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In vitro Release Kinetic Study of Gliclazide from Methocel K 100 MCR and Methocel K100 LVCR Matrix Tablets

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Abstract: The controlled release Gliclazide matrix tablets were prepared using polymeric materials, namely, HPMC, in two grade of DOW chemical patent METHOCEL K100 MCR and METHOCEL K 100 LVCR premium in different amount and different cps. Among the various types of polymers and concentrations studied by UV-spectrophotometer, the dissolution profile of matrix tablets containing 35% HPMC of METHOCEL K 100 LVCR premium (formulation F-4) was found to be best formulation considering release pattern. The drug release data obtained were extrapolated by Zero Order, First Order and Higuchi model. The data were plotted into Korsmeyer-Peppas equation to know the confirmed diffusion mechanism.
Keywords: Controlled release tablets, dissolution profile, hydrophilic polymers.

INTRODUCTION

Gliclazide is one of the sulfonylurea used in the treatment of type II diabetes.[1] Conventional formulation necessitates twice daily administration. A new once daily Gliclazide controlled release preparation has been introduced. In a larger randomized study on type II diabetic patients, once daily Gliclazide controlled release 30-120mg was found as effective in reducing glycosylated hemoglobin, with fewer side effects and less risk of hypoglycemia.[2] Oral sustained release dosage form by direct compression technique is a very simple approach of drug delivery systems that proved to be rational in the pharmaceutical arena for its ease, compliance, faster production, avoid hydrolytic or oxidative reactions occurred during processing of dosage forms.[3] Sustained or controlled drug delivery occurs while embedded within a polymer that may be natural or semi-synthetic or synthetic in nature. The polymer is judiciously combined with the drug or other active ingredients in such a way that the active agent is released from the material in a predetermined fashion and released the drug at constant rate for desired time period.[4] Hydrophilic polymers are extensively used for oral sustained release matrix system.[5] A hydrated viscous layer or gel layer is usually formed at the tablet periphery, which controls the drug release from the hydrophilic matrix tablet.[6] These formulations are relatively flexible, well designed and gives reproducible release profiles. Among the various swellable hydrophilic polymers used to prolong the drug release, hydroxypropylmethyl cellulose (HPMC) has been widely used due to its rapid hydration good compression and gelling characteristics along with its ease of use, availability and very low toxicity.[7, 8] There are three primary mechanisms by which active agents

can be released from a delivery system: diffusion, degradation, and swelling followed by diffusion. The release of drug from the tablet matrix depends on the nature of polymer. Both Methocel K100 MCR and Methocel K100 LVCR are hydrophilic polymers that become hydrated, swollen and facilitates to diffuse the drug.[9] In the present study an attempt has been made to formulate Gliclazide as sustained release tablet matrix with the addition of release retarding polymers Methocel K100MCR and Methocel K100 LVCR in different ratios. The effect of viscosity grade and polymer loading on drug release were recorded and release kinetics was evaluated.

MATERIALS AND METHODS

DRUG: Gliclazide (Shandong Keyuan pharma co. ltd, China), **POLYMER:** Hydroxypropyl methylcellulose-(HPMC) Methocel K100 MCR Premium USP/EP (Colorcon Asia Pvt. Ltd. India), Hydroxypropyl methylcellulose-(HPMC) Methocel K 100 LVCR premium (Colorcon Asia Pvt. Ltd, India). **OTHER EXCIPIENTS:** Microcystalline Cellulose (Avicel PH-102, Comprecel 101, Mingtai Chemical Co. Ltd.Taiwan). Colloidal Silicon Dioxide (Aerosil 200, Source: Deggusa AG, Germany), Magnesium Stearate (Chemical Management Co., Germany).

SOLVENTS AND REAGENTS: Methanol, Disodium hydrogen orthophosphate, Potassium dihydrogen orthophosphate, Sodium hydroxide was from Merck (Germany).

EQUIPMENTS: Clit Tablet Press (model CJD-3, country of origin India) ,Simadzu UV Spectophometer (Japan) , Digital pH meter (Germany), Electronic Hardness tester (Ereweka, Germany), Electrolab Tablet Dissolution Test machine, Sartorius Electronic Balance.

PREPARATION OF MATRIX TABLETS: Drug, polymer and other excipients were weighed separately formulation as per proposed formulations. The proposed formulations were coded as F-1, F-2, F-3, F-4, and F-5. The amounts of drug and excipients are expressed in milligram unit. The active ingredient Gliclazide and HPMC were mixed well about 10 minutes and then Avicel and Aerosil were screened through #24 mesh (701 micron) for 60 minutes. Finally magnesium stearate was added and blended for 2 minutes. Blended mass was taken in the hopper and then die and punch were adjusted to get the desired weight of the tablet (180 mg). After compression the tablets were weighed and tablet weight was found 175 mg -185 mg. The tablets were prepared by direct compression; the types and amounts of polymers used are shown in Table 1.

INVITRO DISSOLUTION STUDIES OF THE MATRIX TABLETS

In vitro drug release studies from the prepared matrix tablets were conducted for a period of 12 h using an USP dissolution apparatus 2(perfect sink conditions) set at 100 rpm and a temperature of 37± 0.5ºC. Initially 28.80 g of disodium hydrogen orthophosphate and 11.45 g of potassium dihydrogen orthophosphate was dissolved in sufficient water to produce 1000 ml. 900ml of medium was placed in each of six vessels. For, P^H adjustment

1 % phosphoric acid was used. Then Apparatus was assembled and temperature raised up to 37°C ± 1 and 1 tablet was placed in each vessel.

According to BP absorbance of both standard and sample preparation was measured at 226 nm and 290 nm against dissolution fluid as blank. Absorbance observed at 226 nm was deducted from the observed absorbance at 290 nm.

DRUG CONTENT ASSAY:

Drug content from formulated tablets were measured by following BP method.[10]

Standard preparation: firstly accurately weighed 40mg of Gliclazide working standard was transferred to a 100ml volumetric flask. Then 0.1N sodium hydroxide was added to adjust the volume. 5ml of this solution was diluted to with 0.1N sodium hydroxide to make volume 100 ml by mixing properly.

Sample Preparation: Average weight of 20 tablets were determined , transferred to a mortar & triturated them with a pestle .Accurately weighed of an amount of powdered sample equivalent to about 40mg of Gliclazide was transferred to 100 ml volumetric flask, and 60 ml of 0.1N sodium hydroxide added to adjust the volume. A portion of the solution was filtered through a no. 1 whattman filter paper and first few ml of the filtrate was discarded. 5ml of this solution was transferred to a 100ml vol. flask and volume was adjusted using .01 N Sodium Hydroxide solution.

The absorbance of both standard and sample preparation was measured at 226nm against 0.1N sodium hydroxide as blank.

KINETIC ANALYSIS OF RELEASE DATA

The release data obtained were treated according to zero-order (cumulative amount of drug release versus time), first-order (log cumulative percentage of drug remaining versus time), Higuchi (cumulative percentage of release versus square root of time) and Korsmeyer-Peppas (log cumulative percentage of drug released versus log time) equation models.

Table 1. Different formulation of Gliclazide matrix tablets

Name of materials	F-1	F-2	F-3	F-4	F-5
Gliclazide	30mg	30 mg	30 mg	30 mg	30 mg
HPMC Methocel k100 MCR premium	45 mg	36 mg	18 mg	-	
HPMC Methocel k100 LVCR premium	-	-	27 mg	63 mg	45 mg
Microcrystalline Cellulose BP (Avicel PH 102)	103.2mg	112.2mg	103.2mg	85.2 mg	103.2 mg
Colloidal Sillicon Dioxide BP (Aerosil-200)	0.90 mg	0.90 mg	0.90 mg	0.90 mg	0.90 mg
Magnesium stearate BP	0.90 mg	0.90 mg	0.90 mg	0.90 mg	0.90 mg
Average weight of tablet	180 mg	180 mg	180 mg	180 mg	180 mg

Table 2. Assay and drug release of different formulations

Formulations	Assay (mg)	Average % of drug release of 6 tablets			
		1 hr	03 hrs	08 hrs	12 hrs
F-1	30.4	11.21	28.50	56.03	62.75
F-2	30	15.11	29.60	57.42	67.24
F-3	30.5	16.18	34.85	62.29	75.53
F-4	30.4	17.06	43.17	74.79	86.10
F-5	30.5	19.5	48.56	81.80	98.1

Where HPMC contents in F1----25% Methocel k100 MCR, in F2----20 % Methocel k100 MCR, in F3 ---- (40% k100MCR+ 60% K 100 LVCR) 25% combination , in F4----- 35 % K100 LVCR, in F5----- 25 % K100 LVCR .

Table 3. Multiple coefficients of determination data in dissolution media

Formulation No	Multiple Coefficient of Determination (r^2)		
	Zero Order	First Order	Higuchi
F-1	0.938	0.975	0.938
F-2	0.948	0.989	0.948
F-3	0.949	0.997	0.949
F-4	0.928	0.998	0.928
F-5	0.937	0.945	0.937

Table 4. Multiple coefficients and slope (n) of dissolution data in korsmeyer –Peppas equation

Formulations	Korsmeyer - Peppas	
	n	r^2
F-1	1.1679	0.5230
F-2	1.0706	0.4850
F-3	1.0598	0.5010
F-4	1.0634	0.5348
F-5	1.0377	0.5456

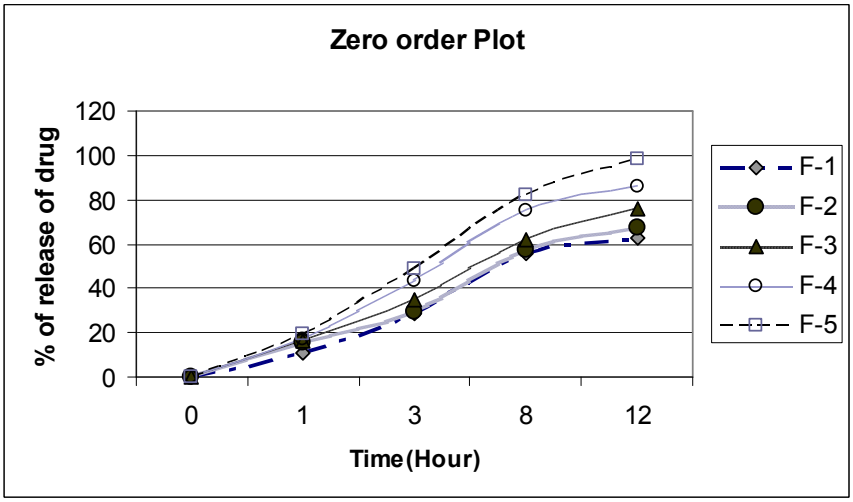

Figure 1. Zero order plot of release of release kinetics of different formulations

Figure 2. First order plot of release kinetics of five different formulations

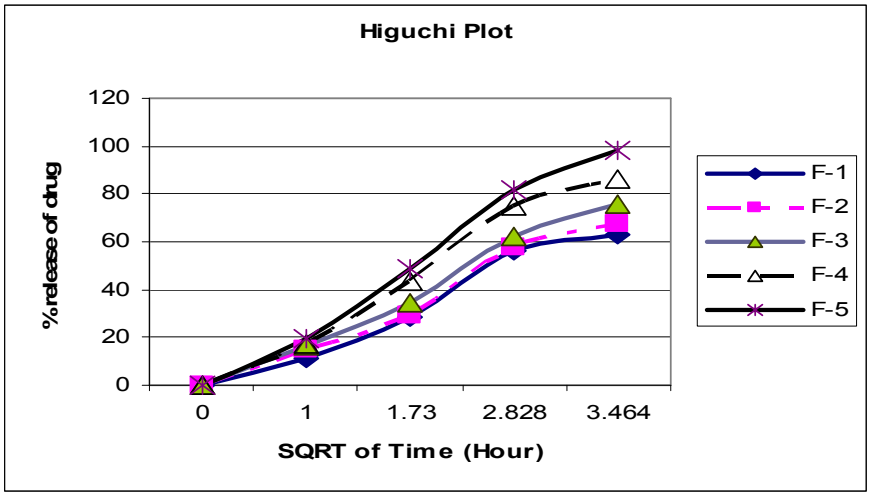

Figure 3: Higuchi plot of release kinetics of five different formulations

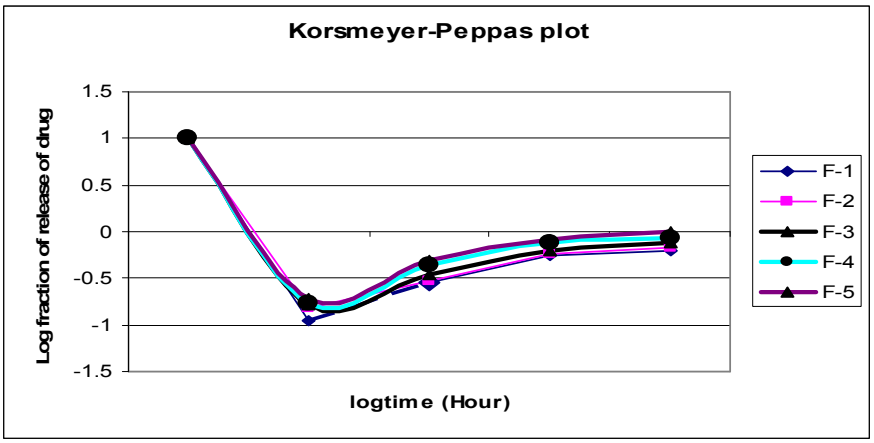

Figure 4: Korsmeyer-Peppas plot of five different formulations

RESULTS AND DISCUSSION

Among all the formulations F1 and F2 were based on methocel k 100 MCR premium HPMC in percentage of 25% and 20% respectively of total tablet weight. Formulation three, F-3 was prepared in combination of both HPMC as Methocel K 100 MCR and Methocel K 100 LVCR in 40:60 ratio and in total wt 25% of tablet wight. Last two formula were from Methocel K100 LVCR premium grade HPMC in two different percentage as 35% of formulation 4 (F-4) and 30% for F-5 of total tablet weight.

Gliclazide is a water insoluble drug so that hydrophilic matrix was chosen. Its water solubility is too slow and from release % of drug it was found that desired released at the end of 12 hours is not achieved for F-1 formulation. It was 62.75% below the In-house specification. Another trial of less percentage at 20% Methocel K 100 MCR of total tablet wt was applied but it shows about no improvement. Though both of these formulations F-1 and F-2 were meet the 8 hours dissolution specification but not well for 12 hours sustained release.

Therefore Low viscosity grade controlled release HPMC as Methocel K 100LVCR was applied for the next batches. Result was improved dramatically. From the Table 3 it was observed that Formulation F-4 met the all time intervals release criteria at the end of 12 hours that was 86.10 %.

So later another trial in less amount of Methocel K 100LVCR at 25% of total tablet wt was tried but it was released earlier. In third hours data it was observed that about half of the drug was released to the medium. That was above the specification. Dissolution data obtained from Formulation F-4 was found satisfactory and met specifications.

In vitro release studies of the formulations demonstrated that the release of drug depends not only on the nature of matrix but also upon the drug polymer ratio. As the percentage of polymer increased, the kinetics of release was decreased. This may be due to structural reorganization of METHOCEL K100MCR Premium and Methocel K 100 LVCR Premium. But decrease in concentration caused failure to generate a uniform and coherent gel for drug release. Processing factors including particle size, hardness, and compressibility index etc. also affect the release rate from the tablets.[11]

Among the five formulations Gliclazide was present within 30 mg ± 5% of the labeled claim as BP. The results of potency and dissolution studies of formulation-1 (F-1), formulation-2 (F-2), formulation-3 (F-3), formulation-4 (F-4), and formulation-5 (F-5) are shown in Table 3. According to USP 29th Edition, 2006 for an ideal sustained release dosage form like Gliclazide SR, percent release in 1st hour should be not more than 30% and in 10th hour not less than 80%.[12]

The drug release data obtained were extrapolated by Zero Order, First Order and Higuchi model.[13]

The drug release data from the proposed formulations F-1 to F-5 were treated in different kinetics order (Zero order plot, First order plot and Higuchi plot) and their correlation coefficients were determined graphically to identify their release mechanism. The drug percent release was plotted against time to get zero order release kinetics, Log % drug remaining against time to get first order release kinetics and the percent release

versus square root of time to get Higuchi release kinetics. From correlation coefficient it can be determined the mechanism of release kinetics. The correlation coefficient getting close to 1.0, the release kinetics will be followed that order of proposed formulations. The correlation coefficients were determined graphically (shown in Table 3).

From the above table it was observed that proposed formulations F-3 and F-4 followed First order release kinetics. In formulation Multiple Coefficient of Determination (r^2) value closely near to 1.0 value proposed strong correlation to the kinetic. Here, F-4 formulation is near about 1 value. It follows first order released kinetic.

For further study, the data were plotted into Korsmeyer-Peppas equation to know the confirmed diffusion mechanism. The formulations with slope (n) values ranging from 1.0377 to 1.1679. Kinetic study of formulations showed aberrant type of release exponent (n) > 0.89 indicating a super case II type of release.
It is difficult to make clear inference regarding the kinetics of drug release from this formulations and these formulation showed very poor fitting with Korsmeyer-Peppas model.[14]

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