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Research Article

FORMULATION AND IN-VITRO EVALUATION OF MODIFIED RELEASE TABLETS OF GLICLAZIDE (ANTIDIABETIC DRUG)

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ABSTRACT

Objective: An attempt was made to formulate the modified release dosages form of Gliclazide using various release retarding polymers *viz.* HPMC K15M, HPMC K100M and EC.

Methods: Modified release tablets containing 120 mg of Gliclazide were developed with different polymers. The tablets were prepared by wet granulation method. The formulations were optimized on the basis of acceptable weight variation, friability, hardness properties and *in vitro* drug release.

Results: The results of dissolution studies suggested that formulations FG3 exhibited good and controlled drug release. Applying the linear regression analysis and model fitting, the selected formulation FG3 have showed diffusion (non-fickian) release mechanism, and shown to follow first order kinetics.

Conclusion**:** The modified release tablets of Gliclazide were prepared and these tablets have advantages of lowering the dose frequency and improve the patient compliance by providing the better management of NIDDM.

Keywords: Gliclazide, Modified release, Wet granulation method, In-vitro dissolution, Linear regression analysis, Release kinetic models.

INTRODUCTION

Solid-dosage forms comprehend the largest category of dosage forms that are clinically used. There are several types of tablet solid dosage form that are designed to optimize the absorption rate of the drug, increase the ease of administration by the patient, control the rate and site of drug absorption and mask the taste of a therapeutic agent. The formulation of tablets involves the use of several components, each of which is present to facilitate the manufacture or to control the biological performance of the dosage form. Sustained/Modified release dosage forms are a convenient means to obtain a reduction in daily administration of drugs with fast absorption and/or elimination. In general, the goal of sustained-release dosages form is to maintain the therapeutic blood or tissue level of drug for an extended period of time and thereby reducing the dose frequency and increasing the patient compliance.

Gliclazide is an oral hypoglycemic agent which used for the treatment and management of non-insulin-dependent diabetes mellitus (NIDDM). It is classified under the category of sulfonylurea drugs and belongs to the second-generation of this group of drugs [1]. It improves faulty insulin secretion and inverts insulin resistance which is observed in patients with NIDDM. These actions are reflected as a step-down in blood glucose levels which is maintained during both short and long term administration, and is comparable with that achieved by other sulphonylurea drugs [2]. Gliclazide has an intermediate half-life of around 11 hours and it is extensively metabolized, and its renal clearance accounts for only 4% of total drug clearance. Gliclazide is highly bound to plasma proteins (more than 90%).

MATERIAL AND METHOD

Gliclazide was generously provided by Dr. Reddy's Laboratories, Hyderabad, HPMC K15M, HPMC K100M, Ethyl Cellulose were gifted by Colorcon Labs, sodium bi-carbonate, mag. sterate, talc, lactose was purchased from CDH Pvt. Ltd, New Delhi. All the ingredients used were of analytical grade.

Manufacture of tablets by wet granulation: Following manufacturing steps were used in the manufacture of tablets by the wet granulation method:

Stage 1*: Mixing of the Therapeutic Agent with the Powdered Excipients (without Lubricant):* This step involves the introduction of the powdered excipients and drug (excluding the lubricant) into a powder mixer. The mixing speed and time must be sufficient to ensure that a homogeneous mixture is produced.

Stage 2: *Wet Granulation of the Powder Mix:* Granulation is a unit operation in which mixed powders are aggregated into and retained as larger particles (approximately 0.2–4.0 mm in diameter). Granulation is done to prevention of segregation of powder components during the tabletting process or during storage, enhancement of the flow properties, enhancement of the compaction properties and to lower incidence of dust production.

Stage 3: *Processing Granules into Tablets:* the prepared granules were compressed in to the tablets using the rotating tablet punching machine (lab instrument). Following stages were followed during the compression of the granules.

1. The filling of the die with the granules/powders.
2. Compression of the powder/granule bed.
3. Tablet ejection.

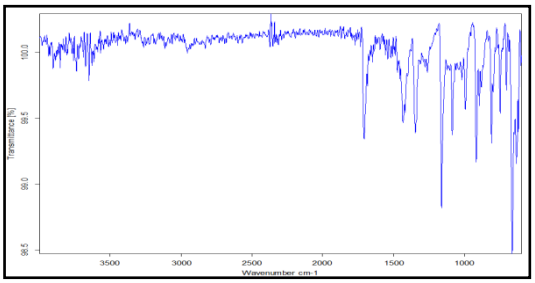

Fig. 1

Drug-Excipient interaction: The drug excipient study was done by FTIR (Fourier Transform Infra Red). In infrared spectroscopy, IR radiation is passed through a sample. Some of the infrared radiation is absorbed by the sample and some of it is passed through (transmitted). The resulting spectrum represents the molecular absorption and transmission, creating a molecular fingerprint of the

sample. Like a fingerprint no two unique molecular structures produce the same infrared spectrum. This makes infrared spectroscopy useful for several types of analysis. Fourier Transform Infrared (FT-IR) spectrometry was developed in order to overcome the limitations encountered with dispersive instruments. The samples were scanned in 400-4000 wave number range, using KBr pellet technique.

Preparation of Modified Release Tablets of Gliclazide: The drug (Gliclazide) and the excipients (without lubricant) were weighed accurately and sifted through sieve # 60. The materials were then subjected to dry mixing in mortar and were mixed thoroughly to produce the homogeneous blend. Purified water was added slowly to the above materials and blending was executed. The blended material was passed through sieve # 60 and dried in a hot air oven at 60^0 C for 1 hour.

The dried granules were then repeatedly passed through sieve # 30. To the dried granules, the previously sifted magnesium stearate was added to the blend to enhance the flow ability and finally the granules were compressed to round, flat tablets. The formulations were prepared as shown in the Table 1.

Table 1: Ingredients for the MR Formulation of Gliclazide (F1-F8)

Ingredients / Formulation Code	FG1	FG2	FG3	FG4	FG5	FG6	FG7	FG8
Gliclazide	120	120	120	120	120	120	120	120
HPMC K15M	2	4	2	4	2	4	2	4
HPMC K100M	10	20	-	-	20	10	-	-
Ethyl Cellulose	-	-	10	20	-	-	20	10
Sodium Bi Carbonate	5	5	5	5	5	5	5	5
Mag. Sterate	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1
Lactose	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Total Weight	500	500	500	500	500	500	500	500

Evaluation of Tablets

Weight variation: All the tablets were evaluated for weight variation as per USP XXIV monograph. Twenty tablets of each formulated batch were used to evaluate weight variation among tablets and mean and standard deviation was calculated [3, 4].

Friability: twelve random tablets of all batches were used to evaluate the friability as per USP XXIV monograph. Friability testing was done by Roche Friabilator, and the SD was determined [5, 6].

Hardness: the hardness of the tablets was determined using Pfizer hardness tester. The test was carried out in triplicate for all batches as per USP XXIV monograph for uncoated tablets [5, 6].

Thickness*:* The thickness of the matrix tablets was determined using vernier caliper and the results were expressed as mean values of 10 determinations, with standard deviations [7, 8].

Drug content: The tablets were powdered, and 120 mg equivalent weight of Gliclazide in tablet powder was accurately weighted and transferred into a 100 ml volumetric flask. The prepared sample was filtered and analyzed at 229.50 nm against a reagent blank solution prepared similarly without drug using Shimadzu 1800 UV-Visible double beam spectrophotometer. The drug content of the each sample was estimated from their previously prepared standard curve [3, 6].

***In-vitro* drug release study:** *In-vitro* drug release was studied using Dissolution Apparatus in 900 ml phosphate buffer pH 7.4, which was maintained at 37±1°C for 12 h, at 100 rpm. 5ml of sample was withdrawn after specified time interval, and was replaced by an equal volume of fresh dissolution medium.

Collected samples were analyzed spectro-photometrically at measured wavelength of 229.50 nm against a reagent blank solution prepared similarly without drug using Shimadzu UV-Visible double beam spectrophotometer, and cumulative percent drug release was calculated [5, 6]. The test was performed in triplicate to assure reproducibility of results.

RESULTS AND DISCUSSION

The prepared Gliclazide Modified Released Tablets were subjected to the above said evaluation parameters and testing was done according to the official methods.

Drug-Excipient Interaction Study: No interaction was found between drug and excipient used. This can be predicted on the basis of no change in peak in the characteristic Fourier Transformation Infrared Spectroscopy was obtained.

Hardness: The results have been shown in Table 2. The result obtained demonstrated that the tablets have good mechanical strength that is capable of withstanding the mechanical shear.

Weight variation analysis: The results of weight variation have been shown in Table 2. The results depicted that the tablets were within the limits.

Friability: The results were shown in Table 2. The values were within the range of 0 - 1.0 %.

Content Uniformity: The results of content uniformity were shown in Table 2.

Table 2: Post-compression evaluation of Formulation F1-F8:

Parameters	Weight Variation	Hardness (kg/cm^2)	Friability (%)	Drug content
FG1	510.7 ± 0.67	4.26 ± 0.25	0.020	95.42% ± 0.063
FG2	511.2 ± 0.79	4.34 ± 0.21	0.039	97.79% ± 0.022
FG3	507.2 ± 0.63	4.35 ±0.24	0.025	96.57% ± 0.039
FG4	511.3 ± 0.67	4.1 ± 0.21	0.031	95.92% ± 0.048
FG5	513.3 ± 1.49	4.3 ± 0.26	0.039	98.28% ± 0.011
FG6	510.7 ± 0.82	4.34 ± 0.21	0.033	96.65% ± 0.013
FG7	507.9 ± 0.74	4.35 ± 0.24	0.020	97.39% ± 0.013
FG8	520.5 ± 0.71	4.29 ± 0.19	0.038	95.75% ± 0.025

Table 3: Correlation Coefficient (R^2) of the Optimized Formulation FG3

Formulation Code	Zero Order	First Order	Higuchi	Korsmeyer-Peppas
FG3	0.805	0.973	0.939	0.914

***In-vitro* Dissolution Studies**

The results of *in-vitro* dissolution studies were obtained and fitted in various mathematical models viz. zero order, first order, higuchi and korsmeyer-peppas models to anticipate the release kinetics. The

results of in-vitro dissolution have been shown in Figure 3-6. From the results obtained and fitting them into the mathematical models, it was confirmed that the drug release from formulations followed first-order kinetics by process ofanomalous (non-fickian) diffusion mechanism.

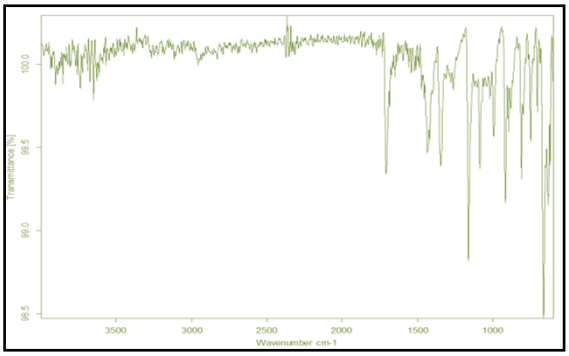

Fig. 2: FTIR of Optimized Formulation (FG3)

Form the *in-vitro* dissolution data, the Formulation FG3 have found to have maximum release for the extended period of more than 12 hrs and as predicted by the correlation coefficient, it seems to follow first order release kinetic.

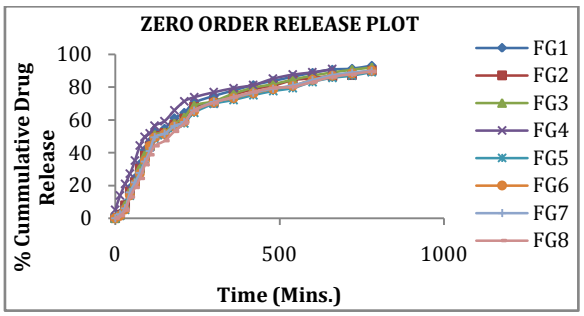

Fig. 3: Zero Order Release Plot for Formulations FG1-FG8

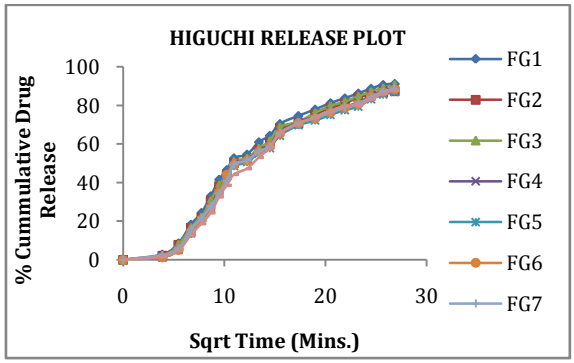

Fig. 4: First Order Release Plot for Formulations FG1-FG8

CONCLUSION

An attempt was made to develop formulations for the sustained release of Gliclazide. In the present work, it was concluded that formulation FG3 shows the best release that follows zero order kinetics with anomalous diffusion method. Therefore, it can be concluded that the Gliclazide Modified Release Tablets have an advantages of lowering the dose frequency and improve the patient compliance by providing the better management of NIDDM.

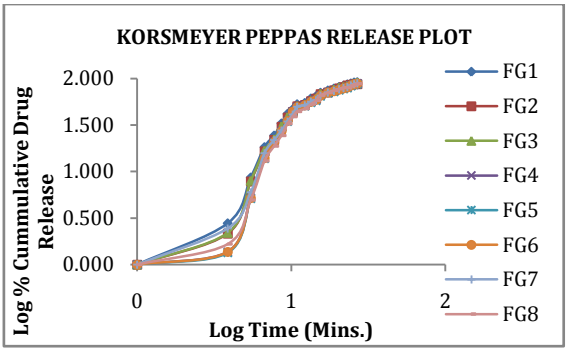

Fig. 5: Higuchi Release Plot for Formulations FG1-FG8

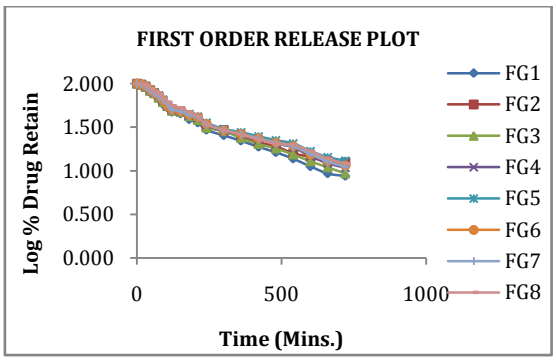

Fig. 6: Korsmeyer-Peppas Release Plot for Formulations FG1-FG8

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