Chronicles of Nanoerythrosomes

Subjects: Pharmacology & Pharmacy

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Nanoerythrosomes (NERs) are the carrier erythrocytes (C-ERs) which are recognized as modern day, novel, and smart drug delivery systems associated with increased bioavailability, improved pharmacokinetics, and low toxicity.

Keywords: nanoerythrosome ; nanoerythrocyte ; nanovesicles

1. Introduction

As a physiological carrier, NERs can release the drug in circulation for weeks, have high loading capacity, are easy to be processed and have good ability to accommodate biologics, antigens, contrasting agents, peptides, proteins, enzymes, and macromolecules using different chemical and physical-based methods [1][2]. Innumerable examples are available in the literature discussing the drug delivery by C-ERs for applications in drug targeting to the reticuloendotehlial system (RES), enzyme therapy, and improvement in the delivery of oxygen to the tissues [3][4]. One of such example is the delivery of bovine serum albumin (BSA) as a model antigen, which can be loaded on the human erythrocytes and delivered to the RES [5]. C-ERs are the unique drug delivery system that is also known to be capable of modulating the immune responses [6]. Amongst different antineoplastic drugs, methotrexate, etoposide, doxorubicin, and carboplatin have been successfully encapsulated in these carriers previously [7]. C-ERs are shown to protect the carried therapeutics such as antibiotics, antineoplastics, corticosteroids, peptides, and enzymes from being inactivated by different endogenous factors. The three main mechanisms, by which these C-ERs work are prolongation of circulation half-life, slow drug release, and organ-specific targeting [8]. Regulatory aspects of carrier erythrocytes and industrial developments are evolving day by day. However, their production scalability, process validation, and quality control are still challenging enough for successful industrialization [9].

2. Applications of NERs in Non-Cancer Therapies

NERs have been extensively investigated for the therapy and diagnosis of various forms of cancers and that has further encouraged the researchers to test their applications for non-cancer diseases. The findings are interestingly very promising which has opened a new vista for the applications of NERs. In one such study, the NERs of antimalarial drug pyrimethamine (PRY) were developed by sonication method which showed good stability and controlled in vivo release. Developed NERs improved the treatment of malaria when combined with artemisinin drug [10]. In another interesting research, artesunate (ART) conjugated NERs were prepared to increase the stability, decrease the toxicity, cost, and drug leakage for the treatment of malaria. The optimized ART-NER nanoformulations were non-aggregated, uniformly sized, with drug loading of 25.20 ± 1.3 µg/mL and when administered IV, showed higher plasma drug concentration as compared to free drug in vivo [11]. For the treatment of atherosclerosis, the nanomaterials can be explored and it is believed that they can serve as a powerful tool in its treatment. In an attempt to achieve this, biomimetic, well defined core-shell-nanocomplexes of rapamycin (RAP)-loaded PLGA-NPs cloaked with RBC were created with negative surface charge. The prepared nanosystems were shown to be safe and effective in the management of atherosclerosis as the biomimetic behavior of RBCs resulted in decreased macrophage-mediated phagocytosis and increased aggregation of NPs in the atherosclerotic plagues using targeted delivery [12]. Most of the applications of NERs were limited to the IV, IP, and sub-cutaneous (SC) routes of administration. To explore other possible routes of administration, they were also investigated as inhalational drug carriers in few studies successfully. In one such study, NERs were conjugated with CARSKNKDC (CAR), a cell permeable peptide and fasudil, a rho-kinase (ROCK) inhibitor using hypnotic-lysis and extrusion method for prolonged pulmonary vasodilation. The NPs obtained were of spherical shape with average size 161.3 ± 1.37 nm and % entrapment efficiency (EE) 48.81 ± 1.96%, which showed stability of around 3 weeks at 4 °C, and the drug fasudil was shown to be released in a controlled release pattern for more than 48 h. The reduction in the pulmonary arterial pressure upon intratracheal administration of CAR-fasudil-NERs was approximately 2-fold more specific to the lungs in comparison to fasudil alone [13]. Few other studies in the literature also suggest that the NERs can effectively be utilized for inhalational delivery of fasudil drug as cell-derived carriers [14][15].

3. Biosensing Applications of RBC-Mediated Carriers Systems

The cutting-edge RBC-mediated anti-cancer drug delivery by NERs is well established along with their applications in some of the non-cancer diseases. Additionally, the in vivo nanobiosensor-based theragnostic application of RBCs has emerged as a topic of interest in present days for advanced medical diagnostics, analytical chemistry, and environmental monitoring [16][17][18]. Their extraordinary profusion, mobility, and loading capacity makes them an attractive tool for sensing the analytes present in the blood. The sensor-loaded ERs or the dubbed erythrosensors can be re-infused in the blood and can be used for the measurement of analyte levels in the blood stream [17]. Previously, 3-D focusing of RBCs in microchannel flows for bio-sensing applications has also been reported [19]. Additionally, the fluorescent sensors were incorporated inside ERs followed by non-invasive monitoring to follow changes in plasma analyte concentrations [19]. For the management of diseases such as diabetes, there exists a need for long-term, minimal-invasive system to monitor blood glucose as analyte. Currently employed methods suffer from disadvantages of low patient compliance for the finger stick test and require regular calibrations for continuous glucose monitoring. The RBCs can act as a biocompatible carrier of sensing assays for such long-term monitoring procedures. They can serve as long-term (˃1 to 2 months), continuously circulating biosensors in the diagnosis and management of such long term diseases [20]. Similarly, the fusion of quantum dots (QD) with living cell membranes for bio-sensing capability in imaging technique is a flexible approach for controlled, hydrophobic QDs-based fluorescence analysis of living cellular membranes [21].

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