

The Potential of α -Mangostin-Loaded Chitosan/Collagen Nanoparticles in Hydrogel Formulation for Enhanced Wound Healing

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Introduction: Chronic and acute wounds remain difficult to manage due to the inability of conventional dressings to provide sustained delivery of poorly soluble bioactives such as α -mangostin. This study investigates the potential of α -mangostin (AMG)-loaded chitosan/collagen nanoparticles (AMG-Ch/Coll NPs) incorporated into a hydrogel system for enhanced topical wound healing.

Methods: Nanoparticles were prepared by ionic gelation and characterized for particle size, zeta potential, morphology (SEM), entrapment efficiency, and physicochemical interactions (FTIR, XRD, DSC). AMG solubility, including its apparent solubility in AMG-Ch NPs and AMG-Ch/Coll NPs was quantified. Subsequently, hydrogels incorporating AMG, AMG-Ch NPs, AMG-Ch/Coll NPs, and Ch-Coll NPs were formulated and evaluated for pH, spreadability, swelling ratio, and in vitro drug release. In vivo wound-healing efficacy was further assessed using a rat excision model.

Results: Mean particle size increased from 297.10 ± 11.64 nm (AMG-Ch NPs) to 317.66 ± 8.76 nm (AMG-Ch/Coll NPs) and 339.62 ± 6.43 nm (Ch-Coll NPs), indicating the influence of collagen on particle size. FTIR, XRD, and DSC analyses confirmed the successful formation of amorphous nanoparticles with strong intermolecular interactions, contributing to enhanced structural stability and solubility. A fourfold improvement in AMG solubility was observed in the nanoparticle formulations, which were subsequently incorporated into hydrogel matrices and evaluated for topical application. All hydrogel (HG) formulations exhibited acceptable pH values (6.50–6.98) suitable for skin application. AMG-Ch NPs-HG demonstrated superior spreadability, swelling ratio, and drug release profiles, followed by AMG-Ch/Coll NPs-HG. Sustained AMG release was achieved, supporting prolonged bioavailability. In vivo wound healing studies in rats revealed that AMG-Ch NPs-HG and AMG-Ch/Coll NPs-HG significantly accelerated wound closure ($99.28 \pm 3.59\%$ and $98.13 \pm 3.26\%$, respectively, on day 21), outperforming AMG-HG ($89.12 \pm 2.58\%$), Ch/Coll NPs-HG ($88.95 \pm 3.14\%$), and the control group ($79.84 \pm 2.25\%$).

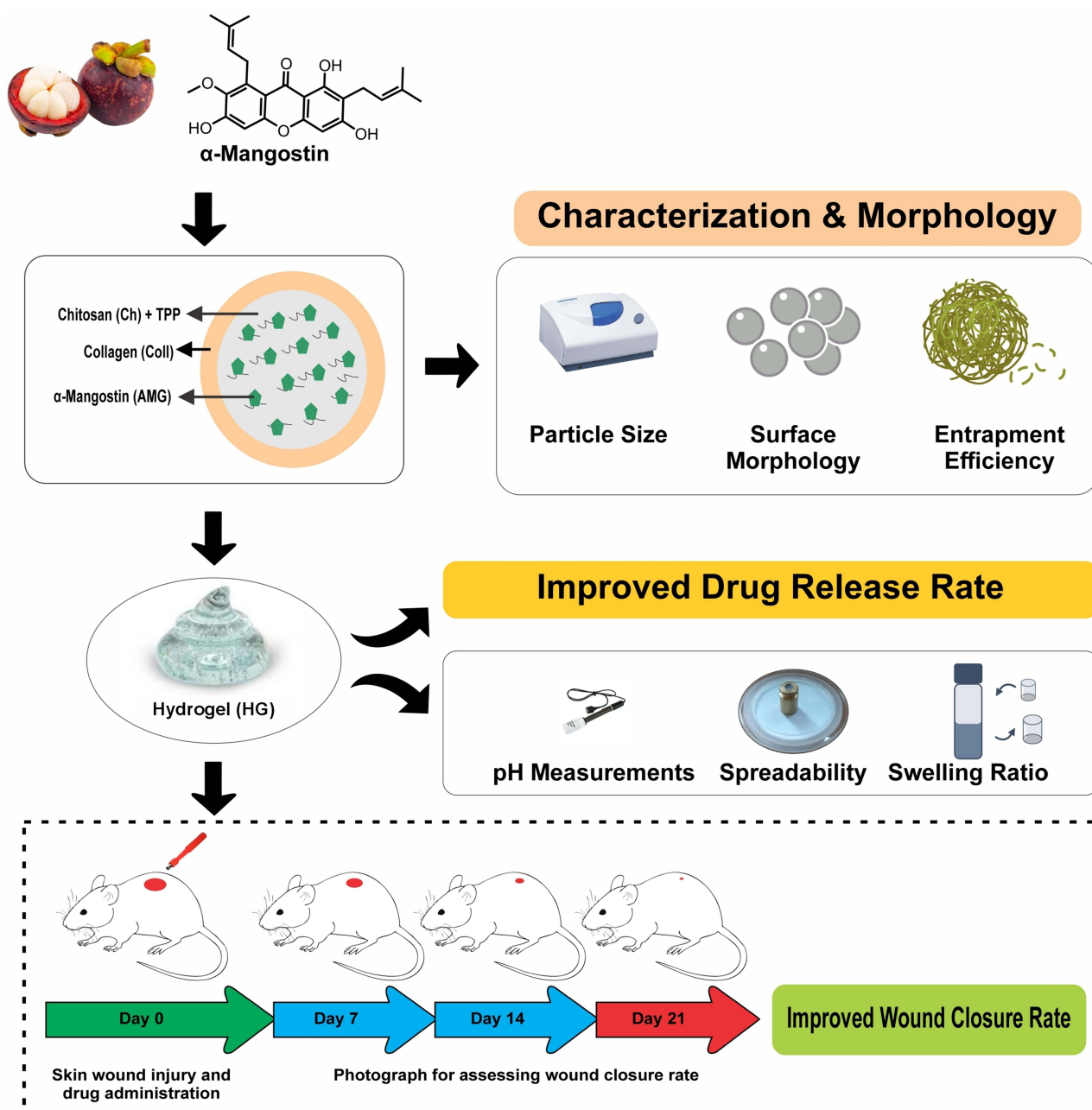
Conclusion: Overall, these findings highlight the synergistic advantages of AMG-loaded Ch/Coll NPs in hydrogel formulations as a promising platform for enhanced topical wound healing.

Keywords: α -mangostin, ionic gelation, particle size, in vitro drug release, wound closure

Introduction

Wound healing is a dynamic and multifaceted biological process involving haemostasis, inflammatory, proliferative, and remodelling phases.^{1,2} It involves various biological processes, including angiogenesis, collagen production, re-epithelialization, and granulation tissue formation.^{3–5} However, the overall Effectiveness of wound healing management is

Graphical Abstract



largely dependent on the type of dressing method applied. Chronic diseases, such as diabetes and cardiovascular disorders, have been shown to delay or impair the normal healing cascade by prolonging inflammation and reducing angiogenesis, whereas autoimmune diseases can exacerbate tissue damage and hinder regeneration.⁶ Although this study primarily investigates an acute full-thickness wound model, recognizing these pathological variations emphasizes the necessity of designing multifunctional and biocompatible dressing systems capable of adapting to various healing environments.⁷

The overall effectiveness of wound healing management is largely dependent on the type of dressing method applied. Synthetic wound dressings have several limitations, including limited biodegradability, potential side effects, and suboptimal therapeutic efficacy.^{8,9} These drawbacks have led to growing interest in alternatives based on bioactive

compounds. In this context, natural compounds derived from medicinal plants are being widely explored for their potential in promoting wound healing.^{10–12} α -mangostin (AMG) is a natural compound with pharmacological properties that support wound healing when applied topically.¹³ However, its clinical use is limited by poor water solubility and low bioavailability, reducing its therapeutic efficacy. Nanoparticle-based drug delivery systems offer a promising solution by improving solubility, stability, and targeted delivery of poorly soluble agents like AMG.^{14,15} These systems also protect bioactive molecules from enzymatic degradation in the wound microenvironment and enable sustained drug release. Recent advances in this field have been driven by the development of multifunctional nanocarriers that enhance encapsulation efficiency and enable sustained release for both topical and transdermal applications.¹⁶ Advances in nanoparticle engineering offer a stronger scientific foundation for the development of next-generation polymeric delivery systems.¹⁷ Specifically, recent reviews have emphasized the promise of soft-matter nanocarriers, particularly nanoparticle-based hydrogels, as versatile and efficient platforms for wound healing and topical drug delivery applications.¹⁸ Building upon these advancements, this study investigates a polymeric nanoparticle-based hydrogel system incorporating chitosan and collagen matrices to enhance the therapeutic efficacy of AMG in wound healing applications. Although some studies have reported improved wound healing using AMG hydrogels formulated with 2-hydroxypropyl- β -cyclodextrin¹⁹ and nanostructured lipid carriers (NLCs),²⁰ neither approaches involved polymeric nanoparticle-based delivery systems. To date, the application of AMG-loaded polymeric hydrogel nanoparticles in wound healing has not been reported. Incorporating AMG into such nanoparticle systems offers a dual advantage by improving the physicochemical properties and stability of the compound, as well as enabling localized and sustained drug release, which is particularly beneficial in wound healing applications.²¹

In this context, nanoparticles have been extensively investigated in the development of wound dressings, both as drug delivery vehicles and as functional components that actively contribute to the healing process.^{22,23} Hydrogels are widely recognized as effective wound dressing platforms due to their ability to retain moisture, facilitate gas exchange, and provide sustained drug release.^{24,25} However, pure hydrogels possess limitations, such as low mechanical strength and inadequate drug retention, which can be effectively addressed by incorporating nanoparticle matrices into the hydrogel system. Natural polymers are commonly applied in the preparation of nanoparticle-based hydrogels, and among these, chitosan has received particular attention due to its biodegradability, biocompatibility, and ability to enhance haemostasis.²⁶

Several studies have formulated chitosan-based nanoparticles hydrogels loaded with bioactive compounds such as curcumin or *Pterocarpus marsupium* extract, which have demonstrated accelerated healing in both normal and diabetic wound models.²⁷ Similarly, curcumin-loaded chitosan nanoparticles incorporated into hydrogels have shown enhanced healing in excisional wound models by improving drug solubility and local retention.²⁸ Moreover, chitosan has been reported to facilitate tissue regeneration through the modulation of inflammation, stimulation of fibroblast proliferation, and promotion of collagen synthesis.^{29,30} Nevertheless, no studies have specifically reported the use of chitosan-based polymeric nanoparticles for AMG in hydrogel formulations for wound healing applications.

Most existing research on chitosan polymer-based AMG nanoparticles has focused on improving their physicochemical properties. Several studies have reported the formulation of chitosan-based AMG nanoparticles using various copolymers, such as alginate,¹³ kappa-carrageenan,³¹ and Eudragit® S100.³² These copolymers not only function as stabilizers but also serve as encapsulating agents to enhance the stability and effectiveness of the nanoparticles. However, based on the literature review, the formulation of AMG-chitosan nanoparticles encapsulated with collagen has not yet been reported.

Collagen is a natural polymer that has been widely applied in therapeutic wound healing due to its favorable rheological, structural, and physicochemical properties.^{33,34} It also exhibits high biocompatibility and biodegradability, along with the ability to promote cell adhesion, migration, and proliferation.³³ However, native collagen hydrogels often suffer from rapid degradation and poor mechanical strength, which limit their long-term clinical application.²⁵ The incorporation of collagen-based nanoparticle matrices into hydrogel systems represents a promising strategy to overcome these limitations by improving stability and therapeutic efficacy.³⁵ Recent studies have explored collagen-based nanoparticles in wound healing, including bioactive tilapia scale collagen nanoparticles³⁶ and collagen nanoparticles coated with macrophage membranes for treating multidrug-resistant bacterial infections.³⁷ Additionally, antimicrobial peptide-loaded nanoparticle nanosheets have shown strong bioactivity in wound therapy.³⁸ These findings underscore the versatility of collagen-based nanoparticles in wound management.

Therefore, the integration of AMG-chitosan nanoparticles encapsulated with collagen matrices into hydrogel systems represents a promising strategy to enhance both the functional and therapeutic performance of wound dressings. In this context, the present study aims to formulate AMG-loaded chitosan/collagen nanoparticles within a hydrogel system and evaluate their wound healing potential. This innovative approach combines the bioactivity of AMG, the functional properties of chitosan and collagen, and the delivery advantages of hydrogel matrices, offering a promising platform for the development of advanced wound dressing technologies.

Materials and Methods

Materials

AMG was purchased from Chengdu Biopurify Phytochemicals (Sichuan, China). Chitosan (Ch, 300 kDa, 81% DDA) was obtained from the PRINT-G Research Laboratory, Padjadjaran University, Indonesia. Collagen (Coll) was supplied by PT Rasanya in Sidoarjo, Indonesia. Sodium tripolyphosphate, Carbopol 940, triethanolamine, propylene glycol, and methylparaben were procured from Brataco (Semarang, Indonesia). All analytical grade solvents including 96% ethanol, glacial acetic acid, and distilled water were provided by local suppliers. All other chemicals and reagents used in this study were of analytical grade and were used as received.

Preparation of NPs (NPs)

Three Categories of NPs Were Synthesized as Detailed Below

- (1) Preparation of AMG-chitosan nanoparticles (AMG-Ch NPs). The preparation of AMG-Ch NPs was executed via the following steps: (Step #1), 200 mg of Ch powder was solubilized in 200 mL of 1% acetic acid ambient temperature (25 °C). (Step #2) 20 mg of AMG powder was solubilized in 20 mL of 96% ethanol at room temperature while stirring at 1500 rpm. (Step #3) The AMG solution was thereafter introduced dropwise into the Ch solution via a micro-pump at a flow rate of 1.5 mL/min, while maintaining continuous stirring for 6 hours to achieve homogeneity. (Step #4) A 1 mg/mL sodium tripolyphosphate (TPP) solution (40 mL) was prepared at ambient temperature. (Step #5) The AMG/Ch mixture was incrementally introduced into the TPP solution while maintaining continuous agitation overnight, leading to the creation of a suspension of AMG/TPP/Ch NPs.³⁹
- (2) Preparation of AMG-loaded chitosan/collagen nanoparticles (AMG-Ch/Coll NPs). (Step #6) A 1 mg/mL Coll solution (10 mL) was prepared in 1% acetic acid. The solution was agitated with a magnetic stirrer at ambient temperature (25 °C) for 6 hours at a velocity of 800 rpm. (Step #7) The AMG/Ch NP suspension from Step #5 was gradually added dropwise to the Coll solution while maintaining continuous stirring overnight. This method led to the creation of a suspension of AMG/TPP/Ch/Coll NPs;
- (3) Preparation of chitosan-collagen nanoparticles (Ch-Coll NPs). The Ch solution formulated in Step #1 was incrementally introduced dropwise into the TPP solution from Step #4 while maintaining magnetic stirring at ambient temperature (25 °C) for a duration of 6 hours at a velocity of 800 rpm. Following the formation of the Ch/TPP solution, it was gradually added dropwise into the Coll solution prepared in Step #6. The mixture was continuously stirred overnight at room temperature to obtain a suspension of Ch/TPP/Coll NPs, as detailed in Table 1.

All suspensions (AMG-Ch NPs, AMG-Ch/Coll NPs, and Ch-Coll NPs) underwent ultrasonication for 30 minutes to decrease particle size and enhance dispersion uniformity. Subsequently, processing was conducted using a microvolume flow titration technique, followed by drying into NP powder through spray pyrolysis at temperatures ranging from 80 °C, with an airflow rate of 5 L/min.³¹

Table 1 NPs Formulation

Formulation	AMG-Ch	AMG-Ch/Coll	Ch-Coll
α -mangostin (mg)	20	20	-
Chitosan (mg)	200	200	200
Sodium tripolyphosphate (mg)	40	40	40
Collagen (mg)	-	10	10

Note: Formulation ratios were optimized based on preliminary experiments (20 mg AMG to 200 mg Ch) and previous studies by Muchtaridi et al¹⁴ and Yedi Herdiana et al³⁹ supporting the 1:10 AMG:Ch ratio and 0.5:10 Coll:Ch ratio.

Characterization of NPs

Analysis of Particle Size and Zeta Potential

The particle size (PS) and zeta potential (ZP) of the NPs were measured using Dynamic Light Scattering (DLS) with a Horiba Scientific SZ-100 instrument. Prior to measurement, the NP powder was dispersed in an aqueous medium, diluted tenfold, and analyzed at room temperature.⁴⁰

Scanning Electron Microscopy (SEM)

The surface morphology of the NPs was examined using scanning electron microscopy (SEM, SU3500; Hitachi, Tokyo, Japan). Powders of AMG-Ch NPs, AMG-Ch/Coll NPs, and Ch-Coll NPs were placed on stubs using double sided adhesive, coated with a thin carbon film, and then sputter coated with platinum for 30 seconds at 10 mA to enhance conductivity. SEM images were acquired at an accelerating voltage of 10 kV at selected magnifications.⁴¹

Encapsulation Efficiency

The entrapment efficiency (EE) of AMG-Ch NPs and AMG-Ch/Coll NPs was determined using UV–VIS spectrophotometry. Briefly, 25 mg of each NP sample was dispersed in ethyl acetate and centrifuged at 10000 rpm for 20 minutes.⁴² The resulting supernatant was collected, and its absorbance was measured at 245 nm to quantify the amount of free AMG using a previously established standard calibration curve. The resulting sediment was then resuspended in ethanol to determine the mass amount of AMG to find the encapsulated drug content. The calibration curve was generated using serial dilutions of AMG in the concentration range of 2–10 $\mu\text{g/mL}$, with absorbance measured at 245 nm.³⁹ The entrapment efficiency was calculated using the following Equation (1):

$$\text{Entrapment efficiency}(\%) = \frac{\text{Mass of the AMG in NPs}}{\text{Mass of AMG used}} \times 100 \quad (1)$$

Fourier-Transform Infrared Spectroscopy (FTIR)

The molecular interactions between AMG, Ch, TPP, Coll, AMG-Ch NPs, AMG-Ch/Coll NPs, and Ch-Coll NPs were analyzed using Fourier-transform infrared (FTIR) spectroscopy (model IR Prestige-21; Shimadzu, Kyoto, Japan). Spectra were recorded over a wavenumber range of 4000–500 cm^{-1} .⁴³

X-Ray Diffraction (XRD)

The molecular structures of AMG-Ch NPs, AMG-Ch/Coll NPs, and Ch-Coll NPs systems were analyzed using X-ray diffraction (XRD) with an X-pert MPD diffractometer (Rigaku International, Tokyo, Japan). The diffraction patterns were recorded over a 2θ range of 10°–60°, using a generator setting of 30 mA and 40 kV. The same experimental conditions were applied for the analysis of raw materials.⁴⁴

Differential Scanning Calorimetry (DSC)

The thermal properties of all raw materials, AMG-Ch NPs, AMG-Ch/Coll NPs, and Ch-Coll NPs were evaluated using differential scanning calorimetry (DSC-60; Shimadzu, Kyoto, Japan), and the data were analyzed using TA-60WS. The

Table 2 Composition of HG Formulations

Composition	AMG-HG	AMG-Ch NPs-HG	AMG-Ch/Coll NPs-HG	Ch-Coll NPs-HG
AMG (w/v)	0.125%	-	-	-
AMG-Ch NPs (w/v)	-	0.125%	-	-
AMG-Ch/Coll NPs (w/v)	-	-	0.125%	-
Ch-Coll NPs (w/v)	-	-	-	0.125%
Carbopol 940 (w/v)	0.75%	0.75%	0.75%	0.75%
Methylparaben (w/v)	0.15%	0.15%	0.15%	0.15%
Propylene glycol (w/v)	10%	10%	10%	10%
Triethanolamine (w/v)	0.75%	0.75%	0.75%	0.75%
Distilled water	Up to 100%	Up to 100%	Up to 100%	Up to 100%

Notes: Where AMG-HG: AMG-based HG; AMG-Ch NPs-HG: AMG-Ch NPs-based HG; AMG-Ch/Coll NPs-HG: AMG-Ch/Coll NPs-based HG; Ch/Coll NPs-HG: Ch/Coll NPs-based HG.

measurements were performed over a temperature range of 30 to 300 °C, at a heating rate of 20 °C/minute under a nitrogen atmosphere.⁴⁵

Solubility Study

Each 60 mg sample of AMG, AMG-Ch NPs, and AMG-Ch/Coll NPs was dispersed in 25 mL of deionized water (Milli-Q) and stirred at 120 rpm for 48 hours at 25 °C. After incubation, the suspensions were centrifuged at 10000 × g for 20 minutes (Hettich EBA 200), followed by filtration through a 0.45 µm syringe filter.⁴⁶ The concentration of AMG was then analyzed using UV spectrophotometry at a wavelength of 245 nm.³¹

Preparation of Hydrogel (HG)

The HG base was prepared by dispersing 0.75% w/v Carbopol 940 into 50% of the total volume of distilled water, which had been preheated to approximately 70 °C to facilitate dispersion. The Carbopol was gradually sprinkled while stirring continuously until a homogeneous dispersion was obtained. Subsequently, each of the formulations (AMG, AMG-Ch NPs, AMG-Ch/Coll NPs, and Ch-Coll NPs) at a concentration of 0.125% w/v was added into the base and mixed until uniform. Methylparaben (0.15% w/v), propylene glycol (10% w/v), and triethanolamine (0.75% w/v) were then incorporated gradually, and the mixture was stirred thoroughly to obtain a stable and homogeneous HG.²⁷ The composition of each formulation is shown in Table 2.

Characterization of HG

pH Evaluation

Each 1 g sample of AMG-HG, AMG-Ch NPs-HG, AMG-Ch/Coll NPs-HG, and Ch-Coll NPs-HG was dispersed in 25 mL of distilled water. A pH electrode was immersed in the dispersion for 10 minutes until a stable reading was obtained. The pH measurements were carried out in triplicate for each formulation.⁴⁷

Spreadability

Each sample of AMG-HG, AMG-Ch NPs-HG, AMG-Ch/Coll NPs-HG, and Ch-Coll NPs-HG (0.5 g) was placed in the middle of a petri dish, forming a circular area with an initial diameter of 2 cm. Another petri dish was then placed inverted

on top, followed by the application of a 100 g weight for 1 minutes. The final diameter of the HG spread was subsequently measured.⁴⁸ The spreadability was calculated using the following formula (Equation 2) and expressed in g.cm/s.

$$\text{Spreadability}(\%) = \frac{ML}{T} \times 100 \quad (2)$$

Where S represents the spreadability of the gel (g.cm/s); M denotes the mass applied to the upper slide (g); L is the distance moved by the slide (cm); and T is the time required for the upper slide to completely detach from the lower slide (s).²⁷

Swelling Ratio

Each sample of AMG-HG, AMG-Ch NPs-HG, AMG-Ch/Coll NPs-HG, and Ch-Coll NPs-HG (0.5 g) was immersed in 50 mL phosphate-buffered saline (PBS) at pH 7.4 for 30, 60, 90, and 120 minutes at room temperature. The swelling ratio was then calculated using Equation (3).

$$\text{Swelling Ratio}(\%) = \frac{W_s - W_d}{W_d} \times 100 \quad (3)$$

Where Wd represents the initial weight of the HG, and Ws indicates the weight of the HG after swelling at a specific time point.⁴⁹

In vitro Drug Release Studies

In vitro drug release studies of the prepared gel formulations were carried out using the dialysis bag method.⁵⁰ A total of 0.1 g of each sample (AMG-HG, AMG-Ch NPs-HG, and AMG-Ch/Coll NPs-HG) was placed into individual dialysis tubes (molecular weight 12,000 Da), each containing 20 mL phosphate-buffered saline (PBS). The sealed dialysis bags were then immersed in 50 mL PBS (pH 7.4) in a beaker and the buffer was stirred continuously at 100 rpm at room temperature. Aliquots of 2 mL were withdrawn from the release medium at predetermined time intervals and immediately replaced with an equal volume of PBS to maintain sink conditions. The amount of AMG released from each formulation was quantified using UV-visible spectrophotometry at a wavelength of 245 nm.

In vivo Wound Healing Assay

The in vivo wound healing assay was conducted to evaluate the therapeutic efficacy of AMG-HG, AMG-Ch NPs-HG, AMG-Ch/Coll NPs-HG, and Ch-Coll NPs-HG an animal model. All experimental procedures were approved by the Ethics Committee of the Faculty of Medicine, Universitas Padjadjaran (approval no: 982/UN6.KEP/EC/2024). The ethical considerations regarding animal experimentation were addressed following the 3R principles (reduction, refinement, and replacement) to promote responsible and humane research practices.⁵¹ Furthermore, these principles were aligned with the 5 Freedoms framework for animal welfare, encompassing freedom from hunger and thirst, freedom from discomfort, freedom from pain, injury, or disease, freedom from fear and distress, and freedom to express normal behavior.⁵² The animals were anesthetized with ketamine (30 mg/kg body weight) and xylazine (3 mg/kg body weight) prior to wound induction to minimize discomfort during the procedure.

The study was performed on Wistar strain rats (*Rattus norvegicus*) weighing between 290–350 g. A total of 25 rats were used and randomly divided into five groups (n = 5 per group), namely: (1) control group (wounded animals receiving no treatment), (2) AMG-HG group, (3) AMG-Ch NPs-HG group, (4) AMG-Ch/Coll NPs-HG group, and (5) Ch/Coll NPs-HG group. Prior to the experiment, the animals were acclimatized under controlled environmental conditions at $26 \pm 2^\circ\text{C}$. The dorsal region of each rat was shaved and disinfected with 70% ethanol, followed by the creation of a full-thickness excisional wound (8 mm in diameter) using a sterile biopsy punch. Each HG formulation was applied topically to the wound area once daily for 21 days at a dose of 50 mg per wound, and the wound was covered with a sterile gauze after each application. Wound healing progression was evaluated on days 0, 7, 14, and 21 through photographic documentation. The wound area was quantitatively measured using ImageJ software and the percentage of wound closure was calculated using the following formula (Equation 4).¹⁹

$$\text{Wound Closure(\%)} = \frac{\text{Initial Wound Area} - \text{Residual Wound Area}}{\text{Initial Wound Area}} \times 100 \quad (4)$$

Statistic

Data were presented as the mean $\pm$ standard deviation (SD). Statistical comparisons were conducted using one-way analysis of variance (ANOVA), followed by Tukey's post-hoc test to evaluate differences between groups. A p-value of less than < 0.05 was considered as statistically significant.⁵³

Results

Characterization of NPs

Analysis of Particle Size (PS) and Zeta Potential (ZP)

The PS of AMG-Ch NPs, AMG-Ch/Coll NPs, and Ch-Coll NPs were 297.10 ± 11.64 , 317.66 ± 8.76 , and 339.62 ± 6.43 nm, respectively. The ZP values were -26.17 ± 0.63 , -26.83 ± 0.37 , and -42.10 ± 0.20 mV for AMG-Ch NPs, AMG-Ch/Coll NPs, and Ch-Coll NPs, respectively (Figure 1).

SEM and Entrapment Efficiency (EE%)

The SEM images revealed that the synthesized NPs (AMG-Ch NPs, AMG-Ch/Coll NPs, and Ch-Coll NPs) exhibited spherical morphology with no apparent agglomeration (Figure 2). The particles appeared well dispersed, with smooth to mildly rough surfaces and minimal aggregation observed across all formulations. The EE of AMG-loaded NPs was evaluated to compare the performance of different formulations. The AMG-Ch NPs exhibited an EE% of $90.52 \pm 1.47\%$, while the AMG-Ch/Coll NPs showed a significantly higher value of $94.19 \pm 0.53\%$.

FTIR Analysis

The FTIR spectra of AMG, Ch, TPP, Coll, and all NP formulations (AMG-Ch NPs, AMG-Ch/Coll NPs, and Ch-Coll NPs) are presented in Figure 3, with detailed wavenumber assignments summarized in Table 3. The NP formulations exhibited characteristic absorption bands corresponding to O–H stretching vibrations at 3294 cm^{-1} (AMG-Ch NPs), 3288 cm^{-1} (AMG-Ch/Coll NPs), and 3300 cm^{-1} (Ch-Coll NPs), along with peaks in the range of $2942\text{--}2946 \text{ cm}^{-1}$ (C–H stretching) and $1629\text{--}1640 \text{ cm}^{-1}$ (C=O stretching). Additional bands were observed for N–H bending ($1561\text{--}1576 \text{ cm}^{-1}$), C–N stretching ($\sim 1375 \text{ cm}^{-1}$), and C–O–C stretching ($\sim 1150 \text{ cm}^{-1}$). Furthermore, distinct peaks around $1065\text{--}1067 \text{ cm}^{-1}$

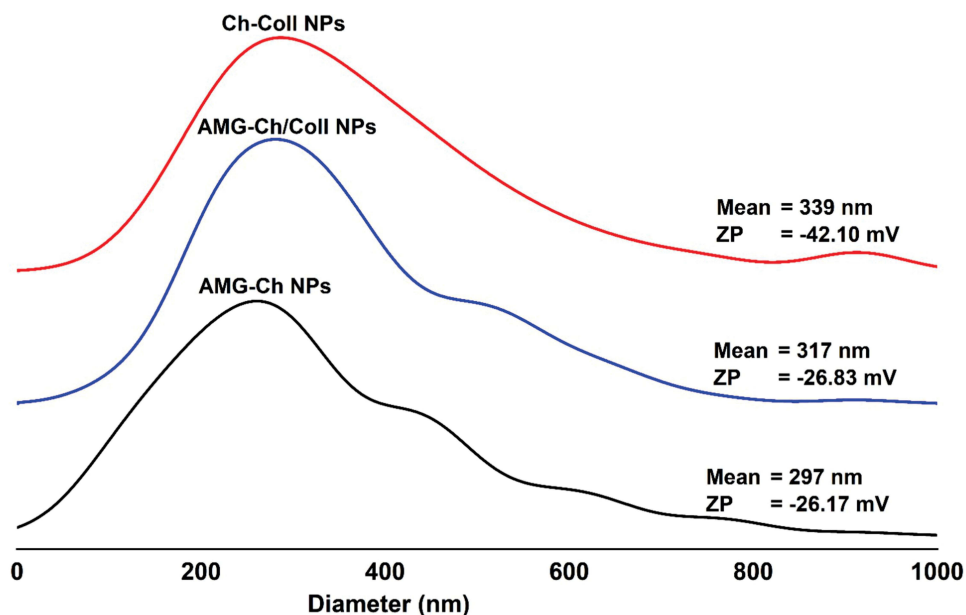


Figure 1 Particle Size (nm) and Zeta Potential (mV) of AMG-Ch NPs, AMG-Ch/Coll NPs, and Ch-Coll NPs.

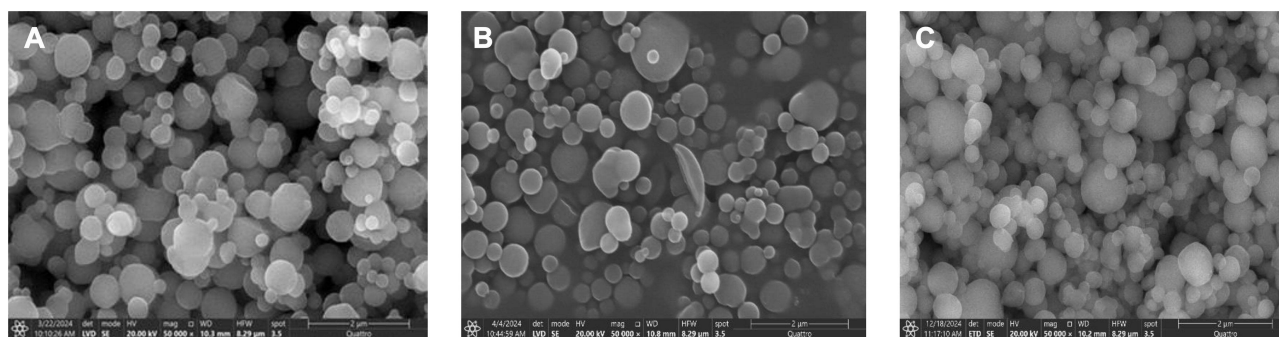


Figure 2 SEM images of (A) AMG-Ch NPs, (B) AMG-Ch/Coll NPs, and (C) Ch-Coll NPs at a magnification of 50,000x.

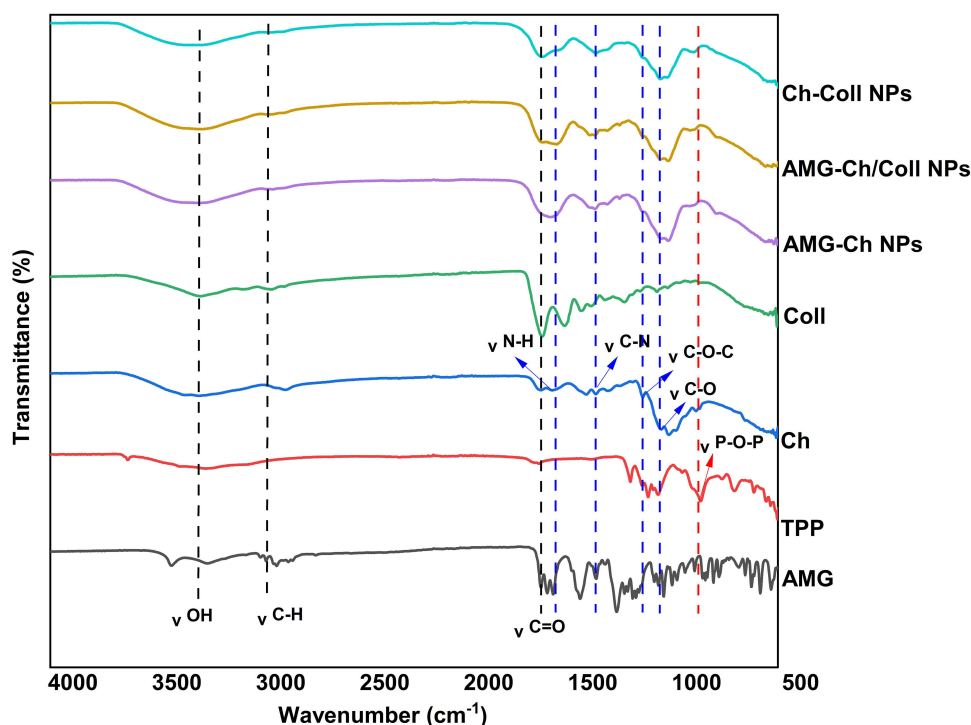


Figure 3 FTIR spectra of AMG, TPP, Ch, Coll, AMG-Ch NPs, AMG-Ch/Coll NPs, and Ch-Coll NPs.

were assigned to C–O stretching. A new band appearing at $\sim 900\text{ cm}^{-1}$, attributed to P–O–P stretching, was evident in all NP spectra.

XRD Analysis

The XRD analysis results are presented in [Figure 4](#). The diffractogram shows that both AMG and TPP exhibit crystalline patterns, as indicated by sharp diffraction peaks in the 2θ range of 14° – 32° . Ch displays a semi-crystalline pattern, with a broad peak observed at a 2θ angle of 29.33° , whereas Coll exhibits an amorphous pattern. The XRD profile of the AMG-Ch NPs, AMG-Ch/Coll NPs, and Ch-Coll NPs also reveals an amorphous structure.

DSC Analysis

The DSC analysis results are presented in [Figure 5](#). The thermogram of pure AMG shows a distinct sharp endothermic peak at 178.78°C , corresponding to its melting point (T_m), while TPP exhibits a characteristic endothermic peak at

Table 3 Wave Number Positions in the FTIR Spectrum and the Respective Functional Groups

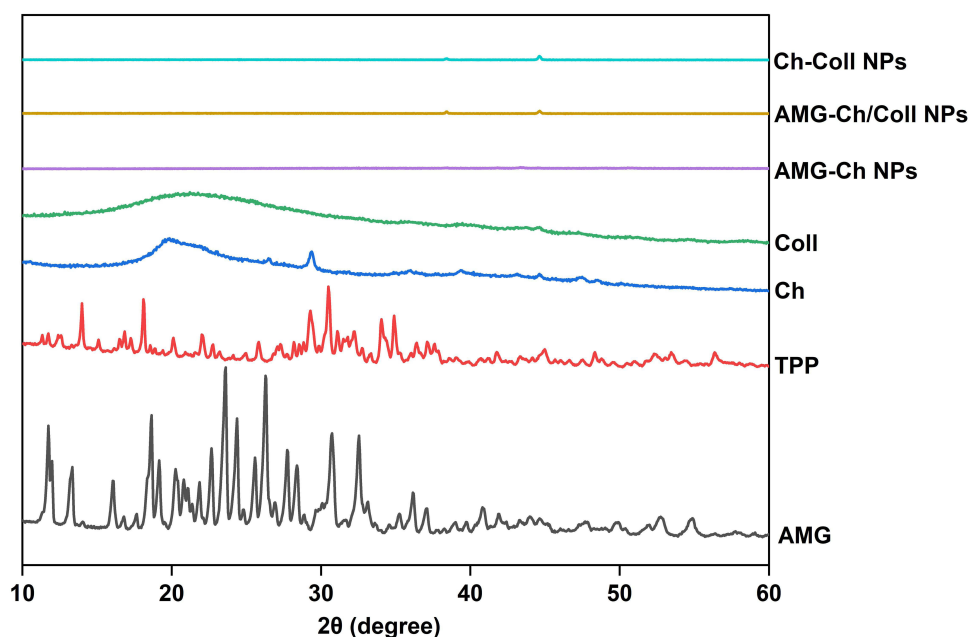
Material	Wavenumber (cm ⁻¹)		Functional Groups	Reference
	Result	Literature		
α -mangostin	3417.01; 3245.78	3420.81	O-H <i>stretch</i>	[31]
	2961.54; 2911.21	2988.75; 2960.78	C-H <i>stretch</i>	
	1639.12	1643.38	C=O	
	1451.18	1454.35	C-C	
	1198.69	1197.82	Orto-OCH ₃ <i>stretch</i>	
	1049.61	1075.33	C-O-C <i>stretch</i>	
Ch	3283.45	3509.54	O-H <i>stretch</i> and N-H <i>stretch</i>	[39]
	2871.38	2894.24	C-H <i>stretch</i>	
	1638.71	1653.02	C=O	
	1586.89	1597	N-H <i>bend</i>	
	1421.30	1419.63	C-H <i>bend</i>	
	1375.53	1378.16	C-N	
	1149.69	1157.31	C-O-C <i>stretch</i>	
	1060.42	1079	C-O	
TPP	1209.47	1211.32	$\nu_{as}P=O$	[31]
	1124.37	1157.31	$\nu_sO-P=O$	
	1076.41	1092.69	$\nu_{as}PO_3$	
	870.79	888.23	$\nu_{as}P-O-P$	
Coll	3273.59	3290	O-H <i>stretch</i> dan N-H <i>stretch</i>	[54]
	2935.81	2876	C-H <i>stretch</i>	
	1636.13	1639	Amide I (C=O)	
	1525.94	1550	Amide II (N-H)	
	1239.32	1242	Amide III (C-N)	
AMG-Ch NPs	3292.67	3509.54	O-H <i>stretch</i> and N-H <i>stretch</i>	[31,39]
	2942.38	2894.24	C-H <i>stretch</i>	
	1629.85	1653.02	C=O	
	1576.72	1597	N-H <i>bend</i>	
	1378.41	1378.16	C-N	
	1153.87	1157.31	C-O-C <i>stretch</i>	
	1065.27	1079	C-O	
	904.55	888.23	$\nu_{as}P-O-P$	

(Continued)

Table 3 (Continued).

Material	Wavenumber (cm ⁻¹)		Functional Groups	Reference
	Result	Literature		
AMG-Ch/Coll NPs	3288.54	3509.54	O-H stretch and N-H stretch	[31,39]
	2946.50	2894.24	C-H stretch	
	1640.15	1653.02	C=O	
	1570.09	1597	N-H bend	
	1374.34	1378.16	C-N	
	1151.81	1157.31	C-O-C stretch	
	1067.33	1079	C-O	
	908.73	888.23	ν_{as} P-O-P	
Ch-Coll NPs	3330.67	3509.54	O-H stretch and N-H stretch	[31,39]
	2944.39	2894.24	C-H stretch	
	1638.03	1653.02	C=O	
	1561.85	1597	N-H bend	
	1376.41	1378.16	C-N	
	1151.81	1157.31	C-O-C stretch	
	1067.33	1079	C-O	
	900.43	888.23	ν_{as} P-O-P	

112.90 °C, also corresponding to its T_m. In contrast, these sharp endothermic peaks are absent in the thermograms of AMG-Ch NPs, AMG-Ch/Coll NPs, and Ch-Coll NPs, indicating that AMG and TPP were dispersed within the polymeric matrices in an amorphous or molecularly encapsulated state rather than remaining as crystalline forms.

**Figure 4** XRD spectra of AMG, TPP, Ch, Coll, AMG-Ch NPs, AMG-Ch/Coll NPs, and Ch-Coll NPs.

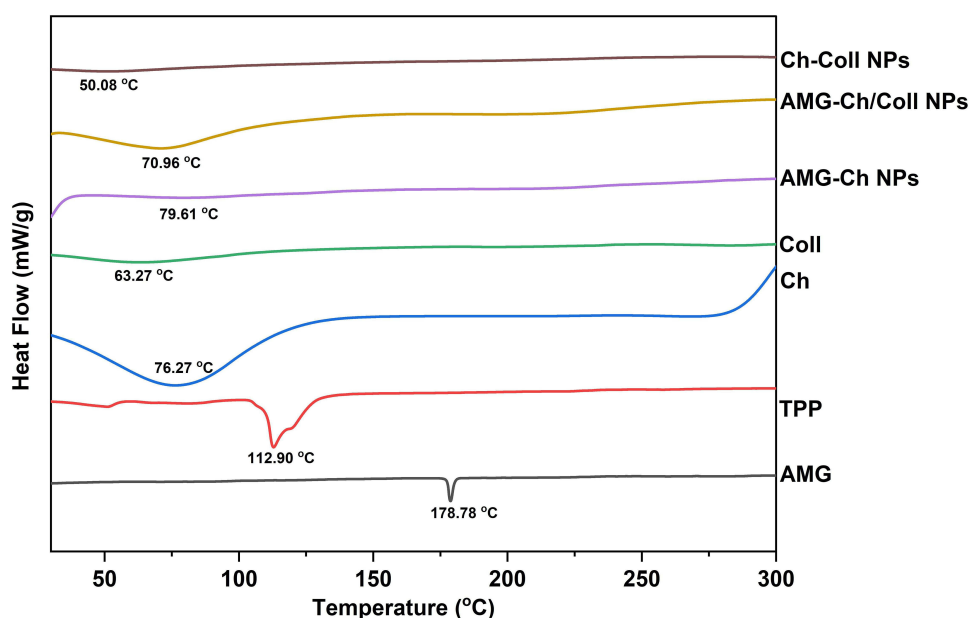


Figure 5 DSC thermograms of AMG, TPP, Ch, Coll, AMG-Ch NPs, AMG-Ch/Coll NPs, and Ch-Coll NPs.

Solubility Study

The solubility study demonstrated a significant enhancement in the solubility of AMG following NP formulation. Both AMG-Ch NPs ($12.97 \pm 1.63 \mu\text{g/mL}$) and AMG-Ch/Coll NPs ($12.88 \pm 1.34 \mu\text{g/mL}$) exhibited solubility values approximately four times higher than that of pure AMG ($3.20 \pm 2.05 \mu\text{g/mL}$), with a statistically significant difference ($p < 0.05$). This enhancement in solubility may be attributed to the reduced PS and improved wettability of the NPs, which facilitate better dispersion in aqueous media.

Characterization of HG

Formulation and pH Measurement of HG

The AMG, AMG-Ch NPs, AMG-Ch/Coll NPs, and Ch-Coll NPs were successfully formulated into HG systems. All formulations were prepared in semisolid form using a consistent composition and fabrication procedure. Each HG exhibited a distinct visual appearance, as shown in Figure 6A. The pH values of the HG formulations ranged from 6.50 to 6.98. The measured values were AMG-HG (6.98 ± 0.13), AMG-Ch NPs-HG (6.68 ± 0.12), AMG-Ch/Coll NPs-HG (6.81 ± 0.15), and Ch-

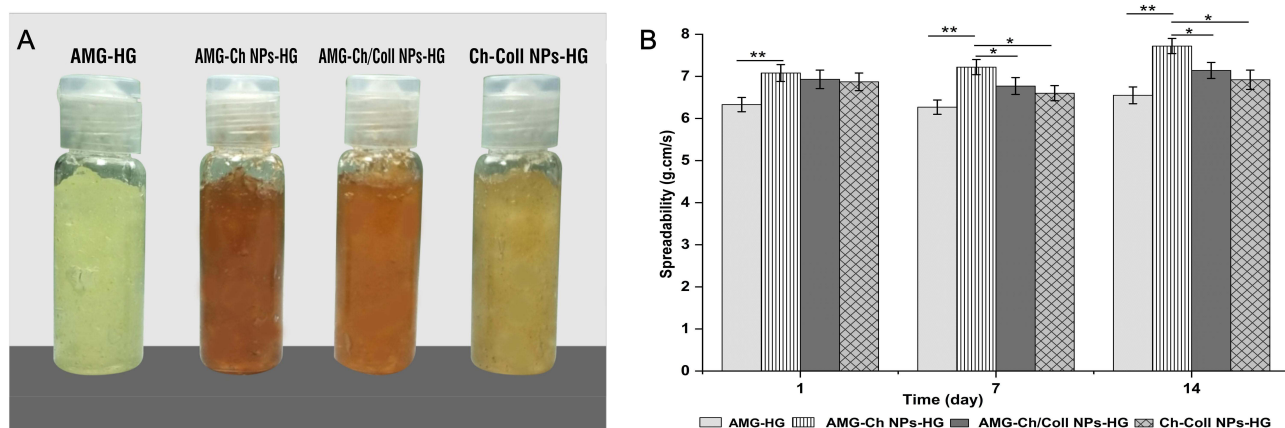


Figure 6 (A) The visual appearance and (B) The spreadability values of various HG formulations. Results are expressed as mean $\pm$ standard deviation ($n = 5$); *indicates statistical significance at $P < 0.05$; **indicates significance at $P < 0.01$.

Coll NPs-HG (6.50 ± 0.11). All formulations thus exhibited pH values within the acceptable physiological range for topical application. Statistical analysis revealed significant differences in pH values among certain formulations ($p < 0.05$). Specifically, AMG-HG (6.98 ± 0.13) exhibited a significantly higher pH compared to AMG-Ch NPs-HG (6.68 ± 0.12) and Ch-Coll NPs-HG (6.50 ± 0.11), whereas no significant difference was observed between AMG-HG and AMG-Ch/Coll NPs-HG ($p > 0.05$).

Spreadability Evaluation

The spreadability values of the HG formulations on days 1, 7, and 14 are presented in Figure 6B. On day 1, spreadability values ranged from 6.33 to 7.08 g.cm/s, whereas on day 7 they ranged from 6.27 to 7.22 g.cm/s. On day 14, the values ranged from 6.55 to 7.72 g.cm/s, with AMG-Ch NPs-HG exhibiting the highest spreadability (7.72 ± 0.18 g.cm/s), followed by AMG-Ch/Coll NPs-HG (7.14 ± 0.19 g.cm/s), Ch-Coll NPs-HG (6.92 ± 0.23 g.cm/s), and AMG-HG (6.55 ± 0.20 g.cm/s). Statistical analysis revealed that AMG-Ch NPs-HG was significantly more spreadable than AMG-HG ($p < 0.01$), while both AMG-Ch/Coll NPs-HG and Ch-Coll NPs-HG also showed significantly higher spreadability compared to AMG-HG ($p < 0.05$).

Swelling Ratio

The swelling ratio of AMG-Ch NPs-HG was the highest among all HG formulations, as shown in Figure 7A. All formulations exhibited a progressive increase in swelling ratio from 30 to 120 minutes. At 120 minutes, AMG-Ch NPs-HG showed the highest swelling ratio ($33.43 \pm 0.85\%$), followed by AMG-Ch/Coll NPs-HG ($31.56 \pm 1.14\%$), Ch-Coll NPs-HG ($30.35 \pm 1.08\%$), and AMG-HG ($27.75 \pm 1.26\%$). These results indicate that the presence of NPs, particularly those loaded with AMG, enhanced the water absorption capacity of the HGs.

In vitro Drug Release

The in vitro release of AMG-Ch NPs-HG was the highest among all HG formulations, as shown in Figure 7B. All formulations exhibited a progressive increase in drug release from 1 to 6 hours. At 6 hours, AMG-Ch NPs-HG demonstrated the highest cumulative drug release ($39.68 \pm 2.25\%$), followed by AMG-Ch/Coll NPs-HG ($35.41 \pm 2.12\%$) and AMG-HG ($12.34 \pm 1.86\%$).

The in vivo Wound Healing Assay

The wound closure rates were assessed for all treatment groups, as shown in Figures 8A and B. Figure 8A presents representative wound images at days 0, 7, 14, and 21, while Figure 8B quantitatively illustrates the progression of wound

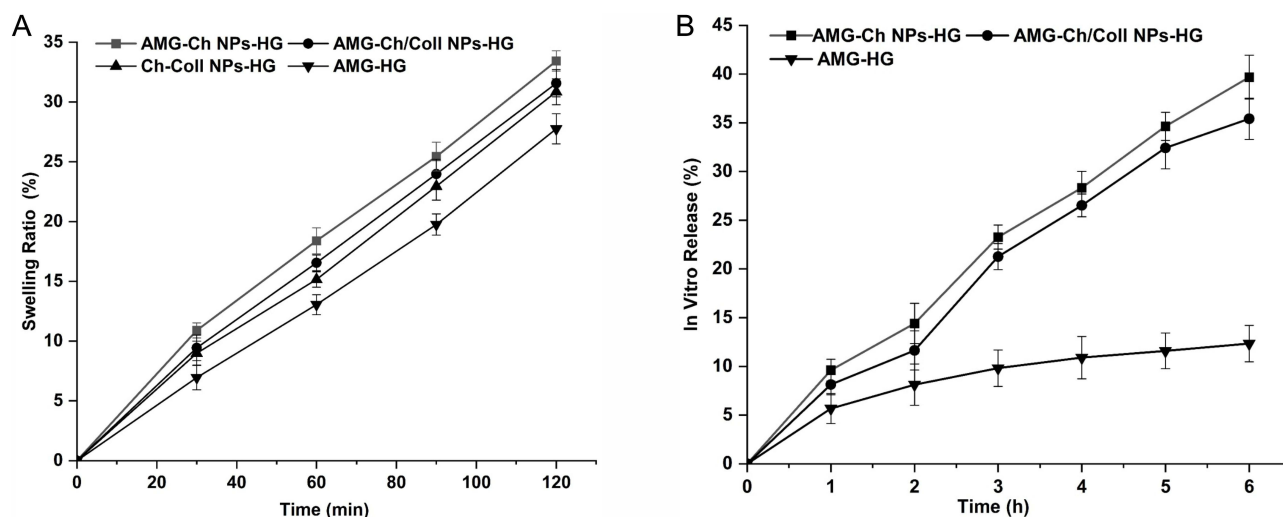


Figure 7 (A) Swelling ratio of AMG-HG, AMG-Ch NPs-HG, AMG-Ch/Coll NPs-HG, and Ch-Coll NPs-HG; (B) in vitro release of AMG-HG, AMG-Ch NPs-HG, and AMG-Ch/Coll NPs-HG.

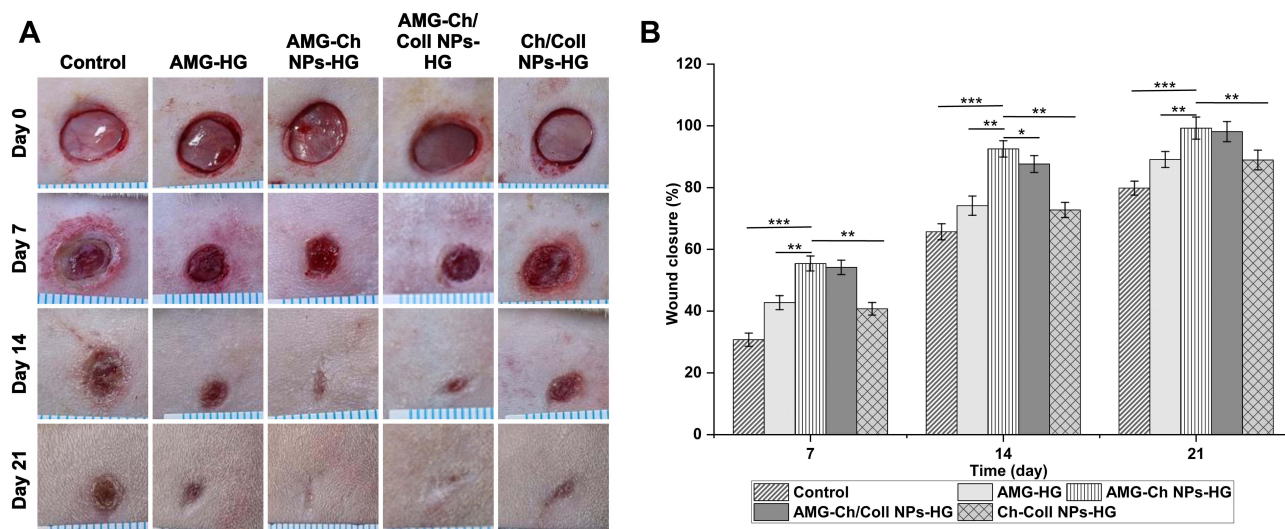


Figure 8 (A) Representative wound closure images taken on days 0, 7, 14, and 21 after treatment illustrate the progression of the healing process over time of (1) control group, (2) AMG-HG group, (3) AMG-Ch NPs-HG group, (4) AMG-Ch/Coll NPs-HG group, and (5) Ch/Coll NPs-HG group; **(B)** Percentage of wound closure measured on days 7, 14 and 21, illustrating the comparative healing progression among the same treatment groups. Results are expressed as mean $\pm$ standard deviation ($n = 5$); * indicates statistical significance at $P < 0.05$; ** indicates significance at $P < 0.01$; *** indicates significance at $P < 0.001$.

closure over time for all treatment groups. After 21 days, the control group showed the slowest closure rate ($79.84 \pm 2.25\%$), while AMG-HG achieved a moderate improvement ($89.12 \pm 2.58\%$). The AMG-Ch NPs-HG and AMG-Ch/Coll NPs-HG groups exhibited the fastest rates ($99.28 \pm 3.59\%$ and $98.13 \pm 3.26\%$, respectively). Ch/Coll NPs-HG showed a comparable effect to AMG-HG ($88.95 \pm 3.14\%$). These results suggest that the incorporation of AMG in NP-based HGs, particularly AMG-Ch NPs-HG and AMG-Ch/Coll NPs-HG, significantly enhanced the wound healing process.

On day 7, both the AMG-Ch NPs-HG ($55.43 \pm 2.43\%$) and AMG-Ch/Coll NPs-HG ($54.17 \pm 2.32\%$) groups exhibited significantly greater wound closure compared to the control ($30.75 \pm 2.14\%$) ($P < 0.001$), AMG-HG ($42.73 \pm 2.27\%$), and Ch/Coll NPs-HG ($40.68 \pm 2.04\%$) groups ($P < 0.01$), although the difference between AMG-HG and Ch/Coll NPs-HG was not statistically significant ($P > 0.05$). By day 14, the AMG-Ch NPs-HG ($92.55 \pm 2.64\%$) group demonstrated a significantly higher wound closure rate than the AMG-Ch/Coll NPs-HG ($87.65 \pm 2.73\%$) group ($P < 0.05$), as well as the AMG-HG ($74.15 \pm 3.12\%$) and Ch/Coll NPs-HG ($72.74 \pm 2.45\%$) groups ($P < 0.01$), and the control group ($65.70 \pm 2.62\%$) ($P < 0.001$). On day 21, the AMG-Ch NPs-HG group continued to show superior wound closure compared to the control ($P < 0.001$), AMG-HG, and Ch/Coll NPs-HG groups ($P < 0.01$), while no statistically significant difference was observed between the AMG-Ch NPs-HG and AMG-Ch/Coll NPs-HG groups ($P > 0.05$). Overall, these results underscore the consistent effectiveness of both AMG-Ch NPs-HG and AMG-Ch/Coll NPs-HG in accelerating wound healing, with their advantages over AMG-HG and Ch/Coll NPs-HG becoming increasingly evident over time. These findings support the potential of both formulations as promising therapeutic agents for the treatment of full-thickness excisional wounds in rats.

Discussion

The present study aims to formulate AMG-loaded Ch/Coll NPs within a HG system and evaluate their wound healing potential. PS plays a crucial role in determining the effectiveness of drug delivery systems for wound healing applications. NPs, especially those within the 20–500 nm range, represent a promising approach to addressing the complex physiological processes of wound healing by enhancing the wound microenvironment, supporting hemostasis, and promoting tissue regeneration.⁵⁵ Their nanoscale size enables targeted delivery to the wound site, offering a clear advantage over larger particles. In line with this consideration, AMG-Ch NPs, AMG-Ch/Coll NPs, and Ch-Coll NPs were selected for further characterization and evaluation of their wound healing potential.

Accordingly, the PS of each formulation was measured to assess its suitability for topical administration. A gradual increase in PS was observed, from 297.10 ± 11.64 nm in AMG-Ch NPs to 317.66 ± 8.76 nm in AMG-Ch/Coll NPs and 339.62 ± 6.43 nm in Ch-Coll NPs. This enlargement is primarily attributed to physical and structural factors arising during the ionic gelation process. Coll, which contains carbonyl groups (C=O) within its carboxyl functional groups, can form hydrogen bonds with the protonated amine groups (NH) of Ch, thereby adding structural complexity to the polymeric network. Moreover, the presence of Coll may impair the cross-linking efficiency between the phosphate groups of TPP and the amine groups of Ch due to charge competition or increased molecular crowding.⁵⁶

In addition, the incorporation of Coll may reduce the degree of Ch protonation due to charge redistribution, resulting in a lower overall surface charge. This reduction in electrostatic repulsion can facilitate NP aggregation, particularly in Ch-Coll NPs, which lack AMG as a hydrophobic stabilizing agent.⁵⁷ In contrast, hydrophobic interactions between AMG and the Ch matrix in AMG-Ch/Coll NPs may enhance colloidal stability. Larger PS are associated with a decreased specific surface area, which may lead to reduced aqueous solubility of the drug.⁵⁸ As solubility is a key factor influencing the availability of active compounds in topical applications, precise control of PS is essential to enhance drug solubility and ensure optimal therapeutic performance.⁵⁹

The ZP values were -26.17 ± 0.63 mV for AMG-Ch NPs, -26.83 ± 0.37 mV for AMG-Ch/Coll NPs, and -42.10 ± 0.20 mV for Ch-Coll NPs. The similarity in ZP values between AMG-Ch and AMG-Ch/Coll NPs suggests that the addition of Coll at a low ratio (10:0.5, Ch/Coll) did not disrupt the electrostatic environment of the NPs. This indicates that Coll contributed to the overall surface characteristics in a manner that helped maintain charge stability, alongside Ch and AMG. Formulations exhibiting a ZP of at least ± 30 mV are generally considered electrostatically stable and provide an energetically favorable particle surface for drug–molecule interactions.⁶⁰ Therefore, the ZP values of approximately -26 mV in AMG-Ch and AMG-Ch/Coll NPs indicate the presence of repulsive forces between similarly charged particles, which help prevent aggregation during storage or application. This level of surface charge is sufficient to maintain good dispersion and provides an energetically favorable interface for drug adsorption.⁶¹ In contrast, the more negative ZP observed in Ch-Coll NPs (-42.10 mV) may reflect increased surface exposure of Coll's polar groups in the absence of AMG. This condition likely reduces the overall positive charge density, which mainly originates from the protonated amine groups (NH) of Ch, and promotes the adsorption of anionic species from the surrounding medium.⁶² Although Ch is typically cationic in acidic media, the observed negative charges can be explained by the presence of anionic phosphate groups from TPP and carboxyl groups of Coll, which dominate the nanoparticle surface during ionic gelation. Moreover, the measurements were performed near neutral pH, at which the protonation degree of Ch is reduced, allowing these anionic groups to predominate at the interface. These combined effects account for the negative surface charge observed in our NP formulations.⁶³

These differences in surface charge characteristics were further supported by morphological observations using SEM. The SEM images showed that AMG-Ch NPs, AMG-Ch/Coll NPs, and Ch-Coll NPs exhibited spherical morphology with slightly rough surfaces, suggesting a porous structure. This porosity, along with minimal agglomeration, indicates the formation of well-dispersed Ch-based NPs with high surface area, beneficial for drug loading, interaction with biological media.^{64,65} The high %EE observed in the AMG-Ch/Coll NPs formulation may be attributed to the additional binding sites and interactive domains provided by Coll, which can facilitate better encapsulation of AMG within the polymeric matrix.⁶⁶ The presence of both Ch and Coll likely forms a more integrated and compact polymeric network, thereby minimizing drug leakage during NP formation and enhancing drug retention.⁶⁷ These findings highlight the influence of polymer composition on particle stability and encapsulation efficiency, warranting a comparative assessment with similar NP-based HG systems reported in recent studies.

Compared with recently reported NP-based HG wound dressings, the developed AMG-Ch and AMG-Ch/Coll NPs fall within the typical nanometric range and exhibit surface charges supportive of colloidal stability. Previous polymeric NP systems have primarily employed polysaccharide-based matrices such as chitosan/alginate (Ch/alginate) for AMG encapsulation. For instance, Muchtaridi et al (2023)¹⁴ reported AMG-loaded Ch/alginate NPs prepared at a 10:0.5 (Ch: alginate) ratio, exhibiting a PS of 374 nm and a ZP of $+45.7$ mV, indicating a stable cationic dispersion and efficient drug entrapment. In contrast, our formulation incorporated Coll at the same polymeric ratio (10:0.5, Ch:Coll), yielding AMG–Ch and AMG–Ch/Coll NPs with smaller PS (297.10 ± 11.64 nm and 317.66 ± 8.76 nm, respectively) and stable negative

surface charges (-26.17 ± 0.63 mV and -26.83 ± 0.37 mV, respectively). This shift in surface potential and nanoscale dimensions suggests enhanced colloidal stability of the NPs, supporting their compatibility within the HG matrix. At the NP level, the system achieved an encapsulation efficiency (EE) of $94.19 \pm 0.53\%$. Furthermore, Nguyen et al (2024) fabricated polycaprolactone (PCL) membranes coated with curcumin–Ch NPs and gelatin for wound dressing applications, showing a curcumin EE of 88.7%, a PS of 102 nm, and a ZP of -35.6 ± 2.8 mV, indicative of stable nanoscale dispersion and strong polymer–drug interactions.⁶⁸ Similarly, Chanmontri et al (2025) developed a quaternized Ch/oxidized pectin HG incorporating AMG– β -cyclodextrin inclusion complexes, exhibiting remarkable cytocompatibility, potent antioxidant activity, and superior wound-healing efficacy.⁶⁹ These findings highlight the therapeutic relevance of AMG-loaded polymeric HGs and support the continued optimization of delivery systems for sustained bioactive release. In comparison, the AMG–Ch and AMG–Ch/Coll NP–HG formulations developed in this study offer additional advantages through nanoscale encapsulation, which enhances colloidal stability and promotes accelerated tissue repair. To further substantiate the structural integrity and confirm the intermolecular interactions underlying these physicochemical characteristics, FTIR analysis was subsequently performed.

The FTIR spectra of AMG, Ch, TPP, Coll, AMG–Ch NPs, AMG–Ch/Coll NPs, and Ch–Coll NPs confirmed the successful formation of NPs through ionic gelation and intermolecular interactions. The NP formulations exhibited characteristic O–H stretching bands around 3294 cm^{-1} (AMG–Ch NPs), 3288 cm^{-1} (AMG–Ch/Coll NPs), and 3300 cm^{-1} (Ch–Coll NPs). This shift and broadening suggest enhanced hydrogen bonding between the polymer matrix and the active compound. Minor shifts were also evident in the C–H stretching region ($2942\text{--}2946\text{ cm}^{-1}$) in AMG–Ch NPs, AMG–Ch/Coll NPs, and Ch–Coll NPs, corresponding to the alkyl chains in Ch and Coll. A strong absorption band in the range of $1629\text{--}1640\text{ cm}^{-1}$ was assigned to C=O stretching, overlapping with N–H bending ($1561\text{--}1576\text{ cm}^{-1}$), indicating the involvement of both carbonyl and amine groups in the crosslinking process.⁶⁶

The C–N stretching ($\sim 1375\text{ cm}^{-1}$), asymmetric C–O–C stretching ($\sim 1150\text{ cm}^{-1}$), and C–O stretching ($1065\text{--}1067\text{ cm}^{-1}$) bands remained visible, confirming the preservation of Ch's primary functional groups. Importantly, the appearance of a distinct band at $\sim 900\text{ cm}^{-1}$ in all NP formulations, which was absent in pure Ch and Coll, corresponds to P–O–P stretching vibrations.³⁹ This confirms the formation of phosphate bridges between TPP and the protonated amine groups of Ch/Coll, validating the ionic gelation mechanism. Collectively, these spectral features demonstrate both intermolecular and intramolecular interactions that contribute to the structural stability of the NPs. Furthermore, the spectral shifts and broadening of characteristic bands in AMG–Ch NPs and AMG–Ch/Coll NPs, compared with pure AMG, indicate the successful incorporation of AMG into the NP matrix through intermolecular interactions with the polymer components.

The FTIR findings were complemented by XRD analysis to gain further insight into the internal structure and physical state of the NPs. The XRD diffractograms of AMG–Ch NPs, AMG–Ch/Coll NPs, and Ch–Coll NPs show a predominantly amorphous pattern, indicating a Transformation from the semicrystalline or crystalline phase to an amorphous phase of the raw material.^{70,71} The absence of AMG's characteristic crystalline peaks in the diffractogram suggests a homogeneous distribution of the compound within the NP matrix and successful encapsulation within the nanoreservoir structure.³¹ In addition, the alteration of Ch's semicrystalline nature is presumed to result from interactions or modifications involving its hydroxyl and amine groups, thereby promoting the formation of amorphous complexes with the polymer encapsulant.⁷²

These structural transitions were further confirmed by the DSC thermogram, which exhibited distinct endothermic peaks at 178.78°C for AMG and 112.90°C for TPP.⁷³ In contrast, Ch displays a glass transition pattern, indicative of its amorphous structure, along with an endothermic peak around 76.27°C , attributed to the evaporation of bound water in the heat-sensitive Ch matrix.⁷⁴ The DSC thermograms of AMG–Ch NPs, AMG–Ch/Coll NPs, and Ch–Coll NPs exhibit profiles consistent with glass transition behavior. Notably, the absence of endothermic or exothermic peaks corresponding to crystalline AMG and TPP suggests a loss of crystallinity.⁷³ These observations, supported by XRD data, indicate molecular dispersion of AMG within the NP matrix and successful encapsulation within the nanoreservoir system.³¹

This amorphous transformation plays a critical role in enhancing the solubility of AMG, as demonstrated by a fourfold increase in its aqueous solubility in AMG–Ch NPs and AMG–Ch/Coll NPs.⁷³ This enhancement can be attributed to the inherent properties of the NPs, combined with the synergistic effect of hydrophilic polymers in the

formulation. Key contributing factors include reduced PS and the presence of polar functional groups in Ch and Coll, which increase surface area exposure to the solvent and improve aqueous dispersion.⁷⁵

The enhanced solubility of AMG, achieved through NP encapsulation, enabled its incorporation into an HG matrix for topical application. Each formulation was prepared using Carbopol as the gelling agent and subsequently evaluated for characterization and suitability as a wound healing formulation.⁷⁶ The first characterization step involved pH analysis, which showed that all HG formulations (pH measured ranges between 6.50–6.98) remained within the acceptable range for skin application (pH 4.5–7.0).²⁷ AMG-HG exhibited the highest pH (6.98 ± 0.13), likely due to the absence of NP matrix interactions. In contrast, Ch-Coll NPs-HG showed the lowest pH (6.50 ± 0.11), which may be influenced by the acidic functional groups present in both Ch and Coll. The slightly lower pH values of AMG-Ch NPs-HG (6.68 ± 0.12) and AMG-Ch/Coll NPs-HG (6.81 ± 0.15) suggest that NP formation helps balance the interaction between acidic and basic groups, contributing to pH stability. Overall, these results indicate that all formulations are suitable for topical use, with NP incorporation enhancing both functional performance and pH compatibility.⁷⁷

In addition to pH, the physical behavior of the HG, particularly its ability to spread uniformly over the wound site, is a critical factor influencing its applicability. The spreadability was assessed to determine the HG formulations' ability to distribute evenly over the skin, which is essential for application, wound coverage, and tissue regeneration.⁷⁸ Among all formulations, AMG-Ch NPs-HG showed the highest spreadability, likely due to the increased solubility and uniform distribution of nanoscale AMG within the Ch matrix. The absence of Coll in this formulation allowed the formation of a more flexible polymeric network, thereby facilitating gel deformation and spreading across the surface.⁷⁹ In contrast, the Coll-containing formulations AMG-Ch/Coll NPs-HG and Ch-Coll NPs-HG showed slightly lower values. Hydrogen bonding and electrostatic interactions with Coll increase the stiffness of Ch-based HGs, which may reduce flexibility and spreadability.⁸⁰ Meanwhile, AMG-HG demonstrated the lowest spreadability, likely due to the poor solubility of pure AMG, which may have caused aggregation and the formation of a denser gel matrix that restricted deformation and spreadability.¹⁹

Another important characteristic of HG formulations for wound healing is their ability to absorb wound exudate. The swelling ratio is essential for wound healing, as it enables HG formulations to absorb wound exudate and maintain a moist environment that supports tissue regeneration.⁸¹ The swelling ratio of the HGs was closely influenced by the polymeric network structure and the PS of the incorporated NPs.⁸² In formulations such as AMG-Ch NPs-HG, the absence of Coll and the presence of smaller NPs favor a more open network structure, which facilitates water uptake and increases the swelling ratio.⁸³ In contrast, AMG-Ch/Coll NPs-HG showed a slightly lower swelling ratio, likely due to increased crosslinking density from hydrogen bonding and electrostatic interactions between Coll and Ch.⁸⁴ The swelling capacity further declined in Ch/Coll NPs-HG, possibly due to the absence of AMG, which in AMG-loaded systems may contribute to colloidal stability and additional hydrophilic interactions. AMG-HG demonstrated the lowest swelling ratio, likely due to the poor solubility and aggregation of free AMG, resulting in a compact and less permeable gel matrix.¹⁹

Polymer composition, matrix flexibility, and PS significantly influenced the *in vitro* drug release profiles of the HGs by affecting their water absorption and retention capacity.⁸⁵ AMG-Ch NPs-HG exhibited the most efficient release, likely due to its smaller PS, enhanced solubility, and better matrix hydration. The nanoscale particles increased surface exposure to the medium, promoting faster water uptake and drug diffusion.⁸⁶ In contrast, the slightly reduced release in AMG-Ch/Coll NPs-HG may be attributed to the presence of both Ch and Coll, which increase matrix rigidity through additional hydrogen bonding and electrostatic crosslinking, thereby slowing drug diffusion.⁸⁷ AMG-HG showed the lowest release performance, likely due to the poor solubility of free AMG and the absence of NP-mediated dispersion, thereby reducing the efficiency of topical drug delivery.²⁰

The improved release behavior of AMG, particularly from AMG-Ch NPs-HG and AMG-Ch/Coll NPs-HG, is expected to translate into enhanced therapeutic performance. This was further evaluated through wound healing studies, in which the percentage of wound closure served as a key indicator of therapeutic efficacy.⁸⁸ Faster and more complete closure reflects a more optimal healing process. Among all groups, the AMG-Ch NPs-HG and AMG-Ch/Coll NPs-HG formulations demonstrated the best performance, achieving the highest wound closure rates on day 21 ($99.28 \pm 3.59\%$ and $98.13 \pm 3.26\%$, respectively). These results were significantly higher compared to the control group ($79.84 \pm 2.25\%$), AMG-HG ($89.12 \pm 2.58\%$), and Ch/Coll NPs-HG ($88.95 \pm 3.14\%$). The enhanced therapeutic efficacy of the AMG-Ch

NPs-HG and AMG-Ch/Coll NPs-HG formulations can be attributed to both pharmacological and pharmaceutical mechanisms. In the AMG-Ch NPs-HG formulation, AMG acts pharmacologically as an anti-inflammatory and antioxidant agent, supporting more effective drug penetration and retention at the wound site.^{89–91} Additionally, the presence of Ch, known for its bioadhesive properties and intrinsic wound healing capabilities, has been reported to support enhanced cell migration and proliferation.^{92,93} From a pharmaceutical perspective, the NP delivery system improves AMG's bioavailability and physicochemical properties by increasing surface area, enhancing water solubility, and enabling a controlled release profile, thereby prolonging the therapeutic action.^{94,95}

Similarly, in the AMG Ch/Coll NPs HG formulation, in addition to the wound healing potential of AMG, the role of Coll combined with Ch as a polymer matrix in the NP system exerts a regenerative effect that is comparatively slower but more sustained.⁹⁶ Although Coll-containing NPs may not accelerate the initial phase of healing, their contribution becomes more prominent during the tissue remodelling stage in the later phase of wound repair.³⁷ These findings suggest that Coll-based NPs can support the long-term healing process by promoting structural integrity and functional tissue regeneration.³⁶

Observations on day 7 revealed that the AMG-Ch NPs-HG group exhibited significantly greater wound closure compared to the control group ($P < 0.001$), AMG-HG, and Ch/Coll NPs-HG ($P < 0.01$), indicating sustained therapeutic activity of the NP system. However, no significant difference was observed compared to the AMG-Ch/Coll NPs-HG group, suggesting that during the early phase of wound healing, both AMG-Ch NPs-HG and AMG-Ch/Coll NPs-HG formulations demonstrated comparable therapeutic effectiveness. This similarity may be attributed to the relatively equivalent initial release of AMG from both systems. By day 14, the AMG-Ch NPs-HG group began to show significantly higher effectiveness than AMG-Ch/Coll NPs-HG ($P < 0.05$), AMG-HG, and Ch/Coll NPs-HG ($P < 0.01$), as well as the control group ($P < 0.001$), indicating continued therapeutic activity. Furthermore, by day 21, both AMG-Ch NPs-HG and AMG-Ch/Coll NPs-HG exhibited significantly superior wound healing performance compared to AMG-HG and Ch/Coll NPs-HG ($P < 0.01$), as well as the control group ($P < 0.001$). These results underscore the potential of AMG-loaded NP HG to provide long-term therapeutic benefits in wound repair.

The observed enhancement in wound closure in the AMG-Ch NPs-HG formulation is consistent with previous studies that reported comparable outcomes using advanced drug delivery systems. In one study, an HG formulation based on AMG complexed with hydroxypropyl- β -cyclodextrin (HP- β -CD)¹⁹ and a sprayable HG containing AMG-loaded nanostructured lipid carriers (NLCs)²⁰ with propolis demonstrated significantly improved wound closure compared to pure AMG. These findings align with the present study and are likely attributed to similar drug release mechanisms, where therapeutic efficacy depends more on the delivery system's ability to enhance the bioavailability of the active compound than on its concentration alone.⁹⁷ The overall enhancement in wound closure observed in the AMG-Ch NP-HG and AMG-Ch/Coll NP-HG formulations is consistent with recent advances in NP-based drug delivery and soft-matter nanocarrier systems. For example, bimetallic oxide (SrO-CoO) NPs embedded within a polyacrylamide HG exhibited a comparable extended-release profile while maintaining biocompatibility for wound healing applications. Such sustained release is known to regulate the wound microenvironment by maintaining steady therapeutic levels, thereby promoting fibroblast activity, enhancing collagen synthesis, and attenuating inflammatory responses—mechanisms previously reported in SrO-CoO HG systems.⁹⁸ Likewise, Ch/Coll matrices have been reported in the literature to provide biointeractive cues that support cellular migration, angiogenesis, and extracellular matrix remodeling, which collectively contribute to the accelerated tissue repair observed in this study. These mechanistic correlations offer a plausible explanation for the improved wound-closure trends observed in the AMG-Ch and AMG-Ch/Coll NP-HG groups.²⁵

Building on this context, beyond polymeric carriers, lipid-based nanostructured systems such as the NLC-P- α M formulation reported by Suhandi et al (2025)²⁰ have also demonstrated high wound-closure efficacy in diabetic models, achieving $85.83 \pm 3.33\%$ wound closure by day 14. However, these lipidic matrices primarily serve as passive encapsulation vehicles with limited biological interaction at the wound interface. In contrast, the Ch/Coll system developed in this study combines the mucoadhesive properties of Ch with the bioactive peptide motifs of Coll, providing both structural stability and biological responsiveness.⁹⁹ By day 14, the AMG-Ch NP-HG and AMG-Ch/Coll NP-HG groups achieved wound closure rates of $92.55 \pm 2.64\%$ and $87.65 \pm 2.73\%$, respectively, outperforming the lipid-based NLC-P- α M formulation ($85.83 \pm 3.33\%$) in terms of wound contraction and tissue recovery.

Although a significant increase in wound closure was observed after 21 days of treatment, nearly complete closure was achieved only in the AMG Ch NPs HG ($99.28 \pm 3.59\%$) and AMG Ch/Coll NPs HG ($98.13 \pm 3.26\%$) groups. This observed sustained therapeutic effect may be attributed to the ability of Ch and Coll to form an HG matrix capable of retaining AMG and prolonging its release, as demonstrated in previous studies on biocompatible HGs for wound healing and drug delivery¹⁰⁰ and further supported by findings highlighting the therapeutic potential of AMG in wound healing.⁹⁰ This enhanced wound closure may be attributed to improved epithelial cell migration and favorable modulation of the wound microenvironment by the biopolymer matrix, which together facilitate faster tissue repair.¹⁰¹ In addition to these mechanistic aspects, the therapeutic effects observed at this dosage are consistent with other preclinical topical formulations employing comparable application amounts. In this study, a daily application of 50 mg AMG per wound was selected based on common practices reported in preclinical HG and other Ch-based topical gel studies.¹⁰² Although a formal dose–response analysis was not conducted, future optimization of active loading and application frequency is planned to determine the minimal effective concentration and further enhance the translational relevance of the developed AMG-loaded NP–HG systems.

Taken together, these findings not only confirm the efficacy of the developed NP–HG systems but also align closely with recent advances in polymeric nanocarrier research. The overall enhancement in wound closure observed in the AMG–Ch NP–HG and AMG–Ch/Coll NP–HG formulations is consistent with recent advances in NP-based drug delivery and soft-matter nanocarrier systems. Recent studies have emphasized that multifunctional polymeric nanocarriers can improve encapsulation efficiency and ensure sustained release, thereby contributing directly to prolonged therapeutic action in topical applications.¹⁶ Furthermore, the integration of soft-matter nanocarriers, particularly NP-based HGs, has been highlighted as a promising strategy to optimize the wound microenvironment and enhance cellular responses during the healing process.¹⁷ These trends support the present findings, in which the polymeric NP–HG systems demonstrated superior wound closure and greater durability of therapeutic effects compared to non–nanocarrier-based formulations.¹⁰³

Consistent with recent reviews on polymeric and soft-matter wound healing platforms,^{18,104} the Ch and Coll-based matrix used in this study provided a biocompatible scaffold that facilitated sustained drug retention and the gradual release of AMG at the wound site. This synergistic interaction between the bioactive polymers and the NP delivery system not only accelerated epithelial regeneration but also ensured long-term stability and safety, thereby confirming the relevance of such soft-matter nanocarrier designs in advanced wound care. The components used in the polymeric NP-based HG formulations, namely Ch and Coll, are known to possess excellent biocompatibility and biodegradability, which are essential for safe topical applications.¹⁰⁵ Ch has been widely reported as a non-toxic, bioadhesive, and hemostatic polymer that promotes fibroblast proliferation and accelerates re-epithelialization.¹⁰⁶ Coll, a natural component of the extracellular matrix, provides a favorable microenvironment for cell adhesion and migration, thereby supporting tissue regeneration without eliciting inflammatory responses.¹⁰⁷ In this *in vivo* study, the wound closure observed over the 21-day period indicates that the formulations were well tolerated locally. These findings are consistent with previous reports demonstrating the biocompatibility of AMG–Ch NP–HG and AMG–Ch/Coll NP–HG systems in wound-healing applications.^{33,34} Similarly, the safety profile of Ch/Coll NPs within HG systems has also been reported in wound-healing applications.

The comparative wound-healing outcomes, beyond confirming local biocompatibility, further emphasize the superior performance of the AMG–Ch NP–HG and AMG–Ch/Coll NP–HG formulations. Collectively, these observations indicate that the developed AMG-loaded Ch/Coll NPs within HG systems not only accelerate wound closure but also maintain excellent local compatibility, suggesting their potential for further preclinical development. In contrast, AMG–HG and Ch/Coll NPs–HG showed only moderate improvements, with no significant differences between them throughout the study period. This suggests that neither AMG without a nanocarrier nor blank NPs without active compounds are sufficient to ensure sustained therapeutic action, underscoring the importance of a well-designed delivery system in topical wound healing.¹⁰⁸

Limitations and Future Directions

A limitation of this study is that we did not directly assess the physical stability of all NP formulations (AMG-Ch NPs, AMG-Ch/Coll NPs, and Ch-Coll NPs) and HG systems under different storage temperatures or durations. In addition, the effects of these NP-based HG formulations (AMG-Ch NPs-HG, AMG-Ch/Coll NPs-HG, and Ch-Coll NPs-HG) and AMG-HG on fibroblast migration and tube-formation assays, which could illustrate their pro-angiogenic potential, were not assessed. Furthermore, the influence of each HG formulation on inflammatory and angiogenic markers, such as IL-6 and TNF- α , was not investigated. The drug-loading efficiency of the NP systems was also not determined. However, quantification of AMG loading in NP-based HG formulations (AMG-HG, AMG-Ch NPs-HG, and AMG-Ch/Coll NPs-HG) using HPLC is planned for future studies. Subsequent work should also include histological examinations of skin tissue sections to evaluate epithelialization, collagen deposition, and inflammatory responses at day 21 post-treatment. Future investigations will further explore cytocompatibility through in vitro cell-viability assays using NIH-3T3 fibroblasts to precisely assess the compatibility of the NP and HG systems. Moreover, bacterial colony-count assays were not performed in this study. Instead, antibacterial performance was preliminarily assessed via disc-diffusion assays against *Staphylococcus aureus* and *Escherichia coli* to determine inhibition zones. Finally, in silico molecular-docking studies are warranted to elucidate the potential interactions between AMG and the Ch-Coll polymer matrix that may contribute to enhanced wound-healing efficacy.

Conclusion

This study successfully demonstrated that AMG-loaded Ch/Coll NPs formulated into an HG system, offer significant potential for enhancing topical wound healing. The NPs exhibited favorable physicochemical characteristics, including suitable PS, spherical morphology, high percentage of entrapment efficiency, and amorphous structure with strong intermolecular interactions, as confirmed by SEM, FTIR, XRD, and DSC analyses. NP encapsulation markedly improved the aqueous solubility of AMG, allowing its stable incorporation into HG matrices. The HG formulations showed acceptable pH values, good spreadability, high swelling ratios, and sustained in vitro drug release, with the best performance exhibited by AMG-Ch NPs-HG and AMG-Ch/Coll NPs-HG matrices.

In vivo wound healing evaluation confirmed that both NP-based HG formulations significantly accelerated wound closure compared to non-NP controls, demonstrating superior therapeutic efficacy. The combination of Ch's bioadhesive and regenerative properties with the long-term structural support of Coll provided a synergistic effect in promoting sustained drug release and tissue repair. These findings emphasize the critical role of NP-based delivery systems in improving the bioavailability and therapeutic effectiveness of poorly soluble compounds like AMG and highlight the promise of AMG-loaded Ch/Coll NPs in HG formulations as an advanced platform for topical wound treatment.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there are no conflicts of interest in this work.

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