ISSN: 2573-962X

Research Article

Journal of Pharmaceutical Research

Design and Development of Controlled Porosity Osmotic Pump Tablets of Zidovudine Using Sodium Chloride as Osmogen for the Treatment of Aids

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Submitted: 28 Dec 2018; **Accepted**: 09 Jan 2019; **Published**: 28 Jan 2019

Abstract

The present study investigates the feasibility of the design and develops controlled porosity osmotic pump (CPOP) tablets to prolong the drug release of an antiretroviral drug zidovudine of 600mg once daily. Five formulations (ZS1to ZD5) were prepared by wet granulation method using various excipients. The CPOP consisted of an osmotic core coated with a micro porous membrane made up of cellulose acetate, poly ethylene glycol and sorbitol as in situ micro pore former. The prepared tablets were evaluated for pre compression parameters, post compression parameters, in vitro drug release study, Fourier Transform Infrared Spectroscopy (FTIR) study, Differential Scanning Calorimetry (DSC) study and scanning electron microscopy (SEM) study. The formulation variables such as effect of osmogen concentration, effect of pore former concentration, effect of membrane thickness of semi permeable membrane were evaluated for drug release characteristics. For the optimized formulation (ZS4) effect of osmotic pressure, effect of pH and effect of agitation intensity was evaluated. 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 model. The result of optimized formulation releases drug up to 16 hrs in a controlled manner and follows Higuchi kinetics and which is independent of the pH and agitation intensity. The optimized formulation was found to be stable up to 3 months when tested for stability study at 40±2°C/ 75±5% RH.

Keywords: CPOP, Wet granulation, In vitro drug release, Stability study.

Introduction

Over the past 36 years AIDS is spreading like a pandemic disease and creating major global health problem in world [1]. WHO estimate in 2015 showed that 36.7 million people globally were living with HIV, AIDS killed 1.1 million people died from AIDS related illnesses and 35 million people have died from AIDS related illness since start from epidemic. AIDS was first recognized in the United States in June 5, 1981. AIDS is a pandemic disease which is infected by human immunodeficiency virus (HIV) and patient experiences infection in immune system causing decline CD4+ cell count of less than 200cells/μL in blood [2, 3]. It is transmitted primarily via unprotected sexual intercourse (including anal and even oral sex), contaminated blood transfusions, and hypodermic needles and from mother to child during pregnancy, delivery or breastfeeding [4]. The management of AIDS can be controlled by antiretroviral therapy, male circumcision, needle exchange program, use of diaphragms, topical protection, use of condoms and alternative medicine [5].

Zidovudine is a synthetic thymidine analog of nucleoside reverse transcriptase inhibitor (NRTI) is extensively used against HIV-1,HIV-2 and human T cell lymphotropic virus 1 and 2.After entering the host cell 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. Treatment of AIDS using conventional formulations of zidovudine is found to have many drawbacks such as adverse side effect due to accumulation of drug in multidose therapy, poor patient compliance and high cost. So controlled release formulations of zidovudine can overcome these problems by reducing dosing frequency and increasing therapeutic effectiveness of the drug [6]. Zidovudine can be administered two times in a day of dose 300mg or three times in a dose of 200mg for adults according

to their body weight for conventional doses. In the present study CPOP tablets of zidovudine were formulated using wet granulation technique in order to reduce dose frequency of 600mg once daily for adults comparing to conventional dose and to enhance patient compliance towards therapy. The biological half life of zidovudine triphosphate is 4 hrs.

The basic rationale for controlled drug delivery is to alter the pharmacokinetic and pharmacodynamics of pharmacological active moieties by using novel drug delivery system or by modifying the molecular structure and physiological parameters inherent in the selected route of administration [7]. However oral controlled drug delivery system may be affected by pH, hydrodynamic condition of the body, presence of food and gastrointestinal motility. But osmotic controlled drug delivery system (OCDDS) utilizes principle of osmotic pressure for controlled delivery of active ingredients [8]. The drug released from OCDDS is independent of pH and hydrodynamic condition of the body and agitation intensity.

CPOP tablet works on the principle of osmotic pressure and osmosis is the phenomenon that makes osmotic controlled drug delivery in a reality. In osmosis the drug moiety moves from its higher concentration to lower concentration area until equilibrium at both sides. Osmotic pressure is created due to imbibitions [9] of fluid from external environment into the dosage form regulates the delivery of drug from osmotic devices. The CPOP core generally consists of a compartment containing drug, excipients and osmotic agents covered with a semi permeable membrane embedded with in situ micro pores forming agent. Water leachable additives are incorporated in semi permeable membrane which gets dissolved when it comes in contact with release media creating in situ micro pore formation generating osmotic pressure within CPOP to release the drug in controlled manner. The rate of drug delivery depends upon the factors such as water permeability of the semi permeable membrane, osmotic pressure of core formulation, thickness and total area of coating [10]. The main objective of the present study was to develop controlled porosity-based osmotically controlled release tablets of zidovudine using different concentrations of osmogen.

Materials and Methods

Materials

Zidovudine was obtained from Hetero Drugs Pvt. Ltd. India., Mannitol and Sodium chloride was purchased from Qualigens Fine Chemicals, India. Cellulose acetate (CA) was obtained from Eastman Chemical Inc, Kingsport, TN. Sorbitol, HPMC E5M LV, magnesium stearate, talc and polyethylene glycol (PEG) 400, 600, 4000, and 6000 were purchased from S.D. Fine Chemicals Ltd, Mumbai, India. Microcrystaline cellulose (MCC) and starch 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 FTIR study [11] of pure drug, formulation and individual excipient were carried out by KBr pellet method. In this method sample mixture and potassium bromide in the ratio of 1:100 was finely ground using mortar and pestle. A small amount of mixture was placed under hydraulic press compressed at10kg/cm to form a transparent pellet which was kept in the sample holder and scanned from 4000cm to 400cm -1in FTIR spectrophotometer (Shimadzu 8400S,Japan).

Differential Scanning Calorimetry (DSC)

Physical mixtures [12] of drug and individual excipients in the ratio of 1:1 were taken and examined in DSC (Shimadzu DSC-50, Japan) by effective heat conduction and scanned in the temperature range of 50-3000C.The rate of heating was 200C/min used to get thermogram. Then the themo grams were compared with pure samples versus optimized formulation.

Methods

Preparation of osmotic pump tablets

The tablets were prepared by wet granulation [13] technique. Formulas of different core formulations of zidovudine are given in Table 1.Required quantities of ingredients mentioned in Table-1 were passed through American Society of Testing and Materials (ASTM) 30 mesh except lubricant and glidant which were passed through ASTM 80 mesh. All the ingredients were manually blended homogenously in a mortar by way of geometric dilution except lubricant (magnesium stearate), glidant (talc).The mixture was moistened with aqueous solution and granulated through ASTM 30 mesh and dried in a hot air oven at 60ºC for sufficient (3-4 hrs). When the moisture content of granules reached to 2-4% in hot air oven then granules were passed through ASTM 30 mesh and blended with talc and magnesium stearate. The homogenous blend was then compressed into round tablets with standard concave punches 10 station rotary compression machine (Mini Press, Karnavati, India).

Table 1: Composition of controlled porosity osmotic pump zidovudine tablets

Ingredients (mg)	ZS1	ZS2	ZS3	ZS4	ZD5
ZD	600	600	600	600	600
MCC	175	150	125	100	200
Starch	40	40	40	40	40
HPMC E5LV	100	100	100	100	100
Sodium Chloride	25	50	75	100	0
Magnesium stearate	5	5	5	5	5
Talc	5	5	5	5	5
Total weight(mg)	950	950	950	950	950

Coating of core tablets

Zidovudine core tablets were coated in perforated [14] coating pan. The coating solution was prepared using mixtures of CA 6gm and 33% w/w of cellulose acetate (CA) of polyethylene glycol 400, 600, 4000, and 6000 respectively with addition of acetone to quantity sufficient maintaining proper viscosity of solution. The composition of coating solutions was mentioned in table 2. Perforated coating pan (GAC-205, Gansons Ltd, Mumbai, India) was employed to coating of tablets bed by spray method. Preheating of tablets was done initially by passing hot air through tablet bed with a rotation of lower speed of pan 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/cm^2 respectively. Inlet and outlet air temperature were 50ºC and 40ºC respectively. Coated tablets were dried at 50ºC for 12 hrs.

Table 2: Coating composition for zidovudine osmotic pump tablets

Ingredients	ZS1	ZS2	ZS3	ZS4	ZD5
CA(g)	6	6	6	6	6
PEG 400(g)	2	0	0	0	0
PEG 600(g)	0	2	0	0	0
PEG 4000(g)	0	0	2	0	0
PEG 6000(g)	0	0	0	2	0
Sorbitol(g)	0	0.6	1.2	1.8	1.8
Acetone(ml)	300	300	300	300	300

Evaluation of Controlled Porosity Osmotic Pump Tablets

Pre compression parameters of osmotic pump granules [15]

Angle of repose (θ)

The angle of repose of granules was determined by fixed funnel and free standing cone method where 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 the angle of repose, h is is the height of heap in cm and r is the radius of the circular support (cone) in cm.

Bulk density (e_b)

Bulk density 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.

Bulk density (e_b) Mass of granules(m)/Bulk volume of granules(V_b) (3)

Tapped density (e_t)

The measuring cylinder containing known mass of granules blend is tapped 1000 times for a fixed time in bulk density apparatus (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.

Tapped density (e_t) Mass of granules (m)/Tapped volume of granules (V_t) (4)

Compressibility index (Carr's index)

The compressibility index indicates the flow property characteristics of granules. The Carr's index can be calculated by the following formula.

$$\%\text{Carr's index (C.I)} = \frac{et-eb}{et} \times 100 \quad (5)$$

Where e_t is the tapped density of granules and e_b is bulk density of granules. It is represented in table no.3.

Hausner's ratio (H.R)

Hausner's ratio indicates of flow properties of granules. The ratio can be calculated by the taking the ratio of tapped density to the ratio of bulk density. It is shown in table no.3.

$$H.R = e_t / e_b \quad (6)$$

Table 3: Scale of flow ability determined by different methods [16]

Flow property	Angle of repose	Compressibility index	Hausner's ratio
Excellent	25-30	≤10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very poor	56-65	32-37	1.46-1.59
Very very poor	>66	> 38	>1.6

Post compression parameters of controlled porosity osmotic pump tablets [17]

Thickness

The thickness of individual tablets is measured by using vernier caliper (Absolute digimatic, Mitutoyo Corp. Japan) which gives the accurate measurement of thickness in mm. The limit of the thickness deviation of each tablet is ± 5%.

Measurement of coat thickness

After dissolution the film was isolated from the tablets and dried at 40^0C for 1hr.Thickness was measured by using electronic digital calipers (Absolute digimatic, Mitutoyo Corp. Japan) and mean values were taken.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of tablets can be determined by using Monsanto hardness tester (Sisco, India) and measured in terms of kg/cm^2

Friability

Friability [18] of tablets was performed in a Roche friabilator (Sisco, India).Twenty tablets of known weight (W_0) were de-dusted in plastic chamber of friabilator for a fixed time of 25 rpm for 4 minutes and weighed again of weight (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

Twenty tablets were randomly selected from each batch and weighed individually [19]. The average weight and standard deviations of 20 tablets was calculated and compared with USP specifications.

Uniformity of drug content test

Ten tablets from each batch of CPOP formulations were taken and triturated to form powder [20]. The powder weight equivalent to

one tablet was dissolved in a 100ml volumetric flask filled with 0.1N HCl using magnetic stirrer for 24hr.Solution was filtered through whatman filter paper No.1 diluted suitably and analyzed spectrophotometrically

Diameter of tablet

The diameter of individual tablets is measured by using vernier caliper (Absolute digimatic, Mitutoyo Corp. 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 test was carried out by using USP type II (paddle) apparatus. The tablet is kept in 900ml of dissolution fluid of 0.1N HCl (pH1.2) and stirrer rotating with 75 rpm and maintaining the temperature 37±0.5^{0}C of dissolution media for first 2 hours then dissolution fluid is changed to phosphate buffer pH 6.8 maintaining same condition for next 14hrs [21]. In specified time intervals an aliquot of 5ml samples of the solution were withdrawn through 0.45-µm cellulose acetate filter from the dissolution apparatus and with replacement of fresh fluid to dissolution medium. Absorbance of these solutions was measured at specific λmax using a UV/Visible Spectrophotometer (SHIMADZU UV-1800, Japan). The drug release was plotted against time to determine the release profile of various batches.

In vitro drug release kinetic studies

To analyze in vitro drug release kinetics from the porous osmotic pump tablet, the in vitro release data were fitted by following equations.

Zero order kinetics for drug release can be expressed by the equation

$$Q_t = Q_0 - K_0 t \qquad (8)$$

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 kinetics for drug release can be expressed by the equation:

$$\text{Log } C = \log C_0 \; K_1 t/2.303 \; (9)$$

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. The first order release constant K_1 can be obtained by multiplying 2.303 with slope.

Higuchi model for drug release from matrix devices can be expressed by the equation.

$$Q = K_H \sqrt{t} \; (10)$$

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. The slope is equivalent to K_H.

Korsmeyer-Peppas model (KP Model) for mechanism of drug release can be expressed as

$$\text{Log } (M_t/M_\infty) \;\; \text{Log } K \;\; n \text{ Log } t \; (11)$$

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. In case of tablets (which are of cylindrical shape) a value of $n < 0.45$ indicates Fickian or Case I release; a value between $0.45 < n < 0.89$ shows non-Fickian or anomalous release; $n = 0.89$ for case II release and $n > 0.89$ indicates super case II release.

Hixson and Crowell model for mechanism of drug release can be expressed by the equation

$$W_0^{1/3} \;\; W_t^{1/3} = \kappa t \qquad (12)$$

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 concentration

To determine 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 concentration

Different concentrations of pore former were used in semi permeable membrane formation. To know drug release characteristics and surface morphology in SPM in vitro drug release data as well as number of formation of micro pores were compared.

Effect of membrane thickness

Tablets with varying coating thicknesses were prepared to determine the effect of coating thickness on drug release. The drug release rate was measured using 0.1NHCl for 2hrs and phosphate buffer pH6.8for rest 14 hrs as a dissolution medium and compared with coating thickness variation of various dosage forms.

Effect of osmotic pressure

To increase the osmotic pressure of the release media pre-equilibrated to 37^{0}C±1°C temperature and osmotically effective solute mannitol was added to produce 30 atm, 60 atm and 90 atm respectively. The drug release rate was tested and compared for various dosage forms.

Effect of pH

In order to measure 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 6.8 phosphate buffer and pH 7.4 phosphate buffer in USP type II dissolution apparatus in 75rpm. The temperature was maintained at 37±0.5°C. The release was studied at predetermined time intervals.

Effect of agitation intensity

To study the effect of agitation intensity 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 and analyzed by UV spectrometer and the drug release for various batches was compared.

Scanning Electron Microscopy (SEM)

In order to predict the mechanism of drug release and surface morphology from the developed optimized formulations surface coated tablets before and after dissolution studies was examined using scanning electron microscope. The specimens 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 (KV) in SEM fitted with ion sputtering device.

Accelerated stability studies

The optimized formulation was subjected to accelerated stability studies as per ICH (The International Conference of Harmonization) guidelines by packing in air tight bottles that can withstand stressed conditions. The packed tablets in air tight container were placed in stability chambers(Thermo lab Scientific equipment Pvt.Ltd., Mumbai, India) maintained at 40 ± 2 ºC, 75 ± 5% RH for 3 months. Tablets were periodically removed and evaluated for physical characteristics, drug content, in-vitro drug release etc..

Results and Discussion

FTIR studies

The study of the FTIR spectra of zidovudine (Figure 1) 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. In the optimized formulation (Figure 2) containing sodium chloride of osmotic pump (ZS4) peak at 3676.84, 1441.18, 789.17 and 571.47cm^{-1} were due to presence of the polymer HPMCE5LV.In the formulation the peaks present due to sodium chloride were 3398.38, and 634.66 cm^{-1}. Peaks at 2075.80 and 1677.90 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 2075.80 and 1677.90 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.

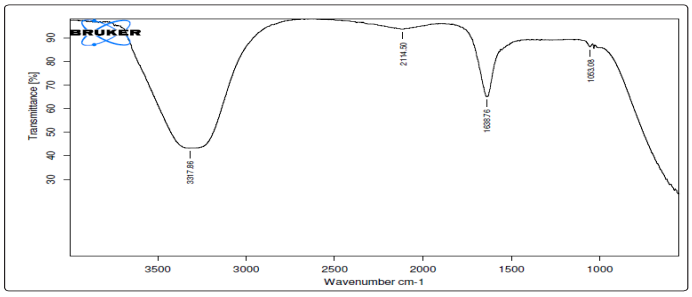

Figure 1: FTIR spectroscopy study of pure Zidovudine

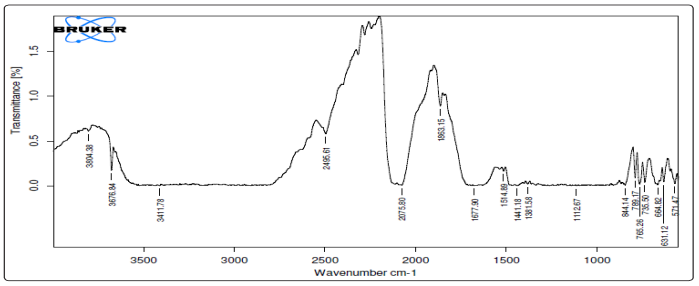

Figure 2: FTIR spectroscopy study of ZS4

DSC

DSC thermo gram showed an endothermic peak at 114.5^{0}C which is corresponding melting point of drug zidovudine in figure 3. DSC thermo gram showed an endothermic peak at 114.3^{0}C in ZS4 formulation (Figure 4). Hence physical mixture showed that there was compatibility with the drug.

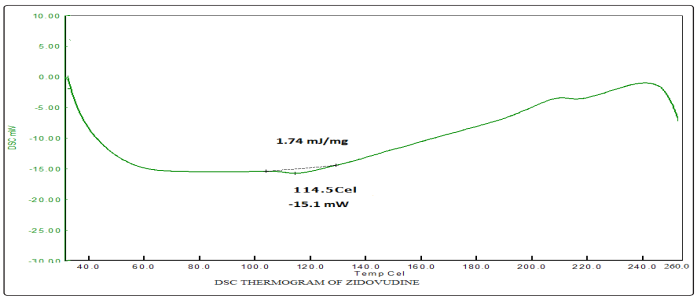

Figure 3: DSC thermogram of Zidovudine

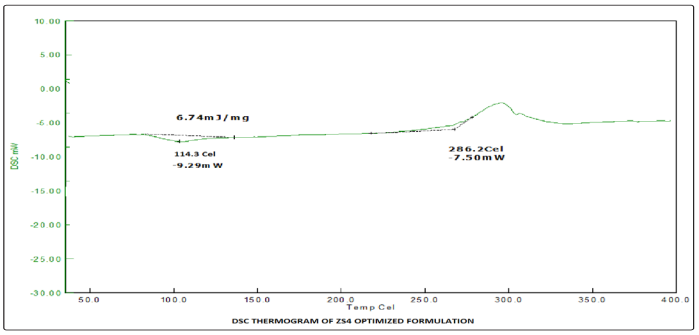

Figure 4: DSC thermo gram of ZS4

Pre compression parameters

The pre compression parameters of various batches of CPOP formulation were evaluated. The angle of repose of pre-compression blends of various batches was in the range of 24.26±0.11 to 29.64 0.12.The bulk density of pre-compression blends was found to be in the range of 0.472±0.06 to 0.487±0.12gm/ml, tapped density in the range of 0.519±0.08 to 0.534±0.03 gm/ml, the Carr's index values were in the range of 7.12±0.07 to 11.11±0.07, and Hausner's Ratio values were ranges of 1.07 ±0.08 to 1.11±0.06.

Table 4: Pre compression parameters of ZD formulations

Formulation code	Angle of repose (degree)[a] ± S.D	Bulk density (g/ml)[a] ± S.D	Tapped density (g/ml)[a] ± S.D	Carr's Index (%)[a] ± S.D	Hausner's Ratio[a] ± S.D
ZS1	28.45±0.11	0.472±0.06	0.531±0.08	11.11±0.07	1.12±0.06
ZS2	29.64±0.12	0.485±0.09	0.527±0.08	7.97±0.08	1.08±0.07
ZS3	25.34±0.06	0.487±0.12	0.528±0.11	7.76±0.08	1.08±0.09
ZS4	24.26±0.11	0.482±0.11	0.519±0.08	7.12±0.07	1.07±0.08
ZD5	26.32±0.08	0.479±0.01	0.534±0.03	10.3±0.04	1.11±0.06

N.B.- All values are expressed as mean ± S.D, [a]n = 3

Post compression parameters

All the post compression parameters for various batches were evaluated shown in table 5.The thickness of formulated batches of tablets were found to be in the range of 4.492±0.01 to 4.534±0.02 mm, coat thickness in the range of 100.4±2.1 to 401.1±2.1µm, the hardness values were in the range of 6.9±0.11 to 7.9±0.13 kg/cm^2,the friability values were in range of 0.11±0.16 to 0.19±0.02, average weight of tablet was in the range of 949.13±1.12 to 951.2±1.06 mg, drug content of tablet was in the range of 98.39±1.12 to 100.0±1.16,diameter of tablets values were ranges of 12.10±0.05 to 12.16±0.04 mm.

Table 5: 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 weight of tablet(mg)[b] ± S.D	%Drug contenta ± S.D	Diameter (mm)[a] ± S.D
ZS1	4.492±0.01	401.1±2.1	7.3±0.14	0.13±0.04	949.13±1.12	98.39±1.12	12.16±0.04
ZS2	4.526±0.02	300.1±2.3	6.9±0.11	0.19±0.02	951.2±1.06	99.03±1.16	12.10±0.05
ZS3	4.507±0.03	200.2±3.3	7.5±0.12	0.12±0.14	950.18±1.03	99.68±1.19	12.14±0.03
ZS4	4.499±0.02	100.4±2.1	7.9±0.13	0.11±0.16	950.1±1.04	100.0±1.16	12.12±0.08
ZD5	4.534±0.02	400.2±2.5	7.3±0.13	0.17±0.01	951.11±1.04	98.71±1.5	12.12±0.06

N.B.-All values are expressed as mean ± S.D, [a]n = 10, [b]n = 20

In vitro drug release study

The in vitro drug release characteristics were studied in 900ml of 0.1N HCl (pH1.2) 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 ZS1, ZS2, ZS3, ZS4 and ZD5 were 90.06, 93.58, 96.11, 98.17 and 81.39% respectively of zidovudine at the end of 16hrs.It is shown in figure 5.

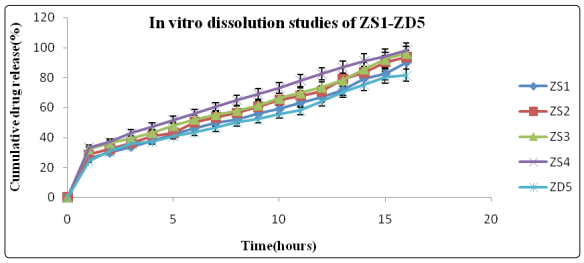

Figure 5: *In vitro* release profiles showing Zidovudine release from various fabricated formulations ZS1-ZD5

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. The optimized formulation ZS4 is showing highest regression values (R^2) in Higuchi model than zero order and first order. Hence the drug release follows Higuchi kinetics. The n value for optimized formulation is 0.421 (n <0.45). Hence it follows Fickian diffusion mechanism. It is shown in table 6.

Table 6: Fitting of IVDR data in various mathematical models

Models	Zero order		First order		Higuchi		Korsmeyer-Peppas			Hixson-Crowell	
Batches	R^2	K^0	R_1^2	K_1	R_H^2	K_H	R_K^2	Kkp	n	R^2	Ks
ZS1	0.952	4.441	0.891	0.1082	0.967	20.37	0.947	21.677	0.456	0.940	0.122
ZS2	0.952	4.727	0.877	0.1335	0.97	21.72	0.942	23.550	0.450	0.939	0.141
ZS3	0.935	4.659	0.824	0.1473	0.964	21.54	0.928	26.730	0.409	0.912	0.148
ZS4	0.935	4.949	0.853	0.1865	0.986	23.14	0.961	28.183	0.421	0.950	0.173
ZD5	0.939	4.09	0.935	0.0898	0.965	18.87	0.946	21.727	0.433	0.953	0.105

Effect of osmogen concentration

The CPOP formulations were prepared with various concentration of osmogen. The drug release profile is shown in figure 6.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 0, 25, 50, 75 and 100mg/tablet for ZD5, ZS1, ZS2, ZS3 and ZS4 respectively. Figure 6 shows that the cumulative percentage drug release lowest for ZD5 (81.39%) and highest for ZS4 (98.17%) respectively of zidovudine at the end of 16hrs

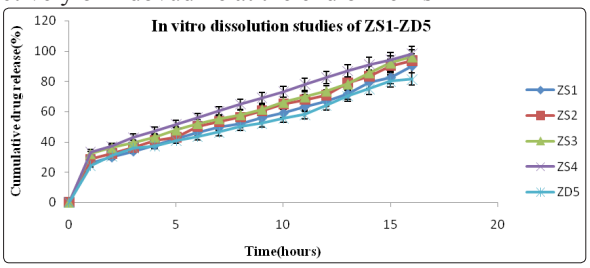

Figure 6: *In vitro* release profiles showing zidovudine release from various fabricated formulations ZS1-ZD5 having different concentration of osmogen

Effect of pore former concentration

The CPOP formulations were coated with various concentration of sorbitol with compared to CA. The coating compositions of pore forming agent towards formulations contains 30%, 0%,10%,20% and 30% w/w of CA of sorbitol for ZD5,ZS1,ZS2,ZS3 and ZS4 respectively.. Release profile from these formulations is shown in figure 7.It shows that as the level of pore former increases the membrane becomes more porous after coming contact with aqueous environment resulting in faster drug release.

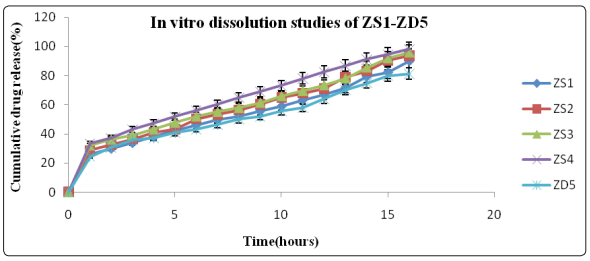

Figure 7: *In vitro* release profiles showing Zidovudine release from various fabricated formulations ZS1-ZD5 having different pore formers

Effect of membrane 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 8.It is clearly evident that drug release is inversely related to coating thickness of the semi permeable membrane.

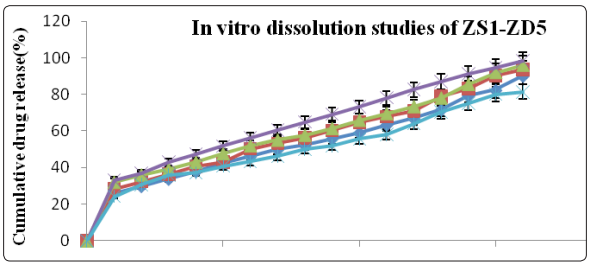

Figure 8: *In vitro* release profiles showing zidovudine release from various fabricated formulations ZS1-ZD5 having different membrane thickness

Effect of osmotic pressure optimized

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 ZS4 was found to be 92.04% for 30 atm, 80.38% for 60 atm and 72.96% for 90 atm respectively. It is shown in figure 9.

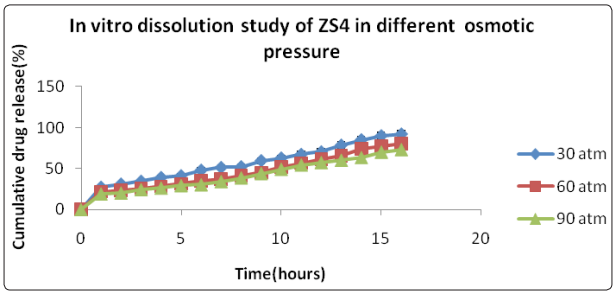

Figure 9: *In vitro* release profiles showing Zidovudine release from optimized ZS4 in different osmotic pressures

Effect of pH

The optimized formulation ZS4 was subjected to in vitro drug release studies in buffers with different pH like pH 1.2, pH 6.8 and pH7.4. 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 10.

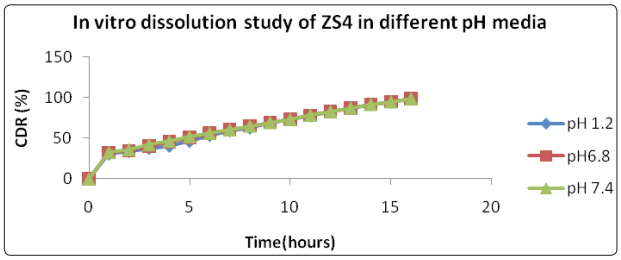

Figure 10: In vitro dissolution study of optimized formulation ZS4 in various pH media

Effect of agitation intensity

The optimized formulation of ZS4 batch was carried out in USP dissolution apparatus type-II at varying rotational speed(50,100 and 150rpm).It shows that the release of zidovudine from CPOP is independent of agitation intensity and the release from the developed formulation is independent of the hydrodynamic conditions of the absorption site. It is shown in figure 11.

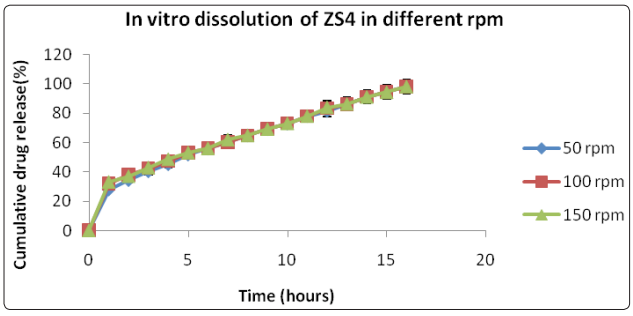

Figure 11: In vitro dissolution study of optimized formulation ZS4 in various agitational speed

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 no pores were found in the coating membrane. But after dissolution 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.

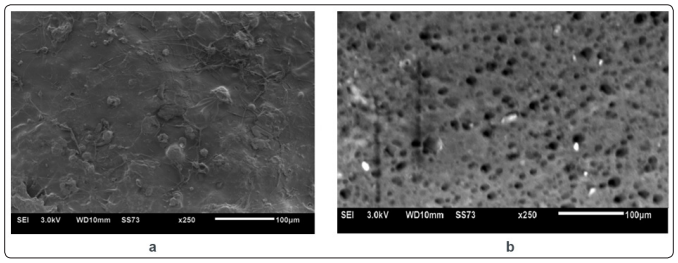

Figure 12: (a) SEM micrograph showing the membrane structure of ZS4 before dissolution, **(b)** SEM micrograph showing the membrane structure of ZS4 after dissolution

Stability studies

The short term stability for optimized formulation ZS4 shows that there was a not significant change in physical appearance, friability, hardness, drug content and in vitro drug release.

Conclusion

CPOP formulations of zidovudine were developed based on osmotic technology. The effect of different formulation variables was studied to optimize the release profile. Drug release was directly proportional to the level of osmogen concentration and inversely proportional to membrane thickness. Release from the developed batches was independent of pH and agitation intensity of release media. Zidovudine release from the optimized formulation was inversely proportional to the osmotic pressure of the release media confirming osmotic pumping to be the major mechanism of drug release.

Acknowledgements

The authors would like to acknowledge the contributions of Pharmaceutics Department, Faculty of Pharmacy, University College of Technology, Osmania University, Hyderabad, Telangana, India for providing necessary facilities to carry out the research work. This study was part of a Ph. D thesis under Osmania University, Hyderabad.

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