



Formulation and Optimization of Controlled Porosity Osmotic Pump Tablets of Zidovudine using Mannitol as Osmogen for the Treatment of Aids

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Abstract : The present study was undertaken to develop controlled porosity osmotic pump tablets of zidovudine a nucleoside reverse transcriptase inhibitor for the treatment of acquired immune deficiency syndrome(AIDS). Zidovudine has the dose of 300mg 2 times daily as conventional dose. In this present study it is designed to prepare controlled release CPOP tablet once daily having 600mg dose. The tablets were prepared by wet granulation method using drug zidovudine as well as various excipients such as hydroxyl propyl methyl cellulose(HPMCE5LV) as controlled release polymer, mannitol as osmogen, microcrystalline cellulose(MCC) as diluent, starch as binder, magnesium stearate as lubricant and talc as glidant. The coating solution of core tablets were prepared by using cellulose acetate as membrane forming material, poly ethylene glycols 400,600,4000,6000 as flux regulating agent, acetone as solvent and sorbitol as porogen. The prepared tablets were evaluated for pre compression parameters, post compression parameters, in vitro drug release study, FTIR, DSC study and scanning electron microscopy study. Among the prepared formulations ZM4 batch shows 94.99% drug release in 16 hrs. The in vitro release kinetics were analyzed for different batches by different pharmacokinetic models such as zero order, first order, Higuchi, Korsmeyer Peppas and Hixson Crowell. The result of optimized formulation releases drug up to 16 hrs in a controlled manner and follows zero order kinetics and which is independent of the p^H and agitational intensity. Short term stability study (at $40\pm 2^\circ C/ 75\pm 5\%$ RH for three months) on the best formulation indicated that there were no significant changes in hardness, %friability, drug content and in vitro drug release. FTIR and DSC study indicated that there was no drug excipient interaction.

Keywords : AIDS, wet granulation, in vitro drug release, stability study.

Inroduction

Oral drug delivery system is the most convenient route¹ for the administration of various drugs, but oral conventional drug delivery system does not control drug release and effective concentration of drug at the target site. It provides uncertain release of drug to site specific delivery over a period of time which often results in constantly changing, unpredictable, often sub therapeutic and supra therapeutic plasma concentrations of drug release. Hence controlled drug delivery systems have been employed to avoid these shortcomings in

conventional drug delivery system. Controlled release dosage forms² cover a wide range of prolonged action which provide continuous release of their active ingredients at predetermined rate and predetermined time. Among various controlled drug delivery systems osmotic controlled drug delivery system (OCDDS) utilizes principle of osmotic pressure³ for controlled delivery of active ingredients. The drug released from OCDDS is independent of p^H, hydrodynamic condition of the body and agitation intensity⁴. The present study is to develop controlled porosity osmotic pump tablets of zidovudine. The delivery system of drug comprises a core with the drug surrounded by semi permeable membrane which is accomplished with different channeling agents of water soluble additives in the coating membrane. The core is coated with cellulose acetate containing in situ micro pore former sorbitol. Further for increasing drug release mannitol was chosen as osmotic agent because it could generate high osmotic pressure gradient to deliver poorly or moderately water soluble drugs^(5, 6). When controlled porosity osmotic pump tablets placed in biological system of fluid low levels of water soluble additives are leached from polymer materials which form sponge like structure in the controlled porosity walls. The rate of drug delivery depends upon the factors^(7, 8) such as water permeability of the semi permeable membrane, osmotic pressure of core formulation, thickness and total area of coating.

Human immunodeficiency virus infection/acquired immune deficiency syndrome (HIV/AIDS) is a disease of human immune system caused by infection with human immune deficiency virus⁹. It is called AIDS when a person infected with HIV has a CD4+ count of less than 200cells/ μ L¹⁰ for a diagnosis of stage 3 infection. CD4 T lymphocytes count of an uninfected adolescent who is generally in good health ranges from 500 cells/ μ L to 1600 cells/ μ L. AIDS is considered one of the most dangerous and a pandemic^(11,12) disease which is transmitted primarily via unprotected sexual intercourse (including anal and oral sex), contaminated blood transfusions, hypodermic needles and from mother to child during pregnancy, delivery or breastfeeding. The management¹³ of AIDS can be controlled by antiretroviral therapy, male circumcision, needle exchange program, use of diaphragms, topical protection, use of condoms and alternative medicine.

Zidovudine the first anti HIV compound approved for clinical use a nucleoside reverse transcriptase inhibitor (NRTI) is extensively used for the treatment of AIDS and related conditions either alone or in combination¹⁴ with other antiviral agents. Zidovudine is phosphorylated to active metabolite zidovudine triphosphate which inhibits the HIV reverse transcriptase enzyme competitively and acts as a chain terminator of DNA synthesis of virus. Zidovudine is administered two times in a day of dose 300mg for adults according to their body weight for conventional dose. The present research aimed to design CPOP tablets by wet granulation method containing dose of 600mg once daily. Zidovudine has low therapeutic index, poor bioavailability of 60-70%, volume of distribution of 1.6litre/kg and protein binding of 20-38%. The biological half life of zidovudine triphosphate is between 3-4hrs. Hence it can be given to control the concentration of drug at the site of action. After oral administration it is rapidly absorbed from the gastrointestinal tract exhibiting a peak plasma concentration¹⁵ of 1.2 μ g/ml at 0.8hrs. The main objective of the present study was to develop controlled porosity-based osmotically controlled release tablets of zidovudine.

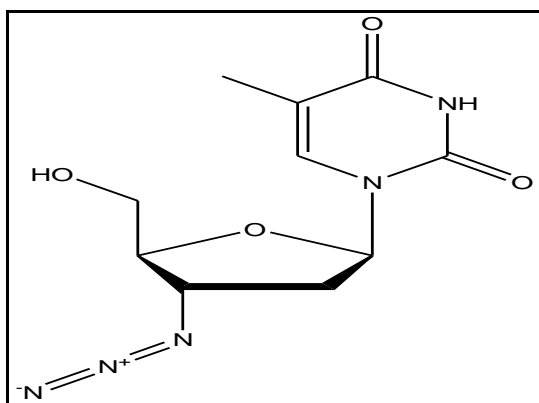


Figure 1: Structure of zidovudine

IUPAC Name-1-[(2*R*,4*S*,5*S*)-4-Azido-5-(hydroxymethyl)oxolan-2-yl]-5-methylpyrimidine-2,4-dione

Materials and Methods

Materials

Zidovudine was obtained from Hetero Drugs Pvt. Ltd. India. Mannitol was purchased from Qualigens Fine Chemicals, India. Cellulose acetate (CA) was obtained from Eastman Chemical Inc, Kingsport, TN. Sorbitol, HPMC E5M LV, magnesiumstearate, talc and polyethylene glycol (PEG) 400,600,4000,6000 were purchased from S.D. Fine Chemicals Ltd, Mumbai, India. Microcrystalline cellulose(MCC),starch all are purchased from Signet Pharma,Mumbai,India.All other solvents and reagents used were of analytical grade.

Compatibility studies

Fourier Transform Infrared Spectroscopy (FTIR)

The use of FTIR technique¹⁶ allows pointing out the implication of the different functional groups of drug and excipients by analyzing the significant changes in the shape and position of the absorbance bands. In this method individual samples as well as the mixture of drug and excipients were ground mixed thoroughly with potassium bromide (1:100) for 3-5 minutes in a mortar and compressed into disc by applying pressure of 10kg/cm to form a transparent pellet in hydraulic press. The pellet was kept in the sample holder and scanned from 4000 to 400 cm^{-1} in FTIR spectrophotometer. Then the characteristics peaks were obtained of all sample as well as mixtures.

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry determines possible incompatibilities¹⁷ between drug excipients of dosage forms. It gives the changes in the appearance, shift or disappearance of melting endotherms, exotherms and variations in the corresponding enthalpies of reaction. Physical mixtures of drug and individual excipients in the ratio of 1:1 were taken and examined in DSC. Individual samples as well as physical mixture of drug and excipients were weighed to about 5mg in DSC pan. The sample pan was crimped for effective heat conduction and scanned in the temperature range of 50-300 $^{\circ}\text{C}$. Heating rate of 20 $^{\circ}\text{C min}^{-1}$ was used and the thermogram obtained was reviewed for evidence of any interactions. Then the themograms were compared with pure samples versus optimized formulation.

Analytical study

UV determination¹⁸ was carried out for zidovudine to estimate λ_{max} at two different pH such as pH 1.2(gastric pH) and pH 6.8(intestinal pH). Primary stock solution of zidovudine having concentration of 1000 $\mu\text{g/ml}$ was prepared using HCl buffer pH 1.2. From the primary stock solution after necessary dilution secondary stock solution having concentration of 10 $\mu\text{g/ml}$ was prepared using HCl buffer pH 1.2. The prepared secondary stock solution was then scanned by UV spectrophotometer at wavelength ranging from 400nm to 200nm and the λ_{max} for solution was determined. It was found as 266nm and utilized for calibration curve determination. Similarly Primary stock solution of zidovudine having concentration of 1000 $\mu\text{g/ml}$ was prepared using phosphate buffer pH 6.8. From the primary stock solution after necessary dilution secondary stock solution having concentration of 10 $\mu\text{g/ml}$ was prepared using phosphate buffer pH 6.8. The prepared secondary stock solution was then scanned by UV spectrophotometer at wavelength ranging from 400nm to 200nm and the λ_{max} for solution was determined. It was found as 265nm and utilized for calibration curve determination.

Methods

Preparation of osmotic pump tablets

The tablets were prepared by wet granulation¹⁹ technique. Accurately weighed quantities of ingredients mentioned in Table-1 were passed through American Society of Testing and Materials (ASTM) 30 mesh and lubricant and glidant were passed through ASTM 80 mesh. All the ingredients except lubricant (magnesium stearate), glidant (talc) were manually blended homogenously in a mortar by way of geometric dilution. The mixture was moistened with aqueous solution and sized through ASTM 30 mesh and dried in a hot air oven at 60 $^{\circ}\text{C}$ for sufficient (3-4 hrs). The dried granules were sized through ASTM 30 mesh and blended with talc and

magnesium stearate. The homogenous blend was then compressed into round tablets with standard concave punches (diameter 10 mm) using 10 station rotary compression machine (Mini Press, Karnavati, India).

Table-1 Composition of controlled porosity osmotic pump zidovudine tablets

Ingredients (mg)	ZM1	ZM2	ZM3	ZM4
ZD	600	600	600	600
MCC	175	150	125	100
Starch	40	40	40	40
HPMC E5LV	100	100	100	100
Mannitol	25	50	75	100
Magnesium stearate	5	5	5	5
Talc	5	5	5	5
Total weight(mg)	950	950	950	950

Coating of core tablets

The different coating solutions²⁰ were prepared using mixtures of cellulose acetate 6gm and 33w/w% of cellulose acetate (CA) of polyethylene glycol 400, 600, 4000, and 6000 respectively with acetone. The CA was passed through sieve No.80 and mixed with polyethylene glycol then acetone was added quantity sufficient maintaining proper viscosity of solution. The coatings of tablets were performed by spray pan coating in a perforated pan (GAC-205, Gansons Ltd, Mumbai, India). Initially tablets were pre heated by passing hot air through the tablet bed and by rotating at a lower speed of 5-8 rpm. Coating process was started with rotation speed of 10-12 rpm. The spray rate and atomizing air pressure were 4-6 ml/min and 1.75 kg/cm² respectively. Inlet and outlet air temperature were 50°C and 40°C respectively. Coated tablets were dried at 50°C for 12 hrs. The coating components of various batches are summarized in Table 2.

Table-2 Coating composition for zidovudine osmotic pump tablets

Ingredients	ZM1	ZM2	ZM3	ZM4
CA (gm)	6	6	6	6
PEG 400 (gm)	2	0	0	0
PEG 600 (gm)	0	2	0	0
PEG 4000 (gm)	0	0	2	0
PEG 6000 (gm)	0	0	0	2
Sorbitol (gm)	0	0.6	1.2	1.8
Acetone (ml)	300	300	300	300

Evaluation of Controlled Porosity Osmotic Pump Tablet

Pre compression parameters of osmotic pump granules

Angle of repose (θ)

The flow property of granules²¹ was determined by measuring the angle of repose. The granules were allowed to flow through funnel freely onto the clean surface. Funnel was placed in such a height that bottom tip of funnel should not touched apex of heap of granules. Angle of repose is calculated using the following equation

$$\tan \theta = h/r \quad (1)$$

$$\theta = \tan^{-1}(h/r) \quad (2)$$

Where θ is the angle of repose, h is the height of heap in cm and r is the radius of the circular support (cone) in cm. According to the specifications the angle of repose value less than 25° indicates excellent flow whereas angle greater than 40° indicates poor flow.

Bulk density (e_b)

Bulk density²² is determined by pouring the granules into a graduated cylinder of bulk density apparatus (Sisco,India). The bulk volume (V_b) and mass (m) of the granules is determined. The bulk density is calculated by using the following formula.

$$\text{Bulk density } (e_b) = \text{Mass of granules}(m) / \text{Bulk volume of granules}(V_b) \quad (3)$$

Tapped density (e_t)

The measuring cylinder containing known mass of granules blend is tapped²³ 1000 times for a fixed time in tap density tester (Sisco,India). The minimum volume occupied in the cylinder (V_t) and mass of the granules (m) is measured. The tapped density is measured by using the following formula.

$$\text{Tapped density } (e_t) = \text{Mass of granules } (m) / \text{Tapped volume of granules } (V_t) \quad (4)$$

Compressibility index (Carr's index)

The compressibility index determines the flow property characteristics of granules developed by Carr²⁴. The percentage compressibility of granules is a direct measure of the potential powder arch and stability. The Carr's index can be calculated by the following formula.

$$\% \text{Carr's index} = \frac{e_t - e_b}{e_t} \times 100 \quad (5)$$

Where e_t is the tapped density of granules and e_b is bulk density of granules.

According to the specifications the Carr's index values between 5-15 indicates excellent flow whereas between 12-16 indicates good flow. Values between 18-21 indicates fair passable where as between 23-35 indicates poor and values between 33-38 indicates very poor and greater than 40 indicates extremely poor.

Hausner's ratio (H_R)

Hausner's ratio is used for the determination of flow properties of granules. The Hausner's ratio²⁵ can be calculated by the following formula

$$H_R = \frac{e_t}{e_b} \quad (6)$$

According to specifications values less than 1.25 indicate good flow (= 20% of Carr's index) whereas greater than 1.25 indicates poor flow(=33% of Carr's index).

Post compression parameters of controlled porosity osmotic pump tablets**Thickness**

The thickness²⁶ of individual tablets is measured by using vernier caliper (Absolute digimatic, Mitutoyo Corp. Japan) which gives the accurate measurement of thickness in mm. It provides information of variation of thickness between osmotic pump tablets. The limit of the thickness deviation of each tablet is $\pm 5\%$.

Coat thickness

After dissolution the film²⁷ was isolated from the tablets and dried at 40°C for 1hr. Thickness was measured by using electronic digital calipers (Absolute digimatic, Mitutoyo Corp. Japan) and mean values were taken.

Hardness test

The hardness²⁸ of a tablet is associated with the resistance of the solid specimen towards fracturing and attrition. The hardness of tablets can be determined by using Monsanto hardness tester (Sisco,India) and measured in terms of kg/cm².

Friability test

Friability test is used to evaluate the ability of the tablet to withstand abrasion²⁹ in packaging, handling and shipping. Friability of tablets was performed in a Roche friabilator (Sisco, India).Twenty tablets were initially weighed (W_0) together and then placed in the chamber. The friabilator was operated for 100 revolutions and the tablets were subjected to the combined effects of abrasion and shock because the Plastic chamber carrying the tablets drops them at a distance of six inches with every revolution. The tablets are then dusted and reweighed (W).The percentage of friability was calculated using the following equation.

$$\% \text{Friability} = F = \left(1 - \frac{W}{W_0}\right) \times 100 \quad (7)$$

Where, W_0 and W are the weight of the tablets before and after the test respectively.

Weight variation test

The weight variation test³⁰ is carried out in order to ensure uniformity in the weight of tablets in a batch. The weight variation test is done by weighing 20 tablets individually in weighing balance (Shimadzu, Japan) calculating the average weight and comparing the individual tablet weights to the average. The percentage weight deviation was calculated and then compared with USP specifications. The tablets meet the USP test if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit. It is shown in table no 3.

$$\text{The weight variation of } n^{\text{th}} \text{ tablet} = \frac{(|\bar{w} - w_n|)}{\bar{w}} \times 100\% \quad (8)$$

Where weight of tablets are $w_1, w_2, w_3, \dots, w_n, \dots, w_{20}$. and average weight of the tablets = \bar{w}

Table.3.USP: Specifications for weight variation of tablets

Average weight of tablets(mg)	Maximum percentage difference allowed
130 or less	± 10
130 to 324	± 7.5
More than 324	± 5

Uniformity of drug content test

Drug content³¹ for ZD tablet was done by the assay method. Ten tablets were weighed and powdered. The powder weight equivalent to 300mg of zidovudine was dissolved in 300ml of 0.1N HCl using magnetic stirrer (Ricon, Hyderabad, India) in a volumetric flask for 24hrs.It gives 1000µg/ml concentration of primary stock solution. The primary stock solution was filtered through Whatman filter paper No.1.From this primary stock solution 1ml of solution is withdrawn and diluted up to 25ml with 0.1NHCl solution to get 40µg/ml concentration of secondary stock solution. From this secondary stock solution 4ml was withdrawn and diluted upto 20ml getting desired concentration 8µg/ml. From the desired concentration the drug content of formulations were calculated using calibrated standard curve equation.

Diameter of tablet

The diameter³² of individual tablets is measured by using vernier caliper (Absolute digimatic, MitutoyoCorp.Japan) which gives the accurate measurement of diameter in mm. It provides information of variation of diameter between osmotic pump tablets.

In vitro dissolution studies

In vitro dissolution test³³ was carried out by using USP type II (paddle) apparatus. The tablet is kept in 900ml of dissolution fluid of 0.1N HCl for first 2 hrs and phosphate buffer pH 6.8 from 3 to 16 hrs maintained at $37 \pm 0.5^{\circ}\text{C}$ with 75 rpm of stirrer. In specified time intervals an aliquot of 5ml sample of the solution was withdrawn through 0.45- μm cellulose acetate filter from the dissolution apparatus and with replacement of fresh fluid to dissolution medium. After appropriate dilution the samples were analyzed for zidovudine using UV/Visible Spectrophotometer (UV-1800, Shimadhu, Japan) at 266nm for 0.1N HCl and 265nm for phosphate buffer pH 6.8. The drug release was plotted against time to determine the release profile of various batches.

Mathematical modeling of in vitro release kinetics

For the determination of the drug release kinetics from the porous osmotic pump tablet, the *in vitro* release data were analyzed by zero order, first order, Higuchi and Korsmeyer and Peppas equations and Hixson-Crowell equation.

Zero order model³⁴

The release of drug which followed zero order kinetics can be expressed by the equation

$$Q_t = Q_0 - K_0 t \quad (9)$$

Where

Q_t is the amount of drug dissolved in time t , Q_0 is the initial amount of drug in the solution and K_0 is the zero order release constant. The release kinetics can be studied by plotting cumulative amount of drug release versus time.

First order model³⁵

The release of the drug which followed first order kinetics can be expressed by the equation:

$$\text{Log } C = \text{log } C_0 - K_1 t / 2.303 \quad (10)$$

Where C_0 is the initial concentration of drug, C is the amount of drug remaining to be released in time t , K_1 is the first order release constant. The release kinetics can be studied by plotting log cumulative percentage of drug remaining versus time.

Higuchi model³⁶

Drug released from the matrix devices by diffusion process proposed by following Higuchi's classical diffusion equation.

$$Q = K_H \sqrt{t} \quad (11)$$

Where Q is the amount of drug release in time t , K_H is the Higuchi dissolution constant. The release kinetics can be studied by plotting cumulative percentage of drug release versus square root of time.

Korsmeyer-Peppas model (KP Model)

Korsmeyer et. al.³⁷ derived a simple, semiempirical model relating exponentially the drug release to the elapsed time for polymeric system. The drug release for this model is expressed as

$$\text{Log } (M_t/M_\infty) = \text{Log } K + n \text{Log } t \quad (12)$$

Where M_t is the amount of drug release at time t , M_∞ is the amount of drug release after infinite time, K is the release rate constant incorporating structural and geometric characteristics of the tablet and n is the release exponent indicative of mechanism of drug release. The release kinetics can be studied by plotting log cumulative percentage drug release versus log time.

Table 4. Interpretation of diffusional release mechanisms³⁸

Release exponent(n) for slab	Release exponent(n) for cylinder	Release exponent(n) for sphere	Drug transport mechanism	Rate as a function of time
0.5	<0.45 or 0.45	<0.43 or 0.43	Fickian diffusion(Case I)	$t^{-0.5}$
$0.5 < n < 1$	$0.45 < n < 0.89$	$0.43 < n < 0.85$	Non Fickian transport(anomalous)	t^{n-1}
1	0.89	0.85	Case II transport	Zero order release
Higher than 1	>0.89	>0.85	Super case II transport	t^{n-1}

Hixson and Crowell model

Hixson and Crowell³⁹ derived the equation for drug powder that having uniform particle size which expresses rate of dissolution is proportional to the cube root of volume of particles. This is expressed by the equation

$$W_0^{1/3} - W_t^{1/3} = \kappa t \quad (13)$$

Where W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is remaining amount of drug in the pharmaceutical dosage form at time t and κ is proportionality constant incorporating the surface volume relation. The release kinetics can be studied by plotting cube root of drug percentage remaining in matrix versus time.

Effect of osmogen concentration⁴⁰

To check the effect of osmogen concentration on drug release formulations were prepared with different concentration of osmotic agents and all other parameters of tablet kept constant. The drug release was compared with the different osmogen concentration of formulated batches by using USP-II dissolution apparatus.

Effect of pore former concentration⁴¹

The pore former is added in coating solution to form in situ micro pores in semi permeable membrane of controlled porosity osmotic pump tablet. Different concentrations of pore former are used in semi permeable membrane formation. In order to compare the effect of different concentrations of pore formers in vitro release profiles as well as number of formation of micro pores are compared.

Effect of coating thickness⁴¹

The osmotic pump coated tablets having varying the coating thickness are evaluated for drug release study. The tablet is kept in 900ml of dissolution fluid 0.1N HCl for first 2hrs and next followed by 3 to 16hrs in phosphate buffer pH 6.8 of USP type II dissolution apparatus and stirrer rotating with 75 rpm and maintaining the temperature $37 \pm 0.5^\circ\text{C}$ of dissolution media. The sample 5ml was withdrawn at different time intervals replaced with fresh medium and analyzed in UV-Visible spectrophotometer for estimation of absorbance taking a suitable blank solution. The percentage cumulative drug release of formulations at various coating thickness was plotted and compared.

Effect of osmotic pressure⁴²

The effect on osmotic pressure on the optimized formulation was studied in media of different osmotic pressure and the release profile with varying osmotic pressure is compared. To increase the osmotic pressure of the release media mannitol was added to produce 30 atm, 60 atm and 90 atm respectively.

Effect of pH⁴³

In order to study the effect of pH of release medium in the drug release of optimized formulation, the *in vitro* release study was carried in dissolution media having different pH media. Dissolution can be carried in 900 ml of 0.1 N HCl (pH 1.2), simulated intestinal fluid (SIF) pH 6.8 and pH 7.4 phosphate buffer in USP type II dissolution apparatus. The temperature was maintained at $37 \pm 0.5^\circ\text{C}$. The sample (5ml) was withdrawn at predetermined intervals and analyzed after filtration through 0.45- μm cellulose acetate filter. The percentage cumulative drug release of optimized formulations at various pH was plotted and compared.

Effect of agitation intensity

To study the effect of agitation intensity⁴⁴ on drug release optimized formulation was subjected to dissolution at various rotation speeds. Dissolution was carried out in USP-II (Paddle) at 50, 100 and 150 rpm. The samples were withdrawn at predetermined intervals through 0.45- μm cellulose acetate filter and analyzed by UV-Visible spectrophotometer. The percentage cumulative drug release of optimized formulations at different agitation intensity was plotted and compared.

Scanning Electron Microscopy (SEM)

In order to observe the mechanism of drug release⁴⁵ from the developed formulations surface coated tablets before and after dissolution studies was examined using scanning electron microscope (Leica, Bensheim, Switzerland). Membranes were dried at 45°C for 12 hrs and stored between sheets of wax paper in desiccators until examination. The samples (membranes) were fixed on a brass stub using double sided tape and then gold coated in vacuum by a sputter coater. Scans were taken at an excitation voltage of 20KV in SEM fitted with ion sputtering device. The surface morphology of coated membrane of optimized formulation film coating before and after dissolution was examined and by comparing the porous morphology the capability of porogen and drug release can be evaluated.

Accelerated stability studies

The purpose of stability study⁴⁶ is to provide evidence on the quality of a drug substance or drug product which varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The formulation was subjected to accelerated stability studies as per ICH (The International Conference of Harmonization) guidelines. The packed tablets in air tight container were placed in stability chambers (Thermo lab Scientific equipment Pvt.Ltd., Mumbai, India) maintained at $40 \pm 2^\circ\text{C}/75 \pm 5\%$ RH for 3 months. Tablets were periodically removed and evaluated for physical characteristics, drug content, in-vitro drug release etc..

Results and Discussion

Fourier Transform Infrared Spectroscopy studies

The study of the FTIR spectra of zidovudine demonstrated that the characteristic absorption peaks for the carbonyl group at 1638.76 cm^{-1} , N=N⁺=N stretching (azido group) at 2114.50 cm^{-1} , C-O stretching at 1063.08 cm^{-1} and amine group stretching at 3317.86 cm^{-1} . This further confirms the purity of zidovudine (Figure 2). The major peaks of HPMCE5LV was found at 3880.71, 3669.20, 2444.13, 2335, 1661.47, 1536.52, 1500.67, 1424.62, 1071.87, 781.05 and 584.97 cm^{-1} .

The major peaks of mannitol were found at 2986.88, 2900.97, 1646.58, 1394.32, 1251.01, 1230.06, 1050.08, 1015.87 and 669.43 cm^{-1} . In the optimized formulation (Figure 3) containing mannitol of osmotic pump (ZM4) peak at 3676.63, 788.62, 1244.26 and 1450.29 cm^{-1} were due to presence of the polymer HPMCE5LV. In the formulation the peaks present due to mannitol were 2980.88, 1244.26 and 1001.03 cm^{-1} .

¹.Peaks at 2082.76 and 1679.28 cm^{-1} were due to presence of the drug zidovudine in the optimized formulation. So from the study it can be concluded that the major peaks of drug 2082.76 and 1679.28 cm^{-1} remain intact and no interaction was found between the drug, polymer and osmogen. Hence drug-excipient mixture reveals that here is no incompatibility was observed between zidovudine.

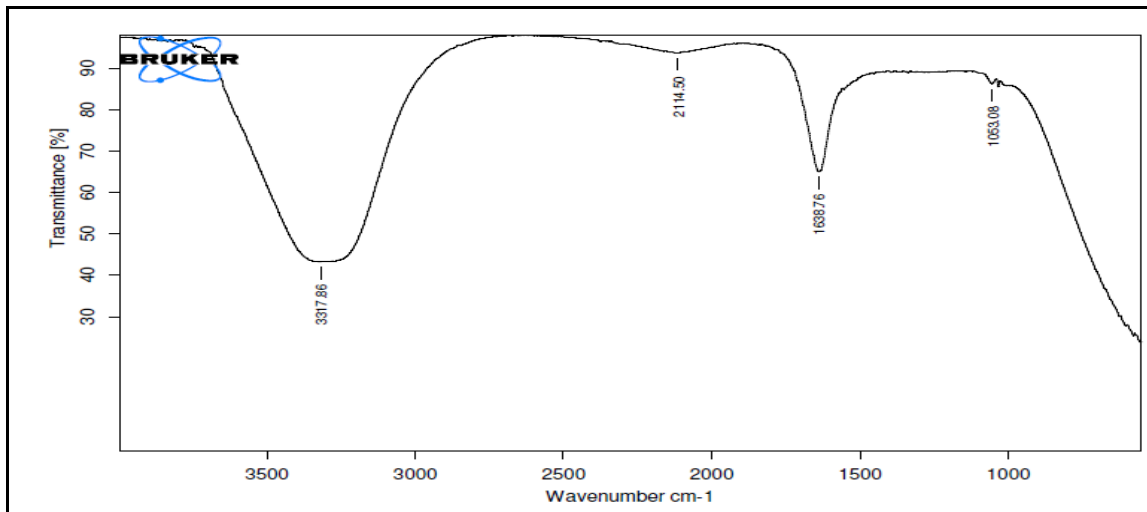


Figure 2: FTIR spectroscopy study of pure Zidovudine

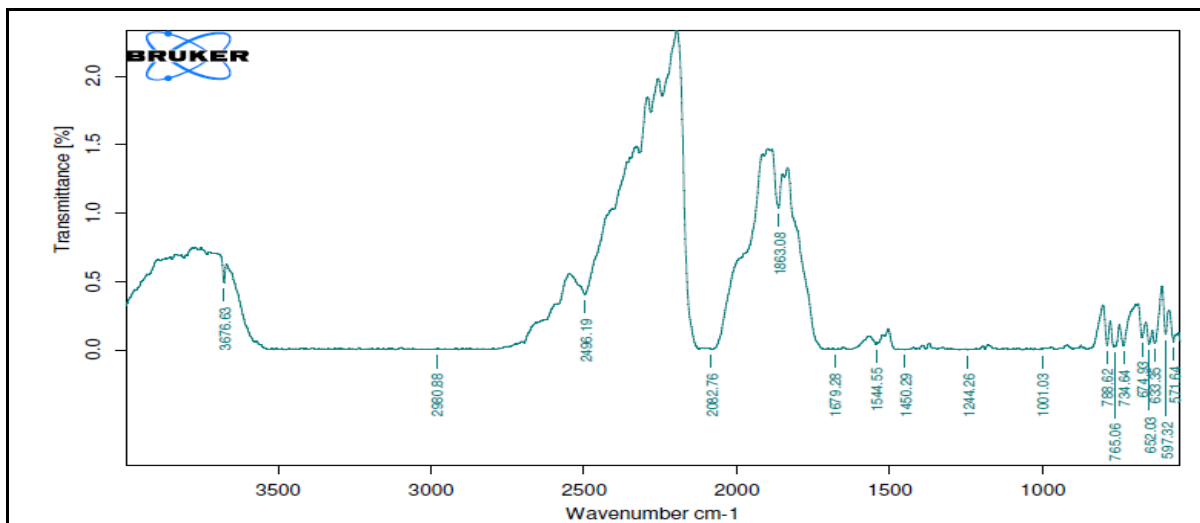


Figure 3: FTIR spectroscopy study of ZM4 formulation

DSC

From the figure 4 it was found that the endothermic peak of zidovudine was at 114.5⁰C. The endothermic peak of ZM4 formulation (Figure 5) was observed at 113.5⁰C. No significant change in the endotherm was observed between drug and formulation. From the DSC thermograms it was clear that no specific interaction between the drug and excipients used in present formulation.

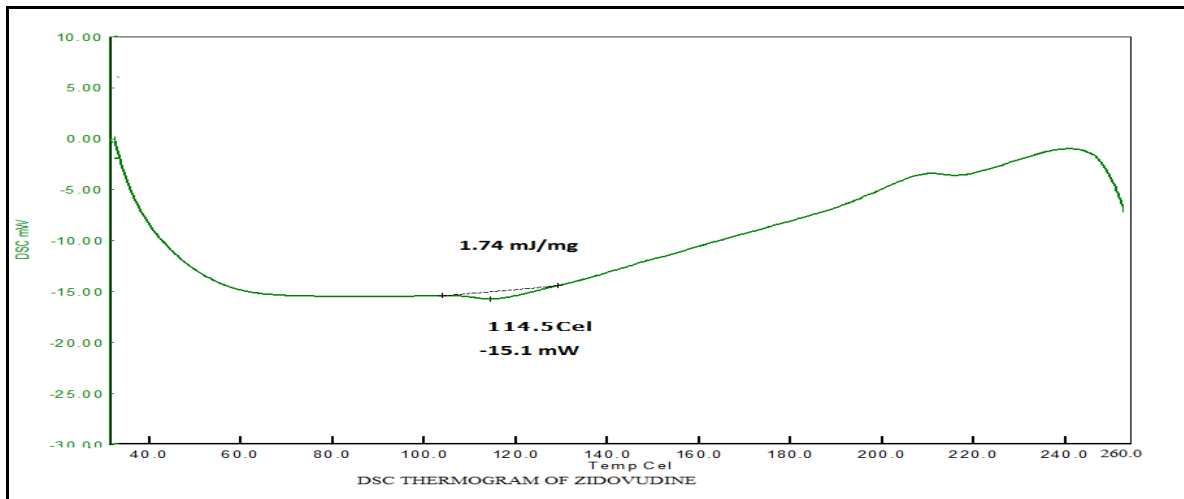


Figure 4: DSC of zidovudine

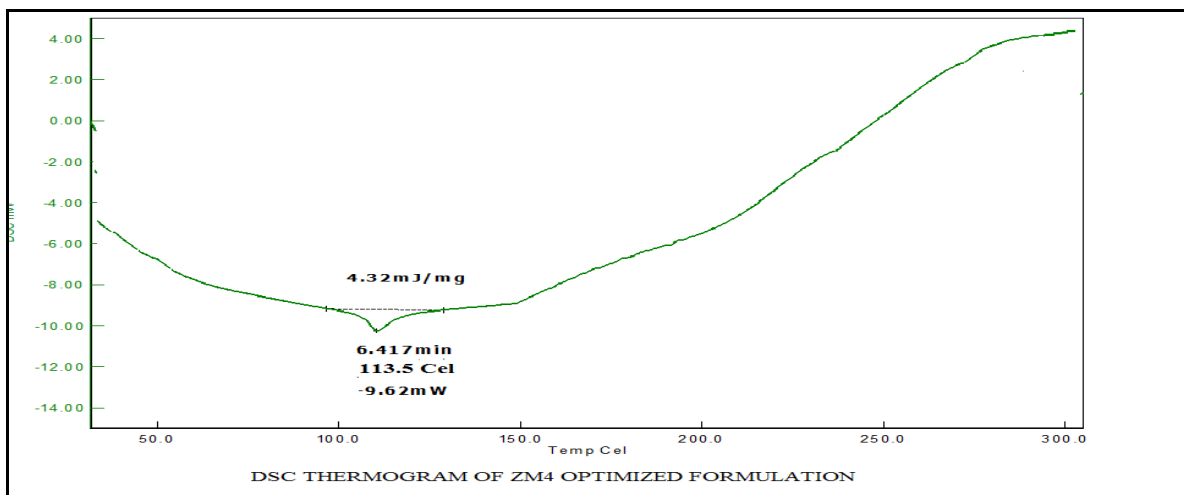


Figure 5: DSC of ZM4 formulation

Analytical study

The wavelength of maximum absorbance λ_{max} was obtained at 266nm for 0.1N HCl. The calibration curve was found to be linear in the range of 2-22 μ g/ml and straight line equation was obtained having regression coefficient value of 0.998. Similarly the wavelength of maximum absorbance λ_{max} was obtained at 265nm for phosphate buffer pH 6.8. The calibration curve was found to be linear in the range of 2-20 μ g/ml and straight line equation was obtained having regression coefficient value of 0.998.

Pre compression parameters

All the compressible excipients for various batches were evaluated for angle of repose, bulk density, tapped density, Carr's index and Hausner's Ratio. The angle of repose of pre-compression blends of various batches was in the range of 25.43 \pm 0.11 to 29.65 \pm 0.13. The bulk density of pre-compression blends was found to be in the range of 0.462 \pm 0.17 to 0.483 \pm 0.11gm/ml, tapped density in the range of 0.529 \pm 0.05 to 0.545 \pm 0.15gm/ml, the Carr's index values were in the range of 9.07 \pm 0.05 to 15.22 \pm 0.14, and Hausner's ratio values were ranges of 1.09 \pm 0.04 to 1.17 \pm 0.16.

Table 5: Pre compression parameters of ZD formulations

Formulation code	Angle of repose (degree) ^a ± S.D	Bulk density (gm/ml) ^a ± S.D	Tapped density (gm/ml) ^a ± S.D	Carr's Index (%) ^a ± S.D	Hausner's Ratio ^a ± S.D
ZM1	29.65 ± 0.13	0.462 ± 0.17	0.545 ± 0.15	15.22 ± 0.14	1.17 ± 0.16
ZM2	28.73 ± 0.12	0.483 ± 0.11	0.536 ± 0.09	9.88 ± 0.06	1.10 ± 0.08
ZM3	26.32 ± 0.08	0.479 ± 0.01	0.534 ± 0.03	10.3 ± 0.04	1.11 ± 0.06
ZM4	25.43 ± 0.11	0.481 ± 0.04	0.529 ± 0.05	9.07 ± 0.05	1.09 ± 0.04

N.B.-All values are expressed as mean ± S.D, ^an = 3

Post compression parameters

All the post compression parameters such as thickness, coat thickness, hardness, % friability, average weight of tablet, drug content and diameter were evaluated accordingly. The thickness of formulated tablets was found to be in the range of 4.502 ± 0.01 to 4.561 ± 0.03 mm, coat thickness in the range of 101.2 ± 3.1 to 400.13 ± 3.1 µm, the hardness values were in the range of 6.8 ± 0.12 to 7.5 ± 0.18 kg/cm², the friability values were in range of 0.10 ± 0.02 to 0.16 ± 0.02, average weight of tablet was in the range of 949.4 ± 1.03 to 951.3 ± 1.02 mg, drug content of tablet was in the range of 100.0 ± 1.32 to 100.96 ± 1.4 and diameter of tablets values were ranges of 12.11 ± 0.03 to 12.14 ± 0.09 mm.

Table 6: Post compression parameters of formulation

Formulation code	Thickness (mm) ^a ± S.D	Coat thickness (µm) ^a ± S.D	Hardness (kg/cm ²) ^a ± S.D	% Friability (%) ^b ± S.D	Average wt. of tablet (mg) ^b ± S.D	% Drug content ^a ± S.D	Diameter (mm) ^a ± S.D
ZM1	4.51 ± 0.01	400.13 ± 3.1	6.8 ± 0.12	0.11 ± 0.03	950.18 ± 1.16	100.0 ± 1.32	12.13 ± 0.02
ZM2	4.523 ± 0.02	301.12 ± 2.4	6.9 ± 0.11	0.16 ± 0.02	949.4 ± 1.03	100.32 ± 1.41	12.11 ± 0.03
ZM3	4.561 ± 0.03	205.16 ± 1.9	7.1 ± 0.16	0.14 ± 0.03	951.3 ± 1.02	100.64 ± 0.98	12.13 ± 0.07
ZM4	4.502 ± 0.01	101.2 ± 3.1	7.5 ± 0.18	0.10 ± 0.02	950.12 ± 1.06	100.96 ± 1.4	12.14 ± 0.09

N.B.-All values are expressed as mean ± S.D, ^an = 10, ^bn = 20

In vitro drug release study

The in vitro drug release characteristics were studied in 900ml of 0.1N HCl (pH 1.2) for a period of first 2hrs and 3 to 16hrs in phosphate buffer pH 6.8 using USP type II dissolution apparatus (Paddle type). The cumulative percentage drug release for ZM1, ZM2, ZM3 and ZM4 were 87.22, 91.56, 93.13 and 94.99% respectively of zidovudine at the end of 16hrs. It is shown in figure 6.

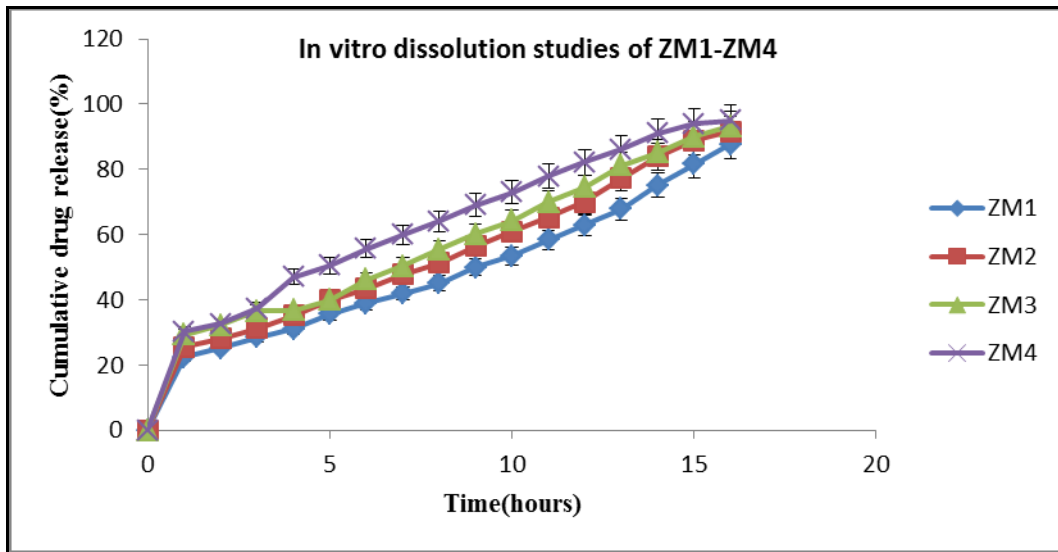


Figure 6: *In vitro* release profiles showing zidovudine release from various fabricated formulations ZM1-ZM4

Kinetic model

The drug release kinetics from the porous osmotic pump tablet, the *in vitro* release data were analyzed by zero order, first order, Higuchi and Korsmeyer and Peppas equations and Hixson-Crowell equation. As clearly indicated in table 7 all the formulations follow non-Fickian transport as n value lies between 0.45-0.89.

Table 7: Fitting of IVDR data in various mathematical models

Models	Zero order		First order		Higuchi		Korsmeyer-Peppas			Hixson-Crowell	
	R ²	K ₀	R ₁ ²	K ₁	R _H ²	K _H	R _K ²	K _p	n	R ²	K _s
ZM1	0.968	4.522	0.879	0.1013	0.936	20.25	0.917	17.298	0.514	0.93	0.118
ZM2	0.970	4.902	0.890	0.1289	0.952	22.11	0.923	19.769	0.503	0.943	0.141
ZM3	0.959	4.895	0.899	0.1381	0.957	22.26	0.904	22.855	0.460	0.949	0.147
ZM4	0.944	5.066	0.936	0.1681	0.991	23.63	0.967	25.176	0.466	0.978	0.166

Effect of osmogen concentration

The core formulations were prepared with various concentration of osmogens. The drug release profile is shown in figure 7. It is observed that osmogen enhances the drug release of drug and thus had a direct effect on drug release. The concentrations of osmogen were 25, 50, 75 and 100mg/tablet for ZM1, ZM2, ZM3 and ZM4 respectively. Figure 7 shows that the cumulative percentage drug release lowest for ZM1 (87.22%) and highest for ZM4 (94.99%) respectively of zidovudine at the end of 16hrs

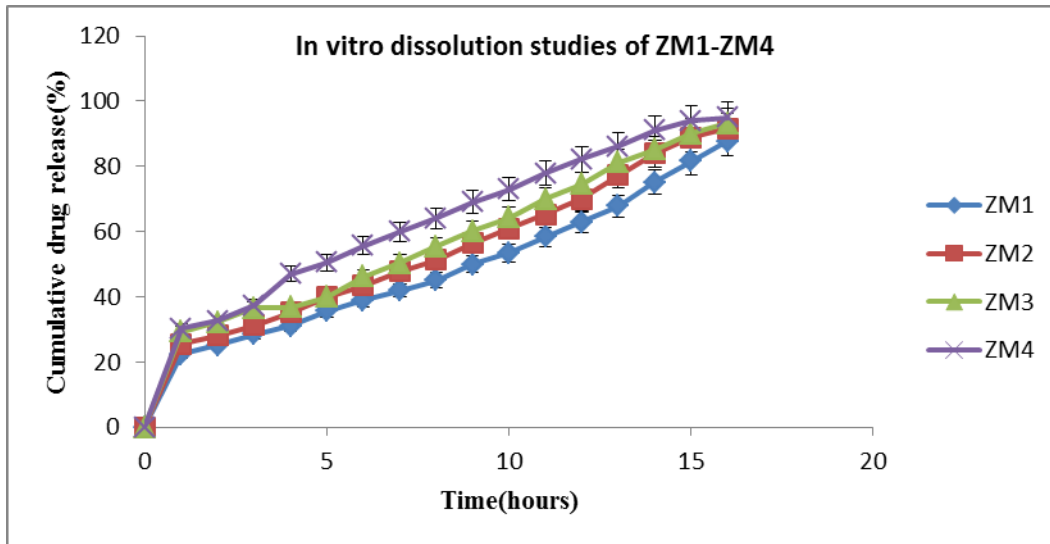


Figure 7: *In vitro* release profiles showing zidovudine release from various fabricated formulations ZM1-ZM4 having different concentration of osmogen

Effect of pore former concentration

To study the effect of pore forming agent core formulations of zidovudine were coated with varying coating compositions of pore forming agent containing 0%,10%,20% and 30% w/w of CA of sorbitol for ZM1,ZM2,ZM3 and ZM4 respectively. Release profile from these formulations is shown in figure 8. It is clearly evident that the level of sorbitol had a direct effect on drug release. As the level of pore former increases the membrane becomes more porous after coming contact with aqueous environment resulting in faster drug release.

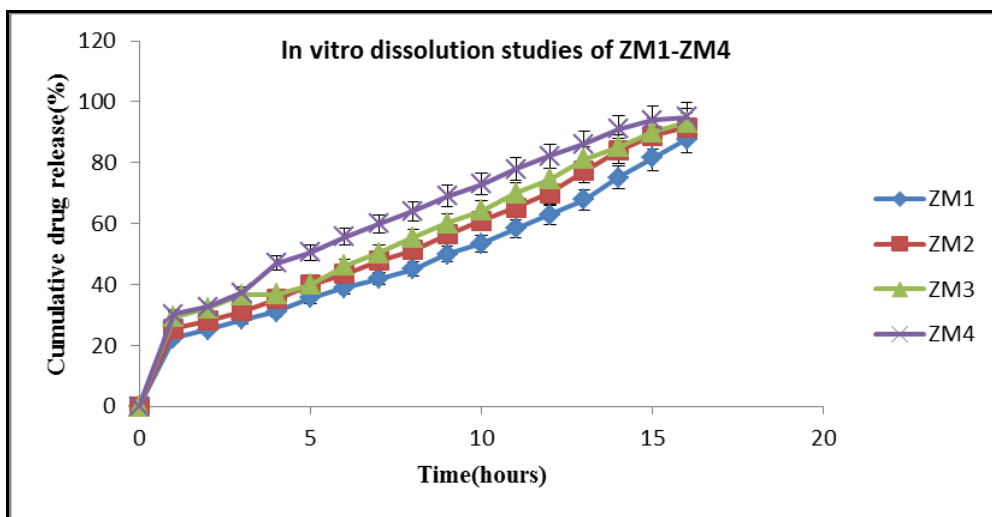


Figure 8: *In vitro* release profiles showing zidovudine release from various fabricated formulations ZM1-ZM4 having different concentrations of pore former

Effect of coating thickness

The osmotic pump coated tablets having varying the coating thickness are evaluated for drug release study. Release profile of zidovudine from these formulations is shown in figure 9. It is clearly evident that drug release decreases with increase in coating thickness of the semi permeable membrane.

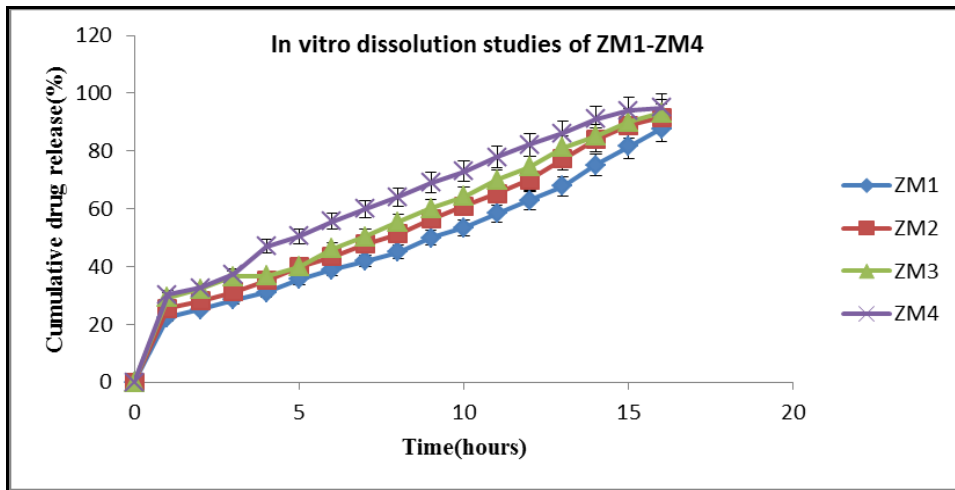


Figure 9: *In vitro* release profiles showing zidovudine release from various fabricated formulations ZM1-ZM4 having different membrane thickness

Effect of osmotic pressure

The results of release studies of optimized formulation in media of different osmotic pressure indicated that the drug release is highly dependent on the osmotic pressure of the release media. The release was inversely related to the osmotic pressure of release media. This finding confirms that the mechanism of drug release is by osmotic pressure. The drug release for ZM4 was found to be 89.96% for 30 atm, 78.97% for 60 atm and 70.14% for 90 atm respectively. It is shown in figure 10.

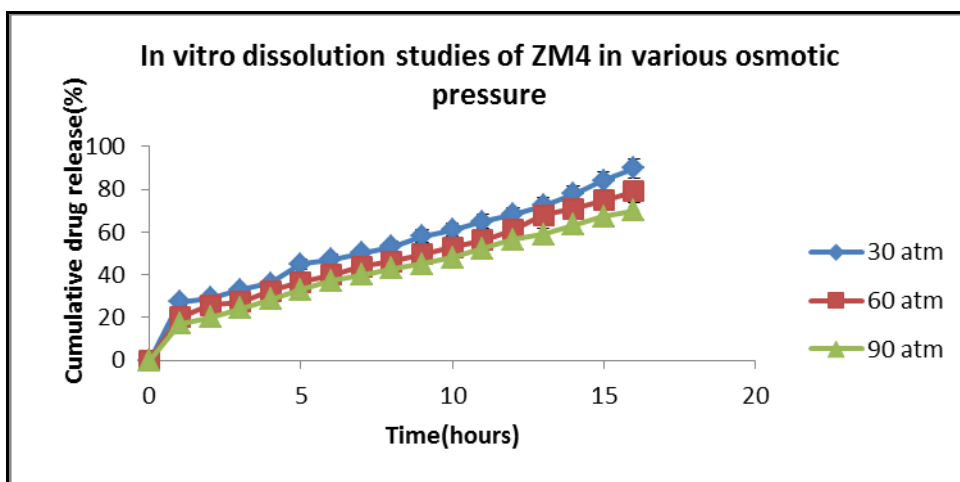


Figure 10: *In vitro* release profiles showing zidovudine release from best ZM4 in different osmotic pressures

Effect of pH

The optimized formulation ZM4 was subjected to *in vitro* drug release studies in buffers with different pH like pH 1.2, pH 6.8 and pH 7.4. It is observed that there is no significant difference in the release profile, demonstrating that the developed formulation shows pH independent release. It is shown in figure 11.

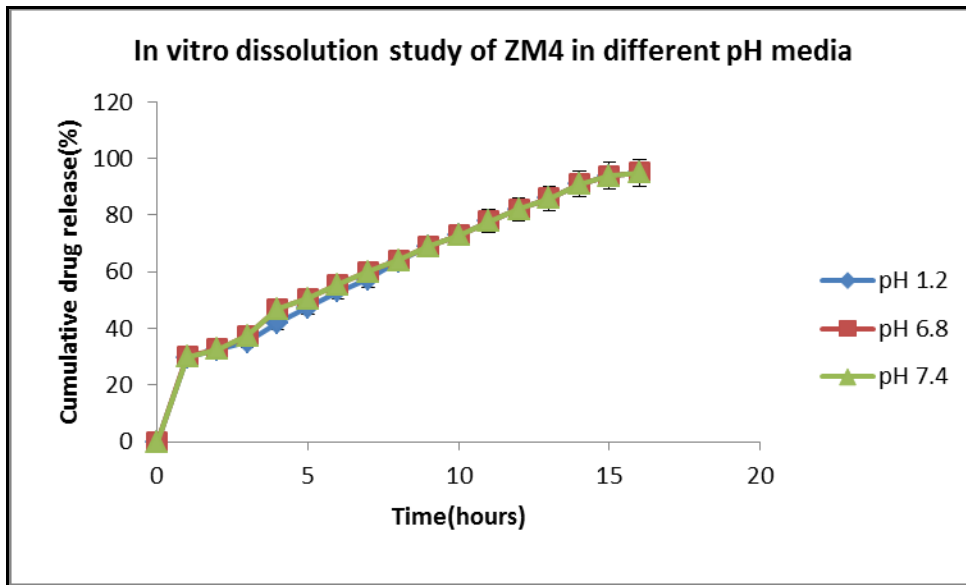


Figure 11: In vitro dissolution study of best formulation ZM4 in various pH media

Effect of agitation intensity

The optimized formulation of ZM4 batch was carried out in USP dissolution apparatus type-II at varying rotational speed (50, 100 and 150 rpm). It shows that the release of zidovudine from CPOP is independent of agitation intensity. Hence it can be expected that the release from the developed formulation will be independent of the hydrodynamic conditions of the absorption site. It is shown in figure 12.

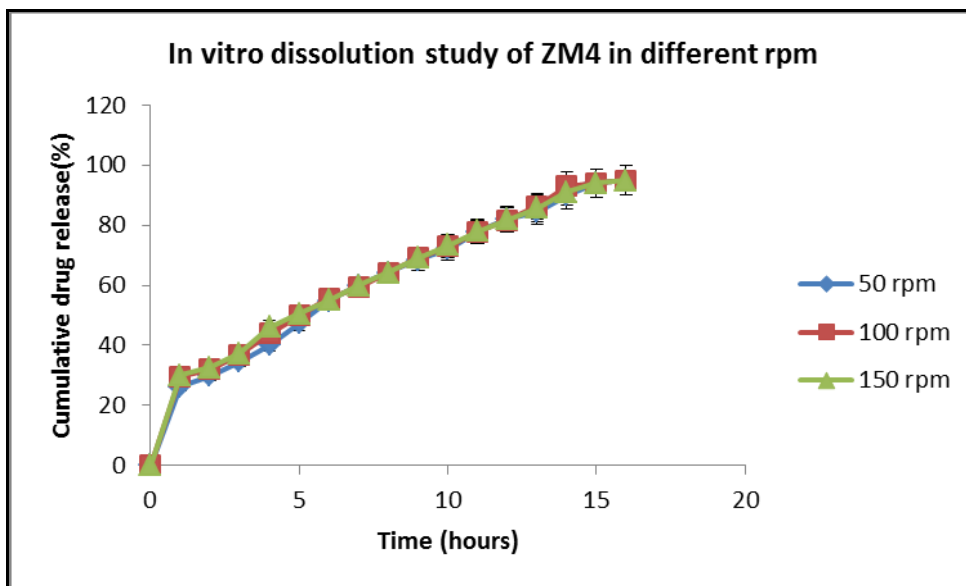


Figure 12: In vitro dissolution study of best formulation ZM4 in various agitational speeds

Scanning Electron Microscopy (SEM)

The coating membrane of the osmotic delivery system before and after dissolution was examined with the help of SEM. Before dissolution (Figure 13) no pores were found in the coating membrane. But after dissolution (Figure 14) comparatively more numbers of pores were found in the membrane might be due to leaching or removal of entrapped drug from the formulation. The porosity nature of the membrane was due to the presence of pore forming agent sorbitol in the formulation.

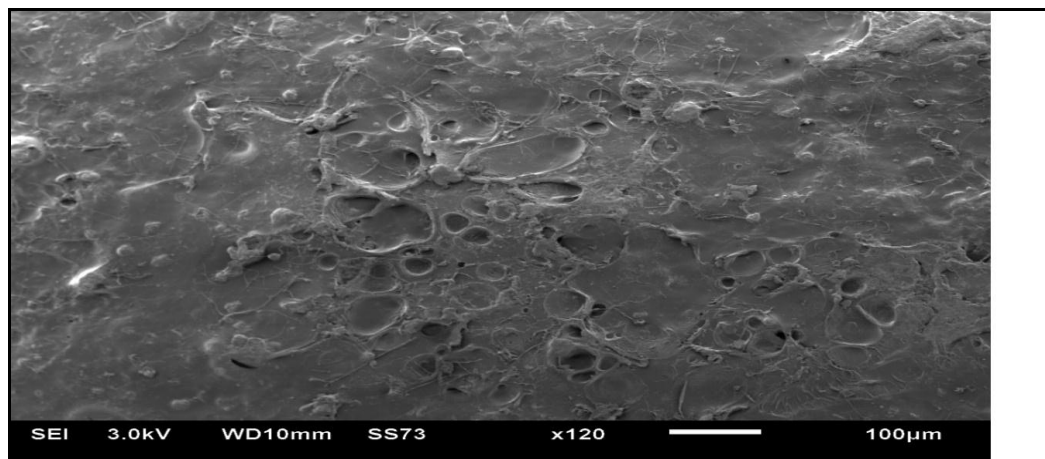


Figure 13: SEM micrograph showing the membrane structure of ZM4 before dissolution

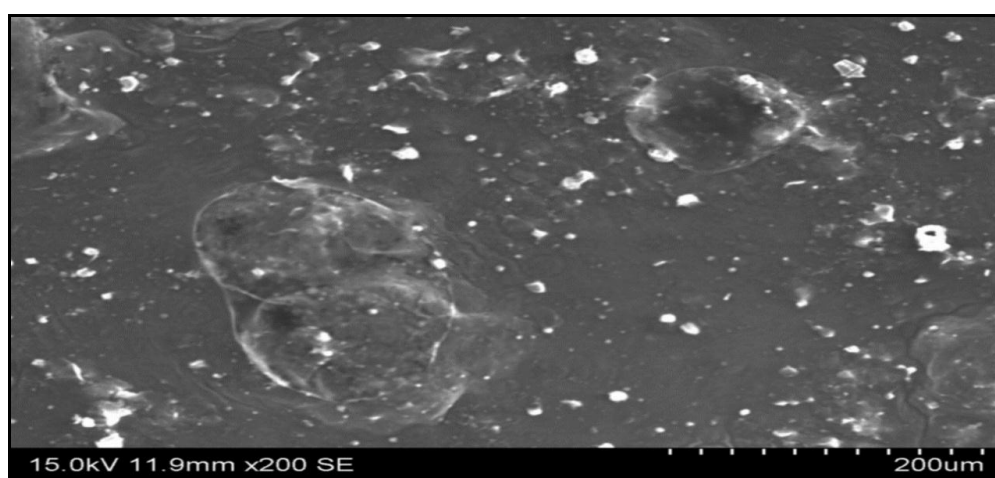


Figure 14: SEM micrograph showing the membrane structure of ZM4 after dissolution

Stability studies

From short term stability studies of optimized formulation ZM4, it was confirmed that there was no significance changes in physical appearance and drug content. It is shown in table 8.

Table 8: Comparative physicochemical characterization of ZM4 at accelerated conditions

Sl.no.	Parameters	Initial	After 30 days	After 60 days	After 90 days
1.	Physical appearance	Pale white,circular,concave smooth surface without any cracks	No change	No change	No change
2.	Thickness(mm) ^a ± S.D	4.502±0.01	4.502±0.01	4.501±0.01	4.500±0.01
3.	Hardness(kg/cm ²) ^a ± S.D	7.5±0.18	7.5±0.18	7.5±0.18	7.3±0.18
4.	Friability(%) ^b ± S.D	0.10±0.02	0.10±0.02	0.10±0.02	0.09±0.02
5.	Weight variation(mg) ^b ± S.D	950.12±1.06	950.12±1.06	950.12±1.06	949.12±1.06
6.	Drug content(%) ^a ± S.D	100.96±1.4	100.96±1.4	100.83±1.4	100.06±1.4
7.	Diameter(mm) ^a ± S.D	12.14±0.09	12.14±0.05	12.14±0.03	12.14±0.11

N.B.-All values are expressed as mean ± S.D, ^an = 10, ^bn = 20

Conclusion

Controlled porosity osmotic pump tablets can be designed for controlled release of zidovudine a highly water soluble (BCS class I) drug using HPMCE5LV as controlled release polymer, mannitol as osmogen and sorbitol as porogen. It was evident from the results that rate of drug release can be controlled through osmotic pressure of the core, the level of pore former and membrane thickness with release to be fairly independent of pH and hydrodynamic conditions of body. From the developed formulations the release of zidovudine was best in ZM4 formulation compared to other batches. The developed formulation ZM4 of zidovudine was inversely proportional to the osmotic pressure of the release media confirming osmotic pumping to be the major mechanism of drug release. The result of SEM studies confirmed the formation of pores in the membrane after coming into contact with the aqueous environment.

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