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AN EXTENSIVE REVIEW ON GELATIN NANOPARTICLES

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ABSTRACT

The current review on gelatin nanoparticles becomes one of the most popular and prominent method of formulation. Gelatin nanoparticles (GNPs) have emerged as a versatile and promising platform for biomedical applications, including drug delivery, gene therapy, imaging, and tissue engineering. Derived from collagen, gelatin is biocompatible, biodegradable, and easily modifiable, making it an ideal candidate for nanoparticle synthesis. Various formulation techniques, such as desolvation, emulsion-based methods, nanoprecipitation, and electro-spraying, have been developed to produce GNPs with controlled size, morphology, and functionality. Crosslinking strategies, both chemical and physical, play a crucial role in stabilizing nanoparticles and tuning their properties for specific applications. GNPs excel in encapsulating and delivering diverse therapeutic agents, offering controlled release and targeted delivery capabilities. Despite significant advancements, challenges such as crosslinker toxicity, scalability, and stability under physiological conditions remain. This review highlights the GNP formulation, characterization, and applications, while also discussing current limitations and future directions for the clinical translation of these nanocarriers.

KEYWORD: Gelatin nanoparticles, Drug delivery systems, Biodegradable nanomaterials, crosslinking techniques, Targeted therapy, Biomedical applications.

INTRODUCTION

Gelatin nanoparticle are one of the most suitable candidates in reducing the toxicity issue associated with most of the drugs and could be used as a promising candidate for controlled drug release. Encapsulation of drug into a gelatin nanoparticles have improve the therapeutic value of various water insoluble drug and improving bioavailability, solubility and retention time.[1] Gelatin is a natural versatile biopolymer. Gelatin is an attractive biodegradable material for use in nano-biotechnology and nano-pharmaceutics. Gelatin nanoparticles (NPs) have been widely used as drug and gene carrier to targeted sick tissues including cancer, tuberculosis, HIV infection along with the treatment of vasospasm and restenosis, due to its biocompatibility and biodegradability.[2] The type of gelatin obtained (type A or type B) is governed by the process of collagen hydrolysis (i.e. acidic and basic hydrolysis, respectively). Types A and B have different IEPs. Type A has IEP 7–9 while type B has IEP 4–5. Each type of gelatin has different drug release potential for different kinds of NPs. It is shown that type B gelatine nanoparticles (GNPs) show better potential in terms of drug delivery than type A.[3] Moreover, gelatin type B physically captures DNA molecule, thus increasing the transfection efficiency of the carriers. Commercially available gelatin is a heterogeneous mixture of polypeptides, presented in varying molecular weights in different ranges, e.g. thousand to million Daltons.[4]

In the human body, gelatin is degraded through enzymatic hydrolysis. Multiple enzymes play a role in breaking down proteins. Protease enzymes, for instance, are capable of cleaving the peptide bonds that connect the amino acids in the gelatin molecule.[5] As a result of this process, gelatin is effectively disassembled into its individual amino acid components (Figure 1). Its biocompatibility and biodegradability make it well-tolerated by the human body, and its versatility allows for use in a range of applications, from tablet binders to coating agents.[6] Gelatin also possesses thermo-reversible gelation properties, which allow it to transition between a fluid and a gel state at different temperatures, enhancing its versatility. One key advantage of gelatin is its ability to form hydrogels, which are networks of polymer chains capable of retaining a large amount of water.[7]

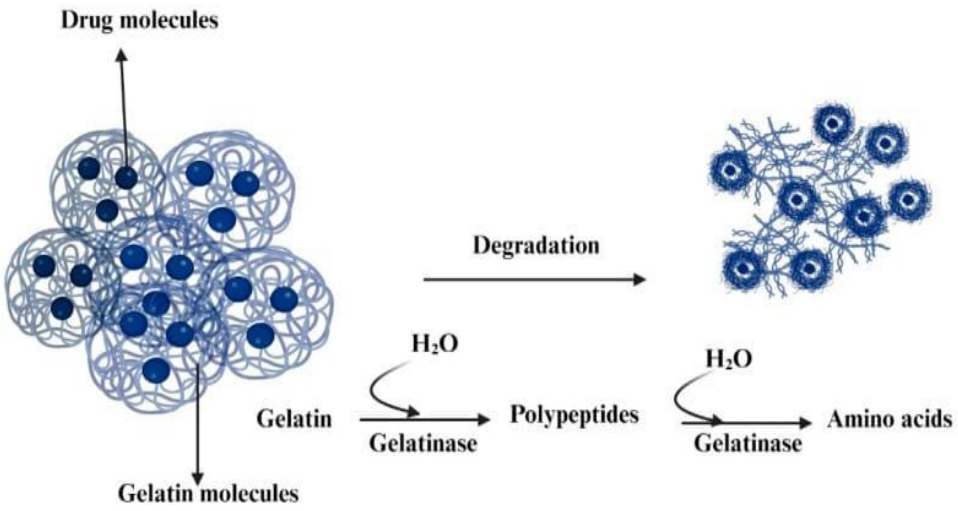

Figure 1: Degradation process of gelatin through enzymatic hydrolysis.

Advantages of gelatin nanoparticles

- ✓ Low cost,
- ✓ Easy availability,
- ✓ Biodegradable and biocompatible nature as well as the presence of abundant active groups,
- ✓ Improved bioavailability and delivery of drug in a controlled and sustained manner,
- ✓ Decreased incidence of side effects and improve patient compliance.[8]

Disadvantages of gelatin nanoparticles

- ✓ **Preparation challenges:** Producing gelatin nanoparticles often faces issues like clumping and uneven particle sizes. Ensuring stability and consistency during the preparation process is a common difficulty.[20]
- ✓ **Weak mechanical strength:** Gelatin nanoparticles can be fragile and may break down easily in the body. Combining gelatin with other materials can help make them stronger.[21]
- ✓ **Low drug encapsulation efficiency:** The amount of drug that can be loaded into gelatin nanoparticles depends on the gelatin concentration. Higher concentrations can hold more drugs but may affect stability and release.[22]

Polymers used in nanoparticles

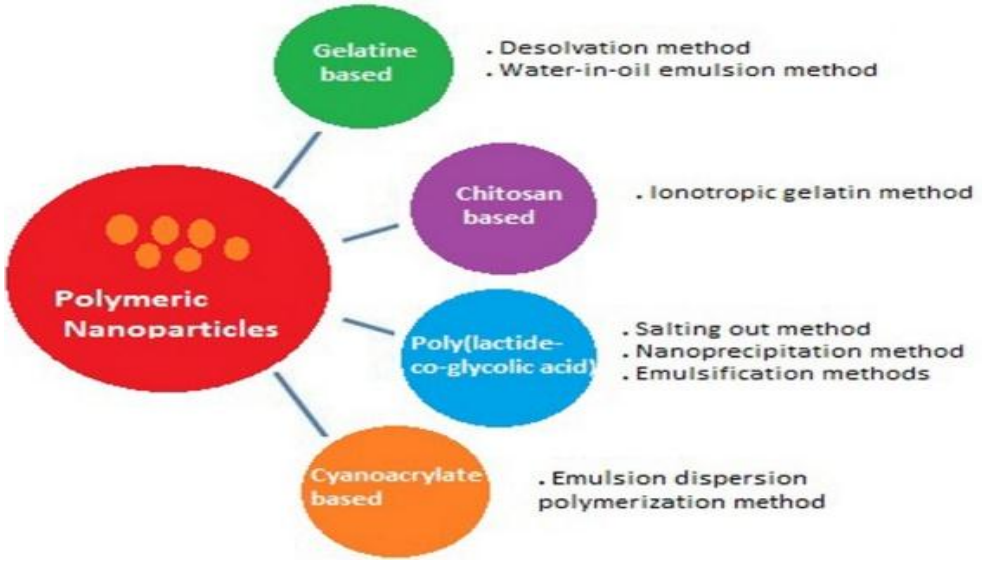

Figure 2: Polymers used in nanoparticles.

a) Natural polymers

Chitosan based nanoparticle

Chitosan is a natural biodegradable copolymer that is derived from the deacetylation of chitin from the exoskeleton of crustaceans[25] Chitosan has many commercial uses; for example, it is used in bandages to reduce bleeding, as an antibacterial agent, and it is also approved by the FDA for the safe use of foods and drugs for humans. As previously mentioned, the negative charge of the mucosal layer along the GIT can be used as a strategic target to ensure the delivery of cationic antigens, like chitosan, to the intestinal epithelium. The

natural composition of chitosan plays a key role in this strategic approach. Chitosan is comprised of copolymers of glucosamine and N-acetylglucosamine. The amino and carboxyl groups in the chitosan molecule can combine with the glycoproteinin the mucus to form hydrogen bonds.[26] The ionic interaction between the cationic primary amine of chitosan and the anionic sialic acid group of mucus, results in an adhesive effect, which facilitates the targeted antigen delivery by enhanced adhesion.

Gelatin based nanoparticles

Gelatin is a natural versatile biopolymer; it has several important applications due to its low cost, easy availability, biodegradable and biocompatible nature as well as the presence of abundant active groups. Gelatin is poly-ampholyte in nature because it contains both cationic and anionic groups. Gelatin polypeptide is composed of repeating triplets of alanine, glycine and proline residues, responsible for typical triple helical structure of gelatin. Gelatin is a protein obtained from the hydrolysis of collagen. The type of gelatin obtained (type A or type B) is governed by the process of collagen hydrolysis (i.e. acidic and basic hydrolysis, respectively). Types A and B have different IEPs. Type A has IEP 7–9 while type B has IEP 4–5. Each type of gelatin has different drug release potential for different kinds of NPs. It is shown that type B gelatine nanoparticles (GNPs) show better potential in terms of drug delivery than type A. Moreover, gelatin type B physically captures DNA molecule, thus increasing the transfection efficiency of the carriers. Commercially available gelatin is a heterogeneous mixture of polypeptides, presented in varying molecular weights in different ranges, e.g. thousand to million Daltons.

The GNPs are nontoxic, biodegradable, bioactive, and inexpensive and are very promising in terms of drug delivery and controlled drug release. Different mechanical properties of GNPs like thermal range and swelling behavior are dependent on the amphetatic interactions on gelatin. Different desired GNPs can be prepared by exploiting the physical and chemical properties of gelatin. Gelatin-based materials need to be cross-linked with glutaraldehyde (GA) or other bifunctional cross-linker such as genipin, carbodiimide/N-hydroxysuccinimide, aldehyde groups, and transglutaminase to render insolubility at high temperatures, reduced swelling in water, and hence drug release from NPs. Drug release was suggested to be dependent on the cross-linking density of gelatin.[21]

b) Synthetic polymers

Poly (lactic-co-glycolic) based nanoparticle

PLGA NPs are a booming topic, especially for the development of NDD treatments (more than 50 articles during the last 5 years on Scopus using “PLGA”, “nanoparticles”, “neurodegenerative disease” as keywords). PLGA, a commercially available synthetic copolymer obtained from lactic and glycolic acid, is approved by the US regulatory agency (Food and Drug Administration: FDA) and the European Medicine Agency (EMA). To date, not based on PLGA but poly-lactic acid (PLA), paclitaxel-loaded PEG-PLA micelles have reached the market in South Korea, India, and Indonesia (Genexol® PM). It is currently undergoing Phase III clinical trials for access to the EU and US markets. For the NPs, only one Phase II clinical trial based on PEG-PLGA/PLA-PEG NPs (BIND-014) for metastatic castration-resistant prostate cancer was reported.[15] However, in the case of NDDs treatment, no PLGA NPs are currently on the market or in clinical trials, are currently only at the preclinical stage.[16] Indeed, several pre-clinical studies based on drug loaded nano-objects are in progress, including delivery of curcumin, levodopa, cholesterol or rapamycin for AD, PD, HD and MS treatment. The advantage of the PLGANPs approach relies on their potential for drug encapsulation, excellent biocompatibility, and biodegradability.[17] PLGA degradation by hydrolysis of its ester bonds in aqueous media releases its two constitutive monomers, which are naturally produced under physiological conditions by several metabolic pathways.[27]

Poly Vinyl Alcohol (PVA) based Nanoparticles

Poly vinyl alcohol (PVA) is a water soluble polyhydroxy polymer that is semi-crystalline and can be obtained from polyvinyl acetate by hydrolysis reaction. They are widely employed for biomedical applications because of their properties such as low cost, compatibility with cells, highly elastic in nature and has tensile strength that matches with that of the articular cartilage. The disadvantages are that it has very less growth of osteoblast cells since it lacks self-adhesion sites. PVA nanoparticles can be fabricated by techniques such as nanoprecipitation or by emulsion technique. The nanoparticles enable widely in cancer treatment by delivering the drug to the tumor site because of the leaky vessels. PVA nanoparticles aid in improving the bioavailability and the stability of the loaded drug. Zinc oxide/PVA nanoparticles were fabricated by sol–gel method for the purpose of reducing the level of glucose. The nanoparticles were found to be spherical in shape and varying amounts of polyvinyl alcohol had an impact on the photocatalytic activity. The in vivo analysis also showed promising results of reduced glucose levels in rats affected with diabetes. Bovine serum albumin was encapsulated in polyvinyl alcohol nanoparticles for the purpose of delivering peptides. The nanoparticles were fabricated by water in an oil emulsion technique and the diameter of the particles were found to be 675.56 nm. The encapsulation efficiency of the drug was 96.26%. The release of the protein, governed by the diffusion process, was held in a sustained manner that lasted up to 30 h. The stability of the drug was raised when it was loaded onto polymeric nanoparticles.[28]

Methods of preparation of gelatin nanoparticles

The GNPs can be prepared by several different techniques, including desolvation, coacervation phase separation, emulsification-solvent evaporation, reverse phase microemulsion, and nanoprecipitation.

Two-step desolvation

In this technique a desolvating agent is added to aqueous gelatin solution to dehydrate gelatin molecules. Low molecular weight gelatin is discarded and remaining high molecular weight portion is dissolved in water and then acetone is added to the solution dropwise, at a controlled pH. Cross-linker is added and stirred at 600 rpm at 40°C for 12 h to obtain hardened uniform spherical NPs. The purification is done with acetone:water (30:70 ratios) followed by extensive centrifugation and finally lyophilization.[9]

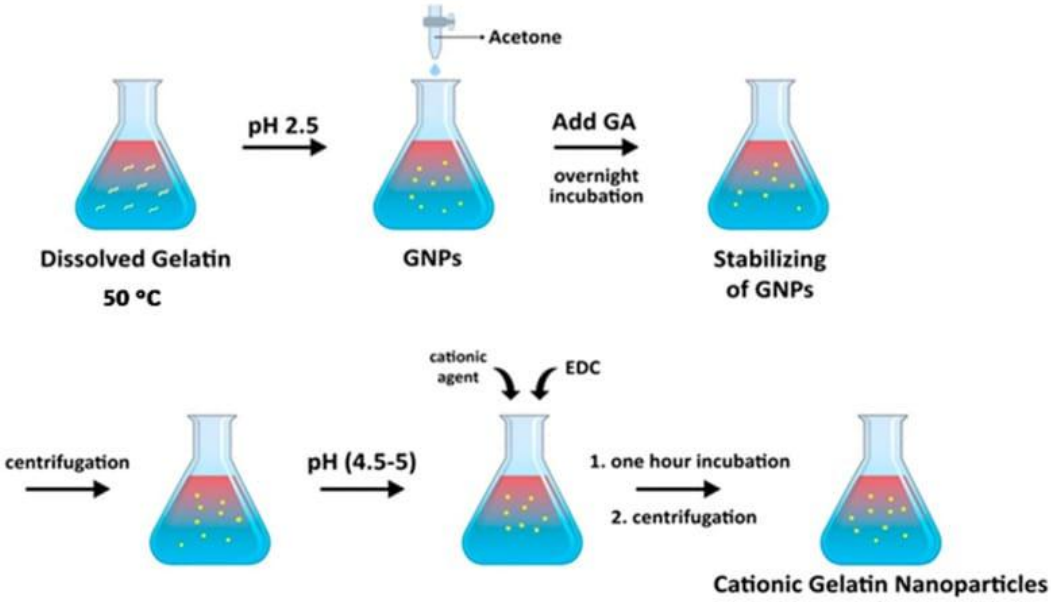

Figure 3: Two-step desolvation method.

Simple coacervation

Simple coacervation is used to prepare stable and small-sized particles. After liquid-liquid phase separation, the polymer settles down in the solution producing two visible, immiscible phases. Natural salts (sodium chloride/sodium sulfate) or alcohols (such as ethanol) are usually used to obtain NPs. However, oppositely charged macromolecules such as proteins or polyelectrolytes are also suggested for coacervation (called complex coacervation). Dehydration of gelatin molecules finally results in the formation of GNPs which are then cross-linked with other cross-linking agents such as GA.[10]

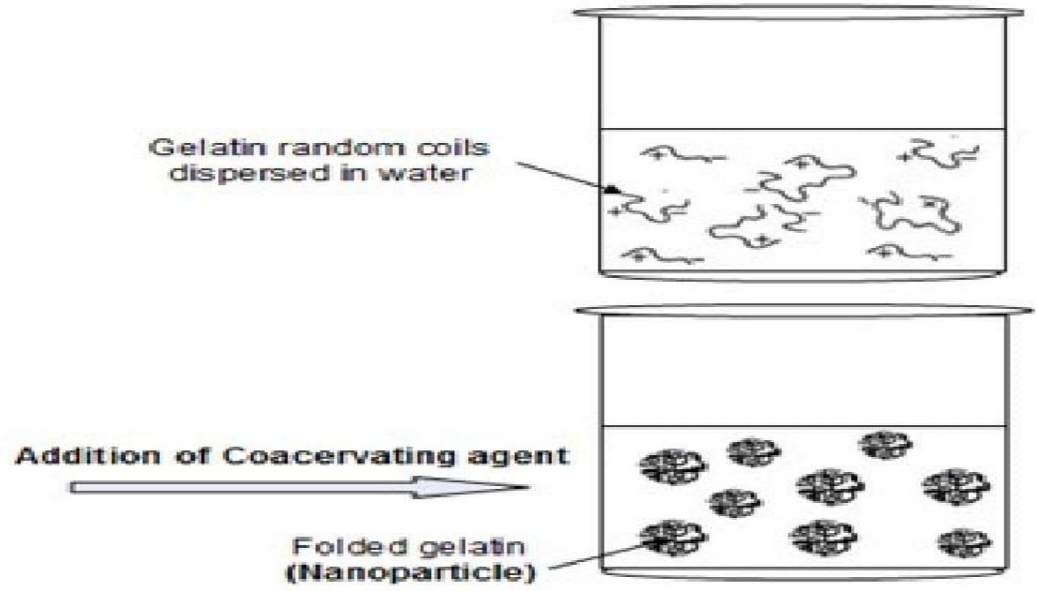

Figure 4: Simple coacervation method.

Solvent evaporation

This technique uses single emulsions or double emulsions for the formation of GNPs. Gelatin and drugs in aqueous phase are homogenized with oil phase (polymethyl methacrylate or paraffin oil) and then cross-linked with GA or genipin. The solvent is then evaporated. The solidified NPs are then collected and washed with distilled water to remove additives such as surfactants, and then lyophilized.[11]

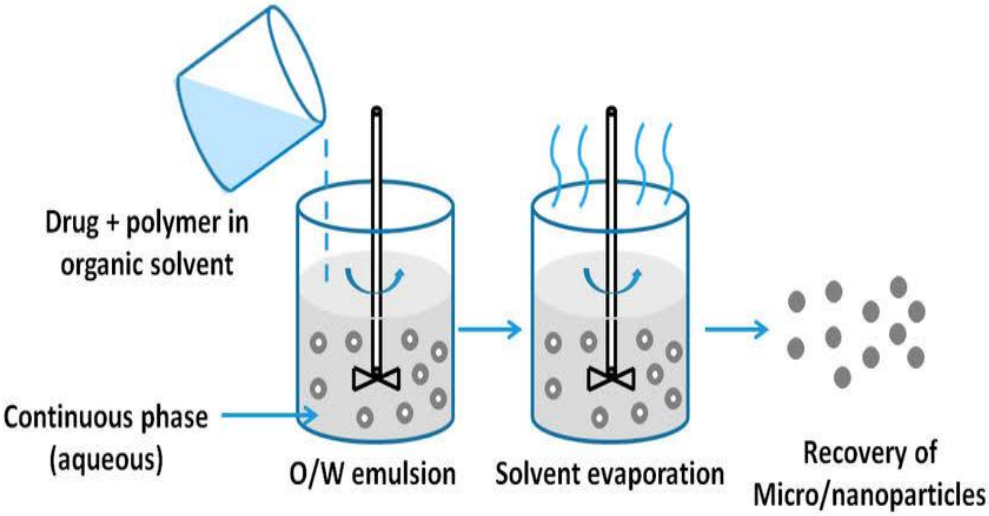

Figure 5: Solvent evaporation method.

Microemulsion

In microemulsion, aqueous gelatin solution is poured into surfactant solution [sodium bis (2- ethylhexyl) sulfosuccinate] in n-hexane, cross-linked with GA and finally n-hexane is evaporated and GNPs are recovered. Microemulsion is considered advantageous because it can control the size of NPs.[12]

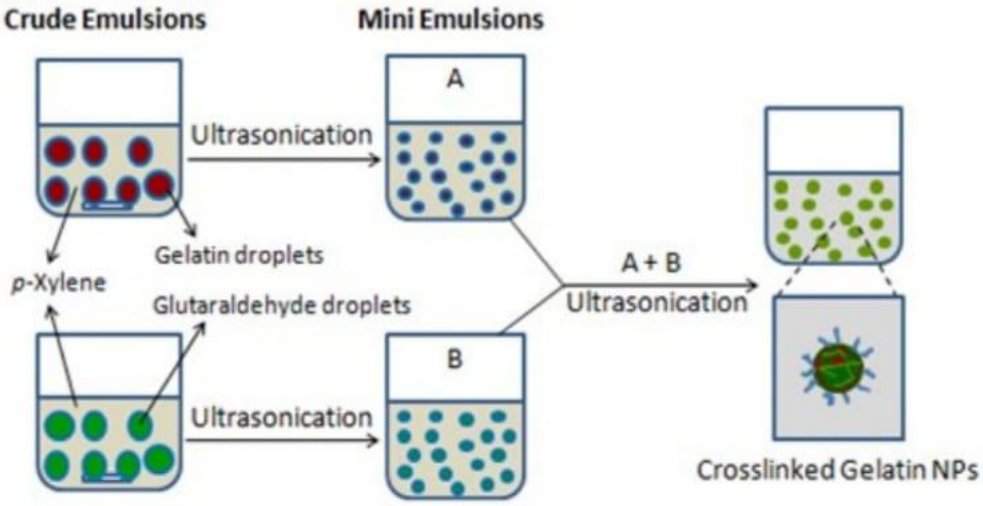

Figure 6: Microemulsion method.

Nanoprecipitation/solvent displacement method

In this technique water is used as a solvent phase in which gelatin and drug molecules are dissolved. This aqueous phase is then added to ethanol as the nonsolvent phase containing poloxamer as a stabilizer. GNPs are formed on the junction of water and ethanol because of Introduction Department of pharmaceutics 6 interfacial turbulence generated during solvent displacement and are subsequently cross-linked using GA.[13]

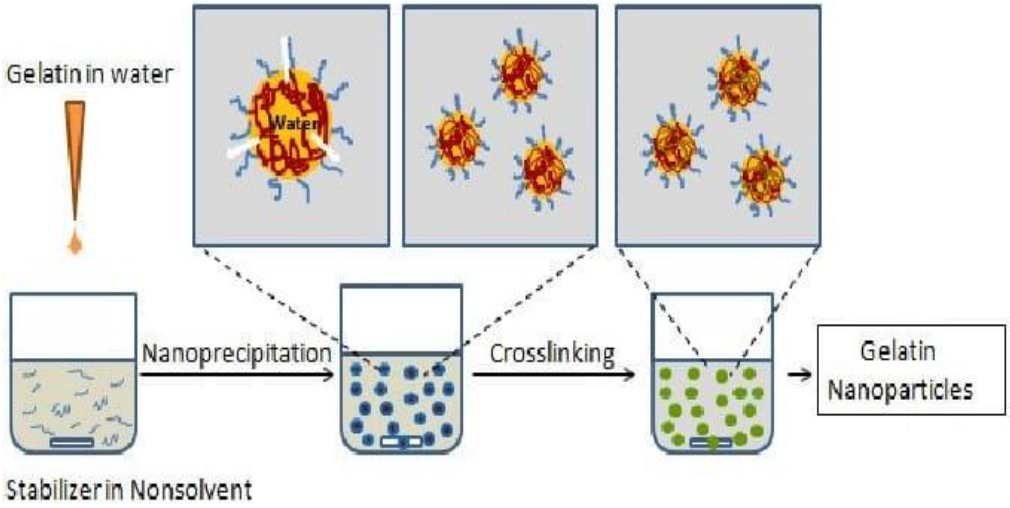

Figure 7: Nanoprecipitation/solvent displacement method.

Mechanisms of drug release from GNPs

There are several possible mechanisms of drug release from gelatin (protein) NPs:

(a) Liberation due to polymer erosion or degradation;
(b) Self-diffusion through pores;
(c) Release via surface erosion of the polymer; and
(d) Pulsed delivery initiated by the application of an oscillating magnetic or sonic field. In most of the drug release pattern, biphasic release is most common, it includes two stages – an initial phase of burst release of immediate discharge surface associated drugs (weakly interacted) from GNPs and then a second phase of covalently bound (tightly bonded) drugs releases in slow diffusion from the matrix, exhibiting prolonged and sustained release.[14]

The initial burst release occurs due to weak adsorption of drugs onto NPs surface. The efficacy of drug release is dependent on the size and loading efficiency of the GNPs as well as drug solubility.

Smaller particle tends to achieve big burst effect while larger particles show Introduction Department of pharmaceutics 7 sustained release thoroughly. Apart from the size, density of gelatin cross-linking is also known to have effect on swelling ratio and drug release pattern from the matrix. Proteolytic enzymes also accelerates drug release by GNPs.[15]

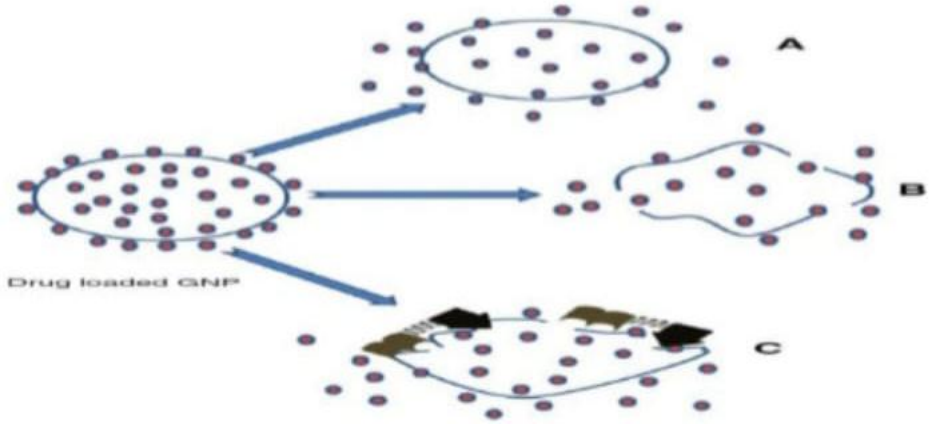

Figure 8: Drug release patterns from gelatin nanoparticles: (A) simple diffusion of drug particle; (b) degradation release; (c) cleavage of the gelatin matrix by proteolytic enzyme.

Applications of GNPs in nano-biotechnology and biomedical science

- ✓ Targeting human malignancies with Gelatin nanoparticles
- ✓ Crossing blood brain barrier
- ✓ Management of infectious tuberculosis via gelatin nanoparticles
- ✓ Gelatin nanoparticle targeting leishmaniasis
- ✓ Gelatin nanoparticle monitoring restenosis (Vascular Malady).[16]

Evaluation test for gelatin nanoparticles

1) Physical characteristics

By visual examination the drug was tested for its physical characteristics like colour, odour and texture.

2) Solubility test

The drug gelatin powder (about 1mg) was taken in a test tube and solubility in ethanol, methanol, chloroform, dichloromethane and water, phosphate buffer was tested.

3) Characterization of gelatin nanoparticles

a) Ftir analysis

FTIR studies were carried to study the presence of functional groups on the synthesized drug loaded GNPs. The Fourier transform infrared (FTIR) spectra of synthesized drug loaded GNPs were measured by a thermos shimadzu FTIR spectrometer with the KBR pellet technique ranging from 4000 cm−1 -400 cm−1.[17]

b) Particle size

The particle Size, and particle size distribution of GNPs were measured with a Malvern instrument. The particle size distribution is reported is reported as poly dispersity index. The sample were placed in the analyzer chamber and reading were performed at 25°C with a detected angle of 90 degrees. The zeta potential of GNPs was measured with a malvern instrument. The sample were diluted and placed in electrophoretic cell and measured in the automatic mode.[18]

c) Zeta potential

Zeta potential is a measure of surface charge. The surface charge (electrophoretic mobility) of nanoparticle can be determined by Zeta sizer (Malvern instrument) having zeta cells, polycarbonate cell with gold plated electrodes and using water as medium for sample preparation. It is essential for characterization of stability of nanoparticle.[18]

d) Entrapment efficiency

The entrapment efficiency of SM-GNP-M were determined by separation of M-GNPs from the supernatant liquid containing non associated silymarin obtained after centrifugation at 12000 RPM for 30 minutes. The amount of free silymarin in the supernatant liquid was measured by UV-VIS spectrophotometer at 288nm. The silymarin entrapment efficiency of M-GNPs was calculated from the following equation.[17]

$$\text{Entrapment efficiency (\%)} = \frac{\text{Total amount of drug-amount of drug}}{\text{Total amount of drug}} \times 100$$

e) Scanning electron microscopy

SEM is a surface imaging method, fully capable of resolving different particle sizes, size distributions, nanomaterial shapes, and the surface morphology of the synthesized particle at micro and nanoscales. SEM analysis nanoparticles were performed to evaluate the surface morphology of nanoparticles. Nanoparticles were prepared and dried well to remove the moisture content and images were taken.[19]

f) drug content

1 ml of drug loaded nanoparticles was saturated with 10 ml methanol in centrifuge tube settled until a day. The following morning, the mixture was vortexed for 15 minutes. Extracted the supernatant liquid from solution after centrifuging it at 5000 rpm for 30 mins. By using UV-spectrophotometer to measure drug at 259nm in the supernatant. Using this formula to calculate the drug content was used.[29]

$$\text{\% Drug content} = \frac{\text{(Amount of drug obtained in particles)}}{\text{(Theoretical amount of drug)}} \times 100$$

g) In-vitro drug release studies

The in-vitro release study of GNPs complex was performed by dialysis bag method. The sample were placed into dialysis bag which are dialysed in 60 ml of phosphate buffer solution with pH 7.4. the drug release assessed to start as soon as the dialysis into reservoir compartment. The reservoir was kept under constant stirring. The sample was collected at regular intervals of time and replaced with equal amount of buffer. The collected sample is filtered and diluted, further analyzed using JASCO V-530 UV 1600 UV-Visible spectrophotometer at 288nm.[23]

h) Stability studies

The optimized formulation was packed in the foil and sealed the glass bottle and hold on at stability chamber at stability chamber at 5 ±20 C / 60 % RH, 25±20 C/60 % RH, 40±20C/75 % RH for 6 months. The formulation was evaluated for modification in appearance, particle size, Entrapment efficiency and dissolution rate. The relative humidity (RH) and temperatue were initiated and maintained in a stability chamber.[24]

CONCLUSION

In conclusion, gelatin is a highly promising biopolymer for the development of drug delivery systems (DDSs) due to its excellent biocompatibility, biodegradability, and low immunogenicity. Its potential spans across various sectors, including biomedicine, cosmetics, and pharmaceuticals, especially in nanomedicine. The synthesis methods for gelatin microparticles and nanoparticles have been extensively explored, with an emphasis on optimizing process parameters to achieve stable and monodisperse products. While preclinical studies demonstrate the efficacy of gelatin-based DDSs in enhancing bioavailability and treating conditions such as tumor pathologies and tissue regeneration, further research is required to refine these systems. There is a need for more research to expand the use of gelatin-based DDSs for broader clinical and industrial applications. The ongoing challenge lies in scaling up the production of these systems while ensuring controlled, sustained, and specific release at target sites, making them suitable for widespread use in the biomedical, pharmaceutical, cosmetic, and food industries.

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Authors contributions
All the authors have contributed equally.

Conflict of interests
Declared none.

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