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Preparation and encapsulation efficiency of surface modified egg albumin nanoparticles

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ABSTRACT: A biocompatible nano-drug delivery vehicle can efficiently deliver the toxic drug to the targeted site in nano-quantity to treat cancer patients. Considering this, the current study aims to fabricate stable egg albumin nanoparticles by using chloroacetic acid to modify their surfaces. The carboxyl functionalized egg albumin (FEA) nanoparticles were prepared through the desolvation process using ethanol as the desolvating agent; the generated nanoparticles were stabilized by glutaraldehyde. To obtain stable nanoparticles of suitable size, various reaction parameters viz concentration of FEA, pH, agitation speed, glutaraldehyde concentration, and rate of ethanol addition were examined. In neutral and alkaline mediums, we can get nanoparticles of 120-160 nm with -32 mV zeta potential. The pH of the medium played a decisive role, which strongly influences the FEA particle diameter and surface charge, while other parameters show little influence. SEM monochrome image of functionalized EA nanoparticles also supported the particle size of around 130 nm. Gallic acid (GA) has been encapsulated under optimal desolvation conditions using the FEA/GA acid ratios of 1:1, 2:1, 4:1, and 8:1. The obtained GA entrapped FEA spherical nanoparticles (GA-FEA) had a -30.9mV zeta potential and were negatively charged. At a 2:1 polymer/drug ratio, an entrapment efficiency (EE) of 90.4 % (w/w) and drug loading capacity of about 28.7 % (w/w) were achieved. This work is beneficial to the scientists involved in the field of cancer research.

KEYWORDS: Egg albumin; surface modification; gallic acid; nanoparticles; desolvation process; drug delivery.

1. INTRODUCTION

A group of diseases known as cancer is recognized as one of the world's leading causes of death. Surgery, chemotherapy, and radiation therapy are the most frequently used modalities in the treatment of cancer [1-4]. Chemotherapy suffers greatly from toxicity and a lack of drug supply in the area of action. Major chemical concerns can be successfully resolved with a biocompatible targeted drug delivery system. By using applications aimed at nano-carrier systems, drug efficacy can be increased [5-16]. In the pharmaceutical industry, nano-carrier systems have proven to be a valuable asset. The active drug molecules can be bound, encapsulated, or adsorbed by nano-carriers, which can also improve their therapeutic target through targeted action and shield the drug molecule from unfavorable metabolic and biodegradation responses [7]. Albumin is a perfect material for creating multifunctional nano-carriers because it is non-toxic, easy to purify, biodegradable, and highly soluble in water. These properties make it convenient to administer by injection [17-20].

There are relative advantages to the various techniques used to fabricate albumin nanoparticles. Desolvation is a better method for synthesizing protein nanoparticles than other methods because it doesn't require removing surfactants and oily residue (emulsification process) [19-20]. This process is better suited for heat-sensitive biological compounds because it doesn't require high temperatures, unlike thermal gelation [21]. Toxic chemicals are also needed for the self-assembly process to break disulfide bonds [22, 23]. Albumin-bound nab-technology is recognized as a safe and appropriate technique for producing protein nanoparticles loaded with lipophilic drugs that have a high drug-loading capacity [24, 25].

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The solubility of less water-soluble drugs is enhanced by the drug-loaded albumin nanoparticles, which have been produced in a number of ways and exhibit high drug-loading and entrapment capacities. Additionally, compared to the bare drug, the nanoparticles show a slower and longer-lasting release of the medication [27]. The incorporation of a target-specific ligand into the albumin matrix increases cancer cells' uptake of albumin nanoparticles because cancer cells have a particular type of ligand-receptor that is overexpressed on their surface [28, 29]. Improved accumulation of drug-loaded albumin nanoparticles in tumors boosts their effectiveness against cancer cells. Albumin nanoparticles release the drug slowly, reducing side effects and increasing animal survival [30].

Numerous foods, including grapes, lemons, gallnuts, green tea, and oak bark contain gallic acid, a natural antioxidant. A suitable carrier can deliver GA, a well-known anticancer substance, to the brain [31]. By increasing the administered drug's therapeutic index and bioavailability, colloidal nanocarriers play an important role in the field of drug delivery. For colloidal drug delivery systems to remain in place and for drugs to be distributed throughout the human body, particle size and surface charge are essential. Smaller nano-carriers (100 nm) after intravenous injection cross lymphatic capillaries and are cleared [32, 33]. Therefore, the drug carrier should be 100-200 nm with narrow size distribution.

Nanoscale structures have a large surface area, so they can be modified or functionalized [28, 34]. As albumin molecules have carboxyl and amine groups on the surface, the incoming ligand can functionalize, enrich, and modify albumin nanoparticles. Several authors have studied albumin's interaction with drugs, poly amino-carboxylate, and metal ions [35-38]. The current communication discusses process optimization for the fabrication of surface-functionalized egg albumin nanoparticles and the application of optimized conditions to create GA-loaded FEA nanoparticles. To obtain stable functionalized EA nanoparticles several preparation conditions viz. glutaraldehyde concentration, FEA concentration, rate of ethanol addition, agitation speed, and pH were studied. Surface charge, drug entrapment efficiency, and drug loading capacity of the prepared GA-FEA nanoparticles were also studied in the present work. The objective of the current work is to enhance the bioavailability of GA via incorporating GA into the FEA during nanoparticles formation. The prepared GA-FEA nanoparticles could be a strong contender for a drug delivery system that targets the brain.

2. RESULTS AND DISCUSSION

2.1. Influence of FEA concentration on zeta potential and particle diameter

The concentration of FEA was changed from 8 mg/ml to 240 mg/ml at 30 ^{o}C to produce preferred-sized nanoparticles. At pH 7, the effect of FEA concentration on particle diameter was checked. Ethanol was added dropwise to the FEA aqueous solution while being stirred (650 rpm) until turbidity appeared. For 6.5 hours after the glutaraldehyde was added, the mixture was stirred continuously to ensure that all of the nanoparticles had been cross-linked. The zeta potential and average diameter of FEA nanoparticles at various FEA concentrations are shown in Figure 1. No discernible change in the surface charge or particle diameter of the FEA nanoparticles was seen in the concentration range under study.

At 60 mg/ml FEA concentration, a surface charge of -32.8 mV with a minimum particle diameter of 132 nm was observed. The earlier studies on albumin also demonstrate that, up to a certain range, the albumin concentration has little effect on the particle diameter [19]. Because of the increased hydrophobic and electrostatic interaction between the protein particles, higher protein concentrations may lead to a larger particle formation, which may result in coagulation [39]. We select 60 mg/ml FEA as the preferred condition to fabricate FEA nanoparticles based on the results of the current investigation and earlier reports.

2.2. Influence of pH on zeta potential and particle diameter

The pH has a significant impact on the charge of protein nanoparticles; more charge (positive or negative) on nanoparticles leads to smaller particle sizes due to electrostatic interaction [19]. The effect of pH on surface charge and particle diameter in the pH range of 2 to 10.5 was investigated in order to obtain stable and appropriate FEA nanoparticles. The findings show that the average diameter increases with increasing pH reaches a maximum at pH 4.0, then decreases up to pH 6.0, after which there is no discernible change in particle diameter with pH (Figure 2). The isoelectric point of EA is 4.5. Following functionalization with chloroacetic acid, the resulting FEA's isoelectric point decreased to 4.0. Larger protein particles are anticipated because of a lower surface charge or electrical neutrality close to the FEA isoelectric point.

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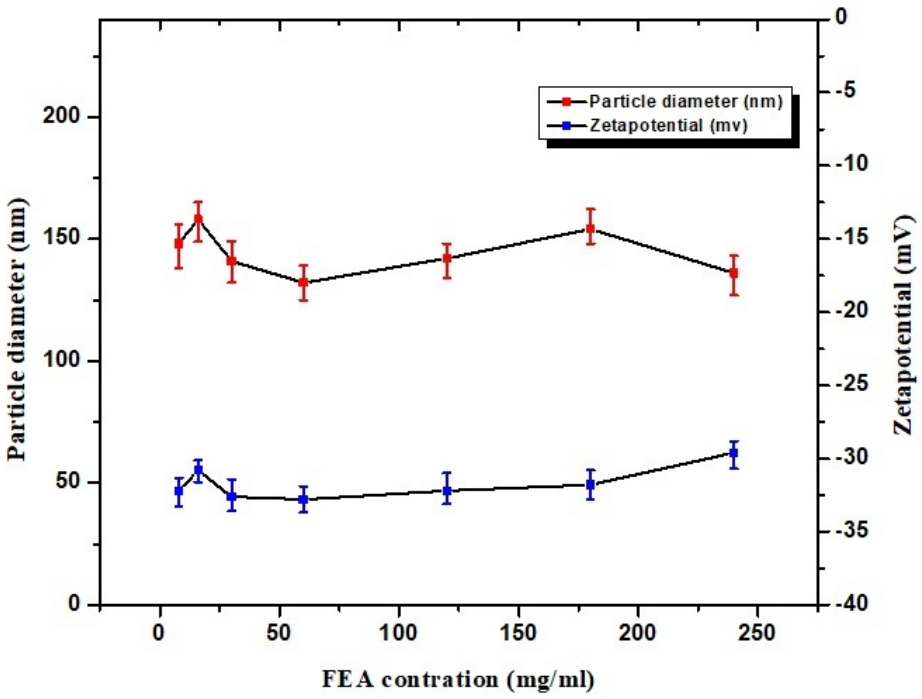

Figure 1. Influence of FEA concentration on zeta potential and particle diameter

At pH 4.0, the incredibly low zeta potential strengthens the hydrophobic interaction betweenprotein molecules, leading to coagulation. Smaller particle sizes result from electrostatic interaction predominating over hydrophobic interaction in an acidic environment (pH 2-3) because of the positive surface charge [40-45]. Hydrogen bonding diminishes the protein hydrophobicity in alkaline and weakly acidic conditions. Strong electrostatic repulsion between FEA nanoparticles occurs in an alkaline environment due to the increased negative surface charge. The smaller particle size is brought on by a combination of reduced hydrophobicity and strong electrostatic repulsion.

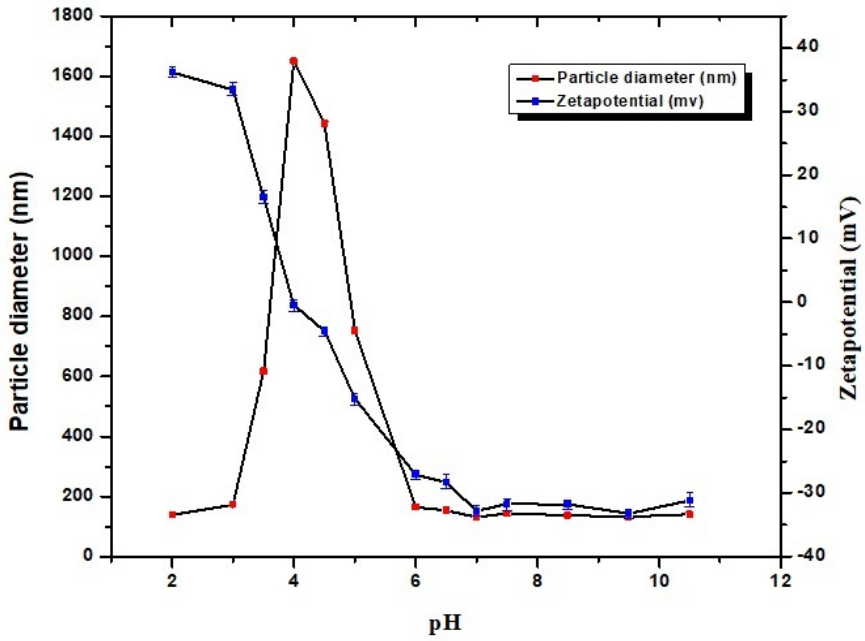

Figure 2. Influence of pH on zeta potential and particle diameter

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2.3 Influence of Ethanol addition rate on zeta potential and particle diameter

The fabrication of FEA nanoparticles involves the use of ethanol, a desolvating agent. By rupturing the disulfide bond, the dropwise addition of ethanol causes the denaturation of FEA [19]. The impact of ethanol addition rate (0.5 to 8.0 ml/min) on particle diameter and the surface charge was investigated after the pH of the aqueous FEA solution was fixed. In the studied range, changing the ethanol addition rate had no discernible impact on surface charge and particle diameter (Figure 3). Larger particle diameters will be produced by the significantly higher addition rate. The outcome differs slightly from earlier reports on EA, HAS, and BSA, which demonstrate that adding ethanol at a rate greater than 1-2 ml/min results in larger nanoparticles [19, 41].

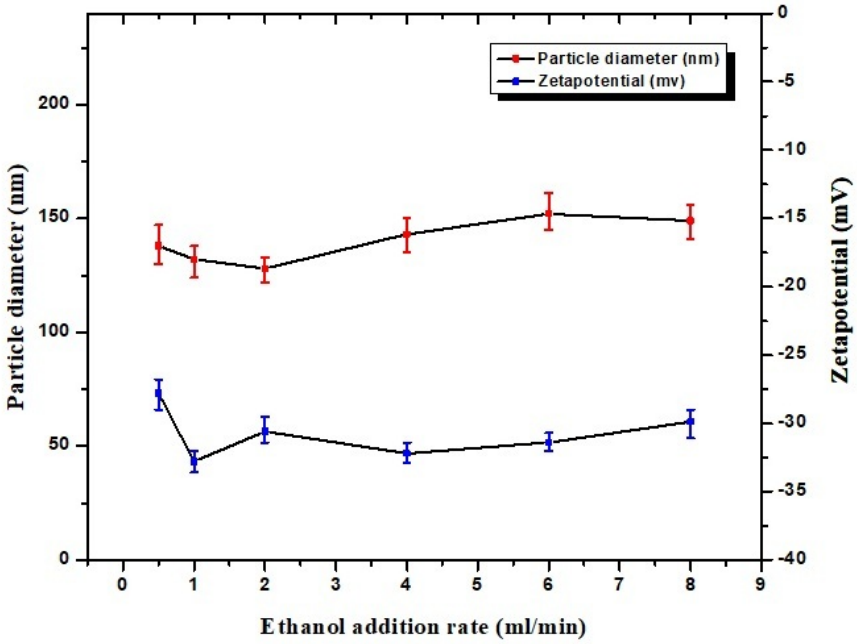

Figure 3: Influence of ethanol addition rate on zeta potential and particle diameter

2.4 Influence of stirring rate on zeta potential and particle diameter

By denaturing the protein, the dropwise injection of ethanol leads to the production of FEA nanoparticles. To prevent the potential for formed nanoparticles to aggregate, the FEA colloidal solution needs to be stirred [46-48]. Previous studies have shown that in order to produce albumin particles with a size in the nanometer range, a stirring rate of at least 450 rpm is necessary [43, 49]. To fabricate stable FEA nanoparticles of the desired size, ethanol was added dropwise to a 60 mg/ml aqueous solution of FEA at pH 7 while stirring at speeds ranging from 200 to 850 rpm.

The experimental results for the FEA particle size and zeta potential at various stirring rates are shown in Figure 4. No discernible effect of stirring rate variation was seen on the zeta potential and particle diameter of prepared FEA nanoparticles. Smaller nanoparticles are also produced at low stirring rates of 200 and 350 rpm, suggesting that FEA nanoparticles aggregate less frequently.

2.5. Influence of crosslinker amount on zeta potential and particle diameter

The nanoparticles produced by ethanol addition while stirring are unstable and can either re-dissolve in water or aggregate [19]. Crosslinker glutaraldehyde was employed to stabilize the nanoparticles. Through condensation crosslinking with the amino moieties found on the surface of albumin nanoparticles, glutaraldehyde hardens the newly formed nanoparticles. For crosslinking, it is advised to use the least amount of glutaraldehyde possible due to its toxicity [45-48]. Various concentrations of glutaraldehyde (1–10%) were used to investigate the impact of crosslinker concentration on zeta potential and particle diameter. The results show that glutaraldehyde concentrations of 1% and 2% result in slightly larger particle sizes (Figure 5), while concentrations of 6-8% of glutaraldehyde were found to produce the smallest particles. Higher concentrations of glutaraldehyde may even cause precipitation.

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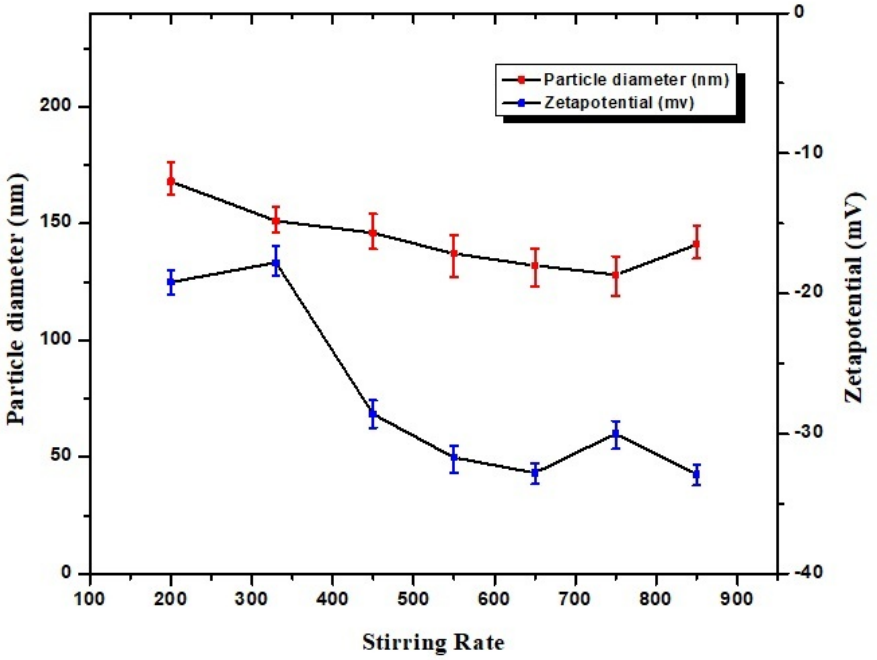

Figure 4. Influence of stirring rate on zeta potential and particle diameter

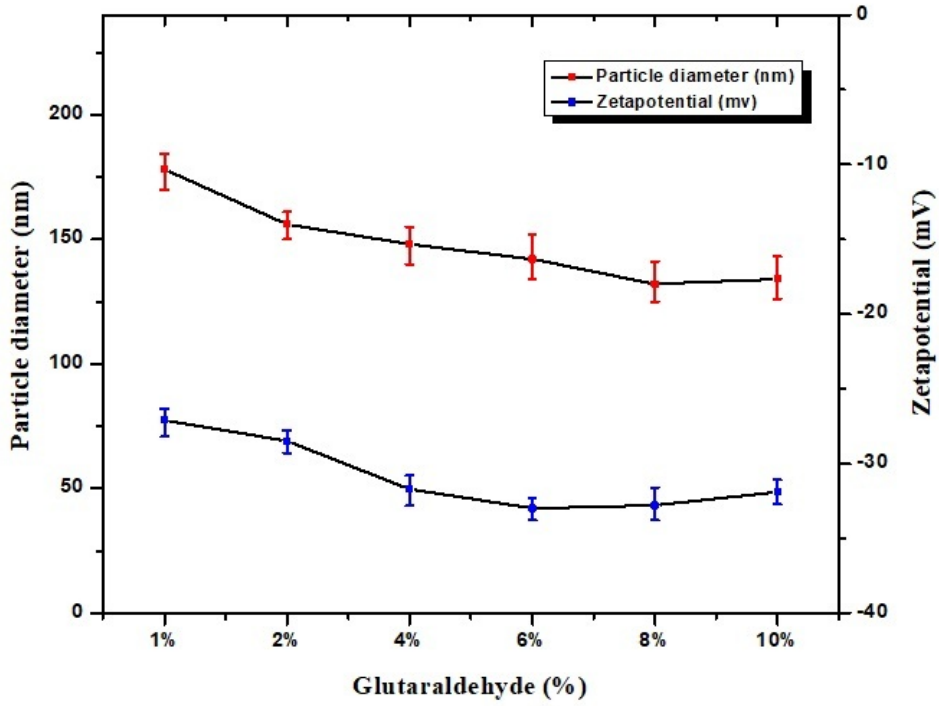

Figure 5. Influence of crosslinker on zeta potential and particle diameter

The SEM monochrome image (Figure 6) of functionalized EA displays that nanoparticles are of approximately 130 nm sizes.

GA-FEA-NP has been prepared under the optimal desolvation conditions (Temperature: 30 °C, Stirring Rate: 650 rpm, FEA: 60 mg/ml, Ethanol Rate: 1 ml/min, and Glutaraldehyde: 8%) in a variety of FEA/GA ratios at pH 7.0. When FEA/GA ratio is 2:1, the maximum loading capacity of 28.7 % with PI 0.124 is seen (Table 1). Due to the increased production of nanoparticles, the GA loading percentage dramatically decreased after that. The GA entrapment efficiency, however, steadily increased to about 90.4 %; this might

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be because more desolvated FEA was engaged in the water-soluble drug's entrapment. The prepared GA-FEA nanoparticles appeared spherical in the typical SEM image, as shown in Figure 7.

Table 1. Zeta potential, particle diameter, PI, loading capacity, and encapsulating efficiency of GA-FEA-NP

FEA: GA	Zeta potential (mV)	Particle Size (nm)	Zeta potential (mV)	PI	Loading Capacity %	Encapsulating Efficiency %
1:1	-31.6	222	-31.6	0.352	16.9	33.1
2:1	-30.9	152	-30.9	0.124	28.7	90.4
4:1	-30.2	141	-30.2	0.178	14.9	86.3
8:1	-31.4	138	-31.4	0.221	13.1	88.2

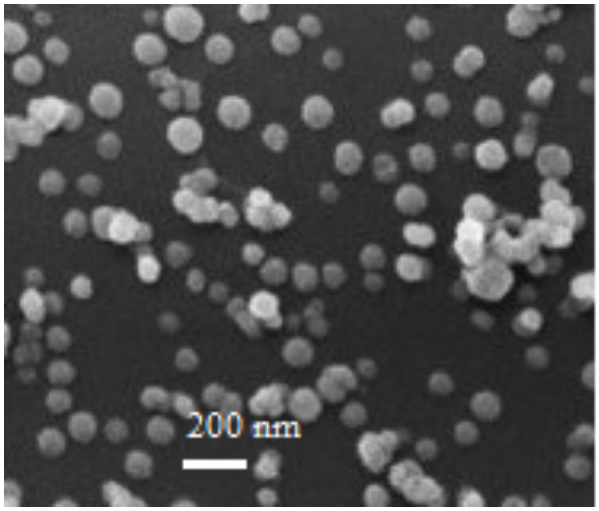

Figure 6: SEM image of FEA nanoparticles

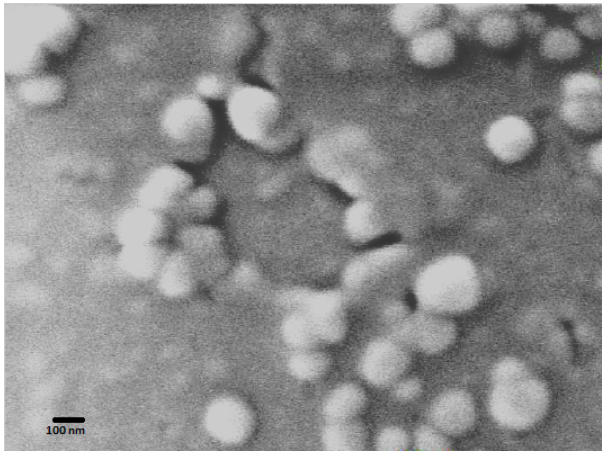

Figure 7. SEM image of GA-FEA nanoparticles

3. CONCLUSION

The current study is concerned with the desolvation process for producing stable FEA and GA-FEA nanoparticles. To obtain stable nanoparticles of suitable size, various reaction parameters viz concentration of FEA, pH, agitation speed, glutaraldehyde concentration, and rate of ethanol addition were examined. With nearly the same surface charge, the FEA concentration has very little impact on particle size. Larger FEA particles were found close to the isoelectric point. pH had a strong impact on the particle diameter and zeta potential. In alkaline, neutral, and acidic mediums, FEA nanoparticles in the 130-150 nm range were obtained. In the studied range, glutaraldehyde amount, stirring rate, and rate of ethanol addition had no discernible impact on particle diameter.At a 2:1 polymer/drug ratio, an entrapment efficiency (EE) of 90.4 % (w/w) and drug loading capacity of about 28.7 % (w/w) were achieved.

4.MATERIALS AND METHODS

4.1. Reagent used

Egg albumin was procured from HiMedia. Gallic acid, acetic acid, ethanol, potassium iodide, chloroacetic acid, Glutaraldehyde 25%, and other chemicals were provided by Merck. For the preparation of all solutions, double distilled water was used throughout. Whatman filter paper of grade 1 has been used for filtration.

4.2. Preparation of modified egg albumin (FEA)

1% aqueous solution of EA was prepared via sonication (2 min) and its pH was fixed at 9.0 using 0.1 N NaOH. The EA solution was then gradually supplemented with dropwise additions of chloroacetic acid (200 mg) containing KI (50 mg) solution, which was maintained at a pH of 7.0 (by NaHCO3) at 25 °C. Following that, the mixture was heated on the water bath for 6 hours at 100 °C. 10% HCl precipitated the formed FEA, which Whatman filter paper then filtered. The resulting precipitate was then dispersed in ammonia and reprecipitated with 10 % acetic acid. The precipitate was then washed three times with cold water after being centrifuged at 4000 rpm to remove any remaining acid. The formed functionalized EA was vacuum-dried.

4.3 Preparation of FEA and GA-FEA nanoparticles

At a temperature of 25 °C, a straightforward desolvation procedure was used to fabricate carboxyl functionalized EA nanoparticles. The pH of the aqueous FEA solution (60 mg/ml) was kept at 7.0 by 0.1 N NaOH during the preparation process. A turbid solution was produced when ethanol was added dropwise at a constant flow rate of 1 ml/min to the aqueous FEA solution while being stirred at a rate of 650 rpm, indicating the formation of FEA nanoparticles. The manufactured nanoparticles were stabilized via chemical cross-linking with glutaraldehyde. The stirring process lasted for 6.5 hours. The resulting orange-brown FEA nanosuspension was centrifuged at 8 °C for 10 minutes at 15000 rpm. To create powdered FEA nanoparticles, the collected nanoparticles were lyophilized. To fabricate GA-encapsulated FEA nanoparticles, gallic acid was added to the FEA solution in the following ratios: 1:1, 2:1, 4:1, and 8:1, and the experiments were carried out in the aforementioned manner.

Quantifying the amount of free gallic acid (GA) in the supernatant phase with a UV-Visible spectrophotometer at 265 nm (λ_{max} of gallic acid) allowed us to determine the drug entrapment efficiency and loading capacity of the successfully fabricated GA-FEA nanoparticles using equation 1 and 2.

GA loading is the ratio of the amount of GA present in the GA-FEA nanoparticle to the total weight of the nanoparticles obtained.

$$\text{GA loading capacity (\%)} = \frac{\text{Total weight of GA} - \text{GA present in supernatant}}{\text{Total weight of nanoparticles}} \times 100 \qquad (1)$$

GA entrapment/encapsulation efficiency can be calculated as the ratio of the GA present in the nanoparticles to the total weight of drug taken.

$$\text{GA Encapsulation Efficiency (\%)} = \frac{\text{Total weight of GA} - \text{GA present in supernatant}}{\text{Total weight of GA}} \times 100 \qquad (2)$$

A standard calibration curve between absorbance and GA concentrations plotted for this purpose was found to linear in 0.5-50 µg/ml range. The data shown are the mean of three runs. The surface charge and average particle diameter were measured at a scattering angle of 173° using a Malvern zeta sizer (Nano ZS series, Malvern Instruments Ltd., Malvern, UK). The SEM image was recorded by Stereoscan-S360 SEM-Leica Cambridge, UK, with a 15,000 magnification under 10 kV accelerating voltage.

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