FORMULATION AND *IN-VITRO* CHARACTERIZATION OF ABACAVIR SULPHATE EFFERVESCENT FLOATING TABLETS

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ABSTRACT

After oral administration of Abacavir, rapid absorption occurs from upper part of gastro intestinal tract with peak concentrations occurring at 0.63 - 1 hr after dosing. Conventional drug therapy with tablets produce relatively rapid and high peak blood levels that requires frequent administration to maintain effective range of plasma drug levels. This conventional therapy leads to reduced effectiveness with poor therapeutic management. To overcome the inadequacy of conventional therapy with tablets, floating sustained release Abacavir tablets were developed. Floating sustained release Abacavir Sulphate tablets were prepared by using direct compression method. Tablet were formulated using Ethyl Cellulose with hydrocolloids like Hydroxypropyl Methylcellulose (HPMC K4M) and Carbopol 974P as release retarding polymers, Sodium bicarbonate (NaHCO₃) and Citric acid as effervescent agents. Tablets were then evaluated for various physical parameters including hardness, thickness, weight variation, friability, drug content, in-vitro buoyancy, Swelling index and In-vitro gastro retentive drug release were conducted. Drug and excipient compatibility studies show that they are compatible with each other. The optimized formulation (F9) shows the hardness of 5.7kg/cm², tablet thickness of 2.74mm, 0.45% of friability, in-vitro buoyancy was up to 6 hours and % drug release was 90.56% in 6 hours. Drug release kinetics was found to follow non-fickian diffusion. Hence, F9 is considered as optimized formulation based on in-vitro buoyancy and % drug release.

Keywords: Abacavir sulphate; Carbopol 974P; HPMC K4M; Ethyl cellulose; Effervescent floating tablets.

INTRODUCTION

Different types of gastro-retentive dosage forms have been created over the past two centuries to prolong gastric residence time. The type of dosage form allows direct administration of drugs with a narrow absorption opening at the apex of the gastrointestinal tract or drug with low colon stabilization. The drug can also act locally within the stomach and extended intimate contact with the absorbing membrane which increases effectiveness^[1-2]. Floating drug delivery systems have a lower bulk density than gastric fluids and therefore remain in the stomach for an extended period of time, without affecting the rate of gastric emptying. The drug is released slowly from the system at the desired rate while the system is floating on the gastric contents^[3-4]. The residual system is emptied from the stomach following the release of the drug. This leads to an increase in gastro retentive time (GRT) and better control of plasma drug concentration fluctuations. It is possible to classify floating systems into two distinct categories: non-effervescent and effervescent^[5].

Acquired immune deficiency syndrome (AIDS), is a threatening disease in present generation. Actually, AIDS is not a disease but it is a collection of 70 or more circumstances that arise from the human immunodeficiency virus (HIV) infection to the immune system and other areas of the body. It is essential that the systematic drug concentration in the treatment is constantly greater than that for AIDS therapy^[6]. There are also a number of drugs that are regarded as anti-HIV. Abacavir sulphate is an antiretroviral HIV reverse transcriptase nucleoside inhibitor. Antiretroviral agents, nucleoside inhibitors are used in the treatment of relatively short half-life plasma drugs, are routinely administered alone or with other anti-retroviral. The treatment of patients with relatively short plasma half-life is common. This study thus formulated effervescent floating tablets of Abacavir sulphate with the use of hydrocolloids to delay the release of drug^[7].

MATERIALS AND METHODS

MATERIALS

Abacavir sulphate was given as gift sample by KP Labs, Hyderabad. Carbopol 974P, HPMC K4M and Ethyl cellulose was obtained from MerckSpecialities Pvt Ltd, Mumbai, sodium bicarbonate, citric acid, microcrystalline cellulose, talc and magnesium stearate was obtained from SD-Fine Chemicals, Mumbai.

METHODS

Analytical Method Development: The UV Spectrophotometric method was selected for the estimation of Abacavir sulphate. 20µg/ml concentration of drug was chosen and absorbance was measured in between the range of 200-400nm.

Drug-Excipient incompatibility studies

Fourier transform infrared (FT-IR) spectroscopy

Drug and excipient compatibility were studied by FT-IR spectroscopy of API with various excipients used in the formulation.

Differential scanning calorimetry (DSC)

1mg of API Abacavir sulphate and effervescent floating tablets were sealed in aluminium pans for DSC scanning. It is carried out to find out the presence of any interaction among drug and the excipients. The various samples along with optimized batch were checked for DSC study^[8-9].

Formulation of effervescent floating tablets of Abacavir sulphate

The tablets were prepared by direct compression technique. The compositions of all formulations were given in the Table 1. All the ingredients were accurately weighed and passed through sieves accordingly. Then except, magnesium stearate all other ingredients were blended uniformly in mortar and pestle. After enough mixing of drug and other components, magnesium stearate was added as lubricant and further mixed for 2-3 minutes. Blended powder mixture was then punched by means of rotary tablet compression machine.

Characterization of powder blend

The flow properties of blend were characterized in terms of angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio. For determination of angle of repose, the powder blend was poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2 cm above hard surface. The formulas are given below:

$$\text{Angle of repose: } \tan \theta = \frac{h}{r} \text{ (or) } \theta = \tan^{-1} \frac{h}{r}$$

Where,

θ = angle of repose,

h = height,

r = radius.

$$\text{Bulk density: } B.D = \frac{M}{V_0}$$

Where,

M = mass of the powder,

V_0 = bulk volume of the powder.

$$\text{Tapped density: } T.D = \frac{M}{V_t}$$

Where,

M = mass of the powder,

V_t = final tapped volume of the powder.

$$\text{Compressibility Index: } C.I = \frac{(\text{Tapped density} - \text{Bulk density}) \times 100}{\text{Tapped density}}$$

$$\text{Hausner's Ratio: } H.R = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Characterization of Abacavir sulphate effervescent floating tablets

The prepared tablets were evaluated for thickness using Vernier caliper, uniformity of weight using Shimadzu sensitive balance, hardness using Monsanto tester and friability using Sisco friability tester.

$$\text{Weight variation} = \frac{\text{Average weight of tablet} - \text{individual weight of tablet}}{\text{average weight of tablet}} \times 100$$

$$\text{Friability: } \% F = \left[1 - \left(\frac{W_0}{W} \right) \right] \times 100$$

Where,

% F = friability in percentage,

W_0 = initial weight of tablet,

W = final weight of tablet.

Drug Content

Tablets were taken, powdered and the powder equivalent to one dose each was transferred to a 100ml volumetric flask and 0.1N HCl pH 1.2 was added. The volume was then made up to the mark with 0.1 N HCl pH 1.2. The solution was filtered and diluted suitably and drug content in the samples was estimated using UV-spectrophotometer at 256 nm.

In-Vitro Buoyancy Studies

The samples were placed in a 100ml beaker containing 0.1N HCl pH 1.2. The time required for the tablet to rise to the surface and float was determined as **floating lag time**^[10-11]. The duration of time for which the dosage form constantly remained on the surface of medium was determined as the **total floating time**.

Swelling Index

The swelling index of tablets was determined in 0.1 N HCl pH 1.2 at room temperature. The swollen weights of the tablets were determined after predetermined time intervals. The swelling index was calculated by the equation given below:

$$\text{Swelling index, S.I} = \frac{(w_t - w_0) \times 100}{w_0}$$

Where,

W_t = weight of the tablet at time t.

W_0 = initial weight of tablet.

In-Vitro drug release studies

The *in-vitro* drug release study was performed for the Abacavir sulphate effervescent floating tablets using USP Type II (paddle method, lab India). The dissolution test was performed using 900ml of 0.1 N hydrochloric acid at $37 \pm 0.5^\circ\text{C}$ and 50 rpm. A sample (5ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium.

Drug Release Kinetics

In order to examine the release mechanism of Abacavir sulphate from the prepared effervescent floating tablets of the optimized formulation (F9), the results of the dissolution study were examined in kinetic models. The regression coefficient R^2 value nearer to 1 indicated the model fitting of the release mechanism.

RESULTS AND DISCUSSION

Analytical Method Development

Abacavir sulphate showed absorption maxima at 256 nm in 0.1N HCl of pH 1.2 (fig 1) by UV Spectrophotometric method.

Fig - 1: UV-Spectrum of Abacavir Sulphate

Preparation of stock and working standard solutions

100mg of Abacavir sulphate was accurately weighed and transferred into a 100ml volumetric flask, dissolve the drug in suitable volume of 0.1N HCl of pH 1.2. Then, further diluted the above solution up to the mark with 0.1 N HCl pH 1.2 to obtain the drug concentration of 1000 μ g/ml. From this solution, 10ml was further diluted using same solvent to obtain drug concentration of 100 μ g/ml as a working standard solution.

Preparation of Calibration Curve in 0.1 N HCl of pH 1.2

Appropriate dilutions were made from stock solution to obtain solutions of 10, 20, 30 and 40 μ g/ml concentrations. Samples were analyzed under the absorbance maxima of 256nm. The standard curve was plotted between areas under curve values against concentrations and the results were shown in the below fig 2.

Fig - 2: Standard Calibration Curve of Abacavir Sulphate in 0.1N HCl

Drug-Excipient incompatibility studies

Fourier transformed infrared (FT-IR) spectroscopy

The FT-IR spectra result (fig3) indicated that there was no drug-excipient interaction. The IR spectra recorded for the API Abacavir sulphate and the optimized formulation showed peaks at 3286 cm^{-1} (O-H stretching), 2920 cm^{-1} ($-\text{CH}_2$ stretching) and 1678 cm^{-1} ($\text{C}=\text{N}$ stretching). In the formulation, peaks were observed at 3282 , 2918 and 1678 cm^{-1} . From the compatibility studies it was observed that the functional groups which are present in API as well in the optimized formulation are having very negligible changes of peaks, this clearly indicates that the drug and excipients have no interactions.

Fig - 3: FT-IR of Abacavir Sulphate and optimized formulation F9

Differential scanning calorimetry

DSC was performed for Abacavir sulphate and optimized formulation i.e. F9 which is represented in fig - 4. The DSC thermo gram of Abacavir sulphate displayed a characteristic peak at 225.8°C . The formulation F9 (Abacavir sulphate + Carbopol 974P + Ethyl Cellulose) exhibits a sharp peak at 226.3°C . Hence, DSC study shows that there is no drug polymer interaction.

Fig - 4: DSC of API and optimized formulation F9

Table – 1: Composition of Abacavir sulphate effervescent floating tablets

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Abacavir sulphate	150	150	150	150	150	150	150	150	150
Carbopol974P	15	-	-	30	-	-	7.5	-	15
HPMC K4M	-	15	-	-	30	7.5	-	15	-
Ethyl cellulose	-	-	7.5	-	-	7.5	7.5	15	15
Micro crystalline cellulose	95	95	102.5	80	80	95	95	80	80
Sodium bicarbonate	30	30	30	30	30	30	30	30	30
Citric acid	4	4	4	4	4	4	4	4	4
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4

HPMC = Hydroxy propyl methylcellulose.

Characterization of powder blend

The flow properties of powder blend have evaluated and the results are shown below in Table - 2. Inter-particle interactions that influence the bulking properties of a powder flow. A comparison of a bulk density and tapped density can give a measure of the relative importance of this interaction in a given powder. The bulk density of powder is good for packaging of the tablets. Carr's index was found to be below 16% for all formulations, which indicated acceptable flow properties. Hausner's ratio for all formulations was less than 2% which also indicated the good flow property of the powders. Angle of repose showed that the flow property of the powder was good and it was within acceptable limits.

Characterization of Abacavir sulphate effervescent floating tablets

The average weight of tablets was found to be in the range of 296 to 299 mg and friability was found to be 0.42 to 0.60%. The thickness was found to be 2.68 to 3.90 mm. The evaluation results show that all the parameters were within acceptable limits. Individual readings of all formulations were tabulated in Table - 3.

Table - 2: Pre-compression studies of formulations

S. No.	Parameters	Bulk density	Tapped density	Carr's index	Angle of repose	Hausner's ratio
1	F1	0.456	0.554	11.9	27.7	1.14
2	F2	0.456	0.527	15	26.4	1.12
3	F3	0.452	0.560	12.4	29.2	1.18
4	F4	0.458	0.572	15.3	28.4	1.16
5	F5	0.461	0.583	12.2	29.5	1.15
6	F6	0.434	0.575	11.2	28.4	1.18
7	F7	0.455	0.528	13.6	29.8	1.08
8	F8	0.460	0.531	12.2	27.5	1.18
9	F9	0.468	0.564	14.8	29.4	1.14

Drug content

The drug content for various formulations was found to be in the range of 67.6% to 97.8 which is shown in Table - 3.

Table – 3:Standard physical test for Abacavir sulphate effervescent floating tablet

Formulations	Thickness (mm)	Hardness (kg/cm ²)	Weight variation (mg)	Friability (%)	Content uniformity (%)
F1	3.80	4.7	298	0.60	88.4%
F2	3.90	5.2	296	0.51	67.6%
F3	3.79	5.1	296	0.54	69.2%
F4	3.68	5.3	299	0.52	89.3%
F5	3.73	5.4	297	0.53	68.5%
F6	3.62	5.5	297	0.48	78.4%
F7	2.75	5.6	299	0.42	92.1%
F8	2.68	5.3	298	0.51	88.4%
F9	2.74	5.7	299	0.45	97.8%

In-Vitro Buoyancy Studies: Sodium bicarbonate was used along with citric acid in the formulation as gas generating agent in contact with acidic aqueous media CO₂ is generated. The observations of all formulations were tabulated in Table 4.

Table – 4: Floating capacity of all formulations

Formulations	Floating lag time (sec)	Total floating time (hours)
F1	95	>3
F2	40	>2
F3	70	>2
F4	85	>4
F5	60	>2
F6	70	>3
F7	95	>5
F8	70	>3
F9	95	>6

Swelling index

Swelling studies revealed that the F-9 formulation showed more swelling in 0.1 N HCl because of its gelling properties of Carbopol 974P and Ethyl cellulose was observed as 98.35%, has attained a sustained release pattern. A comparative value for formulations F-1 to F-9 is shown in Table 5 and fig 5.

Table – 5: % swelling index of formulated batches

Batch	Time (hrs)			
	1	2	4	6
F1	18.55	32.25	47.68	61.24
F2	22.18	44.56	55.89	66.35
F3	30.64	48.25	58.12	70.43
F4	32.55	53.76	65.89	76.14
F5	40.79	60.43	67.79	80.46
F6	47.94	63.52	73.24	89.56
F7	51.10	65.18	77.68	92.87
F8	56.75	66.55	77.98	94.66
F9	76.77	78.10	87.09	98.35

Fig - 5: % Swelling Index

In-Vitro Drug Release Studies

The *in-vitro* drug release characteristics were studied in 0.1N HCl for 7 hours under sink condition using USP dissolution apparatus type II, employing paddle stirrer at 50 RPM and 900ml of 0.1N HCl of pH 1.2 as dissolution medium, the *in-vitro* dissolution data of all the designed formulations are shown and dissolution profiles were kept in the following table 6 and graph in fig 6.

Table 6: %Release pattern of drug from all formulations

Time (hrs)	% Drug Release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	7.9	6.9	6.31	8.23	7.2	8.12	8.96	9.23	10.75
1	8.73	7.5	8.11	9.56	8.23	9.56	10.36	12.85	18.69
1.5	13.65	11.51	10.36	15.42	14.32	17.23	21.23	23.5	29.98
2	19.74	16.75	16.36	22.36	19.62	23.85	29.56	32.69	44.21
2.5	28.45	25.54	24.81	35.23	29.85	36.23	42.7	48.39	58.23
3	37.42	36.84	28.65	45.63	40.65	45.23	51.65	59.65	67.69
4	46.52	43.25	39.85	56.31	49.65	57.68	63.75	67.56	79.56
5	55.32	50.61	46.23	66.21	56.23	69.12	71.56	75.56	87.23
6	61.05	-	53.45	74.23	62.58	-	79.62	-	90.56
7	72.58	-	-	77.25	-	-	82.32	-	87.23

Fig - 6: % release pattern of drug from all formulations

Drug Release Kinetics

The coefficient of regression and release constant values of Korsmeyer - Peppas model was found that the release of Abacavir sulphate effervescent floating tablets follows Korsmeyer- Peppas kinetics.

Table – 7: Release kinetics data of different model for optimized formulation (F9)

Formulation code	Zero order	First order	Higuchi kinetics	Korsmeyer – Peppas (t ₆₀ %)	
F9	R ²	R ²	R ²	n	R ²
	0.8833	0.5509	0.9373	1.1677	0.9959

Fig - 7: Plot of cumulative % drug release vs. time of optimized formulation (F9)

Fig - 8: Plot of log cumulative % drug retained vs. time of optimized formulation (F9)

Fig - 9: Plot of cumulative % drug released vs. root time of optimized formulation (F9)

Fig - 10: Plot of log cumulative % drug released vs. log time of optimized formulation (F9)

CONCLUSION

The prepared effervescent floating tablets were subjected to various pharmaceutical parameters such as bulk density, tapped density, angle of repose, weight variation, thickness, hardness and friability. The results indicated that the parameters drug content, swelling index, *in-vitro* drug release studies and *in-vitro* buoyancy studies are within Pharmacopeia limits. The optimized formulation (F9) shows the hardness of 5.7kg/cm², tablet thickness of 2.74mm, 0.45% of friability, *in-vitro* buoyancy was up to 6 hours and % drug release was 90.56% in 6 hours. These studies revealed that all the parameters are within the range of acceptable limits for the effervescent floating tablets. Drug release kinetics was found that it follows the Korsmeyer - Peppas equation. FT-IR and DSC studies confirmed that there was no interaction between Abacavir sulphate and other ingredients used in the tablet formulations. In which (F9) formulation has showed sustained *in-vitro* drug release, and also good swelling, floating lag time and follows Korsmeyer-peppas kinetics. Hence, it is concluded that F9 formulation (Drug, Carbopol 974P and Ethyl Cellulose) of effervescent floating tablet shows sustained action to 6 hrs.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors are responsible for the content and writing of this paper.

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