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DEVELOPMENT AND OPTIMIZATION OF SUSTAINED RELEASE ABACAVIR MATRIX TABLETS

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ABSTRACT
The aim of the present study was to develop and characterize Abacavir sustained release tablets. These Abacavir solid unit dosage forms were prepared by using direct compression technique and by utilizing synthetic polymers such as ethyl cellulose, eudragit and sodium alginate. Abacavir drug is used in the treatment of human immunodeficiency virus (HIV) infection. It is nucleoside reverse transcriptase inhibitors (NRTIs). The prepared tablets were characterized for hardness, thickness, disintegration time and drug release studies. Optimized formulation of drug delivery was 98.70% in 8 hours along with satisfactory results. It was noted that A5 formulation was the best formulation compared with the other formulations based on the drug release studies and physical parameters.

KEYWORDS: Abacavir, Hydroxypropyl methyl cellulose, sodium alginate, direct compression technique, in-vitro drug release studies.

INTRODUCTION
Oralroute is the most preferred route for administration o f drugs. Tablets are the most popular oral formulations available in the market and preferred by the patients and physicians alike. In long- term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses, and therefore have several disadvantages.[1] Sustained release (SR) tablet formulations are much desirable and preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase safety margin for high-potency drugs.[2]

Direct compression method had been applied for preparation of matrix tablet that involved simple blending of all ingredients used in the formulations and then underwent direct compression. It required fewer unit operations, reduced number of personnel and reduced processing time, increased product stability and faster production rate.[3] Abacavir as a nucleoside and nucleotide reverse transcriptase inhibitors active against Human Immunodeficiency Virus Type 1. It is the treatment of HIV infection in combination with other antiretroviral agents.[4] Oral drug delivery systems have progressed from immediate release to site specific delivery over a period of time.[5] Abacavir is a carbocyclic synthetic nucleoside analogue used for the treatment of HIV/AIDS. To reduce the frequency of administration and to improve patient compliance, a sustained release formulation of Abacavir is developed.[6] The main objective of the present work was to develop sustained release matrix tablets of Abacavir using different polymers.

MATERIALS AND METHOD
Materials: Abacavir was collected as a gift sample from Hetero labs, Hyderabad, Sodium alginate, eudragit and other excipients were purchased from AR chemicals.

Methodology[7,8]
Drug-excipient compatibility studies: The IR absorption spectra of the Abacavir and with various polymers were taken in the range of 3500-3000 cm^{-1} utilizing KBr disc technique, 1-2 mg of the substance to be examined was triturated with 300-400 mg, specified quantity, of finely powered and dried potassium bromide. These quantity are generally enough to give a disc of 10-15mm diameter and pellet of appropriate strength by a hydraulic press.

Formulation Development

Table. 1: Development of Abacavir tablets.

S. No.	Ingredients	A1	A2	A3	A4	A5	A6	A7	A8
1	Abacavir	300	300	300	300	300	300	300	300
2	Sodium alginate	100	-	-	-	50	-	50	50
3	Xantham gum	-	100	-	-	50	-	-	-
4	Ethylcellulose	-	-	100	-	-	50	50	-
5	Eudragit	-	-	-	100	-	50	-	50
6	Microcrystalline Cellulose	195	195	195	195	195	195	195	195
7	Magnesium stearate	3	3	3	3	3	3	3	3
8	Talc	2	2	2	2	2	2	2	2
	Total Wt	600	600	600	600	600	600	600	600

Evaluation studies[9,10,11]

Determination of bulk density and tapped density

Bulk Density

Bulk density is defined as the mass of powder divided by bulk volume.

It is calculated using the following equation:

Bulk density = weight of sample taken /volume noted

Tapped density

An exactly weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (v_o) was measured.

Tapped density = weight of sample taken / tapped volume

Where,

V_o = initial volume

V_f = final volume.

Compressibility index

Based on the apparent bulk density and the tapped density, the percentage Compressibility of the bulk drug was determined by the following formula.

Carr's index = Tapped density - Bulk density / Tapped density X 100

Hausner's ratio: It indicates the flow properties of the powder. The ratio of tapped density to the bulk density of the powder is called Hausner ratio. Hausner's ratio = Tapped density / Bulk density

Angle of repose: The flow characteristics are measured by angle of repose. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

$\tan\theta = h/r$

Where

h = height of pile

r = radius of the base of the pile

θ = angle of repose

Evaluation of tablet

Weight variation: Prepared 20 tablets were selected unsystematically from each batch and separately weighed. After that average weight of tablets were calculated.

Thickness: Ten tablets were selected form single batch and these 10 tablets thickness were determined by using vernier caliper.

Hardness: The hardness of the tablets was measured by utilizing Pfizer hardness tester. It is expressed in kg/cm. 3 tablets were unsystematically chosen and hardness of the tablets were determined.

Friability: Ten tablets were weighed and located in the Roche friabilator, which was then conducted for 25 rpm for 4 min. After revolution, dosage forms were redusted and reweighed.

% F = {1-(Wo/W)} ×100

Where,

% F = friability in percentage

Wo = Initial weight

W = Final weight

Content Uniformity: Twenty tablets from each batch were powdered and weighed accurately equivalent to 100 mg of Abacavir. Required amount of tablet powder transferred into 100 ml of 6.8 phosphate buffer solution by stirring it for 15 min. 1 ml of solution was pipette out into 10 ml volumetric flask the volume was made up with distilled water. The sample solution of the drug was analyzed by taking absorbance at suitable wavelength.

***In- Vitro* Release study:** *In-Vitro* drug release studies were carried out using Tablet dissolution test apparatus USP II at 50 rpm. The dissolution bowls 900 ml of standard buffer 0.1 N Hcl for 2 hr and followed by pH 6.8 and the temperature maintained at 37±5. From that 1 ml sample was withdrawn and placed in a 10 ml volumetric flask, and the volume was adjusted with buffer and the study was analyzed.

Drug release kinetics: The obtained dissolution data was fitted into various kinetic models to understand the pattern of the drug release from sustained microspheres. The models used were zero order, First order, Higuchi model and Koresmeyer Peppas model.

i) zero order release kinetics

$R = K_o t$ -- (1)

Where, R = cumulative percent drug release

Ko = zero order rate constant

ii) First order release kinetics

$\log C = \log Co - K_1 t / 2.303$ -- (2)

Where, C = cumulative percent drug release

K_1 = first order rate constant

iii) Higuchi model

$R = K_H t^{0.5}$ -- (3)

Where R = cumulative percent drug release

K_H = Higuchi model rate constant

iv) koresmeyer peppas model

$M t / M \alpha = K_k t^n$

$\log M t / M \alpha = \log K_k + n \log t$ -- (4)

where K_k = korsrmeyerpeppas rate constant 'M t / M α' is the fractional drug release, n = diffusional exponent, which characterizes the mechanism of drug release.

Diffusional exponent (n)		Drug release mechanism
0.43	--	Fickian diffusion
0.43- 0.85	--	Anamolous (non- fickian) transport
0.85- 1	--	Case II transport
> 1	--	Supercase II transport

The obtained regression co-efficient (which neared 0.999) was used to understand the release pattern of the drug from the sustained release tablets.

Stability studies

The stability testing is to get a stable product which assures its protection from harm and efficiency up to the end of shelf life at defined storage conditions and peak profile. Abacavir tablets were placed on desiccant and stored at ambient conditions such as 37°c and 40±2°c and refrigerated at 2-8°c for a period of 3 months.

RESULTS AND DISCUSSION

Drug - excipient compatibility studies (FT-IR)

The compatibility between the drug and the selected lipid and other excipients were evaluated using FTIR peak matching method. There was no appearance or disappearance of peaks in the API and polymer mixture, which confirmed the absence of any chemical interaction between the drug, polymer and other excipients.

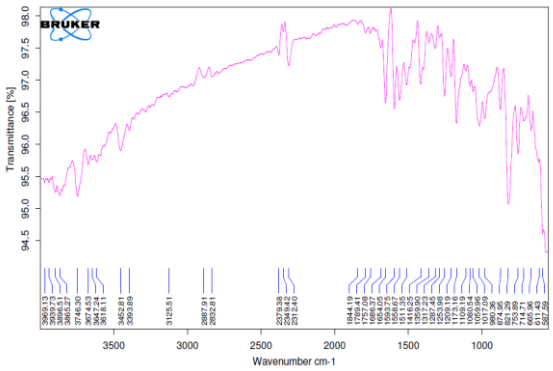

Fig. 1: FT-IR Sample for Abacavir.

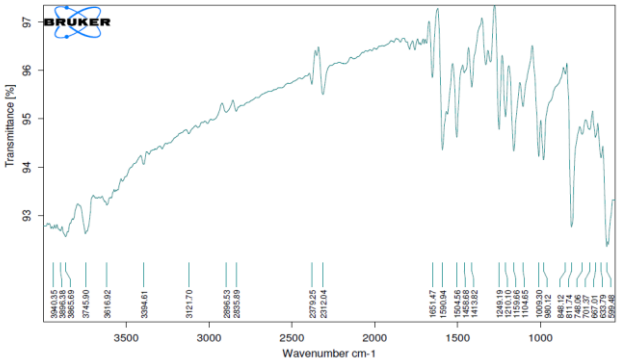

Fig. 2: FT-IR Sample for Optimized Formulation.

Evaluation studies

Pre compression parameters

1. Bulk Density: The bulk density for the formulated blend was carried out for all formulation and was found in the range of 0.521-0.532 g/cc.

2. Tapped density: The tapped density for the formulated blend was found in the range of 0.625-0.637g/cc.

3. Angle of repose: The angle of repose for the formulated blend was carried out. It concludes that all the formulations blend was found to be in the range of 27 ^{0} to 31 ^{0}

4. Compressibility index: Compressibility index was found in between 10% to 17.98 % indicating the powder blend has the required flow property for compression.

Table. 2: Evaluation parameters of Abacavir.

F. NO	Bulk density (g/cc)	Tapped density (g/cc)	Compressibility index	Hausner ratio	Angle of repose(ø)
A1	0.525	0.632	16.93	1.20	27^0
A2	0.523	0.635	17.63	1.21	30^0
A3	0.520	0.634	17.98	1.21	29^0
A4	0.521	0.628	17.03	1.20	28^0
A5	0.532	0.637	16.48	1.19	27^0
A6	0.530	0.625	15.20	1.17	31^0
A7	0.528	0.632	16.45	1.19	29^0
A8	0.522	0.631	17.27	1.20	28^0

Post compression parameters

Weight variation: All the formulated (A1 to A8) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness: Tablets mean thickness (n=3) were uniform in A1 to A8 formulations and were found to be in the range of 2.43mm to 2.46mm.

Hardness: The measured hardness of tablets of each batch ranged between 5.2 to 5.8 kg/cm$^{2.}$

Friability: The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity: The percentage of drug content from A1 to A8 was found to be between 94.19% and 98.10 % of Abacavir, it complies with official specifications.

Table. 3: Results of Pre compression parameters.

F. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
A1	600	5.2	6.20	0.53	95.90
A2	599	5.1	6.18	0.52	94.60
A3	601	5.3	6.15	0.54	95.25
A4	598	5.4	6.14	0.52	96.16
A5	600	5.4	6.15	0.55	98.10
A6	599	5.5	6.10	0.52	94.19
A7	598	5.8	6.09	0.54	97.28
A8	601	5.4	6.10	0.53	96.80

***In-vitro* Dissolution Study:** All the 8 formulation of prepared matrix tablets of Abacavir were subjected to *in-vitro* release studies, these studies were carried out using dissolution apparatus.

Table. 4: Drug release studies of all formulations.

Time	A1	A2	A3	A4	A5	A6	A7	A8
0	0	0	0	0	0	0	0	0
1	25.95	24.70	24.32	28.56	29.65	26.52	22.25	26.78
2	37.70	35.58	34.60	35.72	36.25	35.80	35.48	36.18
3	45.28	45.55	45.92	42.58	49.29	46.28	49.28	48.15
4	59.52	59.70	55.60	53.50	58.30	58.62	55.58	55.80
5	63.26	68.56	62.18	64.40	66.28	62.82	63.72	65.25
6	71.29	73.50	75.25	76.45	78.50	72.28	75.19	73.28
7	80.26	82.95	83.26	84.60	85.29	84.25	82.60	82.27
8	93.40	95.50	94.80	97.63	98.70	96.29	95.65	96.93

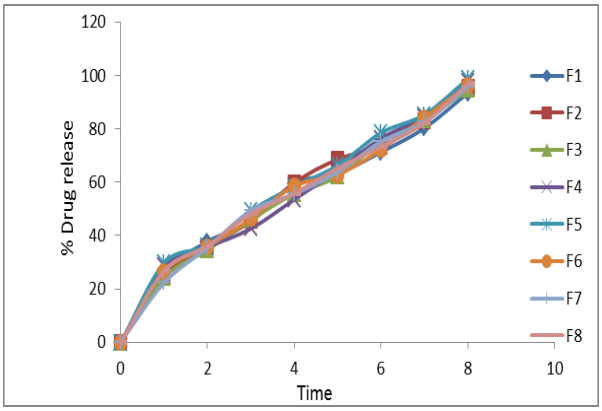

Fig. 3: Dissolution profile of (A1-A8) Formulations.

Kinetic modelling of drug release: All the formulation of prepared of abacavir sustained release matrix tablets were subjected to in vitro release studies these studies were carried out using dissolution apparatus.

Zero order kinetics

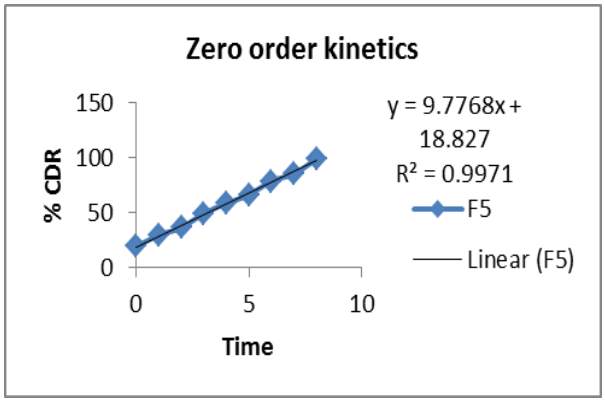

Fig. 4: zero order for optimized formula First order kinetics.

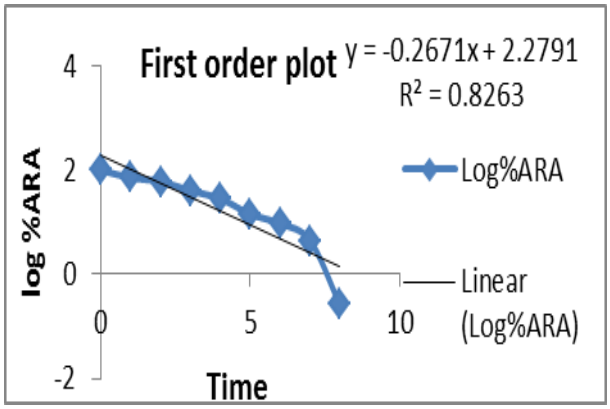

Fig. 5: First order for optimized formula.

Higuchi Model

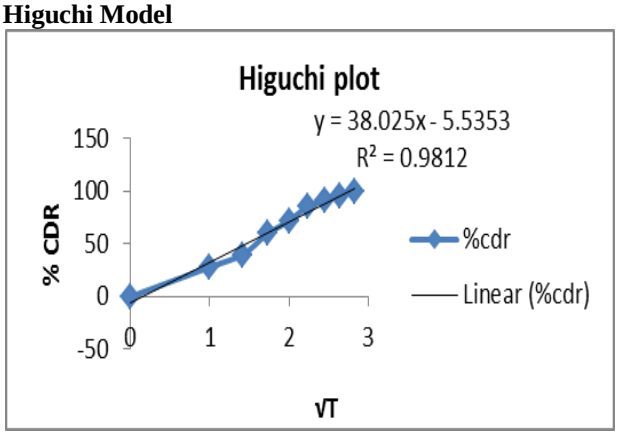

Fig. 6: Higuchi plot for optimized formula.

Koresmayer Peppas

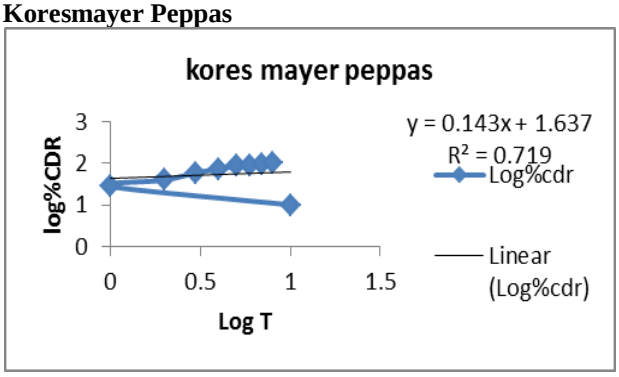

Fig. 7: Korssmayer Peppas plot for optimized formula.

The drug release from the abacavir sustained release tablets was found to follow Zero order release based on the "r" value obtained for Zero order (0.997) and first order (0.826) for A5 formulation. Also, the drug release mechanism was found to be "Diffusion" based on the "r" value of 0.981 obtained for Higuchi's plot. Similarly, the drug release mechanism was found to be of Anomalous diffusion mechanism based on the "n" value of 0.719 obtained for Peppa's equation.

Table. 5: Results of Stability studies of best formulation.

S. no	Zero order	First order	Higuchi	Krossmayer peppas
Code	R^2	R^2	R^2	R^2
A5	0.997	0.826	0.981	0.719

Stability Studies: Sustained release matrix tablets of Abacavir formulated in the present study were subjected to accelerated stability studies. Stability studies of the prepared formulations were performed at ambient humidity conditions, at room temperature, at 40°c and 2-8°c for a period up to 90 days. The samples were withdrawn after periods of 15 days, and 90 days and were analyzed for its appearance, hardness, friability, drug content and in vitro release. The results revealed that no significant changes in appearance, drug content, hardness, friability, and *in-vitro* release for A5 formulation when it was stored at the three storage conditions. However there was slight variation in *in-vitro* release when it is stored at 2-8°c, there was no change when it is stored at 40°c and room temperature.

Table. 6: Results of stability studies of best preparation A-5.

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
A-5	25°C/60%RH % Release	98.70	98.68	98.67	98.69	Not less than 85 %
A-5	30°C/75% RH % Release	98.70	98.65	98.65	98.64	Not less than 85 %
A-5	45°C/75% RH % Release	98.70	98.66	98.66	98.65	Not less than 85 %

CONCLUSION

The sustained release abacavir tablets were prepared by using different excipients. Before going to formulate the tablets the preformulation studies were carried out such as FTIR, calibration, organoleptic characters. The formulation was developed by using polymers such as xantham gum, sodium alginate, ethylcellulose and eudragit used in different trails. The pre compression

parameters such as angle of repose, bulk density, true density, compressibility index, were found to be within the limits. The tablets of abacavir sustained release were prepared by direct compression technique. The talc was used as glidant and lactose was used as lubricant and micro crystalline cellulose was used as filler. The after development of sustained release tablets of abacavir were evaluated for various parameters such as weight variation, thickness, friability, drug content and disintegration and *in-vitro* dissolution studies. They all were found in within the range of limits. The *in-vitro* drug release studies were carried out by USP-II apparatus. The optimized formulation A5 was taken for mathematical modelling to know about the diffusion mechanism. It follows the zero order and Higuchi equation. The stability studies for 90days were done with the optimized formulation. In stability studies the drug content and drug release studies were carried out and there was no degradation in the drug content and drug release studies.

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