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Gellan Gum Immobilized Anticancer Drugs and Gold Nanoparticles in Nanomedicine

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Abstract

This review is devoted to recent progress in the design of anticancer drug delivery systems with participation of unique polysaccharide gellan gum. At first a brief literature survey on conformational and phase behavior of gellan gum as a function of external stimuli, such as temperature, pH, salt addition etc. is presented. Then the immobilization protocol of anticancer drugs and gold nanoparticles within gellan-based hydrogel matrix is discussed. Release of anticancer drugs from gellan gel matrix to outer solution is considered. Cytotoxicity of gellan gum-immobilized gold nanoparticles together with their anticancer activity is summarized.

Keywords: Gellan gum; Coil-helix transition; Hydrogel; Anticancer drugs; Gold nanoparticles; Cytotoxicity; Anticancer activity

Abbreviations: GG: Gellan Gum; EOR: Enhanced Oil Recovery; AgNPs: Silver Nanoparticles; AuNPs: Gold Nanoparticles, AuNR: Gold Nanorods, DDS: Drug Delivery System; PCT: Paclitaxel; Ge-Pred NHs: Gellan-Prednisolone Nanohydrogel; PCT Ge-Pred NHs: Gellan-Prednisolone-Paclitaxel Nanohydrogel; GG-AuNPs: AuNPs Covered by Gellan Gum; GG-AgNPs: AgNPs Covered by Gellan Gum; DOX: Doxorubicin Hydrochloride; SL: Sophorolipid; NIR: Near-IR; PPTT: Plasmonic Photothermal Therapy; CTAB: Cetyltrimethylammonium Bromide; LBL: Layer-By-Layer; SaOS-2: Sarcoma Osteogenic; PVCL: Poly(vinylcaprolactame); TNBC: Triple Negative Breast Cancer

Introduction

Over the past few decades, microbial polysaccharides have been under intense investigation due to their advantageous physicochemical properties. Currently, one of the most widely studied and comprehensively described member of this group is gellan a linear polymer produced by Sphingomonas elodea consisting of a tetrasaccharide repeating unit of 1,3-linked β-D-glucose, 1,4-linked β-D-glucoronic acid, 1,4-linked β-D-glucose, and 1,4-linked α-L-rhamnose [1] (Figure 1). Fermentative production and manufacturing of gellan on industrial scale is described in reviews [2,3].

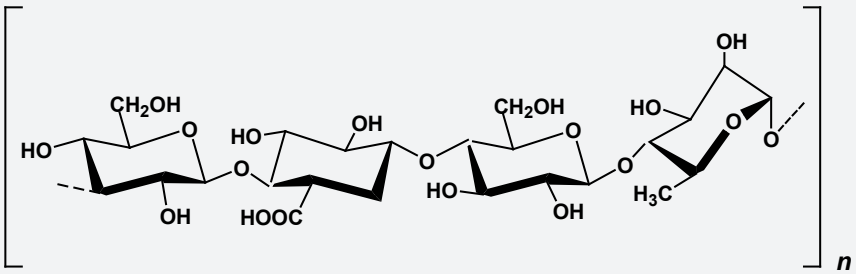

Figure 1: Structure of the repeating monomer unit of gellan.

So far most of the studies have been focused on the application of gellan as a food ingredient. Last year's however, the applicability of gellan gum in EOR was demonstrated [4-12]. Due to the unique structure and beneficial properties, gellan is currently described as a potent multifunctional additive for various pharmaceutical products. Specific gelling properties in different media led to the development of controlled release forms based on gellan. Various formulations have been studied

including oral, ophthalmic, nasal and other [13,14]. Recent report [13] suggests that gellan-based materials can also be used in regenerative medicine, stomatology or gene transfer technology. Gellan gum-based hydrogels exhibit excellent *in vivo* and *in vitro* biocompatibility [15], tunable physical mechanical and injectable properties [16-18] for application in regeneration of cartilage [16,17], tissue engineering [19], cell encapsulation [20], nucleus pulposes regeneration [21]. Recent progress in the design of multi-functional hydrogels with participation of gellan gum in the context of biomedical engineering and regenerative medicine is discussed and summarized in recent review [22]. In spite of a wide application of gellan in medicine, pharmacy and biotechnology it is noteworthy that the gellan based anticancer formulations have not been described.

Conformational and phase behavior of gellan gum in response to external stimuli

Table 1 represents the chemical and physical properties of gellan. The native gellan is composed of high acyl and low acyl precursors [23]. The main difference between them is that the high acyl gellan contains two acyl substituents: acetyl and L-glyceril [24]. Low acyl gellan is obtained by removal of the acyl residues by alkaline hydrolysis [25]. Differences between high- and low acyl gellan are summarized in Table 2 [26]. Authors [1,27] comprehensively reviewed the structure, conformation, gelation, topology, rheology, and application aspects of gellan. The coil-helix conformational and sol-gel phase transitions of gellan gums induced by temperature, salt addition, pH change etc. became the main subject of many studies [28-33]. A series of publications cover formation of interpenetrating networks with participation of gellan and natural polymers [34-42]. It is commonly accepted [43-51] that gellan gum exhibits a conformational change from the disordered state (single chain) to the ordered state (double helix) with decreasing of temperature, and the gelation is considered to be mediated by the double-helix formation and the association of such helices, which is enhanced by the presence of mono- and divalent alkaline and alkaline earth cations [52-55] (Figure 2).

Table 1: Chemical and physical properties of gellan.

Property	Description
Appearance	off-white powder
Types	native, deacetylated, clarified (i.e., filtered deacetylated gum)
Molecular weight	varies within a very wide range ~500,000 >70,000, with 95% above 500,000
Solubility	soluble in hot or cold deionized water soluble in water; insoluble in ethanol
Viscosity	can exhibit high viscosity in solution high-acyl gellan gum is viscous; deacylated gellan gum (treated with an alkali) has relatively low solution viscosity cold dispersions of native gellan gum provide extremely high viscosities, and the solutions are highly thiotropic; the viscosity decreases with heating as the gum hydrates; hot native gum solutions are more viscous than deacylated gellan gum solutions
Gelling property	forms a weak gel in water in its native state, but forms a rigid gel after treatment with an alkali
Ionic nature	anionic
Hydration	native (acylated) gellan gum will swell in deionized water forming a very thick particulate system, and the hydration temperature is reached at ~70°C; the swelling behavior and hydration temperature is altered in the presence of ions deacylated gum will only partially hydrate in cold deionized water, with hydration occurring with a heated deionized water temperature of ~70°C; also, hydration is poor in mildly acidic conditions and in the presence of divalent ions

Table 2: Comparison of the properties of high- and low acyl gellan.

Type of Gellan	Molecular Weight	Solubility	Set Temperature	Thermostability
High acyl gellan	(1-2) ×106 Daltons	Hot water	Hot or cold water	Thermosensitive
Low acyl gellan	(2-3) ×105 Daltons	70-80°C	30-50°C	Heat stable

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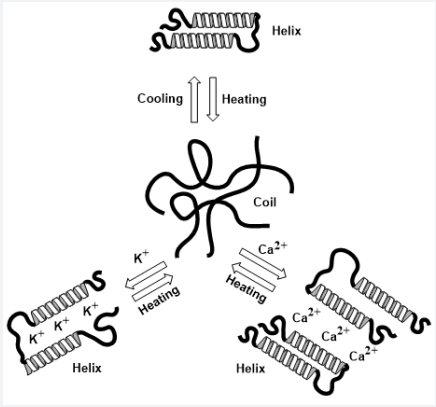

Figure 2: Schematic representation of transformation of gellan gum in aqueous solution from the coil to helix conformation as a function of temperature and salt addition.

As gellan molecules contain the carboxyl groups in the repeating unit, the gelation of gellan is remarkably enhanced by the addition of cations in aqueous solutions. It has been established that the extent of aggregation and effectiveness in promoting gel formation by addition of ions follows this order: Cs^+> Rb^+> K^+>Na^+> Li^+. This sequence follows the Hofmeister series and agrees well with increasing of the ionic radius of cation species. The higher effectiveness of divalent cations in comparison with monovalent ones may be attributed to additional crosslinking of gellan chains due to cooperative binding (or "bridging") of the divalent cations between glucuronate residues according to their ionic radii. Divalent cations seem to bind directly to gellan macromolecules to form aggregates of gellan helices with the effectiveness of Ca^{2+}>Mg^{2+} [56-60]. The main difference between the monovalent and divalent cations is that the monovalent cations shield the electrostatic repulsion between the COO- while the divalent cations, rather than by suppressing electrostatic repulsion, form interchain ionic bonds with carboxylic groups of the glucuronic acid units resulting in the aggregation of the double helices [55,56]. As for the divalent cations, they do not appear to obey the Hofmeister series and the order among the divalent cations is more difficult to rationalize. Gellan salts with the monovalent cation, such as lithium or potassium, form stiff gels and that with divalent cation, Ca^{2+}, make a more rigid gel. The mechanism for conformational change of gellan in the presence of mono- and divalent cations can be represented as shown in Figure 2 [61]. K^+ accelerates the formation of cooperative hydrogen bonds between gellan molecules by the charge-shielding effect and hydrogen bonds reinforces the double-helices and their aggregates. Ca^{2+} forms ionic bonds between carboxylic groups of gellan in addition to hydrogen bonds and leads to the continuous structural change depending on concentration of the divalent cations.

Immobilization of anticancer drugs within gellan hydrogel matrix

Recently authors [62,63] developed gellan-based nanohydrogel systems to deliver multiple drugs: prednisolone and paclitaxel. Prednisolone was chemically linked to the carboxylic groups of gellan while placitaxel was physically entrapped into gel marix. The synergistic anti-inflammatory and anti-cancer effect were reached with respect to malignant cells and tumor inflammatory components.

The kinetics of prednisolone release from gellan hydrogel was measured with respect to NIH/3T3 cells. Figure 3 shows the intracellular release kinetics of gellan-immobilized prednisolone from the gel matrix. It is seen that 40% of total prednisolone is delivered during 30min, 70% after 1h and 100% drug delivery after 24h. It is suggested that the release of prednisolone from gellan-based nanohydrogel is hydrolysis of ester bonds between prednisolone and gellan gum by esterase. Immobilized within gellan nanohydrogel prednisolone exhibits a core-shell structure and allows solubilizing up to 40% water-insoluble drug paclitaxel in hydrophobic environment. The main role of paclitaxel is disrupting of the dynamic equilibrium within the microtubule system and inhibiting the cell replication. The cell-killing drug formulation consisted of gellan-immobilized prednisolone with loaded paclitaxel. The latter released from gellan-prednisolone nanohydrogel kills the cancer cells with higher efficiency (56.1 ± 0.8% cell viability) than free drug (91.6 ± 3.5 cell viability) especially at lower concentration (3nM) (Figure 4).

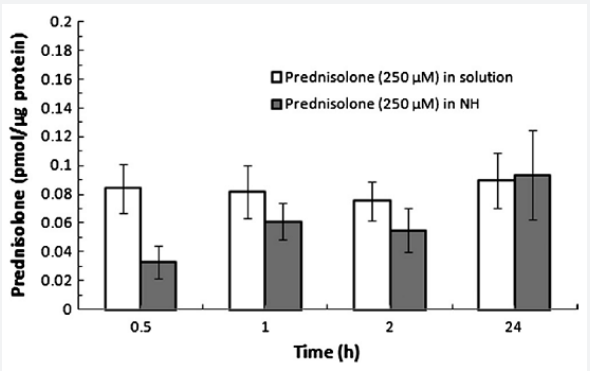

Figure 3: Time-dependent release profile of intracellular prednisolone in NIH/3T3 cells in aqueous solution and in nanohydrogel [62].

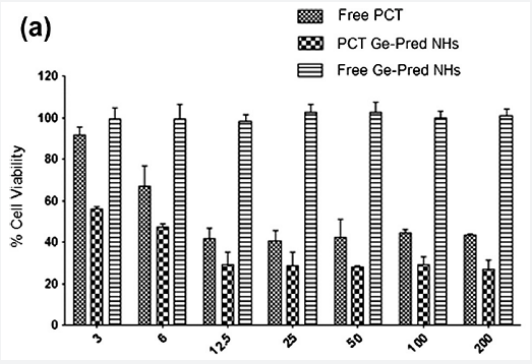

Figure 4: *In vitro* viability of PC-3 cancer cells after incubation with free paclitaxel (free PCT), gellan-prednisolone nanohydrogel (Free Ge-Pred NHs) and gellan-prednisolone-paclitaxel nanohydrogel (PCT Ge-Pred NHs) during 72h [62].

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The cell killing effect of gellan-prednisolone-paclitaxel nanohydrogel was also tested with respect to A2780, MDA-MB-231 and Skov-3 cells. Thus gellan-immobilized anti-inflammatory and anti-cancer drugs can be effective for treatment of malignant and inflammatory cells involved into tumor microenvironment. Analgesic, antipyretic and anti-flammatory drug-diclofenac sodium was immobilized into the matrix of polymethacrylamide-grafted-gellan gum and its sustained *in vitro* release kinetics was studied [64]. It was shown that the diclofenac sodium releases over a period of 8 h and the release profile is described by Higuchi square root kinetic model and release mechanism is governed by Fickian diffusion.

Gellan gum immobilized gold nanoparticles for treatment of cancer cells

It is well known that cancer is one of the leading causes of mortality in the modern world, with more than 10 million new cases every year. Targeting nanoparticles that selectively recognize and destroy cancer cells in the body remain key concept in nanomedicine [65-67]. According to literature survey of authors [68] only 7 out of 1000 administered nanoparticles are applicable in a mouse model limiting their clinical translation. Authors [69] concisely highlighted the current state and recent advances of stimuli-responsive polymers commonly employed in oncology applications.

Gold nanoparticles (AuNPs) with controlled geometrical, optical, and surface-chemical properties are the priority research of intensive studies and applications in cancer diagnosis, treatment and as drug delivery system (DDS) [70]. The effectiveness of many anticancer drugs is limited due to the inability to reach the target site in sufficient concentrations and efficiently exert the pharmacological effect without causing irreversible unwanted injury to healthy tissues and cells. The cellular uptake and toxicity of AuNPs stabilized by gellan gum (GG-AuNPs) was studied on mouse embryonic fibroblast cells, NIH 3T3 and human glioma cell line LN-229 [71]. It was shown that in the cancerous cells the GG-AuNPs were localized mainly in the cytoplasm and perinuclear region of the cells. Oral administration of GG-AuNPs did not cause any toxicity in rats for 28 days and was no any significant difference in hematological, biochemical and histopathology of organs demonstrating potential of GG-AuNPS as DDS.

The AuNPs stabilized by gellan gum was loaded by doxorubicin hydrochloride (DOX) one of the potential and well-known anticancer drugs [72] was conjugated with sophorolipid (SL) [73] and their cytotoxicity were evaluated with respect to human glioma cell line LN 229 and human glioma stem cell line HNGC-2 (Figures 5 & 6).

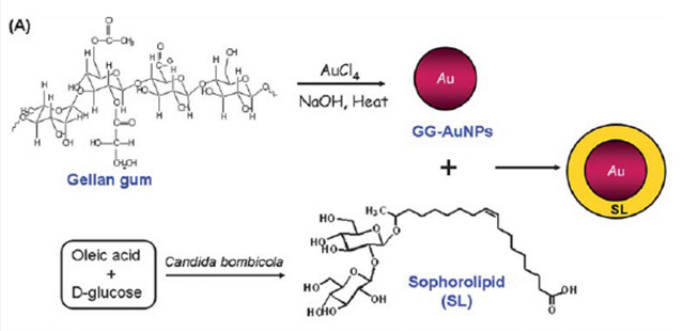

Figure 5: Synthesis of gellan gum reduced and stabilized AuNPs (GG-AuNPs) and sophorolipid-conjugated GG-AuNPs [72].

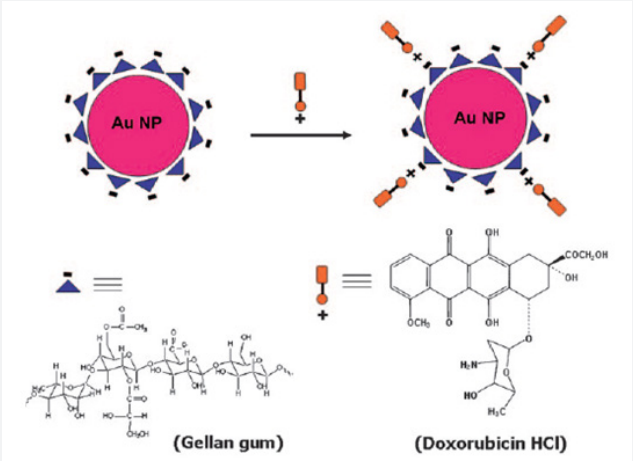

Figure 6: Stabilization of AuNPs by gellan gum and subsequent loading of GG-AuNPs by doxorubicin [71].

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Both SL-conjugated and DOX-loaded gellan gum containing AuNPs exhibited increased effectiveness against glioma tumors. The same authors [74] studied the antibacterial activity of the dispersions of silver nanoparticles (AgNPs) stabilized by gellan gum (GG-AgNPs), the cytotoxicity of GG-AgNPs against mouse embryonic fibroplast cells NIH 3T3 and also evaluated the *in vitro* diffusion of AgNPs dispersions/gels across rat skin. The results show that GG capping effectively passivates the AgNPs and does not display any cytotoxicity against NIH 3T3 and exhibits eligibility for topical treatments.

Photothermal damage of cells is currently one of the most promising research avenues in the treatment of cancer and infectious diseases. The essence of this phenomenon is as follows: AuNPs have an absorption maximum in the visible or near-IR (NIR) region and get very hot when irradiated with corresponding light. If, they are located inside or around the target cells (which can be achieved by conjugating gold nanoparticles to antibodies or other molecules), these cells die. The revolution in thermal cancer therapy is associated with 20-40nm AuNPs that convert the 20ns laser irradiation (514nm) to local heat (up to 40-45°C), and selectively kill the cancer cells (Figure 7). This method called plasmonic photothermal therapy (PPTT) [75] has extensively been researched and used for biomedical application [76]. The PPTT has much potential in diagnosis, treatment and evolution of diseases, in particular cancer [77]. In recent review [78] the advancements of plasmonic nanoparticles and films in the field of biomedicine was overviewed.

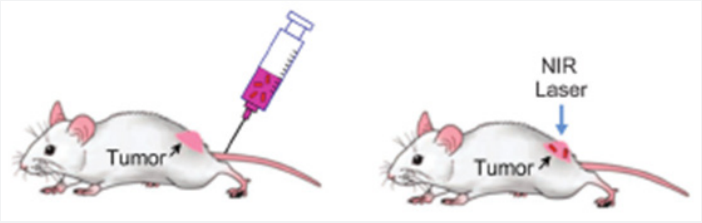

Figure 7: Schematically representation of tumor treatment by NIR laser irradiation.

Among the numerous nanomaterials the best one is gold nanoparticles (AuNPs) because of their biocompatibility, low toxicity, ability to absorb in visible or NIR region, excellent photostability, and availability in various morphologies [79]. Among the gold nanoparticles the gold nanoshells [80] and nanorods (AuNRs) [81] are especially suitable for PPTT due to their tunable longitudinal plasmon band in the NIR region [82].

Small spherical AuNPs exhibit poor NIR absorption, therefore nanoaggregates, nanoshells, nanorods and nanomatryoshkas stabilized by functional polymers are suitable for PPTT [78]. Gellan gum coated gold nanorods (GG-AuNRs) was fabricated by authors [83] and used for intracellular drug delivery and imaging. The preparation strategy of AuNRs includes several steps: at first the fine dispersed AuNRs is synthesized by a seed-mediated growth method using cationic surfactant - cetyltrimethylammonium bromide (CTAB) as surface passivant [84], then the layer-by-layer (LBL) technique is used for coating, and finally AuNRs are coated by gellan gum (Figure 8).

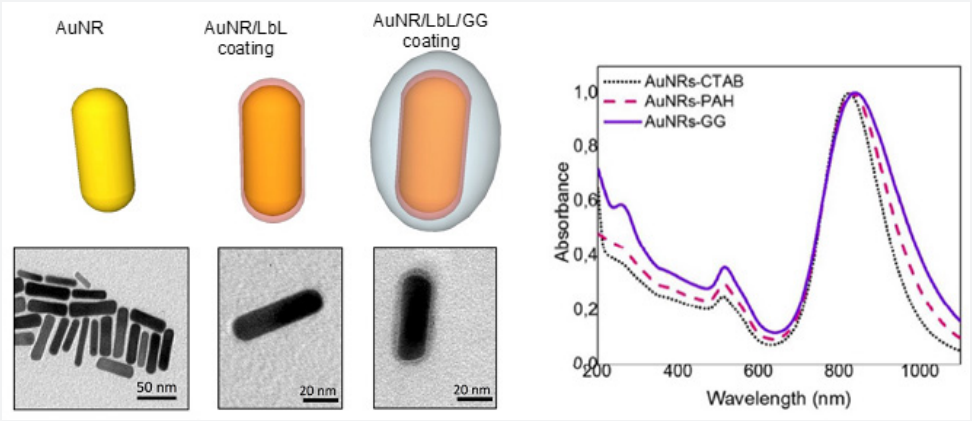

Figure 8: Covering and TEM images of AuNRs by layer-by-layer coatings (AuNRs/LbL) and coating by gellan gum of AuNRs/LbL (left) and visible spectra of AuNRs-CTAB, AuNRs-CTAB-LbL, AuNRs-GG (right) [84].

The direct use of as-prepared AuNRs with biological materials is highly limited because the cytotoxicity of CTAB is high and can lead to cell death. The successive deposition of poly (acrylic acid), poly (allylamine hydrochloride) and GG allows the

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formation of GG shell with nanometric size around individual AuNRs. The cytotoxicity and osteogenic ability of gellan-coated AuNRs was tested with respect to SaOS-2 (Sarcoma osteogenic), a human osteoblast-like cell line commonly used as osteoblastic model [85]. It was found that AuNR-GG were not cytotoxic after 14 days of culturing and were localized inside lysosomes. The images in Figure 9 show that AuNRs-GG is aggregated within multilammelar vesicles identificed as lysosomes.

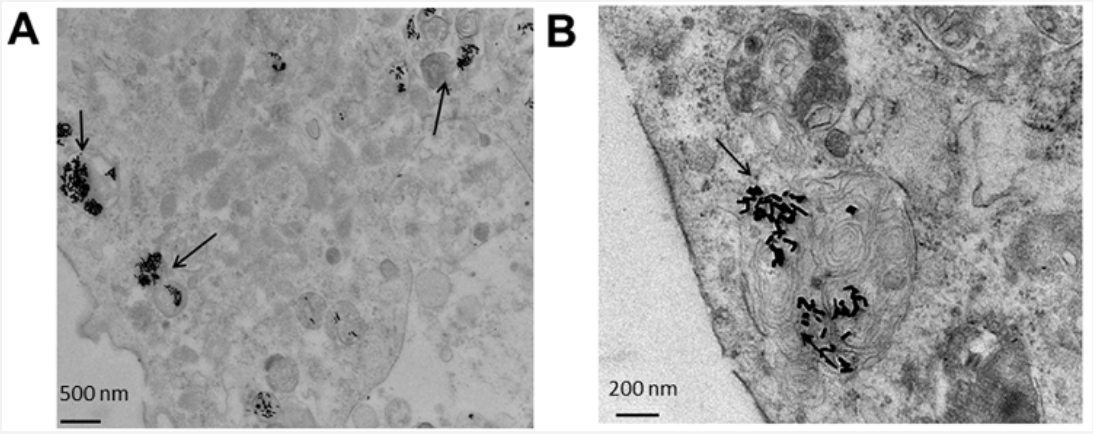

Figure 9: TEM images of SaOS-2 cytoplasm after 14 days of culture with AuNRs-GG. Black arrows point AuNRs-GG clusters [83].

NIR lasers are selected due to higher penetration of human tissue resulting in minimal damage. *In vitro* experiments show that heating of tumor tissues is observed in the presence of NIR-exposed AuNRs, however laser irradiation in the absence of AuNRs causes negligible damage of healthy tissues [78]. Without coating by biocompatible polymers, AuNRs cannot infiltrate the blood vessels and therefore their concentration increases in plasma. *In vivo* tumor ablation requires a tissue temperature of around 48-50°C for successful operation.

Magnetic nanoparticles coated by GG exhibited low cytotoxicity with potential drug delivery applications [86]. Apart from gellan both natural and synthetic polymers can be used for stabilization and coating of AuNRs. Absorption spectra of polymer-coated AuNRs are in NIR region and equal to 770nm (Figure 10a). According to TEM measurements the average size of AuNRs covered by poly(vinylcaprolactame) (PVCL) is < 100nm (Figure 10b).

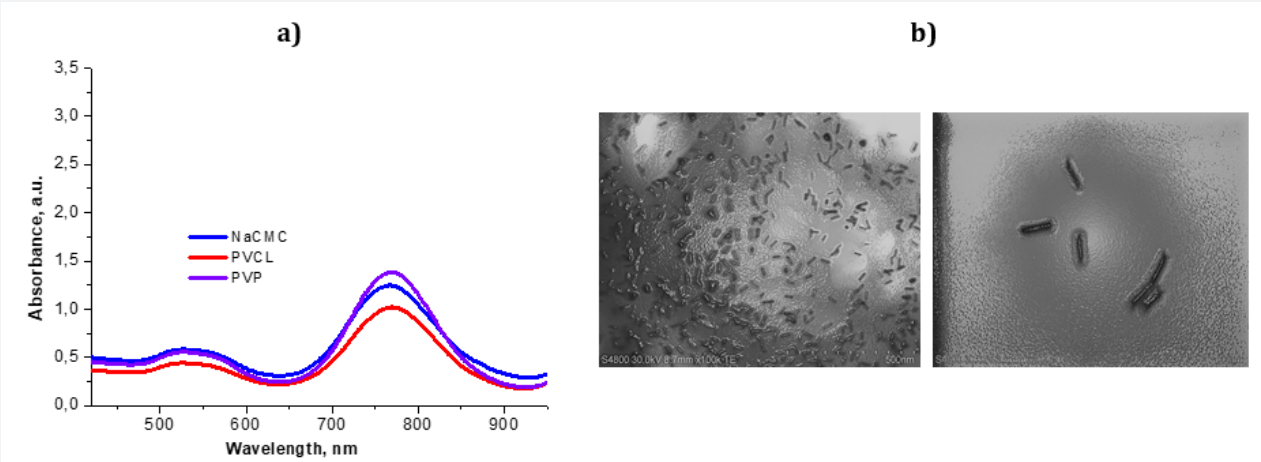

Figure 10: a) UV-Visible spectra of AuNRs stabilized by sodium salt of carboxymethylcellulose (NaCMC), poly(vinylcaprolactame) (PVCL), poly(N-vinylpyrrolidone) (PVP); b) TEM images AuNRs stabilized by PVCL.

Multilayered Au nanoparticles ($Au/SiO_2/Au$ ~ 90nm) called as nano-matryoshkas ("matryoshka" is Russian nesting doll) was tested against triple negative breast cancer (TNBC) tumors [87]. *In vivo* injection of Au nanomatryoshkas and NIR treatment ($2W.cm^{-2}$ for 5min) of TNBC tumor-bearing mice show health improvement and complete recovery for two months (Figure 11a). In contrast, NIR treatment of TNBC in saline water without Au nano-matryoshkas considerably increases the size of tumor for 18 days (Figure 11b).

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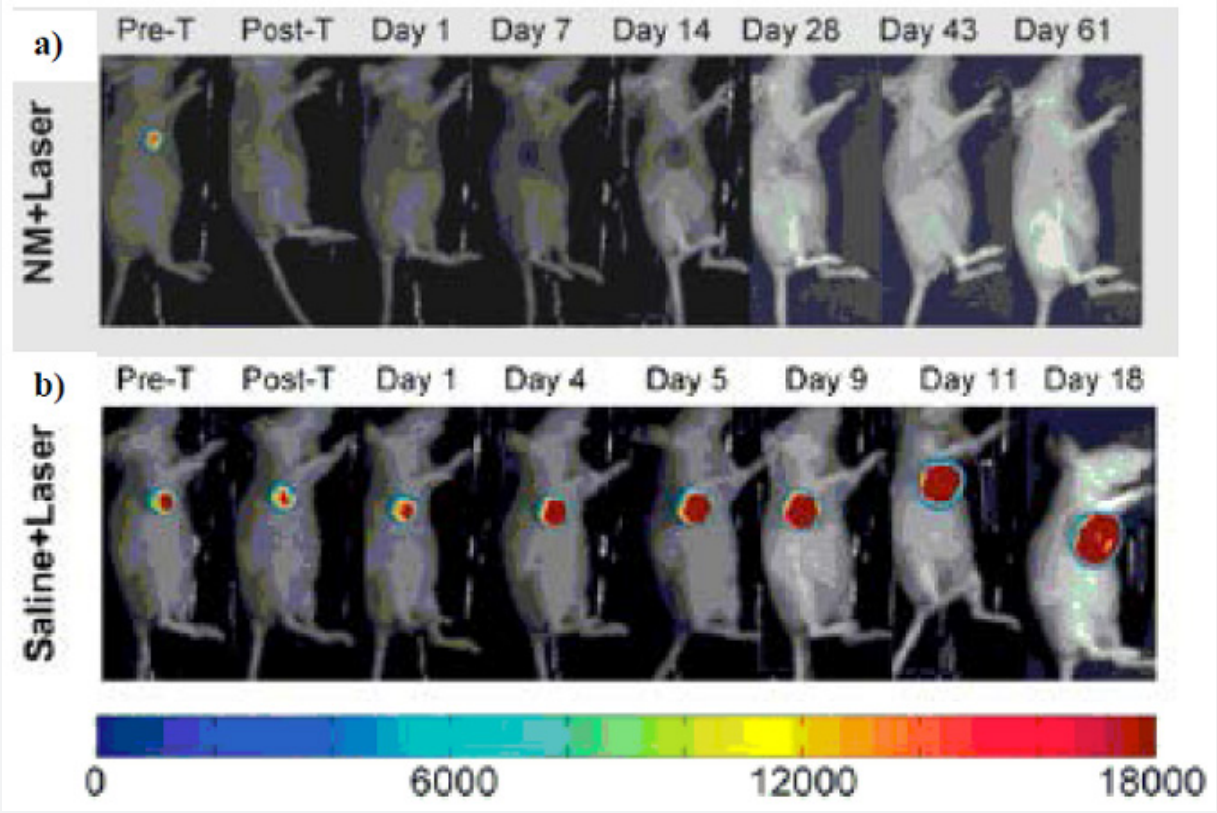

Figure 11: Evaluation of tumor response to photothermal therapy by bioluminescence imaging. The bioluminescence signal is generated only in living cancer cells as a result of luciferase activity [87].

The Au-based nanomaterials have failed in clinical trials as PPTT agents. The further development of PPTT and its acceptance in actual clinical practice depends on success in solving many problems, the most important ones being

a) The choice of nanoparticles with optimal optical properties,

b) The enhancement of nanoparticle accumulation in tumors and the lowering of total potential toxicity, and

c) The development of methods for the delivery of optical radiation to the targets and the search for alternative radiation sources combining high permeability with a possibility of heating AuNPs.

The selection criteria of PPTT depend on

a) The ability of gold nanoparticles to absorb in the near-IR region;

b) Size of nanoparticles (usually less than 100nm);

c) Low toxicity (in terms of excluding or replacement of toxic CTAB);

d) Good biocompatibility and easy biodegradability of polymeric coatings used for entrapment of gold nanoparticles. Moreover, the aggregated AuNPs should be disintegrated and removed from the organs and not cause tissue damage or metal toxicity.

It is expected that in near future the priority research will be focused on probing the fundamental interactions of nanoparticles with organs and tissues that accumulate, sequester or eliminate nanoparticles (such as liver, spleen and kidney), as well as the interactions between nanoparticles and tumors with respect to the physico-chemical properties of the nanoparticles.

Conclusion

The unique properties of gellan gum, in particular, biocompatibility, low toxicity, biodegradability, commercial availability and low cost argue the successful application of this class of polysaccharide in biomedicine, pharmacy and bio- and nanotechnology. The ability of gellan to undergo coil-helix conformational, sol-gel phase transitions, and stimuli-sensitive character of macromolecules to response temperature, pH, salt addition, addition of organic ions and molecules open new perspectives to design drug delivery systems. Anticancer drugs and gold nanoparticles immobilized within gellan gel matrix is effective for treatment of cancer cells. It is expected that in near future the priority research will be focused on probing the fundamental interactions of nanoparticles with organs and tissues that accumulate, sequester or eliminate nanoparticles

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(such as liver, spleen and kidney), as well as the interactions between nanoparticles and tumors with respect to the physico-chemical properties of the nanoparticles. For the successful application of nanoparticles there should be a coordinated research program to establish correlations between the particle parameters (size, shape, and functionalization with various molecular probes), the experimental parameters (model; doses; method and time schedule of administration; observation time; organs, cells and subcellular structures examined; etc.), and the observed biological effects.

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