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Comparative Release Kinetics and Mechanistic Modeling of Mesalazine from PEGylated Chitosan-Coated Niosomes

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Abstract

Mesalazine is widely used in the treatment of Inflammatory Bowel Diseases (IBD); however, its therapeutic efficacy may be limited by rapid drug release and insufficient retention at the target site. In the present study, PEGylated chitosan-coated niosomes (PEG-CS-MEZ-NIO) were developed as a controlled-release delivery system for mesalazine. The formulation was prepared using the thin-film hydration method followed by chitosan surface modification. Encapsulation efficiency, permeability, in vitro drug release behavior, and release kinetics were investigated. The prepared formulation exhibited a high encapsulation efficiency of 95.42%, indicating effective drug entrapment within the vesicular structure. Permeability studies demonstrated excellent storage stability with minimal drug leakage under refrigerated conditions. In vitro release studies revealed a biphasic release profile characterized by an initial burst release followed by a sustained release phase, reaching a cumulative release of 29.8% after 270 min. To elucidate the release mechanism, the experimental data were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas kinetic models. Among the investigated models, the Higuchi model provided the highest correlation coefficient (R^2=0.9990), suggesting diffusion-controlled release as the predominant mechanism. Furthermore, the Korsmeyer–Peppas model yielded a release exponent of n=0.8852, indicating anomalous (non-Fickian) transport involving both diffusion and polymer relaxation processes. The findings demonstrate that PEGylated chitosan-coated niosomes can effectively regulate mesalazine release and represent a promising platform for sustained drug delivery applications.

Keywords: Mesalazine, Niosomes, PEGylation, Release kinetics, Higuchi model, Drug delivery system.

1 | Introduction

Nanotechnology-based drug delivery systems have attracted considerable attention in recent decades due to their potential to enhance the therapeutic performance of conventional drugs by improving solubility,

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stability, bioavailability, and providing controlled release behavior [1–5]. Among various nanocarrier platforms, vesicular systems such as liposomes and niosomes have emerged as promising carriers for both hydrophilic and hydrophobic therapeutic agents [6]. Niosomes are non-ionic surfactant-based vesicles composed of a bilayer structure formed by amphiphilic surfactants, typically stabilized with cholesterol to improve membrane rigidity and reduce drug leakage. Compared to phospholipid-based liposomes, niosomes offer advantages such as improved chemical stability, lower cost, and reduced toxicity, making them suitable candidates for sustained and targeted drug delivery applications [7–12]. Their bilayer architecture enables efficient encapsulation of a wide range of drugs, particularly hydrophilic compounds within the aqueous core and hydrophobic molecules within the lipid bilayer.

Despite these advantages, conventional niosomal systems may still face challenges such as burst release, aggregation, and limited in vivo stability. To address these limitations, surface modification strategies have been widely investigated. Among them, Polyethylene Glycol (PEG) modification, known as PEGylation, has been extensively used to improve the colloidal stability and circulation time of nanocarriers. PEG chains create a hydrophilic steric barrier on the vesicle surface, reducing protein adsorption and recognition by the reticuloendothelial system, thereby enhancing systemic stability and reducing premature drug release [13–15]. In addition, natural polymers such as chitosan have been widely employed for nanocarrier coating due to their excellent biocompatibility, biodegradability, and mucoadhesive properties. Chitosan is a cationic polysaccharide capable of interacting with negatively charged biological membranes, leading to prolonged residence time at mucosal surfaces and enhanced drug absorption. When applied as a coating layer on niosomes, chitosan can act as an additional diffusional barrier, contributing to sustained and controlled drug release profiles [16]. The combination of PEGylation and chitosan coating provides a dual-modification strategy that integrates the advantages of both systems. While PEG improves systemic stability and reduces aggregation, chitosan enhances mucoadhesion and modulates drug release kinetics. This synergistic effect is particularly beneficial for oral and mucosal drug delivery systems, where prolonged retention and controlled release are essential for achieving optimal therapeutic outcomes [17–20]. In this study, a vesicular drug delivery system based on PEGylated and chitosan-coated niosomes was developed for controlled release of mesalazine (5-aminosalicylic acid, 5-ASA). Mesalazine is a first-line anti-inflammatory agent widely used in the treatment of Inflammatory Bowel Diseases (IBD), particularly ulcerative colitis. Its therapeutic action is primarily local, exerted at the intestinal mucosa by inhibiting inflammatory mediators such as prostaglandins and leukotrienes. However, mesalazine is associated with limitations including rapid absorption in the upper gastrointestinal tract, short residence time in the colon, and incomplete delivery to the target site, which can reduce its clinical efficacy and necessitate frequent dosing [21–23]. Encapsulation of mesalazine within niosomal carriers is expected to protect the drug from premature absorption and degradation, enhance its stability, and promote targeted and sustained release in the intestinal environment. Understanding the release mechanism from such nanocarriers is crucial for optimizing therapeutic performance. Mathematical modeling of drug release data provides valuable insights into transport mechanisms. Common kinetic models such as zero-order, first-order, Higuchi, and Korsmeyer-Peppas are widely used to describe release behavior and to determine whether diffusion, erosion, or a combination of mechanisms governs drug release. The Higuchi model typically describes diffusion-controlled release from matrix systems, while the Korsmeyer-Peppas model provides further mechanistic insight through the release exponent (n), indicating Fickian or non-Fickian transport behavior. Although several studies have explored niosomal systems for drug delivery, limited research has focused on the combined effect of PEGylation and chitosan coating on the release kinetics of mesalazine. In particular, comparative mechanistic modeling of dual-modified niosomal systems remains insufficiently investigated. Therefore, a systematic evaluation of how these surface modifications influence release behavior is necessary to better understand transport phenomena in such systems [18–23].

In this context, the present study aims to investigate the in vitro release profile and kinetic modeling of mesalazine-loaded PEGylated chitosan-coated niosomes. The release data were analyzed using multiple mathematical models to determine the best-fit kinetic model and to elucidate the underlying drug release

mechanism. The findings are expected to contribute to the rational design of advanced niosomal systems with improved colon-targeted and sustained release performance.

2 | Materials and Methods

2.1 | Materials

Mesalazine (5-aminosalicylic acid), Span 60 (sorbitan monostearate), Cholesterol, PEG (PEG, molecular weight 2000 Da), chitosan (medium molecular weight), ethanol, glacial acetic acid, and phosphate-buffered saline (PBS, pH 7.4) were used in this study. All chemicals were of analytical grade and used without further purification. Deionized water was used throughout all experiments. Chitosan was selected as a cationic polymer due to its excellent biocompatibility, biodegradability, and mucoadhesive properties, while PEG was incorporated to enhance steric stabilization, reduce aggregation, and improve colloidal stability of the vesicular system.

2.2 | Preparation of PEGylated Niosomes

PEGylated niosomes loaded with mesalazine were prepared using the thin-film hydration technique with slight modifications. Span 60 and cholesterol were dissolved in ethanol at an optimized molar ratio to ensure stable vesicle formation. PEG (2000 Da) was incorporated into the organic phase to achieve surface modification during vesicle formation. The organic solvent mixture was transferred into a round-bottom flask and evaporated under reduced pressure using a rotary evaporator at 40± 2°C to form a thin lipid film on the flask wall. The film was further dried under vacuum overnight to remove residual solvent traces. Hydration of the dried film was performed using phosphate-buffered saline (PBS, pH 7.4) containing mesalazine under continuous agitation at 60°C, above the phase transition temperature of Span 60, to facilitate vesicle formation. The resulting multilamellar vesicular dispersion was sonicated using a probe sonicator (40 kHz) for 10 min to obtain a homogeneous nanosized niosomal suspension.

2.3 | Chitosan Coating of PEGylated Niosomes

Chitosan coating was performed using the electrostatic deposition method. Chitosan was dissolved in 1% (v/v) acetic acid solution under magnetic stirring for 12 h to obtain a clear polymer solution (0.1-0.5% w/v depending on optimization). The freshly prepared PEGylated niosomal suspension was added dropwise into the chitosan solution under continuous stirring at room temperature. The mixture was stirred for 4 h to ensure sufficient electrostatic interaction between positively charged chitosan and the negatively charged niosomal surface. The final formulation was designated as PEG-CS-MES-NIO. The coated vesicles were stored at 4°C for further analysis.

2.4 | Determination of Encapsulation Efficiency (EE%)

The encapsulation efficiency of mesalazine within niosomal vesicles was determined using the indirect method. Briefly, the nanosuspension was centrifuged at 15000 rpm for 30 min to separate free drug from vesicle-encapsulated drug. The supernatant containing unentrapped drug was analyzed spectrophotometrically at the predetermined λmax using UV-visible spectroscopy.

Encapsulation efficiency was calculated using the following *Eq. (1)* [12]:

$$\mathrm{EE}(\%) = \frac{\mathrm{C\ total} - \mathrm{C\ free}}{\mathrm{C\ total}} \times 100, \quad \textbf{(1)}$$

where C total is the initial drug concentration and C free is the concentration of free drug in the supernatant.

2.5 | Stability and Permeability Study

The physical stability of the formulations was evaluated by storing samples at 4°C for up to 30 days. At predetermined time intervals, samples were analyzed for changes in encapsulation efficiency, particle

aggregation, and possible drug leakage. Permeability (or retention efficiency) was calculated based on changes in encapsulation efficiency using *Eq. (2)* [13]:

$$\text{Permeability}(\%) = \frac{\text{E initial} - \text{E final}}{\text{E initial}} \times 100. \quad (2)$$

This study was used to assess the integrity of vesicular systems during storage.

2.6 | In Vitro Drug Release Study

In vitro drug release was performed using the dialysis bag diffusion technique. A known quantity of niosomal suspension equivalent to a fixed mesalazine dose was placed in a dialysis membrane (molecular weight ~12-14 kDa). The dialysis bag was immersed in 100 mL of phosphate-buffered saline (PBS, pH 7.4) maintained at 37±0.5°C under continuous magnetic stirring at 100 rpm to simulate physiological conditions. At predetermined time intervals up to 270 min, 2 mL samples were withdrawn from the receptor medium and replaced with fresh PBS to maintain sink conditions. The amount of released mesalazine was quantified using UV-visible spectrophotometry [12]. All experiments were performed in triplicate, and results were expressed as mean ± standard deviation.

2.7 | Kinetic Modeling of Drug Release

The in vitro release data were fitted to various mathematical models to evaluate the mechanism of drug release from the niosomal systems. The following models were applied (*Eqs. (3)-(6)*) [6–11]:

Zero-order model:

$$\frac{M(t)}{M(\infty)} = k_0 t. \quad (3)$$

First-order model:

$$\frac{M(t)}{M(\infty)} = e^{-k_1 t}. \quad (4)$$

Higuchi model:

$$\frac{M(t)}{M(\infty)} = k_H t^{\frac{1}{2}}. \quad (5)$$

Korsmeyer–Peppas model:

$$\frac{M(t)}{M(\infty)} = k_P t^n, \quad (6)$$

where M(t) is the cumulative amount of drug released at time t, M(∞) is the total drug released at infinite time, k_0, k_1, k_H, k_P are release rate constants, and n is the release exponent indicating the mechanism of drug transport. The model fitting was evaluated using correlation coefficient (R^2) values, and the best-fit model was selected based on highest R^2 and mechanistic consistency.

3 | Results and Discussion

3.1 | Encapsulation Efficiency

The PEG-CS modified niosomal formulation exhibited a high encapsulation efficiency of 95.42%, indicating successful incorporation of mesalazine within the vesicular structure. The elevated entrapment efficiency may be attributed to the presence of Span 60, which possesses a high phase transition temperature and contributes to the formation of a rigid bilayer membrane capable of retaining drug molecules effectively. Furthermore,

the incorporation of PEG and chitosan significantly enhanced vesicle stability and minimized premature drug leakage. PEG provided steric stabilization and reduced vesicle aggregation, while chitosan formed a protective polymeric layer around the niosomal surface. The synergistic effect of PEGylation and chitosan coating increased membrane integrity and improved drug retention within the carrier system. The obtained encapsulation efficiency demonstrates that the PEG-CS modified niosomal system is a suitable platform for mesalazine delivery and may provide prolonged drug release characteristics required for controlled drug delivery applications.

3.2 | Permeability and Storage Stability

The permeability profile of the PEG-CS-MEZ-NIO formulation (*Table 1*) demonstrated excellent storage stability with negligible drug leakage during refrigerated storage conditions. The permeability percentage increased gradually from 0.38% after 1 h to approximately 0.92% after 3 h, indicating strong retention of mesalazine within the vesicular system. The low permeability values suggest that the PEG-chitosan coating effectively acted as a diffusion barrier, reducing drug migration from the vesicular core into the external medium. In addition, electrostatic interactions between chitosan chains and the niosomal surface, together with steric stabilization provided by PEG, contributed to the formation of a compact polymeric network surrounding the vesicles.

The enhanced structural stability observed for PEG-CS-MEZ-NIO can be attributed to the combined effects of membrane rigidification and polymeric surface protection. Such characteristics are highly desirable for controlled drug delivery systems, as they help preserve encapsulated drug content during storage and reduce premature drug release prior to administration.

Table 1. Comparative encapsulation efficiency and permeability profiles of mesalazine-loaded niosomes before and after PEGylation and chitosan coating (mean ± SD, n = 3).

Formulation	Encapsulation Efficiency (%)	Permeability After 1 h (%)	Permeability After 2 h (%)	Permeability After 3 h (%)
MEZ-NIO	88.6 ± 1.4	0.85 ± 0.04	1.34 ± 0.07	1.96 ± 0.08
PEG-MEZ-NIO	92.1 ± 1.1	0.59 ± 0.03	0.88 ± 0.05	1.27 ± 0.06
PEG-CS-MEZ-NIO	95.42 ± 0.9	0.38 ± 0.02	0.67 ± 0.04	0.92 ± 0.05

3.3 | In Vitro Drug Release Behavior

The in vitro release profile of mesalazine from the PEG-CS-MEZ-NIO formulation (*Fig. 1*) demonstrated a characteristic biphasic release pattern consisting of an initial burst release phase followed by a prolonged and sustained release stage. During the first 90 min, a relatively rapid release of mesalazine was observed, which may be attributed to the diffusion and desorption of drug molecules adsorbed or weakly associated with the outer surface of the niosomal vesicles. Following the initial phase, the release rate gradually decreased, indicating the establishment of a controlled diffusion process through the PEGylated and chitosan-coated bilayer membrane. The presence of PEG provided steric stabilization and reduced drug mobility, while the chitosan coating acted as an additional diffusional barrier that prolonged drug transport from the vesicular core into the release medium. The cumulative release of mesalazine reached approximately 29.8% after 270 min, confirming the sustained release capability of the PEG-CS modified niosomal system. The relatively low release percentage observed during the study period can be attributed to the high encapsulation efficiency and enhanced structural integrity of the coated vesicles.

Furthermore, the controlled release behavior suggests that the dual surface modification strategy effectively regulated drug transport kinetics and minimized premature drug leakage. Such a release pattern is desirable for controlled drug delivery applications, where maintenance of therapeutic drug concentrations over

extended periods is required. The obtained findings indicate that PEG-CS-MEZ-NIO possesses considerable potential as a sustained-release carrier for mesalazine delivery.

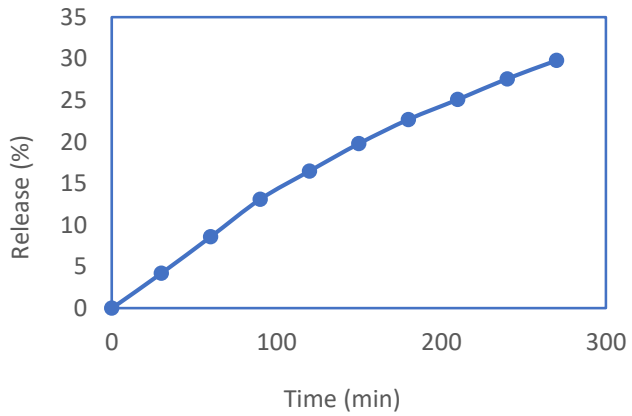


Fig. 1. In vitro release profile of mesalazine from PEG-CS-MEZ-NIO formulation in phosphate-buffered saline (pH 7.4) at 37±1˚C. Data are expressed as mean ± SD (n=3).

3.4 | Kinetic Analysis

Mathematical kinetic models were employed to investigate the mechanism governing mesalazine release from the PEG-CS-MEZ-NIO formulation. The release data were fitted to zero-order, first-order, Higuchi, and Korsmeyer-Peppas models, and the corresponding kinetic parameters are presented in *Table 2* and *Figs. 1.a-1.d.*

3.4.1 | Zero-order kinetics

The zero-order model demonstrated a high correlation coefficient (R^2=0.9839), suggesting a relatively constant release behavior over the experimental period. However, its goodness-of-fit was lower than that of the Higuchi model.

3.4.2 | First-order kinetics

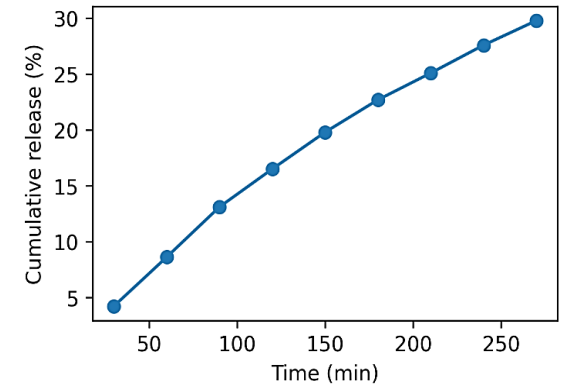
The first-order model exhibited a correlation coefficient of R^2= 0.9931, indicating that concentration-dependent release contributed to the overall release process. Nevertheless, this model did not provide the best description of the experimental data.

3.4.3 | Higuchi model

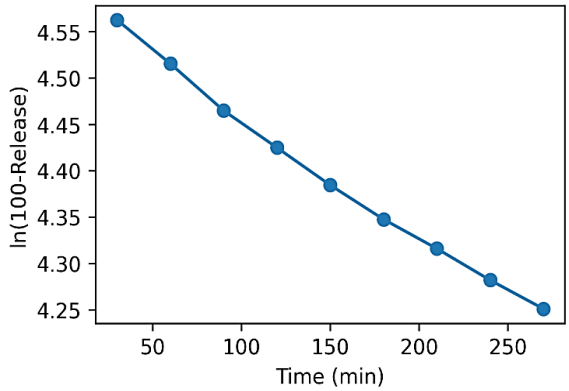
The Higuchi model showed the highest regression coefficient (R^2=0.9990), indicating that diffusion was the predominant mechanism governing mesalazine release from the PEG-CS coated niosomal system. The excellent fit of the Higuchi equation suggests that drug transport mainly occurred through diffusion across the polymer-modified vesicular matrix.

3.4.4 | Korsmeyer-Peppas model

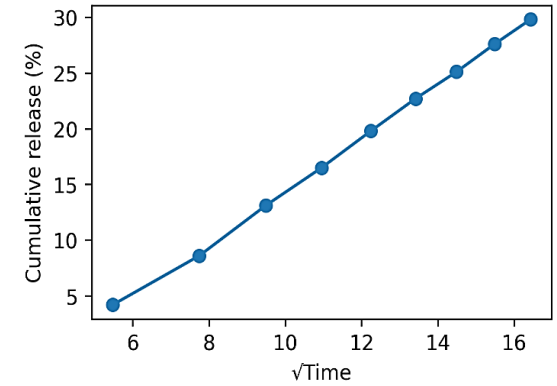
The Korsmeyer-Peppas model also provided a satisfactory fit (R2=0.9920). The release exponent obtained from the model was n=0.8852, indicating anomalous (non-Fickian) transport behavior. This mechanism suggests that drug release was controlled by a combination of diffusion and polymer relaxation processes within the PEG-chitosan coating layer. Overall, the kinetic analysis demonstrated that the PEG-CS modification effectively regulated mesalazine transport and produced a sustained-release system. The predominance of the Higuchi model indicates diffusion-controlled release, while the Korsmeyer-Peppas results confirm the additional contribution of polymer chain relaxation to the overall release mechanism.



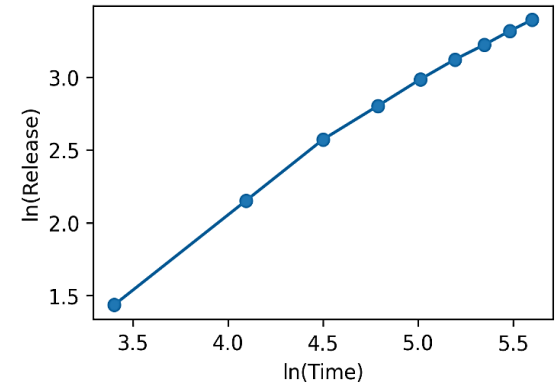
a.



b.



c.



d.

Fig. 2. Linearized kinetic plots for mesalazine release from PEG-CS-MEZ-NIO (mean ± SD, n = 3); a. zero-order, b. first-order, c. Higuchi, and d. Korsmeyer-Peppas.

Table 2. Kinetic parameters, regression equations, and correlation coefficients (R^2) obtained from different release models for mesalazine-loaded PEG-CS niosomes.

Model	Linear Equation	R^2
Zero-order	Qt=0.1053t + 2.80	0.9839
First-order	ln(100-Qt) = - 0.0001248t + 4.5874	0.9931
Higuchi	Qt = 2.3779√t - 9.3383	0.9990
Korsmeyer-Peppas	ln(Qt) = 0.8852ln(t)- 1.4916	0.9920

4 | Conclusion

In this study, PEGylated chitosan-coated niosomes were successfully developed as a nanocarrier system for the controlled delivery of mesalazine. The combination of PEGylation and chitosan surface modification provided enhanced vesicular stability and improved drug retention within the niosomal structure. The prepared PEG-CS-MEZ-NIO formulation exhibited a high encapsulation efficiency of 95.42%, demonstrating the ability of the modified vesicles to effectively incorporate and retain mesalazine. In addition, permeability studies revealed minimal drug leakage during storage, indicating excellent physicochemical stability and the protective effect of the PEG-chitosan coating on the vesicular membrane. The in vitro release study demonstrated a biphasic release pattern consisting of an initial burst release followed by a prolonged sustained-release phase. The limited cumulative release of 29.8% after 270 min confirmed the capability of the PEG-CS modified system to effectively regulate drug transport and reduce premature drug release. Such behavior is advantageous for controlled drug delivery applications, where prolonged therapeutic activity and reduced dosing frequency are desired. To further understand the mechanism governing mesalazine release, the experimental data were analyzed using several mathematical kinetic models. Among the investigated models, the Higuchi model showed the highest correlation coefficient (R^2=0.9990), indicating that diffusion through the polymer-modified vesicular matrix was the predominant release mechanism. Moreover, the Korsmeyer-Peppas model yielded a release exponent (n=0.8852), suggesting anomalous (non-Fickian) transport behavior. This finding indicates that mesalazine release was controlled by a combination of diffusion and polymer relaxation processes, highlighting the important role of the PEG-chitosan coating in modulating drug transport. Overall, the obtained results demonstrate that PEGylated chitosan-coated niosomes provide an efficient and stable platform for mesalazine delivery. The dual surface modification strategy not only improved drug encapsulation and storage stability but also enabled controlled and sustained release behavior. These characteristics suggest that the PEG-CS-MEZ-NIO system has considerable potential for the development of advanced mesalazine delivery formulations. Future studies should focus on in vivo evaluation, pharmacokinetic investigations, and biological performance assessments to further validate the therapeutic advantages of this nanocarrier system and facilitate its potential clinical application.

Authors' Contributions

All aspects of the research and manuscript preparation were carried out by the author. The author has read and approved the final version of the manuscript.

Data Availability

All data are included in the text.

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Conflict of Interest

The author declares that he does not have any conflict of interest.

Consent for Publication

The author has given consent for the publication of this manuscript.

Ethics Approval and Consent to Participate

This study does not involve any research conducted on human participants or animals.

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