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Formulation and Evaluation of Stavudine Sustain Release Matrix Tablets Using Purified Neem Gum as Release Retardant

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ABSTRACT

Stavudine is used for the treatment HIV/AIDS. It is competitive inhibitor of reverse transcriptase enzyme. Stavudine has short half life of 1.5-3 hours and absorption of drug is 86%. To reduce frequency of dosing, adverse effects and to increase patient compliance sustain release matrix tablets of Stavudine was developed. Therefore the main objective of the present work is to prepare sustain release matrix tablets of Stavudine using Neem gum as binder alone and combinations of Neem gum and HPMC K4M (1:1). Sustain release binder property of Neem gum is not evaluated. Tablets were designed in such a way that it releases drug throughout GIT for 12 hours, by retarding the release and thus increase the half life of the drug. Stavudine showed maximum absorbance at a wavelength of 266nm. FTIR studies show no interaction between drug and excipients. Five F1-F5 formulations were developed by using various amount of Neem gum in range of 40-120 mg using non aqueous wet granulation method. Precompressional and post-compressional parameters were evaluated and were found to be within the limits. The dissolution studies were performed it showed that formulation F2 consisting of 80mg of polymer was found to release of the drug perfectly at 12 hour remaining F3, F4 and F5 shown prolong sustain release than required rate. F2 is optimized based on drug release and subjected to different kinetic models, it found to be concentration independent and by diffusion. Stability studies are conducted for optimized F2 formulation tablets, shows no much change.

Keywords: Stavudine, Sustain release matrix tablets, Neem gum, HPMC K4M

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INTRODUCTION

Tablets are most commonly used oral solid unit dosage form, it shows flexibility in drug release. Drugs with low half life less than 6 hrs require multiple dosing. Due to it, elicit adverse effects and sometimes leave patient sub therapeutic leading to patient incompliance. It can be overcome by formulating such drugs in sustain release dosage form. Designing of sustain release drug delivery system mainly to maintain drug concentration in the plasma for prolonged period of time at predetermined rate to elicit efficient therapeutic activity without adverse effects and toxicity. Targeting is not a primary reason but release of drug at predetermined rate is primary concern. Among them sustain release oral matrix tablets are easy to formulate and develop. Sustain release matrix tablets are defined as the drug with release retardant blend is granulated (wet or dry) prior to compression to form matrix tablets. Release retardants (binders) are used to retard the drug release by different mechanisms like impermeability, in-situ forming gels. Sustain release matrix tablets retard the drug release effectively for lone period of time by rate controlling step to drug release is liquid penetration in to tablet matrix. Promote penetration of water in to matrix by channeling agents by dissolution and diffusion. Drug release from matrix tablets alters by using different types and concentrations of binder polymer. Binder polymer should select in such a way that, it prolong drug release for 12 hrs. Many polymers were used as release retardant, show drug release by diffusion and erosion[6]. Neem gum is hydrophilic polymer used as release retardant to check whether it retard drug release at different concentration and it is compared with combination of neem gum and HPMC K4M (1:1) as release retardant. Stavudine drug have very less half life, so it required to give in several doses which may lead to adverse effects. To reduce number of doses and its adverse effects it better to formulate in sustain release dosage form. Hence it is suitable to formulate stavudine as sustained release dosage form. Absorption of stavudine is 85%. Hence it is suitable to formulate stavudine as sustained release matrix tablets. Stavudine sustained release dose is 80mg (marketed formulation 80mg) hence it was found to be suitable for development as a sustained release dosage form. Stavudine is phosphorylated to form active Stavudine triphosphate, it is a analogue of thymidine. Stavudine triphosphate is a competitive inhibitor of enzyme reverse transcriptase of HIV. Some clinical trials have demonstrated comparable HIV suppression with Stavudine and other retroviral combination shows that no resistance towards drugs by virus[2].

MATERIALS AND METHOD

Neem gum is purchased from market in Hyderabad. Stavudine drug is provided by JNTUH University. For purification of neem gum ethanol and acetone were used. Other excipients used in formulation and development of sustain release matrix tablets are HPMC K4M, microcrystalline cellulose, talc, magnesium stearate, povidone and polyvinyl alcohol. All excipients and solvents were provided by Finer chemical (LR).

Purification of Neem gum[1]

Neem gum was purified by precipitation method. Transfer 100g of neem gum in 500ml beaker and hydrated with sufficient amount of distilled water for 5 days with occasional stirring. Extraneous material was removed by using normal filter net. Now filtered slurry was subjected to precipitation using 99.8% ethanol and precipitated gum was filtered. Wash precipitated gum with acetone for several times and dried in a hot air oven at 30ºC for 96 hours. Dried gum powder is subjected to milling and sieving using mesh no. 60 and then stored in amber colored bottle until used.

Characterization of Neem gum[1]

Preliminary tests were performed to conform the presence of polysaccharide and to conform the purity. Neem gum was characterized for various organoleptic properties such as color, odor, taste, touch and texture, Physiochemical characterization such as swelling index, P^H ,solubility, viscosity, true density, Micrometric properties such as flow properties(bulk density, tapped density, Angle of repose, Hausner's ratio and Carr's index.). The X-ray diffraction studies were conducted for Neem gum polysaccharide to determine whether the structure is crystalline or amorphous in nature.

API Characterization[3]

Color:

A small quantity of stavudine powder was taken in a butter paper and views in well illuminated place.

Odour:

A small quantity of stavudine powder was taken in a butter examined for odour. Solid state: free flowing powder.

Determination of λ_{max} in 0.1N HCl and pH 7.4 Phosphate Buffer:

Stavudine was dissolved in 0.1N HCl and pH 7.4 Phosphate Buffer separately. Prepare 10ppm of concentration both solutions. The obtained solutions is then scanned for maximum absorbance in

UV- spectrophotometer (Shimadzu) in the range of 200-400nm. The λ_{max} of the drug was found to be 266 nm in both solutions.

Standard Graph of Stavudine in 0.1N HCl and pH 7.4 Phosphate Buffer:

Stavudine of was accurately weighed and dissolved in 100ml of 0.1N HCl and pH 7.4 Phosphate Buffer to prepare the primary stock solution separately.10ml of above solution was taken and diluted with 0.1N HCl and pH 7.4 Phosphate Buffer to prepare second stock solution. 2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml and10µg/ml of drug per ml samples were prepared using above stock solution using 0.1N HCl and pH 7.4 Phosphate Buffer. The absorbance was measured in a UV-spectrophotometer at 266 nm against HCl 0.1N and pH 7.4 Phosphate buffer.

FTIR Studies of Stavudine:

compatibility studies were important in the preformulation studies. Fourier transform infrared spectrophotometry study was done with Shimadzu Model with wave no. range 4000 to 400 cm^{-1}.

Preparation of sustain matrix tablet granules[3]

Table 1: Formulation Series of Stavudine Sustain Release Matrix Tablets (250mg)

Ingredients(mg)	F1	F2	F3	F4	F5
Stavudine	80	80	80	80	80
Neem gum	40	80	120	40	60
HPMC K4M	-	-	-	40	60
Microcrystalline cellulose	118	78	38	78	38
Magnesium Stearate	6	6	6	6	6
Talc	6	6	6	6	6
Total Weight	250	250	250	250	250

Stavudine matrix tablets granules are prepared by non-aqueous wet granulation method. Granules are prepared using alone neem gum and combination of Neem gum and HPMC K4M. Total weight of sustain release matrix granules formulated was 250mg using different drug and neem gum polymer ratios 1:0.5, 1:1, 1:1.5 as F1, F2, F3. Drug and polymer combination (neem gum and HPMC K4M of 1:1) of 1:1 and 1:1.5 as F4 and F5 were prepared and evaluated. Granules were prepared by non aqueous wet granulation method. According to this method PVP K-30 was dissolved in PVA (5% w/v) as granulating solution was prepared. Stavudine, Neem gum, HPMC K4M and other excipients were weighed in suitable proportion according to Table1. Stavudine is placed in mortar-pestle, mix uniformly after adding binder (neem gum/ neem gum + HPMC K4M) and add microcrystalline cellulose and mix until uniform blend is obtained. Add granulating solution to above uniform blend to prepare granules. The wet mass was passed through sieve no. 20 and dried at 50°C in an oven for 30 minutes. Dried granules were passed

through sieve no. 40 and mixed with Magnesium stearate and talc for a minute and compressed into tablets.

Precompressional evaluation of tablet granules (without adding lubricants and glidants)[3]

Precompressional evaluation of stavudine granules were bulk and flow properties without adding magnesium stearate and talc.

Determination of density parameters of granules:

Bulk and Tapped density of granules were determined by weighing 5gm of powder and transferred to 50ml measuring cylinder. The final volume of cylinder is containing granules is measured; it gives the bulk volume (V_0) of sample. Then Powder in measuring cylinder is subjected to tapping for 100 times. The volume obtained is true volume (Vt) of the powder.

Bulk density = weight of powder / Bulk volume (Vo)

True density = weight of powder /True volume (Vt)

Compressibility Index (Carr's Index):

Carr's index is determined using bulk density and tapped density of powder. It is used to estimate the flow properties of powder.

Compressibility index = $100\ (V_0 - V_t)\ /V_0$

Hausner's Ratio:

It is the ratio of tapped density and bulk density. Hausner found that this ratio was related to interparticle friction and used to predict flow properties of powder.

Hausner's ratio= Tapped density / bulk density.

Angle of Repose:

Angle of repose is defined as maximum angle formed by heap of powder (height) and its horizontal surface. It is used to estimate flow properties of neem gum powder.

$\Theta = \tan^{-1} (h/r)$

Where, h = height; r = radius ,

Θ = angle of repose

An accurately weighed sample was taken. A funnel was fixed to the stand in such a way that the tip of the funnel was at the height of 6 cm from the surface. The sample was passed through the funnel slowly. The height and the circumference of the powder heap formed were measured. The radius was measured and the angle of repose was determined using the above formula. This was repeated five times for a sample.

Preparation of Stavudine matrix tablets

Stavudine granules are subjected to compression to obtain tablet of required hardness by using rotary compressed machine with punch size 11mm diameter and flat faced punches.

EVALUATION OF STAVUDINE MATRIX TABLETS[3]

Tablet Hardness:

Tablet hardness was measured by using Monsanto hardness tester. From each batch six tablets were measured for the hardness and average of six values was noted.

Thickness:

Twenty tablets were randomly taken and individual tablet thickness was measured by using digital vernier calipers. Average thickness was calculated.

Thickness = MSR + [VSR × 0.01]

Where, MSR = Main scale reading

VSR = Vernier scale reading

Friability Test:

Accurately weigh and place tablets in the friability test apparatus (Roche Friabilator). Apparatus was operated at 25 rpm for 4 minutes and tablets were observed. The tablets were then taken after 100 rotations, dedusted and reweighed. The friability was calculated as the percentage weight loss. % Friability was calculated as follows

$$\%F = \frac{W_1 - W_2}{W_1} \times 100$$

Where,

W_1 = Initial weight of the 20 tablets.

W_2 = Final weight of the 20 tablets after testing.

Weight Variation Test:

To study weight variation individual weights (W_I) of 20 tablets were noted using electronic balance. Their average weight (W_A) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets were calculated.

Percentage deviation = $[(W_{avg}) - (W_{initial}) / (W_{avg})] \times 100$

Where,

PD = Percentage deviation,

W_{avg} = Average weight of tablet,

$W_{initial}$ = Individual weight of tablet.

Assay:

Five tablets were weighed and powdered. An accurately weighed portion of the above mixture equivalent to 250mg of stavudine is transferred to a 100ml volumetric flask containing buffer solution. The concentration is measured at λmax (266nm).

***In vitro* Dissolution Studies**:

In vitro dissolution studies were performed using the USP- II (paddle) dissolution apparatus at 50 rpm. The dissolution medium consisted of 900 ml of pH 7.4 phosphate buffer maintained at 37±0.5ºC. An aliquot was withdrawn at specific time intervals for 12 hours and drug content was determined by UV-visible spectrometer at 266nm.

Kinetic Analysis of Dissolution Data:

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The following plots were made using data.

- Zero order kinetic models: Cumulative % drug release vs. time.
- First order kinetic model: Log cumulative of % drug remaining vs. time
- Higuchi model: Cumulative % drug release vs. square root of time

FTIR studies of optimized Stavudine matrix tablets:

FTIR compatibility studies were important to determine the compatibility between drug and excipients. Fourier transform infrared spectrophotometry study was done with Shimadzu Model with wave no. range 4000 to 400 cm^{-1}.

Stability Studies: Stability studies performed for formulated Stavudine sustain release matrix tablets to determine their stability. After 3 months of formulation of tablets hardness, drug content, thickness and friability test are performed.

RESULTS AND DISCUSSION

Neem gum Characterization - Organoleptic evaluation

Table 2: Organoleptic, physicochemical and phyto chemical evaluation

Organoleptic properties of Neem gum	
Properties	**Results**
Description	Powder
Taste	Tasteless
Odour	Odourless
Color	Pale golden yellow
Physicochemical properties of Neem gum	
pH of Neem gum 1% solution	6.67 – 6.8
Swelling index	1.060 ± 0.012
Loss on drying	7.6%

Viscosity	1.48 Poise
Phytochemical properties of Neem gum	
Test	**Results**
Molisch Test	Positive
Starch	Negative
Proteins	Negative
Glycosides	Negative
Alkaloids	Negative
Steroids	Negative
Gum	Positive

Purified Neem gum is pale golden yellow in color, odourless and tasteless. It does not impart any odour and taste to the dosage form. Neem gum shows positive test for Molisch test and gum indicates, it has reducing sugar and gum. Neem gum shows pH 6.67 – 6.8, it was near to water pH. Due to its neutral pH, gum does not cause any irritation and highly suitable for oral dosage forms. Swelling index of 1% solution of neem gum was 1.060 ± 0.012, high swelling of gum is main criteria for drug release by diffusion. Loss on drying was found to be 7.6%, moisture content of neem gum was within range and even suitable for moisture sensitive drugs. Viscosity of neem gum 1% solution found to be 1.48 Poise

Bulk and flow properties

Table 3: Bulk and flow properties of Neem gum

Bulk density	0.714g/cc
True density	0.784g/cc
Carr's index	8.9
Hauser's ratio	1.09
Angle of repose	22.4°

From the results of Carr's index, flow properties of neem gum powder shows excellent compressibility. From the results of hausner's ratio, flow properties of neem gum shows excellent flow properties from the results of angle of repose, flow properties of neem gum powder excellent flow properties.

Solubility

Table 4: Solubility of Neem gum

Water, 0.1N HCl, pH 7.4 buffer	Soluble
Ethanol, Methanol, Acetone	Slightly soluble
Petroleum ether	Insoluble
Chloroform	Coagulate

Gum shows solubility in water, 0.1N HCl, pH 7.4 buffer. It shows it is a hydrophilic polymer.

Analytical methods for characterization of neem gum powder

X-RAY powder diffraction studies

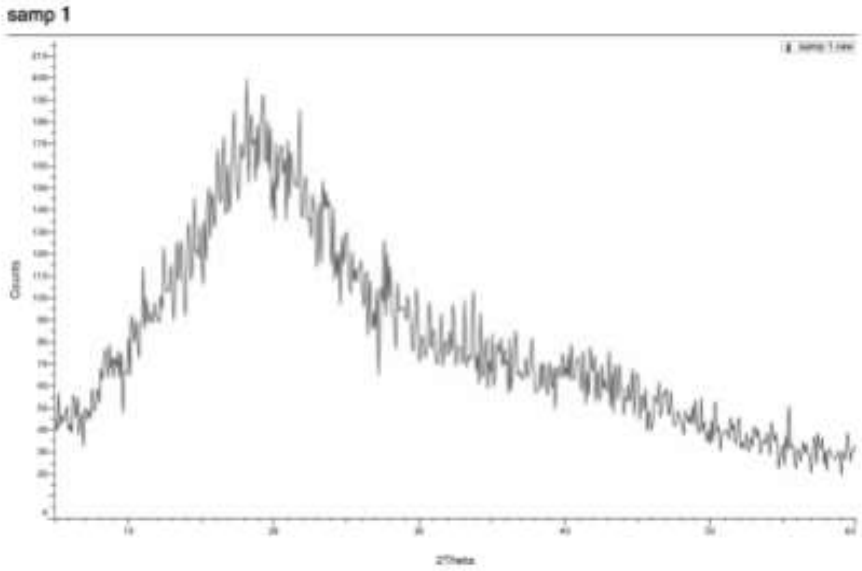


Figure 1: X-ray diffraction of neem gum

Discussion: From XRD studies, neem gum found to be amorphous in nature.

API Characterization:

It includes color, odor, taste; λ_{max} and Standard Graph of Stavudine in 0.1N HCl and pH 7.4 Phosphate Buffer and FTIR studies.

Table 5: Organoleptic properties of Stavudine

Properties	Results
Description	Powder
Taste	Slightly unpleasant
Odor	Odorless
Color	White to Off white

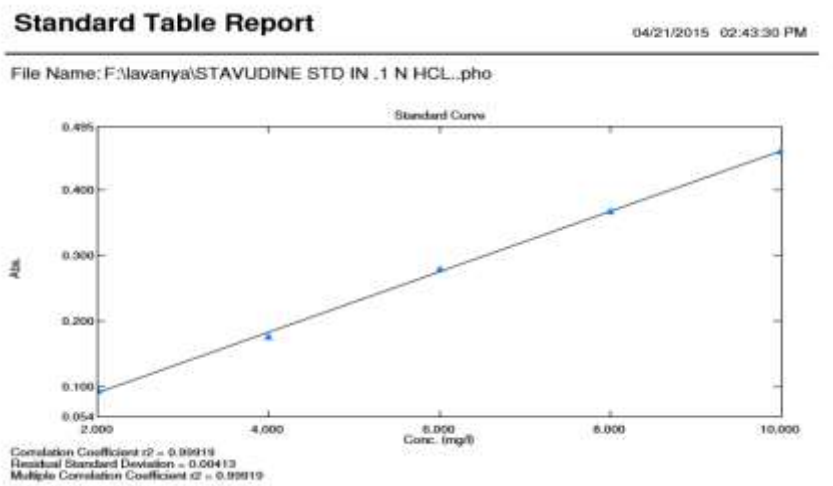


Figure 2: Beer-Lambert's Plot of Stavudine in 0.1NHCl

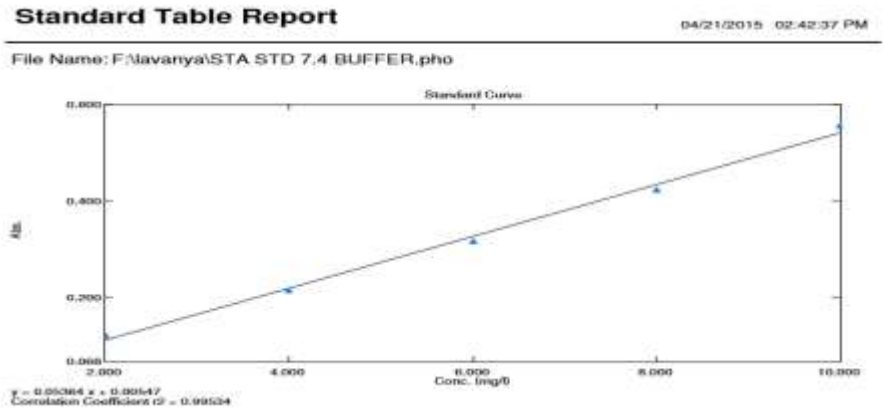


Figure 3: Beer-Lambert's Plot of Stavudine in pH 7.4 phosphate buffer

Bulk and flow properties of Stavudine granules

Table 6: Evaluation of tablet blend (Mean ± SD, n = 6)

Formulation	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner ratio	Angle of repose (θ)
F1	0.372±0.008	0.387±0.001	2.57±0.39	1.02±0.008	32.33±0.27
F2	0.567±0.003	0.583±0.002	2.75±0.3	1.02±0.003	28.6±0.4
F3	0.563±0.004	0.582±0.003	3.24±0.32	1.02±0.006	26.5±0.23
F4	0.469±0.005	0.473±0.005	2.08±0.04	1±0.01	27.8±0.12
F5	0.391±0.008	0.366±0.002	1.01±0.002	1.01±0.002	25.9±0.3

From the results of carr's index, hausner's ratio and angle of repose of F1, F2, F3, F4 and F5 shows excellent compressibility, excellent flow properties, excellent flow properties and F1 show good flow properties.

Evaluation of Stavudine sustain release tablets

Stavudine sustain release tablets are circular, flat, break line on one side. Weight variation, friability, thickness, hardness and drug content of tablets of F1, F2, F3, F4 and F5 found to be

Table 7: Evaluation of Stavudine matrix tablets (Mean ± SD, n = 6)

Formulation	Weight variation		Friability (%)	Thickness (mm)	Hardness (kg/cm²)	Drug Content (%)
	Average wt(mg)	%Deviation				
F1	251.3	3.92±0.04	0.79±0.07	3.92±0.04	6.16±0.18	98.2±0.8
F2	247.8	3.77±0.02	0.31±0.1	3.77±0.02	5.3±0.55	99.4±0.55
F3	250.6	3.66±0.07	0.2±0.07	3.66±0.07	5.2±0.11	97.68±0.78
F4	248.4	3.75±0.05	0.45±0.06	3.75±0.05	5.4±0.08	99.83±0.92
F5	255.5	3.8±0.09	0.26±0.02	3.80±0.03	5±0.1	97.26±0.03

From the results, weight variation of all tablets formulation was in range of 3.66-3.92. According to IP 2010 limits for 250mg tablets were within 7.5. Friability of all tablets formulation was in range of 0.2-0.79. According to IP 2010 limits for friability of tablets was 1%. Thickness of all tablets formulation was in range of 3.66-3.92. According to IP 2010 limits for friability of tablets was 1%. Hardness of all tablets formulation was in range of 5-6.1. According to literature of sustain release matrix tablets should have hardness 5 to 8 kg. Drug content of all tablets formulation was in range of 97.26 - 99.83%. According to IP 2010 limits for drug content of tablets was 90-110%. All formulations are within range.

% Drug release of Stavudine sustain release matrix tablets for 12 hours

Table 8: Evaluation of Stavudine matrix tablets (Mean ± SD, n = 6)

Time (hr)	F1	F2	F3	F4	F5
1	12±0.25	3.7±0.18	2.5±0.41	4.1±0.18	1.48±0.13
2	30.6±0.46	9.7±0.46	6 ±0.17	17.5±0.19	10.6 ± 0.5
3	45.9±0.28	17.2±0.25	19±0.95	27.1±0.39	23.2±0.34
4	51.2 ±0.06	23.5±0.29	24±0.82	39.3±0.54	34.1±0.5
5	67.5±0.25	34.6± 0.65	37.5±0.5	45±0.63	37.1 ±0.45
6	78.7±0.34	48.2±0.64	46.9±0.39	52.9±0.41	44.7±0.29
7	83.1±0.3	54.5±0.34	54.1±0.9	69 ±0.05	48.9±0.32
8	99.4±0.32	65.1±0.87	64.8±0.66	75.6 ±0.09	55.8±0.6
9	-	77.9±0.26	70.1 ±0.85	78.2±0.25	59.7 ±0.37
10	-	84.8±0.79	78.2±0.45	81.6 ±0.25	67.1±0.15
11	-	92.4±0.67	81.7±0.28	87.7±0.37	77.7±0.37
12	-	97.2±0.8	86.6±0.31	91.9±0.39	83.12 ±0.34

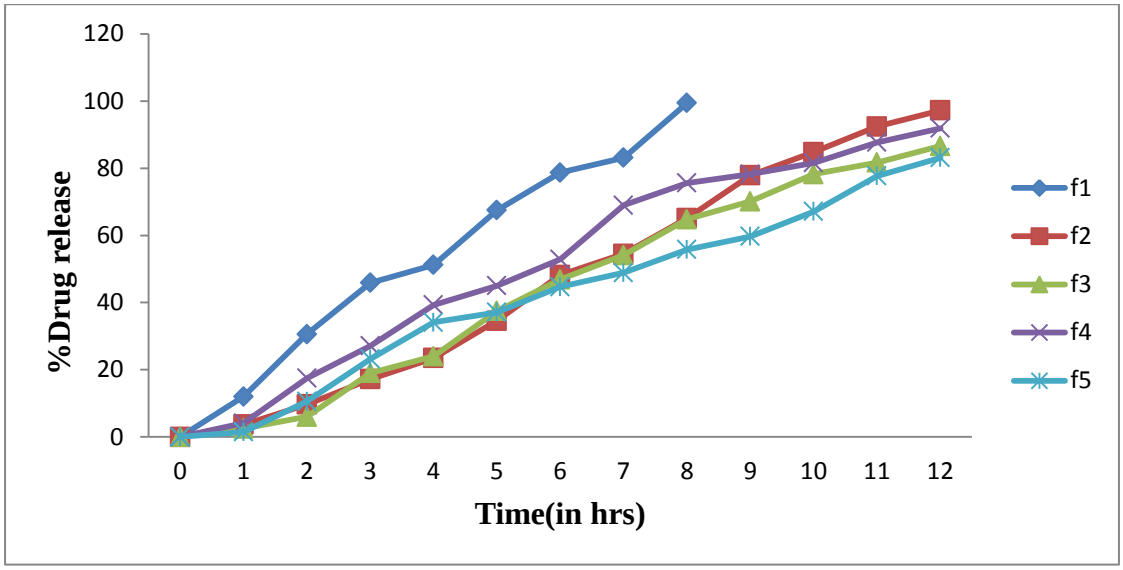


Figure 4: Comparative release profile of Stavudine (F1 to F5)

From the graph, F2 formulation releases 97.3% of drug in 12 hours, whereas F1 released entire drug with 8hours and F3, F4 and F5 fail to release entire drug within 12 hours they have shown high sustainability. So, F2 formulation is optimized.

Kinetic modeling for an optimized formulation

It is performed to determine type of drug release from dosage form of formulation F2.

Table 9: Kinetic modeling for an optimized formulation F2

Time in Hrs	SQRT of time	Log time	%CDR	Log % CDR	Log Cu % Drug remain
0	0	0	0	0	2
1	1	0	3.75	0.57	1.98
2	1.414	0.301	9.7	0.98	1.95
3	1.732	0.477	17.2	1.23	1.91
4	2	0.602	23.5	1.37	1.88
5	2.236	0.698	34.6	1.53	1.81
6	2.449	0.778	48.2	1.68	1.71
7	2.645	0.845	54.5	1.73	1.65
8	2.828	0.903	65.1	1.81	1.54
9	3	0.954	77.9	1.89	1.34
10	3.162	1	84.8	1.92	1.18
11	3.316	1.041	92.4	1.96	0.88
12	3.464	1.079	97.2	1.98	0.44

Table 10: Drug Release Kinetic Parameters

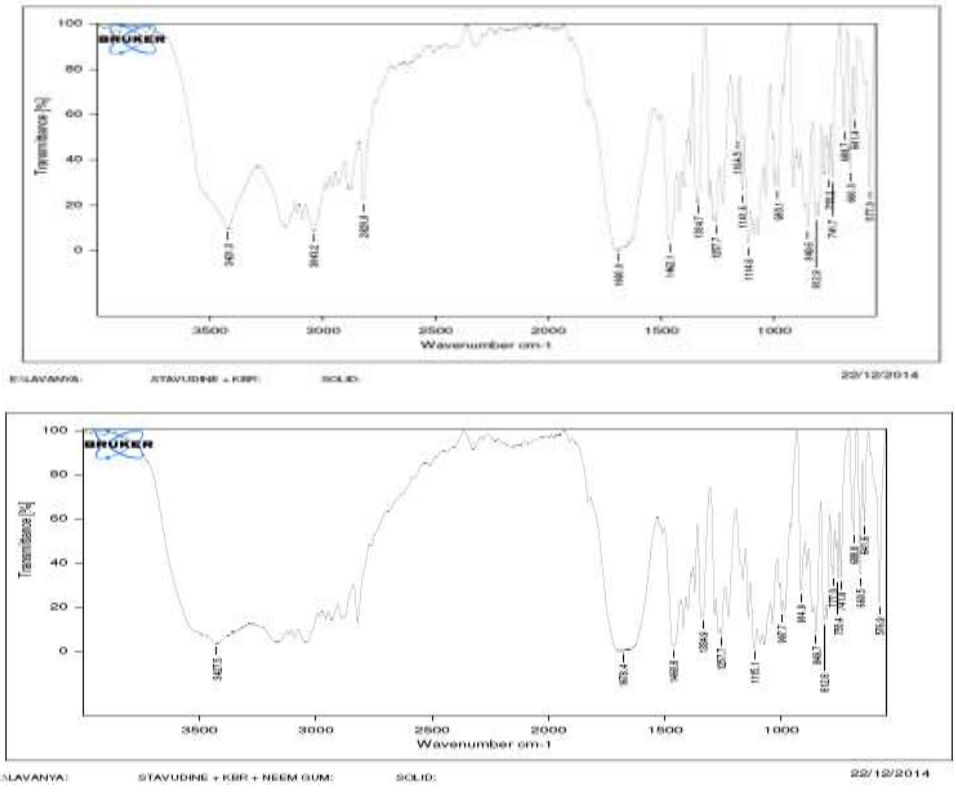
S. No	Kinetic model	R2	n(slope)
1	Zero order	0.9444	7.172
2	First order	0.8388	-0.1126
3	Higuchi plot	0.9445	7.172
4	Korsmeyer peppa's	0.6941	0.1907

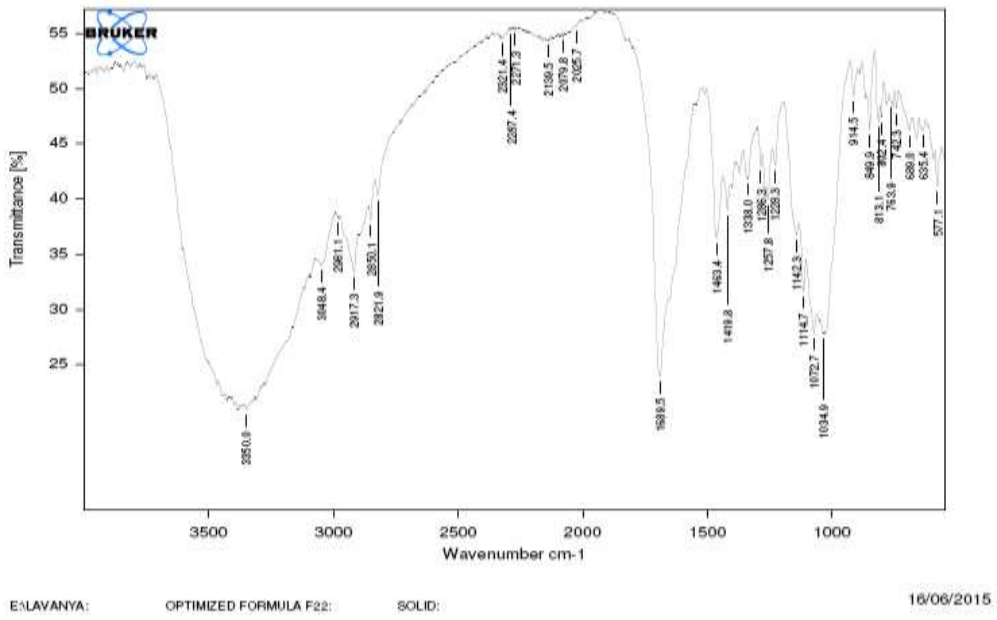
From the kinetic models we can determine the drug release mechanism of optimized formulation. From the regression coefficient, dosage form show 0.6941-0.9445 values range. Drug release from dosage form was concentration independent from zero order kinetic model and by diffusion from Higuchi plot.

Fourier Transformation Infra-red (FTIR) analysis

Table 11: FTIR spectrum analysis

Tablet	API	API+NEEM	Frequency range	Mode of vibration
3473.2	3421.3	3426.3	3500-3300CM^{-1}	N-H stretch
3043.4	3043.2	3042.9	3050-3000CM	Ar-H
2821.4	2820.8	2825.1	3000-2500CM^{-1}	O-H stretch
1689.5	1690	1687.5	1715-1690CM^{-1}	C=O stretch
1257.8	1257.7	1257.6	1270-1200CM^{-1}	C-0 stretch
742.8	741.7	741.8	770-735	C-C de





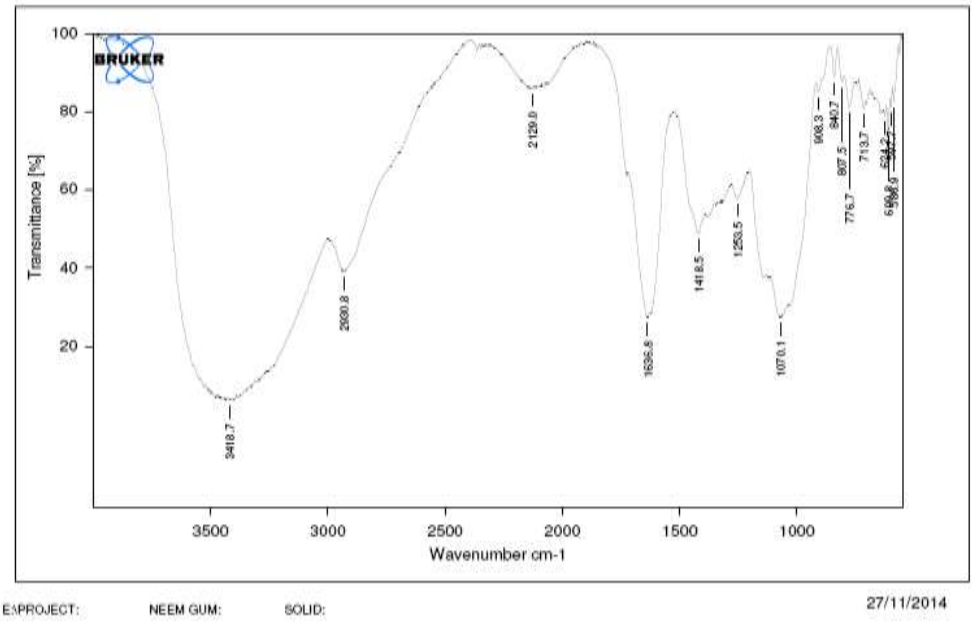


Figure 5: FT-IR spectrum of A- Stavudine, B- Stavudine + Neem gum, C- Neem gum, D- Optimized F2 formulation

From FTIR studies neem gum powder shows following characteristics peaks N-H Stretching at 3418.7 cm-1, O-H Stretching at 3148.70 C-H cm-1, Stretching at 2930.8 cm-1, C=O Stretching at 1636.8 cm-1, C-O Stretching at 1070.1 cm-1.FTIR spectrum of pure drug, drug with neem gum and optimized F2 formulation of Stavudine matrix tablet shows no incompatibility between drug and other excipients even after compression it confirms no effect of compression on tablet blend.

Stability Studies

Stability studies of optimized tablets are performed.

Table 12: Stability studies of Formulation F2 (Mean ± SD, n = 6)

S. No.	Evaluation parameters	Initial amount	after 3 months
1	Weight variation(mg)	3.77±0.028	3.8±0.07
2	Friability (%)	0.31±0.1	0.33±0.2
3	Thickness (mm)	3.77±0.02	3.77±0.3
4	Hardness (kg/cm²)	5.3±0.55	5.6±0.44
5	Drug content (%)	99.4±0.55	98.2±0.8

From the stability studies of optimized tablets found that no much change occur in tablets in drug content, hardness, friability, thickness and weight variation.

CONCLUSION

From the organoleptic, phytochemical, solubility, bulk and tapped density, flow properties shows good results that Neem gum as binder. From analytical method of characterization of Neem gum reveals about their amorphous nature and functional groups. The Sustained released tablets containing Stavudine were successfully prepared by non-aqueous wet granulation method. The granules shows good flow properties. The optimized formulation contains the thickness 3.77±0.02, hardness 5.3±0.13, weight 247.87, and friability 0.11. The optimized formulation F2 releases drug up to 12 hours. FTIR studies confirm compatibility of drug and excipients before and after compression. Stability studies of F2 formulation show no much change.

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