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Formulation and Evaluation of Gastro Retentive Floating Micro balloons of Abacavir Sulphate

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ABSTRACT

The research work was mainly focused on the formulation and evaluation of gastro retentive Abacavir floating microballoons as to retain the formulation for a prolonged period of time and deliver the drug to the site of absorption. This work focused on to investigate the suitability of different viscosities of ethyl cellulose in different concentrations. Abacavir sulphate is a recently approved anti retro-viral drug with very short biological half life (1.0 hrs) and bioavailability (70%), it has better absorption from upper part of GIT. The microballoons were prepared by non-aqueous solvent evaporation method using polymer such as different viscosities of ethyl cellulose (25cps, 100cps), in different ratios and Abacavir sulphate in each formulation. The prepared microballoons were characterized by polymer compatibility (FTIR), The FTIR spectra of drug and different polymers showed no shift in peak, hence no interaction. Micromeritic properties such as Bulk density, Tapped density, Carr's index and Angle of repose. Other properties including percentage of floating buoyancy, drug entrapment efficiency, percentage of yield, *in vitro* drug release and SEM studies. The prepared floating microballoons were found to produce the percentage of yield was in the range of 82.7 - 98.5 %, drug entrapment efficiency was 68 %-98.9 %, percentage of floating buoyancy was 70.2 - 80.6 % and *in vitro* drug release was 94.67 % per 12hrs. Scanning electron microscopy (SEM) confirmed their spherical size, perforated smooth surface and a hollow cavity in them. The best drug release, entrapment efficiency and percentage of floating buoyancy profiles were seen with formulation F10 at the ratio of drug to polymer (EC-100cps) of 1:5.

Keywords: Abacavir sulphate, Ethyl cellulose, Floating microballoons, Floating buoyancy, *In vitro* drug release studies.

INTRODUCTION

Gastro retentive drug delivery system

Gastro retentive drug delivery systems can remain in the stomach for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged the gastric retention improves bioavailability, reduces the drug waste [1]. Their application can be advantageous in the case of drugs absorbed mainly from the upper part of GIT or unstable in the alkaline medium [2]. GRDDS can be used as carriers for drugs having narrow absorption windows. Microballoons are solid spherical particles having central hollow space [3]. Floating microballons are non effervescent multiple unit systems, floated on gastric fluid by low density [4].

Floating Microballoons

Floating microballoons are gastro-retentive drug delivery systems based on non-effervescent approach. Microballoons are in strict sense, spherical empty particles without core. These microballoons are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 micrometer [5]. Solid biodegradable microballoons incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs [6]. Gastro-retentive floating microballons are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. As the system floats over gastric contents, the drug is

released slowly at desired rate resulting in increased gastric retention ith reduced fluctuations in plasma drug concentration [7].

Advantages of floating Microballoons

- It has lower potential for dose dumping and it minimizes the risk of local irritation.
- It has shorter floating lag time and greater gastric retention.
- It distributes more uniformity of drug in GIT.
- It has very low particle size.
- Improve drug absorption.
- Decreasing dosing frequency and cost of the drug
- Avoiding first pass metabolism
- Better patient compliance by reducing repeated administration.
- It was also filled into hard gelatin capsules or compressed into tablets.

The purpose of this research work was to formulate and evaluate gastro retentive floating microballons of Abacavir sulphate using different concentrations of ethyl cellulose [8]. The floating microballons prepared by non-aqueous solvent evaporation technique. To study the effect of various factors like drug polymer ratio of different polymers on the parameters like percentage of floating buoyancy, drug entrapment efficiency and *in vitro drug* release study [9].
Abacavir sulphate is a nucleoside reverse transcriptase inhibitor with antiretroviral activity against HIV. It is administered alone or in combination therapy with other. It is well absorbed following oral administration. It's solubility in stomach pH is higher than intestinal pH [10].

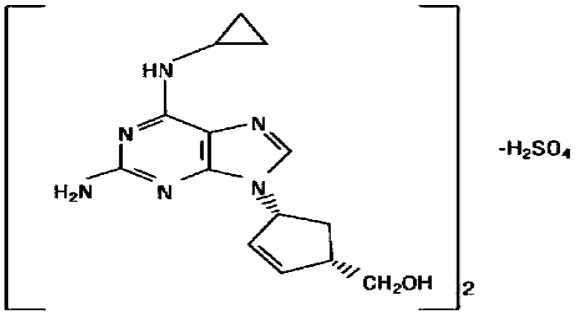

Figure 1: Structure of Abacavir sulphate

MATERIALS AND METHODS

Materials

Abacavir sulphate was obtained as a gift sample from mylon Ltd., (Bangalore). Ethyl Cellulose was used as polymers. Light Liquid Paraffin (SD Fine Chemicals) served as dispersing medium. Dichloromethane (DCM), ethanol served as solvent mixture was also obtained from CDH, New Delhi. All other chemicals/reagents were of analytical grade.

Methods

Drug-excipient compatibility study: FTIR spectroscopy

Compatibility studies were carried out to know the possible interactions between Abacavir sulphate and excipients used in the formulation [11].

Determination of absorption maximum (λ_{max}) of Abacavir sulphate

From the UV spectrophotometric analysis it was conclude that the drug, Abacavir sulphate showed a λmax at 296 nm. Therefore the observed λmax was used for further work to analyze the test samples

Calibration curve

The calibration curves for Abacavir sulphate in 0.1 N HCl, phosphate buffer pH 6.8, pH 7.8 was developed spectrophotometrically at 296 nm [12].

Preliminary Solubility studies Abacavir sulphate

The equilibrium solubility of Abacavir sulphate was measured in 0.1M hydrochloric acid (pH of 1.2), phosphate buffer of pH 6.8 and phosphate buffer of pH 7.8 respectively in order to determine its solubility. Excess amount of the drug were

added to 50 mL-stoppered conical flasks (n=3). The flasks were shaken mechanically at 37°C±0.5°C for 24 hrs, in a horizontal shaker. After 2 days of equilibrium, aliquots were withdrawn and filtered (0.22 µm pore syringe filter). Then, the filtered samples were assayed by UV-spectrophotometer [13].

Preparation of Floating Microballoons

Floating Microballoons containing Abacavir sulphate as a core material were prepared by the non-aqueous solvent evaporation method. Briefly, the polymer was dissolved in the 1:1 ratio of solvent mixture of dichloromethane and ethanol to this mixture drug was added. The solution of drug and polymer mixture was poured drop by drop into light liquid paraffin while being stirred at 600 rpm by a mechanical stirrer equipped with a three bladed propeller at room temperature. The stirred was continued for two hours (2 hrs) to allow to solvents (Dichloromethane, Ethanol) to evaporate completely and the formed microspheres were collected by filtration. The microballoons were washed repeatedly with petroleum ether until free from oil. The collected microballoons were dried at room temperature for 24 hours then store in desiccators [14].

Table 1: Formulation of Abacavir sulphate floating Microballoons

Batch code	Drug: EC25 cps	Drug: EC100 cps	DCM: Ethanol	Dispersion medium (ml)
AS1	1:1	-	1:1	250
AS2	1:2	-	1:1	250
AS3	1:3	-	1:1	250
AS4	1:4	-	1:1	250
AS5	1:5	-	1:1	250
AS6	-	1:1	1:1	250
AS7	-	1:2	1:1	250
AS8	-	1:3	1:1	250
AS9	-	1:4	1:1	250
AS10	-	1:5	1:1	250

Each batch contain 300 mg of Abacavir sulphate **EC -** Ethyl Cellulose, **DCM -** Dichloro methane, **Dispersion medium -** Light Liquid Paraffin, **Speed -** 600 rpm.

Evaluation of floating microballoons of Abacavir sulphate

Physico chemical properties and floating properties of Abacavir sulphate microballoons

Floating microballons were evaluated for physicochemical properties of all batches by measuring the angle of repose [15], and Carr's index [16], mean particle size [17] and floating properties like drug entrapment efficiency [18], percentage yield [19], and floating buoyancy [20].

***In vitro* drug release studies**

Drug release tests on each batch of the microballoons were carried out using a USP type-II dissolution rate test apparatus (DISSO 2000, Lab India). Microballoons equivalent to 300 mg of Abacavir sulphate were spread over dissolution medium containing 900 ml of 0.1 N HCl (pH 1.2) and stirring speed of 75 rpm and temperature of 37 ± 0.5ºC. A 5ml quantity of the dissolution medium was sampled at predetermined time intervals, and fresh dissolution medium was simultaneously used to replenish to maintained sink conditions. The sample was filtered through filter disc and the filtrate was diluted with fresh dissolution medium if necessary. The samples were analyzed using UV-visible double beam spectrophotometer against an appropriate blank. From this percentage drug release was calculated and plotted against function of time to study the pattern of drug release [21].

RESULTS AND DISCUSSION

Preformulation studies

The possible interaction between drug and excipients used in the formulation development of floating microballoons were studied by FTIR spectroscopy.

Drug excipient compatibility studies

The drug excipient compatibility was studied by FTIR studies.

FTIR Studies

The possible interaction between drug and excipient used n the formulation development of floating microballoons was studied by FTIR spectroscopy.The FTIR spectra of abacavir sulphate showed characteristic peaks (in cm^{-1}) at 1674 owing

to C=N aromatic stretch (1630-1690, 1519 due to N-H bending (1500-1650), 1106 due to O-H stretch of alcohols (1050-1150), C-H bending aromatic 773 (700-850), C-H rocking 657 (600-900). The spectra indicated that there was no drug-excipient interaction as the peaks of the drug and other excipients were seen in the drug-excipient mixture and in the optimized formulation (F10), indicating that the drug molecule was present in an unchanged state in the formulation (F10).

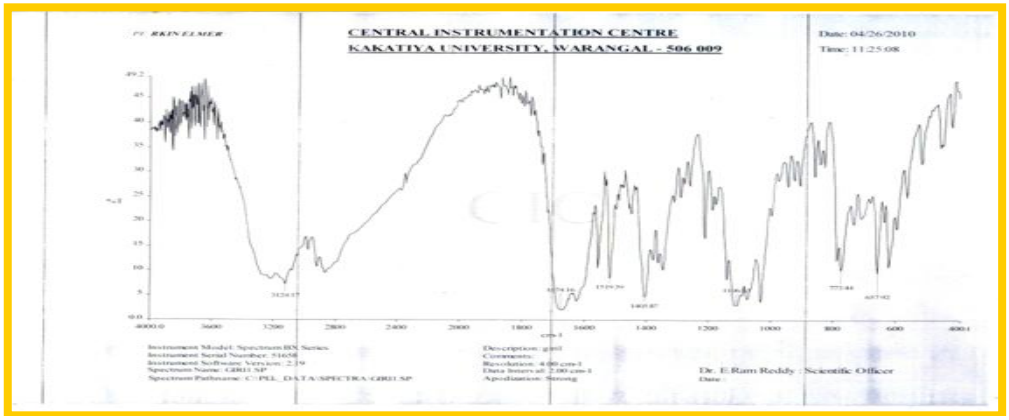

Figure 2: FTIR spectra of Abacavir sulphate

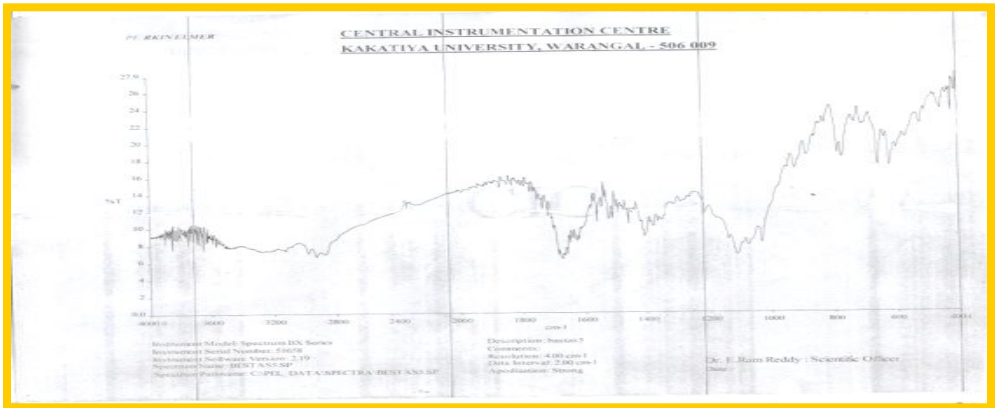

Figure 3: FTIR spectra of optimized batch F10

Determination of absorption maximum (λ_{max}) of Abacavir sulphate

From the UV spectrophotometric analysis it was conclude that the drug, Abacavir sulphate showed a λmax at 296 nm. Therefore the observed λmax was used for further work to analyze the test samples.

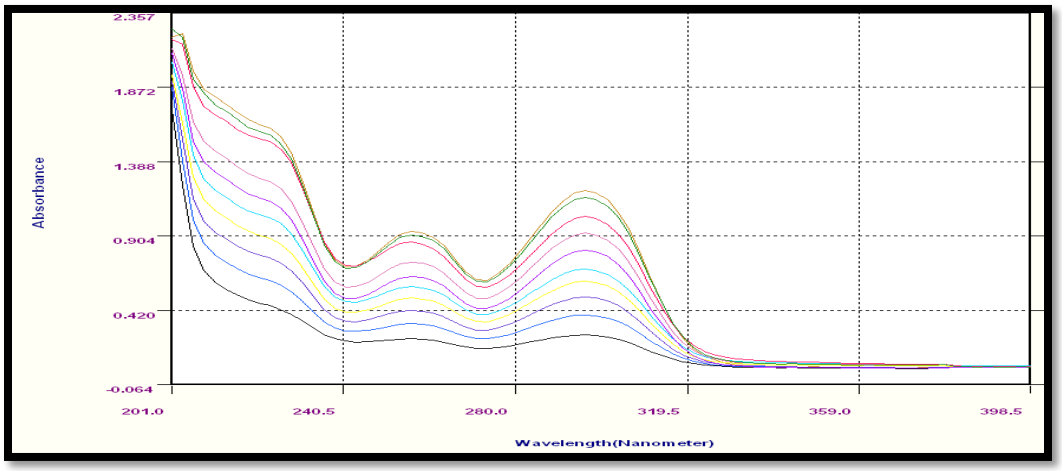

Figure 4: Absorption maximum of Abacavir sulphate in 0.1 N HCl, it was 296 nm.

Calibration curve

The calibration curves for Abacavir sulphate in 0.1 N HCl, phosphate buffer pH 6.8, pH 7.8 was developed spectrophotometrically at 296nm.

Standard graph of Abacavir sulphate in 0.1 N HCl

The concentration of Abacavir sulphate and the corresponding absorbance were given in the table.2 and the plot of concentration verses absorbance was shown in Fig.5. The solution obeyed Beer-Lambert's law over a concentration range of 4 µg -20 µg /ml with a regression co-efficient of 0.995. This standard curve was used further to estimate Abacavir sulphate in the *in vitro* studies.

Table 2: Standard graph values of Abacavir in different media

Concentration (µg /ml)	Absorbance in 0.1 N HCl	Absorbance in PBS pH 6.8	Absorbance in PBS pH 7.8
0	0	0	0
4	0.263	0.202	0.299
6	0.392	0.28	0.359
8	0.510	0.371	0.442
10	0.612	0.461	0.563
12	0.690	0.545	0.668
14	0.813	0.645	0.775
16	0.925	0.713	0.84
18	1.032	0.808	0.923
20	1.158	0.925	0.964

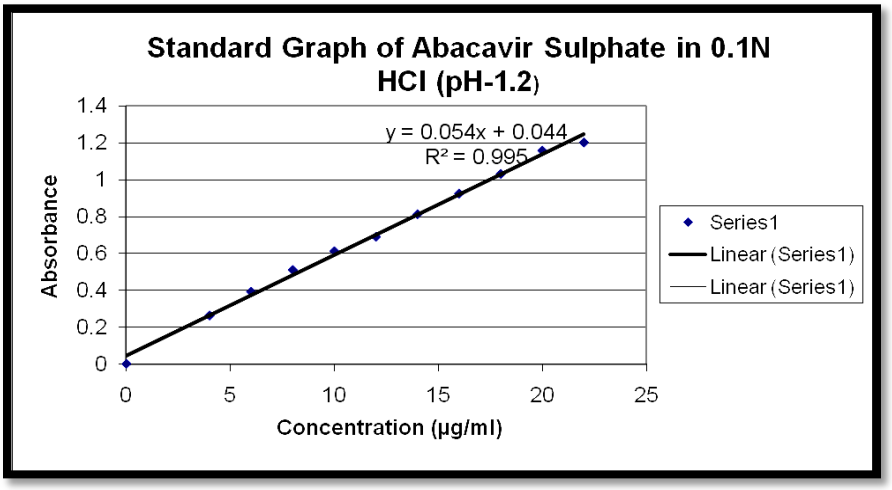

Figure 5: Standard graph of abacavir sulphate in 0.1 N HCl

Solubility studies

The solubility of Abacavir sulphate was determined in various pH ranges. The solubility of Abacavir sulphate was found to be 800 mg/ ml (pH 1.2). 340 mg/ml in phosphate buffer pH 6.8 and 200 mg/ml in phosphate buffer pH 7.8. The results revealed that as the pH of the solution increased, the solubility of Abacavir sulphate decreased. This pH dependent solubility of the drug along with the fact that the drug is mainly absorbed from the upper part of gastrointestinal tract (stomach) necessitates the development of a gastro retentive dosage form, which remain in the acidic conditions and facilitates dissolution and subsequent absorption increase the biological half life of the drug. Therefore, floating microballoons of Abacavir sulphate were developed.

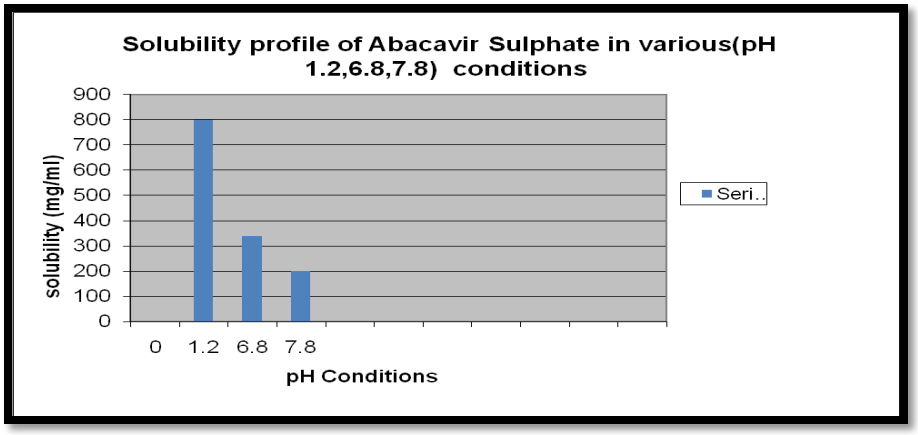

Figure 6: Solubility profile of abacavir sulphate

Results of the evaluated parameters of formulated floating microballoons

Micromeritic properties

Floating microballoons were found to be spherical in and having internal hollow, the flow properties of microballoons were listed in the table 3. Flow properties of batches were evaluated by measuring the angle of repose and compressibility index. In the evaluation of flowability of dry solid ,the substances shows excellent flowability of performance, when the angle of repose have the value less than 22^0 while when compressibility index has value below 14.63, no aid is needed for enhancing the flowability of power. Thus, angle of repose and compressibility index are indicates of good flowability of floating microballoons, showing no need for addition of glidant to enhance flowability. The better flow properties of microballoons indicate that the microballoons produced were non-aggregated. The improved micromeritic properties of formulated microballoons when compared to that of the pure drug alone suggest that they can be easily handled and filled into a capsule.

Table 3: Flow properties of microballoons

Formulation Code	Angle of repose	Bulk density (gm/cm^3)	Tapped bulk density (gm/cm^3)	Carr's Index
AS1	18º96´	0.469	0.508	07.67
AS2	19º73´	0.492	0.505	02.57
AS3	20º21´	0.414	0.545	08.81
AS4	20º14´	0.510	0.56	08.92
AS5	21º61´	0.487	0.503	03.18
AS6	19º74´	0.414	0.485	14.63
AS7	19º81´	0.422	0.490	13.87
AS8	20º33´	0.450	0.515	12.91
AS9	20º73´	0.266	0.30	11.33
AS10	22º21´	0.431	0.480	10.20

The prepared floating microballoons were evaluated for various parameters such as Particle shape, percentage of yield, drug entrapment efficiency, percentage of buoyancy; *in vitro* drug release studies and its results were given below.

Morphology

Surface properties and internal structure of microballoons had been revealed by scanning electron microscopy (SEM). The microphotographs of cross section and surface view of microballoons of optimized batch F10 are shown in figure 7. The cross sectional photomicrographs of the microballoons are shown in A) shows the smooth surface of the microballoons B) shows the round cavity surrounded by the thick shell of the microballoons, SEM indicates that the microballoons produced by the non-aqueous solvent evaporation method are spherical with smooth surface and not aggregated. Their smooth surface indicated that Abacavir was embedded in the shell, as the drug particles were not present on the surface of the floating microballoons

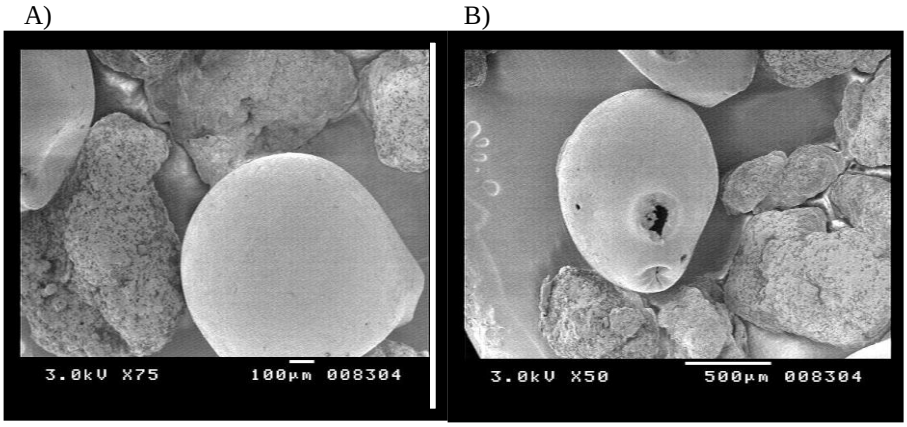

Figure 7: Particle morphology of optimized floating microballoons,
A) Shows the smooth surface of the microballoons, B) shows the round cavity (hollow) surrounded by the thick shell of the microballoons

Percentage yield of abacavir floating microballoons

The yields of the individual formulations were calculated and a bar graph represents the yield of various formulations. The yield was high for the F9 amounting of 98.5% and the yield of F6 was low amount among all formulations to 80.6%.

Figure 8: Prepared floating microballoons of abacavir sulphate

Drug entrapment efficiency (DEE)

The drug entrapment efficiency of the prepared formulations were calculated and the results were given below. The drug entrapment efficiency was higher for F10 formulation (98.9%) and it was lower for F1 (68 %). The results obtained clearly indicated that the drug entrapment efficiency increased as the drug to polymer ratio increased. molecule.

Percentage of floating buoyancy

The *in vitro* floating ability of formulated floating microballoons were evaluated. The floating ability was higher for F5 (80.6) and it was lower for F6. The floating ability was decreased with increase the particle size by increasing viscosity of polymer due to as the size was small, the mass to volume ratio (density) may be more leading to early settling of the microballoons.

Table 4: Percentage of yield, Entrapment efficiency and Percentage of floating buoyancy data for F1-F10 formulations

Batch. No	Yield (%)	DEE (%)	PFB (%)
F1	82.7 ± 2.82	68 ± 2.23	73.8± 2.20
F2	97.5 ± 3.04	72 ± 2.33	74.48± 2.31
F3	92.8 ± 3,51	86 ± 2.41	79.10± 2.34
F4	97.7 ± 2.80	90 ± 2.08	79.54± 2.52

F5	97.7 ± 2.18	93 ± 2.56	80.6± 2.31
F6	80.6 ± 2.80	69 ± 2.24	70.2± 3.01
F7	98.5 ± 2.82	74 ± 2.36	72.6± 2.56
F8	90.6 ± 3.05	89 ± 2.08	75.3± 2.06
F9	98.5 ± 3.06	91.8 ± 2.03	79.6± 3.31
F10	**98.4 ± 3.45**	**98.9 ± 2.51**	**80± 2.81**

*** Average of three preparations ± SD**

DEE- Drug entrapment efficiency, PFB- Percentage of floating buoyancy.

***In vitro* drug release studies**

The results of the *in vitro* drug release studies were given in the tables 5, 6 and figures 9, 10. From the obtained dissolution data following inferences were made. The drug release from the 1:1 ratio of drug: EC showed a burst effect, releasing 41.33 % of the drug with in 0.5 hour and over all release could be sustained only for 6 hours. This may be due to the more effective surface area of the microballoons owing to their small size. The volume of the dissolution media (900ml) to which the microballoons were exposed could be one of the factor influencing the faster release of the drug. Therefore 1:1 core to coat ratio was not sufficient to retard the drug release for a prolonged period time. On increasing the drug to polymer ratio, the drug release could be prolonged. The 1:5 ratio of drug to ethyl cellulose could sustain the release for 12 hours releasing about 94.67 % of the drug.

Table 5: *In vitro* drug release data for F1-F5 formulations

Time (hrs)	AS1	AS2	AS3	AS4	AS5
0.5	41.33	31.57	27.78	12.62	10.83
1	50.09	56.2	52.23	30.37	24.04
2	59.4	60.1	58.6	50.68	44.36
3	62	90.50	79.5	69.75	52.02
4	87.06	93.8	87.9	85.05	72.32
5	92.26	94.12	91.2	89.24	79.96
6	96.06	95.06	92.8	91.58	91.37
7	_	_	94.23	93.63	92.08
8	_	_	95.92	94.91	93.12
9	_	_	_	95.81	94.08
10	_	_	_	_	95.91
11	_	_	_	_	96.51
12	_	_	_	_	96.78

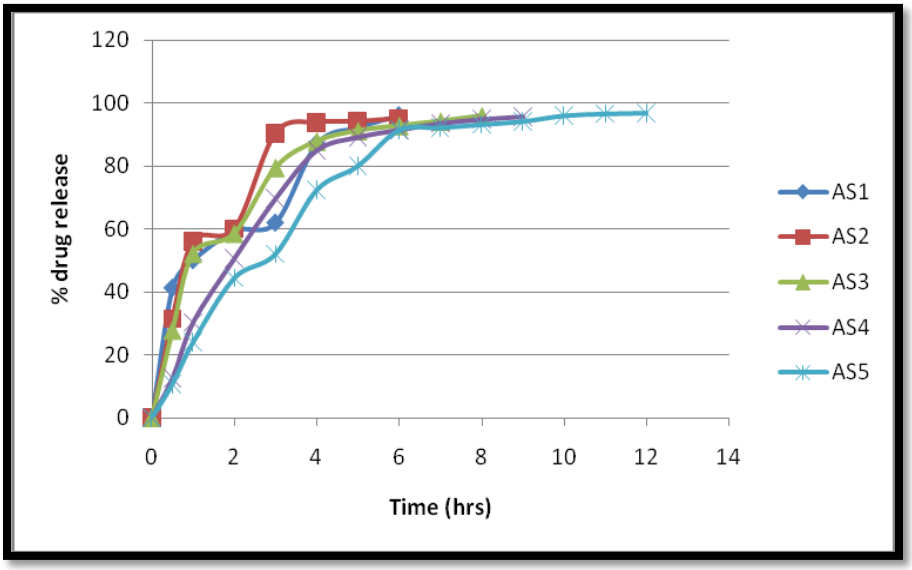

Figure 9: *In vitro* drug release profile of abacavir sulphate for batches F1-F5.

Table 6. *In vitro* drug release data for F6-F10 formulations

Time (hrs)	AS6	AS7	AS8	AS9	AS10
0.5	42.09	33.60	28.01	12.90	**11.04**
1	53.73	48.10	44.36	30.24	**22.69**
2	64.03	53.64	52.07	42.06	**31.62**
3	80.61	73.06	72.32	51.60	**49.53**
4	91.54	80.91	79.96	68.91	**52.01**
5	93.98	84.20	82.61	70.98	**69.84**
6	_	89.10	86.0	84.22	**80.86**
7	_	93.07	90.42	89.10	**87.37**
8	_	_	92.98	90.68	**91.86**
9	_	_	_	92.84	**92.54**
10	_	_	_	94.01	**92.89**
11	_	_	_	_	**93.30**
12	_	_	_	_	**94.67**

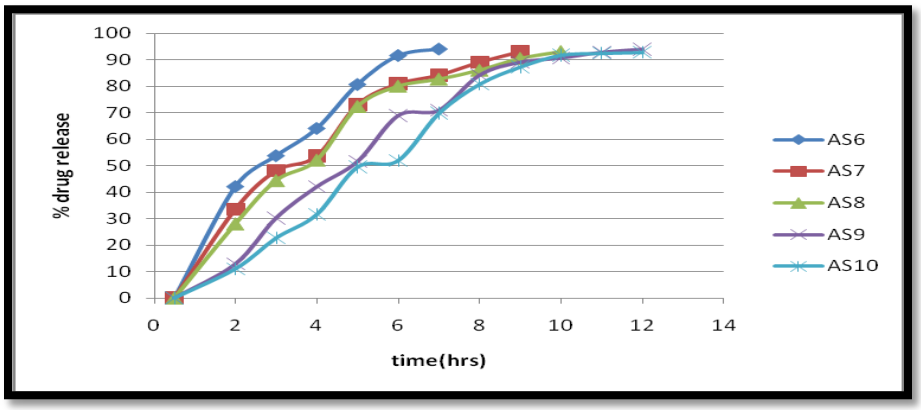

Figure 10: *In vitro* drug release study of abacavir sulphate for batches F6-F10

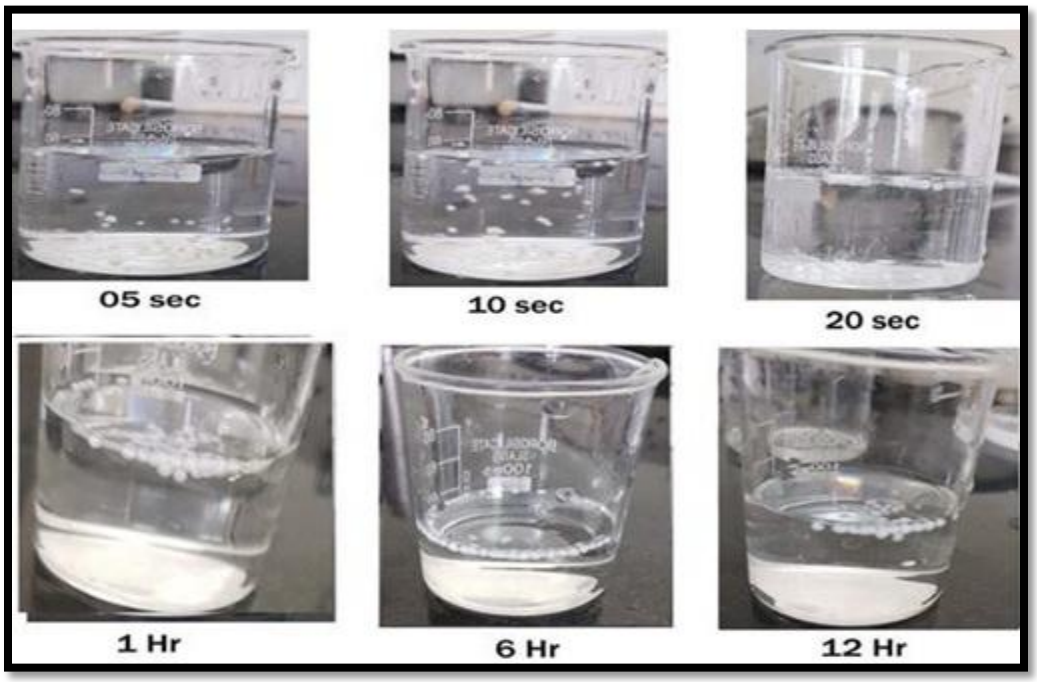

Figure 11: *In vitro* buoyancy of abacavir sulphate floating microballoons in 0.1N HCl

CONCLUSION

Gastro retentive floating microballoons of abacavir sulphate, an anti retroviral agent can be efficiently and successfully formulated by non-aqueous solvent evaporation method. Preformulation studies of abacavir sulphate were performed; such as solubility study revealed high solubility of abacavir sulphate in acidic pH, providing suitable candidate for gastro retentive drug delivery system. Different viscosity grades of ethyl cellulose (25cps, 100cps) were used in the development of floating microballoons. The results of Fourier transform infrared spectroscopy (FTIR) revealed that there was no drug excipient interaction. Formulated floating microballoons of abacavir sulphate gave satisfactory results for various evaluated parameters like angle of repose, bulk density, tapped density, carr's index, percentage of yield, drug entrapment efficiency, percentage of floating buoyancy, *in vitro* drug release and SEM studies. Results of *In-vitro* floating ability study indicated that the microballoons floated in the simulated fluid without enzyme (pH 1.2) more than 12 hrs. The yield of the formulated floating microballoons was in the range of 80.6% to 98.5%.The results of drug entrapment efficiency were in the range of 68% to 98.9%, as the core to coat ratio increased there was an increase in entrapment efficiency. The percentage of floating buoyancy was found that in the range of 70.2% to 80.6% and the floating microballoons had no floating lag time. *In-vitro* release rate studies showed that the sustained drug release was observed in F10 (drug: ethyl cellulose-100cps of 1:5 ratio formulations up to 12 hrs. Drug-excipient interaction of optimized formulation was carried out by using FTIR studies. In this analysis there was no interaction. The SEM photographs revealed that the formulated floating microballoons were spherical in shape smooth textured. Further, the microballoons can also be compressed into tablets and filled into capsules. Further detailed investigation is required to establish bioavailability studies and efficacy including pre-clinical studies and clinical studies of these novel gastro retentive floating microballoons of abacavir.

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