International Journal of Pharmaceutics xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Evaluation of critical formulation parameters in design and differentiation of self-microemulsifying drug delivery systems (SMEDDSs) for oral delivery of aciclovir

Jovana Janković[a], Ljiljana Djekic[b,*], Vladimir Dobričić[c], Marija Primorac[b]

[a] Apoteka Janković, Miloša Bajića 13, 21000 Novi Sad, Serbia
[b] University of Belgrade, Faculty of Pharmacy, Department of Pharmaceutical Technology and Cosmetology, Vojvode Stepe 450, 11221 Belgrade, Serbia
[c] University of Belgrade, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Vojvode Stepe 450, 11221 Belgrade, Serbia

ARTICLE INFO

Article history:
Received 25 August 2015
Received in revised form 4 November 2015
Accepted 6 November 2015
Available online xxx

Keywords:
Self-dispersing drug delivery systems
Self-microemulsifying drug delivery systems (SMEDDS)
Aciclovir
Acyclovir
In vitro drug release
Parallel artificial membrane permeability assay (PAMPA)

ABSTRACT

The study investigated the influence of formulation parameters for design of self-microemulsifying drug delivery systems (SMEDDSs) comprising oil (medium chain triglycerides) (10%), surfactant (Labrasol®, polysorbate 20, or Kolliphor® RH40), cosurfactant (Plurol® Oleique CC 497) (q.s. ad 100%), and cosolvent (glycerol or macrogol 400) (20% or 30%), and evaluate their potential as carriers for oral delivery of a poorly permeable antivirotic aciclovir (acyclovir). The drug loading capacity of the prepared formulations ranged from 0.18–31.66 mg/ml. Among a total of 60 formulations, three formulations meet the limits for average droplet size (*Z*-ave) and polydispersity index (PdI) that have been set for SMEDDSs (*Z*-ave $\leq$ 100 nm, PdI $<$ 0.250) upon spontaneous dispersion in 0.1 M HCl and phosphate buffer pH 7.2. SMEDDSs with the highest aciclovir loading capacity (24.06 mg/ml and 21.12 mg/ml) provided the *in vitro* drug release rates of 0.325 mg cm^{-2} min^{-1} and 0.323 mg cm^{-2} min^{-1}, respectively, and significantly enhanced drug permeability in the parallel artificial membrane permeability assay (PAMPA), in comparison with the pure drug substance. The results revealed that development of SMEDDSs with enhanced drug loading capacity and oral delivery potential, required optimization of hydrophilic ingredients, in terms of size of hydrophilic moiety of the surfactant, surfactant-to-cosurfactant mass ratio (Km), and log *P* of the cosolvent.

1. Introduction

Aciclovir (International Nonproprietary Name, INN) (acyclovir (United States Adopted Names, USAN)) (2-amino-9-(2-hydroxyethoxymethyl)-3H-purin-6-one) (Fig. 1) is an effective small molecule (M_r 225.2 g/mol) antiviral agent against Herpes simplex viruses type 1 (HSV-1 or oral herpes virus) and type 2 (HSV-2 or genital herpes virus), and *Varicella zoster virus* (VZV, chickenpox, herpes zoster, or shingles virus) (Mehta, 2013). The antiviral activity of aciclovir is highly selective, thus it effectively blocks the viral DNA polymerase and the replication of the viruses, while its toxicity to mammalian cells is very low (De Clercq, 2013; Elion, 1982). Oral administration of solid dosage forms (tablets and capsules) with 200–800 mg of aciclovir, are recommended for prophylaxis and treatment of HSV-1, HSV-2, and VZV infections in immunocompetent patients (O'Brien and Campoli-Richards, 1989).

In a dosage of 200 mg and 400 mg aciclovir is classified in the groupe 3 of the Biopharmaceutical Classification System (BCS) of drug substances (Amidon et al., 1995), which indicates high solubility in aqueous media and poor permeability, while in a dosage of 800 mg is a member of the BCS groupe 4, which have the poor solubility and permeability (Arnal, 2008). Although hydrophilic (log *P* −1.56) (Kristl et al., 1999), aciclovir is slightly soluble in water and relevant literature indicates solubility of 1.61 g/l and 1.55 g/l, for hydrated and anhydrous forms respectively (at 25 °C) (Kristl et al., 1996; Lutker et al., 2011), and 2.5 mg/ml at 37 °C (http://www.drugbank.ca/drugs/DB00787). It is an ampholyte with both weak acid and basic groups with reported dissociation constants at 2.27 (pK_{a1}) and 9.25 (pK_{a2}) (Physicians Desk Reference, 2013), and 2.16 (pK_{a1}) and 9.04 (pK_{a2}) at 37 °C (Susantakumar et al., 2011). Absorption of aciclovir, although unaffected by fasted and fed state (Wilson et al., 1987), is slow, variable, and incomplete (Arnal et al., 2008). Low values of log *P*, permeability coefficient (P_{eff} 0.12–2.0 × 10^{-6} cms^{-1}) (Bergstrom et al., 2003; Yee, 1997), and Caco-2 permeability (log P_{eff} (exp) −6.15) (Hou et al., 2004), indicate low permeability and poor absorption of aciclovir, mainly

* Corresponding author. Fax: +381 11 3972840.
E-mail address: ljiljanadjek@gmail.com (L. Djekic).

http://dx.doi.org/10.1016/j.ijpharm.2015.11.011
0378-5173/

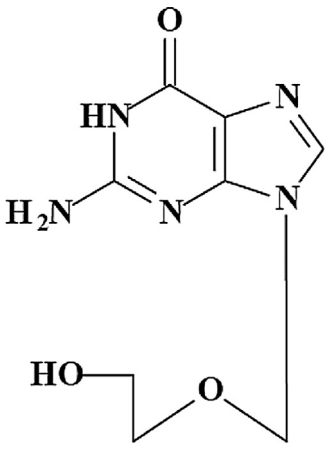

Fig. 1. Chemical structure of aciclovir.

from duodenum and jejunum, in a range of 10–30% when used conventional immediate release pharmaceutical preparations (Arnal et al., 2008; Kristl et al., 1996; Wagstaff et al., 1994). There is a permanent interest to develop an oral formulation which enhances solubility and permeability of aciclovir at the site of absorption. The recent literature documents few attempts for design of aciclovir loaded self-microemulsifying drug delivery systems (SMEDDSs) (Dedakia and Majumdar, 2012; Ghosh et al., 2006; Patel and Sawant, 2007; Satish et al., 2014) that aimed to improve the extent of absorption, however their drug loading capacity was significantly lower compared to its therapeutic doses in conventional solid dosage forms and the influence of formulation parameters on self-dispersing performances was scarcely evaluated.

Development of SMEDDSs is well established as a promising strategy for improvement of oral delivery of drug substances which have limited solubility and/or permeability in the gastrointestinal tract (GIT) (Kohli et al., 2010; Mrsny, 2012; Mu et al., 2013; Porter et al., 2008). SMEDDSs are self-dispersing drug delivery systems consisting of lipids (<20%), surfactants (HLB >12) (20–50%), and hydrophilic cosolvents (20–50%), which form a homogeneous, isotropic mixture in which the drug substance is dissolved, thus they disperse in the GIT to form oil-in-water microemulsions (Pouton, 2000). The compositions of the SMEDDSs may vary in terms of the type and concentration of the used excipients, which create a difference regarding their dispersibility in the biological environment and availability of the active substance for absorption (Kuentz, 2012; Porter et al., 2008; Pouton, 2006). Oil-in-water microemulsions are thermodynamically stable systems with the average oil droplet size less than 100 nm, therefore the SMEDDSs disperse spontaneously and the dispersion process is relatively fast and unaffected by the influence of food and endogenous factors such as digestion of lipids and secretion of bile and pancreatic juice. In addition, since the surface of the oil/water interface film is inversely proportional to the diameter of the droplets of the dispersed oil phase, it is considered that the SMEDDSs provide a large capacity for solubilizing of poorly soluble drug substances and rapid drug release, which are prerequisites for improvement of absorption (Huiling et al., 2013; Porter et al., 2008; Pouton, 2006). Their development requires complex studies in order to optimize the choice of excipients and their concentrations, and to meet the requirements in terms of the solubility of an active substance and dispersibility and solubilization capacity of the carrier formed in the GIT (Charman, 2000; Chen, 2008). Relevant literature usually reports the selection of excipients based on the drug solubility, the investigation of phase behavior of the multicomponent systems in order to determine their quantitative compositions that form oil-in-water microemulsions or nanoemulsions, and/or the evaluation of dispersibility of the drug loaded self-dispersing lipid based formulations in the aqueous medium (usually purified water) (Hauss, 2007). In most cases, the acceptance or rejection of the excipients was based exclusively on the available literature or experimentally obtained data on the drug solubility. In spite of satisfactory drug solubility in the individual excipients, its solubility in the self-dispersing formulations, may be significantly different and insufficient for uploading the therapeutic dose of the drug substance in a suitable unit dosage form (Rane and Anderson, 2008). That shifts the focus on testing the solubility from the individual excipients to the mixtures of the excipients. The concentrations of the ingredients of SMEDDSs are often adjusted by performing extensive and time consuming phase behavior studies, which even may be upgraded with mathematical tools such as artificial neural networks (Djekic et al., 2011) and experimental design (Krstić et al., 2015; Sprunk et al., 2012), however they are limited regarding the number of formulation parameters which can be tested simultaneously, and they were usually performed regardless of the temperature and characteristics of the medium in which the system will be dispersed (*e.g.*, pH value). The pH values of the GIT fluids are significantly different in different parts of the GI system, thus transition of the *in situ* formed colloidal dispersion with the solubilized drug substance, from the stomach into the small intestine, may be associated with a risk for the carrier destabilization, reduction of its capacity for the drug solubilization and subsequent drug precipitation. These risks particularly increase as the hydrophilicity of the self-dispersing formulations is increased (Pouton, 2006) and if solubility of the active substance is pH-dependent. Although high contents of the hydrophilic surfactants and cosolvents are favorable for a self-microemulsification process upon dispersion in aqueous media, the concentration of the hydrophilic excipients at the oil/water interface may decrease progressively and lead to disturbance of physical stability of the carrier which failed to maintain the drug in a solubilized state (Pouton and Porter, 2008). Therefore, the successful development of the SMEDDSs requires a more flexible approach that should include qualitative and quantitative optimisation of the hydrophilic portion regarding their dispersibility and drug solubilization capacity.

The purpose of this study was to systematically investigate the influence of the type and concentration of the surfactants and the hydrophilic cosolvents on the drug loading capacity, dispersibility in aqueous media, and *in vitro* potential for drug absorption enhancement of the SMEDDSs for oral delivery of aciclovir.

2. Materials and methods

2.1. Materials

Excipients used as potential components of the SMEDDSs were: the oil (medium chain triglycerides (Crodamol® GTCC, Croda, UK)); the nonionic surfactants (macrogolglycerol hydroxystearate (Kolliphor® RH40, BASF, Germany)), polysorbate 20 (Ph. Eur. 8.0), caprylocaproyl macrogol-8 glycerides (Labrasol®, Gattefosse, France), and polyglyceryl-3-dioleate (Plurol® Oleique CC 497, Gattefosse, France); the hydrophilic cosolvents (macrogol 400 (Ph. Eur. 8.0), and glycerol (Ph. Eur. 8.0)). Aciclovir was received as a gift sample from Actavis (Belgrade, Serbia). Other reagents that were used within the experimental work were phosphate buffer ingredients (potassium dihydrogen phosphate (Sigma–Aldrich Chemie GmbH, Germany) and sodium hydroxide (Sigma–Aldrich Chemie GmbH, Germany)), hydrochloric acid 0.1 M (Ph. Eur. 8.0) and water, purified (Ph. Eur. 8.0). Dodecane (Sigma–Aldrich Chemie GmbH, Germany) and egg lecithin (Sigma–Aldrich Chemie GmbH, Germany) were used as reagents in the Parallel Artificial

Please cite this article in press as: J. Janković, et al., Evaluation of critical formulation parameters in design and differentiation of self-microemulsifying drug delivery systems (SMEDDSs) for oral delivery of aciclovir, Int J Pharmaceut (2015), http://dx.doi.org/10.1016/j.ijpharm.2015.11.011