ORIGINAL ARTICLE

Implantable vaginal drug delivery system of zidovudine for site specific activity

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The present work aims at the formulation of novel anti-human immunodeficiency virus vaginal compactable inserts to enhance the pharmacological effects of zidovudine (AZT). Attempt was taken to design a dosage form, which provides sustained release of the drug at the site of action so as to minimize the overall dose and dosing frequency that can reduce the risk of side-effects. Different formulations of the vaginal compacts of AZT were prepared employing wet granulation method, utilizing several mucoadhesive polymers such as hydroxypropyl methyl cellulose (HPMC 5, 15, 50, 3000 cps) and methyl cellulose (MC) at 20%, 30% and 40% concentrations. The formulations were evaluated and post-compression parameters including drug content, swelling study, *in vitro* diffusion, dissolution and drug release kinetic studies. Instrumental analysis like differential scanning calorimetry as well as Fourier transform infrared spectroscopy were performed to find the change in thermal properties and the possible interactions between drug-polymer, respectively. X-ray diffraction study was also done to reveal the modification of crystalline nature of drug in the formulation. The compacts prepared by HPMC 50 cps (40%) exhibited the better results in terms of swelling with sustained drug release through the gelled layer. Regardless of good physicochemical parameters, MC did not display a good polymer of choice due to accumulation of spongy gelled blanket around the compact, which is not homogenous but stiff and brittle.

Key words: *Acquired immunodeficiency syndrome, human immunodeficiency virus, hydroxypropyl methylcellulose, vaginal compact, zidovudine*

INTRODUCTION

Human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) statistics (World Health Organization and United Nations Educational Social Cultural Organization) depicted that about 34 million human beings were living with HIV and around 1.7 million people died from AIDS related causes world-wide in 2011.[1] This focused on the huge number of newer HIV infections producing with time, which alarmed the momentous development of approaches to anti-retroviral therapy to abate AIDS associated death in the upcoming years. Women are the fastest growing population with sexually transmitted infection and AIDS world-wide. With no possible cure, HIV continued to spread despite the availability of condoms and other preventive measures.

Modern pharmaceutical technology concentrates on targeting the drug molecule to the site of action for its effective delivery and reduced untoward effects. In mucoadhesive drug delivery systems (DDS), the mean residence time of a formulation is prolonged at the targeted site of action, facilitating higher contact time of the DDS with the absorption surface, focusing on local and systemic delivery of the drug and hence contributing to the increased therapeutic performance of the drug.[2]

Vaginal drug delivery provides site targeted approach with increased permeation of the drug due to high surface area and more vascularized tissues with a vast network of blood capillaries, avoids first pass metabolism and hence reduces the side-effects of metabolites. It also favors possibility of self-insertion

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Access this article online

Quick Response Code:

Website: www.asiapharmaceutics.info

DOI: 10.4103/0973-8398.120089

and removal of the dosage form. In addition, this route also overcomes possible infections, tissue damage as well as an inconvenience and pain caused by parenteral route of drug delivery.[3]

Zidovudine (AZT) is a nucleoside analogue reverse transcriptase inhibitor, which is used as antiviral medication to treat HIV causing AIDS.[4] It is the first approved anti-HIV drug for AIDS used either in combination with other antiretroviral agents or as a single drug.[4] In order to maintain therapeutic levels, oral formulations of AZT in high doses are required to be administered multiple times a day, i.e., 300 mg 2 times a day or 200 mg thrice daily due poor oral bioavailability (65%), presystemic metabolism including short half-life of about 1 h.[4] Furthermore, the other drawbacks of oral administration of AZT include repeated gastric intolerance, anemia, neutropenia, hepatotoxicity, accumulation of drugs during multidose therapy, poor patient compliance and high cost.[4] Other conventional dosage forms such as solutions, emulsions, gels, creams and ointments do not provide controlled release of the drug and also result in short residence and contact time of the drug in the site of action.[3,5]

There have been several approaches reported for the mucosal sustained delivery of this drug. Arkendu *et al*. have developed AZT as bioadhesive films and microencapsulated gel,[6,7] for the vaginal administration of the drug and also extensively researched about its irritation property, *in vitro, in vivo* release studies and the pharmacokinetics.[8,9] AZT was also developed as buccal mucoadhesive patches to enhance the bioavailability and avoid the first pass effect caused by oral tablets.[10] To synergize the therapeutic effect of AZT, a matrix extended release tablet have also been designed in combination with lamivudine.[11] Another novel approach was reported recently for an alternative antiretroviral therapy of AZT using liquid crystal precursor as mucoadhesive vehicle through nasal route.[12]

The present work is a simple, novel and alternative approach, which also aims to overcome the limitations of other systems, with properly designed and optimized dosage form, that provides controlled release of the drug at the site of action and also minimizes the risk of side-effects. To make this drug delivery more efficacious, sustained release vaginal compactable inserts of AZT is designed using different polymer composition.

MATERIALS AND METHODS

Materials

Hydroxypropyl methyl cellulose (HPMC) (5, 15, 50, 3000 cps) and methyl cellulose (MC) were used as release modifier mucoadhesive polymers for the formulation of the vaginal inserts. These polymers were purchased from SD fine chem. Pvt. Ltd. Mumbai. AZT was incurred as gift sample from Matrix Laboratories, Hyderabad. All other chemicals and reagents used in this work were pure and of analytical grade.

Methodology

Preparation of simulated vaginal fluid

SVF was prepared at pH 5 as per british pharmacopoeia (BP) standards dissolving 13.2 g of CH_3COONa and 6 ml of CH_3COOH in ultrafiltered water (Milli-Q Plus, Millipore, USA) until the volume of solvent reached 1 L.[13]

Preparation of the compactable vaginal inserts

The drug loaded compact inserts, each containing 100 mg of AZT was prepared by wet granulation method by employing polyvinylpyrrolidone K30 (PVP K30) in isopropyl alcohol as the granulating binder solution at room temperature. A homogenous blend of the drug with polymers (HPMC [5, 15, 50, 3000 cps], MC [at 20, 30 and 40% concentrations]) and other excipients such as microcrystalline cellulose, lactose, talc, magnesium stearate was prepared using mortar and pestle in the laboratory pilot scale for making 25 tablets [Table 1]. The required quantity of binder solution was added to this blend to form a coherent damp mass, which was passed through sieve no: 22 to form uniform sized granules. The granules were dried in hot air oven at 40°C for 5 min, followed by compression using manual single punch tablet press (Khera Instruments Pvt. Ltd. New Delhi) using 8.8 mm diameter die.[14,15] The operation parameters of the machine was optimized for required compression force and hardness at room temperature, also checking the fill volume of the dies to obtain 700 mg uniform weight compacts.

Pre-compression studies for granules

Quality of the prepared granules was evaluated for its suitability for compression into compact mass. The flow property of the granules was assessed by calculating the angle of repose by funnel method. The tapped density (TD) was determined by observing the change in volume of the granules when the accurately weighed granules was poured in a measuring cylinder and tapped for 200 times. The values obtained from TD and bulk density (BD) were used to calculate Hausner ratio and Carr's compressibility index employing the formula:

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad (1)$$

$$\text{Compressibility index (I)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \quad (2)$$

The evaluations were performed in triplicates.[16]

Post-compression evaluation of the compacts

The post-compression parameters of the compacts were evaluated as per standard quality control procedures adapted for single unit solid dosage forms of tablet. Weight variation

Table 1: Formulation of compactable inserts of AZT with HPMC (5, 15, 50, 3000cps) and MC at 20, 30 and 40% concentrations

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Drug (g)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
HPMC 5 cps (g)	0.14	0.21	0.28	–	–	–	–	–	–	–	–	–	–	–	–
HPMC 15 cps (g)	–	–	–	0.14	0.21	0.28	–	–	–	–	–	–	–	–	–
HPMC 50 cps (g)	–	–	–	–	–	–	0.14	0.21	0.28				–	–	–
HPMC 3000 cps (g)	–	–	–	–	–	–	–	–	–	0.14	0.21	0.28	–	–	–
MC (g)	–	–	–	–	–	–	–	–	–	–	–	–	0.14	0.21	0.28
MCC (g)	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07
PVP K30 (g)	0.035	0.035	0.035	0.035	0.035	0.035	0.035	0.035	0.035	0.035	0.035	0.035	0.035	0.035	0.035
Lactose (g)	0.341	0.271	0.201	0.341	0.271	0.201	0.341	0.271	0.201	0.341	0.271	0.201	0.341	0.271	0.201
IPA (g)	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
Talc (g)	0.007	0.007	0.007	0.007	0.007	0.007	0.007	0.007	0.007	0.007	0.007	0.007	0.007	0.007	0.007
Magnesium stearate (g)	0.007	0.007	0.007	0.007	0.007	0.007	0.007	0.007	0.007	0.007	0.007	0.007	0.007	0.007	0.007
Total weight (g)	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7

qs: Quantity sufficient; AZT: Zidovudine; HPMC: Hydroxypropyl methyl cellulose; MC: Methyl cellulose; PVP: Polyvinylpyrrolidone; MCC: Micro crystalline cellulose; IPA: Isopropyl alcohol

test was performed to demonstrate the uniformity of weight of the formulated compacts and hence the uniformity of the dosage units. The diameter and thickness of individual compacts were measured using a vernier scale (Mitutoyo C/N 532-120), which furnished information of the variations in dimensions if any between the formulations. Hardness of the compacts was measured utilizing Monsanto hardness tester (Dolphin tablet hardness tester-Monsanto type) in kg/cm^2. In-process quality control test such as friability of compacts was ascertained by Roche friabilator (Labindia tablet friability tester FT1020) for all the formulations and the % friability was calculated.[17,18] Uniformity in drug content in the formulated compacts was estimated by preparing required dilutions (10 µg/ml) of the crushed compact formulations in SVF and measuring the absorbance at λmax (267 nm) using ultraviolet (UV) spectrophotometer (thermoscientific evolution 200 UV-Vis). Hence the percentage drug content was calculated using the formula:

$$\%\,\text{Drug content} = \frac{\text{Sample absorbance}}{\text{Standard absorbance}} \times 100 \quad (3)$$

Swelling study

Swelling index of all the formulations was calculated in terms of the percentage weight gained by the compacts at regular time intervals for up to 6 h duration as the sample was exposed to a constant volume of 10 ml SVF as media at pH 5 kept in a petriplate.[19] The % hydration was calculated using the formula:

$$\%\,\text{Hydration} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100 \quad (4)$$

Diffusion study

The study was carried out using Franz diffusion cell as shown in Figure 1, to check the amount of drug diffused across the membrane over a period of time. The receptor was filled with SVF until the neck of the chamber (20 ml). A dialysis membrane (Dialysis Membrane-110, HiMedia Laboratories

Figure 1: *In vitro* permeation study using Franz diffusion cell

Pvt. Ltd. and Mumbai) was mounted in between donor and the receptor cell. The entire apparatus was kept over magnetic stirrer with a magnetic Teflon bead placed in the bottom of the receptor cell. The drug loaded compact was immediately placed on the upper surface of membrane facing the donor cell. The compact was wetted by 0.5 ml of SVF to mimic the vaginal environment fluid, so that the drug could slowly dissolve from the compact and diffuse across the membrane to reach the receptor compartment. Considering this time as the starter, samples of 1 ml were collected from the receptor cell at periodic time intervals and replaced with the same volume to maintain sink level. Absorbance of samples was measured at λmax (267 nm) and the amount of drug diffused through the membrane at each time point was calculated.

In vitro dissolution of the vaginal compacts

The release of AZT from the compacts was investigated *in vitro* under sink conditions, utilizing United States Pharmacopeia (USP) Type II dissolution apparatus (paddle type) at 50 rpm with media composed of 900 ml SVF at

37°C and the study was carried out for 6 h. Aliquots of 5 ml was withdrawn in fixed time periods and displacing with equal quantity of the buffer. The aliquots were filtered and AZT concentration in each sample was measured at λmax of 267 nm (absorption maxima of AZT) using UV spectrophotometer according to predetermined calibration curve ($R^2 = 0.999$) with SVF as blank. Hence, the cumulative % drug release from the compactable inserts was calculated and the experiment was carried out in triplicate.[20]

Characterization of drug release kinetics

Results of the drug release from formulated hydrophilic matrices were fitted into various mathematical models such as zero order, first order, Higuchi model, Korsmeyer-Peppas model and also Hixon-Crowell model with regard to understand the kinetics and mechanism for drug release from the compacts.[21]

Thermogravimetry-differential scanning calorimetry analysis

TG-DSC profile of selected formulations was analyzed to determine the change in thermal properties of the drug due to the process of compression. It was also used to find the compatibility between AZT and polymers. DSC curves of the pure drug, pure polymer and the formulations were obtained using a thermal analyzer (TA Instruments, Q100, USA). Around 5 mg of the sample were placed in alumina pan under a nitrogen flow (10 ml/min). The pans were heated at the rate of 10°C/min, from 25°C to 500°C and the results were represented as weight loss and heat flow against temperature.[22]

Fourier transform infrared spectroscopy studies

FTIR was used to identify possible interactions between the drug and excipient in formulation. Infrared (IR) spectra of pure drug, polymer and selected formulations were recorded by KBr pellet method by an IR spectrophotometer (Perkin Elmer 6701F, USA) between 4000 and 400/cm ranges. Results of the formulations were compared with that of the pure drug and polymer.[23]

X-ray diffraction study analysis

XRD study was carried out to reveal the modifications in crystalline properties of drug in the formulation post-compression. This was performed for the pure drug sample, polymer and formulated compact by powder X-ray diffractometer (D8 Focus, Bruker, Germany) with Cu-Kα radiation at 1.5418 Å.[24]

RESULTS AND DISCUSSIONS

Pre-compression data

Pre-compression studies the drug loaded granules such as the angle of repose, BD, TD, Hausner ratio and Carr's compressibility index were all observed within specified limits as tabulated in Table 2. Decrease in the values of angle of repose of drug loaded granules (20.3423 ± 0.2567-31.6416 ± 0.5465°) was observed with respect to that of pure drug (37.6549 ± 1.0025°). This indicated enhancement in the flow potential of the granules due to the granulation process. The BD and TD of the granules vary between 0.1669 ± 0.0067 g/ml and 0.2863 ± 0.0157 g/ml and 0.1978 ± 0.0097-0.3352 ± 0.0098 g/ml respectively. Hausner ratio was found to be less than 1.25 for all the formulations, which indicated the suitability for compression of granules into compacts. The value of Carr's compressibility index (I) of the pure drug was found to be 38.7895% which indicated very poor flow property. This parameter was enhanced in case of the granules (6.25-17.87%), which displayed a sharp enhancement in the flow ability of the drug loaded formulations. Compressibility index simply indicated the ease by which the granules were induced to flow and compacted. This was an indirect measurement of the coercivity, BD, shape, size and surface area of the granules.[25]

Table 2: Pre-compression studies of the AZT granules

Batch code	Angle of repose (θ)	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (I) (%)	Hausner ratio (E)
F1	20.3423±0.2567	0.2133±0.0076	0.2567±0.0067	16.9069	0.1691
F2	21.8734±1.7563	0.2344±0.0163	0.2674±0.0023	12.3411	0.1234
F3	23.3474±1.4256	0.2443±0.0053	0.2767±0.0156	11.7094	0.1171
F4	26.7663±0.5562	0.2334±0.0076	0.2874±0.0065	14.8423	0.1879
F5	24.4323±1.2311	0.2754±0.0897	0.3234±0.0087	14.5132	0.1484
F6	25.8634±1.7683	0.2845±0.0021	0.3328±0.0198	18.7879	0.1451
F7	28.4259±0.9169	0.2753±0.0261	0.3352±0.0098	17.8699	0.1787
F8	24.1688±0.7227	0.2863±0.0157	0.3244±0.0163	11.7448	0.1174
F9	24.8804±1.7941	0.269±0.0069	0.3036±0.0196	11.3965	0.1139
F10	26.5759±1.9129	0.2316±0.00825	0.2785±0.01792	16.8402	0.1684
F11	21.9899±1.4954	0.2399±0.01368	0.2559±0.01166	6.2524	0.0625
F12	28.5961±2.5197	0.2509±0.0097	0.2735±0.0033	8.2633	0.0826
F13	31.6416±0.5465	0.2219±0.0166	0.2674±0.0067	17.0157	0.1701
F14	30.758±0.8137	0.2017±0.0133	0.2407±0.0145	16.2027	0.162
F15	31.1198±1.0776	0.1669±0.0067	0.1978±0.0097	15.6218	0.1562

AZT: Zidovudine

Post-compression studies

The post-compression properties of the formulated compacts were summarized in Table 3. Visual examination of the formulations showed cylindrical, elongated compacts with smooth surface as in Figure 2.

The purpose of the elongated shape could provide ease of insertion of the compacts into the vaginal cavity hence promote better patient compliance. The average weight of the vaginal inserts was found to be between 0.6934 ± 0.001 g and 0.703 ± 0.003 g, which was within the weight variation limit of ± 5%. Hence the formulations complied with the weight variation requirement of the Indian Pharmacopoeia. It was observed that thickness of the compacts formulated with higher viscosity grade of HPMC (HPMC 50 cps and 3000 cps) was greater compared to other HPMC grades. In case of compact formulated with HPMC 50 cps, there was gradual increase in the thickness with the increased concentration of the polymer. The similar behavior was observed in the case of HPMC 3000 cps formulations. Diameter of all the compactable inserts was in the range of 8.7911-8.9555 mm and the compacts were found to withstand high pressure exhibiting hardness as 7.3333 ± 0.04-13.6666 ± 0.1178 kg/cm^2 except F5 (4.3333 ± 0.062 kg/cm^2) and hence complied with the requirements of USP 29. With an increase in the viscosity grade of HPMC polymer and an elevation in concentration of both HPMC and MC polymer, an increase in hardness of the compacts was observed. Formulation with 40% MC required the highest diameter crushing strength. Furthermore, very good mechanical strength of all the compacts was also evident since the friability values were lesser than 1% (0.02-0.96). Very low friability of the compacts was observed in F11 and F12 compared with all other formulations. Here, also it was evident to show lesser friability with higher viscosity grade and concentration of the HPMC polymer.[26]

The drug content in the formulated compacts estimated showed to measure the mean percentage drug content in range of 94.2935-107.0652% as per the label claim, thus proving the uniformity of the drug distribution in the formulations [Table 4].

Swelling study

The swelling behavior of the formulated compacts carried out in SVF at pH 5 was represented as % hydration with respect to time and summarized in Table 4. An increase in swelling of the compacts was observed proportionally with respect to the increase in concentration and viscosity grade of HPMC, which was due to the hydration nature of the polymer [Figure 3]. All the compacts started swelling by first 15 min showing high % hydration (0.715-0.818%), due to the rapid uptake of the medium through the metastable pores. Formation of a homogenous gelled layer was evident around the surface of the formulations (F7-F12) with increased concentration and time and viscosity grade of the polymer, which resulted in the gradual dissolution and surface erosion of the hydrated matrix hence better swelling of the compacts.[23,26] This was observed because at very high concentrations, the association of hydrophilic polymer network was reduced, with enhanced chain flexibility and thereby result in higher swelling.[22] In case of MC (F13-F15) also, the swelling index increased with an increase in its corresponding concentration. This phenomenon was not predominantly observed with lower viscosity grades of HPMC especially at low concentrations as observed in formulations F1-F4. These compacts when

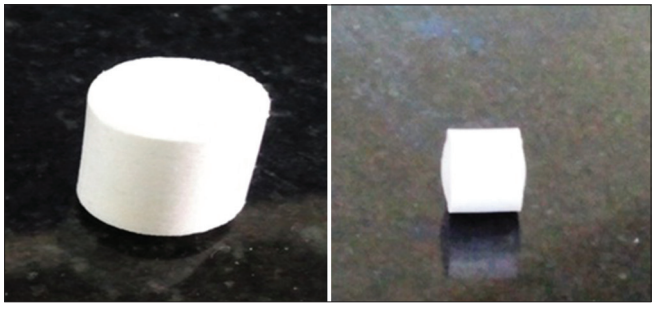

Figure 2: Physical appearance of the formulated compacts

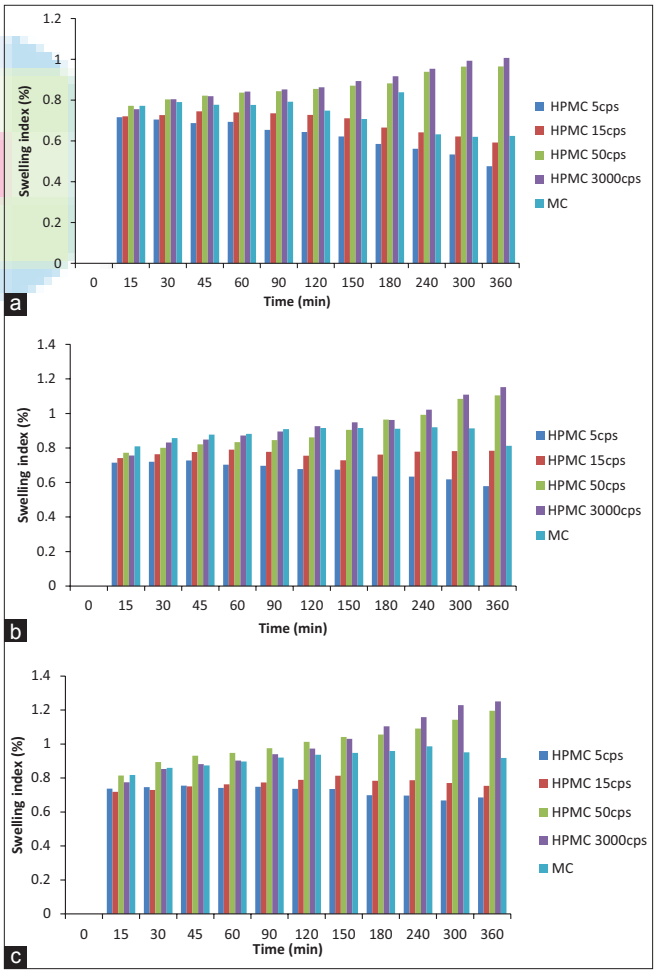

Figure 3: Swelling study of zidovudine vaginal compacts with different polymer concentration (a) 20% polymer (b) 30% polymer (c) 40% polymer

Table 3: Post-compression parameters of AZT vaginal compacts

Batch code	Average weight after punching (g)	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)
F1	0.6953±0.002	11.64±0.07	8.7911±0.01	9.8333±0.47	0.08
F2	0.6961±0.001	11.7622±0.09	8.8022±0.02	8.3333±0.62	0.02
F3	0.6934±0.001	11.0988±0.24	8.8022±0.006	8.0833±0.82	0.08
F4	0.7027±0.001	11.3111±0.07	8.7888±0.24	8.0±0.40	0.02
F5	0.6887±0.003	11.8044±0.06	8.8222±0.01	4.3333±0.062	0.14
F6	0.7000±0.001	11.4688±0.04	8.7911±0.009	7.3333±0.04	0.14
F7	0.6877±0.002	11.7244±0.09	8.8±0.00	10±0.00	0.17
F8	0.6988±0.004	12.7466±0.07	8.8977±0.006	8.9166±0.71	0.08
F9	0.701±0.001	13.4466±0.11	8.9555±0.01	7.3333±0.23	0.31
F10	0.692±0.0161	11.8355±0.1559	8.7977±0.0062	11.75±0.7359	0.11
F11	0.7012±0.007	12.5022±0.062	8.8422±0.0289	12.3333±0.2357	0.49
F12	0.701±0.0027	12.74±0.3400	8.8955±0.0157	12.00±0.4082	0.96
F13	0.703±0.003	11.6022±0.1374	8.8±0.00	12.1666±0.2357	0.05
F14	0.702±0.0046	11.9933±0.0771	8.8±0.00	12.8333±0.4714	0.05
F15	0.701±0.003	12.1844±0.1178	8.8±0.0094	13.6666±0.1178	0.05

Table 4: Drug content uniformity and swelling index of the vaginal compacts

Polymers employed	Batch code	Concentration (%)	Drug content (%)	Swelling index (%)
HPMC 5 cps	F1	20	103.8043	2.68±0.0021
	F2	30	103.5326	5.01±0.0009
	F3	40	102.1739	8.96±0.0042
HPMC 15 cps	F4	20	102.7173	7.55±0.0038
	F5	30	100	14.14±0.0042
	F6	40	101.3587	21.69±0.0037
HPMC 50 cps	F7	20	104.076	39.08±0.0049
	F8	30	101.3589	60.46±0.0039
	F9	40	107.0652	71.46±0.0033
HPMC 3000 cps	F10	20	100	43.89±0.0017
	F11	30	102.4456	65.74±0.0031
	F12	40	100.8152	83.29±0.0013
Methyl cellulose	F13	20	97.2826	20.86±0.0031
	F14	30	96.1957	31.07±0.0058
	F15	40	94.2935	40.82±0.0039

HPMC: Hydroxypropyl methyl cellulose

placed in SVF showed an immediate burst in the swelling by first 1 h and gradually tend to decrease. This was due to absence of a homogenous gel layer around the surface of the compacts, which resulted in breaking and fragmentation of the compacts. Hence, the formulations with lower HPMC viscosity grades with its corresponding concentrations showed low swelling index due to the formation of a brittle, not spongy gel layer, which caused the gradual disintegration and breaking of the compacts, which lead to the release of fragments. Thus by an increase in the amount of HPMC and its viscosity grade, there was a stable and compact gel layer observed after 1-2 h that dissolves gradually in the medium without rapid degradation and fragmentation hence gives better drug release. The excessive hydration can also decrease the bioadhesive strength of the compacts because of the involvement of the huge number of polymer binding sites with the water molecules, thereby decreasing the number of groups interacting with the mucin chains.[24]

In vitro drug release study

Drug release from compacts of all the batches showed a gradual decline with elevated concentration of the polymers. Formulations with HPMC and MC showed sustained release of the drug ranging from 22.6747% to 70.1308% and 38.2594% to 53.3213% respectively at 6 h. As the concentration of the bioadhesive polymers was varied from 20% to 40%, the percentage drug release at each time point was found to decrease proportionately [Figure 4]. Formulation F7 showed a drug release of 70.1309% by 6 h followed by F8 and F9. This polymer exhibited the maximum drug release at 6 h compared with all other formulations. The least drug release was observed with an increase in the HPMC viscosity grade of 3000 cps, i.e. F10 > F11 > F12. F12 formulated with increased concentration of HPMC 3000 cps polymer displayed the least drug release at 6 h. Formulations with MC (F13-F15) showed moderate release in the range of 38.2594-53.3213%.

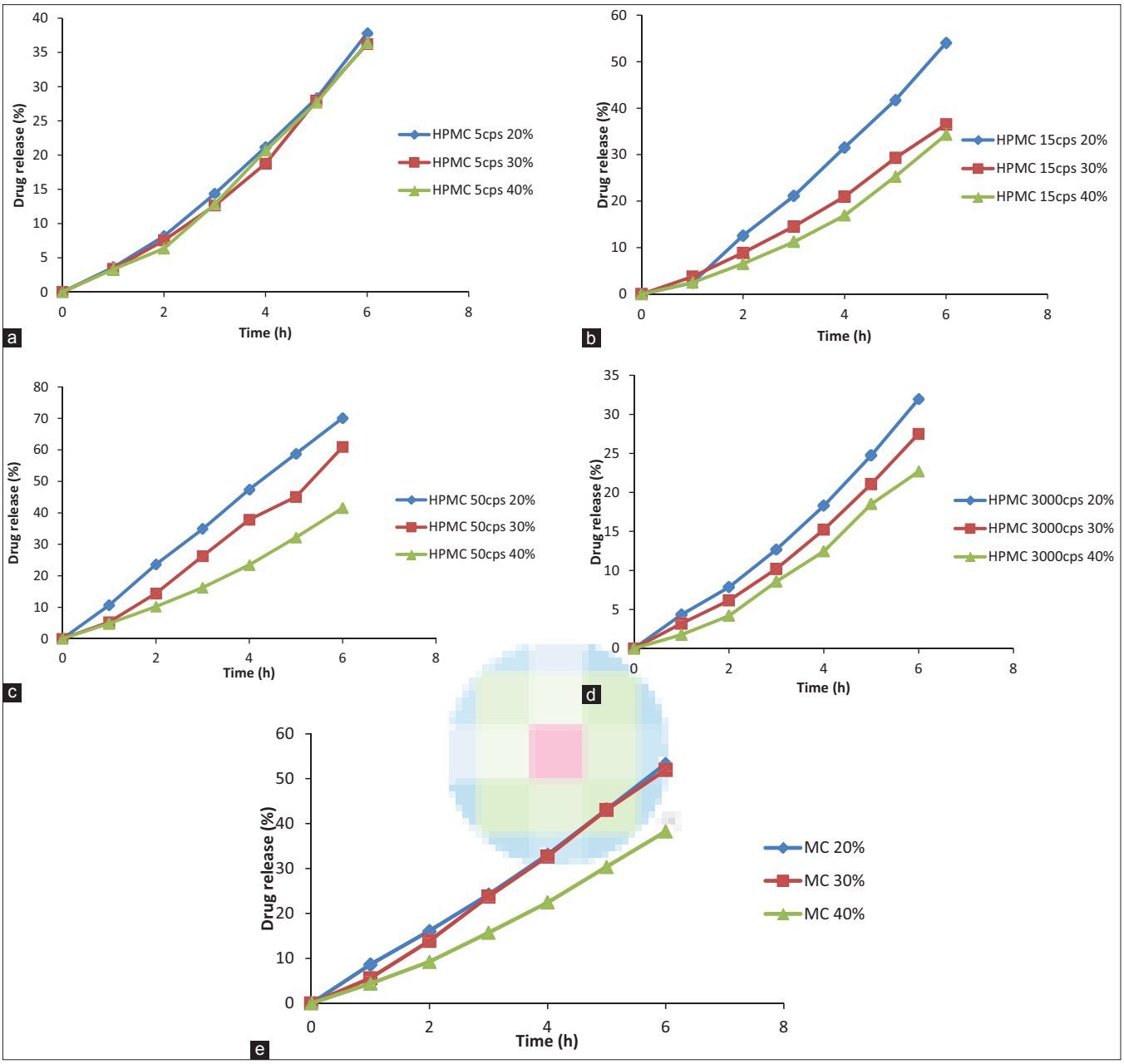

Figure 4: *In vitro* dissolution study of zidovudine vaginal compacts (a) hydroxypropyl methyl cellulose 5 cps (b) HPMC 15 cps (c) HPMC 50 cps (d) HPMC 3000 cps (e) methyl cellulose

Hence from the drug release profile of all batches of formulations, it was evident that all the formulations showed drug release of less than 25% at 1 h. At the 4th h, formulations F1, F3, F4, F5, F8, F9, F13, F14 and F15 released the drug within the USP limits (20%<Q> 40%). Hence, among all the formulations, F9 displayed the required sustained drug release at the end of 6 h, i.e., 5% drug release at 1 h, 23% drug release by 4 h and 42% drug release at the end of 6 h, which satisfied the limits as per USP specifications for sustained release formulations.

Franz diffusion study

The diffusion behavior of AZT from the formulated vaginal compacts was evaluated using Franz diffusion cell with SVF solution as receptor medium. The results revealed a gradual decrease in AZT release to the corresponding increase in concentration of the polymers employed [Figure 5].

Kinetics of *in vitro* diffusion and dissolution

The drug release and diffusion profiles of AZT from the formulated compacts were best fitted to Korsemeyer-Peppas model, as shown by the R^2 values in the range of 0.9991-0.9997 respectively [Tables 5 and 6]. The mechanism of AZT release from the compacts can be correlated to swelling of the polymers present in the compact and the diffusion of drug from the polymer matrix. According to diffusional exponent *n* value, the transportation of drug from the formulated

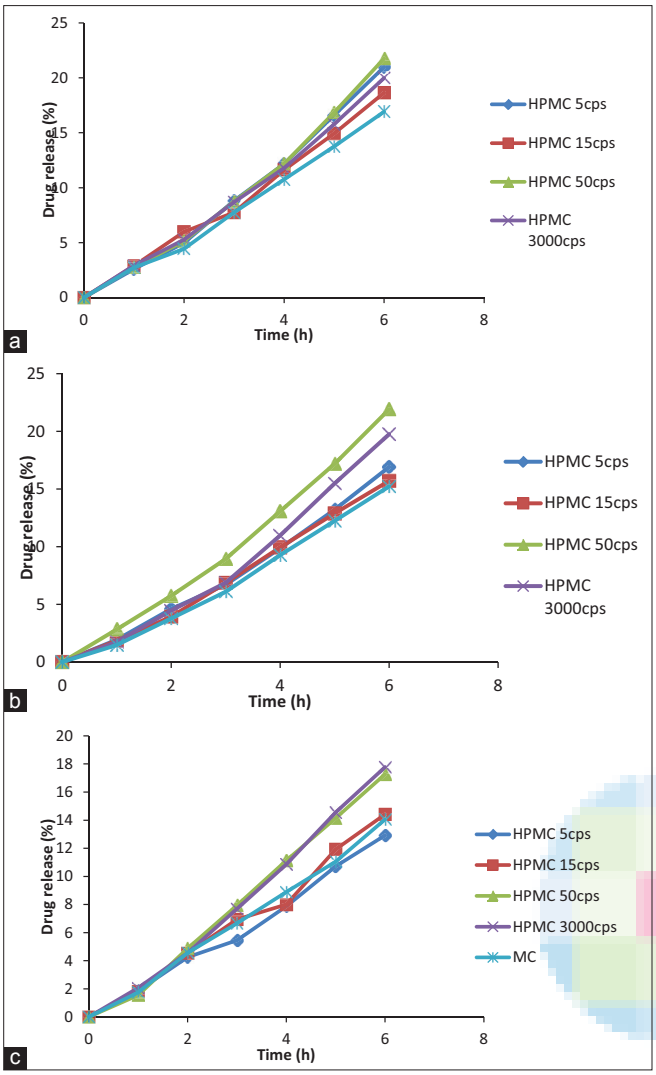

Figure 5: Diffusion study of zidovudine vaginal compacts with different polymer concentration (a) 20% polymer (b) 30% polymer (c) 40% polymer

compactable inserts was classified as non-Fickian super Case II transport ($n > 0.45$). For a DDS displaying super Case II transport, the chief mechanism for drug transport were observed primarily because of polymer relaxation due to gradual swelling of the gelled layer.[27] Hence the matrix system first absorbed the medium followed by hydration cum swelling of the compacts, which governed the gradual and controlled mechanism of drug diffusion.

Differential scanning calorimetry

The TG/DSC thermogram obtained by the thermal analysis of the optimized formulation of AZT vaginal compact was compared with the pure drug. The DSC thermogram of the pure drug AZT showed an endothermic peak at 124.98°C corresponding to melting point of the crystalline drug, followed by a sharp exothermic curve with a peak at 236.60°C which represented the decomposition temperature of the drug. A sharp decline in the TG curve was observed at the same temperatures, which confirmed the sudden weight loss of the drug due to its decomposition [Figure 6]. The TG-DSC curves of the pure polymers HPMC and MC [Figures 7 and 8] depicted their respective thermal behavior and weight changes. The DSC curve of the formulation F9 and F14 showed a slight shift in the endothermic peak of the drug at 122.13°C and 121.07°C respectively and was also less intense as compared with the pure drug [Figures 9 and 10]. This may be attributed to the excessively higher ratio of amorphous polymer and excipients with respect to the drug in the compacts and also the reduction in crystallinity of the drug by granulation process. There was a gradual weight loss observed in the TG curve of F9 and F14 starting from 200°C to 375°C instead of the sharp weight loss at 236°C as observed in the pure drug. Thus, the TG curves of both formulations exhibited a step by step degradation, which can also be attributed to the presence of polymer and excipients. Both F9 and F14 displayed the presence of additional

Table 5: Kinetic modelling of *in vitro* drug release from AZT vaginal compacts

Batch code	R^2					*n*
	Zero order	First order	Higuchi model	Hixon-Crowell model	Korsmeyer-Peppas model	
F1	0.9664	0.9395	0.7684	0.9489	0.9991	1.388
F2	0.9517	0.9233	0.7443	0.9330	0.9979	1.487
F3	0.9517	0.9232	0.7413	0.9330	0.9984	1.483
F4	0.9651	0.9224	0.7631	0.9376	0.9976	1.379
F5	0.9760	0.9524	0.7874	0.9608	0.9994	1.313
F6	0.9360	0.9076	0.7183	0.9172	0.9984	1.599
F7	0.9996	0.9696	0.8759	0.9845	0.9996	1.010
F8	0.9782	0.9348	0.7964	0.9509	0.9953	1.259
F9	0.9762	0.9484	0.7908	0.9583	0.9986	1.309
F10	0.9789	0.9600	0.7996	0.9667	0.9976	1.278
F11	0.9674	0.9492	0.7733	0.9555	0.9981	1.376
F12	0.9532	0.9372	0.7433	0.9427	0.9973	1.462
F13	0.9962	0.9710	0.8529	0.9813	0.9988	1.093
F14	0.9899	0.9599	0.8219	0.9717	0.9992	1.180
F15	0.9807	0.9570	0.7980	0.9655	0.9997	1.277

AZT: Zidovudine

Table 6: Kinetic modelling for the diffusion of drug from AZT vaginal compacts

Batch code	R^2					*n*
	Zero order	First order	Higuchi model	Hixon-Crowell model	Korsmeyer- Peppas model	
F1	0.9811	0.9702	0.8006	0.9740	0.9990	1.269
F2	0.9821	0.9738	0.8045	0.9767	0.9984	1.256
F3	0.9911	0.9873	0.8420	0.9887	0.9952	1.119
F4	0.9920	0.9862	0.8450	0.9883	0.9957	1.113
F5	0.9874	0.9809	0.8148	0.9832	0.9992	1.208
F6	0.9861	0.9818	0.8359	0.9834	0.9905	1.123
F7	0.9763	0.9641	0.7925	0.9683	0.9979	1.303
F8	0.9850	0.9744	0.8115	0.9782	0.9990	1.233
F9	0.9898	0.9839	0.8233	0.9861	0.9980	1.168
F10	0.9885	0.9800	0.8241	0.9830	0.9981	1.189
F11	0.9601	0.9470	0.7571	0.9515	0.9986	1.429
F12	0.9866	0.9787	0.8121	0.9815	0.9997	1.222
F13	0.9930	0.9876	0.8397	0.9896	0.9980	1.130
F14	0.9794	0.9717	0.7935	0.9744	0.9995	1.285
F15	0.9961	0.9933	0.8548	0.9943	0.9978	1.075

AZT: Zidovudine

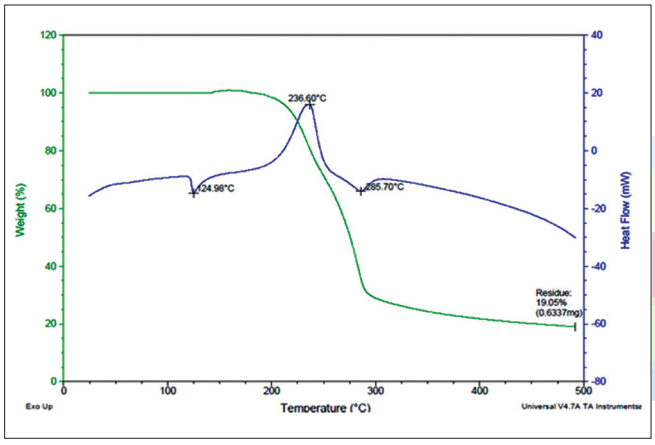

Figure 6: Thermogravimetry/differential scanning calorimetry curve of pure zidovudine

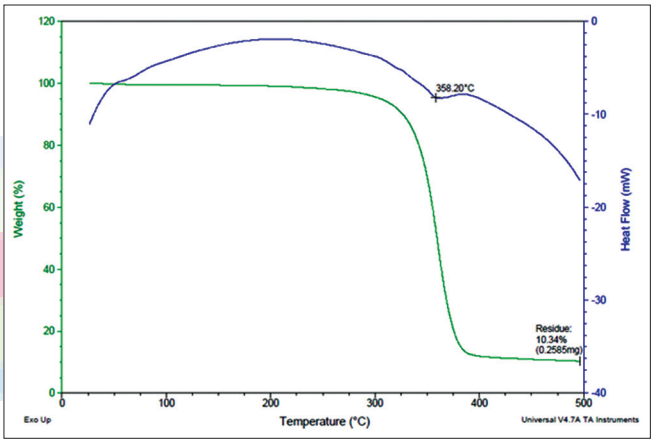

Figure 7: Thermogravimetry/differential scanning calorimetry curve of hydroxypropyl methyl cellulose 50 cps

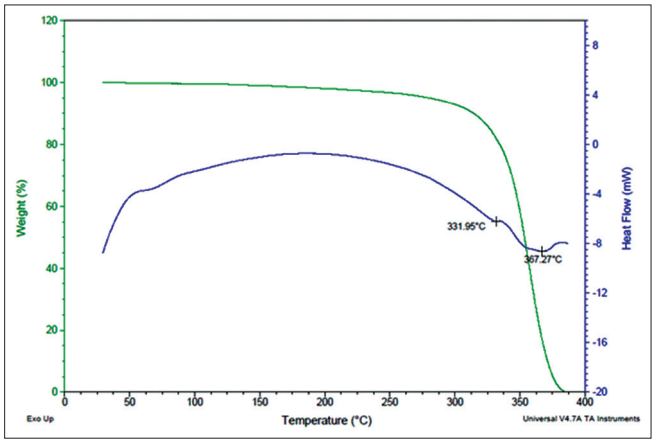

Figure 8: Thermogravimetry/differential scanning calorimetry curve of methyl cellulose

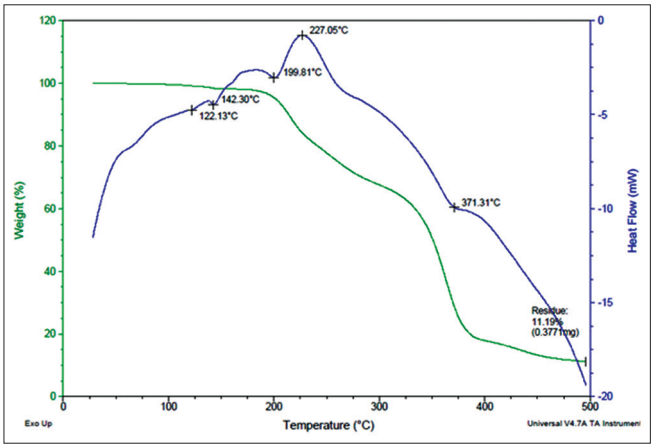

Figure 9: Thermogravimetry/differential scanning calorimetry formulation containing hydroxypropyl methyl cellulose 50 cps (40%)

exothermic peak at 142.30°C and 144.63°C corresponding to the melting point of PVP K30 and endothermic peak at 199.81°C and 202.51°C due the presence of lactose in the formulation respectively [Figures 9 and 10]. Hence, the results of DSC confirmed the absence of any possible interactions between the drug and the polymers in the formulated compacts.[28]

XRD study

The XRD spectra of the pure drug AZT showed the characteristic sharp peaks identifying as a highly crystalline compound. HPMC is amorphous in nature hence displayed blurred and clustered peaks. The AZT compacts formulated with HPMC showed the blurred peaks of semi-crystalline and amorphous polymers and excipients in which the identity peak of the drug was seen with very less intensity. This was due to the change in the solid state crystalline property of the drug by granulation process and also due to the presence of the higher proportion of amorphous excipients and polymers with respect to the drug in the formulation [Figure 11].

FTIR spectroscopy

The comparison of FT-IR spectrum of the optimized formulations with respect to pure drug and pure polymers is shown in Figure 12. The IR spectra of the pure AZT showed the characteristic peaks for the functional groups at the wave numbers represented as 1692.18/cm^{-1} for C = O amide stretching, 1093.77/cm^{-1} for C-N stretching of aliphatic amine group, 2118.48/cm^{-1} for stretching of azide group and a sharp peak at 3463.79/cm^{-1} was also observed which corresponds to O-H stretch. FTIR spectra of the pure HPMC showed its characteristic peaks at 3474.93/cm^{-1} for O-H stretch, 2839.98/cm^{-1} for C-H stretch of –C = O (aldehydes), 2933.98/cm^{-1} for H-C-H stretch of symmetric and asymmetric alkanes and C-O stretch was also observed at 1047.92/cm^{-1} due to the presence of ester in the polymer For pure MC, characteristic peaks of the polymer were observed at 3471.57/cm^{-1} that corresponded to the O-H stretch followed by C-H stretch of aldehyde at 2930.37/cm^{-1}.[29,30]

The FTIR spectra of the formulation F9 and F14 prepared with 40% HPMC 50 cps and 30% MC respectively, did not display any significant difference in the peaks of drug as compared with the pure sample. In formulation F9, the O-H peak was observed at the range of 3444.84/cm^{-1} which was a mild shift with respect to the O-H peaks observed for pure drug and pure polymer. This shift in peak was due to the formation of intermolecular hydrogen bonding. Moreover, the peak was observed to be sharp in the pure drug and pure polymer, but broader in the formulation. This was due to the overlapping of the O-H groups present in the polymer and drug. Other mild shifts observed were 1632.84/cm^{-1} for C = O amide stretch, 1100.31/cm^{-1} for C-N stretch of aliphatic amine group and 2866.20/cm^{-1} for H-C-H stretching. In formulation F14 also, a mild shift in O-H functional group was observed at 3380.63/cm^{-1} in comparison to the pure drug and MC with the appearance of broad peaks due to the interactions between O-H groups of the drug and polymer. Similarly, mild shifts were also observed with respect to the following wave number regions: 1684.61/cm^{-1} for C = O amide stretch, 2900.77/cm^{-1} for C-H stretch of C = O. C-N stretch for the functional group was also observed at 1032.19/cm^{-1}. Hence, all the distinctive peaks of AZT were observed to be in the specified range of their functional groups which proved that no significant interaction occurred between the drug and polymer during the formulation process.

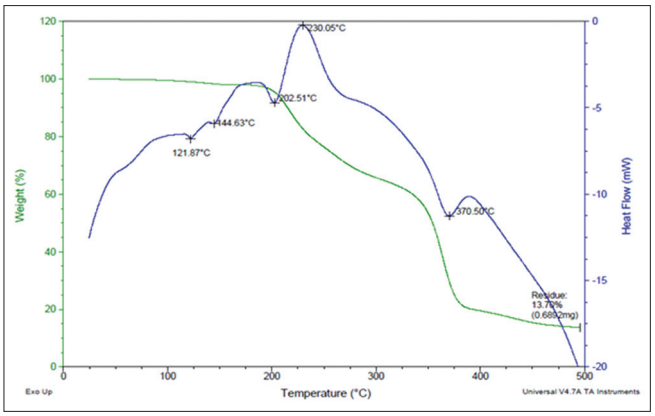

Figure 10: Thermogravimetry/differential scanning calorimetry formulation containing methyl cellulose (30%)

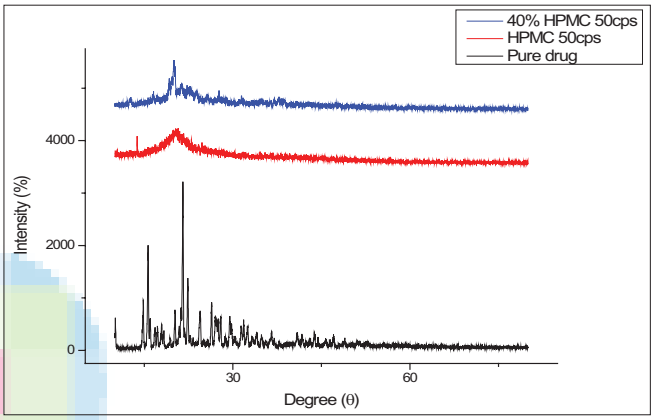

Figure 11: X-ray diffraction study of zidovudine, hydroxypropyl methyl cellulose 50 cps and formulation containing 40% HPMC 50 cps

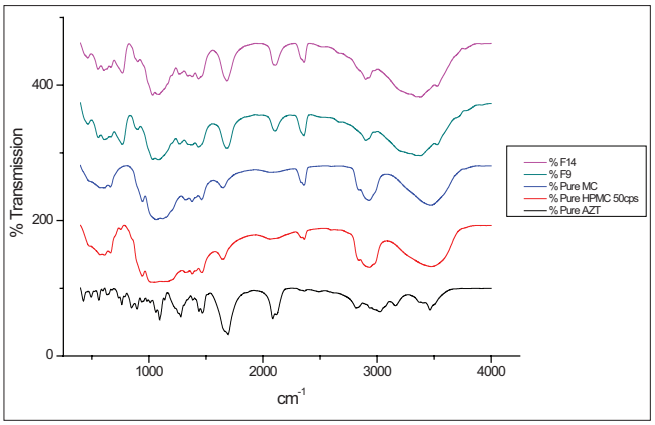

Figure 12: Fourier transform infrared spectroscopy of pure zidovudine, pure hydroxypropyl methyl cellulose 50 cps, pure methyl cellulose, formulations F9 and F14

CONCLUSIONS

From the initial trial formulations, it was evident that the

vaginal compacts prepared by wet granulation method showed greater hardness, friability, compactness and other post-compression parameters when compared to the compacts formulated by dry granulation method. Hence, wet granulation method was chosen for the formulation of compacts with the drug. All the polymers used in the present study were found to be suitable for the preparation of compacts with required hardness and low brittle nature except formulation F5 which displayed least hardness (4.3333 ± 0.062 kg/cm^2). In consideration to the swelling performance, formulations F7-F12 displayed very good hydration capacity with the formation of a stable and homogenous gel layer around the compact with non-releasing fragments.

All the formulations exhibited sustained drug release wherein the formulation F9 showed 5% at 1 h, 23% release at 4 h and 42% drug release at 6 h, which satisfied the required criteria of drug release limits as per USP specifications for sustained release formulations. In addition, F9 also showed a gradual hydration of the compacts for up to 6 h. Presence of the external gel layer in F9 showed gradual diffusion of AZT form the compacts. This swollen layer protected the internal layers of the compact allowing fluid penetration with hydration and swelling. Because of this slow process, F9 formulation could provide prolonged and sustained release of AZT at the target site. Hence, based on these parameters, it was clear that formulation F9 containing HPMC 50 cps at 40% concentration was most suitable in the formulation of vaginal compacts compared to the other polymers employed in this study. Further *in vivo* studies can be performed to correlate the results obtained from *in vitro* drug release studies and formulation can be scaled up at industrial level for once a day administration of AZT vaginal compacts for the effective management of AIDS in women.

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How to cite this article: Nath J, Veda Hari BN, Devi DR. Implantable vaginal drug delivery system of zidovudine for site specific activity. Asian J Pharm 2013;7:140-50.

Source of Support: Nil. **Conflict of Interest:** None declared.