Electrospun cellulose acetate phthalate fibers for semen induced anti-HIV vaginal drug delivery

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ABSTRACT
Despite many advances in modern medicine, human immunodeficiency virus (HIV) still affects the health of millions of people world-wide and much effort is put in developing methods to either prevent infection or to eradicate the virus after infection has occurred. Here, we describe the potential use of electrospun cellulose acetate phthalate (CAP) fibers as a tool to prevent HIV transmission. During the electrospinning process, anti-viral drugs can easily be incorporated in CAP fibers. Interestingly, as a result of the pH-dependent solubility of CAP, the fibers are stable in vaginal fluid (the healthy vaginal flora has a pH of below 4.5), whereas the addition of small amounts of human semen (pH between 7.4 and 8.4) immediately dissolves the fibers which results in the release of the encapsulated drugs. The pH-dependent release properties have been carefully studied and we show that the released anti-viral drugs, together with the CAP which has been reported to have intrinsic antimicrobial activity, efficiently neutralize HIV in vitro.

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1. Introduction

In the last 25 years HIV infection and acquired immune deficiency syndrome (AIDS) became a serious health, social and economical problem all over the world [1]. HIV infection in humans has been proclaimed as pandemic by the World Health Organization (WHO) [2]. Transmission of HIV mostly occurs through sexual contact, by transfusion of contaminated blood or blood products, by sharing contaminated needles or by transmission from mother to child during pregnancy [3]. Fighting HIV has proven to be extremely difficult as it is characterized by a very high genetic variability, resulting in the lack of any currently available vaccine [4]. Because of the difficulties in fighting the virus itself, a lot of effort is put in preventing infection. To date, most emphasis is put on condom use and behavioral modification. However, in high HIV prevalent areas of the world, the use of condoms is low due to social stigmas and their use is often not negotiable for women. Because of this, alternative strategies for the prevention of HIV infection are urgently required.

One possible strategy involves the prophylactic use of microbicides that could be delivered intra-vaginally and which does not require the cooperation or even knowledge of male partners [5,6]. A microbicidal is a chemical entity that can eradicate microbes, including viruses, and thus prevents or reduces the spread of infections. However, currently available vaginal microbicidal formulations suffer from several disadvantages [7]: 1) It has been observed that gel-based formulations tend to be washed away with urination, 2) the broad activity of currently used general microbicides may reduce potency, 3) antiretroviral microbicides can potentially induce resistance of the HIV strain against the therapeutic agent, 4) entry inhibitor microbicides lack activity against other sexually transmitted diseases and 5) they suffer from practical inconveniences. Despite initial high expectations, recent clinical trials with non-specific entry inhibitors such as cellulose...
sulfate and PRO-2000 did not reveal large-scale clinical benefits, which can be explained by possible drug-induced mucosal damage or inconsistent microbicide use [8]. Among the various microbicides, one polymer which has been given due consideration in developing anti-HIV-1 strategies is CAP [9,10]. CAP acts by inducing conformational changes in HIV glycoproteins (gp41 and gp120) which are responsible for recognizing and binding the human CD4 receptor and CCR5 and CXCR4 co-receptors, which is essential for cellular entry. CAP will act on these glycoproteins and form gp41 six-helix bundles which results in a terminal, functionally inactive viral constituent [11]. Furthermore, CAP is a pharmaceutical excipient which is frequently used as an enteric coating agent for tablets and capsules to avoid drug release in the acidic lumen of the stomach. Interestingly, the pKa of CAP equals 5.28 [12], meaning that also at the low pH of the vaginal lumen CAP is expected to be minimally soluble.

As illustrated in Scheme 1, we hypothesized that CAP fibers, produced by electrospinning and loaded with anti-viral drugs, when applied intra-vaginally, should remain intact as long as the environment is acidic. A healthy vaginal flora, which has a pH below 4.5, has nearly no buffering capacity which is in sharp contrast to the high buffering capacity of semen [13]. As such, it has been described under in vivo conditions that minimal amounts of seminal fluid are already sufficient to locally elevate the vaginal pH [13]. As semen maintains its pH near neutral even in the vaginal environment [14], CAP fibers should rapidly dissolve thereby releasing a massive amount of anti-viral drugs locally into the semen possibly contaminated with HIV-1.

2. Materials and methods

2.1. Materials

Dimethylformamide (DMF) and acetone were purchased from Sigma–Aldrich (Steinheim, Germany). Cellulose acetate phthalate (CAP, MW ~ 60,000 g/mol) was purchased from Certa (Braine l’Alleud, Belgium). An MTT kit was purchased from Roche (Vilvoorde, Belgium). TMC 125 was a kind gift from Prof. C. Panwas purchased from Certa (Braine l’Alleud, Belgium). An MTT kit was purchased from Roche (Vilvoorde, Belgium). TMC 125 was a kind gift from Prof. C. Pan-

2.2. Electrospinning of CAP fibers

CAP fibers were obtained by electrospinning a CAP solution (25% w:v) using an acetonelDMF mixture (3:1 v/v) as solvent. The electrospinning setup was composed of a high voltage power supply (up to 40 kV), a syringe, a flat-tip needle and a grounded collector. Typically 1 ml of CAP solution was spun at a flow rate of 1 ml/h. After spinning, the fiber webs were dried in the air at room temperature. Electrospinning of TMC 125, Viread and Rhodamine 6G containing CAP fibers occurred similarly, where different concentrations of the drugs as indicated in the main text and (0.3 mg/0.25 g CAP) Rhodamine 6G were added to the CAP solution prior to electrospinning.

2.3. Scanning electron microscopy

A small amount of CAP fibers was deposited onto a silicon wafer and dried under a nitrogen stream, followed by sputtering with gold. SEM images were recorded with an FEI Quanta 200 FEG scanning electron microscope (FEI Europe, Eindhoven, The Netherlands) operated at an acceleration voltage of 15 kV.

2.4. Preparation of simulated vaginal fluid

SVF was composed as described earlier [15]. NaCl (3.51 g), KOH (1.4 g), Ca(OH)2 (0.222 g), bovine serum albumin (0.018 g), lactic acid (2 g), acetic acid (1 g), glycerol (0.16 g), urea (0.4 g) and glucose (5 g) were dissolved in 1 L water. The pH was then adjusted to 4.2 with hydrochloric acid.

2.5. Behavior of CAP fibers in simulated vaginal fluid and human semen

Mixtures of human semen and SVF were prepared by transferring the appropriate volumes of both samples in an in eppendorf tube and mixing well. The ratios (semen/SVF) 100/0, 50/50, 30/70, 20/80, 0/100 were studied. To monitor the behavior of CAP fibers in these samples, 0.1 ml of the fluids were added to 1 cm² CAP fiber webs on a microscope glass which were imaged in time using an epifluorescence microscope (EZ-C1 Nikon, Nikon Belux, Belgium).

2.6. Cell culture

Immortalized human vaginal epithelial cells were purchased from ATCC and cultured in a humid atmosphere at 37 °C and 5% CO₂. Cells were kept in keratinocyte serum-free medium (Gibco, Invitrogen, Belgium) supplemented with human recombinant EGF (0.1 ng/ml), bovine pituitary extract (0.05 mg/ml) and high calcium chloride concentration (0.4 mM) (Gibco, Invitrogen, Belgium). Cells were passaged when reaching 70–80% confluence and split 1:5. TZMbl cells were obtained from NIBSC and were cultured in DMEM (Lonza), 50 mg/ml gentamycin (Lonza) and 200 mM l-glutamine (Lonza). Cells were given fresh medium twice a week.

2.7. Toxicity assay

To test the viability of vaginal epithelial cells or TZMbl cells, the cells were seeded in 24 well plates (50,000 cells/well) and allowed to settle overnight. The cells were then exposed to CAP solutions and CAP fibers for 5 h. Cell viability was evaluated 24 h later by an MTT assay according to the manufacturer’s instructions and compared to the viability of untreated control cells.

Scheme 1. A) Vaginal epithelium covered by a web of electrospun CAP fibers containing the anti-viral drug before contacting with human semen contaminated with HIV. B) Vaginal epithelium covered by a web of electrospun CAP fibers containing the anti-viral drug after contacting with human semen contaminated with HIV.
2.8. Determination of antimicrobial activity

Lactobacillus crispatus (LMG 11440), Lactobacillus gasseri (LMG 13134) and Lactobacillus plantarum (LMG 5208) were obtained from the BCCM/LMG Bacteria Collection (Ghent, Belgium). Bacteria were maintained on Man/Rogosa/Sharpe (MRS) agar (Oxoid, Drongen, Belgium) at 37 °C in aerobic conditions. Minimal inhibitory concentrations (MICs) were determined in duplo according to the EUCAST broth microdilution protocol using flat-bottomed 96-well microtiter plates (TPP, Trasadingen, Switzerland) [16]. To this end, cells from 10 ml overnight cultures were collected by centrifugation and were then resuspended (10-fold dilution) in double-strength MRS broth. 100 μl of this cell suspension was added to the wells of a 96-well microtiter plate together with 100 μl of CAP fibers dispersed in 0.85% (w/v) NaCl (the concentration range tested was from 0.05 μg/ml CAP to 0.1 mg/ml CAP). The microtiter plate was then incubated for 24 h at 37 °C, after which the absorbance (590 nm) was measured using an Envision Xcite multilabel reader (Perkin Elmer, Vilvoorde, Belgium).

2.9. Rhodamine 6G release study

Rhodamine 6G-loaded fibers (0.1%) were electrospun and air-dried. One mg of such Rhodamine 6G-loaded CAP fibers were placed in Eppendorf tubes containing 1 ml of PBS or SVF. Rhodamine concentration in supernatants was assayed by fluorescence spectroscopy (excitation: 528 nm, emission: 550 nm). Appropriate Rhodamine 6G standard curves (in respectively PBS and SVF; concentration range between 0.5 and 2.5 μg/ml) were used to determine the concentration of the released Rhodamine 6G. For fluorescence microscopy on the Rhodamine 6G-loaded CAP fibers, the fibers were placed in the wells of a 24 well cell culture plate (0.2 mg/well) after which PBS or SVF (0.5 ml/well) was added. The fluorescent fibers were then monitored using a Nikon EZ-C1 epifluorescence microscope, in time.

2.10. HIV-1 infectivity assay

The neutralizing capacity of the fibers against BAL viruses was measured as follows. A stock dispersion of BAL virus (a laboratory strain of HIV-1, subtype B) was diluted 3000 times; the p24 concentration in the stock dispersion equaled 660 ng/ml. The virus titer was determined making use of TZMbl cells expressing luciferase under the control of an LTR promoter as described elsewhere [17]. The TZMbl cells were trypsinized, washed and seeded at 10,000 cells/well in TZMbl medium supplemented with 30 μg/ml DEAE dextran (Lonza).

CAP fiber webs, TMC 125 loaded CAP fiber webs or Viread loaded CAP fiber webs at various concentrations as indicated in the main text, were incubated with the virus suspension in PBS or TZMbl medium for 1 h on the shaker, reaching a total volume of 200 μl with a virus concentration of 220 pg/ml 50 μl supernatant was transferred into wells containing the TZMbl cells. 48 h later, the extent of the infection of TZMbl cells by HIV-1 (or in other words the neutralization of HIV-1 by the fibers) was quantified using SteadyLite (Perkin Elmer) as a substrate for luciferase. Emitted relative light units (RLUs) were quantified on an LB 941 Berthold luminometer (Alabama, US).

2.11. Statistical analysis

All data are expressed as mean standard deviation unless indicated otherwise.

3. Results

3.1. Production and biocompatibility of electrospun CAP fibers

CAP fibers, either pure or with an encapsulated anti-HIV drug (the reverse transcriptase inhibitors TMC 125 or tenofovir disoproxil fumarate (Viread)) were obtained by electrospinning a 25% CAP solution in an acetone/dimethylformamide (DMF) mixture (3/1 (v/v) ratio). Scanning electron microscopy (SEM) data on pure CAP fibers (Fig. 1A) revealed that highly uniform fibers were produced with an average diameter ranging between 500 and 800 nm.
Although electrospun fibers have often been described to show aberrant morphologies and thicknesses, depending on the polymer concentration and type of solvent mixture used, the present conditions appeared to be well suited for the preparation of uniform, small-diameter CAP (nano) fibers. The incorporation of the anti-HIV drugs, at concentrations up to 7.5 μg TMC 125 and 178 μg Viread per 1 mg CAP, did not alter the fiber morphology (Fig. 1B).

Ideally, any compound applied intra-vaginally should be nontoxic toward the vaginal epithelium as a damaged epithelial lining could inadvertently facilitate viral translocation into subepithelial tissues. Therefore, the effect of different concentrations of CAP on the viability of immortalized human vaginal epithelial cells was evaluated by an MTT assay, an established cytotoxicity assay. The data in Fig. 1C demonstrate that free (i.e. dissolved) CAP, in the concentration range used, displayed very low toxicity toward vaginal epithelial cells; a significant toxic effect was only observed at CAP concentrations above 1.8 mg/ml (data not shown). Based on an MTT assay, non-dissolved CAP fibers applied on vaginal epithelial cells were found to be nontoxic at all concentrations up to 2 mg/ml (data not shown). Identical results were obtained on CD4+ T cells which were used in the HIV infection assays described below (Fig. 1D). In all further cell-based experiments, the amount of CAP fibers used was kept at maximally 0.05 mg/ml CAP, which is well below the cytotoxicity threshold for (dissolved) CAP. Besides being nontoxic for the vaginal epithelium, it is of great importance as well that the vaginal flora is not affected by the fibers. The healthy human vaginal flora consists primarily of one or more Lactobacillus species, which are lactic acid producing Gram-positive bacteria and the main cause of the low vaginal pH [18]. In order to verify whether the CAP fibers might affect the vaginal flora, three different Lactobacillus species were tested (L. plantarum, L. crispatus, L. gasseri) which have been described to represent a predominant proportion of the complete vaginal microbial flora [19]. As can be seen in Fig. 1D, CAP fibers (up to 0.1 mg/ml CAP) did not inhibit the growth of the Lactobacillus strains tested. The data in Fig. 1C and D suggest that the CAP fibers are nontoxic under in vitro conditions, suggesting their possible applicability for use within the healthy human vagina. It must still be determined, however, how the fibers act under in vivo conditions and what their effects on the viability of the vaginal epithelium or the vaginal flora may be after longer exposure times.

3.2. The effect of human semen of fiber solubility

To check the ‘sensitivity’ of electrospun CAP fibers to traces of human semen, the fibers were exposed to respectively simulated vaginal fluid (SVF), pure human semen or mixtures of the two (containing respectively 50, 30 and 20% (v/v) semen). Fig. 2 shows representative snapshot images at different time points after exposure times.

The high buffering capacity of semen enables avid fiber dissolution; we observed a complete dissolution of the CAP fibers after respectively 18 s and 10 s in SVF containing 30 and 50% semen (Fig. 2C and D). When the CAP fibers were exposed to pure semen (Fig. 2E) they dissolved nearly immediately. This pH-dependent solubility of the CAP fibers is fully in line with previous data on the solubility of CAP in aqueous solutions which reported lowest solubility at a pH of 4 (and lower) whereas increasing the pH to above 5 significantly improved the solubility [12]. The results in Fig. 2 suggest that CAP fibers will remain intact under physiological intra-vaginal conditions while they will locally dissolve as soon as they become exposed to trace amounts of semen. After heterosexual intercourse, the elevated vaginal pH slowly reduces back to normal levels, where it is expected that the fibers will slowly but continuously dissolve until the pH drops to about 5.3. By manipulating the thickness of the fiber film or altering the polymer constitution, the dissolution kinetics could be optimized in order to allow for repeated and long-term use of a single fiber film.

3.3. The effect of pH on fiber dissolution and release of entrapped compounds

To explore pH-induced release of compounds entrapped during electrospinning in the CAP fibers, CAP fibers were loaded with the fluorophore Rhodamine 6G and subsequently exposed to respectively SVF (pH 4.2) and PBS (pH 7.4). As can be shown in Fig. 3A, the release of Rhodamine 6G from CAP fibers at pH 4.2 was negligible, even after 1 h. In sharp contrast, the fluorophore was very abruptly released from the fibers at pH 7.4, leading to a full release in approximately 2 min. Fig. 3B and C clearly confirm that the CAP fibers keep the Rhodamine 6G at a normal vaginal pH while they easily release it at pH 7. We would like to note that this pH-responsive release profile of electrospun CAP fibers restricts their use to healthy vaginal floras as in bacterial vaginosis, hyp estrogenism or sometimes during menstruation the vaginal pH is increased [2]. If this pH elevation is only transient, such as after sexual intercourse, only a minor portion of the fibers will be dissolved. More data on the behavior of the fibers under in vivo conditions are needed in order to assess the potential limitations of an elevated pH on the use of the electrospin CAP fibers. In view of this potential problem, one could consider the incorporation of colored dyes in the CAP fibers which could help to indicate premature dissolution due to an elevated pH.

3.4. Anti-viral properties of electrospun CAP fibers

In the next part of this study, the anti-viral activity of CAP fibers against HIV-1 was evaluated. To this end, electrospun CAP fibers were applied in cell culture media (pH 7.4) and incubated with free HIV-1 viral particles for 1 h; subsequently the viruses were exposed to CD4+ TZMbl cells and their degree of infectivity was evaluated as described in the Experimental section. CD4+ T cells are stably transfected with CD4, CXCR-4 and CCR-5 receptors to allow HIV-1 attachment and infection and hereby simulate the natural target cells of HIV within the human body, being CD4+ T cells and CD4+ dendritic cells [20]. The data in Fig. 4A show a clear concentration-dependent effect of (dissolved) CAP fibers on the infectivity of HIV-1, resulting in approximately 50% neutralization at 0.05 mg/ml CAP. To further improve the neutralization efficacy of the CAP fibers an FDA-approved nucleotide analog reverse transcriptase inhibitor [21] (Viread) was incorporated in the CAP fibers at various concentrations; note that in this experiment only a low amount of CAP fibers (0.01 mg CAP/ml) was used. The data in Fig. 4B show that the incorporation of Viread into the CAP fibers clearly improves their anti-viral potency achieving complete neutralization of the HIV-1 infection at 0.5 μg Viread/ml. Similar results were obtained upon incorporation of TMC 125, which belongs to the series of diarylpyrimidines, a class of compounds which have been described to be extremely potent against wild-type and various mutant strains of HIV-1 (data not shown) [22].

4. Discussion

To date, the potential use of microbicides in the prevention of HIV is gaining a lot of attention. During the last decade, several
compounds have been discovered which exert potent anti-HIV activity [23] and a number of clinical trials have been setup, mainly using gel-based formulations [24]. However, one of the main issues with the currently available formulations is their poor ability to provide an effective and durable drug barrier along the epithelial lining [9]. Furthermore, the application of these gels, the inherent toxicity of the products and carriers used, often induce the formation of micro-abrasions in the vaginal mucosa, which increases the risk for HIV-1 infection as the virus is likely to pass through the epithelial barrier [25]. In order to overcome these problems and driven forward by the advances made in the development of a dendrimer-based microbicide gel (Vivagel), scientists have turned to nanotechnological developments to improve the vaginal distribution and retention and to create a controlled release environment of anti-viral agents [9]. In line with these developments, several strategies have been evaluated, including, for instance, the delivery of anti-viral agents from biodegradable poly(lactic-co-glycolic acid) nanoparticles [25], the capture of HIV-1 virions by concanavalin-A-immobilized polystyrene nanospheres (360 nm diameter) [26] and the use of 2 nm mercaptobenzoic acid coated gold nanoparticles conjugated to a CCR-5 antagonist (SDC-1721), inhibiting HIV-1 fusion to human T cells [27]. Although these findings may be promising for the prevention of HIV, the vaginal delivery and retention of such nanoparticles remains a huge...
Fig. 3. A) Release profile of Rhodamine 6G from electrospun CAP fibers in respectively SVF and PBS (appropriate standard curves of Rhodamine 6G in SVF and PBS were used to calculate the concentration of released Rhodamine 6G). B–C) Fluorescence microscopy on Rhodamine 6G-loaded CAP fibers after dispersion in SVF (B) and PBS (C).

Fig. 4. A) Inhibition of HIV-1 infection to TZMbl cells by different concentration free CAP powder. B) Inhibition of HIV-1 infection to TZMbl cells by different Viread concentrations in 0.01 mg/ml CAP fiber solution.
challenge. The electrospun fiber webs used in the present study may be applied as vaginal films, resulting in an easier application when compared to nanoparticles and vaginal gels. The combined use of CAP fibers and mucoadhesive fibers in the same web may furthermore improve the (bio)adhesion of the film to the vaginal epithelium and enable a controlled and local release of the antiviral agents, only where the film comes into contact with seminal fluid.

One type of product which has increasingly gained attention, are the so-called vaginal rings. Vaginal rings are flexible, torus-shaped polymer-based devices which lead to a continuous (coitus-independent) sustained release of embedded anti-viral agents over a long period of time (up to several weeks) [28] Several such rings are currently undergoing phase I or II clinical trials. As the continuous release of anti-viral drug requires high amounts of these (costly) products, one of the major concerns also lies in the possible induction of HIV resistance to the applied drug or unwanted secondary effects on the person. To overcome these issues, coitus-dependent release systems have gained a lot of attention. In this respect, also Gupta et al. [29] developed pH-sensitive smart polymer hydrogels composed of a random terpolymer of N-isopropyl acrylamide, butyl methacrylate and acrylic acid, which were stable in simulated vaginal fluid but eroded in the presence of seminal fluid. The present study continues on these interesting findings by making use of electrospun fibers simply prepared from CAP which is, since decades, in use in pharmacy as enteric coating agent for tablets and capsules. Fibers further offer several advantages over the more classical cast hydrogels, such as a very high surface-to-volume ratio, which may greatly enhance drug release rates upon changing the pH [30] These rapid release properties are also apparent in our study, where no release of the Rhodamine 6G can be noted in SVE, whereas in semen, the fibers immediately dissolve (Fig. 4A) and rapidly release the fluorophore within a couple of seconds (Fig. 4B). Such fast release kinetics may greatly enhance the applicability of electrospun fibers in anti-viral strategies as quick-dissolve dosage forms have been reported to offer the most promising platform for the vaginal delivery of microbicides [24].

The intrinsic microbicidal properties of CAP make this an ideal polymer for use in anti-viral therapies. The ease and flexibility of the electrospinning process also allows encapsulating other compounds, such as anti-viral drugs, within the electrospun fibers [31]. In literature, it has been described that a wide range of anti-viral drugs can be readily encapsulated in electrospun fibers without altering the drug’s activity [32]. It is clear from our studies that the encapsulation of anti-viral drugs such as Viread in CAP fibers greatly increases the efficacy of virus neutralization compared with pure CAP fibers. This is in line with previous work by Liu et al. [33] who showed that CAP combined with a reverse transcriptase inhibitor (UC781) had significant synergistic effects on the inhibition of HIV infection. Of interest is also the fact that, in contrast to the HIV-binding gold or polystyrene nanoparticles introduced above, the encapsulated anti-viral compounds may act on both free virus and cell-associated virus present in HIV-infected semen [34]. In addition, the conjoined encapsulation in the fibers of two microbicides which act by different mechanisms may reduce the chance for encountering a resistant mutant HIV strain, as also observed by Liu et al. [33] who found that CAP and UC781 exhibited complementary effects, where CAP was able to inhibit infection of the UC781-resistant HIV-1118B A17 strain.

5. Conclusions

In this study we prepared and characterized CAP electrospun fibers in the context of their potential use in the prevention of HIV-1 infection. It was observed that CAP fibers, even after being dissolved, are not toxic toward vaginal epithelial cells and vaginal Lactobacilli. Our data further showed that CAP fibers remained intact in SVF while they rapidly dissolve upon exposure to low amounts of human semen. The CAP fibers themselves were found to inhibit HIV infection of CD4+ TZMbl cells in vitro. Moreover, CAP fibers could be easily loaded with anti-HIV drugs (TMC 125 and Viread) which were found to inhibit HIV-1 infection even more strongly when released from the fibers by human semen, supporting the potential of CAP fibers in preventing HIV-1 spread during sexual intercourse.

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References


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