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FORMULATION AND EVALUATION OF STAVUDINE EXTENDED RELEASE TABLETS

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ABSTRACT

Stavudine is a prescription medicine used to treat AIDS and HIV infection. Stavudine belongs to a group of medications known as nucleoside reverse transcriptase inhibitors (also known as NRTIs). Stavudine is an extremely metabolized drug on oral administration. Due to its sudden metabolism the t1/2 of Stavudine has been decreased to 0.5 hrs which is major limitation for Stavudine as immediate release dosage form. Therefore the present investigation is concerned with the development of Stavudine extended release (ER) tablets by using different hydrophobic and hydrophilic polymers like Ethocel (ethyl cellulose), Methocel (Hydroxy propyl methyl cellulose) polymers in different ratios. Stavudine along with polymers and other ingredients were directly mixed and compressed by using rotary tablet punching machine (Cadmach). After formulation those tablets were evaluated for weight variation, content uniformity, In-Vitro drug release, and stability. Eight combinations having polymers at different proportions were prepared to access their efficacy. Tablets containing 90% ethyl cellulose and 10% hydroxyl propyl methyl cellulose showed superior organoleptic properties and In-Vitro drug release studies as compared to other formulations. The kinetic model of the release data indicates that Stavudine release from the tablets followed Korsemayer-Peppas model and release was found to be Case-II transport (polymer swelling). Thus the release from the prepared formulations was found to be diffusion controlled.

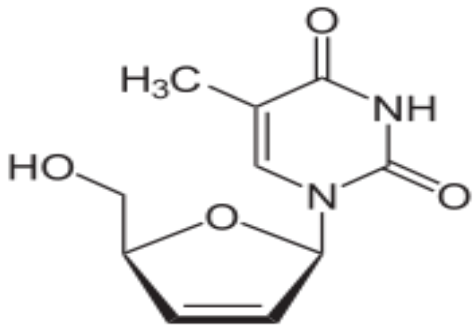
KEY WORDS: Formulation, Evaluation, Stavudine, Extended Release.

INTRODUCTION

The first commercial oral extended-release formulation [1] was the pellet-filled capsule (Spansules®) [2] which was introduced in the 1950 by Smith, Kline and French. Spansule capsules were formulated by coating a drug onto nonpareil sugar beads and further coating with glyceryl stearate and wax. Since then, a number of strategies have been developed to obtain extended release of a drug in the body [3]. These vary from simple matrix tablets or pellets to more technologically sophisticated extended-release systems which have been introduced into the marketplace. Successful commercialization of an extended release dosage form is usually challenging and involves consideration of many factors such as the physicochemical properties of the drug [nature and form of the drug, Biopharmaceutical Classification System (BCS) class, dose and stability of the drug in the gastrointestinal (GI) tract], physiological factors (route of administration, site and mode of absorption, metabolism and elimination) and manufacturing variables (choice of excipients, equipment and manufacturing methods).

Stavudine

Structure of Stavudine



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Systemic (IUPAC) name:
1-((2R,5S)-5-(hydroxymethyl)-2,5-dihydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione
Molecular Formula: $C_{10}H_{12}N_2O_4$
Molecular Mass: 224.213 g/mol
Half-Life: 0.8-1.5 hours (in adults)

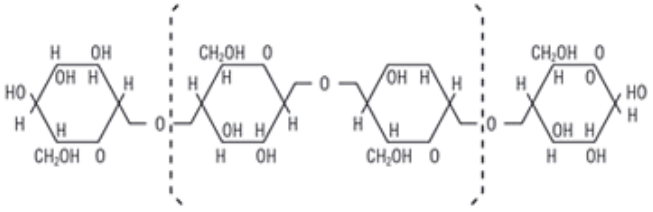
Mechanism of action

Stavudine is an antiviral drug. Stavudine is an analog of thymidine. It is phosphorylated by cellular kinases into active triphosphate [4]. Stavudine triphosphate inhibits the HIV reverse transcriptase by competing with natural substrate, thymidine triphosphate. It also causes termination of DNA replication by incorporating into the DNA strand. Simultaneous use of zidovudine is not recommended, as it can inhibit the intracellular phosphorylation of stavudine. Other anti-HIV drugs do not possess this property.

Uses

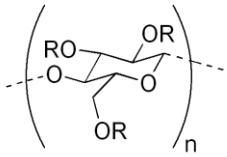
Stavudine is a prescription medicine used to treat AIDS and HIV infection. Stavudine belongs to a group of medications known as nucleoside reverse transcriptase inhibitors (also known as NRTIs) [5]. Acquired Immune Deficiency Syndrome (commonly known as AIDS) was initially reported in the United States in 1981. Since then, it has become a significant, worldwide epidemic. AIDS is caused by the human immunodeficiency virus (HIV).

Cellulose, Microcrystalline
Structural Formula



Nonproprietary Names
BP: Microcrystalline cellulose
JP: Microcrystalline cellulose
PhEur: Cellulosum microcristallinum
USPNF: Microcrystalline cellulose
Synonyms: Avicel PH, Celex, cellulose gel, Celphere, Ceolus KG, crystalline cellulose, E460, Emcocel, Ethispheres, Fibrocel, Pharmacel, Tabulose, Vivapur.
Chemical Name: Cellulose
Empirical Formula and Molecular Weight
$(C_6H_{10}O_5)n$ ≈36 000; Where n ≈220.
Typical properties
Angle of repose: 498 for Ceolus KG; 34.48 for Emcocel 90M.
Density (bulk): 0.337 g/cm3; 0.32 g/cm3 for Avicel PH-102
Density (tapped): 0.478 g/cm3; 0.45 g/cm3 for Avicel PH-102
Density (true): 1.512–1.668 g/cm3
Flowability: 1.41 g/s
Melting point: chars at 260–270^{0}C.
Moisture content: Typically less than 5% w/w. However, different grades may contain varying amounts of water. Microcrystalline cellulose is hygroscopic.
Solubility: slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

Hypromellose
Structural Formula



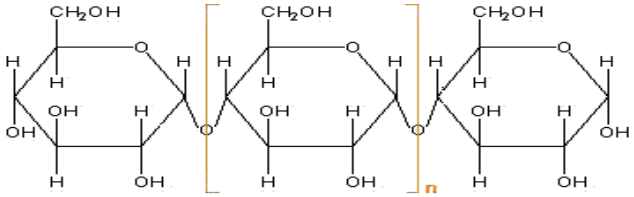
R = H or CH_3 or $CH_2CH(OH)CH_3$

Nonproprietary Names
BP: Hypromellose
JP: Hydroxypropylmethylcellulose
PhEur: Hypromellosum
USP: Hypromellose
Synonyms: Benecel MHPC, E464, hydroxypropyl methylcellulose, HPMC, Methocel, methylcellulose propylene glycol ether, methyl hydroxypropylcellulose, Metolose, Tylopur.
Chemical Name: Cellulose hydroxypropyl methyl ether
Empirical Formula and Molecular Weight

The PhEur 2005 describes hypromellose as a partly Omethylated and O-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 20^{0}C.
Functional Category: Coating agent, film-former, rate-controlling polymer for sustained release; stabilizing agent; suspending agent, tablet binder, viscosity-increasing agent.
Density (bulk): 0.341 g/cm^3
Density (tapped): 0.557 g/cm^3
Density (true): 1.326 g/cm^3
Melting point: browns at 190–200^{0}C; chars at 225–230^{0}C. Glass transition temperature is 170–180^{0}C.
Moisture content: Hypromellose absorbs moisture from the atmosphere; the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air.
Solubility: Soluble in cold water, forming a viscous colloidal solution, practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane and mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone

solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents.

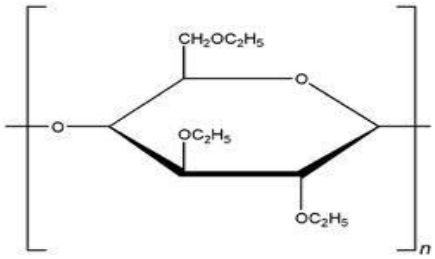
Starch, Pregelatinized
Structural Formula



Synonyms: Compressible starch, Instastarch, Lycatab C, Lycatab PGS, Merigel, National 78-1551, Pharma-Gel, Prejel, Sepistab ST 200, Spress B820, Starch 1500 G, Tablitz, Unipure LD, Unipure WG220.
Chemical Name: Pregelatinized starch
Empirical Formula and Molecular Weight
$(C_6H_{10}O_5)$ n where n = 300–1000

Functional Category: Tablet and capsule diluent, tablet and capsule disintegrant, tablet binder.

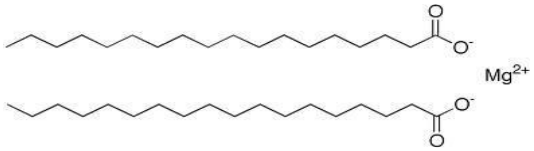
Ethyl Cellulose
Structural Formula



Nonproprietary Names
BP: Ethylcellulose
PhEur: Ethylcellulosum
USPNF: Ethylcellulose
Synonyms: Aquacoat ECD; Aqualon; E462; Ethocel; Surelease.
Chemical Name and CAS Registry Number
Cellulose ethyl ether [9004-57-3]
Empirical Formula and Molecular Weight
Ethyl cellulose with complete ethoxyl substitution (DS = 3) is $C_{12}H_{23}O_6(C_{12}H_{22}O_5)nC_{12}H_{23}O_5$ where n can vary to provide a wide variety of molecular weights. Ethyl cellulose, an ethyl ether of cellulose, is a long chain polymer of b-anhydroglucose units joined together by acetal linkages.
Functional Category: Coating agent; flavoring fixative; tablet binder; tablet filler; viscosity-increasing agent.

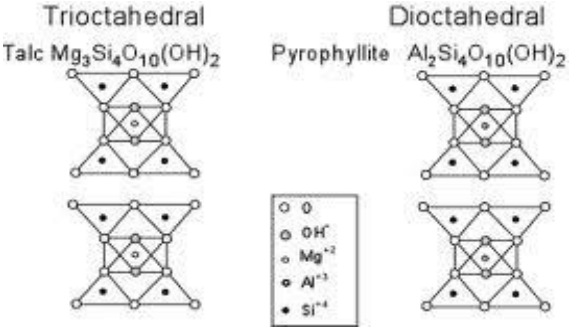
Magnesium Stearate
Nonproprietary Names
BP: Magnesium stearate
JP: Magnesium stearate
PhEur: Magnesii stearas
USPNF: Magnesium stearate

Structural Formula



Synonyms: Magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt.
Chemical Name and CAS Registry Number
Octadecanoic acid magnesium salt [557-04-0]
Empirical Formula and Molecular Weight
$C_{36}H_{70}MgO_4$ 591.34
Functional Category: Tablet and capsule lubricant.

Talc
Structural Formula



Nonproprietary Names
BP: Purified talc
JP: Talc
PhEur: Talcum
USP: Talc
Synonyms: Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Luzenac Pharma; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore.
Chemical Name: Talc
Empirical Formula and Molecular Weight: Talc is a purified, hydrated, magnesium silicate, approximating to the formula $Mg_6(Si_2O_5)_4(OH)_4$. It may contain small, variable amounts of aluminum silicate and iron.
Functional Category: Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

MATERIALS AND METHODS

Determination of the organoleptic properties of Stavudine

Usually it is difficult to measure organoleptic properties since there are no standard laboratory tests for

this and requires personnel that are well experienced with the process. In this study the following organoleptic properties were assessed physical appearance, odor and taste. For these samples of stavudine powder was inspected and assessed using the natural senses (e.g. eyes, nose and mouth).

Standard graph for Stavudine

Step – 1: Preparation of standard stock solution

An accurately weighed quantity of 50 mg of Stavudine was taken in a 100 ml standard flask. To this equal volume of distilled water was added and made up to the volume.

Step – 2: Preparation of sample solution

Different aliquots (0.2, 0.4, 0.6,…… , 2.0 mL) of Stavudine solution were accurately measured from the above primary stock and transferred into a series of 100 mL volumetric flasks and volume made up to the mark with distilled water. Then all dilutions were scanned by UV Spectrophotometer at 265nm against blank and the results were tabulated and a plot was drawn between concentration (µg/ml) on x-axis and absorbance (nm) over y-axis.

Pre compression evaluation parameters

Pre compression parameters mainly includes

Drug-Excipients compatibility study

FT-IR spectroscopy

FT-IR patterns were studied by Shimadzu 8400S, Japan FT-IR spectrometer. The samples (Stavudine and Excipients) were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample: KBr) ratio, respectively [6]. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. The scans were obtained at a resolution of 4 cm^{-1}, from 4000 to 400 cm^{-1}.

Angle of Repose

The angle of repose [7] or the critical angle of repose, of a granular material is the steepest angle of descent or dip of the slope relative to the horizontal plane when material on the slope face is on the verge of sliding. This angle is in the range of 0°–90°. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane.10 gm of powder was allowed to flow by funnel from 4 cm of height from the base. The height of pile and diameter of base was measured and the angle of repose was calculated by following formula

$$\tan \theta = h/r$$

$$\theta = \tan^{-1} h/r$$

Where, Θ = angle of repose, h = Height of the heap, r = Radius of the heap.

Bulk Density

The bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume including the contribution of the inter particulate void volume.

An accurately weighed quantity of powder, which was previously passed through sieve # 40 [USP] and carefully poured into graduated cylinder. Then after pouring the powder into the graduated cylinder the powder bed was made uniform without disturbing. Then the volume was measured directly from the graduation marks on the cylinder as ml. The volume measured was called as the bulk volume and the bulk density is calculated by following formula;

Bulk density = Weight of powder / Bulk volume

Tapped Density

The tapped density is an increased bulk density attained after mechanically tapping a container containing the powder sample. After measuring the bulk volume the same measuring cylinder was set into tap density apparatus. The tap density apparatus was set to 300 taps drop per minute and operated for 500 taps. Volume was noted as (V_a) and again tapped for 750 times and volume was noted as (V_b). If the difference between V_a and V_b not greater than 2% then V_b is consider as final tapped volume. The tapped density is calculated by the following formula

Tapped density = Weight of powder / Tapped volume

Carr's Index [Compressibility Index]

It is one of the most important parameter to characteristic the nature of powders and granules. It can be calculated from the following equation

Carr's index = Tapped density - Bulk density / Tapped density X 100

Hausner's Ratio

Hausner's ratio [8] is an important character to determine the flow property of powder and granules. This can be calculated by the following formula

Hausner's ratio = Tapped density / Bulk density

HR<1.25-indicates good flow property

HR>1.25-indicates poor flow property.

Post-compression evaluation parameters

After compression of desired doses of drug and its excipients into suitable tablet dosage form, each batch was subjected to the following evaluation parameters which includes

Weight variation

Weight variation was measured by weighing 20 Tablets and average weight was found and percentage weight variation of the individual tablet should fall within specified limits in terms of percentage deviation from the mean.

Thickness & Diameter

Thickness & diameter of tablet was measured by Vernier calipers.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablet was determined using Monsanto hardness tester. It is expressed in kg/cm2. It was determined by picking three/more tablets from batch and hardness was determined.

Drug content

20 tablets were collected from each batch, finely powdered and an amount equivalent to 100mg of stavudine was accurately weighed and transferred to a 100ml volumetric flask, then 70ml of buffer pH 2(0.01 N HCl) was added. The flask was shaken for 10 min. Finally, the volume was made up to the mark with the same buffer solution. The resultant solution was then filtered and 1ml of the filtrate was suitably diluted up to 100ml with same buffer solution and analyzed for stavudine content at 265nm using a double beam UV/Vis spectrophotometer by taking 0.01N HCl as blank and the results was tabulated.

Friability

It was determined using Roche friabilator, the percentage loss in tablet weight before (W0) and after (W), 100 revolutions of 10 tablets at 25rpm for 4 min were calculated and taken as a measure for friability. The % friability was then calculated by

$$F(\%) = \frac{(W_{initial}) - (W_{final})}{(W_{initial})} X\,100$$

***In vitro* dissolution studies**

The studies were done on eight station USP dissolution apparatus I (Lab India). All batches of tablets were evaluated using 900 ml of sequential gastrointestinal release medium, i.e. 0.1N hydrochloric acid (pH 1.2) for first two hours, and then phosphate buffer of pH 7.4 for remaining 10 hours. Temperature was maintained at 37 ± 0.5°C throughout the study and stirring at 50 rpm was carried out. Samples were collected periodically, filtered through 0.45 micron filter and replaced with fresh dissolution medium. After filtration samples were properly diluted and Stavudine concentrations were analyzed spectrophotometrically at 265 nm. The percentage drug released at time interval was calculated and plotted against time.

Mathematical modeling for drug release profile

The cumulative amount of Stavudine released from the formulated tablets at different time intervals were fitted in to several kinetic models such as Zero order kinetics, First order kinetics, Higuchi model and Korsemayer-peppas model to characterize mechanism of drug release.

Zero order kinetics

It describes the system in which the drug release rate is independent of its concentration.

$$\mathbf{Q_t = Q_0 + K_0\,t}$$

Where, Q_t = amount of drug dissolved in time "t"
Q_0 = initial amount of drug in the solution
K_0 = Zero order release constant

If the zero order release kinetic is obeyed, then a plot of Q_t vs. t will give a straight line with a slope of K_0 and an intercept at zero. To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as cumulative amount of drug released vs. time.

First order kinetics

It describes the drug release from the systems in which the release rate is concentration dependent.

$$\mathbf{Log\ Q_t = Log\ Q_0 + K_1 t/2.303}$$

Where, Q_t = amount of drug release in time "t"
Q_0 = initial amount of drug in the solution
K_1 = first order release constant
If the release pattern of drug follows first order kinetics, then a plot of log (Q_0-Q_t) versus t will be a straight line with a slope of $K_{1/2.303}$ and an intercept at t=0 of logQ_0. The data obtained are plotted as log cumulative percentage of drug remaining vs. time.

Higuchi model

It describes the fraction of drug release from a matrix is proportional to square root of time [9].

$$\mathbf{M_t/M_\alpha = KHt_{1/2}}$$

Where, M_t & M_α = cumulative amounts of rug release at time "t" and infinite time
KH = Higuchi dissolution constant reflection formulation characteristics.

If the Higuchi model of drug release (*i.e.*, Fickian diffusion) is obeyed, then a plot of M_t/M_α vs. $t_{1/2}$ will be a straight line with a slope of KH. The data obtained were plotted as cumulative percentage drug release vs. square root of time.

Korsemayer-Peppas model (Power law)

The powerful law describes that the fractional amount of drug release is exponentially related to the release time and adequately describes the release of drug from slabs, cylinders and spheres.

$$\mathbf{M_t/M_\alpha = Ktn}$$

$$\mathbf{Log\ [M_t/M_\alpha] = Log\ K + n\ log\ t}$$

Where, Mt & Mα = cumulative amounts of rug release at time "t" and infinite time
K = constant incorporating structural and geometrical characteristics of CR device
n = diffusional release exponent indicative of the mechanism of drug release for drug
dissolution.

A plot of log (drug release) versus log t will be linear with slope of n and intercept gives the value of log k.

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as log cumulative percentage drug release vs. log time.

- n = 0.5, indicates pure Fickian diffusion.
- n = 0.5-1 or 0.45-0.89 indicates anomalous non-Fickian diffusion *i.e.*, the rate of solvent penetration and drug release are in the same range. This deviation is due to increased drug diffusivity from the matrix by the solvent-induced relaxation of the polymers.

n = 0.89 or 1 indicates zero-order release which can be achieved when drug diffusion is rapid compared to the constant rate of solvent induced relaxation and swelling in the polymer (case 2 transport for swellable polymer).

Stability studies

Overall observations from different evaluation studies such as drug-polymer interactions, evaluation of prepared formulations and drug release studies were carried out. Based on the obtained results best formulation was subjected for further stability study. The stability study was conducted as per ICH guidelines for the period of three months at various accelerated temperature and humidity conditions of 25°C/60%RH, 40°C/70%RH, 60°C/80%RH.

Table 1. Standard limits of angle of repose

S. No	Angle of Repose(Θ)	Type of Flow
1	<25	Excellent
2	25-30	Good
3	30-40	Passable
4	>40	Very poor

Table 2. Standard limits of compressibility/Carr's index

S. No	Carr's Index	Type of Flow
1	5-15	Excellent
2	12-18	Good
3	18-23	Fair to passable
4	23-35	Poor
5	35-38	Very poor
6	>38	Extremely poor

Table 3. Standard limits for % deviation of weight of tablets

S. No	Avg. wt. of Tablet	% Deviation
1	<80mg	10
2	80mg-250mg	7.5
3	>250mg	5

Table 4. Diffusional exponent 'n' and mechanism of diffusional release from swellable controlled release systems of different geometrics

Slab	Cylinder	Sphere	Drug release mechanism
0.5	0.45	0.43	Fickian diffusion
0.5-1.5	0.45-0.89	0.43-0.85	Anomalous transport (Non-Fickian)
1.0	0.89	0.85	Zero order
1.0	0.89	0.85	Case 2 transport
1.0	1.0	1.0	Super case 2 transport

RESULTS AND DISCUSSION

Table 5. Calibration curve results for Stavudine extended release tablets at 265nm

S. No	Conc. (µg/ml)	Absorbance at 265 nm
0	0.0	0
1	0.2	0.073
2	0.4	0.162
3	0.6	0.251
4	0.8	0.341
5	1.0	0.428

6	1.2	0.511
7	1.4	0.592
8	1.6	0.681
9	1.8	0.772
10	2.0	0.872

Table 6. Micromeritic parameters for Stavudine extended release tablets

S. No	Bulk density	Tapped density
STV1	0.370	0.495
STV2	0.359	0.515
STV3	0.348	0.535
STV4	0.359	0.515
STV5	0.370	0.495
STV6	0.348	0.535
STV7	0.359	0.520
STV8	0.348	0.515

Table 7. Micromeritic parameters for Stavudine extended release tablets (cont...)

S. No	Angle of Repose (θ)	Carr's index (%)	Hausner's Ratio
STV1	0.564	25.1	1.33
STV2	0.543	30.2	1.43
STV3	0.522	35.1	1.53
STV4	0.543	30.2	1.43
STV5	0.564	25.1	1.33
STV6	0.522	35.1	1.53
STV7	0.552	32.1	1.50
STV8	0.567	34.7	1.55

Table 8. Post compression results for Stavudine extended release tablets

S. No	Tablet dimensions		Weight variation (g)	Hardness (N)
	Thickness (mm)	Diameter (mm)		
STV1	3.52	13	497±0.5	5.2
STV2	3.48	13	498±0.1	5.1
STV3	3.50	13	499±0.4	5.4
STV4	3.55	13	496±0.9	5.5
STV5	3.49	13	497±0.8	5.7
STV6	3.51	13	496±0.5	5.4
STV7	3.54	13	499±0.1	5.5
STV8	3.47	13	498±0.4	5.4

Table 9. Post compression results for Stavudine extended release tablets

S. No	Friability		Content uniformity (%)
	Fines (%)	No of broken tablets	
STV1	0.152	None	98.3±0.5
STV2	0.180	None	98.5±0.1
STV3	0.210	None	99.0±0.6
STV4	0.131	None	96.2±0.7
STV5	0.119	None	97.10±0.1
STV6	0.152	None	99.05±0.6
STV7	0.172	None	98.01±10
STV8	0.110	None	97.01±0.5

Table 10. *In-vitro* drug release profiles of extended release stavudine tablets all formulations

Time (hrs)	Cumulative % drug release							
	STV-1	STV-2	STV-3	STV-4	STV-5	STV-6	STV-7	STV-8
1	12.1	11.89	11.68	11.47	11.26	11.05	10.84	10.6
2	26.3	25.03	23.76	22.49	21.22	19.95	18.68	17.4
3	35.4	34.56	33.72	32.88	32.04	31.2	30.36	29.5
4	46.3	44.88	43.46	42.08	40.62	39.2	37.78	36.3
5	58.4	56.55	54.7	52.85	51	49.15	47.3	45.4
6	69.1	66.85	64.6	62.35	60.1	57.85	55.6	53.3
7	83.4	79.98	76.56	73.14	69.72	66.3	62.88	59.46
8	96.6	97.2	87.85	81.24	79.24	74.4	69.89	67.1
9	---	---	98.2	89.3	88.79	82.55	76.99	78.4
10	---	---	---	97.4	98.3	89.65	84.18	83.2
11	---	---	---	---	---	97.2	91.43	89.2
12	---	---	---	---	---	---	97.8	98.4

Table 11. *In-vitro* drug release kinetics data for formulation F1

Zero order		First order		Higuchi		Korsemayer-peppas	
Time	Cumulative % Drug Release	Time	Log Cumulative % Drug Remaining	SQRT Of Time	Cumulative % Drug Release	Log time	Log Cumulative % Drug Release
1	12.1	1	1.94	1	12.1	0	1.08
2	26.3	2	1.86	1.41	26.3	0.30	1.41
3	35.4	3	1.81	1.73	35.4	0.47	1.54
4	46.3	4	1.72	2	46.3	0.60	1.66
5	58.4	5	1.61	2.23	58.4	0.69	1.76
6	69.1	6	1.48	2.44	69.1	0.77	1.83
7	83.4	7	1.22	2.64	83.4	0.84	1.92
8	96.6	8	0.53	2.82	96.6	0.90	1.98

Table 12. *In-vitro* drug release kinetics data for formulation F2

Zero order		First order		Higuchi		Korsemayer-peppas	
Time	Cumulative % Drug Release	Time	Log Cumulative % Drug Remaining	SQRT Of Time	Cumulative % Drug Release	Log time	Log Cumulative % Drug Release
1	11.89	1	1.945	1	11.89	0	1.075
2	25.03	2	1.874	1.41	25.03	0.30	1.398
3	34.56	3	1.815	1.73	34.56	0.47	1.538
4	44.88	4	1.741	2	44.88	0.60	1.652
5	56.55	5	1.637	2.23	56.55	0.69	1.752
6	66.85	6	1.520	2.44	66.85	0.77	1.825
7	79.98	7	1.301	2.64	79.98	0.84	1.902
8	97.2	8	0.447	2.82	97.2	0.90	1.987

Table 13. Stability testing (Moisture content)

Sample no	Initial weight(g)	Final weight(g)	Difference (g)	Percentage of Moisture (%)
1	0.835	0.822	0.013	1.5 %
2	0.832	0.820	0.012	1.4 %
3	0.833	0.817	0.016	1.9 %
Avg				1.6 %

Table 14. Stability studies In-vitro dissolution profile of STV-8

S. No	Medium	Time	% drug release of STV-8		
			Batch-1 (25°C/60%RH)	Batch-2 (40°C/70%RH)	Batch-3 (60°C/80%RH)
1	0.1 N HCl	1	10.2	11.1	12.9

2		2	17.1	17.8	19.5
3	7.4 Phosphate buffer	3	28.9	29.4	32.5
4		4	35.9	37.3	47.9
5		5	44.7	47.7	55.2
6		6	52.9	54.2	63.4
7		7	59.1	61.5	70.3
8		8	66.6	68.2	79.8
9		9	78.0	79.9	84.6
10		10	82.6	85.4	98.2
11		11	89.1	91.7	-
12		12	98.4	98.9	-

Fig. 1. Calibration curve for Stavudine at 265nm

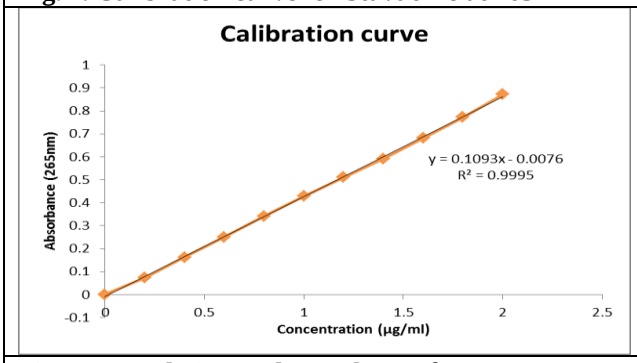


Fig. 2. Cumulative % drug release of STV-1 to STV-4

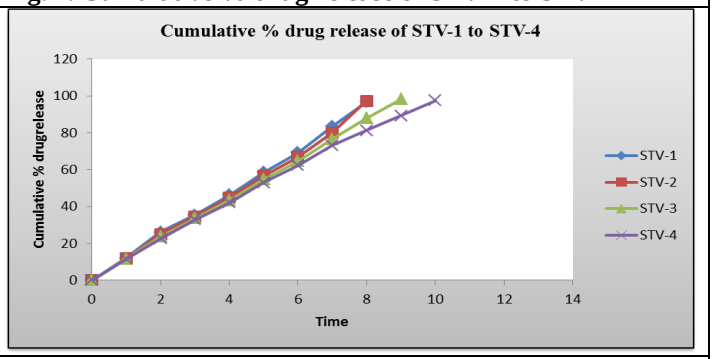


Fig. 3. Cumulative % drug release of STV-5 to STV-8

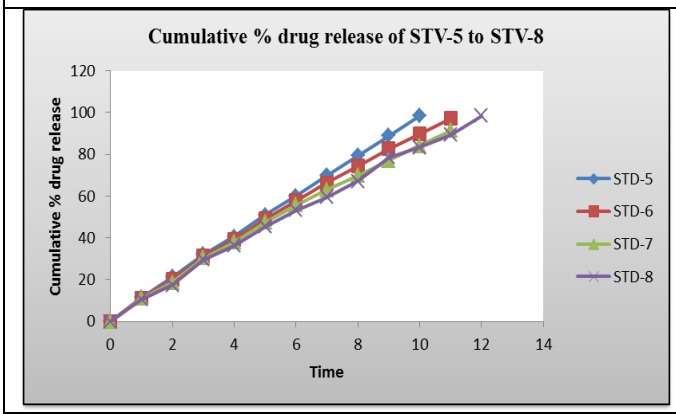


Fig. 4. *In-vitro* drug release kinetics data (Zero order plots) for STV-1 to STV-4

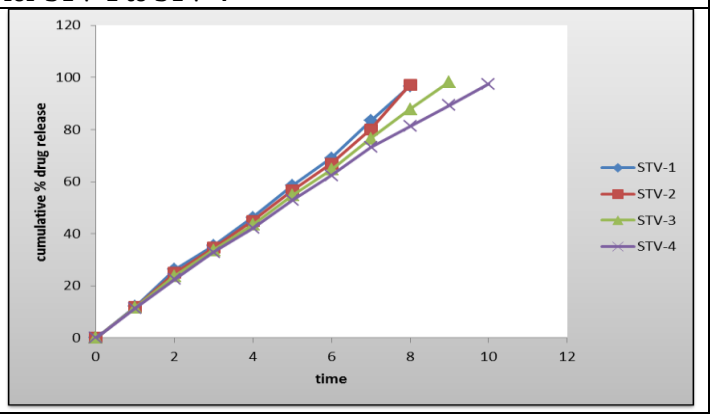


Fig. 5. *In-vitro* drug release kinetics data (Zero order plots) for STV-5 to STV-8

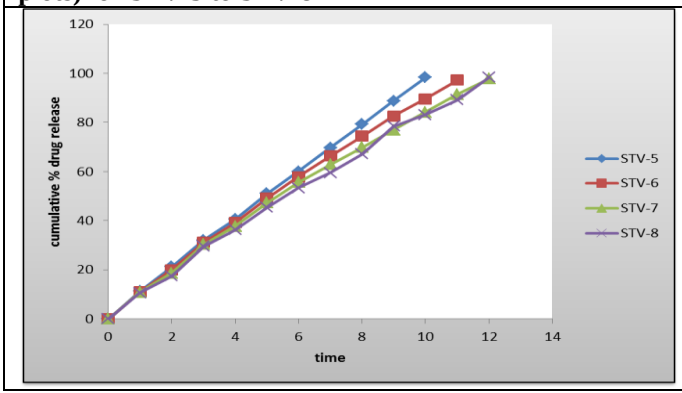


Fig. 6. *In-vitro* drug release kinetics data (First order plots) for STV-1 to STV-4

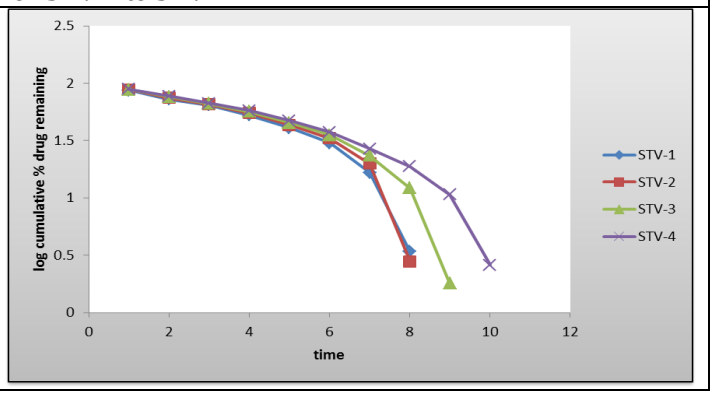


Fig. 7. FT-IR Spectra of Stavudine (pure drug)

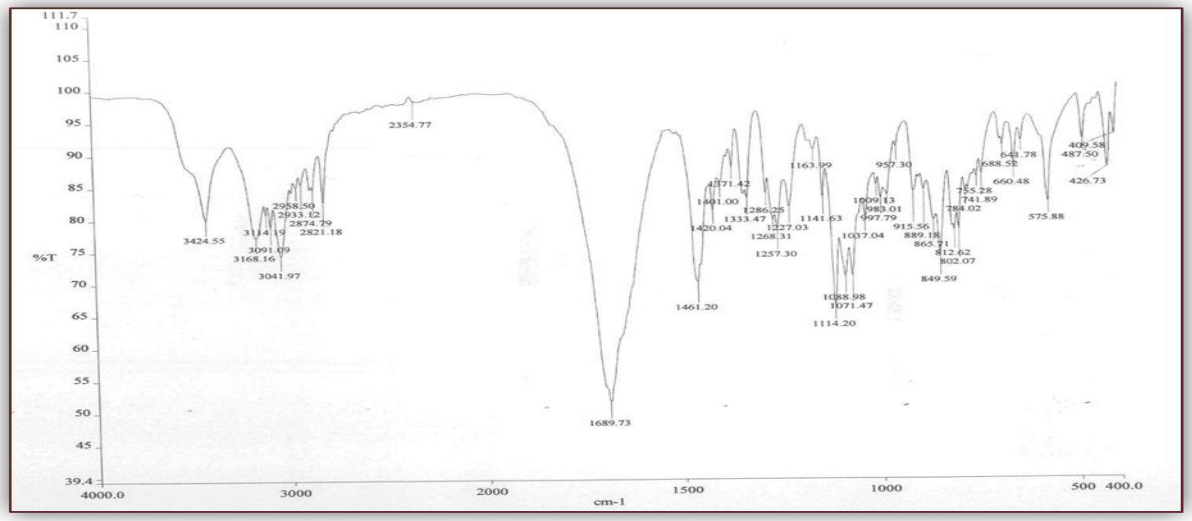


Fig. 8. FT-IR Spectra of HPMC K4M

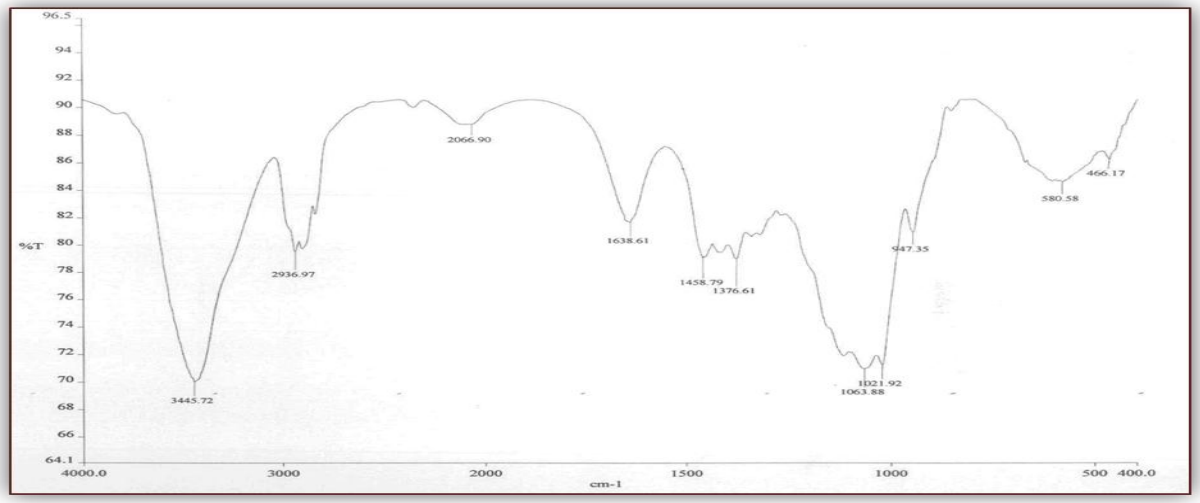
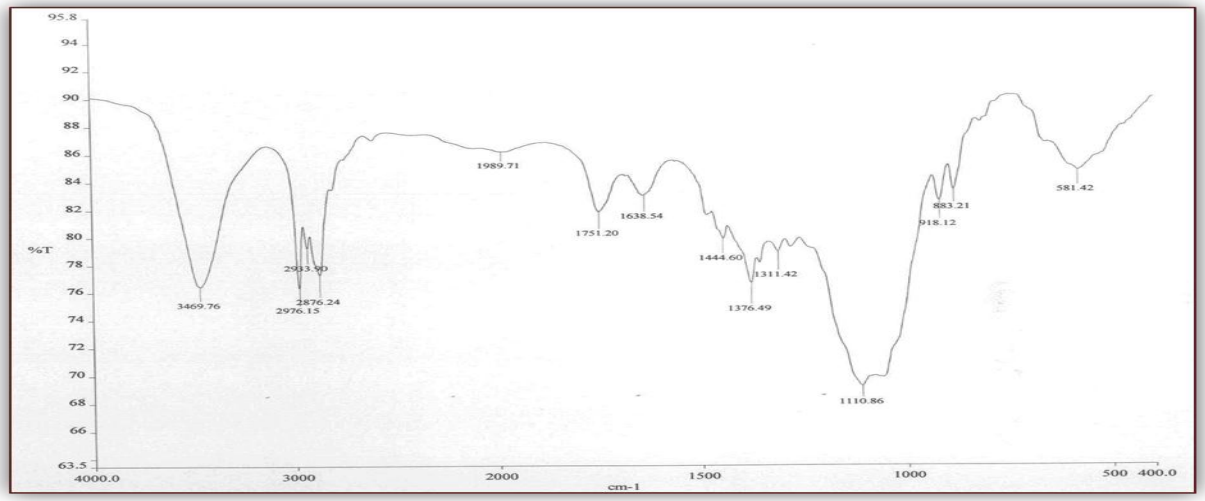


Fig. 9. FT-IR Spectra of Ethyl cellulose



Stavudine belongs to a group of medications known as nucleoside reverse transcriptase inhibitors (also known as NRTIs). From FT-IR results it is evident that pure drug-Stavudine was compared with drug with mixture of excipients and there is no characteristic change in the above peaks. FT-IR results confirm that there was no any chemical interaction between the pure drug and excipients.

From the micromeritic properties it was observed that Stavudine drug alone due to its amorphous nature shows poor flow properties when compared to the formulations which show good flow properties. Post-formulation parameters concluded that there should be certain amount of strength or hardness and resistance to friability for the tablet, so that tablet should not break during handling. However, it has also effect on drug dissolution. Average hardness of Stavudine extended tablet ranges from 7.3±0.34 to 6.2±0.65 kg/cm^2. Friability studies of extended release tablets are in the range of 0.110 % to 0.210%. This indicates that acceptable resistance is shown by the tablets to withstand handling.

In-vitro dissolution studies revealed that, with increase in the concentration of ethyl cellulose, the percent drug release was also increased. In all the formulations the drug release was seen for twelve hours. Among all the formulations, formulation STV-8 showed optimum release profile indicating it to be the best formulation in present research.

The stability tests were conducted on formulation STV-8 which is considered to be the best. The formulation was analyzed for its organoleptic properties, moisture content and dissolution profile. The results showed that the color and gross nature of tablets was slightly changed for batch-3 (which kept at 60°C/80%RH). No changes were found in batch-1&2 (which kept at 25°C/60%RH & 40°C/70%RH). The percentage of moisture content of formulation STV-8 was increased highly when the tablets are kept outside the container at room temperature and relative humidity. STV-8 released the drug at a faster rate when stored at 60°C/80%RH (Batch-3) which may be due to the degradation of polymer.

Although model independent methods are simple and easy to apply, they lack scientific justification. Hence different model dependent approaches (Zero order, First order, Higuchi, Korsemayer- Peppas plots) were performed for dissolution profile comparison of all extended release tablets. The results of these models follow Korsemayer-Peppas model as "best fit model" follows diffusion mechanism. This is due to previously proved fact depending on R^2 value obtained from model fitting. From the results, STV-8 shows more retarding effect. It is thus found that T_{50} % value increases as concentration of EC increases. Korsemayer - Peppas release exponent (n) values of all Stavudine extended release tablets are greater than 0.85 indicating drug diffusion is rapid compared to the constant rate of solvent induced relaxation and swelling in the polymer (case 2 transport for swellable polymer).

CONCLUSION

From the results it was concluded that the formulation STV-8 (Drug with 90% ethyl cellulose and 10% HPMC) of Stavudine has achieved 98% release. Results indicated that, percent drug release has been retarded with increase in the concentrations of hydrophobic polymer. The above formulation may also improve patient compliance with reduction in dosage frequency. Hence it was concluded that Stavudine extended release tablets can be manufactured for future medications.

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