



Contents lists available at SciVerse ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addrPhysical energy for drug delivery; poration, concentration and activation[☆]

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ARTICLE INFO

Article history:

Accepted 31 May 2013

Available online xxxxx

Keywords:

Electroporation

Gene transfection

Magnetoporation

Nanoparticles

Optoporation

Photothermal therapy

Smart drug carriers

Sonoporation

Thermoporation

ABSTRACT

Techniques for controlling the rate and duration of drug delivery, while targeting specific locations of the body for treatment, to deliver the cargo (drugs or DNA) to particular parts of the body by what are becoming called “smart drug carriers” have gained increased attention during recent years. Using such smart carriers, researchers have also been investigating a number of physical energy forces including: magnetic fields, ultrasound, electric fields, temperature gradients, photoactivation or photorelease mechanisms, and mechanical forces to enhance drug delivery within the targeted cells or tissues and also to activate the drugs using a similar or a different type of external trigger. This review aims to cover a number of such physical energy modalities. Various advanced techniques such as magnetoporation, electroporation, iontophoresis, sonoporation/mechnoporation, phonophoresis, optoporation and thermoporation will be covered in the review. Special emphasis will be placed on photodynamic therapy owing to the experience of the authors' laboratory in this area, but other types of drug cargo and DNA vectors will also be covered. Photothermal therapy and theranostics will also be discussed.

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[☆] This review is part of the Advanced Drug Delivery Reviews theme issue on “Editor's Choice 2014.

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1. Introduction

The purpose of a drug delivery system (DDS) [1,2] is to devise a method that enables delivery of a therapeutic agent that may have sub-optimal physicochemical properties in biological tissue, thus enhancing efficacy and safety by controlling the rate, time, and release of the agent [3]. Targeted DDS (TDDS) includes the administration of the therapeutic substance, the release of the active ingredients from the DDS, and the subsequent transport of the active ingredients across the biological membranes to the specific site of action, often using what is so called “smart drug carriers” or “smart nanoparticles (NP)”. Smart NP can improve drug delivery mechanisms based on their particular formulations [4,5]. NP used in such biomedical applications include lipid-based NP (liposomes) [6,7], polymeric micelles [8,9], block ionomer complexes [10,11], water-soluble synthetic polymers (dendrimers) [12,13], inorganic [14] and polymeric NP [15], nanorods [16,17], quantum dots [18,19], carbon nanotubes [20,21], silica-based NP [22], metal and semiconductor NP, upconversion NP [23,24], self-illuminating NP [25,26] and polymer–drug conjugates [27]. However the main limitations of employing NP for drug delivery are the following: 1) the relatively small amount of drug that can be linked to each NP; 2) the possibility of drug deactivation once it is chemically bound to the NP; 3) the possibility of immediate uncontrollable passive release (burst effect); and 4) NP agglomeration producing quick elimination from bloodstream by macrophages before

reaching the target cells [28]. Most of these factors in turn require injection of unnecessarily high concentrations of NP, with potential systemic toxic effects. In order to overcome some of these hurdles, physical energy methods have been explored to enhance not only NP but also drug and gene delivery.

The enhancement of effective drug delivery to the target achieved by the addition of physical energy to the traditional TDDS systems has been widely explored in recent years [29–36]. These techniques have the potential to be used in different biological and medical applications as an advanced TDDS that can minimize the current limitations and unwanted effects. Biophysical energy such as electric fields, magnetic fields, ultrasound and mechanical forces, light and temperature gradients can act as enhancers for drug delivery. Technique-specific terms have been associated with each form of physical energy such as electroporation [37,38] for electric current, iontophoresis for electric potential, magnetoporation [39,40] for magnetic field, sonoporation [41,42], mechanoporation [43] and phonophoresis [44,45] for ultrasound, optoporation [46,47] for pulsed light and thermoporation [48,49] for temperature, respectively (Fig. 1). Table 1 summarizes all of the different types of physical energy used in this review for porating the cells. The advantages and disadvantages of the techniques are analyzed in the table. Synergistic combinations of two or more physical energies such as magnetic-electroporation [50] are also of special interest and have been explored as a potential system for effective drug delivery. The formation of temporary pores in the cell membrane achieved

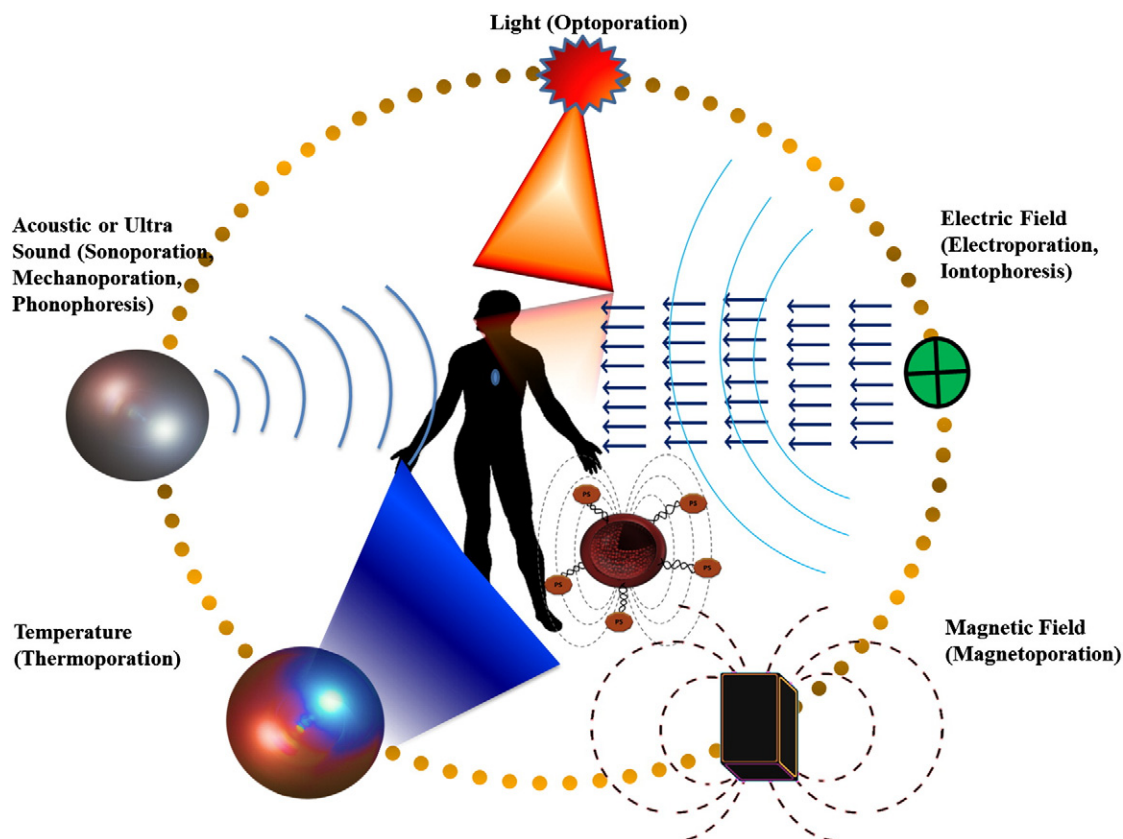


Fig. 1. Different physical energy modules used for drug delivery. Drug delivery enhancers such as electroporation, magnetoporation, thermoporation, sonoporation and optoporation are illustrated.

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