Introduction

The vaginal lumen is affected by several pathologies - most of them are vaginitis caused by bacteria, fungi, protozoa or viruses. A considerable number of antimicrobial, antiviral, antifungal and antiprotozoal drugs have been therefore traditionally administered into this site, as well as spermicidal agents, prostaglandins and steroids [1,2]. It is obvious that topical vaginal application of drugs is advantageous over oral or other systemical route of administration, once important adverse effects such as nausea, vomiting, abdominal pain or menstrual disorders are avoided, even as numerous interactions between drugs could be eliminated [3,4]. Topical absorption, however, is hampered by the physiological removal mechanisms present in the vaginal lumen, which are responsible for the short ER retention time of conventional formulations at the site of action, causing the irregular distribution of the drug through the mucosa. In addition, if one consider vagina is an intimate place, the need for continuous application of conventional topical formulations in this site throughout the day causes discomfort to the patient and reduces therapeutic adherence [5–7].

Since 1980, bioadhesive formulations have been available in market and have proven to be specially important for application in topical drug delivery routes. Previous applications of bioadhesive delivery systems mainly involved the oral cavity and the gastrointestinal tract, but currently, these systems have been developed to target a wider variety of mucosal surfaces including the vaginal mucosa. For drug delivery purposes, the term “bioadhesion” implies binding of a drug delivery system to a specific biological site. If the adhesive is for a mucosa, the phenomenon is referred to as mucoadhesion [8,9].

The mucoadhesion mechanisms involve, first, a contact stage, in which hydration, wetting and scattering are the most important steps, and subsequently a consolidation stage, which involves the strengthening of the polymer-mucin-type junction due to the interpenetration of the chains polymerization in the mucus layer and the occurrence of polymer-mucin binding formation (mainly Van der Waals forces, hydrogen bonds or electrostatic interactions) [5,10].

Mucoadhesion is generally obtained using both natural bioadhesive (such as tragacanth, sodium alginate, Karaya gum, Guar gum, Xanthan gum, soluble starch, gelatin, pectin and chitosan) and synthetic polymers (cellulose derivatives, polyacrylic acid polymers, polyhydroxy ethyl methyl acrylate, polyethylene oxide, poly vinyl pyrrolidone, poly vinyl alcohol and, more recently, thyolated polymers) [11,12]. Among this range of options, polyacrylic acid and hydroxypropyl methyl cellulose are the ones with the highest mucoadhesive strength. In general, traditional vaginal dosage forms include solutions, suspensions, gels, suppositories, creams, foams and tablets [13,14].

Such polymers may further be divided into anionic, cationic or nonionic. Cationic polymers, such as chitosan, form bonds with negatively charged mucin chains and anionic polymers have muco adhesive properties due to hydrogen bonding to the mucosal layer [15]. Anionic polymers are singled out as preferred over cationic polymers for adhesion and toxicity potential. In addition, carboxylated anionic polymers appeared to be favored compared to sulfated [16].

In order for the polymers to succeed in their bioadhesive function on the mucosal surfaces they must have a molecular weight of 100,000 Da or more, excellent polymer concentration, adequate flexibility to control the extent of interpenetration between the polymers and the mucous membranes, surface tensions capable of spreading the bioadhesive polymer on the epithelial surface of the mucosal layer, strong hydrogen bonding groups (-OH, - COOH) and strong anionic charges [4,9]. The duration of the contact, the diffusion coefficient and the solubility of the Se materials at the mucus interface determine their level of muco adhesion [17].

In recent years, a large quantity of studies have focused on the development of systems with bioadhesive properties. Although most bioadhesive vaginal formulations are semi-solid (especially gels), other dosage forms such as tablets and films have also been reproduced [18,19]. An ideal polymer
for a mucoadhesive vaginal delivery system should be non-toxic and non-irritating to the mucosa, adhere rapidly to the tissue, allow easy incorporation of the drug, not obstruct drug release, to possess low cost and have good comfort and convenience [20,21].

One important study developed an intra vaginal bioadhesive table to polystyrene sulfonate loaded with azidothymidine. In general, there, sults suggested the system maybe sufficiently bioadhesive with desirable physicochemical and physicochemical stability for use as a prolonged intra vaginal drug delivery [22]. Another recent study developed a bioadhesive vaginal microbial gel using the two polymers Pluronic® F-127 and Noveon® AA-1 for the administration of anti-HIV agents, demonstrating ideal bioadhesion and drug retention in vaginal tissue [23]. More recently, liposomes coated with natural and synthetic bioadhesive polymers (chitosan and Carbopol, respectively) containing curcumin were evaluated by an in vitro model of vaginal mucus. For control and comparison purposes, liposomes without the coatings were also developed and there sults showed that the bioadhesive polymers allowed significantly greater (p < 0.05) curcumin permeability through the mucosa in comparison to the control [24].

It is evident that in the development of a bioadhesive delivery system, the evaluation of adhesive properties of the formulation is essential. In this way, several in vitro methods have been developed for this purpose, such as: tensile test, shear strength and peel strength [12,25]. Additionally, several physical techniques, such as rheological, optical and spectroscopic have also been applied to evaluate the nature and intensity of mucoadhesive interactions [15]. These methods, however, do not consider biological and anatomical properties of vaginal that are crucial in the formulation performance. In such context, our research group has developed a novel and simplex vivo vaginal drug delivery model. Drug Deliv. 2016; 7544:1-12.

Conclusion

The adhesion property of bioadhesivepolymeric systems offers a potential to prolong the residence time of the dosage form at the vaginal lumen. Consequently, they lead to an increase in drug concentration at the site of action, thus reducing dosing frequency. In addition, patient compliance is improved as well as a better chemical and physical stability of the systems [13,25].

Future Perspectives

The development of new delivery systems with mucoadhesive properties is one of the most challenging research topics in the field of topical drug delivery systems. The use of mucoadhesive polymers to increase contact time for a wide variety of drugs in the vaginal route showed dramatic improvement in therapies and greater patient comfort. Many potential mucoadhesive systems must be investigated so that they can find their way into the market in the near future.

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