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Impact of *Azadirachta indica* Fruit Mucilage on particle size and swelling index in Central Composite Designed Acyclovir mucoadhesive microspheres

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Abstract:

The drive of this exploration is to investigate the mucoadhesive assets of *A. indica* (*Azadirachta indica*) fruit mucilage by incorporating it into mucoadhesive microspheres with Acyclovir (AVR) as a model drug. The study was performed to check the impact of the mucilage proportion on particle size and swelling index. Nine batches of AVR mucoadhesive microspheres were made with varying proportions of Polyacrylic acid 934P and *A. indica* fruit mucilage (AIFM). A central composite design with design expert software to check the impact of dependent variables (*A. indica* mucilage and Polyacrylic acid 934 P levels) on particle size and swelling index as a response. As part of congeniality studies, the batches were examined for their physical constraints, AVR contents, and liberation. The particle size was found to be 35.2 ± 0.3 - $48.1 \pm 0.6 \mu\text{m}$. In batch B-1, the particle was least sized compared to the larger size in B-5. The investigation found that the particle size and the swelling index depended on AIFM and Polyacrylic acid proportions. The research discovered that AVR was systematically released in a controlled manner and that the entrapment efficacy, mucoadhesion, drug content, and other constraints were found to be good. Acyclovir is capable of good stomach-specific drug delivery by Polyacrylic acid 934P and enhanced by *A. indica* fruit mucilage when prepared as mucoadhesive microspheres. Scanning electron microscopy reveals that the microspheres were spherical with a fairly smooth surface.

Keywords: Acyclovir, *Azadirachta indica*, Microspheres, Mucoadhesive, Particle size.

Introduction:

Drug administrations are adopting unique attitudes to increase the gastric availability of drugs with patient consent. Stomach-retentive systems increase the time the formulation remains in the stomach, thereby slowing the fast gastric emptying of the formulations. As a result of gastric emptying and peristalsis, the conventional oral forms are rapidly eliminated from the stomach. A gastro retentive form provides a longer stay in the stomach. It is possible to increase the absorption and bioavailability of AVR in these forms, which reduces the administration frequency. Bioadhesive dosage forms are developed using excipients with bioadhesion properties (for example, polyacrylic acid P 934P). By virtue of their ability to attach naturally to biological surfaces like mucous

membranes, these materials have allowed forms to be imagined that could either prolong local activity or modulate systemic absorption of AVR. The use of these galenic forms enables the slowing down of the elimination of AVR. The gastro retentive microspheres, which are easy to prepare and administer, are of special importance among the various dosage forms^{1,2}.

Acyclovir (AVR) is a purine nucleoside analog that is necessary to tackle viral taints like chickenpox, herpes simplex virus, and herpes zoster. AVR's oral bioavailability has been appraised to be 15-30%. AVR has a half-life of ~2 h. After oral administration, the medication is well absorbed into the stomach³. The properties of the polymer used in mucoadhesive systems greatly

influence their effectiveness. Many patients prefer the oral route for drug administration due to its convenience.

Many polymers have been tried for mucoadhesive drives, which are rare and expensive. In seeking a new polymer from nature that aids mucoadhesion found *Azadirachta indica* fruit mucilage (AIFM) ⁴, which intended to make the mucoadhesive microspheres. AIFM was proved to contain gedunin and azadirachtin which proved their anti-viral activity.

Studies have shown that AIFM has antiviral properties⁵. Antiviral therapy may be aided by AIFM. The objective of making mucoadhesive microspheres of AVR is to achieve a steady-state systemic availability in expanded time. As they are designed for ease, precision liberation systems are an effective solution for short-acting drugs and those that require incessant medicating ⁶.

Traditional research methods tend to focus on one variable at a time due to the ease of manipulating it. Statistically, each variable can be considered only once. Both factors will have an interrelationship, resulting in unreliable results. Design of experiment (DOE) is understood as a treaty with a limited number of variables in multivariate analysis. In DOE, the objective is to screen for response and optimize. Every imitation of a Factorial design (FD) explores all conceivable amalgamations of the factors. In FD, the levels are called 'high' (+1) and 'low' (-1), and the input factors are called FD at two levels. In this study, screening of mucoadhesive microspheres of AVR was studied to assess the impact of independent variables on response using design expert software^{7, 8}. The Design expert version 11.0 trial version software of Stat-Ease corporations was employed in designing and making the formula for the present investigation. For a protracted period, AIFM aims at achieving steady-state systemic availability. Precision liberation systems, designed for ease of use, are an effective way to release short-acting drugs.

Materials and Methods:

Materials

Acyclovir (AP/KA/ACR-B021) was from Actavis Pharma, Bangalore. Polyacrylic acid 934P (PAA 934P), and dichloromethane were from Merck, Hyderabad. *A. indica* fruits (through which mucilage was isolated) were collected from the plants growing in Ananthapuramu, AP, India.

Methods

Extraction of mucilage

As defined by Ahad *et al.*, 2010⁹, expressions were depleted. Following the washing of the *A. indica* fruits, they were soaked in water, boiled for an hour, and cooled. After the seeds were detached, partition was accomplished using petroleum ether (50%), ethyl acetate, and butanol. Using a multilayer muslin bag, the mucilage was extracted to remove the foreign matter. After being divided, parched in an oven at 40°C, poised, grounded, put through a # 80 sieve (Remi), and drained, the mucilage was stored in a desiccator at 30°C and 45% RH.

Cleaning of the Mucilage

As defined by Ahad *et al.*, 2021¹⁰, after homogenization (Biologics 150VT) with 5% trichloroacetic acid, centrifugation (Remi R-303), neutralization with NaOH, and dialysation in the SURDIAL-X, the AIFM was filtered. Lastly, ethanol (95%) was treated with acetone and diethyl ether until it was clean.

Experimental design

Stat-Ease Software (11.0.5.0, Stat-Ease Inc.) to create and judge quadratic response surfaces to optimize the AIFM using 9 runs, and a central composite design (CCD) was used. A quadratic model was created based on determining the key, boundary, and quadratic chattels of independent variables on dependent variables ¹¹.

$$Y = B_0 + B_1 X_1 + B_2 X_2 + B_3 X_1 X_2 + B_1 X_1^2 + B_2 X_2^2 \quad 1$$

The dependent variable is Y, the independent variables are X₁ and X₂, and the regression coefficients are B₀, B₁, and B₂. For AIFM, the dependent variables/responses were Particle Size (PS) (Y₁), and Swelling Index (SI) (Y₂). A total of 9 experimental designs were used to design the variables and their levels used in the AIFM screening ¹².

The ingredients in various AIFM are listed in Table 1.

Table 1. Compositions of AVR based formulations containing different ratios of the AIFM/PAA 934P

Components	Formulations								
	B-1	B-2	B-3	B-4	B-5	B-6	B-7	B-8	B-9
Acyclovir (mg)	200	200	200	200	200	200	200	200	200
Ethyl Cellulose (mg)	50	50	50	50	50	50	50	50	50
AIFM (mg)	50	50	50	75	75	75	100	100	100
PAA 934P (mg)	50	75	100	50	75	100	50	75	100
Dichloromethane (ml)	25	25	25	25	25	25	25	25	25
Span 80 (minims)	5	5	5	5	5	5	5	5	5
Glutaraldehyde (minims)	5	5	5	5	5	5	5	5	5
Liquid paraffin (ml)	250	250	250	250	250	250	250	250	250

Preparation of AIFM

Dichloromethane and acetic acid were used to dissolve the PAA 934P, AVR, EC, and AIFM. Using an IKA-R1385 three-bladed propeller stirrer (300 rpm), this mixture was continuously stirred into liquid paraffin (containing span 80). A concentration of 5 minims of glutaraldehyde was added dropwise (3h of stirring). After centrifugation and washing with petroleum ether, the Acyclovir-A. *indica* mucoadhesive microspheres were removed from the liquid paraffin. In order to remove residual glutaraldehyde from AIFM, it was suspended in sodium bisulfite 5% v/v for 15 min and washed with distilled water. Vacuum desiccators were used to preserve the microspheres so formed¹³.

Quality by Design (QbD) is one of the characteristics of a quality target product profile (QTPP) as described in International Council for Harmonization (ICH) Q8 and Q9. The extraction of the unprejudiced at the beginning of the development of a product is similarly presumptive. A QTPP ensures that a product meets essential quality standards by utilizing product assets¹⁴. Based on previous explorations and literature judgments, and examined the QTPP and Critical Quality Attributes (CQAs) for the AIFM.

Evaluation parameters

Microsphere size, shape, and flow properties

Microsphere sizes were determined using an optical microscope and an eyepiece micrometer. Scanning electron microscopy (SEM) was used to determine the shape and surface morphology of microspheres and to observe them. With double-sided sticky carbon tape, they were mounted directly onto the SEM sample stub and coated with platinum film. SEM was conducted at an accelerating voltage of 15 kV and a chamber pressure of 0.8 mm Hg. An angle of repose (°) as well as Hausner's ratio (HR) were used to measure the flow properties of Acyclovir *Azadirachta indica* mucoadhesive microspheres (AAMM)¹⁵.

% Yield

The weight yield of microspheres for various batches of the drug and polymers was calculated based on the weight of the final product after drying. The formula used was¹⁶:

$$\% \text{Percentage Yield} = \frac{\text{Weight of attained by microspheres}}{\text{Quantity of raw materials taken}} \times 100 \quad 2$$

Entrapment Efficiency

The 100 mg of AAMM dispersed overnight in 0.1 M HCl and the mixture was assessed at 254 nm and the filtrate was spectrophotometrically analyzed (Elico Spectrophotometer, SL-174). Entrapment efficiency was determined by comparing the sum of AVR in the formulation with the amount initially added¹⁷.

$$\text{Entrapment efficacy} = \frac{\text{Drug in the micropsheres}}{\text{Drug took for making microspheres}} \times 100 \quad 3$$

Swelling Measurement

The swelling of microspheres was conducted by keeping them in 0.1M HCl. After 3h, they were removed, centrifuged, and the weight gained was resolute by the difference between the weight gained at time t (Xt) and the initial time (t=0 [X0]) as deliberated from the following equation¹⁸.

$$\% \text{ SI} = \frac{X_t - X_0}{X_0} \times 100 \quad 4$$

Where Xt-weight of the AIFM after time t; X0-Initial weight of the AIFM.

AVR estimation

The AVR amount in the AAMM was determined by suspending 100 mg of AAMM in 100 ml of 0.1 M HCl and stirring for 10h with a magnetic stirrer at 65°C. The solution was then filtered, and the AVR was calculated¹⁹ using UV spectroscopy at 254 nm.

Mucoadhesion Measurement Study

An *in vitro* adhesion testing approach known as the wash-off technique was used to evaluate the AAMM and its mucoadhesive properties. In this investigation, freshly cut sections of goat intestinal mucosa (5.5 x 1.5 cm) were mounted onto glass slides (5.5 x 1.5 cm) with cotton thread. An appropriate support was used to connect the glass slides. Each wetted tissue specimen was rolled out with around 50 microspheres, and the support was quickly placed on the arm of a United States Pharmacopoeia (USP) tablet disintegrating test machine. The tissue specimen was suspended in a moderate up and down motion in the test fluid at 37°C contained in a 1L vessel of the machine when the disintegration test appliance was turned on or in working mode. Readings were taken at the ends of 30 min, 1 h, and hourly intervals up to 6 h. The apparatus was then closed, and the number of microspheres still stuck to the tissue at each reading interval up to 6 h was tallied. The experiment was carried out in 0.1N HCl. The formula involved is as described here²⁰:

$$\% \text{ mucoadhesion} = \frac{\text{Number of AAMM (g)}}{\text{Initial AAMM}} \times 100 \quad 5$$

In Vitro AVR Release Study

Microspheres were dispersed using the USP-II apparatus at a stirring rate of 50±5 rpm at a temperature of 37±0.5°C, using 900 ml of HCl (0.1N HCl) as a dissolution medium. A 5 ml sample at different breaks (replenished the volume of dissolution media at each break) was taken and a spectrophotometric analysis was performed at 254nm on the sample for 10h. The amount of AVR released was recorded^{21, 22}.

Kinetic modeling and release mechanisms of drug

The drug release data of AAMM was fitted to kinetics models, i.e., zero order, first order, Higuchi, Hixon-Crowell, and Korsmeyer-Peppas models²³⁻²⁵ to find out the drug release pattern and mechanism.

Statistical optimization

With Design-Expert, it was estimated independent influences on retorts from contour plots (2D) and response surface plots (3D). Statistical validation of polynomial intentions was obtained by judging ANOVA eatables. The ANOVA endowment created a statistical model to determine model abundance and aptitude, an F value with a p value of 0.05²⁶.

Results and Discussion: Factors screening results

Fit summary

In Table 2, the fit summary for the responses of PS and SI is shown.

Table 2. Fit summary for the responses

Fit summary for the response 1 (Particle size)			
Source	Sequential p-value	Adjusted R ²	Predicted R ²
Linear	0.6251	-0.1400	-0.6848
2FI	0.9511	-0.3669	-2.0150
Quadratic	0.0029	0.9539	0.8585
Cubic	0.9179	0.8835	-1.6534
Fit summary for the response 2: (swelling index)			
Linear	0.0003	0.9131	0.8681
2FI	0.6208	0.9012	0.8257
Quadratic	0.0006	0.9988	0.9965
Cubic	0.9327	0.9970	0.9306

ANOVA for the Quadratic model

ANOVA for the responses, i.e., particle size and swelling index (Table 3).

Table 3. Summary of ANOVA result for the response of AAMM

ANOVA for the response 1: PS (µm)			
Source	Sum of Squares	F-value	p-value
Model	169.21	34.12	0.0076
A-PAA 934P	2.54	2.56	0.2082
B-AIFM	22.43	22.61	0.0177
AB	0.1225	0.1235	0.7485
A ²	0.7606	0.7669	0.4456
B ²	143.37	144.56	0.0012
Residual	2.98		
Cor Total	172.19		
ANOVA for the response 2: SI (%)			
Model	263.17	1369.77	< 0.0001
A-PAA 934P	11.76	306.04	0.0004
B-AIFM	234.38	6099.40	< 0.0001
AB	0.9025	23.49	0.0168
A ²	0.6422	16.71	0.0265
B ²	15.49	403.21	0.0003
Residual	0.1153		
Cor Total	263.29		

The model's F-value of 34.12 designates that the model is significant for the response of PS. There is only a 0.01% chance coincidental that a large F-value would occur as a result of noise. Model terms are significant when P-values are < 0.05. Model terms A, B, AB, B₂ are significant. Values >0.1 indicate the model is not significant. It may be beneficial to reduce model terms (excluding those required for supporting hierarchy) if there are many insignificant terms in your model.

For the PS the Predicted R² of 0.85 is in reasonable agreement with the Adjusted R² of 0.95; i.e., the difference is less than 0.2 with the SD value of 0.99.

Furthermore, the response of SI signposts that the model is significant since its F-value is 1369.77. In this case, A, B, AB, A₂, and B₂ correspond to significant model terms.

On the other hand, for the SI the Predicted R² of 0.99 is in reasonable agreement with the Adjusted R² of 0.99; i.e., the difference is less than 0.2 with the SD value of 0.19.

PS and SI ANOVA details

The ANOVA for PS is shown in Table 3. This model is significant based on the F-value. In these cases, X₁, X₂ and X₃ were significant terms in the model. Any value > 0.1 signposts that the model is not significant. As a result of these coding factors, the final equation for PS was as follows:

$$PS = +47.04 + 0.6500A + 1.93B - 0.1750AB - 0.6167A^2 - 8.47B^2 \quad 6$$

From the above equation, the PS of the AAMM were found to be dependent on the concentration of AIFM. At lower levels of AIFM and PAA 364P (50 mg: 50mg), the mean PS of AAMM was 35.2±1.53µm. At a medium concentration of above combination (75 mg each), the mean particle size was observed to be 48.1±0.6 µm.

As per the coding factors, the final equation for SI was as follows:

$$SI = +54.21 + 1.40A + 6.25B + 0.4750AB - 0.5667A^2 + 2.78B^2 \quad 7$$

Elevation of AIFM improves AVR entrapment. This may be due to an upsurge in the viscosity of AIFM that stabilizes droplets and which prevents the outflow of drug during the hardening phase. For given levels of each factor, the equation in terms of coded factors can be used to predict the response. Factors with a high level are automatically coded as +1 and those with a low level as -1. By comparing the coefficients of the factors, the coded equation can identify the comparative control of the factors.

Diagnostic analysis for PS and SI

Diagnostic plots were used to observe the goodness of fit of the PS (Fig. 1A–D). There are no significant residuals, suggesting the hypothesis of normality holds (Fig. 1A). The PS was within the limits, as shown by the plot of residuals against predicted values. By looking at the random distribution of residuals, it appears that the assumption of constant variance (Fig. 1B) is true. Variables predictive of PS testing were identified by plotting residuals against run numbers. In Fig. 1C, all the points indicate that there were no faraway observations during the run. Based on Fig. 1D, it was observed that the predicted and actual PS were very similar. Similar findings were made at SI (Fig. 2E–H). All the plots showed excellent model fitting, closeness between predicted and observed data, and the absence of outliers.

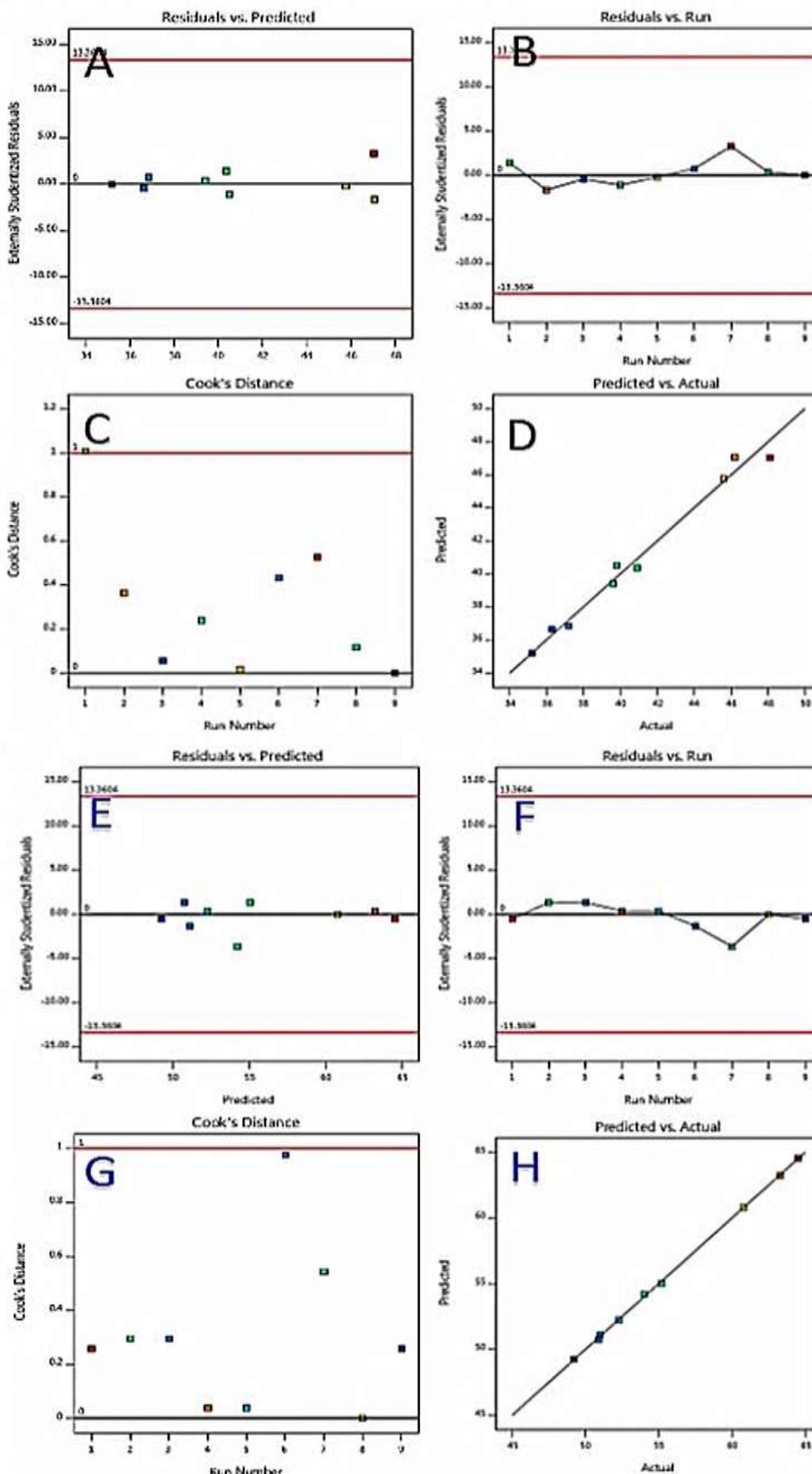


Figure 1. A-H. Plots showing the interaction effects of polymers on PS and SI

In Fig. 2 is the representation of the PS and SI with 3D response plots.

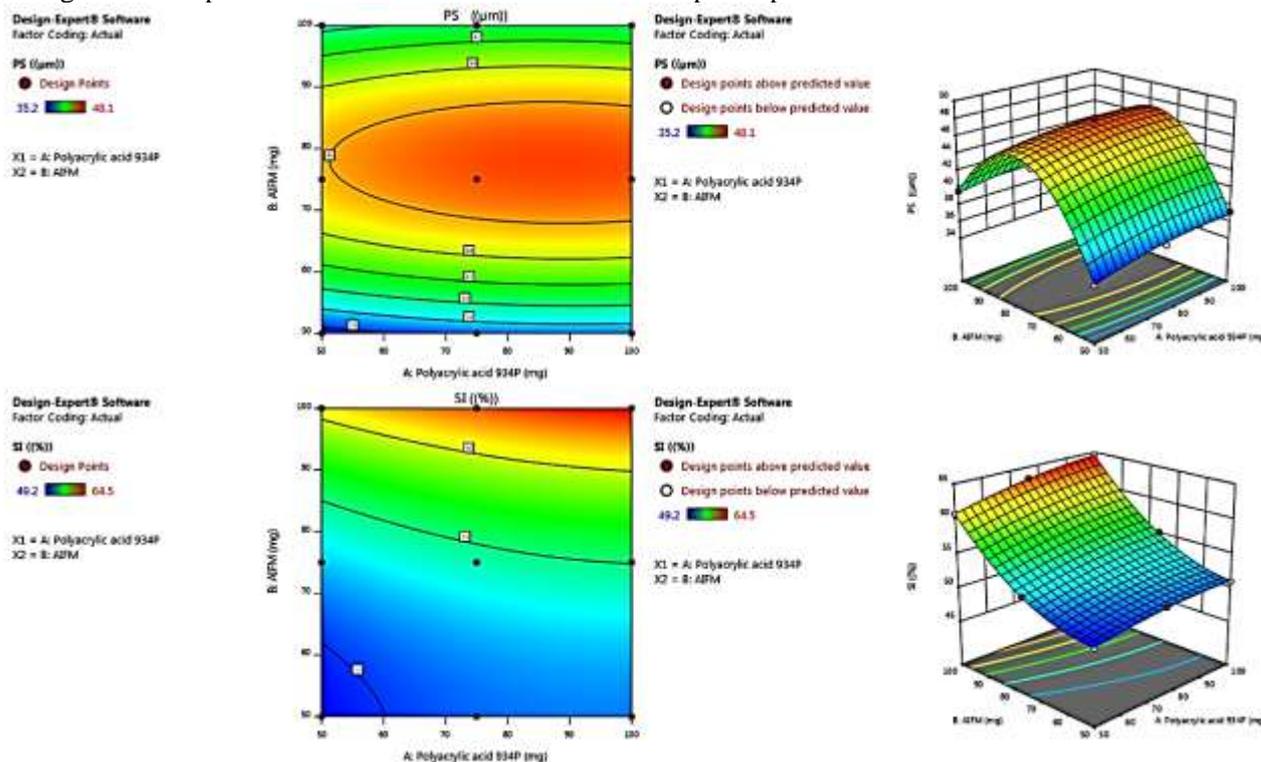


Figure 2. Contour plot and 3D response plots for PS (top) and SI (bottom)

Plots like this show the sway of two factors on the response at the same time. The contour plot and response surface plot (Fig. 2) show an equivalent increase with the concentration of the AIFM.

Optimization

Under the above conditions, to get the desired particle size of 43.44 µm with swelling of 51.70 %, the amount of PAA 934P should be 77.391 mg and AIFM 61.152 mg (Fig. 3).

Design-Expert® Software
Factor Coding: Actual

All Responses

Actual Factors

A: Polyacrylic acid 934P = 77.391
B: AIFM = 61.152

Responses

Desirability = 1
PS ((µm)) = 43.4415
SI ((%)) = 51.7067

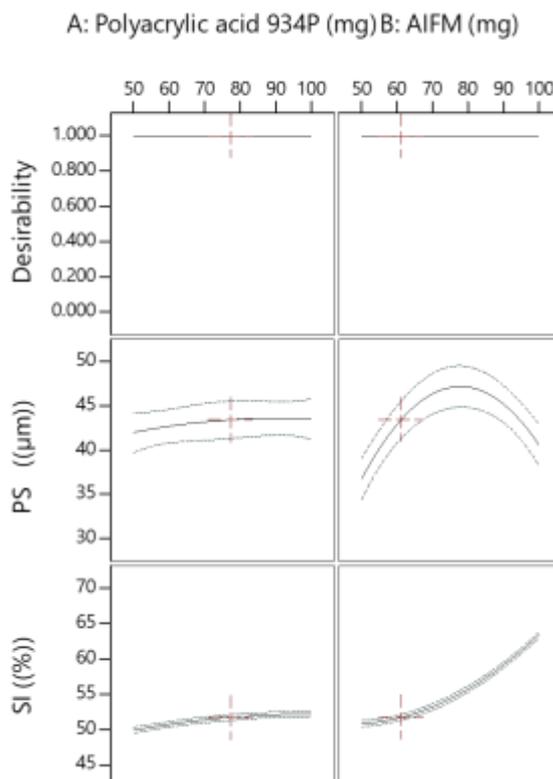


Figure 3. Numerical representation of actual factors influencing AIMM response optimization

Microsphere size, shape, and flow properties

The microspheres were described as separate, non-aggregated, and free-flowing. These also fall into the monolithic matrix group. The AAMM were spherical in shape and have a smooth surface (Fig. 4).

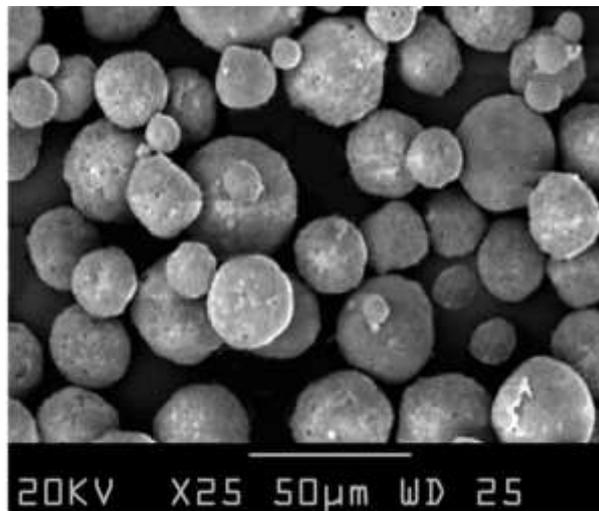


Figure 4. The SEM images of the drug-loaded B-5 batch

The microspheres demonstrated desired flowability because of optimal moisture presence, decreased cohesiveness, and a sphere-shaped shape. Microsphere flow properties, such as angle of repose (25°) and Hausner's ratio (1.00–1.11), show that AAMM have excellent flow properties (Table 4).

An optical microscope was used to discover the distribution of dimensions, particularly the form and size of the AAMM mean diameter. To count at least 100 microspheres, researchers used a compound microscope with an ocular micrometre that had been calibrated in conjunction with a stage micrometre. Mean particle size was taken into account. Each batch of microspheres had a

consistent size, ranging from 31.1 ± 0.2 to 38.2 ± 0.1 m in diameter (Table 4).

% Yield

The manufacturing yield of AAMM was pragmatic and ranged between 78.2 ± 1.8 and 91.3 ± 0.47 (Table 4). The yield of production was not uniform for all formulations. The most likely cause of its low yield was the wastage of formulation ingredients during the manufacturing process.

Entrapment Efficiency

The entrapment efficiency of AAMM (Table 4) was found to range between 72.2 ± 1.7 and 84.3 ± 1.4 . The deal out processing AIFM significantly improved the entrapment efficiency of AAMM. Higher drug extraction into the AIFM could be the cause of the lower entrapment efficiency.

Swelling Measurement

When dipped in 0.1N HCl, all of the formulations swelled dramatically, according to the results. Swelling behavior is highlighted as the most important element that has a substantial impact on the adhesive properties and cohesiveness of mucoadhesive polymers. The swelling, absorption, and capillary effects of mucoadhesive microspheres are expected to start with water from beneath the layer of mucosal tissue, resulting in significantly greater adherence. The higher swelling seen in formulations B-8 and B-9 with a higher proportion of AIFM could be due to its high ionisation in acidic pH, which allows it to absorb a large amount of water (Table 4).

AVR estimation

With a UV-VIS spectrometer, a calibration curve for AVR was obtained for the estimation in 0.1M HCl solution at 254 nm λ_{max} . Beer's law witnessed that the calibration curve was in the range of 0-10 $\mu\text{g/ml}$ (repeated thrice). Data like this is helpful in determining content uniformity.

Table 4. Flow and physicochemical properties of AAMM

Batch	Angle of repose	Bulk Density	Tapped Density	Hausner's Ratio	Particle size (μm)	% yield	Drug entrapment efficacy (%)	Swelling index (%)	AVR content (%)
B-1	18.23 ± 0.9	0.422 ± 0.02	0.461 ± 0.03	1.092 ± 0.01	35.2 ± 0.3	78.2 ± 1.8	72.2 ± 1.7	58.6 ± 1.3	96.5 ± 1.2
B-2	19.68 ± 0.5	0.506 ± 0.01	0.554 ± 0.04	1.094 ± 0.01	36.3 ± 0.4	79.8 ± 0.6	73.5 ± 1.2	60.7 ± 2.5	98.7 ± 2.3
B-3	20.35 ± 0.7	0.446 ± 0.03	0.475 ± 0.03	1.065 ± 0.01	37.2 ± 0.5	80.5 ± 0.3	74.2 ± 1.8	62.4 ± 1.5	99.1 ± 1.6
B-4	23.42 ± 0.4	0.329 ± 0.02	0.361 ± 0.02	1.097 ± 0.01	45.6 ± 0.7	83.6 ± 1.6	78.3 ± 1.6	65.9 ± 1.4	98.2 ± 3.2
B-5	19.81 ± 0.3	0.334 ± 0.02	0.365 ± 0.02	1.092 ± 0.01	48.1 ± 0.6	91.3 ± 0.4	79.4 ± 2.3	68.5 ± 2.7	99.7 ± 2.4
B-6	20.45 ± 0.6	0.498 ± 0.03	0.539 ± 0.03	1.082 ± 0.01	46.2 ± 0.7	90.5 ± 1.3	80.2 ± 1.3	70.1 ± 1.6	98.4 ± 1.5
B-7	19.37 ± 0.2	0.369 ± 0.02	0.401 ± 0.01	1.086 ± 0.01	39.6 ± 0.5	89.6 ± 0.7	83.2 ± 1.6	72.1 ± 1.8	95.3 ± 1.9
B-8	18.65 ± 0.5	0.529 ± 0.02	0.564 ± 0.04	1.066 ± 0.01	39.8 ± 0.8	91.2 ± 0.9	83.6 ± 1.5	73.4 ± 1.2	97.5 ± 1.8
B-9	19.40 ± 0.6	0.385 ± 0.01	0.413 ± 0.03	1.072 ± 0.01	40.9 ± 0.9	88.9 ± 1.2	84.3 ± 1.4	74.3 ± 1.6	98.9 ± 2.4

Values in mean \pm SD, N=5

Mucoadhesion Measurement Study

The percent mucoadhesion of total AAMM with goat intestine (Fig. 5) demonstrated that the viscosity of the polymer was substantially related to adhesion. The mucoadhesion characteristic was proportional to viscosity and molecular weight. When compared to PAA 934 P alone, the microspheres containing a high fraction of PAA 934 P aided by AIFM showed higher mucoadhesive assets in the in-vitro wash-off experiment. The wash-off test revealed that the microspheres had a good mucoadhesive activity, which is necessary for a prolonged residence duration at the absorption site and improved oral bioavailability.

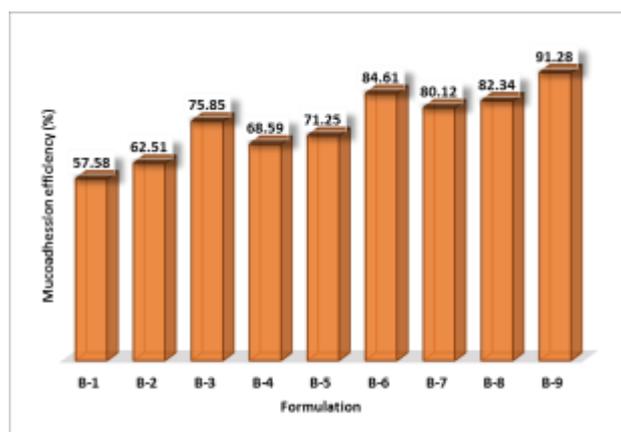


Figure 5. In vitro mucoadhesion of AAMM

In Vitro AVR Release Study

AAMM were studied in 0.1 N HCl for 10 h to determine its in vitro AVR release profile. AAMM showed consistent AVR release during the course of the research. The AAMM's drug release status in vitro is depicted in Fig. 6. Each formulation demonstrated a > 10h in drug release. It's possible that AIFM and PAA 934 P can be

brought together in making AIMM. B-3, B-6, and B-9, out of all the AAMM, had the best-regulated AVR release profile after 10 h, owing to a larger fraction of PAA 934 P. It becomes a thick gel when it comes into contact with aqueous fluids, which could be useful for delivering highly water-soluble medicines in a regulated manner. Effective and rapid drug liberation from hydrophilic matrices was likely due to the effective and faster dissolution of water-soluble pharmaceuticals from the core, which is spreading out of the spheres and creating pores for solvent molecules to pass through.

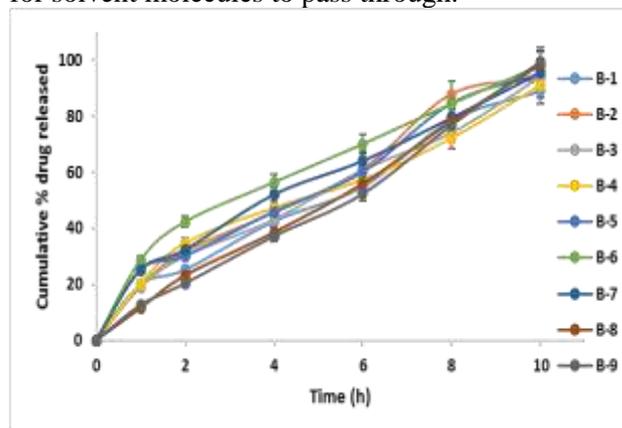


Figure 6. The release profile of AAMM from formulations containing different ratios of AIFM/PAA 934P

Kinetic modeling and release mechanisms of AVR

The release kinetics of the formulation was checked by fitting the release data to various kinetic models. The release was best suited to the Korsmeyer Peppas model. Because the n value was greater than 0.5 in this case, the release mechanism was non-Fickian diffusion (Table 5).

Table 5. Kinetic reports of AAMM

Batch	Correlation (r)					n	Release mechanism
	Zero order	First order	Higuchi	Hixson Crowell's	Korsmeyer Peppas		
B-1	0.9744	0.9176	0.9967	0.9866	0.6878	0.6998	Non fickian
B-2	0.9824	0.9412	0.9554	0.9705	0.6669	0.7286	Non fickian
B-3	0.9865	0.9229	0.9570	0.9866	0.6618	0.7413	Non fickian
B-4	0.9652	0.8769	0.9734	0.9681	0.6345	0.7579	Non fickian
B-5	0.9698	0.8989	0.9692	0.9641	0.6334	0.7641	Non fickian
B-6	0.9295	0.9691	0.9654	0.9514	0.6117	0.7923	Non fickian
B-7	0.9780	0.8764	0.9778	0.9506	0.6043	0.8089	Non fickian
B-8	0.9877	0.7987	0.9554	0.8991	0.5968	0.8173	Non fickian
B-9	0.9809	0.9515	0.9372	0.8408	0.5422	0.8850	Non fickian

Conclusion:

The mucoadhesive polymers control the amount and rate of Acyclovir (AVR) released in the mucoadhesive drug delivery system. When the

microspheres are digested, the AVR is released into the stomach. AVR's formulation includes *Azadirachta indica* fruit mucilage (AIFM) combined with Polyacrylic acid 934 P. Compared to

other formulations, Acyclovir is capable of good stomach-specific drug delivery by polyacrylic acid 934P and enhanced by *A. indica* fruit mucilage when prepared as mucoadhesive microspheres. Scanning electron microscopy reveals that the microspheres were spherical with a fairly smooth surface. AIFM content in all batches increases with an increase in mucoadhesive time. These authors proved the mucoadhesive properties of AIFM. AIFM may assist with antiviral therapy as per the earlier literature it proved anti-viral activity. AVR is released for a protracted period, at steady-state with satisfactory systemic availability. It can be concluded from this study that mucoadhesive microspheres of AVR with AIFM aided by Polyacrylic acid 934 P meet the ideal requirement for mucoadhesive microspheres, which can enhance bioavailability AVR in the stomach. The work can be further processed pre-clinically to reduce the dose of the drug.

Authors' declaration:

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are mine ours. Besides, the Figures and images, which are not mine ours, have been given the permission for re-publication attached with the manuscript.
- Ethical Clearance: The project was approved by the local ethical committee in Raghavendra Institute of Pharmaceutical Education and Research (RIPER).

Authors' contributions statement:

HAA made the protocol of the study. GNB has performed the experiment. MM interpreted the data. All Authors read the manuscript carefully and approved the final version of their MS.

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تأثير صمغ الفاكهة *Azadirachta indica* على حجم الجسيمات ومؤشر الانتفاخ في الكرات المجهرية اللاصقة للأسيكلوفير المصممة مركزياً

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الخلاصة:

الهدف من الدراسة هو التحقيق في أصول اللصق المخاطي لصمغ الفاكهة (*Azadirachta indica*) من خلال دمجه في مجهرية مخاطية مع Acyclovir (AVR) كدواء نموذجي. أجريت الدراسة للتحقق من تأثير نسبة الصمغ على حجم الحبيبات ومؤشر الانتفاخ. تم عمل تسع دفعات من كريات اللصق المخاطي AVR بنسب متفاوتة من حمض البولي أكريليك P934 وصمغ الفاكهة A. إنديكيا (AIFM). وتم تصميم مركب مركزي مع برنامج خبير التصميم للتحقق من تأثير المتغيرات التابعة (الصمغ الإنديكيا ومستويات حمض بولي أكريليك 934 ف) على حجم الجسيمات ومؤشر الانتفاخ كاستجابة. كجزء من دراسات التوافق ، تم فحص الدفعات لمعرفة القيود المادية ومحتويات AVR والتحرير. تم العثور على حجم الجسيمات لتكون $0.3 \pm 48.1 - 0.6 \pm 35.2$ ميكرومتر. في الدفعة B-1 ، كان حجم الجسيم أقل مقارنة بالحجم الأكبر في B-5. ووجدت الدراسة أن حجم الجسيمات ومؤشر الانتفاخ يعتمدان على نسب AIFM وحمض بولي أكريليك. اكتشف البحث أن AVR تم إطلاقه بشكل منهجي بطريقة خاضعة للرقابة ، وأن فعالية الالتحام المخاطي ومحتوى الدواء والقيود الأخرى كانت جيدة. كما اتضح ان الأسيكلوفير قادر على توصيل دواء جيد للمعدة عن طريق حمض بولي أكريليك P934 ومعزز بصمغ فاكهة A. إنديكيا عند تحضيره ككرات مخاطية مجهرية. يكشف الفحص المجهر الإلكتروني أن الكرات المجهرية كانت كروية ذات سطح أملس إلى حد ما.

الكلمات المفتاحية: أسيكلوفير ، أزاديراشتا إنديكيا، كريات مجهرية، لاصق مخاطي، حجم الجسيمات.