Formulation And Evaluation of Stavudine Floating Tablet

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Abstract- *This research aims to enhance the gastric retention time of Stavudine by formulating floating matrix tablets and investigating the effect of various polymers on the drug release profile. The tablets were developed using a melt granulation technique, incorporating beeswax as the hydrophobic meltable base. Hydroxypropyl methylcellulose (HPMC) served as the matrix-forming agent, sodium bicarbonate as the gas-generating component, and ethyl cellulose as the floating enhancer. The final formulations were assessed for several physical parameters, including hardness, weight consistency, friability, buoyancy characteristics (such as lag time and duration of floating), drug content uniformity, stability, and in vitro release behavior. Additionally, interactions between the drug and polymers were analyzed using Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared Spectroscopy (FT-IR).*

Keywords- Stavudine, floating tablet, melt granulation, gastric retention, HPMC, in vitro release, buoyancy

I. INTRODUCTION

The development of innovative drug delivery systems is aimed at overcoming the limitations of conventional dosage forms and enhancing therapeutic outcomes. Among various administration routes, the oral route continues to be the most widely accepted due to its simplicity, cost-effectiveness, and patient compliance. However, traditional oral dosage forms often necessitate frequent dosing to maintain therapeutic plasma concentrations, which can lead to reduced adherence and fluctuating drug levels.

Controlled Release Drug Delivery Systems (CRDDS) have emerged as an effective solution to this challenge, offering prolonged drug action, improved bioavailability, and reduced dosing frequency. One such system, the Gastroretentive Drug Delivery System (GRDDS), is specifically designed to extend the retention time of the dosage form in the stomach. This approach is particularly advantageous for drugs that are primarily absorbed in the upper gastrointestinal tract, are unstable in intestinal pH, or are intended for localized gastric action.

For an ideal GRDDS, the formulation must ensure prolonged gastric residence, patient acceptability, sufficient drug loading, a controlled release profile, and safe degradation or transit after the therapeutic window has been achieved. Additionally, the system should not adversely impact gastric motility or cause local irritation.

Formulation Considerations for GRDDS

Designing an effective gastroretentive drug delivery system (GRDDS) requires careful consideration of multiple formulation aspects to ensure both functionality and patient safety. The system must exhibit reliable gastric retention to maintain the drug at its intended site of absorption for the desired duration. It should be easy to administer, preferably in the form of tablets or capsules to promote patient compliance.

Floating Drug Delivery Systems

Floating drug delivery systems (FDDS) represent a prominent approach within GRDDS, offering significant advantages for drugs that are either locally active in the stomach or have limited stability and solubility in the intestinal environment. These systems are engineered to remain buoyant on gastric fluids, allowing the dosage form to stay in the stomach for an extended period while gradually releasing the drug.

The underlying mechanism relies on the principle of buoyancy, where the system's overall density is reduced below that of gastric contents, enabling it to float. This is typically achieved through the generation of gas (such as CO_2) via effervescent agents like sodium bicarbonate and citric acid, or through the use of low-density materials.

During gastric retention, the drug is released in a controlled manner from the floating system. Once the active agent has been released, the remaining formulation is expected to pass through the gastrointestinal tract safely. To evaluate and optimize floating behavior, specialized apparatuses have been developed that continuously measure buoyant force over time. These measurements help in refining formulation properties such as floating lag time, total floating duration, and stability of the system under simulated gastric conditions.

Advantages of Floating Drug Delivery Systems

- Floating drug delivery systems (FDDS) offer several therapeutic and pharmacokinetic advantages, making them particularly valuable for certain classes of drugs. One of the primary benefits is their ability to maintain the dosage form in the stomach for a prolonged period, thereby enhancing the absorption of drugs that are preferentially absorbed in the stomach or the upper part of the small intestine.
- These systems are especially suitable for medications intended for local gastric action, such as antacids or antibiotics targeting *Helicobacter pylori*. They also support sustained drug release, which helps maintain consistent plasma concentrations and reduce dosing frequency. This contributes to better patient compliance and minimized fluctuations in drug levels.
- Moreover, FDDS are ideal for drugs with a narrow therapeutic window, as they help ensure controlled delivery within the optimal absorption zone, reducing the risk of under- or overdosing. By minimizing exposure to the variable intestinal environment, FDDS can also improve the bioavailability of drugs that are unstable or poorly soluble at higher pH levels. Additionally, they are useful in managing conditions with altered gastrointestinal motility, such as diarrhea, where extended gastric retention can enhance therapeutic outcomes.

Limitations of Floating Drug Delivery Systems

Despite their many benefits, floating drug delivery systems also present certain limitations that must be addressed during formulation. These systems rely heavily on the presence of sufficient gastric fluids to ensure buoyancy. Therefore, in conditions of low gastric volume or fasting states, their floating performance and retention may be compromised. This issue can be partially mitigated by administering the dosage form with a full glass of water.

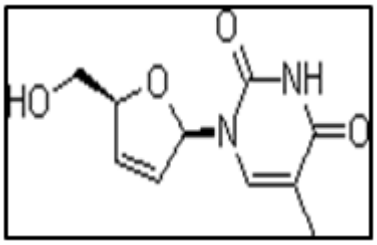
FDDS are not suitable for all types of drugs. For instance, medications that are uniformly absorbed throughout the gastrointestinal tract, or those that undergo extensive first-pass metabolism, may not derive significant benefit from prolonged gastric retention. Similarly, drugs that are unstable or irritating to the gastric mucosa, such as certain non-steroidal anti-inflammatory drugs (NSAIDs), are poor candidates for FDDS due to the risk of local adverse effects.

Another consideration is patient positioning—since gastric emptying accelerates in the supine posture, FDDS are not ideal for administration at bedtime. Furthermore, single-unit floating dosage forms may be subject to "all-or-nothing" gastric emptying, which can lead to dose dumping or treatment failure. This limitation can be addressed by designing multiple-unit systems, such as floating microspheres or beads, to ensure more predictable gastric retention and drug release.

Drug Profile

STAVUDINE

Stavudine is a dideoxynucleoside analog that inhibits reverse transcriptase and has in vitro activity against HIV.



Synonym: Stavudine [Usan:Ban:Inn], Stavudinum [INN-Latin], STV, Estavudina [INN-Spanish]
Drug category: Antiretrtoviral drug. **Proprietary Names:** Zerit, Zeritavir, Stavir**. Structure of Stavudine:**
IUPAC Name: Stavudine is chemically 1 – (2,3 – Dideoxy – β – D – glycerol – pent – 2 – enofuranosyl)thymine.
Molecular Formula : $C_{10}H_{12}N_2O_4$ **Molecular Weight :** 224.21
Physicochemical Properties Melting Point : 159 – 160 C
Description : A white or almost white powder.
Solubility : About 83 mg/ml in water and 30 mg/ml in propylene glycol at 23 C. The n-octanol/water partition coefficient of stavudine at 23 C is 0.144.
Storage : Preserve in tight containers, protected from light and humidity, store at 25^0, excursions permitted between 15^0 and 30^0.
Standard: Stavudine contains not less than 98.0% and not more than 102.0 % of $C_{10}H_{12}N_2O_4$, calculated on an anhydrous and solvent-free basis.

Mechanism of Action:

Stavudine inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural substrate dGTP and by its incorporation into viral DNA.

Pharmacokinetic profile of stavudine:

Stavudine is absorbed rapidly following oral administration producing peak plasma concentrations within 1

hour and with a reported bioavailability of about 86%. Binding to plasma proteins is negligible. The elimination half-life (t) is reported to be about 1-1.5 hours following single or multiple doses. The Intracellular half-life of stavudine triphosphate has been estimated to be 3.5 hrs *in vitro*. About 40% of a dose is excreted in the urine by active tubular secretion and glomerular filtration. Stavudine is removed by haemodialysis.

Adverse Effects:

Common adverse effects seen with the use of stavudine include peripheral neuropathy, arthralgia, hypersensitivity, myalgia, anorexia, chills and fever, rash, asthenia, gastrointestinal disturbances, headache, insomnia, and fat redistribution.

HIV / AIDS – Related Uses:

Stavudine was approved by the FDA on June 24, 1994, for use in combination with other antiretroviral agents and is indicated for the treatment of HIV-1 infection in adults and pediatric patients. (*De Clercq E, 1988*)

II. MATERIALS AND METHODS

Materials

Stavudine, an antiretroviral drug, was received as a gift sample from Aurobindo Pharma Ltd., Hyderabad. Various polymers were employed in the formulation of floating matrix tablets, including Hydroxypropyl Methylcellulose (HPMC K15M), Carbopol 940P, Gum Karaya, Gum Copal, and Gum Dammar. Excipients such as Avicel pH 102 (as a diluent), sodium bicarbonate (as a gas-generating agent), and citric acid (as a component of the effervescent system) were also used. All other chemicals and reagents were of analytical grade.

Instrumentation

The following instruments were utilized during the study:

- Electronic weighing balance (Shimadzu ELB-300)
- Bulk density apparatus (Hexa Tec)
- Ten-station rotary tablet compression machine (Clit Mini Press)
- Roche friabilator (Pharmacon FTA-023)
- Monsanto hardness tester (Tab-Machines, Mumbai)
- Hot air oven (Universal)

Methodology

1. Drug Estimation by UV Spectrophotometry

A simple, sensitive, and validated spectrophotometric method was used to estimate Stavudine concentration. The drug showed maximum absorbance at a wavelength of 266 nm in 0.1N HCl. Standard calibration curves were prepared using solutions ranging from 2–10 µg/mL. Absorbance was recorded using a double-beam UV-Visible spectrophotometer (ELICO), and the linearity was confirmed with a correlation coefficient (R^2) close to 0.999.

2. Preformulation Studies

Drug-excipient compatibility was assessed through physical observation, Differential Scanning Calorimetry (DSC), and Fourier Transform Infrared Spectroscopy (FTIR). These tests helped evaluate potential interactions between Stavudine and the selected polymers or excipients.

3. Preparation of Floating Matrix Tablets

Floating tablets were formulated using the direct compression method. The components were individually weighed, passed through a #60 sieve, and blended uniformly in a double-cone blender. Sodium bicarbonate and citric acid were added last to avoid premature gas generation. The powder blend was lubricated with talc and magnesium stearate and compressed into tablets using 6 mm flat punches.

4. Evaluation of Powder Blend

The powder blends were evaluated for flow properties using:

- **Angle of Repose**: Measured by the fixed funnel method.
- **Compressibility Index** (Carr's Index) and **Hausner's Ratio**: Determined by comparing tapped and bulk densities.

5. Tablet Evaluation

post-compression, tablets were assessed for:

- **Weight variation**
- **Hardness** (using Monsanto tester)
- **Friability** (using Roche friabilator)
- **Drug content uniformity** (by UV spectrophotometry)

6. In Vitro Dissolution Studies

Dissolution studies were carried out using USP Type II paddle apparatus in 900 mL of 0.1N HCl at 37±0.5°C, with a rotation speed of 50 rpm. Samples were withdrawn at regular

intervals up to 12 hours, filtered, and analyzed spectrophotometrically at 266 nm.

7. Swelling Index

The swelling behavior was determined by immersing tablets in 0.1N HCl and measuring weight gain at set time intervals.

8. FTIR and DSC Characterization

FTIR spectra of the pure drug, polymers, and optimized formulations were recorded to identify potential interactions. DSC thermograms were obtained to assess the thermal behavior and confirm the stability of the formulation.

III. EXPERIMENTAL WORK

Estimation of Stavudine:

Several methods have been reported for the estimation of Stavudine by spectrophotometric and chromatographic methods. The variation in the amount of antiretroviral drug content estimated by HPLC and Spectrophotometric methods is below 10 per cent. This suggests that the spectrophotometric method is as accurate as the HPLC method for estimation of Stavudine in tablet. The λmax of Stavudine was found to be 266nm, in the college laboratory, by using UV Spectrophotometer. Thus, In the present investigation a simple, sensitive accurate spectrophotometric method was used for the estimation of Stavudine at a λ_{max} of 266nm.

Preparation of Stavudine Stock Solution:

100mg of Stavudine was weighed and was dissolved in 0.1N HCl. The drug solution obtained was filtered into 100ml volumetric flask and was further diluted to 100ml with 0.1N HCl to get 1mg/ml stock solution.

Preparation of Stavudine Standard Dilutions:

An aliquots of Stavudine stock solution was transferred into 5 volumetric flasks and were further diluted with 0.1n HCl so as to get 2, 4, 6, 8, 10µg/ml of standard dilutions of Stavudine. The absorbance's of the above dilutions were measured in ELICO double beam

UV-VIS spectrophotometer at 266nm using 0.1N HCl as blank. The concentrations of Stavudine and their corresponding absorbance values are given in Table 14. The absorbance values were plotted against concentrations of Stavudine and the corresponding calibration curve was shown as graph 3. The calibration curve values obtained were used to estimate Stavudine in the present investigation.

Stability Analysis of stavudine in 0.1N HCl

Stavudine stability in 0.1N Hcl was analysed by dissolving drug in the 0.1N Hcl. The drug solution was set aside for 24hrs and at specific time intervals, a small volume of sample was withdrawn and a solution with stavudine concentration 6µg/ml, was made with 0.1N Hcl. The dilution was analyzed by UV Spectrophotometric method at 266nm. The absorbance values obtained for the samples at various time intervals were given in Table 15. The amount of drug present in each sample at various time intervals was measured based on the absorbance values.

Preformulation Studies on Stavudine:

The drug and the polymer or excipient interaction studies were evaluated by checking the physical appearance, drug content and by DSC thermographical analytical method.

Preparation of Stavudine Controlled Release Floating Matrix Tablets:

Stavudine controlled release floating matrix tablets were prepared by direct compression process. The controlled release matrix tablet formulations consisted of drug, polymer, diluent, gas generating agent and effervescing agent. The drug concentration was maintained constantly while polymer proportions were varied. The weight of all the tablet formulations was maintained uniformly by using MCC as diluent. The materials were individually weighed, passed through sieve no: 60 and blended for 15 minutes by using double cone blender. Then sodium bicarbonate and citric acid were mixed one by one. The powder blends were evaluated for flow properties such as angle of repose and compressability index. The powder blends lubricated with 1% talc and magnesium stearate were directly compressed as matrix tablets with 6mm flat, round punches by using clit-10 station mini press. To minimize the processing variables all batches of tablets were compressed under identical conditions.

EVALUATION OF POWDER FLOW CHARACTERISTICS

Angle of Repose:

Angle of repose for the powder blends was performed by fixed funnel method and is the measure of the flowability of powder. A funnel with 10 mm inner diameter of stem was fixed at a height of 2 cm over the platform. About 10 gm of powder blend was slowly passed along the wall of the

funnel till the tip of the pile formed and touches the stem of the funnel. A rough circle was drawn around the pile base and the radius of the powder cone was measured *[Lachman L., 1990]*. The results were shown in the tables 25-26 and 29-30.

Compressibility Index:

A simple test was used to evaluate the flowability of a powder by comparing the poured density and the tapped density of a powder and the rate at which it is packed down. The Carr's index can be calculated using the following formula.

Uniformity of Weight:

Twenty tablets from each batch at random were taken and weighed. The average weight was calculated, then each tablet was weighed individually and weights of each tablet were noted. The weights of individual tablets were then compared with the average weight that was already calculated. The deviation if any in the weight of individual tablets from the average weight was checked. This test highly describes that all tablets of a particular batch should be uniform in weight. If any weight variation is there, that should be within the I.P limits *[Lachman L., 1990]*. The test was considered correct if not more than two tablets fall outside the I.P limits out of twenty tablets taken for the test.

Hardness Test:

Hardness of the tablets was determined by using Monsanto hardness tester (Tab- machines, Mumbai). The tablet to be tested is held in fixed and moving jaw and reading of the indicator was adjusted to zero. Then force to the edge of the tablet was gradually increased by moving the screw knob forward until the tablet breaks. The reading was noted from the scale which indicates the pressure required in kg/cm^2 to break the tablet. The hardness of tablet depends on the weight of the material used, space between the upper and lower punches at the time of compression and pressure applied during compression

Friability Test:

Friability test was performed by using Roche friabilator (Remi Equipments, Mumbai). Ten tablets of a batch were weighted and placed in a friabilator chamber and it was allowed to rotate for 100 revolutions. During each revolution these tablets fall from a distance of six inches to undergo shock. After completion of 100 revolutions, tablets were again weighed and the loss in weight indicated friability. The acceptance limits of weight loss should not be more than 1% *[Lachman , 1990]*. This test was performed to evaluate the ability of the tablets to withstand abrasion in packing, handling and transporting.

$$\text{Friability} = \frac{\text{Initial Weight - Final Weight}}{\text{Initial Weight}} \times 100$$

Uniformity of Drug Content:

Lamivudine controlled release floating matrix tablets from a batch was taken at random and was crushed to a fine powder. The powdered material was transferred into a 250ml volumetric flask and 200ml of 0.1N HCl was added to it. It was shaken occasionally for about 30 minutes and the volume was made up to 250ml by adding 0.1N HCl. The resulting solution was set aside for few minutes and the supernatant solution was collected, filtered by using wattman filter paper. Then the filtrate was subsequently diluted and the absorbance was measured at 280nm. This test was repeated six times (n=6) for each batch of tablets. The amount of Lamivudine estimated from different batches were depicted in tables 27-28 and 31- 32.

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IN VITRO DISSOLUTION STUDIES

Dissolution studies on lamivudine floating matrix tablet formulations were performed in a calibrated 8 station test apparatus (LAB INDIA) equipped with paddles (USP apparatus II method) employing 900ml of 0.1N HCl as a dissolution medium. The paddles were operated at a 50rpm and the temperature was maintained at 37±0.5°C throughout the experiment. Samples were withdrawn at regular intervals for 12hrs and replaced with equal volume of same dissolution medium to maintain the constant volume throughout the experiment. Samples withdrawn at various time intervals were suitably diluted with same dissolution medium and the amount of drug released was estimated by ELICO double beam spectrophotometer at 280nm. The dissolution studies on each formulation were conducted in triplicate and the average of 3 values were taken for studies. The release values and

dissolution profiles for all the formulations were shown in tables 33-37 and graph 5-9 respectively. Dissolution studies on stavudine floating matrix tablet formulations were performed in a calibrated 8 station test apparatus (LAB INDIA) equipped with paddles (USP apparatus II method) employing 900ml of 0.1N HCl as a dissolution medium. The paddles were operated at a 50rpm and the temperature was maintained at 37±0.5°C throughout the experiment. Samples were withdrawn at regular intervals for 12hrs and replaced with equal volume of same dissolution medium to maintain the constant volume throughout the experiment. Samples withdrawn at various time intervals were suitably diluted with same dissolution medium and the amount of drug released was estimated by ELICO double beam spectrophotometer at 266nm. The dissolution studies on each formulation were conducted in triplicate and the average of 3 values were taken for studies.
The release values and dissolution profiles for all the formulations were shown in tables 38-42 and graph 10-14 respectively

Swelling Index:

The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in the basket of dissolution apparatus using dissolution medium 0.1N HCl at 37±0.5^{0}C. After 1, 2,4, 6 and 8 hr's, each dissolution basket containing tablet was withdrawn and blotted with tissue paper to remove the excess water and weighed on the analytical balance (Shimadzu, Ax 120).

Infra- Red Spectroscopy:

I.R Spectral studies were carried out on some selected floating matrix tablets of lamivudine and stavudine by using BRUKER FTIR. FTIR spectrophotometer were used for recording spectra in the region of 4000 – 400 cm^{-1} or in some cases down to 200 cm^{-1}. Triturate 1 – 2mg of substance to be examined with 200mg of finely powdered and dried KBr. These quantities were usually sufficient to give a disc of 10-15mm diameter and a spectrum of suitable intensity. FTIR spectra and the interpreted values of various floating matrix tablet formulations were shown in graph 19-26 respectively.

Differential Scanning Calorimetry: A differential scanning calorimeter (DSC 60, Shimadzu) was used to obtain the DSC curves of lamivudine and stavudine controlled release floating matrix tablets prepared by direct compression method representing the rate of heat uptake. About 10mg of sample was weighed in a standard open aluminium pans, were scanned from 0-450ºC, at a heating rate of 10ºC/minute while being purged with dry nitrogen. DSC thermograms and their interpreted values for the optimized formulations were shown in graph 27-34 respectively.

IV. RESULTS AND DISCUSSION

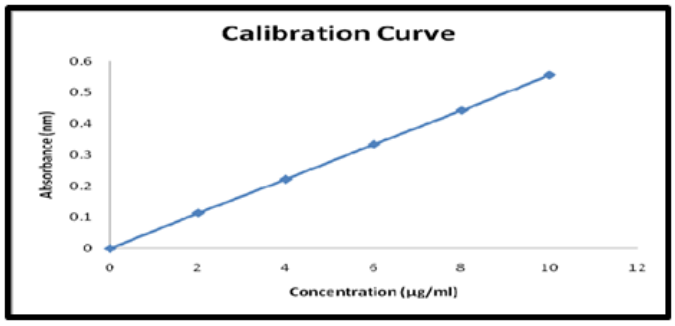
Estimation of Stavudine

The λmax of Stavudine was found to be 266 nm, in the college laboratory, by using UV Spectrophotometer. Thus, in the present investigation a simple, sensitive accurate spectrophotometric method was used for the estimation of Stavudine at a λ_{max} of 266nm 0.1N HCl as a medium.

Reproducibility of the method was tested by analyzing 6 separately weighed samples of Stavudine. The concentrations of Stavudine and their corresponding absorbance values were given in table 14. The absorbance values were plotted against concentrations of Stavudine and the corresponding calibration curve was shown in graph 3. The calibration curve values obtained were used to estimate Stavudine in the present investigation

Table : Calibration Curve for the Estimation of Stavudine in 0.1N HCl

S.No	Concentration (µg/ml)	Absorbance*
1	2	0.114
2	4	0.222
3	6	0.334
4	8	0.443
5	10	0.556



Graph: Calibration Curve for the Estimation of Stavudine in 0.1N HCl

Discussion: Stavudine in 0.1N HCl was estimated by spectrophotometric method at a wavelength of 266 nm. The method used for estimation of Stavudine was found to be liner with the Beers law in the concentration range of 0-10µg/ml.

Pre-formulation Studies on Stavudine:

Table :Preformulation Studies on Stavudine

S.No	Description	Method Evaluated	0th day	1 month	3 months
1	Stavudine	Physical Evaluation	White powder	White powder	White powder
2	Stavudine + HPMC K15M	Physical Evaluation	White powder	White powder	White powder
3	Stavudine + HPMC K15M +MCC	Assay by UV method	complied	Complied	complied
4	Stavudine	DSC Studies	Melting isotherm was observed at 173.5^{0}C	Complied	complied
5	Stavudine + HPMC K15M	DSC Studies	Melting isotherm was observed at 176.1^{0}C	Complied	complied
6	Stavudine	FTIR Studies	3425 cm^{-1} 1115.2 cm^{-1}	Complied	complied
7	Stavudine + Excipients	FTIR Studies	3425 cm^{-1} 1115.2 cm^{-1}	Complied	complied

Discussion:

Preformulation studies on Stavudine and excipients were carried out for a period of three months at an ambient storage conditions. The drugs and excipient interaction were observed physically and by thermal methods. Physical evaluation indicated that there were no physical changes in the colour and amorphous nature of the drug and its excipient blends even after 3 months of storage. UV Spectrophotometric methods exhibited the similar absorbance values of drug alone and excipient indicated that there were no drug excipient interactions. FTIR spectral studies exhibited the same peaks even in the presence of excipients and DSC studies showed the same melting isotherms with or without the presenceof excipients indicated both the drugs selected for the study, Stavudine was stable and hence suitable for further formulation development.

Preparation of Stavudine Controlled Release Floating Matrix Tablets

Controlled release floating matrix tablets for Stavudine were prepared by direct compression method using Elite 10 station mini press. The direct compresion process used for the preparation of matrix tablets was found to be ideal and is easy to reproduce. As many of the polymers and the excipients used are hydrophilic, the involvement of water or moisture makes the wet granulation process highly problematic. Therefore a dry process that produces acceptable powder characteristics and does not intervene with drug release characteristics is desirable. Hence the dry process such as direct compression technique was employed in the present investigation for the preparation of controlled release floating matrix tablets.

Table: Composition of Various Stavudine Controlled Release Floating Matrix Formulations

Ingredients (mg)	S1	S2	S3	S4	S5
Stavudine	40	40	40	40	40
HPMC K15M	40	--	--	--	--
Carbopol 940P	--	40	--	--	--
Copal gum	--	--	40	--	--
Dammar gum	--	--	--	40	--
Gum Karaya	--	--	--	--	40
MCC	116	116	116	116	116
Magnesium stearate	2	2	2	2	2
Talc	2	2	2	2	2
Total tablet weight (mg)	200	200	200	200	200

Discussion:

Controlled release floating matrix tablets for Stavudine were prepared by direct compression method. The direct compression process used for the preparation of matrix tablets was found to be ideal and is easy to reproduce. Polymers such as Hydroxy Propyl Methyl Cellulose (HPMC K15 M), Carbopols, gum Karaya, gum dammar and copal gum

were used in the preparation of matrix tablets with incorporation of Sodium bicarbonate as a gas generating agent and combination of sodium bicarbonate and citric acid as effervescent agents. All the powder blends exhibited good flow properties. These polymers were found to be ideal for the preparation of controlled release matrix tablets. Twenty five floating matrix tablet formulations were prepared with Stavudine by employing various polymers at different concentrations.

Fifty floating matrix tablet formulations were prepared with Lamivudine and Stavudine by employing various polymers at different concentrations. As many of the polymers and the excipients used are hydrophilic, the involvement of water or moisture makes the wet granulation process highly problematic. Therefore a dry process that produces acceptable powder characteristics and does not intervene with drug release characteristics is desirable. Hence the dry process such as direct compression technique was employed in the present investigation for the preparation of controlled release floating matrix tablets.

Floating matrix tablet formulations L1 to L5 and S1 to S5 were prepared by using 1:1 ratio of drug and polymers such as HPMCK15 M, carbopol 940P, copal gum, dammar gum and gum Karaya respectively. L6 to L20 and S6 to S20 formulations were prepared by 1:1 ratio of drug and polymers while sodium bicarbonate as gas generating agent at 15 to 25 % concentration were added in different formulations. Formulation L21 to L23 and S21 to S 23 were prepared b y using 1:0.75:0.25 ratios drug and polymer combinations(HPMCK15 and gum Karaya) with effervescent combination of sodium bicarbonate and citric acid at 2:1 part respectively with a total concentration of 20 to 25 % in the in the matrix formulations of Lamivudine and Stavudine. All the matrix tablet formulations are prepared under identical conditions to avoid processing variables. Before compression of these blends, they were subjected to precompressional studies to check the feasibility of free flowing characteristics.

Evaluation of Powder Flow Characteristics of Stavudine Controlled Release Floating Matrix Tablets

The physical properties of pharmaceutical powders are of upmost importance in the pharmaceutical industry. The knowledge of their flow properties is of critical significance in operations such as blending, tablet compression, capsule filling, transportation, and in scale- up operations. Powders flow properties are measured using a parameters such as, angle of repose, compressibility index (Carr's index) and Hausner ratio.

Table: Flow Properties of Powder Blends of Stavudine Floating Tablets

S. NO	Formulation	Angle of repose (θ)	Hausner's ratio	Compressibility Index (%)
1	S1	23.90	1.12±0.03	14.23
2	S2	22.34	1.12±0.03	12.17
3	S3	24.54	1.12±0.02	11.87
4	S4	23.18	1.12±0.04	11.41
5	S5	22.77	1.12±0.03	13.67
14	S14	23.43	1.11±0.02	12.08

Discussion:

Before compression process the powder blends were evaluated for flow properties such as angle of Repose, compressibility index and Hausner's ratio. The flow property values obtained for various powder blends were in the range of good flow characteristics, as depicted in the tables 29 and 30. The angle of repose values obtained for various powder blends were in the range of 25.42 to 27.32. Carr's index values obtained were in the range of 11.20 to 14.87. Hausner's ratio values obtained were in the range of 1.118- 1.129. Thus all the powder blends were found to be stable and suitable for compression as matrix tablets.

Evaluation of Physical Properties of Stavudine Controlled Release Floating Tablets

Quality of a pharmaceutical product can be assured by evaluating different physical characteristics of the product such as weight variation test, hardness test, friability test etc. following standard methods given by different drug control authorities like USP, BP etc. Evaluation of the physical characteristics can ensure the quality of drug and thereby impart optimum therapeutic activity as well as bioavailability.

Table: Physical Properties of the Stavudine Controlled Release Floating Matrix Tablets

S. NO	Formulation	Weight uniformity(mg)	Hardness (kg/cm²)	Friability (%)	Drug content (mg/tablet)
1	S1	203±2.0	6.0± 0.3	0.12	39.2± 0.5
2	S2	204±2.0	6.0± 0.3	0.12	40.2± 0.5
3	S3	202±2.0	6.0± 0.3	0.18	36.4± 0.5
4	S4	200±2.0	6.0± 0.3	0.17	39.9± 0.2
5	S5	200±2.0	6.0± 0.3	0.15	41.2± 0.3

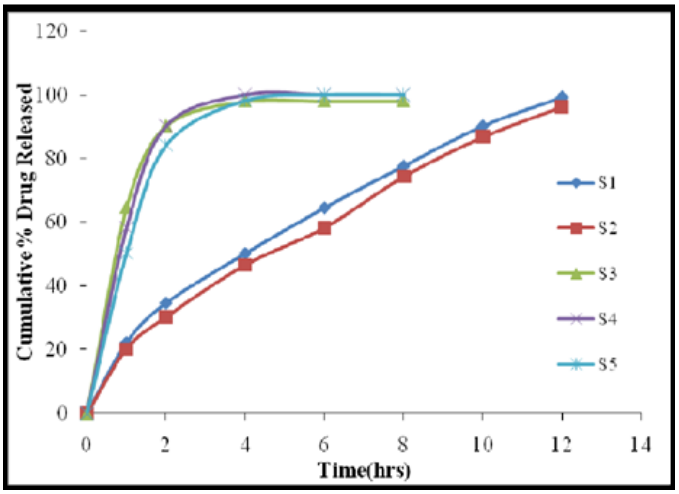
All the batches of matrix tablets were evaluated for the physical parameters such as weight uniformity, hardness, friability and drug content uniformity. All the matrix tablets were evaluated for weight uniformity. The weight ranges of all the matrix tablets were uniform and were within the IP limits. Hardness of the tablets was evaluated by using Monsanto hardness tester. The hardness of all the tablet formulations was in the range of 6.0±0.3 kg/cm^2.Weight uniformity of all the tablet formulations was in the range of 200.0 ± 3.0 respectively. Friability test for all the matrix tablets were performed to determine the ability of tablets to withstand abrasion during packing and transportation. The test was carried out in Roche friabilator. Friability loss of the tablet formulations was negligible and was in the range of 0.1-0.2%. Surface damages to the tablets were found to be negligible and the friability loss values were within the IP limits. Drug content estimated for all the tablet formulations was highly uniform with less than 3% variation. The drug content for the prepared matrix tablets of Lamivudine and Stavudine were evaluated by UV spectrophotometric method. The drug content in all the floating matrix tablet formulations were within the claimed limits.

IN VITRO DISSOLUTION STUDIES OF STAVUDINE FLOATING MATRIX TABLET FORMULATIONS

Dissolution studies on stavudine floating matrix tablet formulations were performed in a calibrated 8 station test apparatus (LAB INDIA) equipped with paddles (USP apparatus II method) employing 900ml of 0.1N HCl as a dissolution medium. The paddles were operated at a 50rpm and the temperature was maintained at 37±0.5°C throughout the experiment. Samples were withdrawn at regular intervals for 12hrs and replaced with equal volume of same dissolution medium to maintain the constant volume throughout the experiment. Samples withdrawn at various time intervals were suitably diluted with same dissolution medium and the amount of drug released was estimated by ELICO double beam spectrophotometer at 266nm. The dissolution studies on each formulation were conducted in triplicate and the average of 3 values were taken for studies.

Table : Drug Release Profile of Stavudine Floating Matrix Tablet

Time(hrs)	Cumulative % Drug Release from Various Formulations				
	S1	S2	S3	S4	S5
0	0	0	0	0	0
1	22.24	20.24	64.66	58.24	50.24
2	34.66	30.26	90.24	90.22	84.22
4	50.24	46.56	98.12	100.00	98.25
6	64.56	58.22	98.14	100.11	100.0
8	77.66	74.22	98.32	100.12	100.0
10	90.24	86.66	---	---	---
12	99.26	96.12	---	---	---



Graph: Release Profiles from Various Controlled Release Floating Matrix Tablet Formulations of Stavudine

Discussion:

Dissolution studies were performed on all the floating matrix tablets of **Stavudine** formulations by using 0.1 N HCl as dissolution medium by USP paddle method (apparatus II). Matrix tablet formulations S1 and S2 containing HPMC and carbopol as polymers extended the drug release upto 12 hours,

where as formulations S3 to S5 containing gum copal, gum dammar and gum Karaya as polymers respectively failed to extend the drug release upto 12 hours.

Characterization of optimized Floating Matrix Tablet Formulations of Stavudine

Based on the dissolution studies performed on all the formulations, some of the optimized formulations were selected for further investigations such as FTIR and DSC Analysis.

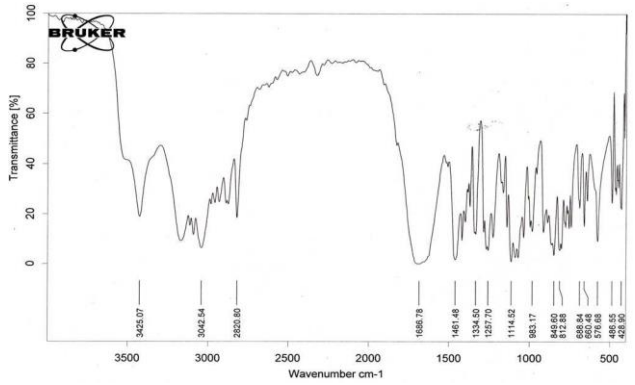


Figure: FTIR Spectra of Stavudine Pure Drug

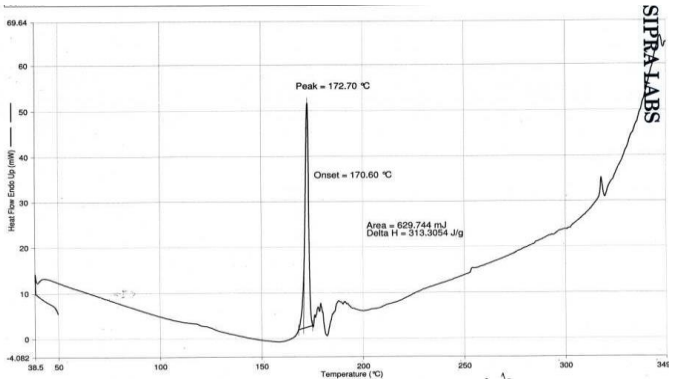


Figure : DSC Thermograms of Stavudine Pure Drug

V. CONCLUSION

The current study reveals that a great attempt has been made in order to formulate and study the drug release behavior of stavudine tablets with improved rapid release and bioavailability.

From all this experimental work we can conclude;

- A drug can be easily analyzed by using UV-Visible spectrophotometry shows maximum absorption. The value of linear regression coefficient was found to be 0.999, which indicates linear relationship between absorbance and concentration.
- IR studies reveals that their no significant interaction between the formulation components.
- From experimentation we can say that as the concentration of superdisintegrants increases there is increase in disintegration time and drug release behavior.
- Various combinations of superdisintegrants have a great impact on Disintegration time and drug release behavior as it improves both of them.
- The formulated tablets showed compliance for various physicochemical parameters such as disintegration, drug content and in-vitro drug release.

REFERENCES

[1] Adeyeye M. Viscoelastic Evaluation of Topical Creams Containing Microcrystalline Cellulose/Sodium Carboxymethyl Cellulose as Stabilizer. *AAPS Pharm Sci Tech,* Vol. 3(2): 76-82, 2002.

[2] Afrasim M, Shivakumar HG. Formulation of sustained-release diltiazem matrix tablets using hydrophilic gum blends. Tropical Journal of Pharmaceutical Research, 9 (3): 283- 291, 2010.

[3] Akhilesh Vikram S, Lila KN, Nihar RP. Development and validation of analytical method for the estimation of lamivudine in rabbit plasma. Journal of Pharmaceutical Analysis, 1; 4: 251–257, 2011.

[4] Akhilesh Vikarm S and Lila Kanta N. Evaluation of Compatibility of Lamivudine with Tablet Excipients and a Novel Synthesized Polymer. Journal of Materials and Environmental Science, Vol. 2(3): 243-250, 2011.

[5] Amelia M, Rakesh R and Shilpa N. Recent Investigations of Plant Based Natural Gums, Mucilages and Resins in Novel Drug Delivery Systems. Indian Journal of Pharmaceutical Education and Research, Vol. 45 (1): 67-73, 2011.

[6] Amit Kumar N, Ruma M and Biswarup D. Gastroretentive Drug Delivery Systems: A Review. Asian Journal of Pharmaceutical and Clinical Research, Vol. 3(1): 1-10, 2010.

[7] Anderson NR. Quantitative Evaluation of Pharmaceutical Effervescent Systems II: Stability Monitoring By Reactivity and Porosity Measurements. Journal of PharmceuticalSciences. Vol. 71(1): 7–13, 1982.

[8] Arunachalam A, Karthikeyan M, Konam K, Sethuraman S, Manidipa S. Floating drug delivery system: A Review. Internatioal journal of research in Pharmaceutical science. 2011; 2, 81-82.

[9] Asari A. Pharmacokinetics of Lamivudine in Subjects Receiving Peritoneal Dialysis in End-Stage Renal Failure British Journal of Clinical Pharmacology, Vol. 6(4): 738–44, 2007.

[10]Asasutjarit R. Viscoelastic Properties of Carbopol 940 Gels and their Relationships to Piroxicam Diffusion Coefficients in Gel Bases. Pharmaceutical Research, Vol. 22(12): 2134–2140, 2005.

[11]Ashok Kumar P, Damodar Kumar S. Effect of hydrophilic polymers on controlled release matrix tablets of acyclovir. INDIAN DRUGS 50(01): 42-49, 2013.

[12]Baaske DM. Stability of Nicardipine Hydrochloride in Intravenous Solutions", American Journal of Health System Pharmacy. Vol. 5(3): 1701–1705, 1996.

[13]Badoni A. Ojha A, Gnanarajan G, Kothiyal P. Review on Gastro Retentive Drug Delivery System, The Pharma Innovation. 2012; 1, 32-42

[14]Banker G. Evaluation of Hydroxypropylcellulose and Hydroxypropylmethyl Cellulose as Aqueous Based Film Coatings. Drug Development and Industrial Pharmacy, Vol. 7(2): 693–716, 1981.

[15]Banker G. Microbiological Considerations of Polymer Solutions used in Aqueous Film Coating. Drug Development and Industrial Pharmacy, Vol. 8(4): 41–51, 1982.

[16]Basak SC, Rao NK, Manavalan R and Rao R. Development and *in Vitro* Evaluation of an Oral Floating Matrix Tablet Formulation of Ciprofloxacin. Indian Journal of Pharmaceutical Sciences, Vol. 66(3): 313-316, 2004.

[17]Bashir Sajid N, Imran Khan, Hafeezullah, Alamgeer, Asad Muhammad H, Fakhar ul, Qamar S. Formulation and in vitro evaluation of nateglinide microspheres using HPMC and carbopol-940 polymers by ionic gelation method. Pakistan Journal of Pharmaceutical Sciences, 26, 6, p 1229, 2013.

[18]Bechgaard H, Ladefoged K., Distribution of pellets in gastrointestinal tract. The influence on transit time exerted by the density or diameter of pellets. J Pharm Pharmacol. 1978; 30: 690-692.

[19]Brahma N. Singh, Kwon H. Kim., Floating drug delivery systems - an approach to oral controlled drug delivery via gastric retention, Journal of Controlled Release,February 2000; 63 (3): 235-259.

[20] Chinna Devi G, Bhaskara Rao R. Formulation and evaluation of sustained release floating tablets of pioglitazone employing olibanum gum and HPMC. Asian Journal of Pharmaceutical and Clinical Research, 5; 1: 157-160, 2012.

[21]Dando TM and Scott L. Abacavir Plus Lamivudine: A Review of Their Combined Use in The Management Of HIV Infection. Drugs; 65: 285–302, 2005.

[22]Davis SS, Stockwell AF, Taylor MJ, et al. The effect of density on the gastric emptying of single and multiple unit dosage forms. Pharm Res. 1986;3:208-213.

[23]De Clercq E. Perspectives for the chemotherapy of AIDS. Chemioterapia**7** (6): 357–64, 1988.

[24]Deshpande SG and Shirolkar S. Sustained Release Ophthalmic Formulations of Pilocarpine. Journal of Pharmacy and Pharmacology, Vol. 4(1): 197–200, 1989.

[25]Debjit B, Chiranjib B, Margret C, B Jayakar. Floating Drug Delivery System: A Review. Der Pharmacia Lettre, 2009; 1(2): 199-218.

[26]Dhirendra Kumar, Vivek Dave, Shaila Lewis, Brajesh Parmar, Kavita R. Gajbhiye, Sarvesh Paliwal. Design andevaluation of sustained-release matrixonce daily formulation of stavudine. International Journal of Drug Delivery, 2: 2010: 125-134

[27]Dixit N. Floating Drug Delivery System. Journal of Current Pharmaceutical Research 2011; 7(1): 6-20.

[28]Suresh V Kulkarni, Ranjit Kumar P, Shankar Ms, Someshwara Rao B, Ashok Kumar P, Ramesh B. Formulation and in vitro evaluation of sustained release matrix tablet of stavudine. Asian Journal of Pharmaceutical and Clinical Research. Vol. 3:215-217, 2010

[29]Farnaz F and Alireza Mortazavi S. Preparation and *In-vitro* Evaluation of Gastroretentive Bupropion Hydrochloride Tablets. Tropical Journal of Pharmaceutical Research*.*, Vol. 13(3): 351-359, 2012.

[30]Fell J T, Whitehead L and Collet H. Prolonged Gastric Retention using Floating Dosage Forms. Pharmaceutical Technology, Vol. 24(3): 82-90, 2000.

[31]Fong IW. Hair loss associated with Lamivudine. *Lancet*, Vol. 1904, 34(4): 1702.

[32]Fulbandhe VM, Jobanputra CR, Wadher KJ, Umekar MJ, Bhoyar GS. Evaluation of release retarding property of gum damar and gum copal in Combination with hydroxypropyl methylcellulose. Indian Journal of Pharmaceutical Sciences, 74(3): 189– 194, 2012.

[33]Garg R and Gupta GD. Development and Evaluation of Gastro Retentive Floating Drug Delivery System of Acyclovir. Asian Journal of Pharmaceutics, Vol. 1(4): 34-40, 2007.

[34]Garg R, Gupta GD. Progress in controlled gastroretentive delivery systems. Trop. J Pharm Res 2008; 7(3): 1055-66.

[35]Gohel M.C., Mehta P.R., Dave, R.K., Bariya, N.H. (2004). A More Relevant Dissolution Method for Evaluation of Floating Drug Delivery System, Dissolutiontech. 11(4): 22-25.

[36]Goodman G. The Pharmacological Basis of Therapeutics, Mac Millan Publishing Company, New York, p. 1357. 6, 2001.

[37]Gopalakrishnan S and Chenthilnathan A. Floating Drug Delivery Systems: A Review. Journal of Pharmaceutical Science and Technology, Vol. 3 (2): 548-554, 2011.

[38]Gu T.H. Pharmacokinetics and Pharmacodynamics of Diltiazem Floating Tablets. *Chung Kao Yao Li Hsuesh Pao*, Vol. 1(3): 527-531, 1992.

[39]Groning R, Heun G. Oral dosage forms with controlled gastrointestinal transit. Drug Development and Industrial Pharmacy. 10; 527-539: 1984.

[40]Harland RS, Gazzaniga A and Peppas NA., Drug /Polymer matrix swelling and dissolution. Pharmaceutical Research, 5(2); 488-494: 1988.

[41]Hemanth Kumar AK, Sudha V, Soumya Swaminathan and Geetha Ramachandran. Comparison of HPLC & spectrophotometric methods for estimation of antiretroviral drug content in pharmaceutical products. Indian J Med. 132; 390-394: 2010.

[42]Hirtz J. The gastrointestinal absorption of drugs in man: areview of current concepts and methods of investigation. Br J Clin Pharmacol, 19; 77S-83S: 1985.

[43]Hiremath SN , Patil SD, Swamy PV, Younus Ali Md. Once-Daily sustained-release matrix tablets of metoprolol Tartrate : Formulation and in-vitro evaluation. Indian Journal of Pharmaceutical Education Research, 44(1), Jan-Mar, 2010

[44]Higuchi T. Mechanism of sustained action mediation, theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci 1963;52:1145-9.

[45]Hoffmann A. Pharmacodynamic aspects of sustained release preparations. Adv. Drug. Deliv. Rev 1998; 33 : 185-199.

[46]Hwang SJ, Park H, Park K. Gastroretentive delivery systems. Crit Rev Ther Drug Carrier Syst 1998; 15(3): 243-84.

[47]Ichikawa M, Watanabe S and Miyake Y. A New Multiple Unit Oral Floating Dosage System: Prepration and *in Vitro* Evaluation of Floating and Sustained-Release Kinetics", Journal of Pharmaceutical Sciences. Vol. 8(3): 1062-1066, 1991.