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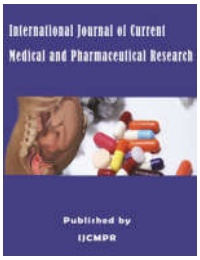

FORMULATION AND EVALUATION OF PARACETAMOL – ACECLOFENAC TABLETS USING ABELMOSCHUS ESCULENTUS MUCILAGE AS BINDING AGENT AND NATURALLY OCCURING GUMS

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ABSTRACT

The study was designed to formulate oral tablet dosage form of Pracetamol – Acelofenac tablets using Abelmoschus esculentus mucilage and compared with a naturally occurring gum like acacia gum as binding agent. The fruits of Abelmoschus esculentus were collected, deseeded, sliced, homogenized and the mucilage was extracted. Phytochemical tests were carried out for the extracted mucilage which showed the presence of mucilage. Physiochemical characteristics like pH and viscosity were also found for the Extracted gum. Pre-compression parameters like Bulk density, Tapped density, Compressibility index (%) and Hausner Ratio were determined. In FTIR analysis, the Principal peaks obtained in IR spectra of samples were almost similar to that of pure drug, indicating no interaction between drug and polymers. Post compression parameters like Content uniformity, Thickness, Hardness, Friability, Weight variation, Swelling index were carried out and were found within the prescribed limits. The matrix tablets were subjected to *in vitro* drug release studies in 5.8 pH and 7.5 pH Phosphate buffer for Paracetamol and Aceclofenac respectively for 5 Hrs. The percent of drug release decreases when the gum concentration increases. Thus Aelmoschus esculentus mucilage could be employed in tablets with sustained release of drugs.

INTRODUCTION

Tablets and capsules are the most preferred dosage forms of pharmaceutical scientists and clinicians because they can be accurately dosed and provide good patient compliance, they can be produced at a relatively low cost and are easy for companies to manufacture [1]. Binders are pharmaceutical excipients that are commonly employed in tablet formulations to impart cohesion on the powder mixture and hence, improve the flow properties on the granules [2]. Natural binders like different starches, gums, mucilages, and dried fruits possess binding capacity as well as some other properties like being a disintegrant, filler, and having sustained release. These natural polymers are much safer and more economical than polymers like polyvinylpyrrolidone [3,4]. Thus, natural biopolymers like Okra gum along with their modification products offer a wide range of properties and applications. Okra gum obtained from the fruits of *Abelmoschus esculentus*, is a polysaccharide consisting of D-galactose, L-rhamnose and L-galacturonic acid [5]. Okra gum had been evaluated as binder in tablet dosage formulation [6,7].

The aim of the present investigation is to study the effect of concentration of gum and the method of preparation on the compressional, Invitro release properties of Okra gum matrices in Paracetamol – Aceclofenac Tablets.

MATERIALS AND METHODS

The fruits of Abelmoschus esculentus were collected from local area. Paracetamol and Aceclofenac were obtained from Bestcare Formulation Pvt.Ltd, Puducherry. Sodium metabisulfite, acetone, lactose monohydrate, talc, magnesium stearate, ethanol, sodium hydroxide, and potassium dihydrogen phosphate were procured from Merck Pvt.Ltd.

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Instruments

The equipments used were Electronic balance (Shimadzu, Japan), Digital pH meter (Elico, India), Tap density apparatus (Campbell Electronics, Mumbai), UV-Visible spectrophotometer (Systronics, Ahmedabad), Microwave oven (Samsung India Electronics Limited), Mechanical stirrer (Remi Motors, Mumbai), Centrifuge (Remi Instruments Limited), Rotary tabletting punching machine (Rimek, Ahmedabad), Friability apparatus (Campbell Electronics, Mumbai), Hardness tester (Campbell Electronics, Mumbai), Disintegration Apparatus and Dissolution Apparatus.

Extraction of the Polysaccharide from Okra Fruits [8]

The Fresh Okra fruits were purchased locally. They were thoroughly washed with water, deseeded, sliced, homogenised with water containing 1% sodium metabisulfite and extracted by filtering through muslin cloth. The crude was centrifuged at 5000 rpm for 30minutes and the mucilage was precipitated from the supernatant with addition of acetone. It was further dried with the help of microwave oven and pulverised.

Preformulation Studies

Phytochemical and Physiochemical characteristics of Extracted gum [9-11]

The extracted gum were tested for the presence of carbohydrates by Molisch's test, presence of alkaloids by dragendroff's test, presence of tannins by ferric chloride test, presence of cardenolides by keller killiani test and finally for the presence of Protein and Amino acid by Biuret Test. Dried mucilage were characterized for pH and viscosity, Bulk Density, Tapped density, Compressibility index, Hausner ratio.

FTIR Study [12]

For all the formulations of Paracetamol and Aceclofenac with Okra gum and Acacia gum were studied by IR spectral matching approach. The pellets have been prepared using potassium bromide (KBr) for FTIR study. The pellets were subjected to FTIR instrument 'Perkin Elmer FTIR spectrometer, spectrum 1000 Germany'.

Development of calibration curve for Paracetamol

1. The standard solutions for the drug having concentration 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 and 24 mg/ml was prepared with phosphate buffer 5.8.
2. From the stock solution. The absorbance of solutions of pure paracetamol drug were measured at 246 nm and a calibration curve was plotted between absorbance v/s concentration to get the linearity
3. Regression equation is shown in fig. 4.

Development of calibration curve for Aceclofenac

1. The standard solutions for the drug having concentration 0,10,20,30,40,50,60, 70, 80, 90 and 90 mg/ml were prepared with phosphate buffer 7.5.
2. From the stock solution. The absorbance of solutions of pure Aceclofenac drug were measured at 273 nm and a calibration curve was plotted between absorbance v/s concentration to get the linearity
3. Regression equation is shown in fig. 5.

Formulation of matrix tablets (13)

Matrix tablets of Paracetamol and Aceclofenac were prepared by wet granulation technique using two naturally occurring biocompatible polymers Okra mucilage and Acacia Gum of 2.5 %, 5% and 7.5 % as binding agents. Lactose was used as diluent. Six formulations each were prepared with different amounts of Natural gum and their formulation codes are F1, F2, F3, F4, F5 and F6 given in Table 1.

Table 1 Paracetamol-Aceclofenac Tablet Formula

Ingredient	Formulation code					
	F1	F2	F3	F4	F5	F6
Paracetamol (mg)	100	100	100	100	100	100
Aceclofenac (mg)	100	100	100	100	100	100
Okra Gum (mg)	10	20	30	-	-	-
Acacia Gum (mg)	-	-	-	10	20	30
Lactose(mg)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

*Weight of each tablet equals 400mg

Post Formulation Studies (14-18)

The formulated Paracetamol – Aceclofenac Tablets were evaluated for parameters like

1. Content uniformity
2. Thickness
3. Hardness
4. Friability
5. Weight variation
6. Swelling index
7. In Vitro release study

RESULTS

Table 2 Phytochemical investigation of *Abelmoschus esculentus* gum

Phytochemical tests	Observations
Mucilage(Ruthenium red test)	Presence
Alkaloids(dragendroff's test)	Absence
Anthraquinones(keller killiani test)	Absence
Tannins(ferric chloride test)	Absence
Carbohydrates(Molisch's test)	Absence
Sterols and steroids(Libermann Burchard Test)	Absence
Proteins and amino acids (Ninhydrin Test, Biuret Test)	Absence

Table 3 Preformulation Studies

S.No	Ingredient	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility index (%)	Hausner Ratio
1.	*Abelmoschus esculentus* gum	0.448	0.660	32.12	1.473
2.	Acacia gum	0.582	0.723	23.94	1.242
3.	Paracetamol	0.620	0.750	18.21	1.2
4.	Aceclofenac	0.338	0.575	41.18	1.7

FTIR Studies

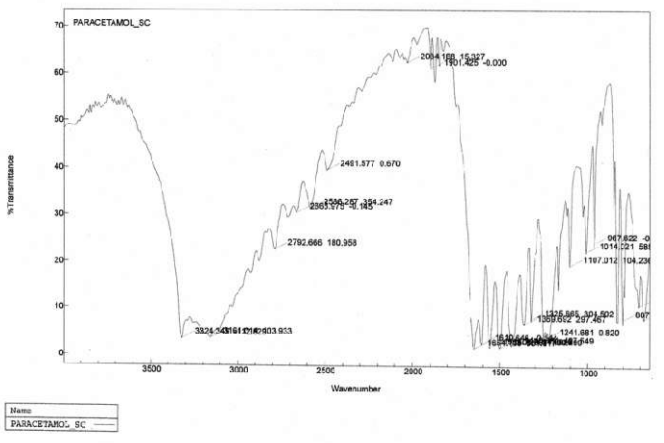

Figure 1 FTIR - Paracetamol

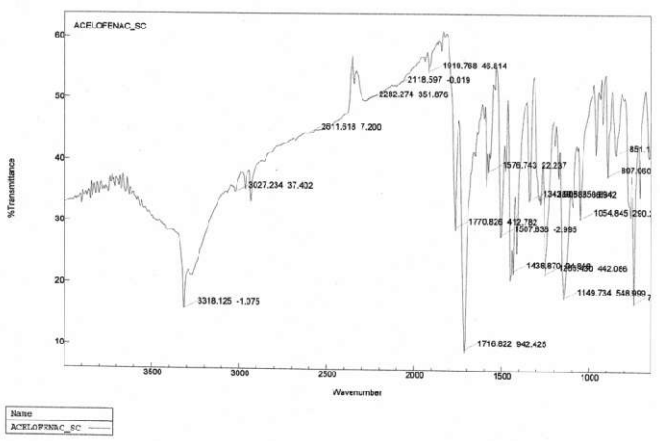

Figure 2 FTIR - Aceclofenac

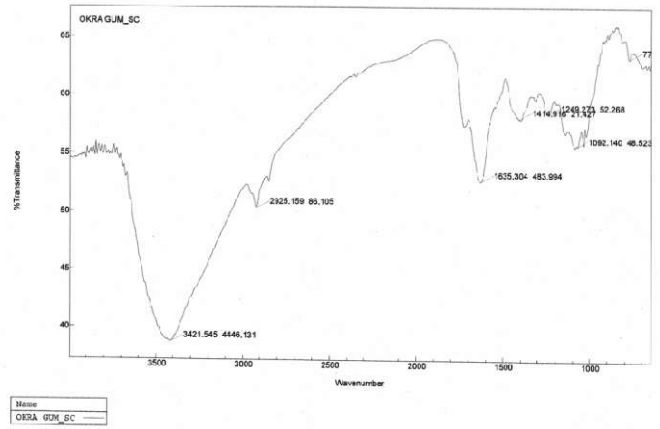

Figure 3 FTIR – Okra Gum

Table 4 Development of Calibration Curve for Paracetamol λmax -246 nm

S.No.	Concentration (µg/ml)	Absorbance At 246 nm
1.	0	0.000
2.	2	0.163
3.	4	0.356
4.	6	0.533
5.	8	0.727
6.	10	0.909
7.	12	1.127
8.	14	1.265
9.	16	1.46
10.	18	1.621
11.	20	1.803

r = 0.999

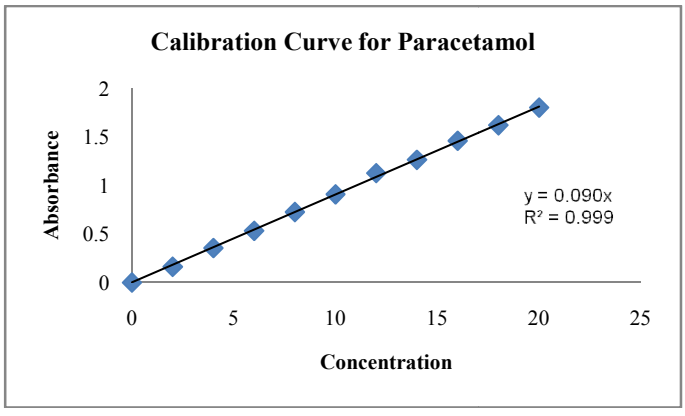

Figure 4 Calibration curve for Paracetamol

Table 5 Development of Calibration Curve for Aceclofenac λmax -273 nm

S.No.	Concentration (µg/ml)	Absorbance At 273 nm
1.	0	0.000
2.	2	0.211
3.	4	0.521
4.	6	0.752
5.	8	1.032
6.	10	1.250
7.	12	1.501
8.	14	1.752
9.	16	2.001
10.	18	2.252
11.	20	2.503

r = 0.999

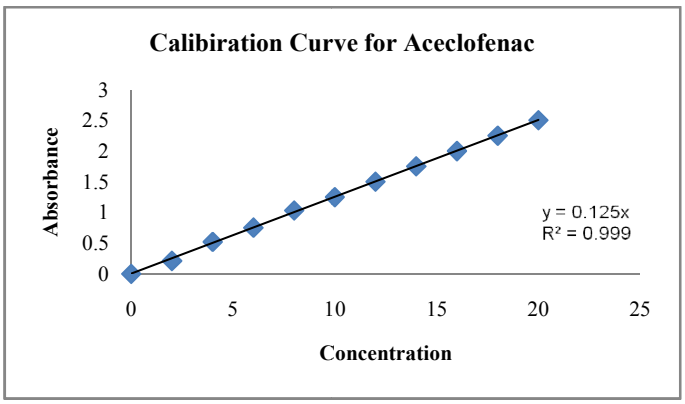

Figure 5 Calibration curve for Aceclofenac

Table 6 Post Formulation Data of Different batches of matrix tablets

S.No	Parameters	Formulation code (Result indicate mean±SD(n=6)					
		F1	F2	F3	F4	F5	F6
1.	Content Uniformity (%)	98.56±0.69	99.19±1.85	98.29±1.77	98.43±2.74	98.89±0.91	98.86±0.12
2.	Thickness (mm)	3.0±0.018	3.0±0.051	3.0±0.044	4.0± 0.02	4.0±0.012	4.0±0.015
3.	Hardness (kg/cm^2)	5.23± 0.28	6.48±0.16	7.52±0.17	5.16±0.28	6.97±0.16	7.49±0.18
4.	Friability (%)	0.58±0.08	0.55±0.03	0.39±0.17	0.34±0.08	0.28±0.10	0.13±0.06
5.	Weight Variation (mg)	401±2.89	400±2.64	399±1.97	401±1.99	400±2.62	401±2.55

Swelling Characteristics

Table 7 Swelling characteristics of matrix tablets

S.No	Time(h)	% Swelling Index					
		F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0	0
2	1	28.39	34.67	69.13	26.0	30.60	41.43
3	2	52.49	57.29	83.15	49.0	53.0	63.15
4	4	78.31	90.63	129.85	76.0	85.0	89.14
5	6	107.62	115.21	149.11	98.0	105.2	107.12
6	12	138.32	148.37	173.25	105.0	108.8	111.25
7	24	151.67	155.56	198.24	118.0	120.5	133.45

In Vitro Release Study

Table 8 *In vitro* release profile of matrix tablets – Paracetamol

S.No	Time(h)	Formulation code {Result indicate mean±SD (n=6)}					
		F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0	0
2	1	1.8465	1.6094	3.0000	2.972	2.0000	3.0048
3	2	2.0000	2.0090	3.0008	2.9456	2.1137	3.0289
4	3	2.3982	2.1001	3.0019	3.0000	3.0000	3.0472
5	4	2.0900	2.0202	3.0015	3.0063	3.0920	3.0792
6	5	3.0980	3.0092	3.0989	3.0364	3.094	3.9782

Table 9 *In vitro* release profile of matrix tablets – Aceclofenac

S.No	Time(h)	Formulation code {Result indicate mean±SD (n=6)}					
		F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0	0
2	1	0.6733	0.6595	0.6979	2.5912	3.2908	3.1002
3	2	1.1007	1.3206	1.3807	3.0000	3.587	3.3802
4	3	1.6249	1.5177	1.8179	3.5878	3.5899	3.5802
5	4	2.2083	2.0971	2.8713	3.0000	3.5878	3.6908
6	5	2.9087	3.0000	3.0010	3.9098	3.7900	3.8092

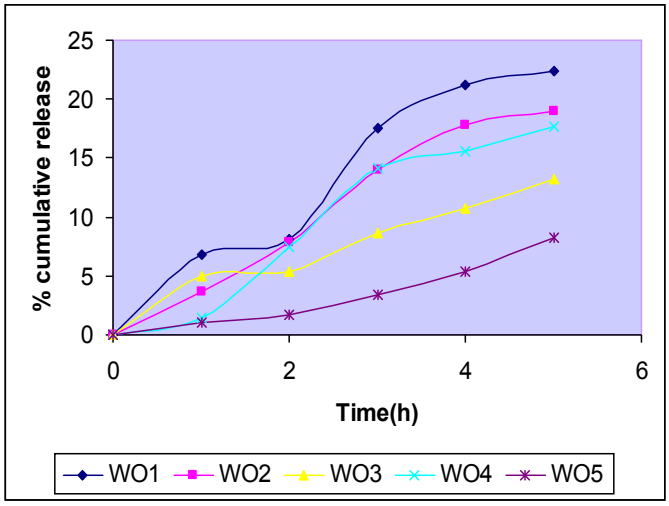

Figure 8 *In vitro* release profile of *Abelmoschus esculentus* gum based matrix tablets

Comparative Studies

Table 10 *In vitro* release study (5h)

Formulation Code Okra Gum	% Cumulative release		Formulation Code Acacia Gum	% Cumulative release	
	Paracetamol	Aceclofenac		Paracetamol	Aceclofenac
F1	3.0980	2.9087	F4	3.0364	3.9098
F2	3.0092	3.0000	F5	3.094	3.70900
F3	3.0989	3.0010	F6	3.9782	3.8092

DISCUSSION

Phytochemical investigations

The Phytochemical investigations performed on the Okra gum showed the presence of mucilage and absence of alkaloids, glycosides , carbohydrates , proteins and amino acids , sterols and steroids and tannins.

Compressibility Index and Hausner ratio values showed that the natural gum under investigation and acacia gum possess poor flow property. Since they are having poor flow properties and is to be incorporated in the matrix tablets in a large proportion, Paracetamol and Aceclofenac tablets were prepared by wet granulation technique. The results are shown in table 3.

FTIR Studies

Compatibility of Paracetamol and Aceclofenac with Okra gum and Acacia gum were studied by IR spectral matching approach. The respective spectra are given in figures (1,2 and 3). By comparing the spectra, it was concluded that there was no significant change in spectral pattern of drug and mucilage, which confirmed the compatibility of Paracetamol and Aceclofenac with the mucilage. The Principal peaks obtained in IR spectra of samples were almost similar to that of pure drug, indicating no interaction between Paracetamol and Aceclofenac with the mucilage.

Calibration curve for Paracetamol and Aceclofenac

Calibration curve for Paracetamol and Aceclofenac were developed in Phosphate buffer pH-5.8 and pH 7.5 respectively using UV spectrophotometer and the results are given in Table 4, 5 and figure 4, 5. The λmax was found to be 246 nm for Paracetamol and 273 nm for Aceclofenac, at which the absorbances of standard solutions (2-20µg/ml) were measured. Calibration between the concentration and absorbance were developed with a regression co-efficient of 0.999, which showed linearity between 2-20µg/ml ranges for both Paracetamol and Aceclofenac.

Evaluation of physical Parameters

pH and Viscosity

Okra gum solution (1% w/v) exhibited a pH of 6.5. The viscosity value of 1% w/v of natural gum is 208.36cp. The viscosity of a polymer plays a vital role in achieving the desired release rate. Higher the viscosity, more resistant the matrix to dissolution and erosion. Thus, viscosity of a polymer gel is a rate controlling factor in drug dissolution.

Content Uniformity

The drug content of all the formulations was found to be within the range of 99.19±1.85% to 98.56±0.69% for Okra gum based formulations and 98.43±2.74% to 98.89±0.91% for acacia gum based formulations (table 6). The minimum intra batch variations revealed the suitability of the process used to prepare tablets.

Tablet Thickness

The data presented in table 12 indicate that the thickness of the Okra gum based formulations vary from 3.0±0.018mm to 3.0±0.051mm while for acacia gum based formulations, it varied from 4.0± 0.02mm to 4.0±0.015mm (table 6). All the formulations exhibited uniform thickness with low standard deviation values ensuring the uniformity of the formulations.

Tablet Hardness

Hardness of the developed formulations varied from 5.23± 0.28 kg/cm^2 to 7.52±0.17 kg/cm^2 for Okra gum and 5.16±0.28 kg/cm^2 to 7.49±0.18 kg/cm^2 for acacia gum. The results are shown in table 6.

Friability

Friability of Okra gum and acacia gum based formulations varied from 0.13±0.06 % to 0.58±0.08 % which were less than 1% as per official requirements of IP. Results are shown in tables 6. Friability values were decreased with increase in concentration of gum.

Weight Variation

The results showed that weights of formulations were ranging from 399±1.97 to 401±2.89 for both formulations. This indicates that there was no significant weight variation in all formulations. The average weight of 20 tablets was calculated for each formulation which was found to be less than 5% deviation. So it is complied the official requirements as per IP. Results are shown in tables 6.

Swelling Index

Tablets composed of polymeric matrices build a gel layer around the tablet core when they come in contact with water. This gel layer governs the drug release. Kinetics of swelling is important because the gel barrier is formed with water permeation. Tablets (F3 and F6) showed significantly higher swelling indices and faster rate of swelling compared with other tablets. The swelling indices are given in table 7. The swelling index behaviour was studied as the function of time. It was seen that with increase in time, the extent of swelling also increased.

In vitro release study

The matrix tablets were subjected to *in vitro* drug release studies in 5.8 pH and 7.5 pH Phosphate buffer for Paracetamol and Aceclofenac respectively for 5 Hrs. The formulations F1, F2, F3, F4, F5 and F6 have shown 3.0980 %, 3.0092 %, 3.0989 %, 3.0364 %, 3.094 % and 3.9782 % for Paracetamol and 2.9087 %, 3.0000 %, 3.0010 %, 3.9098 %, 3.70900 % and 3.8092 % for Aceclofenac. The In vitro release study is given in Table 8, 9 and Figure 8,9. On exposure to the dissolution fluids, the gum gets hydrated and forms a viscous gel layer that slows down further seeping-in of dissolution fluids towards the core tablets. The hydration of gum seems not to be affected by the pH of the dissolution medium. The percent of drug release decreases when the gum concentration increases.

Comparative studies

Okra gum under examination possessed lesser release than the standard carrier in the first 5h of study in 7.5 pH and the release data is shown in Table 10.

CONCLUSION

The present study was planned to develop matrix tablets of Paracetamol and Aceclofenac by using Aelmoschus esculentus mucilage and acacia as binding agent. Matrix tablets were evaluated for various physical parameters and subjected to *in vitro* evaluation. Results of all the evaluation tests were found to be satisfactory. Our efforts to formulate and develop matrix tablets led to the following conclusions, Reliability of the process in the preview of getting uniform drug loading was confirmed by drug content analysis and weight variation data. Interaction study from IR spectra revealed that there was no interaction between the drug and polymer used in the formulations. Release studies shows that the okra gum based formulations possessed minimal release in first 5hrs of study than acacia gum based formulations. Thus, the okra gum under investigation is as effective than acacia gum as binding agent in tablet formulation. Therefore okra gum may be employed as a potential binder in tablet formulation.

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