European Journal of Pharmaceutics and Biopharmaceutics 104 (2016) 171–179

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Development of a multi-layered vaginal tablet containing dapivirine, levonorgestrel and acyclovir for use as a multipurpose prevention technology

Christopher McConville [a,*], Ian Major [b], Brid Devlin [c], Andrew Brimer [c]

[a] School of Pharmacy, Institute of Clinical Sciences, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham, UK
[b] Materials Research Institute, Athlone Institute of Technology, Athlone, Ireland
[c] International Partnership for Microbicide, Silver Spring, MD, USA

ARTICLE INFO

Article history:
Received 29 February 2016
Revised 28 April 2016
Accepted in revised form 3 May 2016
Available online 7 May 2016

Keywords:
Multipurpose prevention technology
HIV microbicides
Contraception
Sexually transmitted infections
Dapivirine
Levonorgestrel
Acyclovir

ABSTRACT

Multipurpose prevention technologies (MPTs) are preferably single dosage forms designed to simultaneously address multiple sexual and reproductive health needs, such as unintended pregnancy, HIV infection and other sexually transmitted infections (STIs). This manuscript describes the development of a range of multi-layered vaginal tablets, with both immediate and sustained release layers capable of delivering the antiretroviral drug dapivirine, the contraceptive hormone levonorgestrel, and the anti-herpes simplex virus drug acyclovir at independent release rates from a single dosage form. Depending on the design of the tablet in relation to the type (immediate or sustained release) or number of layers, the dose of each drug could be individually controlled. For example one tablet design was able to provide immediate release of all three drugs, while another tablet design was able to provide immediate release of both acyclovir and levonorgestrel, while providing sustained release of Dapivirine for up to 8 h. A third tablet design was able to provide immediate release of both acyclovir and levonorgestrel, a large initial burst of Dapivirine, followed by sustained release of Dapivirine for up to 8 h. All of the tablets passed the test for friability with a percent friability of less than 1%. The hardness of all tablet designs was between 115 and 153 N, while their drug content met the European Pharmacopeia 2.9.40 Uniformity of Dosage units acceptance value at levels 1 and 2. Finally, the accelerated stability of all three actives was significantly enhanced in comparison with a mixed drug control.

1. Introduction

Multipurpose prevention technologies (MPTs) are products, preferably single device products, administered via a single route, that are designed to simultaneously address multiple sexual and reproductive health needs, such as unintended pregnancy, HIV infection and other sexually transmitted infections (STIs) [1]. MPTs can fall into a number of categories: (1) a drug delivery device or formulation that releases multiple active agents of which each is effective against a different indication, (2) a drug delivery device or formulation that release a single active agent that is effective against a range of different indications or (3) a barrier device such as a condom or diaphragm in combination with one or more active agents which are effective against multiple indications. According to the Coalition Advancing Multipurpose Innovations (CAMI), every minute a woman is infected with HIV, there are 86 million unplanned pregnancies around the world annually and 1 million people contract an STI every day [2]. MPTs offer a solution to these overlapping reproductive health issues using a single device, which will result in a number of benefits for the users, including convenience, increased adherence, improved effectiveness, reduction in cost and environmental impact [3].

There are currently a number of MPT products on the market, such as the male and female condom and the cervical diaphragm. The male condom is one of the key MPT barrier methods, which when used correctly is highly effective in protecting against pregnancy, HIV infection and many other common STIs [4,5]. However, inconsistent and improper use, as a result of poor acceptability, has resulted in failure rates, after 1 year of use, of approximately 15% and a pearl index of 15 [6], while many women cannot negotiate condom use with their partners [7]. The female condom is a female controlled barrier method, which has been shown to have a comparable or slightly higher contraceptive efficacy when compared to the male condom [8,9] and was just as effective in reducing the recurrence of bacterial STIs [10]. Although there is no actual

* Corresponding author.
E-mail address: C.McConville.2@bham.ac.uk (C. McConville).

http://dx.doi.org/10.1016/j.ejpb.2016.05.003
0939-6411/

data on HIV prevention, mathematical modelling has suggested an effectiveness of 63–82% [11,12]. However, the cost of the female condom is still higher than that of the male counterpart, with strategies, such as the washing, disinfecting and reusing of the female condom being employed to try and reduce its relative cost [13]. Cervical diaphragms are designed to sit on the cervix and are traditionally used for contraception and have a similar rate of effectiveness to the male condom [14]. The cervix has a high density of CD4 cells and CCR5 chemokine receptors and has been shown to be the initial site of infection for HIV and other STIs [15–17]. Therefore, diaphragms may offer protection from HIV and other STIs and thus act as an MPT, while studies have shown that the incidences of gonorrhoea and chlamydia infections are lower in those women who use diaphragms over other barrier methods of contraception [18]. However, a large scale trial comparing the efficacy of using a diaphragm and a condom to condoms alone in preventing HIV-1, gonorrhoea and chlamydia in at-risk women demonstrated that there was no statistically significant difference between the two groups [19,20]. The Program for Appropriate Technology in Health (PATH) has developed a new 'one size fits most' SILCS diaphragm, which is manufactured from silicone and contains a polymer spring, rather than the metal spring used in most standard diaphragms. The SILCS diaphragm performed well in Phase I post-coital barrier effectiveness testing. However, it was recommended that for it to be most effective adjunctive use of a chemical barrier or spermicidal gel was needed [21]. PATH, has investigated the development of a SILCS diaphragm that releases the HIV microbicide dapivirine [22].

Adherence and compliance issues are well understood in contraceptive and microbicide fields, with a recent Phase IIb study of a gel containing 1% w/w of the NRTI tenofovir lowering the risk of HIV infection in sexually active women by 54% provided they reported greater than 80% adherence, which fell to 38% protection if they had between 50% and 80% adherence and to 28% with less than 50% adherence [23]. This study clearly demonstrates the influence of adherence and compliance on the efficacy of a microbicide product and suggests that any future MPT products need to consider patient adherence to the required dosing regimen, particularly for those products which are coitally dependent.

Solid dosage forms such as vaginal tablets may overcome some of the compliance, acceptability and adherence issues associated with other MPT strategies. They are more discrete, easier to administer to the vagina and are coitally independent, especially when they are designed to be sustained release tablets. A study in African women reported that 80% of the women tested liked using a vaginal tablet; while over 85% said they would definitely use them [24]. Sustained-release tablets are designed to slowly release drug at a rate governed predominately by the design of the delivery system. Many sustained release formulations are specifically designed for once-daily per-oral administration and have been shown to improve patient compliance and acceptability compared with conventional multiple daily dosing regimens [25]. Multi-layered tablets are a flexible technology that has been used for modifying the release of drugs as well as delivering multiple drugs [26–29]. Multi-layered tables have been used to achieve, zero order release [30,31], pulsatile release [32] and even bimodal release [33], where an initial immediate release phase is followed by a period of sustained release, and then a second immediate release phase. Melt processing has be used to manufacture solid dosage forms for the purposes of solubility and bioavailability enhancement, through the productions of solid dispersions [34–37] and taste masking of bitter drugs [38–41].

This manuscript describes the development of a range of multi-layered vaginal tablets, with both immediate and sustained release layers capable of delivering the antiretroviral drug dapivirine, the contraceptive hormone levonorgestrel, and the anti-herpes simplex virus drug acyclovir at independent release rates from a single dosage form, manufactured using a combination of melt processing and compression moulding.

2. Materials and methods

2.1. Materials

Dapivirine (DPV) was provided by the International Partnership for Microbicides, which holds exclusive rights to DPV through an agreement with Janssen Sciences Ireland UC, and levonorgestrel (LNG) and acyclovir (ACY) were purchased from Cambridge Biosciences (Cambridge, UK). Sodium dodecyl sulphate (SDS) and methanol were purchased from Sigma Aldrich (Dorset, England). Kollidon® SR, Kollidon® VA and Kolliphor® P 188 were provided by BASF (Ludwigshafen, Germany).

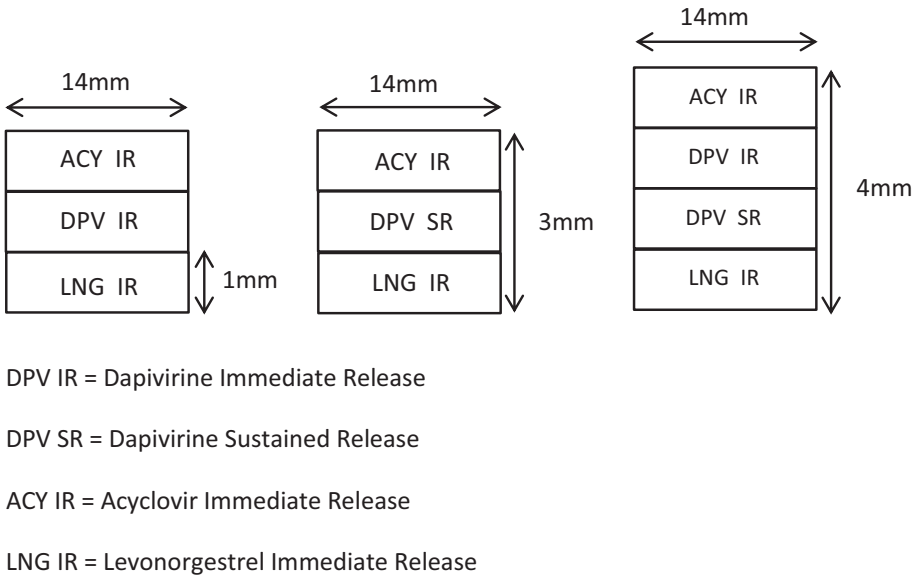

Fig. 1. Schematic of the various multi-layered DPV, ACY and LNG MPT vaginal tablets.