Research Article

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Development and characterization of glime pride controlled release osmotic pump tablets

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ABSTRACT

The current research involves the development of osmotic pump (CPOP) tablets of Glimepride for the treatment of type 2 diabetes. Core tablets were prepared by direct compression method using hydroxyl propyl methyl cellulose (HPMC), Eudragit, Sodium Alginate, potassium chloride as osmogen, MCC as diluents and other additives. The prepared tablets were evaluated for FTIR pre compression parameters, post compression parameters, in vitro drug release study and scanning electron microscopy study. The optimized formulation F4 showed 95.27% at the end of 8 hrs with zero order drug release. Optimized formulation did not show any significant change on the p^H and agitation intensity, but it depends on osmotic pressure of dissolution media indicated that mechanism of drug release was due to osmotic pressure. stability study at 40±2ºC/75±5% RH for three months on the F4 formulation indicated that there was no significant change weight variation, % friability, drug content and *in vitro* drug release.

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

INTRODUCTION

Oral drug delivery is the most preferred and convenient choice as the oral route provides the maximum active surface area among all drug delivery systems for the 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]. An 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 a push-pull osmotic pump (PPOP) and osmotic pump with nonexpanding second chamber.[4, 5] Glimepiride is used with a proper diet and exercise program to control high blood sugar in people with type 2 diabetes. It may also be used with other diabetes medications[6, 7]. Controlling high blood sugar helps prevent kidney damage, blindness, nerve problems, loss of limbs, and sexual function problems[8].Glimepiride stimulates the secretion of insulin granules from the pancreatic beta cells and improves the sensitivity of peripheral tissues to insulin to increase peripheral glucose uptake, thus reducing plasma blood glucose levels and glycated hemoglobin (HbA1C) levels[9, 10]. A multi-center, randomized, placebo-controlled clinical trial evaluated the efficacy of glimepiride (1–8 mg) as

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monotherapy titrated over 10 weeks compared with placebo in T2DM subjects who were not controlled by diet alone[11].

MATERIALS AND METHODS

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

METHODOLOGY

Drug - excipient compatibility studies[12]

The IR absorption spectra of the Glimepiride drug and with different and excipients were taken in the range of 4000-450 cm^{-1} using the KBr disc method, 1-2 mg of the substance to be examined was triturated with 300-400 mg, specified quantity, of finely powdered 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 the presence of principal peaks of the drug, shifting, and masking of drug peaks due to the presence of polymers and excipients.

Formulation development

Preparation of Glimepiride tablets[13]

The drug layer is composed of Glimepiride. Polymers are weighed accurately and passed through 44#. Pass potassium chloride through 60# and mixed properly. The powder is 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 a die cavity and compressed by 6 mm round standard concave punches. (Table 1)

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

Ingredients	F1	F2	F3	F4	F6	F7	F8
Glimepride	4	4	4	4	4	4	4
Kcl	20	20	20	20	20	20	20
Mannitol	20	20	20	20	20	20	20
Povidone	10	10	10	10	10	10	10
Magnesium stearate	3	3	3	3	5	3	3
Microcrystalline cellulose	41	41	41	41	41	41	41
Talc	2	2	2	2	5	2	2
Total wt	100	100	100	100	100	100	100

Coating of core tablets[14]:

Formulation of osmotic pump Tablets by Press Coated Technology. The core tablets were compressed using polymer blend which has a composition of HPMC, Eudragit, Sodium alginate, and Ethyl Cellulose 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 the cavity was filled on the top with the other half of the coating polymer material. Then the tablet was compressed using a Rimek tablet machine, with an 8 mm punch.

Table-:2Formulation table of the Glimepiride osmotic pump tablet

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Core tablet	100	100	100	100	100	100	100	100
HPMC	100	-	50	-	50	-	50	50
Ethyl Cellulose	-	100	50	-	-	50	-	-
Sodium alginate	-	-		100	50	50	-	-
Eudragit	-	-	-	-	-		100	50

Evaluation parameters[15, 16]

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 Vernier calipers

Hardness test

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

Friability test

The friability test is done by using the friability apparatus. The test is for the knowledge of the strength of the tablets. The 10-15 tablets are taken and measure the individual weight of the tablets is the initial weight after that the measured tablets are poured into the Roche friability apparatus. It is operated at 25 rpm for 4mins about 100 revaluations. Tablets were de-dusted and weighed again. The following 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 Glimepiride tablets were tested for their drug content. About to take 20 tablets and crush it properly from crushed powder takes 100 mg of the powder that equivalent to the Glimepiride 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 the solution is taken and it is kept for the absorbance in U.V visible spectroscopy at 250 nm.

In-vitro Dissolution studies

In vitro, drug release studies are performed by using the USP-II apparatus paddle type. The prepared tablets are kept in dissolution studies. The sink condition should be maintained. The temperature is maintained at 37.5^0c. The drug release studies were performed for 8hrs. The 1ml of sample is withdrawn from the basket and the 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 analysis of the absorbance under U.V at 250 nm.

Drug release kinetics

Several theories and kinetic models describe the dissolution of the drug from immediate release and modified release dosage forms. There are several models to represent the drug dissolution profiles where f (t) is a function of time-related to the amount of drug dissolved from the pharmaceutical dosage form. The quantitative interpretation of the values obtained in the dissolution assay is facilitated by the usage of a generic equation that mathematically translates the dissolution curve function of some parameters related to the pharmaceutical dosage forms. Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time' or Q (t). Some analytical definitions of the Q (t) function are commonly used, such as zero order, first order, Higuchi, Korsmeyer-Peppas; these models are used to characterize drug dissolution/release profiles.

Stability studies

The success of an effective formulation can be evaluated only through stability studies. The prepared Glimepiride 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.

RESULTS & DISCUSSION

Drug - excipient compatibility studies (FT-IR)

The similarity between the medication and they chose lipid and different excipients were assessed utilizing FTIR top coordinating technique. There was no appearance or vanishing of tops in the medication lipid blend, which affirmed the nonappearance of any concoction communication between the medication, lipid, and different synthetic compounds. (Fig 1&2)

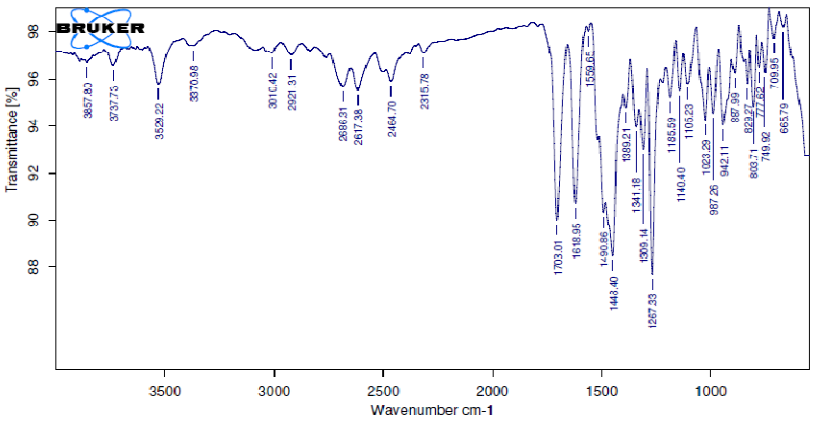

Fig-: 1 FT-IR Sample for Glimepiride

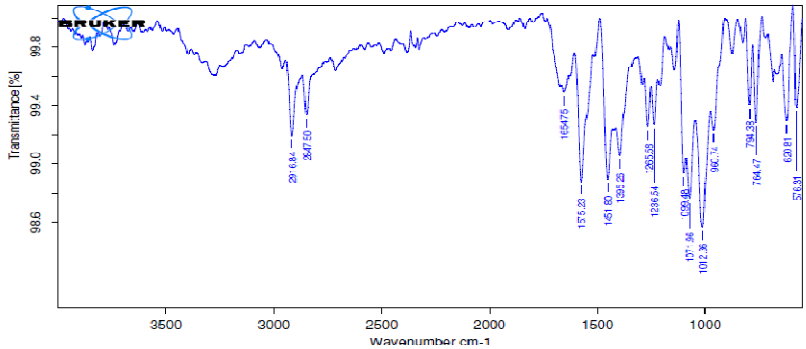

Fig-:2 FT-IR Sample for Optimized Formulation

Evaluation studies

Precompression parameters

1. Bulk Density: The bulk density for the formulated blend was carried out for all formulations and found in the range of 0.217-0.232.

2. Tapped density: The tapped density for the formulated blend was carried out for all formulations and found in the range of 0.320-0.335.

3. Angle of repose: The angle of repose for the formulated blend was carried out. It concludes that all the formulations blend was found to be in the range of 27 ^{0} to 30 ^{0}

4. Compressibility index: Compressibility index was carried out, it found between 10% to 33.10% indicating the powder blend has the required flow property for compression.

Table-: 3 Evaluation parameters of Glimepiride

S. no	Bulk density	Tapped density	Compressibility index	Hausner ratio	THE Angle of repose(0)
F1	0.217	0.323	32.18	1.48	29^0
F2	0.220	0.329	33.1	1.49	28^0
F3	0.231	0.328	29.21	1.41	30^0
F4	0.229	0.332	31.02	1.44	29^0
F5	0.232	0.324	28.39	1.39	27^0
F6	0.218	0.335	34.92	1.53	29^0
F7	0.229	0.327	31.64	1.42	30^0
F8	0.219	0.320	31.56	1.39	26^0

Post compression parameters

Weight variation

The percentage of weight variations for all formulations was tabulated in Table. All the formulated (F1 to F8) tablets passed the weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness

Tablets mean thickness (n=3) were uniform in F1 to F8 formulations and were found to be in the range of 4.8 mm to 5.2 mm.

Hardness

The measured hardness of tablets of each batch ranged between 4.8 to 4.9 kg/cm^2. This ensures good handling characteristics of all batches.

Friability

The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable

Content Uniformity

The percentage of drug content from F1 to F8 was found to be between 86.24% and 92.25% of Glimepiride, it complies with official specifications.

Table-: 4 Results of Precompression parameters

F. No.	Weight variation (mg)*	Thickness (mm)*	Hardness (kg/cm^2)*	Friability (%)	Drug content (%)
F1	199	5.2	4.5	0.39	89.56
F2	200	5.1	4.8	0.40	87.52
F3	198	4.9	4.5	0.38	86.24
F4	197	4.8	4.4	0.39	93.25
F5	198	5.1	4.7	0.46	86.26
F6	199	4.9	4.6	0.39	88.56
F7	200	5.1	4.9	0.41	92.25
F8	197	4.8	4.3	0.48	90.23

In-vitro Dissolution Study

All 8 formulations of prepared osmotic pump tablets of Glimepiride were subjected to in-vitro release studies these studies were carried out using the dissolution apparatus. The dissolution medium consisted of 900 ml of Standard buffer pH 7.4for the 8 hrs.(Fig 3)

Table-:5 Drug release studies of all formulations

Time	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	11.28	12.28	15.28	10.93	11.21	13.56	14.58	11.55
2	31.22	32.14	33.24	30.70	31.56	30.24	31.56	32.15
3	44.56	42.56	42.99	41.28	43.51	41.25	40.87	42.66
4	52.29	51.27	55.27	54.06	50.89	50.28	51.22	50.27
5	61.24	62.85	65.96	63.14	65.45	60.88	62.86	63.46
6	63.21	69.28	71.85	70.12	71.25	69.89	69.55	68.95
7	80.26	81.28	90.60	89.56	88.59	87.88	86.96	82.96
8	85.12	89.45	92.16	95.27	91.16	92.46	93.48	94.12

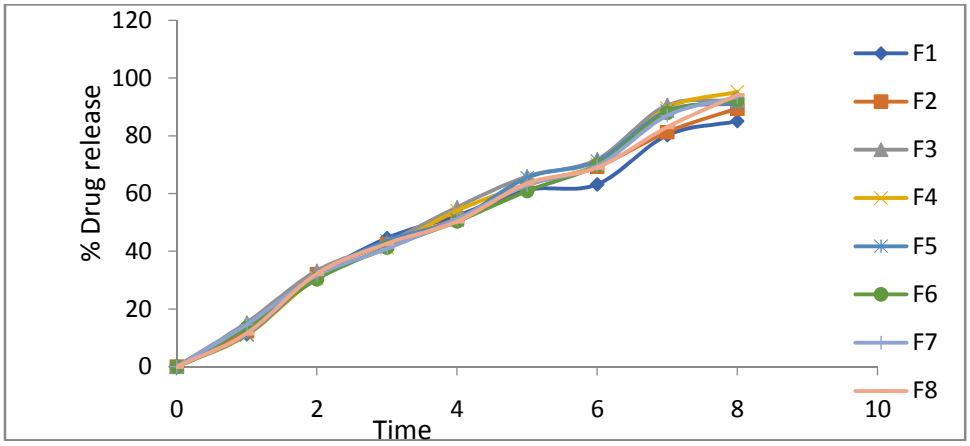

Fig-:3 Dissolution profiles of (F1-F8) Formulations

Kinetic modeling of drug release

All the nine formulations of prepared tablets of Glimepiride were subjected to in vitro release studies these studies were carried out using the dissolution apparatus.(Fig 4,5,6&7)

The results obtaining in vitro release studies were plotted in a different model of the data treatment as follows:

1. Cumulative percent drug released vs. time (zero-order rate kinetics)
2. Log cumulative percent drug retained vs. time (First Order rate Kinetics)

1. Cumulative percent drug released vs. square root of time (Higuchi's Classical Diffusion Equation)
2. Log of cumulative % release Vs log time (Peppas Exponential Equation)

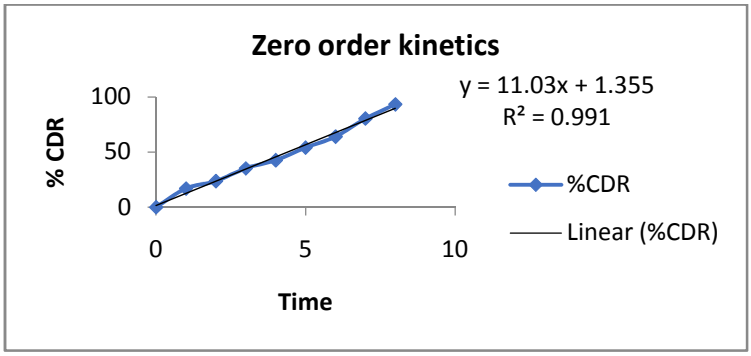

Fig-: 4 Zero-order kinetics

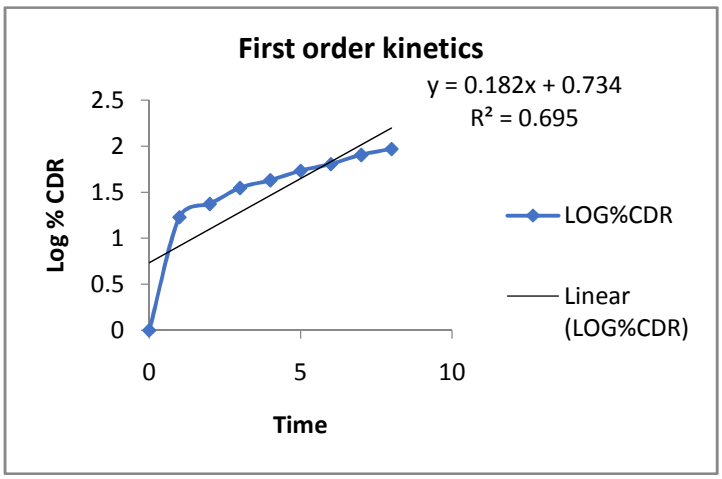

Fig-:5 First order kinetics

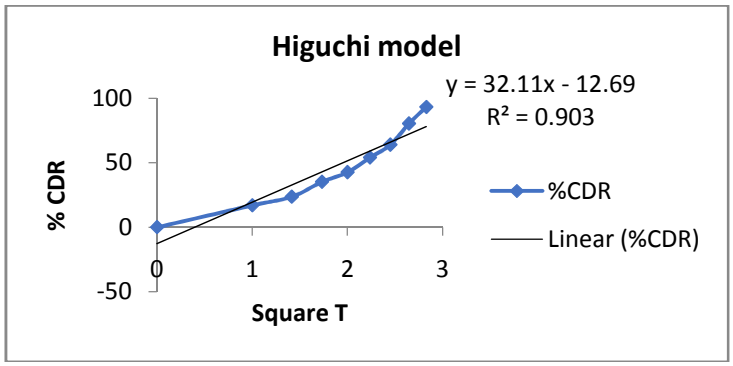

Fig-: 6 Higuchi model

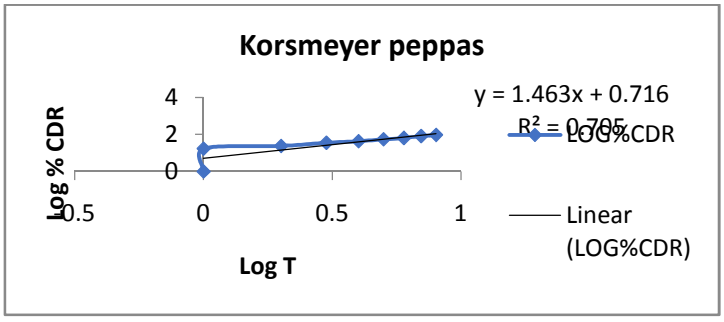

Fig-: 7 Korsmeyer peeps

The values of in vitro release were attempted to fit into various mathematical models. Plots of zero order, first order, Higuchi matrix, Peppas, and Hixson-Crowell.

Regression values are higher with Zero-order release kinetics. Therefore all the Glimepiride follows Zero-order release kinetics.

Stability studies

There was no significant change in the physical and chemical properties of the tablets of formulation F-4 after 3 months. Parameters quantified at various time intervals were shown; (Table 6)

Table-: 6 Results of stability studies of optimized formulation F-4

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-4	25^0C/60%RH % Release	95.27	94.45	93.85	93.63	Not less than 85 %
F-4	30^0C/75% RH % Release	95.27	94.10	93.72	93.52	Not less than 85 %
F-4	40^0C/75% RH % Release	95.27	94.99	93.51	92s.99	Not less than 85 %

CONCLUSION

The present study was undertaken to formulate and evaluate osmotic pump tablets of Glimepiride using different polymers as release retarding agents. A preformulation study was carried out and all the parameters were found within the specification. Hence different batches of Glimepiride were prepared using selected excipients. Powders were evaluated for Bulk density, tapped density, compressibility index, Hausner ratio before being punched as tablets. Various formulations of controlled release tablets of Glimepiride were prepared by using different polymers viz, HPMC, Ethylcellulose and eudragit in different proportions and combinations by direct compression technique. The tablets were evaluated for physical parameters, in vitro release study, and stability studies. All formulations were found to be within the specifications of official pharmacopeias and/or standard references. The in-vitro release indicated that the formulation F4 had a better dissolution profile along with controlled action as compared to other formulations.

A stability study was conducted on tablets of Batch F4 stored at room temperature, 400C, and 2-80C for one month. Tablets were evaluated for hardness, friability, in-vitro release profile, and drug content. No significant changes were observed in any of the studied parameters during the study period (90days), thus it could be concluded that formulation was stable.

From the results, it can be concluded that osmotic pump tablets of Glimepiride containing Ethyl cellulose i.e. F4 can be formulated successfully.

A further detailed investigation is required to establish the in-vivo efficiency of osmotic pump tablets and long-term stability studies were needed.

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