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Development and Evaluation of Fluconazole-Loaded Nanocellulose-Based Three-Dimensional Polymeric Scaffolds Derived from Agricultural Biomass for Sustained Drug Delivery Applications

Maya Kumawat[1]*, Dr. Vaibhav Verma[2]

[1]M.Pharm Scholar (Enrolment No: PU05224EPG12013), Gyanodaya Institute of Pharmacy, Gyanodaya University, Neemuch, Madhya Pradesh, India.

[2]Professor, Gyanodaya Institute of Pharmacy, Gyanodaya University, Neemuch, Madhya Pradesh, India

Abstract:
The development of biocompatible and sustainable polymeric drug delivery systems has gained significant attention due to the increasing demand for controlled release formulations with improved therapeutic performance. Nanocellulose, a renewable nanoscale biomaterial obtained from lignocellulosic sources, possesses unique characteristics including high surface area, biodegradability, mechanical strength, excellent swelling capacity and compatibility with various pharmaceutical polymers. The present research work aimed to design, formulate and evaluate fluconazole-loaded nanocellulose-based three-dimensional (3D) polymeric scaffolds for sustained localized drug delivery applications.

In this investigation, agricultural residues including rice straw and wheat straw were utilized as economical and renewable sources for extraction of nanocellulose. Rice nanocellulose fibers (RNF) and wheat nanocellulose fibers (WNF) were isolated through sequential alkaline treatment, bleaching and acid hydrolysis methods. The extracted nanocellulose was further modified using tetraethyl orthosilicate (TEOS), Eudragit E100 coating and trisodium trimetaphosphate (STMP)-mediated gellan gum crosslinking approaches to enhance structural integrity and drug delivery performance.

The prepared nanocellulose and polymeric scaffolds were characterized using Fourier Transform Infrared Spectroscopy (FTIR), X-Ray Diffraction (XRD), Thermogravimetric Analysis (TGA), Field Emission Scanning Electron Microscopy (FE-SEM), particle size analysis and other evaluation techniques. The developed scaffolds were evaluated for physicochemical characteristics including porosity, swelling behaviour, mechanical strength, mucoadhesive properties, drug release behaviour and antifungal performance.

The results demonstrated successful extraction of nanocellulose from rice and wheat straw with good yield and desirable physicochemical characteristics. Fluconazole-loaded scaffolds showed porous morphology, improved mechanical stability, excellent mucoadhesion and sustained drug release characteristics. Among various modification strategies, Eudragit-coated and STMP-gellan crosslinked scaffolds exhibited superior performance.

The study concluded that agricultural waste-derived nanocellulose-based 3D polymeric scaffolds represent a promising, eco-friendly and effective platform for sustained localized pharmaceutical drug delivery applications.

Keywords: Nanocellulose; Polymeric scaffold; Fluconazole; Sustained drug delivery; Rice straw; Wheat straw; 3D scaffold; Biomaterial.

Corresponding Author: Maya Kumawat †, M.Pharm Scholar (Enrolment No: PU05224EPG12013), Gyanodaya Institute of Pharmacy, Gyanodaya University, Neemuch, Madhya Pradesh, India

1. INTRODUCTION

Recent advancements in pharmaceutical technology have significantly increased the interest toward the development of novel drug delivery systems capable of achieving controlled, sustained and targeted therapeutic action. Conventional dosage forms often suffer from several limitations such as frequent administration, fluctuation in plasma drug concentration, poor patient compliance and reduced therapeutic efficiency. Therefore, the development of advanced polymeric carrier systems has become an important approach for improving drug delivery performance.

Three-dimensional (3D) polymeric scaffolds have attracted considerable attention in pharmaceutical and biomedical fields because of their unique porous architecture, high surface area and ability to incorporate bioactive molecules. These scaffolds provide an interconnected porous network that allows efficient drug loading, controlled diffusion and sustained release of therapeutic agents. Initially, scaffold-based systems were widely investigated for tissue engineering and regenerative medicine; however, their applications have now expanded toward controlled drug delivery, wound healing and localized therapy.

The selection of suitable polymeric material plays a crucial role in determining the performance of scaffold-based drug delivery systems. Natural polymers have gained increasing importance due to their biodegradability, biocompatibility, renewable origin and low toxicity. Among different natural polymers, cellulose and its nanoscale derivatives have emerged as promising biomaterials for pharmaceutical applications.

Nanocellulose is a nanosized cellulose material obtained from various natural sources including plants, microorganisms and agricultural residues. It consists of cellulose fibers with dimensions in the nanometer range and possesses several advantageous properties including high mechanical strength, high aspect ratio, large surface area, excellent water retention capacity, biodegradability and compatibility with other polymers. Due to these characteristics, nanocellulose has been extensively investigated for applications in drug delivery systems, tissue engineering, wound dressing, biomedical implants and pharmaceutical formulations.

Agricultural biomass represents one of the most abundant and sustainable sources for extraction of nanocellulose. Rice straw and wheat straw are generated globally in large quantities as agricultural waste products. These residues contain significant amounts of cellulose along with hemicellulose and lignin. Improper disposal and burning of these wastes contribute to environmental pollution. Conversion of such agricultural residues into valuable nanomaterials provides an eco-friendly and economically beneficial approach.

Extraction of nanocellulose generally involves removal of non-cellulosic components through chemical treatments such as alkaline treatment, bleaching and acid hydrolysis. Alkali treatment removes lignin and hemicellulose from the lignocellulosic matrix, while bleaching improves cellulose purity. Acid hydrolysis further removes amorphous regions of cellulose and produces nanoscale cellulose fibers with enhanced crystallinity and functional properties.

Although nanocellulose possesses excellent biological and mechanical characteristics, modification approaches are often required to improve its performance in advanced drug delivery applications. Surface modification and crosslinking methods can enhance stability, swelling behaviour, mechanical properties and drug release characteristics of nanocellulose-based systems.

Tetraethyl orthosilicate (TEOS) modification has been explored to improve structural strength and functional properties of polymeric materials through silica-based network formation. Similarly, Eudragit E100, a pharmaceutical-grade polymer, has been widely used for controlled release applications due to its film-forming and pH-dependent solubility characteristics. Gellan gum, when crosslinked using trisodium trimetaphosphate (STMP), provides stable polymeric networks suitable for controlled drug delivery.

Fluconazole is a widely used triazole antifungal drug effective against various Candida infections. However, conventional therapy may require repeated dosing and may produce limitations associated with systemic exposure. Localized sustained delivery of fluconazole through polymeric scaffold systems can improve therapeutic effectiveness by maintaining drug concentration at the target site for prolonged periods.

In the present study, rice and wheat straw-derived nanocellulose was utilized for the development of fluconazole-loaded three-dimensional polymeric scaffolds. Different modification strategies including TEOS modification, Eudragit E100 coating and STMP-gellan gum crosslinking were applied to improve scaffold characteristics. The prepared systems were evaluated for physicochemical, structural, mechanical and drug release properties to determine their suitability as sustained localized drug delivery platforms.

The major objective of this research was to develop a sustainable, biodegradable and efficient nanocellulose-based scaffold system that combines agricultural waste utilization with advanced pharmaceutical drug delivery technology.

2. MATERIALS AND METHODS

2.1 Materials

Rice straw and wheat straw were selected as natural lignocellulosic sources for extraction of nanocellulose. The agricultural residues were collected, cleaned and processed before chemical treatment. Sodium hydroxide, hydrochloric acid, sodium hypochlorite and oxalic acid were used during purification and hydrolysis processes.

Fluconazole was selected as a model antifungal drug for incorporation into polymeric scaffold systems. Tetraethyl orthosilicate (TEOS) was used as a silica modifying agent, trisodium trimetaphosphate (STMP) was employed as a crosslinking agent, and Eudragit E100 and gellan gum were utilized as pharmaceutical polymers for scaffold modification and development.

All chemicals and reagents used during the study were of analytical grade.

2.2 Extraction of Nanocellulose from Rice and Wheat Straw

Nanocellulose was extracted from rice and wheat straw using sequential chemical treatment involving alkaline treatment, bleaching and acid hydrolysis.

Initially, rice and wheat straw samples were thoroughly washed with distilled water to remove dust and unwanted impurities. The dried biomass was treated with sodium hydroxide solution to remove hemicellulose, lignin and other non-cellulosic materials from the lignocellulosic structure.

After alkaline treatment, the obtained cellulose-rich material was subjected to bleaching using sodium hypochlorite solution in acidic conditions. This process further removed residual lignin and improved cellulose purity.

The purified cellulose was subsequently treated by acid hydrolysis method to break down cellulose fibers into nanoscale dimensions. After completion of hydrolysis, repeated washing with distilled water was performed to remove residual chemicals.

The obtained rice nanocellulose fibers (RNF) and wheat nanocellulose fibers (WNF) were dried and stored for further scaffold preparation.

2.3 Characterization of Extracted Nanocellulose

The extracted nanocellulose samples were characterized using different analytical techniques to confirm successful isolation and evaluate physicochemical properties.

2.3.1 Fourier Transform Infrared Spectroscopy (FTIR)

FTIR analysis was performed to identify functional groups and structural changes after chemical treatment. The spectra were recorded to confirm removal of lignin and hemicellulose and preservation of cellulose structure.

2.3.2 X-Ray Diffraction Analysis (XRD)

XRD analysis was carried out to evaluate crystalline characteristics of extracted nanocellulose. The crystallinity changes after chemical processing were studied by observing diffraction patterns.

2.3.3 Thermogravimetric Analysis (TGA)

Thermal stability of rice and wheat nanocellulose was determined using thermogravimetric analysis. Weight loss behaviour of samples was observed with increasing temperature.

2.3.4 Morphological Evaluation

The surface morphology and nanoscale structure of prepared nanocellulose were evaluated using electron microscopic techniques including FE-SEM and TEM analysis.

2.4 Preparation of Fluconazole-Loaded Nanocellulose-Based 3D Scaffolds

Fluconazole-loaded polymeric scaffolds were prepared using nanocellulose as a basic structural material. Different modification approaches were applied to enhance scaffold performance.

2.4.1 TEOS Modified Nanocellulose Scaffolds

Nanocellulose was modified using tetraethyl orthosilicate (TEOS) to improve structural properties of the scaffold matrix. Fluconazole was incorporated into the modified polymeric network followed by scaffold formation.

2.4.2 Eudragit E100 Coated Scaffolds

Eudragit E100 coating was applied over nanocellulose-based scaffolds to improve mechanical strength and sustained drug release behaviour.

2.4.3 STMP-Gellan Gum Crosslinked Scaffolds

Nanocellulose was combined with gellan gum and crosslinked using trisodium trimetaphosphate (STMP). Crosslinking was performed to obtain stable porous polymeric structures with improved drug delivery characteristics.

2.5 Evaluation of Prepared Scaffolds

The developed fluconazole-loaded scaffolds were evaluated for various pharmaceutical parameters.

2.5.1 Porosity and Swelling Behaviour

The porous nature and swelling ability of scaffolds were determined to evaluate their capability for fluid absorption and controlled drug release.

2.5.2 Mechanical Strength

Mechanical properties of scaffolds were studied to determine structural integrity and suitability for biomedical applications.

2.5.3 Mucoadhesive Strength

Mucoadhesion studies were performed to determine the ability of scaffolds to remain attached at the application site for prolonged drug delivery.

2.5.4 In Vitro Drug Release Study

Drug release studies were performed to determine the sustained release behaviour of fluconazole from prepared scaffold formulations.

2.5.5 Antifungal Evaluation

The antifungal effectiveness of fluconazole-loaded scaffolds was evaluated against fungal organisms to confirm therapeutic potential.

The obtained results were analyzed to identify the optimized scaffold system suitable for sustained localized drug delivery applications.

3. RESULTS AND DISCUSSION

3.1 Extraction and Characterization of Nanocellulose

Nanocellulose was successfully isolated from rice straw and wheat straw using sequential chemical processing including alkaline treatment, bleaching and acid hydrolysis. The treatment process effectively removed unwanted non-cellulosic components such as lignin, hemicellulose and other impurities from the lignocellulosic biomass.

During alkaline treatment, sodium hydroxide disrupted the complex structure of plant biomass by breaking intermolecular bonding and removing lignin and hemicellulose fractions. Subsequent bleaching treatment further improved cellulose purity by eliminating remaining coloured impurities and lignin residues. Acid hydrolysis reduced the cellulose fibers into nanoscale dimensions by removing amorphous regions and enhancing crystalline cellulose content.

The obtained rice nanocellulose fibers (RNF) and wheat nanocellulose fibers (WNF) appeared as light-coloured fibrous materials, confirming successful purification. The percentage yield of extracted nanocellulose was found to be approximately 62.5% for RNF and 50% for WNF. The higher yield of RNF may be associated with greater cellulose content present in rice straw compared with wheat straw.

3.2 Chemical Composition Analysis

The chemical composition study confirmed enrichment of cellulose after the extraction process. A significant increase in α-cellulose content was observed, indicating successful removal of amorphous components.

The presence of higher α-cellulose fraction suggested improved purity and crystalline nature of extracted nanocellulose. Reduction in β-cellulose and γ-cellulose fractions confirmed efficient elimination of degraded cellulose components and non-cellulosic impurities.

These findings demonstrated that rice and wheat straw can act as suitable renewable sources for pharmaceutical-grade nanocellulose preparation.

3.3 FTIR Spectroscopic Analysis

FTIR spectroscopy was performed to evaluate chemical modifications occurring during nanocellulose extraction and scaffold development.

The FTIR spectra of extracted nanocellulose showed characteristic peaks associated with cellulose functional groups. Broad absorption bands corresponding to hydroxyl (-OH) stretching confirmed the presence of cellulose structure.

The disappearance or reduction of peaks associated with lignin and hemicellulose confirmed their removal after chemical treatment. Preservation of major cellulose peaks demonstrated that the extraction process successfully purified cellulose without damaging its fundamental structure.

FTIR analysis of modified scaffolds further confirmed successful interaction between nanocellulose, fluconazole and polymeric components such as TEOS, Eudragit E100 and gellan gum.

3.4 X-Ray Diffraction Analysis

XRD analysis was performed to determine crystalline behaviour of extracted nanocellulose and prepared scaffold formulations.

The removal of amorphous components during chemical treatment resulted in improved crystallinity of nanocellulose fibers. Characteristic diffraction peaks confirmed the presence of cellulose crystalline regions.

After scaffold formation, a reduction in crystallinity was observed due to polymer interaction and incorporation of fluconazole within the scaffold matrix. The amorphous nature of optimized scaffolds was beneficial for improving drug dispersion and release characteristics.

3.5 Thermogravimetric Analysis

Thermal analysis demonstrated improved thermal behaviour of extracted nanocellulose compared with untreated agricultural biomass.

Removal of lignin, hemicellulose and other impurities enhanced thermal stability. Modified scaffold systems exhibited suitable thermal properties due to formation of stable polymeric networks.

The incorporation of TEOS, Eudragit coating and STMP crosslinking influenced degradation behaviour and provided improved stability required for pharmaceutical applications.

3.6 Morphological Evaluation of 3D Scaffolds

Electron microscopic evaluation confirmed successful formation of three-dimensional porous scaffold structures.

The prepared scaffolds exhibited interconnected porous architecture which is essential for drug loading and controlled release applications. The porous network provides sufficient space for incorporation of fluconazole molecules and allows gradual diffusion of drug from the polymer matrix.

Modification with Eudragit E100 and STMP-gellan crosslinking resulted in improved structural arrangement and mechanical integrity.

3.7 Swelling and Porosity Studies

Swelling behaviour plays an important role in controlling drug release from polymeric scaffold systems. The developed nanocellulose-based scaffolds demonstrated significant swelling ability due to hydrophilic functional groups present in cellulose.

High porosity values indicated the formation of an interconnected network structure. The porous morphology supported fluid uptake and controlled diffusion of fluconazole.

Optimized formulations showed porosity values above 70%, demonstrating their suitability as drug carrier systems.

3.8 Mechanical Properties and Mucoadhesive Strength

Mechanical evaluation demonstrated that modification strategies significantly influenced scaffold strength.

Eudragit-coated scaffolds showed enhanced mechanical performance due to formation of a polymeric coating layer. STMP-gellan crosslinked scaffolds exhibited excellent mucoadhesive characteristics because of stronger interaction with biological surfaces.

The improved mucoadhesive strength indicated prolonged retention ability at the site of administration, which is advantageous for localized vaginal drug delivery.

3.9 In Vitro Drug Release Study

Fluconazole release studies demonstrated sustained drug delivery behaviour from prepared nanocellulose-based scaffolds.

The porous polymeric network-controlled penetration of dissolution medium and regulated diffusion of fluconazole molecules.

Optimized formulations demonstrated prolonged drug release with approximately complete release over the study period. Controlled release behaviour reduces the need for frequent administration and improves therapeutic efficiency.

Among developed formulations, Eudragit-coated scaffolds provided extended release behaviour, while STMP-gellan crosslinked systems showed excellent drug release combined with improved mucoadhesion.

3.10 Antifungal Performance

The antifungal activity study confirmed that fluconazole retained its therapeutic effectiveness after incorporation into nanocellulose scaffolds.

The optimized formulations showed effective inhibition of fungal growth, indicating successful drug loading and release from scaffold systems.

The results suggested that fluconazole-loaded nanocellulose scaffolds may serve as effective localized delivery platforms for management of fungal infections.

Overall, the developed nanocellulose-based 3D scaffolds demonstrated desirable physicochemical properties, controlled release performance and promising pharmaceutical applicability.

4. CONCLUSION

The present research successfully demonstrated the development and evaluation of fluconazole-loaded nanocellulose-based three-dimensional polymeric scaffolds using agricultural biomass-derived cellulose as a sustainable pharmaceutical material.

Rice straw and wheat straw were effectively utilized as renewable sources for the extraction of nanocellulose. The sequential chemical extraction process involving alkaline treatment, bleaching and acid hydrolysis successfully removed lignin and hemicellulose components and produced purified nanoscale cellulose fibers.

The extracted rice nanocellulose fibers (RNF) and wheat nanocellulose fibers (WNF) exhibited desirable physicochemical characteristics including improved purity, suitable crystallinity and enhanced thermal behaviour. The results confirmed that agricultural residues can be converted into valuable biomaterials for pharmaceutical applications.

Different scaffold modification approaches including TEOS modification, Eudragit E100 coating and STMP-mediated gellan gum crosslinking were successfully applied for the fabrication of fluconazole-loaded polymeric scaffold systems. These modifications improved the structural stability, mechanical properties, mucoadhesive behaviour and drug release performance of the prepared formulations.

The developed scaffolds showed interconnected porous morphology, high swelling capacity and suitable mechanical characteristics. The porous three-dimensional structure allowed efficient incorporation of fluconazole and supported controlled release of the drug over an extended period.

Among the prepared formulations, Eudragit-coated nanocellulose scaffolds exhibited superior mechanical strength and sustained drug release characteristics, whereas STMP-gellan crosslinked scaffolds demonstrated enhanced mucoadhesion and drug delivery performance.

The in vitro evaluation confirmed that fluconazole-loaded nanocellulose scaffolds could maintain effective drug release and antifungal activity, making them promising candidates for localized vaginal drug delivery applications.

Overall, the study highlights an eco-friendly strategy for converting agricultural waste into advanced pharmaceutical biomaterials. Nanocellulose-based 3D polymeric scaffolds represent a sustainable, biodegradable and effective platform for controlled drug delivery and future biomedical applications.

Future Perspective

Nanocellulose-based scaffold technology provides significant opportunities for development of next-generation drug delivery systems. Further research involving in vivo evaluation, long-term stability studies and clinical investigations may support the translation of these systems into practical pharmaceutical applications.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this research work.

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Author Contributions

Maya Kumawat contributed to experimental work, data collection, analysis and manuscript preparation.

Mangal Singh Panwar contributed to conceptualization, supervision, guidance and final manuscript review.

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