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Fabrication and *in vitro* evaluation of Gliquidone matrix tablets with *Abelmoschus esculentus* fruit mucilage and Povidone combination

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Abstract

The main objective of the present study was to develop matrix tablets of Gliquidone with *Abelmoschus esculentus* fruit mucilage and Povidone and to study its functionality as a matrix forming agent for controlled release tablet formulations. Physicochemical properties of dried powdered mucilage of *A. esculentus* mucilage were studied. Various formulations containing Gliquidone, *A. esculentus* fruit mucilage and Povidone were prepared. The drug-excipient compatibility studies, physicochemical properties, pre compression and post compression properties were performed and satisfactory results were obtained. These results proved that the dried *A. esculentus* mucilage and Povidone combination can be used as a matrix forming material for making controlled release matrix tablets.

Key words: Gliquidone, *Abelmoschus esculentus*, Povidone, matrix tablets, controlled release

Introduction

Abelmoschus esculentus, (*Malvaceae* family) is an annual/perennial climber, growing up to 2 m tall. The fruit is a capsule up to 18 cm long (Martin 1982). Gliquidone is an oral hypoglycemic agent, which is a commonly prescribed drug for the treatment of patients with type II diabetes mellitus. It belongs to class of sulfonyl ureas. Gliquidone is a weak acid with pKa of 5.3. Gliquidone is practically insoluble in water and acidic environment but highly permeable (class 2) according to the Biopharmaceutical Classification System (BCS) (Kahn and Shechter 1991). The oral absorption is uniform, rapid and complete with nearly 100% bioavailability (Bhattacharyya 2001). Therapy with Gliquidone is usually initiated with 2.5 to 10 mg (Martindale 2005). The pharmacokinetics and dosage schedule supports once daily controlled release formulations for Gliquidone for better control of blood glucose levels to prevent hypoglycemia, enhance clinical efficacy and patient compliance. The objective of present investigation is to design and evaluate controlled release tablets of Gliquidone using *A. esculentus* fruit mucilage and Povidone combination as release retardant.

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Materials and Methods

Materials

Gliquidone was obtained as a gift sample from Dr. Reddy's Laboratories, India. *Abelmoschus esculentus* fruits 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, microcrystalline cellulose (Avicel) and magnesium stearate were procured from SD Fine chemicals, India. All other chemicals used were of analytical reagent grade and double distilled water was used throughout the experiment.

Extraction of mucilage

The fresh *A. esculentus* fruits were washed with water. The fruits 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 (Baveja et al. 1988). The mucilage was extracted using a multi-layer muslin cloth bag to remove the marc from the solution. Acetone (three times the volume of filtrate) was added to precipitate the mucilage. The mucilage was separated, dried in an oven at 40°C, collected, ground, passed through a # 80 sieve and stored in desiccator at 30°C and 45% relative humidity till use (Ahad et al. 2010).

Drug-excipient compatibility studies

Differential scanning calorimetric studies (DSC): DSC analysis was performed using Shimadzu DSC-60, Japan. A 1:1 ratio of drug and excipient was weighed into aluminum crucible. And sample was analyzed by heating at a scanning rate of 30°C per minute over a temperature range of 30-300°C under nitrogen environment.

Fourier transform infrared (FTIR) spectroscopic studies: FTIR spectra were recorded on samples prepared in potassium bromide (KBr) disks using a Shimadzu 1601 FTIR Spectrophotometer, Japan. Samples were prepared in KBr disks by means of a hydraulic press at 6-8 tons pressure. The scanning range was 500 to 4000 cm^{-1}.

Preparation of matrix tablets: Controlled release matrix tablets of Gliquidone with *A. esculentus* fruit mucilage and Povidone were prepared by using different drug: mucilage ratios as shown in Table 1, *A. 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 (Ahad et al. 2010). The compositions of formulations were shown in Table 1. These matrix tablets were evaluated for their physical properties as per official methods.

Table 1. Formulae of matrix tablets

Ingredients (mg)	Batch				
	F-1	F-2	F-3	F-4	F-5
Gliquidone	10	10	10	10	10
Abelmoschus esculentus fruit dried mucilage	2.5	5	7.5	10	12.5
Povidone	2.5	5	7.5	10	12.5
Microcrystalline cellulose (Avicel)	180	175	170	165	160
Magnesium stearate	5	5	5	5	5
Total weight of tablet	200	200	200	200	200

Evaluation for pre compression parameters

Angle of repose: Angle of repose was determined by using funnel method. Granules were poured from a funnel that can be raised vertically until a maximum cone height, h, was obtained. Diameter of heap, D, was measured (Martin 2001). The angle of repose (Θ) was calculated by the following equation.

$$\Theta = \tan\text{-}1\ (h / r)$$

Where, Θ is the angle of repose, h is the height in cm and r is the radius.

Loose bulk density: Loose bulk density was determined by pouring pre sieved drug excipient granules into a graduated cylinder and measuring the volume and weight "as it is". It is expressed in g/mL and is given by the following equation (Lachman et al. 1987, Martin 2001).

$$D_b = M / V_0$$

Where, M is the mass of powder and V_0 is the Bulk volume of the powder.

Tapped bulk density: It was determined by placing a graduated cylinder, containing a known mass of granules on mechanical tapping apparatus. The tapped volume was measured by tapping the powder to constant volume. It is expressed in g/mL and is given by the following equation (Martin 2001).

$$D_t = M / V_t$$

Where, M is the mass of powder and V_t is the tapped volume of the powder.

Carr's index: The compressibility index of the granules was determined by Carr's compressibility index. It is expressed in percentage and it was determined by the following equation (Martin 2001).

$$I = D_t - D_b / D_t$$

Where, I is Carr's index, D_t is the tapped density of the powder and D_b is the bulk density of the powder (Martin 2001).

Hausner ratio: The ratio of tapped bulk density and loose bulk density was related to inter particle friction and could be used to predict powder flow properties. It is expressed in percentage and is expressed by the following equation (Martin 2001)

$$H = D_t / D_b$$

Where, D_t is the tapped density of the powder and D_b is the bulk density of the powder.

Post compression parameters (Banker and Anderson 1986)

Thickness and diameter: The thickness and diameter of the tablets was measured by Vernier Calipers. It is expressed in mm.

Weight variation: 20 tablets were selected at random and average weights were determined. Then individual tablets weighed and the individual weight was compared with the average.

Hardness: The hardness of the tablets was determined by using a Pfizer hardness tester. It is expressed in kg / cm^2.

Friability: The friability of the tablets was determined using Roche Friabilator. It is expressed in percentage. 20 tablets were initially weighed ($W_{initial}$) and transferred into the friabilator. The friabilator was operated at 25 rpm per min for 4 min (100 revolutions). The tablets were weighed again (W_{final}). The % friability (F) was then calculated by the following equation.

$$F = W_{initial} - W_{final} / W_{initial} \times 100$$

Content uniformity: Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 10mg of drug was transferred to 100 mL volumetric flask. The powder was dissolved in 5 mL of Methanol and made up to volume with 0.1N HCl. The sample was mixed thoroughly and filtered through a 0.45µm membrane filter. The filtered

solution was diluted suitably and analyzed for drug content by UV spectrophotometer at a λ_{max} of 230 nm using 0.1 N Hydrochloric acid as blank.

Estimation of Gliquidone: An ultraviolet spectrophotometric method based on measurement of absorbance at 230 nm in Phosphate buffer of pH 7.4. The method obeyed Beer-Lambert's law in the concentration range of 1-20 µg/mL. When a standard drug solution was assayed for 6 times, the accuracy and Precision were found to be 95% and 1.15% respectively. No interference was observed from the excipients used.

Swelling behavior of matrix tablets

The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of batches F-1, F-2, F-3, F-4 and F-5 were studied. One tablet from each batch was kept in a Petri dish containing phosphate buffer of 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 % weight gain by the tablet was calculated by following equation (Killedar et al. 2008).

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

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

Swelling behavior of controlled release matrix tablets were represented in Fig. 6.

In vitro drug release studies

Release of Gliquidone from the matrix tablets was studied in phosphate buffer of pH 7.4 (900 mL) using United States Pharmacopoeia (USP 24/NF19, 1995) 6-station Dissolution Rate Test Apparatus (Electrolab, TDT- 06T, India) with a rotating paddle stirrer at 50 rpm and 37 ± 0.5°C. A sample of Gliquidone matrix tablets equivalent to 10 mg of Gliquidone was used in each test. Samples of dissolution fluid were withdrawn through a filter (0.45 µm) at different time intervals and were assayed at 230 nm for Gliquidone content (USP 24/ NF19, 1995) using a UV/ visible single-beam spectrophotometer-117 (Systronics Corporation, 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, First order, Higuchi's, Korsmeyer-Peppas and Hixson Crowell models (Korsmeyer et al. 1983, Siepmann and Peppas 2000, Muschert et al. 2009).

Scanning Electron Microscopy

Scanning Electron Microscopy (SEM) of optimized batch (F-5) before and different intervals of dissolution were taken. The morphological characters of these scans were compared to hypothesize the mechanism of drug release.

Accelerated Stability Studies of optimized matrix tablets

The promising batch (F-5) was tested for accelerated stability studies for a period of 3 months at a temperature of 40°C and 75% RH. (Remunan et al. 1992).

Results and Discussion

Physicochemical properties of *A. esculentus* fruit mucilage *viz.*, percentage yield, solubility, odour and appearance were studied and showed in Table 2. The mucilage gave positive results for carbohydrates. The average particle size was found to be 189.38±12.84 µm. The weight loss

on drying was 6.66±0.051%, the acid insoluble ash was 1.35±0.008%, the swelling Index was 87±4.19%.

Table 2. Physicochemical properties of *Abelmoschus esculentus* fruit mucilage

Properties	**Observation**
Solubility	Soluble and forms colloidal solution, in Luke warm water. Practically insoluble in ethanol, acetone, ether and chloroform
Odour	Characteristic
Consistency	Lustrous
Identification	
Mounted in 96% ethanol	Transparent angular masses
Mounted in ruthenium red	Particles stained red
Mounted in iodine solution	Particles stained blue
Test for carbohydrate (Mollish test)	+ve
Test for tannis (Ferric chloride test)	-ve
Test for chloride (Silver-nitrate test)	-ve
Test for sulphate (Barium chloride test)	-ve
Uronic acid test	+ve
Average particle size (µm)	189.38±12.84
Weight loss on drying (%)	6.66±0.051
Acid insoluble ash (%)	1.35±0.008
Swelling index (%)	87±4.19
pH	7.1
Test for foreign matter (%)	NMT 0.1
Test for heavy metal (lead)	25±2 ppm
Test for arsenic	<1 ppm
Charring (°C)	Decomposes above 121°
Density of liquid (0.5% w/v)	1.378±0.028
Microbial count (cfu/g)	Bacteria: 18±2; Fungi: 5±1
Flow properties	
Angle of repose (θ°)	28.01±1.25
Loose bulk density (g/cm^3)	0.60±0.03
Tapped bulk density (g/cm^3)	0.81±0.01
Compressebility index (%)	26.41±1.54
Hausner's ratio	1.24±0.07

All the values were represented as mean± S.D; Number of experiments (n) = 3; cfu = colony forming units; NMT = not more than

The pH of the mucilage was 7.1, the amount of foreign matter, heavy metal and microbial levels were within the limits. The density of 0.5% w/v was found to be 1.378±0.028. The mucilage showed good flow properties and satisfactory compressibility index. All these values were shown in Table 2.

The DSC thermogram of Gliquidone and the formulated matrix tablet blend was shown in Fig. 1 and 2. The DSC thermogram of Gliquidone showed a short endothermic peak at 215.50°C. The thermogram of formulated matrix tablets with *A. esculentus* fruit mucilage and Povidone showed an endothermic peak at 166.61°C indicating a slight change in terms of shifting towards the lower temperature. It has been reported that the quantity of material used effects the peak shape and enthalpy. Thus these minor changes in the melting endotherm in the drug could be due to the mixing of the drug with excipients which lower the purity of each component in the mixture and may not necessarily indicate potential incompatibility.

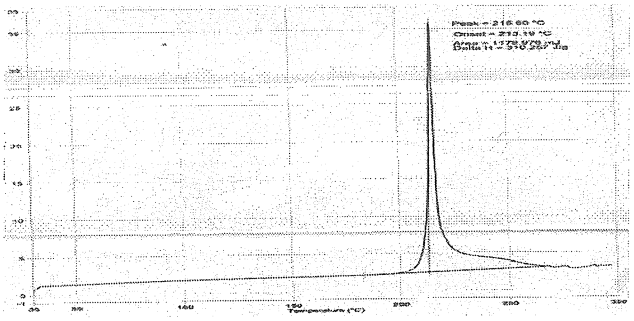

Figure 1. DSC thermogram of Gliquidone

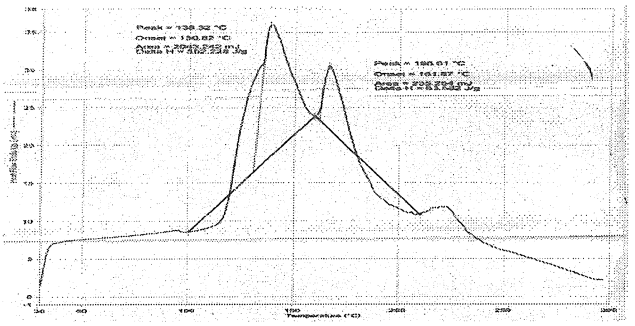

Figure 2. DSC thermogram of formulated matrix tablets

The FTIR spectrum of Gliquidone, placebo and formulated matrix tablets were showed in Fig. 3, 4 and 5, respectively. The characteristic bands 3344.3, 2900.7, 1427.2, 1342.4, 1072.3 and 1033.8 were observed both in pure Gliquidone and formulation.

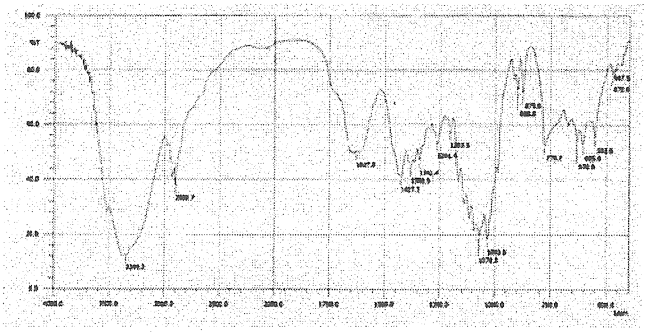

Figure 3. Infrared Spectrum of Gliquidone Pure drug

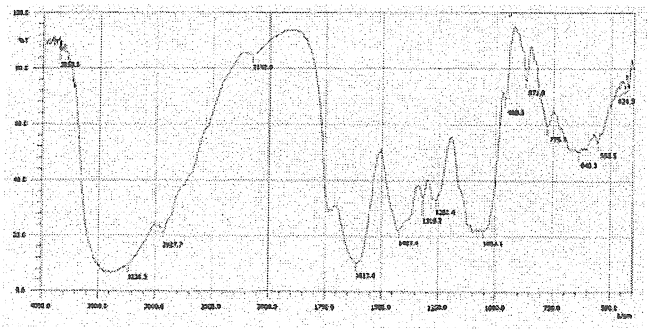

Figure 4. Infrared Spectrum of placebo

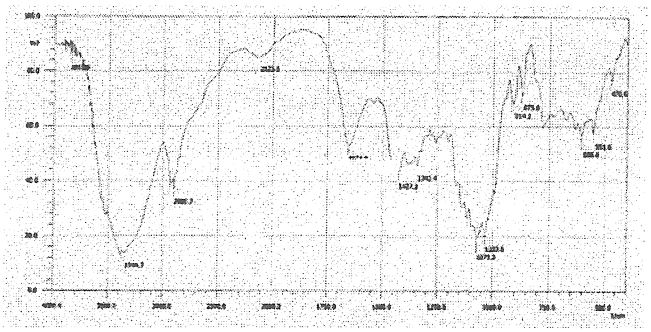

Figure 5. Infrared Spectrum of Gliquidone matrix tablets

This indicates that there is no chemical incompatibility between Gliquidone and the polymers used (*A. esculentus* fruit mucilage and Povidone).

The Angle of repose of granules was found to be 29.45±1.68° indicated the granules had excellent flow properties. The loose bulk density and tapped bulk density of the granules were found to be 0.578±0.08 and 0.788±0.03 g/mL respectively which was used to calculated the Carr's index and Hausner's ratio values. The Carr's index and Hausner's ratio values were found to be 26.59±0.21 % and 1.24±0.04 respectively. The flow properties of granules were shown in Table 3. All these trials were conducted in triplicates (n=3).

Table 3: Flow properties of granules

Parameters	Value
Angle of repose (^{0})	29.45±1.68
Loose Bulk density (g/ml)	0.578±0.08
Tapped Bulk density (g/ml)	0.788±0.03
Carr's index (%)	26.59±0.21
Hausner's ratio	1.24±0.04
Number of experiments (n)= 3	

The thickness of formulated matrix tablets was ranged from 5.4±0.41 to 6.5±0.58 mm; the hardness was ranged from 6.50±1.45 to 8.10±1.40 kg/cm^2. The loss on friability was ranged from 0.44±0.03 to 0.85±0.05%, which is less than 1% indicates the firmness of the formulated tablets. The drug content in the formulated tablets was ranged from 99.5±2.56 to 101.2±5.25%. The physical properties of formulated matrix tablets were shown in Table 4. These trials were conducted for five times (n=5).

Table 4: Physical properties of formulated matrix tablets

Sl. No	Batch	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
1	F-1	6.3±0.21	7.50±1.25	0.50±0.02	100.2±3.95
2	F-2	5.9±0.15	8.10±1.40	0.85±0.05	101.2±5.25
3	F-3	5.4±0.41	6.80±1.35	0.44±0.03	99.5±2.56
4	F-4	6.4±0.39	6.50±1.45	0.62±0.06	99.9±2.16
5	F-5	6.5±0.58	7.40±1.30	0.73±0.07	100.5±3.67
Number of trials (n) = 5					

The formulated tablets were shown good swelling properties which were shown in Fig. 6. The rate of release was faster in F-1 and slower in F-5. The release of Gliquidone was sustained as the proportion of *A. esculentus* fruit mucilage and Povidone increased and the overall time of release of the Gliquidone from the matrix tablet was also increased. The release of Gliquidone form the formulations showed zero order release. The *in vitro* drug release profile of Gliquidone from formulated matrix tablets was further studies using first order, Higuchi, Korsmeyer-Peppas and Hixson-Crowell's models which were tabulated in Tables 5, 6 and shown in Fig. 7-11 respectively. The kinetic plots were perfectly fitting to the formulated *A. esculentus* fruit mucilage- Gliquidone matrix tablets. Drug releases from matrix tablets were by drug dissolution, drug diffusion or a combination of both

Table 5: Kinetic Values Obtained from *In-Vitro* Release Profile for Matrix Tablets of Gliquidone (Zero order and First order)

Batch	Zero Order			First Order		
	Slope	Regression coefficient (r)	k value	Slope	Regression coefficient (r)	k value
F-1	0.00356	0.003560	0.990412	-0.00075	0.001731	-0.97851
F-2	0.00296	0.003025	0.992498	-0.00050	0.001130	-0.99705
F-3	0.00601	0.005024	0.997098	-0.00161	0.003602	-0.97305
F-4	0.00652	0.006524	0.988056	-0.00153	0.003528	-0.99261
F-5	0.00702	0.007014	0.995305	-0.00182	0.004049	-0.98235

Table 6: Kinetic Values Obtained from *In-Vitro* Release Profile for Gliquidone Matrix Tablets (Higuchi, Korsmeyer Peppa's and Hixson-Crowell's models)

Batch	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	1.72506	0.971738	0.16246	0.930215	-0.00043	-0.983549
F-2	1.86582	0.996448	0.17156	0.955709	-0.00032	-0.995741
F-3	3.10345	0.985042	0.28758	0.947342	-0.00064	-0.995174
F-4	3.22809	0.993489	0.31317	0.974431	-0.00083	-0.994409
F-5	3.30859	0.993936	0.30456	0.968608	-0.00092	-0.992139

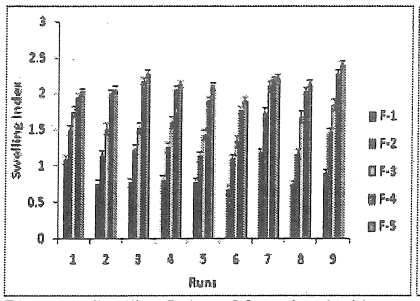

Figure 6: Swelling Index of formulated tablets

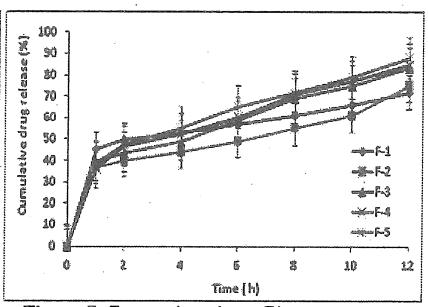

Figure 7: Zero order release Plots

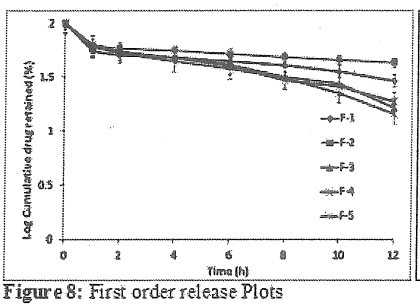

Figure 8: First order release Plots

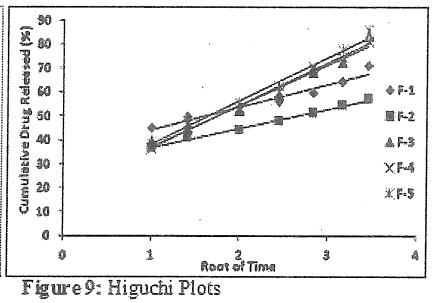

Figure 9: Higuchi Plots

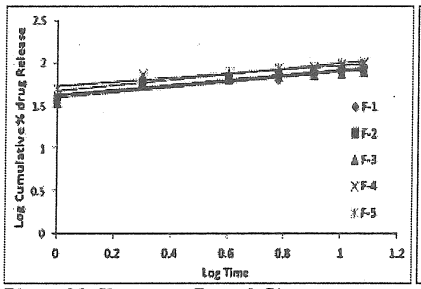

Figure 10: Korsmeyer Peppa's Plots

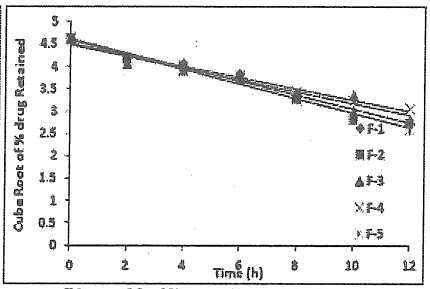

Figure 11: Hixson-Crowell's Plots

The SEM photographs of matrix tablets at time intervals of 0h, 1h, 2h and 4h of dissolution were shown in Fig. 12.

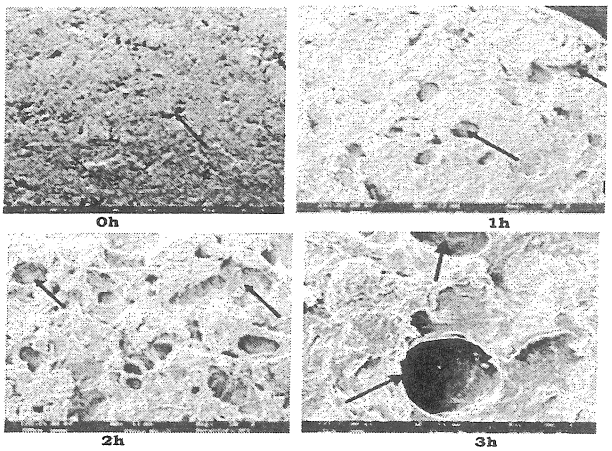

Figure 12. Surface morphology of matrix tablets at time intervals of 0h, 1h, 2h and 4h of dissolution

The formulated tablets retain the physicochemical properties viz., weight of the tablet, diameter, thickness, hardness, friability and drug content were tested before and after accelerated stability

studies. The results were shown in Table 7. The accelerated stability studies further proved the formulation (F-5) is stable even at accelerated environmental conditions.

Table 7: Physicochemical properties of F-5 matrix tablets before and after accelerated stability studies

Parameter	Accelerated stability studies	
	Before	After(90 days)
Weight of the tablet (mg)	200	200
Diameter (mm)	10	10
Thickness (mm)	6.5±0.58	6.5±0.56
Hardness (kg/cm^2)	7.40±1.30	7.20±0.90
Friability (%)	0.73±0.07	0.77±0.05
Drug content (%)	100.5±3.67	100.5±0.59

Conclusion

The present study revealed that *A. esculentus* fruit mucilage and Povidone combination appears to be suitable for use as a release retardant in the manufacture of controlled release matrix tablets because of its good swelling, good flow and suitability for matrix formulations. From the dissolution study, it was concluded that dried *A. esculentus* fruit mucilage in combination with Povidone can be used as an excipient for making controlled release matrix tablets.

Acknowledgement

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