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Review

Nanoparticle-based drug delivery to the vagina: A review

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ABSTRACT

Vaginal drug administration can improve prophylaxis and treatment of many conditions affecting the female reproductive tract, including sexually transmitted diseases, fungal and bacterial infections, and cancer. However, achieving sustained local drug concentrations in the vagina can be challenging, due to the high permeability of the vaginal epithelium and expulsion of conventional soluble drug dosage forms. Nanoparticle-based drug delivery platforms have received considerable attention for vaginal drug delivery, as nanoparticles can provide sustained release, cellular targeting, and even intrinsic antimicrobial or adjuvant properties that can improve the potency and/or efficacy of prophylactic and therapeutic modalities. Here, we review the use of polymeric nanoparticles, liposomes, dendrimers, and inorganic nanoparticles for vaginal drug delivery. Although most of the work toward nanoparticle-based drug delivery in the vagina has been focused on HIV prevention, strategies for treatment and prevention of other sexually transmitted infections, treatment for reproductive tract cancer, and treatment of fungal and bacterial infections are also highlighted.

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1. Introduction

In the nearly 100 years since the early descriptions of drug absorption occurring after topical vaginal administration, research on vaginal drug delivery has recently intensified. Vaginal drug administration has many advantages over conventional oral administration, such as

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avoidance of the harsh gastrointestinal (GI) environment and the hepatic first-pass effect. Absorption from the GI tract can be affected by fed state, drug–drug interactions, microbiota, and GI disturbances. Further, the fraction of drug that is absorbed from the GI tract can then be metabolized and eliminated by first passage through the liver. Thus, vaginal drug administration allows for smaller drug doses and the potential for reduced side effects. Additionally, for drugs that act locally in the female reproductive tract, topical vaginal application results in much higher drug concentrations and improved efficacy.

Typical vaginal dosage forms include rings, films, creams, and gels, each of which has advantages for particular drugs and particular indications, as reviewed elsewhere [1]. More recently, nanoparticle-based platforms for drug delivery to the vagina have received increasing attention. The development of nanoparticle-based vaginal drug delivery formulations has largely been focused on HIV pre-exposure prophylaxis (PrEP). Nanoparticles can provide sustained release of microbicide drugs, which is necessary for maintaining protective drug concentrations between the time of dosing and the time of intercourse. Drug release from nanoparticles can result in more controlled vaginal absorption compared to a drug depot like a vaginal gel, thereby potentially requiring reduced amounts of drug. Nanoparticles can be designed to contain multiple modalities, to target specific cells, and to have intrinsic antimicrobial activity. Achieving adequate vaginal drug distribution can be challenging; appropriately designed nanoparticles can provide improved drug distribution to target cells and tissues, improving efficacy. However, the advantages and unique characteristics of nanoparticle-based vaginal formulations need not be limited to PrEP, as evidenced by demonstrations of nanoparticles applied to the vagina of experimental animals to achieve vaccination, or treatment of cervical cancer and other female reproductive tract infections. The goal of this review is to discuss: (i) factors that influence vaginal drug delivery that should be considered when designing and testing nanoparticle-based platforms, (ii) nanoparticle-based formulations designed for vaginal drug delivery, and (iii) other opportunities for nanoparticle-based vaginal drug delivery formulations to improve prophylactic and therapeutic outcomes.

2. Considerations for the rational design of nanoparticle platforms for vaginal drug delivery

2.1. Physiology of the vagina and implications for drug delivery

Often cited drawbacks of oral drug administration include the lack of predictability in drug absorption due to physiological variations and the hepatic first-pass effect. Drugs absorbed from the vagina enter the peripheral circulation through a venous plexus that empties into the internal iliac veins and the hemorrhoidal veins, thus avoiding the liver [2]. However, similar to oral drug absorption, vaginal drug absorption is affected by numerous physiological factors. First, the vagina is not simply a straight tube as often depicted in anterior drawings of the female reproductive tract. Imaging of the lateral view has demonstrated that the lower portion of the vagina is tilted at approximately 45° leading up to the wider upper portion that is almost horizontal when a woman is standing [3,4]. From a cross-sectional view, the vagina is collapsed with the anterior and posterior walls in contact with each other, forming what is often referred to as an "H" shape [5]. The distended shape of the vagina varies widely between women [6]. The vaginal walls are lined with stratified squamous epithelium containing numerous folds, or rugae, which allow for this distension and increased surface area for absorption [4]. Due to the intra-abdominal pressure that collapses the rugae, high internal surface area, and tortuosity of the vaginal canal, achieving adequate distribution of a vaginal product can be challenging, and is often dependent on the influence of numerous factors [7]. Unfortunately, animal models for vaginal drug delivery fail to recapitulate many of these uniquely human features, including the acidic pH (~3.5–4.0) observed in the human vagina in women with healthy, lactobacilli-dominated microbiota [8,9]. Under certain conditions, such as during a yeast infection or when semen is introduced into the vagina, the pH can be temporarily elevated [10,11], which can affect the ionization and absorption of certain drugs [3,7]. Thus, the basic physiology of the vagina must be considered when designing vaginal dosage forms, and care must be taken in interpreting experimental observations obtained using animal models.

2.2. The mucus barrier and implications for drug delivery

In addition to the epithelium itself, cervicovaginal mucus (CVM) serves as a physical barrier to protect the vagina against infection. CVM can have a significant impact on the penetration, distribution, and residence time of nanoparticle-based systems for vaginal drug delivery applications. Mucus produced at the cervix bathes and coats the vaginal walls, mixing with vaginal epithelial cells and vaginal transudate. The composition of CVM is similar outside of the period of ovulation, and is composed mostly of water (~90–95%) with gel-forming glycoproteins, lipids, soluble proteins, enzymes, and various immune factors [12,13]. During ovulation, cervical mucus becomes watery and mucin proteins align to allow sperm to pass more readily through the cervix into the uterus. However, ovulatory mucus is produced in more copious amounts, thus facilitating clearance and impeding drug absorption [14]. Mucins in CVM from non-ovulatory women and women on hormonal contraceptives form a tight meshwork, acting as a barrier to protect the epithelium [13]. Non-ovulatory human CVM was recently found to have pores in the range of 50–1800 nm, with an average of 340 ± 70 nm [15]. In addition to sterically trapping pathogens and particulates, CVM also traps particles by adhesive interactions [12]. Vaginal dosage forms, such as gels, are often designed to be mucoadhesive to increase residence time in the vagina [16]. It was also found that conventional nanoparticle formulations are inherently mucoadhesive due to interactions between mucus and the hydrophobic polymer nanoparticles [17,18], which was expected to increase residence time [19]. However, it was recently demonstrated that nanoparticles engineered with non-adhesive surface coatings of densely packed polyethylene glycol (mucus penetrating particles, or MPP) can rapidly penetrate human and mouse mucus, reaching deep into the more slowly cleared mucus layers, including those in the collapsed vaginal folds, thereby increasing epithelial coverage and vaginal retention compared to mucoadhesive conventional nanoparticles (CP) (see Polymeric nanoparticles) [17,20,21]. A microbicide drug formulated as an MPP was also found to provide increased protection in a mouse model of vaginal herpes infection, compared to even 10-times the amount of unformulated drug [20]. Thus, it appears as though the barrier properties of CVM to pathogens and nanoparticles must also be considered when designing an effective nanoparticle-based formulation for vaginal drug delivery.

2.3. Immunology of the vaginal mucosa and implications for drug delivery

The immune system of the female reproductive tract must protect against infectious pathogens while tolerating commensal bacteria and the presence of foreign materials, such as sperm. Whether nanoparticle systems are designed to interact directly with the immune system, such as with vaccine delivery and immune cell-targeted delivery, or to be unrecognized by the immune system, a thorough understanding of vaginal immunity is necessary. Although not as highly studied as the immune systems in the respiratory and gastrointestinal (GI) tracts, understanding of how the vaginal immune system strikes a balance between tolerance and pathogen recognition, and how it differs from other mucosae, is progressing [22].

The respiratory and GI tracts are type I mucosae, which is coated with simple columnar epithelia linked by tight junctions and containing organized lymphoid structures (MALT). In contrast, the vaginal and ectocervical epithelia are type II mucosa, covered with squamous epithelia and lacking MALT [23]. Thus, rather than allowing access to underlying MALT for immune surveillance like type I mucosa, the multiple layers

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