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KEYWORD(s):
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COVER
HEADLINE:
Unlocking the power of PEGylation

SUBHEADLINE:
PEGylation, liposomal PEGylation, liposomal pharma manufacturing

A special report from Sigma-Tau PharmaSource
July 2015

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HEADLINE:
Big solutions for small molecules

The world of nanomedicine opened up the door to endless new possibilities for drug researchers to deliver drugs with nanoparticles, which offered drugs that metabolize differently in the body, offering more targeted, potent treatment with fewer side effects. As researchers the world over worked toward these progressive new drug treatments for intractable diseases like cancer, hepatitis B, rheumatoid arthritis and others, one roadblock kept standing in the way of new molecules: drug solubility.

The advent of Nano medicine created a class of drugs with molecules so small, they encouraged a fast renal cycling rate, leading to drugs having too short a therapeutic period in the body. So it's not particularly surprising, then, that the FDA approval of the first PEGylated protein in 1990 caused such a stir, leading to the development of no fewer than 14 important new drugs that represent billions in drug sales, and hope for millions of patients with hard-to-treat diseases.

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SUBHEADLINE: How PEGylation works

PEGylation works by attaching additional polymer chains to a molecule to make it larger. It is the process of both covalent and non-covalent attachment of polyethylene glycol (PEG) chains to molecules and macrostructures, such as drug, therapeutic proteins or vesicles. The covalent attachment of PEG to a drug or therapeutic protein masks the agent from the patient's immune system, allowing it to travel in the body long enough to evenly distribute drugs through the patient's system for longer periods. Molecules constructed in this manner are said to be PEGylated.

SUBHEADLINE: The power of PEGylation

Once PEG is added to the formulation of a drug molecule, it changes everything, from its weight to its shape, to its solubility, to even its function. Because of this, uncovering the capabilities of liposomal PEGylation has been a continuing, robust area of scientific discovery; and one that is likely to continue for years to come.

Numerous studies have noted how PEGylation changes the molecular weight of the molecule, giving it many pharmacological advantages over its original, unmodified form, including:

- Improved drug solubility
- Extended circulating life, in most cases, by more than double
- Increased drug stability
- Enlarged size, keeping the body from breaking the molecule down enzymatically
- Camouflaging the drug, keeping it from being quickly attacked by the immune system
- Changing the elimination of a drug from renal to hepatic pathway
- Reduced dosage frequency
- Protection against proteolysis
- Modification of electro-osmotic flow
- Increased pH and thermal stability
- Low volume of distribution and sustained absorption from the injection site
- Altering the tissue/organ distribution profile, allowing drugs to accumulate better at tissue sites around tumors

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SUBHEADLINE: The properties of PEG

In most cases, the compound used in PEGylation is polyethylene glycol, which has many properties that make it beneficial to drug makers. PEG is inert, non toxic, and non-immunogenic. The polymer is easily cleared through the kidney or liver, with molecular weight below 20 kDa. PEG is a viscous liquid at molecular weights lower than 1000 and solid at higher molecular weights. And, because it is prepared by anionic polymerization, a variety of molecular sizes are possible.

PEG is FDA approved for human administration by mouth, injection, or dermal application, making it a compound suitable for liquid, pill, patch or inhaled formulations. All PEGylated drugs now on the market contain methoxy poly(ethylene glycol) or mPEG.

As years have passed, different types of PEG have been developed based on their suitability for certain applications. At, present, there are:

First generation PEG derivatives – a PEG group that is reactive with hydroxyl groups, typically anhydrides, acid chlorides, chloroformates and carbonates. For proteins, typical reactive amino acids include lysine, cysteine, histidine, arginine, aspartic acid, glutamic acid, serine, threonine and tyrosine.

Second generation PEG derivatives – for this group, PEGylation chemistry uses more efficient functional groups such as aldehyde, esters, and amides, etc.

Third generation PEG derivatives – which are used when PEGS are needed for conjugation to link two entities, and a hydrophilic, flexible and biocompatible spacer is also needed. Preferred end groups include maleimide, vinyl sulfones, pyridyl disulfide, amine, carboxylic acids and NHS esters.

PEG-Based hydrogels – chemically cross-linked PEG can be created to form networks that swell and form “hydrogels.” The biocompatibility of hydrogels makes them ideal for wound-healing applications, such as FocalSeal, a FDA-approved surgical sealant to prevent air leaks in the lungs after lung and chest surgeries, or SprayGel, a biodegradable hydrogel that prevents post-operative formation of skin adhesions.

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SUBHEADLINE: FDA-Approved PEGylated Drugs

DRUG	APPROVED	FUNCTION
Naloxegol (Movantik)	2014, AstraZenica	Treatment of opioid-induced constipation in adults with chronic non-cancer pain
Peginesatide (Omontys)	2012, Affymax/Takeda	Once monthly medication to treat anemia with chronic kidney disease in adult dialysis patients
Pegloticase (Krystexxa)	2010, Savient	PEGylated uricase for the treatment of gout
Certolizumab pegol (Cimzia)	2008, Nektar/UCB Parma	Monoclonal antibody for treatment of moderate to severe rheumatoid arthritis and Crohn's disease
Methoxy polyethylene glycol-epoetin beta (Mircera)	2007, Roche	PEGylated form of erythropoietin to combat anemia associated with chronic kidney disease.
Pegaptanib (Macugen)	2004, Pfizer	Treats neurovascular age-related macular degeneration
Pegfilgrastim (Neulasta)	2012, Amgen	PEGylated recombinant methinonyl human granulocyte colony-stimulating factor for severe cancer chemotherapy-induced neurtropenia
Pegvisomant (Somavert)	2002, Pfizer	PEG-human growth hormone mutein antagonist for treatment of Acromegaly
Peginterferon alfa-2a (Pegasys)	2001. Hoffmann-LaRoche	PEGylated interferon alpha for use in the treatment of chronic hepatitis C and hepatitis B
Doxorubin HCl liposome (Doxil/Caelyx)	2001, Ortho Biotech /Schering-Plough	PEGylated liposome containing doxorubicin for the treatment of cancer
Peginterferon alfa-2 b (PegIntron)	2000, Schering-Plough/Enzon	PEGylated interferon alpha for use in the treatment of chronic hepatitis C and hepatitis B
Pegaspargase (Oncaspar)	1994 Enzon 1990 Enzon	PEGylated L-asparaginase for the treatment of acute lymphobalastic leukemia in patients who are hypersensitive to the native unmodified form of L-asparaginase.
Pegademase bovine (Adagen)	1990 Enzon	PEG-adenosine deaminase for the treatment of severe combined immunodeficiency disease (SCID)

(Source: Biospace.com and www.fda.gov)

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SUBHEADLINE: The Sigma-Tau PEGylation Process

As a contract manufacturer of pharmaceuticals, we specialize in the production of liposomal formulations, especially PEGylated varieties. In fact, we've built our entire operation around liposomal processes, offering our clients only the most cutting edge, GMP-certified, clean room and cold-chain manufacturing machinery and processes.

We believe our proprietary process for PEGylation offers our clients the latest, cutting edge techniques that will help innovation grow. When you work with Sigma-Tau Pharmasource, you can expect these offerings: *(client, please fill in more appropriate detail about your proprietary process, and the results a client can get from these procedures versus the competition.)*

Process/ Procedure	Definition & advantages	Patents	Certifications

SUBHEADLINE: Keeping the Promise

The PEGylation process has helped scientists push the frontiers of nanomedicine for 25 years now, and the applications for it will only continue to grow. Since 1990, much progress has been made to understand the generation of biomolecule therapeutics and PET-bio-molecule conjugates. PEGylation is now considered the method of choice for improving the pharmacokinetics and pharmacodynamics of protein pharmaceuticals.

In the future, you can expect to see more advances, such as more PEGylated drugs that can cross the blood-brain barrier, or the use of DNA-containing liposomes with tethered antibodies to provide targeted gene therapy.

Regardless of where research takes nanomedicine, Sigma-Tau PharmaSource will be there as a help and guide on the road to innovation, ready to provide emerging companies all their contract manufacturing needs. Big progress from small molecules. It's the core of the Sigma-Tau mission.

FINAL PAGE
HEADLINE:
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