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Design, Statistical Optimization and *inVitro-InVivo* Correlation of Extended Release Abacavir Tablets: Influence of *Azadirachta indica* Gum

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Original Research Article

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Abstract: The aim of the present investigation was to develop controlled release tablet of Abacavir sulphate using. *Azadirachta indica* (Neem gum) and comparison with official guar gum (BP). Additionally, physiochemical properties of the gum were evaluated. Totally five batches abacavir containing extended release tablets were designed using neem gum / guargum characterized for preliminary trial. Best formulation was selected for optimization by 2^2 central composite design. In this Input variable were Neem gum/Guargum (X_1) and Microcrystalline cellulose (X_2). The output variables were Hardness (Y_1) friability (Y_2) swelling index (Y_3) and *in vitro* release (Y_4). The optimized formulations were subjected for *inviro-invivo* correlation. The study results revealed optimized batch A2 showed hardness of 5.8 kg / cm^2, friability 0.63 %, swelling index 84.3% and *in vitr*o release of 90% over the period of 12 h. A higher similarity between optimized tablets and Abamune tablets (Cipla) was established with similarity factors f2 was 50 .7.pH 6. 8 phosphate buffer. Also the *in virtro in vivo* correlation coefficient obtain from point –point analysis of optimized tablets was 0.98. The optimized tablets exhibit super case 11 mechanism.
Keywords: *Azadirachta indica* Gum, Abacavir, Extended release tablets, Optimization.

INTRODUCTION

The oral route is the route most often used for administration of drugs. Tablets are the most popular oral formulations available in the market and are preferred by 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. Controlled release (CR) tablet formulations are preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase the safety margin for high-potency drugs.

Neem gum is a plant exudates obtained from the trunk of *Azadirachta indica* family Meliaceae. It contains D-galactose, Larabinose, D-glucuronic acid and some traces of D-xylose. Arabinose is present as furanose form and can be proved by acidic hydrolysis which removes arabinose and fucose in primary stage. Generally gum is found as methyl derivative of acid[1-3].

Response surface methodology (RSM) is a collection of statistical and mathematical techniques useful for developing, improving and optimizing processes. It provides important applications in the design, development and formulation of new product designs. The most extensive applications of RSM, particularly in the situations where several input variables potentially influence some performance measure or quality characteristic of the product or process. This performance measure or quality characteristic of the product is called the response[4]. The input variables are also known as independent variables and they are subjected to be controlled by the formulator.

Abacavir belongs to a class of HIV bioavailability of the drug is 83 %. The drug belongs to BCS 11 drugs. The half life drug is 1.5 h[4]. Therefore, it would be beneficial to develop a extended release delivery system to reduce the frequency of administration. Considering all the factors the primary aim of the research work is to study the characteriszation of neem gum for functionality of binder/ release retardant. The secondary aim is to design and optimization of extended release abacavir tablets using *Azadirachta indica* gum. Additionally, *in vitro in vivo (IVIVC)* correlation was performed to check the improved *invitro release* drug release.

MATERIALS AND METHODS

Material

Abacavir sulphate (Molecules India Pvt Ltd, Chennai) Microcrystalline cellulose (Yarrow Chem products, Mumbai) Magnesium stearate and Talc (Nice Chemicals Ltd, Kochi) Neem gum (Neoteric, Tamilnadu) and Guargum(Urban platter, Mumbai)

Characterization of Neem gum

The physico chemical properties such as pre-compression parameters, visual identification solubility, pH, moisture content, moisture uptake, swelling index and particle size of *Azadirachta indica* gum were determined according to official procedures[5]. All the results are presented in Table 1.

Preparation and optimization of Abacavir sulphate extended tablets

The Extended release tablets of Abacavir sulphate drug were prepared using direct compression method.. After being grinded and sifted required quantities of drug MCC Neem gum, Guargum and other excipients were mixed thoroughly subsequently passed through a mesh #40 to blend the ingredients uniformly. The powders were dried at 55^0C for 2 h. finally the tablets were compressed using a flat faced 10 mm in rotary punch press tablets machine.Each tablet contained 150 mg of abacavir sulphate., keeping hardness between 4 - 6 kg/cm^2.

To study the influence of the tablet formulations abacavir extended release matrix tablets was prepared according to the 2^2 factorial design Two major factors (input variables) was set as follows; the amount of neem gum / Guargum (X_1) and MCC (X_2). Response variables were Hardness(Y_1) Friability(Y_2) Swelling (Y_3) and *In vitro* release Study(Y_4). The composition of tablets and the study results presented in table 2-4.

Hardness test

Tablet hardness was determined for 10 tablets using a Monsanto hardness tester (MHT-20, Campbell Electronics, Mumbai, India. The tablet to be tested is placed between the spindle and anvil and pressure applied by turning the screw knob just to hold the tablet in position .The reading of the indicator on the scale is adjusted to zero. The pressure is applied until the tablet breaks. The reading was noted. In this work, for each formulation the hardness of 6 tablets was evaluated[8].

Weight variation and Friability test

The weight variation was determined by taking 20 tablets using an electronic balance .In weight variation test twenty tablets were selected at a random and average weight was calculated. Then individual tablets were weighed and the weight was compared with an average weight. Friability was determined by testing 10 tablets in a friability tester for 300 revolutions at 25 rpm. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25rpm and dropping the tablets at a height of 6 inches in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were de dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula:

$$F = (1- W_0 / W) \times 100$$

Where, W_0 is the weight of the tablets before the test and W is the weight of the tablet after the test[8].

Swelling Study

The extent of swelling was measured in terms of percentage weight gain by the tablets. The swelling behavior of all the formulations was studied. One tablet from each formulation was kept in Petri dish containing phosphate buffer pH 6.8. At the end of 2, 4, 6, 8, 10 and 12h tablets were withdrawn, soaked on tissue paper and weighed, and then percentage weight gain by the tablet was calculated[8].

Assay

For the determination of drug content, the prepared tablets were divided in triplicate. For each batch, 20 tablets were taken, weighed and finely powdered. An accurately weighed quantity of this powder was taken and suitably dissolved under sonication in pH 6.8 phosphate buffer and filtered. The samples were analyzed by a UV visible spectrophotometer after making appropriate dilutions[8].

In vitro drug release studies

The *in vitro* release study for the self-made tablets and marketed tablets were performed using USP XX111 paddle type apparatus. The set condition was 900ml of pH 6.8 phosphate buffer, 50 rpm, 37 C for 12 h. Aliquots were withdrawn at every one hour and analyzed by UV method at 232nm. The absorbance were changes into drug concentration using a calibration curve **[**9].

Similarity factor

The similarity factor was used as a basis to compare the difference between the optimized self-made tablets and marketed tablets in dissolution profiles, which was calculated by the following equation, *f2 =50+log [{1+(Rt-Tt)*1/n}-0.5]*

where n is the time points of the tested samples, Rt is the dissolution value of the reference batch at time t, and Tt is the dissolution value of the test batch at time t. The similarity factor($f2$) is measurement of the of the similarity in the percent dissolution between the two curves . And $f2$ values greater than 50 (50-100) ensure sameness or equivalence of the two curves[10].

***Drug absorption and Invitro- Invivo* correlation study**

In vivo absorption study for optimized batch was performed by everted sac method. The chicken ileum was removed and cut for 6 cm long, placed in watch glass containing physiological salt solution .The mesentery and adhering tissues were removed . A glass rod was used to evert the intestinal segment without damage to the inner layer of the intestine. After introduction of optimized tablets the opening was closed by tied off and the sac is immersed in a beaker containing pH 6.8 phosphate buffer solution at 37^0 C. The samples were withdrawn at various time intervals, and analyzed by UV method at 232 nm. The absorbance was changed into drug concentration using a calibration curve.

A point to point *invitro - invivo* correlation study was performed ploted the *invitro* release data (optimized batch) on X axis and *Invivo* absorbtion data on Y axis. The linear regression coefficient (R^2) was used to evaluate the correlation between *in vitro* release and *in vivo* absorption data[11].

RESULTS AND DISCUSSION

FT-IR spectrum of Drug and excipients did not differed with major peaks of Abacavir Sulphate ie; all the major peaks of the drug appeared on the blend reveals that there is no possible interaction between drug and excipients

Characterization of Neem gum

The physico chemical parameters of *Azadirachta indica* gum was evaluated. the *Azadirachta indica* gum was very soluble in warm water and partially soluble in cool water. The moisture content values of NMG suggest that the use in formulations containing moisture sensitive active ingredients should be done with caution. It having appreciable amount of polysaccharide and proteins present in neem gum. Hausneris ratio provides an indication of degree of densification of powders/granules that could result from vibration of the feed hopper e.g., during tableting, with values of above 1.2 indicating considerable amount of densification, while Carris compressibility index is a direct measure of the potential powder/granule arch or bridge strength and stability; a less than 20% standard value suggests free-flowing powder/granules. The HR, CI and angle of repose of Neem gum possesses a higher flow that could be useful in direct compression.

Preliminary trial experiment

Four batches of abcavir sulphate extended release tablets were developed by direct compression method for for preliminary trial. The composition of the formulatinons were given in table 1. The formulations were prepared by different concentration of neem gum/guar gum. In all the formulations 150 mg of the drug was incorporated and the final weight was made to 420mg. The formulated tablets were evaluated for weight variation, Hardness, Assay, friability, and *invitro* release profiles. The results are indiated in Table 2.

The friability values decreased with increase in biner concentration. All the evaluation paramenters were found to be with in the pharmacopoeia limits. Percentage friability and weight variation passes the test as per standard pharmacopoeial limit. As the time increase, swelling index was increased, later on it decreases gradually due to dissolution of outermost gelled layer of tablet into dissolution medium. The direct relationship was observed between swelling index and gum concentration, as gum concentration increase swelling index increased. It was observed that the cumulative percent drug release decrease with increasing concentration of gum and swelling index. Among the formulation studied, formulation F4 showed 91.25% release of drug for 12hrs. Among this F 4 batches showed better *invitro* release profile.

Optimization of formulation

Based on preliminary study, two factors factors were choosen as research obects, including X_1 and X_2. Further more, the factors affecting *F2* were studied in the 2^2 factorial design approach. Table 3 showed layout and the results of full factorial design.

Polynomial Equation for factorial fit

$Y=b_0+b_1X_1+b_2X_2+b3X_1X_1+b4X_2X_2+b5X_1X_2$

where,Y= Dependent variable, b_0=Arithmetic mean response of 8 runs, b_1,b_2,b_3 are estimated regression coefficient for factor X_1.

Effect of analysis on hardness

$Y_1= 5.800 + 0.006\ X_1 + 0.041\ X_2 + 0.063\ X_1*X_1 + 0.013\ X_2*X_2 + 0.300\ X_1*X_2$

The result s concentration of X_1 and X_2 increases the hardness of the tablets also increased.

Effect of analysis on Friability

$Y_2 = 0.6200 - 0.0016\ X_1 - 0.0052\ X_2 - 0.0075\ X_1*X_1 - 0.0025\ X_2*X_2 - 0.0450\ X_1*X_2$.

It shows that concentration of X_1 and X_2 increases the percentage of friability decreased.

Effect of analysis on Swelling

$Y_3 = 83.952 - 0.064\ X_1 + 0.060\ X_2 + 0.073\ X_1*X_1 - 0.102\ X_2*X_2 + 0.690\ X_1*X_2$. It shows that The equation revealed concentration of X_1 negatively impact on percentage of swelling . When amount of X_2 increases the percentage of swelling increased. The both effect significantly increasing the swelling (%).

Effect of analysis on drug release

$Y_4 =91.800 + 0.252\ X_1 + 0.046\ X_2 + 0.201\ X_1*X_1 + 0.493\ X_2*X_2 - 1.96\ X_1*X_2$

The counter plot of X_1 and X_2 is actual factor. It shows that concentration of X_1 and X2 increases the percentage of drug relese decreased.

The 3 D shows that with increase in concentration of ----- .It shows increase in release of at some level as observed The factor A has significant influence of the drug release.

Similarity factor

The similarity factor is compared between optimized formulation and marketed formulation. The similarity factor *f2* was 50.7 which ensure sameness of the two curves.

Release kinetics study

The dissolution data was subjected for kinetic treatment. Zero order >First order > Higuchi > Korsemeyer Pappas. From the R^2 values, it was concluded that the drug release profile of optimized batch followed zero order kinetics with super case 11 (n =1.2) mechanism.

Invitro invio correlation

The *IVIVC* for the optimized batch was examined. The *IVIVC* correlation coefficient R^2 was 0.98, suggesting that the prepared tablet followed a strong level correlation.

Table-1: Physicochemical properties of neem gum

S. No	Parameters	Results
1.	pH	6.7
2.	Bulk density (g/ml)	0.7
3.	Carrs index (%)	17.2
4.	Hausners ratio	1.23
5.	Angle of repose^o	22.7
6.	Swelling index	1.04
7.	Solubility	Very soluble in warm water
8.	Moisture content (%)	7.5
9.	Moisture uptake (%)	14.500
10	Particle size (µm)	15.6

Table-2: Composition of extended release Abacavir sulphate tablets for Preliminary Trail

Ingredients(mg)	F1	F2	F3	F4	F5
Abacavir	150	150	150	150	150
Guar gum	100	40	50	60	-
Neem gum	-	60	50	40	100
MCC	135	135	135	135	135
Magnesium stearate	20	20	20	20	20

Talc	15	15	15	15	15
Total weight	420	420	420	420	420

Table-3: Precompression Parameters of Preliminary Trail batch

Code	Bulk Density (g/cc)	Tapped Density (g/cc)	Carr's index (%)	Angle of repose
F1	0.51	0.62	17.74	$25^0 1'$
F2	0.50	0.61	18.03	$26^0 2'$
F3	0.47	0.57	17.54	$26^0 5'$
F4	0.50	0.62	19.35	$26^0 4'$
F5	0.43	0.53	18.86	$25^0 3'$

Table-4: Evaluation of preliminary trail batches of tablets

Formulation	Hardness(kg/cm^2)	Friability(%)	Thickness(mm)	Assay (%)
F1	5.2	0.63	4.08	95.8
F2	5.5	0.61	4.13	95.1
F3	5.7	0.59	4.09	98.9
F4	5.9	0.56	4.10	96.5
F5	4.9	0.71	4.06	99.4

Table-5: Layout of 2^2 factorial designs for optimization of F 4 preliminary trial batch

Run	Independent Variables		Dependent Variables			
	X_1 (Neemgum/Guargum)	X_2 MCC	Hardness (kg/cm^2) Y1	Friability (%) Y2	Swelling index (%) Y3	*Invitro* drug release (%) Y4
1	-1 (90mg)	+1(45mg)	5.4	0.7	82.8	95.6
2	+1 (110mg)	-1(125mg)	5.8	0.6	84.3	90.1
3	-1 (90mg)	-1 (125mg)	5.6	0.6	83.6	91.2
A4	+1 (110mg)	+1 (145mg)	6.4	0.5	84.8	92.1

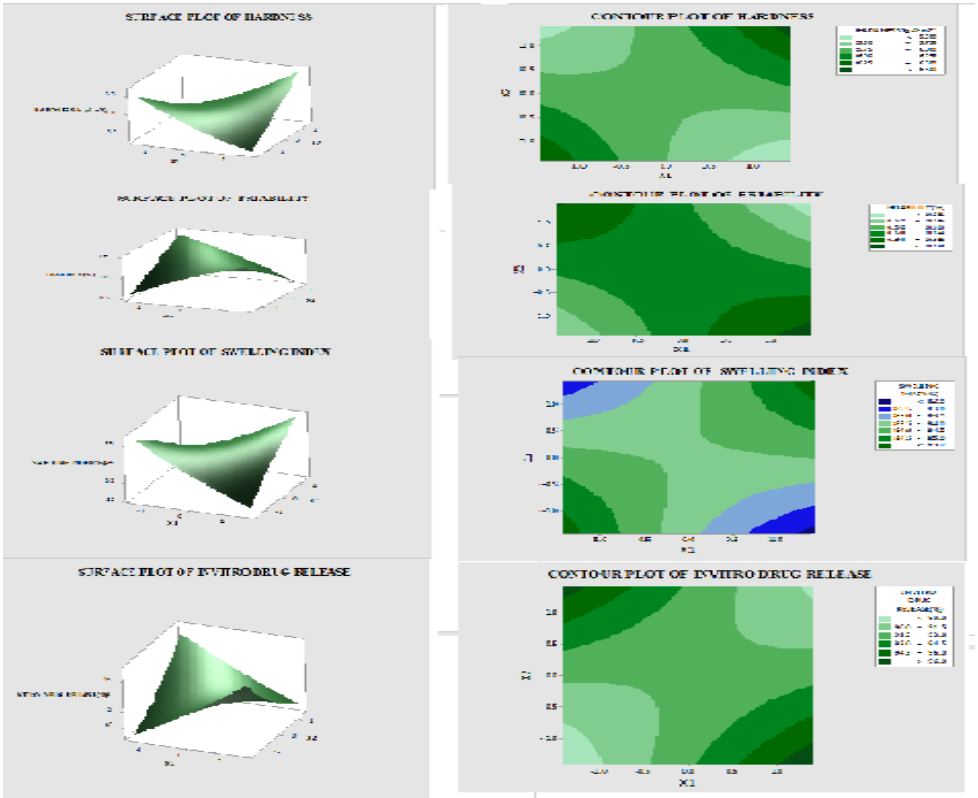

Fig-1: Surface and Contour plots of Optimized self made tablet(A2)

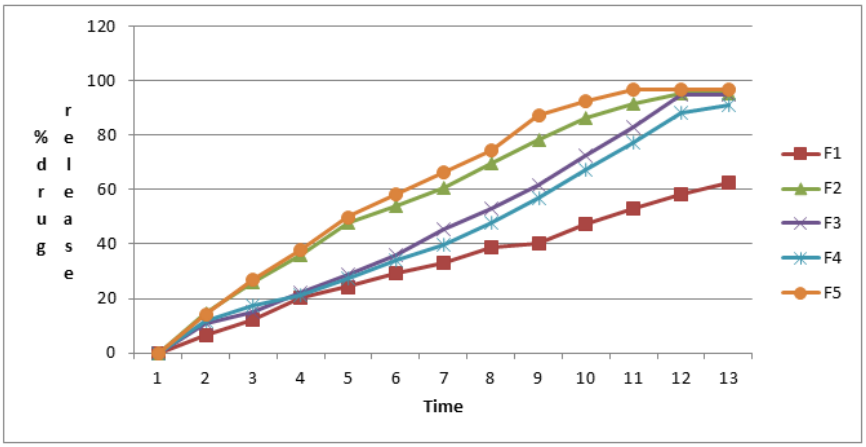

Fig-2: *in vitro* drug release profile of Abacavir extended release tablet

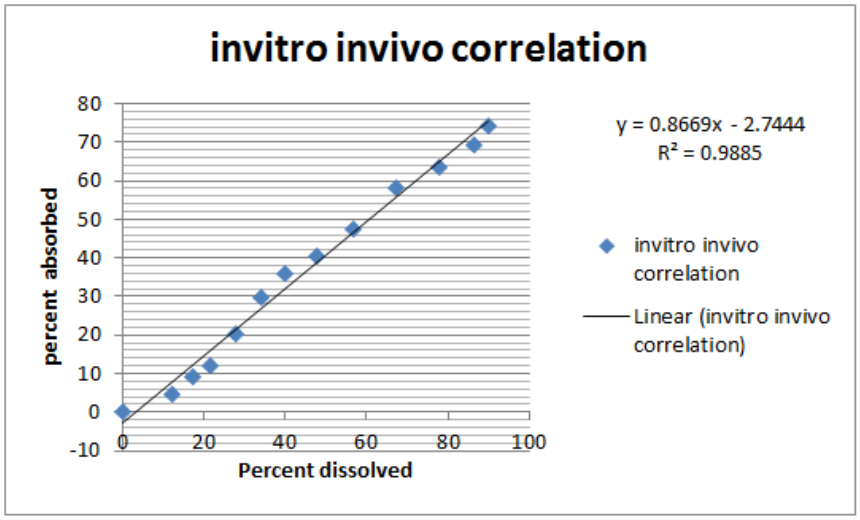

Fig-3: Percentage of drug absorbed and percentage of drug dissolved by *invitro* method

CONCLUSION

The formulated matrix talets of abacavir sulphate using natural polymer neem gum, guargum were cable of exhibiting extended release properties. The evalution of tablets revealed that the binding / release retardant efficacy of tablets prepared using neem gum is of great significance. Therefore, it is concluded that neem gum could be used well as a binding and release retarding agent in the formulation of tablet dosage form.

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