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Research Article

FORMULATION AND EVALUATION OF GLICLAZIDE MODIFIED RELEASE TABLETS USING HYDROXYPROPYL CELLULOSE

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ABSTRACT
The purpose of this research work was to prepare a modified release tablet of gliclazide by using different grades of Hydroxypropyl cellulose. Infrared spectroscopy study showed that drug and other excipients were compatible with each other. The granules were evaluated for angle of repose, bulk density and compressibility index. The tablets were evaluated to weight variation, thickness, hardness, friability, drug content, *in-vitro* drug release. The granules showed satisfactory flow properties. All the tablet formulations showed acceptable pharmacotechnical properties and complied in house specifications for tested parameters. The dug release from each preparation was analyzed by using release kinetic theories. This study showed that release process involved erosion and diffusion. The Accelerated stability study was also performed for optimized formulation for three months indicated that optimized formulation was stable.

KEYWORDS: Gliclazide, Hydroxypropyl Cellulose, Modified release tablet.

INTRODUCTION
Modified release preparations provide an immediate dose required for the normal therapeutic response, followed by the gradual release of drug in amounts sufficient to maintain the therapeutic response for a specific extended period of time. The major advantage of this category is that, in addition to the convenience of reduced frequency of administration, it provides blood levels that are devoid of the peak-and-valley effect which are characteristic of the conventional intermittent dosage regimen[1,2].
Gliclazide (GL) is structurally classified as a sulphonyl ureas second generation analogs. The mean absolute bioavailability of Gliclazide modified release was 97%. It shows linear pharmacokinetics over the 15 to 120mg dose range in patient with diabetes mellitus intraindividual variability is low; at 16%. C_{max} is reached at about 6hr. After administration fasting C_{max} was 0.74mg/L at a t_{max} of 7 hours and the area under the plasma concentration time curve (AUC) is 16.2mg/L. Gliclazide is highly bound to albumin (95%). In patient of type two diabetes mellitus the apperant clearance of Gliclazide modified release was 0.9 L/h, with an apparent volume of distribution of 19L[3,4].
Among the various types of cellulose derivatives, hydroxypropyl cellulose (HPC) polymers are popular in controlled release matrices due to their compatibility with numerous drugs. The adjustment of the polymer concentration and the viscosity grade and the addition of different types and levels of excipients in the HPC matrix can modify the drug release rate[5].
The objective of the present work was to prepare modified release tablets of GL by wet granulation method and to study the effect of concentration of hydrophilic polymer (HPC) on the drug release profile on tablets.

MATERIALS AND METHODS
Gliclazide and Hydroxypropyl cellulose grade like klucel GXF, klucel JXF, klucel EXF were received as a gift samples from Indoco Remedies Pharmaceuticals Research Centre, Mumbai, India. Microcrystalline

cellulose, Povidon and magnesium stearate used were USP/NF quality. All other chemicals and reagents were of analytical grade.

Drug-Excipients Interaction Studies

Assessment of possible incompatibilities between an active drug substance and different excipients forms an important part of the preformulation stage during the development of solid dosage form. Infrared spectroscopy (IR) allows the Evaluation of possible incompatibilities.

Preparation of Tablets

Modified release tablets were prepared by wet granulation technique using HPC polymer shown in table no 1. First seven ingredients with drug were weighed accurately and passed through the sieve no.40. Separately mix it into RMG for 10 min. Wet granulation was carried out at high speed with water. Pass these granules through multi mill sieve no.3 to get fine granules. Dry these granules in Retch dryer to get LOD below 1.45%. Passed these dried granules through the sieve no.1 of multi mill. Lubrication was done by using octagonal blender with aerosol for 15 min and 3 min with magnesium stearate and this lubricated blend was compressed into tablets using 10.1 x 5.1 mm flat face with upper break line on a 16 stationary rotary punching tablet machine[6].

Evaluation of Tablet Blends

Angle of Repose

The fixed funnel and free-standing cone methods employed a funnel that was secured with its tip at given height (h), which was kept 2 cm, above graph paper that was placed on a flat horizontal surface with r, being the radius of base of conical pile. Angle of repose (Θ) can be determined by equation: $\tan \Theta = h/r$[7]

Bulk Density and Tapped Density

An accurately weighed quantity of the granules or powder (W) was carefully poured into the graduated cylinder and volume (V_o) was measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP). The density apparatus was set for 100 tabs and after that the volume (Vf) was measured and continued operation till the two consecutive readings were equal. The bulk density and the tapped density were calculated using the following formulae[8].

$$\text{Bulk density} = W/V_o$$

$$\text{Tapped density} = W/V_f$$

Hausner's Ratio

Hausner's ratio indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density. Hausner's found that this ratio was related to interparticle friction and as such could be used to predict powder flow properties. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index.

$$\text{Hausner's Ratio} = \text{Tapped density}/\text{Bulk density}$$

Carr's Compressibility Index

An indirect method of measuring power flow from bulk densities was developed by Carr. The percentage compressibility of a power was a direct measure of the potential powder arch or bridge strength and stability. Carr's index of each formulation was calculated according to equation given below:

$$\text{Carr's Compressibility Index (\%)} = [(TBD-LBD) \times 100]/TBD$$

Were TBD is the tapped bulk density and LBD is the loose bulk density.

Evaluation of Tablets

Uniformity of Weight

Every individual tablet in a batch should be in uniform weight and weight variation within permissible limits. The weights were determined by using Sartorius balance (BT 124 S). Weight control was based on a sample of 20 tablets.

Thickness

Thickness was determined to within ±0.01mm by using digital vernire calipers.

Hardness

The hardness was measured by using testing apparatus (Dr.Sheleuniger Pharmatron). A tablet hardness of about 6-8 kg was considered adequate for mechanical stability. Determinations were made in triplicate.

Friability

The friability (F) of the tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai). Tablets of a known weight (W_o) or a sample of 400 tablets are deducted in a drum for a fixed time (4000 revolutions) and weighed (Wt) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1%.

$$\% F = \{1-(Wt/Wo)\} X 100$$

Drug Content Uniformity

Crush one tablet on butter paper and transfer an accurately, without loss to 500ml volumetric flask, add 20ml methanol and sonicate for 5min, add 200ml of diluent and shake mechanically for 60 min, make volume up to mark with diluent. Filter the solution with 0.45µm membrane filter. Discard first 3 to 4 ml of filtrate, pipette out 4 ml of this filtrate solution to a 20 ml volumetric flask and dilute up to the mark with diluent. Take the absorbance at 226nm and 290nm using diluent as a blank for a background correction[3,4,9]. Take absorbance in a triplicate of a standard solution and duplicate of a sample preparation.

Corrected absorbance = absorbance at 226nm – absorbance at 290nm.

$$\text{Percentage content Uniformity} = \frac{\Delta At \text{ X } Ws \text{ X } 1 \text{ X } 500 \text{ X } 20 \text{ X } P}{\Delta As \text{ X } 100 \text{ X } 20 \text{ X } 1 \text{ X } 4 \text{ X } LC}$$

Δ At – Corrected absorbance of a sample preparation

Δ As – Average of corrected absorbance of a standard preparation

Ws - Weight of gliclazide working standard taken in mg

P - Potency of gliclazide working standard on as is basis

LC – Label claim of gliclazide as per tablet in mg

***In-Vitro* Dissolution Study**

The release rate of GL Modified release tablet was determined using USP dissolution testing apparatus I (basket method). The dissolution test was performed using 900 ml of phosphate buffer (pH = 7.4), at 37 ± 0.5°C and 100 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at 1, 2, 4, 6, 8, 10, 12 and 14 hours. The samples were replaced with fresh dissolution medium of same quantity. The samples were filtered through a 0.45mm membrane filter. Absorbance of these solutions was measured at 271nm using a UV – 1800; Varian 21 cfr-11 UV/V double beam spectrophotometer[12, 13].

Similarity Factor And Dissimilarity Factor Calculation

The similarity factor (f2) was defined by FDA as the "logarithmic reciprocal square root transformation of one plus the mean squared difference in percent dissolved between the test and reference release profile." f2 value calculated is the simplest among those methods. Moore & Flanner proposed model independent mathematical approach to compare the dissolution profile using two factors f2[9].

$$f2 = 50.\log \{[1+ (1/n) \Sigma_{t=1}^{n} (R_t-T_t)^2]^{-0.5}.100\}$$

Where 'R_t' and 'T_t' are the cumulative percentage dissolved at each of the selected 'n' time point of the reference & test product respectively. Factor f2 is inversely proportional to the averaged squared difference between the two profiles, with emphasis on the larger difference among all the time points. If the f2 value is between 50-100 the release of the test and the reference are identical.

Accelerated Stability Studies

Optimized formulation were packed in blister and stored in ICH certified stability chambers maintained at 40°C±2 °C and 75%±5% RH for three months. The tablets were withdrawn periodically and evaluated for drug content and release studies.

RESULTS AND DISCUSSION

Physical mixture of drug and polymer was characterized by FTIR spectral analysis for any physical as well as chemical alteration of the drug characteristics. From the results, it was concluded that there was no interference in the functional group as the principle peaks of the Gliclazide were found to be unaltered in the drug-polymer physical mixture, indicating they were compatible chemically.

The granules of the different formulations are evaluated for angle of repose bulk density, tapped density, compressibility index, hausner's ratio and the results were shown in Table No: 2.

The prepared tablets were subjected to preliminary characterization such as hardness, thickness, average weight variation, friability and drug content. The evaluated parameters were within acceptable range for all the formulations. The values are indicated in Table No: 3.

The *in-vitro* results of all the formulations were obtained by dissolution testing and similarity factor value f2 value was calculated. The in-vitro release of F2 formulation with concentrations of klucel JXF 21%, F3 (klucel JXF 18%) and F4 (klucel JXF 18% cum klucel EXF 3%) was faster. The desired f2 value was not achieved. The formulation F5, F6 &F7 were formulated with different concentrations of klucel GXF 12%, 13% and 15% cum klucel EXF 12% respectively and the release was sustaining as the viscosity concentration of the polymer was increasing and but the desired f2 value were not achieved. Next batch (F8) was formulated with klucel GXF 18% cum EXF 12 %, the release was found to be higher than that of the innovator F1. So the F9 formulation was decided to formulate with GXF 15% cum EXF 12% and found that release was good and highest f2 (56.9) value was obtained, therefore this F9 formulation was decided to be comparable with innovator F1.

The release data was fitted into various mathematical models to know which mathematical model will best fit the obtained release profile. The regression coefficients of all formulations data were shown in Table No: 4. Based on highest regression value(r) the best-fit model for F4 & F5 was higuchi matrix and remaining all formulations (F2, F3, F6-F9) followed peppa's model. Based on the "n" values ranging from 0.5-1.0, the drug release was found to follow Anomalous (Non-Fickian) transport. This value indicates a coupling of the diffusion and erosion mechanism and indicates that the drug release was controlled by more than one process. Based on the value of "n" (n=0.8363) for innovator product (F1), it was also found to follow the same release mechanism.

Stability studies revealed that there was no significant change in hardness, friability, drug content and dissolution profiles of F9 during the period of 90 days. In light of the aforementioned discussion, it could be concluded that hydroxypropyl cellulose can be used as an effective matrix former, to develop modified release formulation of Gliclazide, which release 30% of drug in the two hours and extend the release up to 14 hours, can overcome the disadvantages associated with conventional tablets formulation of Gliclazide.

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Table 1: Actual values of ingredients taken for Matrix tablet

INGREDIENTS	F2	F3	F4	F5	F6	F7	F8	F9
Gliclazide	30	30	30	30	30	30	30	30
Microcrystalline cellulose	82.3	82.5	82.5	77.8	65.3	75.8	67.3	72.3
Calcium carbonate	5	5	5	5	5	5	5	5
Povidone k-30	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5
HPC[klucel GXF]	-	-	-	20	22	24	30	25
HPC[klucel JXF]	35	30	30	-	-	-	-	-
HPC[klucel EXF]	-	-	5	20	20	20	20	20
Colloidal anhydrous silica	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Magnesium stearate	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Water	qs.	qs.	qs.	qs.	qs.	qs.	qs.	qs.

*All the values are in mg

F1 was Innovator (commercial MR tablet with 30 mg of gliclazide).

Table 2: Physical characteristics of prepared blend of Gliclazide

Batch	Angle of repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility index	Hausner's ratio
F2	$31^0 95''$	0.322	0.523	38.5	1.62
F3	$35^0 89''$	0.453	0.642	29.5	1.41
F4	$36^0 89''$	0.432	0.521	17.1	1.21
F5	$35^0 89''$	0.331	0.431	23.5	1.32
F6	$31^0 89''$	0.412	0.541	23.9	1.31
F7	$30^0 89''$	0.412	0.532	22.2	1.26
F8	$35^0 89''$	0.425	0.521	18.5	1.22
F9	$30^0 89''$	0.432	0.544	20.6	1.25

Table 3: Evaluation properties of Gliclazide compressed tablets

Formulation code	Thickness (mm) ±S.D. (n = 5)	Hardness(kg/cm^2) ±S.D. (n = 5)	Friability (%)	Average weight Variation (mg) (n = 20)	Drug content (%)
Innovator	3.11±0.023	7.32±0.2	0.24±0.005	161.6±0.435	99.4
F2	3.10±0.024	7.92±0.4	0.16±0.020	160.3±1.600	96.0
F3	3.08±0.158	7.31±0.4	0.19±0.020	161.7±0.237	112.0
F4	3.11±0.020	7.98±0.5	0.02±0.015	160.7±0.776	106.4
F5	3.12±0.064	7.9±0.1	0.27±0.005	160.1±1.351	99.4
F6	3.09±0.045	7.36±0.3	0.32±0.066	158.7±2.270	103.6
F7	3.10±0.023	7.38±0.3	0.07±0.015	159.8±1.050	101.2
F8	3.12±0.100	7.65±0.5	0.30±0.026	160.6±1.051	104.3
F9	3.08±0.065	7.88±0.4	0.02±0.017	161.3±2.321	101.7

Table 4: Mathematical modeling of formulated Gliclazide Matrix tablets

Batch	Zero order regression coefficient (r^2)	First order regression coefficient (r^2)	Higuchi equation regression coefficient (r^2)	Slope of krosmeyer's-peppa's plot (n)	Krosmeyer's regression coefficient (r^2)
F2	0.726	0.989	0.919	0.606	0.979
F3	0.902	0.983	0.965	0.692	0.988
F4	0.806	0.924	0.962	0.638	0.941
F5	0.826	0.844	0.967	0.587	0.949
F6	0.910	0.936	0.967	0.659	0.999
F7	0.884	0.953	0.967	0.693	0.969
F8	0.942	0.867	0.971	0.728	0.993
F9	0.932	0.956	0.961	0.732	0.989

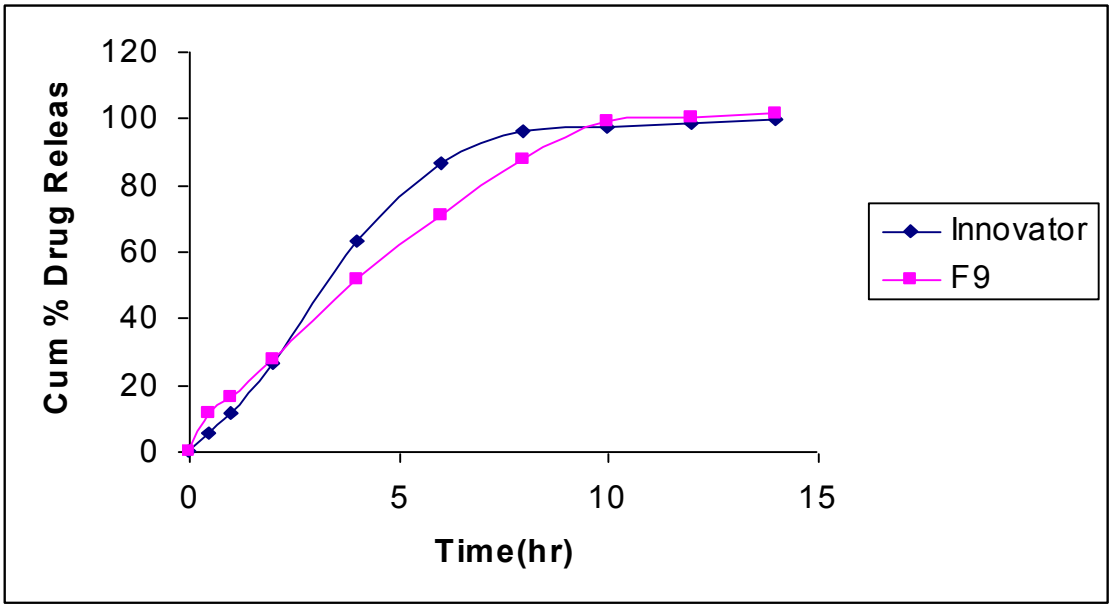

Fig 1: Comparison Of In- Vitro Drug Release Profile Of Gliclazide From Formulated Matrix Tablet (F-9) And Commercial MR Tablet (Innovator-F1).

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