

Use of Silk Fibroin-Based Nanoparticles as a Novel Drug Delivery System

Ms. Iqra Rahat, Satish Kumar Sharma

Department of Pharmacy, Glocal School of Pharmacy

Glocal University, Saharanpur, Uttar Pradesh

Email Id- Iqarahat.rahat37@gmail.com

ABSTRACT: *Silk fibroin (SF) is generally termed as the protein-based bio-macromolecule, with exceptional biodegradability, biocompatibility, and poor immunogenicity. Because of higher bonding ability for various medicines, controlled release drug delivery properties & mild framework of the research, significant attention has been paid to development of nano-particles that are SF-based for delivery of medicine. SF is generally a protein polymer which is obtained naturally with several unique properties making it an appropriate substance for inclusion within a wide range of delivery-automobiles which has ability of providing several varieties of treatment. The adjusted or retroviral polymers dependent on SF can be designed to improve the medicinal effectiveness of drugs found in this nano substance by modifying the particle size, chemical composition and properties. These were utilized for providing tiny polymers medicines (e.g., medicine for cancer treatment), growth factor medicines & protein, gene drugs, and so on. This paper examines recent developments in Nano-particles focused on SF including chemical composition, structures, and methods of preparation. Additionally, the uses of Nano-particles dependent on SF in form of catalysts of medicines which were studied.*

KEYWORDS: *Drug delivery, Nano-particles, Preparation methods, Silk fibroin.*

INTRODUCTION

The composition of the revived silk fibroin protein stock involves sericin extraction (i.e. degumming), which is an important phase in manufacturing hypoallergenic silk fibroin. The much more popular method of degumming is the utilization of high heat acid environment. The removed silk fibers are then drawn out with the help of a chaotropic agent or, as recently written, in molten ionic liquids in conjunction with intense ultrasound to remove frameworks of higher-order silk fibroin. To date, usage has been made of synthetically & naturally produced polymer in context of delivering the medicine. Extensive use has been identified in a broad variety of recycled substance, polyorthoesters, poly-esters, polyphosphazenes, polyphosphoesters & polyanhydrides [1].

The breakdown of the silk protein structure happens throughout degumming and, to a lesser degree, at the time of dissolution in chaotropic agents, decreasing molecular weight & consequently the the biopolymer's polydispersity, with studies documenting the effects on dynamics, self-assembly, deterioration and drug disclosure. That being said, the effect of variability of silk fibroin stocks on the characteristics of nanoparticles remains deeply described, & the structure of silk nanoparticles by particle size is uncertain. During physical or nanofabrication desolvation, the effect of the silk fibroin stock often involves an analysis to decide how this changes the physical properties of the subsequent silk nanoparticles. This research therefore resolved these issues by changing the processing parameters of the silk stock and the dissolving method to determine the impact upon alternative silk-worked nanoparticles, zeta potential, scale, composition, morphology and cytotoxicity. However, given the broad variety of usable products, most regulated drug delivery systems are focused on poly-mer, poly-substance (lactic-co-glycolic acid) (PLGA) authorised by FDA (U.S. Drug and Food Administration) due to features like appropriate pharmaco-kinetics & regulatory

degradable pace. But, due to some of its processing requirements and intrinsic properties, the utility of PLGA was restricted to intermediates. Derived substances (e.g., chitosan, alginates, dextran, collagene, gelatine and pullu-lan) thus provide an enticing option with greater biodegradability and biocompatibility than PLGA.

The arrangement of drug delivery systems still requires careful attention, in addition to their composition. To date, several devices, including gels, films, foams, nanoparticles and micro particles, and have been built with various morphologies and structures. The first Nano-systems licensed for the distribution of drugs and proteins were the liposomal carriers. Nanoparticles have high capacities for chemotherapeutic drugs has also been reported in many studies. In certain situations, the usage of particulate carriers by adding a second restricting measure would reduce the distribution rate of solubilized medicines [2].

In addition, Nanomaterials have many characteristics that are beneficial for the distribution of medications, like a higher ratio volume-to -surface ratio, the capacity to serve as changeable frameworks & the flexible scale. Consequently, applying the nanotechnology principles to the essence of drug carriers will not only increase their diagnostic accuracy but also preserve the property of bio-active compounds. Consideration must be provided to the characteristics associated with nanomaterials in forms of their structure, shape, material performance & function in producing reservoirs for suspended particles drug processing. Silk particles are FDA-approved polysaccharides & were commonly utilized both as regenerative medicine mechanisms & as incisions. These substances have high mechanical strength, robust manufacturing techniques and strong bio-compatibility. So far, several scientific papers have been published on the use of biopolymers in the field of tissue-engineering. Although there are several earlier papers about the application of silk nanomaterials as delivery of drug, no thorough review has ever been released of their use for drug delivery. Thus researchers provide a broad overview in this review of recent efforts to build silk protein nanostructures for delivery of drugs [3]. Present paper aimed to examine modern enhancements in Nano-particles focused on SF including chemical composition, structures, and methods of preparation. Additionally, the uses of Nano-particles dependent on SF as carriers for therapeutic drugs are also studied.

Both the pharmacist and the customer take the appropriate measures to execute the prescription. These measures can involve, but are not limited to, calling various healthcare professionals to explain or change medications, starting medication counselling, informing the patient and/or caregiver(s), arranging the purchase of drugs and/or associated materials, which may involve helping the patient resolve financial or behavioural challenges that may otherwise conflict with the therapy plan; Drug delivery methods have historically been focused on orally delivered or injectable medications. These have, however, been considered inadequate for experimental treatments such as nucleic acids and proteins. Modern innovations are required to distribute modern polymer for decreasing negative impacts, maximize the potency & increase individual enforcement. Nanotechnology has currently contributed to the creation of several innovative aspects that has ability to release and selective distribution of broad variety of tiny polymers, enzymes, peptides & genes. The pharmacist interacts with the patient to optimize patient awareness and participation in the treatment schedule, guarantees that perhaps the patient has and accepts plans for the management of medical treatment (e.g. laboratory assessment, blood pressure control, home blood glucose checking, etc.) and that the patient provides & learns how to correctly utilize the appropriate medications and associated equipment Explanations are adapted to the degree of awareness of the patient, and instructional and implementation aids are utilized as specified.

These instruments that have several various materials, including lipids, microemulsions, dendrimers, carbon nanotubes, ferritin, nano-particles & ferrocene. Nano-particles based on biocompatible & environmentally friendly, and polymers have major cancer treatment implementations & as continuous carriers for the distribution of medicines, among them. Such catalysts are possibly engineered in form of lower-toxicity devices through appropriate chemical & physical architectures & targeted functional features. Particle size has been identified as being the most significant element within design of frameworks associated with the delivery of drugs. The usage of Nano-particles for the distribution and selection of therapeutic molecules therefore is important [4].

These systems have other benefits which include prolonged drug half-life, enhanced hydrophobic drug solubility, Decreased virulence factors & decreased dosing rate. As described in prior research, one of the principal benefits of nanoparticles is the prospect of selective drug delivery. It's also generally accepted that the pronunciation of different ligands with nanostructures may increase their efficacy of tracking correlating to traditional treatments. Limited scale of nano-polymers often impacts on targeting efficiency. Another feature of Nano-based medication delivery technologies relative to traditional methods is the potential to co-deliver several medications. Co-delivery of medications provides many benefits, like the likelihood of synergistic impacts, reduced medication tolerance and the potential to change product dose to one carrier-level of Nano-particles.

The identification of associations among nanoparticles & cell types / fatty acid phospholipid bilayer is important in the areas of chemotherapy, imaging & drug delivery. Explanation for that is that the nanoparticles are low in scale relative to micro particles. Researchers have demonstrated - the cellular absorption of 100-nm nano-particles, respectively, are 2.4 and 6 times more as compared to 1- μm & 10- μm micro-particles to fix this issue. A related research has recorded - cellular absorption of 100-nm nano-particles is 14–240 times higher than micro particles of 1– and 10- μm . They have argued that efficient nanoparticles take-up rely upon sizes [5].

It has been shown that 40-nm gold particle experience much successful absorption. Researchers have also reported that spherical Nano-particles have a five-fold greater absorption than rod-shaped particles. Therefore, scale and form tend to be the two critical variables influencing the cellular absorption of particles. It is also recognized that besides affecting cellular absorption, particle-size may affect drug-packing, releasing of drug, & Nano-particulate reliability. In addition to size & form, features of the Nano product are also significant [6].

METHODS

Surface characteristics including hydrophilicity and hydrophobicity decide the absorbance degree of elements associated with blood. In vitro experiments, however, it's been shown that there is still a relationship among the presence of opsonization & the major group of nano-materials & that there is very little opsonization in rationally energetic materials compared to normal energetic materials. To this end, the use of protecting groups that can prevent the hydrophobic & electrostatic connections resulted in activator being bound to the nano-particle surface. Figure 1 outlines a quick summary of the impacts of molecular weight & surface of nano-particulate characteristics.

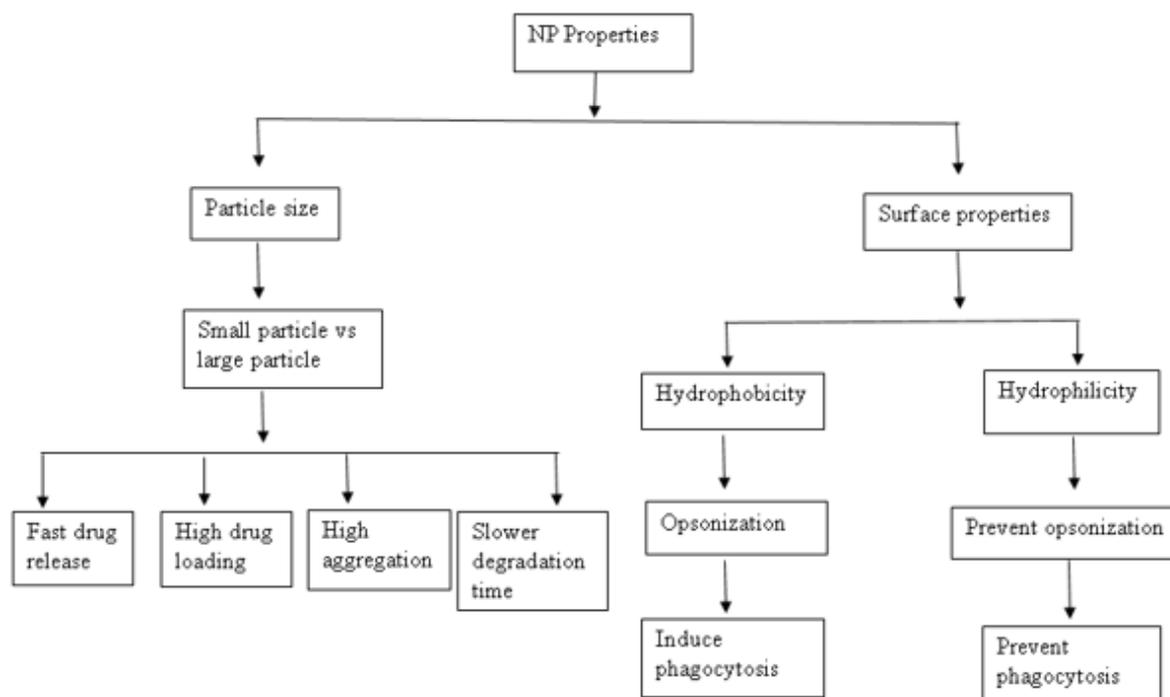


Fig 1: Properties That Define the Behaviour of Silk Nano-particles (SFNPs).

Poly-meric Nano-systems:

In several studies, polymeric Nano-particles have been of significant concern for decades. Several other drug delivery approaches like re-assembled encapsulated & micelles molecules of drug had established dendrimeric-starburst-like polymers introduction. Biodegradable polymeric Nano-carriers are often used for their ability to regulate medication release levels, and They utilized naturally & synthetically produced polymers for this purpose. More basic composition & greater consistency of polymeric materials, rendering Nano-particle formulation more reproducible than polymer which occurs naturally [7].

To drug distribution applications, nevertheless, only synthetic polymers with low cytotoxicity and acceptable biodegradability are suitable. In fact, The capacity of polymeric materials to control levels of drug release is much greater than those of polymeric materials. Polymeric materials can control the drug release of pharmaceutical products over a rather lengthy span of time than polymeric materials with very adequate provision periods. However, their usage was constrained by the tough experimental parameters & utilization of chemical reagents needed for the processing of polymeric materials. Poly (lactic acid), poly (alkylcyano acrylates), poly (glycolic acid) (PGA), and PLGA are the most effective synthetic polymers used for the production of clinical drug delivery systems that are mentioned in Table 1. Natural polymers, by comparison, have higher purity, poorer durability, and need more adjustment and cross-linking before application [8]. Nano-particles based on natural polymer have been generated in several studies which are described in Table 2.

Table 1: Potential Synthetic Nanoparticles for Drug Delivery Applications.

Material	Processing method	Loaded Molecule	Size (nm)	Key findings
PLA ¹	Emulsification solvent evaporation	Aureusidine	231-376	Improving aureusidin's water solubility and light sensitivity
PLGA ²	Double emulsion	Anti-OX40 monoclonal antibody	86	Effective cytotoxic T-lymphocyte responses and tumor antigen-specific cytotoxicity
PCL ³	Solvent displacement	Tamoxifen	250-300	Significant uptake of nanoparticles in the estrogen receptor positive MCF-7 cell line
g-PGA ⁴	Precipitation and dialysis method	Ovalbumin	150-200	Highly negative zeta potential and good biocompatibility of nanoparticles
PVA ⁵	Water-in-oil emulsion technology plus cyclic freezing thawing process	BSA ⁶	675	Prolonged BSA release to 30 h
PBCA ⁷	Anionic polymerization	Moxifloxacin	418	Enhanced encapsulation efficacy, high uptake and retention by macrophages increased drug efficacy against M.tuberculosis residing in macrophages

Silkworms:

Effective polymer-based distribution systems must be biodegradable, bio-compatible, have low toxicity, sufficient mechanical properties, provide requirements for atmospheric processing, and have repeated releases. Silk is a natural polymeric bio-material which can satisfy these criteria owing to its special structural properties, capacity to self-assemble, and mechanical efficiency, durability in the manufacturing, bio-compatibility and biodegradability [9].

Table 2: Potential Natural Nano-particles for Drug Delivery Applications.

Materials	Processing method	Loaded molecule	Size(nm)	Key finding
HSA ¹	Desolvation	Cetuximab	200-250	Targeting colon carcinoma cells
BSA ²	Emulsification dispersion	Tacrolimus	189	Enhanced accumulation in blood rather than other organs e.g kidney
Collagen	Alkaline hydrolysis	17 estradiol-hemihydrate	123	Prolonged estradiol release and absorption
Gelatin	Desolvation	Paclitaxel	600-1000	Rapid drug release, targeting human bladder cancer cells
Protamine	Self-assembly	CpG-oligodeoxynucleotide	215	Suppress T-helper 2 immune response, suitable for immunotherapy of allergy
Casein	Coacervation	Folic acid	150	Folic acid encapsulation, release prevention in an acid environment, enhanced oral bioavailability
Gliadin	Desolvation	All-trans-retinoic acid	500	Good drug loading efficiency, biphasic releasing pattern
Legumin	pH-coacervation	Methylene blue	250	Increased release with decrease in glutaraldehyde/lysine ratio
Elastin	Thermo-responsive self-assembly	BMP ³ -2 and BMP-14	237	High encapsulation efficacy of BMPs with sustained release pattern, maintenance

Several types of silkworms all over the world develop natural silk. Usually the silk substances produced by various silkworms varies in their structure & composition & not all organisms are economically feasible. For e.g., there are eight subspecies of the Bombycoidea genus, & 2 aspects associated with this Saturniidae (non-mulberry) & genus-Bombycidae (Mulberry) are of commercial value. The resource of silk which is frequently obtained from mulberry produced by the Bombycidae group is *Bombyx mori*. The fully selectively bred & require human treatment to replicate & develop which doesn't produce naturally are Mulberry silkworms.

Name of non-mulberry / mulberry-silkworm introduce through patterns of insect-producing silk, which belong to the families of Saturniidae and *Lasiocampidae*. The silkworms which are non-mulberry consist of: shashe silkworms (*Gonometa postica*), tropical (*Antheraea mylitta*), fagaria silkworms (*Attacus atlas*), temperate tasar silkworms, eri silkworms (*Philosamia ricini* / *Samia ricini*), and muga silkworms (*A. assamensis*). These species exist primarily into forests, and were present within form of synthetic-polymer in number of parent-trees across various geographic areas [10].

To create an effective formulation of drug carriers based on nanoparticles, attention must be provided to rate of biodegradation. Several factors influence nano-materials release proportions, such as bonding surfaces & molecules desorption, immersion by metrics of nanoparticles, dissemination of polymer (for Nano-capsules), erosion of the matrix of nanoparticles, and a combination erosion / diffusion method. In particular, synthetic polymers like PGA, PLA, and PLGA, as opposed to natural polymers, generate Acidified substances, as hydrophilic nature whilst also-products & that was theoretically unwanted at target sites.

The susceptibility to enzymatic degradation of natural polymers like collagen, hyaluronic acid and fibrinogen, is often greater as compared with the nano-particles that are synthetic. Whilst, natural polymer, SF is typically subjected to proteolytic degradation which results in non-toxic by-products. Nevertheless, SF has been listed as non-degradable substance by the US Pharmacopeia since it retains 40 percent of its tensile strength 50 days after implant [11].

Many Nano and micro-particulate structures have been used in pharmaceutical and biomedical applications in recent years. These devices are ideal as medication carriers as they are capable of monitoring product release levels and growing the probability of successful clinical outcomes. It's necessary to remember their biodegradability, biocompatibility, scale, drug loading and release while developing polymers associated with delivery of drugs. However, it is difficult to pick the correct forms of biomaterials and to find the best processing methods to prepare the particles.

Silk as a lightweight polymer is generally processed by using a chemical method in a powder form; These are known as working from the ground up. While preparing using this procedure, the macromolecules within β -sheet biopolymers are decomposed by breaking down in various solvents (e.g. oxidizing agents, alkaline compounds, & sulphate adhesives) which contributes to the emergence of silk pellets. Correspondingly, the specimens are normally treated with cosmo-tropic salts like sodium chloride or solvents (usually methan-ol) to induce β -sheet production in order to make the silk particles water insoluble [12]. Another method of handling material of silk is by adopted in hierarchical manner. With specific milling machines, silk fibres are cut for preparation of moderate particles of silk in form of powder mechanically for this process. The main downside to utilizing chemical methods is that of denaturing the surface of protein-silk. Even so, extracting biological catalysts from silk molecules is a lengthy procedure. This downside makes it more desirable to use mechanical methods because it removes the drawbacks found within solutions which are chemically produced & enables procedure of producing the particles of silk.

CONCLUSION

Several types of research have been conducted regarding "Silk fibroin". There has been seen several enhancements related to the drug delivery aspects. Many drawbacks have been discovered regarding the usage of silk fibroin. So, to address this gaps & overcome this drawback the analysis of silk-based nano-particles was conducted, the drug delivery drivers were the main focus in this particular research. The particles of associated with silk fibroin has been examined and enhanced accordingly in order to improve the drug delivery procedures. These nano-particles of silk fibroin have proved to be beneficial to achieve the main goal of this paper.

These systems have other benefits which include prolonged drug half-life, enhanced hydrophobic drug solubility, reduced immunogenicity and reduced intensity of administration. As described earlier, one of the principal benefits of nanoparticles is the prospect of selective drug delivery. The defects in systems may be resolved by utilizing genetically retroviral nanomaterials focused on SF for the distribution of pharmaceutical drugs as substitutes to normal ones. In fact, due to lack of precision and reliability, the drug delivery systems can demonstrate poor therapeutic output and toxic problems. To enhance therapeutic performance, the strategies associated with surface-engineering like genetic-engg. or surface chemical alteration could be created. Nanoparticles focused on silk fibroin has the capacity for broader use with the technology growth.

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