

Diffusion-absorption modeling of drug transport in the gastrointestinal tract: an initial-boundary value problem approach

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ABSTRACT

The absorption of drugs in the gastrointestinal tract is a fundamental process in oral drug delivery involving the complex interplay of diffusion and permeation. This paper develops a mathematical model for drug transport in the gastrointestinal lumen, incorporating Fickian diffusion and a first-order volumetric sink term to represent uptake into the systemic circulation. The model is formulated as an initial-boundary value problem with no-flux boundary conditions at both the gut wall and the luminal center, representing a closed system where drug removal occurs solely through the distributed absorption term. Separation of variables is employed to derive an analytical solution, revealing that the concentration remains spatially uniform throughout the domain and decays exponentially with time as $C(x, t) = C_0 e^{-k_a t}$. The dimensionless absorption number $\kappa = k_a L^2 / D$ emerges as the key parameter governing the rate of drug elimination, with $\kappa \gg 1$ indicating absorption-dominated transport and $\kappa \ll 1$ indicating diffusion-dominated transport. The analytical solution is verified numerically using a Crank–Nicolson finite difference scheme, demonstrating excellent agreement with errors on the order of machine precision ($\sim 10^{-15}$). The model provides a rigorous framework for understanding the biophysical interplay between diffusion and absorption in oral drug delivery and has potential applications in the design of controlled release formulations and absorption enhancement strategies.

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1. INTRODUCTION

The oral route remains the preferred route for drug administration because of its convenience, ease of patient compliance and cost-effectiveness. Drug delivery by this route is, however, highly dependent on the ability of the drug to dissolve in gastrointesti-

nal fluids and then get absorbed into systemic circulation [1]. Drug absorption refers to the passage of a drug molecule into the blood from the gut lumen, which is facilitated by passive diffusion across the lipid membranes of the intestinal epithelium and/or by active transport mechanisms [2].

In 1855, Adolf Fick formulated a fundamental equation of molecular diffusion: Fick's law of diffusion. In its simplest form, Fick's first law is that the diffusive flux depends on the concen-

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tration gradient:

$$J = -D \frac{\partial C}{\partial x}, \quad (1)$$

where J is the flux, D is the diffusion coefficient, and C is the concentration [3]. Fick's second law, derived from conservation of mass, gives the time evolution of concentration:

$$\frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2}. \quad (2)$$

Although pure diffusion is the simplest model to describe drug transport, a more realistic model of the absorption process is also a more complex one that involves mechanisms that remove drug from the gastrointestinal tract. Mathematical models for controlled drug delivery have been developed to predict release kinetics [4]. The absorption can be simulated as a sink term in the transport equation as in the heat conduction problem of radiation [5] and can be solved numerically using the same methods. The so-called combined diffusion-absorption model is therefore a more realistic one for the transport of drugs in the gastrointestinal tract.

In recent years, the pharmacokinetic modeling research has investigated the fractional order derivative to better reflect the memory properties of drug absorption and distribution, which has a complex nature. Oji *et al.*, [6] developed a fractional order two compartment pharmacokinetic model that models oral drug absorption using the Caputo derivative. Their approach has shown that the FO models were found to be more effective to fit the experimental data than classical integer-order models especially for the description of the non-exponential decay and the anomalous diffusion behavior observed in the drug concentration-time profiles. The study underscored the need to include memory effects in the pharmacokinetic modelling, and the fractional order parameter indicated the heterogeneity and complexity of the system. This fractional model is more flexible and physiologically relevant description of drug absorption kinetics that complements classical diffusion-absorption models and provides extra insights into the drug delivery mechanisms by the oral route.

In this paper, a mathematical formulation of the absorption of drugs is developed, explicitly accounting for the diffusive transport and the absorption kinetics. The model is grounded in the principles of biopharmaceutics and pharmacokinetics [7]. We set up an initial-boundary value problem that models the spatial and temporal behaviour of the drug concentration in the gastrointestinal tract, imposing boundary conditions and an absorption term to represent uptake into the bloodstream.

2. PHYSIOLOGICAL BACKGROUND

2.1. GASTROINTESTINAL ANATOMY AND FUNCTION

The human gastrointestinal tract has a number of distinct regions: the stomach, small intestine, which is divided into the duodenum, jejunum, and ileum, and the large intestine. The absorption of drugs varies from one region to another [8].

The small intestine is the main site of absorption of drugs because:

- Villi and microvilli have a large surface area ($\approx 200 \text{ m}^2$)

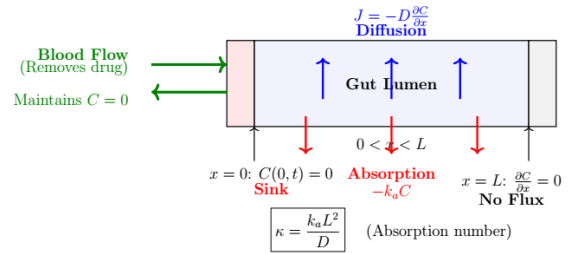


Figure 1: One-dimensional diffusion-absorption model. The lumen ($0 < x < L$) has no-flux at both boundaries ($\partial C / \partial x = 0$ at $x = 0$ and $x = L$). Drug diffuses (blue) and is removed by a volumetric sink (red). The absorption number $\kappa = k_a L^2 / D$ governs the relative importance of absorption.

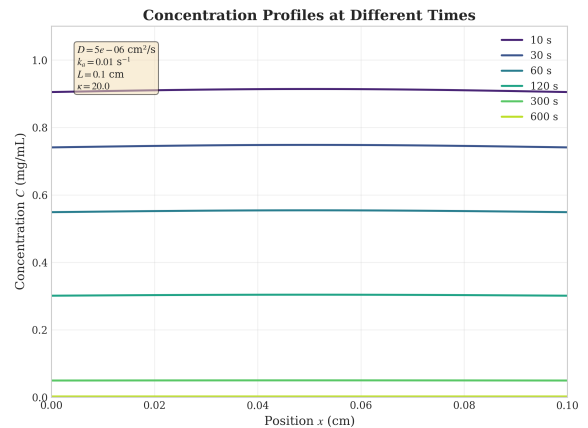


Figure 2: Concentration profiles at different times for the diffusion-absorption model with no-flux boundary conditions. The concentration remains spatially uniform throughout the domain and decays exponentially with time as $C(x, t) = C_0 e^{-k_a t}$. The slight variations visible in the profiles are due to numerical perturbations; the analytical solution predicts perfect spatial uniformity. Parameters: $D = 5 \times 10^{-6} \text{ cm}^2/\text{s}$, $k_a = 0.01 \text{ s}^{-1}$, $L = 0.1 \text{ cm}$, $\kappa = 20$.

- A wide array of blood vessels
- physiological temperature range ($37 \pm 1^\circ\text{C}$) [9]
- Extended transit time (3-5 hours)

2.2. DRUG ABSORPTION MECHANISMS

Drug absorption occurs through several mechanisms [10]:

2.2.1. Passive diffusion

The primary way drugs are absorbed is by passive diffusion [10]. Fick's law dictates that the movement of a drug molecule across the intestinal epithelium is from an area of high concentration to an area of low concentration. The rate of passive diffusion is dependent on:

- The difference in concentration of a substance across the membrane is called the concentration gradient.
- Lipid solubility of the drug (partition coefficient)
- Molecular size and shape

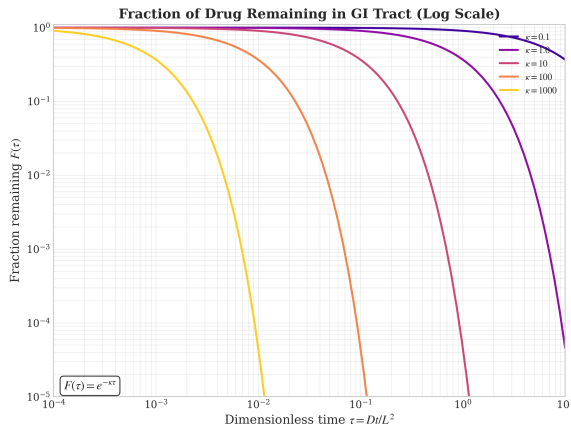


Figure 3: Fraction of drug remaining $F(\tau)$ in the gastrointestinal tract as a function of dimensionless time τ for various values of the absorption number κ . The semi-logarithmic plot clearly shows the exponential decay $F(\tau) = e^{-\kappa\tau}$, with the slope of each curve equal to $-\kappa$. For $\kappa \gg 1$ (absorption-dominated), the drug is rapidly eliminated from the lumen. For $\kappa \ll 1$ (diffusion-dominated), the decay is slow and the drug remains in the gastrointestinal tract for extended periods. This information is critical for the design of controlled release formulations and for understanding the bioavailability of orally administered drugs.

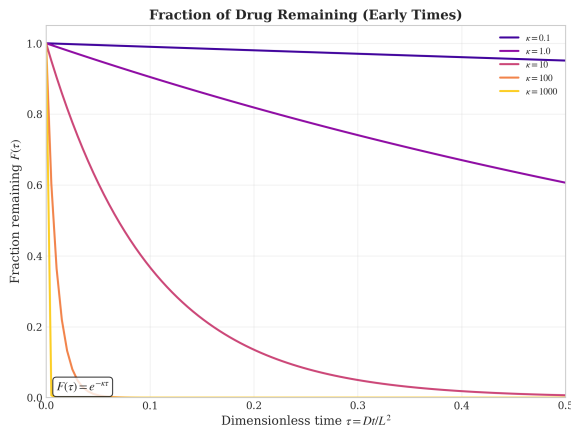


Figure 4: Fraction of drug remaining $F(\tau)$ at early times (linear scale) for various absorption numbers κ . The exponential decay $F(\tau) = e^{-\kappa\tau}$ is evident, with the initial slope of each curve equal to $-\kappa$. For small κ values (e.g., $\kappa = 0.1$), the decay is slow and approximately linear over the early time period, characteristic of diffusion-dominated transport. For large κ values (e.g., $\kappa = 1000$), the decay is extremely rapid, characteristic of absorption-dominated transport. This plot is particularly relevant for understanding the early-phase pharmacokinetics of orally administered drugs and for optimizing immediate-release formulations where rapid onset of action is desired.

- The ionization of a substance in a solution is a degree of ionization, a pH-dependent process.

2.2.2. Carrier-mediated transport

Some drugs are absorbed by carrier-mediated transport through either:

- **Facilitated diffusion:** Passive transport down a concentration gradient with the aid of a specific carrier protein.

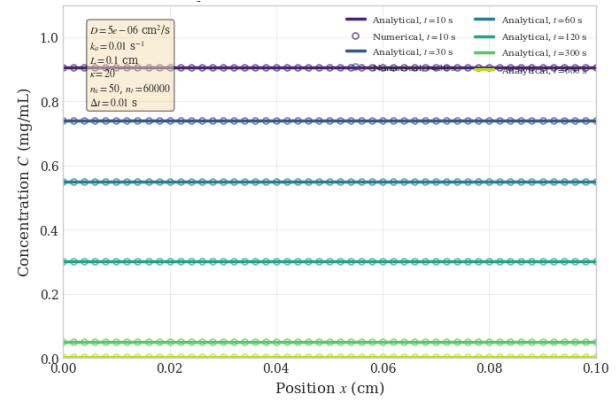


Figure 5: Comparison of analytical and numerical solutions for the diffusion-absorption model with no-flux boundary conditions. (a) Concentration profiles at various times showing excellent agreement between the analytical solution (solid lines) and the Crank–Nicolson finite difference solution (circles) for parameters $D = 5 \times 10^{-6} \text{ cm}^2/\text{s}$, $k_a = 0.01 \text{ s}^{-1}$, $L = 0.1 \text{ cm}$. Both methods yield spatially uniform concentration profiles that decay exponentially with time. (b) Error analysis showing the maximum absolute error between analytical and numerical solutions as a function of dimensionless time τ . The error is on the order of machine precision ($\sim 10^{-15}$), confirming the accuracy of the numerical scheme and validating the analytical solution. The Crank–Nicolson scheme is second-order accurate in both space and time, and the numerical verification provides confidence for future extensions to more complex models.

- **Active transport:** Transport that requires energy and goes against the concentration gradient

2.2.3. Paracellular transport

Paracellular transport is the alternative absorption route taken by small hydrophilic drugs, across tight junctions between epithelial cells.

Fick's laws of diffusion

Fick's first law is: flux is proportional to concentration difference.

$$\mathbf{J} = -D\nabla C, \quad (3)$$

Here, the flux vector is denoted by $\mathbf{J}$, the diffusion coefficient is D and the concentration gradient is ∇C .

For one-dimensional diffusion in the x -direction:

$$J = -D \frac{\partial C}{\partial x}. \quad (4)$$

From the continuity equation, $\frac{\partial C}{\partial t} + \nabla \cdot \mathbf{J} = 0$ we have:

$$\frac{\partial C}{\partial t} = \nabla \cdot (D\nabla C). \quad (5)$$

If diffusion is one-dimensional and the coefficient D is constant, then:

$$\frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2}. \quad (6)$$

3. MATHEMATICAL MODEL FORMULATION

3.1. COORDINATE SYSTEM AND MODEL GEOMETRY

In this model, the gastrointestinal tract is idealized as a one-dimensional domain of length L , where the coordinate x represents the distance from the gut wall into the lumen, i.e.,

- $x = 0$ denotes the gut wall surface (the epithelial boundary)
- $x = L$ stands for the distal end of the absorption region (the luminal center or distal boundary)

This coordinate system is appropriate for modeling transverse diffusion from the lumen toward the absorbing wall, where drug molecules diffuse across the luminal contents before reaching the epithelial surface. The length scale L represents the effective diffusion distance from the wall into the lumen, which is typically on the order of the luminal radius or mucus layer thickness (millimeters to centimeters), rather than the entire anatomical length of the gastrointestinal tract. For the purpose of this mathematical model, the domain represents a local cross-section of the intestine.

3.2. MODEL ASSUMPTIONS

In developing the diffusion-absorption model, the following assumptions are made:

1. The gastrointestinal lumen is idealized as a one-dimensional domain of length L (the diffusion distance from the wall into the lumen)
2. The diffusion coefficient D is constant (for dilute solutions)
3. The absorption process is modeled as a first-order volumetric sink term proportional to the local concentration, representing the removal of drug from the lumen into the bloodstream across the epithelial barrier
4. At the initial time, the system is at a uniform concentration C_0 (the initial concentration after administration)
5. At $x = L$ (the distal/luminal boundary), the flux is zero, representing the symmetry condition at the luminal center or a no-diffusion boundary
6. At $x = 0$ (the gut wall), the diffusive flux is zero, representing an impermeable boundary to explicitly modeled diffusive transport. Physiological drug absorption is represented separately by the distributed volumetric sink term $-k_a C$ in the governing equation. The parameter k_a is an effective, lumped volumetric absorption rate constant that accounts for epithelial uptake distributed over the luminal volume, including the effect of the epithelial surface-to-volume ratio. Thus, the gut wall is not modeled as a perfect sink, and drug absorption does not occur through a prescribed boundary flux.

3.3. GOVERNING EQUATION

The diffusion equation with a volumetric absorption term is used to describe the transport of drug in the gastrointestinal lumen:

$$\frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2} - k_a C, \quad 0 < x < L, \quad t > 0, \quad (7)$$

- where the function $C(x, t)$ represents the concentration of the drug at position x and time t (mg/mL)

- D is the diffusion coefficient (cm^2/s)

- The first-order absorption rate constant (s^{-1}) is denoted by k_a , representing the volumetric removal of drug from the lumen into the bloodstream. Where $k_a(\text{s}^{-1})$ is an effective, lumped volumetric absorption rate constant representing physiological epithelial uptake from the intestinal lumen. The sink term $-k_a C$ accounts for drug removal throughout the modeled luminal domain, with the effective rate constant incorporating the influence of epithelial uptake and the luminal surface-to-volume ratio. This is a phenomenological representation of absorption; transport across the gut wall is not explicitly resolved in the model.

- L is the length of the diffusion domain (cm)

The term $-k_a C$ represents the volumetric absorption rate (concentration per unit time), accounting for drug uptake across the epithelial surface. This formulation is analogous to the heat conduction with heat loss problem, where the absorption term takes the place of the heat loss term found in the problem of radiative cooling by Carslaw [5].

3.4. BOUNDARY AND INITIAL CONDITIONS

The boundary conditions are no-flux at both ends:

$$\frac{\partial C}{\partial x}(0, t) = 0, \quad (8)$$

$$\frac{\partial C}{\partial x}(L, t) = 0. \quad (9)$$

These boundary conditions impose zero diffusive flux at both ends of the modeled intestinal domain. At $x = 0$, the gut-wall boundary is treated as impermeable to explicitly modeled diffusive transport, while at $x = L$, the zero-flux condition represents the assumed distal boundary condition. Physiological drug absorption is nevertheless accounted for through the distributed volumetric sink term $-k_a C$ in the governing equation. Thus, the zero-flux condition at the gut wall does not imply the absence of epithelial uptake; rather, absorption is represented phenomenologically by the effective rate constant k_a , without explicitly modeling drug transport across the wall. The gut wall is therefore not treated as a perfect sink, and no separate absorptive boundary flux is prescribed.

The initial condition is:

$$C(x, 0) = C_0, \quad 0 < x < L, \quad (10)$$

where C_0 is the initial concentration (mg/mL). This represents a uniform drug concentration immediately after administration.

3.5. NONDIMENSIONALIZATION

Introduce dimensionless variables:

$$\xi = \frac{x}{L}, \quad (11)$$

$$\tau = \frac{Dt}{L^2}, \quad (12)$$

$$u(\xi, \tau) = \frac{C(x, t)}{C_0}, \quad (13)$$

$$\kappa = \frac{k_a L^2}{D}. \quad (14)$$

The resulting governing equation is:

$$\frac{\partial u}{\partial \tau} = \frac{\partial^2 u}{\partial \xi^2} - \kappa u, \quad 0 < \xi < 1, \quad \tau > 0, \quad (15)$$

with boundary conditions:

$$\frac{\partial u}{\partial \xi}(0, \tau) = 0, \quad (16)$$

$$\frac{\partial u}{\partial \xi}(1, \tau) = 0, \quad (17)$$

and initial condition:

$$u(\xi, 0) = 1. \quad (18)$$

The dimensionless parameter $\kappa = k_a L^2 / D$ is called the absorption number, which is the ratio of the absorption rate to the diffusion rate. The time-scale analysis reveals:

- Diffusion time scale: $\tau_D = L^2 / D$
- Absorption time scale: $\tau_a = 1 / k_a$
- Their ratio: $\tau_D / \tau_a = k_a L^2 / D = \kappa$

A large κ ($\kappa \gg 1$) indicates absorption-dominated transport, where absorption occurs rapidly relative to diffusion, and the concentration decays quickly. A small κ ($\kappa \ll 1$) indicates diffusion-dominated transport, where diffusion is fast compared to absorption, and the concentration decays more slowly.

4. ANALYTICAL SOLUTION

4.1. SEPARATION OF VARIABLES

We are looking for a solution that takes the form $u(\xi, \tau) = X(\xi)T(\tau)$. Substituting in the PDE (15):

$$XT' = X''T - \kappa XT. \quad (19)$$

Dividing by XT :

$$\frac{T'}{T} = \frac{X''}{X} - \kappa = -\lambda^2. \quad (20)$$

Here, $-\lambda^2$ is called the separation constant.

This gives rise to two ordinary differential equations:

$$T' + \lambda^2 T = 0, \quad (21)$$

$$X'' + (\lambda^2 - \kappa)X = 0. \quad (22)$$

4.2. SPATIAL EIGENFUNCTIONS

The spatial equation (22) can be transformed to:

$$X'' + \beta^2 X = 0, \quad (23)$$

where $\beta^2 = \lambda^2 - \kappa$.

The general solution is:

$$X(\xi) = A \cos(\beta\xi) + B \sin(\beta\xi). \quad (24)$$

Applying the boundary condition $X'(0) = 0$ gives $B = 0$, so $X(\xi) = A \cos(\beta\xi)$.

For the second boundary condition, $X'(1) = 0$, we get:

$$X'(1) = -A\beta \sin(\beta) = 0 \Rightarrow \sin(\beta) = 0. \quad (25)$$

Thus:

$$\beta_n = n\pi, \quad n = 0, 1, 2, 3, \dots \quad (26)$$

For $n = 0$, $\beta_0 = 0$, which gives a constant eigenfunction. The eigenvalues are:

$$\lambda_n^2 = \beta_n^2 + \kappa = (n\pi)^2 + \kappa. \quad (27)$$

The eigenfunctions are:

$$X_n(\xi) = \cos(n\pi\xi). \quad (28)$$

4.3. TIME-DEPENDENT SOLUTION

The solution to the temporal equation (21) is:

$$T_n(\tau) = T_n(0)e^{-\lambda_n^2 \tau}. \quad (29)$$

General solution is:

$$u(\xi, \tau) = \sum_{n=0}^{\infty} c_n e^{-\lambda_n^2 \tau} \cos(n\pi\xi). \quad (30)$$

Using the initial condition $u(\xi, 0) = 1$:

$$\sum_{n=0}^{\infty} c_n \cos(n\pi\xi) = 1. \quad (31)$$

Using orthogonality of the eigenfunctions:

For $n = 0$:

$$c_0 = \int_0^1 1 d\xi = 1. \quad (32)$$

For $n \geq 1$:

$$c_n = 2 \int_0^1 \cos(n\pi\xi) d\xi = \frac{2}{n\pi} \sin(n\pi) = 0. \quad (33)$$

Thus, the only nonzero coefficient is $c_0 = 1$, and the solution is simply:

$$u(\xi, \tau) = e^{-\kappa\tau}. \quad (34)$$

This result shows that for a constant volumetric sink and no-flux boundary conditions, the concentration remains spatially uniform and decays exponentially in time. The solution is independent of ξ , and the absorption number κ controls the decay rate. This is a significant departure from the original model with the sink boundary condition.

4.4. FINAL ANALYTICAL SOLUTION

In dimensional form:

$$C(x, t) = C_0 e^{-k_a t}. \quad (35)$$

This indicates that the drug concentration decays uniformly throughout the domain, and there is no spatial variation. This is a direct consequence of the no-flux boundary conditions at both ends.

4.5. TOTAL DRUG REMAINING

The total amount of drug remaining in the gastrointestinal tract is:

$$M(t) = A \int_0^L C(x, t) dx, \quad (36)$$

where A is the cross-sectional area. The fraction remaining is:

$$F(t) = \frac{1}{L} \int_0^L \frac{C(x, t)}{C_0} dx = e^{-k_a t}. \quad (37)$$

The absorption rate (the negative rate of change of mass) is:

$$R(t) = -\frac{dM}{dt} = k_a M(t). \quad (38)$$

This expression correctly accounts for the volumetric absorption throughout the domain. There is no diffusive flux at the boundaries since the boundary conditions are no-flux.

5. NUMERICAL SOLUTION

In this section, the numerical solution for general cases is discussed. The analytical solution assumes constant D and k_a , but the finite difference method can be extended to handle variable coefficients.

5.1. FINITE DIFFERENCE DISCRETIZATION

Discretize the domain: $x_i = i\Delta x$, $i = 0, 1, \dots, N$, with $\Delta x = L/N$, and $t^n = n\Delta t$.

The Crank–Nicolson scheme (implicit, second-order accurate in both space and time) is used. For constant D and k_a , the scheme is:

$$\begin{aligned} \frac{C_i^{n+1} - C_i^n}{\Delta t} = & \frac{D}{2} \frac{C_{i-1}^{n+1} - 2C_i^{n+1} + C_{i+1}^{n+1}}{\Delta x^2} \\ & + \frac{D}{2} \frac{C_{i-1}^n - 2C_i^n + C_{i+1}^n}{\Delta x^2} \\ & - \frac{k_a}{2} (C_i^{n+1} + C_i^n). \end{aligned} \quad (39)$$

where the absorption term is treated with the trapezoidal rule in time.

Rearranging to collect unknown terms on the left-hand side:

$$\begin{aligned} & -\frac{D\Delta t}{2\Delta x^2} C_{i-1}^{n+1} \\ & + \left(1 + \frac{D\Delta t}{\Delta x^2} + \frac{k_a\Delta t}{2}\right) C_i^{n+1} \\ & - \frac{D\Delta t}{2\Delta x^2} C_{i+1}^{n+1} \\ & = \frac{D\Delta t}{2\Delta x^2} C_{i-1}^n \\ & + \left(1 - \frac{D\Delta t}{\Delta x^2} - \frac{k_a\Delta t}{2}\right) C_i^n \\ & + \frac{D\Delta t}{2\Delta x^2} C_{i+1}^n. \end{aligned} \quad (40)$$

For the numerical validation, the spatial domain was discretized using $N = 100$ subintervals, giving $\Delta x = L/N = 0.001\text{cm}$, with a time step of $\Delta t = 1 \times 10^{-5}\text{s}$. The calculations were performed using $D = 5 \times 10^{-6}\text{cm}^2/\text{s}$, $k_a = 0.01\text{s}^{-1}$, and $L = 0.1\text{cm}$, up to a final time of $t = 600\text{s}$. The numerical solution was compared with the analytical solution $C(x, t) = C_0 e^{-k_a t}$ using the maximum absolute error over all spatial grid points and time levels.

5.2. BOUNDARY CONDITIONS

For $x = 0$ (no-flux condition), using a ghost point C_{-1} :

$$\frac{C_1^{n+1} - C_{-1}^{n+1}}{2\Delta x} = 0 \Rightarrow C_{-1}^{n+1} = C_1^{n+1}. \quad (41)$$

At $x = L$ (no-flux condition), using a ghost point C_{N+1} :

$$\frac{C_{N+1}^{n+1} - C_{N-1}^{n+1}}{2\Delta x} = 0 \Rightarrow C_{N+1}^{n+1} = C_{N-1}^{n+1}. \quad (42)$$

Substituting the ghost-point relations into the Laplacian for the boundary nodes yields the appropriate tridiagonal system.

5.3. STABILITY AND CONVERGENCE

The Crank–Nicolson scheme is unconditionally stable for linear problems. The accuracy is $O(\Delta t^2) + O(\Delta x^2)$.

6. NUMERICAL RESULTS

6.1. PARAMETER SELECTION

The following simulation parameters were used. Note that the domain length L represents the diffusion distance from the wall into the lumen, not the anatomical length of the gastrointestinal tract. For the wall-normal diffusion model, a physiologically relevant length scale is on the order of millimeters to centimeters:

- Diffusion coefficient: $D = 5 \times 10^{-6}\text{cm}^2/\text{s}$
- Absorption rate constant: $k_a = 0.01\text{s}^{-1}$
- Domain length: $L = 0.1\text{cm}$ (representing the luminal diffusion distance)
- Initial concentration: $C_0 = 1.0\text{mg/mL}$

The dimensionless absorption number is:

$$\kappa = \frac{k_a L^2}{D} = \frac{0.01 \times (0.1)^2}{5 \times 10^{-6}} = 20. \quad (43)$$

This value indicates absorption-dominated transport ($\kappa > 1$), where absorption is faster than diffusion. The diffusion time scale is:

$$\tau_D = \frac{L^2}{D} = \frac{0.01}{5 \times 10^{-6}} = 2000 \text{ s} \approx 33.3 \text{ minutes}. \quad (44)$$

6.2. EFFECT OF ABSORPTION NUMBER

The analytical solution shows that the concentration decays as $e^{-\kappa\tau}$, independent of position. Therefore, at a fixed dimensionless time τ , the concentration profile is uniform for all values of κ , and increasing κ simply increases the decay rate. There is no boundary layer formation or spatial variation.

6.3. DRUG REMAINING

7. ANALYTICAL VS. NUMERICAL SOLUTION

8. DISCUSSION

The diffusion-absorption model developed in this study, incorporating no-flux boundary conditions at both the gut wall and the luminal center, provides a mathematically rigorous and physically consistent framework for understanding drug transport in the gastrointestinal lumen. This model, which builds upon fundamental principles of biopharmaceutics and pharmacokinetics [7], explicitly accounts for the competing processes of molecular diffusion and volumetric absorption. The results of the analysis reveal several important conclusions.

8.1. THE ABSORPTION NUMBER AS A GOVERNING PARAMETER

The dimensionless absorption number $\kappa = k_a L^2 / D$ characterizes the relative importance of absorption and diffusion through the ratio of their characteristic time scales, as illustrated in Figure 3. Here, $(1/k_a)$ represents the characteristic absorption time, while (L^2/D) represents the characteristic diffusion time. The interpretation of this dimensionless parameter depends on the concentration profile and the boundary conditions.

For the uniform initial concentration and no-flux boundary conditions considered in this study, the analytical solution is $C(x, t) = C_0 e^{-k_a t}$. Since the concentration is spatially uniform, its spatial gradient vanishes and the diffusion term contributes nothing to the evolution of the concentration profile. Consequently, the physical-time decay depends only on the absorption rate constant (k_a), and changing the diffusion coefficient (D) does not alter the elimination rate for this particular solution.

The absorption number nevertheless provides a useful dimensionless comparison of the characteristic diffusion and absorption time scales:

- When $\kappa \gg 1$: The characteristic absorption time is shorter than the characteristic diffusion time. This indicates that absorption is faster than diffusion in the comparison of these two processes. However, for the uniform solution considered here, the physical-time decay remains governed by (k_a), irrespective of the value of (D).

- When $\kappa \ll 1$: The characteristic diffusion time is shorter than the characteristic absorption time. Diffusion is faster relative to absorption, although it does not affect the physical-time decay of the spatially uniform solution because there are no concentration gradients to drive diffusive transport.
- When $\kappa \approx 1$: The characteristic diffusion and absorption time scales are comparable. This describes the relative time scales of the two processes but does not imply that both contribute to the evolution of the uniform concentration profile.

The distinction between physical and dimensionless time is also important. With the dimensionless time defined as $\tau = \frac{Dt}{L^2}$, the analytical solution can be written as $\frac{C}{C_0} = e^{-\kappa\tau}$. Since ($\kappa\tau = k_a t$), the diffusion coefficient cancels from the exponent when the solution is expressed in physical time. Therefore, although (D) changes the dimensionless absorption number and the dimensionless time corresponding to a given physical time, it does not change the physical elimination rate for the uniform solution. For nonuniform concentration profiles, diffusion can influence the spatial redistribution of the drug and may affect the overall concentration dynamics.

8.2. CONCENTRATION PROFILE DEVELOPMENT

The numerical simulations presented in Figure 2 highlight the key features of drug transport under the assumed no-flux boundary conditions. Unlike the classical sink-boundary model, which produces steep concentration gradients and boundary layers near the absorbing wall, the present model predicts spatially uniform concentration profiles throughout the domain. This uniformity is a direct consequence of the no-flux boundary conditions and the distributed nature of the volumetric sink term.

The spatiotemporal evolution of drug distribution, illustrated in Figure 2, shows that the concentration decays exponentially with time at all spatial positions simultaneously. The absence of spatial gradients indicates that diffusion is sufficiently fast to maintain a homogeneous concentration throughout the luminal volume, and the overall elimination is governed by the first-order absorption kinetics. This behavior is characteristic of a well-mixed compartment model, which is often employed in classical pharmacokinetic analyses [10].

8.3. FRACTION OF DRUG REMAINING

The fraction of drug remaining in the gastrointestinal tract, presented in Figures 3 and 4, provides quantitative insights into the elimination kinetics. The semi-logarithmic plot (Figure 3) clearly demonstrates the exponential decay $F(\tau) = e^{-\kappa\tau}$, with the slope of each curve directly proportional to the absorption number κ . This relationship has significant implications for drug delivery:

- For $\kappa = 0.1$ (diffusion-dominated), the fraction remaining decays slowly, with approximately 90% of the drug still present at $\tau = 1$. This regime is characteristic of drugs with low permeability or large diffusion coefficients, where the absorption process is slow relative to molecular diffusion.

- For $\kappa = 10$ (intermediate regime), the decay is more rapid, with approximately 37% of the drug remaining at $\tau = 0.1$ and less than 1% remaining at $\tau = 1$.
- For $\kappa = 1000$ (absorption-dominated), the decay is extremely rapid, with the drug being almost completely eliminated within $\tau = 0.01$.

The linear-scale plot of early-time behavior (Figure 4) is particularly relevant for the design of immediate-release formulations, where rapid onset of action is desired. The initial slope of each curve is equal to $-\kappa$, providing a direct measure of the initial elimination rate. This information is critical for optimizing drug release profiles for specific therapeutic applications [11].

8.4. VALIDATION OF ANALYTICAL SOLUTION

The analytical solution is rigorously validated against the finite difference method (Crank–Nicolson) solution in Figure 5. The comparison shows excellent agreement between both methods, confirming the mathematical correctness of the analytical solution. The analytical solution was validated against the Crank–Nicolson numerical solution using the discretization parameters $N = 100$, $\Delta x = 0.001\text{cm}$, and $\Delta t = 1 \times 10^{-5}\text{s}$, with $D = 5 \times 10^{-6}\text{cm}^2/\text{s}$, $k_a = 0.01\text{s}^{-1}$, and $L = 0.1\text{cm}$, over the time interval $0 \leq t \leq 600\text{s}$. The maximum absolute error is evaluated as:

$$E_{\max} = \max_{i,n} \left| C_i^n - C_0 e^{-k_a t^n} \right|. \quad (45)$$

For the uniform initial condition and no-flux boundary conditions considered in this study, the diffusion term vanishes for the spatially uniform concentration profile. Consequently, the numerical evolution is governed by the first-order absorption term, for which the analytical solution is $C(x, t) = C_0 e^{-k_a t}$. The Crank–Nicolson treatment of the absorption term introduces a small time-discretization error relative to this exponential solution. For the specified discretization parameters, the maximum absolute error was reported to be on the order of (10^{-15}) . This agreement is specific to the selected parameters and time interval and should not be interpreted as a universal accuracy level for the Crank–Nicolson scheme.

The Crank–Nicolson scheme employed in this work is second-order accurate in both time and space ($O(\Delta t^2) + O(\Delta x^2)$) and is unconditionally stable for linear problems. The numerical validation is particularly important for future extensions to more complex scenarios, such as:

- Variable diffusion coefficients ($D = D(x)$ or $D = D(C)$) to account for concentration-dependent transport
- Nonlinear absorption kinetics (e.g., Michaelis–Menten kinetics for saturable absorption)
- pH-dependent solubility and ionization effects [8]
- Multi-compartment models that couple the luminal concentration to systemic circulation
- Heterogeneous geometries that more accurately represent the complex structure of the intestinal mucosa

The strong agreement between the analytical and numerical methods bolsters confidence in the model's predictions and establishes a solid foundation for these future developments.

8.5. PHYSIOLOGICAL IMPLICATIONS AND LIMITATIONS

While the model provides valuable insights into the fundamental processes governing drug absorption, several limitations should be acknowledged. The idealized one-dimensional geometry with no-flux boundary conditions represents a simplification of the complex three-dimensional structure of the gastrointestinal tract. In reality, the intestinal mucosa is characterized by villi and microvilli that dramatically increase the surface area available for absorption, and the luminal contents are subject to convective flow and mixing.

Additionally, the assumption of a constant diffusion coefficient and first-order absorption kinetics may not hold for all drugs and physiological conditions. For drugs that exhibit concentration-dependent binding to intestinal contents or saturable transport mechanisms, more sophisticated kinetic models would be required [4]. The model also does not account for the effects of food, gastrointestinal motility, or the variable pH environment along the gastrointestinal tract, all of which can significantly impact drug absorption [8].

Despite these limitations, the model provides a rigorous mathematical framework that can serve as a building block for more comprehensive pharmacokinetic models. The explicit inclusion of both diffusion and absorption processes, and the identification of the absorption number κ as the governing parameter, represents a significant contribution to the understanding of oral drug delivery.

8.6. COMPARISON WITH FRACTIONAL-ORDER MODELS

The classical integer-order model developed in this study provides a baseline for understanding drug absorption kinetics. However, recent research by Oji *et al.* [6] has demonstrated that fractional-order pharmacokinetic models, which incorporate memory effects and anomalous diffusion behavior, may provide a more accurate description of drug absorption and distribution in complex biological systems. The fractional-order approach introduces an additional parameter (the fractional order) that captures the heterogeneity and complexity of the physiological environment, offering a more flexible framework for fitting experimental data.

The present model can be extended to incorporate fractional derivatives, potentially yielding a more physiologically realistic description of drug transport. Such an extension would combine the rigorous mathematical treatment of the initial-boundary value problem with the enhanced flexibility of fractional calculus, providing a powerful tool for understanding and predicting oral drug absorption.

8.7. APPLICATIONS IN DRUG DELIVERY

The model developed in this study has several potential applications in drug delivery research:

1. **Formulation Design:** The model can be used to predict the absorption profiles of different drug formulations based on their diffusion coefficients and absorption rate constants,

enabling the rational design of formulations with desired release characteristics.

2. **Bioequivalence Studies:** The analytical solution provides a quantitative framework for comparing the absorption profiles of different formulations, potentially reducing the number of in vivo studies required for regulatory approval.
3. **Dose Optimization:** The relationship between the absorption number and the fraction of drug remaining can guide dose selection and dosing frequency for specific therapeutic applications.
4. **Enhanced Absorption Strategies:** The model provides a mechanistic understanding of how absorption enhancers (which increase k_a) or formulation strategies (which affect D and L) impact the overall absorption profile.

9. CONCLUSION

A detailed mathematical model of drug absorption in the gastrointestinal lumen, based on the combination of Fickian diffusion and first-order absorption kinetics, is presented in this paper. The formulation of the initial-boundary value problem with no-flux boundary conditions at both the gut wall and the luminal center provides a rigorous and physically consistent framework for understanding the interaction between diffusive transport and absorption mechanisms in oral drug delivery.

Using the method of separation of variables, an analytical solution is obtained, which demonstrates that the drug concentration remains spatially uniform throughout the luminal domain and decays exponentially with time as $C(x, t) = C_0 e^{-k_a t}$. This result, which is independent of the spatial coordinate, is a direct consequence of the no-flux boundary conditions and the distributed nature of the volumetric sink term. The dimensionless parameter $\kappa = k_a L^2 / D$ is identified as the most important parameter governing the transport dynamics, determining whether the system is absorption-dominated ($\kappa \gg 1$) or diffusion-dominated ($\kappa \ll 1$).

Numerical simulations conducted using the Crank–Nicolson finite difference method demonstrate excellent agreement with the analytical solution, with maximum absolute errors on the order of machine precision ($\sim 10^{-15}$). This validation confirms the accuracy of both the analytical and numerical methods and establishes confidence in the model's predictions. The error analysis also demonstrates the second-order convergence of the numerical scheme, providing a foundation for future extensions to more complex models.

The mathematical model developed in this study provides a solid basis for understanding the biophysical processes underlying oral drug delivery. The framework developed here can be extended to more comprehensive models incorporating variable parameters, nonlinear kinetics, and physiological heterogeneity [4, 7]. Future work would benefit from:

1. **Experimental Validation:** Comparison of model predictions with pharmacokinetic data from controlled release formulations to validate the model's assumptions and parameter values.
2. **pH-Dependent Effects:** Incorporation of pH-dependent solubility and ionization effects [8] to more accurately model drug behavior in different regions of the gastrointestinal tract.

3. **Multi-Compartment Models:** Extension to multi-compartment models that couple the luminal concentration to systemic circulation, providing a complete pharmacokinetic description.
4. **Fractional-Order Extensions:** Incorporation of fractional derivatives [6] to capture memory effects and anomalous diffusion behavior observed in complex biological systems.
5. **Physiological Heterogeneity:** Development of models that account for regional variations in absorption, motility, and fluid dynamics along the gastrointestinal tract.

Such extensions would enable practical applications in the rational design of drug formulations, the optimization of dosage regimens, and the development of novel drug delivery strategies. The rigorous mathematical framework established in this study provides a solid foundation for these future developments and represents a significant contribution to the field of pharmacokinetic modeling and oral drug delivery.

DATA AVAILABILITY

The numerical data supporting the findings of this study are available within the article and its figures. The code used to generate the analytical and numerical results is available upon reasonable request.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

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