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DESIGN AND EVALUATION OF GASTRIC BIOADHESIVE TABLETS OF GLICLAZIDE

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ABSTRACT

The current work was a successful attempt to develop a bioadhesive drug delivery system for gliclazide, an orally administered anti-diabetic medication, to increase its oral bioavailability and provide long-term drug release. From the results, it can be concluded that gliclazide mucoadhesive drug delivery systems may be made utilizing polymers like guar gum by direct compression method. UV spectrophotometry method of analysis of the drug was developed. In a pH 1.2 buffer (0.1 HCL), gliclazide showed maximum absorption at 226 nm. The regression coefficient (r^2) was determined to be 0.996, indicating that concentration and absorbance have a linear relationship. In the developed formulations, IR spectroscopic tests revealed no drug-polymer interaction. Without capping or chipping, all of the produced tablet formulations were determined to be satisfactory. According to the findings of this study, as the concentration of gum increases, so does the swelling index.

Keywords: Bioadhesive tablet, Gliclazide, Guar gum, FTIR, Mucoadhesive strength

INTRODUCTION

Newer drug delivery systems are created regularly to deliver the therapeutic amount of medication to the correct place inside the body while also increasing the drug's bioavailability. A correctly designed controlled-release medication delivery system is frequently a big step forward in addressing most difficulties, such as delivering drugs to the right place at the right time and regulating drug delivery pace.

Better management of plasma drug levels and fewer frequent doses may be used to achieve this **[1]**. Historically, oral medication administration has been the most common method of drug administration. In recent years, oral dosage forms capable of obtaining an extended retention period within the stomach to increase the duration of drug administration have gotten a lot of attention **[2, 3]**.

MATERIALS & METHODS

Materials

Gliclazide was obtained as a gift sample from Harika Drugs Pvt. Ltd. Telangna, Guar gum was obtained from Loba Chemie Pvt. Ltd., Mumbai, Spray dry lactose was obtained from Research Lab Fine Chem. Mumbai. All the other chemicals used were of analytical grade and were used as a procedure.

Preparation of bioadhesive tablets

In the present investigation, an accurately weighed quantity of Gliclazide and the subjected polymers, remaining excipients were added together in mortar& pestle and triturated. Tablets were prepared by the Direct Compression Method.

Formulation of mucoadhesive tablets of gliclazide

Ingredients	CF1	F1	F2	F3	F4	F5	F6
GLZ	40	40	40	40	40	40	40
Gaur gum	-	40	35	30	25	20	15
Spray dried lactose	55	14	19	24	29	34	39
Talc	3	3	3	3	3	3	3
Magnesium stearate	2	2	2	2	2	2	2
Aerosil	1	1	1	1	1	1	1

All quantities in mg/tablet

Evaluation Parameters [4-9]

1) Bulk density

It's the proportion of powder's total mass to its bulk volume

$Db = M/Vb$ …… (1)

Where, Db = Bulk density, M = Mass of the powder, Vb = Bulk volume of powder

2) Tapped density

Accurately weighed batch (F1 –F6) powder was placed in a 10 ml graduated measuring cylinder. From a distance of 14 + 2 mm, the cylinder was tapped 100 times. To the closest graduated unit, the tapped volume was measured.

$Dt = M/Vt$ …….. (2)

Where, Dt = Tapped density, Vt = Tapped volume of the powder, Dt = Tapped density, M = mass of the powder

3) Angle of repose

The powder mass was allowed to flow through the funnel orifice, kept vertically to a plane paper kept on a

horizontal surface, giving a heap angle of powder on a paper. The powder cone's diameter was measured, and the angle of repose was computed using the equation below.

$\tan\theta = h/r$ ……..(3)

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

4) Hausner's ratio

Hausner's ratio was carried out by tapped density divided by bulk density.

$$\text{Hasusner's ratio}=\frac{\text{Tapped density}}{\text{Bulk density}}$$ …… (4)

5) Carr's consolidation index

Carr developed an indirect method of measuring powder flow from bulk densities. The provided formula was used to compute Carr's index of each formulation.

Carr's index (%) = [(Dt –Db) x 100]/Dt …….. (5)

Post Compression Parameters [10-12]

1) Appearance

The tablets were examined for fractures, pinholes, etc. There should be uniformity in the color and the dimensions of the tablets.

2) Hardness

It was determined using a Monsanto hardness tester.

3) Thickness

It was tested with screw gauze.

4) Friability test

A friability test was performed to determine the hardness and stability of the material in real-time. Initially, 10 tablets were weighed (W0) and placed in a tumbling and rotating device drum in Roche's friability. The pills were then weighed again after being exposed to a 4 minute or 100 rpm. The % loss in weight or friability (F) was calculated by the formula given below.

$$\% \text{ Friability}= \frac{\text{Initial weight}-\text{Final weight}}{\text{Initial weight}}\times 100$$

……. (6)

5) 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 the 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.

$$PD= \frac{Wavg-Win}{Wavg}\times 100$$…….. (7)

Where, PD = percentage deviation, Wavg = average weight of tablets

Wind = individual weight of tablets

6) Uniformity of drug content

This test was performed by taking five tablets that were selected randomly, weighed, and powdered. A tablet triturates

equivalent to 40 mg of drug weighed accurately, dissolved in 10 ml methanol then final volume made up to 100 ml by using 0.1N HCL. Further dilutions were done suitably and absorbance was measured at 226nm using a UV spectrophotometer.

7) Swelling index

Tablet was weighed and put on a Petri plate with 25 ml of 0.1N HCL solutions. The tablet was taken from the plate after each 2-hour interval, the excess buffer was collected using filter paper, and the tablet was weighed again for up to 24 hours. The following formula was used to compute the swelling index.

Swelling index (S.I)= $\frac{Wt-W}{Wo}$×100…… (8)

Where, Wt = Weight of tablet at time t, Wo = Weight of tablet before placing in the Petri plate.

8) *In vitro* dissolution studies

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 dissolving media was 900 ml of 0.1 N HCL, pH 1.2, and the test was done at 37 ± 0.5°C with a rotating speed of 50 rpm. Samples of 5 ml were taken for 24 hours and then replaced with an equivalent volume of the corresponding dissolving medium kept at 37 ± 0.5°C, according to the sampling plan. A UV-VIS double-beam spectrophotometer was used to filter test samples for gliclazide at 226 nm using Whatman filter paper and a blank solution as a reference.

9) *In vitro* mucoadhesive strength

The mucoadhesive strength of the tablets was measured by using modified physical balance. The membrane was the gastric mucus membrane, and the moistening fluid was a 0.1N HCL. For 2 hours, stomach mucosa was maintained in Tyrode solution at 37° C. The mucus membrane carefully cleaned with a pH 1.2 solution. The two sides of the balance were made equal by keeping a 5 g weight on the right pan. The 5 g weight from the right pan was then removed. This lowered the left pan along with the tablet over the membrane with a weight of 5 g. This was kept undisturbed for 3 minutes. Then, the weight on the right-hand side was slowly added in an increment of 0.5 g till the tablet just separated from the membrane surface. The excess weight on the right pan i.e., total weight minus 5 g was taken as a measure of the mucoadhesive strength. From the mucoadhesive strength, the force of adhesion was calculated using the following formula-

Force of adhesion

$=\frac{\text{Mucoadhesive Strength}\times 9.81}{1000}$…… (9)

10) Stability studies

Selected formulations were subjected to determine their shelf life i.e. stability study by using an accelerated stability chamber, according to the WHO guidelines. The tablets were stored in the stability chamber under temperature 40 ± 2^0C and 75 ± 5 % RH (relative humidity) for 90 days. After the specified period, the tablets were subjected to physical appearance, drug content, and dissolution study.

RESULTS AND DISCUSSION

Melting Point Determination

The melting point of Gliclazide was obtained in the range of 177-179^{0}C. The standard melting point value of gliclazide is 179^{0}C. It complies with the melting point of pharmacopeia.

Drug-Polymer Interaction Studies by FT-IR

FT-IR spectra were obtained by using an FTIR – 4100, Jasco, Japan. The Dug sample gliclazide alone and with the treated polymers were pulverized and well mixed with potassium bromide, an infrared transparent matrix, at a ratio of 1:5 (Sample: KBr). The KBr discs were made by compressing particles in a hydraulic press at a pressure of 5 tonnes for 2 minutes.

Drug - excipients compatibility studies

Pure drug gliclazide with polymers was carried out before the formulation of tablets. IR spectra of pure drugs and excipients were taken. The result was given in **Figures 1 & 2**.

Standard Plot of Gliclazide

The λmax of gliclazide was determined in 0.1N HCL which was scanned between 200-400 nm in the UV spectrophotometer. It was found to be 226 nm. The result was given in **Table 3 & Figure 3**.

Evaluation of Powder Properties (Table 1)

Post Compression Parameters (Table 2)

Swelling study

Swelling index was carried out for tablets formulation. The swelling index of the tablets from each formulation (CF1 to F6) was evaluated and the results were hydrated to an extent of 69.1, 200.1, 171.7, 154.7, 131.1, 108.7, and 85.8. The result was given in **Table 4 & Figure 4**.

In vitro dissolution

In vitro drug release studies were performed by using Shimadzu, PharmaSpecUV-1700, Japan at 50 rpm using 900 ml of 0.1N HCL maintained at 37±0.5ºC as the dissolution medium. The result was given in **Tables 5 & 6 and Figures 5 & 6**.

In vitro mucoadhesive strength

In vitro mucoadhesive strength was carried out by using modified physical

balance and measures the Mucoadhesive strength requires to detach the tablet. The Mucoadhesive characteristics were affected by the concentration of gum. An increase in the concentration of gum increases the Mucoadhesive strength of formulation. The result was given in **Table 7**.

Stability study

The rapid stability tests were done by ICH standards. F1 optimized formulations were packed in amber color bottles with aluminum foil laminated on the upper half of the container and stored in ICH-certified stability chambers. Maintained at 40^0C ± 2^0C and 75 % RH ± 5 % (zone III conditions as per ICH Guidelines) for 3 months. The tablets were evaluated before and after one month for a change in appearance, the drug content, and *in vitro* release. The formulation batch showed a circular shape with no cracks. The drug content of the formulation F1 was found to be 97.89 %, 97.19%, and 96.92 % at an interval of 30 days respectively. The % CDR of formulation F1 was found to be 48.29%, 48.13%, and 47.97 % at an interval of 30 days. The result was given in **Table 8**.

Table 1: Micromeritics properties of the powder formulation

Formulation	Bulk Density	Tapped Density	Carr's Index	Hausner's Ratio	Angle of Repose (θ)
CF1	0.3703±0.005	0.4149±0.0011	9.75±0.01	1.1204±0.002	26.56^0±0.125
F1	0.5888±0.006	0.6660±0.005	11.59±0.03	1.148±0.027	19.79^0±0.384
F2	0.5455±0.006	0.6250±0.008	11.12±0.02	1.1261±0.030	20.30^0±0.198
F3	0.5263±0.005	0.5714±0.006	12.22±0.032	1.203±0.032	20.65^0±0.451
F4	0.5000±0.005	0.5494±0.007	12.96±0.01	1.090±0.03	21^0±0.173
F5	0.4761±0.005	0.5154±0.013	11.76±0.02	1.28±0.002	21.30^0±0.467
F6	0.4545±0.003	0.4901±0.011	10.20±0.011	1.22±0.017	22.19^0±0.372
All values in standard deviation in triplicate determination.					

Table 2: Post-compression parameters of tablets formulations

Formulation	Friability (%)	Hardness (kg/cm^2)	Weight Variation (mg)	Thickness (mm)	Drug Content (%)
CF1	0.90	6.93±0.133	99.4±1.658	3.059±0.019	96.43±0.869
F1	0.75	5.01±0.0421	99.8±1.259	3.019±0.033	97.89±1.009
F2	0.77	5.14±0.924	98.6±1.545	2.999±0.079	97.83±0.654
F3	0.79	5.29±0.121	98.9±1.452	2.969±0.054	97.59±0.865
F4	0.82	5.42±0.0421	99.5±1.865	2.959±0.047	96.73±1.001
F5	0.84	5.54±0.119	98.7±1.531	2.919±0.021	96.43±0.869
F6	0.86	5.85±0.113	98.9±1.492	2.899±0.083	96.24±0.586
Where, all the values were mean ± SD for sample sizes 10, 6, 20, 6, 6 respectively.					

Table 3: Calibration data of gliclazide in 0.1N HCL

Sr. No.	Concentration (µg/ml)	Avg. absorbance at 226 nm
1	0	0
2	5	0.3051
3	10	0.476
4	15	0.7808
5	20	0.955
6	25	1.2391
7	30	1.4823

Table 4: % swelling index of tablets formulations

formulation	%Swelling Index Time(hr)					
	2hr	4hr	6hr	8hr	10hr	12hr
CF1	37.7	43.2	50.6	56.4	63.7	69.1
F1	115.5	132.7	149.3	166.8	183.2	200.1
F2	102.7	117.3	135.6	145.9	158.1	171.7
F3	89.1	102.7	115.3	128.9	141.2	154.7
F4	76.1	87.7	98.3	109.8	120.3	131.7
F5	63.4	72.7	81.1	90.8	99.4	108.7
F6	50.2	57.8	64.4	71.8	78.2	85.8

Table 5: % Cumulative drug release of conventional tablets formulations

Time(hr)	%CDR (CF1)
0	0
15	54.37113±1.566
30	75.80412±1.382
45	95.10309±1.719

Table 6: % Cumulative drug release of tablets formulations

Time (hr)	F1	F2	F3	F4	F5	F6
1	4.221649±0.5	4.685567±0.3	6.541237±0.5	8.536082±1.3	11.18041±0.9	12.52577±0.5
2	5.613402±0.3	6.07732±0.5	8.489691±0.7	11.18041±0.5	14.33505±0.3	14.84536±1.5
3	7.979381±0.5	8.536082±0.3	10.85567±0.3	14.0567±1.08	18.69588±0.5	19.15979±1.5
4	9.046392±0.5	10.20619±0.5	13.82474±0.7	18.27835±0.8	22.73196±0.7	23.19588±0.9
5	13.12887±1.5	14.14948±0.5	18.78866±0.5	22.45361±0.7	27.04639±1.5	32.14948±1.3
6	18.32474±0.8	20.45876±1.5	23.6134±0.79	27.37113±0.6	32.01031±0.9	35.81443±0.6
7	20.59794±1.2	22.87113±0.8	27.78866±0.8	32.01031±0.7	38.41237±1.0	42.86598±0.5
8	23.52062±1.1	27.04639±1.3	33.54124±0.5	38.41237±0.9	47.69072±0.6	52.3299±0.79
9	29.2268±0.80	32.10309±1.0	39.80412±1.0	45.83505±1.3	55.1134±0.79	63.92784±0.2
10	36.74227±1.5	38.31959±0.8	45.92784±1.0	55.20619±0.2	64.02062±0.2	73.29897±0.3
11	37.90206±1.8	45.74227±1.5	54.46392±0.3	63.74227±0.5	69.077321.08	80.11856±0.9
12	48.29381±1.3	53.62887±1.8	60.54124±1.0	67.26804±0.7	85.12887±1.0	97.09794±0.7

Table 7: Mucoadhesive strength of tablets formulations

Formulation	Mucoadhesive Strength (g)	Mucoadhesion force (N)
CF1	21.44	2.10
F1	24.67	2.41
F2	24.05	2.35
F3	23.89	2.34
F4	22.72	2.22
F5	22.68	2.22
F6	22.57	2.21

Table 8: Stability study for F1

Time (Days)	Physical appearance	Drug content	% CDR
30	No change	97.89%	48.29
60	No change	96.94%	48.13
90	No change	96.68 %	47.97

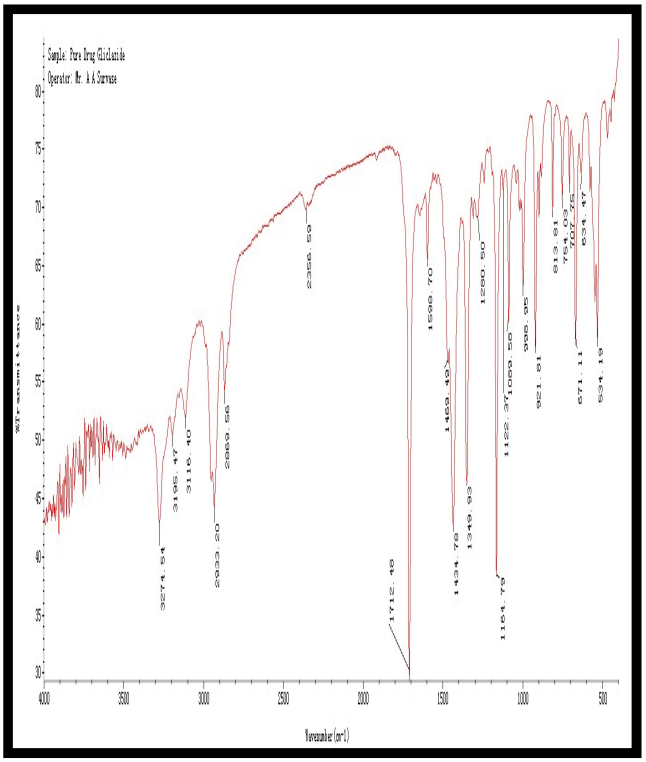

Figure 1: FTIR spectrum of gliclazide

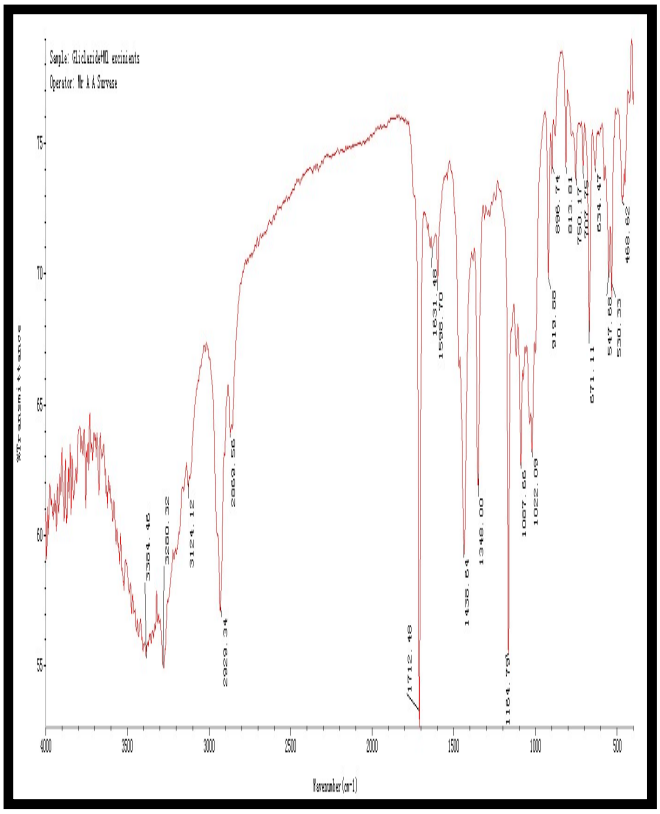

Figure 2: FTIR spectrum of gliclazide and excipients

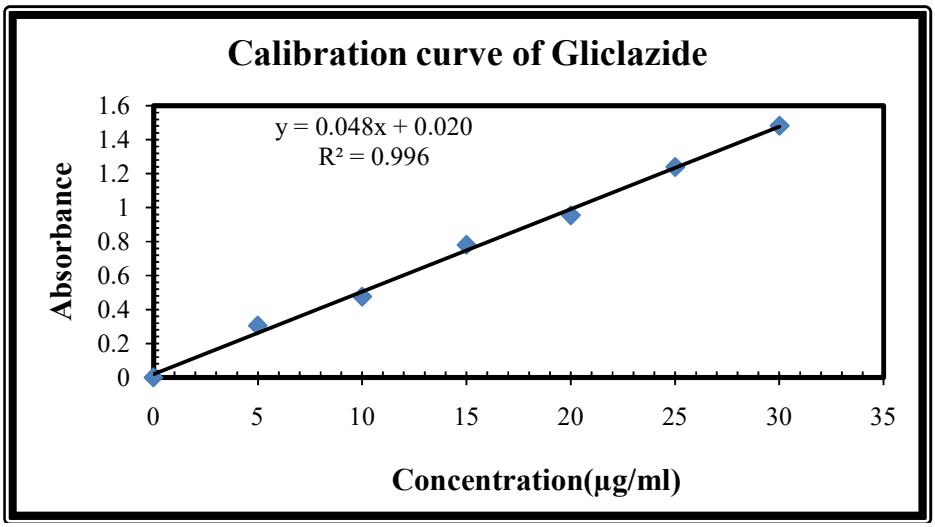

Figure 3: Calibration curve of Gliclazide in 0.1N HCL

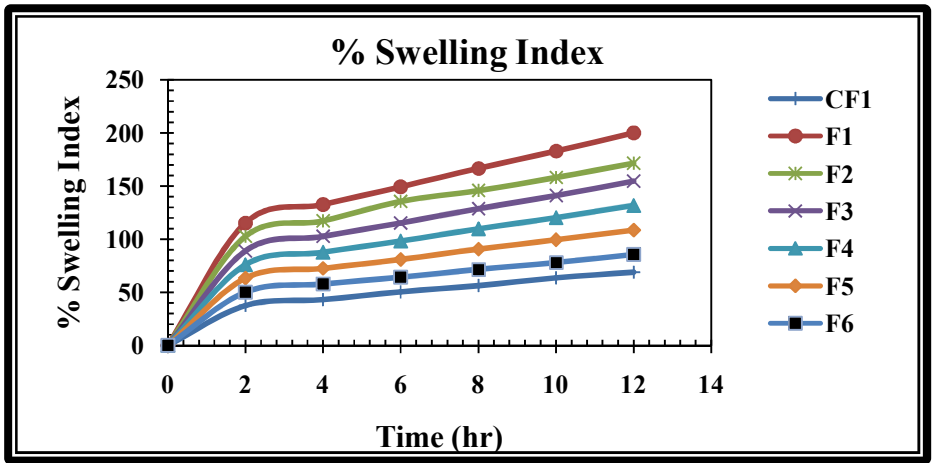

Figure 4: % Swelling index of tablets formulations

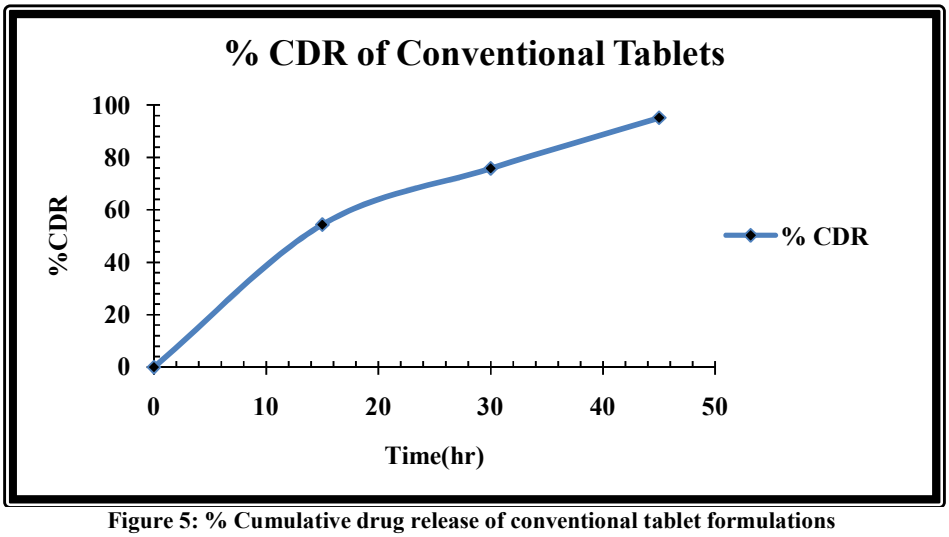

Figure 5: % Cumulative drug release of conventional tablet formulations

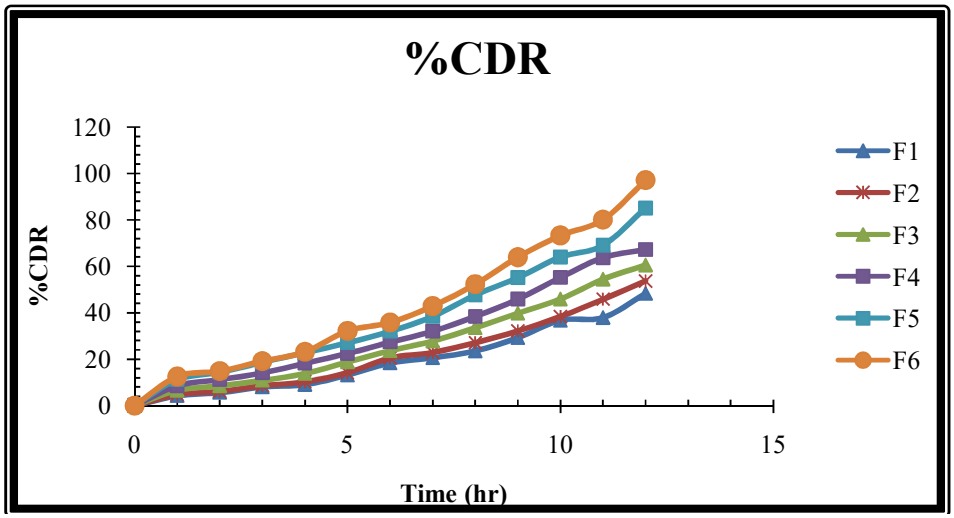

Figure 6: % Cumulative drug release of tablets formulations

CONCLUSION

From the results, it can be concluded that-

- Gliclazide mucoadhesive drug delivery systems may be made utilizing polymers like guar gum by direct compression method.
- UV spectrophotometry method of analysis of the drug was developed. In a pH 1.2 buffer (0.1HCL), gliclazide showed maximum absorption at 226 nm. The regression coefficient (r2) was determined to be 0.996, indicating that concentration and absorbance have a linear relationship.
- In the developed formulations, IR spectroscopic tests revealed no drug-polymer interaction.
- Without capping or chipping, all of the produced tablet formulations were determined to be satisfactory.
- According to the findings of this study, as the concentration of gum increases, so does the swelling index.
- The above results it was concluded that as the concentration of gum increases, so does the in vitro mucoadhesive strength.
- Studies of optimized formulations' short-term stability F1 demonstrates that after 1 month of storage at 40°C ± 20°C, and 75% RH, 5 %t, there are no significant changes in drug content or dissolution parameter values.

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