in silico simulations as complements to in vivo and in vitro experiments, particularly in enhancing our understanding of gastric flow, digestion, and drug dissolution. By synthesizing decades of research on numerical stomach models, this paper highlights the profound impact computational fluid dynamics (CFD) and other simulation techniques have on elucidating the influence of gastric motility and the physical properties of stomach contents on nutrient absorption and drug release. These simulation studies provide more detailed information for us to advance our understanding of drug delivery in stomach and to support the formulation of functional foods tailored for specific metabolic health requirements. Additionally, these models offer valuable forecasts that aid in refining surgical methods and therapeutic approaches, especially for managing conditions such as gastroparesis. By advancing our fundamental understanding of digestive mechanisms, in silico studies contribute significantly to the development of innovative treatments and the enhanced management of gastrointestinal disorders, underscoring the transformative potential of computational tools in nutritional science and biomedicine.

Keywords Computational fluid dynamics · Human stomach · Gastric biomechanics · Food digestion · Drug disintegration

Introduction

Recent research has rigorously explored health issues associated with gastric mechanics, highlighting the significant role of functional foods and digestion management. The impact of gastrointestinal processes on drug absorption has also garnered considerable attention. Individuals with impaired digestion require easily digestible foods, while those with metabolic syndrome, a disorder increasingly linked to obesity prevalence [13], may benefit from foods that are less readily digested to limit nutrient uptake. Accordingly, functional foods have been developed to meet these needs, such as dextrin-enriched products to mitigate lipid absorption for weight management [56] and the use of Konjac glucomannan (KGM) in creating satiety-enhancing foods due to its high viscosity [23, 54, 63]. Understanding gastric digestion is crucial for preventing health risks and managing diseases.

In the realm of biopharmacy, understanding gastric mechanics is vital for optimizing drug delivery, particularly for pills targeting the proximal gastrointestinal tract [42]. Gastro-retentive techniques have been developed to prolong gastrointestinal residence time, thus enhancing the efficacy of therapeutic agents [4, 10, 68]. As Schneider et al. [59] emphasize, variations in gastric fluid volumes, pH, chyme viscosity, and motility patterns significantly impact drug dissolution and gastro-retentive dosage forms. Predictive models must consider these factors to ensure reliability and effectiveness. Furthermore, the interaction between food and drug release from solid oral dosage forms is a significant biopharmaceutical issue [33]. The dissolution of a tablet is intricately linked to the gastric system's fluid dynamics, where shear strains and stresses affect mass-transfer coefficients and tablet release kinetics. These principles also apply

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to the erosion process in food disintegration, characterized as a mass-transfer phenomenon [32, 41].

Investigations into gastric digestion mechanisms encompass in vivo (within living organisms), in vitro (outside living organisms in simulated conditions), and in silico (computational models) studies. In vivo studies, which include animal and clinical trials, are considered the most comprehensive, reliable and accurate but are invasive, ethically complex, and challenging to control for specific variables. In vitro digestion studies play a critical role in the field of food engineering, offering a controllable, ethical, and reproducible method to simulate human gastric conditions. They are essential for evaluating the digestibility and bioavailability of nutrients and pharmaceuticals, as well as understanding the breakdown and release of bioactive compounds within food matrices [8, 48, 61]. However, the accuracy of in vitro models must be validated through comparison with in vivo models [6]. Advancements in computational capabilities have also made in silico models a valuable tool, offering detailed insights into the dynamics of food mixing and breakdown within the gastric environment. Consequently, it is imperative to advance the development of in silico models that can aid in interpreting experimental data and contribute to comprehensive models of the digestive process.

The objective of this review is to comprehensively examine in silico studies on fluid flow, food digestion, and drug dissolution in the human stomach. It aims to describe key gastric processes, summarize computational methodologies, evaluate model strengths and limitations, and propose future directions to enhance their relevance. Specifically, the review will explore three primary in silico methods: 0-dimensional (0D) system simulations, computational solid mechanics (CSM) simulations, and multi-dimensional computational fluid dynamics (CFD) simulations. Each of these models offers distinct advantages and limitations in gastric simulations, see Table 1 for comparison. 0D models are computationally efficient and ideal for system-level analyses, such as gastric emptying and drug dissolution, but lack spatial resolution. CSM models excel at simulating mechanical behaviors like the deformation and disintegration of food boluses or drug tablets under gastric motility, though they have limited integration with fluid dynamics. CFD models provide detailed spatial and temporal resolution for analyzing gastric flow, mixing, and chemical reactions but require significant computational resources and experimental validation. It is important to acknowledge that in silico studies fundamentally dependent on experimental data obtained from in vivo and in vitro studies to validate and refine computational models, thereby ensuring their accuracy and applicability. This interdependence underscores the importance of integrating these approaches to create physiologically realistic gastric models capable of addressing key challenges in food and drug design.

Anatomy and Functions of the Stomach

The configuration of the stomach is influenced by both the volume of its contents and the individual's posture [40]. The minimal gastric fluid volume in the fasted state has been reported to vary across studies. For example, Mudie et al. [55] reported a minimal volume of approximately 35 mL, while Grimm et al. [19] found the resting gastric fluid volume to be approximately 25 mL. Despite these minimal volumes, the stomach's inherent distensibility allows it to expand and accommodate up to 4 L of content [26]. This variability underscores the importance of considering gastric adaptability and interindividual differences when developing and validating in silico models. When moderately filled, the organ measures about 25 to 30 cm in length and has a capacity close to 1.5 L [70]. Although variations exist, the predominant morphology resembles a "J" shape, extending from the esophagus at the upper extremity to the duodenum at the lower end. The gastric wall, with a thickness ranging from 3 to 4 mm, is structurally composed of four primary layers as depicted in Fig. 1: the serosa, muscularis, submucosa, and mucosa, each layer progressing inwardly [7]. The interior surface of the stomach is replete with rugae or gastric folds, with the mucosal layer forming numerous folds each measuring approximately 5–10 mm in width and 2–4 mm in depth [9]. These folds significantly enhance the stomach's surface area, facilitating its extensive digestive functions. As a soft biological tissue, the stomach wall exhibits nonlinear viscoelastic characteristics,

Table 1 Comparison of 0D, CSM, and CFD models for human stomach simulations

Feature	0D Models	CSM Models	CFD Models
Computational Efficiency	High	Moderate	Low
Spatial Resolution	None	Partial	High
Applicability	System-level analysis	Mechanical behavior analysis	Fluid dynamics and chemical behavior analysis
Advantages	Fast, simple, suitable for macro-level analysis	Captures deformation and fracture of solids	High precision, suitable for complex multiphysics problems
Limitations	Lacks local detail	Limited fluid dynamics support	High computational cost and complexity

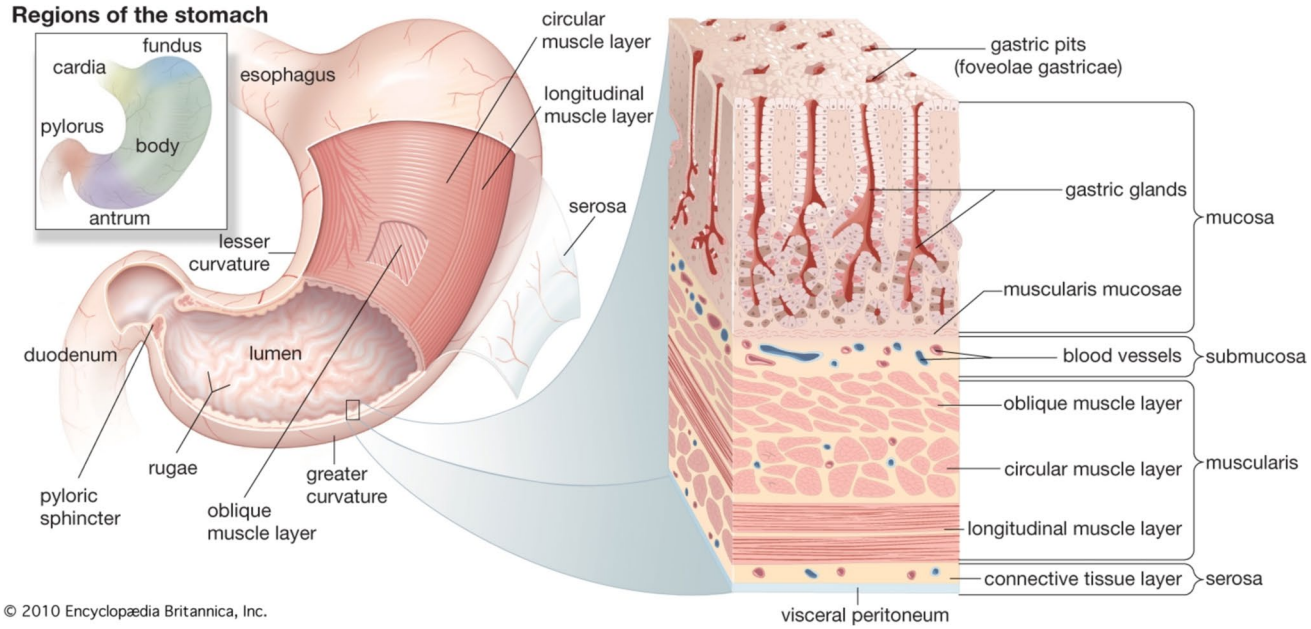

Fig. 1 Structure of the human stomach (left) and a zoomed view of the gastric wall (right). By courtesy of Encyclopædia Britannica, Inc., copyright 2010

where the relationship between stress and strain is non-linear, resulting in material stiffness variability during deformation processes. This property allows the stomach to maintain its structural integrity while adapting to varying degrees of distension and mechanical stress during the digestive process.

The stomach's functionality is highly localized, as delineated in Fig. 1, exhibiting regional differentiation into five distinct areas [37]. The cardia serves as a valve preventing the retrograde flow of gastric contents into the esophagus during the gastric peristaltic activity. The fundus and the body are designed to expand to accommodate ingested food and house glands that produce digestive secretions. The gastric antrum's peristaltic activity is a pivotal contributor to stomach motility. The pylorus regulates the transfer of chyme to the duodenum. Additionally, the stomach's internal lining is characterized by rugae that not only stretch to increase food capacity but also facilitate the mechanical processing of food, thereby enhancing the disintegration and amalgamation of food with gastric secretions, which are significant in the digestive process [9]. Gastric secretions, crucial for protein digestion, contain hydrochloric acid, which activates pepsinogen, converting it to pepsin. The gastric wall movements encompass tonic contractions (TCs) and antral contractions (ACs), as identified by Ebara et al. [12]. TCs are continuous, low-intensity contractions that generate a pressure gradient directing content from the stomach to the duodenum, aiding in its transit. ACs are instrumental in the mechanical breakdown of food, involving two types of motions: antral contraction waves (ACWs) and terminal antral contraction waves (TACs). ACWs originate in the mid-gastric body and proceed toward the terminal antrum, while TACs represent the terminal phase of ACWs, characterized by increased velocity and contraction strength, resulting in enhanced intragastric fluid dynamics [60].

0D and CSM Simulations

0D system simulations, characterized by low computational demand, are primarily focused on temporal dynamics, making them adept at forecasting the overall behavior of digestion processes. For instance, the Elashoff model employs a power exponential function to describe gastric emptying dynamics [14]: $f = 2^{-\left(\frac{t}{t_{\frac{1}{2}}}\right)^{\beta}}$, where f represents the fraction of gastric content remaining at time t, $t_{\frac{1}{2}}$ is the gastric emptying half-time, and β is a shape parameter capturing the nature of the emptying curve. The model's adaptability to various physiological conditions allows it to predict gastric emptying under different meal types and patient states, making it particularly useful for analyzing clinical and experimental gastric emptying data.

Kondjoyan et al. [31] utilized both in vitro experiments and 0D mathematical modeling to assess the digestibility of myofibrillar proteins by pepsin, incorporating models for predicting digestion kinetics and evaluating the thermal effects linked to protein denaturation mechanisms. The main models are summarized in Table 2. Specifically, the hydrolyzed product concentration (P) serves as a quantitative

Table 2 Mathematical models for assessing the digestibility of myofibrillar proteins by pepsin Kondjoyan et al. [31]

Model	Equation	Description
Linearized Michaelis function	$\frac{E_T^{\mathrm{pH}}}{E_T} = \frac{1}{1+\frac{10^{-\mathrm{pH}}}{K_{a1}}+\frac{K_{a2}}{10^{-\mathrm{pH}}}}$	The proportion of pepsin in its active form E_T: Total enzyme concentration E_T^{pH}: Active pH-dependent enzyme concentration K_{a1}, K_{a2}: Constants of pepsin dissociation
First order	$P \approx E^*_{max}\frac{E_T^{\mathrm{pH}}}{E_T^{\mathrm{pH}}+K}(1-\exp(k_f t_{OD}))$	Formation of the hydrolysis product P: Concentration of hydrolyzed protein products E^*_{max}: Maximum concentration at protein cleavage sites K: Pseudo rate constant of reaction k_f: Product formation rate constant
First order	$\mathrm{X}^{th} = \left(\mathrm{X}^0 - \mathrm{X}^{end}\right)\exp\left(-\alpha t_h\right) + \mathrm{X}^{end}$	Thermal denaturation of myofibrillar proteins is tracked by measuring surface hydrophobicity (X^{th}) X^0: Initial hydrophobicity X^{end}: Stable value achieved following extended heat treatment duration α: Time scale of heat denaturation

measure of protein breakdown, providing a direct indicator of digestibility. The hydrophobicity parameter (X^{th}) reflects changes in cleavage site availability resulting from protein denaturation during thermal processing. While heating increases the number of accessible cleavage sites, it may simultaneously reduce the digestion rate due to protein aggregation, highlighting the complex interplay between structural modifications and enzymatic activity. Their findings highlighted that factors such as pH, enzyme concentration, and heating duration significantly influence digestibility. By integrating these factors, the model provides insights into how physiological parameters and processing conditions influence the rate and extent of protein breakdown, which are directly related to digestibility.

Sicard et al. [64] created a 0D reaction–diffusion mathematical model to simulate the digestion of meat proteins in the human stomach, considering aspects like meat's pH buffering, pepsin action, and proton diffusion within the bolus. Compared to the model proposed by Kondjoyan et al. [31], pepsin and acid diffusion are rate-limiting factors, yielding a non-constant value of $E^{*\mathrm{pH}}_{max}\frac{E^{\mathrm{pH}}(t)}{E^{\mathrm{pH}}(t)+L}$. The main models are outlined in Table 3. They discovered that bolus particle size, gastric pH fluctuations, and meat's pH buffering capacity markedly affect protein digestion. Additionally, their research indicated that mass transfer between gastric fluid and bolus particles plays a crucial role in digestibility, whereas pepsin quantity has a minimal impact.

In CSM simulations, the focus is on understanding the mechanical behavior of food under various forces, with recent applications increasingly exploring food disintegration in the stomach. Skamniotis et al. [66] advanced the use of CSM in simulating gastric processes, identifying bolus separation due to backward extrusion or peristaltic wave

Table 3 Mathematical models for evaluating meat protein digestion in the human stomach [64]

Model	Equation	Description
Fick's second law	$\frac{\partial E}{\partial t} = D_{Pepsin}\Delta E$	The diffusion of pepsin within the meat bolus particles Neumann boundary condition: $\Phi_{Pepsin} = k_{Pepsin}\left(E - E_{gastric}\right)$, k_{Pepsin} is the mass transfer coefficient describing pepsin exchange at the particle surface
Fickian diffusion	$\frac{\partial H^+_{Free}}{\partial t} = D_{HCl}\Delta H^+_{Free} - f(H^+_{Free})D_{HCl}\Delta H^+_{Free}$	Local pH variation inside these particles depends on proton diffusion in the matrix and pH buffering capacity $\mathrm{pH} = -\log_{10}[H^+_{Free}]$ Neumann boundary condition: $\Phi_{H^+_{Free}} = k_{HCl}\left(H^+_{Free} - H^+_{Free\,gastric}\right)$, k_{HCl} is the mass transfer coefficient of HCl
Dimensionless number	$\mathrm{Sh} = k/(D/L_{car})$ $\mathrm{Re} = (\rho \times v \times L_{car})/\mu$ $\mathrm{Sc} = \mu/(\rho \times D)$ $\mathrm{Sh} = 0.14 \times \mathrm{Re}^{1/3} \times \mathrm{Sc}^{1/3}$	To the mass transfer coefficients: $k = \mathrm{Sh}\frac{D}{L_{car}}$
First order	$P(t) + \frac{1}{l_f}\frac{\mathrm{d}P(t)}{\mathrm{d}t} = E^{*\mathrm{pH}}_{max}\frac{E^{\mathrm{pH}}(t)}{E^{\mathrm{pH}}(t)+L}$	Rate-limiting digestion of meat bolus by active pepsin l_f: Product formation rate constant L: Pseudo rate constant of reaction

intrusion and bolus agglomeration driven by hydrostatic compression near the pylorus as key factors affecting the surface-to-volume ratio of the bolus during digestion. These findings highlight the relevance of CSM simulations in capturing the complex mechanical dynamics of food breakdown in the gastric environment.

However, much of the foundational work in CSM simulations has focused on food cutting mechanics, providing essential insights that can be extended to gastric studies. McCulloch et al. [52] introduced a coupled thermal-stress finite element model for ultrasonic cutting of toffee, emphasizing the role of temperature-dependent material properties and blade-material interactions. This work demonstrated how thermal and mechanical factors influence fracture behavior, laying a foundation for broader applications in food mechanics. Vandenberghe et al. [73] examined critical stress and distance criteria for crack propagation during cheese cutting, integrating experimental and numerical methods to predict material failure with high precision. Similarly, Witt et al. [75] investigated oblique wire cutting of soft food materials, refining models to predict how cutting angle and wire geometry influence structural integrity. Skamniotis and Charalambides [65] further demonstrated the effectiveness of Eulerian finite element methods in modeling the deformation and fracture of ultra-soft solids. Additionally, Skamniotis et al. [67] focused on large-strain deformation in soft, viscous foods, providing insights into oral food breakdown and disintegration across digestive stages.

Together, these studies demonstrate the versatility of CSM simulations in food mechanics, transitioning from foundational work in cutting processes to advanced applications in simulating the mechanical breakdown of food in the stomach. This evolution highlights the potential of CSM to bridge the gap between external mechanical manipulation and internal digestive processes.

CFD simulations

A range of computational techniques have been employed to numerically model the gastric digestion process in the human stomach [38, 50]. These models utilize diverse methodologies and geometries, including variations in dimensions and volumes. Each model incorporates different properties of chyme and gravity conditions, enabling the simulation of specific gastric functions such as wall motions, secretions, and stomach emptying.

Flow Behaviors in the Stomach

CFD simulations have profoundly advanced our understanding of gastric digestion, particularly through the examination of fluid dynamics within the stomach. Pioneering work by Pal et al. [58] utilized magnetic resonance imaging (MRI) to create the first two-dimensional (2D) CFD model using the lattice Boltzmann method (LBM), which incorporated gastric geometry and motility. This model analyzed the flow and mixing of a Newtonian fluid with a viscosity of 1 Pa·s, identifying two primary fluid movements: retrograde jets generated by ACWs and circulatory flow between these waves. The ACWs created a mixing zone confined to the antrum, where increased occlusion and narrower ACWs enhanced the mixing process. This pioneering study laid the groundwork for further interdisciplinary research in gastric hydrodynamics.

Kozu et al. [35] developed a symmetrical 2D computational model focusing on the distal region of the human stomach, investigating the flow behavior of various Newtonian fluids with viscosities ranging from 7.3×10^{-4} to 4.7×10^{3} Pa·s. Their results demonstrated that while viscosity minimally affected peak flow velocity and shear rates, it significantly shaped the overall velocity profile within the computational domain. This highlighted the role of gastric peristalsis in mixing pepsin secreted from the stomach walls. Subsequent studies by Kozu et al. [36] further explored retropulsive flow dynamics and concluded that liquid viscosity, despite varying between 1×10^{-3} and 0.1 Pa·s, had limited impact on maximum flow velocity.

Ferrua and Singh [17] introduced the first three-dimensional (3D) model to analyze how viscosity influences flow behaviors in the stomach, revealing that higher viscosity obstructs retropulsive jet-like motions and eddy structures essential for effective mixing. This challenges the idea of rapid homogenization during digestion. Ferrua et al. [16] emphasized the significant impact of gastric fluid rheology on flow dynamics, particularly in the antropyloric region, where increased viscosity led to localized flow patterns and reduced velocities. Building on this, Ferrua et al. [18] examined the mixing efficiency of Newtonian and pseudoplastic fluids, finding that large retropulsive and vortex structures had limited effects on overall flow dynamics. Their research indicated that while gastric advection seems chaotic, it is relatively inefficient, with viscosity's influence becoming negligible beyond a certain threshold. Collectively, these studies enhance our understanding of fluid dynamics and mixing during gastric digestion, informing in vitro system design. Figure 2 shows the instantaneous streamlines affected by varying rheological properties of the gastric fluids.

Later investigations, such as those by Imai et al. [24] and Berry et al. [5], explored the complex interplay between gastric motility and mixing efficiency, revealing that body posture affects recirculation patterns and mixing outcomes. These studies underscored the significance of peristaltic contractions and electrical activity in enhancing antral recirculation, which is critical for effective digestion. Miyagawa et al. [53] found that properties such as

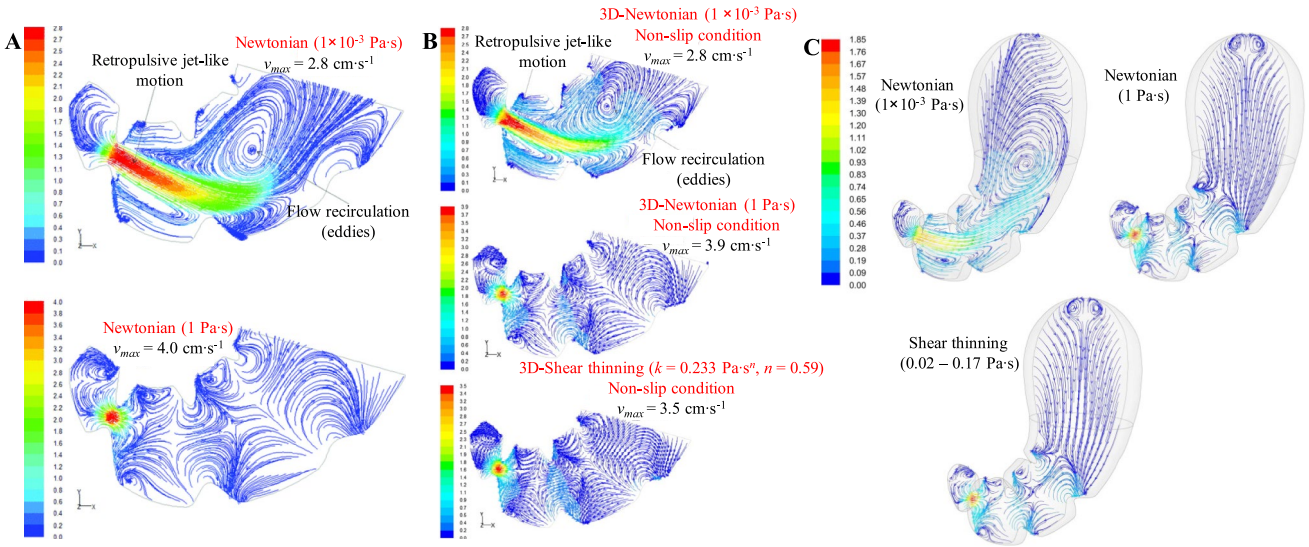

Fig. 2 (**A**) Influence of viscosity on retropulsive jet-like motion and eddy formation, reproduced with permission from Ferrua and Singh [17]. (**B**) Fluid flow streamlines in the stomach's median plane, reproduced with permission from Ferrua et al. [16]. (**C**) Instantaneous streamlines during the terminal phase of ACW, reproduced with permission from Ferrua et al. [18]

contraction velocity and frequency significantly influence mixing efficiency, highlighting how retropulsive flow near the pylorus enhances mixing through extensive flow separation. Additionally, Feigl and Tanner [15] analyzed droplet behavior in peristaltic flow, demonstrating that peristaltic dynamics significantly affect droplet deformation and breakup, influenced by factors like wave velocity, viscosity, and droplet size. This research underscores the potential for optimizing these conditions to improve digestive and drug delivery processes. Further studies by Alokaily et al. [2] and Dufour et al. [11] assessed how variations in viscosity and wave parameters influence flow characteristics, especially the dynamics of retropulsive jets and food disintegration within the antrum. Recent work by Toniolo et al. [69] and Kuhar et al. [39], have begun to address the biomechanical implications of gastric interventions, underscoring the necessity of understanding flow dynamics to optimize surgical techniques and mitigate complications. Table 4 summarizes the fluid properties (rheology, density, and viscosity), and associated simulation outcomes, including typical flow patterns and maximum velocity.

Modelling of Gastric Emptying

The dynamics of gastric emptying have been extensively explored through various computational models, revealing critical insights into how different factors influence this complex process. The concept of Magenstrasse or stomach road, as discussed by Pal et al. [57] using LBM-based 2D simulations, identifies a specific pathway in the stomach facilitating the rapid transport of liquid content from the fundus to the intestines (see Fig. 3A), driven by coordinated fundic and antral contractions. Unlike traditional views that depict a sequential movement from the antrum to the fundus, this study reveals that ACWs create a narrow channel for swift transport of liquid to the duodenum, enabling transit in as little as 10 min, which is critical for drug delivery. However, in vivo studies [20, 34] performed a novel investigation on the Magenstrasse, confirming its existence but suggesting that ingested liquids are rapidly evacuated along the entire inner wall of the stomach, enveloping the chyme, rather than exclusively following a path along the lesser curvature. A model developed by Kiyota et al. [30] incorporates the Magenstraße into simulations of gastric emptying, emphasizing its role as a critical pathway during the fed state. This model successfully predicts the in vivo performance of liquid-filled soft gelatin capsules and oral solutions, outperforming traditional approaches by including gastric secretion dynamics and the Magenstraße kinetics. Li et al. [47] developed a 3D CFD model that found a rapid transport pathway for hydrogen ions near the lesser curvature during water emptying, yet observed that the dynamics of mixing high-viscosity foods with water revealed that food empties more quickly than water, indicating that neither viscosity nor motility alone can explain Magenstrasse formation. This study incorporated an open pylorus in the simulation of gastric emptying, with the outflow rate of gastric contents regulated by the transient TCs. Subsequent simulations incorporated a food matrix to represent solid food accumulation, which significantly slowed the emptying process, taking hours for complete evacuation. This

Table 4 Fluid properties and corresponding simulations results

Rheological properties	Density (kg·m^3)	Viscosity (mPa·s)	Typical flow patterns	Maximum velocity (mm·s^{-1})	Ref.
Newtonian	1000	1000	Retropulsive flow Recirculating flow Eddy flow	7.5	[58]
Newtonian	989—1379	0.73—4760	Retropulsive flow Eddy flow	12/10.4	[35, 36]
Newtonian	1000	1	Retropulsive flow Eddy flow	76	[17]
Newtonian, Shear-thinning	*Water/honey, 5.8% T.S. tomato concentrate	1/1000, k = 233 mPa.s$^{0.59}$	Retropulsive flow Recirculation flow	28/39, 35	[16]
Newtonian	1000	1000	Retropulsive flow, Antral recirculation	30	[24]
Newtonian	1000	12.5	Retropulsive flow	11.1	[5]
Newtonian	1000/1360	1—10,000	Retropulsive flow Recirculation flow	94.3	[2]
Newtonian, non-Newtonian	1070, 1000	3.2/150/2070, Initial value: 2470/1590	Retropulsive flow Recirculation flow	19.52—78.71	[11]
Newtonian	1000	100/1000/ 10,000	Reflux flow	15	[69]
Newtonian	1000	1/50	Retrograde and pyloric jet	100	[39]

*Density data is unavailable in the cited reference. Typically, the density of water is approximately 1000 kg·m^3, honey varies between 1380 and 1450 kg·m^3, and 5.8% total solids tomato concentrate has a density ranging from 1030 to 1060 kg·m^3

matrix caused water to bypass the chyme, flowing along the stomach's inner wall (see Fig. 3B). These findings highlight that the formation of the Magenstrasse is influenced by the interplay of food viscosity, the physical presence of the food matrix, and gastric motility mechanisms, challenging conventional understandings of gastric emptying dynamics.

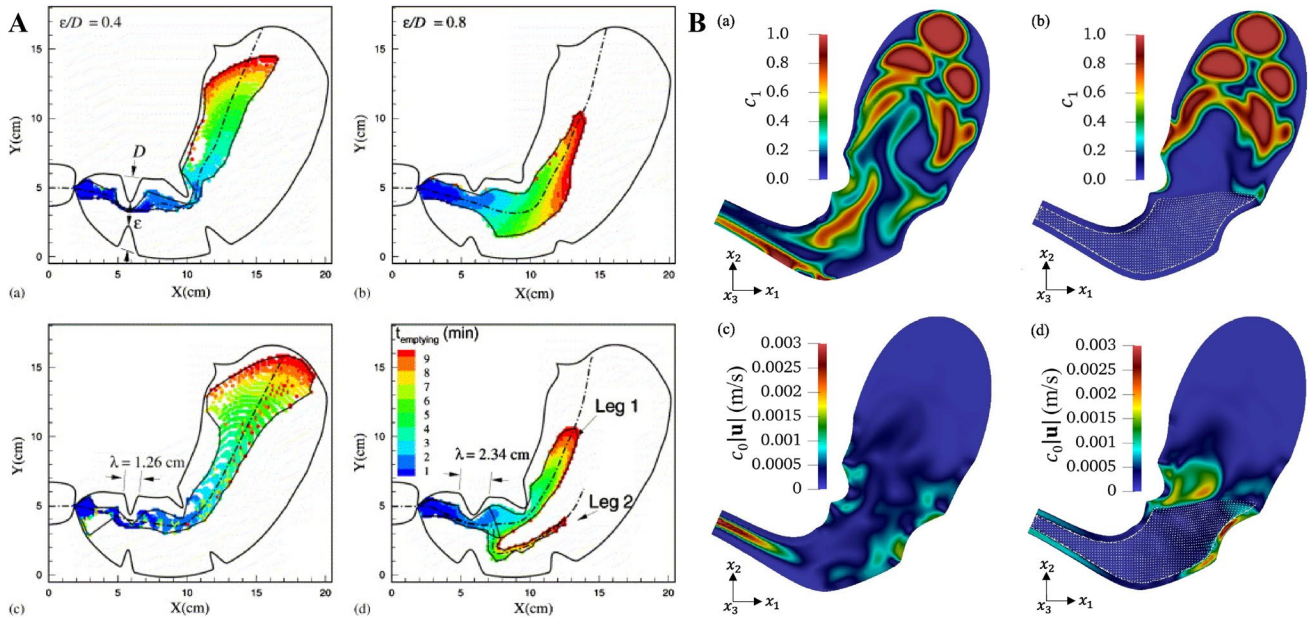

Fig. 3 (**A**) Initial locations of fluid particles emptied from the stomach after 10 min of release, highlighting the influence of ACW geometry, including maximum occlusion (ε/D) and width (λ). (**B**) The cross-section of the stomach at $t = 250$ s showing the food mass fraction (c_1) and water-velocity magnitude ($c_0|u|$), with the food matrix denoted by white dots. Both images are reproduced with permission from Pal et al. [57] and Li et al. [47], respectively

The importance of gastric motility and food properties is further highlighted by Hao et al. [21], who demonstrated how microparticle density affects gastric retention, and by Harrison et al. [22] whose biomechanical model revealed that contraction behavior and content viscosity significantly influence emptying rates. These studies underscore the importance of antral contractions in mixing and transporting contents. In both cases, the pylorus remained open; however, the former utilized a fixed emptying rate, while the latter allowed free-surface flow, with the emptying rate determined by the combined effects of gravity and ACWs. Avvari [3] added to this understanding by illustrating how pyloric resistance, influenced by pressure gradients and channel diameter, plays a crucial role in gastric emptying dynamics. Ishida et al. [25] emphasized the role of pyloric function, showing that impaired coordination between pyloric closure and antral contractions can accelerate emptying, which may lead to complications like dumping syndrome. This study directly modeled the pyloric closure mechanism to investigate its impact on emptying rates.

Advanced modeling techniques have further explored the mechanics of gastric emptying. Li and Jin [45] examined the emptying behaviors of various liquid foods, the pylorus kept open, and the emptying rate was specified based on the caloric content of the ingested food, revealing that peristaltic contractions significantly increase kinetic energy within the stomach, enhancing mixing and emptying rates. They found that properties like viscosity and density affect emptying behavior and gastric juice mixing efficiency, with higher caloric foods showing slower emptying rates. Acharya et al. [1] developed a multiphysics model capturing fluid–structure interaction (FSI) in the upper gastrointestinal tract, highlighting the roles of gravity and density in emptying dynamics. This model incorporated dynamic pyloric opening and closure mechanisms to simulate how the pylorus regulates content outflow during coordinated peristaltic movements. Their model illustrated how coordinated peristaltic movements drive the transport and mixing of gastric contents, providing insights for surgical interventions such as gastric bypass. Ebara et al. [12] employed a model in which the pylorus opened and closed in synchrony with peristaltic contractions. Their findings demonstrated that variations in peristaltic amplitude and frequency critically influence emptying rates, emphasizing the need for optimized peristaltic motion for effective gastric function. Zhang et al. [76] evaluated stomach-partitioning gastrojejunostomy using a static and open pylorus model, showing it significantly improves gastric emptying and postoperative recovery compared to conventional methods.

Finally, Li et al. [44] investigated the effects of reduced gravity on food mixing and emptying in the human stomach through numerical simulations. This study assumed a continuously open pylorus and neglected its contractile behavior. They found that reduced gravity, particularly in microgravity, significantly alters gastric emptying dynamics. In zero gravity, food retention increases during the first six minutes compared to normal gravity, with notable effects on food distribution and pH levels across different stomach sections. The simulations indicate that stomach contents do not settle under zero gravity, resulting in a more uniform distribution of food and gastric juices, contrasting with the stratified layering observed on Earth. Additionally, TACs were shown to enhance mixing and emptying in the distal stomach but had minimal impact on proximal regions. These findings highlight the complex interplay between gravity and gastric fluid dynamics, which is essential for preparing astronauts for space missions, as altered digestion could affect nutrient absorption and overall health. Table 5 presents a summary of parameters that may influence gastric emptying dynamics and the associated emptying times, as derived from CFD simulations.

Modelling of the Gastric Digestion

Recent advancements in modeling gastric digestion have significantly enhanced our understanding of the complex interactions between food, digestive enzymes, and gastric motility. Trusov et al. [71] introduced a mathematical model simulating the dynamics of food particle distribution and digestive mixture flow in the stomach, emphasizing the impact of functional disorders on digestion. Their work elucidated the critical role of active contractions and waveforms

Table 5 Summary of parameters and results from CFD simulations of gastric emptying

Volume of food (mL)	Content composition	Motility patterns	Pylorus diameter (mm)	Simulated emptying time (s)	Ref.
NA	Air–water	ACWs, speed of 1.8/2.5 cm·s^{-1}	1.2	1100	[21]
337	Liquid, 0.01/0.1/1.0 Pa·s	ACWs, period of 20/30/60 s	23	180	[22]
650	Liquid, 4.2×10^{-3} to 4.2 Pa·s	ACWs, speed of 2.5 cm·s^{-1}	9	600	[25]
1170	Water/orange juice/whole milk	ACWs, TACs	20.4	1800	[45]
850	Liquid, 0.01 Pa·s	ACWs	16	3.5	[1]
650	Olive oil, 0.125 Pa·s	ACWs, speed of 2.5 cm·s^{-1}	9	60	[12]

(ACWs) in gastric digestion, highlighting how these factors influence food hydrolysis from the point of oral ingestion through stomach processing. Building upon this foundation, Trusov et al. [72] developed a multiphase flow model for the gastrointestinal tract, revealing the influence of secretory dysfunctions on food dissolution and acidity. Their findings underscored the importance of understanding the physical properties of food and digestive enzymes in facilitating hydrolysis, as well as the role of stomach motility and food rheology in effective digestion.

Further expanding this area of research, Kamaltdinov et al. [28] modeled the flow of a multi-component mixture within the stomach and duodenum, assessing how functional disorders affect secretion rates and acidity, and their subsequent impact on the mucosal lining. This study highlighted the dynamic nature of acidity and the volume of ingested liquids throughout the digestion process. More recently, Kamaltdinov et al. [27] employed a CFD model to study the stomach and duodenum, incorporating gas phase effects and enhancing the understanding of multiphase flow and biochemical reactions, see Fig. 4A. This research demonstrated how food particle density affects phase distribution, enzyme activities, and pH levels, providing a more detailed representation of gastric processes and emphasizing the critical role of rheological properties in analyzing food hydrolysis and gastric emptying.

In another study, Li and Jin [46] explored meat protein digestion in the human stomach using a CFD model, considering gastric motility and secretory activity. They represented large, deposited food particles within the stomach using a porous media model, simulating the disintegration of these particles into smaller ones through a reaction–diffusion-convection mechanism. Their findings indicated a notable decrease in the digestion rate of large food particles in the presence of stomach disorders, such as reduced gastric motility or H^+ secretion. The study also observed that increasing the processing temperature of the meat could facilitate faster digestion and gastric emptying, as illustrated in Fig. 4B, which compares the volume fractions of different meat samples at time of 1800s. Moreover, they discovered that the presence of TACs, which generate backflows, significantly enhances the transport of H^+ and enzymes, thereby accelerating the digestion process. This study contributes to understanding the complex interactions between temperature, gastric motility, and chemical reactions in protein digestion and gastric emptying.

Kuhar et al. [37] examined the effects of stomach motility on food hydrolysis. It explored how the stomach's peristaltic movements and digestive enzyme secretion influence the breakdown of protein in a liquid meal, see Fig. 4C. The research quantified the velocities of retropulsive jets induced by peristalsis, and the extent of protein hydrolysis under different motility conditions, including those simulating reduced motility due to conditions like diabetes mellitus. The study highlighted that stomach motility significantly impacts the efficiency of food hydrolysis. It also demonstrated the importance of mixing in the stomach, driven by wall motion, in facilitating the enzymatic breakdown of food, providing a detailed understanding of the interplay between mechanical actions and chemical processes in gastric digestion. In a later investigation, Liu et al. [51] explored buoyancy-driven flow in the stomach, highlighting how density differences between stomach contents (e.g., fats and aqueous liquids) impact food hydrolysis. Their findings illustrated that buoyancy effects can lead to rapid stratification of different density layers within the stomach, which occurs much faster than peristaltic movements and overall digestion timescales. This stratification may influence gastric mixing and the efficiency of floating drug delivery systems, underscoring the need for further exploration of buoyancy's role in optimizing gastric residence time and therapeutic effectiveness. Table 6 provides a summary of the parameters that may influence gastric digestion and the corresponding simulated digestion times, as derived from CFD simulations.

Modelling of the Drug Dissolution

Gastric digestion can influence the pharmacokinetics of orally administered drugs by affecting their dissolution and bioavailability, particularly for immediate-release formulations in the fed state. However, the extent of this influence varies depending on the drug formulation, with certain dosage forms, such as enteric-coated or controlled-release formulations, designed to resist dissolution in the stomach. Understanding the dynamics of drug dissolution within the gastric environment in the fed state is essential for optimizing oral drug delivery systems. Recent advancements in computational modeling have provided insights into the complex interactions between gastric flow, motility, and drug behavior under postprandial conditions.

The study by Seo and Mittal [62] developed a computational model to investigate drug dissolution in the human stomach, focusing on the interaction between gastric flow and orally administered drugs in tablet form, see Fig. 5A. By incorporating FSI and mass transport simulations, the model examined how gastric motility and fluid dynamics influence drug dissolution. Key findings include the significant role of the retropulsive jet and recirculating flow in the antrum in tablet motion and drug distribution. This study demonstrates that gastric flow enhances drug dissolution mass flux, particularly when the tablet exhibits substantial relative motion within the gastric fluid. Two tablet densities were analyzed, revealing the impact of gastric flow and gravity on tablet motion and dissolution. The study advances understanding of how physical and dynamic properties within the stomach

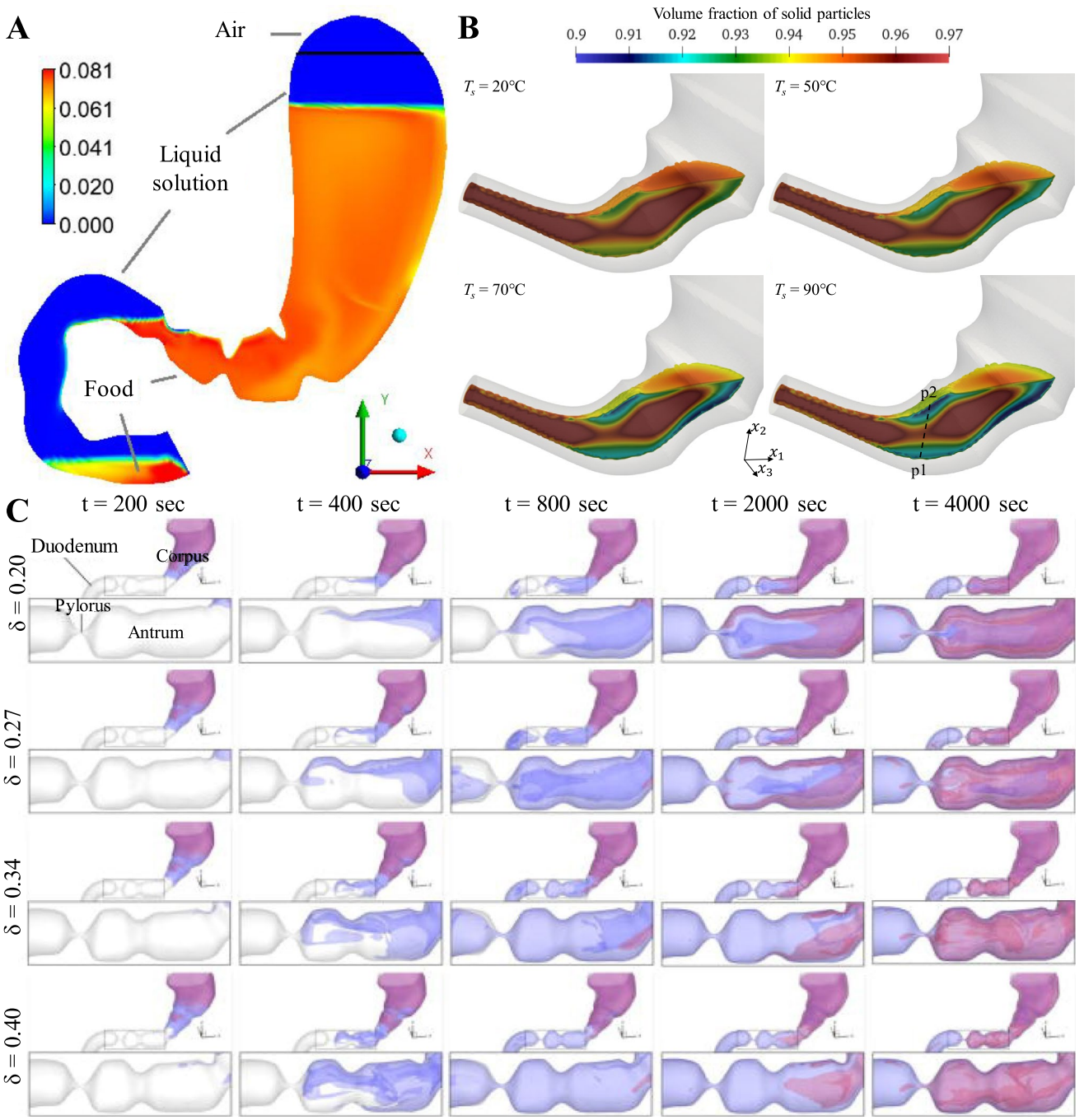

Fig. 4 (**A**) Volume fraction of the largest food particles at $t = 120$ s, adapted from Kamaltdinov et al. [27]. (**B**) The volume fraction of large particles within the food matrix at $t = 1800$s, after processing the meat samples at different temperatures, adapted from Li and Jin [46]. (**C**) Iso-surfaces of concentration at a normalized level of 0.01 for pepsin (red) and digesta (blue) in the antral region, adapted from Kuhar et al. [37]

affect drug dissolution, aiding the design of oral drug delivery systems.

Physiologically based pharmacokinetic (PBPK) models, such as those described in Litou et al. [49] and Wagner et al. [74], rely on biorelevant dissolution media to simulate fed-state gastric environments. These models are effective in predicting drug absorption by considering factors such as pH, bile salt concentrations, and drug solubility. However, PBPK models typically do not include explicit representations of gastric motility or the dynamics of fluid motion within the stomach, including the role of the Magenstraße. This limitation may lead to inaccuracies when predicting

Table 6 Overview of key parameters and outcomes from CFD simulations of gastric digestion

Food viscosity (mPa·s)	Phases of food*	Gastric secretion	Gastric motility	Simulated digestion time (s)	Ref.
20 + 74	Aqueous liquid + Oil	No	No	8	[51]
1	Liquid + solid	$NaHCO_3$, HCl, pepsin	ACWs	864	[72]
1	Liquid	$NaHCO_3$, HCl	ACWs	330	[28]
0. 7	Liquid + Solid + Gas	$NaHCO_3$, HCl, pepsin	ACWs	1800	[27]
1	Liquid + Solid	H^+, pepsin	ACWs, TACs	1800	[46]
1	Liquid	Pepsin	ACWs, TACs	5000	[37]

*In this context, the liquid, solid, and gas phases are all represented as components of a continuous phase within the model

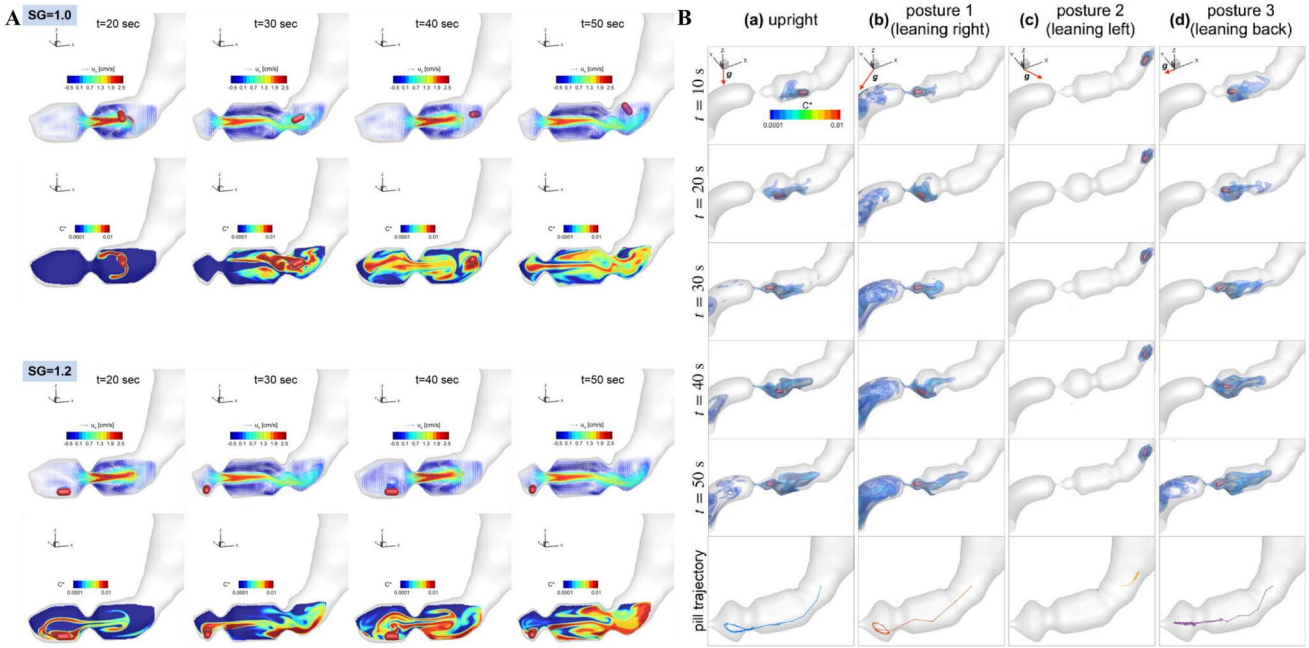

Fig. 5 (**A**) velocity vectors and active pharmaceutical ingredient (API) concentration contours on the antrum's cross-sectional plane, adapted from Seo and Mittal [62]. (**B**) Volumetric distributions of the dissolved API concentrations in the antrum and duodenum regions for varying postures, adapted from Lee et al. [43]

drug dissolution and bioavailability for dosage forms affected by gastric emptying and motility.

The physiologically based biopharmaceutics modeling (PBBM) approach, as utilized by Kiyota et al. [29], builds upon PBPK methods by integrating dynamic changes in gastrointestinal fluid characteristics, such as reacidification and bile secretion, into dissolution models. While this approach successfully predicts food effects on solid dosage forms, including weak base drugs, it still lacks detailed representations of gastric motility mechanisms such as the Magenstraße. Thus, although PBBM offers a more refined simulation compared to traditional PBPK models, it does not fully capture the dynamic interplay between gastric motility and drug dissolution.

Extended from the previous work [62], Lee et al. [43] explored the impact of posture and gastroparesis on drug dissolution and bioavailability in the stomach using a CFD model, see Fig. 5B. This work further highlights the importance of incorporating dynamic gastric biomechanics in drug dissolution models, particularly under conditions of impaired motility or altered gastric emptying. Such insights are less emphasized in biorelevant PBPK/PBBM studies, which rely on simplified hydrodynamic assumptions. The model reveals that body posture can significantly influence the dissolution rate of drugs and their emptying into the duodenum, with changes in posture potentially altering drug bioavailability by up to 83%. The study also examines gastroparesis, a condition that impairs gastric motility,

finding that it significantly reduces drug dissolution and gastric emptying. The simulations indicate that neuropathic gastroparesis, affecting antral contractility, has a more pronounced effect on gastric emptying compared to myopathic gastroparesis. The research highlights the complex interplay between gastric biomechanics and fluid dynamics in drug dissolution, offering valuable insights for optimizing oral drug delivery systems.

These findings underscore the complementary roles of PBPK/PBBM and advanced computational models. While PBPK/PBBM approaches are invaluable for assessing biorelevant dissolution properties, dynamic modeling of gastric motility and fluid dynamics is essential for a more mechanistic understanding of drug dissolution and absorption in the fed stomach. Future studies should aim to integrate these methodologies to provide a holistic approach to oral drug delivery system optimization.

Beyond fundamental insights, CFD models hold significant potential for real-world applications, including functional food design, drug delivery systems optimization, and personalized treatment plans. These simulations reveal how food components (e.g., proteins, fats, carbohydrates) mix, dissolve, and digest, providing data to optimize nutrient release. They have guided the development of fiber-enriched or viscosity-modifying formulations to delay gastric emptying and enhance satiety. Additionally, CFD models predict drug dissolution and distribution, minimizing localized irritation and informing gastro-retentive dosage design. By incorporating individual physiological data, such as gastric motility, stomach capacity, and pyloric function, they support personalized interventions, including optimizing drug release for gastroparesis or tailoring food formulations for specific populations like children or the elderly. CFD models also provide detailed insights into gastric fluid dynamics, such as shear forces, vortex patterns, and mixing efficiency, guiding the optimization of in vitro gastric models. They predict key parameters like pH gradients, enzyme distributions, and fluid viscosity, enabling the design of more physiologically relevant systems. Additionally, these models streamline experimental design by simulating drug dissolution and mixing under various conditions, identifying optimal parameters. By integrating mechanical, chemical, and biological processes, in silico models support the development of advanced gastric simulators that replicate motility and enzymatic activity, offering a comprehensive understanding of gastric digestion.

Conclusions and Future Outlooks

The application of in silico models, particularly CFD, has significantly deepened our understanding of stomach dynamic, revealing how gastric flow, motility, and the mechanical properties of stomach contents influence key processes like mixing, breakdown, and transport, essential for digestion and drug delivery. In food engineering and manufacturing, these models can be potentially used to optimize formulations and processes by linking material properties to digestive behaviors, such as mixing efficiency and nutrient release. This enables the development of functional foods tailored to nutritional and therapeutic needs, while also accelerating product innovation through rapid prototyping and reduced reliance on experiments. Furthermore, computational models have the potential to support personalized dietary and treatment plans by accounting for individual gastric motility patterns and digestive kinetics. Realizing this potential requires collaboration between gastroenterologists, pharmacologists, food scientists, and computational modelers.

Despite their potential, current in silico models have notable limitations. They often simplify gastric emptying by focusing on short time scales or uniform conditions, failing to fully capture the complexity of gastric behavior over extended timeframes. Many models overlook the non-Newtonian properties of food materials, which significantly influence their flow and digestion. Adding to these challenges is the limited availability of experimental data to validate these models, a constraint stemming partly from the complex nature of digestion and the gaps in our understanding of its fundamental mechanisms. These factors limit their ability to accurately simulate real-world digestive processes, particularly for diverse foods or intricate drug formulations. Bridging these gaps is key to improving the models' relevance.

One way to overcome this limitation is to develop multiscale models, linking short-term gastric dynamics with long-term processes like enzymatic hydrolysis and nutrient absorption. Advances in computational power and the use of machine learning-assisted modeling can also enable efficient simulation of complex, long-duration digestive processes. Incorporating dynamic FSI and chemical kinetics into these models will further improve model realism. Future research should also explore the role of gastric contraction waves in dosage form disintegration, an important yet underexplored aspect of drug release. Mechanical forces exerted by these waves, such as pressure-wave-triggered capsule rupture, are essential for drug disintegration but are rarely modelled. Developing multiphysics simulations that integrate these mechanical effects can fill this gap.

Moreover, improving the accuracy of gastric digestion models will require rigorous experimental validation. Future research should involve detailed comparisons between CFD simulations and in vivo/in vitro experiments to ensure computational models reflect actual physiological conditions. This validation is particularly important for food engineering applications, as it establishes confidence in using computational models to predict food behavior during digestion.

Finally, chemical processes, such as enzymatic reactions and acid interactions during digestion, should also be integrated into future simulations to provide a more comprehensive understanding of food hydrolysis and nutrient absorption. Together, these advancements will make in silico models more precise and expand their use in nutrition and drug delivery.

Author Contributions Changyong Li: Conceptualization, Investigation, Formal analysis, Figure design, Writing – original draft, Writing – review & editing. Jie Xiao: Writing – review & editing. Xiao Dong Chen: Conceptualization, Writing – review & editing. Yan Jin: Investigation, Writing – review & editing.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Ethical Approval Not applicable.

Competing Interests The authors declare no competing interests.

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