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Duodenum-triggered delivery of pravastatin sodium via enteric surface-coated nanovesicular spanlastic dispersions: Development, characterization and pharmacokinetic assessments

Saadia Ahmed Tayel, Mohamed Ahmed El-Nabarawi, Mina Ibrahim Tadros *, Wessam Hamdy Abd-Elsalam

Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Cairo University, Kasr El-Aini, 11562 Cairo, Egypt

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ABSTRACT

Pravastatin sodium (PVS) is a hydrophilic HMG-CoA reductase inhibitor that is mainly absorbed from duodenum. PVS has a short elimination half-life (1–3 h), suffers from instability at gastric pH, extensive hepatic first-pass metabolism and low absolute bioavailability (18%). The current work aimed to develop enteric surface-coated spanlastic dispersions as controlled-release duodenum-triggered systems able to surmount PVS drawbacks. PVS-loaded spanlastic dispersions were prepared by ethanol-injection method using span® 60. Tween® 60 and Tween® 80 were explored as edge activators. As a novel approach, the fine spanlastic dispersions were surface-coated with an enteric-polymer (Eudragit® L100-55) via freeze-drying. The systems were evaluated, before and after enteric-coating, for particle size, zeta potential, PVS entrapment efficiency (EE%), morphology and PVS release studies. PVS pharmacokinetics from the best achieved system and an aqueous solution were estimated in rats by UPLC–MS/MS. The best achieved enteric surface-coated spanlastic dispersion (E-S6) displayed spherical nanosized vesicles (647.60 nm) possessing negative zeta potential (−6.93 mV), promising EE% (63.22%) and a biphasic drug-release pattern characterized by a retarded-release phase (0.1 N HCl, 2 h) and a controlled-release phase (pH 6.8, 10 h). The higher C_{max}, delayed T_{max}, prolonged $MRT_{(0-\infty)}$, longer elimination $t_{50\%}$ and enhanced oral bioavailability unravel E-S6 potential for oral PVS delivery.

1. Introduction

The design of new therapeutic strategies strives to improve the pathways of drug administration, the required doses, the specificity of response and the combination of multifunctional systems to allow greater patient-oriented treatment (Tanner et al., 2011). Approaches are being adapted to control the drug biodistribution by incorporating the drug in a suitable carrier system, by altering the drug structure at the molecular level or by controlling the direct drug input into the bioenvironment (Biju et al., 2006). The colloidal drug carriers such as nanoparticles and nanovesicles (like liposomes, niosomes, transfersomes, ethosomes, pharmacosomes, etc.) have been investigated to protect labile drugs from degradation in the GIT, to protect the GIT from possible drug toxicity and to promote targeted drug penetration into cells (Barratt, 2000).

Recently, Kakkar and Kaur developed spanlastic systems as novel nanovesicular colloidal drug carriers based on non-ionic surfactants and explored their potential for the ocular and dermal delivery of ketoconazole (Kakkar and Kaur, 2011, 2013). The spanlastic system consists of Span® 60, as a non-ionic lipophilic surfactant, along with an edge activator. The latter includes other hydrophilic surfactant molecules that provide flexibility to the lipid bilayers of spanlastic systems by inducing pores and causing destabilization of these membranes (Kaur et al., 2012). Like liposomes and niosomes, spanlastic systems are spheroid structures consisting of amphiphilic molecules acting as suitable matrices for bioencapsulation (Balakrishnan et al., 2009).

Pravastatin sodium (PVS) is a lipid-lowering agent that inhibits HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase activity and regulates hepatic low-density lipoprotein (LDL) receptors in animals and humans (Komai et al., 1992). Following oral administration, PVS is rapidly absorbed showing a maximum drug-plasma concentration within one hour. Previous studies on

* Corresponding author. Tel.: +20 1223620458; fax: +20 223628426.
E-mail addresses: mina_ebrahim@yahoo.com, mina.tadros@pharma.cu.edu.eg (M.I. Tadros).

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PVS suggested that the upper part of the small intestine (the duodenum) represents the main site for absorption through the GIT. Unfortunately, the oral bioavailability of PVS is 18% only (Hatanaka, 2000). This could be related to many factors including; (i) PVS instability under the acidic milieu of the stomach and transformation to 3′α-isopravastatin and 6′-epipravastatin by non-enzymatic acid-catalysed isomerisation before absorption. These isomers have markedly lower HMG-CoA reductase inhibitory activity than PVS (Quion and Jones, 1994). (ii) The incomplete absorption and low permeability of PVS through the intestinal membrane because of its hydrophilic properties (log *P* of – 0.84). (iii) About half of PVS taken up by the intestine undergoes a first-pass metabolism. In fact, the short elimination half-life of PVS (1–3 h) does not guarantee a prolonged drug-plasma concentration suitable for daily dosing (Singhvi et al., 1990). To surmount these limitations and conceivably improve oral PVS bioavailability, controlled-release duodenum-triggered nanocarriers could be suggested. These systems not only have the abilities to protect the entrapped-drug from degradation in gastric fluid but also possess the attributes to enhance the intracellular drug penetration, to adjust the rate of drug release as well as to improve the oral drug bioavailability (Hao et al., 2013).

Two approaches were reported for the enteric-coating of nanocarriers. The first one involves the coating of the lyophilized product-loaded capsules in coating pans or fluid bed equipment till a certain increase in capsule weight is achieved (Gupta et al., 2013). This technique necessitates high expertise to deal with many limitations including; (i) insufficient adhesion of the film on the smooth capsule shell with possible splintering and peeling of coat, (ii) increased cracking on handling the medicament, (iii) separation of the capsule shells due to movement in the coating pans and (iv) altered coating permeability due to the presence of residual moisture or solvents (Petereit and Weisbrod, 1999; Thoma and Oschmann, 1991).

The surface-coating technique is the second approach that could be achieved via different methods like emulsification-solvent diffusion (Dai et al., 2004), oil-in-oil emulsification (De Oliveira et al., 2009), drug-interpolyelectrolyte complexation (Palena et al., 2012), coaxial electro-spray deposition (Zhang et al., 2011), aerosol flow reactor (Eerikäinen and Kauppinen, 2003), ultrasonic dispersion – diffusion solidification (Hao et al., 2013) and spray drying (Bejugam et al., 2008). Unfortunately, most of these methods suffer from many limitations including; (i) the use of organic solvents, (ii) the lengthy production steps as well as (iii) the need of special sophisticated equipment (Bejugam et al., 2008).

In the current work, the controlled drug-release potential of oral spanlastic systems was explored for the first time to the best of the authors' knowledge. As a novel approach, the promising spanlastic systems were enteric surface-coated with Eudragit® L100-55 (in a single step and without the need of organic solvents) via freeze drying. To explore the aptitude of the developed techniques, the pharmacokinetics of PVS following oral administration of the best achieved enteric surface-coated system and an aqueous drug solution were evaluated in rats by UPLC–MS/MS.

2. Materials and methods

2.1. Materials

Pravastatin sodium (PVS) and rosuvastatin calcium (RVC; internal standard in UPLC/MS/MS analysis) were kindly provided by Hi-Pharm (Obour city, Egypt) and Chemipharm, (6th October city, Egypt), respectively. Eudragit® L100-55 was donated by Rohm Pharma GmbH (Weiterstadt, Germany). Sorbitan monostearate (Span® 60), Polyoxyethylene sorbitan monostearate (Tween® 60) and Polyoxyethylene sorbitan monooleate 80 (Tween® 80), trehalose, ortho-phosphoric acid solution (HPLC grade), formic acid solution (HPLC grade) and methanol (HPLC grade) were purchased from Sigma Chemical Co. (St. Louis, USA). Spectra Por© semi-permeable membrane tubing (MWCO 12,000–14,000) was obtained from Spectrum Laboratories Inc. (CA, USA). Disodium hydrogen phosphate and potassium dihydrogen phosphate were purchased from Merck (Darmstadt, Germany). Ethanol (95%) and concentrated hydrochloric acid were acquired from El-Nasr pharmaceutical chemicals Co. (Cairo, Egypt). All other chemicals were of analytical grade and were used as received.

2.2. Preparation of PVS-loaded spanlastic dispersions

PVS-loaded spanlastic dispersions were prepared by the ethanol injection method as described by Kakkar and Kaur (2011). Briefly, PVS and Span® 60 were dissolved in ethanol and injected into a preheated aqueous phase in which an edge activator (Tween® 60 or Tween® 80) was previously dissolved. The organic phase to the aqueous phase ratio was fixed at 1:5. The investigated Span® 60: edge activator ratios were 1:0, 9:1, 4:1, 7:3, 3:2 and 1:1, respectively. The spanlastic vesicles were formed spontaneously and turned the resulting hydroalcoholic solution slightly turbid. Continuous stirring of the latter solution on a magnetic stirrer was performed to allow complete evaporation of ethanol and subsequent formation of PVS-loaded aqueous spanlastic dispersions. To promote the development of fine spanlastic dispersions, ultrasonic water-bath sonication (Crest Ultrasonics Corp., NJ, USA) was performed for 5 min. The composition of the investigated formulae is shown in Table 1.

2.3. In vitro characterization of PVS-loaded spanlastic dispersions

2.3.1. Determination of vesicle size, zeta potential and polydispersity index

The hydrodynamic vesicle diameter (*z*-average) and the polydispersity index (PI) of the systems were evaluated by the dynamic light scattering (DLS) technology via a Zetasizer Nano ZS (Malvern instruments; Worcestershire, UK). The technique analyzes the fluctuations in light scattering due to the Brownian motion of vesicles and consequently estimates *z*-average. Triplicate measurements were carried out, at 25 ± 0.5 °C, after appropriate dilution with deionized water to obtain a suitable scattering intensity at 90° with respect to the incident beam (Tayel et al., 2013). PI values <0.3 indicate homogenous vesicle size distribution (Dragicevic-Curic et al., 2009).

The zeta potential (ζ) values of the systems were determined according to the electrophoretic light scattering (ELS) technology using a Laser Doppler Anemometer coupled with the same equipment. The technique analyzes the electrophoretic mobility of vesicles under an electric field. Triplicate measurements were

Table 1
The composition (mg/ml) of the investigated PVS-loaded spanlastic dispersions.

Formulae	PVS concentration	Span® 60 concentration	Tween® 60 concentration	Tween® 80 concentration
S1	20	200	–	–
S2	20	180	20	–
S3	20	160	40	–
S4	20	140	60	–
S5	20	120	80	–
S6	20	100	100	–
S7	20	180	–	20
S8	20	160	–	40
S9	20	140	–	60
S10	20	120	–	80
S11	20	100	–	100