Formulation, Development and Evaluation of Mucoadhesive Tablet of Giclazide.

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ABSTRACT AND KEYWORDS

i. ABSTRACT

Extending the residence time of a dosage form at a particular site and controlling the release of drug from the dosage form are useful especially for achieving controlled plasma level of the drug as well as improving bioavailability. The objective of this study was to extend the GI residence time of the dosage form and control the release of Gliclazide using mucoadhesive tablet to achieve controlled plasma level of the drug which is especially useful for 12 hrs. Matrix tablets of Gliclazide were formulated using different mucoadhesive polymers namely HPMC K4M, HPMC K15M and HPMC K100M, Carbopol 934. Formulations were evaluated for preformulation parameters, *in vitro* drug release profile and release kinetics. The formulations were found to have good preformulation characteristics. FTIR and DSC indicated the absence of any significant chemical interaction within dug and excipients. The develop mucoadhesive tablet, which is pharmaceutically equivalent and robust formulation of gliclazide by using complexation method and in this method we use microwave irradiation technique and its evaluation and also compare with kneeding method. Optimized formulation showed results near to predicted result and stability studies showed no changes in tablets after 1 month of accelerated stability studies. By using different polymers (HPMC

K4M, HPMC K15M, HPMC K100M and Crbopol 934) and 3^2 factorial design with gliclazide in appropriate proportions matrix mucoadhesive, sustained and stable release tablets could be prepared which shoes prolonged therapeutic effect and improves patient compliance and drug efficiency.

ii. Keyword:

Mucoadhesive tablet, Solubility enhancement, Microwave irradiation, kneeding method, Gliclazide.

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to proper site in the body to achieve and maintain therapeutic concentration within range and increase the solubility of gliclazide because it is BCS class II drug. To achieve this goal one should maintain dosing frequency and suitable route of administration. The oral administration is the most convenient from any of drug delivery to the systematic circulation. It achieves improved therapeutic advantages, such as ease of dosing administration, patient compliance. The development process is affected by several physiological difficulties, such as highly variable nature of gastric emptying process. Improved bioavailability.[1,2] Mucoadhesive dosage forms deliver drug for longer period of time and help to produce therapeutic effect for more than 12hr for those drugs which are having poor solubility.[3] Drugs that have narrow absorption window in the GIT (gastro intestinal tract) will have poor absorption[4,5]. The MDDS is advantageous for these drugs, gastro retentive dosage forms help in maintenance of constant therapeutic levels for prolong period, increase therapeutic efficacy and decrease dose administration.

Gliclazide binds to the β cell sulfonyl urea receptor (SUR1). This binding subsequently blocks the ATP sensitive potassium channels. The binding results in closure of the channels and leads to a resulting decrease in potassium efflux leads to depolarization of the β cells. This opens voltage-dependent calcium channels in the β cell resulting in calmodulin activation, which in turn leads to exocytosis of insulin containing secretorty granules Mecanism. Gliclazide have poor absorption. By formulating with mucoadhesive drug delivery system, it remains longer time in gastro intestinal tract and improves bioavailability of drug rational.

MATERIALS AND METHODS

Materials

Materials used in present investigation were Gliclazide (Healthy Life Pharma, Mumbai, India), HPMC K4M (Chemodyes corporation, Ahmadabad), HPMC K15M (Chemodyes corporation, Ahmadabad),

HPMC K100M (Chemodyes corporation, Ahmadabad), Lactose (Oxford laboratory, Mumbai), Microcrystalline Cellulose (Astron chemicals, Mumbai), Talc and Magnesium stearate (Oxford laboratory, Mumbai).

Preparation of Mucoadhesive tablets:

Direct compression technique used to prepared tablet. Gliclazide was mixed with different excipient according to formulation. Then powder blend was lubricated by adding magnesium stearate and compressed on tablet punching machine. To maintain constant tablet weight as well as to counter balance the poor water solubility of drug, water soluble filler micro crystalline cellulose (MCC), lactose was used. Prepared tablets were compressed to get hardness within range of 5-7 Kg/cm^2.

Solubility enhancement techniques of Gliclazide:

This technique involves the microwave irradiation reaction between the gliclazide and complexing agent using a microwave oven. The gliclazide and CD in definite molar ratio are dissolved in a mixture of water and organic solvent in a specified proportion into a 250 ml round bottom flask. The mixture is reacted for short time of about one to two minutes at 60 °C in the microwave oven. After the reaction completes, adequate amount of solvent mixture is added to the above reaction mixture to remove the residual, uncomplexed free gliclazide and CD. The precipitate so obtained is separated using whatman filter paper, and dried in vaccum oven at 40 °C for 48 hrs. [12]

Table 1: Formulation chart of 9 each Mucoadhesive tablet of Gliclazide

Batches	Drug (mg)	HPMC K15 M	Carbopol (mg)	MCC (mg)	Lactose (mg)	Talc (mg)	Mg. stearate (mg)	Total (mg)
F-1	80	75	60	40	25	10	10	300
F-2	80	75	45	49	31	10	10	300
F-3	80	75	30	58	37	10	10	300
F-4	80	60	60	49	31	10	10	300

F-5	80	60	45	58	37	10	10	300
F-6	80	60	30	67	43	10	10	300
F-7	80	45	60	58	37	10	10	300
F-8	80	45	45	67	43	10	10	300
F-9	80	45	30	76	49	10	10	300

Evaluation of prepared tablets:

a) Thickness

Tablet thickness was measured using vernier caliper. Ii is expressed in millimeter[12].

b) Hardness

The hardness of core tablets was measured using Monsanto Pfizer[12].

c) Friability

6.8gm weighed and placed in a Roche friabilator and rotated at 25 rpm for 4 mins. The tablets were taken out, dedusted, and reweighed.[12]

The percentage friability of the tablets was calculated using the equation:

% F = {1-(Wt/W)} ×100

Where, % F is friability in percentage, W is the initial weight of tablet and Wt is the final weight of tablets after revolutions. Values of friability of 1 % are considered as an acceptable.

d) Mucoadhesive strength

An instrument was designed to evaluate the tensile force. This instrument consists of a modified physical balance. This method was used for determination of the *ex-vivo* bio adhesion strength. The balance was modified by replacement of one pan with the metal shaft 5 gm heavier in weight than pan. An artificial membrane was wash with the distilled water followed by 0.1 N HCl. An artificial

membrane was fixed in a petri dish with instant adhesive, which was filled with 0.1 N HCl so, that it just touched the mucosal surface. The tablet was stuck to the lower side of a shaft with instant adhesive. The two sides of the balance were made equal before the study, by keeping 5 gm weight on the right hand pan. A weight of 5 gm was removed from the right hand pan, which lowered the shaft along with the tablet over the mucosa. The balance was kept in this position for 3 minutes contact time. The weight was added slowly to the right hand pan until the tablet detached from the mucosal surface. This detachment force gave the bioadhesion strength of the mucoadhesive tablet in gm. The excess weight on the left pan *i.e.,* total weight minus 5 g was taken as adhesive strength. Three films of each formulation is tested for mucoadhesive strength, average and standard derivations was calculated-

Fabricated bio-adhesion= bio-adhesive strength X 9.81/100

Whereas, 9.18 is acceleration due to gravity (m/sec^2).

e) In vitro drug release study

In vitro release study of gliclazide were evaluated using a USP dissolution testing apparatus type II (paddle method) at 37±0.5 °C with rotation speed of 100 rpm in 900 ml of 0.1 N hydrochloric acid buffer pH 1.2 for 12 hr. From this, 5 ml of the dissolution medium were withdrawn at regular time intervals, replaced with an equal volume of fresh dissolution fluid then analyzed for the drug content using UV-Vis spectrophotometer at 226 nm[14].

f) Drug content

Equivalent to 100 mg of gliclazide was taken and transferred to 100 ml volumetric flask, dissolved and diluted with 0.1N HCl pH 1.2 buffer. The absorbance of the resulting solution was measured at the λmax of 226.80 nm using a UV spectrophotometer after filtration through whatmann filter paper. The drug content was calculated using equation given below[12]:

% Drug content (%) = Conc. (µg / ml) × Dilution factor × 100 /50

g) Weight variation

20 tablets from each formulation were randomly picked up and weighed individually and the average weight was calculated. The individual weights were then compared with the average weight.[12]

% Deviation = Avg. weight of tablet–Individual tablet weight/Avg. weight of tablet×100

h) Stability study

To determine the change in performance of dosage form on storage, stability study was carried out for 1 month at 40° C in a humidity jar having 75% RH according to ICH[15].

RESULTS

1) Drug-Excipient compatibility study

1.1 Drug-Excipient compatibility study by IR

IR analysis of pure drug and drug mixed with excipients of all were done on IR. It was found that all the prominent functional group picks [Alkenes C=C stretching (3263), Aromatic C-C stretching (1701), Aromatic C-C stretching (1433), Aromatic amines CN stretching (1239), Aromatic CH stretching (810)] were observed in physical mixture. From the figure it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers.

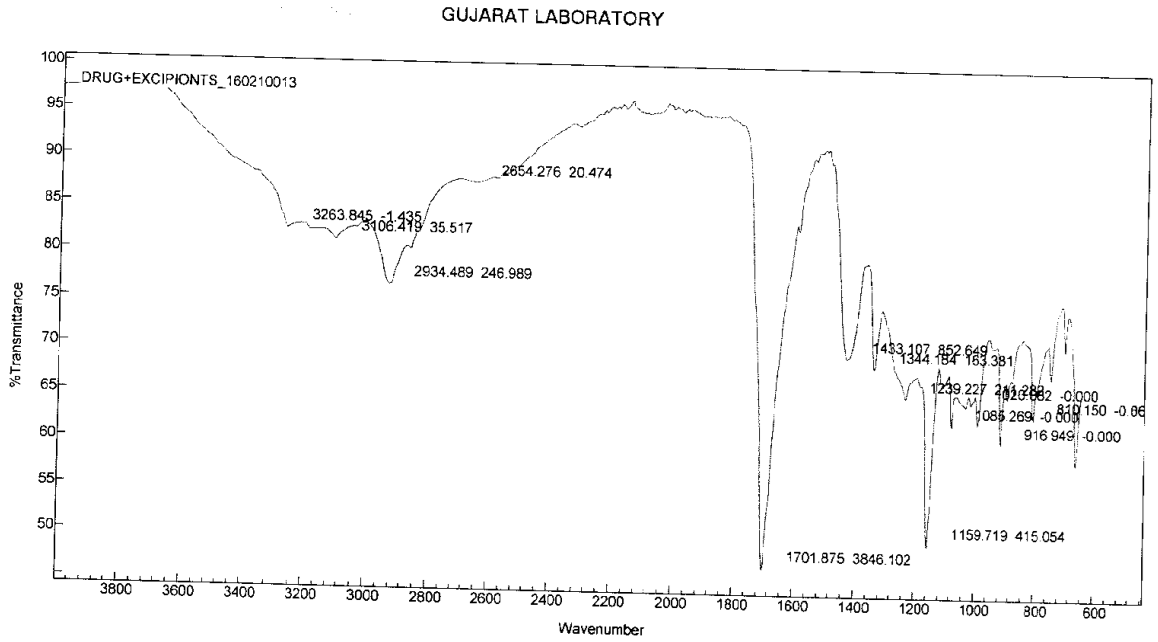

Figure.1. IR spectrum of Drug + Excipients

1.1 Drug-Excipient compatibility study by DSC

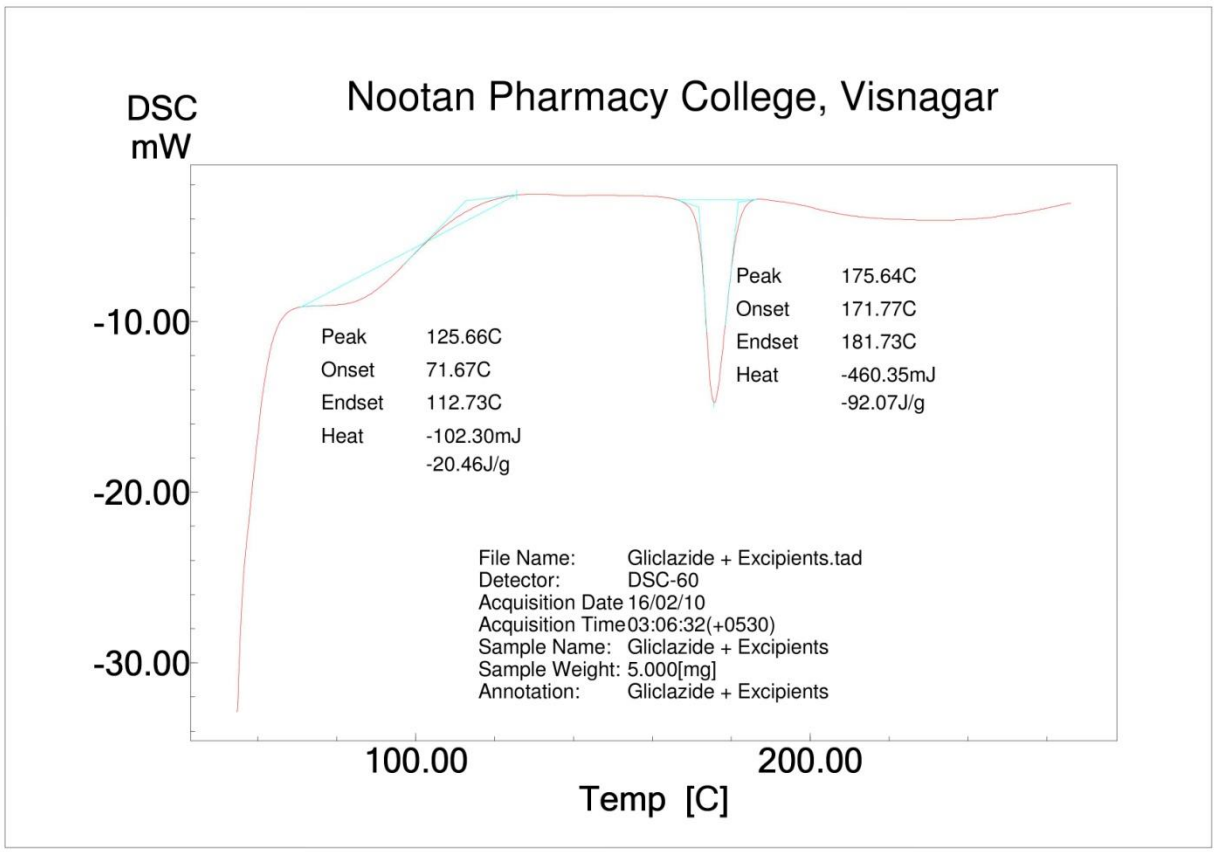

Figure.2. DSC of Drug + Excipients

Evaluation of gliclazide solid dispersion

Complexation of gliclazide in PEG 4000, PEG 6000, PEG 8000 and poloxamer 407 were prepared with different ratio like 1:1, 1:3, 1:5. The methods used for the preparation of these complexations were kneeding method and microwave irradiation method.

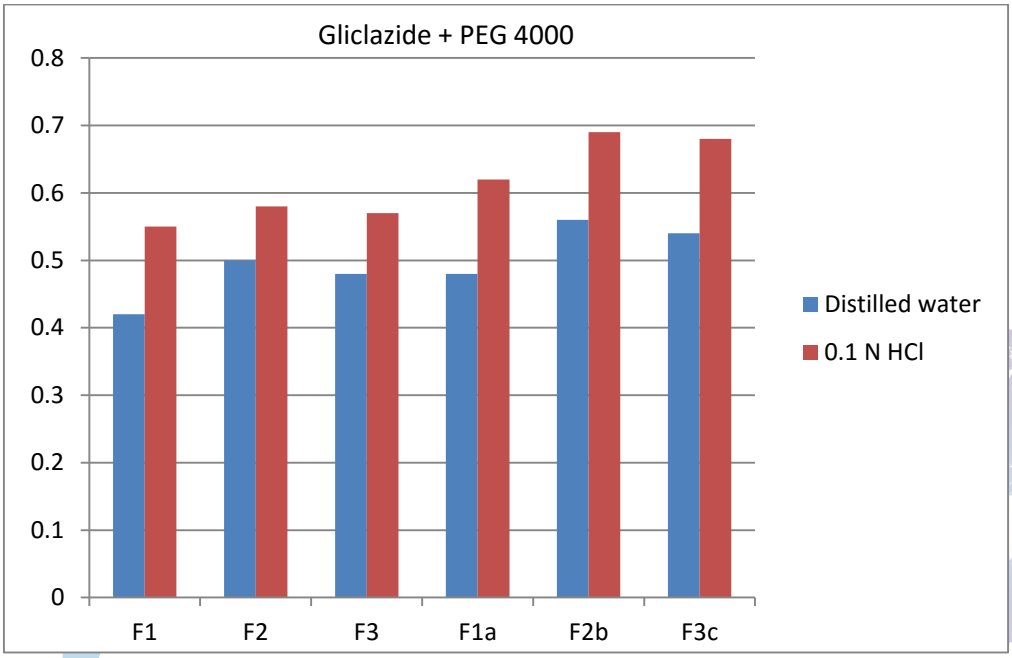

Figure.3. Comparison of kneeding method and microwave irradiation method by using gliclazide + PEG 4000

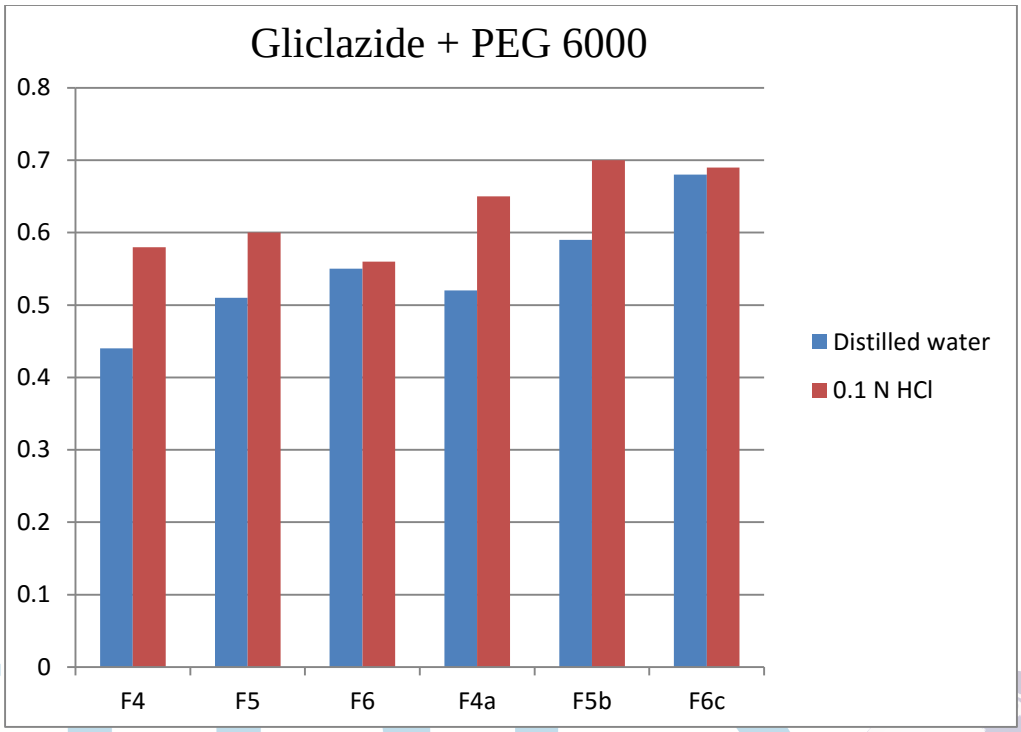

Figure.4. Comparison of kneeding method and microwave irradiation method by using gliclazide + PEG 6000

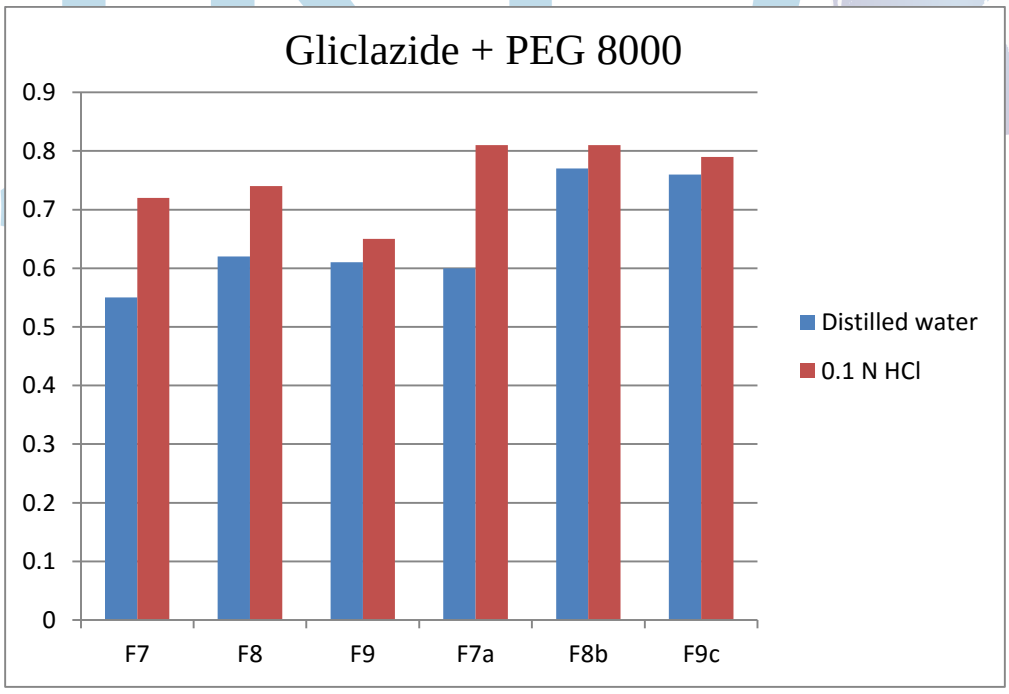

Figure.5. Comparison of kneeding method and microwave irradiation method by using gliclazide + PEG 8000

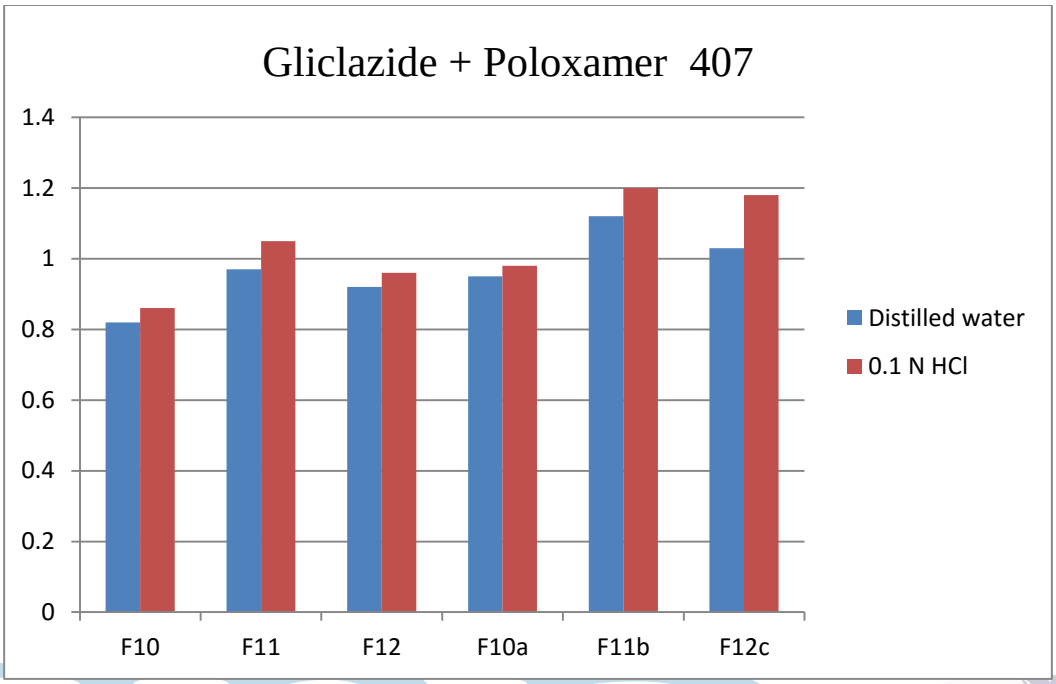

Figure.6. Comparison of kneeding method and microwave irradiation method by using gliclazide + Poloxamer 407

2) Physico chemical characterization of prepared tablets

Table 2. Physico-chemical characterization of Mucoadhesive tablets of Glicalzide

Sr No.	Formulation code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	Mucoadhesive strength (N)	Weight variation (%)
1	F-1	2.0±0.10	6.42±0.15	0.75	96.20±3.14	0.425	Pass
2	F-2	2.2±0.15	5.50±0.12	0.68	95.30±2.12	0.420	Pass
3	F-3	2.10±0.18	5.72±0.09	0.75	94.32±2.75	0.412	Pass
4	F-4	2.20±0.18	5.70±0.18	0.65	94.60±2.81	0.410	Pass
5	F-5	2.0±0.15	5.62±0.12	0.65	94.20±3.55	0.381	Pass
6	F-6	2.2±0.15	5.5±0.13	0.74	94.37±3.74	0.350	Pass
7	F-7	2.2±0.10	4.7±0.09	0.75	93.56±1.61	0.375	Pass
8	F-8	2.4±0.10	4.8±0.15	0.55	90.21±2.67	0.343	Pass
9	F-9	2.3±0.15	4.8±0.12	0.60	90.03±1.34	0.365	Pass

4) Swelling index

Table 3.Swelling index

Batch code	Time						
	0hr	1hr	2hr	3hr	4hr	5hr	6hr
F-1	0	3.6±0.49	6.52±1.27	11.95±2.41	14.32±1.83	18.21±2.49	22.57±2.57
F-2	0	3.92±0.35	6.87±0.79	12.56±1.22	17.22±2.37	20.12±1.41	24.45±2.24
F-3	0	2.85±0.73	5.75±1.05	9.45±2.42	14.52±1.90	19.36±1.53	22.85.±1.68
F-4	0	3.6±0.49	5.75±1.05	11.95±2.42	14.32±1.83	18.21±2.49	22.57±2.57
F-5	0	3.25±0.49	6.52±1.27	11.95±2.41	14.32±1.83	18.21±2.49	22.57±2.57
F-6	0	3.10±0.68	6.86±0.89	10.73±1.18	14.45±1.89	18.11±2.72	22.46±2.29
F-7	0	3.26±0.73	6.45±0.68	11.32±0.98	14.70±1.72	18.45±2.57	23.16±3.19
F-8	0	3.89±0.84	7.02±1.58	12.45±2.39	16.58±1.65	21.12±2.74	25.82±3.58
F-9	0	3.65±1.22	6.43±0.87	11.20±1.38	15.35±2.10	19.74±2.24	24.21±2.87

*Values all mean ± SD (n=3)

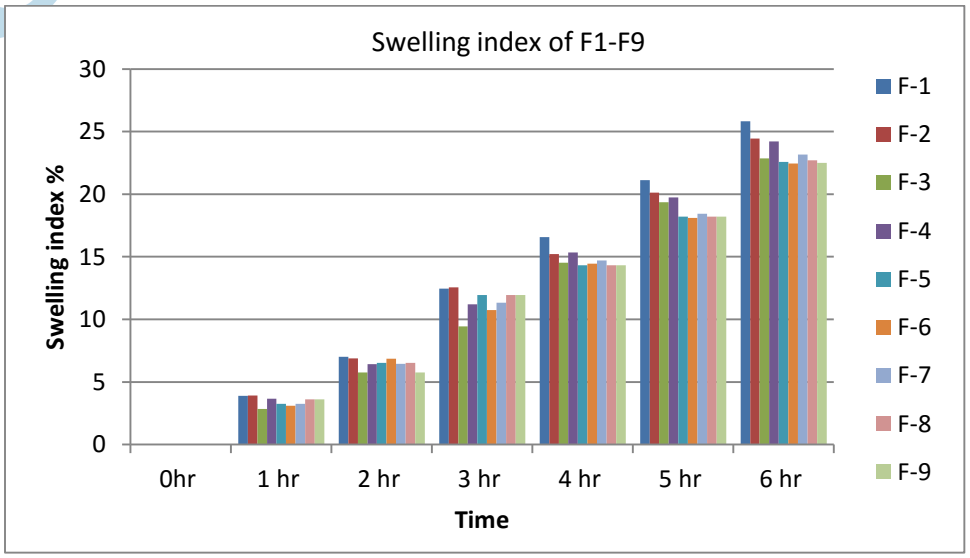

Figure.7. Swelling index

4) In vitro release study

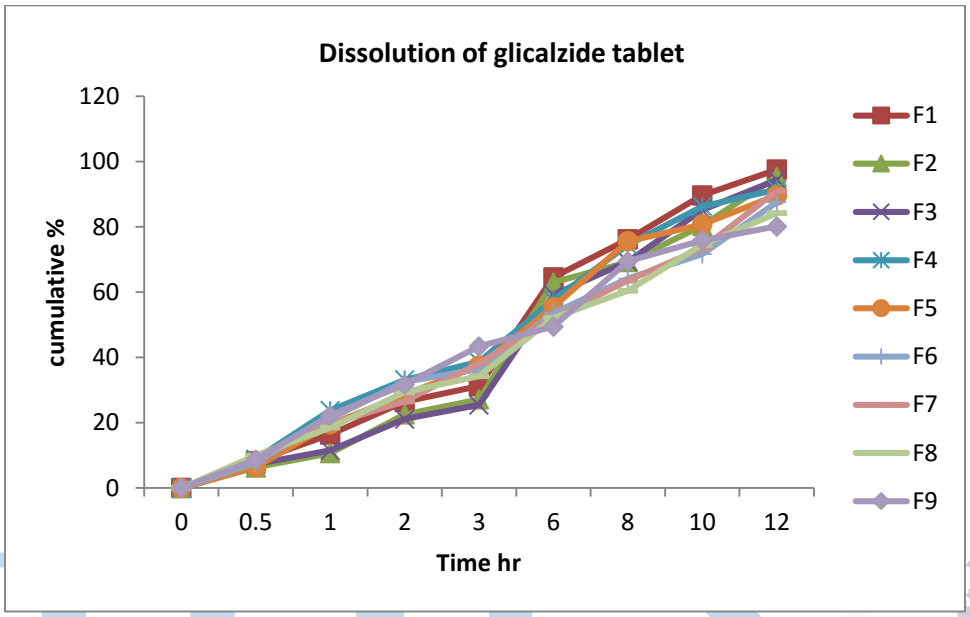

Figure 3. In vitro drug release profile of Gliclazide from Mucoadhesive tablet formulations.

5) Stability study

The tablets were stored for 1 month at 40˚C/ 75% RH. The result do not show any significant change in physical appearance, mucoadhesive strength and dissolution behavior of mucoadhesive tablets in comparison with initial values. Similarity factor f2 was found to be 83%.

DISCUSSION

The angle of repose was found to be in the range of 23.21 to 35.80 having excellent or good flow property. Hausner's ratios of preliminary trials were found to be in the range of 1.13 to 1.35 having moderate flow property. Carr's index were found to be in the range of 16.67 to 25 having passable flow property. The thickness all tablets was found to be in the range of 3.37 to 3.40mm. Sufficient strength of all tablets was also evident since the friability was less than 1%, indicating compliance with the requirements of Indian pharmacopeia. Hardness of tablets were found to be between 4.70 to 6.42K Pascal indicated good strength. The average weight of the prepared tablets were in the range of from 295to 302 mg. Tablets of all batches complied with the mass variation requirement of Indian

Pharmacopoeia, here no batch variation > 5% of average weight which indicates that consistency in the preparation of the tablet having minimum batch to batch variation. The mucoadhesive strength of all tablets was found to be in the range of 0.343 to 0.425 (N). There was proper distribution of the drug in the mucoadhesive matrix tablets according to results of drug content analysis and well within the range of 90.03 to 96.20 % of the total amount of the drug added in mucoadhesive matrix tablets so, comply with the pharmacopoeial limit. Compatibility study performed with various excipients, the physical attributes of the tablet were found to be satisfactory. Then the solubility enhancement of gliclazide was successfully done using solid dispersion technique with different ratio of polymers. Then the dosage form was formulated using direct compression technique. Results for other physical evaluations were also found to be within the limit. Optimization of tablet formulation using 3^2 factorial designs was carried out. There were two response considered in factorial design, dissolution at 6 hr and dissolution at 12 hr. Analysis of variance carried out for this 2 responses. 2 factor interaction model selected for response 1 and linear model selected for response 2. Contour graph and 3D surface graph of these two responses created after choosing model. Optimized batch find out using software minitab 17 and dissolution study carried out of optimized batch. Stability study of optimized batch was carried out at 40Ċ in a humidity jar having 75% RH specified by ICH. Results of the stability studies showed that there were no significant changes in the drug content and physical appearance of tablets

CONCLUSION

The present study was aimed to develop prolong release stable, pharmaceutically equivalent formulation of gliclazide using polymers HPMC K15M and Carbopol 934 optimized by 3^2 full factorial design. Formulation of gliclazide had potential application as ant diabetic for sustained delivery of drug following in oral administration.

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