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Research Article

Fabrication and Characterization of Acyclovir Matrix Tablets Using *Azadirachta indica* Fruit Mucilage for Tackling Viral Infections

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ABSTRACT

The authors were targeted to make extended discharge Acyclovir (ACR) tablets with a combination of natural and artificial polymers. ACR matrix tablets were made with the combination of *Azadirachta indica* fruit mucilage (AIFM) and Ethylcellulose. The blend was tested for compatibility, flow possessions, official and non-official tests including ACR discharge. The ACR matrix tablets possess good ACR with possible pre and post formulation parameters. The study explored no chemical interactions between ACR with polymers used. This was also noted that AIFM can be a good polymer in grouping with other synthetic polymers for controlling the drug release.

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Introduction

The viral infections trouble the entire globe. As viruses keep their vitality even, they present outside the human body and infects when it gets into the living beings (Qu & Morris, 2005).

Acyclovir (ACR) is a BCS class III drug with t ½ of 2-4 h. Its absorption in the gut is sluggish, variable and incomplete (Lennernas, *et al* 2005). The bioavailability of ACR after oral administration ranges from 10 to 30%. Approximately 80% of an oral dose is never absorbed and excreted through faeces (Dey, *et al* 2009). The absorption was enhanced with the aid of Dimethyl sulfoxide (DMSO) (Tyring, *et al* 2002). Also, the frequency of administration of Acyclovir is high, being 200 to 400mg five times a day depending upon the type of infection (Ahad, *et al* 2010).

Prolonged drug delivery systems with zero-order drug release can be achieved by various tactics

among them matrix system is simple, economical and effective (Bigoniya*et al.*, 2012). Using costly polymers can be released by economical and easily available herbal mucilages that have antiviral activity (Singla, *et al.*, 2018) in addition to binding and release retarding activity (Rawat, *et al* 2018). The author selected *Azadirachta indica* fruit mucilage (AIFM) as a release retardant in this investigation.

Materials and Methods

Material

The materials required in this work are illustrated in Table 1.

Table 1: List of Materials

Materials	Suppliers/Manufacturer
Acyclovir	Gift sample by Torrent Pharma, Mumbai
Ethyl Cellulose	Fischer Chemic Ltd, Hyderabad
Dimethyl sulfoxide	Fischer Chemic Ltd, Hyderabad
Lactose	Fischer Chemic Ltd, Hyderabad
Magnesium stearate	Fischer Chemic Ltd, Hyderabad
Talc	Fischer Chemic Ltd, Hyderabad

Methods

Identification of Acyclovir

Identification of ACR was scrutinized for a physical look, melting point and solubility.

Method to estimate Acyclovir

ACR was dissolved in 0.1N KOH to obtain 10 µg/ml solutions. Further diluted with the same and scanned for λ_{max} in a double beam UV-VIS Spectrophotometer, at 200 to 400 nm and λ_{max} was found to be 256nm and 253 nm (Ahad, Rajesh, et al., 2010).

Acyclovir calibration curve

The procedure for plotting ACR calibration curve (Hindustan *et al* 2012) was illustrated in charts 1 and 2.

Chart 1: Procedure for obtaining Acyclovir calibration curve in 0.1 N HCl

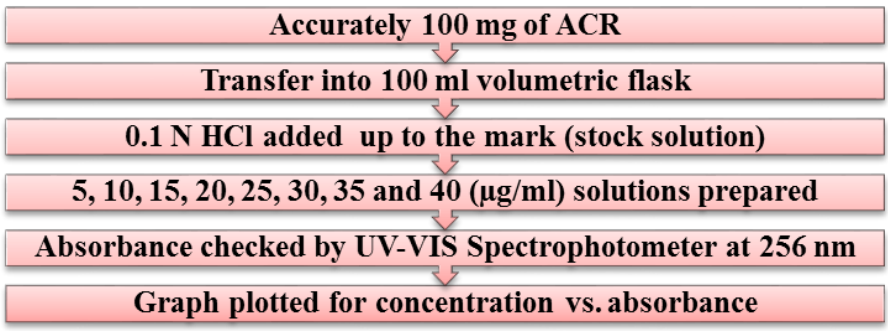
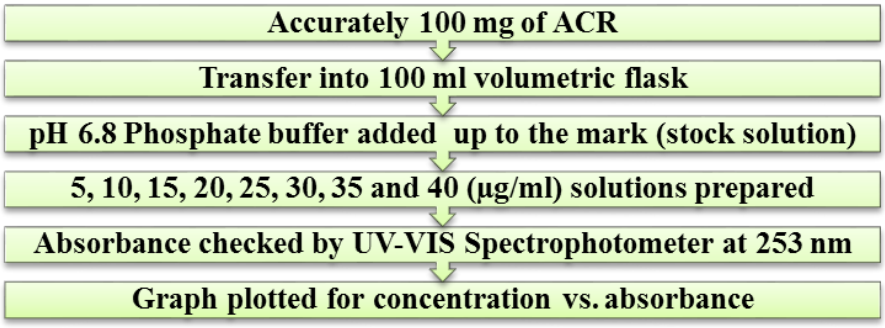


Chart 2: Procedure for obtaining Acyclovir calibration curve in pH 6.8 phosphate buffer



Extraction of mucilage

The extraction and purification were performed as styled by Ahad *et al*., 2010 (Lachman, *et al* 1986). The fresh *Azadirachta indica* fruits were washed, soaked and boiled in water. Later filtered isolated with Acetone, dried, # 80 sieved. Formulations made in this study shown in table 2.

Table 2: Formulae of Matrix Tablets

	Formulations					
Ingredients	**AMT-1**	**AMT-2**	**AMT-3**	**AMT-4**	**AMT-5**	**AMT-6**
Acyclovir	200	200	200	200	200	200
DMSO	5	5	5	5	5	5
Ethyl cellulose	20	20	20	20	20	20
AIFM	10	20	30	40	50	60
Lactose	105	95	85	75	65	55
Magnesium stearate	5	5	5	5	5	5
Talc	5	5	5	5	5	5

Drug excipient compatibility studies

Differential scanning calorimetry (DSC)

The DSC analyses of ACR and formulation blend were achieved with Perkin Elmer, FTIR spectrophotometer to check any drug-excipient interaction. Each sample was placed in an aluminium pan separately with heating rates of 10°C/min from 50-300°C under nitrogen 50 ml/min.

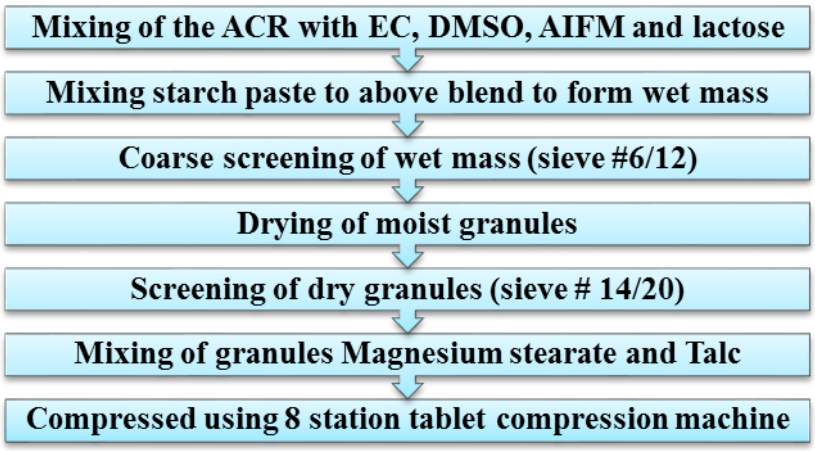
FTIR study

FTIR spectra and characteristic peaks of ACR and ACR with excipient blend were made by Bruker IR spectrophotometer.

Formulation of tablets by wet granulation technique

Steps involved in the preparation (Martin*et al* 2006) of AMT are shown in chart 3.

Chart 3: Steps involved in matrix tablet preparation



Pre formulation studies

The dried granules were subjected to flow patterns for checking their easy movement from hopper to tablet die mould for compression (Ahad*et al*2020; Narasimha *et al* 2011).

Post formulation studies

The prepared tablets were characterized by the following parameters (Avachat & Kotwal, 2007; Jaya & Divya, 2019).

Thickness of tablets

A sliding caliper was used to know the thickness of 5 tablets from each batch.

Uniformity of weight

20 tablets from each batch were weighed solely and the mean weight was also resolute. Later the unorthodoxy of individual weights was calculated.

Tablet hardness

5 tablets were randomly taken from each batch and hardness was dogged by using Pfizer tester.

The loss on friability

A pre-weighed 10 tablets from each batch were allowed for 100 falls (4 min) from 6 inches and weighed after de-dusting.

Determination of drug content in tablets

ACR content in the AMT was dogged by the procedure explained in chart 4.

In vitro dissolution studies

The dissolution conditions adopted for drug dissolution (Fuertes, *et al* 2006) were concise in Table 3.

Chart 4: Procedure for determining the drug content in prepared tablets

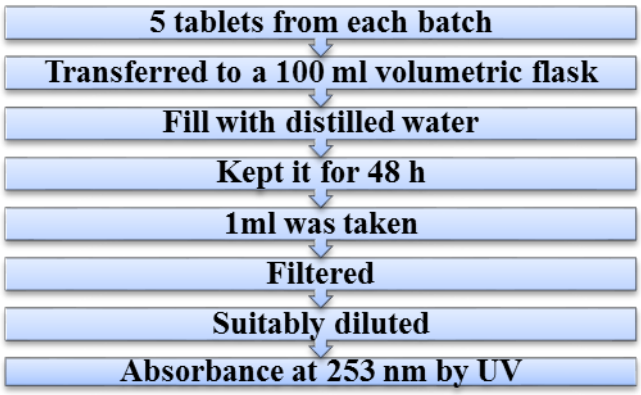


Table 3: *In vitro* dissolution conditions

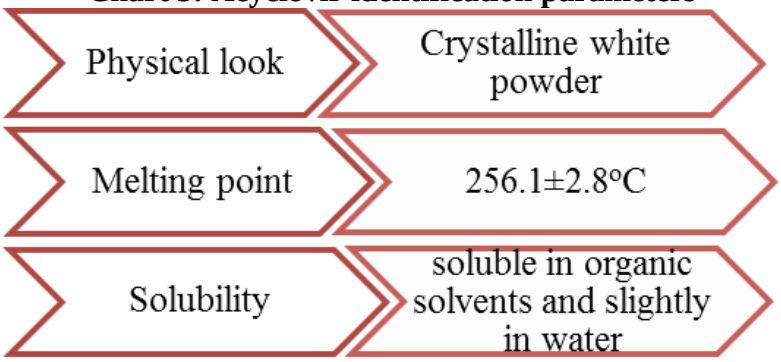
Parameter	Description
USP Apparatus	II
Rotation (rpm)	100
Medium	0.1N HCL (for 2h) then in pH6.8 Phosphate buffer
Volume	900 ml
Temperature	37±0.5°C
Sampling at	1, 4, 6, 8, 10 and 12 h
Wavelength	256nm (0.1N HCL); 253 nm (pH 6.8 PBS)

Results and Discussion

Results API characterization

ACR appearance, melting point, and solubility were listed in chart 5.

Chart 5: Acyclovir identification parameters



Compatibility studies

Neither loss of specific peaks nor emissions of new peaks were seen in the DSC of ACR thermogram when compared to pure ACR which indicates no incompatibility of ACR with polymers used (Table 4). The FTIR spectra expressed that the typical bands of ACR were not rehabilitated in the physical mixtures, which confirms no negative dealings between ACR and EC and DS polymers (Fig. 1).

Table 4: DSC thermograms of drug and polymers used

DSC sample	Endothermic events (°C)			ΔH Fusion	Inference
	T onset	T peak	T end	Enthalpy (J)	
Acyclovir	224.54	255.11	284.91	-287.25	An endothermic peak
Acyclovir+ Polymers	231.29	252.89	285.96	-291.96	A shift in peak to left due to positive blending of Acyclovir with polymers

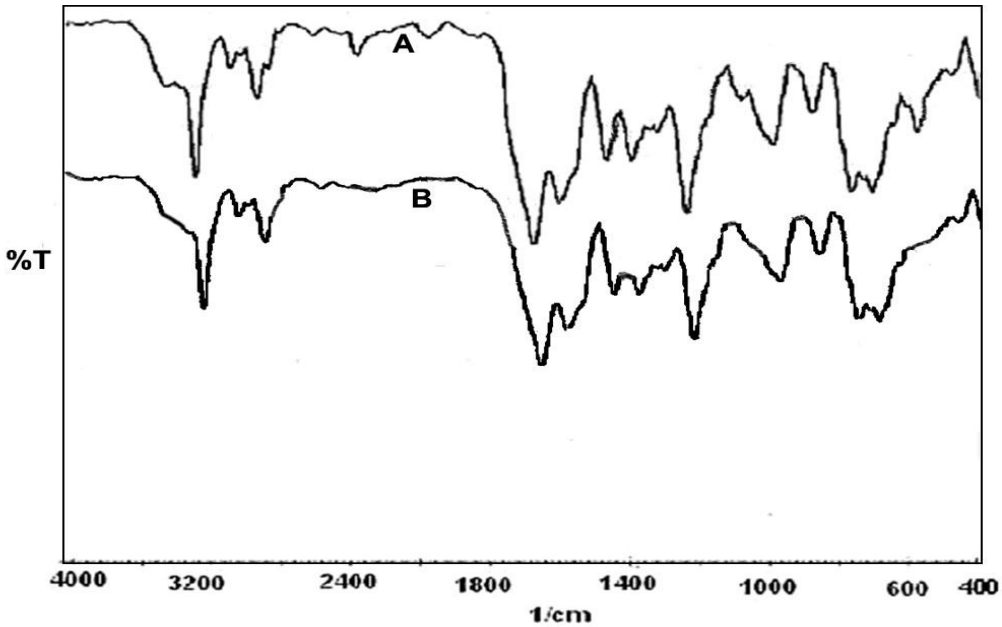


Fig. 1: FTIR spectra of A) Pure Acyclovir B) Acyclovir with excipients blend

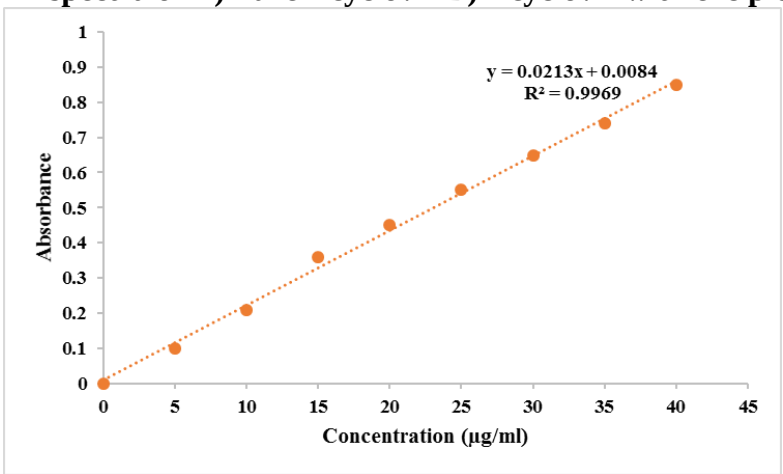


Fig. 2: Calibration curve of Acyclovir (in 0.1 N HCl)

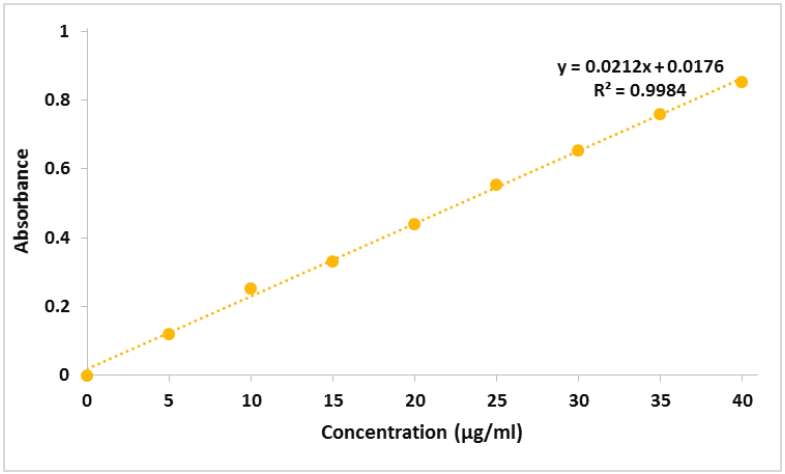


Fig. 3: Calibration curve of Acyclovir (in pH 6.8 phosphate buffer)

Calibration curve

ACR calibration curve (in 0.1 N HCl) shows a slope of 0.057x +0.0545 with a regression (R^2) value of 0.9991 (Fig. 2), where as in phosphate buffer (pH 6.8) shows a slope of 0.0212x +0.0176 with a regression (R^2) value of 0.9984 (Fig. 3).

Pre formulation studies

The results of angle of repose was ranged from 25.11±0.02 to 29.12±0.05^o, indicate good flow properties. Bulk density (BD) of the blends was ranged from 0.625±0.05 to 0.958±0.04 g/cm^3 and tapped density (TD) was ranged from 0.645±0.04 to 0.986±0.07g/cm^3. The BD and TD values were considered in calculating compressibility index, which was ranged from 1.644±0.02 to 3.100±0.01 % and Hausner ratio ranged from 1.016±0.01 to 1.032±0.01. These values indicate that the formulated powder blend shows satisfactory flow properties. All these values were represented in Table 5.

Table 5: Flow parameters of prepared granules

Formulation	Flow properties				
	Angle of repose (^{o})	Bulk Density	Tapped Density	Carr's Index	Hausner's Ratio
AMT-1	25.11±0.02	0.795±0.02	0.811±0.03	1.972±0.06	1.020±0.01
AMT-2	28.95±0.09	0.854±0.01	0.869±0.08	1.726±0.07	1.017±0.01
AMT-3	27.52±0.07	0.658±0.03	0.669±0.05	1.644±0.02	1.016±0.01
AMT-4	27.82±0.14	0.958±0.04	0.986±0.07	2.839±0.05	1.029±0.01
AMT-5	27.06±0.15	0.625±0.05	0.645±0.04	3.100±0.01	1.032±0.01
AMT-6	29.12±0.05	0.775±0.02	0.798±0.03	2.882±0.01	1.029±0.02

Readings in mean ±SD; The number of trials (n=3)

Post formulation studies

The prepared AMT were found to have a uniformity in thickness (4.5 mm) and weight which represents the drug and excipients were added and blended systematically. The loss on friability was negligible (<1%) and the hardness was > 4 Kg/cm^2 indicates that the AMT having appreciable strength. The ACR content in AMT was found to be satisfactory as per the specifications (Table 6). The *in vitro* release indicates a controlled release of ACR from the formulation. Among the formulations, AMT-5 showed a controlled release for a prolonged period (Fig. 4).

Release kinetics and mechanism

To know the mechanism of release and kinetics of ACR optimized formulation, AMT-5 was subjected to fit into mathematical models. The 'n', and R^2 values for zero-order, first-order, Hixson Crowell's and Korsmeyer Peppas models were illustrated in Table 7. This study revealed that the ACR release from the devices followed non-fickian release as the 'n' value is >0.5.

Table 6: Physical Characteristics of the prepared matrix table

	Physical parameter				
Formulation	**Uniformity of weight (mg)**	**Hardness (cm^2)**	**Thickness (mm)**	**Friability (%)**	**Assay (%)**
AMT-1	350.2±3.67	5.8±0.02	4.52±0.04	0.58±0.03	98.8±1.86
AMT-2	351.4±5.28	5.7±0.06	4.51±0.02	0.65±0.04	98.9±2.19
AMT-3	350.2±2.56	6.8±0.02	4.53±0.02	0.57±0.04	97.3±3.26
AMT-4	352.7±2.17	5.8±0.08	4.53±0.03	0.74±0.02	99.6±2.36
AMT-5	351.1±2.96	7.0±0.01	4.51±0.09	0.36±0.01	97.4±2.15
AMT-6	350.3±4.15	6.6±0.04	4.50±0.01	0.46±0.01	98.8±1.28

Values in mean ±SD; The number of trials (n=3)

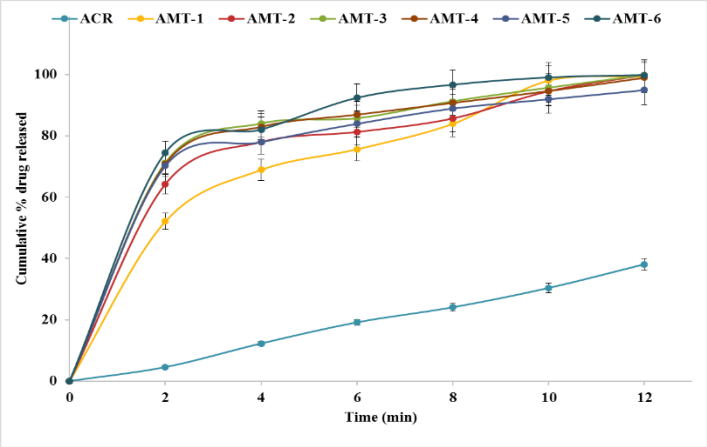


Fig. 4: Zero-order plots of prepared matrix tablets

Table 7: Kinetic data of prepared matrix tablets

Formulation	**Model with correlation values**				
	Zero-order	**First-order**	**Hixson Crowell's**	**Korsmeyer Peppas**	
	R^2	**R^2**	**R^2**	**R^2**	**n**
AMT-1	0.9941	0.9936	0.9752	0.9868	0.528
AMT-2	0.9458	0.9878	0.9837	0.9734	0.572
AMT-3	0.9865	0.9922	0.9761	0.9926	0.558
AMT-4	0.9399	0.9867	0.9945	0.9263	0.535
AMT-5	0.9676	0.8809	0.9285	0.9236	0.589
AMT-6	0.9401	0.8882	0.9269	0.9925	0.523

Conclusion

The authors in this study found that Acyclovir matrix tablet sustained the emission of the drug for an extended duration (beyond 12 h) with elevation in bioavailability and devoid of monotonous dosing and administration. This was also noted that *Azadirachta indica* fruit mucilage can be a good polymer in combination with Ethylcellulose for controlling the Acyclovir release with minimal adverse effects and cost and with appreciable patient happiness and effectiveness.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgement

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