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FORMULATION AND EVALUATION OF GASTRORETENTIVE MUCOADHESIVE TABLET OF GLICLAZIDE BY USING SYNTHETIC POLYMERS

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Abstract:
Gliclazide is a oral anti hyperglycemic agent used to treat non-insulin dependent diabetes mellitus. Aim of the present work is to formulate and evaluate mucoadhesive tablet of Gliclazide by using synthetic polymers like HPMC K4M, and carbopol 940. The tablets were formulated by Direct compression method and then evaluated pre-compression and post compression such as hardness, friability, thickness, weight variation, drug content, drug release, FTIR, mucoadhesive strength. Polymers and drug have no interactions in IR. The formulation were found to have good preformulation characteristics. Formulation (F3) showed good mucoadhesive strength (22.720g) and maximum drug release of 57.4 % in 10 h. The drug content shown 96.56%. All the evaluation parameters given the positive result and comply with the standards. Advantage of mucoadhesive tablet is increase the residence time and control the release of drug as well as inhence bioavailability. It also improve patient compliance, drug efficacy, and therapeutic effects .

Keywords: *Gliclazide, mucoadhesive tablet, in vitro drug release,*

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INTRODUCTION:

The primary goal of sustain drug delivery system is to deliver drug for longer period of time to achieve better bioavailability, which should be predictable and reproducible. But it is difficult due to the number of physiological problems such as fluctuation in the gastric emptying process, narrow absorption window and stability problem. To overcome these problems, different approaches have been proposed to retain dosage form in stomach. These include mucoadhesive systems, swelling and expanding systems, floating system, and other delayed gastric emptying devices. [1,2]

Gastric mucosa is the preferred site for both system local and systemic action. The mucosa has a rich blood supply and relatively permeable. In the mucoadhesive drug delivery systems mucoad hesion is the key element. In this adhesion ability of a biological or synthetic material to stick to a mucus membrane, resulting in adhesion of the material to the tissue for a protracted period of time. Various binding agents can be useful in achieving various tablet mechanical strength and drug release.[3]

Gliclazide bind to the β cell sulfonyl urea receptior (SUR1). This binding blocks the ATP sensitive potassium efflux leads to depolarization of the β cell. This opens voltage- dependent calcium channels in the β cell resulting in calmodium activation, which in turn leads to exocytosis of insulin. [4]

MATERIALS AND MATERIALS:

List of Material Used

S. No.	Name	Supplier/Manufacturer
1.	Gliclazide	Gift Sample from Pharmaceuticals
2.	Methanol	Central Dug House Pvt. Ltd
3.	HPMC K4M	Central Dug House Pvt. Ltd
4.	Carbopol 940	Central Dug House Pvt. Ltd
5.	MCC	Central Dug House Pvt. Ltd
6.	Lactose	Central Dug House Pvt. Ltd
7.	Talc	Central Dug House Pvt. Ltd
8.	Magnesium Stearate	Central Dug House Pvt. Ltd
9.	Hydrochloride	Central Dug House Pvt. Ltd

Formulation of Mucoadhesive Tablets:

In the case of prepared tablet, the method of direct pressing is used. Gliclazide was mixed together different ingredients according to formula. The powder mixture was then lubricated with magnesium stearate and compressed with on a tablet punching machine. Micro crystalline cellulose and lactose was used to keep the tablet weight constant and optimize poor solubility of the drug.

Formulation of mucoadhesive tablets of gliclazide:

All quantities in mg/tablet

Batches	HPMC K4M	Carbopol 940	Micro C.C.	Lactose	Talc	Magnesium Stearate	Drug	Total
F1	**60**	**45**	**58**	**37**	**10**	**10**	**80**	**300**
F2	**45**	**30**	**40**	**85**	**10**	**10**	**80**	**300**
F3	**75**	**30**	**40**	**55**	**10**	**10**	**80**	**300**
F4	**45**	**60**	**40**	**55**	**10**	**10**	**80**	**300**
F5	**75**	**60**	**40**	**25**	**10**	**10**	**80**	**300**
F6	**45**	**60**	**76**	**19**	**10**	**10**	**80**	**300**
F7	**35**	**45**	**58**	**62**	**10**	**10**	**80**	**300**
F8	**85**	**45**	**58**	**12**	**10**	**10**	**80**	**300**
F9	**60**	**70**	**58**	**12**	**10**	**10**	**80**	**300**

Evaluation tests

Precompression parameters: [5]

1) Bulk density
2) Tapped density
3) Angle of repose
4) Hasusner's ratio
5) Carr's consolidation index

1) Bulk density:

It is the ratio of total mass of powder to the bulk volume of powder. Accurately weighed batch (F1 – F9) powder was placed in 10 mL graduated measuring cylinder. Initial volume was observed. The $D_b$andwas calculated in gm/ mL using following formulae,

$$D_b = M/V_b$$

Where, D_b = Bulk density

M = Mass of the powderV_b = Bulk volume of powder

2) Tapped density:

Accurately weighed batch (F1 –F10) powder was placed in 10 mL graduated measuring cylinder. The cylinder was tapped initially 100 times from a distance of 14 + 2 mm. The tapped volume was measured to the nearest graduated unit. Again, the tap volume was measured to the nearest graduated unit. The $D_t$were calculated in g/ mL using following formulae,

$$D_t = M/V_t$$

Where, D_t = Tapped density

V_t = Tapped volume of the powder

D_t = Tapped density
M = mass of the powder

3) Angle of repose:

Good flow properties are critical for the development of any pharmaceutical tablets, capsule or powder formulations. Angle of repose is defined as the maximum angle possible between the surface of the pie of powder and horizontal plane. It is performed to determine the flow property of powder done by the funnel method. The powder mass was allowed to flow through the funnel orifice, kept vertically to a plane paper kept on horizontal surface, giving a heap angle of powder on a paper. The diameter of the powder cone was measured and angle of repose was calculated using the following equation

$$\text{Tan } \theta = h/r$$

Where, h and r are the height and radius of the powder cone, respectively.

4) Hasusner's ratio:

Hasusner's ratio carried out by tapped density divided bulk density.

Hasusner's ratio = Tapped Density/Bulk Density

5) Carr's consolidation index:

Carr developed an indirect method of measuring powder flow from bulk densities. The % compressibility of the powder was direct measure of the potential powder arch or bridge strength and stability. Carr's index of each formulation was calculated using thegiven formula.

Carr's index (%) = $[(D_t - D_b) \times 100]/D_t$

Post compression parameters: [6]

1)Appearance:

The tablets were checked for presence of cracks, pinholes etc. There should be uniformity in the color and the dimensions of the tablets.

2)Hardness:

This test is used to check the hardness of the tablet, which may undergo chipping or breakage during storage, transportation, and handling. In this, three tablets were selected randomly and the hardness of each tablet was measured with Monsanto hardness tester. The hardness is usually measured in terms of kg/cm^2.

3)Thickness:

Thickness of tablet was important for uniformity of the tablet size. In these three tablets were selected randomly and the hardness of each tablet was measured with using screw gauze.

4) Friability test:

Friability test was carried out to evaluate the hardness and stability instantly. In roche Friabilator, 10 tablets were weighed (W_0) initially and put in a tumbling and rotating apparatus drum. Then they were subjected for completion of 4 min or 100 rpm, the tablets were again weighed. The % loss in weight or friability (F) was calculated by the formula given below.

$$\% \text{ Weight Loss} = \frac{W1 - W2}{W1} \times 100$$

Where, W1 = Intial weight
W2 = Final weight

6) Weight variation:
This test was performed to maintain the uniformity of weight of each tablet, which should be in the prescribed range. This was done by weighing 10 tablets at random and average weight was calculated. Not more than two of individual weight deviates from the average weight. The weight data from the tablets were analyzed for sample mean and percent deviation.

Weight variation = **(IW – AW)/ AW ×100**

Where, IW: Individual weight

AW: Average weight

7) Uniformity of drug content: [7]
The content uniformity was mandatory for tablets. This test was performed by taking five tablets were selected randomly, weighed and powdered. A tablet triturate equivalent to 40 mg of drug weighed accurately, dissolved in 10 mL methanol then final volume made up to 100 mL by using pH 1.2 buffer. Further dilutions were done suitably and absorbance was measured at 230nm using UV spectrophotometer.

8) Swelling index: [8]
The swelling of tablet involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle results to saturation of capillary spaces within the particles. The liquid enters the particles through pores and bind to large molecule breaking the hydrogen bond and resolution in the swelling of particle. One tablet from each batch was weighed and placed in a Petri plate containing 25 mL of pH 1.2 buffer solution. After each 2 hrs interval the tablet was removed from plate, removes excess of buffer by using filter paper and weighed again up to 24 hrs. The swelling index was calculated using following formula.

9) *In vitro* dissolution studies [8]
Dissolution tests were performed in USP dissolution eight dissolution apparatus II (paddles) at 37±0.5°C. The baskets were rotated at a speed of 50 rpm. The test was performed in 37±0.5°C with a rotation speed of 50 rpm using 900 mL of 0.1 N HCl, pH 1.2, as a dissolution medium. According to the sampling plan, samples of 5 mL were withdrawn till 24 hrs and immediately replaced with an equal volume of the respective dissolution medium maintained at 37±0.5°C. Test samples were filtered through Whatman filter paper for Gliclazide at 230 nm using a blank solution as reference with a UV-VIS double-beam spectrophotometer.

***10) In vitro* mucoadhesive strength:** [8]
Mucoadhesion strength of the tablet was measured by using sheep stomach mucosa as model mucosal membrane. Fresh sheep stomach mucosa was obtained from a local slaughter house and was used within 2-3 h of slaughtering. The mucosal membrane was washed with distilled water and then with pH 1.2.

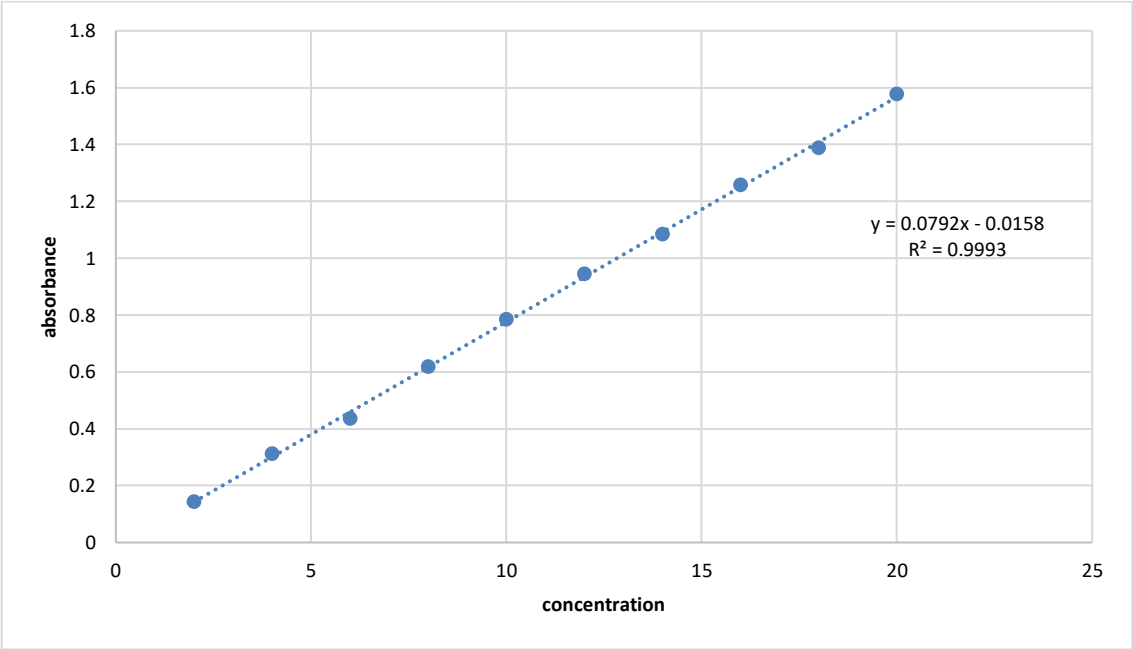
The mucoadhesive strength measurement apparatus was fabricated locally. The mucoadhesive strength of the tablets was determined using this locally fabricated apparatus. The weight at which the tablet was detached was recorded. The mean value of three trials was taken for each set of formulations. After each measurement, the tissue was gently and thoroughly washed with phosphate buffer and left for 5 minutes before placing a new tablet to get appropriate results for the formulation.

RESULT AND DISCUSSION:

Preparation of calibration curve in 0.1N HCL:

Data for Standard curve of Gliclazide

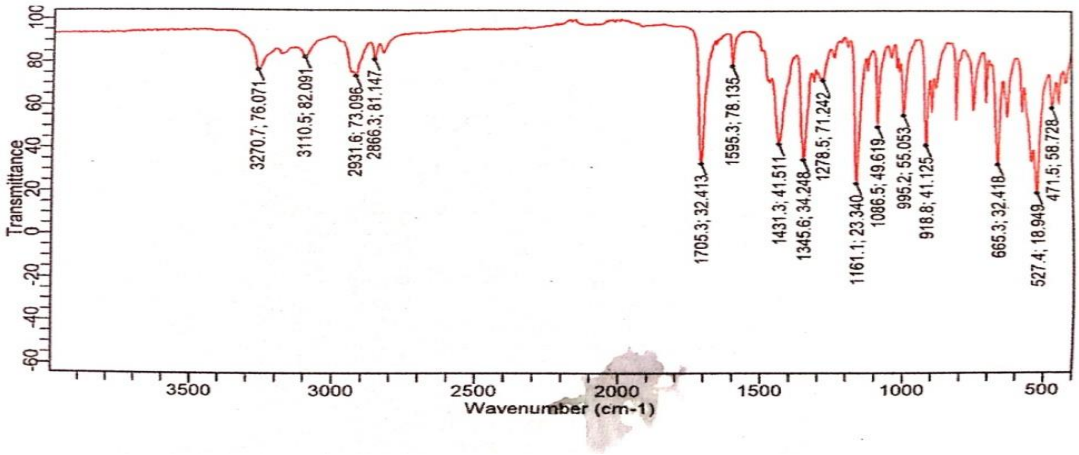
S. No.	Concentration(µg/ml)	Absorbance(nm)
1	2	0.1428
2	4	0.3120
3	6	0.4360
4	8	0.6191
5	10	0.7845
6	12	0.9450
7	14	1.0844
8	16	1.2581
9	18	1.3881
10	20	1.5784



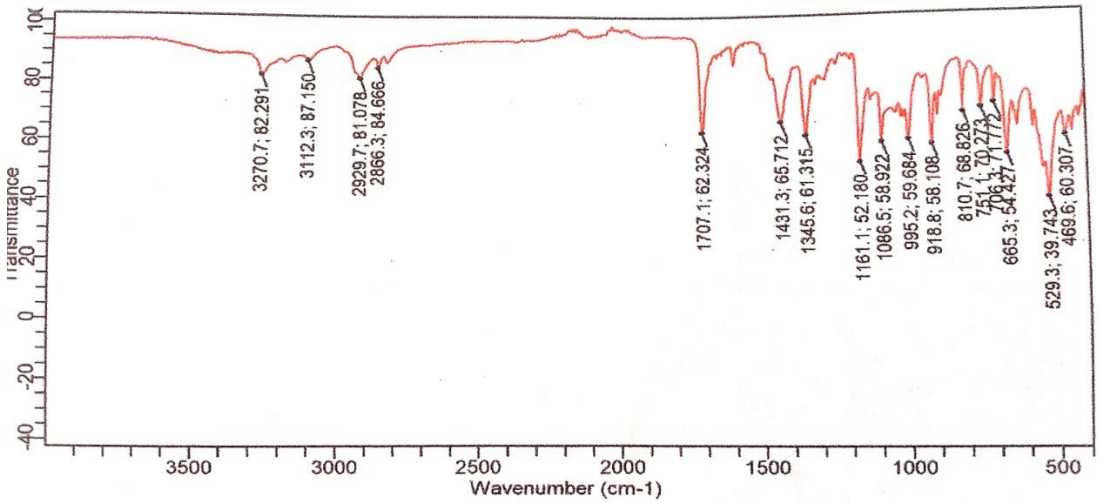
S.No.	Parameters	Observation
1	Absorbance maxima	230nm
2	Slope	0.079
3	Intercept	0.015
4	Coefficient of correlation	0.9992

Infrared Spectrum Analysis:
In the IR study, it was found that there was no interaction exhibited between Gliclazide and polymers used.

IR SPECTRUM OF PURE DRUG (GLICLAZIDE)



IR SPECTRUM OF GLICLAZIDE + HPMC K4M



EVALUATION OF PRE-COMPRESSION PARAMETERS OF POWDER

Formulation code	Bulk density (g/ml)	Tapped density(g/ml)	Hausner's ratio	Compressibility index(%)	Angle of repose
F1	0.4176	0.5067	1.1245	14.23	23 ^{0}.11
F2	0.4108	0.5243	1.1943	13.43	24.58
F3	0.4201	0.5389	1.1390	15.51	21.43
F4	0.4283	0.5361	1.1485	12.50	22.43
F5	0.4387	0.5120	1.1189	13.72	23.52
F6	0.4261	0.4849	1.1567	13.89	22.12
F7	0.4350	0.5186	1.1409	10.49	20.38
F8	0.4283	0.4976	1.1265	11.12	21.76
F9	0.4289	0.4865	1.1121	10.85	20.93

EVALUATION OF PREPARED MUCOADHESIVE TABLET OF GLICLAZIDE:

Formulation Code	Weight Variation (mg)	Drug Content (%)	Friability (%)	Hardness (Kg/Cm$^{2)}$	Thickness (mm)
F1	298.5	95.03	0.73	5.32	2.312
F2	297.6	95.21	0.88	5.12	2.462
F3	300.9	94.56	0.91	6.49	2.214
F4	299.1	96.37	0.89	5.50	2.215
F5	295.9	94.20	0.82	5.43	2.220
F6	301.7	94.60	0.72	6.21	2.267
F7	298.9	93.32	0.82	5.56	2.712
F8	299.3	90.30	0.90	5.17	2.671

F9	296.6	90.24	0.78	5.84	2.540

***In vitro* mucoadhesive strength**

Formulation code	Mucoadhesive strength (g)	Mucoadhesion force(N)
F1	23.471	2.302036
F2	22.300	2.187184
F3	22.720	2.228378
F4	21.350	2.094008
F5	20.580	2.018486
F6	23.890	2.343131
F7	22.576	2.214254
F8	22.680	2.224454
F9	24.053	2.359118

Swelling Index of The Developed Tablet

FORM. CODE	% Swelling index Time (hrs)								
	0Hrs	**1Hrs**	**2Hrs**	**3Hrs**	**4Hrs**	**5Hrs**	**6Hrs**	**7Hrs**	**8Hrs**
F1	0	4.6	8.42	12.65	15.85	18.29	22.65	28.75	31.43
F2	0	4.2	8.67	11.28	13.67	17.76	21.98	27.72	31.67
F3	0	3.5	5.76	10.37	14.12	18.87	23.76	27.11	33.76
F4	0	4.2	8.83	12.43	13.75	20.34	24.48	29.85	33.99
F5	0	4.35	7.76	11.22	17.56	20.10	24.31	28.65	32.12
F6	0	5.12	8.75	10.98	15.65	18.65	24.11	28.02	32.87
F7	0	4.36	7.65	11.67	13.09	18.06	23.90	29.11	35.78
F8	0	4.89	8.98	12.39	17.23	19.91	22.78	27.67	35.10
F9	0	3.75	7.21	11.25	16.49	20.27	25.01	28.88	35.89

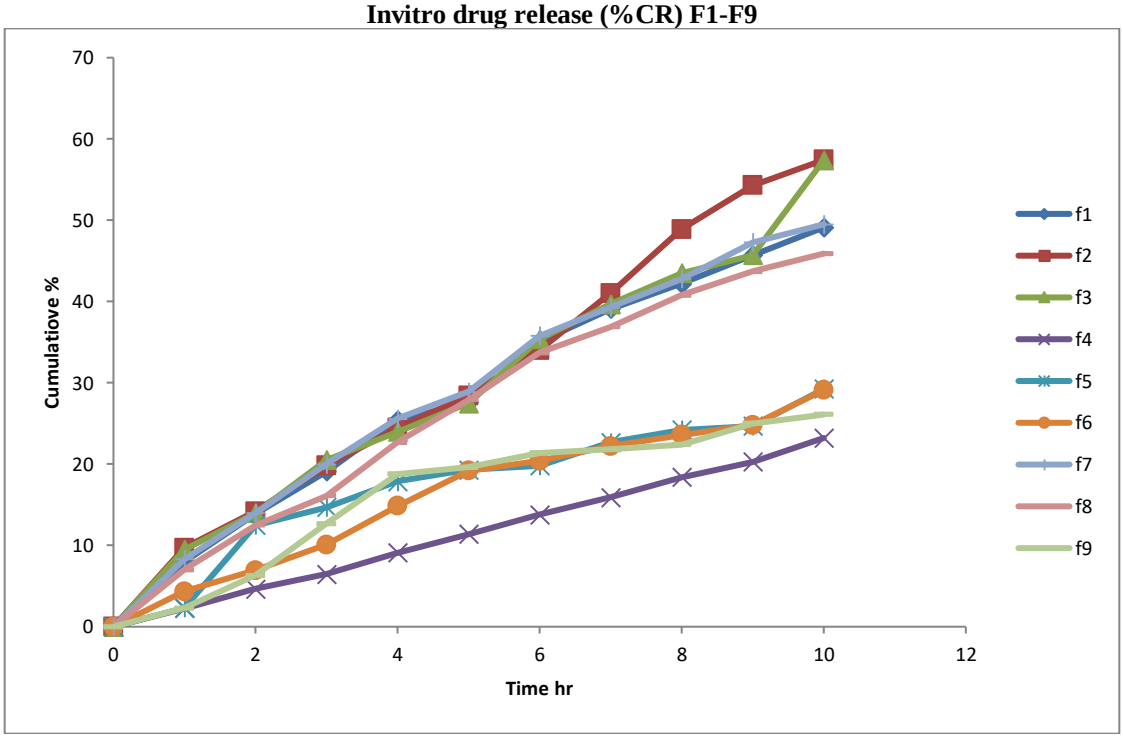
***In vitro* dissolution studies**

In vitro drug release studies were performed by using USP XXIII dissolution test apparatus- II at 50rpm using 900 mL of 1.2 pH buffer maintained at 37±0.5ºC as the dissolution medium.

***In-vitro* release profile study**

Time (Hrs)	Dissolution media 0.1N HCL (% drug release) Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	8%	9.7%	9.5%	2.25%	2.32%	4.33%	8.3%	7.0%	2.3%
2	13.9%	14.2%	14.0%	4.67%	12.5%	6.95%	14.0%	12.5%	6.3%
3	19.1%	19.8%	20.5%	6.46%	14.7%	10.08%	20.0%	16.1%	12.7%
4	25.4%	24.4%	24.0%	9.09%	17.9%	14.87%	25.6%	22.7%	18.8%
5	27.6%	28.4%	27.5%	11.4%	19.3%	19.2%	28.9%	27.9%	19.6%
6	35.1%	34.1%	35.4%	13.8%	19.8%	20.4%	35.8%	33.7%	21.4%
7	39.1%	41.3%	39.7%	15.9%	22.7%	22.2%	39.3%	36.9%	21.8%
8	42.2%	48.9%	43.5%	18.4%	24.2%	23.6%	42.8%	40.8%	22.4%
9	45.7%	54.2%	45.7%	20.3%	24.7%	24.8%	47.3%	43.7%	25.0 %
10	49.2%	57.4%	57.4%	23.2%	29.2%	29.1%	49.5%	45.9%	26.1%

Invitro drug release (%CR) F1-F9



RELEASE KINETICS DATA OF ALL THE FORMULATION

FORMLN. CODE	Mathematical models (kinetics)				
	Zero order (R)	First order (R)	Higuchi(R)	Korsmeyer-Peppas	
				(N)	(R)
F1	0.9848	0.9970	0.9156	0.79	0.9973
F2	0.9935	0.9786	0.9069	0.80	0.9069
F3	0.986	0.9691	0.9055	0.76	.9873
F4	0.9994	0.9973	0.9182	1.007	0.9991
F5	0.9049	0.9274	0.9366	0.9060	0.8383
F6	0.968	0.9775	0.9219	1.8758	0.9941
F7	0.984	0.9976	0.9181	0.7911	0.9981
F8	0.984	0.9955	0.9190	0.8450	0.9949
F9	0.895	0.9121	0.9436	1.0109	0.9138

RESULTS AND DISCUSSION:

Formulation and evaluation parameters have been performed in satisfactory data. The aim of study to prolong residence time and bioavailability. The percent drug content of the optimized formulation was found to be 90.24 w/w to 96.37w/w. Hardness of the tablets was found to be in a range of 5.12 to 6.49 kg/cm^2 and it was found that hardness will increase with increase the amount of carbopol 940. Weight variation of the tablets range is found to be 296.6 to 301.7 and % deviation in a specified limit. Hence all formulations complied with the test for weight uniformity. All the tablet were circular with no cracks and with average thickness of 2.214mm to 2.712. Friability value also considered and weight loss was found to less than 1%. All the formulations were studied and its results indicate that all the formulations possess good Swelling index. The mucoadhesion force were affected by amount of polymer. The highest mucoadhesive force by optimum formulation was found to be 2.09N to 2.35

CONCLUSION:

The present study was aimed to develop prolong release stable, pharmaceutically equivalent formulation of gliclazide using polymers HPMC K4M, and Carbopol 940 optimized by 3^2 full factorial design.

The satisfactory formulation shows a zero-order drug release profile depending on the regression value and shows a satisfactory dissolution profile. Slow, controlled release of Gliclazide over a period of 10 hrs was obtained from F3formulation.

Further work is to be carried out in order to determine its efficacy and safety by long term pharmacokinetic and pharmacodynamic studies.

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