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Mucoadhesive and thermogelling systems for vaginal drug delivery ☆

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ABSTRACT

This review focuses on two formulation approaches, mucoadhesion and thermogelling, intended for prolonging residence time on vaginal mucosa of medical devices or drug delivery systems, thus improving their efficacy. The review, after a brief description of the vaginal environment and, in particular, of the vaginal secretions that strongly affect *in vivo* performance of vaginal formulations, deals with the above delivery systems. As for mucoadhesive systems, conventional formulations (gels, tablets, suppositories and emulsions) and novel drug delivery systems (micro-, nano-particles) intended for vaginal administration to achieve either local or systemic effect are reviewed. As for thermogelling systems, poly(ethylene oxide–propylene oxide–ethylene oxide) copolymer-based and chitosan-based formulations are discussed as thermogelling systems. The methods employed for functional characterization of both mucoadhesive and thermogelling drug delivery systems are also briefly described.

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1. Introduction

The vaginal lumen is the site of various pathologies such as vaginitis caused by bacteria, fungi, protozoa or virus and has been traditionally employed for the delivery of antimicrobial and antiviral drugs. Recently, the vagina has been exploited as a possible administration route, in

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alternative to the parenteral one, for the delivery of drugs, endowed with systemic effects, that cannot be profitably administered *per os* due to hepatic or gastrointestinal degradation or to the induction of side-effects in the gastrointestinal tract [1].

A drawback of such a route is represented by the physiological removal mechanisms, which are active in the vaginal lumen and are responsible for a scarce residence time of conventional formulations at the action/absorption site, causing an erratic drug distribution onto the mucosa.

Two are the main approaches proposed in the literature to withstand the abovementioned problems: one is represented by mucoadhesive formulations able to prolong drug permanence into the vaginal cavity thanks to the formation of physical and chemical bonds with the mucosa, the other is constituted by thermogelling liquid systems that are subjected to a sol–gel transition upon vaginal administration. Both approaches will be discussed in the review after a brief description of the vaginal environment, with particular regard to the vaginal secretions, that strongly affect *in vivo* performance of vaginal formulations. The methods employed for the functional characterization of both mucoadhesive and thermogelling drug delivery systems will also be described.

2. Vaginal environment

Vaginal epithelium is uncornified and pluristratified and its thickness (200–300 μm) is strongly dependent on age and hormonal levels, especially estrogens. Although it is considered a mucosa, it lacks goblet cells. Vaginal surface is anyway lined and protected by cervical mucus [2]. Besides cervical mucus, endometrial and tubal fluids and vaginal transudate, Bartholin's and Skenes's gland secretions contribute to vaginal fluid amount and composition. An exhaustive survey of the literature [3] suggests a production of vaginal fluid of about 6 g/day, and a volume present in the vagina of approximately 0.5–0.75 ml. Such compounds as lactic acid, acetic acid, glycerol, urea, and glucose are present in significant concentrations in vaginal fluids. Glycogen, which is present in large amount, is a substrate of microbial and enzymatic processes that result in the production of lactic acid, whose concentration is estimated between 3 and 5 g/l, and that contributes to maintain the vaginal pH to slightly acidic values, usually in the range 4–4.5 [3].

Mucus production varies with hormonal changes, with higher rate occurring during the ovulatory phase. Mucus production rate decreases to approximately 50% and 30% during the follicular and luteal phases, respectively [2].

Even the characteristics of cervical mucus are variable according to the different phases of the menstrual cycle. During the first half of the cycle, when estrogen exposure predominates, mucus is thinner and easily penetrable, while it is produced in lower amount and is thicker in consistence in the second part of the cycle due to progesterone effect. The use of contraceptive hormones increases mucus viscosity. Modifications of vaginal flora occurring in bacterial vaginosis reduce mucus viscosity compared to women with normal flora. The main representative microorganisms of vaginal flora belongs to *Lactobacillus* spp., which are responsible for the relatively low pH of vaginal environment [4–6].

Amount and composition of vaginal fluids can however change according to sexual stimulation, that strongly increases their volume and can also affect sodium and chloride concentration.

Quite important changes occur during menopause. In this condition, the epithelium becomes thin and atrophic. The changes in hormonal levels are responsible for the decrease in vaginal fluids and glycogen concentration, so that the environment becomes hostile to the protective lactobacilli that are responsible for lactic acid production and, as a consequence, vaginal pH increases. The environment faced by drug delivery systems can therefore vary depending on hormonal changes, but also on sexual intercourses or pathological conditions, with possible consequences in their performance.

3. Mucoadhesive vaginal drug delivery systems

Mucoadhesion is an attractive interaction that involves a pharmaceutical dosage form and either secreted mucus or a mucosal membrane [7]. The main components of secreted mucus are soluble mucins. These are highly glycosylated glycoproteins consisting of about 500 kDa subunits jointed by disulfide bridges to give large structures that entrap high amount of water to give a viscoelastic protective layer over the mucosa surface. Mucoadhesive properties allow better contact of the formulation with the vaginal surface and longer residence times. In most cases mucoadhesion is imparted to a formulation by the employment of polymeric excipients. The mechanisms of mucoadhesion involve firstly a contact stage, in which hydration, wetting and spreading are the most important steps, and subsequently a consolidation stage, that involves the strengthening of polymer–mucin joint, thanks to the interpenetration of the polymer chains into the mucus layer and the occurrence of polymer–mucin bonding (mainly weak van der Waal and hydrogen bonds or electrostatic interactions) [7]. According to these mechanisms, polymers with promising mucoadhesion properties are those having high number of functional groups, for example hydroxyl groups or unionized carboxylate groups. Molecular weight should be not so high to impair hydration and chain entanglement with mucins but not so low to give poor cohesion. Flexibility is important to improve interpenetration with mucus. Ionizable groups can help mucoadhesion if they are able to determine electrostatic interactions in the vaginal environment with the anionic moieties of mucins [1,8]. Hereafter the different types of vaginal mucoadhesive formulations reported in literature are discussed.

3.1. Gels

Gels are well accepted products, used for vaginal applications of various drugs/actives endowed with moisturizing and lubrication effect, physiological pH restoring effect, contraceptive, labor inducer and microbicide activity [9,10].

The mucoadhesive polymers proposed in the literature and used in commercial formulations for vaginal application are numerous. Among the most common polyacrylic acid derivatives, such as carbomer and polycarbophil, cellulose derivatives, chitosan and its derivatives, hyaluronic acid, alginate, carrageenan and sulphated polysaccharides, and gums are listed [4].

Thanks to the high content in water that characterizes these preparations, gels based on mucoadhesive polymers, without addition of drugs, are proposed for moisturization of the vagina in cases of vaginal dryness, experienced especially during menopause, and for lubrication to facilitate or enhance sexual intercourse [11,12].

An example of this kind of application of vaginal gels is represented by some polycarbophil gels that form the basis of well-consolidated marketed products (Replens®, Miphil®), and by a hydroxyethylcellulose (HEC) based product (K-Y® jelly), that is commercialized as lubricant.

Other products, more specifically intended to buffer the vagina environment with the aim of restoring the physiological pH against vaginal infections, have been developed. The buffering capacity of polycarbophil has been demonstrated capable of normalizing vaginal pH during the menopause [13] and in cases of bacterial vaginosis [14]. An acid buffering bioadhesive vaginal gel was based on guar gum, xanthan gum (XG) and hydroxypropylmethylcellulose (HPMC K4M) combination, associated with monosodium citrate as buffering agent to provide acidic pH (4.4). Clotrimazole (CTZ) (antifungal), metronidazole (MTZ) (antiprotozoal as well as antibacterial) and *Lactobacillus acidophilus* was added to treat mixed vaginal infections [15].

Mucoadhesive chitosan (CS) lactate gels, based on medium (AM) and high (FH) chitosan viscosity grades, were developed for the controlled release of lactic acid onto vaginal mucosa. CS medium molecular weight showed better mucoadhesive properties, likely due to the less rigid structure of the gel. A full factorial design evidenced an interaction

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