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DEVELOPMENT OF LEVODOPA LOADED ALBUMIN NANOPARTICLES FOR NOSE-TO-BRAIN DELIVERY

Toshtemirov Shukhrat
Development of Drugs and Health Products (D2HP) University of Paris-Saclay
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Abstract. Parkinson's disease is a progressive neurodegenerative disorder characterized by the degeneration of dopaminergic neurons and a reduction in dopamine levels in the brain. Levodopa (L-DOPA) remains a principal pharmacological agent for the management of motor symptoms associated with Parkinson's disease. However, its therapeutic performance may be limited by peripheral metabolism, variable systemic exposure, and challenges associated with delivering sufficient drug concentrations to the central nervous system. Intranasal administration has attracted considerable interest as a potential route for nose-to-brain drug delivery.

Keywords: Levodopa; albumin nanoparticles; nose-to-brain delivery; intranasal administration; Parkinson's disease; nanotechnology; drug encapsulation; brain targeting.

Introduction. Nanoparticles are particles with at least one dimension in the range of 1 to 100 nanometers (nm). Due to their extremely small size, they exhibit unique physical, chemical, and biological properties that differ significantly from their bulk counterparts. These properties include a high surface-area-to-volume ratio, enhanced reactivity, and novel optical or magnetic behaviors. Nanoparticles are widely utilized in various fields such as medicine and environmental science for applications including drug delivery, biosensing, catalysis, and pollution control.

Over the past few decades, nanomedicine has emerged as a prominent area of focus in pharmacological research and development, particularly for improving the efficacy of drug therapies. A wide range of nanocarriers—including polymeric, lipid-based, and protein-based systems—are under investigation for their potential to enhance bioavailability and provide alternative routes of administration. Among protein-based delivery systems, albumin nanoparticles have demonstrated especially favorable characteristics. Albumin is recognized for its biocompatibility, biodegradability, non-immunogenic nature, wide availability, and low toxicity. Additionally, it exhibits physicochemical properties beneficial for drug delivery, such as increased water solubility, improved stability, and enhanced permeability. By adjusting formulation parameters, albumin-based carriers can achieve various drug release patterns, including sustained and controlled release.

Albumin-based nanoparticles have been extensively studied for multiple delivery routes, including intranasal (IN) administration, which is gaining traction as a promising, non-invasive approach for targeting the central nervous system (CNS). This is especially relevant for treating neurodegenerative diseases like Parkinson's disease, a progressive brain disorder characterized by tremors, bradykinesia, and postural instability. In such conditions, drugs like levodopa (L-DOPA)—a dopamine precursor used to restore dopamine levels in the brain—require efficient CNS delivery to alleviate motor symptoms. Various techniques are available for fabricating albumin nanoparticles, such as desolvation (coacervation), emulsification, thermal gelation, self-assembly, and nab® technology. Of these, the desolvation method is most commonly employed due to its simplicity, utilizing agents like ethanol to induce protein precipitation and subsequent gelation for nanoparticle

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formation.

Bovine serum albumin (BSA) is among the most widely researched forms of albumin for nanoparticle development. Due to its approximately 80% amino acid sequence similarity with human serum albumin, BSA exhibits comparable properties while offering cost-effectiveness and ease of purification. BSA is a highly water-soluble protein with a molecular weight of approximately 69 kDa, composed of around 585 amino acids. Its favorable attributes—biocompatibility, biodegradability, chemical modifiability, and non-toxicity—make it suitable for pharmaceutical use. Moreover, it remains stable across a broad pH range (4–9) and can tolerate heat exposure up to 60 °C for 10 hours without denaturing.

BSA nanoparticles provide multiple benefits for drug delivery:

- **Protection of Labile Drugs**: They shield sensitive drugs from enzymatic degradation and environmental instability.
- **Controlled Release**: They facilitate sustained drug release, enhancing therapeutic outcomes and reducing dosing frequency.
- **Targeted Delivery**: Surface modification enables site-specific delivery to targeted tissues or cells.
- **Simple Production**: BSA is low-cost, readily available, and easy to formulate.
- **Versatility**: Effective for carrying small molecules, proteins, peptides, and nucleic acids.

The current study aimed to develop and optimize BSA nanoparticles for the intranasal delivery of L-DOPA, a cornerstone therapy in Parkinson's disease management. BSA was solubilized in purified water, and levodopa was incorporated without the use of ethanol or other desolvating agents. Various formulations were prepared by adjusting the ratios of BSA, water, and L-DOPA. These were characterized in terms of average hydrodynamic diameter (Z-average), polydispersity index (PdI), zeta potential (ZP), and drug encapsulation efficiency to assess their suitability for nasal application. Additionally, the impact of the ethanolic environment on the secondary structure of BSA was examined using Differential Scanning Calorimetry (DSC), Thermal Gravimetry (TG) and Fourier-transformed infrared spectroscopy (FT-IR). L-DOPA release profiles and mucoadhesion of the formulations were also evaluated to support the development of an effective, non-invasive nasal drug delivery system for brain targeting in Parkinson's disease therapy.

In case of IN delivery drugs are administered via the nasal cavity, offering a direct axonal pathway to the brain and effectively bypassing the blood-brain barrier (BBB). This route provides several advantages, such as ease of administration, rapid onset of action, and avoidance of first-pass hepatic metabolism. IN delivery is especially advantageous for managing neurodegenerative diseases due to its ability to deliver therapeutic agents directly to the CNS via olfactory and trigeminal nerve pathways. With its richly vascularized mucosal surface, the nasal cavity allows both local and systemic drug absorption. More importantly, it provides direct access to the brain through the olfactory epithelium, enabling efficient nose-to-brain transport.

In the context of Parkinson's disease—where dopamine depletion in the brain is central to pathophysiology—IN administration of levodopa may enhance CNS targeting, reduce peripheral side effects, and improve drug bioavailability. The use of mucoadhesive systems, such as BSA-based nanoparticles, further improves nasal drug delivery by prolonging residence time, enhancing epithelial permeability, and protecting the drug from enzymatic degradation. These characteristics make BSA nanoparticles a promising platform for levodopa delivery through the nasal route, offering a patient-

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friendly and potentially more effective approach to treating Parkinson's disease.

Materials and methods. BSA (lyophilized powder, purity ≥ 97%), ethanol 96% v/v, L-DOPA was used as a model drug (Merck, Ltd., Budapest, Hungary), mucin from the porcine stomach (Type III), Simulated Nasal Electrolyte Solution (SNES) which consisted of 2.98 g/L potassium chloride (KCl), 8.77 g/L sodium chloride (NaCl), 0.59 g/L anhydrous calcium chlo-ride ($CaCl_2$) dissolved in purified water (pH 5.6), and all other reagents were pur-chased from Merck Ltd. (Budapest, Hungary) if not indicated otherwise. Analytical-grade methanol was purchased from Molar Chemicals (Budapest, Hungary). Purified water was obtained through a Gradient Water Purification System (Millipore Mil-li-Q®, Merck Ltd., Budapest, Hungary). All reagents and solvents were of pharmaceutical grade.

BSA—L-DOPA were prepared using a coacervation method. A certain amount of BSA (5, 10, 15 and 20 mg/ml) was dissolved in 2 mL of purified water under magnetic stirring for 15 minutes. A certain amount of L-DOPA (10 mg) was added to the BSA solution and the pH value was adjusted to 8.0 with NaOH 0.1 N and the solution was kept stirring for 30 minutes. Then, using a syringe pump, certain amount of ethanol (EtOH) was injected dropwise at a constant flow rate of 1 mL/min until turbidity appeared in the solution. Afterwards, all prepared formulations were transferred into vials and then lyophilized using a freeze-dryer (ScanVac CoolSafe, LaboGene, Lynge, Denmark) for 16 hours (at −40 °C, 0.013 mbar pressure), and then continued with secondary drying for four hours at 25 °C. Subsequently, all of the freeze-dried cakes were stored in the fridge at 4 °C for further analysis, and immediately redispersed with 2 mL of purified water prior to each investigation.

The measurement of the Z-average, PdI, and ZP (ζ) of formulations redispersed in water was carried out through via the dynamic light scattering (DLS) method, using a Malvern Zetasizer Nano ZS (Malvern Instruments, Worcestershire, UK) instrument at 25 °C.

Thermogravimetric analysis (TGA) was carried out using a METTLER-Toledo TGA/DSC 1 thermal analyzer (Mettler-Toledo GmbH, Gießen, Germany) to investigate the thermal stability and compositional characteristics of the samples. Approximately 5 mg of each freeze-dried sample was accurately weighed into 40 µL aluminum crucibles, which were hermetically sealed using standard crimping techniques to minimize atmospheric exchange.The analysis was performed over a temperature range of 25 °C to 300 °C**,** with a linear heating rate of 10 °C/min, under a continuous flow of high-purity nitrogen gas (50 mL/min) to provide an inert atmosphere and prevent oxidative degradation. Data was evaluated with STARe software, version 9.00.

Differential scanning calorimetry (DSC) measurements were performed using a Mettler-Toledo DSC 1 instrument (Mettler-Toledo GmbH, Gießen, Germany) to assess the thermal transitions and heat flow characteristics of the samples. The analyses were carried out over a temperature range of 25 °C to 300 °C**,** employing a heating rate of 10 °C/min under an inert atmosphere maintained by a constant argon purge flow of 150 mL/min. Approximately 5 mg of each freeze-dried sample was weighed into 40 µL standard aluminum crucibles**,** which were then sealed to prevent mass loss or interaction with the environment during the thermal scan. All measurements were normalized to sample mass to ensure quantitative comparability of the heat flow data. Thermograms were acquired and evaluated using STARe software, version 9.00**.**

The FT-IR spectra of BSA—L-DOPA formulations (homogenized in 0.15 g KBr disks) were recorded in the spectral range of 400-4000 cm^{-1} with the help of an AVATAR 330 FT-IR spec-trometer (Thermo Nicolet, Unicam Hungary Ltd., Budapest, Hungary), equipped with a deuterated triglycine sulfate detector. The spectral resolution was 2 cm^{-1} and 32 scans were performed. OriginPro 8.6

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software (OriginLab Corporation, Northampton, United States) was used for the spectral analysis. During sample preparation, the pressure was 10 tons, and the diameter of the pressings was 13 mm; a Specac Hydraulic Press was used (Specac Inc., Orpington, UK)

In this study, EE% was determined using a modified centrifugation method. Briefly, 3 mL acetonitrile with formic acid 0.1% v/v was added to 1 mL of each redispersed nanoparticle formulation to precipitate the albuminnanoparticles. Then, the precipitated formulation was centrifuged at 14,000 rpm for 15 minutes at a controlled temperature of 4 ± 1 °C. This high-speed centrifugation process separates the nanoparticles (pellet) from the unencapsulated, free drug (remaining in the supernatant).

The L-DOPA content of the products were analyzed with a 1260 HPLC Agilent system (Agilent Technologies, San Diego, CA, USA). The mobile phase consisted of acetate buffer (20 mM, pH 5.0)

:methanol=90:10 (v/v). A Chrome-Clone™ 5 µm C18 100 Å column (150 x 4.6 mm, Phenomenex, Torrance, CA, USA) was applied connected with a C-18 security guard cartridge. 10 µL of the sample was injected and isocratic elution was applied with 1ml/min flow for 8 min at 30 °C. Data were evaluated with ChemStation B.04.03. software (Agilent Technologies, Santa Clara, CA, USA). Both APIs were analyzed at 280 nm with a diode array detector.

To investigate the in vitro drug release behavior of different BSA—L-DOPA formulations (5, 10, 15 and 20 mg/ml) at nasal conditions, the modified paddle method was employed using a Hanson SR8-Plus™ dissolution tester (Teledyne Hanson Research, Chatsworth, CA, USA). Briefly, the redispersed formulations were placed into a dialysis bag with a molecular weight cut-off (MWCO) of 12–14 kDa (Spectra/Por®, Spectrum Labs, San Francisco, CA, USA) and immersed in 100 mL of freshly prepared simulated nasal electrolyte solution (SNES) as the release medium. The dissolution study was conducted at 100 rpm and 32 ± 0.5 °C. At predetermined time intervals (15, 30, 60, 120, and 240 mins), 1 mL samples were taken from medium and replaced with 1 ml SNES at the same time. The amount of L-DOPA released was then analyzed using the HPLC method, as described below.

To evaluate the in vitro drug release profile of different BSA—L-DOPA formulations at cerebrospinal conditions, a modified paddle method was employed using a Hanson SR8-Plus™ dissolution tester (Teledyne Hanson Research, Chatsworth, CA, USA). The redispersed formulations were placed into a dialysis bag as described above. The bags were then immersed in 100 mL of freshly prepared phosphate-buffered saline (PBS pH 7.4), which served as the release medium. The dissolution study was carried out at 100 rpm and a controlled temperature of 32 ± 0.5 °C. At predetermined intervals (15, 30, 60, 120, and 240 minutes), 1 mL of the release medium was withdrawn and immediately replaced with an equal volume of fresh PBS to maintain constant volume. The concentration of released L-DOPA from the BSA formulations was subsequently quantified using HPLC, as described below.

To evaluate the in vitro nasal permeability of formulations a modified Side-bi-side® type horizontal diffusion system was used, in which cellulose membrane filters (Whatman, pore size 0.45 µm; Germany) were positioned between the donor and acceptor chambers. Prior to assembly, the membranes were lightly moistened with isopropyl myristate (IPM), which served as a penetration enhancer to improve mucosal absorption due to its hydrophobic properties. The donor compartment was filled with 8 mL SNES, pH 5.6, and the acceptor compartment was filled with 9 mL of PBS, pH 7.4. Subsequently, 1 mL of redispersed formulation and a reference solution were added to the SNES in the donor chamber. Samples of 0.5 mL were withdrawn from the acceptor compartment (PBS side)

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at predefined time intervals: 5, 10, 15, 30, and 60 minutes. After each sampling, the removed volume was immediately replaced with an equal volume of fresh PBS to maintain a constant volume and sink conditions. The collected samples were analyzed to determine the concentration of the drug using HPLC, as detailed in the following section.

The mucoadhesive characteristics of BSA—L-DOPA formulations were evaluated by assessing their interactions with mucin using Zeta Potential (ZP) Measurement (Indirect). The mucoadhesion was assessed based on the interaction and complex formation between mucin and BSA—L-DOPA. 4 ml volumes of reconstituted BSA—L-DOPA formulations and 4 ml mucin solution (0.5% w/v in simulated nasal electrolyte solution, SNES) were thoroughly mixed. The total volume is 8 ml and then the mixtures were incubated at 37 °C for 2 hours to facilitate interaction. At predetermined time intervals (15, 30, 60, and 120 minutes) we took 1 ml samples zeta potential was analyzed using a Zetasizer (Malvern Zetasizer Nano ZS, Malvern Instruments, Worcestershire, UK).

RESULTS AND DISCUSSION

The particle size (Z-average), polydispersity index (PdI) and zeta potential (ZP) value of formulations was measured (Table 1). Each formulation met the particle size requirements of intranasal administered nanoparticles (<200 nm) even. The narrow PdI (<0.300) indicates monodisperse size distribution, which ensures the homogeneity of nanoparticles in the formulation. The highly negative ZP suggests high repulsion, therefore decreased aggregation tendency in liquid form.

Table 1. Colloidal parameters of BSA—L-DOPA formulations.

Formulation	Z-average (nm)	PdI	ZP (mV)
BSA—L-DOPA 5 mg/ml	71.71	0.116	-32.9
BSA—L-DOPA 10 mg/ml	90.17	0.143	-30.5
BSA—L-DOPA 15 mg/ml	81.64	0.150	-29.1
BSA—L-DOPA 20 mg/ml	99.1	0.162	-28.3

Thermal decomposition and weight loss behavior were monitored and recorded throughout the heating process. The onset decomposition temperatures, mass loss steps, and residual content was investigated. This setup ensured high sensitivity and reproducibility for the thermal characterization of the investigated materials. The sample is heated at a constant rate, and any mass loss (or gain) is recorded, indicating physical or chemical changes such as decomposition, dehydration, desolvation, oxidation, or phase transitions. TG analysis was performed to determine the residual ethanol content. TG thermograms revealed BSA undergoes denaturation above 60 °C as indicated by the weight loss (Figure 1). Ethanol evaporates in the same temperature range (45-110 °C), therefore the investigation of weight loss in the mentioned temperature interval and comparison with the TG curve of initial BSA. As ethanol belongs to Class 3 solvents, its residual concentration should be less than 50 mg; 5000 ppm or 0.5% in the daily dose of the final product, a requirement of the International Conference for Harmonisation (ICH) Q3C (R5) guideline for residual solvents. It has been revealed, that comparing the weight loss of BSA—L-DOPA formulations to initial BSA no remarkable difference was obtained,

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indicating the residual ethanol content is under limit of detection; it fits the acceptance criteria of ICH (Table 2).

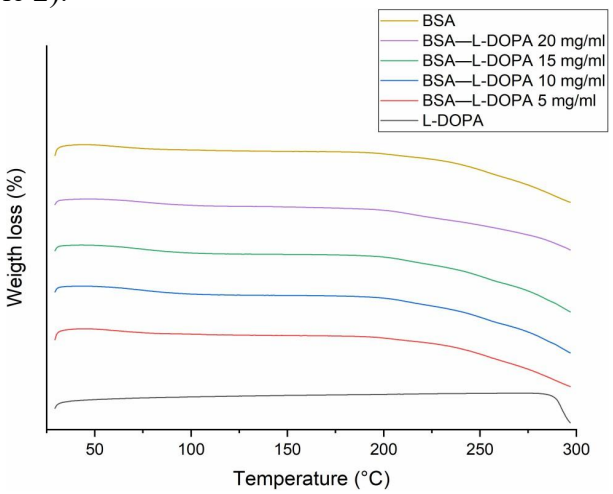


Figure 1. TG curves of BSA—L-DOPA formulations, as well as initial components.

Table 2. Weight loss results of BSA—L-DOPA formulations in comparison to initial BSA. Formulation

Formulation	**Weight loss (%)**	**Ethanol content (%)**
initial BSA	5.49	-
BSA—L-DOPA 5 mg/ml	5.53	0.04
BSA—L-DOPA 10 mg/ml	5.59	0.1
BSA—L-DOPA 15 mg/ml	5.54	0.06
BSA—L-DOPA 20 mg/ml	5.61	0.12

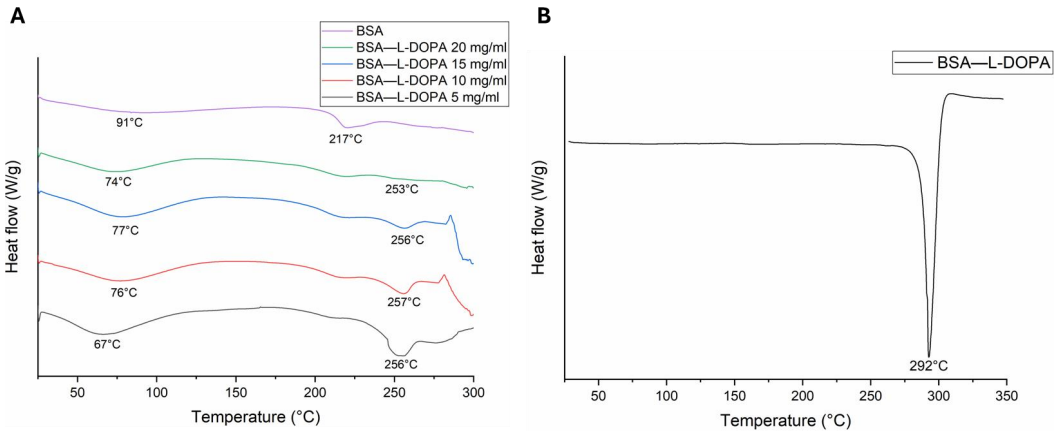
DSC analysis is allowing for accurate determination of thermal events such as glass transition temperature (Tg), melting point (Tm), and enthalpy changes (ΔH). This analytical configuration ensured high sensitivity and reproducibility in the thermal profiling of the investigated materials. DSC study was conducted in order to further investigate the thermal behaviour of BSA-Levodopa nanoparticle formulations (Figure 2). In accordance with the TG results, the endothermic peak at 91°C of the DSC thermogram of initial BSA indicated the denaturation temperature of protein, while the endothermic peak at approximately 217°C belongs to its melting point. The DSC curve of Levodopa revealed that the drug has the melting point at

292°C. In case of nanoparticulate formulations, the denaturation peak of BSA was remarkably shifted to a lower temperature proportional to the BSA content of formulations. Furthermore, no endothermic melting peak of Levodopa was observed in case of the formulations, which indicated Levodopa was dispersed at a molecular state within the nanoparticles either in an amorphous or in disordered crystalline state. However, the melting point of BSA increased in corresponding Levodopa-loaded nanoparticulate formulations, supporting the existence of drug in the composition and the

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formation of drug-albumin complex.

Figure 2. DSC thermograms of BSA—L-DOPA formulations (A) and initial



The addition of ethanol to BSA solution up to 30% v/v can cause unfolding of albumin, indicating a change in the α-helical structure. Therefore, FTIR studies were performed (Figure 3) to investigate the refolding behavior of BSA after the removal of ethanol through the freeze-drying process. There was no shift observed in the amide I peak (1655 cm^{-1}) and amide II peak (1545 cm^{-1}) in comparison to initial BSA, which indicates no specific interaction of BSA with Levodopa. Some characteristic peaks of Levodopa can be also observed in the FT-IR spectra of formulations at 1120 cm^{-1} and 819 cm^{-1} ,which proves a nanocomplex of BSA and Levodopa was successfully formed (Figure 3A).

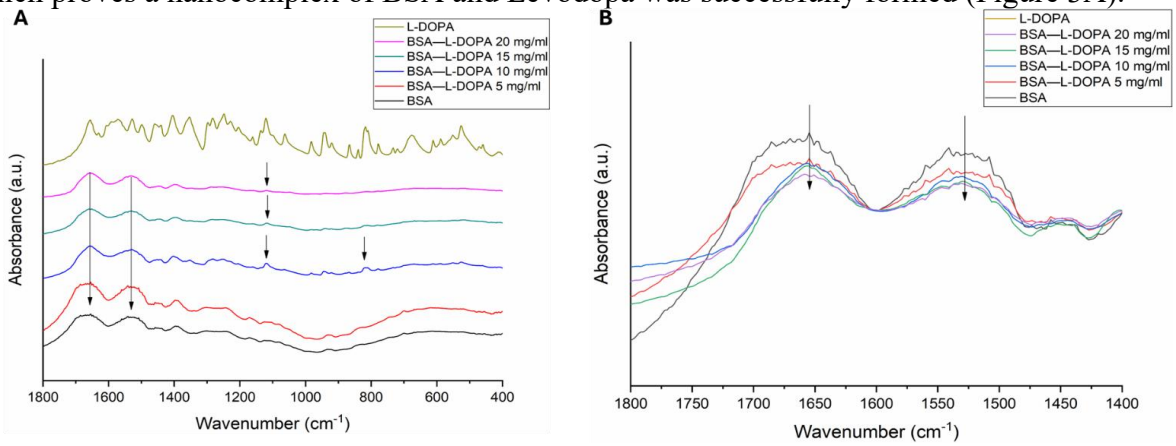


Figure 3. FT-IR spectra of BSA—L-DOPA formulations (A) and the magnification of amide regions (B).

Focusing on the amide I and amide II region the intensity changes of the peak at 1655 cm^{-1} and 1545 cm^{-1} indicate the unfolding and refolding of the protein (Figure 3A). In the FT-IR spectrum of BSA—L-DOPA formulations, the decreased intensity of amid I peak suggests the unfolding of BSA, moreover this tendency is proportional with the concentration of BSA. According to these results BSA—L-DOPA 5 mg/ml seems to be the most stable formulation.

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EE% refers to the proportion of the total drug that is successfully encapsulated or entrapped within the nanoparticles relative to the total amount of drug initially used in the formulation (Figure 4). It is an important parameter that reflects the effectiveness of the drug loading process and the ability of the nanoparticle system to retain the drug. In Figure 4, the highest EE% (64.2%) was achieved in case of 15 mg/ml BSA. BSA concentrations lower or higher than 15 mg/ml led to lower EE%, suggesting that there's an optimal balance at 15 mg/ml for most efficient loading or incorporation of L-DOPA into BSA.

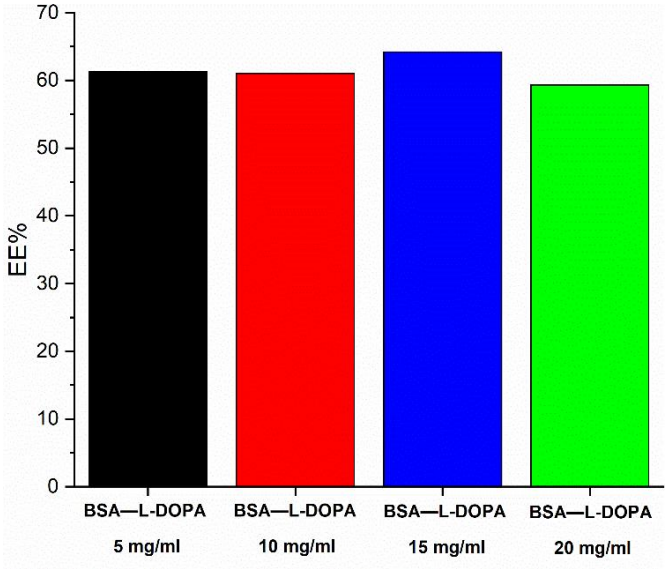
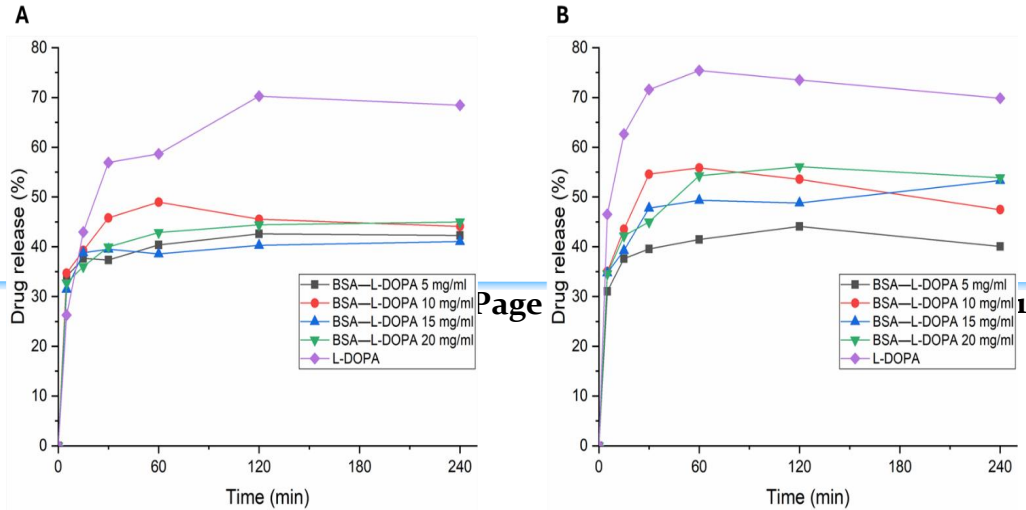


Figure 4. Drug encapsulation efficiency of L-DOPA-loaded formulations.

In vitro drug release studies at nasal conditions revealed, the BSA—L-DOPA 10 mg/ml formulation consistently shows the highest drug release percentage among the encapsulated formulations in SNES, reaching nearly 50% (Figure 5A). The BSA—L-DOPA 5 mg/ml, 15 mg/ml, and 20 mg/ml formulations exhibit remarkably similar and sustained release profiles, all plateauing around 40-43%, while free L-DOPA releases rapidly, reaching ~70% by 120 mins. physiologically the residence time of intranasally administered formulations is about 15 mins, so these release results support, only low amount of drug may be released in the nasal cavity, the major fraction of L-DOPA will be released after absorption.

Figure 5. In vitro drug release profiles of BSA—L-DOPA formulations in pH 5.6 SNES (A) and pH 7.4 PBS (B).The release profiles at cerebrospinal conditions indicated similar results, initial L-



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DOPA showed a rapid and high initial release, approximately 75% release within the first 30 minutes and then plateaus, indicating that the free drug readily dissolves and is available in the medium (Figure 5B). All BSA—L-DOPA formulations (5 mg/ml, 10 mg/ml, 15 mg/ml, 20 mg/ml) exhibited a sustained release pattern compared to free L-DOPA. The release is much slower and extends over a longer period. An initial burst release for all BSA—L-DOPA formulations was observed within the first 15-30 mins, followed by a slower, more gradual release. This burst is common for nanoparticles, where drug molecules on or near the surface are released quickly. BSA—L-DOPA 5 mg/ml showed the lowest overall drug release among the nano formulations, reaching just over 40% release by 60 minutes and maintaining that level, whereas BSA—L-DOPA 10 and 15 mg/ml showed similarly highest drug release rate (~55%). The drug release study in PBS confirmed that BSA—L-DOPA provided sustained drug release compared to free L-DOPA, suggesting a saturation point or intrinsic nanoparticle factors govern release rather than initial concentration, which implies some drug may remain entrapped, this could be advantageous in reaching the therapeutic goal.

Conclusion. The development of levodopa-loaded albumin nanoparticles offers a research opportunity to investigate protein-based nanocarriers for intranasal drug delivery. Albumin may provide a useful formulation matrix for drug incorporation and physicochemical modification, while intranasal administration offers a potential pathway for delivering therapeutic agents toward the central nervous system.

The proposed work will focus on nanoparticle preparation, formulation optimization, physicochemical characterization, encapsulation efficiency, drug release, stability, and preliminary nasal compatibility. These investigations will establish whether the developed formulation meets the basic requirements for further evaluation.

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