An Overview on Polyethylene Glycol Gelation for Anti-Cancer Activity

Keywords: PEG, PEGelation, Polymer, Anti-cancer Activity

ABSTRACT
The advanced drug delivery systems using Polyethylene glycol (PEG) is an important development in anti-cancer therapy. PEGelation has the ability to enhance the retention time of the therapeutics like proteins, enzymes, small molecular drugs, liposomes and nanoparticles by protecting them against various degrading mechanisms active inside a tissue or cell, which consequently improves their therapeutic potential. PEGelation effectively alters the pharmacokinetics (PK) of a variety of drugs and dramatically improves the pharmaceutical values. Recent development of which includes, fabrication of stimuli-sensitive polymers/smart polymers and polymeric micelles to cope of with the pathophysiological environment of targeted site with less toxic effects and more effectiveness. This overview discusses PEGelation involving proteins, enzymes, low molecular weight drugs, liposomes and nanoparticles that has been developed, clinically tried for anti-cancer therapy during the last decade.
INTRODUCTION

Cancer is one of the leading causes of death worldwide. Metastases are the primary cause of death from cancer. Cancer cells proliferate at much faster rate than the normal cells. The available traditional cancer chemotherapy is not essentially selective as it depends on the kinetics of the cell growth. Targeted cancer therapies are expected to be more effective and beneficiary in comparison to available conventional treatment procedures. The last few decades of research in the particular area are focused on exploring the treatment of cancer at its molecular level. This will be helpful in developing better therapeutics.\textsuperscript{1,2} Polymer therapeutics is establishing as an innovative and reliable method for its ability to conjugate with protein, enzymes, nanoparticles, liposomes and low molecular weight drugs. In this regard, polyethylene glycol (PEG), a water soluble and biocompatible polymer, is the most commonly used non-ionic polymer in the field of polymer-based drug delivery. Passive targeting with PEGs in combination with active targeting i.e. entry into the tumor cell via ligand receptor, antigen antibody interaction, delivery systems has been effectively employed to achieve better therapeutic index of anti-cancer drugs.

Further, with the introduction of stimuli-responsive chemical moiety in PEGelated prodrugs, the sensitiveness of the drug molecule toward the pathophysiological environment of tumor cells involved as a new era of site-specific targeted drug delivery system. Hence this overview deals with the development and recent advancement in various aspects of PEGelationin cancer treatment and its future perspective in a comprehensive way.\textsuperscript{3}

This chapter reviews the preparation methods of hydrogels from hydrophilic polymers of synthetic and natural origin with emphasis on water soluble natural biopolymers. Recent advances in radiation cross-linking methods for the preparation of hydrogel are particularly addressed. Additionally, methods to characterize these hydrogels and their proposed applications are also reviewed. A class of biomaterials that has been the subject of intense research interest is hydrogels. Hydrogels are extensively investigated as two- and three dimensional scaffolds for cells because they closely mimic the natural environment of cells, both chemically and physically. Hydrogels can be formed from synthetic (e.g., poly(ethylene glycol) and naturally occurring polymers (e.g., collagen, hyaluronic, heparin), and are useful 3D models of tissue culture due to their high water content and ability to form in the presence of cells, proteins and
Depending on the reactivity of the constituent materials, gelation can be induced using pH, temperature, columbic interactions, covalent bonding, non-covalent interactions, or polymerization.\(^4\)

**Mechanism of Gel Formation:**

Gelation refers to the linking of macromolecular chains together which initially leads to progressively larger branched yet soluble polymers depending on the structure and conformation of the starting material. The mixture of such polydisperse soluble branched polymer is called ‘sol’. Continuation of the linking process results in increasing the size of the branched polymer with decreasing solubility. This ‘infinite polymer’ is called the ‘gel’ or ‘network’ and is permeated with finite branched polymers. The transition from a system with finite branched polymer to infinite molecules is called ‘sol-gel transition’ (or ‘gelation’) and the critical point where gel first appears is called the ‘gel point’.\(^5,6,7\) Gelation can take place either by physical linking (physical gelation) or by chemical linking (chemical gelation). Physical gels can be subcategorized as strong physical gels and weak gels. Weak physical gels have reversible links formed from temporary associations between chains. These associations have finite lifetimes, breaking and reforming continuously. Examples of weak physical bonds are hydrogen bond, block copolymer micelles, and ionic associations. On the other hand, chemical gelation involves formation of covalent bonds and always results in a strong gel. The three main chemical gelation processes include condensation, vulcanization, and addition polymerization.\(^8,9\)

**PEGelation and its Significance:**

It is the technique of covalently attaching polyethylene glycol (PEG) to a given molecule is known as “PEGelation” and is now a well-established method in the field of targeted drug delivery systems. The general structure of monomethoxy PEG (mPEG) can be represented as \(\text{CH}_3\text{O–(CH}_2\text{-CH}_2\text{O)}\text{n–CH}_2\text{-CH}_2\text{–OH}.\(^10\) At the beginning of PEG chemistry, in the late1970s, Professor Frank Davis and his colleagues had shown that the immunological properties as well as the stability of bovine serum albumin and bovine liver catalase can be successfully altered by covalently linking them to methoxy PEG (mPEG) using cyanuric chloride as an activating agent.\(^11\) The process of PEGelation can be extended to liposomes, peptides, carbohydrates, enzymes, antibody fragments, nucleotides, small organic molecules and even to different
nanoparticle formulations. mPEG is the most useful unit for polypeptide modification.\textsuperscript{12} Now several derivatives of PEG molecules are available that vary in molecular weight and structure, such as linear, branched, PEG dendrimers and more recently multi-arm PEGs. The first step of PEGelation is to activate PEG by conjugating a functional derivative of PEG at one or both the terminals of PEG chain. PEGelation conjugation techniques can be classified into two categories:

i) First-generation random PEGelation, and

ii) Second generation site-specific PEGelation.\textsuperscript{13,14}

Thanks to the second generation PEGelation processes that resulted in well-defined conjugated products with improved product profiles over those obtained through non-specific random conjugations. Irreversibly conjugating PEGs had some adverse effects on the specific biological activity of many therapeutics. Thus, to minimize the loss of activity, a reversible (or releasable prodrug) PEGelation concept has been formulated.\textsuperscript{15,16} Reversible PEGelation concept deals with attachment of drugs to PEG derivatives through cleavable linkages. The release of drug occurs by therapeutic agents through enzymatic, hydrolytic cleavage or reduction \textit{in-vivo} at a predetermined kinetic rate over a time period.\textsuperscript{17} The objective of most PEG conjugation techniques aims at increasing the circulation half-life without affecting activity. It is to be noted that the distinct advancement in the PEG conjugation processes and diversity in the nature of the PEGs used for the conjugation has attributed to the increased demand for PEGelated pharmaceutical products.\textsuperscript{18,19} PEGelation enhances the therapeutic efficacy of the drugs by bringing in several advantageous modifications over the non- PEGelated products. Increase in the serum half-life of the conjugate is the major way of enhancing therapeutic potential of the PEGelated conjugate. PEGelation prolongs the circulation time of conjugated therapeutics by increasing its hydrophilicity and reducing the rate of glomerular filtration. Few factors such as protection from reticuloendothelial cells, proteolytic enzymes and decreased formation of neutralizing antibodies against the protein by masking antigenic sites by formation of a protective hydrophilic shield are the key components of PEG molecule that attributes to the improved pharmacokinetic profile (PK) of the conjugates. It has also been reported that PEGelation increases the absorption half-life of subcutaneously administered agents and is associated with a decreased volume of distribution.\textsuperscript{19,20}
Figure 1: Significance of PEGelated Therapeutics

Role of PEGelation in passive and active targeting of drugs

Passive targeting drug delivery technique is mostly depends upon the concentration gradient between the intracellular and extracellular space, created due to high concentration of the drug in the tumor area. PEG conjugates takes the advantage of enhanced permeation and retention (EPR) effect executed by the tumors and gets accumulated in the pathophysiological environment of tumor vessels through leaky vasculature and poor lymphatic drainage. However, this effect cannot be studied with low molecular weight drugs that freely extravagate causing systemic toxicity, and this is a size dependent effect. PEGelation increases the solubility, size, molecular mass and serum stability of the drugs. For all these reasons, PEGelation is considered to be one of the best methods for passive targeting of anti-cancer therapeutics. 21,22

The concept of active targeting of drugs is based on the idea of conjugating drug molecules to targeting entities (antibodies, ligands, etc.) for specific interaction with the structures present on the cell surface for targeted delivery of the anti-cancer agent. The fate of the pro-drug is dictated by the targeting molecule and the linker molecule present on the prodrug. 23 The targeting moiety essentially decides the type of cancer cell for the act of therapeutics. Further, depending on the linker molecule, drug gets entry into the tumor cell by either of the two ways:
(i) Receptor-mediated internalization of the whole pro-drug by endocytosis and subsequent degradation by endosomal/lysosomal pathway, or

(ii) Receptor independent internalization of the drug into targeted cells after extracellular cleavage of the pro-drug.\textsuperscript{24}

PEGelation pro-drugs can be efficiently conjugated to targeting moieties by different conjugation chemistry in order to achieve the goal of active targeting. The targeted delivery of the PEGelation drugs at the desired site causes high bioavailability and low systemic toxicity.\textsuperscript{25}

**PEGelation Proteins in Anti-cancer Therapy**

PEGelation of proteins is a well-established method in the pharmaceutical field, but the significance of PEGelation peptides and proteins for anti-cancer therapy has only been realized in the last several years as more and more PEG conjugates make it to late-phase clinical trials. Enzymes, monoclonal antibodies and cytokines are the three major class of proteins used in anti-cancer therapy or as adjuvant therapy.\textsuperscript{26}

![Figure 2: A passive targeting with acid-sensitive PEG-prodrugs that cleave in the extracellular space](image)

*Figure 2: A passive targeting with acid-sensitive PEG-prodrugs that cleave in the extracellular space*
**PEGelated Monoclonal Antibody Fragment**

In the field of anti-cancer therapy, monoclonal antibodies represent the major class of protein therapeutics. Antibodies act by binding to the specific antigens/cell surface receptors. This task is taken care by the fragment antigen-binding (Fab’) region on an antibody. Depending upon the receptor and the binding site on the receptor against which the antibody is designed, it can either activate cellular signaling pathways leading to apoptosis, cell growth arrest, or block the pathways leading to cell growth that eventually causes tumor cell death (apoptosis). The major drawback associated with Fab’s antibody fragment is its short serum half-life as it lacks the Fc region of the antibody that limits its potential as a therapeutic agent. Hence, suitable PEGelation method and PEGs are used to ensure minimal loss of the antibody-antigen/cell surface receptor interaction keeping in view the enhancement of serum half-life. It has been reported that the hinge region cysteine residues on Immunoglobulin-G (IgG antibody isotype) Fab’ antibody fragments can tolerate attachment of one or two PEG moieties (up to a total of 40 kDa molecular weight) with little effect on antigen binding affinity. This process also enables significant increase in the half-life of the circulating plasma antibodies by reducing the glomerular filtration and lower immunogenicity than the parent IgG.

**PEGelated Cytokines**

Cytokines represent another class of protein therapeutics employed mainly as adjuvant therapy in classical anti-cancer chemotherapy protocols either to control or bring improvements in patient conditions. These small secreted proteins belong to the immunotherapy category and mobilizes the body’s immune system to fight cancer.

**PEG-interferon-alpha conjugates:**

This process is illustrated as PEG-interferon-α2b (PEG-INTRON®/Sylatron™) and PEG-interferon-α2a, which are discussed as follows:

**PEG-interferon:**

The PEGylated version of interferon-α2b was synthesized by conjugating interferon-α2b, with a single chain 12 kDa PEG-SC via a urethane bond. It displayed a half-life of 27–37 h with 10-fold
lower clearance and minor change in the volume of distribution in comparison to native form. Based upon the outcome of clinical studies in the year 2011, the PEGylated drug PEG-interferon alfa-2b got FDA approval for adjuvant treatment of melanoma patients with microscopic or gross nodal involvement following definitive surgical resection including complete lymphadenectomy. Sylatron™ is another brand name for PEG-interferon alfa-2b exclusively approved by FDA for adjuvant therapy in cancer treatment.30,31

**PEGelated Enzymes in Anti-cancer Therapy**

Therapeutic enzymes represent a growing class of biopharmaceuticals, and PEGelation has played a major role in improving several of these products. Many depleting enzymes are active against tumors. Enzymes intrinsic property of degrading amino acids is essential for cancer cells existence. The fate of the tumor cell is dictated by the different cellular pathways regulated by the substrate (amino acid) to be degraded. The normal cells are not affected because the normal cells can synthesize the amino acids for their growth. This situation is particularly the most advantageous aspect of using depleting enzymes in cancer therapy. Therefore, during PEGelation procedure, a combination of these enzymes, low molecular weight (5–10 kDa) PEGs and random amine conjugation strategies are employed.32

**PEG-arginine depleting enzymes:**

Arginine is a nonessential amino acid in humans. It has been reported that arginine deficiency inhibits tumor growth, angiogenesis and nitric oxide synthesis. Two types of arginine degrading enzymes are,

i) Arginine deiminase (ADI) and

ii) Arginase(ARG),33,34

Which can be utilized as antitumor agents, are discussed below:

**PEG-arginine deiminase:**

The PEGelation of arginine deiminase proved to be a better therapeutic approach for anti-cancer treatment. Among the several PEGelated ADI formulations the ADI-PEG20000, formulated by
conjuncturing 10–12 chains of 20 kDa PEG with ADI by using the succinimidylic succinate linker, is proved to be the acceptable one from in-vivo study results. Clinical studies have shown better efficacy of ADI PEG 200,000 in terms of antitumor activity and tolerability. Currently, ADI PEG 200,000 versus placebo is under phase III clinical trial for advanced hepatocellular carcinoma. Further, Phase II for acute myeloid leukemia/non Hodgkin’s lymphoma and Phase I are under trial.35

**PEG-arginase:**

The depleting enzyme arginase is an endogenous protein expressed in humans. The conjugate, PEGrhArg, has 10 to 12 polymer chains of PEG 5000 per protein molecule that is covalently attached via a succinimide propionic acid (SPA) linker.36 This conjugate remains in fully active condition. The PEGelated form executes sufficient catalytic activity at physiological pH with a prolonged plasma half-life of 3 days in comparison to the native form, which has a half-life of several minutes only. Currently, this conjugate is under phase I/II clinical trials.37

**PEG-asparagine depleting enzyme (PEG-L-asparaginase):**

Depletion of asparagine eventually results in leukemic cell death. Leukemic cells lack the enzyme asparagine synthetase, an enzyme required for asparagine synthesis, and depend on the exogenous supply of asparagine for their growth and survival. Therefore, asparaginase, the depleting enzyme for asparagine, plays a critical role as a therapeutic enzyme in treating acute lymphoblastic leukemia. Oncaspar is a modified form of the enzyme L-asparaginase approved by FDA in 1994. Oncaspar consists of tetrameric enzyme L-asparaginase derived from E. coli, and it is covalently conjugated with approximately 69–82 molecules of monomethoxy polyethylene glycol (MPEG), each having molecular weight of 5 kDa.38-40 Oncaspar proves to be a better treatment option for patients who were allergic to the native form of the drug. The U.S. Food and Drug Administration granted approval to PEGasparagase in July 2006 for the first-line treatment of patients with acute lymphoblastic leukemia as a component of a multi-agent chemotherapy regimen.41
PEGelated Low Molecular Weight anti-Cancer Drugs

Various PEGelated low molecular weight anti-cancer drugs are currently under development. For example, topoisomerase I inhibitor camptothecin-based drugs (irinotecan, topotecan, SN38, exetecan, etc.) are reported to be useful in the treatment of many solid tumors. However, the hydrophobicity of such material limits their therapeutic efficacy, are discussed below:

PEG-SN38

EZN-2208, the product Enzon Pharmaceuticals, Inc, is a PEGelated SN38 (10-hydroxy-7-ethyl-camptothecin (a derivative of camptothecin)). SN38 is the active moiety of CPT-1 and reported to be a potent topoisomerase I inhibitor. In this PEGelated product, the 20-OH group of SN38 was selectively coupled with a 4 arm PEG of 40 kDa through a glycine spacer to preserve the E ring of SN38 in the active lactone form while leaving the drug 10-OH free. PEGelation was able to enhance the solubility of SN38 by about 1000-fold. In fact, EZN-2208 showed a 207-fold higher exposure to SN38 compared to irinotecan in treated mice.42

The conjugate showed promising antitumor activity both in-vitro and in-vivo. However, following phase II trial, Enzon Pharmaceuticals, Inc. announced the discontinuance of its EZN-2208 clinical program.43

PEGelated Nanoparticles in Anti-cancer Therapy

Nanoparticles (NPs) are synthetic materials with dimensions from 1 to 1000 nano-meters. NPs have large payloads, stability and the capacity for multiple, simultaneous applications due to their unique size and high surface area: volume ratio. Despite these advantages, the major drawbacks associated with NP drug delivery system for clinical studies are associated with short circulating half-life due to uptake by the reticuloendothelial system (RES) for larger NPs, whereas smaller NPs are subjects to tissue extravasations and renal clearance. Liposomes, solid lipids nanoparticles, dendrimers, polymers, silicon or carbon materials, and gold and magnetic nanoparticles are examples of nano-carriers that have been studied as drug delivery systems in cancer therapy. Therefore, surface modification of the nanoparticles with PEGs of various chain length, shape, density, molecular weight and incorporation of different targeting moieties
(ligands, antibodies, etc.) is emerging as a more promising and technologically advanced drug delivery system in anti-cancer therapy.\textsuperscript{44}

There are currently more than 35 US FDA-approved PEGelated NPs, with a larger number in pre-clinical studies for both imaging and therapy. Among several PEGelated nanoparticle formulations for anti-cancer therapy, liposomes have been most extensively studied.

**PEGelated Liposomes in Anti-cancer Therapy**

Liposomes are spherical, self-closed structures formed by one or more concentric lipid bilayers with an encapsulated aqueous phase in the center and between the bilayers composed of natural or synthetic lipids. The development of long circulating liposomes with inclusion of the synthetic polymer poly-(ethylene glycol) (PEG) in liposome composition could be able to solve the issue of low serum half-life associated with liposomes. PEG can be incorporated on the liposomal surface in a number of ways. However, anchoring the polymer in the liposomal membrane via a cross-linked lipid, PEGdistearoylphosphatidylethanolamine [DSPE], is reported to be the most widely accepted method. Preclinical studies with PEGelated liposomes reported that the cytotoxic agents entrapped in PEGelated liposomes tend to accumulate in tumors. However, recent preclinical studies of anti-cancer drug enclosed in PEGelated liposomes in rodents and dogs have shown the rapid blood clearance of the pegylated drug carrier system due to the increased anti-PEG-IgM production. An example of PEGelated liposomal formulations, PEGelated liposomal doxorubicin (PLD), and most extensively studied is discussed below:

**Doxil (PEGelated liposomal doxorubicin):**

DOXIL is the trade name for PEGelated liposomal doxorubicin formulated to achieve better drug efficacy for cancer chemotherapy. This product contains doxorubicin (Adriamycin) enclosed in an 80–90 nm size unilamellar liposome coated with PEG. The modification increases the circulatory half-life of the drug leading to its enhanced bioavailability at the tumor site. PEGelated liposomal doxorubicin has fewer side effects on healthy cells than regular doxorubicin. PLD has improved pharmacokinetic features, such as long circulation time of about 60–90 h for doses in the range of 35–70 mg/m\textsuperscript{2} in patients with solid tumors. After PLD administration, nearly 100\% of the drug in the plasma remains in the encapsulated form. Moreover, in comparison to free doxorubicin PLD, plasma clearance is dramatically slower.
and its volume of distribution remains very small, which is roughly equivalent to the intravascular volume. After obtaining approval from FDA, PEGelated liposomal doxorubicin (PLD) is currently used to treat Kaposi’s sarcoma and recurrent ovarian cancer.\(^{45}\)

**PEGelated Smart Polymers in Anti-cancer Therapy**

Smart polymers are defined as polymers that undergo reversible large, physical or chemical changes in response to small external changes in the environmental conditions, such as temperature, pH, light, magnetic or electric field, ionic factors, biological molecules, etc. Smart polymers show promising applications in the biomedical field as delivery systems of therapeutic agents. Among various smart polymers currently in use in biomedical field of research, the temperature sensitive systems are the most studied systems. The greater therapeutic index of the targeted drug delivery systems can be achieved by adjusting the transition temperature (Tt) of thermally responsive polymers, i.e., between body temperature\((37^\circ C)\) and the temperature approved for mild clinical hyperthermia \((42^\circ C)\). Within the temperature ranges, these polymers facilitate tissue accumulation by localizing the aggregation of systemically delivered carriers to the heated tumor volume. For example, ThermoDox, a temperature sensitive doxorubicin-loaded PEGelated liposome (DPPC), releases encapsulated doxorubicin at elevated tissue temperature. DPPC has a transition temperature of 41.5\(^\circ C\), which makes it suitable for temperature-sensitive technology. The temperature can be achieved by radiofrequency ablation technique. For ThermoDox, the concentration of the drug is up to 25 times more in the treatment area than IV doxorubicin, and several fold the concentration of other liposomal encapsulated Doxorubicins. Currently, it is under phase III clinical trial for hepatocellular carcinoma.\(^{46}\)

**PEGelated Polymeric Micelles in Anti-cancer Therapy**

Polymeric micelles are colloidal dispersions prepared by block copolymers, consisting of hydrophilic and hydrophobic monomer units. Self-assembling amphiphilic polymeric micelles represent an efficient drug delivery system for poorly soluble or insoluble drugs. Different varieties of amphiphilic polymeric micelles (i.e. Diblock AB type, Triblock ABA type or graft copolymers) can be designed by arranging the monomeric units in different ways and orders. The hydrophobic block constitutes the core and the hydrophilic block makes the corona of the micelles.\(^{47}\) The water-soluble PEG blocks with a molecular weight from 1 to 15 kDa are
considered as the most suitable hydrophilic corona-forming blocks. Various preclinical and clinical studies have shown the potential use of PEGelated polymeric micelles with different hydrophobic blocks such as PLGA poly(D,L-lactide-co-glycolide), poly aspartate, γ-benzyl-L-glutamate, polyglutamate, and poly(D,L-lactic acid) in anti-cancer therapy. 48,49

**PEGelated Nanoparticles for Sirna Delivery in Anti-cancer Therapy**

RNA interference is a natural phenomenon employed to selectively turn off the genes expressed in some diseases. Molecular therapy using small interfering RNA (siRNA) has shown great therapeutic potential for tumors and other diseases caused by abnormal gene overexpression or mutation. 50

It is a highly specific process for gene silencing. However, naked molecules of siRNA are vulnerable to premature renal clearance and nuclease degradation. The negative charge and hydrophilicity of siRNA also limit its permeability through cellular and endolysosomal membranes. Therefore, in order to overcome these issues, siRNA requires a carrier system for effective delivery. Modification of drug delivery systems with PEGs of suitable chain length, molecular weight and percent composition was proven to be efficient in overcoming intracellular and systemic siRNA delivery barriers. A nanoparticle formulation (Calando Pharmaceuticals) formulated by using cyclodextrin nanoparticles conjugated to transferrin and coated with PEG, is the first one to enter under phase I clinical trials for solid tumors, in addition to few more which are currently under development. 51
Table 1: PEGelated polymeric micelles in clinical development as anti-cancer therapy

<table>
<thead>
<tr>
<th>Trade name for polymeric micelles</th>
<th>Block copolymer</th>
<th>Parent Drug</th>
<th>Clinical trial status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NK105</td>
<td>PEG-P (aspartate)</td>
<td>Paclitaxel</td>
<td>Phase II, advanced stomach cancer</td>
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<td></td>
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<tr>
<td>NK012</td>
<td>PEG-PGlu(SN-38)</td>
<td>SN-38</td>
<td>Phase II, breast cancer</td>
</tr>
<tr>
<td>NC6300</td>
<td>PEG-P(aspartate)</td>
<td>Epirubicin</td>
<td>Phase I, breast cancer, stomach cancer, lymphoma</td>
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<tr>
<td></td>
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<tr>
<td>NC6004</td>
<td>PEG-PGlu(cisplatin)</td>
<td>Cisplatin</td>
<td>Phase I/II, solid tumors</td>
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<tr>
<td>Genexol PM</td>
<td>PEG-P(D,L-lactide)</td>
<td>Paclitaxel</td>
<td>Phase IV, breast cancer</td>
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<tr>
<td></td>
<td>Paclitaxel</td>
<td></td>
<td>Phase II, pancreatic cancer</td>
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</tbody>
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CONCLUSION

The PEGelationis offers a great advantage for bioactive molecules in pharmaceutical and biological applications by way of reducing protein immunogenicity and increased serum half-life of the drugs. This overview highlighted on the use of PEGelated proteins, low molecular weight drugs and PEG micelles. PEGelation improves the therapeutic efficacy of a drug by passive targeting in a novel way. The process can also be combined effectively with active targeting and stimuli-responsive targeted therapies for the development of new methodologies for the treatment of cancer. It is an important to note that the efficacy of PEGelated drugs depends on the overall exposure and its relationship to the pharmacodynamics of the drug. Molecular weight of PEG chain and its structural modifications carries strategic importance for conjugation with drug molecule for effective PEGelation process. The research in this direction shall be helpful in effective cancer treatment process in near future.
REFERENCES


Citation: Raju J. Asole et al. Ijppr.Human, 2016; Vol. 6 (4): 702-718.

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