Original Research Article

Formulation and evaluation of floating matrix tablet of stavudine

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Abstract

Background/Aim: The purpose of the study was to prolong the gastric residence time of stavudine by designing its floating tablets and to study the influence of different polymers on its release rate. **Materials and Methods:** The floating mix matrix tablets of stavudine were prepared by melt granulation method. Beeswax was used as hydrophobic meltable material. Hydroxypropyl methylcellulose (HPMC), sodium bicarbonate, and ethyl cellulose were used as matrixing agent, gas generating agent, and floating enhancer, respectively. The prepared tablets were evaluated for physicochemical parameters such as hardness, weight variation, friability, floating properties (floating lag time, total floating time), drug content, stability study, and in vitro drug release. The drug- polymer interaction was studied by Differential Scanning Calorimetry (DSC) thermal analysis and Fourier transform infared (FT-IR). **Results:** The floating lag time of all the formulations was within the prescribed limit (<3 min). All the formulations showed good matrix integrity and retarded the release of drug for 12 h except the formulation F5.The concentration of beeswax (X_1), HPMC K_4M (X_2), and ethyl cellulose (X_3) were selected as independent variables and drug release values at 1 (Q_1), at 6 (Q_6) and at 12 h (Q_{12}) as dependent variables. Formulation F7 was selected as an optimum formulation as it showed more similarity in dissolution profile with theoretical profile (similarity factor, f_2 = 70.91). The dissolution of batch F7 can be described by zero-order kinetics (R^2 = 0.9936) with anomalous (non-Fickian) diffusion as the release mechanism (n = 0.545). There was no difference observed in release profile after temperature sensitivity study at 40°C/75% relative humidity (RH) for 1 month. **Conclusion:** It can be concluded from this study that the combined mix matrix system containing hydrophobic and hydrophilic polymer minimized the burst release of drug from the tablet and achieved a drug release by zero-order kinetics, which is practically difficult with only hydrophilic matrix.

Key words: Antiretroviral agent, bees wax, HPMC, *in vitro* buoyancy, melt granulation technology

INTRODUCTION

Acquired Immunodeficiency Syndrome (AIDS), which threatens to cause a great plague in the present generation, was first identified in California in 1981. AIDS is a disease in which the body's immune system breaks down and is unable to fight off infections caused by human immunodeficiency virus (HIV). HIV infects human cells and uses the energy and nutrients provided by those cells to grow and reproduce, so it is necessary to take many medicines for longer periods of time. This can lead to an increase in noncompliance of drugs. This problem is very serious in case of drugs having shorter biological half-life because they must be taken more number of times. It is crucial for the success of AIDS therapy to maintain systemic drug concentration consistently above its target antiretroviral concentration throughout the course of the treatment.[1,2] Oral drug delivery systems have progressed from immediate release to site-specific delivery over a period of time. Every patient would always like to have an ideal drug delivery system possessing the two main properties, i.e. single dose or less frequent dosing for the whole duration of treatment and the dosage form must release the active drug directly at the site of action.[3] Sustained release (SR) gastroretentive dosage forms (GRDF) enable prolonged and continuous input of the drug to stomach and upper parts of the gastrointestinal (GI) tract. These systems are designed to be retained in the stomach for longer period of time, and hence significantly prolong the gastric residence time of drugs. Therefore, different approaches have been proposed to retain the dosage form in the stomach,

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including bioadhesive systems, swelling and expanding systems, floating systems, and delayed gastric emptying devices.[4-6] Among these, the floating dosage form has been used most commonly. This technology is suitable for drugs with an absorption window in the stomach or in the upper part of the small intestine, drugs acting locally in the stomach, and for drugs that are poorly soluble or unstable in the intestinal fluid. The floating systems include single, multiple, and raft forming systems. The principle of these systems offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release. The present investigation is concerned about the development of mix matrix floating drug delivery systems by melt granulation technique that generates CO_2, and thus reduces the density of the system in the stomach for prolonged period of time and releases the drug slowly at the desired rate. Stavudine is used as a part of highly active antiretroviral therapy. Stavudine, a nucleoside analog of thymidine, is phosphorylated using cellular kinases to the active metabolite, stavudine triphosphate. Stavudine triphosphate inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate thymidine triphosphate and by causing DNA chain termination following its incorporation into viral DNA.[7] Stavudine is typically administered orally as a capsule and an oral solution. The drug has a very short half-life (1.5 h), thus necessitating frequent administration to maintain constant therapeutic drug levels. Formulation of extended release effervescent floating tablets of stavudine improves patient compliance and minimizes the dose-related side effects. Therefore, this study aims at formulating once a day floating mix matrix tablets using hydroxypropyl methylcellulose (HPMC) as the hydrophilic polymer and bees wax as the hydrophobic material release rate modifying polymer, and $NaHCO_3$ and ethyl cellulose were used as the floating aid and release modifier.

MATERIALS AND METHODS

Materials

Stavudine was a gift from Emcure Pharmaceutical Ltd. (Pune, India). HPMC K15M and bees wax were purchased from Yarrow chemicals (Mumbai, India). Ethyl cellulose was purchased from SD Fine Chem. Ltd. (Mumbai, India). Lactose and talc were obtained from Chemdyes Corporation (Ahmedabad, India). Magnesium stearate and sodium bicarbonate were purchased from Shakti Chemicals (Mehsana, India).

Method

Calculation for the dose of drug in the tablets

The total dose of stavudine for an SR formulation was calculated by the following four equations[8] using available pharmacokinetic data from a design of one compartment model with simultaneous release of loading dose and a zero-order release, maintenance dose, as described by Robison and Eriksen:[9]

$K_0 = D_iK_e$……..(1)

$D_m = K_0T$……..(2)

$D_l = Di\text{-}K_0T_p$…….(3)

$D_t = D_l + D_m$…….(4)

D_m = maintenance dose; T = time for sustained action; T_p = time to reach peak plasma concentration; elimination half-life of stavudine $t_{1/2}$ = 0.8–1.5 h (average 1.175); time to reach peak plasma concentration (T_P) = 1 h; initial dose (D_I) = 25 mg.

Elimination rate constant (K_e) = $0.693/t_{1/2}$

= 0.693/1.175

= 0.589 h

Zero-order release constant ($K_0 = D_I \times K_e$

= 25×0.589

= 14.74 mg/h

Loading dose (D_l) = $D_I - (K_0 \times T_P)$

= $25 - (14.74 \times 1)$

= 25 – 14.74

= 10.26 mg.

So, maintenance dose = total dose – loading dose

= 40 mg – 10.26 mg

= 29.74 mg.

Hence, the matrix tablet should contain a total dose of 40 mg for 12 h SR dosage form and it should release 25 − 14.74 = 10.26 (25.62%) mg in the 1st h like conventional dosage form and the remaining dose (40 − 10.26) in remaining 11 h, i.e. 29.74 (74.35%) mg or 2.70 (1.08%) mg per hour up to 12 h.

Hence, the theoretical drug release profile can be generated using the above value which is shown in Table 1.

Table 1: Theoretical profile of stavudine

Time (h)	Amount of drug release (mg)	% Drug release
1	10.25	25.62
2	12.96	32.4
3	15.66	39.15
4	18.36	45.9
5	21.06	52.65
6	23.76	59.04
7	26.46	66.15
8	29.16	72.9
9	31.86	79.65
10	34.56	86.4
11	37.26	93.15
12	40	100.00

Preliminary screening

Preliminary screening was carried out using three different grades of HPMC K_4M, three different concentrations of sodium bicarbonate, and three different concentrations of bees wax to select proper total floating time, floating lag time, and sustain the release up to 12 h. The formulas of batch HF1 to HF3 are shown in Table 2. NF1 to NF3 are shown in Table 3. BF1 to BF3 are shown in Table 4. Tablets prepared using different polymers were tested for total floating time, floating lag time, % drug content, weight variation, hardness, friability, *in vitro* drug release, etc.

Optimization by 2^3 full factorial design

A 2^3 randomized full factorial design was used in the present study. In this design, three independent factors were evaluated, each at two levels, and experimental trials were performed for all eight possible combinations. The concentrations of bees wax (X_1), HPMC K4M (X_2), and ethyl cellulose (X_3) were chosen as independent variables in 2^3 full factorial design. *In vitro* drug release values at 1 h (Q_1), 6 h (Q_6), and 12 h (Q_{12}) were taken as dependent variables. The formulation layout for the factorial design batches (F1–F8) is shown in Table 5a and b. Prepared tablets were evaluated for weight variation, hardness, thickness, % drug content, friability, buoyancy lag time, and *in vitro* drug release.

Preparation of stavudine floating tablets by melt granulation

Bees wax was melted in a large Petri dish at 60°C and the required quantity of stavudine was added to the melted mass. Previously prepared geometric mixture of HPMC K4M, sodium bicarbonate, and filler was added to the molten stavudine–beeswax and stirred well to mix. The mass was removed from the hot plate and subjected to scraping until it attained room temperature. The coherent mass was passed through 60 #. The granules was collected and mixed with talc (2%) and magnesium stearate (1%). The lubricated blend was compressed using round tooling on a Rimek-I rotary tablet machine (Karnavati Engineering, Kadi, India). Compression was adjusted to obtain tablets with hardness in the range of 2–3 kg/cm^2.

Evaluation of tablets

The prepared tablets were evaluated for weight variation, friability, hardness, content uniformity, *in vitro* dissolution study, floating lag time, and total floating time.

Weight variation

Twenty tablets were selected at random, weighed, and the average weight was calculated. Not more than two of the individual weights should deviate from the average weight by more than 7.5%.

Friability

For each formulation, pre-weighed tablet sample (20 tablets) was placed in the Roche Friability test apparatus (USP) EF-02 (Electrolab, Mumbai, India), which was then operated for 100 revolutions. The tablets were deducted and reweighed.

Table 2: Composition for preliminary screening of the polymer (different grades of HPMC) for total floating time

Name of ingredient	HF1 (%)	HF2 (%)	HF3 (%)
Stavudine	20	20	20
Bees wax	20	20	20
HPMC K4M	30	-	-
HPMC K100M	-	30	-
HPMC K15M	-	-	30
Ethyl cellulose	10	10	10
Sodium bicarbonate	5	5	5
Magnesium stearate	1	1	1
Talc	2	2	2
Lactose	q.s.	q.s.	q.s.

Table 3: Formulation of stavudine floating tablet using different amounts of sodium bicarbonate

Name of ingredient	Quantity (%)		
	NF1	NF2	NF3
Stavudine	20	20	20
Bees wax	20	20	20
HPMC K4M	30	30	30
Ethyl cellulose	10	10	10
Sodium bicarbonate	5	7.5	10
Magnesium stearate	1	1	1
Talc	2	2	2
Lactose	q.s	q.s	q.s

Table 4: Formulation of stavudine floating tablet using different amounts of polymer and wax

Name of ingredient	Quantity (%)		
	BF1	BF2	BF3
Stavudine	20	20	20
Bees wax	15	20	25
HPMC K4M	25	30	20
Ethyl cellulose	10	10	10
Sodium bicarbonate	5	5	5
Magnesium stearate	1	1	1
Talc	2	2	2
Lactose	q.s	q.s	q.s

Table 5a: Formulation layout

Batch	X_1	X_2	X_3
F1	−1	−1	−1
F2	+1	−1	−1
F3	−1	+1	−1
F4	+1	+1	−1
F5	−1	−1	+1
F6	+1	−1	+1
F7	−1	+1	+1
F8	+1	+1	+1

Table 5b: Compositions of formulations of factorial design

Ingredients	Quantity (mg/tablet)							
	F1	F2	F3	F4	F5	F6	F7	F8
Stavudine	40	40	40	40	40	40	40	40
Bees wax	30	40	30	40	30	40	30	40
HPMC K4M	40	40	50	50	40	40	50	50
Ethyl cellulose	10	10	10	10	20	20	20	20
$NaHCO_3$	10	10	10	10	10	10	10	10
Mg. stearate	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4
Lactose	64	54	54	44	54	44	44	34

Conventional compressed tablets that lose <0.5–1% of their weight were considered acceptable.

Hardness

Hardness of tablet was determined before and after sintering using Monsanto Hardness Tester.

Content uniformity

The drug content in each formulation was determined by triturating ten tablets and a quantity of powder equivalent to the mass of one tablet was extracted with pH 1.2 buffer and the solution was filtered through 0.45 μm membranes. The absorbance was measured at 266 nm after suitable dilution using UV visible spectrophotometer at λmax of 266 nm and the amount of stavudine was found using the calibration curve method.

In vitro floating studies

The *in vitro* floating of the tablets was studied at 37 ± 0.5°C in 100 ml of 0.1 N HCl. The time duration of tablet floatation was observed visually.[10,11]

In vitro dissolution study

The *in vitro* dissolution study of stavudine tablets was performed using USP apparatus (model TDT-08T; Electrolab, Mumbai, India) fitted with paddle (50 rpm) at 37 ± 0.5°C using simulated gastric fluid (SGF) (pH 1.2; 900 ml) as the dissolution medium. At predetermined time intervals, 10-ml samples were withdrawn, filtered through a 0.45-μm membrane filter, diluted, and assayed at 266 nm using a Shimadzu UV-1800 double-beam spectrophotometer (Shimadzu, Kyoto, Japan). Cumulative percentage release (CPR) of the drug was calculated using an equation obtained from a calibration curve.

Drug–excipient interaction compatibility study

FT-IR study

Fourier transform infrared (FT-IR) technique was used to study the physical and chemical interaction between the drug and excipients used. FT-IR spectra of pure drug and floating tablet were recorded using KBr mixing method on FT-IR instrument available at central instrument laboratory of the institute (FT-IR-1700, Shimadzu).

Differential Scanning Calorimetry (DSC)

DSC was used to study physical and chemical interaction between the drug and excipients used. DSC spectra of pure drug and drug composite mixture were recorded on DSC-60 instrument available at central instrument laboratory of the institute (DSC-60, Shimadzu).

Kinetic modeling of dissolution data

The dissolution profile of all factorial batches was fitted to various models such as zero order, first order, Higuchi,[12] Hixon Crowell,[13] and Korsemeyer and Peppas[14] to ascertain the kinetics of drug release. The method described by Korsemeyer and Peppas was used to describe the mechanism of drug release.

Short term stability study

To determine the change in *in vitro* release profile and on storage, a short-term stability study of the optimal batch was performed at 40°C in a humidity jar with 75% relative humidity (RH). Samples were withdrawn at 1 month interval and evaluated for any change in *in vitro* drug release pattern.[15]

RESULTS AND DISCUSSION

Results of preliminary screening

The evaluation results for different batches showed that batch HF1 which contained HPMC K4M (30%) gave maximum total floating time of more than 12 h [Table 2]. Hence, HPMC K4M was selected for further study. NF1 which contained 5% sodium bicarbonate gave a floating lag time of 137 sec and a total floating time of more than 12 h [Table 3]. Hence, 5% sodium bicarbonate was selected for further study. BF1 which contained 15% bees wax gave *in vitro* drug release of 95.75% [Table 4]. Hence, 15% bees wax selected for further study. Final prototype formulation is shown in Table 6 which was considered in full factorial design.

Results of full factorial design

The average weight of the tablet was found to be between 192.39 mg and 198.81 mg. The maximum variation from average was found to be ±2.30% from all the formulations. Hardness of the tablets for all the formulations was found to be between 2 and 3 kg/cm^2, with an average of 2.34 kg/cm^2. The percentage deviation in hardness was 0.265 kg/cm^2. Percentage friability for all formulations was found to be between 0.02 and 0.91%, with an average of 0.48%. Percentage drug content for all formulations was found to be between 97.00 and 101.10%. It was concluded that there was no loss of drug. Thickness of all the formulations was found to be between 1.80 and 2.30 mm. All these results are shown in Table 7.

In vitro drug release studies indicated that the drug release was higher in case of F1, F2, and F7. It indicates that as the concentration of bees wax increase in formulation the drug release decrease. Batch F7 showed the maximum drug release at 12 h, whereas batch F4 showed the minimum drug release at 12 h, as shown in Table 8.

The dissolution profile of all factorial batches was fitted to various models such as zero order, first order, Higuchi, Hixon Crowell, and Korsemeyer and Peppas to ascertain the kinetics of drug

Table 6: Prototype formulation of stavudine floating tablet

Ingredient	Quantity (%)
Stavudine	20
Bees wax	15
HPMC K4M	25
Ethyl cellulose	5
Sodium bicarbonate	5
Magnesium stearate	1
Talc	2
Lactose	q.s

Table 7: Evaluation parameter of factorial batches

Batch code	Weight variation (mg)	Hardness (kg/cm²)	Thickness (mm)	% Drug content	Friability (%)	Buoyancy lag time (sec)
F1	192.39 ± 2.38	2.00 ± 0.15	2.10 ± 0.025	100.20 ± 0.59	0.148	129
F2	196.71 ± 2.98	2.75 ± 0.26	1.92 ± 0.032	99.00 ± 1.04	0.020	93
F3	192.6 ± 2.86	2.00 ± 0.12	2.26 ± 0.031	97.00 ± 1.27	0.289	66
F4	197.37 ± 2.07	2.75 ± 0.17	2.05 ± 0.070	98.55 ± 0.93	0.90	58
F5	196.41 ± 3.89	2.00 ± 0.25	2.30 ± 0.045	99.50 ± 0.63	0.57	41
F6	193.21 ± 1.97	1.50 ± 0.15	1.90 ± 0.036	100.10 ± 0.73	0.573	182
F7	198.81 ± 3.02	2.75 ± 0.21	1.80 ± 0.062	100.80 ± 0.67	0.43	94
F8	193.62 ± 2.42	3.00 ± 0.10	1.90 ± 0.035	101.10 ± 0.95	0.91	102

Table 8: *In vitro* drug release profile of factorial batches

Time (h)	Cumulative percentage release (CPR)							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.25	15.89	10.45	14.29.	4.52	20.35	15.49	15.49	3.91
0.5	23.64	14.04	24.09	10.48	37.71	27.94	18.92	10.74
1	35.82	19.16	29.73	14.18	52.44	32.08	26.93	12.69
2	38.35	34..67	45.65	19.14	69.89	44.2	32.24	15.79
3	52.83	48.54	52.28	24.05	78.33	55.67	40.34	17.62
4	58.52	51.05	58.47	28.63	82.45	58.07	48.54	21.47
5	66.82	55..2	68.82	30.54	85.8	68.66	56.86	25.16
6	70.44	58.38	75.27	35.15	90.51	82.18	60.24	27.75
7	79.14	74.67	83.7	35.33	93.25	86.38	72.44	30.73
8	87.36	83.38	87.65	41.32	96.69	93.94	79.19	33.15
9	90.84	86.31	90.36	43.2	100.7	98.76	83.45	35.27
10	92.04	88.74	93.6	48.13	97.64	100.82	89.98	41.81
11	95.01	90.68	96.36	52.43	96.86	98.28	98.75	43.43
12	98.02	91.44	98.11	56.72	96.30	96.47	99.98	46.43

Table 9: Kinetic treatment of dissolution data

	F1	F2	F3	F4	F5	F6	F7	F8
Zero order								
b	7.194	7.469	7.46	3.528	4.922	8.357	7.380	2.915
a	28.487	28.423	28.423	12.529	58.283	27.093	18.678	9.828
R^2	0.9859	0.9721	0.9721	0.9791	0.8693	0.9841	0.9936	0.995
First order								
b	−0.105	−0.109	−0.109	−0.022	−0.146	−0.187	−0.081	0.055
a	1.998	1.995	1.995	1.9499	1.8141	2.226	2.007	1.086
R^2	0.9477	0.9809	0.9809	0.9860	0.9791	0.8435	0.9585	0.970
Higuchi								
b	29.312	30.873	30.87	14.50	21.002	34.201	29.867	11.838
a	1.578	−0.456	−0.455	−0.939	37.843	−4.482	−8.487	−0.991
R^2	0.9784	0.9927	0.9927	0.9888	0.9460	0.9850	0.9726	0.9809
Hixon Crowell								
b	0.243	0.253	0.252	0.069	0.2613	−0.353	0.2098	−0.120
a	0.257	0.263	0.2630	0.185	0.9431	−0.008	20.134	2.375
R^2	0.9771	0.9927	0.9927	0.9846	0.9777	0.9490	0.9781	0.9822
Korsemeyer and Peppas								
a	−0.494	−0.517	−0.517	−0.859	−0.254	−0.508	−0.621	−0.936
n	0.457	0.505	0.506	0.5091	0.269	0.5199	0.545	0.487
R^2	0.9584	0.9931	0.9931	0.9930	0.9696	0.9868	0.9682	0.9703

b = Slope, a = Intercept, R^2 = Correlation coefficient, n = Diffusion exponent

release [Table 9]. For batches F2, F3, F4, F6, and F7, the values of n were 0.505, 0.506, 0.5091, 0.5199, and 0.545, respectively, indicating non-Fickian release; whereas for batches F1, F5, and F8, the values of n were 0.457, 0.269, and 0.487, respectively, indicating Fickian release. F7 batch gave zero-order release.

Dissolution data of all batches were subjected to find f_2 similarity for the selection of optimum batch. Theoretical profile of stavudine was taken as reference. F7 batch showed maximum similarity (70.91) compared with other batches [Table 10]. Hence, formulation F7 was optimized based on the highest f_2 similarity (70.91) it showed zeroorder drug release.

Drug–excipient compatibility study was carried out using FT-IR 1700 (Shimadzu) and DSC-60 (Shimadzu). Drug–excipient interaction plays a vital role in the release of drug

from formulation. The drug exhibits carbonyl peak (C=O) at 1647.10 cm^{-1}, alkyl peak (=C–H) at 3024.18 cm^{-1}, and carbonyl amide group peak (N–H) at 3417.63 cm^{-1}. It was observed that there were no changes in these main peaks in the IR spectra of a mixture of drug and excipient [Figures 1 and 2].

DSC thermograms were obtained for pure stavudine and mix matrix floating tablet containing stavudine and other excipients. Pure powdered stavudine showed a melting endotherm at 172.10°C [Figure 3]. DSC thermograms of floating tablet showed the melting peak of the drug at 169.36°C [Figure 4]. There was no significant difference in the melting point of drug in both samples. It indicates that the drug was present in its characteristic physical and chemical form. It was compatible with all the excipients present in the tablet and there was no major interaction of the drug with the excipients.

Table 10: Comparison of *in vitro* drug release after stability study

Time (h)	CPR (initial) F7	CPR (after storage at 40 ± 2°C/75 ± 5% RH) after 1 month
1	26.93	28.34
2	32.24	34.16
3	40.34	43.68
4	48.54	46.98
5	56.86	57.23
6	60.24	65.41
7	72.44	69.30
8	79.19	75.74
9	83.45	81.39
10	89.98	89.45
11	98.75	96.17
12	99.98	98.44

Stability study was carried out by storing optimized formulation at 40 ± 2°C and 75 ± 5% RH for 1 month. At the end of the studies, samples were analyzed for the drug content, *in vitro* drug release, and floating lag time. There was not any change in morphological condition during the stability study and also not any measurable change in the remaining parameter, as shown in Table 7. *In vitro* drug release was 98.44% after 12 h [Figure 5]. Similarity factor of the batch after stability study was 77.09, which was comparable to the initial drug release profile.

CONCLUSION

It can be concluded from this study that the combined mix matrix system containing hydrophobic and hydrophilic polymer minimized the burst release of drug from the tablet and achieved a drug release by zero-order kinetics, which is practically difficult with only hydrophilic matrix. Bees wax used as hydrophobic material and HPMC K4M as hydrophilic material gave zero-order release of stavudine mix matrix floating tablet.

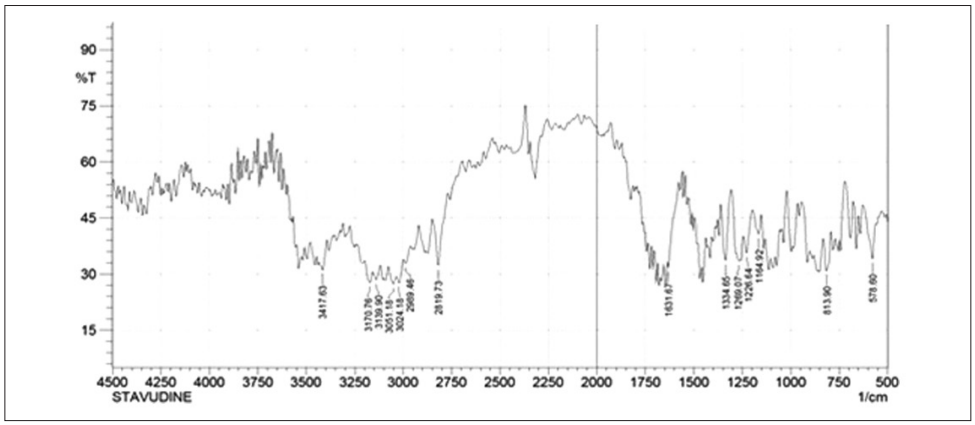

Figure 1: FT-IR spectrum of stavudine

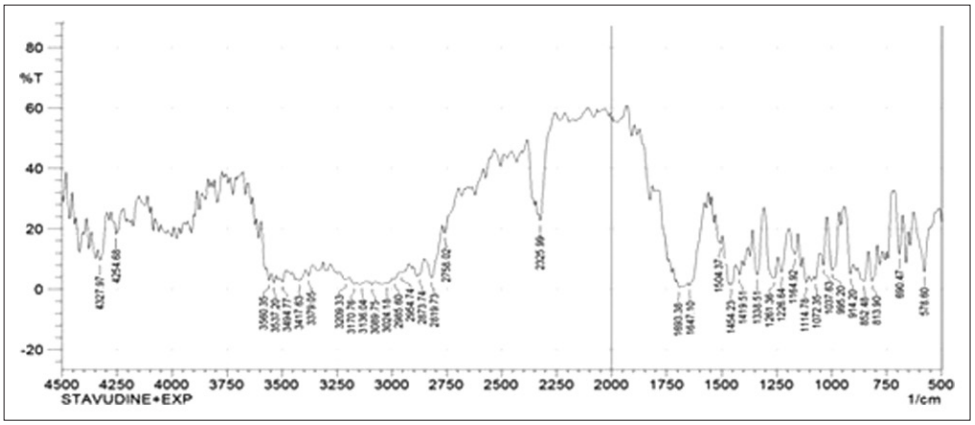

Figure 2: FT-IR spectrum of stavudine & excipients

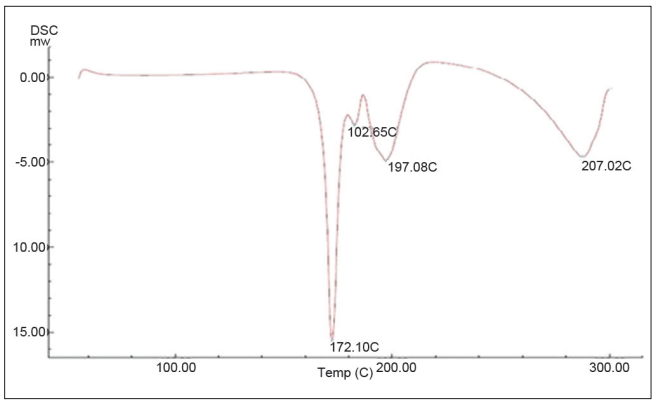

Figure 3: DSC thermogram of stavudine

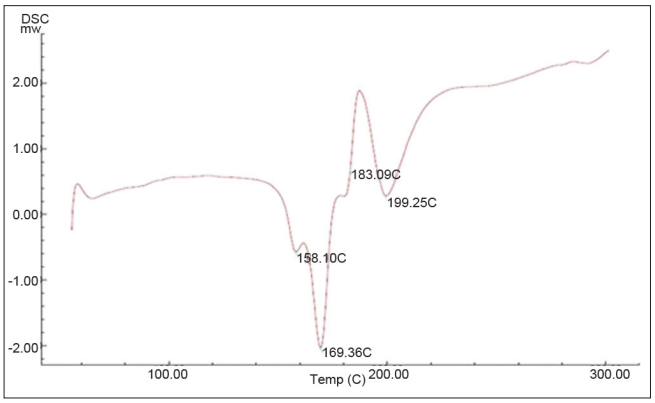

Figure 4: DSC thermogram of stavudine mix matrix floating tablet

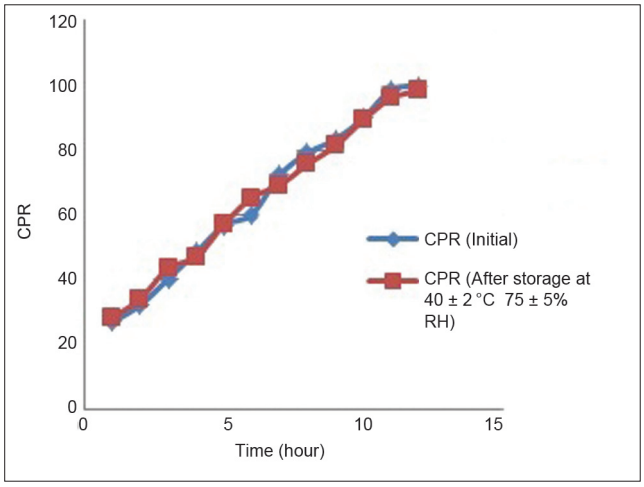

Figure 5: Comparison of release profile initially and after stability studies

Ethyl cellulose and sodium bicarbonate were used as floating enhancers and gave a total floating time of more than 12 h. From the regression analysis, insignificant factors were omitted. Formulation F7 was selected as an optimum formulation as it showed more similarity in dissolution profile with theoretical profile (similarity factor, $f_2 = 70.91$). The dissolution of batch F7 can be described by zero-order kinetics ($R^2 = 0.9936$) with anomalous (non-Fickian) diffusion as a release mechanism ($n = 0.545$). There was no difference observed in the release profile after temperature sensitivity study at 40°C/75% RH for 1 month.

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