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Lyophilized tablets for focal delivery of fluconazole and itraconazole through vaginal mucosa, rational design and *in vitro* evaluation

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ABSTRACT

The present work deals with the rational design and *in vitro* evaluation of vaginal tablets for focal delivery of fluconazole (FLZ) and itraconazol (ITZ). Drug loaded liposomes with and without D-alpha-tocopheryl polyethylene glycol 1000 succinate (vit E TPGS) were prepared by direct sonication of the components and mixed with albumin to obtain albusomes. Tablets were obtained by direct compression of the lyophilized cake. The influence of vit E TPGS on size, zeta potential and entrapment efficiency (EE%) of liposomes and albusomes was evaluated. Tablet swelling and drug release were studied by *in vitro* assays. Vit E TPGS neither affected the zeta potential nor the EE% of liposomes and albusomes, but affected the liposomes size and the tablet disintegration time. A rapid erosion was observed for the tablets with the highest content of vitamin, while a slow swelling for those lacking the vitamin (swelling index = 57.76 ± 13.51%). A faster drug release profile was obtained for the former compared to the latter. The *in vitro* assay showed that FLZ diffused and solved in the vaginal fluid simulant while ITZ remained into the albusomes, which slowly released ITZ-albumin complex and ITZ-loaded liposomes, both suitable carriers for drug transport to deeper vaginal endothelium.

1. Introduction

Vulvovaginal candidiasis (VVC) affects most women at least once in their lifetime. The increasing incidence of diabetes, malignancy and chemotherapy, and the widespread use of immunosuppressive drugs and broad-spectrum antibiotics have all contributed to the rise of *Candida* infections. The impact and morbidity of VVC and recurrent VVC (RVVC) are well recognized and warrant continued efforts toward improving patient outcomes (Sobel, 2016). Conventional vaginal formulations cannot maintain effective drug concentration for prolonged periods of time and therefore new vaginal formulations based on micro or nanoparticles, largely focused in the human immunodeficiency virus (HIV) profilaxis have received increasing attention (Cunha-Reis et al., 2016; Fetherston et al., 2013; Gupta et al., 2012; Notario-Pérez et al., 2018). In addition, the vaginal route is being considered for systemic drug delivery and innovative formulations are being designed to overcome the physiological factors that hinder formulation retention and drug absorption (Krogstad et al., 2014; Sawant and Khan, 2017). Liposomes are one type of nanocarriers which offer several advantages over other drug delivery systems for vaginal delivery (Patel et al., 2018). Liposomes have been proposed for acyclovir (Pavelić et al., 2005), resveratrol (Joraholmen et al., 2015) and curcumin (Berginc et al., 2014) delivery at the vaginal mucosa. In these cases vesicles are incorporated into a Carbopol® gel (acyclovir) or coated with chitosan (resveratrol and curcumin) for mucoadhesion. Nevertheless, there is currently a debate on whether mucoadhesiveness is advantageous for improving drug delivery at the mucosal sites or disadvantageous (das Neves et al., 2018, 2011). It was recently shown that non-adhesive nanoparticles can penetrate human and mouse mucus. Polyethylene glycol coated nanoparticles are able to reach deeper into the more slowly cleared mucus layers increasing epithelial coverage and vaginal retention as, compared to mucoadhesive nanoparticles (Joraholmen et al., 2017; Lai et al., 2007; Yang et al., 2014). While mucoadhesive nanoparticles aggregate and remain trapped within the mucus, Pluronic F127-coated particles achieve a more uniform distribution and close proximity to cervical tumour (Yang et al., 2014). Although vaginal formulations for local release face fewer obstacles than systemic delivery, local release still requires a rational design for the vaginal

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