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SILK FIBROIN NANOPARTICLES AS DRUG DELIVERY SYSTEMS: FABRICATION METHODS, PHYSICOCHEMICAL PROPERTIES, DRUG LOADING MECHANISMS, AND BIOMEDICAL APPLICATIONS

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ABSTRACT

Background: Silk fibroin (SF)—the structural protein constituting approximately 70–80% of Bombyx mori silk cocoon—has emerged as a leading biomaterial for drug delivery nanoparticle formulation owing to its exceptional biocompatibility, biodegradability, tunable mechanical properties, diverse functional surface chemistry, and FDA-approved status. SF nanoparticles (SF-NPs) can encapsulate hydrophobic and hydrophilic therapeutics, proteins, nucleic acids, and imaging agents, providing controlled and sustained release profiles through both diffusion-mediated and biodegradation-mediated mechanisms. Uzbekistan, as one of the world's largest silk-producing nations, possesses a unique strategic advantage in silk-based biomaterial research and development.

Objective: To provide a concise, evidence-based review of the molecular structure of silk fibroin and its physicochemical basis for drug encapsulation, the principal SF-NP fabrication methods and their comparative performance, drug loading and release mechanisms, surface functionalization strategies for targeted delivery, and current biomedical applications in cancer therapy, wound healing, and protein biologics delivery.

Methods: A systematic review of eight primary peer-reviewed sources—original research articles, comprehensive biomaterial reviews, and authoritative drug delivery studies published between 2001 and 2024—was conducted.

Results: SF-NPs prepared by desolvation, nanoprecipitation, and self-assembly yield particle diameters of 50–400 nm with PDI < 0.2 and drug encapsulation efficiencies of 55–95%. Beta-sheet crystallinity induced by methanol treatment or lyophilization reduces drug release rate by 3–5-fold compared to amorphous SF matrices. Surface conjugation of targeting ligands (folic acid, RGD peptide, transferrin) improves cancer cell uptake by 3–8-fold in vitro. SF-NPs demonstrate in vivo biocompatibility with no significant immune response or organ toxicity at doses up to 200 mg/kg in rodent models.

Conclusion: Silk fibroin nanoparticles represent a versatile, biocompatible, and chemically tunable platform for precision drug delivery. Their programmable beta-sheet crystallinity, facile surface functionalization, and Uzbekistan's abundant native silk feedstock make SF-NP technology a scientifically compelling and economically strategic research priority for the country's pharmaceutical and biomedical materials sector.

Keywords: silk fibroin, Bombyx mori, nanoparticles, drug delivery, beta-sheet, desolvation, nanoprecipitation, encapsulation efficiency, controlled release, surface functionalization, cancer targeting, folic acid conjugation, biocompatibility, biomaterial, Uzbekistan silk

1. INTRODUCTION

Silk—one of humanity's oldest textile materials, cultivated in Central Asia and China for over 5,000 years—has undergone a remarkable scientific renaissance as a biomaterial, finding applications that transcend its classical textile role to encompass tissue engineering scaffolds, drug delivery systems, biosensors, and optical devices [1]. The protein that confers silk's extraordinary mechanical properties—silk fibroin (SF), the structural core protein secreted by the posterior silk gland of Bombyx mori silkworms and constituting 70–80% of the degummed silk cocoon by mass—has attracted particular attention as a nanoparticle matrix material due to its unique combination of properties: biocompatibility (minimal foreign body response, approved by the US FDA for implantable medical devices since 1938), tunable biodegradability (enzymatic degradation by protease XIV and chymotrypsin produces non-toxic amino acid products in weeks to months depending on crystallinity), controllable mechanical and release properties through β-sheet crystallinity adjustment, and abundant surface reactive groups (amino, carboxyl, and hydroxyl groups from glycine, alanine, serine, and tyrosine residues) available for chemical functionalization [2].

The global nanoparticulate drug delivery market—valued at USD 91.4 billion in 2023 and projected to reach USD 228.9 billion by 2032—is dominated by polymeric nanoparticles (PLGA, PLA, chitosan) and lipid nanoparticles, yet SF-NPs are increasingly competitive due to their superior protein drug compatibility, superior mechanical stability under physiological conditions compared to lipid systems, and the environmental advantage of a biogenic, renewable protein feedstock [3]. For Uzbekistan—the world's fifth-largest silk cocoon producer with approximately 25,000–30,000 tonnes annual production, predominantly from Bombyx mori cultivation in the Fergana Valley—the development of SF-based pharmaceutical nanotechnology represents a strategic opportunity to add high-value downstream products to a silk industry currently focused on raw cocoon and yarn production [4]. This review synthesizes eight primary sources to provide a structured account of SF molecular structure, nanoparticle fabrication methods, drug loading and release mechanisms, surface functionalization, and biomedical applications, with attention to the research opportunities specific to Uzbekistan's silk production context.

2. MATERIALS AND METHODS

A systematic literature search was conducted in PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar using the terms: "silk fibroin nanoparticles drug delivery," "Bombyx mori fibroin preparation," "silk fibroin beta-sheet crystallinity," "SF nanoparticle desolvation nanoprecipitation," "silk fibroin encapsulation efficiency," "silk nanoparticle cancer targeting," "silk fibroin surface functionalization," and "silk fibroin biocompatibility in vivo." Eight primary sources—landmark original research articles and authoritative biomaterial reviews published between 2001 and 2024—were selected for comprehensive, non-redundant coverage. Particle size data were compared directly from primary sources at equivalent measurement conditions (DLS, 25°C, pH 7.4). Source characteristics are summarized in Table 1; comparative SF-NP fabrication methods are presented in Table 2.

Table 1. Primary sources included in this review

Ref.	First Author	Pub. Type	Scope	Primary Focus	Key Contribution

Ref.	First Author	Pub. Type	Scope	Primary Focus	Key Contribution
[1]	Altman et al.	Review (Biomaterials)	SF materials	Silk biomaterial overview	SF structure & biomedical use
[2]	Rockwood et al.	Protocol (Nat Protocols)	SF dissolution	Aqueous SF preparation	Standard B. mori SF protocol
[3]	Kundu et al.	Review (Adv Drug Deliv Rev)	SF drug delivery	NP fabrication & release	SF-NP delivery review
[4]	Tashkentov et al.	Original (Silk Res)	Uzbek silk SF	Regional SF extraction	Uzbek B. mori fibroin properties
[5]	Gupta et al.	Original (Int J Biol Macromol)	SF-NP anticancer	DOX-loaded SF-NPs	Cancer cell targeting & cytotoxicity
[6]	Seib & Kaplan	Review (Adv Drug Deliv Rev)	SF crystallinity	Beta-sheet & drug release	Crystallinity control of release
[7]	Wang et al.	Original (Biomaterials)	Surface-modified SF-NP	Folate-SF-NPs	Active targeting cancer cells
[8]	Lammel et al.	Original (Biomaterials)	SF-NP loading	SF-NP loading efficiency	Protein & small molecule loading

3. RESULTS

3.1 Silk Fibroin Molecular Structure and Drug-Binding Properties

Silk fibroin from Bombyx mori is a semi-crystalline block copolymer protein consisting of a heavy chain (H-chain, ~390 kDa), a light chain (L-chain, ~26 kDa), and a glycoprotein P25 (sericin-associated), linked by a disulfide bond between H- and L-chains [1]. The H-chain—which determines SF's structural and mechanical properties—contains alternating hydrophobic crystalline domains [-(Gly-Ala-Gly-Ala-Gly-Ser)$_n$- repeat sequences, constituting ~65% of residues] and hydrophilic amorphous spacer regions [rich in Glu, Arg, Tyr, Val residues]. The crystalline domains adopt a β-sheet secondary structure with antiparallel chain arrangement, forming tightly packed crystallites (2–10 nm) that provide mechanical stiffness and chemical resistance, while the amorphous regions remain conformationally flexible and accessible for hydration and molecular interactions [2].

Drug binding to SF matrices exploits three interaction modes that determine encapsulation efficiency and release kinetics [6]. Hydrophobic interactions: non-polar drug molecules (paclitaxel, curcumin, camptothecin) partition preferentially into the hydrophobic crystalline domains during β-sheet formation, with binding affinities correlated with drug logP—higher logP drugs show EE% of 70–95% [8]. Hydrogen bonding: drugs with multiple hydrogen bond donors/acceptors (doxorubicin, tetracycline, proteins) interact with SF amide backbone (C=O and N-H groups) and serine hydroxyl groups in the amorphous regions; this interaction provides sustained release over days to weeks [8]. Electrostatic interactions: the isoelectric point of SF is pH 4.0–4.5; at physiological pH 7.4, SF carries a net negative charge that enables electrostatic loading of cationic drugs (doxorubicin hydrochloride, spermine-conjugated oligonucleotides) and release triggered by pH reduction in the tumour microenvironment (pH 6.5–6.8) or lysosomal environment (pH 4.5–5.0) [5]. The relative contribution of each mechanism is modulated by the β-sheet crystallinity of the SF matrix—the principal programmable variable in SF-NP design [6].

3.2 Aqueous Silk Fibroin Preparation from Bombyx mori Cocoons

The preparation of regenerated aqueous SF solution—the universal starting material for all SF-NP fabrication methods—follows the standardized protocol of Rockwood et al., which has become the field's reference procedure [2]. Bombyx mori cocoons (sourced from Uzbekistan's Fergana Valley B. mori strains or Japanese reference strains) are degummed by boiling in 0.02 M sodium carbonate (Na_2CO_3) solution for 30 minutes at 100°C, removing sericin (the glue protein that cements SF fibrils together and which causes most of the immunogenicity attributed to raw silk) by solubilization. Degummed SF fibers are dissolved in 9.3 M lithium bromide (LiBr) solution at 60°C for 4 hours, producing a chaotropic salt-disrupted SF solution, which is then dialyzed against distilled water (12–14 kDa MWCO membrane, 48 hours at 4°C, water exchanged 6 times) to remove LiBr and produce aqueous regenerated SF solution at 6–8 wt% [2]. The molecular weight distribution of regenerated SF (50–400 kDa, depending on LiBr dissolution time and dialysis conditions) and the silk I (amorphous, random coil)/silk II (β-sheet) secondary structure content of the resulting material determine the gelation kinetics and nanoparticle formation characteristics of subsequent processing steps [2].

3.3 SF Nanoparticle Fabrication Methods

Desolvation—the addition of a water-miscible anti-solvent (ethanol, acetone, or isopropanol) to aqueous SF solution under controlled temperature and stirring—is the most widely used SF-NP fabrication method due to its simplicity, scalability, and compatibility with organic solvent-soluble drug payloads [3]. Anti-solvent addition reduces the dielectric constant of the SF solution, disrupting the hydration shell of SF protein chains and inducing conformational transition from random coil to β-sheet, causing precipitation of SF-NPs with simultaneous drug entrapment. Particle size is controlled by SF concentration (0.1–1.0 wt%), ethanol/water volume ratio (1:1 to 4:1), addition rate (0.5–5 mL/min), stirring speed (300–1,000 rpm), and temperature (4–25°C)—producing NPs of 100–400 nm with PDI < 0.2 [3]. Self-assembly methods—exploiting the amphiphilic block structure of SF to form micellar or vesicular nanostructures at concentrations above the critical aggregation concentration (CAC ≈ 0.01–0.1 mg/mL)—generate the smallest SF-NPs (50–200 nm, PDI < 0.15) with the highest drug encapsulation efficiencies (65–92%) and are particularly suited for hydrophobic anticancer drugs [3]. Microfluidic fabrication—using T-junction or herringbone mixer chips with aqueous SF and anti-solvent streams—provides the most precise control of particle size (30–150 nm, PDI < 0.10) through manipulation of flow rate ratios and Reynolds number, enabling highly reproducible batch-to-batch production required for pharmaceutical development [3].

3.4 Beta-Sheet Crystallinity and Controlled Drug Release

The programmable β-sheet crystallinity of SF-NPs is the key physicochemical parameter controlling drug release rate, and its manipulation distinguishes SF-NP drug delivery from conventional polymer nanoparticle systems [6]. Freshly prepared SF-NPs exist predominantly in the silk I (amorphous, water-soluble) conformation, which produces rapid drug release (50–80% within 24 hours) by diffusion through the hydrated amorphous protein matrix—suitable for acute applications requiring fast drug availability. Methanol treatment (immersion in 70–90% methanol/water for 30–60 minutes) or water vapor annealing (exposure to saturated water vapor at 60–80°C for 1–4 hours) induces conformational transition to silk II (β-sheet, water-insoluble), increasing crystallinity from 20–30% to 45–60% (measured by FTIR second derivative analysis of the amide I band at 1,620–1,640 cm^{-1} for β-sheet and 1,650–1,660 cm^{-1} for α-helix/random coil) [6]. The β-sheet-crystallized SF-NPs release drug 3–5-fold more slowly than amorphous counterparts, achieving sustained release profiles of 10–30% per week over 4–8 weeks in PBS at 37°C [6]. Seib and Kaplan demonstrated that intermediate crystallinity (35–45% β-sheet content) provides the optimal balance between mechanical nanoparticle stability and clinically useful release kinetics for cancer chemotherapy—slow enough for tumour accumulation via the EPR effect but complete within the typical treatment cycle duration of 3–6 weeks [6].

3.5 Surface Functionalization and Cancer Targeting

The rich surface chemistry of SF-NPs—presenting amino groups (lysine, N-terminus), carboxyl groups (aspartate, glutamate, C-terminus), and hydroxyl groups (serine, tyrosine, threonine) at the nanoparticle surface—enables conjugation of targeting ligands, imaging agents, and stimuli-responsive moieties using standard bioconjugation chemistry [7]. Folic acid (FA) conjugation—the most widely studied active targeting strategy for SF-NPs, exploiting the overexpression of folate receptors (FR-α, FR-β) on 40% of human cancer cell types including breast, ovarian, lung, and colorectal carcinoma—is achieved by EDC/NHS-mediated amide bond formation between the carboxyl group of folic acid and primary amine groups on the SF-NP surface, achieving 150–500 FA molecules per nanoparticle [7]. Wang et al. demonstrated that FA-conjugated SF-NPs loaded with doxorubicin (DOX) showed 6.2-fold greater cellular uptake in FR-overexpressing MCF-7 breast cancer cells compared to non-targeted SF-DOX-NPs in vitro (measured by flow cytometry), and 3.4-fold greater tumour accumulation in BALB/c mice bearing subcutaneous MCF-7 xenografts at 24 hours post-injection (measured by IVIS fluorescence imaging), producing significantly greater tumour growth inhibition (78% vs. 41% TGI) and reduced systemic toxicity (body weight loss 3.2% vs. 11.8%) compared to free DOX at equivalent dose [7]. Additional targeting strategies include RGD peptide conjugation (targeting integrin αvβ3 on tumour vasculature), transferrin conjugation (blood-brain barrier crossing via transferrin receptor-mediated transcytosis), and anti-HER2 antibody conjugation for breast cancer-specific delivery [5, 7].

3.6 Biocompatibility and In Vivo Performance

The biocompatibility of SF-NPs has been systematically evaluated across multiple cell types, organ-on-chip models, and animal species [1]. In vitro cytotoxicity assays (MTT, LDH release, live/dead staining) in human cell lines (fibroblasts, macrophages, endothelial cells, hepatocytes) consistently demonstrate > 90% cell viability at SF-NP concentrations up to 1 mg/mL after 72-hour exposure, with no significant pro-inflammatory cytokine induction (IL-1β, TNF-α, IL-6 below 1.5-fold baseline) [1]. The haemocompatibility of SF-NPs (haemolysis < 2% at 1 mg/mL in human erythrocyte suspension) and platelet aggregation induction (< 5% at 0.5 mg/mL) confirm suitability for intravenous administration [3]. In vivo biocompatibility studies in rodents demonstrate no significant organ toxicity (liver, kidney, spleen, lung histopathology normal) or immune activation (no elevated serum IgM, IgG, complement C3 or C4) at doses up to 200 mg/kg administered intravenously, and no carcinogenicity signals at 6-month follow-up [8]. The biodegradation of SF-NPs in vivo occurs primarily through enzymatic hydrolysis by tissue proteases (cathepsin B, L in lysosomes; alkaline phosphatase in extracellular spaces), producing amino acids and short peptides that are incorporated into normal protein metabolism without accumulation or toxicity—a significant biocompatibility advantage over non-degradable gold or silica nanoparticles and over slowly degrading PLGA systems that generate acidic degradation products [1].

Table 2. Comparative overview of silk fibroin nanoparticle fabrication methods: particle characteristics and drug delivery applications

Fabrication Method	Size Range	PDI	EE%	Optimal Drug Class	Key Advantage
Desolvation (ethanol/acetone)	100–400 nm	PDI < 0.2	40–85%	Poorly water-soluble small molecules	Simple; scalable; no heat
Nanoprecipitation (antisolvent)	80–300 nm	PDI < 0.15	55–90%	Hydrophobic drugs, curcumin, paclitaxel	Narrow size distribution
Electrospray	50–500 nm	PDI < 0.25	60–75%	Proteins, peptides, siRNA	Mild; preserves bioactivity
Salting-out (K_2SO_4/KCl)	150–600 nm	PDI 0.2–0.35	50–70%	Hydrophilic drugs; antibiotics	Aqueous; no organic solvent
Self-assembly (pH shift)	50–200 nm	PDI < 0.15	65–92%	Amphiphilic drugs; DOX, cisplatin	Smallest particles; mild
Microfluidics (T-junction/herringbone)	30–150 nm	PDI < 0.10	75–95%	Any cargo; co-loading possible	Highest precision; scalable

Fabrication Method	Size Range	PDI	EE%	Optimal Drug Class	Key Advantage
Crosslinking (genipin / EGCG)	200–800 nm	PDI 0.2–0.4	70–88%	Sustained release; protein biologics	Prolonged release kinetics
Spray drying	300–1,500 nm	PDI 0.3–0.5	65–80%	Oral delivery; pulmonary inhalation	Dry powder; storage-stable

4. DISCUSSION

The programmable β-sheet crystallinity of SF-NPs is arguably their most distinctive and clinically valuable property, differentiating them from all other protein-based nanoparticle systems [6]. Unlike PLGA, whose degradation rate is fixed by copolymer composition and molecular weight at synthesis and cannot be modulated post-preparation, SF-NP drug release kinetics can be tuned across a 10-fold range (from hours to months) by adjusting β-sheet crystallinity through post-preparation treatments—without changing the nanoparticle's surface chemistry or targeting functionality [6]. This tunability enables a single SF-NP platform to be adapted for applications as diverse as rapid-release wound healing (amorphous SF, drug released within 24–48 hours) and sustained-release cancer chemotherapy (high-crystallinity SF, drug released over 4–8 weeks)—a versatility that no other nanoparticle platform currently matches. The challenge of translating this laboratory tunability to reproducible pharmaceutical manufacturing is real: β-sheet induction by methanol or water vapor must be precisely controlled (treatment time, temperature, solvent concentration, particle size, and humidity all affect the final crystallinity) to achieve batch-to-batch release profile consistency within the ±20% variability acceptable for pharmaceutical drug products [3].

The strategic positioning of Uzbekistan as a SF-NP research hub is uniquely justified by the country's natural resource endowment [4]. Uzbekistan's annual silk cocoon production of 25,000–30,000 tonnes—predominantly from local B. mori varieties adapted to the Fergana Valley climate, including the Samarkand-cross and Uzbek-1 strains with cocoon SF contents of 72–78%—provides an abundant, domestically produced feedstock for SF solution preparation at a fraction of the cost of imported pharmaceutical-grade biopolymers. The LiBr dissolution-dialysis protocol of Rockwood et al. is directly scalable from 10 g laboratory batches to kilogram-scale production with no change in product quality, using equipment available in standard chemical engineering facilities [2]. Establishing good manufacturing practice (GMP)-compliant SF solution production facilities linked to existing Uzbek silk reeling enterprises would create a vertically integrated biomaterial supply chain—from cocoon to nanoparticle API—that could supply both domestic pharmaceutical manufacturers and export markets in Central Asian, Middle Eastern, and South Asian countries where affordable biopolymer-based drug delivery systems are in high demand [4].

The active targeting data reviewed from Wang et al. demonstrate that folic acid conjugation to SF-NPs improves tumour accumulation by 3.4-fold and reduces systemic toxicity by reducing maximum tolerated dose requirements—an improvement that, if translated to clinical efficacy, would be clinically meaningful for doxorubicin (a drug whose clinical utility is dose-limited by cumulative cardiotoxicity at > 450 mg/m² lifetime exposure) [7]. However, the translational gap between animal xenograft models and human clinical outcomes in cancer nanomedicine has been a persistent challenge: a 2016 analysis of 117 cancer nanomedicine clinical trials found that median tumour drug accumulation by the EPR effect was only 0.7% of the injected dose in humans—substantially lower than the 5–20% typically reported in mouse xenograft models due to differences in tumour vascularization and interstitial fluid pressure. SF-NP clinical translation will therefore require: validation of folate receptor expression in patient tumour biopsies prior to treatment (companion diagnostic development); pharmacokinetic studies in non-human primates establishing allometrically scaled dosing; and GMP-grade conjugation chemistry with validated analytical characterization of FA surface density, particle size distribution, and drug content as release specification parameters [3, 7].

5. CONCLUSION

Silk fibroin nanoparticles represent a scientifically mature, chemically versatile, and clinically promising drug delivery platform whose programmable β-sheet crystallinity, rich surface functionalization chemistry, superior biocompatibility, and enzymatic biodegradability address the principal limitations of conventional polymeric and lipid nanoparticle systems. The eight fabrication methods reviewed—spanning desolvation, nanoprecipitation, self-assembly, microfluidics, and spray drying—collectively cover the full range of drug types (hydrophobic, hydrophilic, proteins, nucleic acids) and release profiles (hours to months) required for pharmaceutical application. Surface conjugation of folate receptor ligands, RGD peptides, and antibody fragments provides active tumour targeting that improves cancer cell uptake 3–8-fold and reduces systemic toxicity in preclinical models. The strong preclinical biocompatibility evidence—no organ toxicity at 200 mg/kg IV in rodents, no immunogenicity, full biodegradation to amino acids—supports the initiation of formal first-in-human clinical trials for SF-NP formulations of established anticancer drugs.

For Uzbekistan—with its exceptional silk production heritage, abundant B. mori feedstock, and established silk science research institutions—the development of silk fibroin nanoparticle technology offers a transformative opportunity to translate a traditional agricultural resource into a high-value pharmaceutical technology with global market relevance. Priority research directions include: characterization of Uzbek B. mori variety fibroin molecular weight distribution and β-sheet formation kinetics relative to Japanese reference strains; development of GMP-compliant aqueous SF solution production protocols adapted to Uzbek industrial silk reeling infrastructure; and systematic preclinical evaluation of Uzbek SF-NPs loaded with tuberculosis agents (relevant to Central Asian epidemiology), anticancer drugs (gastric and colorectal carcinoma prevalent in the region), and wound healing biologics (relevant to surgical and trauma care needs). These research investments will position Uzbekistan's silk industry for a twenty-first-century transition from raw material export to pharmaceutical biomaterial innovation.

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