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Development and characterization of remogliflozin etabonate loaded Chitosan based nanoparticles as enhanced drug delivery system

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Abstract
This study reports the development and characterization of chitosan-based nanoparticles (CNPs) for the controlled delivery of Remogliflozin etabonate, addressing its pH-dependent solubility and bioavailability challenges. Nanoparticles were synthesized through ionic gelation using polyvinylpyrrolidone (PVP) as a crosslinker, achieving a mean particle size of 47-55 nm (SEM) and high encapsulation efficiency. XRD analysis confirmed amorphization of the drug within the matrix, while FTIR spectra verified successful polymer-drug interaction. The optimized formulation exhibited sustained release kinetics, with around 90% cumulative release over selected duration following anomalous transport (Korsmeyer-Peppas exponent: n=0.510) and Higuchi diffusion (R^2=0.993). Swelling studies demonstrated pH-responsive behavior, with prolonged gastric retention. Accelerated stability studies showed no significant alterations in drug content and dissolution profile, or physicochemical properties. The developed CNP system presents a robust platform for enhancing the oral bioavailability of Remogliflozin etabonate through synergistic pH-modulated release, mucoadhesion, and controlled dissolution kinetics, with potential clinical applications in diabetes therapy.

Keywords: Remogliflozin etabonate, chitosan nanoparticles, ionic gelation, controlled release, stability studies

Introduction
Nanotechnology has revolutionized drug delivery systems by enhancing therapeutic efficacy while minimizing adverse effects. Among the various biomaterials explored, chitosan (CS)—a biocompatible, biodegradable, and nontoxic biopolymer derived from chitin—has emerged as a promising candidate for nanoparticle-based drug delivery. Chitosan nanoparticles (CNPs) have garnered significant attention for their ability to facilitate targeted drug delivery, particularly in oncology, where precision and reduced systemic toxicity are paramount [1-3].
Chitosan, the N-deacetylated derivative of chitin, is composed of β-(1-4)-linked D-glucosamine and N-acetyl-D-glucosamine units. Unlike cellulose, chitin possesses an acetamide group at the C-2 position, contributing to its unique biological properties. The solubility and functionality of chitosan largely depend on its degree of deacetylation (DD), which influences its applicability in drug delivery systems [8-10]. Over the past decade, chitosan-based formulations—including films, hydrogels, microparticles, and nanoparticles—have been extensively investigated for the controlled release of small-molecule drugs, proteins, peptides, and nucleic acids. Notably, chitosan's mucoadhesive properties enhance drug absorption across mucosal surfaces in the gastrointestinal tract, respiratory system, and ocular tissues, further broadening its therapeutic potential [4-7].
Recent advancements in drug delivery have leveraged nanotechnology, stimuli-responsive systems, and computational modeling to optimize drug release kinetics and targeting efficiency. Artificial intelligence (AI) and in silico simulations have accelerated the design of tailored drug delivery systems, enabling precise predictions of their pharmacokinetic and pharmacodynamic behavior [11, 12]. Despite these innovations, challenges such as inconsistent drug release profiles and immunogenicity remain critical hurdles. Ongoing research focuses on functionalizing chitosan through chemical modifications, integrating theranostic capabilities (combining therapy and diagnostics), and developing stimuli-responsive platforms for personalized medicine [13].
A key aspect of chitosan-based drug delivery is the mechanism of drug release, which can be

governed by diffusion, polymer degradation, or environmental triggers (e.g., pH, temperature, or enzymatic activity). Understanding these mechanisms is essential for designing efficient, controlled-release systems that maximize therapeutic outcomes. This review highlights the latest developments in chitosan nanoparticles for targeted drug delivery, emphasizing their formulation strategies, release mechanisms, and applications in cancer therapy. Furthermore, it explores future directions, including the integration of smart nanomaterials and AI-driven design, to advance precision medicine and overcome existing limitations in drug delivery.

Materials

The study utilized high-purity chemicals and reagents, including acetonitrile (HPLC grade), methanol (HPLC grade), toluene (AR grade), and water (HPLC grade) from Merck Specialties Private Ltd. (Mumbai, India) and Qualigens Fine Chemicals (Mumbai, India). Additional reagents such as triethylamine (HPLC grade), hydrochloric acid (AR grade), sodium hydroxide (AR grade), hydrogen peroxide, orthophosphoric acid, and potassium dihydrogen orthophosphate were procured from Research Lab. (Mumbai, India) and S.D. Fine-Chem. Ltd. (Mumbai, India).

The active pharmaceutical ingredient, Remogliflozin etabonate, was obtained from Alkem Laboratories Ltd. (Mumbai, India). Polymers and excipients, including chitosan, sodium alginate, hydroxypropyl methylcellulose (HPMC), carboxymethylcellulose (CMC), pregelatinized starch, and polymethylmethacrylate, were sourced from Loba Chemicals India Pvt. Ltd., Merck India Limited, and Sigma-Aldrich, India.

Instrumentation: The following instruments were employed for synthesis, characterization, and analysis: Digital Balance (AUX 120, Shimadzu, Japan) for precise weighing, Differential Scanning Calorimeter (METTLER DSC 30 S, Mettler Toledo India Pvt. Ltd.) for thermal analysis, Infrared Spectrophotometer (IR Affinity 1, Shimadzu, Kyoto, Japan) with KBr press (TSI, Mumbai) for FT-IR studies, Dissolution Test Apparatus (Electrolab TDT 08 L Plus, Mumbai, India) and Disintegration Tester (USP ED-2L, LAB-HOSP, Mumbai) for drug release studies, Sonicator, Digital pH Meter and Stability Chamber (Remi Lab, Mumbai) for sample preparation and stability testing, Jaguar tablet compression machine for formulation development.

Experimental

Preformulation Studies

- **Drug dentification:** The identity of Remogliflozin etabonate was confirmed using FT-IR spectroscopy (KBr pellet method) and melting point determination (capillary method).
- **Solubility Studies:** The solubility of the drug was assessed in various solvents by preparing saturated solutions under continuous shaking (Remi Mechanical Shaker, Mumbai) at 37±0.5 °C for 24 h. The solutions were filtered (0.45 µm pore size) and analyzed via UV spectrophotometry at 276 nm.
- **Standard Calibration Curve:** A stock solution (100 µg/mL) of Remogliflozin etabonate was prepared in pH 1.2 buffer serial dilutions (10-60 µg/mL) were analyzed spectrophotometrically and a calibration curve was plotted (absorbance vs. concentration).

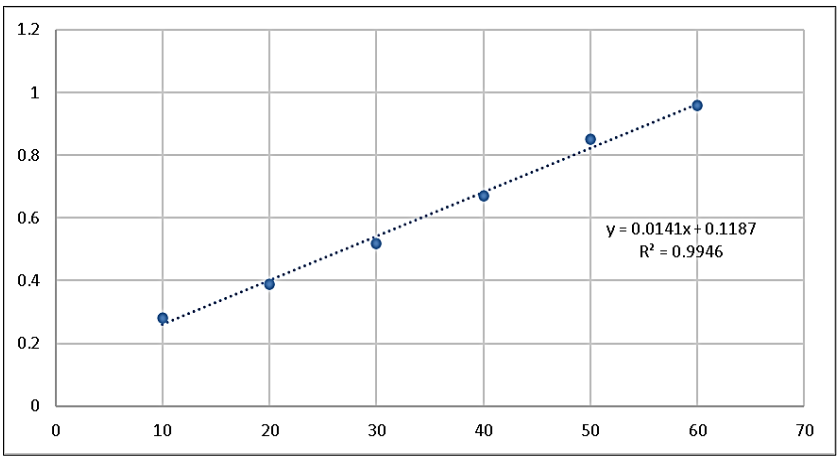

Fig 1: Standard calibration curve of Remogliflozin etabonate in pH 1.2

- **Preparation of Water-Soluble Chitosan:** Chitosan (1 g) was dissolved in 0.1 N HCl (50 mL) and treated with 30% hydrogen peroxide at 60°C for 1 h. The solution was cooled, mixed with ethanol (100 mL), and stored at 5 °C for 24 h. The precipitate was freeze-dried to obtain water-soluble chitosan.
- **Nanoparticle Formation via Ionic Gelation:** Water-soluble chitosan was reacted with potassium pyrophosphate in varying ratios (1:0.5, 1:1, 1:2) under 0-5 °C with continuous stirring. The nanoparticles were collected via centrifugation (1200 rpm, 20 min), washed, and lyophilized.

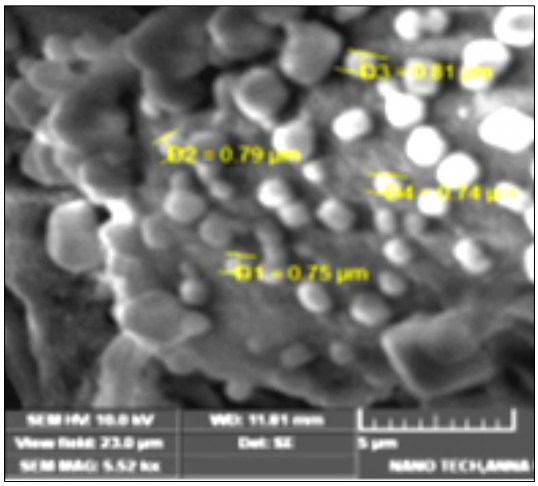

Fig 2: SEM image of chitosan nanoparticle after one-step de-solvation method

SEM image of chitosan nanoparticle after one-step de-solvation method

- **Drug Loading and Optimization:** Selection of Crosslinking Agents:
  Three crosslinkers were evaluated for drug encapsulation efficiency. Remogliflozin etabonate was incorporated into chitosan nanoparticles using a one-pot ionic gelation technique, maintaining a 1:1 drug-to-polymer ratio. The mixture was stirred (0-5°C, 1 h), centrifuged, and freeze-dried.
- **Preliminary Trials for Nanoparticle Synthesis:** Chitosan was dissolved in distilled water, and pH was adjusted (3.0, 5.0, 7.0) using phosphoric acid. Nanoparticles were precipitated by acetone addition, centrifuged and lyophilized.
- Characterization of Nanoparticles SEM Analysis: Morphology and particle size were examined using, FT-IR Spectroscopy: Functional group interactions were analyzed, XRD: Crystallinity of nanoparticles was assessed using XRD.
- **Formulation of Nanoparticle-Loaded Tablets:** Tablets were prepared via direct compression (3500 psi) using a single-punch tablet press (Korsch Erweka, Germany). The formulation contained drug-loaded nanoparticles, HPMC, CMC, and pregelatinized starch (1:1:0.2 w/w).
- ***In Vitro* Drug Release Studies:** Dissolution studies were conducted using USP Apparatus II (paddle type, 50 rpm, 37±0.5 °C). The medium was initially 0.1 N HCl (2 h), followed by phosphate buffer (pH 6.8). Samples were withdrawn periodically and analyzed via UV spectrophotometry.
- **Drug Release Kinetics:** Release data were fitted to zero-order, first-order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas models using PCP Dissolution software (v2.08). The best-fit model was selected based on regression coefficient (R^2).
- **Swelling Studies:** Tablet hydration and gel-layer formation were evaluated to understand buoyancy, mucoadhesion, and drug release kinetics.
- **Stability Studies:** Optimized formulations were stored at 40 °C/75±5% RH for 3 months (ICH guidelines). Samples were analyzed monthly for drug content, mucoadhesion and dissolution profile. This systematic approach ensured the development of an optimized chitosan nanoparticle-based drug delivery system with enhanced therapeutic efficacy.

Results and Discussion

Preformulation Characterization and Drug Analysis

The structural integrity of Remogliflozin etabonate was confirmed through comprehensive spectroscopic and thermal analyses. Fourier-transform infrared spectroscopy revealed characteristic absorption bands at 3343 cm^{-1} (N-H stretching of primary amide), 1746 cm^{-1} (C=O stretching of ketone), and 1591 cm^{-1} (N-H bending), which matched the reference spectrum (Manirul Haque *et al*., 2023). The sharp melting point range of 152-156 °C further corroborated the drug's purity and crystalline nature, consistent with pharmacopeial standards (IPC, 2023). Solubility studies demonstrated significant pH-dependent behavior, with maximum solubility in acidic conditions (5.60 mg/mL in pH 1.2) and poor solubility in neutral/alkaline media (0.37 mg/mL in pH 6.8), highlighting the necessity for a gastroretentive delivery approach to enhance bioavailability.

Development and Characterization of Chitosan Nanoparticles

The two-step desolvation technique effectively reduced chitosan particle size from 700-800 nm to 47-55 nm, as evidenced by scanning electron microscopy. This size reduction was crucial for improving drug loading capacity and release characteristics. X-ray diffraction analysis showed a transition from semi-crystalline bulk chitosan (peaks at 11.59° and 20.77°) to amorphous nanoparticles, which significantly enhanced drug encapsulation efficiency. FT-IR spectroscopy confirmed successful crosslinking with polyvinylpyrrolidone (PVP), demonstrated by new absorption bands at 1705 cm^{-1} (C=O stretching of PVP lactam) and 1268 cm^{-1} (C-N stretching).

Optimization of Drug Loading and Release Characteristics

Comparative evaluation of crosslinking agents revealed PVP's superior performance over polyethylene glycol (PEG), achieving 21% process yield at a 1:1 chitosan:PVP ratio. The optimized formulation (F2) exhibited controlled release kinetics, with only 12% drug release in the first hour and 90% cumulative release over 300 minutes. Kinetic modeling indicated the release followed Higuchi diffusion (R^2=0.993) with Korsmeyer-Peppas exponent (n=0.510) confirming

anomalous transport a combination of diffusion and polymer relaxation mechanisms. This dual mechanism is particularly advantageous for maintaining consistent plasma drug levels.

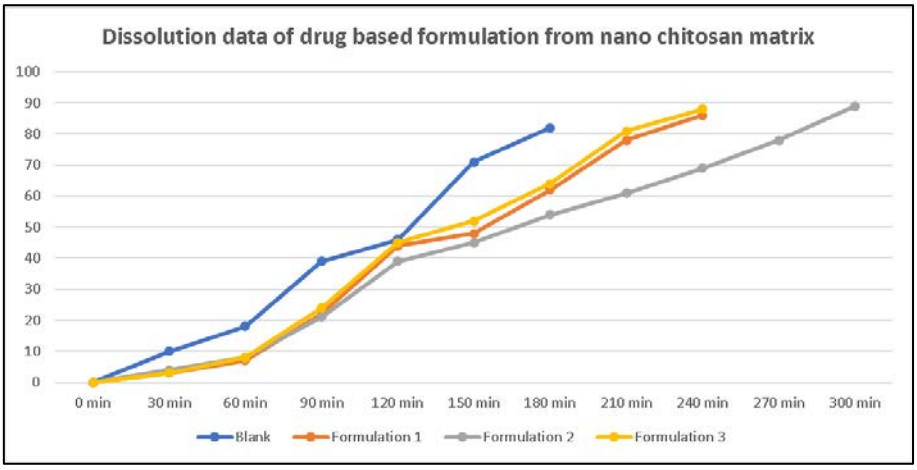

Fig 3: Zero order release graphical representation of drug loaded nano chitosan matrix

Swelling Behavior and Matrix Performance

Hydroxypropyl methylcellulose (HPMC)-based matrices demonstrated progressive swelling, forming a stable gel layer that maintained integrity for over 240 minutes. Formulation F2 (1:1 chitosan: PVP ratio) showed optimal performance, with minimal initial burst release (1-12%) in acidic conditions and sustained release over 300 minutes. The swelling index reached 88% at 240 minutes, indicating effective water uptake while controlling erosion rates. This behavior is attributed to HPMC's high water retention capacity combined with PVP's crosslinking effect.

Stability Assessment

Accelerated stability testing (40°C/75% RH for 3 months) confirmed the formulation's robustness. No significant changes were observed in drug content (90.00 ± 0.824%), tablet hardness (10.5 kg/cm²), or dissolution profile. These results demonstrate the formulation's resistance to humidity-induced degradation, a critical factor for tropical climate storage and long-term stability.

Conclusion

The developed chitosan-PVP nanoparticle system successfully addressed key challenges in Remogliflozin etabonate delivery. The pH-responsive swelling behavior, combined with optimized crosslinking, created an effective gastroretentive system with controlled release properties. The amorphous nature of nanoparticles enhanced drug loading, while the 1:1 chitosan: PVP ratio provided optimal release modulation. The anomalous transport mechanism ensures consistent drug release through combined diffusion and swelling processes. Excellent stability under accelerated conditions positions this formulation as a promising candidate for clinical translation, particularly for drugs requiring prolonged gastric residence and pH-dependent solubility enhancement.

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