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Magneto-electric nanocarriers for drug delivery: An overview

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ABSTRACT

There is an increasing interest to develop new nanocarriers that are capable of controlled and targeted drug delivery. To satisfy this motivation, the body-temperature magneto-electric nanocarriers (ME-NCs) were developed in the form of multi-functional nanostructures possess unique coupling of both magnetic and electric properties at physiological condition. These novel nanocarriers achieve on-demand drug release in response to low-field external magnetic stimulation in an energy-efficient dissipation (heat)-free mechanism. This platform technology proved promising potential for the treatment of cancer, AIDS and for Parkinson's disease management via high efficiency noninvasive deep brain stimulation. However, these studies are limited to *in vitro* models and must be explored for clinical applications. Therefore, efforts should be accelerated to prove the therapeutic and diagnostic potentials of ME-NCs in *in vivo* models. Unfortunately, significant knowledge gaps still exist on a complete toxicological profile of these nanocarriers and intensive studies have to be performed. This mini-review explores the rationale of ME-NCs for controlling and site-specific drug release, mechanism of action, advantages over conventional magnetic nanocarriers, preparation methods, characterization techniques, therapeutic and diagnostic applications, toxicity assessment and future directions.

Contents

1. Introduction

The development of a technology that is capable of high-specificity targeted delivery of therapeutic agents would be a significant breakthrough in health quality. The confinement of the

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drug specifically inside the target cell without affecting the healthy cells challenges the natural ability of the circulatory system to deliver a drug to every cell in the body. Besides, the attainment of tunable release profiles along with biocompatibility offer additional obstacles [1]. Recently, attention has been focused toward the nanoscale manipulation of drug delivery systems offering unique properties for navigation and controlled drug release, that cannot be attained in conventional- and microscale-drug carriers [2].

Nanoscale stimuli responsive systems (Fig. 1) enable controlling drug biodistribution in response to appropriate exogenous/endogenous stimuli [3,4]. However, the released drug from nanocarriers-drug formulation in the bloodstream results in possible binding of the drug with unspecific sites. This causes drug concentration loss at active target site, undesirable side effects and reduced efficacy [2].

These challenges can be overcome via designing multifunctional nanocarriers with the combined properties to achieve target-specific delivery of on-demand and controlled drug release [3]. The choice of nanocarrier materials and its surface modification to architect the formulation is crucial in achieving high drug loading, suitable navigation and controlled drug release with the proper selection of stimuli-responsive [2].

Based on these principles, **ME-NCs** were developed as novel nanocarriers to deliver and release therapeutic agents on the target site. These nanocarriers are characterized by ideal properties of high loading capacity, site-specificity and accurate on-demand controlled drug delivery. Only few reports are available on the ME-NCs-based drug delivery and their biological-related applications [2]. This mini-review aims at providing an insight into these novel nanocarriers.

2. Rationale of magneto-electric nanocarriers

The magneto-electric (ME) effect is defined as the dielectric polarization of a material in an applied magnetic field or an induced magnetization in an external electric field [5]. Magneto-electric nanocarriers are a subgroup of multiferroic materials possessing the strong coupling ability of its magnetic and electric fields at body temperature [6,7]. Structurally, ME-NCs are core shell structures, where a magnetic core is preserved with a shell of desired electrical properties [8]. Consequently, these novel carriers have been adopted for on-demand controlled drug delivery on application of remote low-energy direct (d.c.) and/or alternating current (a.c.) magnetic field [2].

3. Mechanism of action of magneto-electric nanocarriers

Due to the strong magneto-electric coupling properties of ME-NCs, they can function as localized magnetic-to-electric-field nano-converters in biological microenvironments allowing remote control and generation of the electric signals that underlie the intrinsic molecular interactions [9,10].

This unique electromagnetic capability can exploit the cell membrane's intrinsic properties. The voltage-gated ion channels in cell membranes are kind of electrically polarized medium that can be affected by the resulting electric field. This property explored to open up and/or create pores in the cell membrane in a mechanism called "**Nano-electroporation**" referring to the scale down of electroporation to the nanoscale [1,2]. The process is relatively energy efficient as most of the energy is directed to fulfill the main operation (of opening up the local pores) without potential

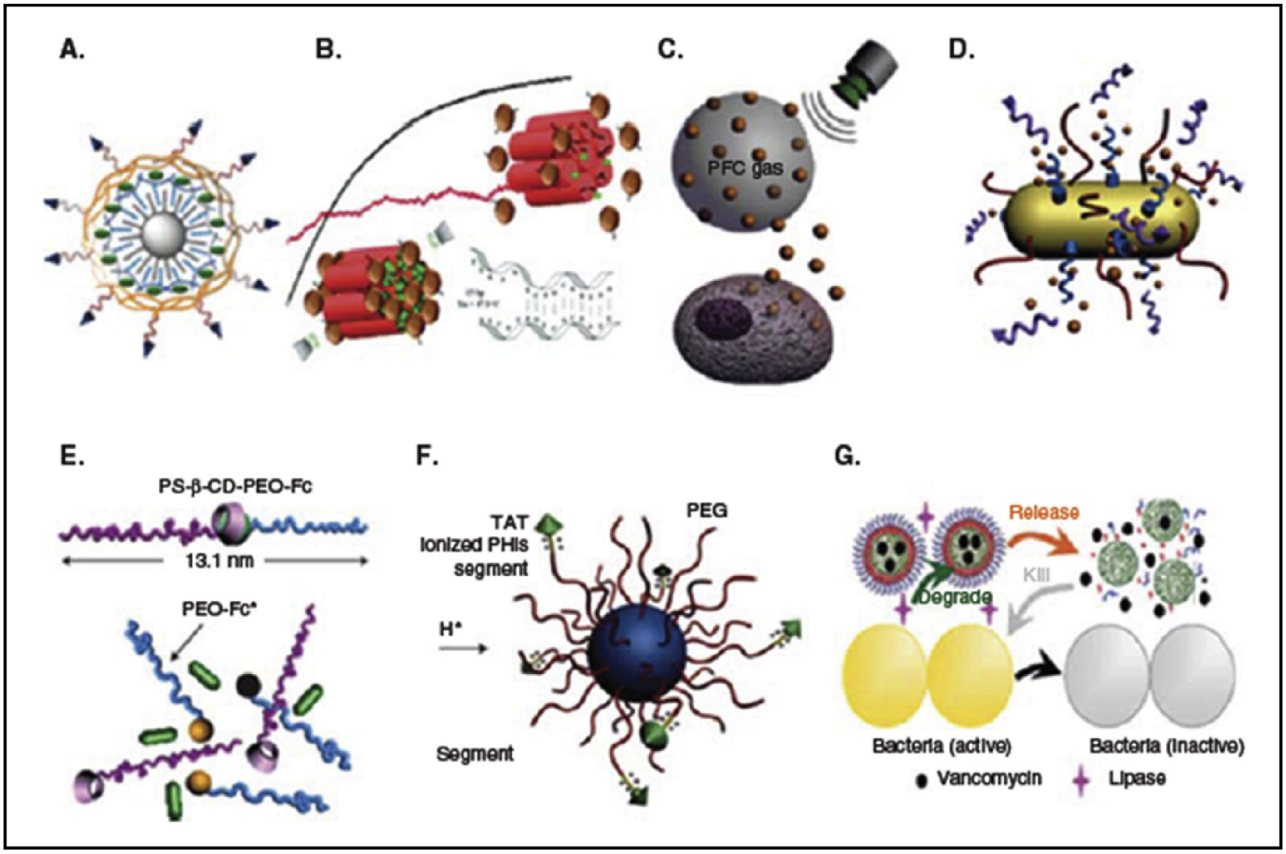

Fig. 1. Stimuli-responsive nanocarriers in drug delivery. A) Temperature-based liposomal drug delivery, **B)** Heat generated stimulation from nanocarriers due to an alternating magnetic field, **C)** Ultrasound stimulated drug delivery from nanoemulsions, **D)** Near-infrared-triggered release of drug, **E)** Voltage-responsive controlled drug delivery, **F)** pH-sensitive nanocarriers for efficient drug release and **G)** Enzyme-sensitive drug delivery [2].