A Diffusion-based Model of Doxorubicin Release from Liposomes: Effects of Size and Membrane Permeability

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Received: 22nd July 2025; Revised: 21st August 2025; Accepted: 23rd August 2025

Abstract – *Liposomes are widely used as nanocarriers in cancer therapy due to their ability to encapsulate chemotherapeutic agents and modulate drug release. Among these, doxorubicin-loaded liposomes, such as Doxil®, have demonstrated enhanced safety and efficacy profiles. However, predicting the kinetics of drug leakage remains critical for optimizing liposome design and therapeutic performance. In this study, a first-order mathematical model based on Fick's law of diffusion was developed to predict the leakage kinetics of doxorubicin from liposomes. The model captures key behaviors, including the effects of liposome size and lipid composition on membrane permeability and leakage. Simulations show that lower permeability coefficients, associated with increased membrane rigidity, slow down drug leakage, whereas smaller liposomes exhibit faster leakage due to their higher surface-area-to-volume ratios. Despite its simplicity, the model successfully captures experimental trends, reproduces permeability coefficients on the same order of magnitude as those observed in other doxorubicin-loaded liposomal systems, and demonstrates robustness to minor structural variations. It serves as a practical tool for early-stage design of liposomal drug delivery systems and highlights the sensitivity of drug leakage to key formulation parameters.*

Keywords: *Diffusion equation; drug delivery; liposomes; drug release kinetics;.membrane permeability.*

1. Introduction

Liposomal drug delivery systems have become a cornerstone of nanomedicine, especially in oncology, by enhancing therapeutic efficacy, reducing systemic toxicity, and improving drug stability [1,2]. These nanoscale vesicles (Figure 1), composed of one or more lipid bilayers, can encapsulate both hydrophilic and hydrophobic drugs, thereby optimizing pharmacokinetics, biodistribution, and tissue-specific accumulation [3]. Doxorubicin, a widely studied anthracycline antibiotic, exerts potent antitumor effects through DNA intercalation, topoisomerase II inhibition, and reactive oxygen species generation, ultimately inducing apoptosis [4,5]. Encapsulation within liposomes protects doxorubicin from premature degradation and off-target interactions while enabling targeted release in tumor tissues [6].

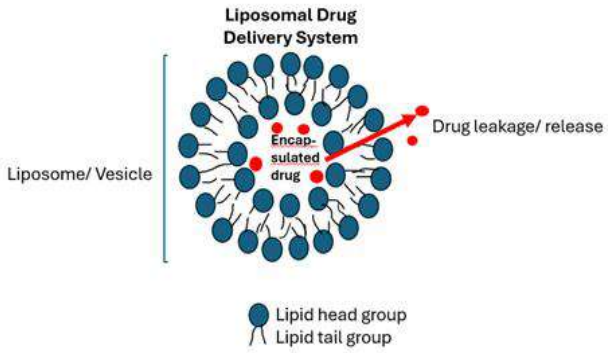

Figure 1. Liposomal drug delivery system.

The kinetics of drug release from liposomes critically influence therapeutic outcomes. Achieving controlled, site-specific drug release maximizes efficacy and minimizes adverse effects [7]. Drug translocation across lipid membranes occurs via active or passive mechanisms; passive diffusion driven by concentration gradients is the predominant route for small-molecule drugs leaking from liposomes [8].

Mathematical modeling and simulation have become indispensable for predicting liposomal drug release, enabling systematic evaluation of formulation parameters such as liposome size, membrane composition, and temperature prior to experimental validation [7]. First-order kinetic models, which assume drug release rates proportional to the remaining encapsulated drug concentration, are widely used and have been validated for various drugs including iodide [9], 5-fluorouracil [10], AR-67 [11], and doxorubicin [12]. However, many existing models rely on empirical fitting, limiting their predictive capacity outside experimental conditions.

To address this, the present study introduces a physically grounded mathematical model based on Fick's law of diffusion under ideal sink conditions. Liposomes are idealized as perfect spheres with drug release governed by passive diffusion across the lipid bilayer, producing an exponential decay in internal drug concentration dependent on permeability and liposome size.

Despite its simplicity, the model captures fundamental physical factors influencing drug release membrane permeability and liposome radius, and aligns well with experimental data. Permeability coefficients calculated for varying lipid compositions, modulating the ratio of distearoylphosphatidylcholine (DSPC) to dipalmitoylphosphatidylcholine (DPPC), agree with literature values [12,14]. Simulations reproduce observed trends including slower leakage with increased DSPC content, which enhances membrane rigidity and reduces permeability.

This diffusion-based model supports rational design of thermosensitive liposomal formulations, aiming to minimize drug leakage at physiological temperature (37 °C) while enabling rapid release under mild hyperthermia (~42 °C). By adjusting permeability and size, the model can simulate diverse release profiles to guide formulation optimization. Its mechanistic clarity and accessibility make it a valuable tool for early-stage development and screening.

In summary, this work advances liposomal drug delivery modeling by bridging theoretical principles with experimental validation, overcoming limitations of empirical approaches. The permeability coefficient, central to drug diffusion across lipid bilayers, directly impacts therapeutic concentration, duration, and side effects [15,16]. Factors affecting permeability include acyl chain length and saturation: longer saturated chains like DSPC (C18:0) promote tighter lipid packing and lower permeability, whereas shorter chains like DPPC (C16:0) increase membrane fluidity and permeability [17]. Saturation levels further influence membrane order, with unsaturated lipids disrupting packing and raising permeability [18,19].

2. Research Methods

To systematically investigate the influence of liposome size and lipid composition on doxorubicin leakage, we developed a mathematical model grounded in well-defined assumptions. The model represents each liposome as a perfect sphere with a fixed radius *R*, assuming no morphological changes occur during the leakage process. Drug release is modelled exclusively as passive diffusion of doxorubicin molecules through the lipid bilayer membrane. This diffusion process is governed by Fick's First Law, with a constant permeability coefficient *P* characterizing the rate of doxorubicin transport across the membrane. The permeability coefficient *P* is assumed to be independent of time and drug concentration, reflecting steady membrane properties during the leakage timeframe.

The model further assumes ideal sink conditions in the external medium, meaning the concentration of doxorubicin outside the liposome remains negligible and does not affect the diffusion gradient. Inside the liposome, doxorubicin is uniformly distributed initially, providing a well-mixed starting concentration. Together, these assumptions simplify the complex release dynamics, allowing us to derive an analytical expression for drug leakage kinetics. The core diffusion equation based on Fick's First Law used in this model is presented in Eq. (1).

$$J = -D\frac{dC}{dx} \tag{1}$$

where J is the flux of the drug, D is the diffusion coefficient of the drug in the bilayer, and $\frac{dC}{dx}$ is the concentration gradient across the bilayer.

Assume the bilayer has a thickness h. The flux across the bilayer can be approximated as:

$$J \approx -P(C_{in} - C_{out}) \tag{2}$$

where $P=D/h$ is the permeability coefficient, C_{in} is the drug concentration inside the liposome (near the inner surface), and C_{out} is the drug concentration outside the liposome (near the outer surface, assumed to be 0 under sink conditions).

The rate of change of the amount of drug inside is equal to the flux times the surface area of the liposome:

$$\frac{dM}{dt} = -J \cdot A = -P.C_{in} \cdot 4\pi R^2 \tag{3}$$

where M is the total amount of drug inside the liposome, and $A=4\pi R^2$ is the surface area.
The concentration inside the liposome is:

$$C_{in} = \frac{M}{V} = \frac{M}{\frac{4}{3}\pi R^3} \tag{4}$$

Substitute Eq. (4) into the mass balance Eq. (3) to get a differential equation for the concentration C_{in} as a function of time:

$$\frac{dC_{in}}{dt} = \frac{dM}{Vdt} = -3P\frac{C_{in}}{R} \tag{5}$$

The solution of Eq. (5) is:

$$C_{in}(t) = C_0 \exp(-\frac{3P}{R}t) \tag{6}$$

where C_0 is the initial drug concentration inside the liposome. The fraction of drug released is then

$$1 - \frac{C_{in}(t)}{c_0} \tag{7}$$

This mathematical model was computationally implemented using the Python programming language, taking advantage of the numerical efficiency of the NumPy library and the plotting functionality of Matplotlib. A linearly spaced array of time points was generated using NumPy, and vectorized calculations were performed to determine the time-dependent drug concentration within the liposomes. The leakage profile for each defined liposome radius was calculated using a first-order exponential decay function, derived from the analytical solution to Fick's law under the specified assumptions. The resulting fractional leakage values, representing the proportion of drug diffused out at each time step, were visualized using Matplotlib's pyplot module. Comparative line plots were generated with time on the x-axis and fractional doxorubicin leakage on the y-axis, enabling clear visualization of how liposome size influences the rate and extent of drug release.

Model validation was performed using experimental data from Lokerse et al. [14], who measured doxorubicin release from four liposomal formulations composed of varying molar ratios of short saturated DPPC (C16:0, C16:0) and long saturated DSPC (C18:0, C18:0), each containing 5 mol% DSPE-PEG2000. The tested compositions were DPPC:DSPC:DSPE-PEG2000 at 50:45:5 (Liposome A), 60:35:5 (Liposome B), 70:25:5 (Liposome C), and 80:15:5 (Liposome D).

Using our Fick's law-based model, we estimated the membrane permeability coefficient for each formulation by fitting the model to the reported liposome diameters and corresponding fractional leakage after 1 hour at 37 °C. We then investigated the effect of permeability by fixing the liposome diameter and varying the permeability coefficient, allowing its influence on release kinetics to be isolated. To illustrate this relationship, simulations were performed for two fixed diameters 82 nm (Liposome A2-D2) and 77 nm (Liposome A3-D3) using the permeability range estimated for Liposomes A–D.

Finally, to examine the effect of liposome size, we simulated leakage from two diameters: Liposome 1 with a diameter of 75 nm and Liposome 2 with a diameter of 140 nm, while keeping the membrane permeability coefficient constant at $P = 1\times10^{-14}$ m/s.

3. Results and Discussion

3.1. *Effect of permeability coefficient*

Table 1 is showing estimated permeability coefficients for different liposome formulations. The calculated permeability coefficients (Table 1) were on the order of 10^{-14} m/s, consistent with values reported for Doxil®—a clinically approved PEGylated liposomal doxorubicin formulation (HSPC:Cholesterol:DSPE-PEG2000, 56:39:5 molar ratio)—as well as other similar Doxil-like analogs [12].

Table 1. Estimated permeability coefficients for different liposome types.

Liposome Type	Liposome Size (nm) [14]	Fractional Leakage at 1 hour (%) [14]	Estimated *P* (m/s)
A	82	1	3.82×10^{-14}
B	80	1	3.72×10^{-14}
C	78	1	3.63×10^{-14}
D	77	8	2.97×10^{-13}

As expected, increasing DSPC content, due to its higher transition temperature ($T_m \approx 55$ °C vs. 41 °C for DPPC) and longer saturated tails, resulted in reduced bilayer fluidity and tighter packing, which significantly decreased permeability. This trend is clearly reflected in the permeability values calculated for Liposomes A through D. Interestingly, Liposome D, which contains the highest proportion of DPPC, showed the highest permeability coefficient, consistent with its relatively disordered membrane structure at physiological temperature.

These results demonstrate that, given reliable experimental drug release data, our model is capable of quantitatively estimating the permeability coefficient for liposomes of varying lipid compositions. This capability is valuable in rational liposome design, enabling researchers to predict how modifications in lipid makeup influence drug release rates, and to tailor delivery systems for specific therapeutic windows or drug release profiles.

Table 2 summarizes the simulated times required to achieve 50% and approximately 100% doxorubicin release for liposomes of fixed size, while Figure 2 illustrates the influence of the membrane permeability coefficient on the release profile under the same size constraint. The simulations were performed for two liposome diameters: 82 nm (Liposome A2–D2) and 77 nm (Liposome A3–D3). The permeability coefficients applied in these simulations correspond to previously estimated values for Liposomes A through D, representing variations in membrane composition and the associated differences in rigidity and permeability.

Table 2. Simulated time to 50% and ~100% doxorubicin release at fixed liposome size.

Liposome	Diameter (nm)	Permeability (m/s)	Time to 50% Release (h)	Time to ~100% Release (h)
A2	82	3.82×10^{-14}	68.88	915.32
B2	82	3.72×10^{-14}	70.74	939.92
C2	82	3.63×10^{-14}	72.49	963.23
D2	82	2.97×10^{-13}	8.86	117.73
A3	77	3.82×10^{-14}	64.68	859.51
B3	77	3.72×10^{-14}	66.42	882.61
C3	77	3.63×10^{-14}	68.07	904.49
D3	77	2.97×10^{-13}	8.32	110.55

They reveal a consistent trend: for a given liposome size, higher permeability coefficients lead to significantly faster doxorubicin release. For example, at a constant diameter of 82 nm, increasing the permeability from 3.63×10^{-14} m/s to 2.97×10^{-13} m/s reduces the time to 50% release from ~72 hours to just under 9 hours.

This finding reinforces the importance of accurate permeability characterization in the rational design of liposomal drug carriers. It also demonstrates the utility of our model in simulating and predicting release kinetics based on physicochemical parameters.

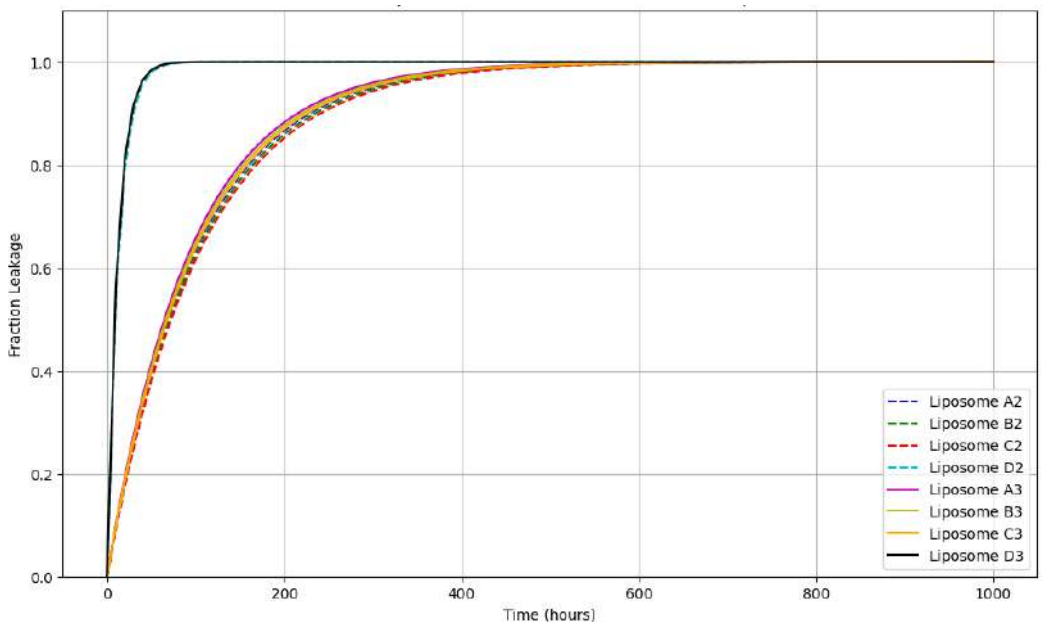

Figure 2. Effect of membrane permeability coefficient on doxorubicin release at fixed liposome size.

3.2. *Effect of liposome size*

Table 3 reports the fractional doxorubicin leakage at selected time points, while Table 4 presents the simulated time required to reach near-complete (100%) leakage. Figure 3 depicts the leakage profiles over a 3000-hour period. Together, these results demonstrate the model's ability to capture the influence of liposome size on drug release kinetics. The simulations compare two systems: Liposome 1, with a diameter of 75 nm, and Liposome 2, with a diameter of 140 nm, both evaluated under a constant membrane permeability coefficient of $P = 1\times10^{-14}$ m/s.

Table 3. Fractional doxorubicin leakage at specific time points.

Time (h)	Liposome 1 (%)	Liposome 2 (%)
24	14.37	7.98
240	78.80	56.44
336	88.60	68.76

Table 4. Time to achieve near complete (100%) doxorubicin leakage.

Liposome	Diameter (nm)	~100% Leakage Time (h)
1	75	1427.69
2	140	2665.03

From Tables 3 and 4, along with the simulation plot in Figure 3, we can see that the smaller liposome (75 nm) exhibited substantially faster drug release than the larger one (140 nm). This behavior is rooted in fundamental geometric principles.

Smaller liposomes have higher surface-area-to-volume (SA:V) ratios, which increase the area available for diffusion relative to the internal drug volume. For a spherical liposome, the surface area scales with the square of the radius ($4\pi r^2$), while the volume scales with the cube of the radius ($(4/3)\pi r^3$), resulting in a surface area-to-volume ratio that is inversely proportional to the radius ($1/r$). Additionally, drug molecules in smaller liposomes have shorter diffusion paths to traverse before reaching the membrane. Both effects accelerate release. Mathematically, for spherical liposomes undergoing passive diffusion, the release rate constant k is given by [9, 13, 15]:

$$k \propto \frac{P.A}{V} \alpha \frac{P}{r} \tag{8}$$

where: P is the permeability coefficient (m/s), A is the surface area, V is the internal volume, r is the radius of the liposome. Thus, smaller r results in a larger k, yielding faster release, even at constant permeability.

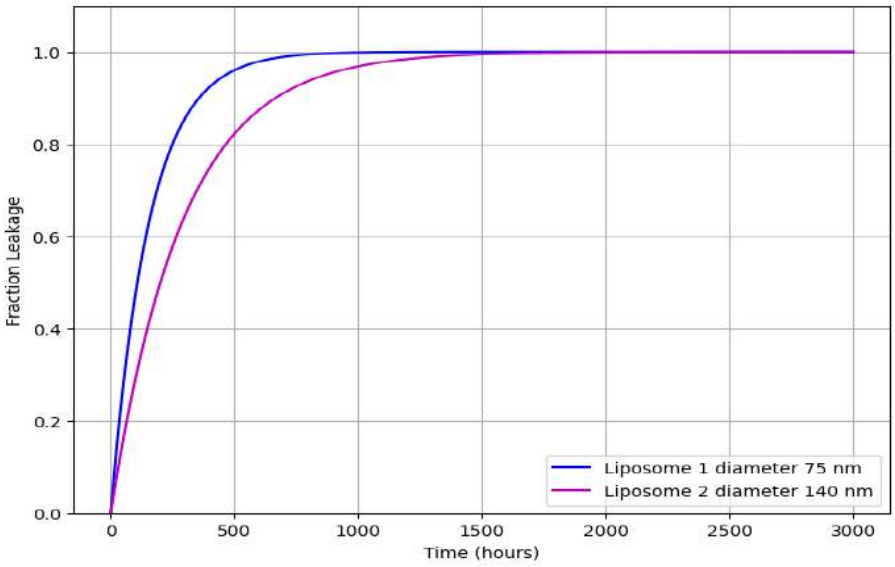

Figure 3. Fractional doxorubicin leakage over 3000 h.

This finding aligns with experimental observations. For instance, Nagayasu et al. [20-21] showed that daunorubicin-loaded liposomes composed of HEPC:Cholesterol:DCP (5:4:1) with 50 nm diameter released the drug gradually in circulation, while 100 nm liposome showed no drug release over 240 minutes.

Overall, our model confirms that liposome size is a critical determinant of drug release rate and provides a valuable framework for predicting and tuning liposomal performance in therapeutic contexts.

3.3. *Comparison with experimental liposome leakage data*

To further validate the predictive capability of our model, we incorporated experimental data reported by Lokerse et al. [14], utilizing both the liposome size and estimated permeability coefficients summarized in Table 1 to simulate the fractional release of doxorubicin. Table 5 and Figure 4 present the time-dependent leakage profiles over a 60-minute period for four different liposome formulations. Liposomes A–C, which share similar low permeability values ($P \approx 3.63–3.82 \times 10^{-14}$ m/s), exhibit markedly slower drug release compared to Liposome D ($P = 2.97 \times 10^{-13}$ m/s). This trend mirrors the experimental observations of Lokerse et al. [14], providing confidence in the model's ability to reproduce key behaviours associated with liposomal drug retention.

Table 5. Fractional doxorubicin leakage over 60 minutes.

Time (minutes)	Liposomes A–C (P = 3.63–3.82×10⁻¹⁴ m/s)	Liposome D (P = 2.97×10⁻¹³ m/s)
0	0.00	0.00
10	0.17	1.38
20	0.33	2.74
30	0.50	4.08
40	0.67	5.40
50	0.83	6.71
60	1.00	7.99

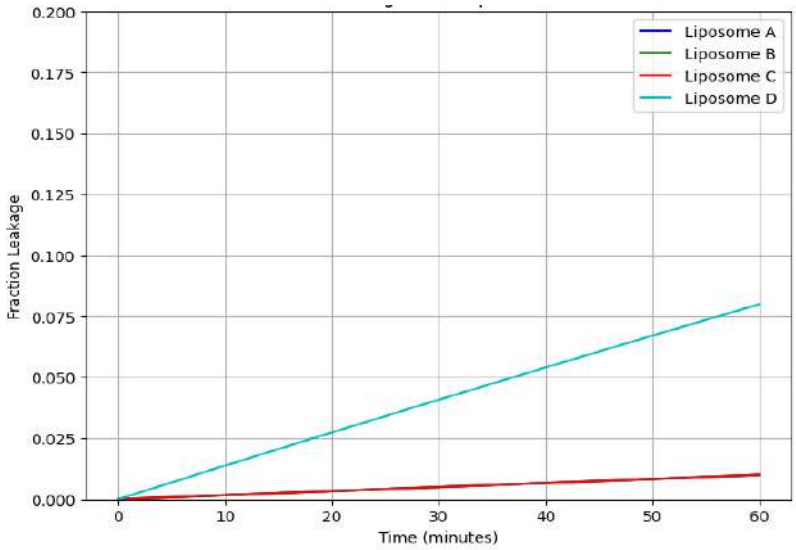

Figure 4. Fractional doxorubicin leakage over 60 minutes.

Furthermore, Table 6 and Figure 5 highlight the estimated time required for each formulation to reach 50% and 100% cumulative doxorubicin release. Liposome D releases its entire drug load in approximately 110 hours, while Liposomes A–C maintain encapsulated drug for substantially longer durations, requiring over 900 hours to fully release their contents. Notably, the time to 50% release is around 8.3 hours for Liposome D, compared to nearly 69 hours for Liposomes A–C, illustrating a near ninefold difference in leakage kinetics.

Table 6. Time to achieve 50% and 100% doxorubicin leakage.

Liposome Type	~50% Leakage (h)	~100% Leakage (h)
A	68.88	915.32
B	69.01	917.00
C	68.95	916.24
D	8.32	110.55

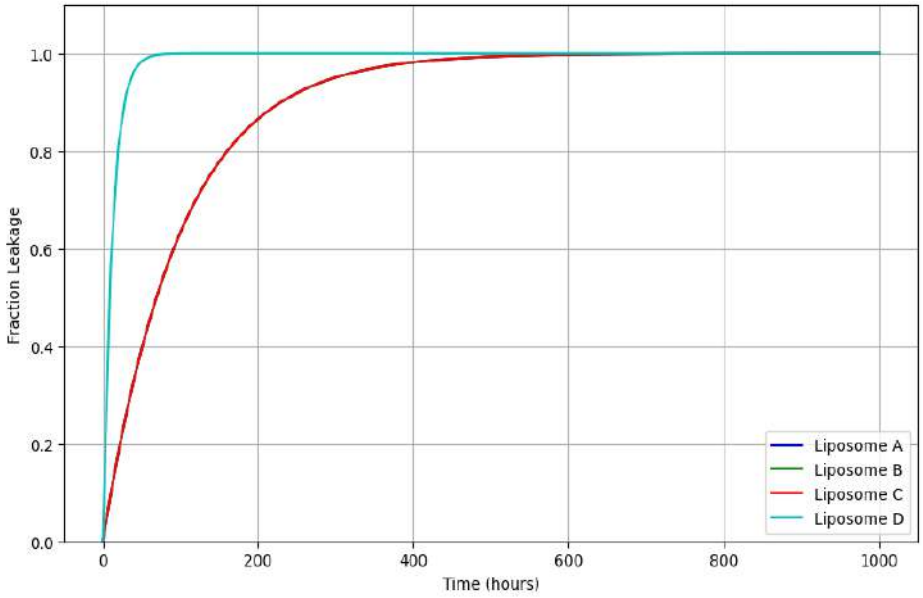

Figure 5. Fractional doxorubicin leakage over 1000 hours.

These outcomes reinforce the validity of the model and the central role of membrane composition in regulating drug permeability. As reported by Lokerse et al. [14], increasing the DSPC content from 25% to 45% in Liposomes A–C enhances membrane rigidity (bending modulus, κ) by promoting tighter lipid packing. This structural alteration yields lower permeability coefficients and results in slower drug release, despite only marginal differences in liposome size across the formulations. Accordingly, the release curves for Liposomes A–C are nearly superimposed, suggesting that, within this compositional window, the release kinetics are robust against minor physicochemical fluctuations. Such stability underscores the reliability of these liposomal constructs for drug delivery and affirms the utility of simplified diffusion-based models for predicting release behaviour in well-characterized systems.

Importantly, these findings support the design principles emphasized by Lokerse et al. [14], which prioritize minimal drug leakage at normothermic conditions (37 °C) and rapid, temperature-triggered release under mild hyperthermia (≈42 °C), a hallmark of thermosensitive liposomal (TSL) strategies. Model predictions further suggest that Liposomes A–C meet these design objectives effectively: at 37 °C, the estimated time to complete release exceeds 900 hours, indicating strong membrane integrity and minimal passive leakage, ideal for reducing systemic toxicity and prolonging circulation time. In contrast, Liposome D, which contains a higher proportion of DPPC (a lipid associated with looser packing and increased fluidity), demonstrates faster release kinetics and significantly higher permeability, potentially compromising its suitability for long-circulating applications unless used in a hyperthermic-triggered context.

Collectively, these simulations emphasize the therapeutic advantages of Liposomes A–C, particularly for oncology applications requiring prolonged circulation and site-specific, heat-triggered release. Their stability and predictable behaviour render them strong candidates for controlled delivery platforms, where maximizing drug bioavailability at the tumour site while minimizing off-target exposure is critical for achieving optimal therapeutic outcomes.

4. Conclusions

This study introduces a diffusion-based mathematical model for doxorubicin leakage from liposomes, grounded in Fick's law and first-order kinetics under ideal sink conditions. By incorporating key factors such as liposome size and membrane permeability, the model captures the main mechanisms of passive drug release and highlights the critical influence of lipid composition, particularly the DSPC to DPPC ratio on membrane rigidity and drug leakage. Simulations show that membrane composition, reflected in permeability changes, strongly affects release rates, while liposome size plays a lesser role when permeability is fixed. The model closely matches experimental data, accurately predicting permeability coefficients and drug retention times. Increased DSPC content significantly reduces leakage by enhancing membrane rigidity, prolonging drug release, whereas higher DPPC content leads to faster leakage. The model's robustness to small compositional changes supports its use for early formulation screening. Future improvements could include factors like temperature effects and non-sinking conditions to better mimic physiological environments. Overall, this model provides a reliable and practical tool for understanding and optimizing liposomal drug delivery systems.

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