



Application of nanogels in reduction of drug resistance in cancer chemotherapy

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ABSTRACT

Different mechanisms in cancer cells become resistant to one or more chemotherapeutics is known as multidrug resistance (MDR) which hinders chemotherapy efficacy. Potential factors for MDR includes enhanced drug detoxification, decreased drug uptake, increased intracellular nucleophiles levels, enhanced repair of drug induced DNA damage, over expression of drug transporter such as P-glycoprotein(P-gp), multidrug resistance-associated proteins (MRP1,MRP2), and breast cancer resistance protein (BCRP). New chemotherapeutic drug delivery systems have been developed to combat drug resistance and multidrug resistance. Nanogel are being used to deliver drugs more effectively in cancer chemotherapy. These novel applications and techniques include: Nanogels for loading siRNA. This is a small interfering RNA (siRNA) is a class of double-stranded RNA molecules consisting of 21–23 nucleotides, involved in inhibition of protein synthesis encoded by the messenger RNAs. Nanogels are used as carriers to deliver siRNA. Another technique and application is hyaluronic acid-based nanogel-drug conjugates with enhanced anticancer activity designed for targeting of cd44-positive and drug-resistant tumors. In this technique small nanogel particles with a hydrophobic core and high drug loads formed after ultra-sonication and demonstrated a sustained drug release following the hydrolysis of biodegradable ester linkage. Other techniques and applications which will be discussed in this review article include; Novel anticancer polymeric conjugates of activated nucleoside analogs, Nanogel formulations with phosphorylated nucleoside analogs and Crosslinked Polymeric Nanogel Formulations of 5'-Triphosphates of Nucleoside analogs.

Key words: Applications of nanogel; Drug resistance cancer chemotherapy; Nanogel in cancer chemotherapy.

INTRODUCTION

The term 'nanogels' defined as the nanosized particles formed by physically or chemically crosslinked polymer networks that swell in a good solvent. The term "nanogel" (NanoGel™) was first introduced to define cross-linked bi-functional networks of a polyion and a nonionic polymer for delivery of polynucleotides (cross-linked polyethyleneimine (PEI) and poly (ethylene glycol) (PEG) or PEG-cl-PEI). Sudden outbreak in the field of nanotechnology have introduced the need for developing nanogel systems which proven their potential to deliver drugs in controlled, sustained and targetable manner. [1]

The management of cancer involves procedures, which include surgery, radiotherapy and chemotherapy. Development of chemo-resistance is a persistent problem during the treatment of local and disseminated disease. A plethora of cytotoxic drugs that selectively, but not exclusively, target actively proliferating cells include such diverse groups as DNA alkylating agents, antimetabolites, intercalating agents and mitotic inhibitors. Resistance constitutes a lack of response to drug-induced tumor growth inhibition; it may be inherent in a subpopulation of heterogeneous cancer cells or be acquired as a cellular response to drug exposure. Principal mechanisms may include altered membrane transport involving the P-glycoprotein product of the multidrug resistance (MDR) gene as well as other associated proteins, altered target enzyme (e.g. mutated topoisomerase II), decreased drug activation,

increased drug degradation due to altered expression of drug metabolizing enzymes, drug inactivation due to conjugation with increased glutathione, subcellular redistribution, drug interaction, enhanced DNA repair and failure to apoptosis as a result of mutated cell cycle proteins. Attempts to overcome resistance mainly involve the use of combination drug therapy using different classes of drugs with minimal overlapping toxicities to allow maximal dosages and with narrowest cycle intervals [2].

Drug resistance, intrinsic or acquired, is one of the most described limitations of cancer therapy. Drug resistance comprises up-regulation of the target enzyme (e.g. TS), up-regulation of proteins that effectively transport anticancer compounds out of the cell (e.g. some of the multidrug resistance associated proteins), down-regulation of influx nucleoside transporters (e.g. the human equilibrative nucleoside transporter, hENT), down-regulation of key-activating enzymes (e.g., one of the dNKs), low levels of intracellular accumulation, and increased intracellular deactivation (e.g., CDA or a nucleotide). Strategies aimed to improve these drugs include the chemical modification of compounds by changes in the molecular structure or enhanced delivery by liposomes or nanoparticles [3]. In this review article we try to explore different nanogel formulations that are being used to reduce drug resistance in cancer chemotherapy.

Nanogels show promise as a suitable nanomedicine carrier as compared to other nanoparticles especially in terms of drug loading. Nanogels can be prepared or synthesized even in the absence of the drug to be loaded as drug loading in nanogels can be efficiently done later on when the nanogels are swollen and equilibrated in water or biological fluid. Drug loading occurs spontaneously in nanogels.

As compared to other conventional nanoparticles, nanogels allow much higher drug loading (up to 50% of weight). Moreover the methods of preparation of nanogels are simpler and do not involve the use of mechanical energy or organic solvents. Hence the loaded drug or therapeutic is not exposed to any vigorous condition during preparation. After administration the nanogels safely carry the payload, move within the cells and release the contents in the desired place in vivo. Nanogels can be designed to facilitate the encapsulation of diverse classes of bioactive compounds and following applications of nanogels show their utility as a potential nanomedicine carrier:

1. Upon intravenous injection, nanogels can reach the areas which are not easily accessed by hydrogels.
2. Nanogels are ideal candidates for intracellular delivery and can be safely delivered into the cytoplasm of the cell.
3. Nanogel dispersions have a larger surface area which is important for in vivo applications.
4. Nanogels have sizable drug loading capacity, low buoyant density and high dispersion stability in aqueous media.
5. Nanogels enhance the efficacy of therapeutic nucleoside analogs.
6. Nanogels can encapsulate delicate compounds with low or high molecular weights and can significantly prolong their activity in biological environments.
7. Weakly cross-linked polyelectrolyte nanogels can incorporate biomacromolecules of the opposite charge. Whereas; biomacromolecules are not able to accommodate in hydrogels due to the effects of excluded volume and cross-linking density.
8. Nanogels can be chemically modified to incorporate various ligands for targeted drug delivery, triggered drug release or preparation of composite materials.
9. Nanogels can be used for efficient delivery of biopharmaceuticals in cells as well as for increasing drug delivery across cellular barriers.
10. The nanoscale dimension of nanogels makes them to respond rapidly to environmental changes such as pH and temperature [4]

NANOCARRIERS AS POTENTIAL DRUG DELIVERY SYSTEMS IN CANCER THERAPY

Nanovehicles such as polymeric nanoparticles, solid lipid nanoparticles, magnetic nanoparticles, dendrimers, liposomes, micelles, quantum dots, etc. are extensively explored for cancer diagnosis, treatment, imaging, and as ideal vectors to overcome drug resistance by diverting ABC-transporter mediated drug efflux mechanisms. The major classes of nanocarriers utilized for chemotherapeutic drug delivery are listed in Table 1.

Table 1: Chemotherapeutic nanodrug delivery systems [5]

Nanocarriers	Properties	Characteristics
Solid lipid nanoparticles (SLNs)	Release drug in acidic microenvironment of multidrug resistance cells	Delivers anticancer drugs to overcome P-gp mediated multidrug resistance
Polymeric nanoparticles (NPs)	Versatile platform for controlled, sustained and targeted delivery of anticancer agents including small molecular weight drugs and macromolecules (gene and protein)	Enhanced drug accumulation, reduction in tumor size/volume, increased animal survival rate in rat models, minimal cytotoxicity in cancer cell lines, high transfection activity, potential to overcome multidrug resistance
Liposomes (LIPO)	Made of lipid bilayers encapsulating both hydrophilic and hydrophobic drugs, improved stability, long circulation	Selective targeting, P-gp inhibitory action, altered drug internalization and sub-cellular localization properties
Mesoporous silica nanoparticles (MSNPs)	Inorganic nanocarriers with tunable size and shape, high drug loading due to high pore volume and surface area, multi functionalization for targeted and controlled delivery	Enhanced cellular uptake and bioavailability, circumvents unwanted biological interactions delivers therapeutics at cellular levels for therapeutic and imaging in cancer
Inorganic nanoparticles (a) Iron oxide magnetic nanoparticles	Unique optical, electrical, magnetic and/or electrochemical properties, inert, stable, ease of functionalization	Circumvents drug resistance associated with over expression of ATP-binding cassette transporters, increased intracellular drug retention, enhanced loss of cell viability
(b) Gold nanoparticles (AuNPs)	Shape and size dependent on electronic characteristics, versatile drug delivery system due to tunable optical properties	Induces cellular DNA damage
(c) Quantum dots (QD)	Semiconductor inorganic fluorescent nanocrystals, small (1-20nm), and uniform size, high surface to volume ratio, surface conjugation with multiple ligands, biocompatible, fluorescence properties help real time tracks within target cells	Release of toxic compounds (cadmium) and generation of reactive oxygen species can result in long term toxicity

CHEMOTHERAPEUTIC NANOGEL DRUG DELIVERY SYSTEMS

I. Nanogels for loading siRNA

A small interfering RNA (siRNA) is a class of double-stranded RNA molecules consisting of 21–23 nucleotides, involved in inhibition of protein synthesis encoded by the messenger RNAs (mRNA). The siRNA mediates post transcriptional gene silencing of a specific target protein by disrupting mRNA when introduced into cells. They show promise to be used for any disease-causing gene as well as for targeting any cell or tissue. siRNA as a gene regulating tool has a tremendous therapeutic potential in the areas of cancer treatment.

However, the clinical application of siRNA is hindered by its poor stability, degradation by endogenous enzyme, low cellular uptake efficiency, low endosomal escape efficiency and short half-life in blood. Also the naked siRNA is unable to penetrate cellular membranes due to its large size and high negative charge. Such obstacles restrict the delivery of siRNA in vivo and require a suitable delivery carrier. Among different carriers, nanogels show promise as a novel transport medium for siRNA.

Dickerson et al. suggest targeted delivery of siRNAs by nanogels may be a promising strategy to increase the efficacy of chemotherapy drugs for the treatment of cancer. It is difficult to load siRNA into nanogel carrier with high encapsulation efficiency as it easily leaks from the carrier due to its hydrophilic character. To increase siRNA loading efficiency it is complexed with cationic excipients to enhance the affinity between the siRNA and the particle matrix. Mimi et al. used polyethyleneimine (PEI) nanogels as an effective siRNA carrier. The negative charge of siRNA allows it to form a strong electrostatic interaction with the positively charged polyethyleneimine. The consequential polyionic complexes also protect siRNA against enzymatic degradation. Other negatively charged complexing agents used are dioleoyl trimethyl ammonium propane and polyamines.

Chitosan has been shown to be useful as a carrier for improving the cellular uptake of naked siRNA both in vitro and in vivo via different administration routes. Chitosan is also useful for preventing the rapid degradation of siRNA in vivo.

Lee et al. explored the potential possibility of Hyaluronic acid as a biocompatible and biodegradable nanogel for delivery of siRNA. These nanogels crosslinked with disulfide linkages showed target-specific intracellular delivery of siRNA to HA-specific CD44 receptor over-expressing cancer cells.

Cationic dextran hydroxyethyl methacrylate (dex-HEMA) based nanogels are promising carriers for siRNA delivery since they can be loaded efficiently with siRNA, taken up by cells in vitro and were able to deliver intact siRNA into the cytosol of cells. Raemdonck et al. used the photopolymerization method to load siRNA into dextran nanogels (dex-HEMA-co-TMAEMA) using UV induced emulsion. These nanogels were used as a siRNA depot from which siRNA released at the desired time to prolong the gene silencing effect. It was reported that in this way the siRNA

dose was more efficiently deployed. Photochemical internalization was used as a trigger to induce endosomal escape of siRNA through the use of amphiphilic photosensitizers.

PEGylate cationic dex-HEMA nanogels by covalent attachment of NHS-PEG to the reactive amine groups of the nanogels with an aim to deliver siRNA *in vivo*. It was shown that dex-(HE)-MA-co-AEMA-co-TMAEMA nanogels retained their high loading efficiency of siRNA after PEGylation. The diffusion of the negatively charged siRNA molecules inside the gels occurred very slowly and that the siRNA was trapped by the cationic charges in the nanogels. Also, siRNA-loaded PEGylated dex-(HE) MA-co-AEMA-co-TMAEMA nanogels were able to successfully down regulate EGFP without causing severe toxicity in a HuH-7 EGFP cell line [4].

II. Nanogel-encapsulated active triphosphates of nucleoside analogs (NATP)

These are small particles of biodegradable cationic nanogels loaded with anionic NATP efficiently interacted with cancer cells and released active drug compounds into the cytoplasm. The potential of novel drug formulations was evaluated in the nucleoside transport-deficient (CEM/araC/C8) or nucleoside activation-deficient (RL7/G) lymphogenic cancer cells. Compared to nucleoside analogs, NATP-loaded nanogels demonstrated increased cytotoxicity, reducing the drug resistance index 250 to 900-fold in CEM/araC/C8 cells and 70 to 100-fold in RL7/G cells. The strong cytotoxic effect of nanoformulations was accompanied by characteristic cell cycle perturbations, usually observed in drug-treated sensitive cells, and resulted in the induction of apoptosis in all studied drug-resistant cells. Efficient cellular accumulation of nanogels and the consequent increase in intracellular levels of NATP were found to be the major factors determining cytotoxic efficacy of nanoformulations. Decoration of nanogels with multiple molecules of tumor lymphatic-specific peptide (LyP1) enhanced the binding efficacy of nanocarriers with lymphogenic cancer cells. The targeted nanoformulation of activated gemcitabine (LyP1-NG-dFdCTP), when injected in subcutaneous RL7/G xenograft tumor model, demonstrated two-fold more efficient tumor growth inhibition than gemcitabine at a higher dose. Nanogel-drug formulations exhibited no systemic toxicity during the treatment, hence extending the versatility of nucleoside analogs in the treatment of drug-resistant lymphogenic tumors [5].

III. Hyaluronic acid-based nanogel-drug conjugates with enhanced anticancer activity designed for targeting of cd44-positive and drug-resistant tumors

Many drug-resistant tumors and cancer stem cells (CSC) express elevated levels of CD44 receptor, a cellular glycoprotein binding hyaluronic acid (HA). Here, we report the synthesis of nanogel-drug conjugates based on membranotropic cholesteryl-HA (CHA) for efficient targeting and suppression of drug-resistant tumors. These conjugates significantly increased the bioavailability of poorly soluble drugs with previously reported activity against CSC, such as etoposide, salinomycin, and curcumin. The small nanogel particles (diam. 20–40 nm) with a hydrophobic core and high drug loads (up to 20%) formed after ultra-sonication and demonstrated a sustained drug release following the hydrolysis of biodegradable ester linkage. Importantly, CHA-drug nanogels demonstrated 2–7 times higher cytotoxicity in CD44-expressing drug resistant human breast and pancreatic adenocarcinoma cells compared to free drugs and non-modified HA-drug conjugates. These nanogels were efficiently internalized via CD44 receptor mediated endocytosis and simultaneous interaction with the cancer cell membrane. Anchoring by cholesterol moieties in the cellular membrane after nanogel unfolding evidently caused more efficient drug accumulation in cancer cells compared to non-modified HA-drug conjugates. CHA-drug nanogels were able to penetrate multicellular cancer spheroids and displayed higher cytotoxic effect in the system modeling tumor environment than both free drugs and HA-drug conjugates. In conclusion, the proposed design of nanogel-drug conjugates allowed us to significantly enhance drug bioavailability, cancer cell targeting, and the treatment efficacy against drug-resistant cancer cells and multicellular spheroids [6].

IV. Novel anticancer polymeric conjugates of activated nucleoside analogs

Previously, we have actively promoted the idea that the nanodelivery of active nucleotide species, e.g. 5'-triphosphates of nucleoside analogs, can enhance drug efficacy and reduce nonspecific toxicity. In this study we report the development of a novel type of drug nanoformulations, polymeric conjugates of nucleoside analogs, which are capable of the efficient transport and sustained release of phosphorylated drugs. These drug conjugates have been synthesized, starting from cholesterol-modified mucoadhesive polyvinyl alcohol or biodegradable dextrin, by covalent attachment of nucleoside analogs through a tetraphosphate linker. Association of cholesterol moieties in aqueous media resulted in intramolecular polymer folding and the formation of small nanogel particles containing 0.5 mmol/g of a 5'-phosphorylated nucleoside analog, e.g. 5-fluoro-2'-deoxyuridine (floxuridine, FdU), an active metabolite of anticancer drug 5-fluorouracil (5-FU). The polymeric conjugates demonstrated rapid enzymatic release of floxuridine 5'-phosphate and much slower drug release under hydrolytic conditions (pH 1.0–7.4). Among the panel of cancer cell lines, all studied polymeric FdU-conjugates demonstrated an up to 50 times increased cytotoxicity in human prostate cancer PC-3, breast cancer MCF-7 and MDA-MB-231 cells, and more than 100 times higher efficacy against cytarabine-resistant human T-lymphoma (CEM/araC/8) and gemcitabine resistant follicular

lymphoma (RL7/G) cells as compared to free drugs. In the initial *in vivo* screening, both PC-3 and RL7/G subcutaneous tumor xenograft models showed enhanced sensitivity to sustained drug release from polymeric FdU-conjugate after peritumoral injections and significant tumor growth inhibition. All these data demonstrate a remarkable clinical potential of novel polymeric conjugates of phosphorylated nucleoside analogs, especially as new therapeutic agents against drug-resistant tumors [7].

V. Nanogel formulations with phosphorylated nucleoside analogs

Many prospective nucleoside analogs have been discarded in earlier preclinical studies, or withdrawn later from clinical studies as their intracellular conversion into NTP was inefficient within an acceptable dosage range. The choice of available anticancer drugs could be considerably broadened given that these drugs are delivered into the cytosol in a preactivated NTP form. However, only a limited number of efforts were made to directly administer NTP encapsulated in special drug-delivery vehicles, as this drug form was found to be too unstable to be used in chemotherapy. In one example, 5'-triphosphate of 2', 3'-dideoxycytidine was found to be well-protected in circulation and delivered to mononuclear phagocyte system in PEG stabilized liposomes. Recently, the authors have demonstrated successful application of cationic nanogels for encapsulating 5'-triphosphates of natural nucleosides and nucleoside analogs. Phosphate moieties of NTP formed ionic complexes with protonated amino groups of PEI and compacted into the nanogel network core, surrounded by a layer of PEG loops. Based on these findings, nanogels can be used for direct delivery of immediately active NTPs (instead of nucleoside analogs) into infected or cancerous cells. Therefore, nanogels may be developed into a promising therapeutic formulation. To test this strategy, nanogel/NTP formulations of several cytotoxic nucleoside analogs, such as 2'-fluoroadenine arabinoside, AZT and cytosine arabinoside were studied. Initial nucleosides were converted into NTP, using well-developed chemical phosphorylation methods. A polyionic drug complex with nanogel was formed immediately by the direct mixing of an aqueous dispersion of the carrier with the NTP solution. Complex formation could be traced by marked reduction of the hydrodynamic diameter of Nanogel particles, observed by dynamic light scattering. An alternative approach involved titration of the dispersion of nanogel-containing deprotonated amines with NTP in an acidic form, until a neutral pH of the resulting solution was reached. In both cases, lyophilised formulations were obtained that could be stored in dry form at 4°C, without any trace of NTP decomposition for at least 1 year. Drug (NTP) loading depended directly on the PEI content in nanogels, and was equal to 15 – 30% of the weight of dry formulation, or 0.5 mmol of NTP/g on average. Drug-loaded nanogel particles swelled and retained enough water in their interior to ensure a high solubility and dispersion stability in aqueous media. Experiments on *in vitro* drug-release demonstrated a sustained release of nucleotide drugs from nanogels in physiological medium, reaching ~ 30% of the initial drug loading during the first 24 h of incubation at 37°C. Evidently, *in vitro* release of free drug from nanogels in circulation is slow enough to cause no serious problems associated with nonspecific toxic effects of unbound nucleoside analogs.

Nanogels provided significant protection of encapsulated phosphorylated nucleosides from degradation by ubiquitous intra- or extra-cellular dephosphorylating enzymes. In model experiments, 30–60% of encapsulated NTP was protected and kept intact, depending on the nanogel loading capacity, compared with only 10% of the free NTP following incubation with alkaline phosphatase. In addition, ~ 60% of degraded nucleotide was found in the form of mono- and di-phosphates that are also active drug species. Drugs may be released from nanogel/ NTP formulations by a multi-variant mechanism. Nanogel can slowly release a considerable amount of the encapsulated drug in the form of nucleoside 5'-phosphates, which are formed as a result of partial dephosphorylation at physiological conditions and dissociate more easily from the nanogel interior. However, a remaining fraction of the formulated NTP may be unbound only in the event of binding with competitive cellular polyanions. Previously, a putative mechanism of drug release including interaction of nanogel cationic network with negatively charged phospholipids and other components of the cellular membrane has been suggested. Membrantropic properties of nanogels were clearly illustrated recently by dose-dependent interactions of tritium-labelled nanogels with isolated cellular membranes, and by direct visualisation of these events using transmission electron and atomic force microscopy. These findings could clearly be observed in a cellular system of rhodamine-labelled nanogels loaded with a fluorescein-labelled ATP. Initial accumulation of nanogel on the cellular membrane was evident on these confocal images taken earlier, after cell treatment. This process was accompanied with a fast release and accumulation of the green fluorescent ATP into the cytosol. At a later time point (60 min), most of the drug loaded nanogels, as well as membrane-bound unloaded nanogels, were taken up by endocytosis (yellow and red dots) and accumulated in endosomes. However, membrane binding and the process of drug release continued inside the endosomes, and a much higher level of green fluorescent ATP was now observed in the cytosol. This process has been called membrane triggered drug release from nanogel-ATP complexes. In this process, positively charged nanogel competitively formed more stable complexes with phospholipids of the cellular membrane, fusing into the lipid bilayer and releasing NTP directly into the cytosol on the other side of the membrane. The feature provides an evident advantage over many existing drug delivery systems, as nanogel can release the drug rapidly, by means of bursting, as soon as the carrier reaches the target site.

Several cytotoxic nucleoside analogs in the form of NTP have been formulated with nanogel. Surprisingly, the cytotoxicity of these formulations tested in various human breast carcinoma cell lines was approximately two orders of magnitude higher compared with the parental nonphosphorylated drug. This additional cytotoxic effect was independent of the inherent cytotoxicity of the carrier, as similar Nanogel-ATP complexes exhibited markedly lower cytotoxicity. Based on previous findings, the authors have attributed the observed cytotoxic efficacy of Nanogel-NTP formulations to the rapid creation of an excessive inhibitory NTP concentration higher than the cytosolic pool of cellular nucleotides.

Toxicology of many novel drug carriers constitutes a serious challenge for polymer chemists and chemical engineers. By analogy to the therapeutic index of antiviral drugs (usually determined as a ratio of drug cytotoxic concentration [IC₅₀] to the drug effective concentration [EC₅₀]), various drug delivery systems may be also compared by their own therapeutic index, which may be determined as a ratio of cytotoxic concentration of the carrier to the cytotoxic concentration of the carrier-loaded drug. The higher the therapeutic index, the better the drug carrier formulation. In the case of cationic nanogel-NTP formulations, the therapeutic index value was usually > 50, which is considered to be a very good ratio for many drugs [8].

VI. Crosslinked Polymeric Nanogel Formulations of 5'-Triphosphates of Nucleoside analogs

Activation of cytotoxic nucleoside analogs *in vivo* depends primarily on their cell-specific phosphorylation. Anticancer chemotherapy using nucleoside analogs may be significantly enhanced by intracellular administration of active phosphorylated drugs. However, the cellular transport of anionic compounds is very ineffective and restricted by many drug efflux transporters. Recently developed cationic nanogel carriers can encapsulate large amounts of nucleoside 5'-triphosphates that form polyionic complexes with protonated amino groups on the polyethylenimine backbone of the nanogels. In this paper, 5'-triphosphate of an antiviral nucleoside analog, 3'-azido-2', 3'-dideoxythymidine (AZT), was efficiently synthesized and its complexes with nanogels were obtained and evaluated as potential cytotoxic drug formulations for treatment of human breast carcinoma cells. A selective phosphorylating reagent, tris-imidazolylphosphate, was used to convert AZT into the nucleoside analog 5'-triphosphate using a one-pot procedure. The corresponding 3'-azidothymidine 5'-triphosphate (AZTTP) was isolated with high yield (75%). Nanogels encapsulated up to 30% of AZTTP by weight by mixing solutions of the carrier and the drug. The AZTTP/nanogel formulation showed enhanced cytotoxicity in two breast cancer cell lines, MCF-7 and MDA-MB-231, demonstrating the IC₅₀ values 130–200 times lower than those values for AZT alone. Exact mechanism of drug release from nanogels remains unclear. One mechanism could involve interaction with negatively charged counterions. A high affinity of nanogels to isolated cellular membranes has been observed, especially for nanogels made of amphiphilic block copolymer, Pluronic® P85. Cellular trafficking of nanogel particles, contrasted by PEI-coordinated copper (II) ions, was studied by transmission electron microscopy (TEM), which revealed membranotropic properties of nanogels.

A substantial release of encapsulated drug was observed following interactions of drug-loaded nanogels with cellular membranes. A drug release mechanism triggered by interaction of the drug loaded nanogels with phospholipid bilayer is proposed.

The results illustrate therapeutic potential of the phosphorylated nucleoside analogs formulated in nanosized crosslinked polymeric carriers for cancer chemotherapy [9].

CONCLUSION

It can be concluded that Nanogels have potential application as carriers for cancer chemotherapy.

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