ORIGINAL ARTICLE

Formulation and evaluation of controlled release floating matrix tablets of Stavudine

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The purpose of this research was to prepare and evaluate floating drug delivery systems of Stavudine. Floating matrix tablets of Stavudine were developed to prolong gastric residence time and increase its bioavailability. Rapid gastrointestinal transit could result in incomplete drug release from the drug delivery system above the absorption zone leading to diminished efficacy of the administered dose. The matrix tablets were prepared by direct compression technique, using polymers such as hydroxylpropylmethyl cellulose (HPMC K15M), karaya gum and other standard excipients. Sodium bicarbonate was incorporated as a gas-generating agent. The effect of different concentrations of polymers on drug release profile and floating properties were investigated. Comparable release profiles between the commercial product and the designed system were obtained. The matrix formulations were evaluated for physical parameters, drug release by *in vitro* dissolution studies and *in vitro* buoyancy studies. Surface characteristics, drug-excipient interactions and crystal morphology of optimized formulations were evaluated by SEM analysis and DSC studies.

Key words: *Anti HIV agent, floating tablets, gastroretentive, Stavudine*

INTRODUCTION

Oral administration is the most versatile, convenient and commonly employed route of drug delivery for systemic action. Indeed, for controlled release system, oral route of administration has received the more attention and success because gastrointestinal physiology offers more flexibility in dosage form design than other routes. Development of a successful oral controlled release drug delivery dosage form requires an understanding of three aspects: (1) gastrointestinal (GI) physiology, (2) physiochemical properties of the drug and (3) dosage form characteristics.[1,2] Novel oral controlled dosage form that is retained in the stomach for prolonged and predictable period is of major interest among academic and industrial research groups. One of the most feasible approaches for achieving prolonged and predictable drug delivery profile in the GI tract is to control gastric residence time (GRT). Dosage form with prolonged GRT or gastro-retentive dosage form (GRDF) provides an important therapeutic option.[3-7] Various approaches for preparation of gastroretentive drug delivery system include floating drug delivery systems, swellable and expandable systems, high density systems, bioadhesive systems, altered shape systems, gel forming solutions or suspension system and sachet systems.[8] Compared to these approaches the gastric floating drug delivery systems (FDDS) developed has provided several advantages as shown by the encouraging results reported earlier. The floating systems include gas generating systems, non effervescent systems and raft forming systems.[9,10] Furthermore, the buoyancy action provided by the FDDS seems to offer a greater safety for clinical uses than some of the above mentioned approaches. Infact, no adverse effects due to floating devices have been reported till date, but the sudden gastric emptying often affects their therapeutic efficacy.[11-14]

Stavudine is a dideoxynucleoside analog that inhibits reverse transcriptase and has *in vitro* activity against HIV. Stavudine is absorbed rapidly following oral

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administration producing peak plasma concentrations within 1 hr and with a reported bioavailability of about 86%. The virustatic drug has a very short half-life of 1-1.5 hrs.[15,16]

Based on the above physicochemical and biopharmaceutical properties, Stavudine was selected as a drug candidate for developing floating drug delivery systems to reduce the severity of toxicity and also to improve patient compliance. In the present investigation the drug Stavudine was selected for the design of FDDS. The drug has its absorption window in upper GIT. The physicochemical properties and short half-life of Stavudine make it as a suitable candidate for floating drug delivery. Hence, it is aimed to design and evaluate FDDS of Stavudine, with swellable polymers, gel forming hydrocolloid such as hydroxylpropylmethyl cellulose (HPMC K15M) and gum karaya by employing gas generating agent such as sodium bicarbonate.

MATERIALS AND METHODS

Materials

Stavudine was a gift sample from M/s Aurobindo Pharma Ltd., Hyderabad, Hydroxypropylcellulose (Methocel K15M) was a gift sample from Colorcon Asia Pvt. Ltd., Mumbai and karaya gum was commercially procured from Yarrow chem. Products, Mumbai., Avicel PH 112 was a gift sample from M/s Aurobindo Pharma Ltd., Hyderabad. Sodium bicarbonate was commercially procured from Qualigens Fine Chemicals, Mumbai. Magnesium stearate and talc were commercially procured from Colorcon Chemicals Asia pvt. Ltd., Mumbai. All other materials used were of pharmacopoeial grade.

Determination of stability of Stavudine in 0.1N HCl

The stability of Stavudine in 0.1N HCl was analyzed by dissolving it in the 0.1N HCl. The drug solution was set aside for 24 hrs and at specific time intervals; a small volume of sample was withdrawn and subsequently diluted with 0.1N HCl to get 10 µg/ml standard dilution. The dilutions were analyzed by UV Spectrophotometric method at 266 nm. The absorbance values were obtained for the samples at various time intervals.

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. 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 compositions of various tablet formulations are given. The materials were individually weighed, passed through sieve no: 60 and blended for 15 minutes by using double cone blender. The powder blends were evaluated for flow properties such as angle of repose and compressibility index and their corresponding results are given. The powder blends lubricated with 0.5% talc and magnesium stearate and were directly compressed as matrix tablets with 6 mm flat, round punches by using clit-10 station mini press. To minimize the processing variables all batches of tablets were compressed under identical conditions. The composition of various floating matrix tablets of Stavudine are given.

Evaluation of physical parameters

The physical parameters such as weight uniformity, hardness, friability and drug content were evaluated for the prepared floating matrix tablets as per the Indian Pharmacopoeial standards.[17] The physical parameters results are given.

Dissolution rate studies on Stavudine floating matrix tablets

Dissolution studies on each formulation were performed in a calibrated eight station test apparatus (LAB INDIA) equipped with paddles (USP apparatus II method) employing 900 ml of 0.1N HCl as a dissolution medium. The paddles were operated at a 75 rpm and the temperature was maintained at 37 ± 2°C throughout the experiment. Samples were withdrawn at regular intervals for 12 hrs 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 266 nm. The dissolution studies on each formulation were conducted in triplicate.

Pharmacokinetics of drug release

To analyse the mechanism of drug release studies from the obtained dissolution data, various kinetic calculations based on the equations of first order constant, higuchi constant and koresmeyer peppas constant respectively were used. The following are the equations:

$$\ln Q = k.t \quad (1)$$

$$Q = k.t^{1/2} \quad (2)$$

$$M_t/M_\infty = kt^n \quad (3)$$

Where Q in the equation (1) is cumulative percent drug remained, while Q in equation (2) is cumulative amount of drug released, M_t/M_∞ is the fraction of drug released, t is the release time and k is the constant incorporating the structural and geometrical characteristics of the release device. If the value of $n = 0.45$ indicates case I (Fickian) diffusion or square root of time kinetics, $0.45 < n < 0.89$ indicates anomalous (non fickian, drug diffusion in the hydrated matrix and the polymer relaxation) diffusion, $n = 0.89$ indicates case II transport and $n > 0.89$ indicates super case II transport. Linear regression analysis was performed for all these equations and regression coefficients (r) are determined.[18,19]

In vitro buoyancy studies

Floating time was determined by using USP XXIII dissolution apparatus-II at 75 rpm using 900ml of 0.1N HCl. and temperature was maintained at 37 ± 0.5°C, throughout the study. The duration of floating (floating time) is the time the tablet floats in the dissolution medium (excluding floating lag time, which is the time required for the tablet to rise to the surface) is measured by visual observation.[20] The results were summarized.

Characterization

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

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°C. After 1, 6, and 10 hrs, each dissolution basket containing tablet was withdrawn and blotted with tissue paper to remove the excess water and weighed on the analytical balance.[21] The experiment was performed in triplicate for each time point. Swelling index was calculated by using the following formula. The swelling indexes for various selected formulations of matrix tablets are shown.

$$\text{Swelling index} = \frac{(\text{Wet weight of tablet} - \text{Dry weight of tablet})}{\text{Dry weight of tablet}} \quad (4)$$

Scanning electron microscopy

The samples were coated with a thin gold layer by sputter coater unit (SPI, Sputter, USA). Then, the SEM photographs were taken by a scanning electron microscope (Scanning electron microscope JSM-6390, Japan) operated at an accelerated voltage of 15kV.

Differential scanning calorimetry

A differential scanning calorimeter (DSC 60, Shimadzu) was used to obtain the DSC curves of Stavudine controlled release floating matrix tablets prepared by direct compression method representing the rate of heat uptake. About 10 mg of sample was weighed in a standard open aluminium pans, were scanned from 20-300°C, at a heating rate of 10°C/minute while being purged with dry nitrogen.

RESULTS AND DISCUSSION

Stavudine stability in 0.1N HCl was performed for 24 hrs period. The values obtained at various time intervals were found to be linear. This showed that the drug remains stable in 0.1N HCl over a period of 24 hrs [Table 1]. The absorbance values were measured at 266 nm. Floating matrix tablet formulations were prepared as per the compositions shown in Table 2. Before compression process the powder blends were evaluated for flow properties such as angle of repose and carr's index. The angle of repose and carr's index values for all the powder blends prepared established good and free flowing characteristics. The flow property results are given in Table 3.

All the batches of tablets were compressed under identical conditions to minimize processing variables. The compressed matrix tablets were further evaluated for physical parameters such as weight uniformity, hardness, friability and drug content.[17] These studies revealed that all the tablet formulations were found to be stable and meeting Indian Pharmacopoeia specified limits for weight uniformity, friability and drug content. The hardness of all the tablet formulations was in the range of 6-6.5 kg/cm^2. Weight uniformity of all the tablet formulations were in the range of 198 ± 3.0 to 200 ± 3.0 mg. Friability loss of the tablet formulations were negligible and were in the range of 0.1-0.2%. Drug content estimated for all the tablet formulations were highly uniform with less than 3% variation. The physical parameters results are given in Table 3.

Dissolution studies were performed on all the tablet formulations by using USP paddle method (apparatus II). The drug release from the matrix tablet formulations were extended up to 12 hrs in the formulations F1, F2 containing HPMC K15M at 20% and 40% concentrations respectively as rate controlling polymer. The formulations F3, F4 prepared by using gum karaya at 20% concentration in tablet formulations as rate controlling polymer have failed to extend drug release up to 12 hrs. The formulations F5–F16 containing HPMC K15M and combination of HPMC K15M with gum karaya, showed initial rapid drug release due to presence of gas generating, while extending the drug release up to 12 hrs. It was found that the drug release from the matrix tablet formulations were dependent on the concentration of the polymer. As the concentration of HPMC K15M increases the drug release from the matrix tablets were extended the drug release over a prolonged period of time. But the combination of HPMC K15M and gum karaya in some of the tablet formulations such as F11

Table 1: Stability of Stavudine in 0.1N HCl

Time (hr)	Absorbance	Amount of drug
1	0.552	9.92
2	0.545	9.80
3	0.555	9.98
4	0.561	10.08
8	0.558	10.03
12	0.548	9.85
16	0.559	10.05
20	0.556	10.00
24	0.549	9.87

Table 2: Composition of various Stavudine controlled release floatingmatrix formulations

Ingredients (mg/tab)	Formulations															
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
Stavudine	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
HPMC K15M	40	80			40	40	40	20	20	20	40	40	40	60	60	60
Gum Karava			40	80				60	60	60	40	40	40	20	20	20
Sodium bicarbonate					15	25	35	15	25	35	15	25	35	15	25	35
MCC	116.5	765	116.5	76.5	101.5	91.5	815	61.5	51.5	41.5	615	515	41.5	615	515	415
Talc	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Mg stearate,	1.5	1.5	1.5	1 5	1.5	1 5	1.5	1 5	1 5	1 5	1 5	1 5	1 5	1 5	1 5	1.5
Total wt (mg)	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200

Table 3: Evaluation of Stavudine controlled release floating matrix tablets

Formulation	Angle of repose (θ)	Compressibility Index (%)	Weight uniformity (mg)	Hardness (kg/cm²)	Friability (%)	Drug content (mg/tablet)
F1	23.90	14.23	197±2.0	6.5±0.3	0.12	39.2±0.5
F2	22.34	12.17	198±3.0	6.5±0.3	0.12	40.2±0.5
F3	22.54	14.98	199±3.0	6.5±0.3	0.16	39.6±0.5
F4	23.30	15.77	201±3.0	6.5±0.3	0.18	40.8±0.3
F5	22.57	13.63	203±2.0	6.2±0.3	0.15	40.5±0.2
F6	21.36	11.57	202±3.0	6.2±0.3	0.13	39.4±0.3
F7	25.74	13.37	197±3.0	6.2±0.3	0.16	41.3±0.2
F8	22.14	12.61	201±2.0	6.2±0.3	0.18	40.7±0.5
F9	21.74	12.27	198±4.0	6.2±0.3	0.13	39.9±0.4
F10	24.62	12.37	197±4.0	6.2±0.3	0.15	41.5±0.3
F11	23.74	13.42	203±3.0	6.2±0.3	0.18	40.4±0.2
F12	21.37	12.87	201±3.0	6.2±0.3	0.19	39.7±0.5
F13	24.85	12.81	197±2.0	6.2±0.3	0.16	40.4±0.2
F14	24.54	13.83	199±4.0	6.2±0.3	0.14	40.2±0.3
F15	27.68	13.27	203±5.0	6.2±0.3	0.19	39.4±0.5
F16	25.73	13.07	198±4.0	6.2±0.3	0.18	41.3±0.4

and F14 formed good matrix and extended the release over a prolonged period of time. It was also observed that as the gas generating agent proportion increased the initial drug release from the matrix tablets. Among the formulations F14, F15 and F16 were found to extend the drug release over a prolonged period of time than compared to marketed formulation due to high proportion of HPMC K15M at 30% concentration along with 10% of gum karaya.

All the floating matrix tablet formulations were found to be linear with first order release rate with R^2 values in the range of 0.93-0.99. Thus the rate of drug release from all the matrix tablet formulations were concentration dependent and were linear with first order release rate constant (K_1). The higuchi constants for all the floating matrix tablet formulations except F3 and F4 were in the range of 10-13 $mg^{1/2}$ indicating the controlled drug release from the dosage form. The amount of drug released *v/s* square root time plots were found to be linear with R^2 values in the range of 0.91–0.99. The drug release from the matrix tablet formulations were by diffusion process. The release exponent (*n* values) for all the matrix tablet formulations were in the range of 0.5-0.8, indicated that the drug release was by non-fickian diffusion. Thus the drug release from the matrix tablet formulations was by diffusion of the drug from the polymeric matrix followed by erosion of the polymer. The mechanism of drug release from all the matrix tablet formulations was by both polymer erosion and diffusion of the drug from the matrix systems. The dissolution profiles of marketed and prepared formulations are shown in Figures 1-6. The R^2 values and release rate constants are given in Table 4.

The formulations F1 and F2 containing HPMC K15M alone floated with a floating lag time of 14-20 min and remained floating throughout duration up to 12 hrs. The formulations F3, F4 containing gum karaya floated with a floating lag time of 10-30 min but failed to float throughout duration up to 12 hrs. The formulations F5–F16 floated with a minimum

floating time due to gas generating agent, and continued to float throughout duration up to 12 hrs. It was observed that, floating lag time decreased with increase in concentration of sodium bicarbonate sin formulation F16. The results were summarized in Table 5.

Table 4: Drug release profile of Stavudine controlled release floating matrix tablets

Formulation	First order		Higuchi		Peppas	
	K (hr^{-1})	R^2	K ($mg^{1/2}$)	R^2	*n* value	R^2
F1	0.2855	0.977	12.15	0.985	0.628	0.987
F2	0.2635	0.990	11.94	0.973	0.661	0.947
F3	0.5112	0.977	16.31	0.961	0.760	0.975
F4	0.5329	0.996	17.06	0.990	0.784	0.985
F5	0.2910	0.955	12.24	0.959	0.538	0.983
F6	0.3170	0.966	12.66	0.987	0.605	0.987
F7	0.3110	0.955	12.96	0.961	0.538	0.985
F8	0.2990	0.974	12.25	0.977	0.750	0.952
F9	0.3310	0.977	12.86	0.980	0.743	0.962
F10	0.3008	0.966	13.03	0.979	0.734	0.975
F11	0.2216	0.984	11.49	0.951	0.531	0.977
F12	0.2849	0.947	12.49	0.950	0.535	0.986
F13	0.2903	0.945	12.50	0.936	0.593	0.971
F14	0.1934	0.987	10.50	0.948	0.583	0.980
F15	0.1965	0.984	10.56	0.953	0.612	0.968
F16	0.2057	0.963	10.90	0.969	0.646	0.966

Swelling index characteristics were performed on selected floating matrix tablet formulations. The floating matrix tablet formulation F1 and F2 containing HPMC K15M as polymer tends to swell at a rapid rate. The formulation F16 was found to have low swelling rate. It was observed that in formulation F16 the swelling rate was initially high due to presence of high concentration of sodium bicarbonate and the swelling was suppressed at the late duration due to the presence of gum karaya. The swelling indexes for various selected formulations of matrix tablets are shown in Table 6. The SEM photographs

Table 6: Swelling index of controlled release floating matrix tablets of Stavudine

Formulation	Swelling index (%)		
	1 hr	6 hr	10 hr
F1	70.25	100.51	103.50
F2	79.14	109.28	117.71
F16	87.5	98.50	89.75

Table 5: The floating lag times and floating times of matrix tablets of Stavudine

Formulations	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
Floating lag time(min)	20	14	25	30	2	1.5	1	6	4	2.5	4	3	2	3	2	1
Total floating time (hrs)	>12	>12	>8	>6	>12	>12	>12	>12	>12	>12	>12	>12	>12	>12	>12	>12

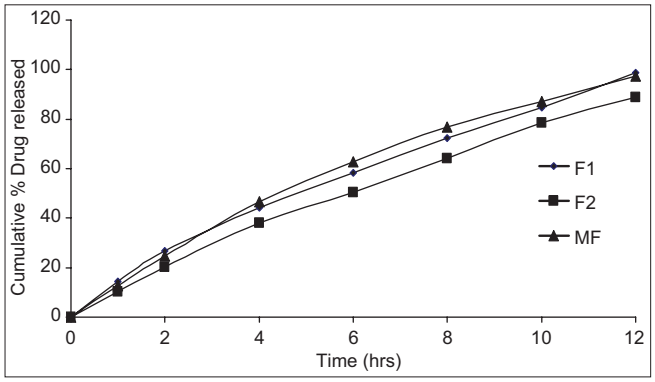

Figure 1: Dissolution profiles of Stavudine floating matrix tablets

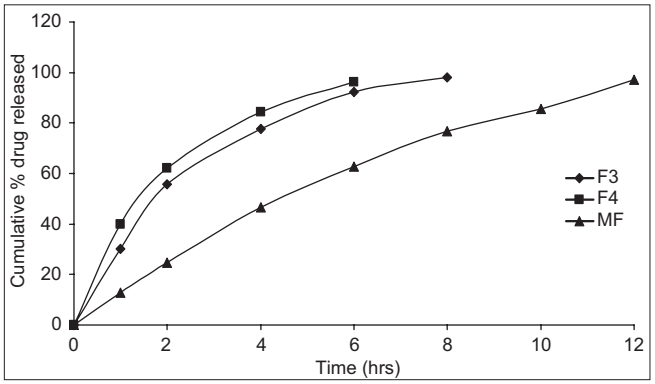

Figure 2: Dissolution profiles of Stavudine floating matrix tablets

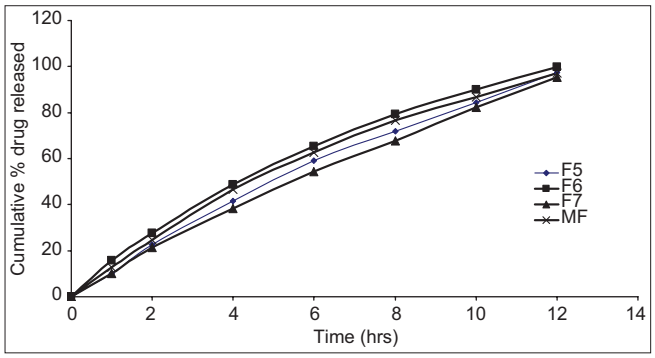

Figure 3: Dissolution profiles of Stavudine floating matrix tablets

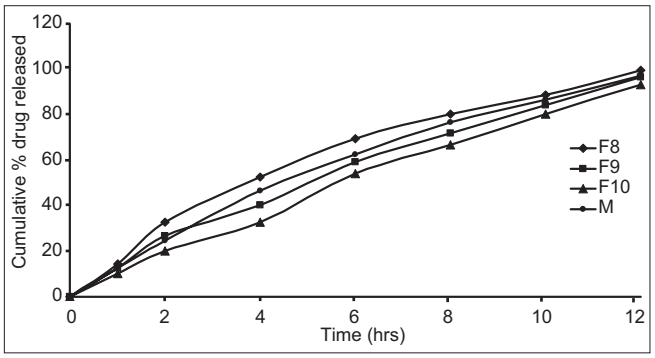

Figure 4: Dissolution profiles of Stavudine floating matrix tablets

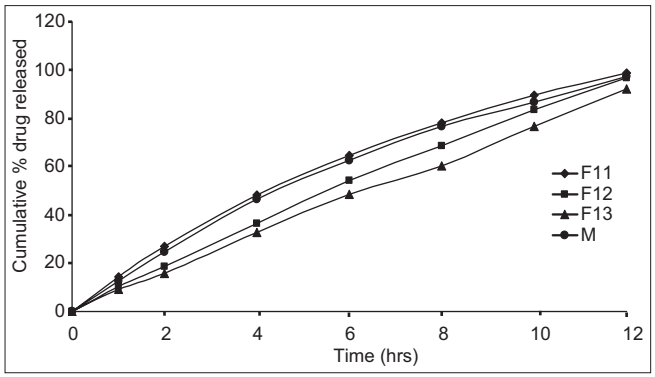

Figure 5: Dissolution profiles of Stavudine floating matrix tablets

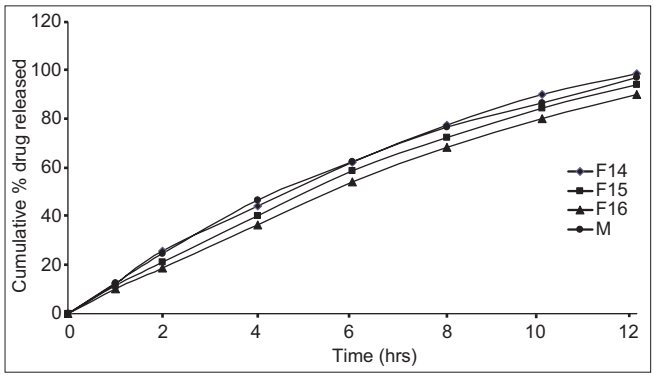

Figure 6: Dissolution profiles of Stavudine floating matrix tablets

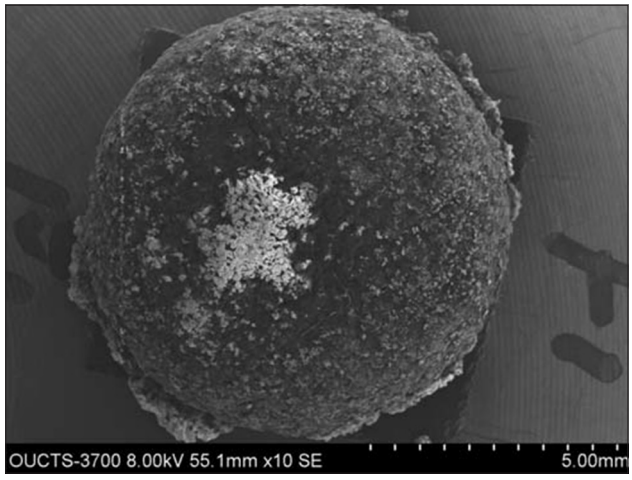

Figure 7: Scanning electron microscope photographs of Stavudine floating matrix tablets containing HPMC K 15M as polymer in formulation F1

were taken for F1, F16 are shown in Figures 7 and 8. The SEM photographs of formulations F1 showed minimum pores on the surface. Erosion of the polymer was observed in the photograph. This indicated the drug release by both drug diffusion and polymer erosion. The SEM photograph of formulation F16 showed erosion of the surface and formation of pores on the surface due to presence of gas generating agent, which indicated the drug release by both drug diffusion and polymer erosion.

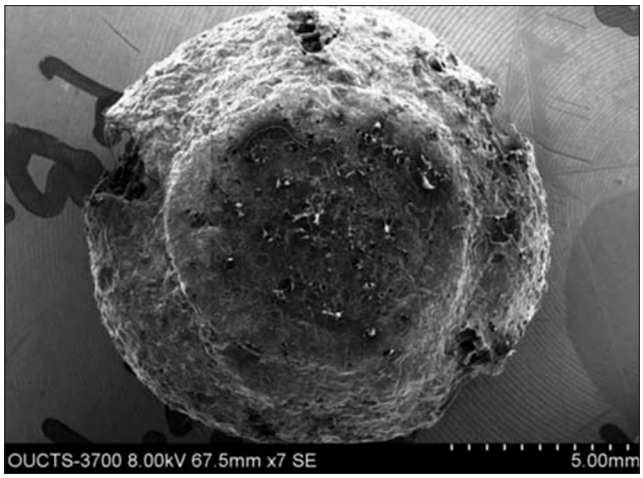

Figure 8: Floating matrix tablets of Stavudine containing combination of HPMC K 15M and gum Karaya along with a gas generating agent in formulation F16

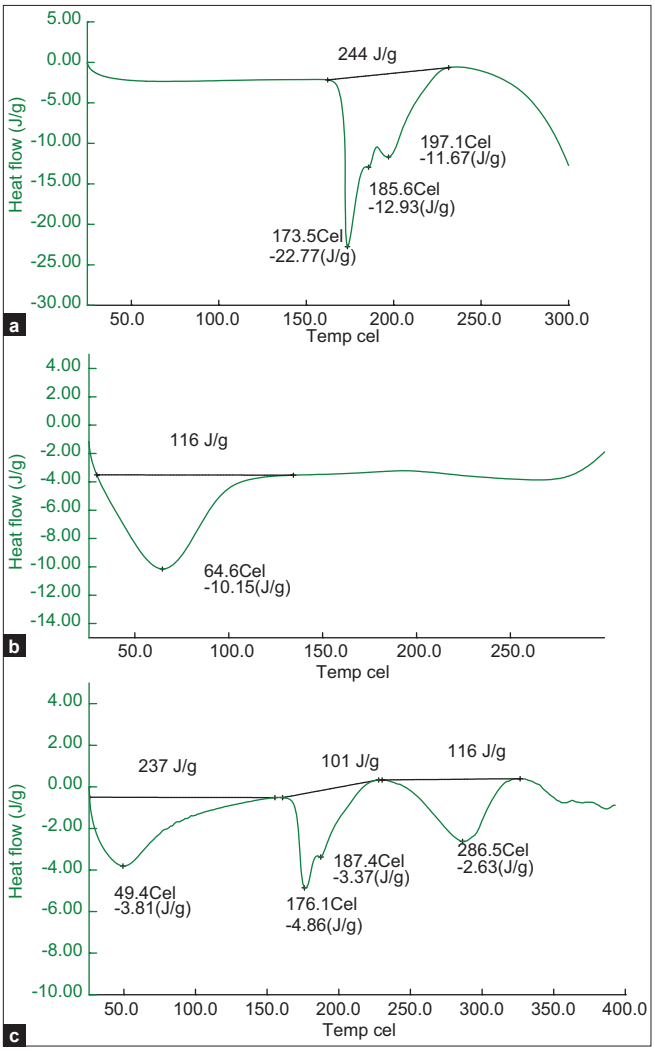

Figure 9: Differential scanning calorimetry curves for Stavudine pure drug, HPMC K15M, Stavudine + HPMC K15M and optimized formulations (a) Stavudine (b) HPMC K15M (c) Stavudine + HPMC K 15M + Gum Karaya

The DSC thermogram in Figure 9 of Stavudine showed sharp endothermic peak at 173.5°C, while that of HPMC K15M showed broad endothermic peak at 64.6°C. The DSC thermograms of admixture of Stavudine with HPMC K15M and gum karaya in formulations F1 and F16 showed sharp endothermic peaks for Stavudine at the temperatures similar to that of the peak of Stavudine alone. This indicated that there were no drug excipient interactions in the formulations.

CONCLUSION

From the evaluation studies of all the formulations, the formulations F14, F15 and F16 containing HPMC K15M and gum karaya showed the best results regarding buoyancy lag time as well as total buoyancy time and also showed extended release for a prolonged period than compared to marketed formulation. Hence it can be concluded that floating matrix tablets showed the best results when the polymer ratio of HPMC K15M and gum karaya was maintained at 3:1. Hence the floating matrix tablet of Stavudine was a novel approach so as to avoid the disadvantages of anti-retroviral conventional dosage forms.

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