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Review

Nanopharmaceuticals for improved topical vaginal therapy: Can they deliver?

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ABSTRACT

Nanopharmaceuticals have the potential to revolutionise medical treatment by permitting the design of more potent, less toxic "smart" therapeutics, ultimately leading to personalised medicine. This review summarises the challenges and potential uses of nanodelivery system for the topical drug therapy of vaginal diseases. The vaginal route of drug administration remains a challenge in the development of novel drug therapies, including nanomedicines. We attempted to provide an unbiased overview of currently investigated nanodelivery systems, some of which remain to be extensively studied under laboratory conditions, and some of which are already in clinical trials. Most nanodelivery systems are aimed at improving the treatment of vaginal infections, including HIV prevention. Promising new approaches in nanopharmaceutical design are discussed in this review, as well as the controversies related to mucoadhesiveness of nanopharmaceuticals.

Contents

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1. Introduction

Nanomedicine has the potential to revolutionise medical treatment by permitting the design of more potent, less toxic "smart" therapeutics. It has been extensively described in numerous reviews, which have discussed the rationales, challenges, efficacy, safety, and regulatory issues related to the development of nanoscale drug delivery systems, i.e., nanopharmaceuticals (Desai, 2012; Duncan and Gaspar, 2011; Riehemann et al., 2009; Svenson and Tomalia, 2005). The aim of this review is to focus on the potential uses of nanopharmaceuticals as delivery systems for topical vaginal therapies. We attempted to provide an unbiased overview of currently investigated nanodelivery systems, some of which still require extensive study under laboratory conditions, and some of which are already in the clinical trial stages. Throughout the review, we have used the terms "nanodelivery systems" and "nanopharmaceuticals" as defined in the recent review by Duncan and Gaspar (2011), i.e., in terms of what is defined as nanomedicine, nanopharmaceuticals and the flexibility/rigidity of the size boundaries. We have included delivery systems with size ranges below 1 μm, although some of these systems may be considered either nano- or micro-delivery systems. In writing this review, we have focused on the potential of each proposed nanodelivery systems with respect to topical vaginal drug delivery, considering the uses of nanodelivery systems in other routes of drug administration to be beyond the scope of this review.

2. The vaginal environment

Although it is referred to as mucosal tissue, the vagina does not have secretory glands; rather, a mixture of fluids originating from a number of different sources composes the moist surface film of this tissue. This mucus coating has several important physiological functions and plays an important role in drug absorption. The composition, volume, and rheological properties of vaginal fluids are affected by age, the stage in the menstrual cycle, and sexual arousal, thus influencing the release pattern of a drug delivery system administered into the vagina. Furthermore, it is well established that changes in the volume, viscosity, and pH of the vaginal fluid may affect the efficacy of administered drug delivery systems. Importantly, due to the self-cleansing action of the vaginal tract, the residence times of dosage forms and delivery systems will be reduced, unless they are modified for this specific route of drug administration (das Neves et al., 2011b; Robinson and Bologna,

Table 1
Overview of liposomal formulations investigated for topical vaginal delivery.

Lipid composition	Drug (active compound)	Vehicle formulation	Type of study	Reference
HPC/Chol/stearic acid	*Interferon α*	–	*In vivo* (humans)	Foldvari and Moreland (1997)
SPC	*Clotrimazole, Metronidazole, Chloramphenicol*	–	*In vitro*, *in situ* (cow vaginal mucosa)	Pavelić et al. (1999)
EPC/PG	*Calcein*, *FITC-dextrans*	Carbopol gels	*In vitro* stability, release, rheology	Pavelić et al. (2001, 2004a)
EPC/PG	*Clotrimazole, Metronidazole, Chloramphenicol*	Carbopol gel	*In vitro* release studies, stability	Pavelić et al. (2004b, 2005b)
EPC/PG; EPC; EPC/SA	*Acyclovir*	Carbopol gel	*In vitro* stability and release	Pavelić et al. (2005a)
EPC/SDCh; EPC/T80; EPC/S80	*Metronidazole*	–	*In vitro* permeability (Caco-2 cells)	
SPC, pectin and chitosan coating	*Clotrimazole, Metronidazole*	–	*In vitro* release, mucoadhesion	
EPC; HPC; HPC/Chol	–	Carbopol and Natrosol gel	Rheology	Mourtas et al. (2008)
SPC/Chol/SA; SPC/Chol/PEG_{2000}DSPE		Carbopol gel	Rheology	Boulmedarat et al. (2003)
HPC/Chol	*MC1220*	Natrosol, Carbopol gels	*In vivo* (rhesus macaques)	Caron et al. (2010)
HPC/Chol	*MC1220*	Natrosol, Carbopol gels	*In vivo* (rabbits)	Mourtas et al. (2010)
PC	*Octylglycerol*	Carbopol and poloxamer gels	*In vitro*, *ex vivo*, *in vivo* (macaque monkeys)	Wang et al. (2012)
DOPE/DOTAP/Chol	*Amphotericin B*	Poloxamer gels	*In vitro* release, cytotoxicity	Kang et al. (2010)
SPC/DOPE/Chol/$mPEG_{2000}$-Hz-CHEMS	*Arctigenin*	Poloxamer gels	*In vitro* release, pH sensitivity, toxicity	Chen et al. (2012)
SPC/Chol EPC/CholEPC/Chol/SA; EPC/Chol/DMPG	*Matrine*	Hydrogel foam aerosol	*In vitro* release, mucoadhesion	Wei-Ze et al. (2012)
DOTAP/Chol/DOPE; DOTAP/Chol/DOPE/	*CN54gp140*	Lyophilized liposomal gel-rods	*In vitro* evaluation, rheology	Gupta et al. (2012)
$PEG_{2000}C16_{ceramide}$	*siRNA*	Alginate scaffold system	*In vitro* evaluation, *in vivo* (mice)	Wu et al. (2011)
SPC	*Metronidazole*	Tablets	*In vitro* drug release	
SPC	*Curcumin*		*In vitro* efficacy	Basnet et al. (2012)
SPC	*Curcumin*		*In vitro* vaginal permeability	Berginc et al. (2012)

Chol cholesterol; DMPG dimyristoylphosphatidylglycerol; DOPE dioleoylphosphatidylethanolamine; DOTAP dioleoyltrimethylammoniumpropane; EPC egg phosphatidylcholine; HPC hydrogenated egg phosphatidylcholine; mPEG-2000-Hz-CHEMS methoxy polyethylene glycol 2000-hydrazone-cholesteryl hemisuccinate; PEG_{2000}DSPE poly(ethylene glycol)-2000-distearoylphosphatidylethanolamine; PG phosphatidylglycerol; SA stearylamine; SDCh sodium deoxycholate; SPC soya phosphatidylcholine; T80 Tween 80; S80 Span 80.