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PREPARATION AND EVALUATION OF ANTIHYPERTENSIVE ACTIVITY OF SUSTAINED RELEASE TABLET CONTAINING JACKFRUIT MUCILAGE

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ABSTRACT:
Sustained release dosage form is useful especially for achieving controlled plasma level of drugas well as improving bio-availability. An oral sustained release formulation can reduce fluctuation in plasma concentration and allow longer dosing interval. The aim of the current research work was to isolate and evaluate Jackfruit mucilage to develop Verapamil HCl tablets using varying concentration of jackfruit mucilage and it has been found that as the concentration of jackfruit mucilage increases, sustained release action of tablet also increased.
Key words: sustained release tablet, verapamil HCL, anti- hypertensive, jackfruit mucilage.

INTRODUCTION:
Oral delivery of drugs is the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation etc. Many of the drug delivery systems available in the market are oral drug delivery type systems.[1]
Now a day's conventional dosage forms of drugs are rapidly being replaced by the new and the novel drug delivery systems. Amongst these the controlled release/sustained release dosage formhave become extremely popular in modern therapeutics.[2]
In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of sustained drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.[3]
Natural polymers are remained attractive primarily because they are capable of chemical modification, having high drug holding capacity and thermal stability[4]. Natural polymers are easily available and have some advantages when employed in controlled release drug delivery system such as bio-acceptability, bio-compatibility, bio-degradability and non-toxicity[5]. Mucilageis most commonly used adjuvant in pharmaceutical preparation as binding, disintegrating, suspending, emulsifying and sustaining agent, because of their low cost, readily availability and non-toxicity.[6]
Among this Jack fruit mucilage is used as a natural tablet retardant polymer for thedevelopment and optimization of an oral sustained release tablet.[7]
Verapamil HCL is belong to the class of calcium channel blocker widely use in the treatment ofhypertension, not only in hypertension but also in angina and (for some CCBs) arrhythmias due to its short biological half-life (2.8-7.4hrs) and high-water solubility make it a potential candidate for sustained release preparations. In the present study Jackfruit mucilage is used as natural polymer for formulation of sustained release tablets.[8,9]

MATERIALS AND METHODS

Wet granulation method was used for all tablet production. Calculation was made for 100 tabletsin each batch.

Isolation of mucilage from Jackfruit:[10]

The fresh fruits were obtained from the local market, in the month of June. The fruits were thoroughly washed with water to remove dirt and debris. The seeds which were present inside the fruit were removed. Pulps of the fruits were made into slices and dried in oven at 35ºC till itdried completely. collected, grounded, passed through a # 80 sieve, and in desiccator till use.

i. Preparation of starch paste: Starch past was prepared by adding a required quantity of starch powder to the boiling water on water bath till it gives paste consistency. This mixture wasthen used as binder solution in the preparation of granules.

ii. Preparation of damp mass: In each case, accurately weighed quantities of Verapamil HCl, Microcrystalline cellulose, Dicalcium phosphate, Magnesium stearate, Bentonite and Jackfruit mucilage, were mixed in a mortar and the starch paste was added to obtain a damp coherent mass. The damp mass was sieved with 1.7mm sieve and dried at 37ºC in oven for 30mins.

iii. Punching of Tablets: The dried granular mass was passed through a 1.0 mm sieve to obtain uniform sized granules. The different batches of the granules were then mixed with calculated equal quantities of Talc and then compressed the tablets of 150mg using 8mm round flat punches on 12 station rotary tablet machine.

EVALUATION OF TABLETS:

Compatibility study using FT-IR:

A successful stable and effective formulation of a dosage form depends on careful selection of the excipients that are added to facilitate administration that promote the consistent release and bioavailability of the drug and protect it from degradation. Compatibility study was carried outfor Drug and Jackfruit mucilage.

pre-compression parameters

Pre-compression studies were carried out of blend powder mixtures for flow properties, bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose,

post-compression parameters

The formulations were subjected to various post compression parameters such as Color, shape, odour, weight variation, hardness, thickness, friability, drug content, disintegration time, *In-vitro* release profile, Kinetic Analysis of *In-Vitro* release rates and Stability studies.

Drug content uniformity

Sustained release tablets of Verapamil HCl equivalent to 150 mg are weighed and dissolved in little amount of methanol in100ml volumetric flask, sonicate for 5min and volume is made up to 100 ml with the 0.1N HCl and filtered through membrane filter. Subsequent dilutions are madeand absorbance is measured at 278 nm against blank (0.1N HCl) and drug content is calculated using standard curve. Each test is performed in triplicate.[9]

***In-vitro* dissolution studies:**

Dissolution of the tablets was carried out on USP XXIII dissolution type II apparatus using paddle. The dissolution medium consisted of 900 ml of pH 1.2 buffer (0.1N HCl) for first two hours and the phosphate buffer pH 6.8 from 3- 12 hours maintained and the temperature of the medium was set at 37±0.5º C. The rotational speed of the paddle was set at 50 rpm. 5ml of sample was withdrawn at predetermined time interval of 1 hour up to 10 hour and same volume of fresh medium was replaced. The withdrawn samples were diluted to 10ml with pH 6.8. filtered

and analyzed on UV spectrophotometer at 278nm using pH 6.8 as a blank. Percentage cumulative drug release was calculated.

***in-vitro* drug release kinetics and mechanism**

To describe the kinetics and % releases of the drug release from sustain release Verapamil HCl formulation. The drug release data from trial and factorial batches were fitted in to various kinetic release mathematical models such as zero order, first order, Higuchi, Korsmeyer-Peppas models by using PCP-Disso-v3 software. The regression coefficient (r2) value compared to each other and selected best fit model, the release mechanism of Verapamil HCl from system were decided from release exponent value.

The zero-order kinetic describes the system in which the drug release rate is independent of its concentration. The first order kinetic describes the system in which the drug release rate is concentration dependent. Higuchi describe the release of drug from an insoluble matrix as squareroot of time dependent process.

- Zero order Kinetics Q = K0t
- First order Kinetics Log C = Log C0-Kt/2
- Higuchi's Square root of time Equation (Diffusion model) Q = Kt½
- Korsmeyer-Peppas model Equation (Diffusion/Relaxation Model)Mt/M0 = k5tn

Stability studies

The optimized formulation was subjected for stability study. The selected formulations were packed in aluminum foil in tightly closed container. They were then stored at 40ºC / 75% RH and evaluated for their physical appearance, drug content and dissolution.

RESULTS AND DISCUSSIONS:

Results of all the evaluations parameters such as Bulk density, Tapped density, Carr's index, Hausner's ratio, Angle of repose, weight variation, Hardness, Thickness, Friability, Drug content and Disintegration were found to be within the limits. are found to be within the acceptable official limit. compatibility studies not shown presence of any extra peaks for new functional groups indicating no chemical interaction between drug and mucilage, hence stable formulation could be prepared. *in-vitro* drug release shown as the concentration of jackfruit mucilage increases, drug release decreases. the drug release was by super case II mechanism. stability studies showed that there was no change in case of physical appearance.

CONCLUSION:

Sustained release tablets of Verapamil HCl was successfully formulated by using Jackfruit mucilage and it indicate that as the concentration of Jackfruit mucilage increases rate of drug release decreases. All the formulations were best fitted to first order kinetic model and the drugrelease from the formulation was by super case I mechanism.

Table No 1: Formulation developed for different batches

Sl.no	Ingredients (mg)	F1	F2	F3	F4	F5	F6
1	Verapamil HCl	40	40	40	40	40	40
2	Microcrystalline cellulose	55	45	40	35	30	30
3	Dicalcium phosophate	45	25	25	25	25	20
4	Magnesium staerate	5	2	2	2	2	2
5	Talc	5	2	2	2	2	2
6	Bentonite	_	26	26	26	26	26
7	Jackfruit mucilage	_	10	15	20	25	30
8	Starch paste	q. s	q. s	q. s	q. s	q. s	q. s
9	Total tablet weight	150	150	150	150	150	150

Table No.2: Pre-compression parameters results.

Code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index%	Hausner's ratio	Angle ofrepose(°)
F1	0.521±0.094	0.625±0.120	17.24±0.03	1.19	28.56±0.04
F2	0.529±0.101	0.626±0.034	16.64±0.094	1.14	26.19±0.067
F3	0.528±0.074	0.627±0.069	16.37±0.065	1.17	23.89±0.051
F4	0.523±0.089	0.632±0.091	13.49±0.074	1.20	25.21±0.079
F5	0.521±0.093	0.623±0.113	14.83±0.093	1.19	27.97±0.084
F6	0.476±0.112	0.555±0.108	14.23±0.034	1.16	24.61±0.099

Table No 3: Physicochemical Properties of tablets

Formulationcode	Color	Shape	Odor
F1	White color	Flat and circular	Odorless
F2	Cream colour	Flat and circular	Odorless
F3	Cream color	Flat and circular	Odorless
F4	Cream color	Flat and circular	Odorless
F5	Cream color	Flat and circular	Odorless
F6	Cream color	Flat and circular	Odorless

Table No.4: Post-Compression Parameter results

Code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability(%)	Drug content (%)	Disintegration Time
F1	148.91±0.22	4.02±0.10	3.12±0.01	0.39±0.15	93.51±0.57	25min

F2	145.12±0.36	5.05±0.09	3.14±0.03	0.36±0.11	95.00±0.42	36min
F3	154.10±0.49	5.01±0.04	3.11±0.03	0.33±0.09	96.85±0.32	48min
F4	152.30±0.41	5.07±0.007	3.44±0.02	0.43±0.62	95.79±0.27	60min
F5	146.60±0.32	5.07±0.05	3.16±0.01	0.42±0.44	97.01±0.89	72min
F6	149.20±0.91	6.06±0.03	3.18±0.04	0.32±0.53	96.15±0.42	88min

Table No.5: *In-vitro* drug release profile

SL.NO	**TIME (hrs)**	**% CUMULATIVE DRUG RELEASE(CDR)**					
		FORMULATION CODE					
		F1	F2	F3	F4	F5	F6
1	0	0.00	0.00	0.00	0.00	0.00	0.00
2	0.5	24.32	20.23	18.14	12.24	8.78	4.45
3	1	49.83	32.88	26.66	18.42	12.61	6.62
4	1.5	79.33	46.67	35.98	26.66	24.48	12.12
5	2	97.43	59.89	39.68	29.98	28.45	20.24
6	3	-	68.98	45.55	37.78	34.44	28.89
7	4	-	75.98	57.89	45.67	41.11	34.44
8	5	-	82.23	59.11	50.98	49.92	36.62
9	6	-	95.27	66.24	58.84	54.42	45.72
10	7	-	-	78.89	66.67	62.66	49.85
11	8	-	-	86.66	74.48	70.77	54.44
12	9	-	-	91.17	79.94	75.55	60.69
13	10	-	-	96.52	86.66	80.12	68.89
14	11	-	-	-	92.01	85.99	76.86
15	12	-		-	96.66	89.82	81.89

Kinetic Release Study

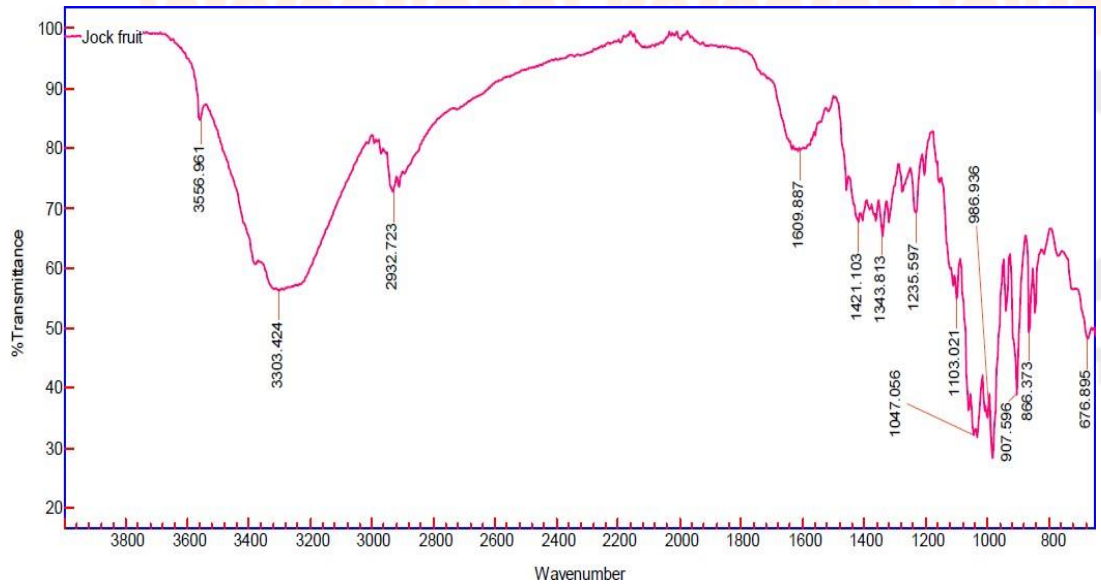
Table No 6: Results of Kinetic data of various models for release study

Formulation code	Zero order release Plots	First order release Plots	Higuchi'splots	Korsmeyer'sand Peppas plots	
	Regression coefficient(R^2)	Regression coefficient(R^2)	Regression coefficient(R^2)	Regression coefficient(R^2)	Exponential value (n)
F1	0.995	0.998	0.945	0.534	1.312
F2	0.706	0.987	0.897	0.765	1.050
F3	0.882	0.988	0.901	0.861	1.066
F4	0.989	0.991	0.916	0.914	1.008
F5	0.889	0.921	0.712	0.911	0.983
F6	0.854	0.951	0.813	0.906	1.085

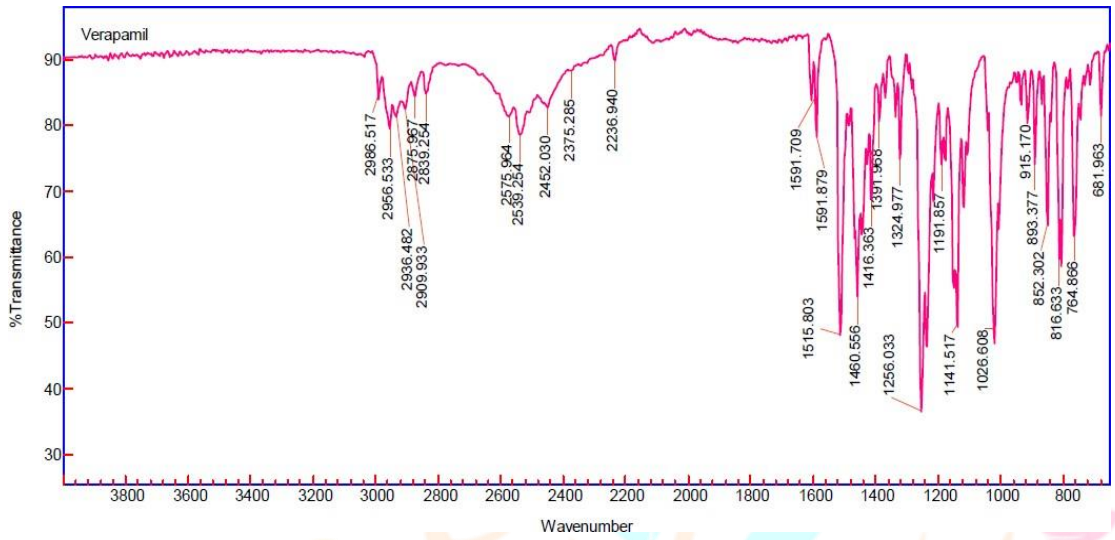
Table No. 7: Results of Stability studies for F4 formulation at 40ºC/75%RH

Time	**Evaluation parameters**			
	Color	**Hardness**	**Drug content**	**%CDR**
15 days	Cream	5.07	95.79	98.89
30 days	Cream	5.05	95.54	98.73
45 days	Cream	5.01	95.34	98.66
60 days	Cream	5.00	94.99	98.24

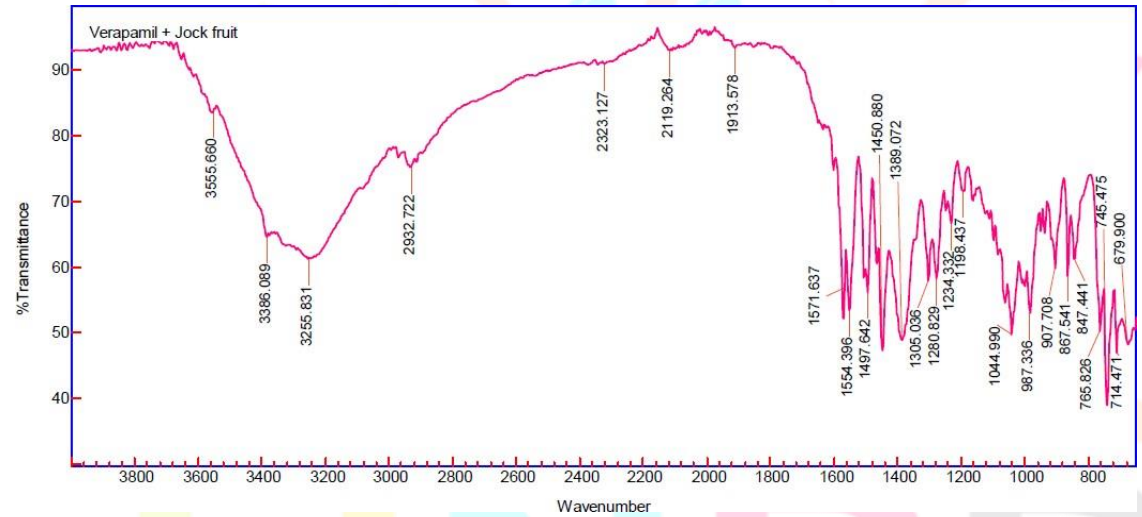
Spectra No 1: FT-IR Spectra of Jackfruit mucilage

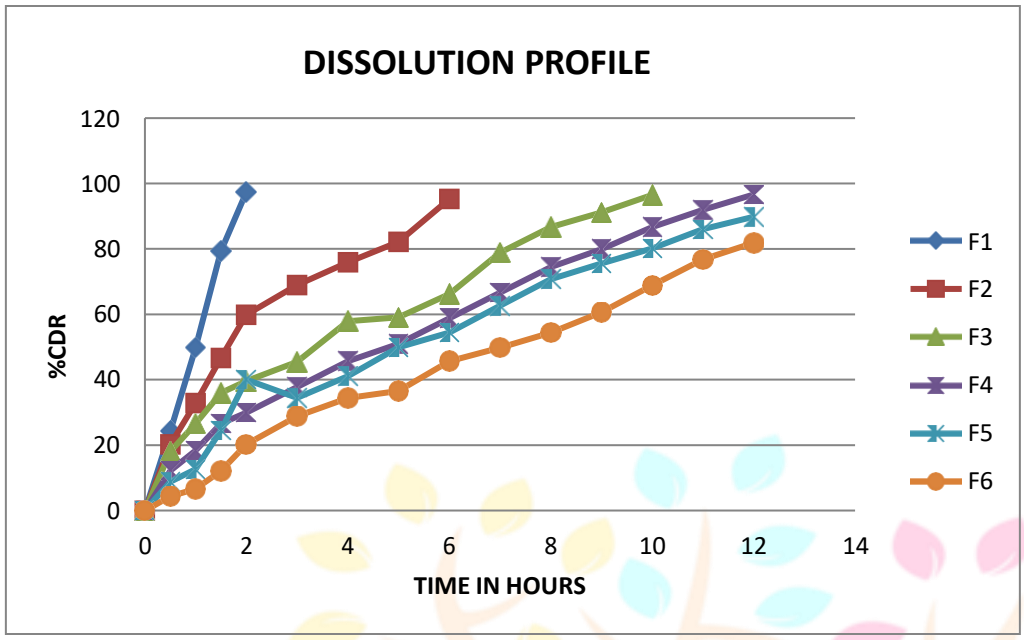


Spectra No 2:FT-IR spectra of verapamil HCl



Spectra No 3: FT-IR Spectra off Verapamil HCl + Jackfruit mucilage





Graph No.4: *In-vitro* Cumulative percentage drug released V/S Time for Formulations F1 to F8

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