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Formulation, *In Vitro* and *In Vivo* Pharmacokinetics of Anti-HIV Vaginal Bioadhesive Gel

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ABSTRACT

Inexpensive and female-controlled pre-exposure prophylaxis strategies to prevent mucosal transmission of the virus, is urgently needed with the rising prevalence of human immunodeficiency virus (HIV-1 and HIV2) infections in women. Zidovudine-loaded bioadhesive vaginal gel may become one of the very useful strategies, as it can be used not only for controlled release but also for enhancing bioavailability. Drug delivery through vaginal gel is a promising area for continued research with the aim of achieving controlled release with enhanced bioavailability over longer periods of time. The aim of the study was to develop a newer prolong releasing Zidovudine (AZT) bioadhesive vaginal gel to treat HIV infections with increased patient convenience. AZT-loaded bioadhesive vaginal gel was prepared successfully by using cold mechanical method. F3 formulation containing carbopol–HPMC (1:3) was selected and evaluated in order to achieve objectives of this study. *In vitro* drug release study of F3 showed in 24 h drug released following case I Fickian ($n \leq 0.5$) transport mechanism, and *in vivo* drug release was found much better (T_{max}), (C_{max}), and bioavailability (F) comparison with oral pour drug solution. It was also showed good extrudability, spreadability, and bioadhesive strength. A generalized protocol, for the further research, in this area will surely expected to yield significant outcome with improved drug delivery system.

Key words: Bioadhesive, human immunodeficiency virus, pharmacokinetics, vaginal gel, zidovudine

INTRODUCTION

The women (15.4 million) are approximately 50% of people (33.2 million) infected and living with HIV, as reported in 2007 UN AIDS summary.[1] In most regions of the world, HIV is affecting women and girls in increasing numbers. Vaginal drug delivery is a very challenging and less explored research area. Gel as dosage forms were successfully used as drug delivery systems with their ability to prolong the drug release. Topical, self-administered products containing HIV microbicides were aimed to prevent and to reduce HIV infection in women and may represent the most promising strategy for combating the HIV/AIDS epidemic at the present time. The vagina is an efficient route[2] for drug administration due to presence of dense blood vessels network and avoids first-pass.[3,4] Ideally, anti-HIV vaginal gels (F) should adheres in vaginal medium; provide uniform drug–hydrogel coating of vaginal tissue, resulting in intravaginal biomimetic lubrication during intercourse, and retention of this gel layer before and after intercourse. Most importantly, controlled release of anti-HIV drugs form this gel inactivates the viral load potentially

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introduced during sexual activity. Zidovudine (AZT) with short elimination half-life of about 1 h, high dose (250 mg in every 4 h while 300 mg twice a day, in some cases), low systemic bioavailability (64%) due to rapid hepatic fast-pass metabolism, was chosen as a model drug of choice.[5] The use of prolong-release bioadhesive vaginal gel was thought to offer numerous benefits including prolong residence time of the dosage form at the site of absorption due to bioadhesion to the vaginal mucosa, prolong drug release, improved bioavailability and decreased side effect of drug, and ultimately improved patient compliance. Keeping in view of the above uniqueness, this study was designed to develop a newer formulation for prolong release of AZT to treat HIV infections with increased patient convenience.

MATERIALS AND METHODS

Materials

Zidovudine was obtained from Arbindo Pharmaceutical Ltd. (Hydrabad, India). Carbopol 940P were received as gift sample from Corel Pharma Chem (Ahmedabad, India). HPMCK4M was obtained from LOBA Chemicals (Kolkata, India). All other chemicals and reagents used were of analytical grade and used as received.

Methods

Preparation of Zidovudine-loaded vaginal gel

Vaginal gels were prepared by cold mechanical method described by Schmolka.[6,7] The required quantity of drug (AZT) and polymer (Carbopol 940P and HPMCK4M) was weighed, then it was sprinkled slowly on surface of purified water for 2 h. After that it was continuously stirred by mechanical stirrer, till the polymer was soaked in the water. Finally solution was kept for overnight for complete hydration of polymer. With continuous stirring, triethanolamine was added to neutralize the gel and to maintain the pH of the gel. Now the appropriate quantity of dimethyl sulphoxide (DMSO) was added to the gel, which behaved as the penetration enhancer, followed by addition of required quantity of ethanol to make the soft gel. Care should be taken to avoid incorporation of air into gel. In this way, four formulations (F1–F4) of gel were prepared by combinations of carbopol 940 and HPMC. Finally, the preparations were packed in wide mouth plastic jar covered with screw capped plastic lid after covering the mouth with an aluminum foil and were kept in dark and cool place. The formulations were preserved for further study. The generalized bioadhesive gel preparation protocol depends on choice of solvent, stirring speed of mechanical stirrer, and optimization at every preparative steps. AZT incorporated into bioadhesive gel intended for vaginal was successfully prepared using mechanical stirring technique as designed in Table 1.

Percent yield of vaginal gel

The percent yield was calculated[8] as the weight of the formulations (Fs) recovered from each batch divided by total weight of drug containing microparticles and other all ingredients used to prepare Fs multiplied by 100. The percentage yield of each formulation was replicated three times. The yield of Fs was calculated using the following formula:

$$Y = \{P_m - Z_g\}/T_m[P + \text{Ig}] \times 100,$$

where Y = yield, P_m = practical mass, Z_G = vaginal gel, T_m =theoretical mass, P = polymer, and Ig = ingredients.

Drug content evaluation

Drug content was determined by Sanjay *et al*.,[9] dissolved accurately weighed quantity of bioadhesive vaginal gel with 20 mL of simulated vaginal fluid (SVF, acetate buffer I.P. pH 4.7) in a 50 mL of volumetric flask with continuous stirring. The volume was adjusted up to 50 mL with SVF. Blank bases were also treated in similar manner for blank determination. Both the test sample and blank were allowed to stand on mechanical stirrer for 2 h and kept for 24 h. In the next day, all the solutions were filtered using Whatmann filter paper no. 44. Then, the filtrate solution was kept as a stock solution. After suitable dilution, the absorbance of the solution with the blank was measured by UV–visible spectrophotometer (UV-1700, Shimadzu, Japan) at 267 nm. Drug content was calculated from the standard calibration curve, $Y = 0.038 \times X$, where Y = absorbance and X = concentration of the drug. $D_c = [C_c \times D_f \times V]/C_F$, where as D_c = drug content, C_C = concentration, D_F = dilution factor, V = volume taken, and C_F = conversion factor.

Bioadhesive strength of Fs using isolated goat vagina

Isolated goat vaginal tissue (*Capra hircus*, local breed,

Table 1: Formulation design of bioadhesive vaginal gels (F1–F4)

Ingredients	Formulation			
	F1	F2	F3	F4
Zidouvdine (mg)	100	100	100	100
Carbopol (mg)	100	100	100	100
HPMC (mg)	100	200	300	400
DMSO (mL)	0.2	0.2	0.2	0.2
Triethanolamine (mL)	0.9	0.9	0.9	0.9
Methyl Paraben (mg)	15	15	15	15
Alcohol (mL)	5.0	5.0	5.0	5.0
Water (up to mL)	100	100	100	100