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Research Article

Optimization and Characterization of Stavudine from Controlled Porosity Osmotic Pump Tablets Using Osmotic Agent and Porogen

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ABSTRACT

The present work was aimed to develop controlled porosity osmotic pump tablets of stavudine.Wet granulation technique was adopted for the preparation of all these formulations. Conventional spray coating pan was used to develop coating upon core tablets by using cellulose acetate as wall forming material and sorbitol as pore former. The developed 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 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 optimized formulation was found to be stable up to 3 months when tested for stability study at 40±2ºC/ 75±5% RH.

INTRODUCTION

AIDS is a pandemic and serious infection [1] is caused by human immunodeficiency virus (HIV) and patient experiences infection in immune system causing decline CD4+ cell count of less than 200cells/µL in blood. It is transmitted by unprotected sexual intercourse, contaminated blood transfusions, needles, from mother to child during pregnancy, delivery, breastfeeding and infected body fluids like semen, vaginal fluid etc. The management of AIDS can be controlled by antiretroviral therapy [2], male circumcision, needle exchange program, use of diaphragms, topical protection, use of condoms and alternative medicine.

The main reason for controlled drug delivery [3] 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. But oral controlled drug delivery system is affected by p^H, hydrodynamic condition of the body, presence of food and gastrointestinal motility. Hence the most advance is osmotic controlled drug delivery system (OCDDS) over oral controlled drug delivery system because the drug release from OCDDS is independent of p^H and hydrodynamic [4] condition of the body and agitation intensity. The basic principle is osmotic pressure to control drug delivery from OCDDS.The current work is to design controlled porosity osmotic pump tablets of stavudine a part of osmotic drug delivery system.

CPOP tablet 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

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CPOP to release the drug in controlled manner. Osmotic pressure is created due to imbibitions [5] of fluid from external environment into the dosage form regulates the delivery of drug from osmotic devices. Water permeability of the semi permeable membrane, osmotic pressure of core formulation, thickness and total area of coating affect the drug delivery of CPOP tablet.

Stavudine is a nucleoside reverse transcriptase inhibitor (NRTI) with activity against Human Immunodeficiency Virus Type 1 (HIV-1) which is chemically 2',3'-didehydro-3'-deoxythymidine. The active metabolite stavudine 5' triphosphate is an inhibitor of the HIV reverse transcriptase and acts as a chain terminator during DNA synthesis.Stavudine [6] is absorbed rapidly orally producing peak plasma concentration within 1hour with 86% bioavailability and elimination half life of 1 to 1.5 hour following single or multiple doses. The conventional dose of stavudine is 40mg twice daily. Converting twice daily regimen of stavudine into once daily formulation of controlled release dose enhances the effectiveness of antiretroviral therapy. The main objective of the present study was to develop controlled porosity-based osmotically controlled release tablets of stavudine using different concentrations of osmogen.

MATERIALS AND METHODS

Materials

Stavudine was obtained from Hetero Drugs Pvt. Ltd. India. Fructose and Mannitol were purchased from Qualigens Fine Chemicals, India, and Cellulose acetate (CA) was obtained from Eastman Chemical Inc, Kingsport, TN. Sorbitol and polyethylene glycol (PEG) 400,600,1500,4000,6000 was purchased from S.D. Fine Chemicals Ltd, Mumbai, India. All other solvents and reagents used were of analytical grade.

Calculation of dose in sustained release tablets containing single drug

For a sustained release matrix tablet formulation containing single drug, the dose required for loading dose and sustained release layer was estimated by using following four equations. The equations that were given by Robinson and Erikson [7] are based on the available pharmacokinetic data following one compartment model with simultaneous release of loading dose and maintenance dose with a zero order release kinetic. The equations are presented as follows:

$$K_0 = D_I K_E \ldots\ldots\ldots\ldots\ldots \quad (1)$$

$$D_M = K_0 T \ldots\ldots\ldots\ldots\ldots \quad (2)$$

$$D_L = D_I - K_0 T_{max} \ldots\ldots\ldots \quad (3)$$

$$D_T = D_L + D_M \ldots\ldots\ldots\ldots\ldots \quad (4)$$

D_L=Loading dose, D_M = maintenance dose, D_I=Initial dose; T = time for sustained action; T_{max} = Time to reach peak plasma concentration;

Conventional dose 40mg 2 times daily above 60kg BW adult Cmax is 536 ng/ml

Controlled release dose 80mg once daily concentration (T_{max}) = 0.72 hour; initial dose (D_I) = 40 mg.

Elimination rate constant

$$K_E = {}^{0.693}/_{t_{1/2}} \quad \ldots\ldots\ldots\ldots \quad (5)$$

= 0.693/1.8h
= 0.385 h^{-1}

Zero-order release constant
$K_0 = D_I \times K_E$
= 40 mg × 0.385 h^{-1}
= 15.4 mg/h

Loading dose
$D_L = D_I - (K_0 \times T_{max})$
= 40 – (15.4 × 0.72 h)
= 40 – 11.088
= 28.912 mg

So, maintenance dose = Total dose – loading dose
= 80 mg – 28.912 mg
= 51.088 mg.

Hence, the CPOP tablet should contain a total dose of 80 mg for 18 hours in dosage form and it should release 40 – 11.088 = 28.912 (36.14%) mg in the 1st hour like conventional dosage form and the remaining dose (80 – 28.912) in remaining 17 hour, i.e. 51.088 (63.86%) mg or 3.005(3.756%) mg per hour up to 18 hours. The theoretical profile of stavudine is shown in Table 1.

Compatibility studies

Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR study [8] 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^{-1} in FTIR spectrophotometer (Bruker, Germany).

Table 1: Theoretical profile of stavudine

Time(hours)	Amount of drug release(mg)	%DR
1	28.912	36.14
2	31.917	39.896
3	34.922	43.652
4	37.927	47.408
5	40.932	51.164
6	43.937	54.92
7	46.942	58.676
8	49.947	62.432
9	52.952	66.188
10	55.957	69.944
11	58.962	73.7
12	61.967	77.456
13	64.972	81.212
14	67.977	84.968
15	70.982	88.724
16	73.987	92.48
17	76.992	96.236
18	80	100

Differential Scanning Calorimetry (DSC)

Physical mixtures [9] 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 50-300^{0}C.The rate of heating was 20^{0}C/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 technique. Formulas of different core formulations of stavudine are given in Table 2. Required quantities of ingredients mentioned in Table 1 were passed through 30 mesh except lubricant (magnesium stearate) and glidant (talc) which were passed through 80 mesh. All the ingredients were manually blended homogenously in a mortar by way of geometric dilution except magnesium stearate and talc. The mixture was moistened with aqueous solution and granulated through 30 mesh and dried in a hot air oven at 60ºC for sufficient time (3-4 hrs). When the moisture content of granules reached to 2-4% in hot air oven then granules were passed through 30 mesh and blended with talc and magnesium stearate. The homogenous blend was then compressed into round tablets with standard concave punches (diameter 8 mm) 10 station rotary compression machine (Mini press,Karnavati, India).

Coating of core tablets

The coating solution was prepared taking required ingredients from table 3 and acetone was added quantity sufficient maintaining proper viscosity of solution. The coatings [10] of tablets were performed by spray pan coating in a perforated pan (GAC-205, Gansons Ltd, Mumbai, India). Hot air is supplied to tablet bed by rotating lower speed 5-8 rpm initially. The coating of tablets was carried out with the 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.

EVALUATION OF CONTROLLED POROSITY OSMOTIC PUMP TABLETS

Pre compression parameters of osmotic pump granules

The prepared granules were evaluated for pre compression parameters [11,12] such as angle of repose, bulk density, tapped density and compressibility index (Carr's index).Fixed funnel method was used to determine angle of repose. The bulk density and tapped density were determined by bulk density apparatus (Sisco, India).

The Carr's index can be calculated by the following formula.

$$\% \text{ Carr's index } = \frac{etap - ebulk}{etap} \quad \ldots\ldots (6)$$

Where etap is the tapped density of granules and ebulk is bulk density of granules.

The Hausner's ratio can be calculated by the taking the ratio of tapped density to the ratio of bulk density. The scale of flowability is mentioned in Table 4.

Post compression parameters of controlled porosity osmotic pump tablets [14]

Thickness

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

Table 2: Composition of controlled porosity osmotic pump stavudine tablets

Formulation code	SD (mg)	MCC (mg)	PVP k30 (mg)	HPMC E5LV(mg)	Sodium chloride (mg)	Magnesium stearate (mg)	Talc (mg)	Total weight (mg)
SS1	80	175	20	100	20	2	3	400
SS2	80	155	20	100	40	2	3	400
SS3	80	135	20	100	60	2	3	400
SS4	80	115	20	100	80	2	3	400
SS5	80	95	20	100	100	2	3	400
SD6	80	195	20	100	0	2	3	400

Table 3: Coating composition for controlled porosity osmotic pump tablets

Formulation code	CA (g)	PEG 400 (g)	PEG 600 (g)	PEG 1500 (g)	PEG 4000 (g)	PEG 6000 (g)	Sorbitol (g)	Acetone (ml)
SS1	6	2	0	0	0	0	0.4	300
SS2	6	0	2	0	0	0	0.8	300
SS3	6	0	0	2	0	0	1.2	300
SS4	6	0	0	0	2	0	1.6	300
SS5	6	0	0	0	0	2	2	300
SD6	6	0	0	0	0	0	2	300

Table 4: Scale of flowability determined by different methods [13]

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

Measurement of coat thickness

Film was isolated from the tablets after 18hrs of dissolution and dried at 40^0C for 1hr.Thickness was measured by using electronic digital calipers (Absolute digimatic, Mitutoyo Corp. Japan).

Hardness

The hardness of tablets can be determined by using Monsanto hardness tester (Sisco,India).

Friability

Friability of tablets was performed in a Roche friabilator (SISCO, India).Twenty tablets of known weight ($W_{initial}$) were de-dusted in plastic chamber of friabilator for a fixed time of 25 rpm for 4 minutes and weighed again of weight (W_{final}).The percentage of friability was calculated using the following equation.

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

Where, $W_{initial}$ and W_{final} are the weight of the tablets before and after the test respectively.

Weight variation test [15]

The weight variation test is performed by weighing 20 tablets individually 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.

Uniformity of drug content test

Powder is made after triturating 10 CPOP tablets from each batch with mortar and pestle.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 spectro photometrically.

Diameter of tablet

The diameter of individual tablets is measured by using vernier caliper (Absolute digimatic, Mitutoyo Corp. Japan).

***In vitro* dissolution studies**

The *in vitro* dissolution studies were carried out using USP apparatus type II (Lab India 8000) at 75 rpm. For the first 2 hr the dissolution medium was 0.1N HCl (pH1.2) and phosphate buffer pH 6.8 from 3-18 hr (900 ml), maintained at 37±0.5^{0}C. At each time point 5 ml of sample was withdrawn and it was replaced with 5 ml of fresh medium. The drug release at different time interval was measured by UV-visible spectrophotometer (UV-1800, Shimadzu, Japan)

Statistical data analysis by model independent approach [16]

The difference factor (f_1) calculates the percent error between the drug release profiles of two formulations usually one is test and other is standard over predetermined time points. It is expressed as:

$$f_1 = \frac{\sum_{j=1}^{n}(Rj-Tj)}{\sum_{j=1}^{n} Rj} \times 100 \quad \ldots\ldots\ldots (8)$$

Where n is the sampling number,Rj and Tj are the percent dissolved of the reference and test products at each time point j. Dissolution profile of test formulations are usually said to be satisfactory if f_1 values lie below 15.

The similarity factor (f_2) is a logarithmic transformation of the sum squared error of differences between the test Tj and reference products Rj over all time points.

$$f_2 = 50 \times \log\left[1+\frac{1}{n}\sum_{j=1}^{n} wj(Rj - Tj)2\right]^{-0.5} \times 100 \quad \ldots\ldots (9)$$

Where, wj is an optional weight factor. The similarity factor fits the result between 0 and 100. Generally if f_2>50, the release profiles are deliberated to be similar. For the calculation of similarity and difference factors of all the mentioned formulations in present studies three time points were taken i.e. Ist, 2nd and 3rd hours and dissolution profiles of theoretical release(reference) and test formulations at same time point were used.

***In vitro* drug release kinetic studies [17, 18]**

In order to determine the mode of release from tablets, the release data of formulation was analyzed zero order kinetics, first order kinetics, Higuchi model, Korsmeyer-Peppas equations and Hixson-Crowell equations.

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

$$Q_t = Q_0 - K_0 t \quad \ldots\ldots\ldots (10)$$

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.

First order kinetics for drug release can be expressed by the equation:

$$\text{Log } C = \log C_0 - K_1 t/2.303 \quad \ldots\ldots\ldots (11)$$

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.

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

$$Q = K_H \sqrt{t} \quad \ldots\ldots\ldots (12)$$

Where Q is the amount of drug release in time t, K_H is the Higuchi dissolution constant.

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

$$\text{Log } (M_t/M_\infty) = \text{Log } K + n \text{ Log } t \quad \ldots\ldots\ldots (13)$$

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.

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

$$W_0^{1/3} - W_t^{1/3} = \kappa t \quad \ldots\ldots\ldots (14)$$

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.

Effect of osmogen concentration

Different osmogen [19] concentrations were used to prepare core tablets, considering all the parameters constant. The drug release was compared for different formulated batches by using USP-II dissolution apparatus.

Effect of pore former concentration
Pore former concentrations were varied for various batches in SPM [20]. The effect of pore former on *in vitro* release profile is compared as well as number of formation of micropores were determined.

Effect of membrane thickness
Tablets having varied coating thicknesses were prepared to analyze the effect of coating thickness on drug release. The drug release rate was observed using 0.1N HCl and phosphate buffer pH6.8 as a dissolution medium.

Effect of osmotic pressure [21]
Osmotic pressure effect was analyzed by adding different amount of mannitol of an osmotic agent to produce 30 atm,60 atm and 90 atm respectively in dissolution media 0.1N HCl for 2hrs and phosphate buffer pH 6.8. The drug release rate was carried out in USP type II (Paddle) apparatus at 75 rpm maintained at 37±0.5^{0}C and compared for various dosage forms.

Effect of pH
The effect of pH for core tablets were observed by performing the release studies of optimized formulation in different media 0.1 N HCl (pH 1.2), pH 6.8 phosphate buffer and pH 7.4 phosphate buffer in USP type II dissolution apparatus at 75rpm. The temperature was maintained at 37±0.5°C. The release was studied at predetermined time intervals.

Effect of agitation intensity [22]
Agitation intensity effect were demonstrated by performing the release studies of optimized formulation in USP Type II(Paddle) dissolution apparatus containing 0.1NHCl for first 2hrs and phosphate buffer pH 6.8 for remaining hours at different rotational speeds of 50,100 and 150rpm with maintaining temperature at 37±0.5°C.The samples were withdrawn at predetermined intervals and analyzed by UV spectrophotometer.

Scanning Electron Microscopy (SEM)
Porous morphology [23] of membrane can be studied by taking coating membrane of core formulation before and after complete dissolution of core contents by scanning electron microscope (Leica, Bensheim, Switzerland).The mechanism of drug release was analyzed.

Accelerated stability studies [24]
The packed tablets in air tight container were placed in stability chambers(Thermo lab Scientific equipment Pvt.Ltd.,Mumbai,India) maintained at 40±2^{0}C/75±5% RH conditions for accelerated testing) for 3 months. Tablets were periodically removed and evaluated for physical characteristics, drug content, *in-vitro* drug release etc.

RESULTS ANS DISCUSSION
FTIR studies:
The study of the FTIR spectra of stavudine demonstrated that the characteristic absorption peaks for the N-H bending at 1640.34 cm^{-1},C-H stretching at 2981.35 cm^{-1},C-O stretching at 1054.71 cm^{-1} (Fig. 1) and amine group stretching at 3336.44 cm^{-1}.In the optimized formulation SS5 peaks at 1039.35 and 2916.48cm^{-1} were due to presence of the drug stavudine,peak at 1066.15cm^{-1} was due to presence of the polymer HPMCE5LV and peaks present due to sodium chloride was 670.26 cm^{-1}. Hence from the study it can be observed that the major peaks of drug 1039.35 and 2916.48 cm^1 (Fig. 2) remain unchanged and no interaction was found between the drug, polymer and osmogen.

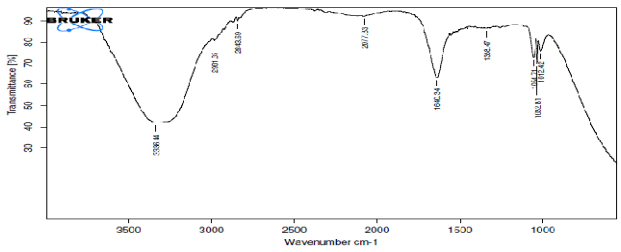


Figure 1: FTIR spectroscopy study of pure stavudine

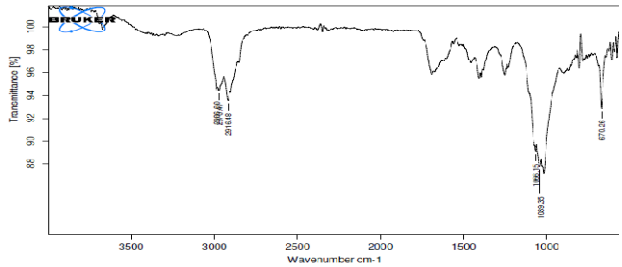


Figure 2: FTIR spectroscopy study of SS5

DSC study
Figure 3 indicates that the endothermic peak of stavudine is at 160.1^{0}C.The endothermic peak of SS5 formulation (Figure 4) is observed at159.8^{0}C.There was no significant changes in the endotherm peak between drug and formulation.

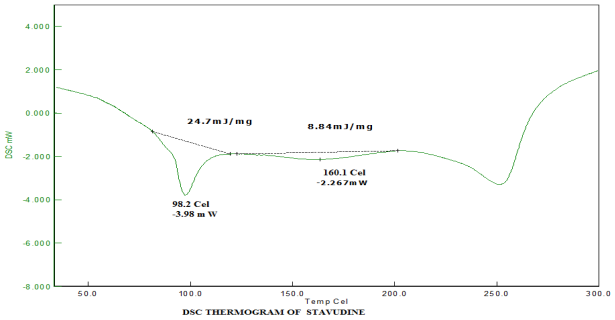


Figure 3: DSC study of stavudine

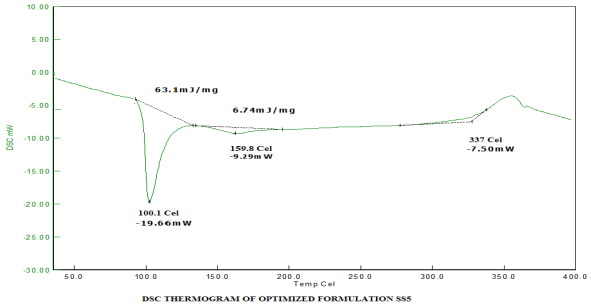


Figure 4: DSC study of SS5

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. It is observed all the parameters fall within specified limit. It is shown it Table 5.

Post compression parameters
All the post compression parameters for various batches evaluated accordingly such as thickness, coat thickness, hardness, friability, weight variation, drug content and diameter of tablet etc. It is observed all the parameters fall within specified limit. It is mentioned in Table 6.

***In vitro* drug dissolution 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 18hrs in phosphate buffer pH 6.8 using USP type II dissolution apparatus (Paddle type).The cumulative percentage drug release for SS1, SS2, SS3, SS4, SS5and SD6 were 83.57, 85.96, 87.42, 90.11, 99.02 and 80.36 respectively of stavudine at the end of 18 hrs.It is shown in figure 5. Similarity (f_2) and difference (f_1) factor were mentioned in Table 7.

Kinetic model
From the kinetic it is observed that SD6 follows non-Fickian transport mechanism and SS1, SS2, SS3, SS4 and SS5 show Fickian diffusion mechanism. It is shown in Table 8.

Effect of osmogen concentration
The various batches of stavudine were developed with various concentrations of osmogens. It was observed that osmogent enhances the drug release of drug and thus had a direct effect on drug release. The drug release profile was shown in figure 6.

Effect of pore former concentration
The core formulations were coated with various concentration of sorbitol with compared to CA. It confirms that as the level of pore former increases the membrane becomes more porous after coming contact with aqueous environment resulting in faster drug release. Release profile of various batches was shown in figure 7

Effect of membrane thickness
Release profiles of stavudine from various batches varying the coating thickness were evaluated. It was clearly evident that drug release was inversely proportional to coating thickness of the semi permeable membrane. It is shown in figure 8.

Effect of osmotic pressure
The drug release for SS5 was found to be 93.01% for 30 atm, 87.28% for 60 atm and 83.14% for 90 atm respectively. Hence it was concluded that drug release was inversely proportional to the osmotic pressure of release media. It is shown in figure 9.

Effect of pH
The optimized formulation SS5 was evaluated for *in vitro* drug release studies in buffers with different pH like 0.1NHCl (pH 1.2), phosphate buffer pH 6.8 and phosphate buffer pH7.4. It was concluded that there was no significant difference in the release profile, demonstrating that the developed formulation showed pH independent release. It is shown in figure 10.

Effect of agitation intensity
The optimized formulation of SS5 batch was carried out in USP dissolution apparatus type-II at varying rotational speed(50,100 and 150rpm).It showed that the release of stavudine from core was independent of agitation intensity and the release from the developed formulation was independent of the hydrodynamic conditions of the absorption site. It is shown in figure 11

Table 5: Pre compression parameters of powder blend

Formulation code	Angle of repose (degree)[a] ± S.D	Bulk density (gm/ml)[b]± S.D	Tapped density (gm/ml)[c] ± S.D	Carr's Index (%)[d] ± S.D	Hausner's Ratio[a] ± S.D
SS1	27.36±0.09	0.476±0.08	0.514±0.12	7.39±0.08	1.07±0.12
SS2	26.63±0.08	0.485±0.12	0.521±0.06	6.91±0.06	1.07±0.08
SS3	25.14±0.06	0.499±0.11	0.544±0.13	8.27±0.14	1.09±0.12
SS4	24.92±0.08	0.491±0.12	0.539±0.06	8.90±0.06	1.09±0.08
SS5	24.36±0.02	0.488±0.08	0.521±0.06	6.33±0.07	1.06±0.08
SD6	26.02±0.06	0.487±0.08	0.538±0.06	9.48±0.07	1.10±0.04

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

Table 6: Post compression parameters of controlled porosity osmotic pump tablets

Formulation code (FC)	Thickness of tablet (mm)[a] ± S.D	Coat thickness (μm)[a] ±S.D	Hardness (kg/cm²)[a] ±S.D	Friability (%)[b] ± S.D	Average weight of 1tablet(mg)[b] ± S.D	%Drug content (%)[a] ± S.D	Diameter (mm)[a] ± S.D
SS1	3.16±0.04	499.9±3.9	7.2±0.04	0.16±0.04	401.2±1.06	101.23±1.13	8.2±0.03
SS2	3.18±0.02	401.7±3.8	6.6±0.02	0.27±0.11	402.3±1.04	98.45±1.09	8.1±0.02
SS3	3.12±0.04	300.8±3.9	7.5±0.01	0.17±0.12	400.8±1.12	99.07±1.05	8.1±0.06
SS4	3.11±0.02	200.4±3.4	7.7±0.03	0.12±0.06	400.2±1.06	99.69±1.04	7.9±0.03
SS5	3.12±0.03	100.9±3.2	7.8±0.04	0.14±0.08	400.1±1.12	100±1.03	8±0.02
SD6	2.99±0.03	501.2±3.5	7.1±0.08	0.21±0.14	400.9±1.12	99.07±1.07	7.9±0.08

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

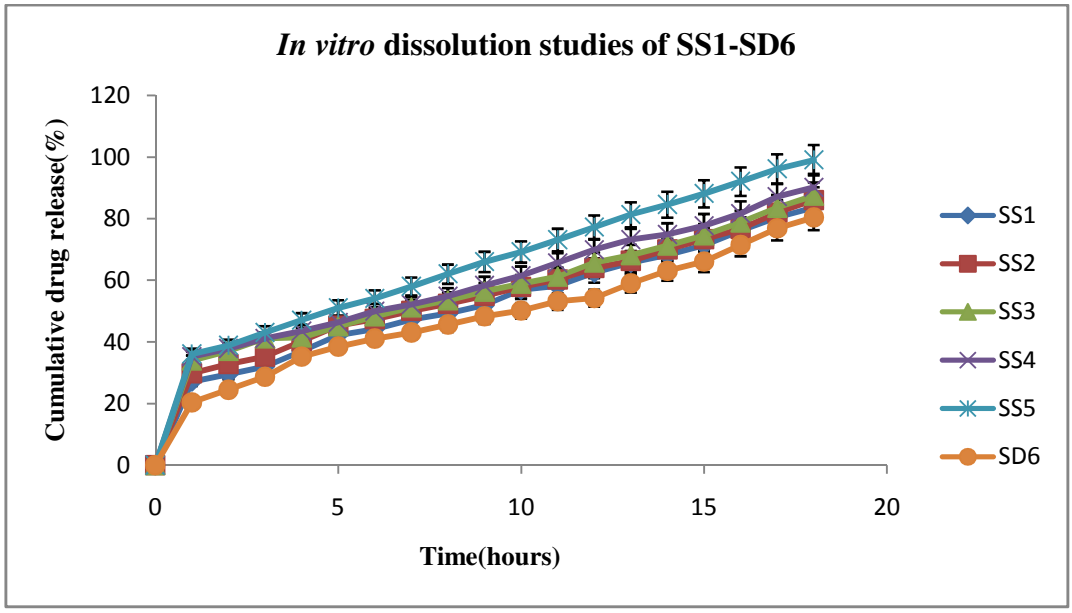


Figure 5: *In vitro* release profiles showing stavudine release from various fabricated formulations SS1-SD6

Table 7: Similarity (f_2) and difference (f_1) factor with dissolution profile of all formulations (SS1 to SD6)

F.No.	Difference factor (f_1)	Similarity factor(f_2)	Dissolution profiles
SS1	25.96	49.01	Dissimilar
SS2	18.32	56.45	Dissimilar
SS3	6.3	78.26	Similar
SS4	4.64	82.85	Similar
SS5	1.41	95.78	Similar
SD6	38.64	40.55	Dissimilar

Table 8: 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
SS1	0.941	3.638	0.953	0.0806	0.978	18.04	0.949	22.490	0.408	0.968	0.095
SS2	0.921	3.571	0.938	0.0829	0.976	17.87	0.952	25.409	0.371	0.956	0.096
SS3	0.902	3.500	0.923	0.0875	0.960	17.57	0.919	28.973	0.326	0.942	0.097
SS4	0.910	3.701	0.925	0.0990	0.966	18.55	0.917	29.444	0.337	0.951	0.108
SS5	0.926	4.262	0.798	0.1750	0.979	21.33	0.941	30.060	0.374	0.929	0.156
SD6	0.949	3.533	0.938	0.0713	0.972	17.40	0.975	18.238	0.461	0.957	0.087

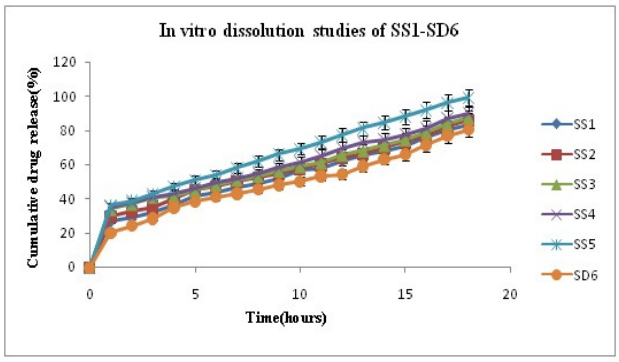


Figure 6: *In vitro* release profiles showing stavudine release from various fabricated formulations SS1-SD6 having different concentration of osmogen

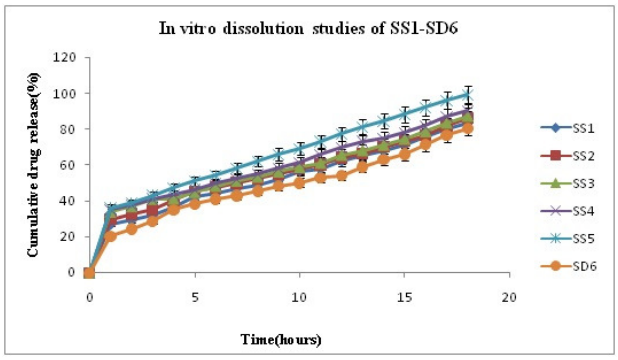


Figure 7: *In vitro* release profiles showing stavudine release from various fabricated formulations SS1-SD6 having different pore formers

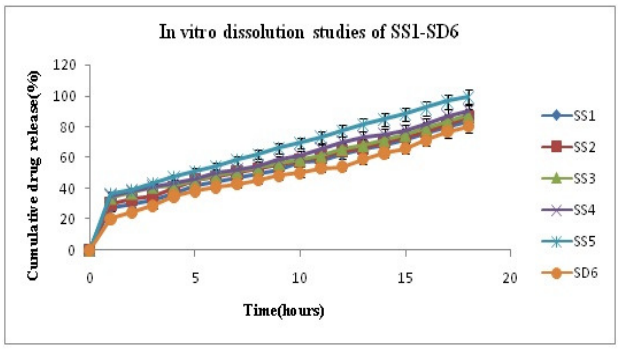


Figure 8: *In vitro* release profiles showing stavudine release from various fabricated formulations SS1-SD6 having different membrane thickness

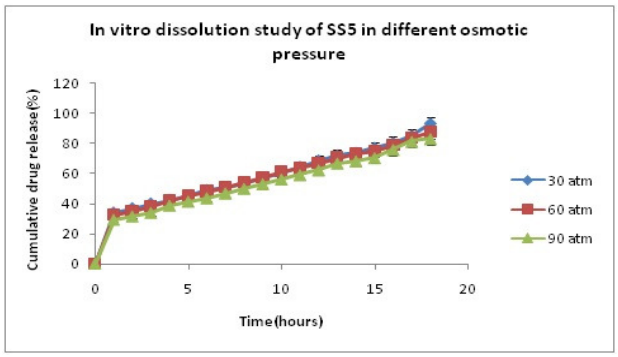


Figure 9: *In vitro* release profiles showing stavudine release from optimized SS5 in different osmotic pressures

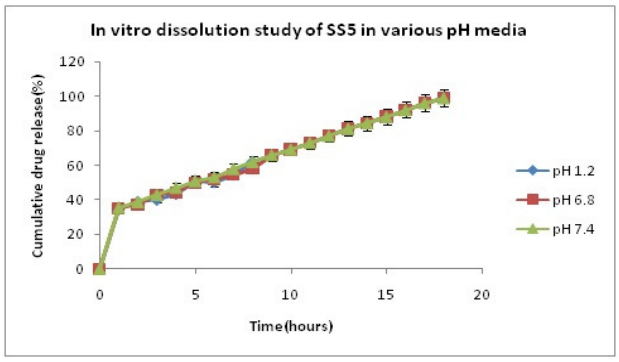


Figure 10: *In vitro* dissolution study of optimized formulation SS5 in various pH media

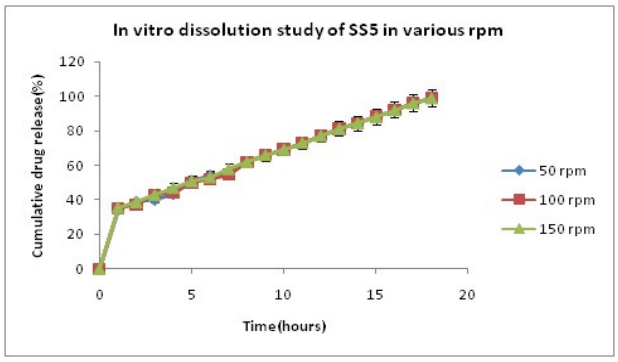
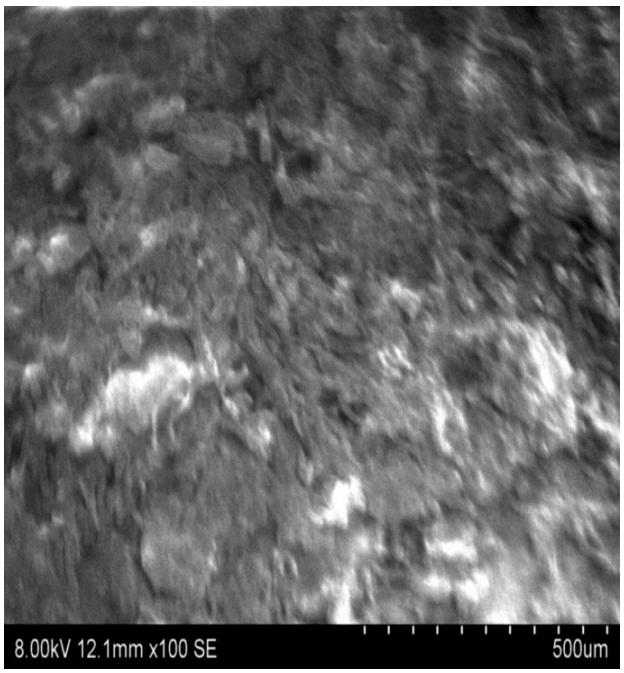
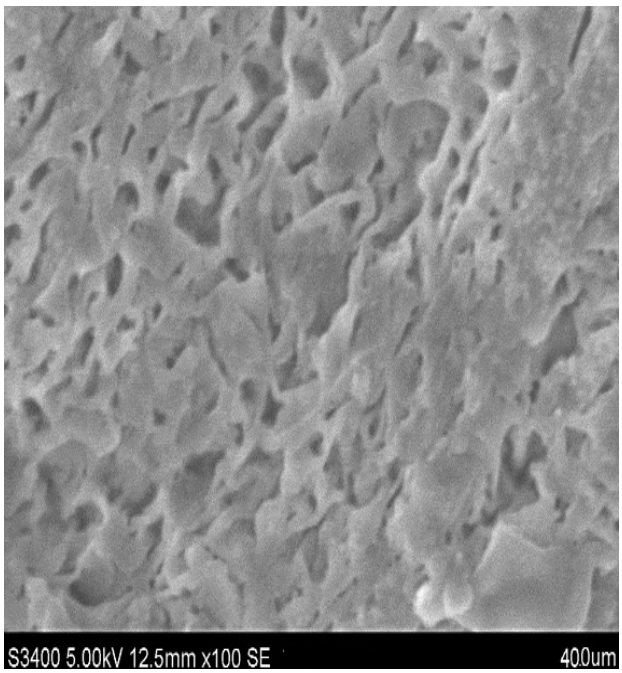


Figure 11: *In vitro* dissolution study of optimized formulation SS5 in various agitational speeds



(a)



(b)

Figure 12: a) SEM micrograph of SPM before dissolution, b) SEM micrograph of SPM after dissolution

SEM analysis

Figure 12a suggesting that there is no evidence of development of pores in the membrane before dissolution study of SS5.On the other hand figure 12b shows that more pore formation after dissolution. When comparison was studied of the membranes containing different levels of porogen, it was observed that the membrane that contained a higher level of porogen became more porous after dissolution studies.

Stability studies

From short term stability studies of optimized formulation SS5, it was confirmed that there was no significance changes in physical appearance, weight variation, %friability, drug content and % drug release.

CONCLUSION

The optimized formulation follows Higuchi kinetics. The release from the optimized formulation was independent of pH and agitation intensity of release media.Stavudine release from the core tablets was directly related to the level of osmotic agent and porogen concentration, but drug release was inversely proportional to the level of coat thickness of membrane. Developed tablets were found to be stable during 3 months of storage at accelerated stability condition. Finally it can be concluded the developed CPOP tablets can control the drug release as well as it can reduce the side effects of conventional tablets.

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