Research Article

Evaluation of Sustained Release Tablet of Metformin in Alloxan Induced Diabetic Rat

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ABSTRACT

Currently, the use of natural gums is of increasing importance in pharmaceutical formulations as valuable drug excipients. Natural plant-based materials are economic, biocompatible and biodegradable with no side effect. Therefore, Metformin matrix tablets were formulated by employing Guar gum as natural polymer and HPMC K100M as a synthetic polymer to sustain the drug release from matrix system. Direct compression method was used to develop sustained released (SR) matrix tablets. The formulated matrix tablets were evaluated for pre and post compression parameters, compatibility studies and *in vitro* drug release. The dissolution studies of formulated tablets revealed sustained drug release up to 24 hrs compared to the reference drug GLYCIPHAGE 500mg SR tablets. Furthermore, the formulation was evaluated for glycemic control with marketed formulation of Metformin (GLYCIPHAGE 500mg SR) in alloxan induced diabetic rat. The obtained results reveals, granules of formulations showing compliance with pharmacopoeial standards. Dissolution data later were fitted into kinetic models such as zero order equation, first order equation, Higuchi equation, Hixson Crowell equation and Korsmeyer-Peppas equation to study the release of drugs from each formulation. With the increase in concentration of polymer, drug release was found to be retarded for both natural and synthetic polymers. The best formulation was found to be F7 having 1:2 ratio of both polymers showing sustained release of drug for 12 hrs with 98.28% and showed comparable dissolution profile to the reference drug with 97.95%. The release kinetics of this formulation has shown to follow Higuchi's equation for all the formulations with higher correlation (r^2 = 0.98). Additionally, the *in vivo* results indicated that there were significant changes in blood glucose level in treated and untreated rats. However, treatment of diabetic rats with F7 significantly decreases blood glucose level for a prolonged period compared to pure Metformin HCL and Marketed Glyciphage treated rats.

Keywords: Metformin hydrochloride, HPMC K100M, Guar Gum, Sustained release, Matrix tablet.

INTRODUCTION

Sustained-release (SR) oral delivery systems are designed to achieve therapeutically effective concentrations of drug in systemic circulation over an extended period of time[1] towards novel drug delivery of pharmaceutical technology; SR matrix tablets have given a new evolution. [2] Reservoir type of dosage forms designed to release drug constantly and continuously over satisfactory prolonged period of time to maintain plasma drugs concentration within therapeutic level. [3] The desire to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use. [4] As per its popularity and availability in the market due to its ease of manufacturing, administration convenience, dosing accurateness and better stability than other dosage forms, SR tablets are adopted. [5] Matrix systems are widely used in oral controlled drug delivery system and were chosen as formulation approach since their preparation involves few processing variables and they can be easily manufactured by direct compression with conventional tabletting facilities. [6, 7, 8] It is investigated that various natural, synthetic and semi-synthetic polymeric materials are used in SR tablets. Hydroxyl propyl methylcellulose (HPMC), sodium carboxy methylcellulose (CMC), Eudragit (polymethacrylate)

polymer,[9, 10] ethyl cellulose[11] are synthetic in nature whereas natural gums like guar gum and xanthan gum are widely used as release retardants.[12]

In the development of oral sustained release dosage forms, generally natural polymers are considered to be stable and safe which is due to their non-toxicity, cost effectiveness as well as easy availability. [13, 14] Guar Gum is an acidic polysaccharide containing D-galactose, L-arabinose, L-rhamnose and D-glucuronic acid. [15] It can protect the drug in the stomach and small intestine environment, leading to the final delivery of the drug, as it is not affected by ionic strength or pH at moderate temperature due to its non-ionic nature.[16]

As an oral anti-hyperglycaemic agent mainly Metformin used to treat patients with type 2 diabetes mellitus. [17] Different from Insulin and the Sulfonylurea, Metformin does not promote weight gain; therefore it becomes the first choice for treatment of type 2 diabetes and is even used in obese patients with type 1 diabetes to reduce insulin resistance.[18] Chemically, metformin (N, N-dimethylimidodicarbonimidic diamide hydrochloride) [19] belongs to the class of biguanides, hydrophilic, BCS class-III drug, with oral bioavailability of 50 -60%. [20] Biological half-life of Metformin hydrochloride is (1.5-1.6) hour and the drug is commonly administered at high doses (500mg

or 1000 mg) 2-3 times per day to achieve effective glucose-lowering treatment. [21, 22]

The overall objective of present investigation was to develop matrix tablet of Metformin Hydrochloride for sustained release using Hydrophilic synthetic polymer (HPMC K100M) and Natural polymer (Guar gum) as the retardant polymers. Matrix tablets were prepared by direct compression method and prepared tablets were evaluated for pre and post compression parameters. The excipients used in this study do not alter physicochemical nature of drug as tested by IR and DSC. The optimized formulation was evaluated for glycemic control with marketed formulation of Metformin (GLYCIPHAGE 500mg SR) in alloxan induced diabetic rat.

MATERIALS AND METHODS

Metformin hydrochloride was a generous gift sample from Micro Labs Ltd, Hosur, India. Hydroxy propyl methyl cellulose (HPMC K 100 M) and Guar gum were purchased from LOBA CHEMIE, Mumbai. All other chemicals used were of analytical grade.

Animals

Adult albino Wistar rats of either sex weighing between180-200 were used for the study. The animals were housed in well ventilated cages in an air-conditioned animal house with a 12h light and dark control conditions. The animals were fed with standard pellet diet and water *ad libitum*. Prior to experiments, the procedure and protocols used in the study were approved by Institutional Animal Ethical committee (Approval number. 03/16/IAEC/SPS/SOAU) under School of Pharmaceutical Sciences, SOA University. Bhubaneswar , India in accordance with the Committee for the purpose of control and supervision of Experiments on Animals (CPCSEA) guidelines, Chennai, India.

Preliminary Study (Compatibility study)

Fourier transform infrared spectroscopic study (FTIR)

Infrared spectrum was taken by scanning the samples of pure drug and the polymers individually over a wave number range of 4000 to 400 cm cm−1 using Fourier transform infrared spectrophotometer (FT-IR, Shimadzu 8400S, Shimadzu, Japan). The change in spectra of the drug in the presence of polymer was investigated which indicates the physical interaction of drug molecule with the polymer. [23]

Differential scanning calorimetry (DSC)

DSC study of untreated and spray-dried metformin hydrochloride samples were carried out on a differential scanning calorimeter (model DSC7, Perkin Elmer, and UK). Samples, of 2 mg each, of untreated drug and spray-dried powder of the optimized batch were held for 1 minute at 50 °C and then heated gradually at 10 °C min^{-1} in crimped aluminium pans under a nitrogen atmosphere from 50 to 270 °C. The onsets of melting points and enthalpies of fusion of samples were automatically calculated by the instrument. [24]

Formulation of Sustained Release Tablet of Metformin

Matrix tablets each containing 500 mg metformin hydrochloride was prepared by direct compression method. The composition of various formulations of the tablets with their codes is listed in Table 1. The ingredients were passed through a 60 mesh sieve. Calculated amount of the drug, polymer (HPMC K100 M, Guar gum) and filler (MCC) was mixed thoroughly. Magnesium Stearate was added as lubricant. Appropriate amount of the mixture was weighed and then compressed using an eight station rotary press, at a constant compression force equipped with a 14-mm flat - faced punch at a compression force required to produce tablets of about 7-8 kg/cm^2 hardness. All the tablets were stored in airtight containers for further study. Prior to compression, granules were evaluated for their flow and compressibility characteristics.

Pre-compression parameters

Bulk Density

The bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume including the contribution of inter particulate space.

$$\text{Bulk density} = \frac{\text{Mass[M]}}{\text{Bulk volume[Vb]}}$$

Tapped Density

The tapped density is the ratio of mass of the blend and tapped volume.

$$\text{Tapped Density} = \frac{\text{Mass[M]}}{\text{Tapped volume [Vt]}}$$

Angle of Repose

The angle of repose of the granules was determined by the height cone method, which indicate the flow ability of the granules.

It is calculated by

$$\text{Tan } \theta = \frac{h}{r}$$

Where, θ = angle of repose, h= height of pile, r = radius of pile

Compressibility Index

% Compressibility or Carr's index

$$\text{Carr's index (\%)} = \frac{\text{poured density – Tapped density}}{\text{Poured density}} \times 100$$

Hausner's Ratio

Hausner's ratio was calculated using the formula

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{poured density}}$$

Evaluation of Sustained Release Tablet of Metformin

Post Evaluation Parameter

Hardness

The hardness of the tablets is determined by using Monsanto hardness tester. It is expressed in kg/cm^2. Minimum 10 tablets are randomly picked and hardness of the tablets is determined. [25]

Thickness

By using Vernier calliper, the thicknesses of the tablets can be determined. Minimum five tablets are required, and average values are calculated. Variation in tablet may cause problems in counting and packaging. Tablet thickness should be controlled within a ±5% of a standard value. [26]

Weight Variation

Minimum 20 tablets are randomly selected and individually weighed to check the weight variation.

Friability

Minimum 20 tablets from each batch are selected randomly and weight. The friability of tablets is determined by using Roche Friabilator for 100 revolutions. [27]

$$\%friability = \frac{(\text{Initial Weight} - \text{Final Weight})}{\text{initial weight}} \times 100$$

In-Vitro **Drug Release Studies**

Drug release studies were conducted using USP-22 dissolution apparatus-2, paddle type (Electro lab, Mumbai, India) at a rotational speed of 50 rpm at 37±0.5 ^{o} C. The dissolution media used were 900 mL of pH 6.8 phosphate buffer solutions for 12 h. Sink condition was maintained for the whole experiment. Samples (10 mL) were withdrawn at regular intervals and the same volume of pre warmed (37±0.5 ^{o} C) fresh dissolution medium was replaced to maintain the volume constant. The samples withdrawn were filtered through a 0.45 μ membrane filter (Nunc, New Delhi, India) and the drug content in each sample was analysed after suitable dilution with a UV spectrophotometer (Shimadzu UV-1700) at 232 nm. The dissolution test was performed in triplicate. Drug dissolved at specified time periods was plotted as cumulative percent release versus time (h) curve. [28]

In vivo **study**

The optimized F7 formulation (500mg/kg, p.o.) was suspended in 1%w/v CMC in distilled water, pure drug Metformin HCL (500mg/kg, p.o.) and Marketed Drug (Glyciphage SR) (500mg/kg, p.o.) suspended in 1%w/v CMC in distilled water used as reference control in this study. The laboratory acclimatized rat were kept overnight fasting and injected (80mg/kg, i.p.) alloxan monohydrate in normal saline. The rats were considered diabetic when the blood glucose level was beyond 200mg/dl and this condition was observed at the end of

48 hour after alloxanisation, which is 0th hour of experiment. [29] The diabetic rats were divided into four groups.

Group I- diabetic control and rats received only vehicle (i.e 1%CMC).

Group II- F7 formulation (500mg/kg, p.o.) suspended in 1%w/v CMC in distilled water

Group III- Pure Metformin HCL (500mg/kg, p.o.)

Group IV- Marketed Drug (Glyciphage SR) (500mg/kg, p.o.). The blood glucose was measured by glucometer from the rat tail tip on 0th ,6th ,12th,24th,48th,72th,120th hour of administration of test drugs.

RESULTS AND DISCUSSION

Compatibility study

FTIR study

An FTIR study suggests that there was no interference in the functional group. The principle peaks of Metformin Hydrochloride were found to be unaltered in the drug polymer physical mixture as shown in Figure1. Furthermore, FTIR studies revealed that metformin hydrochloride showed two typical bands at 3369 and 3296 cm^{-1} due to N-H primary stretching vibration ; a band at 3170 cm^{-1} due to N-H secondary stretching; characteristics bands at 1626 and 1567 cm^{-1} assigned to C=N stretching in Metformin Hydrochloride. No significant shifts of reduction in intensity of the FTIR bands of metformin hydrochloride were observed.
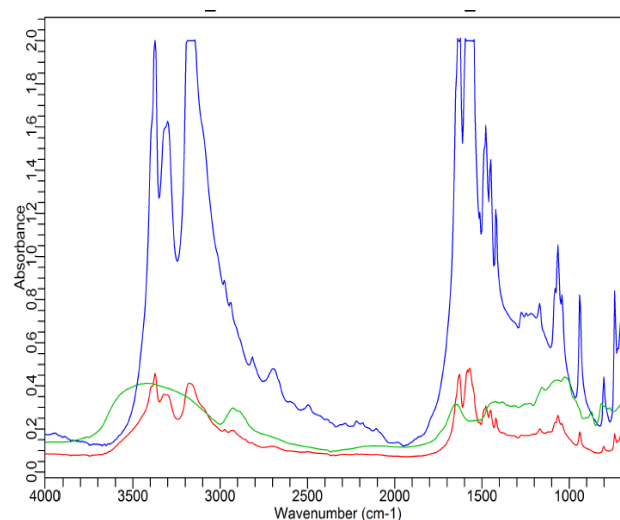

Figure 1: FTIR Spectra of Physical Mixture.

DSC Analysis

The thermal curves of pure components and physical mixture are shown in Figure 2. The DSC curve of pure Metformin exhibited an initially flat profile, followed by a single sharp endothermic peak representing the melting of the substance in the range 223–237 ºC (T onset = 231.2, T peak = 233.33 and Fusion = -313.51 J/g). The thermal curves of physical mixtures, obtained by simple blending corresponded to the superimposition of those of

the single components, indicating the absence of solid-state interactions and allowing assessment of drug–polymers compatibility in all the examined formulations. As a further confirmation of the absence of any incompatibility problem, no variations in the thermal behaviour of physical mixtures were observed after their tabletting and subsequent powdering. Thus, no definite solid-solid interaction could be concluded by examination of all the DSC thermograms as shown in Figure 2.
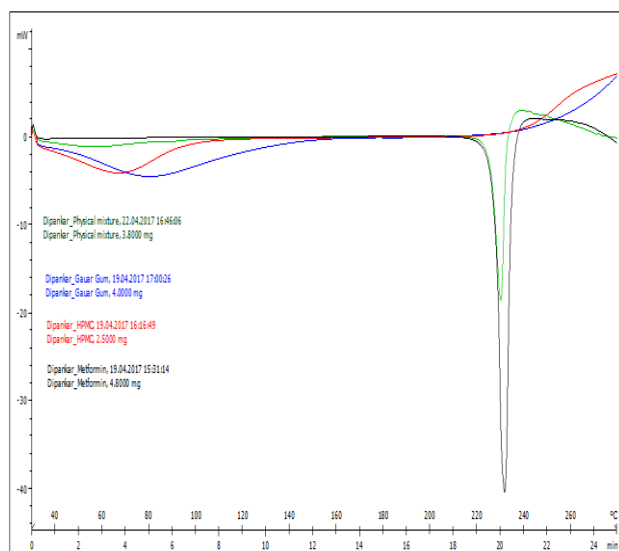

Figure 2: DSC of Physical Mixture

Formulation of Metformin SR Tablets

SR tablet was prepared by using the drug Metformin and the polymer i.e. Guar gum, HPMC K100M in varying proportions as shown below.

Evaluation of post -compression parameters

From the physical parameters of each batch as shown in Table 3, it was concluded that the tablets of all batches had desirable physical characteristics. Results of various batches of prepared formulations i.e. Thickness (4.22-4.53mm), Hardness (7.10 –7.94 kg / sq. cm.) and Friability (0.12 – 0.29 %) indicates that the tablets having sufficient strength to withstand physical abrasion. Tablets of all batches pass the weight variation test and uniformity in content was as per the pharmacopoeial standard limits.

In-Vitro Drug Release Study

Table 4 and Figure 3, indicates the dissolution data of various batches of Metformin HCl sustained release tablets. The percentage drug release from batch F1 to F8 vary from 79.58 to 98.28%. The results of dissolution studies as shown in Table 4 indicate that formulations F1, F2 and F3 containing only HPMC K100 M in varying ratio release 97.34, 97.09 and 84.45% of drug after 12hrs. Formulations F4 and F5 containing Guar gum released 97.56, 92.12% of drug respectively after 12 hrs. The dissolution profile of Formulations F6, F7 and F8 containing combinations of a hydrophilic polymer HPMC with Guar gum in the different polymer/polymer ratio (1:1, 1:2 and 1:3, respectively) released 96.78, 98.28 and 79.58% of the drug respectively, after 12 hrs. Marketed formulation Glyciphage 500mg SR showed 97.95 % at 12 hrs.

Table 1: Formulation table

Formulation code	Metformin HCL	Guar Gum	HPMC K100M	Mg. Stearate (1%)	MCC	Total
F1	500	-	60	8	232	800
F2	500	-	120	8	172	800
F3	500	-	180	8	112	800
F4	500	60	-	8	132	800
F5	500	120	-	8	172	800
F6 (1:1)	500	60	60	8	172	800
F7 (1:2)	500	60	120	8	112	800
F8 (1:3)	500	60	180	8	52	800

Evaluation of pre-compression parameters

Table 2, indicates the powder characteristics of various batches of sustained release tablets. All the formulations show good flow properties. Results of Bulk density (0.36 – 0.39), Tapped density (0.41 – 0.48), Compressibility index (12.06 – 20.63), Angle of repose (24.14 – 28.41) shows satisfactory results, which is required for better bioavailability.

From the data it is clear that by increasing the amount of polymer in the formulation, the amount of drug release is decreased. The obtained data reveals that by combining the natural (guar gum) and synthetic (HPMC K100M) polymers, the drug release is prolonged. Further increasing the amount of polymer causes the incomplete release of drug from the matrix. Hence, Formulation F7 having 1:2 ratio of both polymers i.e. Guar gum and HPMC is the best formulation, since it meets the dissolution specification as per USP. Finally the optimized

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F7 formulation is compared with the marketed GLYCIPHAGE 500mg SR Tablets. At higher polymer loading, the viscosity of the gel matrix is increased which results in a decrease in the effective diffusion coefficient of the drug and is more likely to be resistant to drug diffusion and erosion .This indicates that drug/polymer ratio is an important factor affecting the rate of release drugs from HPMC matrices.

Table 2: Micromeritic Properties of Blend

Formulation	BulkDensity (g/ml) (± SD)	Tapped Density (g/ml) (± SD)	Compressibility Index (%) (± SD)	Angleof Repose (± SD)
F1	0.39±0.52	0.46±0.62	15.22±0.78	24.14±0.67
F2	0.39±0.43	0.47±0.78	17.88±0.33	27.25±0.48
F3	0.37±0.91	0.46±0.24	18.45±0.64	24.41±0.50
F4	0.36±0.35	0.42±0.46	14.29±0.80	25.73±0.45
F5	0.38±0.71	0.48±0.34	20.63±0.77	27.68±0.57
F6	0.39±0.12	0.45±0.93	15.22±0.42	28.21±0.90
F7	0.37±0.20	0.41±0.32	12.06±0.71	27.41±0.66
F8	0.37±0.43	0.46±0.74	19.3±0.49	28.41±0.32

Table 3: Physical properties of the sustained release Metformin HCL formulations

| Formulation code	Hardness (kg/cm^2)	Friability (%)	Weight Variation	Drug Content (%)	Thickness (mm)
F1	7.39±0.36	0.12±0.14	780±0.12	99.54	4.42±0.06
F2	7.10±0.58	0.28±0.11	788±0.24	99.84	4.53±0.04
F3	7.55±0.63	0.29±0.12	785±0.16	97.23	4.29±0.07
F4	7.83±0.12	0.25±0.29	798±0.23	99.24	4.33±0.04
F5	7.94±0.32	0.15±0.27	786±0.12	98.54	4.39±0.06
F6	7.82±0.54	0.27±0.31	789±0.15	97.34	4.22±0.08
F7	7.20±0.83	0.24±0.15	800±0.23	99.94	4.52±0.05
F8	7.52±0.28	0.23±0.18	799±0.31	98.44	4.32±0.02
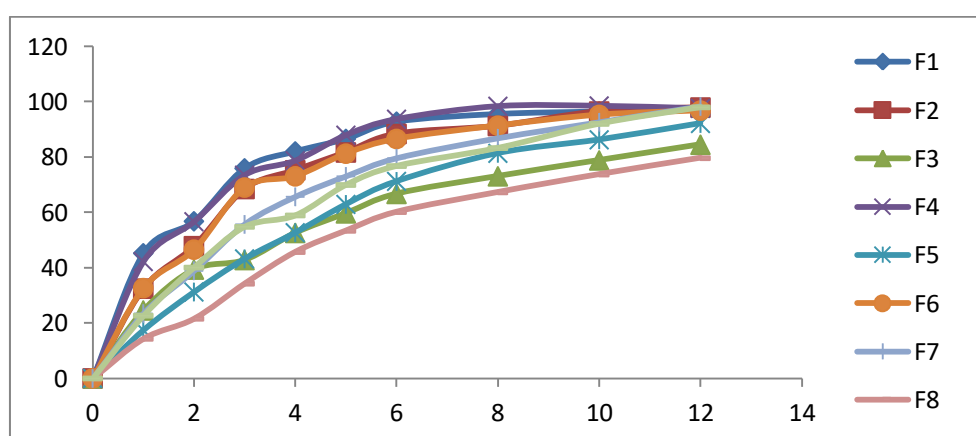
Figure 3: *In-vitro* dissolution study of formulations (F1-F8) & Mkt Glyciphage SR Tablets

Release kinetics

In order to study the drug release mechanism of the examined tablets, the dissolution profile was analysed according to the different zero-order, first-order and Higuchi square root kinetic equations. The best fit with higher correlation (r^2 = 0.98) was found with Higuchi's equation for all the formulations. This model fails to allow for the influence of swelling of the matrix (upon hydration) and gradual erosion of the matrix. Therefore, the dissolution data were also fitted according to the well-known exponential Korsmeyer -Peppas equation [30] which is often used to describe drug release behaviour from polymeric systems. The results of R^2 for Higuchi and Korsmeyer Peppas were obtained.

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Table 4: *In-vitro* dissolution study of Formulations (F1-F8) & Marketed Glyciphage500mg SR tablets

Time	F1	F2	F3	F4	F5	F6	F7	F8	MKT
0	0	0	0	0	0	0	0	0	0
1	45.23±0.12	32.45±0.17	24.56±0.14	42.23±0.16	17.45±0.16	32.63±0.22	23.45±0.22	14.32±0.23	22.67±0.12
2	56.67±0.24	47.78±0.12	39.34±0.26	56.64±0.18	31.23±0.22	46.54±0.14	38.89±0.16	21.56±0.22	40.05±0.13
3	75.89±0.22	68.45±0.19	42.78±0.12	73.45±0.28	43.21±0.19	68.98±0.12	55.67±0.18	34.23±0.16	54.78±0.23
4	82.32±0.23	75.21±0.23	52.56±0.15	78.67±0.16	52.67±0.16	73.03±0.22	65.63±0.14	45.67±0.17	58.89±0.21
5	86.56±0.33	81.65±0.25	59.65±0.22	87.89±0.12	62.89±0.14	81.23±0.16	73.01±0.15	53.34±0.19	69.91±0.11
6	92.78±0.13	88.34±0.22	66.67±0.18	93.67±0.23	71.21±0.25	86.54±0.25	79.56±0.24	60.12±0.18	76.74±0.24
8	95.56±0.12	91.21±0.32	73.03±0.22	98.34±0.32	81.34±0.15	91.34±0.22	86.78±0.17	67.23±0.14	83.23±0.17
10	96.45±0.16	96.45±0.21	78.78±0.27	98.47±0.16	86.32±0.22	95.23±0.15	92.56±0.21	73.67±0.21	90.97±0.22
12	97.34±0.14	97.09±0.12	84.45±0.25	97.56±0.12	92.12±0.21	96.78±0.23	98.28±0.22	79.58±0.24	97.95±0.12

STABILITY STUDY

According to ICH guidelines, 90 days stability study at 40 °C ± 2°C and 75±5% RH of optimized formulation F7 was carried out. It showed negligible change over time for parameters like appearance, drug content, and dissolution. No significant difference in the drug content between initial and final formulations stored at 40 °C ±2°Cfor 90 days at RH 75±5% for 90 days.

IN-VIVO STUDY

There were significant changes in blood glucose level in treated and untreated rats. Treatment of diabetic rats with F7, Pure Metformin HCL and Marketed Glyciphage significantly decrease the blood glucose level in comparison with solvent treated diabetic rats. Treatment of diabetic rats with F7 significantly decreases blood glucose level for a prolonged period compared to pure Metformin HCL and Marketed Glyciphage treated rats.
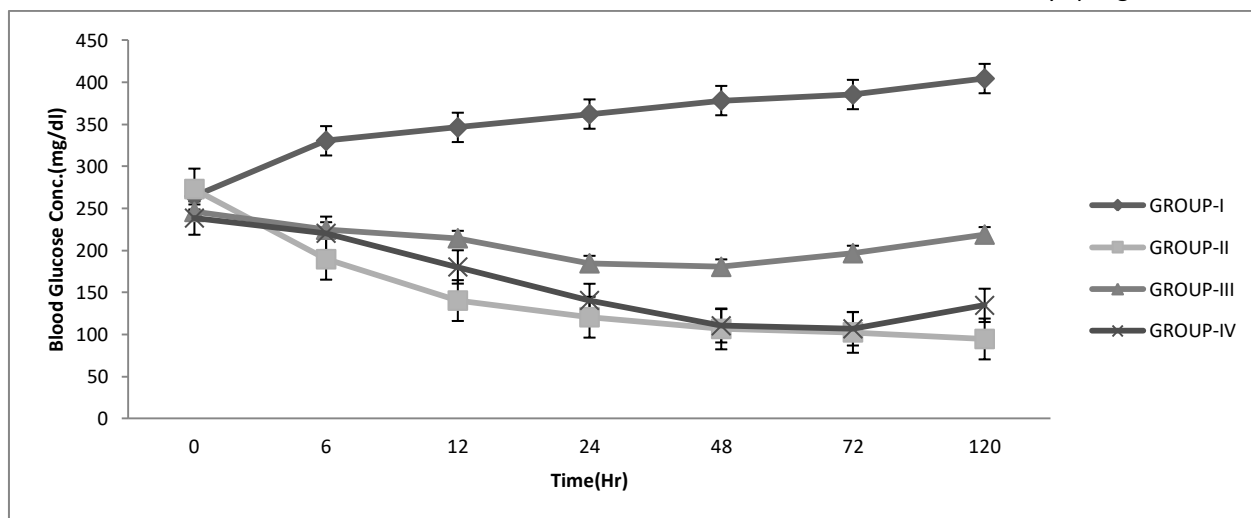

Figure 4: Effect of different formulations in alloxan induced diabetic rat.

Values are expressed in mean± SEM from 6 animals in each group. *$p < 0.05$.One way ANOVA followed by Dunnet's t-test. Group-II is compared with Group-I. Group-III and IV are compared with Group-II.

CONCLUSION

Our results demonstrated that the hydrophilic matrix of HPMC alone could not control the Metformin HCL release effectively. Furthermore, when combined with Guar gum could slow down the release of drug from their matrices and can be successfully employed for formulating SR matrix tablets. Diffusion coupled with erosion might be the mechanism for the drug release which can be expected to reduce the frequency of administration and decrease the dose-dependent side effects associated with repeated administration of conventional Metformin HCL tablets.

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