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Mini Review

The Usage of PEG in Drug Delivery Systems- A Mini Review

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Abstract

Designing polymeric delivery systems for drugs and genes to implement individual biological functions is an area of continuing interest. Poly (Ethylene Glycol) (PEG) is one of the most successfully adopted materials for designing this kind of drug delivery systems and it exhibits a controllable and sustained release profile. Due to its unique structure, PEG molecules are used to reduce the immunogenicity of drug delivery systems and active substances and to avoid unwanted enzymolysis. PEG based copolymers also play a very important role as biomedical materials due to their biocompatibility, biodegradability and easily controllable characters. This mini review summarizes the state-of-the-art use of PEG in therapeutic applications.

Keywords: Polyethylene glycol; Drug delivery; Hydrogels

Abbreviations: PEG: Polyethylene Glycol; FDA: Food and Drug Administration; BSA: Bovine Serum Albumin

Introduction

Polymers, which are formed by the formation of larger molecules by establishing bonds between simple structures called monomers, have recently become a frequent subject of research in the field of medicine and biotechnology [1]. These high molecular weight substances, which are formed because of the combination of the word's "poly" used to mean "many" in Greek and "meros" used to mean "part/section", are called "Polymer" [2,3]. Natural polymers, like synthetic polymers, consist of simple and repetitive parts, and new polymers synthesized because of development studies on natural polymers are called semi-synthetic polymers [4]. When the idea of using water- soluble polymers for innovative drug delivery systems, particularly parenteral systems, was first proposed, the industry viewed the idea as an impractical and very risky scientific curiosity, then because of studies on polymers, these high molecular weight molecules began to take place in controlled drug release systems as rate-controlled membranes or biodegradable implants [5-7]. PEG is one of the most important of these water-soluble polymers. After the discovery of PEG in the 1950s, the first pegylation process took place in the late 1970s and thus PEG gained an important place in drug delivery systems [8]. Besides the high water- soluble nature of PEG, it is a non-toxic, non- immunogenic and non-antigenic and FDA- approved conjugate. Therefore, PEG is frequently preferred in drug delivery systems [9,10]. Also, the trend towards biotechnological drugs in recent decades shows that PEG will take place more in drug delivery systems in the future [11].

Polyethylene glycol (PEG)

The emergence of PEG chemistry began in 1977 with the findings of Abuchowski et al. reported that alteration of the immunological properties of Bovine Serum Albumin (BSA) was achieved by the covalent attachment of poly(ethylene) glycol, more appropriately termed PEG [12]. Polyethylene Glycols (PEGs) are polymers of ethylene oxide with the generalized formula HO $(CH_2\_CH_2\_O)_n$-H, and "n" indicating the average number of oxyethylene groups and are

composed of polyether compounds repeating ethylene glycol units according to the constituent monomer or parent molecule (Figure 1) [13,14]. They are FDA approved synthetic polymers used in food, cosmetics and pharmaceutical industries in non-toxic, white solid form, it is soluble in water, most organic solvents and aromatic hydrocarbons, but slightly soluble in aliphatic hydrocarbons [15,16]. Apart from its use in drug delivery systems in pharmacy, it is used as a water-soluble lubricant in rubber molds, textile fibers and metal forming processes. It is also commonly used in foodstuffs and their packaging, hair preparations and cosmetic preparations. It is also used as a stationary phase in gas chromatography. PEG content is also found in watercolors, paper coatings, lacquers and ceramics [17-19].

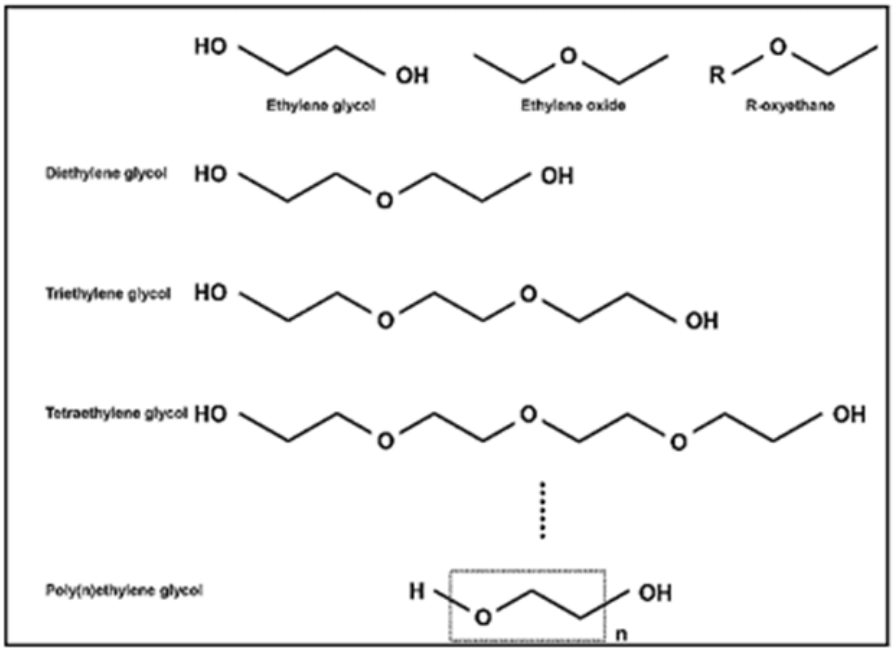

Figure 1: Polymerization of ethylene glycol [14].

PEG in Controlled Drug Delivery Systems

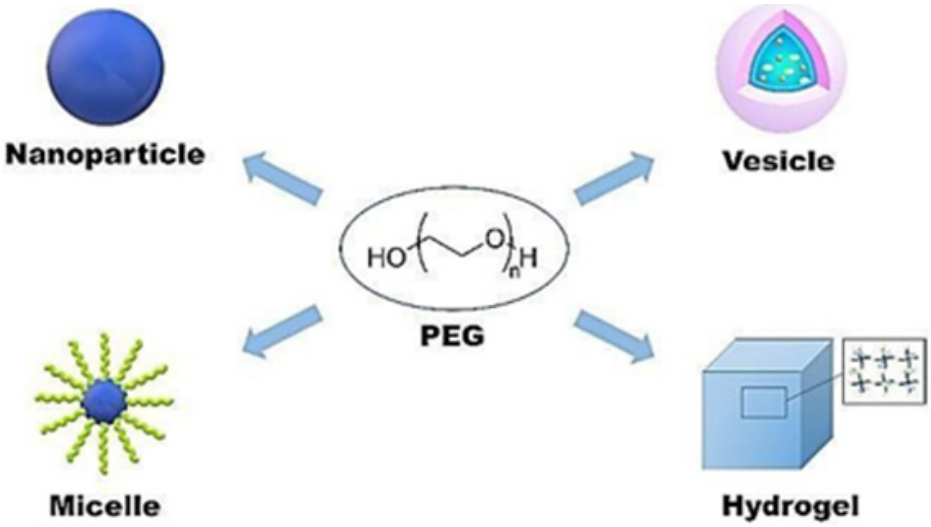

Figure 2: Controllable and sustainable antidiabetic drug delivery systems [29].

Many fundamental studies have revealed the structural properties of PEG-based hydrogels, such as swelling properties, mechanical properties, and molecular transport properties. Based on these studies, PEG-based controlled release systems containing large biomacromolecules such as nucleic acids, peptides and proteins have been prepared from small molecular weight drugs [20-25]. Two important considerations in the design of PEG hydrogels are stability and bioavailability. To obtain the desired therapeutic efficacy from a designed drug, PEG hydrogels must be stable and capable of releasing the correct dosage of active

substance [26-28]. The release of an active substance from PEG-based hydrogels depends on multiple factors such as the method of loading of the drug, its size, molecular properties, the dose required for administration, and the release profile [30-32]. The most important feature of PEG that enables it to be used in controlled release systems is its protein resistance (Figure 2) [33-35]. Due to the hydrophilic nature of PEG, the polymer chain is firmly attached to hydrogen bonds in water, which inhibits or inhibits protein adsorption to the PEG chain [36-38]. Due to this feature, PEG chains on the surface prolong activities such as endocytosis, phagocytosis, liver effects and adsorptive processes in the body, allowing the therapeutic proteins to bound to it to remain in the circulation for a longer time [41-42].

PEGylation in Drug Delivery

PEGylation describes the modification of a protein, peptide, or non-peptide molecule by the attachment of one or more Polyethylene Glycol (PEG) chains [31,43,44]. PEG-drug conjugates have some advantages, prolonged residence in the body, a reduced degradation by metabolic enzymes and reduction or elimination of protein immunogenicity. Due to these properties, PEGylation plays a very important role in drug delivery today, increasing the potential of peptides as well as proteins as therapeutic agents. There are PEGylated pharmaceutical products on the market today and they play a very important role in the drug delivery system [9,30,43]. From 1995 to 2022, 27 macromolecules, 2 small molecules and 1 nanoparticulate drug have been approved by The United States Food and Drug Administration (FDA) and in addition, Comiranty® (COVID-19 vaccine, mRNA by Pfizer/BioNTech) in which PEGylation technology was used in the rapid development of mRNA-based COVID-19 vaccine received full approval by the FDA in August 2021 [44,45].

Conclusion

Thanks to its unique structure, PEG provides enhanced physicochemical properties and biodegradability to natural or artificial materials. Drug delivery systems composed of PEG can protect drugs with PEGs long hydrophilic chains. And this property prolongs internal life, and promote the stability of particles, leading to improved therapeutic effects. Therefore, the expected effect from the drug will be achieved with a lower amount of active agent. This will increase the safety of the treatment by providing a significant increase in the therapeutic effect/side effect ratio. Hence, passive targeting of destructive drugs used in cancer treatment with PEG is a very useful approach. In addition, hiding foreign protein structures from the reticuloendothelial system with PEG is among the factors that pave the way for novel biotechnological drugs. Studies on the search for new ligands and the development of non-chromatographic affinity strategies for PEG- modified proteins will proliferate. Also, in the future, new PEGylated agents will increase the demand for stable and long-lasting drugs.

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