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Formulation and Physicochemical Characterization of Chitosan-Coated Simvastatin Nanoparticles

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Abstract

Simvastatin is an effective antihyperlipidemic agent whose clinical utility is limited by poor aqueous solubility, low gastrointestinal absorption, and extensive first-pass metabolism, resulting in reduced oral bioavailability. This study aimed to formulate and characterize chitosan-coated simvastatin nanoparticles as a strategy to improve its physicochemical performance and controlled release properties. Nanoparticles were prepared using the ionic gelation method involving electrostatic interaction between chitosan and sodium tripolyphosphate. The developed formulation was evaluated by in vitro drug release studies, scanning electron microscopy (SEM), and Fourier transform infrared spectroscopy (FTIR). The release profile demonstrated a biphasic pattern with an initial burst release during the early phase, followed by sustained drug release reaching approximately 70–75% over 300 minutes, indicating effective controlled-release behavior. SEM analysis showed clear morphological transformation from loosely aggregated crystalline simvastatin particles to denser and more cohesive nanoparticulate structures after chitosan coating, confirming successful encapsulation. FTIR spectra retained the characteristic peaks of both simvastatin and chitosan with only minor shifts in band positions, suggesting structural integrity of the drug and absence of significant chemical incompatibility between formulation components. The combined findings indicate that chitosan coating improved the physicochemical characteristics of simvastatin while providing sustained release potential. Therefore, chitosan-coated simvastatin nanoparticles represent a promising oral nanocarrier system for enhancing simvastatin delivery and therapeutic performance.

Keywords: Phytochemical characterization, Chitosan, Simvastatin, Nanoparticles.

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INTRODUCTION

There has been a significant rise in particle engineering and nanosizing of therapeutic agents such as simvastatin over the decades (Selvasudha et al., 2017). This shift has been driven by the inherent limitations of conventional drug delivery systems and the expanding potential of nanotechnology-based carriers in pharmaceutical science (Khan et al., 2013). Traditional dosage forms often fail to deliver drugs effectively to their intended site of action, and oral administration is frequently associated with presystemic metabolism in the liver, resulting in gastrointestinal irritation, poor absorption, and reduced bioavailability. Parenteral routes, although effective, are limited by high production costs and poor patient compliance, necessitating the exploration of alternative and more efficient drug delivery strategies (Sharma et al., 2013). Nanotechnology-based drug delivery systems, particularly nanoparticles, have emerged as a promising approach to overcome these challenges. Nanoparticles are capable of improving the physicochemical properties of drugs by altering key characteristics such as solubility and permeability through particle size reduction and surface modification. These particulate systems include microparticles, microspheres, and nanoparticles, with the latter representing the forefront of modern drug delivery innovation (Abo-zeid et al., 2020). Nanocarriers enhance the bioavailability of encapsulated drugs by prolonging systemic circulation, enabling controlled release, and maintaining steady-state plasma concentrations, thereby reducing dose-related side effects (Macedo et al., 2020). Simvastatin, a widely used lipid-lowering agent and HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitor, is particularly suitable for nanoparticle-based delivery systems due to its poor aqueous solubility, extensive first-pass metabolism, and low oral bioavailability (<5%) (Wong et al., 2010; Chen et al., 2011). It is a lipophilic drug with very limited gastrointestinal absorption and a maximum aqueous solubility of approximately 30 µg/mL, making it an ideal candidate for formulation into nanoscale drug delivery systems aimed at improving therapeutic efficiency and pharmacokinetic performance (PrakashKatakam et al., 2014; Kongsong et al., 2014). The development of simvastatin nanoparticles is therefore aimed at overcoming its inherent limitations, including low solubility, poor bioavailability, short half-life, and dose-dependent adverse effects (PrakashKatakam et al., 2014). Nanoparticles are particularly advantageous for oral delivery of gut-labile or poorly soluble drugs, as they can traverse mucosal barriers and enhance drug uptake via intestinal absorption mechanisms (Wong et al., 2010; Chen et al., 2011). The performance of nanoparticle formulations is strongly influenced by formulation variables, including polymer type, stabilizer selection, surfactants, and process parameters such as stirring speed and temperature. Among these, stabilizers play a critical role in ensuring physical stability and preventing particle aggregation, which directly affects drug bioavailability (Peltonen et al., 2010). Commonly used stabilizers include polymers such as PVP, PVA, HPMC, PEG, and CMC, as well as surfactants such as Pluronic F68, Pluronic F127, Tween 80, Tween 20, sodium lauryl sulfate (SLS), and lecithin (Mahesh et al., 2014; Danhier et al., 2014). Stabilizers may be ionic or non-ionic in nature, and nanoparticle stability is largely governed by electrostatic interactions. While single stabilizers may be sufficient in some cases, combinations are often employed to achieve narrow particle size distribution and improved formulation stability (Valo et al., 2013; George et al., 2013). Although stabilizers are often regarded as pharmaceutically inactive excipients, emerging evidence suggests that they may influence cellular interactions and permeability, thereby indirectly modifying drug bioavailability. This highlights the importance of rational stabilizer selection in nanoparticle formulation design. In addition to stabilizers, polymers are central to nanoparticle formulation. They may be natural or synthetic in origin and are responsible for controlling drug release and optimizing pharmacokinetic behavior. Biodegradable natural polymers are advantageous due to their elimination via normal metabolic pathways, while synthetic polymers offer greater structural control and reproducibility, although natural polymers may exhibit variability and mild immunogenicity (Crucho & Barros, 2017). Among natural polymers, chitosan has gained significant attention as a drug delivery excipient. It is a cationic polysaccharide composed of glucosamine and N-acetylglucosamine linked via β-(1→4) glycosidic bonds and is widely regarded as the second most abundant natural biomaterial after cellulose. Chitosan is extensively used in pharmaceutical formulations due to its biodegradability, biocompatibility, mucoadhesive properties, in-situ gelation capability, and non-toxic nature (Nilay, 2019). These properties make it particularly suitable for enhancing drug retention and absorption across biological membranes. Chitosan nanoparticle formation is commonly achieved through ionic gelation with sodium tripolyphosphate (TPP), a multivalent anionic cross-linker. In this process, electrostatic interactions occur between the positively charged amino groups of chitosan and the negatively charged phosphate groups of TPP, leading to intra- and intermolecular cross-linking and subsequent hydrogel or nanoparticle formation (Kim et al., 2006 & Severino et al., 2016). Sodium TPP is widely preferred due to its low toxicity, rapid gelling ability, and capacity to form stable complexes with chitosan (Shavi et al., 2011). The increasing global burden of cardiovascular diseases further underscores the need for improved therapeutic strategies. Ischemic heart disease remains the leading cause of death worldwide, accounting for approximately 16% of total mortality, followed by stroke and chronic obstructive pulmonary disease (COPD) (Tulbah et al., 2019). Simvastatin, an HMG-CoA reductase inhibitor, plays a critical role in reducing lipid levels and preventing cardiovascular events such as myocardial infarction and stroke. However, its clinical

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efficacy is limited by poor oral bioavailability, extensive first-pass metabolism, and poor gastrointestinal absorption, making it a strong candidate for nanoparticulate drug delivery systems (Kongsong et al., 2014 & Selvasudha et al., 2014). The present study on Formulation and Physicochemical Characterization of Chitosan-Coated Simvastatin Nanoparticles was undertaken to develop an optimized nanoparticulate drug delivery system capable of improving the solubility, bioavailability, and therapeutic performance of simvastatin, while systematically evaluating the influence of formulation variables on key physicochemical and release characteristics.

Materials and Methods

Chemicals and Reagents

The chemicals and reagents utilized in this study were of analytical grade and were obtained from reputable suppliers including Sigma-Aldrich (USA), British Drug House (BDH, England), and Andalucia (Spain). Simvastatin (SIM) was sourced from PharmaCompass Bangalore, Karnataka, India, while Chitosan (low molecular weight) and sodium tripolyphosphate (TPP), along with ethanol, acetic acid, trichloroacetic acid (TCA), hydrochloric acid (HCl), phosphate-buffered saline (PBS), sodium hydroxide (NaOH), and potassium chloride (KCl), were used as supporting reagents throughout the study. Standardized reagents and analytical-grade chemicals from commercial test kits manufactured by Randox (USA) and Teco Diagnostics (USA) were employed to ensure methodological consistency.

Instruments and Equipment

The equipment used for this study were those present in the laboratory of Department of Biochemistry, University of Nigeria Nsukka and others procured from scientific shops. They were beakers (Pyrex, England), centrifuge (Vickas Ltd. England), conical flasks (Pyrex, England), filter papers (Whatman), glass funnel (Pyrex, England), measuring cylinder (Pyrex, England), spectrophotometer (Spectronic 20D, Germany), test tubes (Pyrex, England), refrigerator (Thermocool, England), rotary evaporator (IKA, Germany), water bath (Gallenkamp, England) and weighing balance (Mettler HAS, U.S.A).

Formulation of Chitosan-coated Simvastatin nanoparticles (CCSNs)

The Chitosan-coated Simvastatin nanoparticles were formulated using the ionic gelation technique, which leverages electrostatic interactions between Chitosan and sodium tripolyphosphate to form stable nanoparticles (Elsaadany et al., 2021). Chitosan (4 g) was weighed and dissolved in 200 mL of 5% acetic acid under continuous stirring using a magnetic stirrer until a homogeneous solution was obtained. Simvastatin (2 g) was separately dissolved in 100 mL of distilled water to ensure complete solubilization. While maintaining constant stirring, the Simvastatin solution was gradually added dropwise into the Chitosan solution to facilitate uniform dispersion and encapsulation of the drug. Subsequently, sodium tripolyphosphate (2 g) was dissolved in 200 mL of distilled water and added dropwise to the Chitosan–Simvastatin mixture under continuous stirring. This step initiated the crosslinking process, leading to nanoparticle formation through ionic interactions between the positively charged Chitosan and the negatively charged tripolyphosphate ions. The resulting nanoparticles were allowed to stabilize before further characterization and use in the study.

In Vitro Release Studies of Chitosan-coated Simvastatin nanoparticles

In-vitro release studies of Simvastatin from CCSNs formulations were performed using a dialysis membrane as described by Chinaeke et al. (2014).

Fourier transform infrared (FTIR) spectroscopy

Interaction between drug and formulation components was studied using FTIR spectroscopy (FT-IR 8300 Spectrophotometer Shimadzu, Tokyo, Japan). FTIR analyses were performed on Simvastatin, Chitosan and the CCSNs.
To perform FTIR analysis on Simvastatin, Chitosan and the CCSNs., the first step involved preparing the samples appropriately. For Simvastatin, a small amount (usually 1 to 2 mg) of the pure drug waas weighed and thoroughly mixed with about 100 mg of dry potassium bromide (KBr) powder, which is transparent to infrared light. This mixture is then ground into a fine powder using a mortar and pestle. The powder is compressed into a thin, transparent pellet using a hydraulic press under high pressure, typically between 5 and 10 tons. A similar procedure is followed for chitosan, where 1 to 2 mg of the polymer was mixed with KBr powder and pressed into a pellet. For the chitosan-coated simvastatin nanoparticles, the samples are first dried, commonly by freeze-drying or oven drying, to remove moisture. A small quantity of the dried nanoparticles was then mixed with KBr and pressed into a pellet in the same way. The FTIR analysis was conducted using a spectrophotometer, with the scanning range set from 4000 to 400 cm^{-1} and a spectral resolution of around 4 cm^{-1}. Multiple scans were averaged to improve the signal quality. The resulting spectra provided characteristic absorption bands corresponding to the different chemical bonds and functional groups present in the samples.

Determination of Surface Morphology

The surface morphology of Simvastatin, Chitosan, and Chitosan-coated Simvastatin nanoparticles was determined using scanning electron microscopy (SEM). Samples were first dried to remove moisture. A small amount of each dried sample was then mounted on aluminum stubs using double-sided carbon adhesive tape. To improve conductivity and prevent charging during imaging, the samples were coated with a thin layer of gold using a sputter coater. SEM imaging

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was performed at various magnifications to observe the surface characteristics, shape, and size of the particles. Simvastatin appeared as irregular crystalline structures, Chitosan exhibited a relatively smooth surface, and the chitosan-coated simvastatin nanoparticles showed spherical morphology with a distinct coating layer, confirming successful nanoparticle formation.

Results

In Vitro Drug Release Studies of Chitosan-coated Simvastatin nanoparticles

The drug release profile in figure 1 below shows an initial burst phase within the first 50 minutes, where a significant portion of the drug is rapidly released. After this burst, the release rate slows and follows a sustained, stepwise increase up to 200 minutes. Between 200 and 250 minutes, the release plateaus around 70%. A minor dip around 200 minutes is observed. By 300 minutes, the drug release reaches approximately 70–75%. The overall profile indicates a combination of initial burst and sustained release.

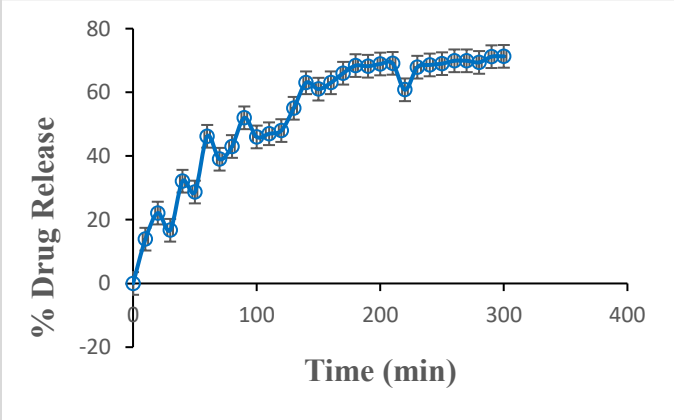

Figure 1: Release profile of Chitosan-coated Simvastatin nanoparticles

Morphological Characterization of Chitosan, Simvastatin, and Chitosan-Coated Simvastatin Using Scanning Electron Microscopy (SEM)

The morphological Characterization of Chitosan, Simvastatin, and Chitosan-Coated Simvastatin Using Scanning Electron Microscopy (SEM) is shown in figure 8 (a, b and c) below. At 2000× magnification and an accelerating voltage of 3.00 kV, the SEM image of Chitosan (figure 2a) revealed a distinctly rough and porous structure with small clusters and horizontal lines across the surface. The SEM image of pure Simvastatin (figure 2b) showed loosely packed particles with visible voids, a rough texture, and particle aggregation. Upon coating Simvastatin with Chitosan, the SEM image (figure 2c) demonstrated an apparent increase in particle size, formation of cohesive clusters, reduced porosity, and a denser surface morphology.

Fourier Transform Infrared Spectroscopic Characterization of Chitosan-Based Simvastatin Nanoparticles

The FTIR spectrum of Chitosan (figure 3a) below showed characteristic absorption bands at 3852.07 cm^{-1} (O–H stretching), 2361.78 cm^{-1} (C≡C or C≡N stretching), 1698.72 cm^{-1} (C=O stretching), 1539.73 cm^{-1} (aromatic C=C stretching), 1465.56 cm^{-1} (C–H bending), and 910.97 cm^{-1} (C–H out-of-plane bending). The FTIR spectrum of Simvastatin (figure 3b) exhibited peaks at 3734.63 cm^{-1} (O–H stretching), 2899.26 cm^{-1} (C–H stretching), 2158.78 cm^{-1} (C≡C or C≡N stretching), 1698.36 cm^{-1} (C=O stretching), 1557.88 cm^{-1} (aromatic C=C stretching), 1456.29 cm^{-1} (C–H bending), and 899.36 cm^{-1} (C–H out-of-plane bending). In Chitosan-coated Simvastatin nanoparticles (figure 3c), the FTIR spectrum presented a combination of peaks from both Chitosan and Simvastatin, including 3734.63 cm^{-1} (O–H stretching) and modifications in the C=O and C=C regions, with slight shifts and intensity changes.

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Morphological Characterization of Chitosan, Simvastatin, and Chitosan-Coated Simvastatin Using Scanning Electron Microscopy (SEM) and Fourier Transform Infrared Spectroscopic

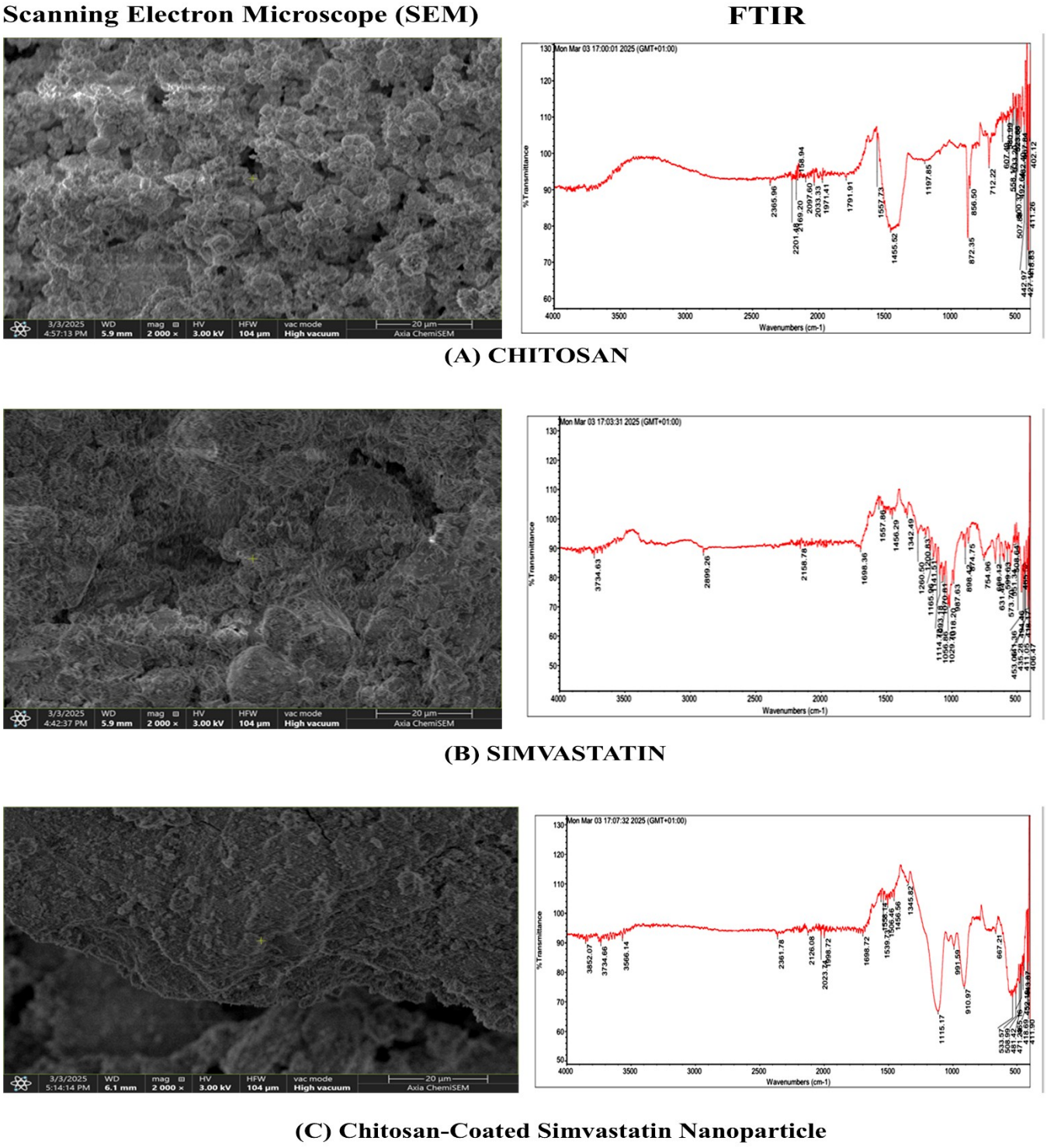

Figure 2: *FTIR and Scanning Electron Microscope (SEM) image of Chitosan, Simvastatin and Chitosan-coated Simvastatin nanoparticles at 2000× magnification, taken under high vacuum conditions at 3.00 kV accelerating voltage.*

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Discussion

Following the formulation of Chitosan-coated Simvastatin nanoparticles, the *in vitro* release profile was determined. As shown in Figure 1, the nanoparticles demonstrated a biphasic release pattern characteristic of effective controlled drug delivery systems. An initial burst release was observed within the first 50 minutes, likely due to the rapid dissolution of surface-bound or loosely associated drug molecules. This phase may be advantageous for prompt therapeutic action, particularly in acute hypercholesterolemia management. Following this, a sustained release phase extends up to 200 minutes, suggesting that the drug diffuses gradually through the Chitosan matrix, potentially influenced by the polymer's degradation dynamics. The release gradually plateaus between 200 and 250 minutes at approximately 70%, indicating a balance between drug diffusion and polymer erosion. Minor fluctuations around this point could be attributed to experimental variability or nanoparticle aggregation. By 300 minutes, the cumulative drug release reaches about 70–75%, implying that a portion of the drug remains tightly bound within the matrix or exhibits limited solubility. Overall, this release profile highlights the nanoparticle formulation's potential for sustained and controlled drug delivery, aligning with the study's objective to enhance Simvastatin's therapeutic efficacy. While this study focused on Chitosan-coated nanoparticles and characterized a ~70–75% release with biphasic behavior, Faris et al. (2020) on his study emphasized pH-dependent release and the superior release of nanoparticles over pure Simvastatin, with a more extended 8-hour observation period. Together, these findings reinforce the potential of Nano formulation strategies for improving Simvastatin bioavailability and therapeutic performance. While comparing this study with the study by Selvasudha and Koumaravelou (2017), this study reported a burst release within the first 50 minutes, while Selvasudha and Koumaravelou (2017), observed 22.18% release within 2 hours. Therefore, this study showed a more rapid initial release, suggesting a more pronounced burst effect. In the sustained phase, their study reported a gradual release up to 66.18% over 8 hours, which aligns with my observation of a stepwise, sustained release up to 200 minutes, though the total duration and extent differ. Scanning Electron Microscopy (SEM) analysis was conducted to evaluate the morphology of the formulated Simvastatin-loaded Chitosan nanoparticles. The SEM images revealed that the Chitosan nanoparticles possessed a rough and porous surface, a characteristic that favors higher drug loading and enables sustained drug release. In contrast, pure Simvastatin appeared as loosely packed particles with visible voids, indicating its crystalline nature and potential issues with uniformity and solubility. Upon encapsulation, the Chitosan-coated Simvastatin nanoparticles exhibited a more cohesive and well-structured morphology, confirming successful drug incorporation and suggesting improved delivery performance. These findings align with a study by Shinde and Harinath (2014), in which Simvastatin encapsulated in PLGA nanoparticles showed a significant morphological transformation from needle-shaped crystalline particles to nearly spherical, uniformly sized nanoparticles (~122 nm) with no residual crystals demonstrating the advantages of nanoparticle-based systems in enhancing drug solubility and stability. Similarly, in another comparative study using field emission scanning electron microscopy (FE-SEM), ChN (Chitosan nanoparticles) and ChSimN (Simvastatin-loaded Chitosan nanoparticles) displayed morphological changes, with ChSimN appearing more spherical and slightly larger (~47.1 nm) than unloaded ChN (~35.3 nm). This structural transformation further corroborates the role of Chitosan encapsulation in achieving uniformity and stability. Collectively, these studies underscore the effectiveness of nanoparticulate carriers, whether Chitosan- or PLGA-based, in modifying drug morphology to enhance solubility, encapsulation efficiency, and overall therapeutic potential. Fourier Transform Infrared (FTIR) spectroscopy was employed in this study to investigate potential chemical interactions between Simvastatin and Chitosan during nanoparticle formulation. The FTIR spectra of pure Chitosan exhibited characteristic peaks corresponding to functional groups such as O–H, C=O, and C–H, while Simvastatin displayed distinct absorption bands indicative of its molecular structure. In the spectra of the Chitosan-coated Simvastatin nanoparticles, these characteristic peaks were preserved without significant shifts or disappearance, indicating that the encapsulation process maintained the chemical integrity of Simvastatin and that no strong chemical interactions occurred between the drug and the polymer matrix. This finding aligns with previous studies. Sarathchandiran et al. (2019) reported similar retention of functional peaks in Simvastatin-loaded Chitosan nanoparticles, confirming that no new covalent bonds formed during encapsulation. Likewise, Ullah et al. (2022) observed preserved FTIR signatures for Simvastatin in lipid-based nanoparticles, with characteristic peaks at 3545 cm^{-1} (O–H stretching), 2914 and 2849 cm^{-1} (C–H stretching), and 1732 cm^{-1} (C=O stretching), reinforcing the drug's structural stability post-loading. Additionally, Harisa et al. (2018) reported comparable FTIR profiles in Chitosan-based nanoparticle systems, where the retention of key functional group peaks confirmed the absence of chemical modification. Collectively, these findings demonstrate that Chitosan serves as a chemically inert and stable carrier matrix, capable of physically encapsulating Simvastatin without altering its molecular structure supporting its suitability for drug delivery applications.

Conclusion

Chitosan-coated simvastatin nanoparticles were successfully formulated using the ionic gelation technique with sodium tripolyphosphate as crosslinking agent. The developed formulation exhibited favorable physicochemical

characteristics, including modified morphology, structural stability, and a controlled biphasic drug release profile. SEM analysis confirmed successful encapsulation of simvastatin within a denser chitosan matrix, while FTIR results demonstrated compatibility between the drug and polymer without significant chemical interaction. The sustained release pattern observed suggests the potential for prolonged therapeutic action and improved drug availability. Overall, chitosan-coated nanoparticles represent a promising delivery platform for overcoming the limitations of simvastatin such as poor solubility and low oral bioavailability. Further studies involving particle size analysis, entrapment efficiency, stability assessment, and *in vivo* pharmacokinetic evaluation are recommended to establish their full pharmaceutical potential.

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