FORMULATION AND EVALUATION OF GLICLAZIDE OSMOTIC PUMP TABLETS

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ABSTRACT : Gliclazide (GZ) which is oral hypoglycemic drug belongs to BCS Class II was selected as a model drug to prepare controlled porosity osmotic pump (CPOP) tablet. The effect of different formulation variables - such as the level of solubility modifier in the core, membrane weight gain, and level of pore former in the membrane - were studied. Drug release was found to be affected by the level of solubility modifier present in the core. GZ release was inversely proportional to the membrane weight but directly related to the initial level of pore former (in the membrane. Controlled porosity osmotic pump (CPOP) based drug delivery system contains active ingredient, osmogens, semi permeable membrane, channelling agent and water soluble additives. In this system, when water comes in contact with water soluble additives it results in an in situ formation of a Microporous membrane. The main driving force for the release of drug is osmotic pressure. Osmogens maintain concentration gradient across the membrane. The present study deals with Controlled porosity osmotic pump tablets and its basic components.

Key words: Gliclazide, osmotic drug delivery, osmosis, direct compression technique, coating and in vitro drug release studies.

I.INTRODUCTION

Oral drug delivery is the most preferred and convenient choice as the oral route provides maximum active surface area among all drug delivery system for administration of various drugs. [1] Oral osmotically controlled release (CR) delivery systems exploit osmotic pressure for controlled delivery of active agents [3]. Drug release from these systems is independent of pH and other physiological parameters to a large extent and it is possible to modulate the release characteristics by optimizing the properties of drug and system [2]. Oral osmotic pump pertains to an osmotic device for delivering an active ingredient into the oral cavity of patients. The osmotic device comprises a shaped semi permeable membrane surrounding a compartment containing an active ingredient that is insoluble to very soluble in an aqueous fluid. The passage through the semi permeable membrane connects the exterior of the device with the compartment containing the active agent for delivering the agent from the device into the oral cavity. Based on the chamber the oral osmotic pump is classified into single chamber osmotic pump e.g. elementary osmotic pump (EOP) and multi chamber osmotic pump such as push pull osmotic pump (PPOP) and osmotic pump with nonexpanding second chamber. [4,5,6] Gliclazide is a second generation anti-diabetic drug used for the treatment of type II diabetes. Chemically it is (1-(3-azabicyclo-[3, 3, 0]-Oct-3-yl)-3-(p-tolyl sulfonyl) urea). The drawback of the drug is, it is practically insoluble in water and so possesses poor solubility, GI abruption and bioavailability.[7] Controlled release formulation is needed for glicalzide for better control of blood glucose levels to prevent hypoglycaemia and enhance clinical efficacy, to reduce gastrointestinal disturbances and to enhance patient compliance so, gliclazide is a suitable drug for oral controlled release tablets and it would be a great advantage to slow down its release in GI, where not only therapeutic action can be prolonged but minimize the side effects.[8] To improve the therapeutic efficacy of gliclazide and reduce the severity of upper GI tract side effect through alternative dosage form of gliclazide, can be achieved by modifying release of the formulation to optimize drug delivery.[9]

II.MATERIALS AND METHODS

Gliclazide was collected as a gift sample from Hetero labs, Hyderabad and various excipients like HPMC, ethyl cellulose, sodium alginate, tragacanth were purchased from AR chemicals, Hyderabad.

Methodology

Pre compression parameters[10,11]

Angle of repose: Weighed amount of the drug was transferred through a funnel kept at a height 2 cm from the base. The material is transfer till it forms a heap and touches the tip of the funnel. The radius the base of the conical pile, and the height of pile were measured.

$$\tan\theta = h/r$$

Where

h= height of the pile
r= radius of the base of the conical pile
θ= angle of repose

Bulk density and Tapped density

Weighed amount of the Gliclazide was transferred into 100 ml measuring cylinder without significant mechanical stresses during transfer. The volume employed by the drug was measured, and then control to 500, 750, 1250 taps in the tap density tester (electro lab USP II), the blend was subjected to 500, 750.taps respectively then the % variation in volume was calculated, if it is more than 2 then the blend has to be subjected for 1250 taps and the percentage variation in volume has to be calculated.

Bulk density is denoted by (ρ_i)

$\rho_i = m/v_i$

Tapped density is denoted by (ρ_t)

$\rho_t = m/v_t$

m=mass of the blend

V_i = initial volume

V_t =tapped volume

Compressibility index (CI)

The compressibility index was expressed in percentage calculated using the formula

$$CI = \left(\frac{v_i - v_t}{v_i}\right) \times 100$$

$$CI = \frac{TD - BD}{TD} \times 100$$

Hausner's ratio

It is measured by the ratio of tapped density and bulk density.

$$\text{Hausner's ratio} = \left(\frac{v_i}{v_i}\right) \text{or} \frac{TD}{BD}$$

Drug - excipient compatibility studies[12]

The IR absorption spectra of the Gliclazide drug and with different and excipients were taken in the range of 4000-450 cm^{-1} using KBr disc method, 1-2 mg of the substance to be examined was triturated with 300-400 mg, specified quantity, of finely powered and dried potassium bromide. These quantities are usually sufficient to give a disc of 10-15mm diameter and pellet of suitable intensity by a hydraulic press. The scans were evaluated for presence of principle peaks of drug, shifting and masking of drug peaks due to presence polymers and exipients.

Formulation development[13,14]

Preparation of Gliclazide tablets:

Drug layer composed of Gliclazide. Polymers are weighed accurately and passed through 44#. Pass Sodium chloride through 60# and mixed properly. The powder are lubricated with Magnesium stearate and talc as a glidant, which is passed through 60#. Blend it in a blender for 5 minutes. The prepared blend was placed in die cavity and compressed by 6 mm round standard concave punches.

Table-1: Formulation table of the Gliclazide osmotic pump core tablets

Ingredients	F1	F2	F3	F4
Gliclazide	100	100	100	100
Nacl	50	50	50	50
Magnesium stearate	5	3	3	3
Microcrystalline cellulose	40	40	40	40
Talc	5	2	2	2
Total wt	200	200	200	200

Coating of core tablets: Formulation of osmotic pump Tablets by Press Coated Technology. The core tablets were compressed using polymer blend which has composition of HPMC K15 M, Eudragit L100, Sodium alginate and tragacanth in different concentrations. Half of the coating polymer material was placed in the die cavity, then the core tablet was carefully sited in the centre of the die and cavity was filled on the top with the other half of the coating polymer material. Then the tablet was compressed using Rimek tablet machine, with 8 mm punch.

Table-2: Formulation table of the Gliclazide osmotic pump tablets

Ingredients	F1	F2	F3	F4
Core tablet	200	200	200	200
HPMC	100	-	-	-
Eudragit	-	100	-	-
Sodium alginate	-	-	100	-
Tragacanth	-	-	-	100

Evaluation parameters[15,16,17]

Weight variation

The prepared osmotic pump tablets are under kept for the weight variation study the randomly about 20 tablets are taken and measure the individual weight of the tablet.

$$\text{Percentage Deviation} = \frac{\text{Individual weight} - \text{average weight}}{\text{Average weight}} \times 100$$

Dimensions

The prepared tablets are under kept for the Thickness by using Verniar calipers

Hardness test

The hardness test is also done by using Pfizer hardness tester. The six Tablets were randomly selected from each batch and hardness of each tablet was determined by using a Pharma instruments.

Friability test

The friability test is done by using the friability apparatus. The test is for the knowing of the strength of the tablets. The 10-15 tablets are taken and measure the individual weight of the tablets that is initial weight after that the measured tablets are poured in the Roche friability apparatus. It is operated at 25 rpm for 4mins about 100 revaluations. Tablets were de-dusted and weighed again. The fallowing equation is used for the calculating of the %of friability,

$$\mathbf{F} = \frac{\text{Initial wt} - \text{final wt}}{\text{Initial wt}} \times \mathbf{100}$$

Drug content estimation

The Gliclazide tablets were tested for their drug content. About to take 20 tablets and crush it properly from cursched powder take 100 mg of the powder that equivalent to the Gliclazide drug substance. The powder is taken in the 100ml of the volumetric flask with the 6.8 ph phosphate buffer solution. The phosphate buffer solution is kept on the sonication for 30mins. The 1ml of solution is taken and it is kept for the absorbance in U.V visible spectroscopy at 225 nm.

In-vitro Dissolution studies

In vitro drug release studies are performed by using USP-II apparatus paddle type .The prepared tablets are under kept in the dissolution studies. The sink condition should be maintained. The temperature is maintained for 37.5^0c. The drug release studies performed for 9hrs. The 1ml of sample is withdrawn from the basket and same amount of sample is placed in the basket to maintain the sink conditions. The 6.8 buffer solution is used for the In-vitro drug release studies. The medium is about 900ml. The sample is withdrawn and under kept for the analyzing of the absorbance under U.V at 225 nm.

Stability studies

The success of an effective formulation can be evaluated only through stability studies. The prepared Gliclazide osmotic pump tablets were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40 ± 2^oc and refrigerator $2\text{-}8^o$c for a period of 30days.

III.RESULTS & DISCUSSION

Compatibility Study

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied. The characteristic absorption peaks of Gliclazide were obtained at 3500 cm^{-1}, 1084 cm^{-1}, 3095cm^{-1}, 1745cm^{-1}. The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components.

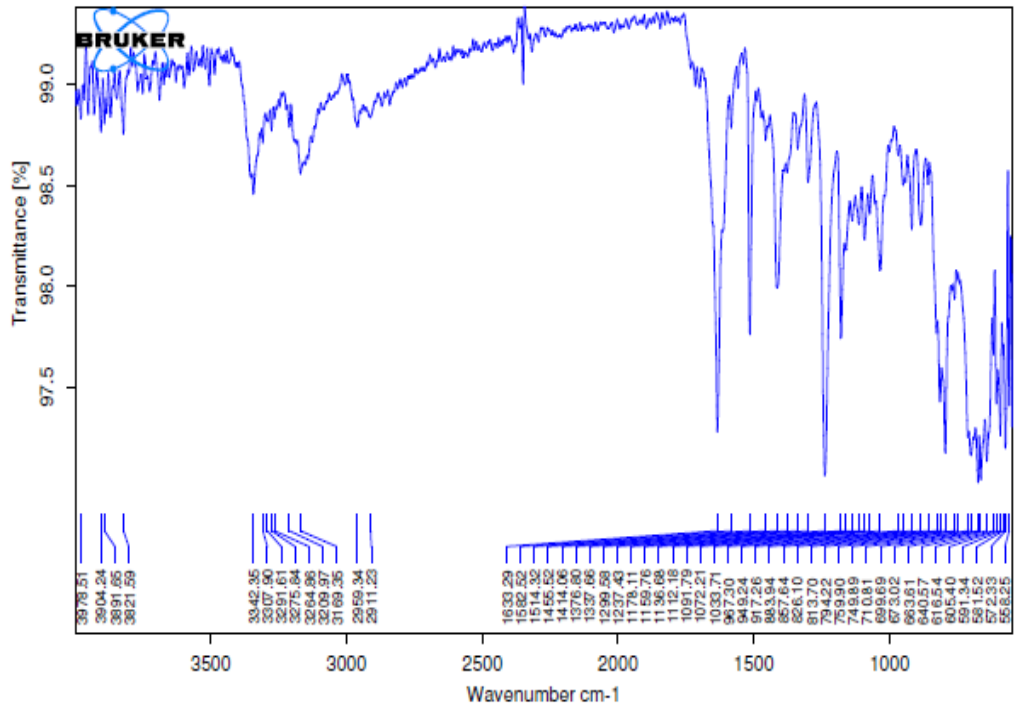

Fig-1: FTIR Spectra of Gliclazide

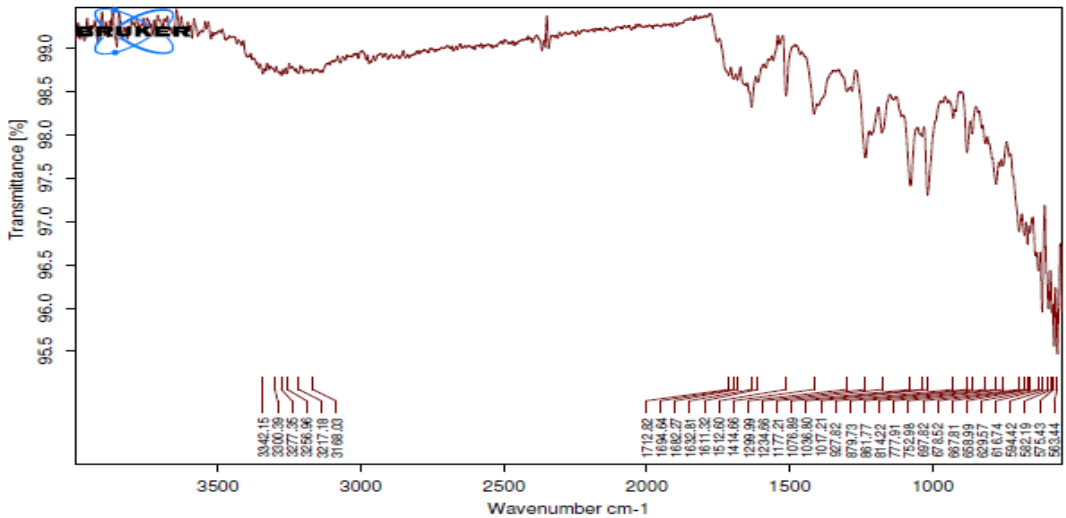

Fig-2: FTIR Spectra of Optimized formulation

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of Pure drug and physical mixture of drug and excipients were studied. The characteristic absorption of peaks were obtained as above and as they were in official limits (±100 cm-1) the drug is compatible with excipients.

Evaluation

Physical Properties of Gliclazide:

Interparticulate interactions influence the physical properties of powder flow. A comparison of the bulk density and tapped density can give a measure of the relative importance of this interaction in a given powder. Such a comparison is often used as an index of the ability of the powder to flow. Physical properties of Gliclazide like

bulk density, tapped density, compressibility index, Hausner's ratio, and angle of repose.

Table-2: Average values of pre-compressive parameters of tablet blend

F. No	**Bulk density**	**Tapped density**	**Compressibiliy index**	**Hausner ratio**	Angle of repose(0)
F1	0.512	0.611	16.2	1.19	30^0
F2	0.525	0.615	14.6	1.17	29^0
F3	0.519	0.625	16.9	1.22	30^0
F4	0.528	0.623	15.2	1.17	28^0

Evaluation of core Tablets:

The tablet formulations were subject to various post-compressive evaluation tests, such as, Hardness, Friability and Weight variation, drug content uniformity.

Weight variation test: It was carried out as per official method and the average percentage deviation of all the formulation was found to be within the limit (as per USP standard).

Content uniformity: Was also carried out as per official method and it was found that all batches shows good content uniformity. The values for all the formulations were in the ranges from 89.42-95.90%.

Hardness test: States that all the formulations were found in the range 5to 8 kp.

Friability test: Compressed tablets have lose less than 1 % of their weight are generally considered acceptable. All the formulations have less than 1% friability.

Table-3: Results of Evaluation parameters of tablets

F. No.	**Weight variation (mg)**	**Thickness (mm)**	**Hardness (kg/cm^2)**	**Friability (%)**	**Drug content (%)**
F1	300	6.09	5.82	0.65	95.90
F2	299	5.99	5.65	0.64	89.42
F3	300	6.05	5.42	0.61	93.80
F4	400	6.12	5.22	0.60	92.82

The tablets of 4 formulations were tested and analyzed for thickness, weight variation, hardness, friability, content uniformity

Table-4: Cumulative % of drug release

Time (hrs.)	F_1	F_2	F_3	F_4
0	0	0	0	0
1	28.44	22.40	20.30	21.52
2	32.51	32.28	29.75	30.52
3	43.79	42.65	34.80	41.21
4	50.72	50.20	48.40	49.85
5	59.18	55.81	52.50	58.62
6	65.22	63.76	60.75	63.86
7	79.21	73.53	71.90	78.82
8	92.32	85.32	86.25	90.12

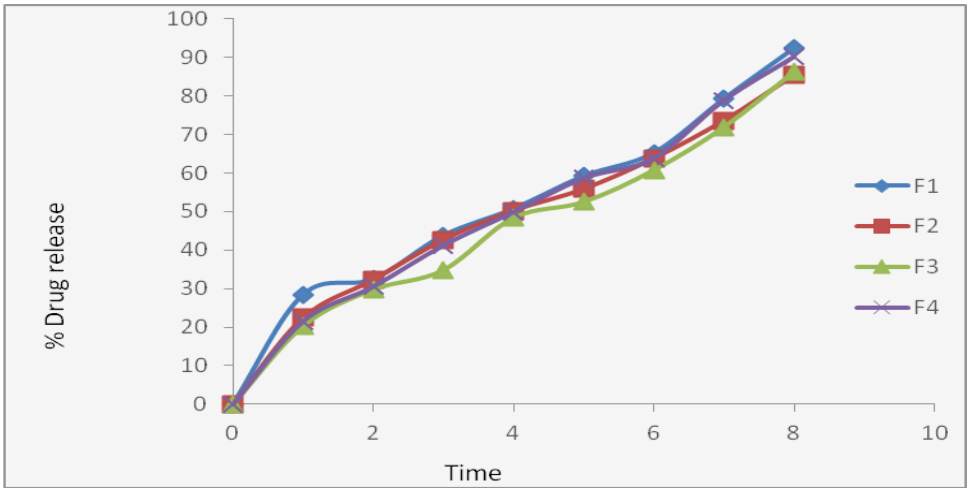

Fig-3: Invitro drug release of all formulations

Stability studies

There was no significant change in physical and chemical properties of the tablets of formulation F-1 after 1 month. Parameters quantified at various time intervals were shown

Table-5: Results of stability studies of optimized formulation F-1

Formulation Code	Parameters	Initial	1st Month	Limits as per Specifications
F-1	**25^0C/60%RH % Release**	92.32	92.30	**Not less than 85 %**
F-1	**30^0C/75% RH % Release**	92.32	92.28	**Not less than 85 %**
F-1	**40^0C/75% RH % Release**	92.32	92.26	**Not less than 85 %**

CONCLUSION

Extended release formulations of Gliclazide were developed based on controlled porosity osmotic pump technology. Core tablets of Gliclazide were successfully prepared by direct compression for drug layer using Gliclazide, microcrystalline cellulose, sodium chloride, Magnesium stearate. After compression core tablets coated with HPMC as a polymer. *In vitro* release profile of formulation F1 was found to be release profile were found to be 92.32%. Finally the F1 formulation was optimized. The effect of different formulation variable was studied to optimize release profile. Drug release was directly proportional to the pore former, When we increase the concentration of pore former from 30 to 50% along with increase in osmogent ratio, the drug release also found to be increased. Drug release from the developed formulations was found to be independent of Hydrodynamic conditions of the body and depends on pH, because the solubility of the drug is pH dependent.

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