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## Formulation and Evaluation of Sustained Release Matrix Tablets of Glimepiride Based on Combination of Hydrophilic and Hydrophobic Polymers

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### ABSTRACT

The objective of this study was to develop sustained release tablets of glimepiride by wet granulation method based on combination of hydrophilic (HPMC15cps, HPC) and hydrophobic (Ethyl cellulose) polymers. The drug excipient mixtures were subjected to pre-formulation studies. The tablets were subjected to physicochemical studies, *in-vitro* drug release, kinetic studies and stability studies. FTIR and DSC studies shown there was no interaction between drug and polymers. The physicochemical properties of tablets were found within the limits. Glimepiride is a first third generation sulphonyl urea agent for the treatment type II diabetes mellitus. The drug release from the optimized formulation was extended for a period of 12 hrs. The kinetic treatment showed that the release of drug follows first order models. The optimized formulations were subjected to stability studies and shown there were no significant changes in drug content, physicochemical parameters and release pattern. Results of the present study indicated the suitability of the above mentioned polymers in the preparation of sustained release formulation of glimepiride.

**Keywords:** Glimepiride, Sustained release, Matrix tablets, Wet granulation.

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### INTRODUCTION

The oral route of administration is considered as the most widely accepted route because of its convenience of self administration, compactness and easy manufacturing (Sastry et al, 2000; Seager et al, 1998). Nevertheless, it is probable that at least 90% of all drugs used to produce systemic effects are administered by oral route (Fig 1).

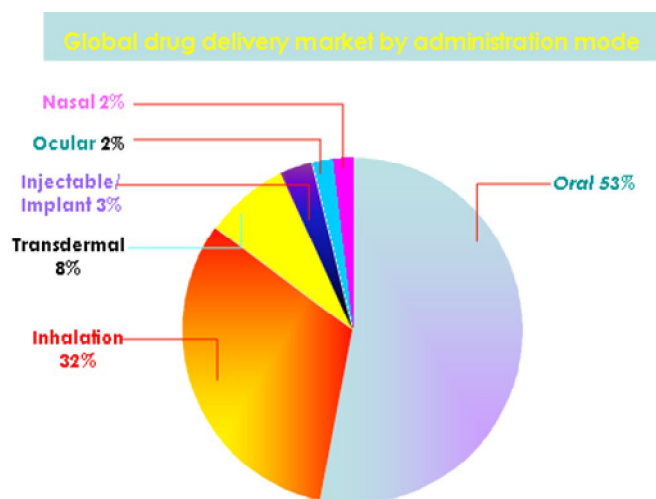


Fig. 1: Global drug delivery market by administration mode.

Diabetes mellitus is a condition in which a person has a high blood sugar level, either because the body doesn't produce enough insulin, or because body cells don't properly respond to the insulin that is produced. Insulin is a hormone produced in the pancreas which enables body cells to absorb glucose, to turn into energy. If the body cells do not absorb the glucose, the glucose accumulates in the blood, leading to vascular, nerve, and other complications (International Diabetes Federation, 2006; Rother et al, 2007). The recent estimation that there were 171 million people in the world with diabetes in the year 2000 and this will increase to 366 million by 2030 [Wild et al, 2004]. Diabetes is a condition primarily defined by the level of hyperglycemia giving rise to risk of microvascular damage (retinopathy, nephropathy and neuropathy). It is associated with reduced life expectancy, significant morbidity due to specific diabetes related microvascular complications, increased risk of macrovascular complication (ischemic heart disease, stroke and peripheral vascular disease), and diminished quality of life. The American Diabetes Association (ADA) estimated the national costs of diabetes in the USA for 2002 to be \$US 132 billion, increasing to \$US 192 billion in 2020 (Diabetes Care, 2003).

Diabetes mellitus is mainly classified as four types. They are, Type -I, Type -II, Gestational diabetes, other types of diabetes. Glimepiride is the first III generation sulphonyl urea it is a very potent sulphonyl urea with long duration of action. It is practically insoluble in water. Soluble in dimethyl formamide, slightly soluble in methanol, sparingly soluble in methylene chloride. It also dissolves in dilute alkali and in dilute acids. Half life is Approximately 5 hours following single dose. Completely (100%) absorbed following oral administration. Over 99.5% bound to plasma protein. Glimepiride is used with diet to lower blood glucose by increasing the secretion of insulin from pancreas and increasing the sensitivity of peripheral tissues to insulin. The mechanism of action of Glimepiride in lowering blood glucose appears to be dependent on stimulation the release of insulin from functioning pancreatic beta cells, and increasing sensitivity of peripheral tissues to insulin (Sekhar et al, 2011).

For sustained release systems, the oral route of drug administration has received the most attention as it is natural, uncomplicated, convenient and safer route. The aim of the present work was to prepare sustained release matrix tablets of glimepiride by using various concentrations of hydrophilic polymers (HPMC 15cps, HPC) and hydrophobic polymer (Ethyl cellulose) by wet granulation method and to study the effect of *in-vitro* release characteristics, kinetics of the prepared formulations and stability studies.

## MATERIALS AND METHODS

### Materials

Glimepiride was obtained as a gift sample from Dr. Reddy's Laboratories, Hyderabad, India. HPMC 15cps and Microcrystalline cellulose were purchased from Rajesh chemicals, Mumbai. Ethyl cellulose was purchased from Loba Chemie Pvt. Ltd, Mumbai. Hydroxyl propyl cellulose, Magnesium stearate and Talc were purchased from Himedia Chem Lab, Mumbai.

### Experimental Methods

#### Drug-excipient compatibility studies

Assessment of possible incompatibilities between an active drug substance and different excipients forms an important part of the pre-formulation stage during the development of solid dosage form. Therefore, the pure drug and the formulations mixed with polymers were subjected to infra-red (IR) studies [Kannan et al, 2010; Patel et al, 2009].

#### Fourier Transform Infrared (FTIR) spectral analysis

The compatibility of drugs and excipients used under experimental condition were studied. The study was performed by taking 2 mg sample in 200 mg KBr (Perkin Elmer, spectrum-100, Japan). The scanning range was 400 to 4000  $\text{cm}^{-1}$  and the resolution was 1 $\text{cm}^{-1}$ . This spectral analysis was employed to check the compatibility of drugs with the excipients used. [Reddy et al, 2011].

#### Preformulation studies

##### Micromeritic properties [Lachman et al, 2009]

##### Angle of repose

The fixed funnel and free standing cone methods employ a funnel that is secured with its tip at a given height,  $h$ , which was kept 2cm above graph paper that is placed on a flat horizontal surface. With  $r$  being the radius, of base of conical pile, angle of repose can be determined by following equation:

$$\theta = \tan^{-1} (h/r)$$

Where,  $\theta$  is the angle of repose,

$h$  is height of pile,  $r$  is radius of base of the pile

##### Bulk density and tapped density

Both loose bulk density and tapped bulk density were determined. A quantity of 2gm of granules from each formula, previously light Shaken for the break of any agglomerates formed, was introduced into the 10ml of measuring cylinder. After the

initial volume was observed, the cylinder was allowed to fall down its own weight from the hard surface from a height of 2.5cm at 2 sec Intervals. The tapping was continued until no further change in the volume was noted

LBD and TBD were calculated using the following formulas:

**LBD:** Weight of the powder/volume of the packing.

**TBD:** Weight of the powder/Tapped volume of the packing.

#### Compressibility index

The compressibility index of the granules was determined by Carr's

Compressibility index.

Carr's index (%) = [(TBD-LBD) \* 100] / TBD

Where,

LBD: Weight of the powder/volume of the packing.

TBD: Weight of the powder/Tapped volume of the packing.

#### Hausner's ratio

Hausner's ratio can be determined by the following equation,

Hausner's ratio = TBD / LBD

Where, TBD -Tapped bulk densities & LBD- Loose bulk densities

#### Preparation of tablets [Ahad et al, 2012]

According to the formula given in **Table 1**. A total number of four formulations were prepared by wet granulation method. Sustained release matrix tablets of glimepiride were prepared by using HPMC (15cps), HPC and ethylcellulose as matrix forming materials, while lactose as a diluent, Magnesium stearate as a lubricant and talc as an anti-adherent. All ingredients used were passed through a # 100 sieve, weighed and blended. The granules were prepared by wet granulation technique and evaluated for its flow properties. The granules were compressed by using 10 mm flat faced punches using in a rotary tablet press (Rimek mini press, model RSB-4, M/S: Karnavathi engineering, Ahmadabad).

#### Evaluation of physical properties of matrix tablets [Prajapati et al, 2010]

##### Hardness test

The hardness of the tablets were determined using Monsanto Hardness tester. It is expressed in kg/cm<sup>2</sup>. Six tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

##### Friability

A friability test was conducted on the tablets using an veego friabilator. Twenty tablets were selected from each batch and any loose dust was removed with the help of a soft brush. The tablets were initially weighed ( $W_{initial}$ ) and transferred into friabilator. The drum was rotated at 25 rpm for 4 minutes after which the tablets were removed. Any loose dust was removed from the tablets as before and the tablets were weighed again ( $W_{final}$ ). The percentage friability was then calculated by,

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

% Friability of tablets less than 1% is considered acceptable.

#### Weight variation

The weight variation test was conducted by weighing 20 randomly selected tablets individually, calculating the average weight and comparing the individual tablet weights to the average. The specification of weight variation is 10%.

#### Uniformity of thickness

The tablet thickness was measured using screw gauge.

#### Drug content uniformity (Banker et al, 2006)

Five tablets of each formulation were weighed and powdered. The quantity of powder was equivalent to 8 mg. The equivalent weight of glimepiride was transferred into 100 ml volumetric flask and by using pH 7.8 as the extracting solvent and samples were analyzed spectrophotometrically by using UV/Visible spectrophotometer at 226 nm.

#### In Vitro-Release Testing (Banker et al, 2006)

Dissolution studies were carried out for all the formulations combinations in triplicate, employing USP - II paddle method and 900ml of pH 7.8 phosphate buffer as the dissolution medium. The medium was allowed to equilibrate to temp of 37°C±0.5°C. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 24 hrs in pH 7.8 phosphate buffer at 50 rpm. At definite time intervals of 5 ml of the aliquot of sample was withdrawn periodically and the volume replaced with equivalent amount of the fresh dissolution medium. The samples were analyzed spectrophotometrically at 226 nm using UV-spectrophotometer. And this dissolution data was further treated for kinetic modeling.

#### Kinetics of in-vitro drug release [Londhe et al, 2010]

Setti et al, 2009; Shoib et al, 2006]: To study the release kinetics in-vitro release data was applied to kinetic models such as zero-order, first order, Higuchi and Korsmeyer-Peppas.

##### Zero-order

$$C = K_0 t \quad (1)$$

expressed in units of concentration/time,  $K_0$  is zero order release constant and  $t$  is the time in hrs.

##### First-order

$$\log C = \log C_0 - Kt / 2.303 \quad (2)$$

Where  $C$  is the concentration,  $C_0$  is the initial concentration of drug,  $K$  is the first-order rate constant, and  $t$  is the time.

**Higuchi**

$$Q_t = K_H \cdot t^{1/2} \quad (3)$$

Where  $Q_t$  is the amount of release drug in time  $t$ ,  $K$  is the kinetic constant and  $t$  is the time in hrs.

**Korsmeyer peppas,**

$$Mt / M_\infty = K \cdot t^n \quad (4)$$

Where  $Mt$  represents amount of the released drug at time  $t$ ,  $M$  is the overall amount of the drug (Whole dose). The value of  $n$  indicates the drug release mechanism related to the geometrical shape of the delivery system, if the exponent  $n = 0.5$ , then the drug release mechanism is Fickian diffusion. If  $n < 0.5$  the mechanism is quasi-Fickian diffusion, and  $0.5 < n < 0.5$ , then it is non-Fickian or anomalous diffusion and when  $n = 1.0$  mechanism is non-Fickian case II diffusion,  $n > 1.0$  mechanism is non-Fickian super case II.

**Accelerated Stability studies [8]**

Accelerated stability study was carried out to observe the effect of temperature and relative humidity on selected formulation (F3), by keeping at  $40^\circ \pm 2^\circ\text{C}$ , in air tight high density polyethylene bottles for three months, at RH  $75 \pm 5\%$ . Physical evaluation was carried out in each month.

**RESULTS AND DISCUSSION****Compatibility study**

Spectra of the pure drug, excipient and physical mixture of drug and excipient were recorded in between 400-4000 wave number ( $\text{cm}^{-1}$ ). The FTIR spectral analysis showed that there is no appearance or disappearance of any characteristic peaks of pure drug glibenclamide and in the physical mixture which confirms the absence of chemical interaction between drug and polymers.

Peak in pure drug and Functional group	Peak in physical mixture and Functional group
NH stretching at $3369 \text{ cm}^{-1}$	NH stretching at $3369 \text{ cm}^{-1}$
C-H stretching at $2932\text{-}2842 \text{ cm}^{-1}$	C-H stretching at $2936\text{-}2883 \text{ cm}^{-1}$
C=O stretching at $1707 \text{ cm}^{-1}$	C=O stretching at $1708 \text{ cm}^{-1}$
C-N stretching $1542 \text{ cm}^{-1}$	C-N stretching at $1543 \text{ cm}^{-1}$

**Micromeritic properties**

Granules of all the formulations were subjected for various pre-compressional evaluations such as angle of repose, bulk and tapped density, compressibility index and Hausner's ratio. Results of all the pre-compressional parameters performed on granules for formulations shown in **Table 2**.

The angle of repose was found to be ranging from  $21^\circ.30' \pm 0.04$  to  $26^\circ.16' \pm 0.02$  for the granules of all the formulations. Compressibility index was found to be ranging from  $11.92 \pm 0.07$  to  $14.77 \pm 0.04$  % for the granules of all the formulations. The results of Hausner's ratio were found to be lesser than 1.25 which indicates better flow properties. The results of angle of repose ( $< 30$ ) indicates good flow properties of the powder. This was further supported by lower compressibility index values. Generally compressibility values up to 15% results in good to excellent flow properties.

**Evaluation of prepared tablets**

The results of physical evaluation of tablets were given in **Table 3**. The tablets of different batches were found uniform with respect to hardness within the range of  $3.20 \pm 0.40$  to  $4.00 \pm 0.55 \text{ kg/cm}^2$ .

Another measure of a tablet's strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. Results of friability test were also has been found within limit. In weight variation test, the pharmacopoeial limit for percentage deviation for tablets of more than 250 mg is  $\pm 5\%$  and all the formulations were found to comply with the specifications given in I.P. for weight variation test. Good uniformity in drug content was found among the formulations, and percentage of drug content was more than 95%. All the tablet formulations showed acceptable pharmaco technical properties.

**In - vitro drug release study**

The release profile of glibenclamide from different batches of formulated matrix tablets were illustrated in **Table 4** and plotted in **Figure 3**. Based on the results of in-vitro dissolution testing it was known that the formulations compressed with either HPMC (15cps) or HPC shown the drug release for a period of only upto 4-6 hours. But when combination of three polymers (ethylcellulose, HPMC 15cps and HPC) were taken and to some extent the polymers concentration were increased the drug release was extended for a period of 12 hours.

It is due to the reason that used concentrations of polymers have increased the viscosities of formulations which lead to the sustained-release of drug. But the formulation F-3 shown maximum amount of drug release i.e. 99.93 % for a period of 12 hours in a sustained-manner and hence was considered as the best formulation. It was also found to be optimum for stability studies.

**Table 1:** Composition of sustained release matrix tablets:

Ingredients	F 1	F 2	F 3	F 4
Glibenclamide	8 mg	8 mg	8 mg	8 mg
HPMC (15cps)	30 mg	---	20 mg	20 mg
HPC	---	20 mg	20 mg	10 mg
Ethyl cellulose	30 mg	40 mg	30 mg	40 mg
Microcrystalline cellulose	76 mg	76 mg	66 mg	66 mg
Magnesium stearate	3 mg	3 mg	3 mg	3 mg
Talc	3 mg	3 mg	3 mg	3 mg
Total	150 mg	150 mg	150 mg	150 mg

**Table 2:** Results of physical evaluation of Pre-compression Blend.

Formulations	Angle of repose (degree± SD)	Bulk Density (g/mL± SD)	Tapped Density (g/mL± SD)	Carr's Index (%± SD)	Hausner's ratio (%± SD)
F1	21°.30'±0.04	0.224±0.04	0.264±0.02	14.77±0.04	1.17±0.03
F2	22°.24'±0.06	0.222±0.04	0.260±0.06	14.61±0.02	1.17±0.04
F3	26°.16'±0.02	0.251±0.06	0.289±0.04	13.14±0.07	1.15±0.06
F4	25.26'±0.01	0.229±0.01	0.260±0.03	11.92±0.07	1.13±0.05

**Table 3:** Evaluation of Sustained release matrix tablets of Glimepiride.

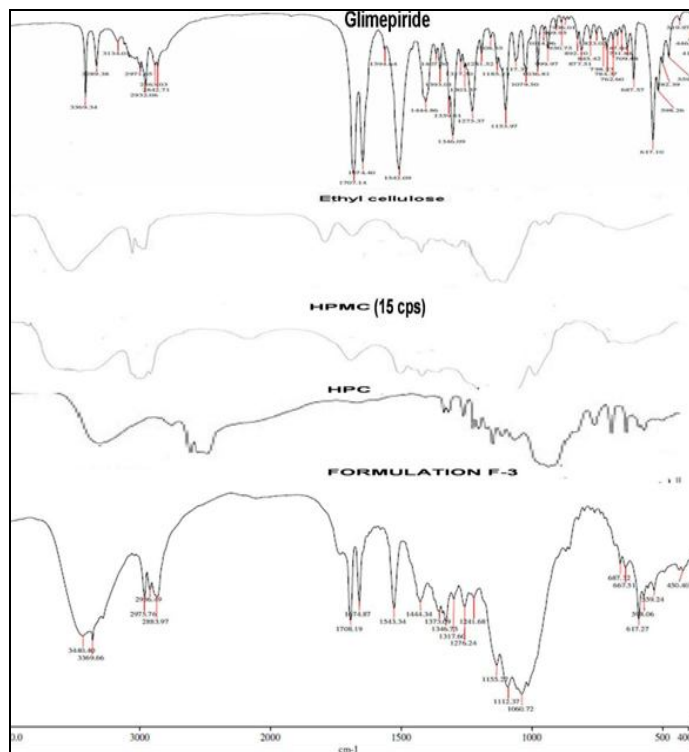
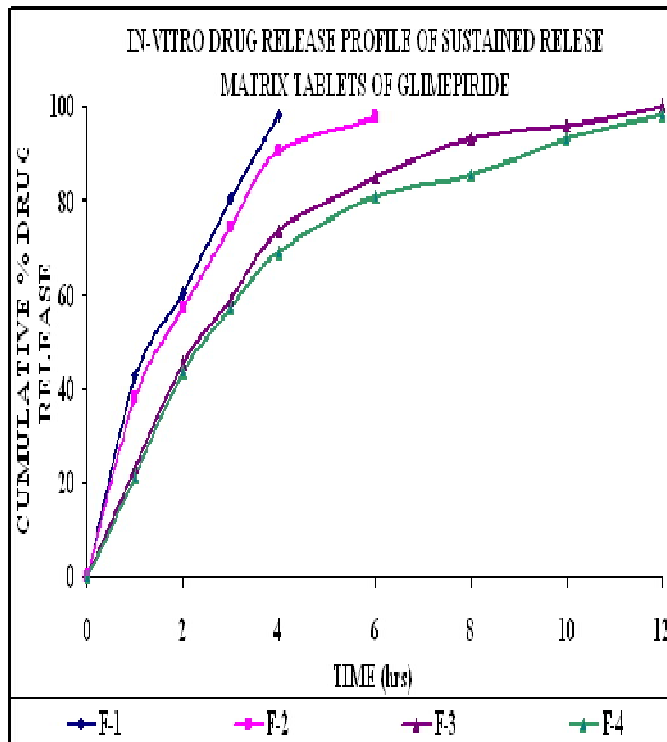
Formulation	Weight Variation (mg)	Hardness (kg/cm <sup>2</sup> )	Thickness (mm)	Friability	Drug Content (%)
F1	150±1.22	3.34±0.10	3.65±0.25	0.40±0.08	99.16±0.56
F2	149±0.56	4.00±0.55	4.05±0.40	0.35±0.10	98.28±0.60
F3	149±0.30	3.20±0.40	3.80±1.20	0.24±0.12	99.42±1.46
F4	150±0.45	3.80±0.20	4.00±0.28	0.16±0.06	99.22±0.84

**Table 4:** Data of In-Vitro Drug Release Studies of sustained-release matrix tablets of Glimepiride.

Time	F1	F2	F3	F4
1	42.93286	38.16254	23.13604	21.46643
2	60.58304	57.24382	45.31802	43.40989
3	80.61837	74.41696	59.15194	57.24382
4	98.26855	90.39753	73.70141	69.16961
6		97.79152	85.15018	81.09541
8			93.25972	85.38869
10			96.12191	93.0212
12			99.93816	98.26855

**Table 5:** Summary of physical properties of F-5 before and after accelerated stability studies.

Parameter	Before stability studies (Initial)	After stability studies
Thickness (mm)	3.80±1.20	3.80±1.10
Hardness (kg/cm <sup>2</sup> )	3.20±0.40	3.20±0.26
Friability (%)	0.24 ± 0.12	0.20 ± 0.10
Drug content (%)	99.42±1.46	99.00 ± 1.14
In-vitro release study (at the end of 12 hours)	99.93	99.43
Number of trials (n) = 5		

**Fig. 2:** IR spectra of a) Pure drug Glimepiride b) Ethyl cellulose c) HPMC (15 cps) d) HPC e) Formulation F-3.**Fig. 3:** In-vitro drug release profile of Sustained-release matrix tablets of glimepiride.

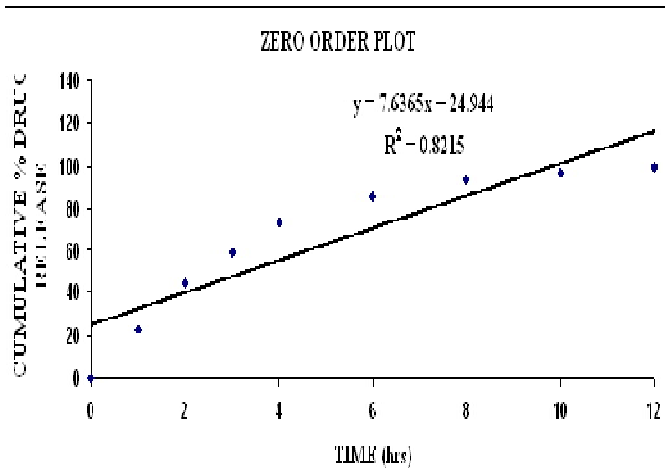


Fig. 4: Zero order plot of Formulation F-3.

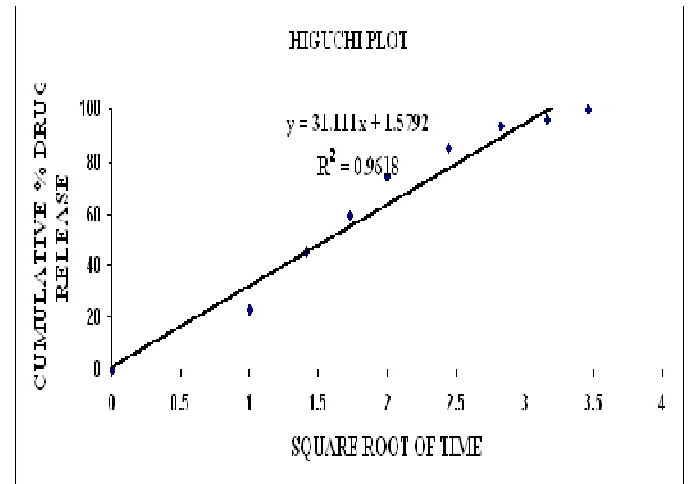


Fig. 6: Higuchi plot of Formulation F-3.

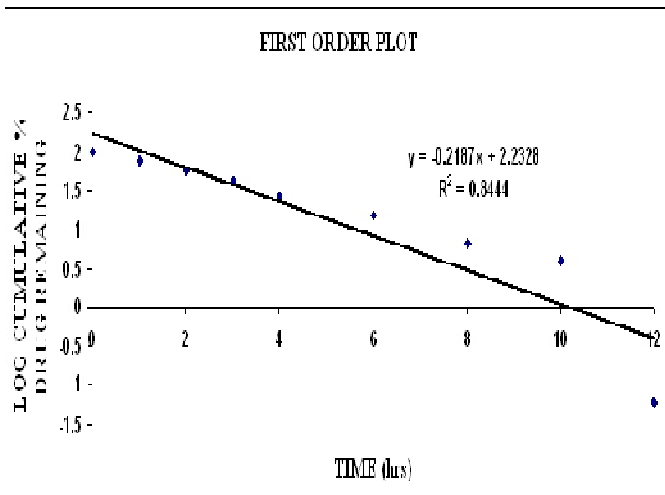


Fig. 5: First order plot of Formulation F-3.

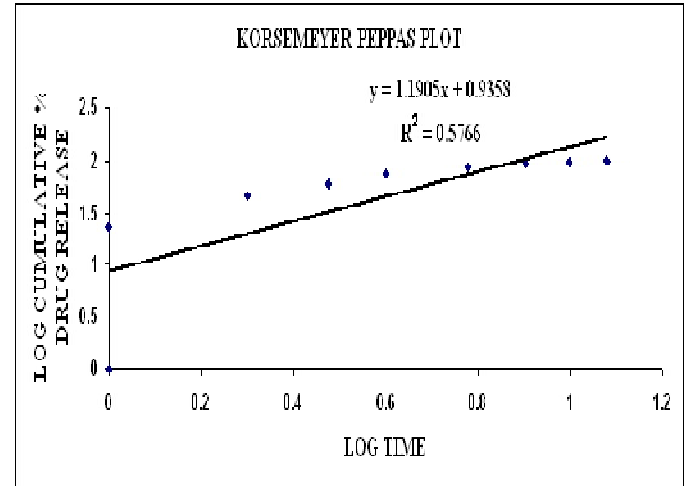


Fig. 7: Korsmeyer-Peppas's plots of Formulation F-3.

### Drug release study

The kinetic data of all the formulations are graphically represented in **Figures 4-7**. In order to determine the mechanism of drug release from the formulations, the *in-vitro* dissolution data was fitted to Zero order, First order, Higuchi plot and Korsmeyer-peppas's plot was drawn for optimized formula and interpretation of release exponent value (*n*) was calculated. The results of R2 for zero and first order were obtained as 0.8215 and 0.8444 respectively. Based on that we have confirmed that the optimized formulation followed first order release.

Higuchi's model was applied to the *in-vitro* release data, linearity was obtained with high 'r' value indicating that drug release from the sustained-release tablets through diffusion. The *in-vitro* release data was further fitted to Korsmeyer-Peppas model which is generally used to analyze the release mechanism when more than one type of release phenomenon is operational. Good linearity was observed with high 'r' values. The value of release exponent 'n' is an indicative of release mechanism. The value of 'n' obtained for the optimized formulation F-3 was found to be 1.19 suggesting probable release by super case-II transport.

### Stability studies

The results of accelerated stability studies shown in **Table 5** carried out according to ICH guidelines indicated that the tablets did not show any physical changes (color change, friability and hardness), assay and dissolution characteristics during the study period.

### CONCLUSION

The study was undertaken with the aim to Formulation and evaluation of glimepiride sustained-release matrix tablets using various concentrations of polymers.

From the above results and discussion, it is concluded that the formulation of sustained release tablet of glimepiride containing HPMC (15cps), HPC, ethylcellulose and microcrystalline cellulose which are taken as ideal or optimized formulation for 12 hours release fulfills all the requirement of sustained release tablet. From the kinetic studies it was known that all the formulations released at first-order rate and were even found to be optimum for stability studies.

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