



Research Article

FORMULATION DEVELOPMENT AND EVALUATION OF BIO-ADHESIVE CARBOPOL 974P NF POLYMER MATRIX BASED SUSTAINED RELEASE GLICLAZIDE TABLET

Md. Anisuzzman ^{*1}, Shaista Islam ², A.H.M. Arif-Ur-Rashid ¹, Md. Nazmul Alam ¹ and Amit Kumar Acharzo ¹

¹Pharmacy Discipline, Khulna University, Khulna-9208, Bangladesh

²University of Asia Pacific, Dhaka, Bangladesh

*Corresponding Author Email: jony5rija7@gmail.com

Article Received on: 03/03/17 Approved for publication: 20/04/17

DOI: 10.7897/2230-8407.080444

ABSTRACT

The aim of the present study was to develop a sustained release bio-adhesive matrix based Glliclazide tablet to match the *in-vitro* and *ex-vivo* experimental profile, and can be used to the treatment of Type II Diabetes Mellitus. It will be expected that single Glliclazide tablet reduce glycosylated hemoglobin and overcoming individual large fluctuation of oral bioavailability. Eleven types of tablets were formulated by wet granulation technique which contains 30 mg of Glliclazide and different concentrations of diverse bio-adhesive polymers which conforming to the USP/BP monograph. The prepared tablets were evaluated for their physicochemical parameters, bio-adhesive behavior and also *in-vitro* release pattern and *ex-vivo* residence time. Formulated F-6 tablet (300 mg) contains 30 mg Glliclazide, 90 mg Carbopol 974P NF, 155 mg Lactose, 15 mg Povidone, 5 mg Magnesium Stearate and 5 mg Talc. Carbopol based F-6 tablets showed highest significance adherence (164.1 gm) property and also exhibited greater than 300 minutes *ex-vivo* residence time. *In-vitro* release pattern of F-6 formulation was 44.74% (Mean Dissolution Time 52.86 hrs) which was studied for 8 hours in phosphate buffer media at pH 7.4. Different kinetic models including zero order, first order, Higuchi and Korsmeyer pattern were applied to evaluate drug release behavior. Zero order and Korsmeyer pattern indicated most appropriate model for describing the release profile of F-6 formulation. The drug release mechanism was consequently found to be diffusion, swelling and erosion. The results point out that Carbopol 974P NF bio-adhesive matrix Glliclazide tablets have marked sustained release properties.

Keywords: Glliclazide, Bio-adhesive Polymer, Sustained Release, Residence Time

INTRODUCTION

Diabetes mellitus is a global health crisis, which has been persistently affecting the humanity. Several drugs are available for this life threatening disease. Glliclazide is an oral hypoglycemic agent, classified as both first-generation and second-generation sulfonylurea which selectively binds to sulfonylurea receptors (SUR-1) to protect from hyperglycemia induced apoptosis and also revealed in an antiatherogenic effect in Type II Diabetes ¹⁻⁴.

Its conventional formulation requires twice daily administration. However, a new once daily Glliclazide modified release formulation has been found to be effective as twice daily Glliclazide to reduce the glycosylated hemoglobin (HbA1c) with fewer side effects and less risk of hypoglycemia. To design a muco-adhesive tablet with potential use in the treatment of Type II Diabetes Mellitus, different types and levels of bio-adhesive polymers will be investigated and evaluated for their efficacy in formulating Glliclazide (30 mg) dosage form. Glliclazide judiciously combined with different polymers e.g. HPMC 100 cps, Carbopol 974P NF, Eudragit NE 30D, and Sodium Alginate, and other excipients to achieve requisite bio-adhesion and physiochemical properties which ensure prolong residence in the gastrointestinal tract. Prepared granules were evaluated for their flow and compression characteristics prior to wet granulation compression. Then compressed tablets were subjected to various mechanical tests (thickness, diameter, friability and weight variation etc.) and *in-vitro* bio-adhesive properties were also evaluated to prove that the tested

parameters were found to be acceptable and compliant with BP/USP specifications. The dissolution profiles of the tablets were treated by model dependent methods so as to determine the dominant type of release pattern. Common sustained release mechanisms are diffusion, dissolution, osmotic, swelling, erosion, stimulation and mechanical methods etc. The concept of bio-adhesive drug delivery systems is based on the self-protecting mechanism. Our current research deals with improving the retention time in the GI tract and therefore contact time with the absorbing surface of Carbopol 974P NF bio-adhesive matrix based Glliclazide tablets in treatment of Type II Diabetes Mellitus.

MATERIALS AND METHODS

The active ingredient, excipients and other materials are used to prepare Glliclazide 30 mg sustained release tablet (Table 1).

Reference Product

For experiment, ADMIRA MR (Glliclazide 30 mg) tablet manufactured by Unimed & Unihealth Manufacturers Ltd. is considered as reference listed drug (RLD).

Formulation

In this research work, Glliclazide 300 mg sustained release matrix tablets are formulate by using different bio-adhesive polymers to measure the actual amounts in each formulated tablet.

Granules Preparation

At first, active drug and different additives were appropriately weighed and mixed together by hand for 10 minutes. Then binding solution was prepared by using Povidone and Isopropyl Alcohol which added continuously drop by drop to the dry mixture and continued for further 10 minutes after all the binding solution has been added. Then wet mass was dried in an oven for 30 minutes at 60 °C, and then passed through a 22 mesh sieve to obtain very fine particles. Finally, declared quantities of talc and mg stearate mixed to the formed granules and sieved through a 40 mesh screen to obtain granules with the pre-requisite flow properties.

Matrix Tablet Preparation

At first individually measured granules fed into the die punch cavity then 2.5 tons pressure was applied for 2 minutes for compression.

Evaluation of Prepared Granules

Physical properties of granules such as bulk density, compressibility index, Hauser's ratio and angle of repose were evaluated as per reference ⁵⁻⁷.

Evaluation of Physicochemical Properties of Matrix Tablets

The formulated tablets were assessed for average weight, diameter, thickness, hardness, friability and drug content ⁸. *In-vitro* dissolution study, *ex-vivo* muco-adhesive strength and *ex-vivo* residence time were also evaluated ⁹⁻¹⁰.

In-vitro Dissolution Study

Dissolution study of Gliclazide sustained release matrix tablets was carried out according to the process outlined by Hermann et al. ⁹. Dissolution studies were conducted according to the USP method (USP XXII) using apparatus 2. In all cases, the rpm was maintained at 100 while the temperature maintained always at 37± 0.5 °C in dissolution vessels. Into each of the six vessels, 900 ml of the prepared buffer was poured. The dissolution machine was then set up with paddles and the tablets directly placed in the dissolution vessel. The dissolution machine was then started and 10 ml of sample was withdrawn after 1 hr, 2 hrs etc. time interval. At each withdrawal, 10 ml of fresh dissolution medium was immediately added to maintain the sink condition. The dissolution was carried out for 8 hrs. This was done to get a simulated picture of drug release in the *in-vivo* condition. The withdrawal sample was first filtered and then diluted before being assayed at 225.5 nm using UV spectrophotometer. The amount of drug released was calculated with the help of a straight line equation, obtained from the standard curve of Gliclazide at the same λ_{max} . The drug release percentage was calculated and plotted against time. This drug release profile was fitted into several mathematical models to get an idea of the release mechanism of the drug from the dosage form.

Preparation of Standard Curve

Standard solution of Gliclazide was prepared in different concentration range between 2 and 20 µg/ml. Phosphate buffer (pH 7.4) used as solvent to ensure complete dissolution of the active drug into media. The prepared standard solution was placed in the sonicator for few minutes. The absorbance of this standard solution was then observed in the double beam spectrophotometer at 225.5 nm. From the observed absorbance, the standard curve of Gliclazide was prepared.

Determination of *Ex-vivo* Muco-adhesive Strength

The *ex-vivo* muco-adhesion strength was estimated according to the method of Krishnarajan *et.al.* ¹⁰. Firstly, fresh excised pieces of goat intestinal mucosa was washed with distilled water and then with phosphate buffer (pH 7.4) at 37 °C. With the help of cyanoacrylate glue, it was then attached to an open petri dish and constantly wetted by adding single drop of the buffer of the stated pH. Then tablet was made to adhere to the flat end of a syringe by means of cyanoacrylate glue again and a nylon rope was attached to the other end of which a plastic bottle cap was suspended. The whole arrangement was hung from the clamps of a burette stand. While suspended, the end surface of the syringe tablet lightly pressed on to the mucosal tissue specimen and held there for 2 minutes. When suitable adhesion had taken place, the plastic cap was slowly loaded with calibrated weights and the load at which the tablet shot free of the tissue specimen was considered to be an estimate of its muco-adhesive strength using the formula:

$$\text{Force of adhesion} = (\text{muco-adhesive strength} \times 9.81) \div 1000$$

Determination of *Ex-Vivo* Residence Time

The *ex vivo* muco-adhesion time was studied according to method stated by Puratchikody *et.al.* ¹¹ with slide modification. At first excising freshly cut intestinal mucosa (4 x 3 inches) from the goat and then fixing them into inner side of a beaker with cyanoacrylate glue. Then formulated tablet pressed onto wet rinsed tissue specimens with a light force for 30 seconds. Once suitable adhesion had taken place, the beaker was filled with 750 ml of phosphate buffer (pH 7.4) and immediately transferred to the disintegrating machine where tissue specimen given a slow, regular up and down movement to simulate the duodenal area movement. Then film adhesion for five hours and time required for the film to detach from the goat intestinal mucosa was monitored that recorded as the muco-adhesion time.

Successive Fractional Dissolution Time

To characterize the drug release rate in different experimental conditions, $T_{25\%}$, $T_{50\%}$ (mean dissolution time) and $T_{80\%}$ was calculated by the equation of $T_{25\%} = (0.25/K_k)^{1/n}$, $T_{50\%} = (0.5 / K_k)^{1/n}$, $T_{80\%} = (0.8 / K_k)^{1/n}$ respectively. Mean Dissolution Time can be calculated by the following equation-

$$\text{MDT} = (n/n+1). K^{-1/n} \quad 12.$$

Stability Analysis

Stability study was performed due to fix the shelf-life of the prepared tablets and to confirm the valid formulation. The international conference on harmonization (ICH) guideline has been used to develop valid accelerated testing method. Formulated tablets were studied at 40 °C± 2 °C temperature and relative humidity 75%±5% and at 30 °C±2 °C temperature and relative humidity 65%±5% for 3 and 6 months respectively. After 3 and 6 months' the formulated tablets were tested as per instructions ¹³.

RESULT

The physicochemical properties of the prepared granules and blend powders of different formulations (F1–F11) were passed through 22 and 40 mesh size subsequently. Bulk density result ranged from 0.408 to 0.588 gm/cm³ while the tap densities ranged from 0.435 to 0.625 gm/cm³. Formulation F-6 showed higher compressibility index value 16.327%, higher Hausner ratio 1.195 and also estimated lower angle of repose 30.964°

value (Table 2). Estimated physical properties of formulated granules met the U.S Pharmacopeia standard for wet granulation tableting. In case of all formulated tablets, the average weight variation ranged from 0.297 to 0.301 mg, average thickness ranged between 2.67 and 2.96 mm, average diameter ranged from 10.0 to 10.09 mm, hardness ranged from 7.82 kg to 26.74 kg, friability varied from 0.11 to 0.6%, radial tensile strength and axial tensile strength ranged were 0.19 to 0.62 kg/mm² and 0.10 to 0.34 kg/mm² respectively (Table 3). The F-6 formulated tablets showed the greatest hardness and negligible variation of average weight, thickness, diameter, friability and also showed highest significant radial tensile strength and axial tensile strength value. Formulations bearing increased polymer concentration Carbopol 974P NF and Eudragit NE 30D were observed to increase in bio-adhesive strength and retained for longer than five hours which ensure escalation of *ex-vivo*

residence time (Table 4). The high values of R² (R² near about 0.999) indicate the best fitted models for the respective formulations (Table 5). The dissolution data of F-6 was the best fitted in Zero order and Korsmeyer models (Table 6 and Figure 5, 8) where swelling and erosion are thought to play the leading role for Zero order release kinetics to be dominant. In general, formulations bearing Carbopol 974P NF showed the highest MDT while those containing HPMC 100 cps were comparatively low (Figure 9). A higher value of MDT indicates a higher drug retaining ability of the polymer and vice versa. Rest of the formulated batch revealed the Pharmacopeias specifications. Average weight was gained during storage condition while drug content was insignificantly changed after 3 and 6 months which met the specifications as per ICH guidelines (Table 8).

Table 1: Formulation of Gliclazide Sustained Release Matrix Tablets

Formulation	Drug mg	HPMC 100 cps mg	Carbopol 974P NF mg	Eudragit NE 30D mg	Na Alginate mg	Lactose mg	Povidone mg	Mg Stearate mg	Talc mg	Total tablet mg
F-1	30	30				215	15	5	5	300
F-2	30	60				185	15	5	5	300
F-3	30	90				155	15	5	5	300
F-4	30		30			215	15	5	5	300
F-5	30		60			185	15	5	5	300
F-6	30		90			155	15	5	5	300
F-7	30			30		215	15	5	5	300
F-8	30			60		185	15	5	5	300
F-9	30				30	215	15	5	5	300
F-10	30				60	185	15	5	5	300
F-11	30				90	155	15	5	5	300

Table 2: Physicochemical Properties of Prepared Granules

Formulation	Bulk Density (g/cm ³)	Tapped Density (g/cm ³)	Compressibility Index (in per cent)	Hausner Ratio	Angle of Repose (Degree)
F-1	0.533	0.571	6.667	1.071	42.614
F-2	0.500	0.533	6.250	1.067	38.660
F-3	0.476	0.500	4.762	1.050	34.216
F-4	0.500	0.556	10.000	1.111	35.754
F-5	0.444	0.513	13.333	1.154	34.216
F-6	0.408	0.488	16.327	1.195	30.964
F-7	0.408	0.435	6.122	1.065	38.660
F-8	0.381	0.417	8.571	1.094	35.754
F-9	0.588	0.625	5.882	1.063	37.235
F-10	0.571	0.615	7.143	1.077	35.754
F-11	0.556	0.597	6.944	1.075	34.216

Table 3: Physicochemical Properties, Radial Tensile Strength and Axial Tensile Strength of Compressed Tablets

Formulation	Average Weight (gm)	Average Diameter (mm)	Average Thickness (mm)	Friability (in per cent)	Hardness (Kg)	Radial Tensile Strength (kg/mm ²)	Axial Tensile Strength (kg/mm ²)
F-1	0.297	10.00	2.67	0.39	7.82	0.19	0.10
F-2	0.300	10.09	2.91	0.44	9.96	0.22	0.12
F-3	0.299	10.06	2.92	0.49	12.64	0.27	0.16
F-4	0.299	10.01	2.85	0.49	12.91	0.29	0.16
F-5	0.300	10.00	2.79	0.23	18.9	0.43	0.24
F-6	0.299	10.01	2.75	0.11	26.74	0.62	0.34
F-7	0.301	10.00	2.96	0.17	9.41	0.20	0.12
F-8	0.300	10.01	2.94	0.16	10.2	0.22	0.13
F-9	0.299	10.02	2.75	0.50	11.04	0.26	0.14
F-10	0.301	10.01	2.74	0.54	9.8	0.23	0.12
F-11	0.298	10.01	2.71	0.60	8.94	0.21	0.11

Table 4: Muco-adhesive Parameters and General Appearance of Different Formulated Tablets

Formulation	Mucoadhesive force (g)	Force of adhesion (N)	Ex vivo residence time (min)	General appearance of formulated tablet
F-1	71	0.697	> 300	No displacement of the tablets from the initial point, only swelling occurs.
F-2	50	0.491	> 300	
F-3	40	0.392	> 300	
F-4	118.05	1.158	> 300	
F-5	120	1.177	> 300	
F-6	164.1	1.610	> 300	Very much swelling occurs and thickness of tablet was increased but no displacement of the tablets from the initial point.
F-7	70	0.589	> 300	Not swelling and displacement of the tablets from the initial point.
F-8	60	0.687	> 300	
F-9	60	0.589	125	Displaced of tablet
F-10	20	0.196	115	Displaced of tablet
F-11	15	0.147	85	Disintegration of tablets without displacement from the initial point.

Table 5: Release Rate Constants and R² Values for Different Release Kinetics of Formulated Drugs

Formulation	Zero order		First order		Higuchi		Korsmeyer			MDT
	K _o	R ²	K ₁	R ²	K _H	R ²	R ²	K _k	n	
F-1	8.417	0.706	-0.158	0.614	28.775	0.888	0.833	0.531	0.232	6.20
F-2	9.574	0.886	-0.150	0.611	30.148	0.945	0.931	0.030	0.474	6.79
F-3	9.18	0.950	-0.078	0.962	28.239	0.967	0.973	0.050	0.697	10.74
F-4	8.043	0.884	-0.072	0.837	24.636	0.892	0.763	0.275	0.409	2.89
F-5	8.609	0.984	-0.065	0.931	25.056	0.897	0.946	0.123	0.795	30.39
F-6	5.391	0.994	-0.031	0.982	15.744	0.912	0.974	0.075	0.817	52.56
F-7	7.481	0.917	-0.057	0.972	23.714	0.992	0.977	0.243	0.483	6.11
F-8	3.255	0.959	-0.017	0.971	9.960	0.967	0.945	0.087	0.538	32.8
F-9	7.952	0.911	-0.665	0.927	24.494	0.930	0.785	0.269	0.423	6.66
F-10	5.647	0.794	-0.039	0.894	18.919	0.959	0.972	0.299	0.297	11.72
F-11	5.720	0.925	-0.036	0.959	17.858	0.971	0.924	0.180	0.477	13.31

Table 6: Release Mechanisms and Best Fitted Model of Formulated Matrix Tablet

Formulation	Best fitted models	n value Korsmeyer model	Release mechanism
F-1	Higuchi and Korsmeyer	0.232	Diffusion
F-2	Higuchi	0.474	Both diffusion and erosion
F-3	Korsmeyer	0.697	Both diffusion and erosion
F-4	Higuchi	0.409	Diffusion
F-5	Korsmeyer and Zero order	0.795	Both diffusion and erosion
F-6	Korsmeyer and Zero order	0.817	Both diffusion and erosion
F-7	Higuchi	0.483	Both diffusion and erosion
F-8	Higuchi	0.538	Both diffusion and erosion
F-9	Higuchi	0.423	Diffusion
F-10	Korsmeyer	0.297	Diffusion
F-11	Higuchi	0.477	Both diffusion and erosion

Table 7: Release Profile of F-6 Formulation Tablets

Zero Order release profile		First Order release profile		Higuchi release profile		Korsmeyer release profile	
Time h	Cumulative % Release	Time h	Log % of Drug Remaining)	SQRT h	Cumulative % Release	Log h	Log % release
0 h	0	0h	2	0 h	0	0	0
1 h	8.61	1 h	2	1	8.61	0	0.93
2 h	11.98	2 h	1.96	1.414	11.98	0.301	1.08
3 h	16.62	3 h	1.94	1.732	16.62	0.477	1.22
4 h	21.31	4 h	1.92	2	21.31	0.602	1.33
5 h	27.28	5 h	1.90	2.236	27.28	0.699	1.44
6 h	32.09	6 h	1.86	2.449	32.09	0.778	1.51
7 h	39.81	7 h	1.83	2.646	39.81	0.845	1.60
8 h	44.74	8 h	1.78	2.828	44.74	0.903	1.65

Table 8: Stability Analysis Data of F- 6 Formulation Tablets

Frequency of analysis		1 st Month	3 rd Month		6 th Month	
Date of analysis		16.11.15	16.02.16		16.05.16	
SIN	Parameters	Initial Result	30 ⁰ C / RH 55%	40 ⁰ C / RH 75%	30 ⁰ C / RH 65%	40 ⁰ C / RH 75%
1	Physical Appearance	Complies	Complies	Complies	Complies	Complies
2	Average Weight	299.9 mg	300.00 mg	300.0 mg	300.1 mg	300.1 mg
3	Hardness	27.11 kg	27.00 kg	27.08 kg	26.64 kg	26.49 kg
4	Friability	0.08 %	0.09 %	0.11 %	0.11 %	0.12 %
5	Ex-vivo Residence Time	>300	>300	>300	>300	>300
6	Mucoadhesive Strength	163.9	163.4	164.2	164.1	163.9
7	MDT	52.56 hours	52.40 hours	52.51 hours	52.57 hours	52.50 hours
8	Assay	30.08 mg	29.97 mg	30.09 mg	30.02 mg	30.05 mg

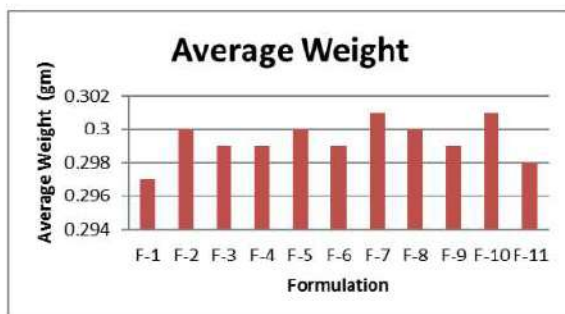


Figure 1: Average weight of formulated tablets

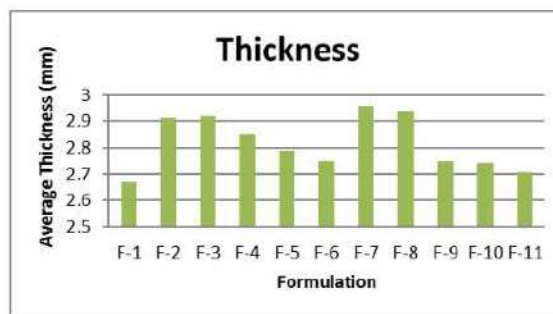


Figure 2: Average thickness of formulated tablets

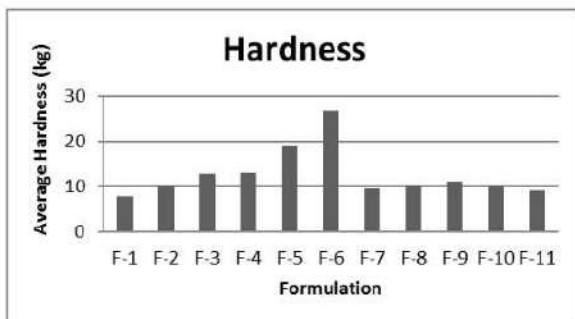


Figure 3: Average hardness of formulated tablets

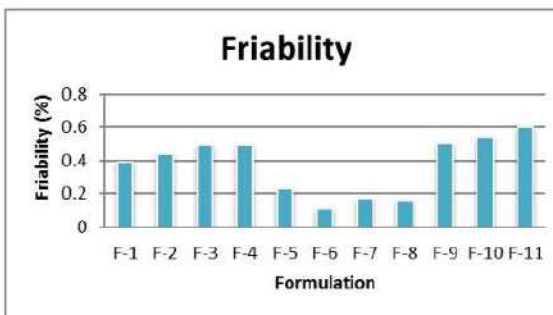


Figure 4: Friability value of formulated tablets

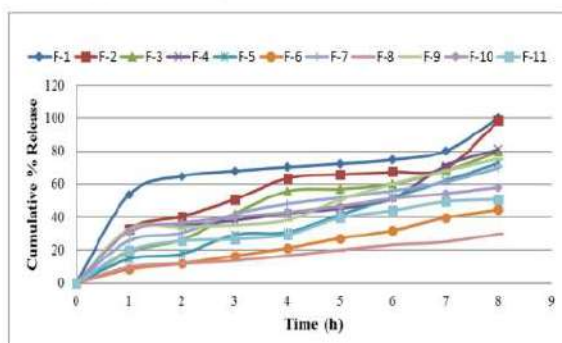


Figure 5: Zero order release profile of formulated tablets

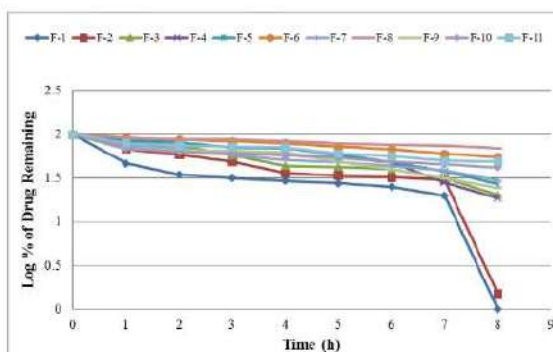


Figure 6: First order release profile of formulated tablets

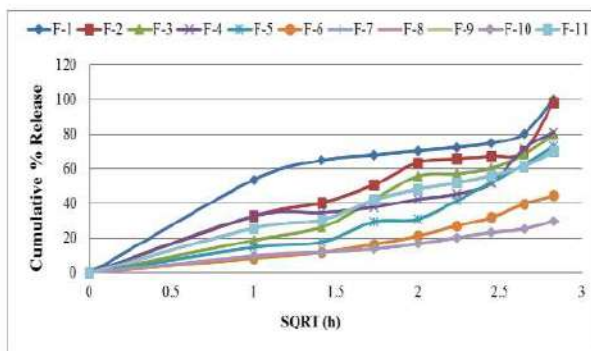


Figure 7: Higuchi model analysis of formulated tablets

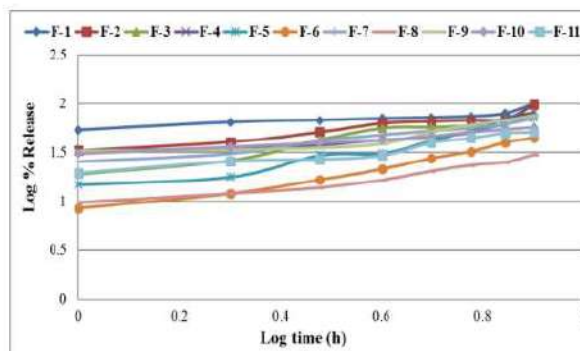


Figure 8: Korsmeyer-Peppas model analysis of formulated tablets

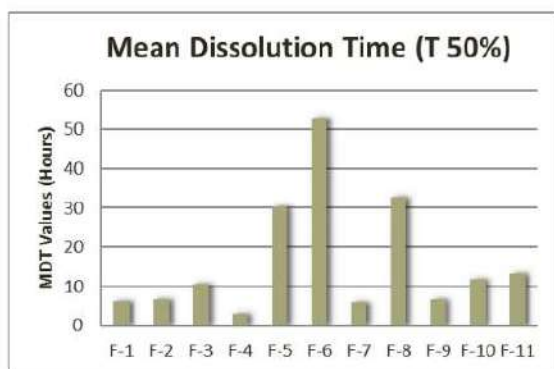


Figure 9: Mean dissolution time (MDT) of formulated tablets

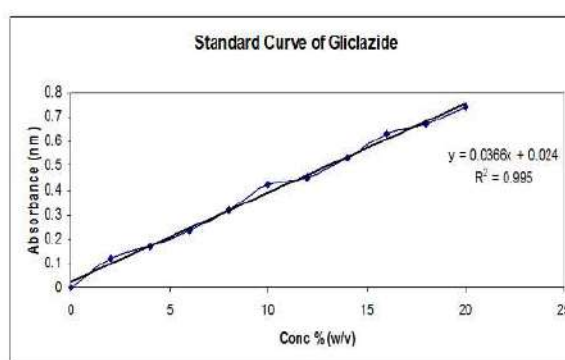


Figure 10: Standard curve of Glucoside solution

DISCUSSION

Glucoside is an effective and inexpensive oral hypoglycemic agent that is widely used to the treatment of Type II Diabetes Mellitus. A new once daily Glucoside modified release formulation has been found to be effective as twice daily dose in reducing glycosylated hemoglobin (HbA1c) with fewer side effects and less risk of hypoglycemia. The aim of this research paper is to develop a dosage form that not only shows sustained release but also bio-adhesive in nature. Eleven possible formulations have proposed, using four different bio-adhesive polymers. The combinations of excipients with different concentration of HPMC 100 cps, Carbopol 974P NF, Eudragit NE 30D, and Sodium Alginate polymer plays on the physiochemical properties of dosage form which sufficiently involve in sustain release and bio-adhesive properties of the tablet. The estimated micrometric properties of granules ensure satisfied level for compression of the matrix tablets by wet granulation method. Formulations containing Carbopol 974P NF polymer showed higher bulk density and lower tapped density with increase in concentration. This could be possibly due to the fact that the higher percentages of specific polymer usually leads to growth in mean particle size which causes a higher volume to be occupied by the granules. The lower value of angle of repose of formulations showed moderate flow properties¹⁴. Carbopol 974P NF polymer increased flow property of granules when used upsurge amount while the percentage of lactose was decreased. In case of F-6, angle of repose was 30.964° due to lower amount of lactose. Hausner ratio of F-6 formulation was 1.195 which indicates good flow-ability (<1.20)¹⁵. Compressibility Index of greater than 25% is considered to be an indication of poor flow-ability and below 15% an indication of good flow-ability of powders¹⁶. The granules of most of the formulations exhibited a compressibility index of less than 15%,

thus depicting satisfactory flow-ability. Only formulation F-6 show a slightly higher compressibility index of 16.327 % but that too is within the stated range of 25%. Thus, we find a very good correlation. The average weight of the tablets was practically found to be remarkably consistent and somewhat uniform, which approximated to 300 mg. The average diameter was also found to be pretty much consistent varying insignificantly, the friability values for none of the formulations exceeded 1%¹⁷. The average thicknesses of the tablets were not alarming and remained within the acceptable range. All formulation showed greater than 5 Kg hardness which was considerably accepted¹⁸. The tablets of F-6 had the greatest hardness (26.74 Kg). The presence of 10% Carbopol 974P NF claimed good hardness. Hardness, diameter and thickness of the tablets are factors of radial tensile strength and hardness and diameter measures for the axial tensile strength^{19,20}. The lowest value of radial tensile strength had been seen formulation requiring less force to break up while highest values formulation F-6 requiring most breaking force. In general, as the Carbopol 974P NF polymer concentration of a particular polymer rises, the radial tensile strength was seen to increase. The axial tensile strength followed the same trend as the radial tensile strength. *Ex-Vivo* residence time will correlate to the *in-vivo* muco-adhesive strength and force of adhesion performance of the dosage form. As the muco-adhesive strength and force of adhesion was seen to increase, *ex-vivo* residence was also observed to rise because stronger binding between the tablet and gastrointestinal mucosa so retained on the gastrointestinal mucosa for a long time. F-6 formulation bearing Carbopol 974P NF was observed to increase in bio-adhesive strength due to function of its own contact time with mucus, swelling rate of the polymer and the biological membrane. Mean dissolution time (MDT) value used to characterize the drug release rate from the dosage form and the retarding efficiency of the polymer. A

higher value of MDT indicates a higher drug retaining ability of the polymer and vice versa. The MDT value was also found to be a function of polymer loading, polymer nature and physicochemical properties of the drug molecule ²¹. *In-vitro* release studies demonstrated that the release of Gliclazide from all tablet formulations was generally sustained. The dissolution data of F-6 was the best fitted in Zero order and Korsmeyer models where swelling and erosion mechanisms are thought to play the sustain release. Most formulations physical parameters were unchanged while little bit change in disintegration and dissolution time which comply with standards set by pharmacopoeias during the accelerated stability test. Among the eleven formulations, F-6 formulation finally select as bio-adhesive matrix polymer based sustain release dosage form of Gliclazide tablet due to appreciable bio adhesive strength, *ex-vivo* residence time and physical parameters which comply with the standards set by pharmacopoeias.

ACKNOWLEDGEMENT

The authors are thankful to the faculty, management and laboratory staff of Pharmacy Discipline, Khulna University and University of Asia Pacific, Bangladesh for providing the all facilities.

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Cite this article as:

Md. Anisuzzman *et al.* Formulation development and evaluation of bio-adhesive Carbopol 974p NF polymer matrix based sustained release gliclazide tablet. *Int. Res. J. Pharm.* 2017;8(4):28-34 <http://dx.doi.org/10.7897/2230-8407.080444>

Source of support: Nil. Conflict of interest: None Declared

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