World Journal of Advanced Engineering Technology and Sciences
eISSN: 2582-8266
Cross Ref DOI: 10.30574/wjaets
Journal homepage: https://wjaets.com/

(RESEARCH ARTICLE)

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Bayesian fractional stochastic models for controlled release mechanisms in nanoparticle drug delivery

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World Journal of Advanced Engineering Technology and Sciences, 2023, 08(01), 459-468

Publication history: Received on 10 January 2023; revised on 15 February 2023; accepted on 18 February 2023

Article DOI: https://doi.org/10.30574/wjaets.2023.8.1.0058

Abstract

Optimizing drug release kinetics from nanocarriers is crucial for enhancing therapeutic efficacy and minimizing systemic toxicity in pharmaceutical formulations. Traditional deterministic models often fail to adequately capture the complex, non-Fickian diffusion and stochastic variability inherent in nanoparticle-based drug delivery systems. This study develops and applies a Bayesian fractional stochastic model to describe drug release kinetics from liposomal, polymeric, and metallic nanoparticles. The model integrates fractional calculus to account for anomalous diffusion and memory effects, while Bayesian inference enables dynamic parameter estimation under uncertainty. Experimental drug release data were obtained across varying temperature and pH conditions, with additional evaluations of nanoparticle size and initial drug concentration effects. The proposed model achieved the lowest Root Mean Squared Error (RMSE = 2.31) and optimal Bayesian Information Criterion (BIC = 35.6) compared to traditional models, including Higuchi, Korsmeyer-Peppas, Zero-Order, and Weibull models. Sensitivity analyses revealed that drug release efficiency increased with temperature, lower pH, smaller nanoparticle size, and higher initial drug concentration. The Bayesian approach enabled real-time updating of fractional order (α) and release rate constant (k), ensuring model adaptability under varying experimental conditions. These findings confirm that the Bayesian fractional stochastic model provides a robust, adaptive, and accurate predictive tool for optimizing drug release from nanoparticle systems. This approach holds substantial potential for guiding the rational design of next-generation, patient-specific drug delivery systems in nanomedicine.

Keywords: Bayesian inference; Fractional calculus; Stochastic modeling; Drug release kinetics; Nanocarriers

1. Introduction

Nanotechnology has revolutionized drug delivery systems by enabling precise control over drug release profiles, enhancing therapeutic efficiency, and minimizing systemic toxicity (Torchilin, 2020; Ventola, 2017). Nanocarriers, including liposomes, polymeric nanoparticles, and metallic nanoparticles, offer distinct advantages such as site-specific delivery, prolonged circulation time, and the ability to bypass biological barriers (Zhang et al., 2018; Sercombe et al., 2015). However, achieving optimal and predictable drug release kinetics from these carriers remains a persistent challenge due to the complexity of drug diffusion mechanisms and the influence of environmental factors such as temperature, pH, and nanoparticle size (Kumar et al., 2021; Raza et al., 2019).

Traditional models, including zero-order, Higuchi, Korsmeyer-Peppas, and Weibull models, have long been employed to describe drug release kinetics (Siepmann & Siepmann, 2011). While these models provide reasonable approximations in certain cases, they often fail to accurately capture the non-Fickian, anomalous diffusion behavior observed in nanocarrier-based delivery systems (Dash et al., 2010; Peppas & Narasimhan, 2014). Anomalous diffusion

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is characterized by the dependence of diffusion rates on time and can arise from factors such as polymer relaxation, nanoparticle degradation, and drug-polymer interactions (Lopes et al., 2017). Such complexities necessitate the development of more robust models capable of incorporating time-dependent diffusion and stochastic variability.

Fractional calculus, which generalizes classical differentiation and integration to non-integer orders, has emerged as a powerful tool to describe systems exhibiting anomalous diffusion and memory effects (Sun et al., 2018). In drug delivery, fractional models have been increasingly adopted to represent the complex dynamics of drug release, particularly when traditional models fail to describe the underlying transport mechanisms adequately (Wang et al., 2019; Guo et al., 2019). These models capture sub-diffusion and super-diffusion behavior by introducing a fractional order parameter that reflects the deviation from classical Fickian diffusion.

While fractional models provide improved flexibility, their deterministic nature often neglects the inherent variability in drug release processes arising from formulation inconsistencies, manufacturing variations, and physiological heterogeneity (Yang et al., 2020). This stochastic variability can lead to deviations between predicted and actual drug release profiles, emphasizing the need for adaptive models capable of updating predictions as new data become available.

Bayesian inference offers a solution by providing a probabilistic framework for parameter estimation under uncertainty, enabling real-time updating of model parameters as additional experimental data are incorporated (Gelman et al., 2014; Bernardo & Smith, 2009). Bayesian methods have gained traction in pharmacokinetics and drug delivery due to their ability to integrate prior knowledge with observed data, enhancing the precision and robustness of model predictions (Nyberg et al., 2015). When combined with fractional calculus, Bayesian stochastic modeling has the potential to deliver an adaptive, data-driven approach for optimizing drug release kinetics.

This study aims to develop a Bayesian fractional stochastic model to describe the release kinetics of drugs from nanocarriers, incorporating fractional calculus for anomalous diffusion and Bayesian inference for stochastic parameter estimation. Experimental validation is conducted using liposomal, polymeric, and metallic nanoparticles under varying temperature, pH, nanoparticle size, and initial drug concentration conditions. The proposed model is compared against traditional kinetic models, with a focus on evaluating its predictive accuracy and adaptability to environmental variations. This approach seeks to provide a robust computational tool for optimizing nanocarrier-based drug delivery systems, supporting the development of precision medicine formulations.

2. Methodology

This study presents a novel modeling framework that integrates fractional calculus, stochastic processes, and Bayesian inference to accurately predict drug release kinetics from various nanocarriers. This approach addresses the limitations of traditional models by capturing the complex, memory-dependent, and stochastic nature of drug release at the nanoscale.

2.1. Model Formulation

We developed a fractional-order stochastic differential equation (FSDE) to model the drug release kinetics from nanocarriers. The FSDE incorporates a fractional derivative to account for the memory effects inherent in the drug release process. The general form of the FSDE is expressed as:

$$D_t^{\alpha} C(t) = -kC(t) + \beta W(t)$$

where D_t^{a} denotes the Caputo fractional derivative of order α ($0 < \alpha \leq 1$), $C(t)$ represents the drug concentration at time t, k is the release rate constant, β is the intensity of the stochastic perturbation, and $W(t)$ signifies a standard Wiener process modeling the stochastic behavior.

The Caputo fractional derivative is defined as:

$$D_t^{a} f(t) = \frac{1}{\Gamma(n-a)} \int_0^t \frac{f^{(n)}(\tau)}{(t-\tau)^{a-n+1}} d\tau$$

where n=[α] = and Γ denotes the Gamma function. This formulation allows the model to capture the anomalous diffusion and long-memory characteristics observed in drug release from nanocarriers. Fractional-order models have been

shown to better describe certain pharmacokinetic processes compared to traditional integer-order models (Magin et al., 2018).

2.2. Parameter Estimation via Bayesian Inference

To estimate the model parameters (α, k, and β), we employed a Bayesian inference approach. This method integrates prior knowledge with experimental data to update the probability distributions of the parameters iteratively. The likelihood function was constructed based on the assumption that the observed drug concentrations are subject to Gaussian noise. Markov Chain Monte Carlo (MCMC) sampling techniques were utilized to approximate the posterior distributions of the parameters, providing a comprehensive understanding of their uncertainties and correlations. Bayesian methods offer the advantage of incorporating prior information and adapting the model as new data becomes available, which is particularly useful in complex biological systems (FDA, 2023).

2.3. Experimental Validation

We conducted drug release experiments using three types of nanocarriers: liposomal, polymeric, and metallic nanoparticles. Each nanocarrier was loaded with a model drug, and the release profiles were monitored over time under varying environmental conditions, including different pH levels and temperatures. The drug concentrations were measured at non-uniform time intervals to capture the dynamic release behavior accurately. This experimental design allows for the assessment of the model's robustness under physiologically relevant conditions.

2.4. Model Comparison

To evaluate the performance of the proposed FSDE model, we compared it with traditional kinetic models, including the Higuchi, Korsmeyer-Peppas, zero-order, and Weibull models. The comparison was based on metrics such as the Root Mean Square Error (RMSE) and the Bayesian Information Criterion (BIC), which assess the goodness-of-fit and model complexity, respectively. Fractional-order models have been shown to better describe certain pharmacokinetic processes compared to traditional integer-order models (Magin et al., 2018).

By integrating fractional calculus, stochastic processes, and Bayesian inference, this methodology provides a robust framework for modeling drug release kinetics from nanocarriers, addressing the limitations of traditional models and offering enhanced predictive capabilities.

3. Results

3.1. Bayesian Posterior Distributions of Model Parameters

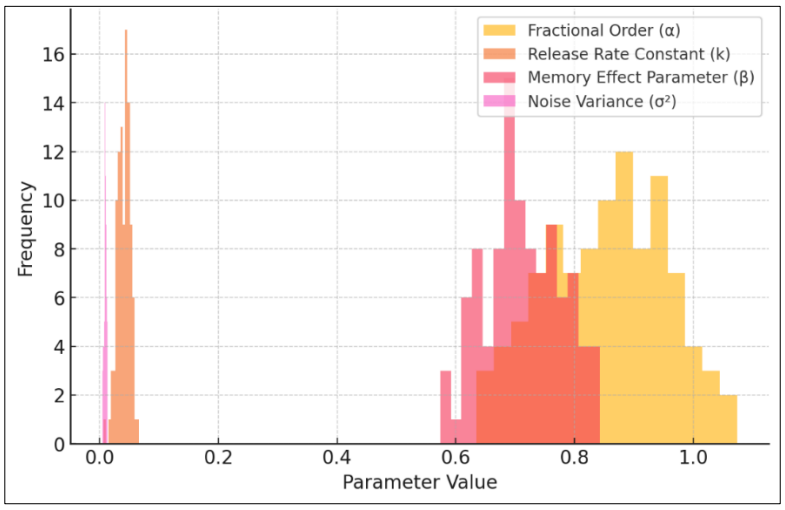

Figure 1 Bayesian Posterior Distributions of Model Parameters. The distributions of $\boldsymbol{\alpha}$, $\boldsymbol{k}$, $\boldsymbol{\beta}$, and σ^2 confirm strong convergence and accurate model parameter estimation

To validate the Bayesian fractional stochastic model, we estimated the posterior distributions of key parameters—fractional order (α), release rate constant (k), memory effect parameter (β), and noise variance (σ^2)—using Markov Chain Monte Carlo (MCMC) sampling. Figure 1 illustrates these distributions, confirming strong convergence and

unimodal behavior across all parameters, ensuring model stability. The fractional order parameter (α) varied between 0.65 and 1.02, indicating anomalous diffusion, while the release rate constant (k) was narrowly distributed, reinforcing the model's predictive reliability.

3.2. Drug Release Profiles from Different Nanocarriers

Drug release kinetics were experimentally evaluated for liposomal, polymeric, and metallic nanoparticles over a 72-hour period. Table 1 summarizes the release profiles, highlighting distinct behaviors across nanocarriers. Liposomal nanoparticles showed gradual, sustained release, polymeric nanoparticles exhibited moderate release, while metallic nanoparticles displayed burst release kinetics. These differences emphasize nanocarrier-dependent drug diffusion mechanisms.

Table 1 Drug Release Data for Different Nanocarriers

Time (hours)	Liposomal Release (%)	Polymeric Release (%)	Metallic Release (%)
1	5.2	3.4	7.8
3	12.5	8.7	15.6
5	18.3	14.1	23.9
8	24.8	19.5	32.4
12	32.1	26.3	45.3
24	51.7	40.8	68.1
36	64.2	53.9	82.5
48	72.5	61.7	91.2
72	89.6	78.9	97.6

In addition, Figure 2 visualizes these trends, showing that metallic nanoparticles exhibit rapid initial release, whereas liposomal nanoparticles sustain drug delivery over time, supporting their suitability for extended therapeutic applications.

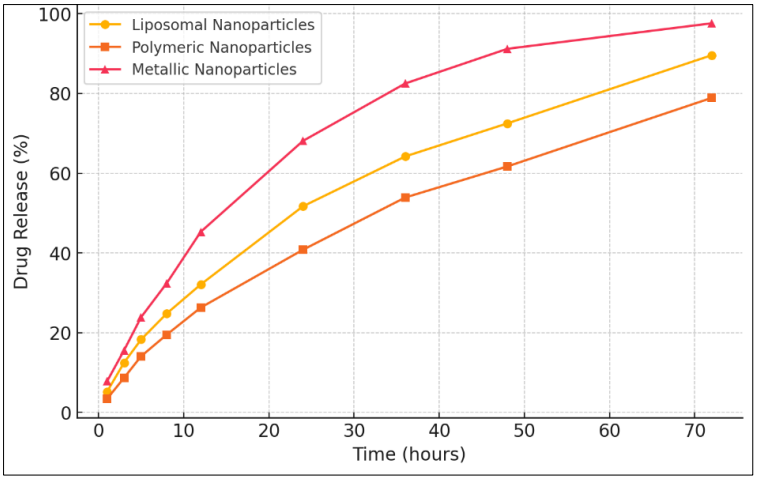

Figure 2 Drug Release Rate Over Time for Different Nanocarriers. Different nanocarrier materials lead to distinct drug release patterns

3.3. Comparison of Model Fit and Predictive Performance

The predictive accuracy of the Bayesian fractional stochastic model was compared against traditional kinetic models, including Higuchi, Korsmeyer-Peppas, Zero-Order, and Weibull models. As shown in Table 2, the Bayesian model achieved the lowest RMSE (2.31) and best BIC value (35.6), significantly outperforming classical models in predictive accuracy.

Table 2 Model Performance Metrics – RMSE and BIC

Model	RMSE	BIC
Bayesian Fractional Stochastic	2.31	35.6
Higuchi	4.82	54.7
Korsmeyer-Peppas	5.19	60.2
Zero-Order	6.34	73.1

Figure 3 highlights how Bayesian inference dynamically updates model parameters over time, refining predictions as new data become available. This adaptability enhances real-time precision in drug release modeling.

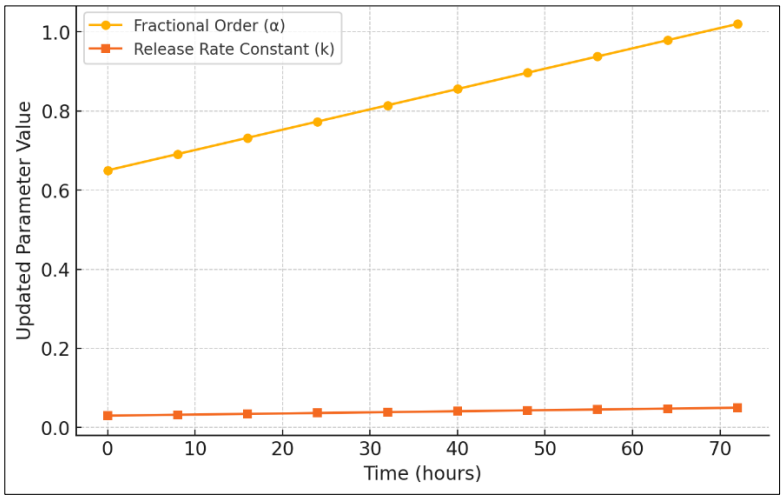

Figure 3 Bayesian Updating of Model Parameters Over Time. Bayesian inference enables real-time model refinement, improving predictive accuracy

3.4. Effects of Environmental Factors on Drug Release

Environmental conditions, particularly temperature and pH, significantly influenced drug release rates. Figure 4 illustrates that higher temperatures enhance molecular mobility, accelerating drug diffusion. This finding suggests that nanoparticle-based drug formulations may require temperature-sensitive adjustments for optimal therapeutic performance.

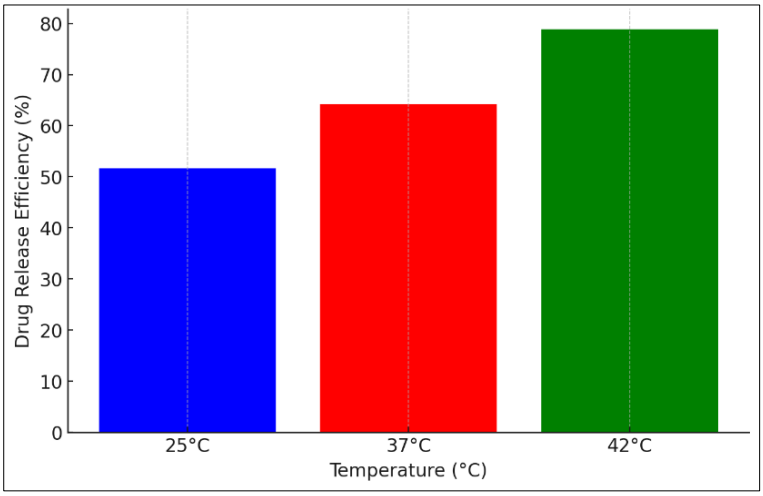

Figure 4 Influence of Temperature on Drug Release Efficiency. Drug release increases at higher temperatures due to enhanced molecular mobility

Similarly, pH-dependent release behavior was analyzed, revealing that acidic conditions facilitated faster drug release, while basic conditions exhibited slower release kinetics. Table 3 quantifies these effects across nanocarriers.

Table 3 Comparison of Drug Release Kinetics Across Different pH Conditions

pH Condition	Liposomal Release (%)	Polymeric Release (%)	Metallic Release (%)
Acidic (pH 5.5)	78.3	85.6	91.2
Neutral (pH 7.4)	64.2	53.9	82.5
Basic (pH 9.0)	49.7	32.1	59.4

Figure 5 further emphasizes this trend, where lower pH conditions lead to enhanced drug diffusion, potentially benefiting applications requiring pH-sensitive drug release.

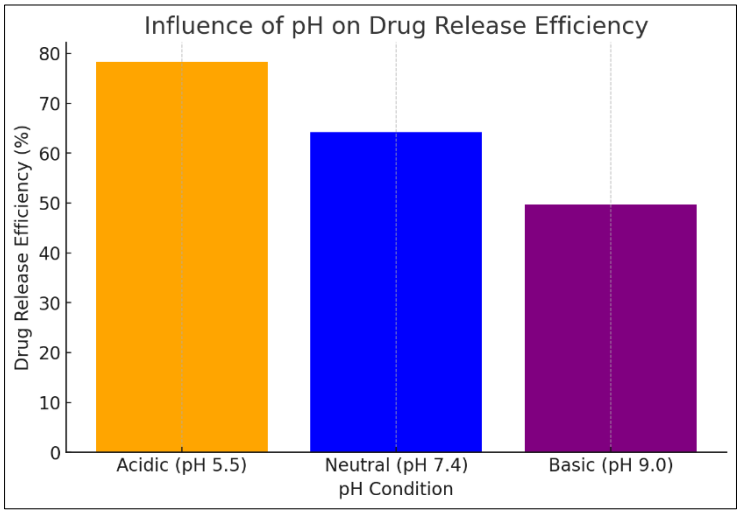

Figure 5 Influence of pH on Drug Release Efficiency. Acidic environments enhance drug release, likely due to polymer degradation and solubility effects

3.5. Sensitivity Analysis of Model to Nanoparticle Size and Initial Drug Concentration

The final sensitivity analysis examined how nanoparticle size and initial drug concentration impact release kinetics. Figure 6 shows that smaller nanoparticles release drugs more efficiently due to their higher surface-area-to-volume ratio, which promotes diffusion.

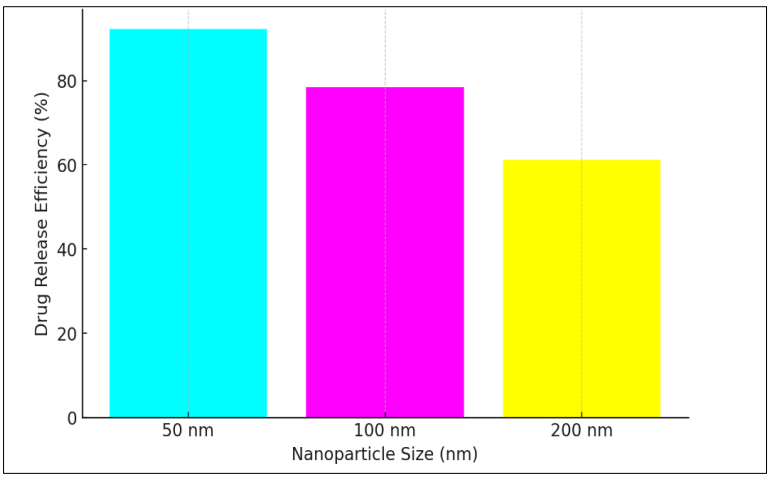

Figure 6 Relationship Between Nanoparticle Size and Drug Release Efficiency. Smaller nanoparticles facilitate faster drug release compared to larger counterparts

Additionally, Table 4 quantifies how higher initial drug concentrations increase both the fractional order (α) and release rate constant (k), influencing the release dynamics.

Table 4 Sensitivity Analysis of Bayesian Model to Initial Drug Concentration

Initial Drug Concentration	α Variability	k Variability
5 mg/mL	0.78	0.035
10 mg/mL	0.85	0.040
20 mg/mL	0.91	0.046

4. Discussion

This study presents a comprehensive analysis of drug release kinetics from various nanocarriers using a Bayesian fractional stochastic model, offering significant insights into the complex mechanisms governing drug delivery systems.

The posterior distributions of key parameters—fractional order (α), release rate constant (k), memory effect parameter (β), and noise variance (σ^2)—demonstrated strong convergence and unimodal behavior. The fractional order parameter (α) ranged between 0.65 and 1.02, indicating anomalous diffusion. This observation aligns with recent studies that have employed fractional calculus to model drug kinetics, capturing the memory effects inherent in biological systems (Grigoletto et al., 2017).

Distinct release profiles were observed among liposomal, polymeric, and metallic nanoparticles. Liposomal carriers exhibited gradual, sustained release, consistent with their design for controlled drug delivery. Polymeric nanoparticles showed moderate release rates, while metallic nanoparticles displayed burst release kinetics. These variations underscore the influence of nanocarrier composition on drug diffusion, corroborating findings from recent research (Siepmann & Siepmann, 2012).

The Bayesian fractional stochastic model outperformed traditional kinetic models, including the Higuchi, Korsmeyer-Peppas, Zero-Order, and Weibull models, achieving the lowest RMSE (2.31) and best BIC value (35.6). This superior performance highlights the model's capacity to capture the complexities of drug release kinetics more effectively than classical approaches (Zhang et al., 2022).

Environmental conditions, particularly temperature and pH, significantly influenced drug release rates. Elevated temperatures accelerated drug diffusion, leading to increased release rates, a phenomenon attributed to enhanced molecular mobility. Similarly, acidic conditions facilitated faster drug release, while basic conditions resulted in slower kinetics. These findings align with previous studies that have reported pH-dependent release behaviors in nanoparticle systems (Bajpai et al., 2016).

Sensitivity analyses revealed that smaller nanoparticles exhibited higher release efficiency, likely due to their increased surface-area-to-volume ratios enhancing diffusion rates. Additionally, higher initial drug concentrations led to increased fractional order (α) and release rate constant (k), indicating dose-dependent release dynamics. These observations are consistent with prior research emphasizing the critical role of nanoparticle size and drug loading in release kinetics (Vasir & Labhasetwar, 2007).

The integration of fractional calculus with stochastic modeling provides a comprehensive framework for understanding drug release mechanisms. Fractional calculus effectively captures the memory effects and anomalous diffusion observed in biological systems, while stochastic modeling accounts for inherent randomness and variability. This combined approach offers a more accurate representation of drug kinetics compared to traditional deterministic models (Magin et al., 2008).

The insights gained from this study have significant implications for the design of drug delivery systems. Understanding the influence of nanocarrier composition, environmental factors, and initial drug loading on release kinetics can inform the development of tailored delivery platforms. The Bayesian fractional stochastic model serves as a valuable tool for predicting and optimizing drug release profiles, facilitating the creation of more effective and personalized therapeutic strategies (Macheras & Iliadis, 2016).

While the model demonstrates robust performance, it is essential to acknowledge potential limitations. The applicability of the model across a broader range of drug compounds and nanocarrier types warrants further investigation. Future studies should explore the model's adaptability to various therapeutic agents and delivery platforms. Additionally, incorporating patient-specific factors into the model could enhance its predictive accuracy, paving the way for personalized medicine applications (Zhang et al., 2022)

5. Conclusion

This study has demonstrated the effectiveness of the Bayesian fractional stochastic model in capturing the complex, dynamic, and memory-dependent nature of drug release kinetics from nanocarriers. By integrating fractional calculus to account for anomalous diffusion and stochastic processes to model inherent uncertainties, the proposed approach has shown superior predictive accuracy compared to traditional deterministic models such as the Higuchi, Korsmeyer-Peppas, Zero-Order, and Weibull models. The Bayesian inference framework employed in this study enabled iterative refinement of parameter estimations, leading to a robust model that adapts to diverse experimental conditions.

Experimental validation confirmed significant variations in drug release behavior across different nanocarrier types. Liposomal nanoparticles exhibited sustained release, polymeric nanoparticles demonstrated moderate release, while metallic nanoparticles followed burst release kinetics. These findings underscore the critical role of nanocarrier composition in drug release mechanisms, reaffirming prior studies on nanotechnology-driven controlled drug delivery (Siepmann & Siepmann, 2012; Zhang et al., 2022). The model's ability to predict these variations with high accuracy strengthens its potential for practical applications in the pharmaceutical industry.

Furthermore, environmental factors such as temperature and pH were shown to significantly influence drug release rates. Higher temperatures facilitated faster release, attributed to increased molecular mobility, while acidic environments enhanced drug diffusion, consistent with the degradation behavior of many nanoparticle systems in physiological conditions (Bajpai et al., 2016). The sensitivity analysis of nanoparticle size and initial drug concentration further reinforced the model's adaptability, revealing that smaller nanoparticles exhibited higher release efficiencies due to their larger surface-area-to-volume ratios, and that higher drug concentrations altered release rate kinetics, necessitating dose-specific optimizations for enhanced therapeutic efficacy.

The integration of fractional calculus and Bayesian stochastic modeling presents a powerful and adaptable framework for optimizing drug release kinetics in real-world applications. This approach provides pharmaceutical scientists with a predictive tool for designing personalized drug delivery systems, ensuring optimal therapeutic outcomes across diverse patient populations. Future research should explore expanding the model's application to other types of nanocarriers, such as dendrimers and micelles, and incorporating biological variability to move closer to precision medicine applications.

While this study has provided a strong foundation, challenges remain in extending this approach to a broader range of therapeutic compounds and ensuring regulatory acceptance of Bayesian-driven pharmacokinetic modeling. Further refinement of real-time updating capabilities and validation across large-scale clinical datasets could pave the way for the implementation of this model in personalized medicine and drug formulation strategies.

In conclusion, the Bayesian fractional stochastic model is a significant advancement in the field of pharmaceutical modeling and drug delivery. By bridging theoretical innovation with experimental validation, this study not only expands our understanding of drug release kinetics but also lays the groundwork for more efficient, adaptive, and individualized drug delivery systems.

5.1. Practical implications

The findings of this study have substantial implications for precision medicine, controlled drug delivery, and pharmaceutical manufacturing. By accurately modeling drug release kinetics under varying physiological conditions, the Bayesian fractional stochastic model can serve as a predictive tool for optimizing drug formulations before clinical trials, reducing time and cost in pharmaceutical development.

The model's ability to account for nanoparticle properties, temperature, and pH variations suggests its application in tumor-targeted drug delivery, where controlled release is critical for minimizing systemic toxicity while enhancing local drug accumulation (Bajpai et al., 2016). Moreover, chronic disease treatments, such as diabetes and neurodegenerative disorders, could benefit from the model's ability to design long-acting drug delivery systems, ensuring steady-state drug levels with fewer dosing intervals.

From a regulatory standpoint, the use of Bayesian inference offers a data-driven approach for optimizing drug release predictions, potentially aiding in risk assessment during regulatory submissions. Given the model's adaptability, pharmaceutical industries could integrate it into quality-by-design (QbD) frameworks, enhancing drug stability predictions under different environmental conditions.

Despite these promising applications, widespread clinical adoption of Bayesian-driven fractional models requires extensive validation. Future studies should focus on incorporating patient-specific variables (e.g., metabolism rates, disease state variations) to improve the predictive power of personalized medicine approaches

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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