Design, Development and Characterization of Giliclazide Delayed Release Tablet for better Therapeutic Efficacy

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Received Date: July 09, 2022; Published Date: August 10, 2022

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Citation: Sameer Shaikh Shakur, Harsha Rameshwar Barde, Mohammad Zishan Ibrahim, Shaikh Abid Shaikh Shabbir. Design, Development and Characterization of Giliclazide Delayed Release Tablet for better Therapeutic Efficacy. ICARE. 2022;1(1):1006.

Abstract

Gliclazide Sustained release tablets were prepared by Direct Compression method by using various polymers such as HPMC & Eutragit and when these two (HPMC & Eutragit) are used in combination then results in retardation of drug release. In the dissolution studies of all formulations, the formulation containing HPMC alone that is F1, F2 show 95% dissolution but there is a fluctuation in the drug release. The formulation containing Eudragit that is F3, F4 doesn't show proper or desirable dissolution profile. In F2, F5, F6 formulations the first two formulations release of drug is completed within 8 to 10 hours. The later formulation gives a drug release in a sustain manner. The formulation F5, F6 drug release profile is 99%. In the formulation F5 and F6 having swellable polymer HPMC K4M and non-swellable polymer (Eudragit L-100) showing desirable drug release profile. Hence the combinations of both polymers are better suitable for sustained release delivery. Thus, formulation F5 and F6 having both two polymers such as HPMC and Eudragit in the proportion of 1:1 show 99% drug release for longer duration of time.

Introduction

Tablets are unit solid dosage forms each containing a active pharmaceutical substance with an excipient. It is possible to incorporate the one or more active Pharmaceutical substance in tablets dosage form. Tablets are solid, flat or biconvex discs (as the shape od die cavity use), unit dosage form, prepared by compressing a drug or a powder mixture of drugs, with or without excipients

Oral route is most common route of drug delivery drug delivery. It has been known for decades as the most widely utilized route of administration from all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical product of different dosage form. For many decades, treatment of acute disease or a chronic disease has been mostly accomplishes by administration of drugs to patient by using various pharmaceutical dosage forms including tablets, capsules, suppositories, pills, creams, ointments, liquids, aerosols, and all injectable as a drug carrier. Drug administered by numbers of routes but oral administration is adopted ware ever possible. Oral drug delivery is considered the holy grail of drug delivery because easy to administer and more patients compliance. Oral route is the most commonly employed route of administration. All though different route of administration is used for the delivery of drugs, oral route remains the most preferred one. It is safest, easiest, and most economical route of drug administration. Most of drugs that are administered orally solid oral dosage forms i.e. tablets and capsules, are the most preferred class of dosage form. Out of the two oral

solid dosage forms, the tablets have number of advantages like temper proof, low, cost and speed of manufacturing (direct compression), ease of administration, patient compliance, and flexibility in formulation etc.

Materials and Methods

Table 1: Materials and name of suppliers

Material	Name of the Supplier
Gliclazide HPMC K4M	Oxford laboratory, Mumbai
Ethyl Cellulose	Thomas Chemicals Pvt. Ltd.
Microcrystalline cellulose (MCC)	Oxford laboratory, Mumbai
Potassium dihydrogen	Ranbaxy Fine chemical Ltd.
phosphate	
Eudragit L- 100	Thomas Chemicals Pvt. Ltd.
Magnesium Stearate	Oxford laboratory, Mumbai
Talc	Thomas Chemicals Pvt. Ltd.

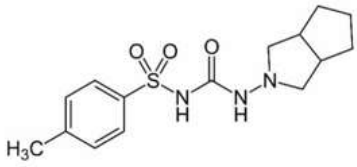
Table 2: Equipment's and name of manufacturer

Equipment's	Manufacturers
Single pan digital balance	Citizen CY 107, Mumbai
Digital bulk density apparatus	Jyoti scientific Ind. Gwalior (M.P.)
UV-visible Spectrophotometer	Shimadzu 2100
Hardness tester	Mutotoyo, japan
Melting point apparatus	Jyoti scientific Ind. Gwalior (M.P.)
Dissolution apparatus	Jyoti scientific Ind. Gwalior (M.P.)
Fournier- transform	Shital scientific machinery
Table punching machine	Skylab, Mumbai
Friabilator	Jyoti scientific Ind. Gwalior (M.P.)

Drug Profile

Gliclazide

Structural formula



Chemical Name: N-(hexahydrocyclopenta[c]pyrrol-2(1H)-ylcarbamoyl)-4-methylbenzenesulfonamide

Molecular formula: C15H21N3O3S

Molecular weight: 323.41 g·mol−1

Melting point: 180 to 182 °C (356 to 360 °F)

PKA: 5.8

Protein binding: >99.5%

Biological half-life: 10.4 hours

Solubility

Gliclazide is freely soluble in ethanol, methanol and completely insoluble in water.

Pharmacology

Pharmacokinetics and metabolism:

Absorption: Gliclazide is extensively absorbed from the gastrointestinal tract. Following oral administration of 3 mg/kg of gliclazide to four healthy subjects, the peak plasma levels (mean 5.0 µg/mL) were achieved between 4 to 6 hours. The absorption half-life in man is 1.3 hours.

Distribution: That means apparent volume of distribution in 4 healthy subjects was 20 to 40% of their total bodyweight.

Protein binding: Using equilibrium dialysis, it was found that the majority of the drug is protein bounded. At a plasma concentration of about 8 µg/mL, 94.2% of the drug was protein bound and 5.8% was free or unbound.

Metabolism: Although more than 90% of unchanged gliclazide is found in plasma after administration, this is intensively metabolized with little of the unchanged compound (<1%) found in urine. Five principal metabolites have been found in urine, essentially oxidised and hydroxylated derivatives, the majority of which undergo type-II metabolic reactions, i.e. glucuroconjugation.

Excretion: About 60 to 70% of Gliclazide is essentially eliminated through the urine and 10 to 20% through faeces.

Half-life: The elimination half-life of Gliclazide is near about 10.4 h.

Pharmacodynamics

Gliclazide acts primarily by increasing the secretion of endogenous insulin. Clinical studies demonstrate that the sulphonylureas are ineffective in completely in the patients with pancreatic disease and in juvenile onset diabetic patients. The mechanism of action is not completely understood. Sulphonylureas including gliclazide cause degranulation of the pancreatic beta-cells, this phenomenon results in an increasing the rate of insulin secretion.

Extra pancreatic effects of sulphonylureas have been reported and some of these may increase the effects of secreted insulin. These effects include deduction in hepatic uptake of endogenous insulin and the increased sensitivity of insulin to peripheral tissues. Sulphonylureas agents may increase hyperplasia of the beta-cells.

In normal therapeutic dose of gliclazide, it has been shown that the reduced platelet aggregation. When these are close to normal at the inclusion time, no significant difference is observed.

Indications

To control of hyperglycaemia in gliclazide responsive diabetes mellitus of stable, mild, non-ketosis prone, maturity onset or adult type which cannot be controlled by proper dietary management and exercise, or when insulin therapy is not appropriate.

Contraindications

- Known hypersensitivity or allergic reactions to gliclazide, other sulfonylureas, sulphonamides, or to any of the excipients of this product.
- Unstable and/or insulin dependent diabetes mellitus, particularly juvenile diabetes,
- diabetic ketoacidosis, diabetic pre-coma and coma.
- During stress conditions such as serious infection, trauma or surgery.
- In the presence of severe hepatic impairment.
- In presence of various renal disease.
- Treatment with miconazole via systemic route or oromucosal gel.
- Pregnancy and lactation.

Side Effects

- Common side effects of Gliclazide
- includes followings
- Constipation.
- Stomach ache.
- Feeling sick (nausea)
- Being sick (vomiting) or diarrhoea

Experimental Work

Performulation study [1-3]

Organoleptic characteristics:

Colour: A small quantity of active constituent's powder was taken on butter paper and viewed in well-lighting place.

Odour: some amount of drug was used to get the odour of drug.

Melting point determination

The melting point was determined by the capillary method using digital melting point apparatus. The capillary tube was filled by the pressing the open end gently into pure drug sample and packed by tapping the bottom of the capillary on a hard surface so that the drug pack down into the bottom of the tube. When the drug was packed into the bottom of the tube, the tube was placed into the slot of the apparatus, the apparatus was started and the temperature was noted at which the drug melting.

Determination of wavelength of maximum absorbance (lambda max)

50mg of drug was weighed accurately and transferred to 100ml of volumetric flask. Then 0.1N HCL. Was added to dissolve the frag completely. The volume was made up to 100 ml with 0.1N HCL and the sample is observed the UV spectroscopy to determine the maximum wave length.

FT-IR determination

The FT-IR Analysis of the pure drug was carried out for qualitative compound identification. The FT-IR spectra for pure drug were carrier out by KBr disc method, the spectrum was recorded in the range of 4000 cm-1 and 400 cm-1.

Partition coefficient

The partition coefficient of a gliclazide may be determined by shaking it with equal parts of two immiscible solvents

(the organic layer, which is saturated with water, and the aqueous drug solution) until equilibrium is attained. The 50g of drug was dissolved in 50ml of distilled water and 50ml of n-octanol in separating funnel. Shake well the flask then stand for phase separation. After that the two phases was separated out and measure the concentration of drug in water and n-octanol.

Solubility

Determination of Solubility of Drug by visual observation. A fixed amount of drug was taken and dissolves in to distilled water and observe the solubility visually. The same procedure was followed for glacial acetic acid, dichloromethane, methanol, phosphate buffer and 0.1N HCL.

Evaluation of Precompression Parameters

Hardness: [3,4]

The application of hardness testing enables you to evaluate a material's properties, such as strength, ductility and wear resistance, and so helps you determine whether a material or material treatment is suitable for the desired purpose. The term hardness indicates the ability of a tablet to a withstand shocks while handling and travelling. Its generally expressed in Kg/cm or in Newton (N).There are six main hardness tests that can be performed to evaluated hardness includes; Vickers, Rockwell, Brinell, Mohs, Shore and Knoop, Which one to use its depends on the type of material to be tested and the equipment available. Most common method which is used to determine the hardness of a tablet was Monsanto Hardness Tester.

Weight variation test: [5,6]

To study weight variation, 20 tablets of each formulated batch were collected randomly during compression and weighed using an electronic balance to obtain average weight of each tablet. And also, the individual tablet was weighted. IP limit for weight variation in case of tablets weighing more than 325mg is ± 5%.

Average weight of tablet(mg)	Percentage deviation (±)
130 or less	10
More then 130	7.5
More then 325	5

Friability: [7]

The friability test was carried out by using Roche Friability test apparatus. The 10 tablets were taken and carefully weighted before testing. The Friabilator was allowed to rotate 100 times, and that the tablets were removed. Removed loose dust from the Friabilator of tablets, and weighed accurately.

Angle of repose: [8]

The angle of repose was determined by fixed funnel method. A funnel was kept vertically in a stand at specific height above a paper on a horizontal surface. The funnel bottom was closed and granules were filled in funnel.

Table 3: Relationship between Angle of repose and Flow properties

Angle of Repose	Flow property
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk density and tapped density [3]

An accurately weighed quantity of the powder drug (W), was carefully poured into the graduated cylinder and the volume of that powdered drug (Vo) was Properly measured. Then the graduated cylinder was closed with lid, set into the density determination apparatus. The density apparatus was set for 100 taps and after that, the final volume (Vf) was measured.

***In Vitro* dissolution studies [9]**

In Vitro drug release studies of tablets dosage form was carried out in USP dissolution apparatus type 2(paddle). The dissolution test was performed using 900ml of 0.1 N HCL, at 37 ± 0.5ºC with 50rpm for first 2hr then after dissolution media using phosphate buffer of pH 6.8. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus and volume equipment to the amount of sample withdrawn was replaced with fresh dissolution medium.

In -Vitro drug release study [10]

Kinetic studies

Kinetic mode had described drug dissolution from solid dosage from where the dissolved amount of drug is a

function of test time. In order to study the exact mechanism of drug release from the tablets. Drugs release data was analysed according to zero order, first order, Higuchi square root. Korsmeyer peppas model. The regression coefficient R2 value nearer to 1 indicated the model fitting of the release mechanism

Results

Characterization of gliclazide

Organoleptic characterization and melting point determination:

Table 4: Organoleptic characterization and melting point Determination of drug

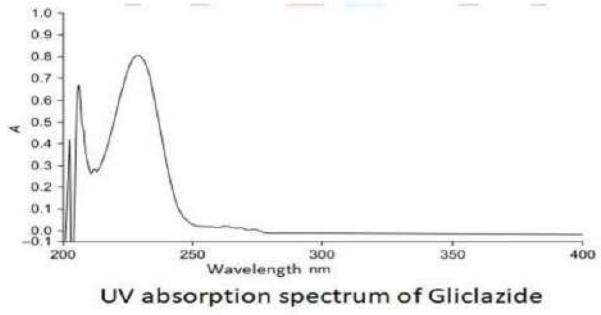
Characteristics	Observations
Colour	White
Odour	Odourless
Melting point	183-184°C

Solubility of gliclazide:

Sr. No.	Solvent	Solubility
1	Water	Insoluble
2	Ethanol	Soluble
3	Methanol	Soluble
4	DMSO	Soluble

Spectroscopic studies:

UV spectroscopy: The UV spectrum of Gliclazide in phosphate buffer pH 6.8 showed maximum absorption at 229.5 nm. Hence it has been prove that the drug used in the formulation was found to be pure according to USP specification. The UV spectrum of the Gliclazide in solution of phosphate buffer of pH 6.8 is given in following figure.



UV absorption spectrum of Gliclazide

Standard calibration curve of gliclazide: A standard curve was prepared by dissolving 10 mg of Gliclazide dissolved in required quantity of methanol and make up 100 ml with phosphate buffer pH 7.4 to get solutions in concentration ranges between 2 µg/ml to 8 µg/ml. The absorbance of these solutions was determined spectro-photometrically at 220 nm. The absorbance values were noted as shown in table 5 and figure 1,2 shows standard calibration curves with slope 0.0814 and regression value of 0.9995. The curve was found to be linear in the range between 2 to 8 µg/ml at the wave length of 229.5 nm.

Table 5: observations of standard calibration curve of gliclazide.

Concentration	Absorbance
2	0.0872
4	0.128
6	0.1695
8	0.2061
10	0.2101

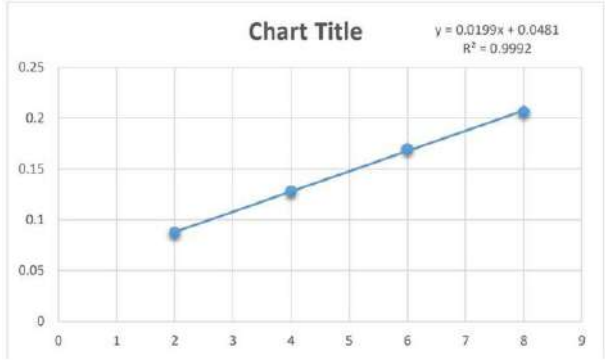


Figure 1: Calibration Curve of Gliclazide

FT-IR Spectra of Gliclazide

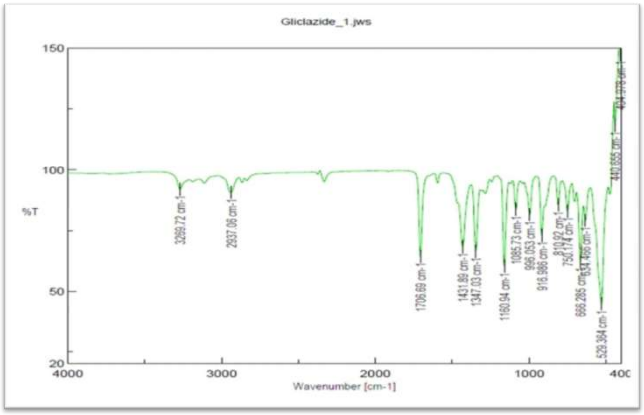


Figure 2: FT-IR Spectra of Gliclazide

Table 6: Pre-compression parameters of gliclazide

Formulations	Bulk density (gm\ml)	Tap density (gm\ml)	Angle of repose
F1	0.499	0.602	30.01
F2	0.502	0.606	26.98
F3	0.505	0.598	25.99
F4	0.517	0.597	28.78
F5	0.51	0.605	26.29
F6	0.503	0.599	27.25

Table 7: Post compression parameters of gliclazide

Formulation	Avg. Wt (mg)	Diameter (mm)	Thickness (mm)	Friability	Hardness (Kg\cm2)
F1	122	6	4.19	0.04	5.9
F2	124	6	4.6	0.09	5.4
F3	120	6	4.1	0.08	5.6
F4	121	6	4.49	0.07	5.4
F5	124	6	4.78	0.23	5.8
F6	120	6	4.58	0.14	5.5

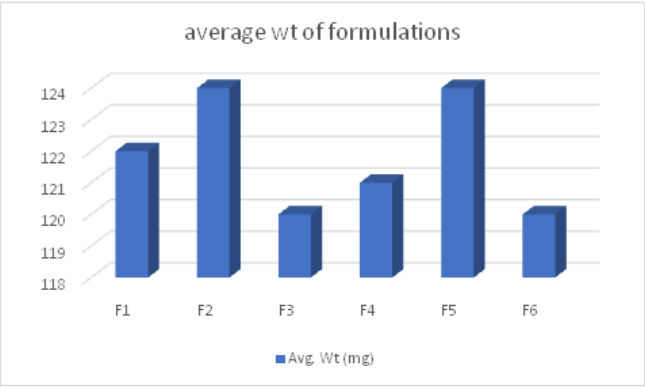


Figure 3: Bar diagram of average wt of formulations

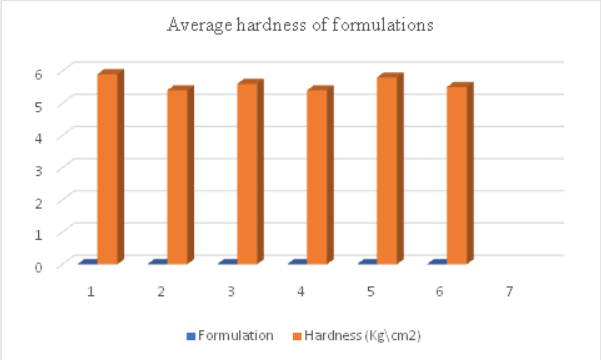


Figure 4: Bar diagram of Average hardness of formulations

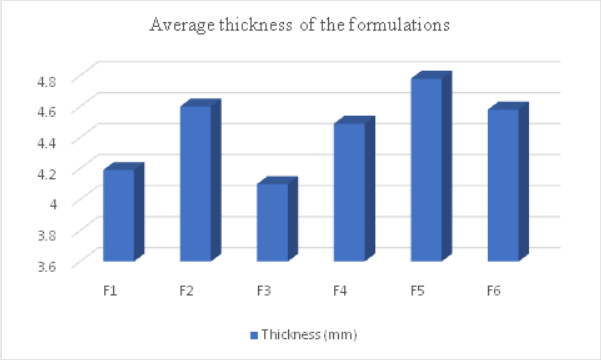


Figure 5: Bar diagram of Average thickness of the formulations

Table 8: Dissolution table of formulations in 6.8 Phosphate buffer

Time	0 hr	1hr	2hr	4hr	6hr	8hr	10 hr	12 hr	14 hr
F1	0	23.74	33.43	53.24	65.87	74.91	81.89	93.11	94.67
F2	0	24.87	32.56	55.51	67.98	75.98	79.97	92.16	98.01
F3	0	22.98	36.67	53.76	66.44	73.99	82.17	93.67	97.94
F4	0	21.87	35.43	54.45	67.71	76.56	80.98	90.93	95.46
F5	0	23.22	34.59	54.63	68.45	77.36	82.87	90.03	98.45
F6	0	25.08	35.19	52.99	69.17	75.36	81.57	90.87	98.46

Figure 6: Dissolution profile of batch F1 to F6

Conclusion

The present study was aimed to developed sustain release tablet of Gliclazide. Before formulation of sustain release dosage form, pre-formulation studies were performed such as organoleptic characteristics, solubility study and drug polymer interaction study by FT-IR. In the result of all above study was found that the drug and polymer used are desirable and there is no incompatibility between drug and the polymers used. Gliclazide Sustained release tablets were prepared by Direct Compression method using different polymers, such as HPMC K4M & Eutragit L-100 and when these two used in combination results in the drug release in a sustain manner. The Gliclazide, has an antidiabetic activity which is derivatives of sulphonyl urea mostly used to treat Type II diabetis can be delivered by using Matrix tablet by sustain drug delivery to enhance their pharmacological action with a reduced dose and frequency.

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