REVIEW

Vaginal Films for Drug Delivery

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ABSTRACT: Vaginal dosage forms have been studied in relation to many drugs as the vagina presents several advantages as a site for drug delivery, such as large surface area, rich blood supply, avoidance of the first-pass effect, relatively high permeability to several drugs, and self-insertion. Traditional vaginal dosage forms have been associated with disadvantages such as low residence time and discomfort and have been surpassed by newly designed drug delivery systems, particularly those based on bioadhesive polymers. Vaginal films are solid dosage forms that rapidly dissolve in contact with vaginal fluids and are unlikely to be associated with leakage and messiness. They have been studied for some female genital problems, aiming either contraceptive, antimicrobial, or microbicide effects. Precise and complex processes of manufacturing and characterization are required to achieve successful film formulation. Although scarce, the available user's acceptability studies show promising results. Vaginal films gather a lack of opportunities for both therapeutic and prophylactic actions, and therefore should be considered when designing and developing new vaginal drug delivery systems. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:2069–2081, 2013

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INTRODUCTION

Vaginal drug delivery is an important approach for the treatment of both local and systemic diseases.[1–4] The vaginal route has several advantages due to its large surface area, rich blood supply, avoidance of the hepatic first-pass effect, relatively high permeability to many drugs, and self-insertion.[1,3,5] These particular characteristics of the vagina provide significant potential for the delivery of a wide range of bioactive compounds, including peptides and proteins, and offer an alternative to the parenteral route of administration.[4] On the other hand, several drawbacks, including cultural background, personal hygiene, gender specificity, local irritation, and influence on sexual intercourse, need to be addressed during the design of a vaginal formulation.[3]

Vaginal drug delivery systems have traditionally been used to deliver contraceptives and drugs intended to treat vaginal infections. Over time, the intravaginal route has been mainly used for the delivery of locally active drugs such as antibacterials, antifungals, antiprotozoals, antivirals, labor-inducers, spermicidal agents, prostaglandins, and steroids,[4,6] although systemic delivery of hormones and other drugs has also been explored.[7] In the last few years, microbicides largely stimulated research on vaginal formulations. Microbicides are chemical substances that when inserted into the vagina before sexual intercourse, have the potential to either prevent or reduce the risk of sexually transmitted infections (STIs) and recent researches are particularly focused on human immunodeficiency virus (HIV) transmission.[4,8–16] Looking beyond traditional vaginal formulations and drugs, novel biopharmaceuticals, nanoparticles, and combinations of mucosal vaccines and microbicides are under active investigation. Vaginal delivery of these agents can be accomplished through gels, films, tablets, and vaginal rings. Studies

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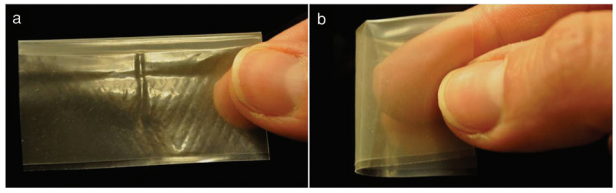

Figure 1. Vaginal film (VCF®, Apothecus Pharmaceutical) folded in half (a) and placed over the fingertip for insertion (b).

in animal models suggest that these new approaches deserve further investigation.[14]

The vagina is a highly expandable, longitudinally S-shaped fibromuscular, collapsed canal connecting the cervix to the vestibule[17] and although deprived from secreting glands is usually referred to as mucosa. The vaginal canal extends from approximately 7–15 cm with the posterior wall being longer than the anterior one due to an asymmetrical positioning of the cervix.[18] Under a transverse cross-section view it has a figure of H configuration, with the anterior and posterior walls contacting one each other.

The vaginal wall consists of the following cell layers: the nonkeratinized stratified squamous epithelium, the lamina propria (mainly composed of connective tissue with multiple blood and lymphatic vessels, which drain into the internal iliac vein thus allowing for avoidance of hepatic first-pass effect following drug absorption), the muscular layer and the tunica adventitia, highly rich in blood and lymphatic supply.[17,19] The vaginal epithelium is coated with a thin layer of fluid composed by endometrial, cervical, and vestibular secretions, tissue transudate, and residues of urine and presents acidic pH in healthy reproductive age women.[20]

Changes in anatomical and physiological parameters mainly in epithelial thickness do occur during puberty, pregnancy, menopause, and even menstrual cycles and must be taken in account when developing vaginal dosage forms. Permeation of locally applied drugs through the vaginal wall may occur by passive diffusion (through the transcellular or paracellular pathways) or, to a minor extent, by active transport-mediated mechanisms and is influenced by drug factors (molecular weight, lipophilicity/hydrophilicity), formulation characteristics, and physiological conditions (pH, amount of fluid, epithelial thickness).[19]

Traditional vaginal dosage forms, including creams, gels, vaginal suppositories and tablets, have been associated with some limitations such as leakage, messiness, and relatively low residence time due to the self-cleaning action of the vaginal tract.[1,6,15,21] In fact, the major challenge in vaginal dosage forms design is the ability to fulfill functional criteria such as product dispersion throughout the vagina, prolonged residence time, adequate physicochemical interaction with vaginal content, release profile of active ingredients, and effects on targets.[22] Bioadhesion has been defined as the attachment of synthetic and natural macromolecules to a biological tissue and mucoadhesion is considered a particular case of bioadhesion where the biological tissue is covered by mucus.[23] Mucoadhesive polymers have been explored in the development of either semi-solid and solid vaginal drug delivery systems to circumvent some of the outlined limitations of traditional dosage forms gathering user compliance and improving therapeutic outcomes.[1,15,24,25] Moreover, some polymers have shown microbicidal activity as is the case for kappa carageenan (absorption inhibitor, *in vitro*), carbomers (interruption of HIV cell binding, *in vivo*), cellulose acetate phthalate [inactivation of HIV and herpes simplex virus (HSV), *in vivo*], and polystyrene sulfonate (PSS) (activity against HIV and HSV, *in vitro*).[4]

The progress in polymer science has provided thin films with the flexibility to meet the demands and requirements for use as drug delivery systems.[6,10] Vaginal films are polymeric drug delivery systems usually square in shape, with soft and homogeneous surfaces with approximate side measurements of 5–10 cm that can be applied without the use of an applicator. They can be folded before insertion into the vagina[19] (Fig. 1). These dosage forms are thin strips of polymeric water-soluble substances which disperse/dissolve when placed in the vaginal cavity to release the active pharmaceutical ingredients.[10,15,26] Films are designed to rapidly disperse or dissolve in contact with fluids to form a smooth, viscous, and bioadhesive gel while possessing good appearance (preferably colorless and odorless), softness, flexibility, and absence of any sharp edges to avoid mechanical injuries during insertion. These desirable features are expected to facilitate insertion, gather user's acceptability and compliance, and result in the immediate formation of a bioadhesive dispersion that could be retained in the vagina for prolonged periods of time.[22,27]

Vaginal films are formulated with the drug, water soluble polymers, plasticizers, fillers, color, and flavor.[26] The chosen polymers should be nontoxic, nonirritant, devoid of leachable impurities, possess good wetting properties and spreadability, exhibit sufficient peel, shear, and tensile strength; and inexpensive to manufacture and pack. Polyacrylates,