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RESEARCH ARTICLE

Impact of Gastric Emptying Kinetics on Dipyridamole Dissolution Using a Gastrointestinal Simulator

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Abstract

Gastric emptying plays a crucial role in the dissolution and absorption of oral drugs, particularly those with pH-dependent solubility, such as dipyridamole. This study evaluates the impact of gastric emptying kinetics on dipyridamole dissolution using a Gastrointestinal Simulator. A dynamic dissolution model incorporating first-order and Weibull kinetics was applied to simulate different gastric emptying profiles. Results indicate that dissolution behavior is significantly influenced by the rate and pattern of gastric emptying, affecting drug solubility and potential bioavailability. The Weibull model provided a more flexible fit to experimental data, but the external control shows that significant differences exist between theorical and experimental gastric volumes. These findings highlight the importance of integrating physiologically relevant gastric emptying models into biopharmaceutical assessments to improve the prediction of *in vivo* drug performance. This approach could enhance the design of oral formulations by optimizing dissolution profiles for weak base drugs.

Keywords dipyridamole · dissolution kinetics · gastric emptying · gastric volume · gastrointestinal simulator

Introduction

The process of drug release, encompassing both disintegration and dissolution processes, plays a critical role in determining the bioavailability of orally administered drugs. Disintegration refers to the breakdown of the solid dosage form into smaller fragments, while dissolution involves the subsequent solubilization of the active pharmaceutical ingredient (API) in gastrointestinal fluids (1). These processes are highly dependent on the physicochemical properties of the drug, the formulation design, and the gastrointestinal environment (2).

Gastric emptying is a pivotal physiological factor influencing drug bioavailability (3). It governs the transit time of pharmaceutical formulations within the stomach and their subsequent release into the small intestine, where drug absorption primarily occurs (4). The dynamics of gastric emptying are complex, being affected by factors such as the migrating motor complex (MMC), food intake, gastric motility, and physicochemical properties of the formulation (5). Particularly under fasting conditions, gastric emptying follows a cyclic pattern in which strong peristaltic contractions during phase III of the MMC promote the rapid expulsion of stomach contents into the duodenum (2). This phenomenon is crucial for weak base drugs with dissolution rates that are pH-dependent, as prolonged gastric retention may alter their solubility profile and, consequently, their bioavailability (4).

Several methodologies have been developed to study the influence of gastric emptying on weak base drugs bioavailability (6). Additionally, physiological-based pharmacokinetic (PBPK) models and *in vitro* dissolution testing methods, such as the Gastrointestinal Simulator (GIS), provide valuable insights into how gastric emptying modulates drug dissolution and absorption (5, 7). Recent advances have also introduced stochastic models that better capture the variability in gastric emptying patterns, providing a more physiologically relevant approach to predicting *in vivo* drug performance (5, 8).

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Understanding the interplay between drug release, gastric emptying, and bioavailability is essential for optimizing oral weak base drug formulations (9, 10). By integrating experimental and computational methodologies, researchers can develop more predictive models that enhance drug development and regulatory evaluation (11).

Dynamic dissolution testing has emerged as a crucial tool in pharmaceutical sciences for accurately simulating the *in vivo* drug dissolution and absorption processes (12). Unlike conventional compendial dissolution methods, which rely on static media and fail to replicate physiological variability, dynamic dissolution models integrate time-dependent changes in pH, volume, and composition of the gastrointestinal environment (13). These models are particularly relevant for weak base drugs with pH-dependent solubility, supersaturation behavior, or complex dissolution kinetics (14).

One of the most widely used dynamic dissolution approaches is the two-stage dissolution model, which mimics the transition from the gastric to the intestinal environment. This method is essential for evaluating the precipitation risk of poorly soluble drugs upon gastric emptying, a phenomenon that significantly affects bioavailability (14). Additionally, advanced multicompartmental models such as GIS allow for a more accurate representation of gastric emptying kinetics, including first-order and Weibull-based kinetics, which are crucial for predicting *in vivo* dissolution profiles (15). Moreover, supersaturation methods, as described by O'Dwyer *et al*. (16), enable the assessment of transient solubility enhancement strategies, aiding in the development of bioavailable formulations for BCS Class II and IV drugs.

By incorporating dynamic fluid flow and pH gradients, these models enhance the predictive power of dissolution studies, bridging the gap between *in vitro* and *in vivo* performance. The adoption of dynamic dissolution methods is, therefore, essential for optimizing drug formulations, reducing reliance on animal models, and improving BCS-based predictions (16).

Biopredictive dissolution methods are crucial in accurately forecasting the *in vivo* performance of oral drug formulations. Among these, GIS stands out as a multi-compartment dissolution model capable of modulating gastric emptying dynamics to better mimic physiological conditions. By incorporating variables such as pH fluctuations, motility patterns, and gastric transit time, the GIS provides a more comprehensive assessment of weak base drug dissolution and absorption potential (2).

This study will focus on investigating gastric emptying by applying first-order and Weibull kinetics to volume emptying, two well-established mathematical models used to describe drug transit and dissolution behaviors under dynamic conditions (4). A custom-developed control program, designed by the research team, will be employed to regulate and analyze gastric emptying profiles within the GIS, ensuring a controlled and reproducible experimental setup for evaluating dissolution kinetics.

Material and Methods

Gastrointestinal Simulation (GIS)

A dynamic *in vitro* gastrointestinal simulation system (GIS) was employed to evaluate the effect of gastric emptying kinetics on the dissolution behavior of dipyridamole. The GIS model consists of three interconnected compartments simulating the stomach, duodenum, and jejunum, allowing physiologically relevant control of fluid dynamics. In addition, two reservoir compartments were included to simulate gastric and duodenal secretions, enabling continuous input of media and maintenance of physiologically accurate pH and volume conditions. Fluid transfer between compartments was regulated using programmable peristaltic pumps to mimic gastric emptying under controlled experimental conditions.

Gastric Emptying Models

To investigate the influence of gastric emptying kinetics on drug dissolution, GIS was employed as a dynamic *in vitro* model. This system allows the modulation of gastric emptying to simulate physiological conditions, providing insights into drug dissolution and absorption behavior. The study focused on evaluating two different emptying kinetics: first-order and Weibull models, selected based on previous research by Talattof *et al*. (5).

First-order

$$Volume = V_0 \cdot exp^{-k_d \cdot t} \tag{1}$$

Weibull

$$Volume = V_0 \cdot exp^{-(t/\beta)^{\alpha}} \tag{2}$$

The parameters for these two kinetics were selected based on two criteria: that they be representative of the gastric emptying profiles described by Talattof, and that the resulting flow rates could be achieved using the available software and peristaltic pump.

The kinetics of gastric empty tested can be seen in Fig. 1.

The parameters of six different gastric emptying kinetics tested and presented in Table I.

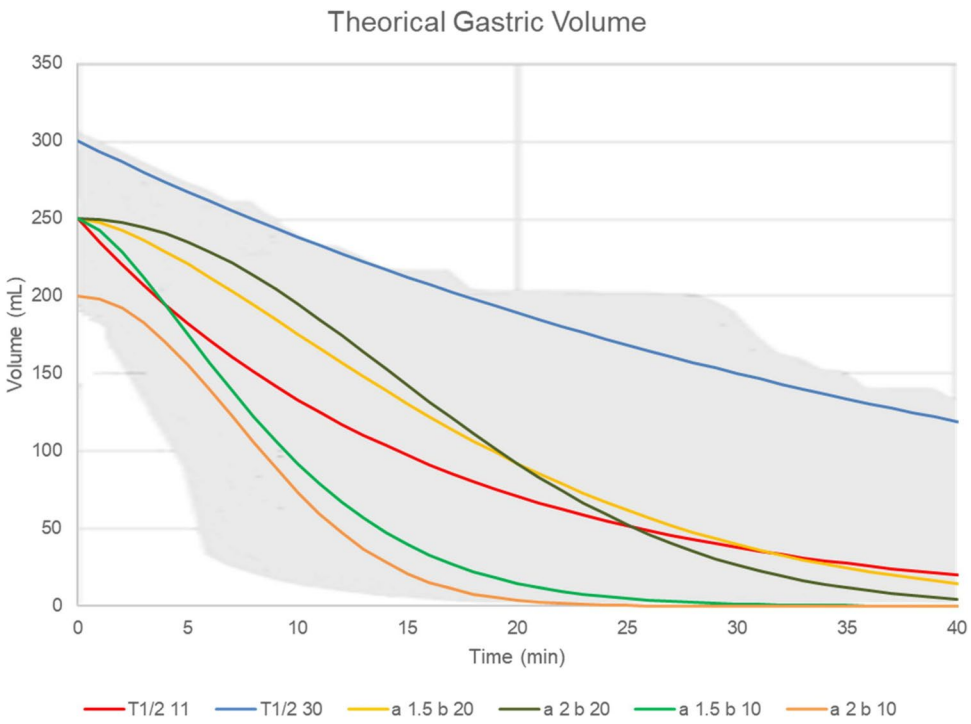

Fig. 1 Gastric Empty, Volume (mL) *vs* time (min). The grey area represents the possible gastric emptying obtained experimentally and with simulations by Talattof *et al.* (5). Thick lines are the gastric empty kinetics studied. First-order with two different half-live, 11 min and 30 min and four Weibull kinetics. Adapted with permission from Talattof 2018 Copyright 2018 American Chemical Society

Table I Gastric Emptying Kinetics Tested

Model	Gastric half emptying time (min)	Alpha	Beta	Initial Volume (V0)
First-order	11	—	—	250 mL
First-order	30	—	—	300 mL
Weibull	15.66	1.5	20	250 mL
Weibull	16.65	2	20	250 mL
Weibull	7.83	1.5	10	250 mL
Weibull	8.33	2	10	200 mL

Dissolution Media

The dissolution media were designed to replicate the physiological conditions of the human gastrointestinal tract:

- Gastric medium: 1.2 pH hydrochloric buffer (50 mL) + water (150–250 mL). 200–300 mL total initial volume.
- Intestinal medium: 50 mM phosphate buffer at pH 6.8 (50 mL). 50 mL initial volume and it will be constant during experiment.
- Reservoirs:
  - Gastric: pH 1.2 hydrochloric acid. (1 mL/min).
  - Intestinal: 100 mM phosphate buffer, ensuring stable pH conditions. (1 mL/min).

Experimental Procedure

Prior to the start of each experiment, the entire gastrointestinal simulation system was assembled and calibrated. Peristaltic pumps were first calibrated to ensure accurate flow rates. Tubing was connected as follows:

One tube connected the gastric compartment to the duodenal compartment. Another tube connected the duodenal to the jejunal compartment. These two flow paths were regulated by variable-speed peristaltic pumps that controlled gastric emptying dynamics throughout the experiment.

In addition, two reservoir compartments—for gastric and duodenal secretions, respectively—were connected to their target compartments via separate peristaltic pumps operating at a constant flow rate of 1 mL/min.

Agitation and pH monitoring were implemented to simulate physiological mixing:

- The gastric compartment was stirred at 100 rpm.
- The duodenal compartment was stirred at 50 rpm.
- The jejunal compartment remained unstirred.

Both the gastric and duodenal compartments were equipped with pH electrodes for real-time monitoring.

Initial volumes were added according to the conditions described in Table I:

- The gastric compartment was filled with a volume specific to each kinetic model.

- The duodenal compartment was always initialized with 50 mL.
- The jejunal compartment started empty and progressively accumulated volume from the duodenal output.

The duodenal compartment must contain exactly 50 mL at the end of the experiment; otherwise, the run was considered invalid and discarded.

Once the system was fully assembled and operational parameters confirmed, the dosage form was introduced into the gastric compartment, and the timer was started.

Each experiment lasted 60 min, during which:

- Peristaltic pumps were active for the first 40 min, enabling dynamic transfer between compartments.
- Samples were collected from the gastric, duodenal, and jejunal compartments at 13 time points: 2, 4, 6, 8, 10, 15, 20, 25, 30, 35, 40, 45, and 60 min.
- The final two samples were taken with the peristaltic pumps deactivated, simulating a post-emptying phase.

Collected samples were processed as follows:

- Each sample was centrifuged at 10,000 rpm for 2 min (AccuSpin Micro 17, Fisher Scientific).
- The supernatant was diluted 1:1 with drug-free medium: pH 1.2 hydrochloric buffer for gastric samples, and phosphate buffer at pH 6.8 for intestinal samples.
- Drug concentration was determined using UV spectrophotometry (Biomate 3S).
- The gastric compartment was placed on a precision balance (Acculab Atilon ATL-6201) to record mass in real time, enabling continuous fluid volume calculations.

Drug Choice

The drug used in this study was dipyridamole (Persantin 100 mg film-coated tablets commercialized by GmbH, manufactured by Delpharm Reims S.A.S.). It is classified as a Class II compound in the Biopharmaceutics Classification System (BCS) with a pka of 6.4 (17). Due to its pH-dependent solubility (slightly soluble in water, and soluble in dilute acid having a pH of 3.3 or below) (18), dipyridamole has a high tendency for supersaturation and precipitation in the gastrointestinal tract, which may subsequently reduce its absorption and bioavailability (19). Dipyridamole concentrations were measured at a wavelength of 450 nm in the UV spectrum.

Software Developed

A comprehensive control system has been developed to integrate a Reglo ICC peristaltic pump and a pH sensor connected to an Orion Versa Star Pro datalogger. The Reglo ICC peristaltic pump features four independent channels, each configurable for rotation direction, speed, and flow rate or volume after calibration. This allows for precise and automated liquid handling in various experimental and industrial applications. The Orion Versa Star Pro serves as an advanced data acquisition system, capable of simultaneously measuring pH, electrochemical potential (mV and ORP), conductivity, dissolved oxygen, and ion concentration.

Communication with the devices is handled using proprietary protocols over an RS-232 link, based on ASCII commands. This enables full control of the devices and facilitates their integration into automated laboratory or industrial processes. The pH sensor has been programmed with a specific protocol to manage data acquisition, storage, and data download.

A graphical application in C + + using Qt5 framework has been developed to manage the system. Graphical User Interface (GUI), Device Control Layer and an Experiment Management Module have been development. These components were communicated using Qt signals.

The design of experiment control system is based on state graphs (GRAFCET) and the graphical interface allows to configure an execute experiments, real-time monitoring of variables through a SCADA system, and pump calibration (Fig. 2).

On the SCADA screen, the occupied volumes, pH, and output flow rates from the stomach and duodenum will be displayed, as well as the flow rates from the peristaltic pumps. Using the tab calibration, the user can perform a precise calibration of the flow rates for each pump roller.

Validation from *In Vivo* Data

Plasma levels from a human clinical study (20, 21) were used to fit a two-compartment disposition model to obtain the value of the distribution constants k_{12} and k_{21} and the disposition β constant and the elimination rate form central compartment kel. Those parameters were used for the convolution of the cumulative experimental fractions dissolved (obtained from the sum of fractions dissolved in the three GIS compartments).

In order to use the fractions dissolved for convolution a linear time-scaling procedure was used from 1 h *in vitro* to 24 h *in vivo* and an extent normalization taking as 100% the highest value obtained *in vitro* and scaling up all the values. Those scaled up in time and extent fractions dissolved with each kinetic model were convoluted with the disposition parameters using a reverse Loo-Riegelman procedure as described in Prieto-Escolar et.al. (22, 23).

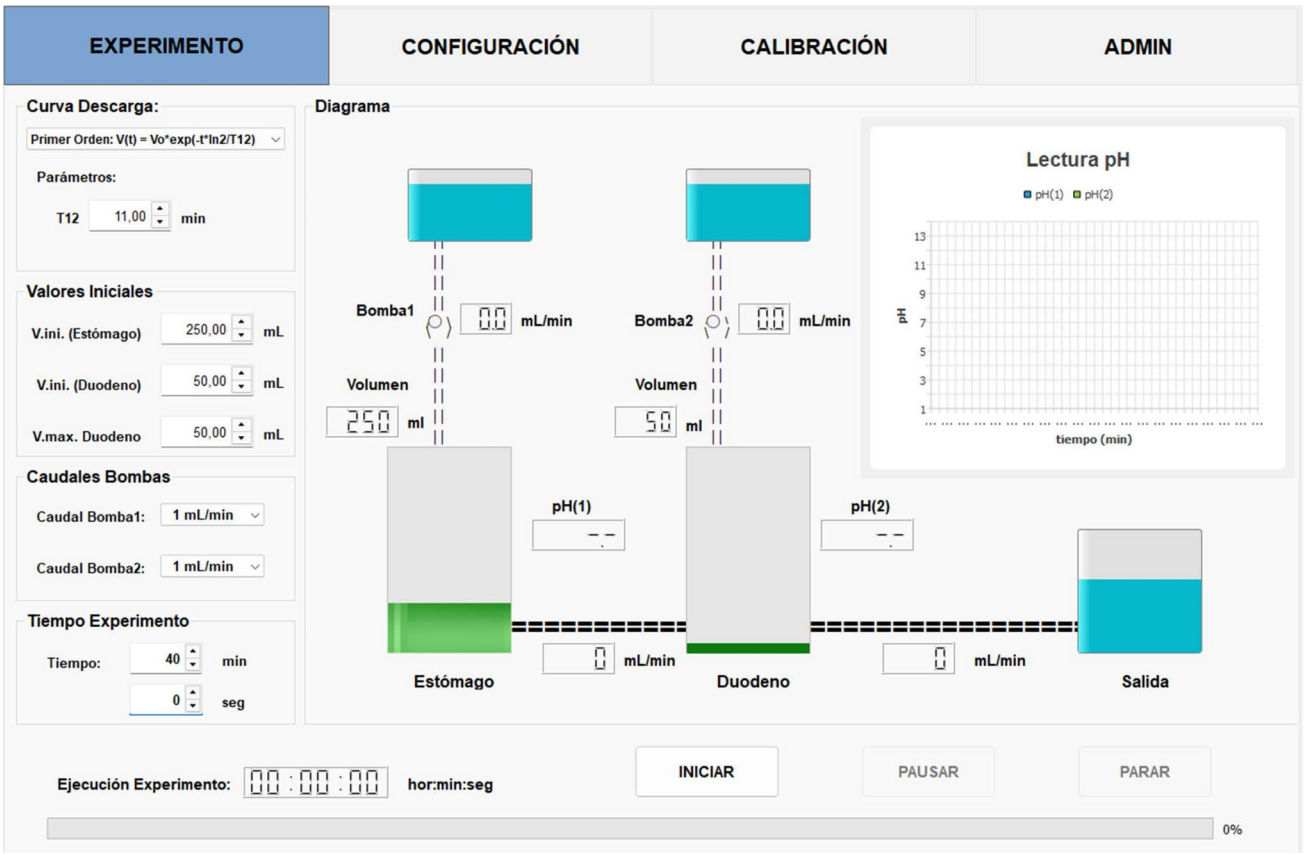

Fig. 2 Example of the interface of the program used

Results

A comprehensive control system has been developed to integrate a Reglo ICC peristaltic pump and a pH sensor connected to an Orion Versa Star Pro datalogger. This setup provides precise fluid handling and real-time monitoring of pH and other electrochemical properties.

Communication with the devices is handled using proprietary protocols based on ASCII commands and this enables full control of the devices and facilitates their integration into automated laboratories or industrial processes.

The software employs multithreaded architecture, ensuring efficient separation of functionalities into dedicated execution threads:

- Graphical User Interface (GUI): Provides an interactive environment for real-time control and visualization.
- Device Control Layer: Manages communication with the Reglo ICC pump and Orion Versa Star Pro pH meter.
- Experiment Management Module: Implements automated execution and data handling.

Communication between these components is asynchronous using Qt signals, ensuring smooth interaction.

The design of experiment control system is based on state graphs (GRAFCET), allowing a structured definition of any experiment defining process steps, associated actions, and transitions.

- Steps represent the control system states, managed through internal variables.
- Actions define device operations associated with each step (e.g., setting pump speed, logging pH readings).
- Transitions determine the conditions for moving from one step to another, triggered by signals and asynchronous events.

Execution of time-based experiments is carried out through periodic timers based on the required process speed.

The graphical interface allows to configure an execute experiments, real-time monitoring of variables through a SCADA system, and pump calibration (Fig. 2). This approach enhances control, supervision, and automation, leading to higher precision and efficiency in laboratory and industrial settings. The system's modular design allows for future expansion, supporting additional sensors and actuators as needed.

Specifically, the user interface allows the user to configure the type of stomach emptying curve model (first-order or Weibull), the pump flow rate values, the initial volumes of the stomach and duodenum, and the experiment duration.

In Fig. 3, the concentrations in the different compartments from the conducted experiments are presented.

To reach the validation of the software the comparison between theorical and experimental data were compared. First of all, comparison between theoretical and experimentally measured gastric volumes are presented in Fig. 4, highlighting potential discrepancies in the emptying process. These curves allow visualization of how each kinetic model influences fluid retention and transit within the system.

The volume in the duodenal compartment was visually monitored to remain constant at 50 mL throughout the experiment. The volume of the jejunal compartment was inferred from the other two compartments, considering that it starts at 0 mL and that the outflow from the duodenum to the jejunum is 1 mL/min faster than the gastric-to-duodenal transit rate.

Subsequently, the dissolution profiles obtained under each of the six conditions are analyzed. The percentage of drug dissolved is compared using theoretical volumes *versus* experimental volumes, aiming to assess the impact of dynamic gastric volume variations on drug dissolution behavior (Figs. 5–6).

To compare the dissolution profiles within the GIS system, the AUCs of the total dissolved profiles (three chambers) were compared with the theoretical ones. As shown in Table II, gastric emptying kinetics provide better approximations than Weibull kinetics.

The pH progression in the Gastric and Duodenal compartments is summarized in Fig. 7.

Predicted plasma levels are depicted in Fig. 8 overlapped with the Dipyridamole clinical data. Figure A was obtained with the experimental fraction dissolved and B with the theoretical ones.

Cmax ratios of the predicted *versus* the human data are displayed in Table III.

Discussion

In Vitro Data

In dynamic dissolution studies, both the volume of the dissolution medium and its movement play a critical role in accurately predicting drug solubility, dissolution kinetics, and subsequent bioavailability. Unlike static dissolution tests, where volume remains constant, dynamic systems simulate the physiological changes in gastric and intestinal fluids, including secretion, emptying, and mixing. These factors directly influence the rate and extent of drug dissolution, particularly for compounds with weak base drugs (pH-dependent solubility) or those prone to supersaturation and precipitation (14).

As observed in Fig. 3, dipyridamole preferentially dissolves in the gastric compartment. A lower concentration can also be noted when gastric emptying is calibrated with first-order kinetics and a gastric half emptying time of 11 min. This may be due to the rapid disintegration of the tablet and the fast flow of undissolved particles into the duodenal compartment.

The results of the gastric compartment volume study revealed that the GIS can be successfully fitted to first-order kinetics. However, the differences between the theoretical and experimental volumes are significant when fitted to Weibull kinetics.

As shown in Fig. 9, the actual volumes obtained from the experiments remain within the range of possible gastric emptying profiles.

Table IV presents the ratios comparing the AUCs of the dissolution rate profiles for the entire GIS across the different gastric emptying kinetics studied. As observed, the kinetic model with the highest AUC is the first-order model with a gastric half emptying time of 30 min and an initial volume of 300 mL. This result was expected, as theoretical curves had already indicated that this model would maintain the highest volume in the stomach throughout the experiment. However, the kinetic model with the lowest AUC was the first-order model with a gastric half emptying time of 11 min.

According to theoretical estimates, the kinetic model expected to result in the lowest gastric volume during the experiment was the Weibull model with an alpha of 2, a beta of 10, and an initial volume of 200 mL. However, the actual volumes obtained show that this experimental kinetic model, like all Weibull models, stabilized at a minimum volume higher than anticipated. The differences in the dissolved percentages among the various experiments further emphasize the importance of properly modulating volumes in dynamic dissolution experiments.

Moreover, the fluid dynamics within the gastrointestinal compartments impact the shear forces acting on solid drug particles, modulating their disintegration and dissolution rates. Peristaltic movements and gastric emptying patterns introduce variability in local drug concentrations, which can alter precipitation tendencies and absorption profiles. Studies utilizing multicompartmental models, such as the GIS, have demonstrated that inaccuracies in volume control can lead to significant deviations between theoretical and experimental dissolution profiles (15). Additionally, as highlighted by O'Dwyer *et al.* (16), the precise calibration of peristaltic pumps and fluid transfer rates is essential to ensure reproducibility in dissolution testing, particularly for complex Weibull-type emptying kinetics.

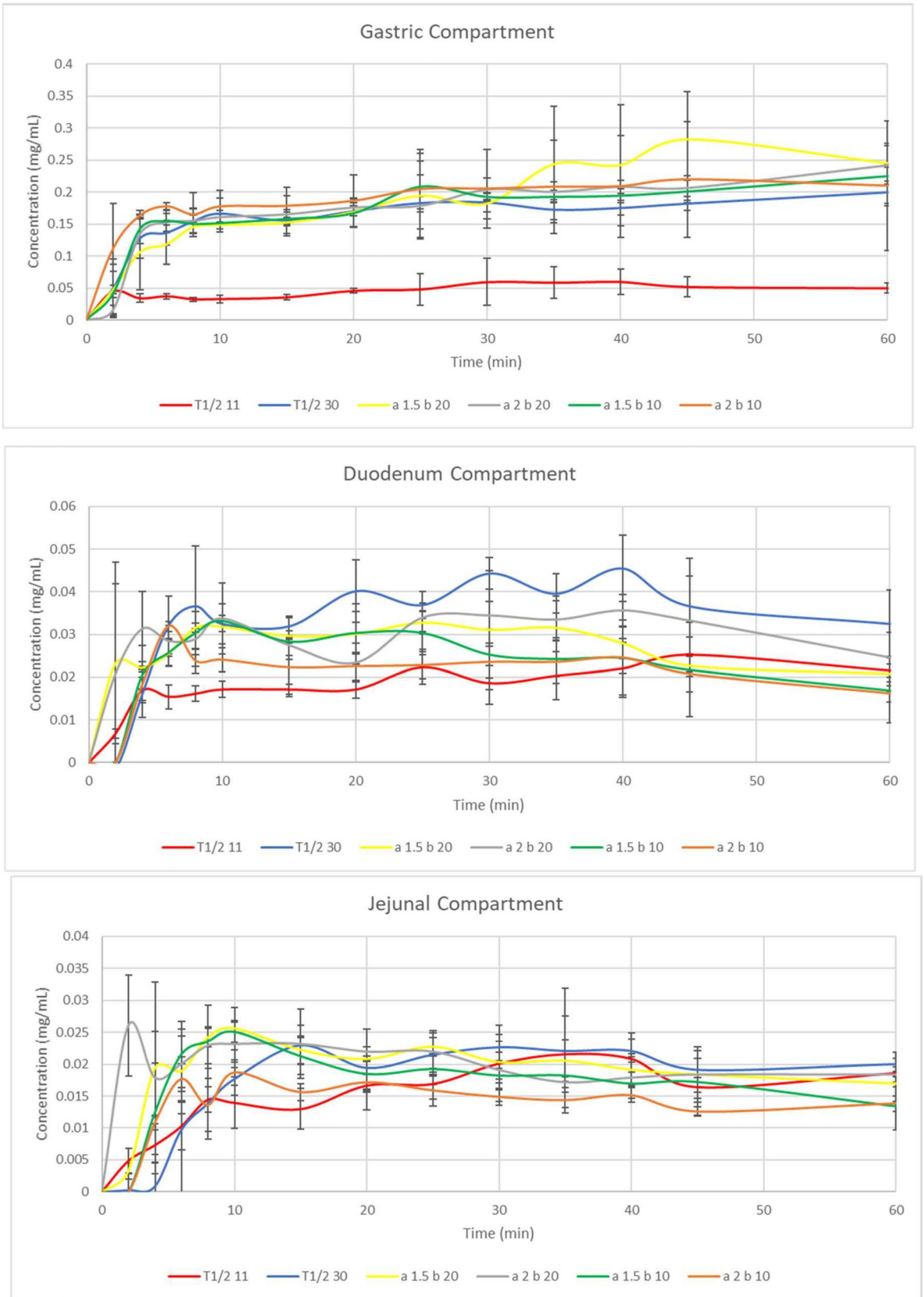

Fig. 3 Dipyridamole concentrations in the different compartments of the GIS. All studied gastric emptying conditions (First-order and Weibull) are shown

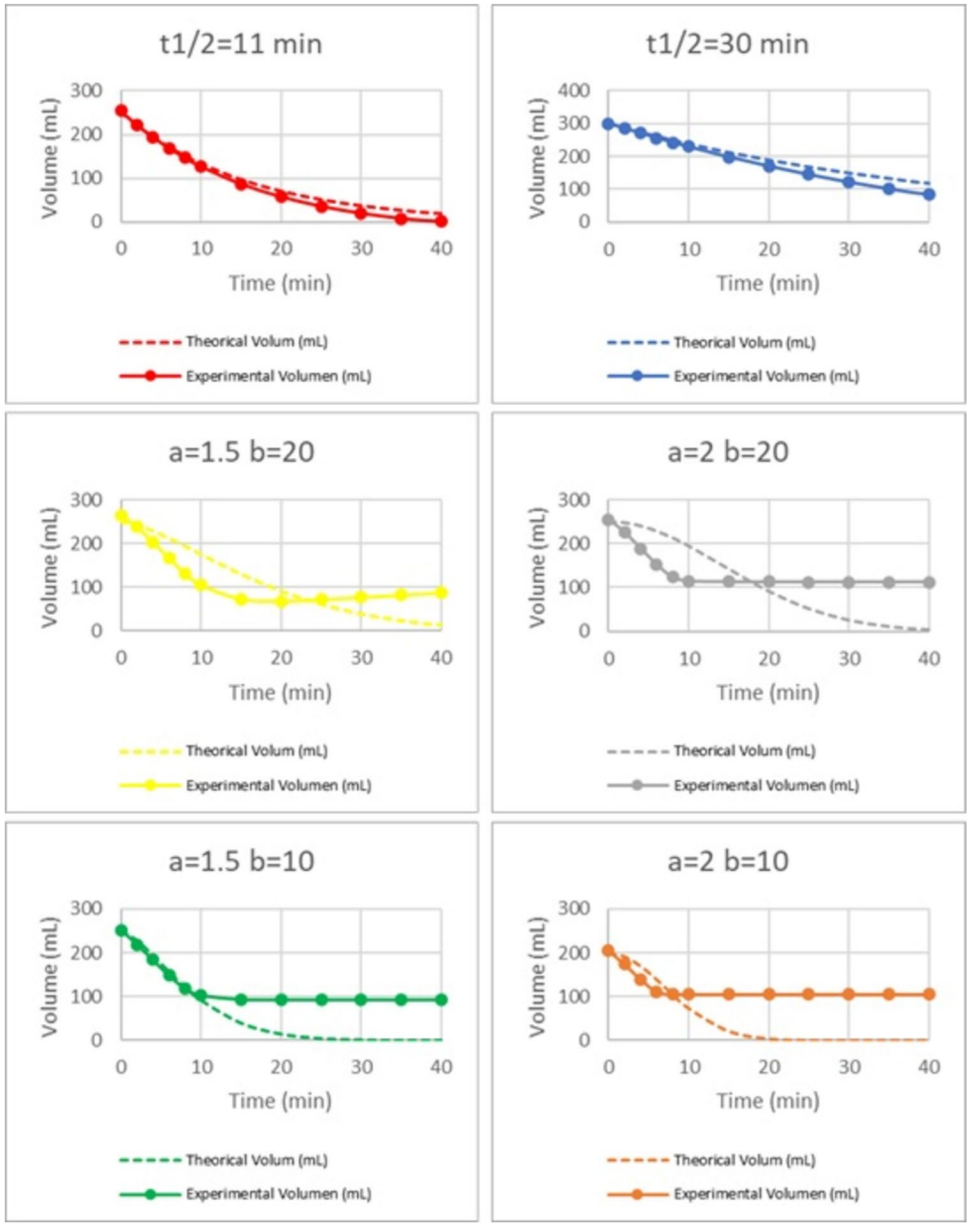

Fig. 4 Gastric emptying kinetics studied, with the X-axis representing time (minutes) and the Y-axis showing the remaining volume in the gastric compartment

Thus, controlling both the absolute volume and its dynamic changes is essential for obtaining physiologically relevant dissolution data. Failure to account for these factors may result in misleading *in vitro-in vivo* correlations (IVIVC), ultimately affecting drug formulation decisions and regulatory approvals.

The differences observed between theoretical and experimental gastric volumes can be attributed to limitation in the calibration method used for the peristaltic pumps. The calibration was performed using a single-point method, where a fixed volume was pumped over a set time interval, so only one velocity reference was used to calibrate. While this approach is adequate for the reservoir channels, which maintain a constant flow rate of 1 mL/min throughout the experiment, it introduces a potential source of error for the transfer channels (gastric to duodenum and duodenum to jejunum). These channels operate at variable flow rates, adjusting dynamically as the gastric emptying process progresses.

For simpler kinetic models, such as first-order kinetics, this limitation does not appear to significantly affect the results, as show in Fig. 5 and Table II. Since the flow rate in these models decreases gradually from the beginning, no substantial deviations were observed in either the measured volumes or drug concentrations. However, for Weibull kinetics, the effect is more pronounced. In these cases, gastric emptying rates increase and decrease at different phases of the process, making the single-point calibration less accurate

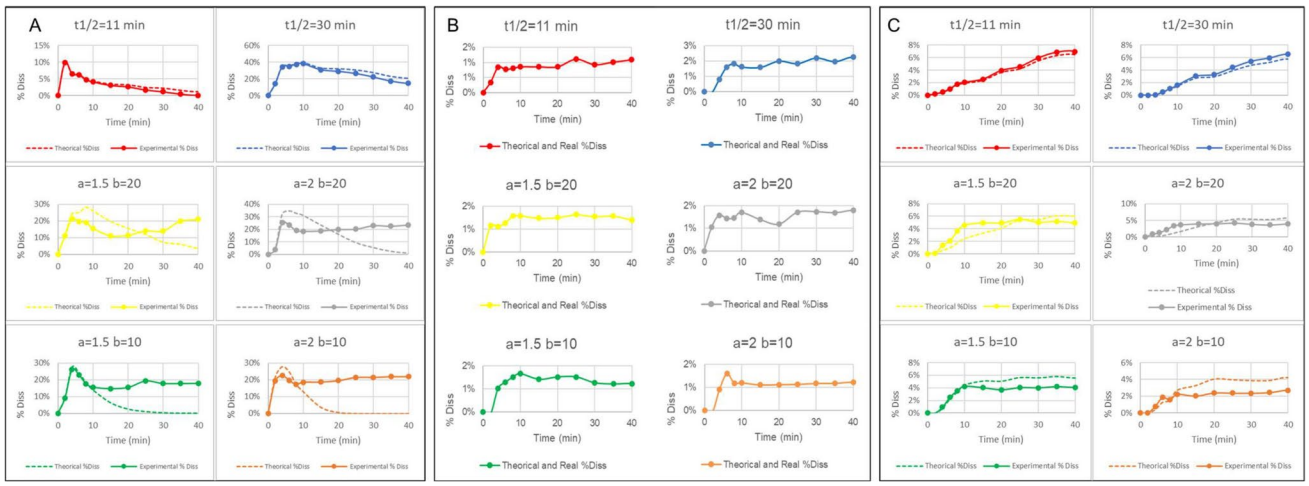

Fig. 5 Percentage dissolved of Dipyridamole in Gastric (**A**), duodenum (**B**), and jejunum compartment (**C**) using Theorical and Experimental Volume. The X-axis representing time (minutes) and the Y-axis showing the % Dissolved in the gastric compartment

Fig. 6 Percentage dissolved of Dipyridamole in GIS 3 compartments using Theorical and Experimental Volume. The X-axis representing time (minutes) and the Y-axis showing the % Dissolved in the gastric compartment

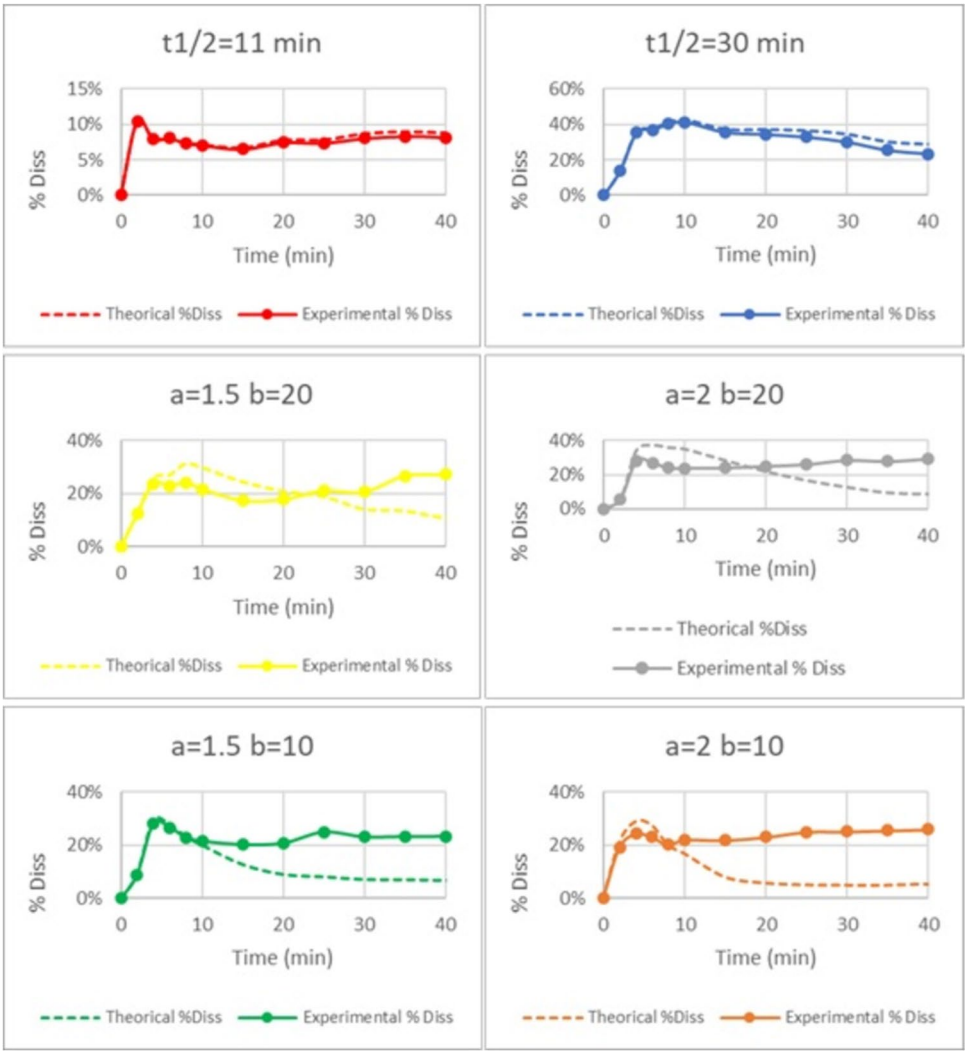

Table II Ratio of Actual Total AUC to Theoretical Total AUC for the Dissolution Profiles of all Three Compartments Combined Across all Studied Gastric Emptying Kinetics

Model	Condition	Theorical AUC	Real AUC	Ratio AUC (Real/theoretical)
First-order	11 min	4.86	4.44	0.91
First-order	30 min	19.45	17.14	0.88
Weibull	a 1.5 b 20	10.03	14.01	1.40
Weibull	a 2 b 20	9.76	15.84	1.62
Weibull	a 1.5 b 10	6.12	13.47	2.20
Weibull	a 2 b 10	5.10	14.38	2.82

in capturing these variations. This discrepancy suggests that for more complex kinetics, multi-point calibration or real-time flow adjustments may be necessary to improve the accuracy of experimental simulations.

In Vivo

The dissolution profiles obtained under the different gastric emptying kinetics revealed clear variations in the percentage of dipyridamole released. These differences were anticipated, given the drug's well-established pH-dependent solubility. This observation naturally leads to the question of whether such variations could be of relevance under *in vivo* conditions following oral administration. To address this, both precipitation and absorption phenomena were evaluated, as they play critical roles in determining oral bioavailability.

Dipyridamole's solubility is significantly affected by pH, which contributes to marked inter-individual variability in bioavailability. This is particularly evident in individuals with hypochlorhydria, a condition commonly found in infants, the elderly, and patients suffering from HIV or Helicobacter pylori infections (24–26).

Despite differences in the applied kinetic models, pH monitoring results indicated no meaningful variation among the profiles. The pH values remained stable, suggesting that the emptying kinetics did not influence the acid–base environment within the compartments. Notably, pH values in the gastric compartment were consistently higher than in the duodenum, a gradient that favors precipitation upon transfer of drug material into the more alkaline intestinal region.

Regarding the precipitation phenomenon, Fig. 6 shows that the fraction of dipyridamole dissolved never approached 100%. This can be explained by the transfer of both dissolved and undissolved material via the peristaltic system. Undissolved tablet fragments entering the intestinal compartments may fail to dissolve further due to the less favorable pH. In Fig. 5, dissolution profiles in the intestinal compartment do not exhibit a clear supersaturation-precipitation pattern; rather, the dissolved fraction remains relatively constant over time. This could be attributed to the continuous volume flow in the duodenum and jejunum, which may limit the degree and visibility of local precipitation.

Interestingly, no clear signs of precipitation were observed in the jejunal compartment either. These results are consistent with *in vivo* findings reported by Psachoulias *et al*. (27), who observed that dipyridamole precipitation in the upper small intestine was generally limited and occurred gradually over extended periods (up to 48 h), rather than as an immediate or pronounced event.

Given that dipyridamole absorption is known to occur primarily in the duodenum and proximal jejunum, the dissolved fraction in these compartments serves as a proxy for the bioavailable portion of the dose (ref: *In vitro* dissolution of fluconazole and dipyridamole in GIS). To quantify and compare these effects, the sum of the dissolved fractions in the duodenal and jejunal compartments was used to calculate the area under the curve (AUC) for each kinetic profile (28). The ratios between AUC values for the different conditions are presented in Table V.

Analysis of Table V reveals that most kinetic profiles resulted in comparable AUC values, suggesting no significant differences in the extent of drug available for absorption.

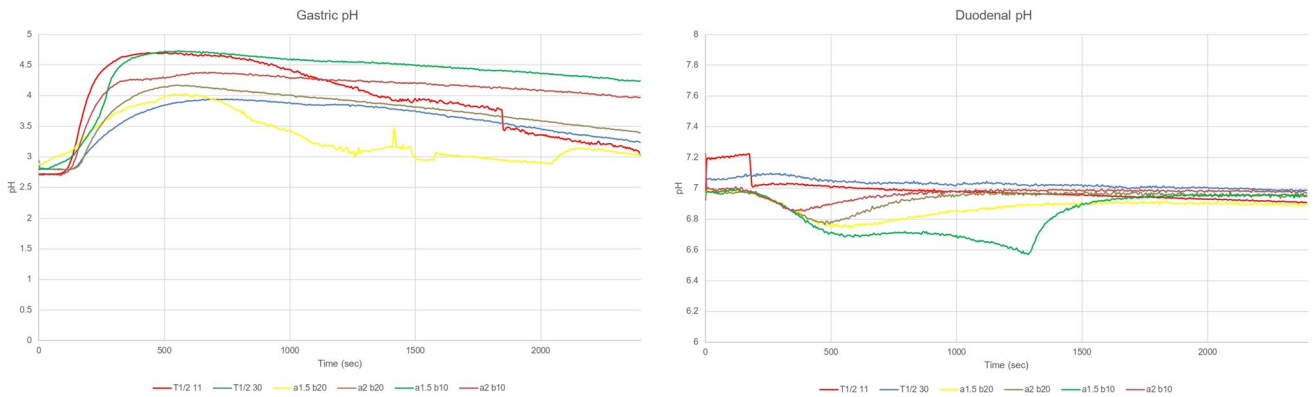

Fig. 7 Measured pH values in the Gastric and Duodenal compartments for the tested kinetic profiles throughout the experiment

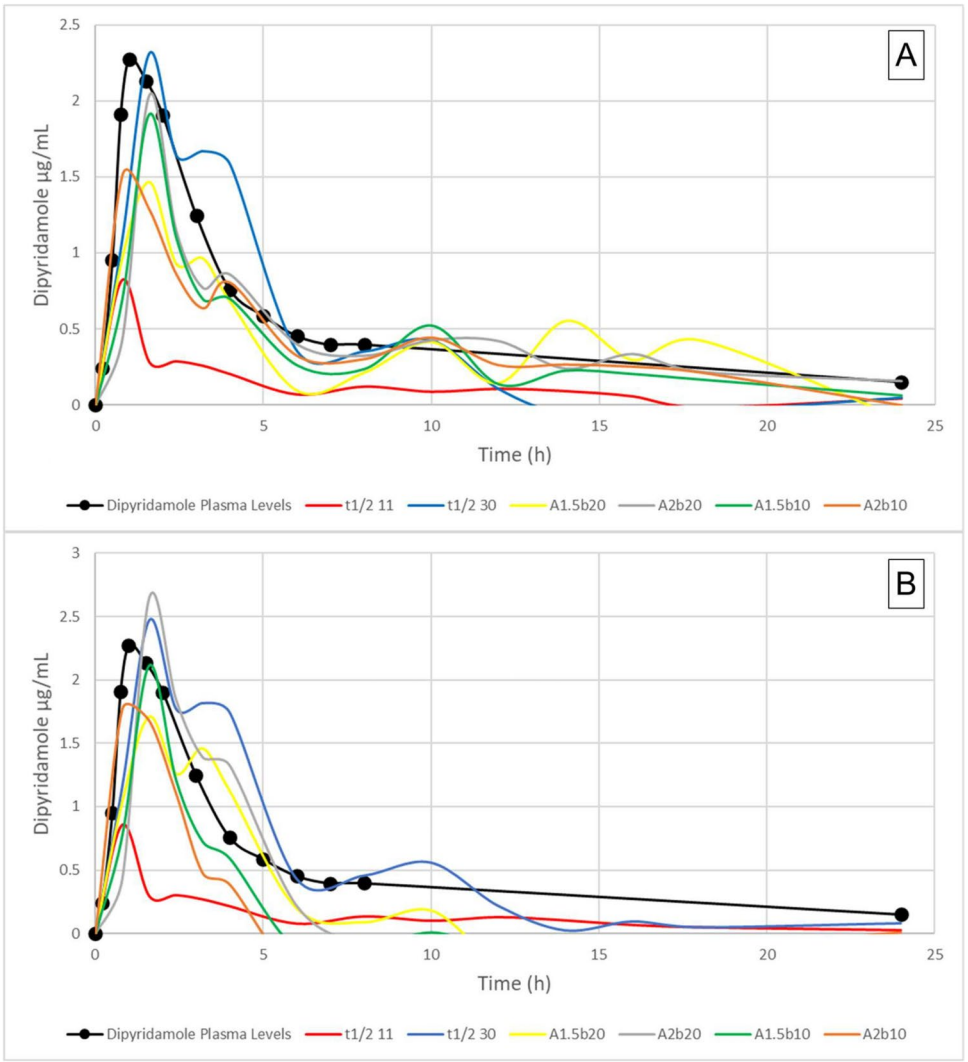

Fig. 8 Predicted plasma levels overlapped with the Dipyridamole clinical data. Figure A was obtained with the experimental fraction dissolved and B with the theoretical ones

Table III Concentration Maxima Calculated with Predicted and Theoretical for the Dissolution Profiles

Cmax ratio	t1/2 11	t1/2 30	A1.5b20	A2b20	A1.5b10	A2b10
Predicted	0.36	**1.02**	0.65	**0.90**	**0.84**	0.67
Experimental	0.38	**1.09**	0.75	**1.16**	**0.93**	0.78

However, an exception was observed for the Weibull profile with $\alpha = 2$ and $\beta = 10$, which showed an AUC approximately 30% lower than the others. Notably, this profile also used a reduced initial gastric volume (200 mL), which may have limited the amount of drug available for dissolution and subsequent transfer, thus explaining the observed discrepancy.

Taken together, these findings suggest that, with the possible exception of cases involving reduced gastric volume, the variation in gastric emptying kinetics does not appear to significantly affect dipyridamole's *in vivo* bioavailability.

Dipyridamole is best described by a three-compartment disposition model (20), but the two-compartment model was reasonably fit and made easier the convolution of the fractions dissolved to get plasma concentrations. As the kinetic model is approximate, only the predicted Cmax values were used to compare the predictive ability of each gastric emptying kinetic.

As can be seen in Fig. 8 and Table III the first order gastric emptying kinetic with a half emptying time of 30 min gave the best Cmax prediction followed by two of the Weibull kinetics. These results can be explained considering the pH dependent solubility of Dipyridamole which dissolves easily in the gastric acidic environment and could supersaturate and precipitate after emptying in the alkaline intestinal environment. With a short gastric half emptying time it might

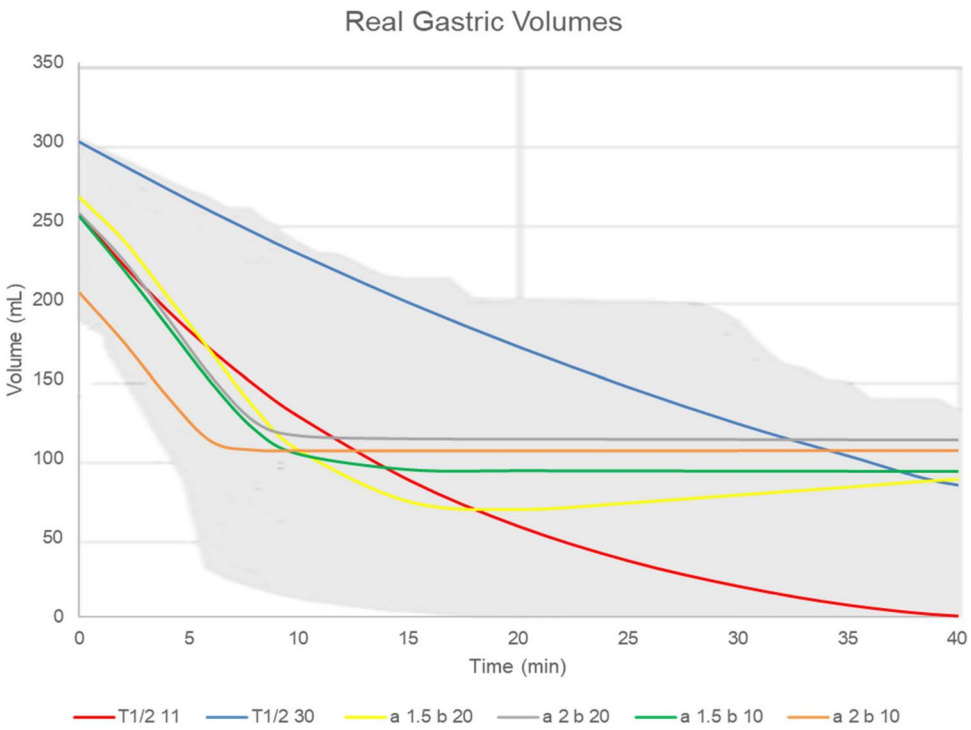

Fig. 9 Real Gastric Emptying, Volume (mL) *vs*. Time (min). The grey area represents the possible gastric emptying profiles obtained experimentally and through simulations by Talattof *et al.* (5)

Table IV Ratios Between the Total AUCs of the Dissolution Rate Profiles in the GIS for the Different Studied Kinetics. The Calculations were Performed Using the Results Obtained from the Actual Volumes

Ratio experimental Total AUC		First-order		Weibull			
		11 min	30 min	a 1.5 b 20	a 2 b 20	a 1.5 b 10	a 2 b 10
First-order	11 min	1.00					
	30 min	3.86	1.00				
Weibull	a 1.5 b 20	3.16	0.82	1.00			
	a 2 b 20	3.57	0.92	1.13	1.00		
	a 1.5 b 10	3.03	0.79	0.96	0.85	1.00	
	a 2 b 10	3.24	0.84	1.03	0.91	1.07	1.00

Table V Ratios of AUC Values (duodenal + jejunal) for each Gastric Emptying Kinetic Profile, Based on Real Volume Measurements

Ratio experimental AUC (Duodenum+Jejunum chambers)		First-order		Weibull			
		11 min	30 min	a 1.5 b 20	a 2 b 20	a 1.5 b 10	a 2 b 10
First-order	11 min	1.00					
	30 min	1.09	1.00				
Weibull	a 1.5 b 20	1.05	0.96	1.00			
	a 2 b 20	0.94	0.86	0.90	1.00		
	a 1.5 b 10	0.87	0.80	0.83	0.92	1.00	
	a 2 b 10	0.58	0.54	0.56	0.62	0.67	1.00

happen that the incomplete disintegration of the tablets did not allowed complete drug dissolution and consequently the amount being transferred to the next segments was slower. In contrast, when the emptying is slower either with a first order kinetic or with two of the Weibull kinetics, drug dissolution can be higher and the dissolved drug being transferred slowly to the next segment suffered a slower precipitation in duodenum (27). Weibull kinetic with parameters a = 2 b = 20 is the one with theoretical gastric volumes closer to the first order with t1/2 30 min, so it is consistent that the predictions were also good with this Weibull kinetic. Nevertheless, then the other Weibull model that should produce good predictions would be a = 0.5 and b = 20 and this is not the case. The problem might have arisen as the different Weibull kinetics produced in the experiments similar gastric volumes, but the estimation using the theoretical volumes gave similar results.

We have shown the technical difficulties of reproducing Weibull kinetic for gastric emptying, at least with the direct implementation of the theoretical emptying rates into the system. It might be necessary to use linear or constant emptying rates in time intervals and change them more abruptly to approximate the Weibull curve and check if the experimental volumes reproduce better the theoretical ones.

Conclusions

A new software as control of a Reglo ICC Peristaltic Pump and a pH Sensor with Orion Versa Star Pro Datalogger was development and validation of equipment was carried out. This approach enhances control, supervision, and automation, leading to higher precision and efficiency in laboratory and industrial settings. The system's modular design allows for future expansion, supporting additional sensors and actuators as needed. For first-order kinetics the equipment has demonstrated perfect correlation between theorical and experimental data, however, real-time volume control will be necessary to adjust gastric emptying to Weibull kinetics.

Although variations in gastric emptying kinetics influence the dissolution behavior of dipyridamole, these differences do not appear to translate into significant alterations in its *in vivo* bioavailability under most conditions. Notably, the intestinal environment—specifically in the duodenum and proximal jejunum—does not exhibit abrupt precipitation despite the pH shift, indicating that drug precipitation is both limited and gradual. However, a reduced initial gastric volume markedly impairs the extent of drug dissolution and transfer, leading to a measurable decrease in absorption. Overall, aside from scenarios involving constrained gastric volume, dipyridamole demonstrates pharmacokinetic resilience to variable gastric emptying profiles.

Since the kinetic profile does not appear to significantly influence the outcomes, and given the technical difficulty of accurately representing gastric emptying following a Weibull kinetic model, it is recommended to use first-order kinetics to modulate gastric emptying in this type of dynamic dissolution rate assays.

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Data Availability Data_Impact of Gastric Emptying Kinetics on Dipyridamole Dissolution Using a Gastrointestinal Simulator https://zenodo.org/records/15873012.

Declarations

Conflicts of interest The authors declare no conflict of interest.

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