RESEARCH PAPER

Curcumin-Loaded Casein Nanoparticle-based Biocomposite Films: Fabrication, Characterization and Drug Release Studies

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ABSTRACT

In this study, casein nanoparticle-based biocomposite films were fabricated for possible drug delivery applications. To enhance the flexibility and film-forming abilities of this biocomposite film, the casein nanoparticles were embedded in the biocomposite film matrix, with the addition of glycerol as a plasticizing agent. Scanning electron microscopy (SEM) and Fourier transform infrared spectroscopy (FTIR) were used to investigate the surface morphological and functional group interaction attributes of the fabricated films. The synthesized casein nanoparticle biocomposite films were also loaded with curcumin, a natural bioactive compound with therapeutic potential and analyzed for drug loading efficiency and in vitro drug release behaviour. The curcumin-loaded films showed effective drug incorporation and a sustained release performance, which make casein nanoparticle-based biocomposite films as a promising platform for controlled drug delivery applications. The results indicate that GMCNFs have potential as biodegradable carrier system for curcumin delivery.

Keywords: Casein nanoparticles, Biocomposite films, Curcumin delivery, Drug loading, In vitro release

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1. INTRODUCTION

Biodegradable and biocompatible materials in the development of controlled drug delivery have been on the trend of the research and development in the pharmaceutical and biomedical fields in recent years. In the past, drugs were delivered via conventional methods that could be limited by poor solubility in water, low bioavailability, degradation of therapeutic molecules, and their uncontrolled release. To address these issues, nanotechnology-based delivery systems have been developed to improve the stability and therapeutic efficiency of drugs and to enable longer active compound release [1].Protein-based nanoparticles have been the focus of considerable interest among other biomaterials as they possess good functional properties, biocompatibility and biodegradability. The casein protein is one of the largest proteins in milk, and has a unique amphiphilic conformation with both hydrophobic and hydrophilic regions, allowing it to interact with a variety of bioactive molecules. The nanogels are self-assembled casein particles which can bind poorly water soluble molecules and enhance their bioavailability [2].Numerous studies have been conducted to investigate the potential of casein nanoparticles as natural nanocarriers for pharmaceutical and nutraceutical uses. They can also provide protection for encapsulated compounds against environmental degradation and increase the stability of the compounds, which makes them good candidates for controlled drug delivery. Moreover, the existence of functional groups like amino, hydroxyl and carboxyl groups helps to interact with bioactive molecules through hydrophobic interaction and hydrogen bonding, which results in efficient drug incorporation and controlled release behaviour [3]. Biopolymer based films are becoming more significant alternative delivery system due to their biodegradability, safety and sustained delivery of the incorporated compounds. Nanoparticles can be included in polymeric films to enhance the structural properties and develop a multifunctional material with increased drug carrier capabilities. Nanocomposite film is a combination of both the benefits of nanoscale delivery systems and film-based delivery systems and these films are suitable for biomedical and pharmaceutical applications [4].Glycerol has been considered as a natural plasticiser in protein films preparation because of its ability to increase the flexibility and decrease the brittleness of the films, and to improve

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their film forming properties. The intermolecular interaction among the polymer chains is changed by the addition of glycerol and it enhances the mechanical/handling characteristics of biopolymer films. Thus, the incorporation of glycerol is an important factor to be considered for the development of flexible casein based film system [5].The rhizome of Curcuma longa is a source of a naturally occurring polyphenolic compound called curcumin, which has been studied for its antioxidant, anti-inflammatory, antimicrobial and therapeutic effects. The main limitation to the use of curcumin in practical applications is its limited water solubility, poor bioavailability, and rapid metabolism. Hence, several methods of nanoformulations have been explored for improving the stability, bioavailability and controlled delivery of curcumin [6].The study revealed that curcumin and casein nanoparticles interaction is a promising approach to enhance the incorporation and release properties of curcumin. Casein molecules can interact with hydrophobic compounds, such as curcumin, by hydrophobic interactions to enhance the dispersibility in an aqueous medium and to protect the drug molecule. To date, casein based nanocarriers have been shown to be efficient for curcumin encapsulation and the resulting sustained release behaviour, which make them suitable for pharmaceutical applications [7].

Fabrication of casein nanoparticle-based biocomposite films is an innovative approach to introduce natural protein-based nanocarriers in a biodegradable film matrix. These systems can offer benefits such as controlled drug release, drug stability, and better compatibility for biomedical applications. Surface morphology and molecular interactions in the developed film system are key factors that can be determined with characterization techniques such as scanning electron microscopy (SEM), and Fourier transform infrared spectroscopy (FTIR).The present work is thus aimed at developing casein nanoparticle based biocomposite films with plasticizer glycerol. SEM and FTIR analysis were performed to characterize developed films, then loaded with curcumin. The study aimed at evaluating the potential of curcumin-loaded casein nanoparticle biocomposite films for controlled drug delivery, the drug loading efficiency and in vitro drug release behaviour were studied.

2. MATERIALS AND METHODS

Casein was purchased from Merck (India) and used as the primary biopolymer for the preparation of casein nanoparticle-based biocomposite films. Glycerol and curcumin were obtained from Sigma-Aldrich. All chemicals and reagents used were of analytical grade and used without further purification. Distilled water was used throughout the experimental procedures.

2.1 Synthesis of Casein Nanoparticles

Casein nanoparticles were synthesized by the desolvation method as reported by Bora and Mishra [8] with slight modifications. Briefly, 1% (w/v) casein solution was prepared in double-distilled water, and the pH was adjusted to 9 using 1 M NaOH solution. The solution was stirred continuously for 30 min at room temperature to ensure complete hydration. Absolute ethanol was then added dropwise under constant stirring until the solution became slightly turbid, indicating nanoparticle formation. Subsequently, 0.01 mL of 4% calcium chloride solution was added, followed by glutaraldehyde as a cross-linking agent. The suspension was stirred for 3 h to obtain stable nanoparticles. The nanoparticles were collected by centrifugation at 6000 rpm for 30 min, washed with absolute ethanol, re-dispersed using ultrasonication, and stored at 4°C until further use in the fabrication of casein nanoparticle-based biocomposite films.

2.2 Preparation of Casein Nanoparticle-Based Biocomposite Films

The nanoparticle-based biocomposite films were prepared using the solution casting method with slight modifications to incorporate the synthesized casein nanoparticles. Initially, a precise amount of glycerol (acting as a plasticizer) was blended with the synthesized casein nanoparticles in designated ratios based on the total solids. The mixture was then dispersed in deionized water, maintaining a ratio of ten times the volume relative to the nanoparticle mass. The pH of the suspension was adjusted to 10 by the dropwise addition of approximately 6mL of 1M sodium hydroxide (NaOH) solution to facilitate appropriate matrix interaction, monitored continuously using an electronic pH meter. The nanoparticle suspension was subsequently stir-heated in a regulated water bath maintained at 80^0C. The warmed solution was then carefully cast onto glass plates covered with a silicone-oil substrate to form consistent sheets. Finally, the cast films were dried in a hot-air oven at 60^0C for 8h to obtain the developed nanoparticle-based biocomposite film [10].

2.3 Characterization of Casein Nanoparticle-Based Biocomposite Films

2.3.1 FT-IR Analysis

For FTIR measurement, Casein – Based biocomposite films were pulverised and compressed in KBr to form pellets. The Nicolet 750 FT- IR spectrometer was used to analyse the sheet.

2.3.2 Scanning Electron Microscopy (SEM)

Surface morphology of the films was analyzed using SEM (VEGA3 TESCAN). The images were used to study the structure of the prepared films.

2.4 Preparation of Curcumin Loaded Casein Nanoparticle-Based Biocomposite Films

The casein nanoparticle-based biocomposite films were prepared and loaded with curcumin with slight modification from the reported protocol [7] by immersion loading technique. In brief, the drug loading solution was prepared by dissolving the curcumin in ethanol. Then, the biocomposite film was prepared using casein nanoparticles and placed in the curcumin solution and stirred continuously to allow the diffusion of curcumin molecules in the film matrix. Once loaded the films were taken out from the solution and dried in a controlled environment before being stored for further studies.Casein

nanoparticles interacted with curcumin molecules, which helped the incorporation of curcumin into the biocomposite film matrix. The fabricated biocomposite films, containing curcumin loaded casein nanoparticles were then subjected to drug loading efficiency and in vitro drug release assessment.

2.5 Determination of Drug Loading Efficiency

The drug loading efficiency of curcumin loaded casein based biocomposite films were determined by estimating the unbound curcumin in the loading solution by UV-Visible spectrophotometric analysis. Once loading, the curcumin concentration in the solution was measured at the characteristic absorption of curcumin. The quantity of curcumin added to the biocomposite film was determined by subtracting the amount of free curcumin found in the solution from the original amount of curcumin added to the solution.

Figure 1 Schematic illustration of curcumin-loading into casein nanocomposites

The drug loading efficiency was calculated using the following equation:

Drug Loading Efficiency (%) = [(Initial amount of drug − Amount of free drug) / Initial amount of drug] × 100

The obtained values were expressed as percentage drug loading efficiency.

2.6 *In Vitro* Drug Release Study

The drug release behaviour of curcumin loaded casein nanoparticle based biocomposite films was studied in vitro by dialysis membrane method with few modifications of the procedure reported earlier.These drug loaded films were inserted into an appropriate release medium and kept in a dialysis membrane with continuous stirring. Every so often the release medium was sampled and replaced with an equal volume of new medium to keep the sink conditions. The amount of curcumin released from the biocomposite films was quantified using UV–Visible spectrophotometric analysis at the characteristic absorption wavelength of curcumin. The controlled release behaviour of the developed film system was evaluated by calculating the cumulative percentage of the drug released [9].

Figure 2 Schematic representation of the in vitro release study using a dialysis membrane

3. RESULTS & DISCUSSION

3.1 Characterization of Casein Nanoparticle-Based Biocomposite Films

3.1.1 FT-IR Analysis

The FTIR spectrum of the casein nanoparticle based biocomposite film **(Figure 3)** shows characteristic absorption peaks, verifying the suitable molecular interaction between casein and glycerol, which is suitable for advanced drug delivery applications.

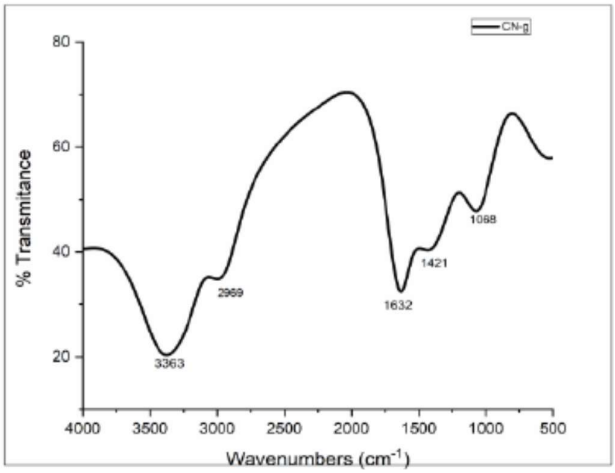

Figure 3 FTIR Spectrum of Casein Nanoparticle-Based Biocomposite Film

The broad absorption band around the 3363 cm^{-1} is due to hydroxyl (-OH) and amine (-NH) group oscillations and suggests that the protein-plasticizer system is hydrogen-bonded. Such functional groups are key to creating strong intermolecular interactions that help ensure the secure binding of bioactive molecules for long-lasting drug delivery. The peak at 2969 cm^{-1} is due to aliphatic C-H stretching vibrations. Protein Backbone (Amide Bands): The most intense peaks related to the Amide I (1632 cm^{-1}) and Amide II (1421 cm^{-1}) bands of casein protein structure showed that the structural integrity of the protein is well maintained during the film fabrication. Plasticizer Integration: Also, the peak at 1068 cm^{-1}, which is associated with the C-O stretching interaction, signifies the same integration of glycerol as a plasticizer [13]. This structural compatibility reduces the brittleness and creates a stable, flexible matrix with good controlled release of drugs in practical drug delivery applications. Such intermolecular cross-linking and plasticizer integration play an important role in the optimization of the structure in protein-based films.

3.1.2 Scanning Electron Microscopy (SEM)

The surface and cross sectional morphology of the fabricated casein nanoparticle based biocomposite films (GMCNFs) were well studied with Scanning Electron Microscopy (SEM) as shown in Figure 4 which shows that the fabricated films are structurally suited for effective biocomposite application.

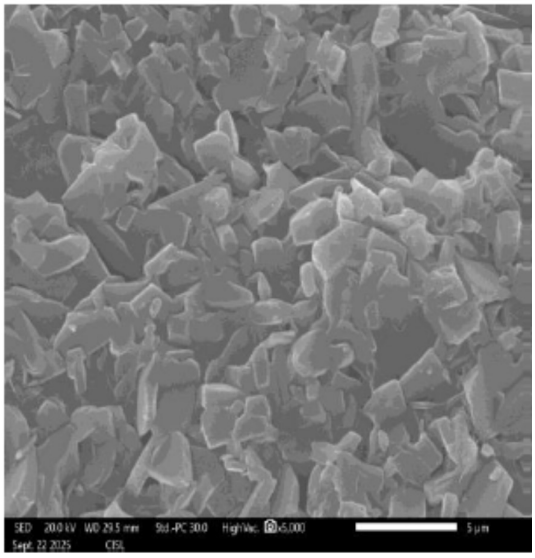

Figure 4 SEM image of Casein Nanoparticle-Based Biocomposite Film

The micrograph shows that the surface morphology is structurally integrated, homogeneous and dense with no obvious change throughout the film matrix. The casein nanoparticles are well dispersed in the continuous biopolymer network without significant agglomeration, similar to the well-dispersed nanostructured systems, showing good phase miscibility between casein nanoparticles and glycerol plasticizer [4]. Glycerol effectively lowers the intermolecular forces between the rigid casein chains, yielding a smooth and solid surface topology with less tendency to be brittle, and improving the flexibility of the film as a whole. Such plasticizers and intermolecular cross-linking play an important role in the optimization of the structure of protein-based films. Implications for Matrix Performance: The uniform morphology is compact, which means the active molecules are distributed uniformly in the matrix.

3.2 Drug loading efficiency

The drug loading efficiency of the curcumin loaded casein nanoparticle biocomposite films was found by measuring the free (unbound) curcumin in the loading solution by UV-Visible spectrophotometric method. The loading efficiency of drugs in the fabricated films was found to be high and effective, of 79.30%. The high percentage is due to the amphiphilic structure of the casein nanoparticles, having both hydrophobic and hydrophilic regions that are effective in entrapping and binding the hydrophobic bioactive molecules such as curcumin by strong intermolecular and hydrophobic interactions [12]. The biocomposite system is particularly effective for practical applications of drug delivery, for poorly soluble pharmaceutical compounds, due to its exceptionally good properties as protein-based nanoparticles as carriers.

3.3 *In Vitro* Drug Release Study

The functional behaviour of the casein nanoparticle based biocomposite films was measured in a dialysis membrane system as shown in **Figure 2** and **Table 1** for 48 hours in a simulated medium.

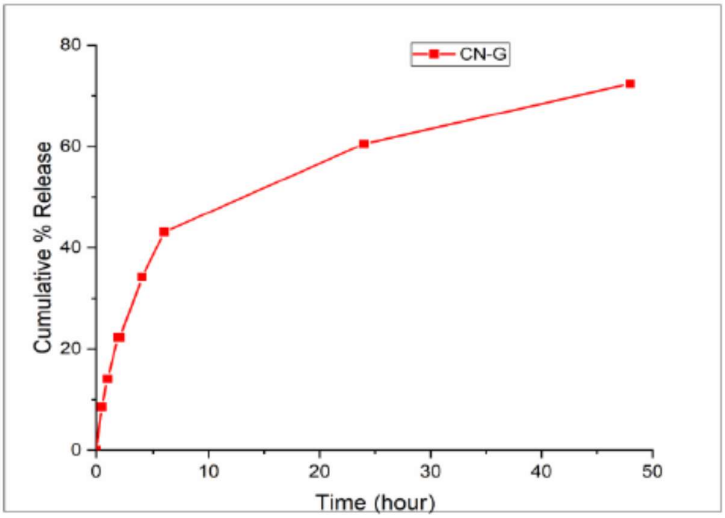

Figure 5 Cumulative percentage release profile of the casein nanoparticle-based biocomposite film as function of time

Table.1 *In vitro* cumulative release data of the casein nanoparticle-based biocomposite film over 48 hours.

Time (hour)	Cumulative Release at 48 h
0	0.00
1	8.35
2	13.92
4	22.14
8	34.20
12	43.15
24	60.50
48	72.40

The cumulative profile shown in the release graph shows that the release profile is stable with a two-stage release profile, an initial stage and a longer, steady stage throughout the film matrix [11].The active molecules in the vicinity of the surface of the casein nanoparticle-based biocomposite film lead to an observed initial percentage of about 8.35% within the first hour as detailed in the release graph. This is followed by a controlled and steady increase up to 72.40% in 48 hours, showing that the biocomposite film is a good bio-compatible system for the controlled delivery of bioactive molecules, such as casein. The structural integrity is maintained and the desired steady

state kinetics are obtained with the success of the polymer-based nanoparticle systems for advanced biocomposite applications.

CONCLUSION

Casein nanoparticle based biocomposite films were successfully prepared using solvent casting method with glycerol as an effective plasticizing agent in this study. FTIR confirmed successful intermolecular interactions and hydrogen bonding between the casein matrix and glycerol, and SEM showed a homogeneous, compact and evenly distributed morphology of the nanoparticles throughout the film. Fabricated biocomposite films exhibited a high drug loading efficiency (79.30%) for curcumin in the films due to the special amphiphilic properties of the casein nanoparticles. The in vitro drug release study showed a biphasic release which exhibited a minor burst release and a sustained release of 72.40% in 48 hrs. Overall, the results indicate that the developed biocomposite film of casein nanoparticles loaded with curcumin is a good carrier system for controlled drug delivery applications which is biodegradable as well as biocompatible.

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