

Drug Release Kinetics in Biopolymer-based Drug Delivery Systems: A Study

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ABSTRACT

Biopolymer-based drug delivery systems (DDS) offer a promising avenue for achieving sustained and controlled drug release to targeted sites within the body, maximizing therapeutic response while minimizing adverse side effects. This study aims to elucidate the drug release kinetics from various DDS based on the different release mechanisms governing drug release, using mathematical models. The release kinetics depend on a complex interplay among the physicochemical properties of drugs, biopolymers, and their interactions within the matrix. Mathematical modeling is vital for explaining key mechanisms of drug release kinetics, enabling the systematic development of novel pharmaceutical products rather than relying on costly and time-consuming trial-and-error approaches. Therefore, understanding these mechanisms and their influence on release dynamics is essential for modifying drug release profiles to achieve optimal therapeutic efficacy. It also facilitates the rational design of DDS with customizable release kinetics, suitable for precision-targeted drug delivery. This is particularly important in cases such as neurological disorders, where the presence of the blood-brain barrier (BBB) severely hinders the efficacy of current drug delivery methods to the brain. This study outlines future research objectives and provides practical insights into medication release kinetics.

Contents

1. Introduction	3
2. Results and Discussions	4
2.1. Drug release mechanisms of various drug delivery systems(DDS)	4
2.2. Mathematical models based on various mechanisms	7
2.3 Comparative analysis of mathematical models for biopolymer-based DDS	11
2.4. Key findings across the drug release models and their implications for DDS design	13
3. Conclusions	15

References

1. Introduction

Biopolymer based drug delivery systems (DDS) are changing the prospects of controlled & sustained pharmaceutical administration. There are many polymers (**Table-1**) currently used in the development of controlled and sustained drug delivery systems, with biopolymers being among the most prominent. Their strong biocompatibility and biodegradability make them safe and flexible carriers that allow for targeted, localized drug delivery while minimizing systemic adverse effects and promising that medications remain at consistent therapeutic levels in the body. Unlike traditional delivery systems (such as pills, capsules, or syrups), where drug level in the body fluctuates very much and is difficult to maintain consistent release whereas biopolymer-based DDS offers a solution to that problem by allowing consistent, and extended drug release directly to particular areas.

Biopolymers' ability to transport and precisely distribute therapeutic components at a regulated rate enhances medicinal efficacy and safety. This control is especially important when dealing with sensitive or potent pharmaceuticals that require exact dosing to minimize negative effects. Thus, interest in biopolymers has increased tremendously as they have the potential to greatly increase bioavailability and stability, as well as open avenues for regulated, predictable release patterns, hence improving therapeutic results across a wide range of medical therapies.

As a result, understanding drug release mechanisms and the physicochemical processes that determine release rates is critical for designing and developing novel DDS. The three major release methods ([K.W. Leong & R. Langer, 1987](#)) that are associated with the release of pharmaceuticals from diverse drug delivery systems are diffusion-, swelling-, and erosion-controlled mechanisms, with some including both diffusion and swelling. However, there are other factors and events that impact the pace of drug diffusion or degradation-kinetics, including interactions like drug-polymer, drug-water, drug-receptors etc. Thus, a thorough understanding of the underlying mechanisms is required to produce a regulated and sustained medication release rate.

Table-1: Polymers that are currently being used to achieve controlled or sustained release.

Category	Polymers
Natural polymers	Alginates, Chitosan, Dextrans, Starches, Cyclodextrins (α , β , γ), Collagen, Gelatine, Cellulose, Gums (acacia, tragacanth, guar gum), Microbial polymers (polyhydroxybutyrate)
Synthetic polymers	Polylactic acid (PLA), Poly(lactic-co-glycolic acid) (PLGA), Polycaprolactone, Ethyl cellulose, Hydroxypropyl methyl cellulose (HPMC), Eudragits, Poly methyl methacrylate (PMMA), Polyvinyl Pyrrolidone (PVP)
Stimuli-responsive	pH-responsive polymers (e.g., Chitosan, Alginates, Polymethacrylate), Thermo-responsive Polymers (e.g., PNIPAM), Electric-responsive polymers (e.g., Sulfonated polystyrenes, Poly(thiophene)s), Ultrasound-responsive polymers (e.g., Ethylene-vinyl acetate), Light-responsive polymers (e.g., Modified poly(acrylamide)s)
Biodegradable polymers	Non-biodegradable polymers
Alginates, Chitosan, Dextrans, Starches, Cyclodextrins (α , β , γ), Collagen, Gelatine, Cellulose, Gums (Acacia, Tragacanth, Guar gum), Microbial Polymers (Polyhydroxybutyrate), Polylactic acid (PLA), Poly(lactic-co-glycolic acid) (PLGA), Polycaprolactone	Ethyl cellulose, Hydroxypropyl methyl cellulose (HPMC), Eudragits, Poly methyl methacrylate (PMMA), Polyvinyl Pyrrolidone (PVP)

2. Results and Discussions

2.1. Drug release mechanisms of various drug delivery systems(DDS)

Drug release mechanisms are crucial for designing effective drug delivery systems(DDS) and understanding release kinetics in depth. They are broadly classified into three types([K.W. Leong & R. Langer, 1987](#)): diffusion, swelling, erosion- controlled, and certain processes that combine them. Each kind represents a distinct physical or chemical process that governs the drug's release from its matrix or carrier over time. Discussed in **Table-2:**

Table–2:

Mechanisms	Description	Important factors	Application
A. Diffusion-Controlled Release	<p>Drug is released through diffusion driven by the concentration gradient explained by Fick's second law of diffusion. Occurs in two formats based on matrix region:</p> <ul style="list-style-type: none"> a) Matrix systems: Drug is dispersed throughout the polymer matrix and released as it diffuses through the network. b) Reservoir systems: Drug is stored in a core and released through a semipermeable membrane. 	<p>Polymers' features: Porosity, cross-linking, and molecular weight impact diffusion rate.</p> <p>Drug properties: Smaller, hydrophilic drugs diffuse more easily.</p> <p>Environmental factors: Temperature, pH, and solvents/fluids can alter diffusion rates.</p>	Applicable for sustained-release formulations, especially for applications needing slow, steady release (e.g., cancer).
B. Erosion-Controlled Release	<p>Drug is released as the biopolymer degrades over time via:</p> <ul style="list-style-type: none"> a) Surface Erosion: Surface erosion causes the microsphere's diameter to diminish as the polymer erodes at the matrix boundary. Layer-by-layer erosion from the outer surface provides a constant release rate. It follows zero-order kinetics. b) Bulk Erosion: It occurs when external fluid 	<p>Polymer Composition: Biodegradable polymers like PLGA and polyanhydrides erode, aiding release.</p> <p>Environmental factors: pH, temperature, and enzymes affect degradation rate.</p>	Ideal for implants and injectables where long term, steady delivery is desired without frequent dosing.

	penetrates a constant diameter microsphere, causing erosion of the polymer. Polymer matrix degrades throughout, causing faster release as structural integrity weakens. This follows first-order kinetics.		
C. Swelling-Controlled Release	It allows better control over drug release, especially when diffusivity in the polymer is minimal. Polymer swells upon exposure to biological fluids, creating channels for drug diffusion. It is non-fickian or anomalous in nature.	Polymer hydrophilicity: Hydrophilic polymers swell more readily, allowing quicker release. Cross-Linking Degree: Higher cross-linking restricts swelling and slows release. Environmental: Changes in pH and temperature can induce swelling in responsive polymers.	Useful for responsive or on demand delivery, especially for localized DDS in wound healing or cancer treatments.
D. Combined mechanisms	Integrates diffusion, erosion, and swelling, providing complex release profiles adaptable to therapeutic goals. Initial diffusion may be followed by erosion- or swelling-induced release for sustained delivery.	Polymer blend: Combining hydrophilic/hydrophobic polymers or using block copolymers creates a balance of swelling, diffusion, and erosion. External Stimuli: Stimuli responsive polymers (e.g., pH- or thermosensitive) control release under specific conditions.	Common in sophisticated DDS like multi-layered nanoparticles or implants targeting cancer, cardiovascular, and CNS.

2.2. Mathematical models based on various mechanisms

Mathematical modeling of drug release kinetics offer insights into mass transport and various chemical processes that are involved in drug delivery systems, as well as the impact of design parameters. Key mathematical models that help us understand drug release kinetics, characterizing how a medication is released from various delivery systems over time and aiding in the design and optimization of DDS include –

2.2.1. Zero-Order Kinetics

Zero-order kinetics implies that the drug release is constant, independent of concentration. It follows diffusion or erosion controlled mechanisms. This model is ideal for applications requiring steady drug levels, like in transdermal patches or implant-table devices, and it suits surface-eroding DDS where each layer erodes sequentially, releasing a constant amount of drug over time.

$$Q = Q_0 + k \cdot t$$

Q: drug released at time t

Q_0 : Initial drug concentration

k: Zero-order release rate constant

2.2.2. First-Order kinetics

First-order kinetics describes that the rate is proportional to the concentration of the drug present in the system. The drug release rate decreases over time as the drug concentration in the DDS decreases. It follows diffusion-controlled mechanisms. This model is common for systems where drug release slows as the concentration gradient between the DDS and surrounding medium decreases. Useful for oral dosage forms like tablets or capsules, where drug release slows down as the reservoir is depleted.

$$\frac{Q}{Q_0} = 1 - e^{-kt}$$

Q: Amount of drug released at time t

Q_0 : Initial drug concentration

k: First-order rate constant

2.2.3. Higuchi Model ([Higuchi, T., 1963](#))

The Higuchi model describes drug release from a matrix system and the release is diffusion-controlled. Release rate is proportional to the square root of time, indicating a decreasing rate of release over time as the drug near the surface of the matrix diffuses out. This model is commonly used for semi-solid and solid matrices, such as topical creams or hydrogels, where drug diffusion occurs through a porous structure. The total drug release,

$$Q = \sqrt{D \cdot t \cdot (2A - C_s) \cdot C_s}$$

Q: Drug release over time per unit area(planar system)

D: Diffusivity of the drug in the matrix.

A: Total drug amount in the matrix per unit volume.

C_s: Solubility of the drug in the matrix.

A more simplified version of this model,

$$Q = k \cdot t^{1/2}$$

Q: Cumulative amount of drug released at time t

K: Higuchi release constant(dependent on factors
like drug solubility and matrix properties)

22.4. Baker-Lonsdale Model ([Baker R.W. & Lonsdale H.S., 1974](#))

The Baker-Lonsdale model is used for spherical matrix systems where the drug release is governed by diffusion from a spherical particle. It corrects the Higuchi model for geometry, considering that the release from spherical matrices will vary based on surface area. Often applied to spherical microparticles and nanoparticles where diffusion governs drug release.

$$\left(1 - \left(1 - \frac{Q}{Q_\infty}\right)^{\frac{2}{3}}\right) Q_o = \frac{2}{3}kt$$

Q: Drug released at time t

Q_∞: Total amount of drug available for release

K: Baker-Lonsdale rate constant

2.2.5. Hixson-Crowell Model ([Hixson & Crowell, 1931](#))

The Hixson-Crowell model addresses DDS where drug release is controlled by changes in the surface area and particle size of the drug formulation. As the matrix erodes, the surface area available for release decreases, affecting the release rate. This model applies well to tablets or particles undergoing surface erosion. Its equation—

$$Q_0^{1/3} - Q^{1/3} = k \cdot t$$

Q: Drug remains at time t

Q₀: Initial drug concentration

k: constant for surface-volume relation

2.2.6. Korsmeyer-Peppas Model ([Korsmeyer R.W. et al., 1983](#))

The Korsmeyer-Peppas model is an empirical model that describes various release mechanisms (Fickian diffusion, non-Fickian transport, or swelling). The exponent n provides insight into the release mechanism, where n=0.5 indicates Fickian diffusion, n=1 suggests case II transport (swelling-controlled), and values between 0.5 and 1 indicate anomalous transport. Commonly used for polymeric systems, such as hydrogels and biodegradable implants.

$$\frac{Q}{Q_0} = k \cdot t^n$$

Q: Total drug released at time t

Q₀: Total amount of drug in the system

k: Korsmeyer-Peppas release rate constant

n: Diffusion exponent indicating the release mechanism

2.2.7. Peppas-Sahlin Model ([N.A. Peppas & J.J. Sahlin, 1989](#))

The Peppas-Sahlin model extends the Korsmeyer-Peppas model by accounting for both Fickian diffusion and polymer relaxation. The constants K₁ and K₂ distinguish between the two mechanisms, allowing for more accurate modeling of systems where both mechanisms contribute to release. Used for polymer matrices where both diffusion and swelling/relaxation are significant, such as in pH-sensitive or temperature-sensitive DDS.

$$\frac{Q}{Q_\infty} = K_1 \cdot t^m + K_2 \cdot t^{2m}$$

Q: Amount of drug released at time t

Q_∞ : Total amount of drug in the system

K₁, K₂: Constants for Fickian and relaxation mechanisms

m: Exponent indicating release type

2.2. 8. Hopfenberg Model ([Hopfenberg & H. B., 1976](#))

The Hopfenberg model describes drug release from surface-eroding systems with different geometries. The exponent n varies based on geometry (1 for slabs, 2 for cylinders, and 3 for spheres), allowing for geometry-specific predictions. Typically applied to surface-eroding polymers like polyanhydrides, often used in implants.

$$\frac{Q}{Q_\infty} = 1 - \left[1 - \frac{k \cdot t}{C_L \cdot a} \right]^n$$

Q: Cumulative amount of drug released at time t

Q_∞ : Total amount of drug to be released

k: Release rate constant(zero-order)

n: Exponent indicating geometry

C_L :initial drug loading throughout the system,

a:system's half-thickness (like, radius for a sphere or cylinder)

2.2.9. Gompertz Model

The Gompertz model is a sigmoidal model often used for controlled release systems exhibiting an initial lag phase, followed by an acceleration phase, and finally a plateau phase. It is effective for characterizing delayed release profiles. Applied in systems where drug release follows a growth pattern, useful for pulsatile or on-demand release systems. ([Sheilu Chang Ed, 2003](#))

$$\frac{Q}{Q_0} = e^{\alpha e^{\beta \ln(t)}}$$

Q: Amount of drug released at time t

Q_0 : Initial drug amount

α, β : Model parameters describing growth rates

2.2. 10. Lao Model (Lao et al., 2008)

Lao and his colleagues developed a combined mathematical model that incorporates numerous drug release mechanisms such as burst release, diffusion, and degradation, as well as multiple biodegradable polymers such as PLGA and PCL. The model development process included forecasting the release kinetics of each material component. One model was built for pure PCL films, with the first term indicating the burst phase and the second depicting diffusion-controlled release, but no degradation terms. The PLGA model accounts for all three processes. The total fraction of drug release in each case –

$$\left. \frac{M_t}{M_\infty} \right|_{\text{PLGA}} = \phi_{b,\text{PLGA}} [1 - \exp(-k_{b,\text{PLGA}} t)] + \phi_{r,\text{PLGA}} [\exp(k_{r,\text{PLGA}}(t - t_{b,\text{PLGA}})) - 1] + \phi_{d,\text{PLGA}} \left[1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2 \pi^2} \exp\left(-\frac{D_{\text{PLGA}}(2n+1)^2 \pi^2 (t - t_{r,\text{PLGA}})}{4l^2}\right) \right]$$

In case of PLGA, it is the total of the drug release resulting from the initial burst, diffusion-controlled release, and degradation-controlled release.

$$\left. \frac{M_t}{M_\infty} \right|_{\text{PCL}} = \phi_{b,\text{PCL}} [1 - \exp(-k_{b,\text{PCL}} t)] + \phi_{d,\text{PCL}} \left[1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2 \pi^2} \exp\left(-\frac{D_{\text{PCL}}(2n+1)^2 \pi^2 (t - t_{r,\text{PCL}})}{4l^2}\right) \right]$$

For PLC, total drug release is the sum of release due to initial burst and diffusion controlled release.

$$\left. \frac{M_t}{M_\infty} \right|_{\text{combined}} = \left. \frac{M_t}{M_\infty} \right|_{\text{PCL}} + \left. \frac{M_t}{M_\infty} \right|_{\text{PLGA}}$$

It's the total functional drug release in case of polymeric blend of PLGA and PLC

2.3 Comparative analysis of mathematical models for biopolymer-based DDS

A comparison(Table-3) has been made among various mathematical models based on different drug release mechanisms, including mechanistic models (which account for physicochemical phenomena involving chemical reaction processes and diffusional mass transfer) and empirical models (which do not account for complex physicochemical phenomena and are typically developed for systems that follow zero-order kinetics)

(Arifin et al., 2006)

Table-3: Comparative analysis of various mathematical models

Model	Equation	Mechanism	Limitations
Zero-order	$Q = Q_o + k*t$	Diffusion or Erosion-Controlled	Limited to systems with constant release rates; not suitable for all matrices
First-order	$\frac{Q}{Q_o} = 1 - e^{-kt}$	Diffusion-Controlled	Concentration-dependent; release rate decreases over time
Higuchi	$Q = k * t^{1/2}$	Diffusion-Controlled	Only applies to systems with homogeneous drug distribution; assumes planar geometry
Baker-Lonsdale	$(1 - (1 - \frac{Q}{Q_\infty})^{2/3}) \frac{Q}{Q_o} = \frac{2}{3} k * t$	Diffusion-Controlled in spherical matrix systems	Assumes spherical geometry; complex mathematical form
Hixson-Crowell	$Q_o^{1/3} - Q^{1/3} = k * t$	Erosion-Controlled (typically bulk erosion)	Assumes uniform particle size; not suitable for all particle systems
Korsmeyer-Peppas	$\frac{Q}{Q_o} = k * t^n$	Diffusion, Swelling, or Diffusion + Swelling	Limited to the first 60% of drug release; n-value interpretation may vary with system geometry
Peppas-Sahlin	$\frac{Q}{Q_\infty} = K_1 * t^m + K_2 * t^{2m}$	Combination of Diffusion and Swelling	Requires fitting of multiple parameters; complex interpretation
Hopfenberg	$\frac{Q}{Q_\infty} = \frac{1 - (1 - k * t / C_L * a)^n}{1 - (1 - k * t / C_L * a)^n}$	Erosion-Controlled	Geometry-dependent; assumes erosion dominates release
Gompertz model	$\frac{Q}{Q_o} = e^{\alpha e^{\beta \ln(t)}}$	Complex, Often Swelling or Diffusion-Limited Growth	Non-linear behaviour; best suited for systems with slow initial release

2.4. Key findings across the drug release models and their implications for DDS design

A. Early vs. Late release

Rapid Initial Release: Models such as First-Order, Higuchi, and Hixson-Crowell have a high initial release rate that diminishes with time. This is commonly known as "burst release," in which a considerable percentage of the medication is released fast, followed by a slower, decreasing release rate. These profiles are useful for therapies that need a fast therapeutic impact, such as pain relief or anti-inflammatory medicines, where quick drug availability is preferable with some disadvantages such as, If a large dosage is administered too rapidly, the rapid initial release may result in adverse consequences. These models may not be suitable for chronic diseases that require consistent blood levels.

Sustained Release: Models like Zero-Order and Peppas-Sahlin provide a more controlled release pattern, with the medication being administered at a relatively constant rate throughout time. These kind-of release profiles are beneficial for pharmaceuticals that require long-term, consistent drug levels, such as in the case of hypertension, diabetes, or chronic pain treatments. This constant release lowers the frequency of dose and increases patient adherence. Although achieving zero-order release is difficult in reality since maintaining a constant rate sometimes necessitates complex materials or system designs, such as implanted devices.

B. Mechanism-specific release profiles:

Diffusion-controlled release: The Higuchi and Korsmeyer-Peppas models are typical of diffusion-driven release, in which the drug progressively diffuses out of the matrix. The release rate slows over time as the residual drug concentration within the matrix declines. This release mechanism is typically found in tablets and patches, where the medicine gently diffuses through the outer layer to reach the surroundings. This approach is useful for creating a moderate to slow release rate, which is suitable for topical treatments and some oral sustained-release systems.

Erosion-controlled release: Models such as Hopfenberg and Hixson-Crowell describe systems in which the drug release rate is affected by deterioration or erosion of the delivery medium (e.g., polymer matrix or particle surface).These profiles are appropriate for biodegradable implants or controlled- release particles that release pharmaceuticals

as they degrade. And, for the medications that require consistent release while also ensuring full degradation of the delivery device, such as some implants or injectables.

Swelling-controlled and multi-mechanism systems: Peppas-Sahlin and other complicated models take into consideration several processes (such as swelling, diffusion, and erosion) that might interact to influence drug release. They are useful in sophisticated systems where the release rate may be controlled by variables such as hydration or environmental cues. Hydrogels, for example, can be used to make wound dressings or eye drops because they swell in reaction to moisture and release medications by both diffusion and swelling.

C. Application suitability

1. Immediate-release vs. Sustained-release:

Immediate-release systems (such as the early stages of First-Order release) are appropriate for short-term therapies that require quick therapeutic effects. And,

Sustained-release systems (such as Zero-Order or controlled-release Peppas-Sahlin) are preferable in chronic illness treatment because they provide constant release to maintain steady-state medication levels, reducing dosage frequency and increasing patient adherence.

2. Design considerations for specific therapeutic needs

Threshold-based or sigmoidal release (e.g., Gompertz model): A sigmoidal profile is useful for treatments that need delayed or triggered release, such as medicines that activate at specific pH or temperature levels. The Gompertz model, with its sluggish start followed by an increasing release phase, represents this and is useful in biological systems that require a threshold or environmental trigger.

Surface Erosion for Localized or Implantable Systems: Hopfenberg models are beneficial for implantable systems because they allow for sustained drug release directly at the target location (for example, an erodible polymer implant at a tumour site). This reduces systemic exposure and distributes the medicine where it is most needed.

D. Challenges to achieving the ideal release:

1. Critical challenges like establishing zero-order release kinetics for achieving consistent therapeutic outcomes. Real drug delivery systems may use a variety of processes, necessitating hybrid models such as Peppas-Sahlin to better mimic actual release behaviour.

- 2.** Complex models may fit experimental data well but lack generalizability across different systems. Validation often requires extensive experimental data, which may not always be feasible or available.
- 3.** There are no generally applicable mathematical models for release kinetics in non-degradable or degradable polymer systems due to the complex nature of solute transport. The existing models appear to be material, drug, and formulation-specific. Before applying a model to experimental data, it's important to carefully review its applicability. This includes material structural characteristics, drug properties, delivery device dimensions and geometry, and any model assumptions or limitations.
- 4.** Choosing materials that correspond to the intended release mechanism is critical. For example, non-biodegradable polymers can be employed to create diffusion controlled releases while biodegradable polymers are appropriate for erosion-based release while careful engineering is required to regulate the erosion rate.

3. Conclusions

The current study conducts an in-depth analysis of multiple mathematical models, both empirical and mechanistic, to understand drug release kinetics based on distinct release mechanisms. The findings here provide significant insights into the design of new biopolymer-based drug delivery systems with potential future applications in targeted and sustained drug delivery to achieve optimal therapeutic efficacy in a variety of diseased conditions, where traditional drug delivery has been hopeless, particularly in the case of CNS drug delivery. However, the mathematical models provide valuable insights into drug release and serve as initial guides; their limitations in dealing with complex DDS such as—Over simplification of complex processes, lack of mechanistic insights and challenges in parameter estimation emphasize the need to look for other computational avenues, such as machine learning, to account for the complexity of real-world systems.

References

1. Arifin, D. Y., Lee, L. Y., & Wang, C. H. (2006). Mathematical modeling and simulation of drug release from microspheres: Implications to drug delivery systems. *Advanced Drug Delivery Reviews*, 58(12–13), 1274–1325. <https://doi.org/10.1016/j.addr.2006.09.007>
2. Baker, R. W., & Lonsdale, H. S. (1974). Controlled release of biologically active agents. *Plenum Press*.
3. Ford Versypt, A. N. (2013). Mathematical modeling of drug delivery from autocatalytically degradable PLGA microspheres: A review. *Journal of Controlled Release*.
4. Higuchi, T. (1963). Mechanism of sustained-action medication: Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *Journal of Pharmaceutical Sciences*, 52(12), 1145–1149. <https://doi.org/10.1002/jps.2600521210>
5. Hixson, A. W., & Crowell, J. H. (1931). *Ind. Eng. Chem.*, 23, 923.
6. Hopfenberg, H. B. (1976). Controlled release polymeric formulations. *American Chemical Society*.
7. Korsmeyer, R. W., Peppas, N. A., Gurny, R., Doelker, E., & Buri, P. (1983). Mechanisms of solute release from porous hydrophilic polymers. *International Journal of Pharmaceutics*, 15(1), 25–35. [https://doi.org/10.1016/0378-5173\(83\)90064-9](https://doi.org/10.1016/0378-5173(83)90064-9)
8. Leong, K. W., & Langer, R. (1987). Polymeric controlled drug delivery. *Advanced Drug Delivery Reviews*, 1, 199–233.
9. Lao, L., Venkatraman, S. S., & Peppas, N. A. (2008). Modeling of drug release from biodegradable polymer blends. *European Journal of Pharmaceutics and Biopharmaceutics*, 70(3), 796–803. <https://doi.org/10.1016/j.ejpb.2008.05.024>
10. Peppas, N. A., & Sahlin, J. J. (1989). A simple equation for the description of solute release. III. Coupling of diffusion and relaxation. *International Journal of Pharmaceutics*, 57(2), 169–172.
11. Chang, S. (Ed.). (2003). *Encyclopedia of biopharmaceutical statistics*. Informa HealthCare.