Original Article

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Design and Development of Nanoparticles Containing α-Mangostin for Wound Application

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Abstract:

Objective: The objective of this research was to design and develop nanoparticles containing α-mangostin (α-MG) for wound applications.

Material and Methods: The nanoparticles were composed of polycaprolactone (PCL) and Eudragit® S 100 (EDG), with 10% wt of α-MG; wherein, the optimal compositions of the nanoparticles were studied using a mixture-typed simplex lattice design. The amount of PCL (5-20 milligram/milliliter (mg/mL)) and EDG (5-20 mg/mL) were varied, and the effects of the components toward particle size, size distribution, zeta potential; drug content, and drug release were examined. The physicochemical properties of the nanoparticles were analyzed using a zetasizer. The content of α-MG was quantified using High Pressure Liquid Chromatography.

Results: It was found that the nanoparticles having different mixtures of PCL and EDG did not affect the physicochemical properties nor the drug content. However, the release of α-MG can be tuned by varying the nanoparticle composition. Formulations with higher EDG showed greater drug release at pH 7.4, because of the polymer dissolution at a specified pH. The composition of the optimized formulation composed of 16.5 mg/mL of EDG and 8.5 mg/mL of PCL. The optimized nanoparticle showed a controlled release profile of up to 12 h, which was superior to the α-MG solution.

Conclusion: The developed nanoparticles of PCL and EDG can be considered as a promising platform to deliver α-MG for wound applications.

Keywords: α-mangostin, Eudragit® S 100, nanoparticles, polycaprolactone, wound healing

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Introduction

The skin is the largest and most expansive organ of the human body. It plays a vital role as a protective barrier, exhibits essential functions; such as immune defense, sensory perception, and protects the internal organs from external environments[1]. The integumentary system serves as the first-line defense against environmental factors that may harm to the body. However, cuts, burns, accidents, and constant exposure to these external elements can lead to skin damage, with subsequent tissue injury; even extending to the development of wounds[2]. Sometimes, wounds can get infected with microorganisms, which can lead to infections and inflammations. Gram-positive bacteria; such as Staphylococcus spp. and Streptococcus spp., are known to cause delayed wound healing[3]. Therefore, the incorporation of topical antimicrobial agents becomes necessary to effectively manage such infections and promote wound healing[4].

Numerous herbal plants have demonstrated efficacy in promoting wound healing, due to their potent pharmacological properties and safety. One such plant is the mangosteen (Garcinia mangostana Linn.), a native Southeast Asian plant commonly found in Thailand and Indonesia. The health benefits of the pericarp of mangosteen were reported to be attribute to the compounds known as xanthones[5]. The most important phytochemical of the pericarp is α-mangostin (α-MG), which is hydrophobic in nature. The compound is known to possesses antibacterial, antioxidant, and anti-inflammatory effects that are favorable in wound care[5-7]. Considering its antimicrobial activity, α-MG is known to possess antibacterial activity against several strains and fungi. This is achieved by penetrating and breaking down the microbial membrane through attachment on the bacterial surface via electrostatic bonds and hydrophobic bonding[8,9]. The utilization of natural antibacterial agents offers numerous benefits in the treatment of diverse medical conditions; including localized infections, non-healing wounds, and challenging lesions that pose significant management difficulties[10,11]. Through the utilization of natural antibacterial compounds, the obstacles presented by antibiotic-resistant pathogens containing multidrug resistance (MDR) genes can be successfully surmounted. This presents an encouraging solution for effectively combating these microorganisms[12,13]. Additionally, α-MG have DPPH radical scavenging activity, and it can reduce the reactive oxygen species (ROS), which are related to antioxidant activity[14,15]. Furthermore, studies have also demonstrated that α-MG could effectively promote wound healing[16]. However, the use of α-MG in wound healing is impeded by its low water solubility, rendering it a challenge to be absorbed and penetrate the skin. This poses a significant obstacle in harnessing the full potential of α-MG for wound treatment purposes[17].

To date, novel drug delivery systems have been developed to aid the delivery of hydrophobic substances by enhancing their solubility and improving their absorption. Drug delivery systems also help to control and prolong drug release[18]. Polymeric nanoparticles (NPs) have become attractive drug delivery systems over the past decade due to several advantages. NPs are defined as small solid particles, with sizes ranging from 100 to 1000 nm[19]. NPs possess distinct characteristics due to their small size, which enable them to display diverse physical and chemical properties that differ greatly from larger materials[20]. There are several advantages to utilizing NPs for wound management. Firstly, these particles are not harmful to the skin and can effectively moisturize the affected area. In addition, they have been shown to accelerate the healing process by stimulating tissue repair. NPs are capable of penetrating through cellular barriers and accessing the cytoplasmic layer, leading to improved drug retention and targeted drug delivery[21]. Additionally, NPs possess a remarkable ability to protect drugs from protease enzymes that are present in the wound; thereby, enhancing their therapeutic effectiveness.

Furthermore, NPs facilitate a controlled drug release, which reduces the frequency of drug administration, simplifies the drug regimen, and may lead to a reduction in the overall cost of wound treatment[22].

This study aimed to design and develop NPs containing α-MG for controlled delivery in wound application. Polycaprolactone (PCL) and Eudragit® S 100 (EDG) were acquired to formulate a pH-sensitive NPs. The amount of α-MG was fixed at 10%wt, and the content of each polymer was optimized using an experimental design by a mixture-typed simplex lattice design. The NPs were prepared using the nanoprecipitation method, and α-MG was incorporated through entrapment technique. Then; particle size, size distribution, zeta potential (ZP), drug content, and drug release were examined. Herein, this study proposes an optimized NP composition for the delivery of α-MG for wound application.

NP=NPs ?

Material and Methods

α-MG extract was prepared following the previously published protocols, using the maceration method in 70% ethanol for 24 hr. (α-MG 183 milligram/milliliter (mg/mL) extract)[23]. Absolute ethanol, acetonitrile, and methyl alcohol (HPLC grade) were bought from Merck & Co. (Darmstadt, Germany). Polysorbate 80, polyvinyl alcohol, and polycaprolactone were purchased from Sigma Aldrich (St. Louis, MO. USA). Eudragit® S 100 was bought from Evonik (Essen, Germany).

The design and optimization of NPs

The design of the experiments was utilized for the optimization of the EDG and PCL content used in the NP formulation. The DesignExpert® software (version 11) was used to design the experiment, for which a mixture-type simplex lattice design was performed. The independent variables were the concentration of EDG, ranging from 5–20 mg/mL (X_1), and PCL; ranging from 5–20 mg/mL (X_2). The responses acknowledged (dependent variables) were particle size (Y_1), polydispersity index (PDI) (Y_2), ZP (Y_3), drug content (Y_4), and drug release at 6 hr (Y_5). The amount of α-MG was kept constant at 10% wt. Through a comprehensive evaluation, the impact of concentrations of each polymer on the properties and characteristics of the NPs were analyzed by the software; in which an optimized condition was generated.

use h or hr? homogeneous

Preparation of polymeric NPs containing α-MG

The NPs were constructed using the nanoprecipitation method. The organic phase was prepared by dissolving EDG (5–20 mg/mL), PCL (5–20 mg/mL), and α-MG extract; equivalent to 10% wt α-MG, in 25 mL of acetone, and at varying concentrations as determined by the DesignExpert® software. To prepare the water phase, polyvinyl alcohol (PVA) (2.5 mg/mL) and polysorbate 80 (10 mg/mL), as stabilizers, were dissolved in 50 mL of water, and the pH was adjusted to 5.5 using 1 N hydrochloric acid (HCl) or sodium hydroxide (NaOH). Afterwards, the organic phase was added to the water phase under a homogenizer (5000 rpm), via vigorous stirring with a magnetic stirrer for 30 min. The obtained solution was left stirring overnight in a fume hood to allow the organics to evaporate. The solution was then collected, and underwent either characterizations or was stored after a freeze-drying process.

Characterization

Particle size, PDI, and ZP

In order to assess the properties of the NPs; including their particle size, PDI, and surface charge, a zetasizer (Malvern Instruments, Malvern, UK) was used. The samples after the organic phase removal were aliquoted and diluted to 1:99 with ultrapure water (pH 5.5) before the measurement at a 90° angle and 25°C: experiments were conducted in triplicate.

Drug content

The freeze-dried α-MG-loaded NPs (α-MG-NPs) were accurately weighed, dissolved in 1 mL of methanol, and shaken overnight to extract α-MG. The amount of α-MG loaded in the NPs was determined using HPLC, with a C-18 column (250 mm x 4.6 mm, 5 µm) detected using a UV detector, at a wavelength of 320 nm. An injection volume of 10 µL and a flow rate of 0.7 mL/min were used. The mobile phase was an isocratic elution of 80% solution A (2% acetic acid) and 20% solution B (acetonitrile: methanol (75:25)). The concentration of α-MG was calculated against the prepared standard curve (R^2>0.999). The loading capacity and % loading efficiency (%LE) were calculated using the Eq. 1 and Eq. 2, respectively.

$$\text{Loading capacity} = \frac{\text{The amount of α-MG found}}{\text{The amount of α-MG-NPs}} \quad \text{Eq. 1}$$

$$\%\text{Loading efficiency} = \frac{\text{The amount of α-MG found}}{\text{The amount of α-MG added}} \quad \text{Eq. 2}$$

Drug release

Firstly, 5 mg of NPs was resuspended in 1 ml of PBS pH 5.5, and filled in a dialysis bag with a molecular weight cut off of 6000-8000 Da. Then the dialysis bag was immersed in 10 mL of PBS pH 7.4 as a medium, and placed in an incubator shaker at a temperature of 37±0.5 ºC, with a speed of 50 rpm. At different times of up to 12 hr, the medium was collected and fresh PBS was added back into the system to maintain a sink condition. The amount α-MG released at each timepoint was quantified using HPLC.

Statistic analysis

Experiments were carried out in triplicate, and the results were reported as means±standard deviation (S.D.). The data was assessed using one-way ANOVA, followed by Tukey's test. A significance level was established at a p-value<0.05.

Results

The design and optimization of polymeric NPs

The DesignExpert® software was used to create a mixture-type simplex lattice experimental design. The formulation consisted of PCL ranging and EDG ranging from 5-20 mg/mL, and 10%wt α-MG. This resulted in a total of 8 formulations, which are listed in Table 1.

Table 1 The experiments designed for the optimization of NPs containing 10%wt α-MG

Run	PCL (mg/mL)	EDG (mg/mL)
1	16.25	8.75
2	12.50	12.50
3	20.00	5.00
4	20.00	5.00
5	5.00	20.00
6	12.50	12.50
7	8.75	16.25
8	5.00	20.00

NPs=polymeric nanoparticles, α-MG=α-mangostin, PCL=polycaprolactone, EDG=Eudragit® S 100

Table 2 presents the particle size, PDI, ZP, drug content, and drug release data of each NP formulation. The results show that all of the formulations had small particle sizes, between 15 to 65 nm, and a narrow size distribution (PDI<0.4). The ZP values of all formulations ranged from: 1.76 to -0.06. The NPs attributes of those that were freshly prepared and those after lyophilization were comparable; as shown in Table 3. The drug loading capacity was desirable, and ranging between 203.20 to 241.78 µg/mg. As to the drug release at 6 hr of different NP formulations, this varied when considering the different NP composition; with the lowest drug release being 47% and the maximum drug release at 6 hr being 99%. This highlighted the significant differences in drug release behavior among the formulations.

NP=NPs ?

Table 2 Particle size, PDI, ZP, and drug content of the NP formulations containing 10% wt α-MG (n=3)

Run	Particle size (nm)	PDI	ZP (mV)	Drug content (μg/mg)	Drug release at 6 h (%)
1	33.37	0.095	-0.24	203.20	49.75
2	65.01	0.108	-0.50	226.28	60.27
3	14.94	0.341	-0.74	241.78	64.46
4	23.05	0.274	-0.44	203.73	47.05
5	35.15	0.228	-1.76	228.26	99.04
6	24.37	0.314	-0.06	215.38	95.39
7	29.84	0.063	-0.28	219.99	92.31
8	51.87	0.077	-1.17	225.24	99.20

PDI=polydispersity index, ZP=zeta potential, NP=.....? NP=Polymeric nanoparticles (NPs) ?

Table 3 The attributes of α-MG-NPs having been freshly prepared and after lyophilization

Run	Size (nm)		PDI		ZP (mV)	
	Freshly prepared	After lyophilization	Freshly prepared	After lyophilization	Freshly prepared	After lyophilization
1	33.37±1.14	38.76±0.73	0.095±0.030	0.089±0.027	-0.24±0.65	-0.22±0.62
2	65.01±0.84	71.93±0.63	0.108±0.039	0.121±0.022	-0.50±0.17	-0.50±0.17
3	14.94±0.34	22.07±0.98	0.341±0.017	0.317±0.026	-0.74±0.67	-0.75±0.68
4	23.05±0.38	29.25±0.61	0.274±0.056	0.262±0.058	-0.44±0.57	-0.44±0.57
5	35.15±0.78	42.06±0.44	0.228±0.020	0.215±0.028	-1.76±0.29	-2.88±1.69
6	24.37±0.42	31.33±0.25	0.314±0.033	0.324±0.057	-0.06±0.21	-0.06±0.22
7	29.84±0.91	37.49±0.39	0.063±0.009	0.065±0.013	-0.28±0.27	-0.28±0.27
8	51.87±0.39	59.79±0.51	0.077±0.002	0.081±0.009	-1.17±0.81	-1.14±0.77

PDI=polydispersity index, ZP=zeta potential

Selection criteria for the optimized NPs

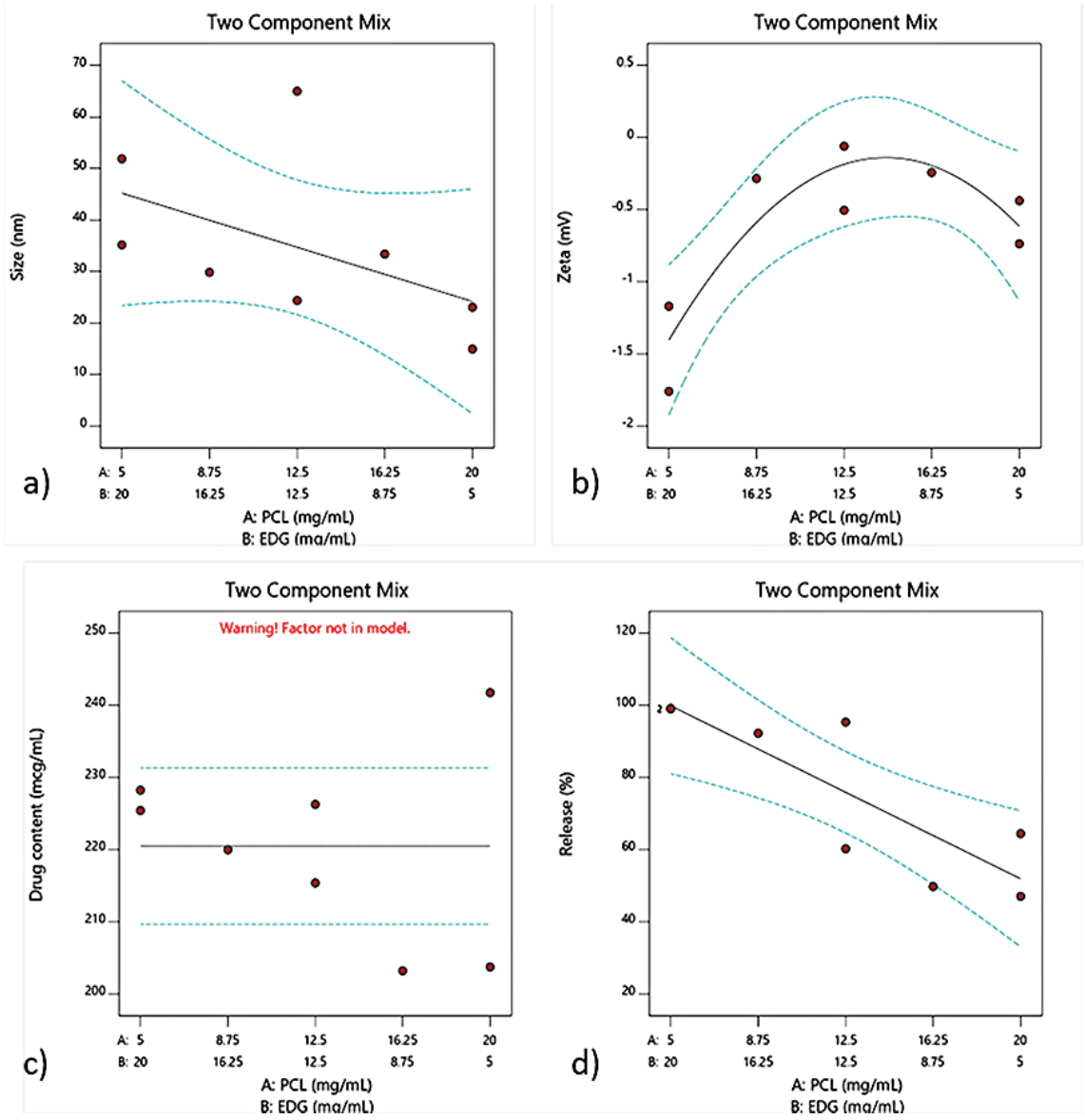
According to the analysis of the obtained responses; Figure 1 presented the findings on the effects of varying concentrations of PCL and EDG on particle size, ZP, drug loading, and drug release. Figure 1(a) and (c) indicated that neither PCL nor EDG have an impact on particle size or drug loading. However, the ZP of the NPs decreased as the amount of EDG increased (Figure 1(b)). Also, Figure 1(d) reveals that the amount of EDG significantly impacted the drug release; wherein, a higher percentage of α-MG was released when the amount of EDG in the NPs was increased.

To select the optimal formulation for α-MG-NPs, the criteria for each independent variable and significant dependent variables were chosen; as shown in Table 4. The optimized solution generated was 16.25 mg/mL of EDG and 8.75 mg/mL of PCL. This formulation exhibited a desirability value of 1.0; indicating both acceptability and excellence. Desirability served as a valuable tool to assess the multi-response optimization value, with an acceptable and excellent range falling between 0.8 and 1; indicating the formulation has high-quality characteristics[24].

Table 4 Criteria for optimized α-MG-NPs formulation

Variables	Criteria	Solutions	Desirability
EDG concentration (mg/mL)	In range	16.25	1.00
PCL (mg/mL)	In range	8.75	
Size (nm)	In range	39.95	
PDI	None	0.151	
ZP (mV)	None	-0.59	
Drug content (μg/mL)	Is in range	220.51	
Drug release (%)	Is in range	87.94	

α-MG=NPs=.....?, EDG=Eudragit® S 100, PCL=polycaprolactone, PDI=polydispersity index, ZP=zeta potential



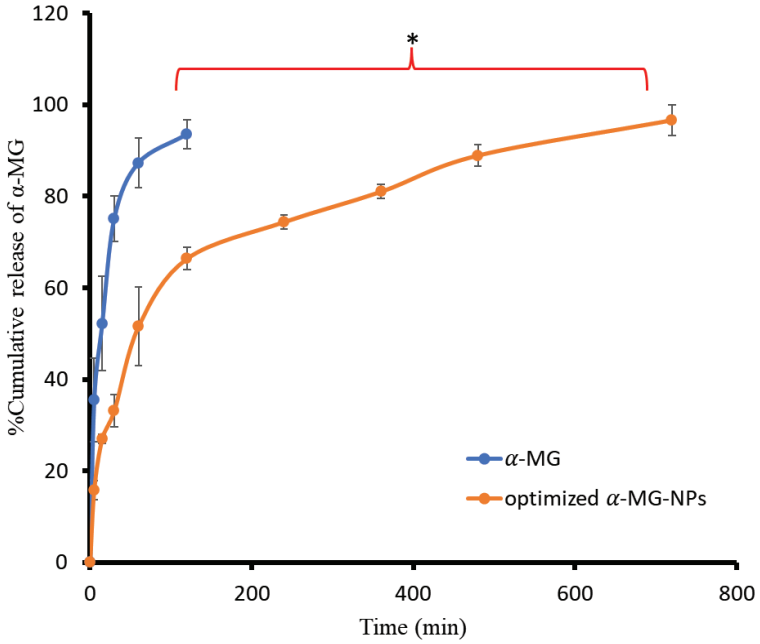
EDG=Eudragit® S 100, PCL=polycaprolactone, ZP=zeta potential

Figure 1 The effect of the concentrations of EDG and PCL on a) particle size, b) ZP, c) drug content, and d) the drug release

Table 5 Prediction results of particle size, PDI, ZP, drug content and drug release

Results	Particle size (nm)	PDI	ZP (mV)	Drug content (μg)	Drug release at 6 h (%)
Predicted result	39.95	0.151	−0.59	220.51	87.94
Actual result	45.19±1.64	0.142±0.012	0.03±0.04	222.71±3.86	81.01±1.52

PCL=polycaprolactone, ZP=zeta potential



*Significant difference, p-value<0.05

Figure 2 The release profile of the optimized α-MG-NPs and α-MG (n=3)

Confirmation of the optimization

Once the optimized condition was acquired, and the NPs according to the solution were prepared, the characteristics of the optimized NPs were evaluated to compare the actual responses with the predicted responses, so as to ascertain the optimization. The results are shown in Table 5. It can be observed that the optimized NP formulation was reliable, with no significant difference between the predicted and the actual value (p-value>0.05). Additionally, the optimized NP formulations represent small sized particles, with an appreciable PDI of 0.142, and neutral ZP. The drug content was also not significantly different between the predicted and the actual value, with an α-MG amount of 222.71±3.86 μg/mg (p-value>0.05). Moreover, the drug release at 6 hr of the predicted and the actual value did not exhibit any significant difference: 81.01±1.52%. However, further calculation of the % LE from the yield obtained was found to be 13.1±0.23%.

Drug release

The drug release profiles of the optimized α-MG-NPs compared with the α-MG extract solution are depicted in Figure 2. The findings indicated that the 6-hr α-MG release from the NPs was comparable to the predicted value and all α-MG was completely released from the solution after 720 mins. On the contrary, the α-MG release from the extract solution was rather more rapid and completed within 120 min.

Discussion

In this study, the design of experiments was utilized to formulate the NPs containing α-MG. The mixture-type simplex lattice design of 2 independent variables generated 8 experiments to be conducted. The responses, these being: particle size, PDI, ZP, drug content and 6-hr drug release, were characterized. Thus, several factors may affect the differences in the results seen though the experimental runs

were equivalent, mainly the pouring speed when the organic phase was added to the water phase. Also, some differences presented in Table 2 were not significant. The particle size of all NP formulations exhibited remarkably small particle sizes at a nanoscale. Moreover, the PDI of all formulations was consistently less than 0.4, indicating uniformity and narrow size distribution among the NPs. Interestingly, the result in Figure 1(b) found that the concentration of EDG had an effect on the surface charge. The surface charge of the NPs decreased as the amount of EDG increased. This effect can be attributed to the negative charge of the carboxylic acid anions in the structure of EDG. However, the difference, though significant, may be negligible as the overall surface charge is only slightly negative, and possibly have no impact on the colloidal stability of the NPs. Thus, these findings emphasized the promising attributes of the NP formulations, as they exhibited both small particle sizes and uniform size distributions, along with a consistent range of slightly negative zeta potentials. Moreover, the difference in the ratio of EDG and PCL did not affect the amount of α-MG that was encapsulated within the NPs. This might be due to the total polymer weight for each formulation being equivalent, and that the composition difference had no effect on the amount of dug that could be loaded. Also, it was noted that 1 mg of α-MG-NPs contained approximately 220 µg α-MG, which may be considered low in relative to the amount of α-MG added. Additionally, the %LE presented that the loading method may be further improved to obtain more efficient drug loading, since a great amount of the active compound was excluded. However, due to the small particle size and the amount of α-MG found the drug content was considerable desirable. It was discovered that the amount of EDG had a significant impact on the release of the drug. The more EDG presented, the higher the percentage of α-MG was released from the NPs. This is due to the properties of the polymer structure. At a pH of 7.4, EDG (Eudragit® S 100) dissolved and demolished the structure of the NPs enabling the drug to be released from the NPs. This dissolution process plays a crucial role in regulating the drug release rate, which in turn affects the therapeutic effectiveness and pharmacological response.

After the optimized formula was obtained (16.25 mg/mL of EDG+8.75 mg/mL of PCL+10% wt α-MG), a comprehensive analysis and comparison of the anticipated results, derived from the DesignExpert® program and the subsequent experimental measurements, were investigated. It was revealed that the developed NP formulations exhibited highly favorable attributes in relation to the predicted data. Thus, the validity of the optimization and their suitability for the preparation of α-MG-NPs was ascertained.

From Figure 2, it became evident that there was a noticeable difference in the release pattern of α-MG between the extract solution and the α-MG-NPs. The α-MG solution showed a prompt and swift release profile, characterized by a rapid release of the compound. In contrast, the α-MG encapsulated within polymeric NPs demonstrated a prolonged and controlled release pattern, in which the release of α-MG continued gradually and steadily over a duration of up to 12 hr. The difference in release kinetics highlights the advantage of the α-MG-NPs to achieve a prolonged and sustained release of the drug. Therefore, this holds promising implications for wound application, which would require controlled and prolonged drug delivery to maintain the activity of the drug with reduced dosing frequency or less frequent would dressing application.

Conclusion

This study designed and demonstrated the effects of different components on the physicochemical properties of α-MG-loaded NP formulations for wound healing. The parameters; including particle size, size distribution, surface charge, drug content and drug release, were examined. Our findings revealed that EDG had a significant impact on drug

release, but did not affect other properties. The optimized NP formulation consisted of 16.25 mg/mL of EDG, 8.75 mg/mL of PCL, and 10% wt α-MG. This formulation led to a prolonged drug release profile compared to α-MG extract alone. Further investigation could be conducted to explore the potential of the NP formulation loaded with α-MG to effectively inhibit bacterial growth, while also exhibiting antioxidant properties. This research leads to potential applications in the treatment of infected wounds.

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Conflict of Interest

There is no conflict of interest to declare.

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