STM JOURNALS

Nano Trends:
A Journal of Nanotechnology and Its Applications

ISSN: 0973-418X
Volume 27, Issue 1, 2025
January–April
DOI (Journal): 10.37591/NTs

https://journals.stmjournals.com/nts

Research NTs

Synthesis and Characterization of PF-127 Stabilized Metformin Encapsulated Chitosan-TPP Nanoparticles

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Abstract

Metformin is widely used to manage Type 2 Diabetes, but its effectiveness is limited by low intestinal absorption, high dose requirements, and short half-life. To tackle these challenges, several nano-drug delivery systems have been designed to optimize the delivery of metformin and enhance its therapeutic efficacy. Nanoparticles (NPs) have emerged as key players in medicine, biology, and pharmacology, gaining considerable attention for their potential applications. Polymeric NPs are among the most utilized nanomaterials in nanomedicine due to their diverse applications. Chitosan (CS)-based polymeric NPs offer several key benefits, including biodegradability, biocompatibility, non-toxicity, bioactivity, ease of synthesis, and targeted delivery, making them highly suitable as drug carriers. CS NPs formed through ionic gelation are amongst the most studied nanosystems for drug delivery. Chitosan is also widely recognized as an effective mucoadhesive polymer, capable of enhancing the bioavailability of drugs and improving cellular permeability. In this study, metformin-loaded chitosan TPP nanoparticles, stabilized by PF-127, were formulated, and characterized. We have incorporated the Ionic Gelation method for the formulation of nanoparticles. Physiochemical analyses, such as FTIR and DLS were conducted. From the FTIR results, the successful synthesis of nanoparticles was confirmed. Also, the formulated nanoparticles showed a mean hydrodynamic size of 188.8 nm, a zeta potential of -18.3 mV, and a drug entrapment efficiency of up to 41%.

Keywords: Polymeric, metformin, ionic gelation method, chitosan

INTRODUCTION

Diabetes is currently one of the most grave and life-threatening health conditions [1]. Metformin (MET) has been a staple drug for treating type 2 diabetes mellitus (T2DM) over the years [2]. However, it faces several limitations that hinder its therapeutic effectiveness, including poor intestinal absorption, the need for high doses, and frequent administration attributing to its short half-life [3]. To overcome these challenges, several nano-drug delivery systems have been designed for the improvised delivery of MET [4].

Polymers are often recommended as ideal carriers for drug encapsulation [5]. They are not only biodegradable and biocompatible but also capable of releasing drugs in a controlled manner through methods like conjugation, surface modification, and responses to changes in pH or temperature [6]. This makes polymeric nanocarriers highly effective for enhancing drug targeting, permeability, bioavailability, and controlled release [7]. Among the various types of polymers available, chitosan

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Received Date: October 15, 2024
Accepted Date: November 22, 2024
Published Date: January 02, 2025

Citation: Sakshi Tyagi, Shalini Mani. Synthesis and Characterization of PF-127 Stabilized Metformin Encapsulated Chitosan-TPP Nanoparticles. Nano Trends: A Journal of Nanotechnology and Its Applications. 2025; 27(1): 34–38p.
DOI: https://doi.org/10.37591/NTs.v27i01.186054

(CS), alginate, pectin, and gums are some of the most commonly used [8]. Chitosan-based materials are broadly considered for oral drug delivery because of their beneficial properties, including mucoadhesion, biocompatibility, and adaptability for controlled release [9, 10]. Chitosan is procured from chitin, a natural polysaccharide presents within the shells and exoskeletons of various crustaceans, making it the second most abundant polysaccharide in nature [11, 12]. Nanoparticles, with their nanoscale size and large surface area, can interact more efficiently with biological systems, resulting in improved therapeutic outcomes [13, 14]. Chitosan nanoparticles (CS NPs) can be synthesized using the ionic gelation method, where crosslinking occurs as positively charged amino groups in chitosan bond with the negatively charged sodium tripolyphosphate (TPP) from an anionic polymer [15, 16]. These CS-based nanoparticles are highly favored as drug carriers due to several advantages, such as reduced risk of systemic toxicity, minimized local irritation, predictable gastric emptying, enhanced bioavailability, improved pharmacokinetic profiles, greater stability, and better patient compliance.

In the current study, we have fabricated the metformin-loaded CS-TPP nanoparticles (MET-CS-TPP NPs) and stabilized them with Pluronic F-127 (PF-127). The prepared NPs were physicochemically characterized using Fourier-transform infrared spectroscopy (FTIR) and Dynamic Light Scattering (DLS) techniques. FTIR was used to identify and confirm the functional groups involved in NPs formation and the successful encapsulation of MET. Moreover, DLS technique was used to analyze the particle size, polydispersity index (PDI), and zeta potential, providing insights into the colloidal stability and uniformity of the nanoparticles. These techniques collectively ensured the successful fabrication of MET-CS-TPP NPs with desired properties for potential biomedical applications.

MATERIALS AND METHODOLOGY

Materials

Metformin Hydrochloride (Cat No. RM10257), Chitosan, Pluronic F-127 (PF-127), and Sodium Tripolyphosphate (TPP) were obtained from the Himedia Laboratories, India. All reagents, chemicals, and solvents used in the experimental procedures were of analytical grade.

Spectrophotometric Detection for the Quantitative Analysis of Metformin

To determine the amount of residual metformin in various nanoformulations, a standard calibration curve of metformin was prepared. For the stock solution, metformin was first dissolved in Milli-Q water and then further diluted to concentrations within the range of 2 to 20 µg/ml. The sample's absorbance was measured at 234 nm, with the R^2 value optimized to be 0.99.

Fabrication of Metformin-Loaded Chitosan-TPP Nanoparticles

The Metformin hydrochloride nanoparticles were prepared using the ionic gelation process, with TPP serving as a cross-linker. Chitosan was first dissolved in 3% glacial acetic acid, while TPP was prepared in water. PF-127 was used as a stabilizer and combined with TPP before being added to the chitosan solution. The final mixture was homogenized overnight at 37°C. To optimize the combination of TPP and chitosan, varying concentrations were tested. Metformin (50 mg/ml) was added to a CS solution (ranging from 1% to 2%), and this mixture was combined with a TPP (0.1% to 0.3%) and PF-127 (1% to 2%) solution. The TPP+PF-127 solution was carefully added dropwise using a syringe dispenser over a period of 45 minutes. The solution was gradually mixed while stirring continuously to form the nanoparticles.

Encapsulation efficiency

The encapsulation efficiency of the synthesized NPs was determined by centrifuging them at 10,000 rpm for 20 minutes. The amount of free metformin in the supernatant was measured by a UV spectrophotometer at 234 nm. The amount of drug encapsulated within the nanoparticles was then estimated as follows:

$$\text{Encapsulation efficiency (\%)} = [\text{Total amount of metformin added} - (\text{Free Metformin} * 100)] / \text{The Total amount of metformin added}$$

Physicochemical Characterization of MET-CS-TPP Nanoparticles

The hydrodynamic particle size, zeta potential, and polydispersity index (PDI) of the nanoparticles were analyzed using a DLS particle size analyzer (Malvern NANO-series Zetasizer, Worcestershire, United Kingdom). To determine the numerous molecular components on the nano formulation's surface, FTIR was employed, detecting vibrational peaks of different functional groups in the 400 to 4000 cm^{-1}range [17]. FTIR operates on the principle that when infrared light passes through a sample, distinct components absorb or emit light at specific infrared wavelengths based on their unique properties [18].

RESULTS AND DISCUSSION

Fabrication and Characterization of MET-CS-TPP Nanoparticles

We have used the Ionic Gelation process for the synthesis of MET-CS-TPP NPs. From the UV spectrophotometric analysis, the encapsulation efficiency was estimated to be 41%. Next, the average hydrodynamic size and of NPs was observed to be 188.8 nm and PDI was observed to be 0.248, respectively (Figure 1A). The average hydrodynamic size of 188.8 nm indicates that the NPS are within the nanometric range, making them well-suited for numerous biomedical applications, including drug delivery. Their nanoscale size allows them to effectively penetrate biological barriers, facilitating efficient distribution of the encapsulated drug. The lower PDI value indicates the monodispersity of the fabricated NPs making them suitable for several biomedical applications. Electrostatic interaction amongst oppositely charged molecules is the main driving force of NPs formation through ionic gelation. The zeta potential represents the stability index of the NPs. It is anticipated that stability will increase with increasing magnitude, regardless of the type of charge. The zeta potential of formulated MET-CS-TPP NPs was observed to be –18.3 mV (Figure 1B). FTIR spectra of pure Metformin HCl was used to check the chemical stability of metformin in fabricated NP. FTIR of the pure MET exhibited the peak at 3369 cm^{-1} (NH stretching of NH2), 3148 cm^{-1} (CH stretching), 1624 cm^{-1} (C-N stretching), 1564 cm^{-1} (C=N stretching), 936 cm^{-1} (C-H distortion). Since there is no prominent peak for the standard in the MET-CS-TPP nanoparticles, we can deduce that the MET is probably encapsulated within the nanoparticle or not present on its surface (Figure 2). The FTIR analysis suggests that no interaction is taking place amongst the drug and the formulation excipients.

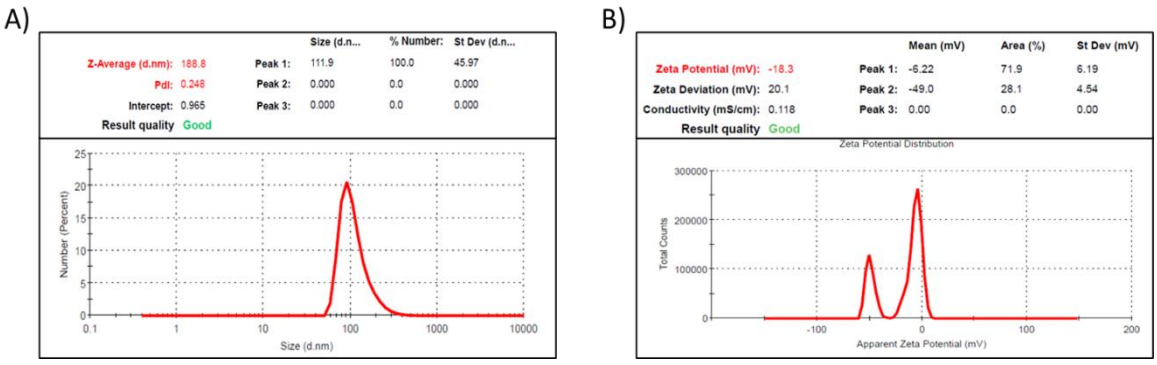

Figure 1. Characterization of MET-CS-TPP nanoparticles. (A) Dynamic light scattering (DLS), (B) Zeta potential.

CONCLUSIONS

In the present study, we have first reported the preparation and physicochemical characterizations of novel MET-CS-TPP NPs using stabilizer. From this study, we also confirmed that ionic gelation method is an appropriate technique for the fabrication of MET-CS-TPP NPs with improved encapsulation efficiency. From the FTIR analysis, the encapsulation of metformin inside the NPs was confirmed. These novel MET-CS-TPP NPs were fabricated to enhance the delivery and therapeutic efficacy of metformin, a widely used anti-hyperglycaemic drug. The structural integrity and overall stability of the nanoparticles are ensured through crosslinking between the polymer chitosan and TPP as a crosslinking agent. DLS studies confirm that the nanoparticles formed were in the nanometric range with a

homogeneous distribution. Analysis from the zeta potential results demonstrated that the NPs exhibit sufficient surface charge to maintain colloidal stability, which is an important aspect for biomedical use. Based on these promising results, MET-CS-TPP NPs can be potentially used for several biomedical applications, such as targeted drug delivery and controlled release system. Encapsulating metformin within polymeric nanoparticles has the potential to significantly enhance its bioavailability, potentially reducing both the required dosage and frequency of administration. Consequently, the developed formulation presents a promising alternative to traditional methods of managing T2DM. However, animal model studies could be explored for further validation and refinement of this novel formulation.

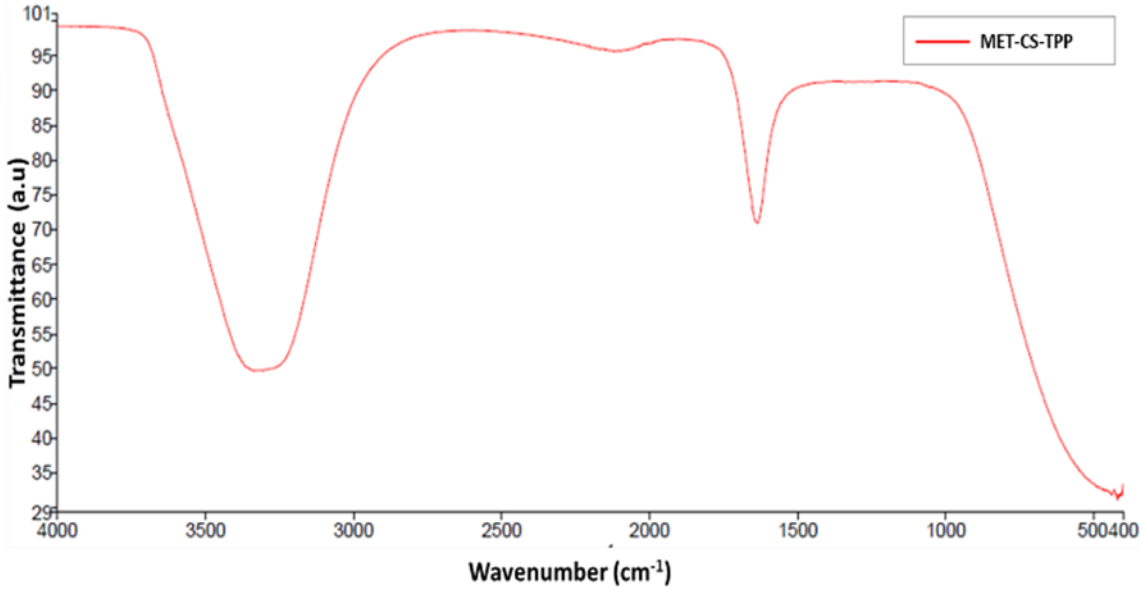

Figure 2. Image representing the FTIR spectra of MET-CS-TPP nanoparticles.

Acknowledgment

The authors are grateful to the Jaypee Institute of Information Technology, Noida for offering the infrastructure and amenities for the completion of this work. The authors would also like to acknowledge the Indian Council of Medical Research (ICMR) for providing the financial support required for completing the study.

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