



DEVELOPMENT AND EVALUATION OF NUCLEOSIDE ANALOG REVERSE TRANSCRIPTASE INHIBITOR DRUG (NRTI) BASED FLOATING DRUG DELIVERY SYSTEM

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ABSTRACT

HIV is a virus that attacks the immune system, which is our body's natural defence against illness. The virus destroys a type of white blood cell in the immune system called a T-helper cell, and makes copies of itself inside these cells. T-helper cells are also referred to as CD4 cells. The present study involves formulation and evaluation of sustained release floating microspheres of Abacavir sulphate. Endeavour's with respect to floating mechanism are inculcated in the formulation to achieve longer stay of microsphere in stomach which happen to better site of absorption for the selected drug. Preformulation studies involving organoleptic bulk density, tapped density, angle of repose, compressibility of index, hausner ratio, melting point range, pH, solubility were carried out as per IP specification. Drug excipient compatibilities were carried out and evaluation and FT-IR, SEM. This showed no significant change in any way to the Mixture. Different polymers like sodium alginate, sodium carboxy methyl cellulose, HPMC K4M, HPMC K100M were utilized in the trials. All the physical evaluations are carried in preformulation studies were carried out on all the three different polymers utilized. All the formulations exhibited values within the acceptable range. Microspheres were evaluated for buoyancy studies, drug entrapment efficient. Release studies were carried out in 0.1N HCL for 12 hours. Evaluated samples for all the four polymer system. Results indicated that formulation F7, gave 90.12% release up to 12 hrs which is formulated with HPMC K100M and HPMCK4M combination. Assay was carried out for formulation F7 and was found to be 88.69%. The mechanism of drug release from microspheres follows Non-Fickian release. Remaining formulations gave fluctuating release profiles. The formulation F7 was considered to be better among the trials accomplished.

KEYWORDS: HIV, Floating Microspheres, In- vitro Drug release.

INTRODUCTION

HIV is a virus that attacks the immune system, which is our body's natural defence against illness.^[1] The virus destroys a type of white blood cell in the immune system called a T-helper cell, and makes copies of itself inside these cells. T-helper cells are also referred to as CD4 cells.^[2] As HIV destroys more CD4 cells and makes more copies of itself, it gradually breaks down a person's immune system. This means someone living with HIV, who is not receiving treatment, will find it harder and harder to fight off infections and diseases.^[3]

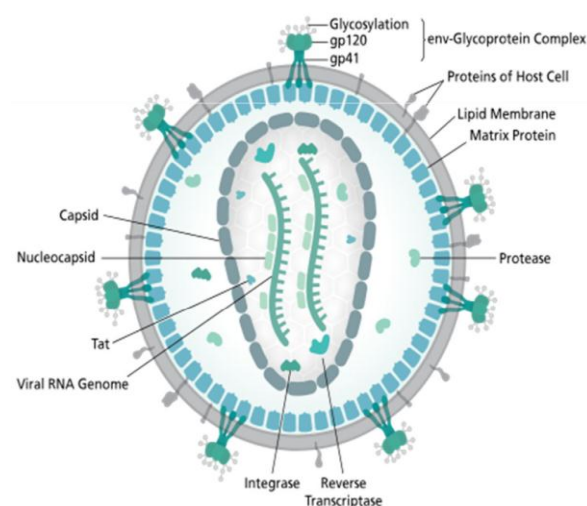


Fig.: Structure of HIV Virus.

If HIV is left untreated, it may take up to 10 or 15 years for the immune system to be so severely damaged it can no longer defend itself at all.^[4] However, the speed HIV progresses will vary depending on age, health and background. Human immunodeficiency virus (HIV) needs this enzyme to make copies of itself. In 2015 about 7.3 million people were living with HIV and it resulted in 1.2 million deaths. Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000µm.^[5] They are made of polymeric, waxy or other protective materials, that is biodegradable synthetic polymers and modified natural products such as starches, gums, proteins, fats and waxes.^[6] The natural polymers include albumin and gelatin, the synthetic polymer include poly lactic acid and polyglycolic acid. The solvents used to dissolve the polymeric materials chosen according to the polymer and

drug solubilities and stabilities, process safety and economic considerations.^[7] Microspheres are small and have large surface-to-volume ratio. At the lower end of their size range they have colloidal properties. The interfacial properties of microspheres are extremely important, often indicating their activity.^[8]

Polyethylene and polystyrene microspheres are two most common types of polymers microspheres.^[9] Polystyrene microspheres are typically used in biomedical applications due to their ability to facilitate procedures such as cell sorting and immune precipitation.^[10] Proteins and ligands adsorbed onto polystyrene readily and permanently, which makes polystyrene microspheres suitable for medical research and biological laboratory experiments.^[11]

MATERIALS AND METHODS

Materials

S. No	MATERIALS	SUPPLIERS/MANUFACTURERS
1	Abacavir sulfate	Molecules India Pvt Ltd, Chennai
2	Sodium alginate	S.D.fine chem. Ltd. Mumbai
3	Sodium carboxy methyl cellulose	S.D.fine chem. Ltd Mumbai
4	Hydroxy propyl methyl cellulose K4M	Otto chem. Laboratories Pvt.Ltd
5	Hydroxy propyl methyl cellulose K100M	Otto chem. Laboratories Pvt.Ltd
6	Sodium phosphate dibasic dehydrate	RANKEM, RFCL Ltd, New Delhi
7	Potassium dihydrogen ortho phosphate	RANKEM, RFCL Ltd, New Delhi
8	Sodium chloride	RANKEM, RFCL Ltd, New Delhi
9	Paraffin liquid colorless light	Molychem, Mumbai
10	Polysorbate 80 (tween 80)	Sisco Research laboratories Pvt.Ltd.
11	Dichloromethane	RANKEM, RFCL Ltd, New Delhi
12	Methanol	Merck Specialities Pvt.Ltd, Mumbai
13	n-Hexane	S.D.fine chem. Ltd, Mumbai

FORMULATIONS OF ABACAVIR SULFATE FLOATING MICROSPHERES

Floating microspheres were prepared by the solvent evaporation method using 1000 mg of Abacavir sulfate and with different polymer as shown in Table, were dissolved in methanol (5 ml), dichloromethane (5 ml) with vigorous agitation to form uniform drug polymer dispersion. This was slowly poured into the dispersion medium consisting of light liquid paraffin (100ml) containing 1.1% tween 80. The system is stirred using propeller at 1000 rpm at room temperature for 1hr 30

min – 2 hr. The liquid paraffin was decanted and the microparticles were separated by filtration through a whatmann filter paper, was washed thrice with 180 ml of n-Hexane and air dried for 6-8 hrs.

Table: FORMULATIONS.

INGREDIENTS in mg	FORMULATION BATCHES									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Abacavir sulfate	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000
HPMC K4M	1000	-	-	-	500	500	500	-	-	-
Sodium alginate	-	1000	-	-	500	-	-	500	500	-
Sodium CMC	-	-	1000	-	-	500	-	500	-	500
HPMC K100M	-	-	-	1000	-	-	500	-	500	500
Methanol	5	5	5	5	5	5	5	5	5	5
Dichloromethane	5	5	5	5	5	5	5	5	5	5



Fig.a: Preparation of Microspheres.



FIG. B: AFTER DRYING MICROSPHERE

Organoleptic properties

Table Organoleptic properties.

Test	Specifications/limits	Observations
Color	White to off white	Off White powder
Odour	odorless	odorless

The results complies as per specifications

Angle of repose

Table: Flow properties.

Material	Angle of repose
Abacavir sulphate	29°.28"

Bulk density and tapped density

Table: Density.

Materials	Bulk Density(gm/ml)	Tapped density(gm/ml)
Abacavir sulphate	0.19	0.26

Powder compressibility

Table: Powder compressibility.

Material	Compressibility index	Hausner ratio
Abacavir sulphate	28.04%	1.34

Melting point

Table. Melting point.

Material	Material point range	result
Abacavir sulphate	165 °C	Complies

SOLUTION PROPERTIES**pH of the solution**

Table. pH.

Material	Test	Specification	Observation
Abacavir sulphate	pH	7.5	7.5

Solubility

Table. Solubility.

Test	Specification	Result
solubility	Freely soluble in water, Sparingly soluble in DMSO, ethanol, methanol	Complies

DRUG-EXCIPIENT COMPATABILITY STUDIES

Table. Drug – Excipients Compatibility Study Results.

Drug + Excipients	Initial	After 1 month at		Compatible
		40°C/75%RH	60°C	
Drug	White powder	No change	No change	Yes
Drug + Methanol	White powder	No change	No change	Yes
Drug + Tween 80	White powder	No change	No change	Yes
Drug + HPMC K100M	White powder	No change	No change	Yes
Drug + HPMC K4M	White powder	No change	No change	Yes
Drug + Dichloromethane	White powder	No change	No change	Yes

FT-IR GRAPHS

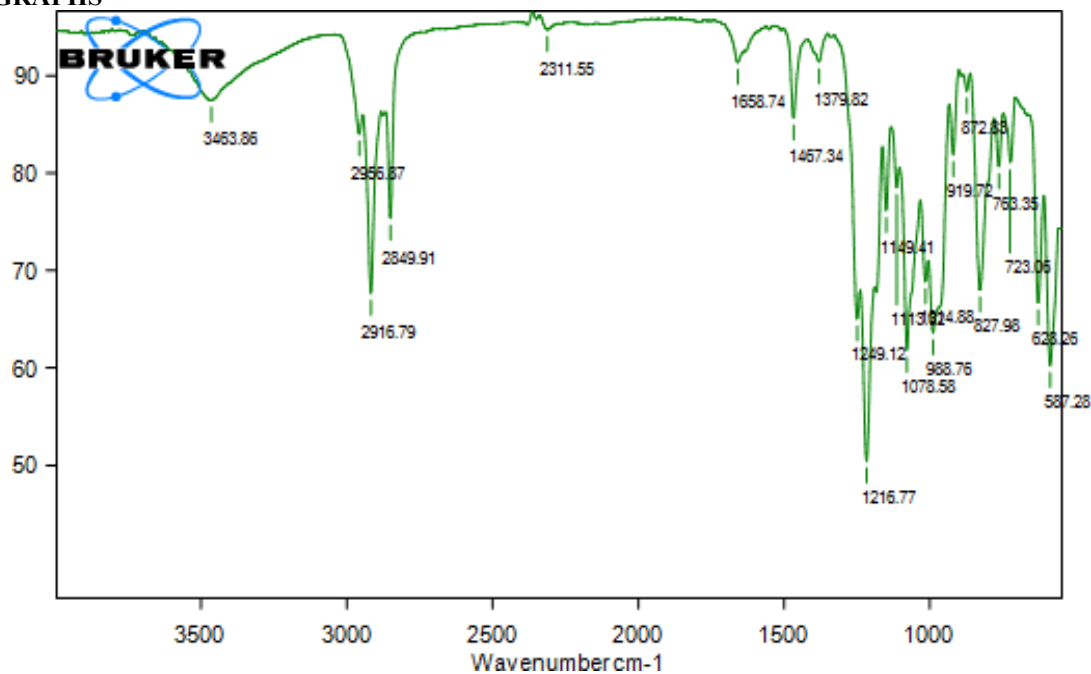


Fig. (a): FT-IR of Abacavir Sulphate.

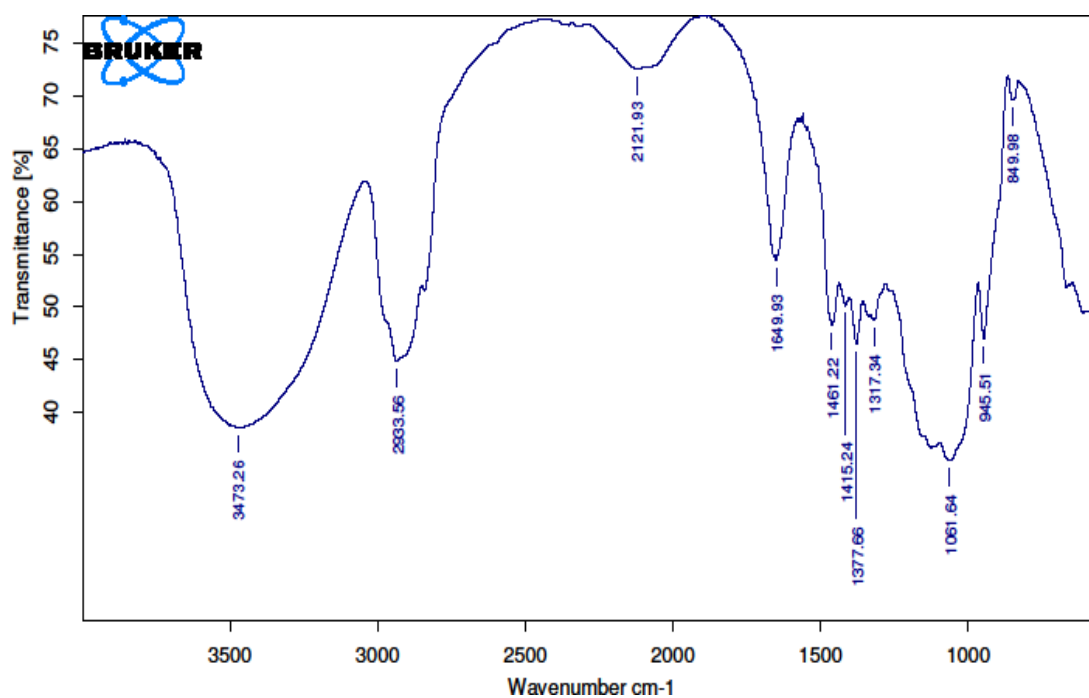


Fig. (b): FT-IR Graph of HPMC K4M.

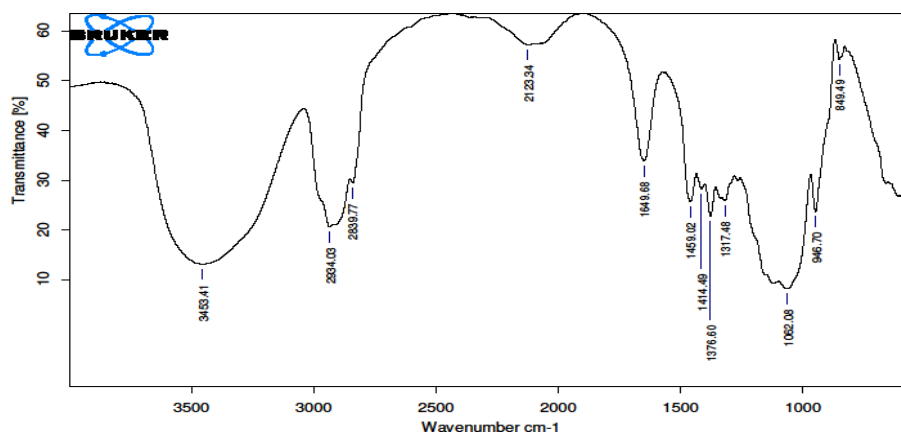


Fig. (c): FT-IR Graph of HPMC K100M.

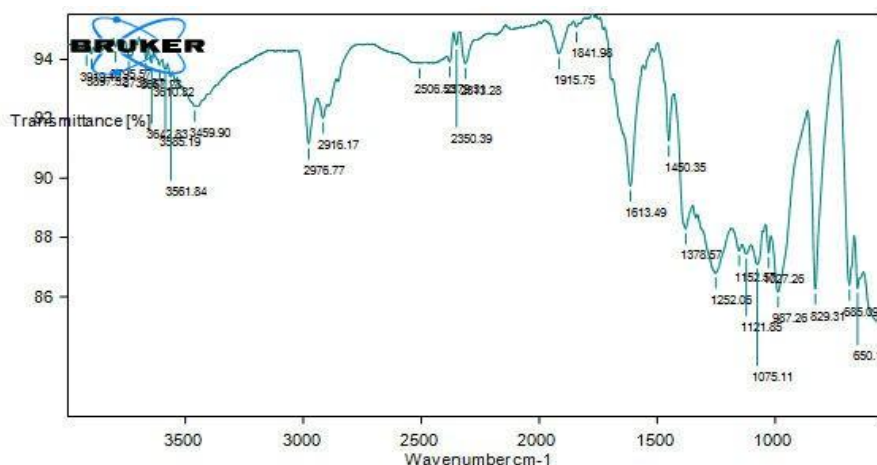


Fig. (d): FT-IR Graph of Mixture of Abacavir Sulphate + HPMC K4M + HPMC K100M.

Table. No.: Band Assignments for the Infrared Absorption Spectrum of Abacavir Sulphate

Band Energy (cm-1)	Assignment
3463.2	tertiary amine hydrochloride (N-H) stretch
2958.6	O-H stretch
2849.7	C-H Stretch
1660.0	Cyclopentene Ring C=C stretch
1451.6	C-H bending (CH ₂ Scissoring)

In the present study, it has been observed that there is no chemical interaction between Abacavir sulphate and the polymers used. From the figures (a),(b),(c) and (d) it was observed that there were no changes in these main

peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymer.

Table. Evaluation of Microspheres.

Batch No.	Angle of Repose(°)	Bulk Density (g/ml)	Tapped Density(g/ml)	Carr's Index (□)	Huasner Ratio
F1	25□08□	0.2826	0.3177	10.38	1.11
F2	23□52□	0.2671	0.3242	14.07	1.19
F3	24□24□	0.2841	0.3318	16.47	1.15
F4	27□62□	0.2853	0.3420	16.13	1.19
F5	24□09□	0.2965	0.3446	14.47	1.16
F6	27□37□	0.2924	0.3321	11.94	1.13
F7	26□64□	0.2768	0.3394	13.68	1.22
F8	24□71□	0.2891	0.3503	16.04	1.21
F9	26□14□	0.2965	0.3446	13.54	1.16
F10	25□50□	0.2721	0.3242	15.07	1.19

The angle of repose for the formulations F1-F10 was found to be in the range 23°52' to 27°62' shows good flow property.

Compressibility index for the formulations F1-F10 found between 10.38% to 16.13% indicating the good flow property.

Table. Percentage Yield, *Invitro* Buoyancy, Drug Entrapment Efficiency of Floating Microspheres of Abacavir Sulphate

batch No.	Percentage yield	<i>Invitro</i> Buoyancy	Entrapment efficiency
F1	84.52	85.65	82.60
F2	82.98	83.75	81.73
F3	83.54	84.82	82.17
F4	79.89	80.23	78.61
F5	85.15	86.24	83.04
F6	88.91	89.54	87.39
F7	90.21	91.66	88.69
F8	86.78	87.26	83.92
F9	85.59	86.92	83.47
F10	87.66	88.22	85.21

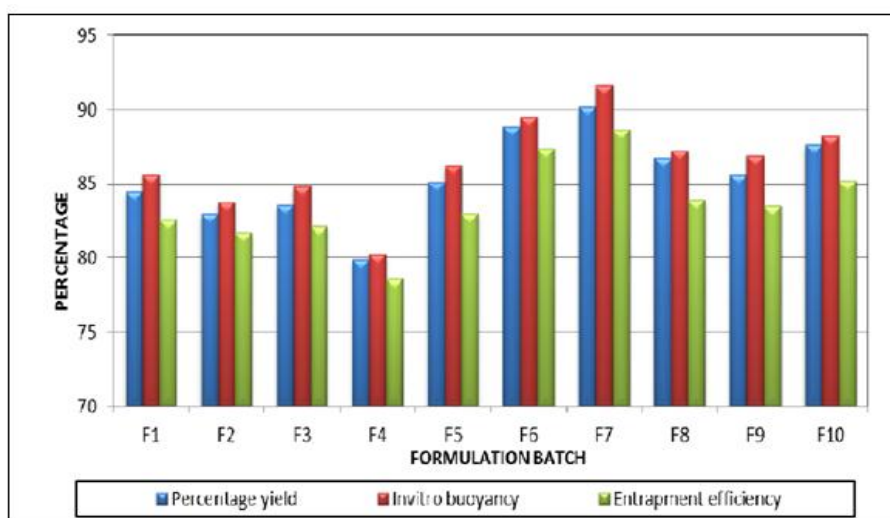


Fig.: Buoyancy, Entrapment efficiency Study of Floating Microspheres.

Percentage yield

The maximum percentage yield was found in F7 formulation and was noted to be 90.21% among all formulations.

The floating microspheres were prepared with different and combination of two polymer of HPMC K4M, HPMC K100M, Sodium Alginate and Sodium CMC to investigate the influence of encapsulation efficiency and were used to determine its influence on floating behavior.

Invitro Buoyancy

The different polymers with same ratios of formulation were selected for optimization of their buoyancy property. The formulations in which combination of HPMC K4M, HPMC K100M are giving the better results.

The formulations, are selected as the best formulations depending upon their buoyancy, encapsulation efficiency. From the results of all the ten formulations, it is confirmed that the change in polymers of Sodium

Alginate, Sodium CMC, HPMC K4M, K100M influences the properties of the formulations. The formulation F7 with drug and combination of two polymer 1:1 ratio, is giving the best result of buoyancy property.



Fig.: Buoyancy Study of Floating Microspheres.

Entrapment efficiency

The percentage entrapment efficiency of various formulation parameters of the prepared microspheres were shown in table. The entrapment efficiency varied from 78.61 to 88.69.

The formulation F7 is having high encapsulation efficiency of 88.69% and F4 is having low encapsulation efficiency of 78.61%.

The low encapsulation is because of using single polymer of HPMC K100M than the drug concentration where the quantity of HPMC K100M is insufficient to entrap the drug. The high encapsulation efficiency is because of using combination of polymers of HPMC K100M, HPMC K4 where the increase in the HPMC concentration forms larger microspheres encapsulating more amount of drug.

Table: *Invitro* Release Profile.

Time (hours)	BATCH NO.									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	20.03	12.05	14.18	10.01	12.91	10.56	8.25	15.23	12.11	9.54
2	35.56	32.56	31.56	28.19	22.12	15.99	13.11	25.76	22.77	13.84
4	54.14	53.29	45.25	62.43	35.12	28.21	24.72	37.45	30.99	24.15
6	69.65	77.38	63.14	76.37	52.64	44.14	40.99	53.28	48.12	43.09
8	89.14	96.38	92.02	98.24	78.11	58.98	56.25	79.54	69.82	54.69
10					94.42	78.68	72.84	90.47	93.51	72.74
12						87.04	90.12			85.25

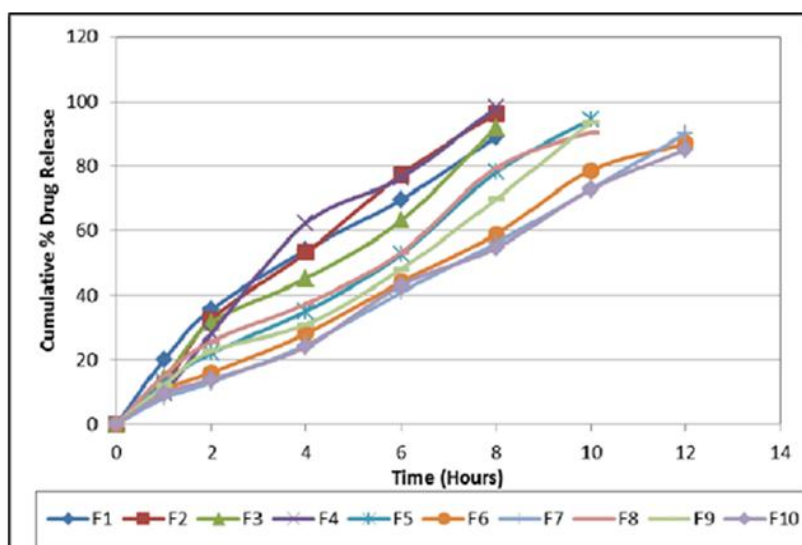


Fig.. *Invitro* Dissolution Release Profile for F1 – F10 Formulations

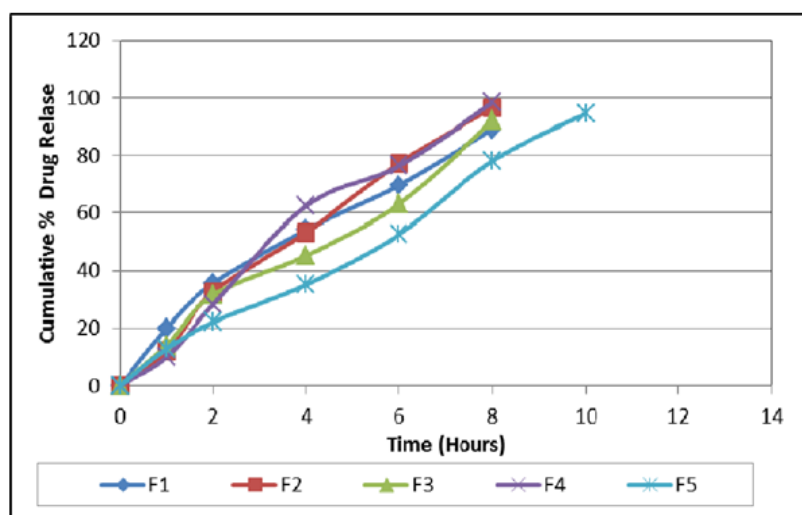


Fig.. *Invitro* Dissolution Release Profile for F1 – F5 Formulations.

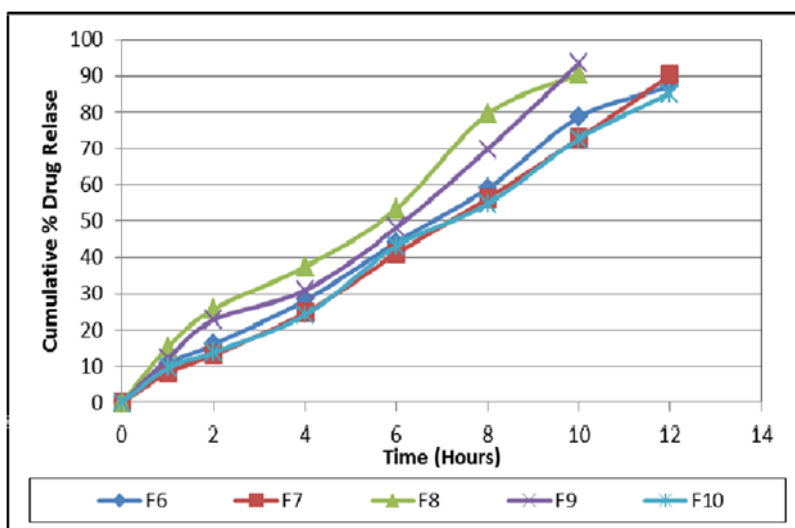


Fig.. *Invitro* Dissolution Release Profile for F6 – F10 Formulations.

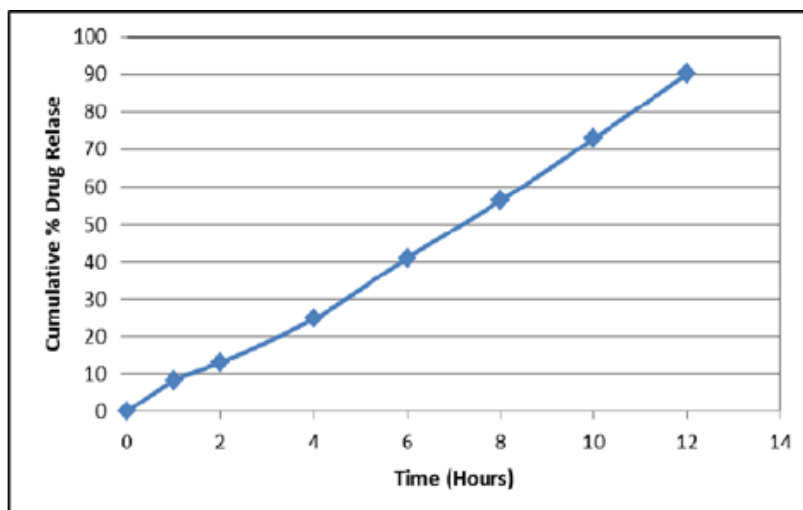


Fig.. *Invitro* Dissolution Release Profile for best Formulation F7.

From the *Invitro* dissolution study of all formulations (F1-F10), formulation F7 release around 90.12% of drug at the end of 12 hours for a sustained release.

Therefore the F7 formulation chosen as the best formulation from all ten batches.

Scanning Electron Microscopy (SEM)



Fig SEM (a)

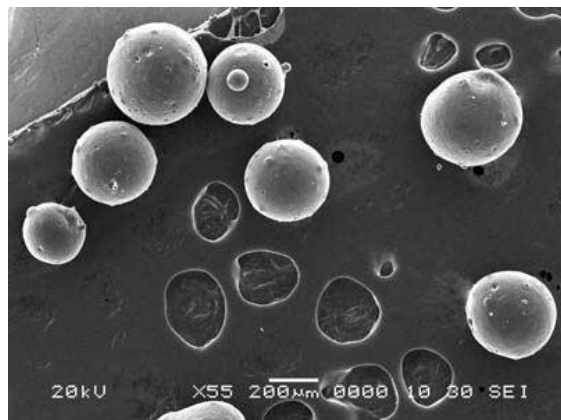


Fig SEM (b)



Fig. SEM(c).

Fig. SEM Scanning electron microphotographs of floating microsphere of Abacavir sulphate: SEM (a) & SEM(b) smoothness of the surface of spherical shaped microsphere SEM(c) Internal view of the shell having porous structure.

Morphology of floating microspheres was examined by scanning electron microscopy. The view of the microspheres showed hollow structure with a smooth surface morphology exhibited range of sizes within each batch. The outer surface of microspheres was smooth and dense, while the internal surface was porous. The shell of microspheres also showed some porous structure it may be caused by evaporation of solvent entrapped within the shell of microsphere after forming smooth and dense layer.

CONCLUSION

The ultimate goal for sustained drug release is to maximize therapeutic activity while minimizing the negative side effects of the drug. In this regard, floating microspheres have emerged as a novel drug delivery system to treat HIV with Abacavir sulphate.

The type of polymer affects the drug release rate and the mechanism. Polymer swelling is crucial in determining the drug release rate and is also important for flotation. A lesser FLT and a prolonged floating duration could be achieved by using different polymer combinations. In this study sustained release Floating Microsphere approach for Abacavir sulphate purposes that with hydrophilic polymers the GI retention can be enhanced and reduce frequency of dosing, thereby minimizing the occurrence of side effects, site specificity, increase the effectiveness of the drug and better patient compliance This gives a signal to extending this approach to similar combinations of drugs used in clinical practice so as to improve bioavailability of poorly absorbed drugs in GIT.

When these floating microspheres compared to other floating dosage forms like floating tablets have bulk density less than gastric fluid and so remain buoyant in the stomach for prolonged period of time and these are used as multiunit dosage form and drug release optimization and show efficiency level. So, Sustained release floating microspheres of Abacavir sulphate may

provide a convenient dosage form for achieving best performance and release and show good bioavailability.

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