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Sericin-Based Paclitaxel Nanoparticles: Preparation and Physicochemical Evaluation

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Abstract

The aim of this study is the formulation of Paclitaxel (PTX) as self-assembled nanoparticles (NPs) by using silk sericin protein in conjunction with the presence of poloxamer 407 to increase the solubility of practically insoluble PTX. In this study, poloxamer 407 and silk sericin protein were mixed in various proportions in the presence of dimethyl sulfoxide (DMSO) to create nine formulas of self-assembled nanostructures that could transport the hydrophobic anticancer medication paclitaxel (PTX). The produced NPs were then examined to determine their size distribution, percent of entrapment efficiency (EE%), morphology, compatibility and *in vitro* drug release studies. The selected formula was spherical and had a particle size (145 nm), a PDI of (0.25). and EE% of 82. The FT-IR data show that PTX and excipients are compatible, and the *in vitro* data show that PTX releases continuously over a 24-hour period.

Keywords: Paclitaxel, Protein nanoparticles, Sericin, self-assembly

Introduction

Paclitaxel (PTX) is a chemotherapy medicine that has been authorized by the FDA to treat a variety of malignancies, namely colon, breast, ovarian, brain, lung, and AIDS-related tumors [(1)]. Although, its powerful anticancer activity against a wide spectrum of tumors, PTX's limited solubility in water (practically insoluble) offers a significant barrier to its practical usage[(2)]. Taxol® is now manufactured containing Cremophor EL in a 1:1 v/v combination with dehydrated ethanol, a potent solubilizer chemical. Many patients may have nephrotoxicity, neutropenia, bone marrow suppression, as well as liver damage after receiving a PTX injection. Unfortunately, this excipient Cremophor EL has been linked to severe hypersensitivity, bronchospasms, and hypotension [(3)]. As a result, there has been a need to enhance water solubility while avoiding hazardous organic solvents, which have major adverse effects. One method for improving PTX solubility while avoiding the use of harmful chemical solvents is to formulate PTX as NPs comprised of various materials. In light of its biocompatibility, easiness of surface changes, localized activity, and less systemic toxicity, NPs are possibly suitable to be used in the treatment of a number of malignancies [(4)]. Because of their controlled release, stability *in vitro* or *in vivo*, and substantial drug loading capacity, NPs have also attracted a lot of interest in the field of tumor therapy. NPs can increase a drug's stability by preventing it from breaking down quickly once it enters the human body. Additionally, by altering the carrier's structure and function, the release rate and duration of NPs may be changed, extending the drug's duration of action in the body and producing a sustained release effect[(5)].Natural polymers have garnered interest as viable materials for nanocarriers due to their superior biological compatibility, *in vivo* biodegradability, and plentiful renewable supplies [(6)]. A natural protein called sericin is taken out of silkworm cocoons. Its great biological compatibility with tissues and cells, biodegradability, lack of immunogenicity, and variety of bioactivities have made it a popular choice for creating scaffolds for tissue engineering or for delivering drugs using nanocarriers. Sericin is a hydrophilic macromolecular protein with a high degree of chemical reactivity that is attributed to its abundance of polar side chains composed of amino, carboxyl, and hydroxyl groups [(7)]. The current work aims to manufacture protein-based NPs of the anti-cancer medication PTX and assess the *in vitro* and physicochemical aspects of this formulation.

Materials and Methods

Paclitaxel and sericin were procured from Wuhan Senwayer Century Chemical co., China. Dialysis membrane M.wt 100 kd was procured from HiMedia laboratories, Mumbai India.

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Dimethylsulphoxide DMSO and Methanol were procured from BDH Chemicals, Ltd., Liverpool, England. Poloxamer 407 was procured from Sigma-Aldrich, Germany.

Preparation of sericin-based PTX NPs

The NPs were prepared by desolvation method with modification. Desolvation means the addition of hydrophobic solvents (usually acetone, alcohols, or acetonitrile) dropwise to the aqueous protein solution under stirring in order to dehydrate the protein resulting in conformational change from stretched to coil conformation that ended with nanoparticles formation[8]. Sericin and poloxamer 407 were dissolved in 10 mL deionized water by aiding of bath sonicator to obtain clear solutions of different concentrations of the two substances (first mixture). PTX (6 mg) was dissolved in 1mL DMSO until obtaining clear solution (second mixture). Afterward, paclitaxel solutions in DMSO were added drop by drop to deionized water mixture while being stirred at 600 rpm for 20 min with a magnetic stirrer (Vision scientific, Korea) at 25 °C, permitting construction of PTX NPs by self-assembly. Using cellulose dialysis membrane (100 kDa), the resulting NPs suspension has been dialyzed against deionized water (for 72 h, with frequent change of deionized water every 4-6 h). After that the formulations were stored in refrigerator until use [9]. Table 1 showed the composition and variable condition of the prepared formulas.

Table1.Composition of sericin-based PTX NPs

Formula No.	Paclitaxel (mg)	Poloxamer 407 (%)	Sericin (%)	DMSO: Water
F1	6	1.5	1	1:10
F2	6	3	1	1:10
F3	6	4.5	1	1:10
F4	6	1.5	2	1:10
F5	6	3	2	1:10
F6	6	4.5	2	1:10
F7	6	1.5	3	1:10
F8	6	3	3	1:10
F9	6	4.5	3	1:10

Particle size/PDI analysis

The dynamic light scattering (DLS) procedure (Zetasizer, Malvern, UK) was implemented for assessing the size and PDI of sericin-based PTX NPs. One milliliter of each preparation was tested for particle size and (PDI) by means of the Zetasizer Ultra. The quartz cuvettes were employed. All tests were conducted in triplicate [10].

Assessment of entrapment efficiency

One mL of NPs suspension was combined with 9 mL methanol before sonication for 5 min through a bath sonicator to determine the EE% of the generated self-assembled NPs formulations. This takes into account the actual drug content, which was determined spectrophotometrically (Carry win UV, Varian, Australia) through measurement of its UV absorbance at 230 nm after appropriate dilution. Additionally, another (1 mL) of NPs suspension was ultra-centrifuged for 60 min at 20000 rpm, 4 °C using a cooling centrifuge (Eppendorf AG, Germany). The remaining supernatant was thrown away then the remainder was dissolved in 10 mL methanol then sonicated for 5 min in a bath sonicator to determine the amount of entrapped PTX spectrophotometrically [11]. Methanol was used as a solvent and to precipitate protein to avoid UV spectroscopic interaction with PTX measurements [12]. All tests were performed in triplicate.

EE% of PTX was calculated by equation:

$$EE\% = \frac{Amount\ of\ entrapped\ drug}{\text{Actual drug content}} \times 100$$

Determination of saturated solubility of PTX in acetate buffer

The shaking flask technique was used to determine the PTX's saturation solubility. Two acetate buffer pH 5.4 solutions were made, one of which had 0.5% polyethylene glycol lauryl ether (brij-35). To create saturated solutions, an excess PTX was added to 2 mL of each solvent. The mixture was then shaken on a water bath agitator for 72 h at 37 °C with continuous vibrations. After that, those solutions were ultra-centrifuged for 20 min at 10,000 rpm in a suitable 2-mL Eppendorf tube in order to extract the supernatant. The supernatant was filtered using a 0.22 µm filter syringe, diluted appropriately with its medium, and examined using a UV–vis spectrophotometer at the drug's λ max [13]. For every sample, three determinations were made.

In vitro release study

Using the dialysis technique, the *in vitro* drug release performance of PTX from self-assembled sericin-based PTX NPs was

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investigated. In summary, a previously soaked dialysis bag was filled with 1 mL of NPs dispersion, which is equivalent to 0.5 mg of PTX (the molecular weight cut-off was 8.0 to 14 kDa). After being hermetically sealed, the dialysis bag was incubated at 37 ± 0.5°C with moderate shaking (100 rpm) in 75 mL of acetate buffer (pH = 5.4) containing brij-35 (0.5% w/v). 1.5 mL of the media were removed at each scheduled time and replaced with freshly released media that had been pre-warmed to 37 °C. Centrifuging the extracted release material for 15 min at 12,000 rpm was done. The supernatant was collected for the analysis. At a wavelength of 230 nm, UV-vis spectroscopy was used to measure the quantity of PTX released [14].

The release of marketed PTX (Abraxane®) as reference standard and free PTX were performed as follows: 10 mg of lyophilized powder was dissolved in 2 mL deionized water, from this suspension 1mL (equal to 0.5 mg of PTX) was placed in dialysis bag and performed the release same as the colloidal dispersion of NPs. For free PTX, 5 mg was dispersed in 10 mL deionized water, from this suspension 1 mL was taken and placed in the dialysis bag as in method describe for colloidal dispersion NPs and marketed product. The formula used to determine the release rate was RR% = (Wi/W total) × 100%, where Wi is the quantity of PTX measured at the given time and W total is the entire amount of PTX loaded in dialysis bag. A similarity factor (*f*2) was used to statistically verify the data obtained from the two release profiles using equation below:

$$f2 = 50.\log\{100.[1+\frac{1}{n}\sum_{t=1}^{n}(Rt-Tt)^2]^{-0.5}\}$$

Where (n) is the number of dissolution time points. (Rt) and (Tt) are the reference (Abraxane® or free drug) and test (PTX NPs) release values at time t, respectively. The two release profiles are considered similar when *f*2 values are greater than 50 (50–100); otherwise, the profiles are not similar[15].

Fourier transform infrared spectroscopy (FT-IR) study

The drug's compatibility with the excipients was validated by FT-IR. The potassium bromide (KBr) disc method was used to determine the spectra of pure drug, excipients and the optimum formulation. PTX, poloxamer 407, sericin, a 1:1:1 physical combination (PTX: sericin: poloxamer 407), and F3 were all recorded in the spectrum. After combining the samples and KBr and pressing them into a disc shape, the mixture was examined using FTIR spectroscopy at 4000-400 cm^{-1} [16].

Field emission scanning electron microscope (FESEM) study

FESEM was implemented for analyzing the morphology of the recommended liquid formula. FESEM (INSPECT F50, FEI Company, Eindhoven, The Netherlands) was used to examine a little portion of the NPs sample. At different magnification power, the samples were inspected then the obtained data will transform electronically into computer[17].

Statistical analysis

The results in this experiment were expressed as the mean ± (SD). One-way analysis of variance (ANOVA) was used to analyze the difference between the samples at the level of significance ($p<0.05$).

Results and Discussion

Formulation of sericin-based PTX NPs

The solvent/anti-solvent precipitation method was used to create NPs, which will ultimately result in the self-assembly of NPs growing spontaneously. Poloxamer 407 is a copolymer comprising hydrophobic and hydrophilic domains capable of self-assembling to form micellar aggregates in an aqueous solution. The desolvation and dialysis procedures were implemented to generate NPs[18]. Through the desolvation process, the addition of DMSO solution into the aqueous phase encompassing poloxamer 407 and protein sericin triggers the fast miscibility of DMSO with water, and the water in the protein solution becomes substituted with DMSO, where the protein is insoluble. The fundamental micellar architecture in an aqueous medium consists of a polypropylene oxide core that is mostly dehydrated and hydrophobic, encased in a polyethylene oxide/water shell that is hydrophilic[19]. It is more plausible that the hydrophobic interior of the micellar architecture contains the hydrophobic medication "PTX". However, because sericin is hydrophilic, it may exist outside the poloxamer 407 micellar structure's core, within its corona.

Particle size and PDI of sericin-based PTX NPs

It is essential to create NPs with a particle size of less than 200 nm because this will dictate features such as solubility, dissolution, tissue distribution, cellular uptake of cancer cells through the enhanced permeability and retention effect (EPR), and escape from the reticulo-endothelial system[20]. The size distribution of NPs was found to be varied, and their average particle sizes ranged from around 145±3 nm to 567±32 nm, with a PDI of 0.25±0.025-0.93±0.147 as in Table 2. It was found that adding more poloxamer 407 to the formulation resulted in an overall significantly ($p<0.05$) smaller particle size because it lowers the surface tension between the organic and aqueous components and causes tiny solvent droplets to

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form, which also reduces particle size. Like earlier studies, it also prevents particle aggregation and stabilizes newly generated surfaces[21, 22]. On the other hand, the results indicated a substantial ($p<0.05$) increase in particle size with an increase in protein concentration. High protein concentrations cause the polymer solution's viscosity to increase to the point where the resistance of NPs in the external aqueous phase reduces dispersion performance and, as a result, produces larger particle sizes[23]. A similar result was determined by other researcher [24, 25]. The consistency of the produced NPs is impacted by the homogeneity of particle size. Producing NPs with a PDI less than 0.7 which is regarded as an appropriate PDI value is essential [26]. PDI values are classified as follows: 0.05–0.05 are regarded as almost monodisperse, 0.08–0.7 are considered mid-range polydisperse, and more than 0.7 are considered extremely polydisperse[27]. The PDI values illustrate the fluctuation in particle size homogeneity, as seen in Table 2.

From Table 2, it was shown that sericin concentration and PDI are directly correlated. Because sericin is a globular protein that forms tiny linear aggregates at low doses, it has a substantial effect ($p<0.05$) on PDI. However, as they interacted with one another at higher protein concentrations, these little linear aggregates gradually grew into enormous macroaggregates, affecting the uniformity of the particle size distribution[28]. In contrast, there was an inverse association between poloxamer 407 concentration and PDI because it stabilizes NPs by inhibiting coalescence and aggregation, which lowers PDI values. Additionally, because it is a surfactant, it lowers surface tension, which results in a narrow size distribution. The impact was not statistically significant ($p > 0.05$). The researcher came up with the same outcome[29]. Figure 1 shows the particle and distribution sizes of one measurement for F3 with lowest particle size.

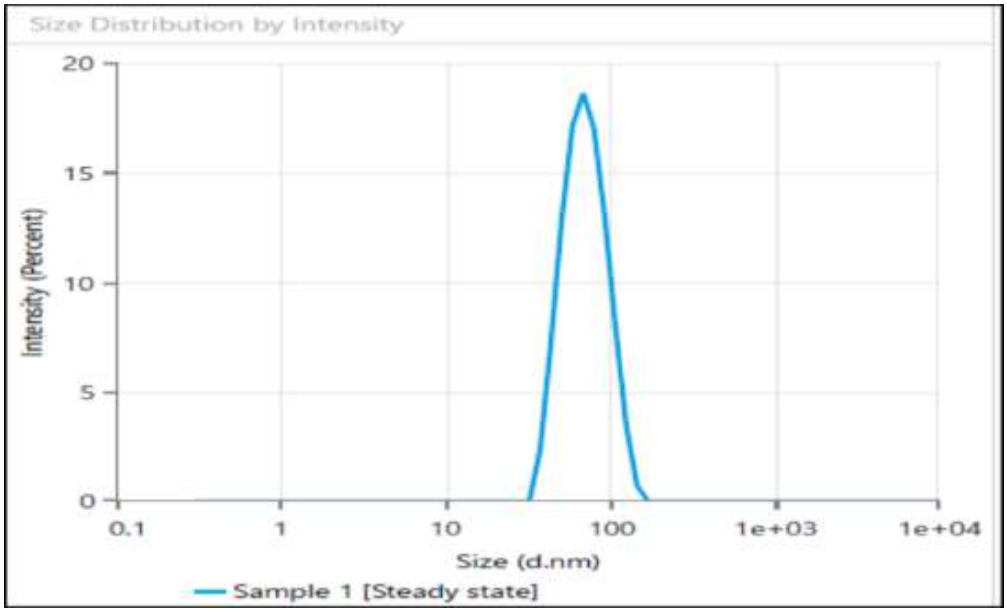

Figure 1. Particle size analysis of formulation F3

Entrapment efficiency analysis

Table 2 displays the EE% of sericin-based PTX NPs, which varied from 46.6±5.13 to 82.8±5.19. From Table 2, it was shown that the concentration of poloxamer 407 and EE% are directly correlated. As the concentration of poloxamer 407 rose, the percentage of EE also increased considerably ($p<0.05$). This is because more poloxamer 407 at a given concentration causes more self-assembled NPs to form, which in turn will trap PTX in their core. The amounts of poloxamer 407 that we employed are greater than its critical micelle concentration, which is 34.2 mg/L at 37 °C [30].

Since PTX is a hydrophobic medication, it may be inserted into the hydrophobic poloxamer 407 core, acting as a "pool" that will boost the drug's solubility, stability, and duration of circulation[31]. Regarding the effect of the concentration of sericin on the EE% of PTX, our theory of the makeup of self-assembled NPs, which is made up of a hydrophilic tail that holds the hydrophilic drug and other carriers and a hydrophobic core that holds the hydrophobic drugs. Since sericin is a hydrophilic protein, it will attach itself to the hydrophilic tail of

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poloxamer 407 and may end up outside the micellar structure's core, inside the corona. Therefore, there is no correlation between concentration of sericin and EE% of PTX loaded in the core of poloxamer 407.

Table 2. Particle size, PDI and EE% of different sericin-based PTX NPs

Formula No.	Particle size (nm)*	(PDI)*	(EE%) *
F1	312±14	0.39±0.076	71.4±3.14
F2	176±11	0.27±0.084	80.5±6.22
F3	145±3	0.25±0.025	82.8±5.19
F4	307±15	0.66±0.172	59.1±4.83
F5	283±12	0.53±0.116	75.7±6.39
F6	266±21	0.41±0.098	79.4±6.07
F7	567±32	0.93±0.147	46.6±5.13
F8	540±27	0.79±0.123	58.3±7.61
F9	494±18	0.70±0.161	65.7±5.47

*(Mean ±SD), n=3

Determination of saturated solubility of PTX in acetate buffer

In order to calculate the volume of release media that would give the sink condition (that is, a saturation solubility which should be at least threefold greater than the drug concentration contained in the dissolving medium as specified by USP), the saturation solubility of PTX was tested[32]. The nonionic surfactant Brij-35 has been utilized in the release medium to create a sink situation[33]. Table 3 showed that the solubility of PTX was considerably greater in the acetate buffer pH 5.4 with 0.5% brij-35 ($P < 0.05$) than in the acetate buffer pH 5.4 without 0.5% brij-35, due to surfactants, such as Brij-35, have the capacity to lower the surface tension, either between liquids or between a liquid and a solid, enhancing the wetting qualities of substances and perhaps increasing the wettability of poorly soluble medications. Surfactants can increase the solubility and dissolution of poorly soluble medications, improving their bioavailability by making them more wettable [34]. In order to exclude any potential interference between PTX and Brij-35 during UV spectroscopy, PTX in an acetate buffer pH 5.4 was scanned independently with and without 0.5% Brij-35. The identical PTX λ max of 230 nm was seen in the UV scan findings for both media. This behavior might be attributed to the absence of a conjugation system in the Brij-35 structure, which would allow it to absorb UV light. Therefore, because they provide a wide range of polarity, do not absorb UV light, and exhibit low sensitivity to ions, non-ionic surfactants like brij-35 can be particularly helpful in analytical separations[35].

Table 3. Saturated solubility of PTX

Acetate buffer pH 5.4	With 0.5% brij-35	(21.63±2.61*) µg/mL
	Without 0.5% brij-35	(8.38±1.06*) µg/mL

(Mean ±SD*), n=3

In vitro release study of sericin-based PTX NPs

Formula 3 was selected as the best formula for the release profile study because it has the lowest PDI, lowest particle size, and the highest EE% compared with the other formulas. Furthermore, this particular formula's release profile was contrasted with marketed (Abraxane®) and free drug as in Figure 2. In contrast to Abraxane®, which only releases 76% of the medication after the same length of time, F3 demonstrated a 68% PTX release after 24 h in acidic solutions that mimicked the tumor microenvironment. Because of PTX's strong affinity toward the hydrophobic interior of the NPs, the formulations under study F3 and Abraxane® showed a delayed and prolonged release of the drug. The drug included in these NPs may release gradually owing to their capacity as drug reservoirs [36].

Furthermore, it was believed that the dialysis release technique had some bearing on the modest release and prolonged release of PTX in both formulations. The dialysis membrane directly may act as a diffusion barrier in this release approach, delaying drug diffusion and maybe even pushing poorly water-soluble medicines to reprecipitate into bigger aggregates [37]. Although, the drug release from Abraxane® as reference standard was higher than observed in F3, both of them had similar release profile (*f2*= 65). The in vitro release profile for free PTX suspension showed only 40% drug release over a period of 24 h. The PTX loaded in NPs showed significantly higher release ($p < 0.05$) than pure PTX suspension. The calculated

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similarity factor (*f2*=36) indicating difference between these profiles.

The elaboration of this result relies on the fact that NPs have a larger surface area compared to the pure drug, which allows for more interactions with the surrounding environment, this in turn enhances PTX solubility and thus facilitates faster release of the drug. PTX is known for its poor solubility, but when encapsulated in NPs, its solubility can be enhanced, leading to more efficient release from the NPs[38]. For this reason, F3 was examined in further detail.

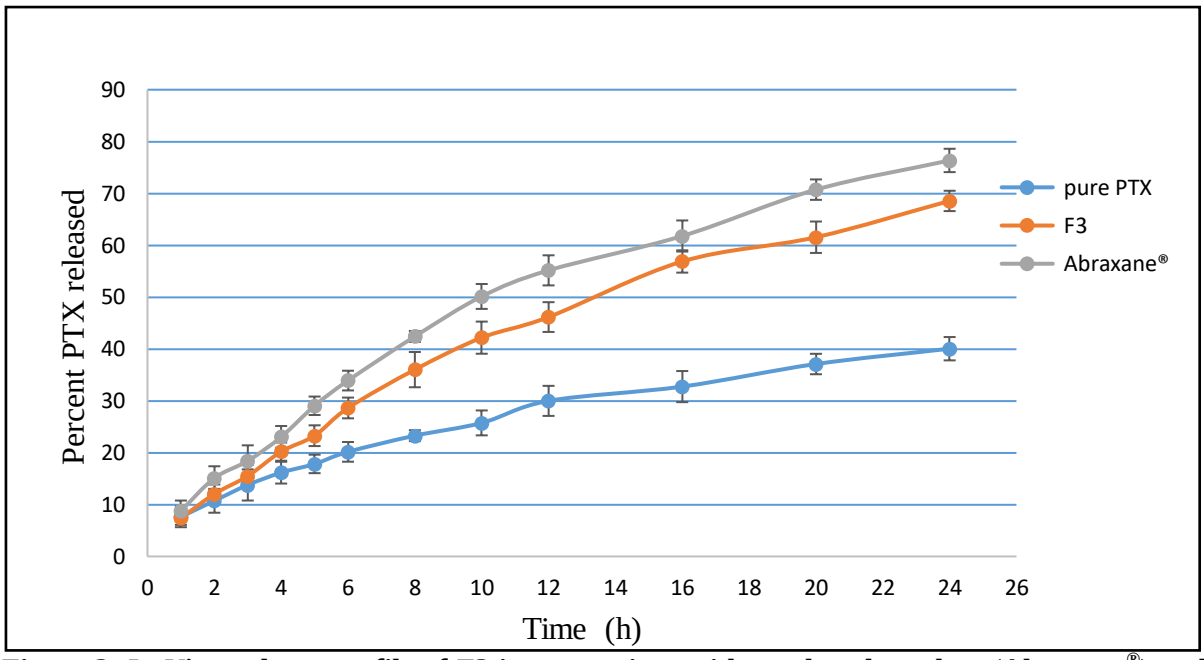

Figure 2. *In Vitro* release profile of F3 in comparison with marketed product (Abraxane®) and Pure PTX in acetate buffer (pH 5.4) at 37°C.

FESEM analysis

The FESEM was utilized to analyze the F3 formulation, and Figure 3 displays the results. Particle sizes detected through DLS (145–567 nm) were larger than those seen by FESEM, which varied between 79 and 92 nm. This is not surprising because DLS measurements provide the hydrodynamic diameter which comprises layers of water enclosing the NPs, leading to greater sizes in solution while FESEM-submitted particles are in the dry form[39]. The data acquired indicated that the NPs had a roughly spherical morphology. The same outcomes from earlier research were attained[40].

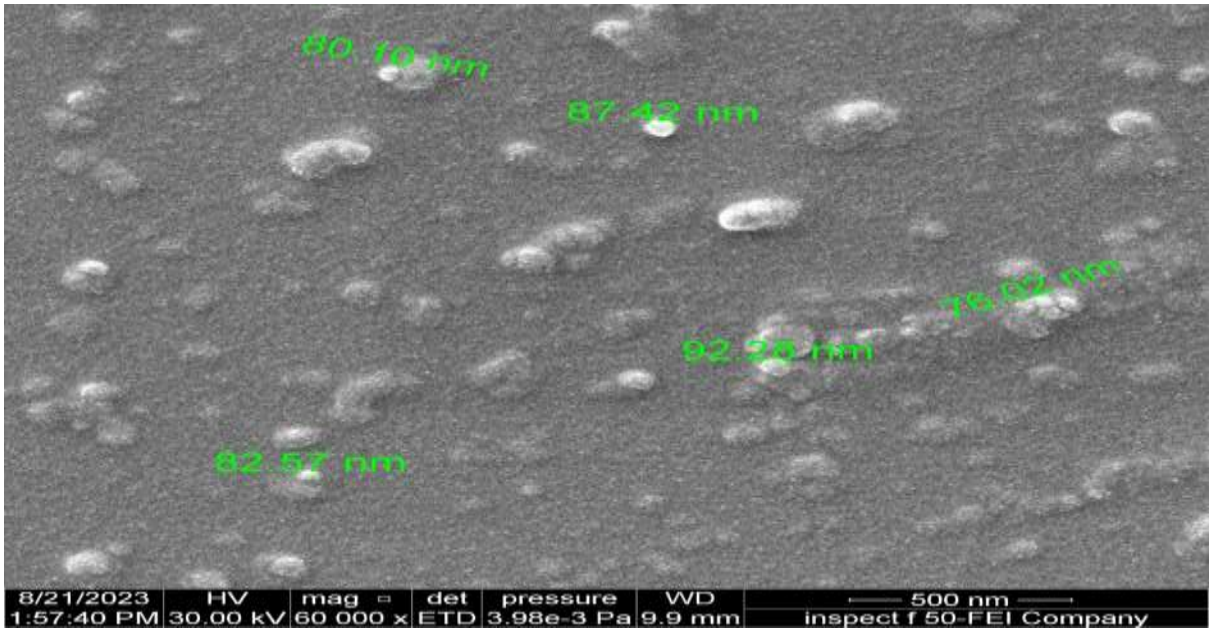

Figure 3. FESEM of formulation F3 NPs (scale 500 nm)

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FT-IR analysis

FT-IR spectroscopy was used to examine the component functional groups and structural alterations that occurred during the creation of NPs. Figure 4 displays the IR spectrum of PTX, poloxamer 407, sericin, and the physical combination of PTX, sericin, and poloxamer 407 (1:1:1), as well as sericin-based PTX NPs (F3).

The characteristic peaks in the FTIR spectrum of pure PTX are found at 3400–3500 cm^{-1} (N-H stretching), 3307 cm^{-1} (O-H stretching), 1734 cm^{-1} (C=O) stretching of ester, 1707 cm^{-1} (C=O) stretching of amide, 1645 cm^{-1} (C-C) stretching, 1242 cm^{-1} (C-N) stretching, 1176 cm^{-1} (NC-O) stretching, and 1072 cm^{-1} (C-O) stretching[41]. The spectrum of poloxamer 407 shows a band at 2881 cm^{-1} (C–H) stretching vibration, a band at 1467 cm^{-1} (C–H) bending vibration and its distinctive band at 1109 cm^{-1} (C-O) stretching[42]. Sericin showed characteristic bands of C=O stretching at 1649 cm^{-1} and N-H bending at 1539 cm^{-1} of amides I and II, respectively, and broadband peaked at 3342 cm^{-1} owing to the stretching of the N-H bond of amides in conjunction with the absorption of the O-H groups[43]. The majority of the distinctive peaks for both the drug and the protein were visible in the physical mix spectrum: PTX: sericin: poloxamer 407 at a ratio of 1:1:1, suggesting that there was no drug-excipient interaction. The absence of all the primary peaks in the FT-IR spectrum of the F3 optimum PTX NPs formulation is caused by PTX becoming entrapped in the self-assembled sericin-based PTX NPs. The following bands, which correspond to the properties of poloxamer 407, were seen in formulation F3: a band at 2883 cm^{-1} from C-H stretching vibration, a band at 1467 cm^{-1} from C-H bending vibration, and a distinctive band at 1112 cm^{-1} from C-O stretching. In addition, while they have moved to higher wavenumbers 1647 and 1535 cm^{-1}, respectively—the distinctive bands of the sericin N-H bond of amides 3362 cm^{-1}, amide I, and II are still discernible, indicating the existence of the protein in the polymer system.

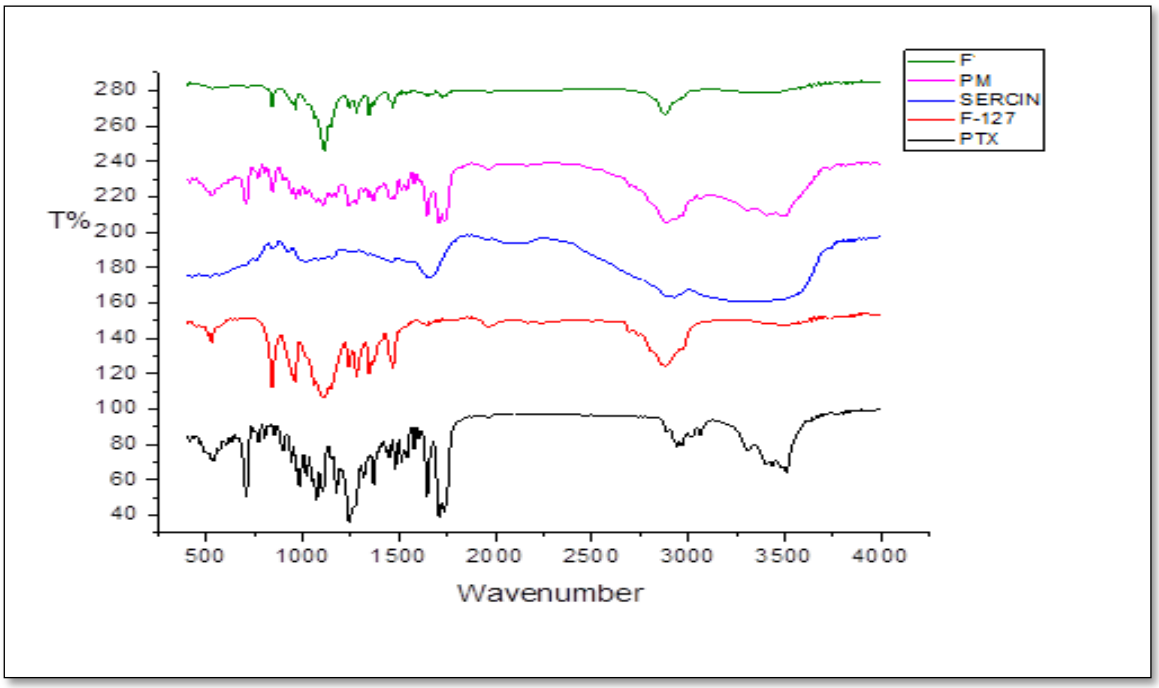

Figure 4. FT-IR absorption spectrum of pure PTX, sericin, poloxamer 407, physical mixture and F3

Conclusion

This work describes the effective synthesis of sericin-based PTX NPs as nanocarriers drug delivery system using the desolvation and dialysis approach. For the production of PTX NPs, DMSO was anticipated to be the ideal desolvating agent. A useful parameter for the produced NPs' particle size, PDI, and EE is the poloxamer 407: sericin ratio. The *in vitro* release profile of commercialized Abraxane® and encapsulated PTX is comparable and lasts for 24 h. The spherical-shaped NPs were visible in the FESEM picture. The medication was fully encapsulated within the NPs, and the FT-IR analysis of the chosen formula demonstrated compatibility between the medicine and other formula excipients. The capacity of encapsulation to delay and regulate the release of PTX may enhance its therapeutic efficacy and create new opportunities for the use of this active ingredient. Additionally, naturally occurring protein silk sericin as a form of NPs may be used as efficient and successful carriers for drugs through biomedical applications involving tissue engineering.

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Conflicts of Interest

The author declares that there are no conflicts of interest regarding the publication of this manuscript.

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Ethics Statements

Neither human subjects nor living animals were used in this study thus no consents were required.

Author Contribution

The authors confirm contribution to the paper as follows: performed data analysis and interpretation of the results and writing: Mustafa Egla. Study conception, design, validation, review and editing: Nawal Ayash Rajab.

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جسيمات الباكليتاكسل النانوية المعتمدة على بروتين السريسين: التحضير والتقييم الفيزيائي والكيميائي

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الخلاصة

الهدف من الدراسة هو تصييغ عقار الباكليتاكسل على شكل هياكل نانوية متجمعة ذاتيا باستخدام بروتين الحرير (السريسين) مع البولاكسامر ٤٠٧ لغرض زيادة ذوبانية الباكليتاكسل. في هذه الدراسة، تم خلط بولوكسامر ٤٠٧ وبروتين الحرير السيريسين بنسب مختلفة بوجود ثنائي ميثيل سلفوكسيد لانشاء تسع اشكال من هياكل نانوية متجمعة ذاتيًا يمكنها نقل دواء مضاد للسرطان كاره للماء مثل باكليتاكسيل. تم فحص الجسيمات النانوية المنتجة لتحديد توزيع حجمها، ونسبة كفاءة حصر للدواء وشكلها، وتوافق المواد مع بعضها وتحرر الدواء في المختبر. كانت الجسيمات النانوية الكروية الناتجة لها مجموعة من أحجام الجسيمات (١٤٥نانوميتر)، و PDI (٠,٢٥)، ونسبة كفاءة حصر للدواء (٨٢) . وتظهر البيانات في مطياف الاشعة تحت الحمراء أن عقار باكليتاكسيل والمضافات متوافقة مع بعضها، ايضا أن عقار باكليتاكسيل يتم تحرره في المختبر بشكل مستمر على مدى ٢٤ ساعة.

الكلمات المفتاحية: باكليتاكسل، الجسيمات النانوية البروتينية، بروتين الحرير، التجمع الذاتي.