Drug Delivery and Development of Anti-HIV Microbicides

edited by
José das Neves
Bruno Sarmento
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Prevention of sexual HIV transmission remains the cornerstone to bend the curb of the pandemic. Campaigns to promote behavioral changes, including avoidance of high-risk sexual practices and consistent condom use, remain key, but they need to be supplemented with biomedical interventions [1]. Treating the seropositive partner is an efficacious means of preventing HIV transmission in stable relationships [2]. If this option is not available, pre-exposure prophylaxis (PrEP) of non-infected at risk individuals with antiviral drugs, either systemically or locally, could be an alternative. Clearly, the local PrEP option, referred to as “microbicides,” seems preferable (especially in order to avoid systemic exposure to drugs) but its development over two decades has been an intellectual and logistical challenge [3].

As explained in Chapter 1, the field of microbicides has moved from simple broad-spectrum microbicidal-virucidal products (such as nonoxynol-9) to specific anti-HIV drugs. The first and yet only successful microbicide clinical trial (CAPRISA 004), using the nucleotide analogue tenofovir as a vaginal gel, showed significant protection against both HIV-1 and human herpes simplex virus type 2 (HSV-2), a known co-factor for HIV acquisition. This success has boosted the search for locally applicable highly active antivirals of various classes and combinations thereof. This endeavor is currently pursued by several international organizations, e.g., the European program CHAARM (“Combined Highly Active Anti-Retroviral Microbicides,” more information available at http://chaarm.eu/) and the International Partnership for Microbicides (IPM, more information available at http://www.ipmglobal.org/), amongst others. Since HIV transmission is linked to other sexually transmitted infections (STIs), research on “Multiple Purpose Technology” (MPT) to prevent HIV, other STI and pregnancy is a new logical trend.

Besides a good (combination of) active pharmaceutical ingredient(s) (API), however, suitable drug delivery (i.e., formulation)
is essential for success: The API has to be delivered in a format that is affordable, easy to use, culturally adapted and, of course, able to release the API at the right time and place, i.e., vaginally or rectally. Formulation issues are often underestimated by "basic" scientists performing in vitro research, but also by clinicians, who generally only think about the API, when they evaluate success or failure. In that sense, this book is revealing as it provides a very thorough and state-of-the-art overview mainly from the perspective of the "formulators," but clearly intended to inform all scientists and clinicians who are involved in microbicide development.

The biological aspects of transmission, modeling, and the challenges for drug delivery are discussed in Chapters 2 and 3, providing a good basis to frame the formulation efforts, explained throughout this book. In Chapter 4, safety assessment of microbicide formulations is addressed. The importance of this aspect cannot be over-emphasized, in view of the early failures of microbicide clinical trials, due to a low therapeutic index. The biophysical aspects of drug transport and microbicides formulation are then highlighted in Chapter 5. Chapter 6 on advantages and pitfalls of microbicide formulation provides a general overview on requirements of a good microbicide formulation, whereas several specific formulations are being discussed in the next chapters.

Traditional vaginal gels have been used in most microbicide trials until now, but they have several disadvantages such as messiness and coital dependency (i.e., need to be applied shortly before intercourse). Vaginal rings (Chapter 7) offer a first alternative, as they provide sustained local delivery over several weeks with low systemic exposure, as well as the ability to deliver multiple APIs. They are easy to use and therefore may also improve acceptability and adherence. Rings with the non-nucleoside reverse transcriptase inhibitor (NNRTI) dapivirine or/and maraviroc (a CCR5 inhibitor) are at the forefront of clinical trials today. Vaginal films (Chapter 8) constitute another format with a possibly higher acceptance than gels, since they are a convenient, portable, dry solid dosage form that dissolves rapidly once in contact with the vaginal fluid. Vaginal films containing some of the non-specific candidate microbicides have been succeeded by more potent antiviral drugs, including the nucleoside analogue zidovudine and the non-nucleosides IQP0528 and dapivirine, the latter being prepared for a clinical trial soon.
Chapter 9 attracts our attention to the fact that not only homosexual but also a lot of heterosexual transmission occurs via anal intercourse. Obviously, the challenges to develop an effective microbicide for anal use are even bigger than those associated with vaginal use, in view of the (much) larger area to protect and the higher susceptibility of the rectal mucosa both to HIV transmission and to possible toxic effects of applied products. Nevertheless, a number of candidate rectal microbicides show anti-HIV activity in colorectal explants, and encouraging macaque rectal protection trials (with tenofovir) have already been reported. At the same time, human Phase 1 clinical trials have been performed, are ongoing, or are being prepared.

The next four chapters discuss further innovative aspects of formulation. Chapter 10 explains how gels, rings, films, and nanoparticles could be conceived to respond to stimuli associated with the vaginal environment and with intercourse in order to release their antiviral API with appropriate timing. Some of the most advanced products are based on Eudragit® S 100, a pH-sensitive anionic copolymer, which can be used for co-formulation and timely release of combinations of hydrophilic and hydrophobic APIs (e.g., tenofovir and dapivirine). In Chapter 11, polymeric nanoparticles (NPs) are presented as a delivery system for APIs, with potentially better stability of the encapsulated drug, sustained release, lower toxicity, and more even distribution as compared to traditional gel formulations. Similarly, electrospun fibers (Chapter 12) have already been shown to incorporate and deliver a variety of anti-HIV compounds, including tenofovir, zidovudine, maravir, and NNRTI. These and other APIs could effectively be combined into composites or nanostructured carriers, such as layered mats or coaxial fibers, and be made responsive to relevant stimuli such as pH changes and vaginal enzymes, among others. In Chapter 13, genetic engineering of commensal Lactobacilli (part of the natural vaginal defense) to deliver anti-HIV molecules is discussed. Thus long-lasting protection might be provided at low cost, but this approach, of course, faces particular regulatory challenges.

The final chapters put all this work into a larger societal context, including affordability and intellectual property issues (Chapter 14), regulatory issues (Chapter 15), and behavioral as
well as socioeconomic factors (Chapter 16). Basic and clinical scientists should be well aware of those aspects during the development of their candidate microbicides, as those will define whether or not a product that has shown efficacy in clinical trials will ultimately be used by the population who needs it.

In summary, the present book provides a reference for all those who want to be informed on the state-of-the-art of microbicide formulation, starting from basic science over technicalities to the wider social context. All contributors hope that their work will inspire the scientific community joining forces to develop an effective, safe, and affordable microbicide for all those who need it.

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June 2014

References

Preface

The worldwide impact of HIV/AIDS is well recognized. In the absence of a cure, pre-exposure prophylaxis (PrEP) represents a cornerstone in the battle against HIV infection. Different strategies were shown to be useful in slowing down the spread of the virus and put into practice, while others are being actively developed. One promising approach comprises the use of microbicides (also referred to in recent years as topical PrEP), which have been traditionally defined as vaginal and/or rectal products intended to be used around the time of intercourse in order to prevent the sexual transmission of HIV and, potentially, other pathogens. In 2010, the CAPRISA 004 clinical trial testing a gel containing 1% tenofovir provided proof-of-concept that microbicides may prevent male-to-female vaginal HIV transmission, even though observed protection was only partial. There was renewed interest and significant development in the field ever since, and other products also advanced significantly toward clinical testing. Even though follow-up studies for gels containing tenofovir did not produce so far the expected confirmatory outcomes, researchers and advocrators are now kept in suspense while waiting for the results of two ongoing Phase 3 clinical trials testing a dapivirine vaginal ring, expected to be released in late 2014 or early 2015.

Once a somewhat neglected topic, it is now accepted that specific development of drug dosage forms and/or drug delivery systems is an indispensable aspect for future microbicides success. Different groups strived over the last decade to optimize the technological, biophysical, and safety performance of traditional dosage forms, particularly gels, tablets, and suppositories (or ovules), in order to fulfill the specificities of microbicides use, without neglecting the preferences of users and affordability issues. Moreover, other formulation approaches, such as vaginal rings and films, nanotechnology-based systems, stimuli-sensitive formulations, and targeted delivery systems, among others, have been proposed and are currently undergoing pre-clinical or even clinical testing.
We hope this book will provide a thorough and critical overview of current aspects and developments, as well as new trends, in the formulation and drug delivery concerning anti-HIV microbicides by leading scientists in the field. Additionally, the book discusses pertinent large-scale production, affordability, and regulatory aspects, as well as socioeconomic issues related to the subject.

Finally, we would like to express our deepest gratitude to all the contributors for taking the time and expertise to make this book real, as well as to everyone at Pan Stanford Publishing who assisted in the production of the book. Also, a special word of appreciation is due to Guido Vanham for kindly accepting to write the Foreword.

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