Journal of Pharmaceutical Sciences xxx (2021) 1-11

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutical Nanotechnology

Self-Emulsifying Drug Delivery Systems: Mucolytic Action of N-acetylcysteine (NAC)-Polymer Hydrophobic Complexes for Effective Mucopermeation

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ARTICLE INFO

Article history:
Received 21 December 2020
Revised 25 January 2021
Accepted 10 February 2021

Keywords:
SEDDS
Nanoemulsions
Ion pairing
Intestinal mucus
Mucopermeation
Viscoelasticity
Sustained release

ABSTRACT

The mucolytic function of N-acetylcysteine (NAC) is necessary for the diffusion of mucoactive self-nanoemulsifying drug delivery systems (SEDDS) through the intestinal mucus gel layer. NAC instantly released from SEDDS leads to nonsignificant mucolytic activity and poor mucopermeation. It was the aim of this study to develop a novel mucoactive SEDDS based on the mucolytic function of NAC with improved mucopermeation. Therefore, NAC hydrophobic complexes with the cationic polymers polyethyleneimine (PEI), Eudragit E and RS were loaded in SEDDS and evaluated for size, polydispersity index (PDI), zeta potential and cytotoxicity. NAC release from the mucoactive SEDDS followed Ellman's method at pH 6.8. Interaction of mucoactive SEDDS with mucus was assayed using *in vitro* rheology, a Transwell diffusion model and intestinal residence time. SEDDS showed size stability in the range of 76 ± 12 nm over 4 h, as indicated by < 0.3 PDI and caused zeta potential increase from −17.3 mV to −7.7 mV. SEDDS showed no cytotoxicity on Caco-2 cells. The immediate release of NAC in a few seconds from SEDDS of PEI was significantly more sustained in 40–80 min with Eudragit E ($p \leq 0.05$) and RS ($p \leq 0.001$). Similarly, the SEDDS complexes showed a concentration- and time-dependent decrease of 52.55 ± 19.88% in mucus dynamic viscosity. Finally, Transwell diffusion showed approximately 2- and 1.8-fold higher amounts of diffused SEDDS anchoring NAC complexes with Eudragit E/RS ($p \leq 0.05$), respectively. Mucoactive SEDDS slowly releasing low NAC levels while permeating exhibit better mucolytic targeting, which improves overall *in vitro* mucopermeation.

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Introduction

The demand for oral drug delivery has led to the development of self-nanoemulsifying drug delivery systems (SEDDS) in which many drugs can be solubilized. With a surfactant-oil-cosolvent mixture, these systems spontaneously form an oil-in-water (o/w) emulsion upon contact with gastrointestinal (GI) fluids, providing a valuable means of intestinal mucosal drug delivery.[1,2] However, the mucus gel layer lining the absorptive mucosal epithelium presents a challenge. SEDDS have to diffuse through this dynamic barrier from the intestinal luminal side to the epithelial side, encountering steric hindrance that may contribute to poor systemic bioavailability of the loaded essential drug.[3] Several strategies can be proposed to overcome the mucus barrier. These are either dependent on altering the physicochemical properties of the SEDDS themselves or designing systems that actively interact with the mucus.[4] These can be, for instance, SEDDS composed of excipients providing slippery droplet surfaces, small droplet sizes and droplets with negative surface zeta potentials, described as diffusion enhancers.[5,6] Furthermore, changing the negative zeta potential of permeating SEDDS droplets to a positive value guarantees the prevention of reverse diffusion.[7,8] Despite the achieved success in using mucus-inactive approaches, altering the conformation of the cross-linked glycoprotein-based mucin fibers forming the mucus robust network is necessary when the optimized setup of muco-diffusing droplets is not sufficient to achieve the desired goal for the

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https://doi.org/10.1016/j.xphs.2021.02.010
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