NATURAL MODIFIED STARCH USED AS A CARRIER FOR ENHANCING DISSOLUTION AND BIOAVAILABILTY OF GLIPIZIDE

Amaresh Chandra Sahoo[1*], Sujit Dash[2], Prabhat Kumar Sahoo[3], Minaketan Sahoo[4], Sushanta Kumar Behera[5], Sradhanjali Behera[6]

Abstract

Objective: The objective of this research is to use a natural modified starch obtained from *Aponogeton natans* to improve the solubility and bioavailability of glipizide, a BCS class II drug.

Methods: *Aponogeton natans* starch was isolated and modified into starch citrate form by interacting with citric acid at high temperatures. The physio-chemical characteristics of starch citrate shows that it is water insoluble, has good flow characteristics, and a high swelling index without gelling properties. Drug and starch citrate compatibility was demonstrated using FTIR and DSC spectra. The solid dispersion of glipizide with *Aponogeton natans* starch citrate was prepared by solvent evaporation method with varying proportions such as 1:1, 1:2, and 1:3.

Results: The results show that the drug content of all formulations is more than 99 %.In vitro dissolution study reveals the F6 formulation exhibits more than 90% drug dissolution within 30 minutes .Bioavailability study of F6 formulation shows greater AUC and Emax value than pure glipizide. The F6 formulation was then compressed and formulated into an IR tablet by direct compression method. The tablets are then put through a series of quality control tests. In vitro dissolution study of tablet reveals that over 90% of the medication is dissolved in 30 minutes.% DE 30 was found more than 99% in 30 minute. Lowest time of T_{50} was observed for F10 i.e. 7.36 min indicating higher dissolution potential of starch citrate based immediate release tablet.

Conclusion: The research showed that tablet prepared with starch citrate of *Aponogeton natans* shows improved dissolution and has higher bioavailability.

Keyword- *Aponogeton natans*, glipizide, super disintegrant, bioavailability, pharmacodynamic method.

[1*, 2, 3,4,5,6] Institute of Pharmacy & Technology, Salipur, Cuttack, Odisha-754202, India

***Corresponding Author:** Amaresh Chandra Sahoo,
*Assistant Professor, Institute of Pharmacy & Technology, Salipur, Mail:amareshchandrasahoo@gmail.com, Mobile: 6370799114

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INTRODUCTION

Glipizide is a BCS Class II oral hypoglycaemic drug with low water solubility. Because dissolution is the rate determining step for bioavailability, improving the solubility and dissolution rate of Glipizide in gastrointestinal fluids might improve bioavailability. Several strategies have been employed to improve the solubility, dissolution rate, and bioavailability of poorly soluble pharmaceuticals, including micronization, cyclodextrin complexation, solid dispersion, microemulsions, and nano disperse systems. Solid dispersions in water dispersible excipientsis a simplistic, industrially applicable strategy among the different approaches for the solubility, dissolution rate and bioavailability of poorly soluble drugs.

The drug is molecularly dispersed or exists in an amorphous state in solid dispersions, which may result in increased solubility. The primary goal of this study is to develop, characterise, and evaluate Aponogeton natans starch citrate, a new modified starch, as an effective carrier in solid dispersions for increasing glipizide dissolution rates. *Aponogeton natans* Starch citrate has also been reported to be a promising directly compressible carrier for the direct compression method of tablet manufacturing. The feasibility of compressing glipizide solid dispersions in starch citrate into compressed tablets with a faster dissolving rate was also examined [1, 2, 3.]

MATERIALS AND METHODS

Glipizide, was obtained as a gratis sample from M/S Yarrow Chem Products, Mumbai. *Aponogeton natans* were collected from local area. All other chemicals and reagents used were of analytical grade.

Isolation of starch from *Aponogeton natans*

The hot water extraction method was used to extract the starch from Aponogeton natans[4]. Aponogeton natans tubers were soaked for 24 hours in a one-litre beaker in a thermostatic water bath at a constant temperature of 40°C.For 3 minutes, one part drenched tubers and three parts distilled water were mashed. The resulting slurry was then filtered through a muslin cloth and centrifuged for 20 minutes at 5000 rpm. The supernatant was then discarded and the dregs were resuspended in sodium hydroxide in excess of 0.02 percent to remove any residual proteins and phenolic compounds. The resulting suspension was allowed to stand for 4 hours before the supernatant was discarded. This procedure was repeated 6-8 times more until the supernatant became colourless. The resulting material was suspended in distilled water and filtered through a 0.045 mm strainer, neutralised to pH 7.0, filtered and rinsed with distilled water using the Buchner channel. The cake was separated and dried at room temperature before being pulverised into powder and stored in an airtight container.

Preparation of Starch Citrate

30 gm of citric acid were dissolved in 40 ml. of water the pH of the solution was adjusted to 3.5 using 10 M of NaOH and the final volume was adjusted to 100 ml by water. This citric acid solution was mixed with 50 g of *Aponogeton natans* starch, spread on a tray and conditioned for one day at room temperature (27°C). The starch citrate was then dried in a hot air oven at 60°C for 6 hours. To eliminate untreated citric acid, the dried blend was repeatedly rinsed with water. The purified starch citrate was dried at 60°C until it was completely dry. The acquired product will be ground and sieved[5].

Characterisation of the starch citrate

The starch citrate was subjected to FTIR analysis. The Starch Citrate's solubility was assessed in water, buffer of pH 1.2, 4.5, and 7.4, as well as organic solvents such as alcohol, dichlorome thane, chloroform, and acetone. The pH of a 1% w/v slurry of Starch Citrate was determined by using apH metre. The melting point was determined using a melting point apparatus as well as a DSC apparatus. Using a Brookfield viscometer, the viscosity of a 1% solution in water was measured. The swelling index of Starch Citrate was determined by mixing 200 mg of Starch Citrate with 10 ml of water and light liquid paraffin in two graduated cylinders. The cylinders were let to stand for 12 hours to allow the dispersion to settle. The sediment volumes in the two cylinders were measured[6, 7.]

The Swelling index of the Starch Citrate was determined as follows.

$$\%SI = \frac{\text{volume of sediment in water} - \text{volume of sediment in light iquid paraffin}}{\text{volume of sediment in light liquid paraffin}} \times 100$$

The gelling property (gelatinization) of the Starch and Starch Citrate was assessed by warming 7% w/v dispersion of each in water at 100°c for 30 min. The hygroscopic nature of starch citrate was assessed by IR moisture balance. Bulk density,

tapped density, angle of repose, Compressibility index was determined.

Preparation of standard curve of glipizide

10 mg glipizide was transferred to a 100 mL volumetric flask. Then glipizide was dissolved by adding a little amount of solvent (ACN: K2HPO4 = 17: 83) and shake well, make up the volume to 100ml.Assemble a series of dilute solutions with concentrations of 10, 20, 30, 40, and 50 µg/ml from the aforementioned stock solution, Assess the absorbance of the solution at 275nm[8]. A Graph is Plotted by taking concentration on the X - axis and absorbance on the Y- axis and the linearity can be determined by using equation i.e.y = mx + c.

Drug-Excipient Interaction Study FT-IR spectroscopy Glipizide-carrier interaction (1:1) was assessed using FTIR spectroscopy (Brooker-Alpha II). FT-IR spectra of pure drug glipizide and its 1:1 physical blend with starch of Aponogetonnatans and its starch citrate were recorded. FT-IR spectra

Differential Scanning Calorimetry (DSC) Analysis

DSC analysis was performed on the physical mixture of glipizide and its 1:1 starch citrate to investigate the interaction between the active drug ingredient and the carrier.

Preparation of solid dispersions of glipizide with *Aponogeton natans* starch citrate

By solvent evaporation technique, solid dispersions of glipizide with *Aponogeton natans* native starch and its starch citrate were prepared in various proportions such as 1:1, 1:3, and 1:5 of the drug: carrier. Glipizide was dissolved in 10 ml of dichloromethane to get a transparent solution; The starch and Starch citrate were then dispersed in the clear drug solution. The suspension was homogenised for 15 minutes to allow complete dichloromethane evaporation, and then dried at 60°C until completely dry. The dried mass was crushed and sieved with a mesh size of 40[9]

Characterization of solid dispersion.

Percentage Yield, Drug Content, Solubility, Flow ability and compressibility of solid dispersion were determined. For determination of drug content, a quantity equal to 10 mg of glipizide was calculated, weighed and so nicated in a phosphate buffer of pH 6.8for 10 minutes, strained, diluted with the same solvent and drug content was assessed. Solubility of solid dispersion was determined by placing an excess quantity of glipizide and its various solid dispersions separately into bottles of 25 ml size, each containing 20 ml of de-ionized water and shaking continuously at 25 ± 0.5 °C for 24 h on a Remi mini rotary shaker till equilibrium. The filtered solutions were diluted correctly and spectro photo metrically analysed. Percent compressibility index (%CI), Hausner's ratio (H.R) and angle of repose of solid dispersion were determined to measure the flow properties[10].

In-vitro dissolution test of solid dispersion

The U.S.P. apparatus-2 was used to measure the dissolution of glipizide from its solid dispersion. 900 ml of pH 6.8 phosphate buffer was measured and placed into the dissolution flask, at37 ± 0.2 °C with the paddle rotating at 50 RPM. At 5, 15, 30, 45, 60, and 90 minutes, 5 ml of samples were withdrawn, filtered, and supplemented with an equivalent amount of fresh dissolution medium. Thereafter, the samples were properly diluted and spectro photo metrically assessed at 275 nm. Experiments on dissolution were carried out in triplicates. The dissolution profiles were analysed and the amount of drug released during the first 30 minutes (Q30 min) and T50, i.e. the time required for 50% of glipizide to dissolve was calculated [11,12].

Assessment of therapeutic efficacy (bioavailability study) of glipizide solid dispersion

The bioavailability study was conducted on glipizide and its solid dispersion, that was selected based on the results of the dissolution tests. A single dose and a parallel group design were used in this study on diabetic rats.10-14 days prior to the diabetes-inducing trial, male Wistar rats weighing 180-240 g were fed a normal diet, fasted for 24 hours, and injected intraperitoneally with streptozotocin (50 mg/kg). These rats were placed into three groups, each with three rats. A Glucometer (Smart Scan®) was used to determine the amount of fasting blood glucose. The blood glucose level (BGL) was measured at various time periods up to 24 hours after intragastric tube administration of a single dose of 20 mg/kg of the drug or its equal solid dispersion. Blood was taken from the orbital sinus of the animal[13]. The hypoglycaemic response was then calculated as a percentage decrease in blood glucose levels as follows:

$$\%\ \text{Decrease in BLG} = \frac{\text{BLG at t = 0} - \text{BLG at t}}{\text{BLG at t = 0}} \text{X100}$$

The pharmacodynamic parameters taken into consideration were maximum percentage decrease in blood glucose level (E_{max}), time for maximum response (t_{max}), and area under percentage

decrease in BGL versus time curve ($AUC_{0–24h}$) which was calculated adopting the trapezoidal rule

Preparation of glipizide Immediate Release (IR) Tablet

The solid dispersion demonstrates highest solubility and dissolution rate was commixed with super disintegrate cross caramel lose sodium and lactose. The formulation was then compressed on a 16- station single rotary tableting press (Type – CMD3-16. Cadmach Machinery Pvt. Ltd., Ahamadabad) using an 8-mm standard flat punch by direct compression technique to produce glipizide tablets containing equivalent of 20 mg of *glipizide* (SD) product[14].

Quality control tests forglipizide IR tablets

The weight variation, hardness, friability, drug content, disintegration time, In vitro analysis of dissolution, were assessed for prepared tablets. The weight variation was estimated by weighing 20 tablets individually, assessing the average weight, and resolving the percentage variance of each tablet. Hardness was determined from tablets of each formulation using the Monsanto Hardness Tester. Friability was assessed by placing Ten pre-weighed tablets in the friability tester (VEEGO).

for 4 minutes at 25 rpm. After elimination of fines (using no. 60 mesh screen), the tablets were then reweighed and the percentage of friability was computed. Disintegration test was performed using a programmable tablet disintegration tester by using water as medium (LABINDIA-DT1000) and the time for the tablets to disintegrate was determined[15].

In-vitro dissolution test for glipizide immediate release (IR) tablets

The release of glipizide from IR tablets formulated by starch citrate was determined by the USP paddle-type Dissolution Tester (LABINDIA-DS8000) at 50 rpm. Using 900 ml of phosphate buffer, pH6.8 at a temperature of 37 ± 0.2°C. At 5, 15, 30, 45, 60 and 90minutes interims, 5 mL of sample were pipetting out, and replaced with an equal amount of fresh dissolution media to preserve sink condition.

The samples were filtered and spectro photo metrically analysed at 275 nm.The dissolution profiles were tested for the quantity of drug released in the initial 30 minutes (Q_{30}min) and time to release 50% of the drug (T_{50}). Other parameters like dissolution efficiency,

RESULTS AND DISCUSSION

Physical properties of the starch citrate

The starch citrate obtained from *Aponogeton* as reported to be a white, crystalline, non-hygroscopic powder. The physicochemical parameters of starch citrate are displayed in (Table 1). In both aqueous and organic solvents, it was insoluble. The pH of a 1 % aqueous dispersion was found to be 6.3. Starch citrate has no melting point, but it charred at 203^0C. Starch citrate has a bulk density of 0.721 g/cc and a tapped density of 0.806 g/cc, respectively. The compressibility index and angle of repose are 17 and 10.54, respectively, indicating satisfactory flow characteristics. Starch citrate swelled nicely in water. It was revealed that the swelling index was 1300. When native starch was heated, it hydrolyzed and turned to gel, while starch citrate did not.

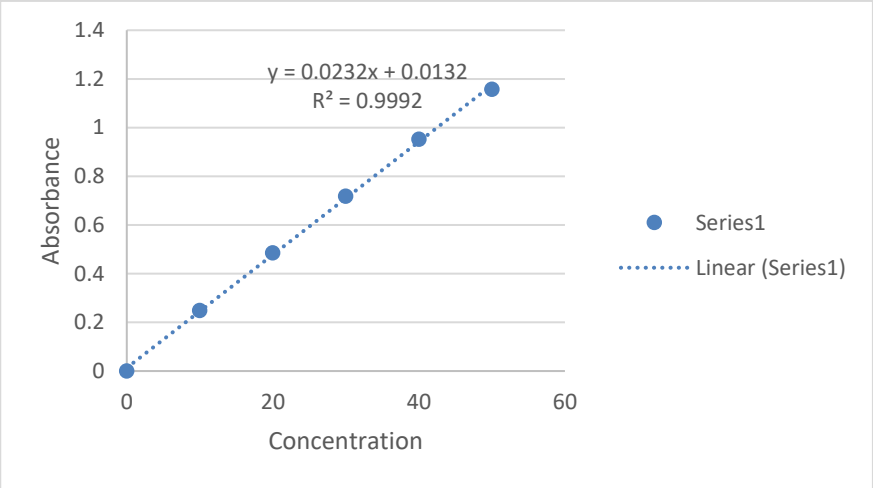
Table 1: Physical properties of the starch citrate

s.no.	Physical properties of the starch citrate	Results
1	Solubility	Insoluble in aqueous and all organic solvent tested
2	pH(1%w/v aqueous dispersion	6.3
3	Melting point	Charred at 203º C
4	Viscosity (1% w/v aqueous dispersion	1.12 CPS
5	Swelling index	1300
6	Gelling property	No gelling and swelling particles of the starch separated from the water
7	Moisture absorption	3.5
8	Bulk density	0.721 g/cc
9	Tapped density	0.806g/cc
10	Compressibility index	10.54 %
11	Angle of repose	17

In Acetonitrile: potassium hydrogen orthophosphate, the calibration curve of glipizide was prepared. At 275 nm, it showed maximum absorbance. In the concentration range of 10 to 50µg/ml, Glipizide obeyed Beer Lambert's law. The absorbance value at the corresponding concentration as seen in (Table 2) and the standard curve. in Fig.1. A correlation coefficient (r2) of 0.9992 was seen in the calibration curve and the straight line equation is y = 0.0232x + 0.01322 + 0.01322.

Table 2: Standard Graph of Glipizide

Serial no.	Concentration	Absorbance
1	0	0.000
2	10	0.249
3	20	0.486
4	30	0.718
5	40	0.953
6	50	1.157



"Figure 1: The standard curve of Glipizide"

Drug-Excipient Interaction Study

FTIR of glipizide with starch citrate The Characteristic FT-IR peaks of Glipizide appeared at 3351.49, 3322.24cm^{-1} (N-H stretching of Amide), 3030.62cm^{-1} (Aromatic C-H stretching), 2852.96cm^{-1} (methylene C-H asymmetric stretching), 1688.24 cm^{-1} (C=O stretch amide), 1648.48 cm^{-1} (C=O stretch urea) 1597.24 cm^{-1}(C=N stretch) 1533.24 cm^{-1} , 1526.56 cm^{-1}, 1484.00 cm^{-1} (aromatic C=C streching) , 1330 cm-1 (SO2NH stretching)1204.18 cm^{-1} (lactone C-O-C asymmetric bend), 1154 cm (cyclohexyl), 1076.12 cm^{-1} (lactone C-C symmetric bend), All the above peaks were also observed for the physical mixture of Glipizide with starch (1:1) and Glipizide with starch citrate (1:1). Hence there was no interaction between Glipizide and carriers used in the studyas shown in the (Fig. 2, 3, 4)

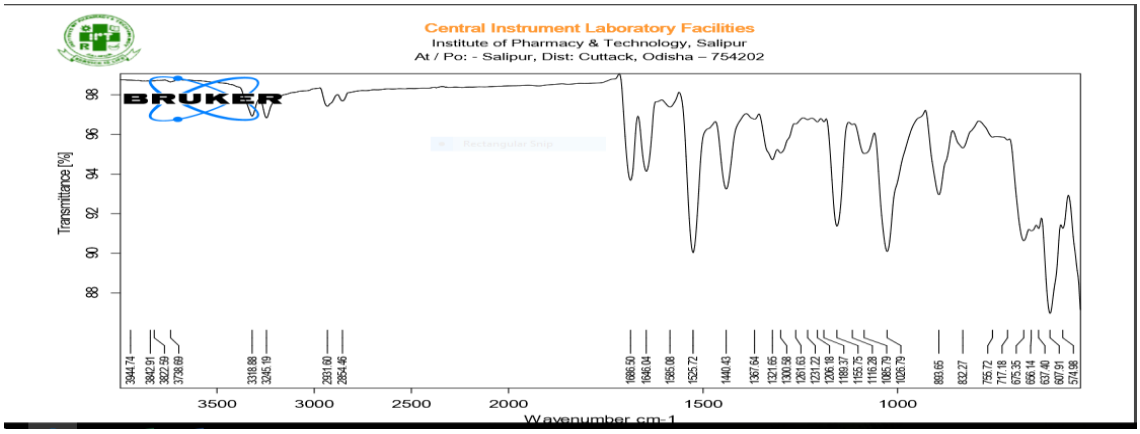


Figure 2: FTIR spectra of glipizide

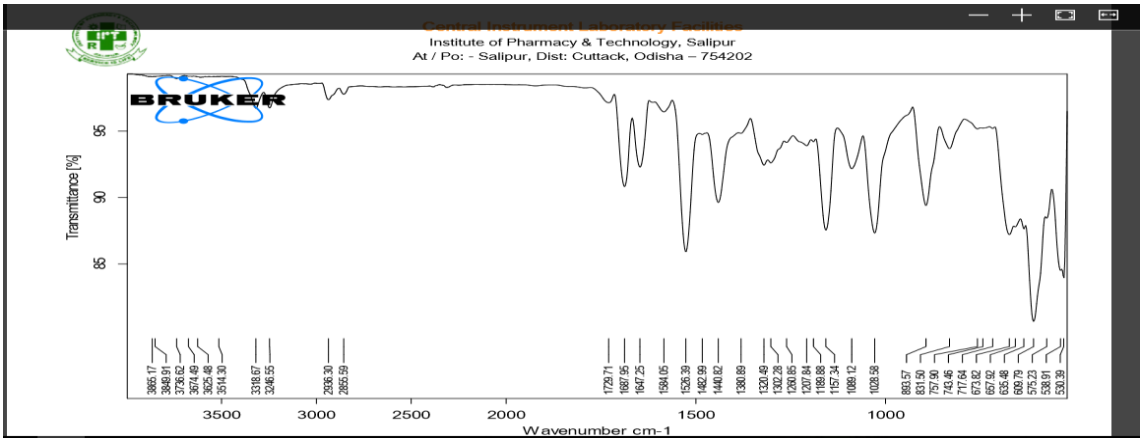


Figure 3: FT-IR study of glipizide with starch

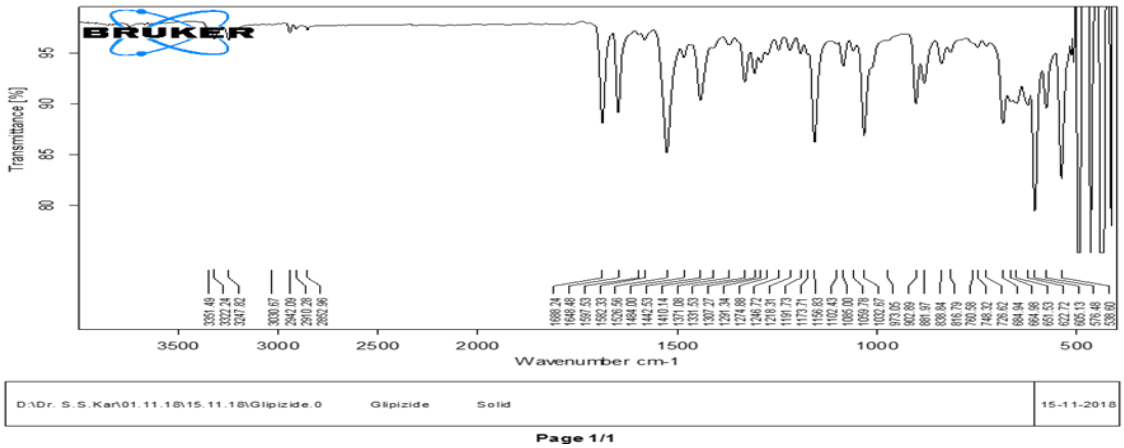
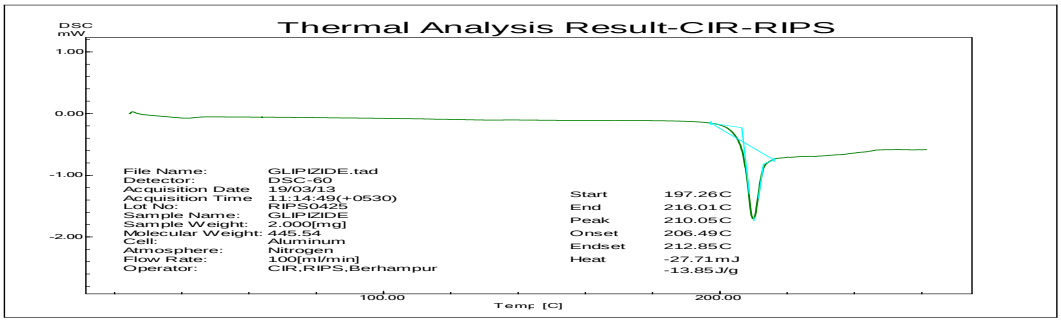


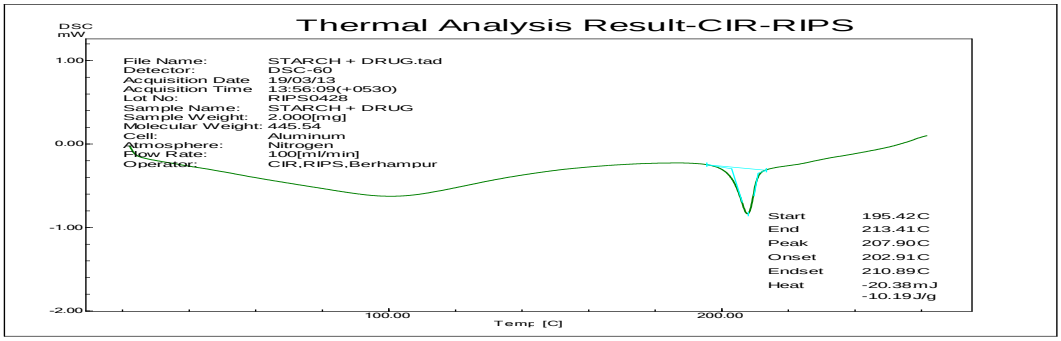
Figure 4: FTIR study of glipizide with starch citrate

Differential Scanning Calorimetry of glipizide with starch citrate

In the present study DSC was used to analyse the thermal behaviour of Glipizide and its physical mixture with starch citrate. At 210 ^{0}C, the Glipizide had shown a sharp melting peak that revealed that it is a pure and crystalline material. Fig.5 displays the DSC thermograms of the physical mixture of starch citrate. A sharp melting peak at 207.7^{0}C C reveals thatthere is also no association between the carriers and Glipizide in the present analyses which are shown in (Fig. 5, 6, and 7).



"Figure 5: DSC Spectra Of Glipizide"



"Figure 6: DSC Spectra of Glipizide with starch"

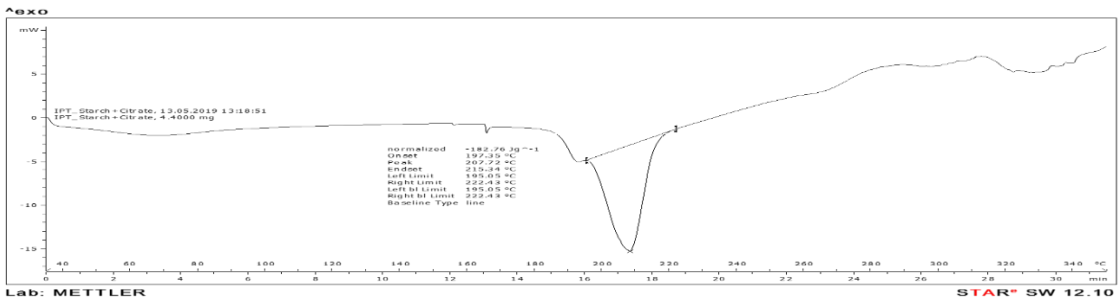


Figure 7: DSC Spectra of glipizide with Starch Citrate

Composition of glipizide solid dispersion

Solid dispersions were developed using the native starch of Aponogeton natans and its starch citrate in various drug to carrier ratios such as 1:1, 1:3, and 1:5 in order to improve solubility and dissolution rate. The composition of solid dispersions made by solvent evaporation is shown in (Table 3).

"Table 3: The composition of solid dispersions made by solvent evaporation."

Sl no	Formulations	Glipizide	Starch	Starch citrate
1	F1	1	1	
2	F2	1	3	
3	F3	1	5	
4	F4	1	-	1
5	F5	1	-	3
6	F6	1	-	5

Characterization of Formulations

The practical yield and drug content of Glipizide solid dispersions are shown in (Table 4). More than 99 %yield was observed in all the formulations. Drug content were found more than 97 %indicating uniform mixing of drugs with carriers.

Table 4: Practical Yield and Drug Content

Formulations	Practical Yield (%)*	Drug Content (%)*	Solubility* (µg/mL)
Glipizide	-	-	810 ± 4
F1	99.1 ± 2.2	98.5 ± 1.3	820 ± 7
F2	99.5 ± 1.5	99.2 ± 0.8	834 ± 3
F3	99.7 ± 1.3	97.2 ± 1.2	840 ± 4
F4	99.2 ± 2.3	97.1 ± 2.3	835 ± 2
F5	99.4 ± 2.1	97.3 ± 1.3	834 ± 3
F6	99.5 ± 1.3	98.1 ± 0.5	841 ± 2

* Mean ± SD, n=6

Flow ability and compressibility

The angle of repose, Carr's index (C.I), and Hausner's ratio (H.R) values for Glipizide drug powder indicate that it has poor flowability. However, the values of the above three parameters shown in (Table 5) indicate that all of the formulations have significantly improved flowability andcompressibility, indicating that they are suitable for tablet Formulation.

Table 5: Flowability and compressibility parameters of formulations

Formulations	Angle of Repose (^{0})*	Compressibility Index(%)*	Hausner' sratio*
Glipizide	32 ± 3	25 ± 1.5	1.15 ± 0.4
F1	17 ± 3	11 ± 2	1.05 ±0.2
F2	19 ± 2	10 ± 1	1.04 ±0.1
F3	18 ± 3	13 ± 2	1.0 ± 0.3
F4	21± 2	10 ± 3	1.01 ±0.4
F5	20± 1	12 ± 2	1.02±0.5
F6	21 ± 2	11 ± 1	1.01±0.4

* Mean ± SD, n=6

In-vitro dissolution test

The cumulative percentage of drug release from starch-based solid dispersion i.e. F1, F2, F3 is 40%, 55% and 62 %respectively as shown in (Fig.8). Cumulative percentage of drug release for the starch citrate based solid dispersion i.e.F4, F5, F6 is 71%, 87% and 100 %respectively. In case of Starch Citrate based solid dispersions (F4-F6) ,an increase in the dissolution rate was found with increase in the drug- carrier ratio as shown in (Fig. 9).This could be due to the uniform and homogeneous distribution of Glipizide in the Starch Citrate crust as a result of solid dispersion. In the case of solid dispersion prepared with Starch Citrate, i.e. in formulation F6, over 90% of the drug was dissolved in 30 minutes, whereas only 50% of the drug was dissolved in 30 minutes in Starch based solid dispersion, i.e. in formulation F3.The dissolution related parameters like Q_{30}, T_{50}, % DE_{30}, and MDT for all formulation are calculated and are provided in (Table 6).The percent dissolution efficiency in case of solid dispersion prepared with Starch Citrate, i.e. in F6 formulation, is 96.59%, while in case of solid dispersion prepared with Starch, i.e. in F3 formulation, is 65.23 %, indicating that the solid dispersion prepared with Starch Citrate has a higher dissolution efficiency than the solid dispersion prepared with starch. Lower MDT values For F6 formulation i.e.7.65 min were observed than F3, i.e. 17.37 min.

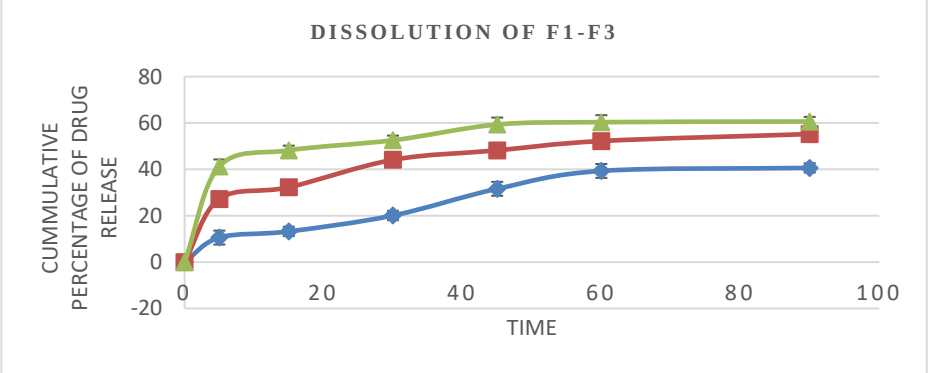
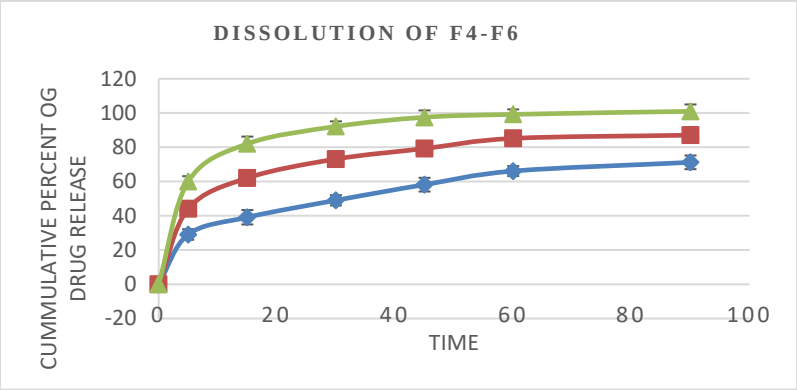


Figure 8: Dissolution of Glipizide solid dispersion prepared with starch



* Mean ± SD, n=6

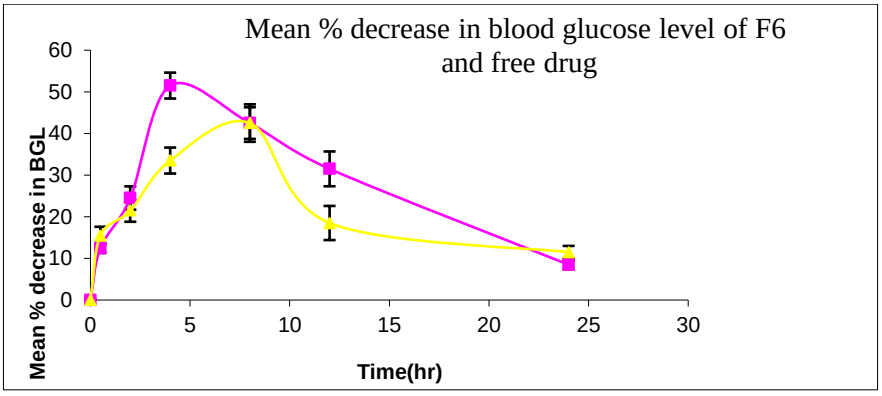
"Figure 9: Dissolution of Glipizide solid dispersion prepared with starch citrate"

Table 6: Dissolution parameter of glipizide solid dispersion					
Formulations	**Q_{30}**	**T_{50} (min)**	**% DE_{30}**	**MDT (min)**	**Hixson crowell cube root constant (r^2)**
F1	20.09	*	37.31	27.12	0.912
F2	44.11	45	54.45	22.71	0.923
F3	52.54	30	65.23	17.37	0.924
F4	49.05	30	67.43	15.23	0.935
F5	73.14	6	83.60	13.32	0.916
F6	93.16	4	96.59	10.65	0.941
* Mean ± SD, n=6					

Assessment of Therapeutic Efficacy

The percentage decrease in blood glucose following administration of F6 is higher ($p<0.001$) than the corresponding values of the free drug product at 12 and 24 hrs shown in (Fig. 10). The difference of maximum percentage decrease in blood glucose conc.between F6 and pure glipizide is extremely significant($p<0.001$) indicating that F6 has a stronger intensity of action than the free drug. With regard to the time period for a maximal percentage reduction in blood glucose level (tmax), it is obvious from results that the F6 has a lower tmax value than the free drug which suggest, the F6 has a quicker onset of action as compared to the free drug. There is a highly significant difference between the tmax value of F6 with that of the free drug ($p<0.01$).The Emax values for F6 are higher than the free drug values. As a result, F6 will have a marginally longer duration of effect than the glipizide. From area under percentage decrease in the bloodglucose level-time curve i.e.$AUC_{0\text{-}24h}$, it is clear that the F6 has a higher value than the free drug. The results demonstrated that the F6 shows greater bioavailability and improved therapeutic effectiveness relative to the free drug. The tmax, Emax, $AUC_{0\text{-}24h}$ and the mean % level decrease by the formulation F6 has been demonstrated in (Table 7, Fig. 10)

Table 7**:** The percentage decrease in blood glucose of F6 and free drug			
Formulations	t_{max}(h)	E_{max}(%)	$AUC_{0\text{-}24h}$
Free drug	8	42.5±4.23	535.65±11.5
F6(starch citrate based solid dispersion)	4	61.14±5.23	893.04±25.50
* Mean ± SD, n=6			



* Mean ± SD, n=6

"Figure :10 The percentage decrease in blood glucose"

Preparation of Tablets

The solid dispersions prepared with different carriers were evaluated for subsequent formulation into tablets. The most significant dissolution was reported in solid dispersions based on starch citrate. The F6 formulation was chosen for further tablet development because it demonstrated more than 90% drug dissolution in less than 30 minutes. The various formulations of the tablet were prepared with different concentrations of super disintegrant i.e. cross-caramellose sodium. One formulation was compressed without starch citrate based solid dispersion (F7). Cross carmellose sodium was added as a super disintegrating agent in various amounts 1, 2 and 3 percent of total tablet weight (F8-F10). The tablet composition is shown in Table 8

Table 8: Composition of Glipizide Tablets

Formulations	Glipizide(mg)	Starch citrate	CCS(mg)	Lactose(mg)	Talc(mg)	Total
F7	20	-	**6**	**171**	**3**	**200mg**
F8	20	100**mg**	2	**75**	**3**	**200mg**
F9	20	100**mg**	4	**73**	**3**	**200mg**
F10	20	100**mg**	6	**71**	**3**	**200mg**

Quality Control Tests for Tablets

The drug content values of Glipizide ensured uniform blending and mixing with starch citrate, cross-caramellose sodium, and lactose (97-99 %). The tablets have a hardness of 4.1 to 4.5 kg/cm2. The friability values ranges from 0.49 to 0.67 %, confirming that the tablets were not caped or laminated. All of the formulations passed the weight variation test, suggesting good and acceptable flow ability. Formulation F8 had a longer disintegration period of 11.3minutes, which could be attributed to the low disintegrate concentration.

As the amount of cross-caramellose sodium increased, the disintegration time of tablets reduced from 11.3 to 2.6 minutes (F8 to F10).This was due to cross-caramellose sodium's higher swelling and hydration ability. Table 9 summarizes the outcomes of the appraisal results

Table 9:Quality Control Tests of Glipizide tablets

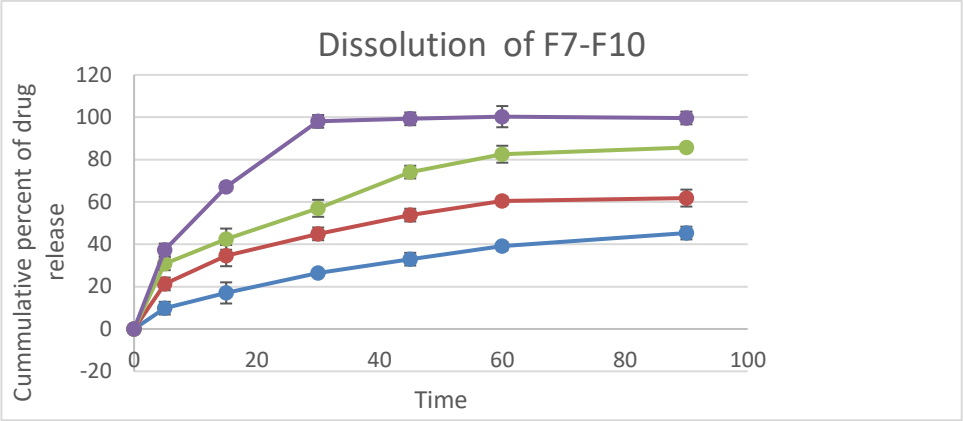
Formulation code	Hardness (Kg/cm^2)*	D.T. (min)*	Friability (%)*	Weight Variation	Drug Content (%)*
F7	4.1 ± 0.31	3.50 ± 1	0.61	PASS	99.01± 1.6
F8	4.3 ± 0.16	11.3± 1	0.49	PASS	98.4 ± 2.2
F9	4.5 ± 0.29	5.9 ± 0. 6	0.55	PASS	99.07 ± 3.1
F10	4.5 ± 0.52	2.60 ± 0.2	0.67	PASS	97.5 ± 1.2
* Mean ± SD, n=6					

In-vitro dissolution of glipizide immediate release tablet

Because of Glipizide's low solubility, in vitro dissolution tests with glipizide tablets produced without starch citrate, i.e. F7, revealed approximately 40% drug dissolution in 90 minutes. With solid dispersion, a remarkable dissolving rate of more than 90% in 30 minutes was reported in F6.However, when the same formulation was compacted into a tablet (F8), the rate of dissolution was significantly reduced due to a slower tablet disintegration time of 11.3 minutes. As a result, the surface area was constrained to the dissolution medium.

The dissolution rate increased as the proportion of cross-caramellose sodium increased (F8-F10) from 1 to 3%. In 30 minutes, the tablet formulation (F10) showed more than 99 % dissolution. For glipizide solid dispersion tablets, dissolution efficiency (% DE30), percent of the drug dissolved in 30 minutes (Q30), and time in which 50% of the drug dissolved (T50) were calculated (F8 to F10). Table 10 shows the measured values for each formulation. With an increase in the proportion of cross-caramellose sodium from 1% to 3%, the % DE30 rises from 20.09 to 99.41 over 30 minutes.

In comparison to pure glipizide products, Q30 values for F10 formulations showed a more than nine fold increase in dissolution rate.T_{50} values for pure drug glipizide could not be determined as only 27 % of drug dissolved in 2 hour of dissolution study. T50 was found to be the lowest for F10, of 7.36 minutes, indicating that the starch citrate-based immediate release tablet has a higher dissolving potential.



"Figure : 11 In –Vitro Dissolution of glipizide Immediate Release tablet"

Table 10: Dissolution parameters for glipizide tablet					
Formulations	**% DE_{30}**	**Q_{30}**	**T_{50} (min)**	**MDT(min)**	**Hixson Crowell's cube root constant (r^2)**
F7	20.09	--	37.38	27.12	0.912
F8	45.54	42	43.72	31.56	0.912
F9	90.13	87	9.07	21.37	0.945
F10	99.41	99	7.56	12.35	0.989
* Mean ± SD, n=6					

CONCLUSION

As a result of the foregoing research, it can be concluded that *Aponogeton natans* starch citrate can be used to improve the dissolution of a poorly water soluble drug called glipizide. The presence of cross-caramellose sodium as a super disintegrant also helped to improve the drug's dissolution. Among the carriers, starch citrate exhibited better solubility and dissolution enhancement potential than simple starch of *Aponogeton natans*.In-vivo study revealed nearly two times improvement in bioavailability of glipizide solid dispersion as that of pure drug.

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