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Fabrication of Glimepiride *Hibiscus esculentus* Fruit Mucilage and Povidone Sustained Release Matrix Tablets: *In vitro* evaluation

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ABSTRACT

The main purpose of the present work was to develop matrix tablets of Glimepiride with Hibiscus esculentus fruit mucilage and Povidone and to study its functionality as a matrix forming agent for sustained release tablet formulations. Mucilage from Hibiscus esculentus fruit was extracted, isolated, purified and characterized. Physicochemical properties of the dried powdered mucilage of Hibiscus esculentus fruit were studied. Various formulations of Glimepiride Hibiscus esculentus fruit mucilage and Povidone were prepared. The formulated tablets were tested for mechanical properties, friability, swelling behavior, in vitro drug release pattern and the dissolution data was treated with mathematical modeling and the optimized formulation was tested for accelerated stability studies. The formulated tablets were found to have good mechanical properties, good swelling properties. The in vitro dissolution data was perfectly fitting to zero order and the release of drug from the formulation followed Higuchi's release. The accelerated stability studies revealed that the tablets retain their characteristics even after stressed storage conditions. From this study it was concluded that the dried Hibiscus esculentus fruit mucilage and Povidone combination can be used as a matrix forming material for making sustained release matrix tablets.

Key words: Glimepiride, *Hibiscus esculentus*, Povidone, matrix tablets, sustained release.

INTRODUCTION

Hibiscus esculentus belongs to *Malvaceae* family is an annual or perennial climber, growing up to 2 m tall. The fruit is a capsule up to 18 cm long [1].

Glimepiride is an oral hypoglycemic agent, which is a commonly prescribed drug for the treatment of patients with type II diabetes mellitus. It belongs to sulfonyl ureas drug class.

Glimepiride is a weak acid with PKa of 5.3. Glimepiride is practically insoluble in water and acidic solutions but highly permeable (class 2) according to the Biopharmaceutical classification System (BCS) [2]. The oral absorption is uniform, rapid and complete with nearly 100% bioavailability. The pharmacokinetics and dosage schedule supports once daily sustained release formulations of Glimepiride for better control of blood glucose levels to prevent hypoglycemia, enhance clinical efficacy and patient compliance [3, 4]. The purpose of present work was to design and evaluate sustained release matrix tablets of Glimepiride using *Hibiscus esculentus* fruit mucilage and Povidone combination as release retardant.

MATERIALS AND METHODS

Materials

Glimepiride was obtained as a gift sample from Dr. Reddy's Laboratories, Hyderabad, India. *Hibiscus esculentus* fruit were collected from plants growing in local areas of Anantapur, India. The plant was authenticated at the Department of Botany, Sri Krishnadevaraya University, Anantapur, India. Povidone, Micro crystalline cellulose (Avicel**)** and Magnesium stearate were procured from SD Fine chemicals (Mumbai, India). Tri chloro acetic acid, Acetone, Ethanol (95%), diethyl ether and all other chemicals used were of analytical reagent grade and double distilled water was used throughout the experiments.

Extraction of mucilage

The fresh *Hibiscus esculentus* fruits were washed with water. The fruit were crushed and soaked in water for 5–6 h, boiled for 30 min and left to stand for 1 h to allow complete release of the mucilage into the water. The mucilage was extracted using a multi-layer muslin cloth bag to remove the marc from the solution. Acetone (in the quantities of three times the volume of filtrate) was added to precipitate the mucilage. Later the mucilage was separated, dried in an oven at 40^0C, collected, ground, passed through a # 80 sieve and stored in desiccator at 30^0C & 45% relative humidity till use [5].

Purification of the Mucilage

The crude mucilage (1%) was homogenized (Potter homogenizer, Sartorius AG, Germany) with cold dilute tri chloro acetic acid solution (5%). The solution was centrifuged (3500 rpm for 20 min), neutralized with sodium hydroxide by drop wise addition and then dialyzed for 30 h against distilled water. The mucilage was precipitated by adding three volumes of 95% ethanol and washed successively with ethanol, acetone and diethyl ether [5, 6].

Drug-excipient compatibility studies

Differential scanning calorimetric (DSC) analysis [7]

The DSC analysis was carried out using Differential Thermal Analyzer (Shimadzu DSC-60, Shimadzu Limited, Japan). A 1:1:1 ratio of Glimepiride: *Hibiscus esculentus* fruit mucilage: Povidone were weighed into aluminum crucible and the DSC thermo grams were recorded at a heating rate of 10^0C/min in the range 20^0C to 280^0C, at a nitrogen flow of 20 ml/min.

Fourier Transform Infrared (FTIR) spectral analysis [7]

FTIR spectrums were recorded on samples prepared in potassium bromide (KBr) disks using FTIR spectrophotometer (Model-1601 PC, Shimadzu Corporation, Japan). Samples were prepared in KBr disks by means of a hydrostatic press at 6-8 tons pressure. The scanning range was 500 to 4000 cm^{-1}. The FTIR spectrums of pure Glimepiride, 1:1:1 ratio of Glimepiride: *Hibiscus esculentus* fruit mucilage: Povidone and formulation blend (F-5) were taken.

Preparation of matrix tablets

Sustained release matrix tablets of Glimepiride with *Hibiscus esculentus* fruit mucilage and Povidone were prepared by using different drug: mucilage ratios. *Hibiscus esculentus* fruit mucilage and Povidone were used as matrix forming materials while microcrystalline cellulose as a diluent and Magnesium stearate as a lubricant. All ingredients used were passed through a # 100 sieve, weighed and blended. The granules were prepared by wet granulation technique and evaluated for its flow properties. The granules were compressed by using 10 mm flat faced punches [8, 9]. The compositions of formulations were showed in Table 1.

Table 1: Formulae of matrix tablets

Ingredients (mg)	**Formulation**				
	F-1	**F-2**	**F-3**	**F-4**	**F-5**
Glimepiride	2	2	2	2	2
Hibiscus esculentus fruit dried mucilage	2.5	5.0	7.5	10.0	12.5
Povidone	5.0	5.0	5.0	5.0	5.0
Micro crystalline cellulose (Avicel)	185.5	183	180.5	178	175.5
Magnesium stearate	5	5	5	5	5
Total weight of tablet	**200**	**200**	**200**	**200**	**200**

Evaluation for granules

The granules so obtained were evaluated for flow properties viz., Angle of repose [10], Loose Bulk Density [11], Tapped Bulk Density [11], Carr's Index [12] and Hausner ratio [12].

Evaluation of tablets

The formulated tablets were evaluated for uniformity in thickness, uniformity in weight [13, 14], hardness [14], Friability [15] and uniformity in drug content [16].

Swelling behavior of matrix tablets

One tablet from each formulation was kept in a Petri dish containing phosphate buffer with pH 7.4. At the end of 2 h, the tablet was withdrawn, kept on tissue paper and weighed, repeated for every 2 h till the end of 12 h. The swelling index was calculated by following equation [17].

$$S.I = \{(M_t - M_0) / M_0\} \times 100$$

Where, S.I = Swelling Index, M_t = Weight of tablet at time 't' and
M_o = Weight of tablet at time 0.

***In vitro* drug release studies**

Release of Glimepiride from the matrix tablets was studied by 900 ml phosphate buffer (pH 7.4) using United States Pharmacopoeia (USP) 6-station Dissolution Rate Test Apparatus (Model Electro lab, TDT- 06T, Mumbai, India) with a rotating paddle stirrer at 50 rpm and 37 ± 0.5^0C. A sample of Glimepiride matrix tablets equivalent to 2 mg of Glimepiride was used in each test. Samples from dissolution fluid were withdrawn at regular intervals filtered (0.45 µm) and absorbance was measured at 229 nm for Glimepiride content [18] using a UV/ visible double-beam spectrophotometer (Elico SL210, India). The drug release experiments were conducted in triplicate (n = 3).

Drug release kinetics

To analyze the mechanism of drug release from the prepared formulations, the data obtained from *in vitro* release studies were subjected to Zero order [19], First order [19], Higuchi's [20], Korsmeyer Peppa's [21] and Hixson Crowell models [19].

Scanning Electron Microscopy

The optimized formulation (F-5) was selected for Scanning Electron Microscopy (SEM) analysis. The tablet surface morphology was studied at zero time and 4^{th} h of dissolution.

Accelerated Stability Studies of optimized matrix tablets

The promising formulation (F-5) was tested for a period of 3 months at accelerated storage conditions (temperatures of 40^0C with 75% RH) and the drug content was estimated [22].

RESULTS AND DISCUSSION

The thermo gram of Glimepiride showed a short endothermic peak at 209.13^0C (Figure 1). The thermo gram of formulated matrix tablets with *Hibiscus esculentus* fruit mucilage and Povidone showed an endothermic peak at 193.20^0C (Figure 2) indicating a slight change in terms of shifting towards the lower temperature. Thus these minor changes in the melting endotherm in the drug could be due to the mixing of the drug and excipients which lower the purity of each component in the mixture (may not indicate the potential incompatibility).

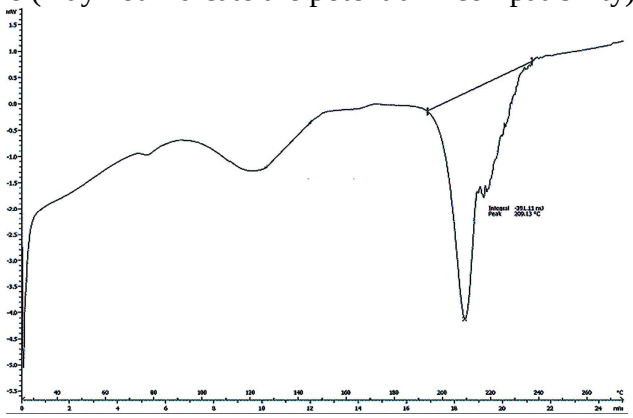

Fig.1: DSC thermo gram of Glimepiride

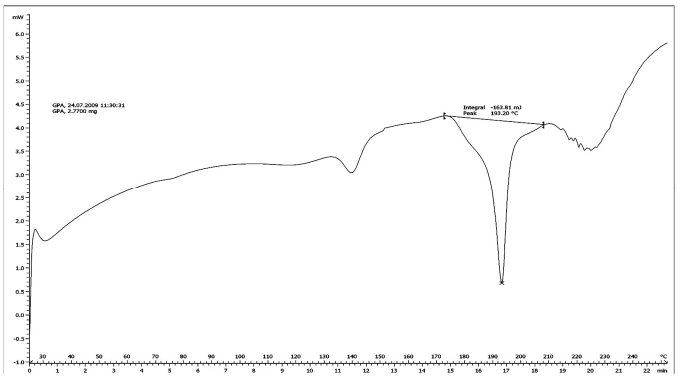

Fig.2: DSC thermo gram of Glimepiride: *Hibiscus esculentus* mucilage: Povidone (1:1:1)

The FTIR spectrum of Glimepiride showed characteristic peaks at wave numbers were 3344.3 (3300-3500) (N-H), 2900.7 (2850 – 3000) (C-H), 2900.7 (3300 - 2500 (O-H), 1427.2 and 1342.4 (1350 –1550) (N=O), 1072.3 (1220 -1020) (C-N) and 1033.8 (1000 –1300) (C-O) (Figure 3).

Infrared absorption spectrum of *Hibiscus esculentus* fruit mucilage and Povidone (1:1) spectrum shows prominent peaks at wave numbers 2920.0 (2850 – 3000) (C-H), 3379.1 (3300 – 3500) (NH), 1029.1 (1000 – 1300) (C-O) (Figure 4). The major FTIR peaks observed in matrix tablets were 3344.3 (3300-3500) (N-H), 2900.7 (2850 – 3000) (C-H), 2900.7 (3300 - 2500 (O-H), 1427.2 and 1342.4 (1350 –1550) (N=O), 1072.3 (1220 -1020) (C-N) and 1033.8 (1000 –1300) (C-O). (All these values were represented as cm^{-1}). This indicates that there were no chemical incompatibility between Glimepiride and the polymers (*Hibiscus esculentus* fruit mucilage and Povidone) used.

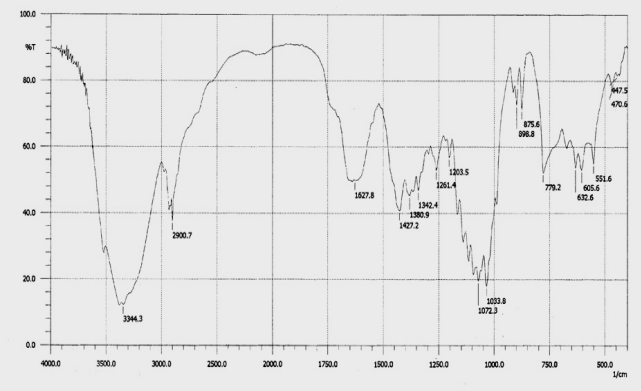

Fig.3: FTIR spectrum of Glimepiride

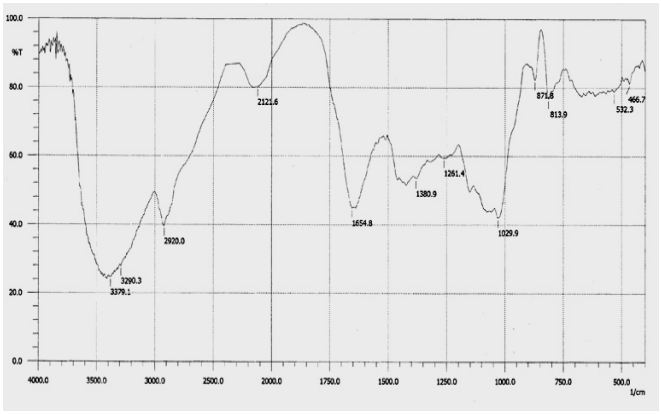

Fig.4: FTIR spectrum of *Hibiscus esculentus* fruit mucilage: Povidone (1:1)

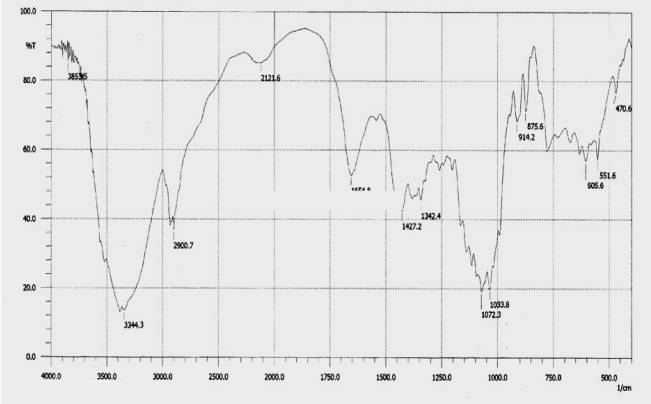

Fig.5: FTIR spectrum of formulation (F-5) blend

The Angle of repose of granules was found to be 26.94^0±2.157 indicates that the granules had excellent flow properties. The Loose Bulk density and Tapped Bulk density were found to be 0.58±0.084 and 0.81±0.046 g/ml respectively which was used to calculate the Carr's index and Hausner ratio. The values of Carr's index and Hausner ratio were found to be 26.84 ± 2.989 % and 1.25±0.046 respectively. All the values of flow properties were showed in Table 2.These trials were conducted in triplicates (n=3).

Table 2: Flow properties of granules

Parameters	Value
Angle of repose (^{0})	26.94±2.157
Loose Bulk Density (g/ml)	0.58±0.084
Tapped Bulk Density (g/ml)	0.81±0.046
Carr's index (%)	26.84±2.989
Hausner's ratio	1.25±0.046
Values were mentioned in mean ± SD; Number of experiments (n) =6	

The thickness of formulated matrix tablets was ranged from 2.98±0.045 to 3.11±0.153 mm and the hardness was ranged from 6.45±1.313 9.15±1.464 kg/cm^2, which was more than 5 kg/cm^2 and passes the hardness test. The loss on friability was ranged from 0.44±0.044 to 0.85±0.041 % (less than 1%). The formulated tablets were found to have good hardness and minimal weight loss on friability indicates that the tablets can with stand the mechanical shocks during their handling and transport. The drug content in the formulated tablets was ranged from 99.97±4.687 to 101.34±8.592 %. These trials were conducted for five times and shown in Table 3. The formulated tablets showed increase in swelling index as the concentration of *Hibiscus esculentus* fruit mucilage increased (Figure 6).

Table 3: Physical properties of formulated matrix tablets

Formulation	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F-1	3.05±0.079	8.50±1.244	0.50±0.012	100.12±6.955
F-2	3.11±0.153	9.15±1.464	0.85±0.041	101.34±8.592
F-3	3.04±0.048	7.80±1.348	0.44±0.044	99.97±4.687
F-4	3.08±0.048	7.55±1.419	0.65±0.071	99.99±5.846
F-5	2.98±0.045	6.45±1.313	0.78±0.071	100.15±8.267
Values were mentioned in mean ± SD; Number of experiments (n) =6				

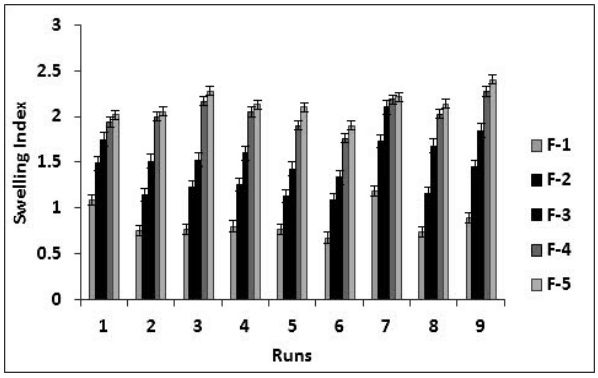

Fig. 6: Swelling behavior of matrix tablets

The drug release rate was faster in F-1 and slower in F-5. The release of Glimepiride was sustained as the proportion of *Hibiscus esculentus* fruit mucilage increased and the overall time

of release of the Glimepiride from the matrix tablet was also increased. The release of Glimepiride form the optimized formulation (F-5) showed zero order release and the formulations gave slope (n) and regression coefficient (r) values, which were 0.006714, 0.995289 respectively and shown in Table 4. The *In-vitro* drug release profile of Glimepiride from formulated matrix tablets was further studied using first order, whose slope and regression coefficient values of F-5 were -0.001763 and -0.982313 respectively and represented in Table 4. The slope and regression coefficient values of F-5 for Higuchi model were 3.308517 and 0.993937 respectively, for Korsmeyer Peppa's they were 0.304559 and 0.968567 and for Hixson-Crowell's Model they were -0.000926 and -0.992145 respectively. These values were represented in Table 5 and shown in Figures 7, 8, 9, 10 and 11. The *in vitro* drug release data was perfectly fitted to zero order release and Higuchi's matrix models. Drug releases from matrix tablets were by drug dissolution, drug diffusion or a combination of both.

Table 4: Kinetic Values for dissolution Profile of Glipizide Matrix Tablets

Formulations	First Order values		Zero Order values	
	Slope (n)	Regression Co-efficient (r)	Slope (n)	Regression Co-efficient (r)
F-1	-0.000752	-0.978458	0.003561	0.990382
F-2	-0.000499	-0.996849	0.002959	0.992587
F-3	-0.001566	-0.972615	0.005978	0.996664
F-4	-0.001532	-0.992596	0.006496	0.988148
F-5	-0.001763	-0.982313	0.006714	0.995289

Table 5: Kinetic values for Glipizide matrix tablets

Formulation	Higuchi's values		Korsmeyer Peppa's values		Hixson Crowell's values	
	Slope (n)	Regression Coefficient (r)	Slope (n)	Regression Coefficient (r)	Slope (n)	Regression Coefficient (r)
F-1	1.725018	0.971716	0.162459	0.930223	-0.000445	-0.983565
F-2	1.865834	0.996464	0.171526	0.955648	-0.000349	-0.995775
F-3	3.103446	0.985078	0.287584	0.947334	-0.000661	-0.995143
F-4	3.227641	0.993492	0.313174	0.974435	-0.000838	-0.994416
F-5	3.308517	0.993937	0.304559	0.968567	-0.000926	-0.992145

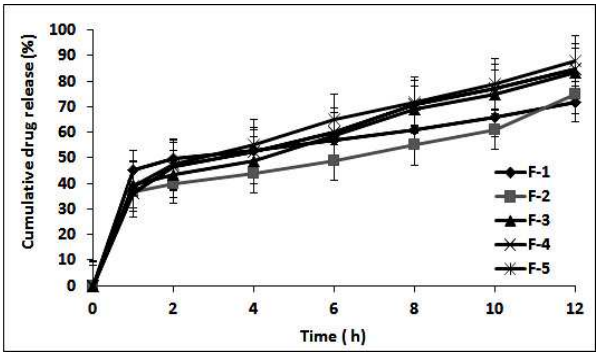

Fig. 7: Zero order release plots

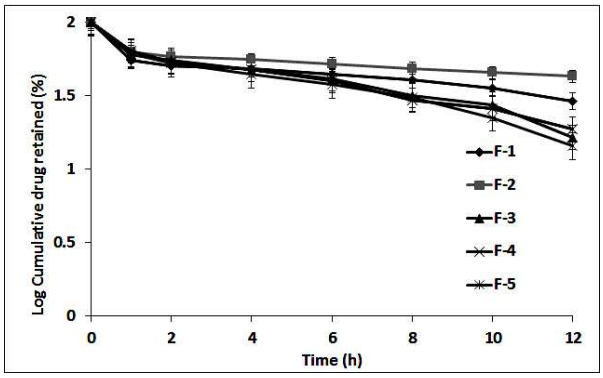

Fig. 8: First order release plots

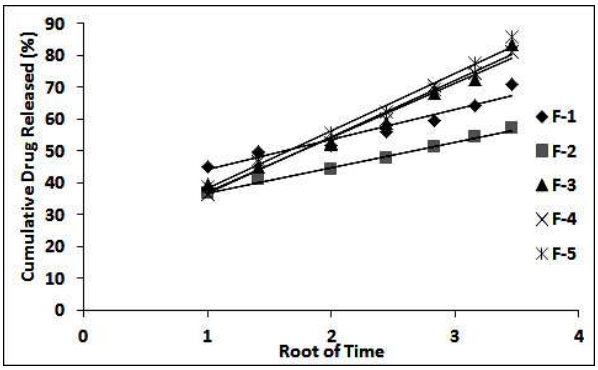

Fig. 9: Higuchi plots

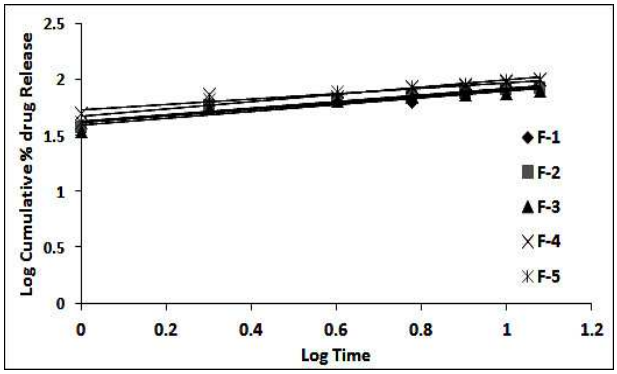

Fig.10: Korsmeyer Peppa's plots

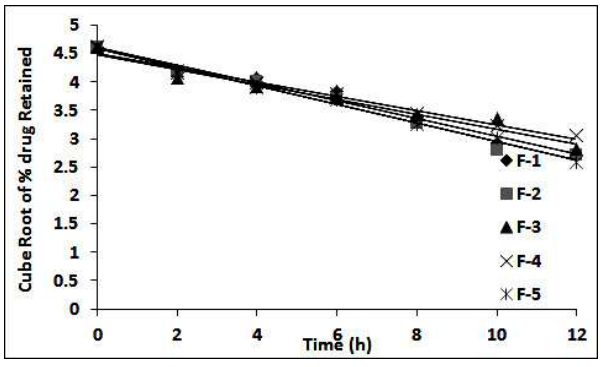

Fig.11: Hixson Crowell's plots

The surface morphology of optimized formulation (F-5) at zero time and at 4th h of dissolution were observed which indicates that the release of drug from dosage form by diffusion mechanism. The SEM photographs of tablet (F-5) were shown in Figure 12.

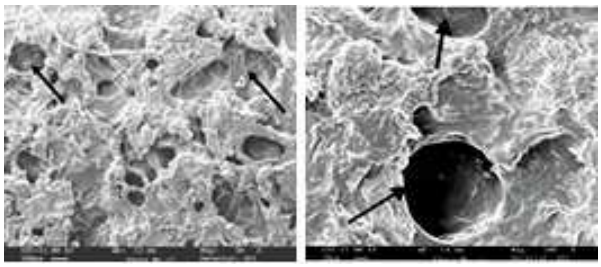

Fig.12: Surface morphology of matrix tablet (F-5) at zero time and at 4th h of dissolution

The accelerated stability studies further proved the formulation (F-5) was stable even at accelerated storage conditions. The physicochemical properties of F-5 tablets, before and after stability studies were shown in Table 6.

Table 6: Summary of properties of F-5 before and after accelerated stability studies

Parameter	Before stability studies	After stability studies
Thickness (mm)	2.98±0.045	2.98±0.059
Hardness (kg/cm^2)	6.45±1.313	6.44±1.458
Friability (%)	0.78±0.071	0.79±0.054
Drug content (%)	100.15±8.267	100.15±5.958
Values were mentioned in mean ± SD; Number of experiments (n) =3		

CONCLUSION

The present study revealed that *Hibiscus esculentus* fruit mucilage and Povidone combination appears to be suitable for use as a release retardant in the manufacture of sustained release matrix tablets because of its good physicochemical and swelling properties and suitability for matrix formulations. The *in vitro* dissolution data, mathematical modeling and accelerated stability studies revealed that the dried *Hibiscus esculentus* fruit mucilage in combination with Povidone can be used as a release retardant for making sustained release matrix tablets.

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