Metformin hydrochloride sustained release tablet using different matrixing tablet

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ABSTRACT

Sustained release dosage forms continue to draw attention in the search for improved patient compliance & decreased incidences of adverse drug reactions. The objective of this work was to prepare & evaluate sustained release matrix tablets of Metformin HCl using different polymers. Metformin HCl is a water soluble drug indicated to improve glycemic control in patients with type II diabetes. Metformin HCl Matrix tablets were prepared using different polymers like Carbopol 971, Xanthan gum, hydroxypropyl methyl cellulose K100M, Carbopol 71G by wet granulation technique. Prepared tablets were evaluated for weight variation test, hardness, friability, uniformity of content, assay & in vitro drug release. Influence of different parameters like pH, agitation intensity on drug release was studied for optimized batch. Metformin HCl sustained release matrix tablets prepared using HPMC K100M was found to have higher drug content 99±0.5 % w/w & better drug release profile 95±3 % after 12 hrs & hence it was optimized. In vitro release profile of optimized formulations was found to be similar to that of commercial marketed products. The average f2 values were found to be 56.47 for matrix tablets. Likewise other water soluble drugs can also be formulated for sustained release matrix system.

Key words: Sustained release drug delivery system, Matrix tablets, Metformin hydrochloride, HPMC

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to the target site, to achieve promptly & then maintain the desired therapeutic drug concentration that elicits the desired therapeutic action & to minimize the incidence & the severity of unwanted adverse effects. To achieve this goal, it would be advantageous & more convenient to maintain a dosing frequency to once, or at most, a twice-daily regimen. An approximately designed extended release dosage form can be completely justified in view of their biopharmaceutical & pharmacokinetics advantages over the conventional immediate release dosage forms.[1]

Among various technologies available, Monolithic Sustained Release Matrix tablets are possibly the most common for controlling the release of drugs because they are relatively easy to fabricate, compared to reservoir devices, simple processing technologies required, reproducibility, & stability of the materials & dosage form as well as ease of scale-up operation.[2] There is not the danger of an accidental high dosage that could result from the rupture of the membrane of a reservoir device. This

gives a higher initial release rate & can be made to release at a nearly constant rate. The polymer when incorporated into pharmaceutical dosage forms such as tablets had shown a tendency to linearize the drug release curves & gives zero order release. In such a system the active agent is present as dispersion within the polymer matrix, & they are typically formed by the compression of a polymer/drug mixture or by dissolution or melting.[3]

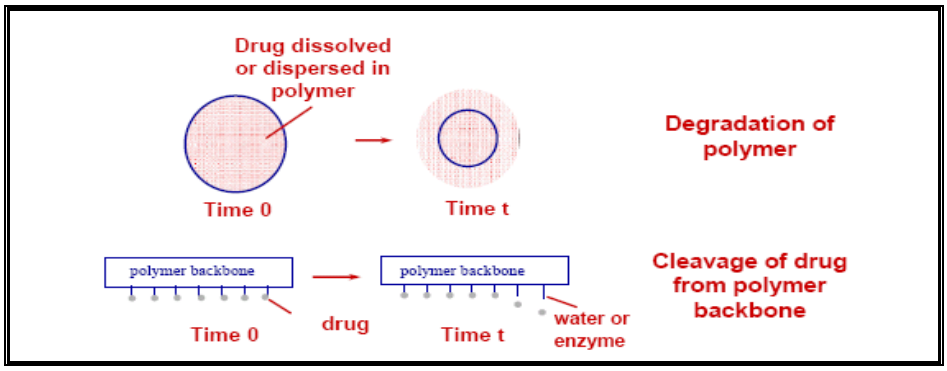

Figure 1: Drug release mechanism from Matrix system by time

Diabetes is not a disease, but a disorder which requires continuous use of drugs for its maintenance. Metformin Hydrochloride, a biguanide, is an orally active antidiabetic agent. It is effectively used in the treatment of non-insulin dependent diabetes mellitus (NIDDM). It has a plasma elimination half-life of 3 hours. Hence, recommended dosage of conventional tablets is 3 times a day. Its daily oral dose is 0.5 to 3 g/day in divided doses. Therefore, metformin HCl is suitable candidate for development of a sustained release dosage form.

Adverse events associated with metformin HCl use are often gastrointestinal in nature (e.g. anorexia, nausea, vomiting, & occasionally diarrhea, etc.). These adverse events may be partially avoided using sustained release dosage form.

EXPERIMENTAL STUDIES

Materials

Metformin Hydrochloride was a gift sample from Nir-life Healthcare, Sachana. Carbopol 971 & Carbopol 71 were obtained from Corel Pharma Chem, Ahmedabad; Xanthan Gum from Anil Starch, Ahmedabad. Hydroxy Propyl Methyl Cellulose (HPMC K100M), Micro crystalline Cellulose MCC, Polyvinyl Pyrollidone (PVP K30), talc, Mg Stearate, Aerosil was obtained from Nir-life Healthcare, Sachana. All chemicals were of analytical grade.

Compatibility Studies

Compatibility of metformin HCl with different excipients was tested using FT-IR Spectrophotometer & DSC thermoanalysis.

Micromeritic Properties[4]

The drug and blend of drug with excipients was evaluated for bulk density, tapped density, compressibility index, and angle of repose.[3]

FORMULATION OF MATRIX TABLETS

The matrix tablets each containing 500 mg of metformin HCl were prepared by wet granulation technique with varying ratio of the three different polymers (Table

1). Carbopol 971, Carbopol 71G, Xanthan gum, HPMC K100M selected as polymer (all in varying concentration of 10 %, 15 % & 20 %); Binder plays a major role in a formulation. As metformin HCl was supposed to be granulated with water then the hydrophilic binder selected for study.[5] PVP K30 was a versatile binder, used in the study. Talc, Magnesium Stearate & aerosil used as lubricant.

Required quantities of Metformin HCl, MCCP, and HPMC K100M were passed through mesh no.60 & mixed thoroughly. The granulating solution (PVP K30 dispersed in water) was added & mixed properly to form uniform dough mass. The mass was granulated using mesh no.20 & dried at 50 °C for 2 hours. The dried Granules were passed through mesh no.20 again to break the aggregates. The granules were lubricated. Granules then were compressed into tablets on a 16-station rotary compression machine (Cadmach, Ahmedabad).

Table 1: COMPOSITION OF MATRIX TABLETS OF METFORMIN HCl

Ingredients*	**F01**	**F02**	**F03**	**F04**	**F05**	**F06**
Metformin HCl	500	500	500	500	500	500
Carbopol 971	75	112.5	150	-	-	-
Carbopol 71G	-	-	-	75	112.5	150
MCC	140.5	103	65.5	140.5	103	65.5
PVP K30	22.5	22.5	22.5	22.5	22.5	22.5
Mg Stearate	4.5	4.5	4.5	4.5	4.5	4.5
Talc	6	6	6	6	6	6
Aerosil	1.5	1.5	1.5	1.5	1.5	1.5
Ingredients*	**F07**	**F08**	**F09**	**F10**	**F11**	**F12**
Metformin HCl	500	500	500	500	500	500
Xanthan Gum	75	112.5	150	-	-	-
HPMC K100M	-	-	-	75	112.5	150
MCC	140.5	103	65.5	140.5	103	65.5
PVP K30	22.5	22.5	22.5	22.5	22.5	22.5
Mg Stearate	4.5	4.5	4.5	4.5	4.5	4.5
Talc	6	6	6	6	6	6
Aerosil	1.5	1.5	1.5	1.5	1.5	1.5
Total Wt (mg)	**750**	**750**	**750**	**750**	**750**	**750**

*all values were in mg

EVALUATION PARAMETERS

Appearance[6]

The tablet should be free from cracks, depressions, pinholes etc. The color and the polish of the tablet should be uniform on whole surface. The surface of the tablets should be smooth.

Tablet Dimensions[7]

The dimensions of the tablets are thickness and diameter. Thickness and diameter of a tablet were measured using vernier calipers.

Uniformity of weight[7]

According to the official test, twenty tablets from each batch were selected randomly & weighed individually using a highly sensitive electronic balance. Their

mean weight was calculated for each batch. The percent deviation was calculated using the following formula.

$$\%\ Deviation = \frac{individual\ weight - mean}{mean}\ X\ 100$$

Tablet Hardness[7]

The resistance of tablet for shipping or breakage, under conditions of storage, transportation and handling, before usage, depends on its hardness (diametric crushing strength). The hardness of 6 tablets of each formulation was measured by using Monsanto hardness tester.

Friability[7]

Friability is a measure of tablet strength. Roche friabilator was used to measure the friability by noticing initial weight of 10 tablets (W1) and placed in a friabilator for 4 min at a rate of 25 rpm dropping the tablets through a distance of six inches with each revolution. After 100 revolutions the tablets were reweighed and noted as (W2). The difference in the weight is noted and expressed as percentage. Permitted friability limit is 1.0%. The percent friability was determined using the following formula.

$$\%Friability = \frac{W1 - W2}{W2} X\ 100$$

Drug Content[8]

Ten tablets were weighed and ground. The powder equivalent to 500mg of drug was taken, dissolved in purified water. The absorbance of the resulting solution was measured at 233 nm. The amount of metformin HCl was calculated & compared with standards stated in the monograph. All the batches should fall within the limit of 95 – 105 %.

Content Uniformity[8]

Twenty uncoated tablets were randomly selected & average weight was calculated. Tablets were crushed in a mortar individually and accurately weighed amount of tablet triturate from each blend was taken. Samples were transferred to twenty different volumetric flasks and were diluted up to the mark with purified water. The content was shaken well for some time and kept for 30 minutes for dissolving of drug completely. The mixtures were filtered and appropriate dilutions were made. The drug content in each tablet was estimated at λ_{max} 233 nm against blank reference and reported.

In vitro drug release[9]

In vitro drug release studies were carried out using USP – type II dissolution apparatus (paddle type) at 50 rpm. The dissolution medium consisted of 900 ml purified water maintained at 37 $\pm$ 0.5 °C. Aliquots from the release medium were withdrawn & filtered, the concentrations of metformin HCl were determined spectroscopically. The withdrawn samples were replaced with equal quantity of the media to maintain constant volumes. The cumulative percentage drug release was calculated.

Effect of pH of dissolution medium on drug release10

In order to study the effect of pH of release medium in the drug release of optimized formulation, the in vitro release studies can be carried out in buffers of different pH, like pH 1.2 buffer, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer in USP type II dissolution apparatus. The temperature was maintained at 37±0.5°C. The release was studied at predetermined time intervals.

Effect of agitation intensity on drug release10

To study the effect of agitation intensity (rpm) of the dissolution medium, studies were conducted using USP type II dissolution apparatus (paddle type) at rotational speeds of 50, 75, and 100 using purified water. The samples were withdrawn at 1, 2, 4, 6,8,10 and 12 hours and passed through 10 µm filters. Samples were suitably diluted with purified water and were analyzed at 233 nm. Cumulative percentage drug release was calculated.

Accelerated Stability Study11

Optimized Metformin HCl matrix tablets were packed in 0.04 mm thick aluminum foil strips laminated with PVC. The packed tablets were placed in stability chamber maintained at 40±2°C and 75±5% RH for 1 month. The samples were withdrawn after one month and were observed for changes on the physical parameter (i.e. change in color, appearance of spot, any bad odor, smoothness). Samples were evaluated for drug content and *in*-vitro drug release.

Release Kinetics of the Optimized Formulation12

The dissolution profile of most satisfactory formulation was fitted to zero order & first order model to ascertain the kinetic modeling of the release. The methods were adopted for deciding the most appropriate model.

1. Zero order kinetic model (Cumulative % drug release v/s time)
2. First order kinetic model (log cumulative % drug remaining v/s time)

RESULTS & DISCUSSION

Compatibility Studies

From the FT-IR study the drug was found to be compatible with all the excipients. The Metformin HCl powder blends were free flowing as indicated by the values of bulk density (0.573 to 0.591 gm/cc), tapped density (0.708 to 0.722 gm/cc) and Carr's compressibility index (17.37 to 19.86%). Angle of repose ranged from 20.26 to 24.0. The values are given in Table 2.

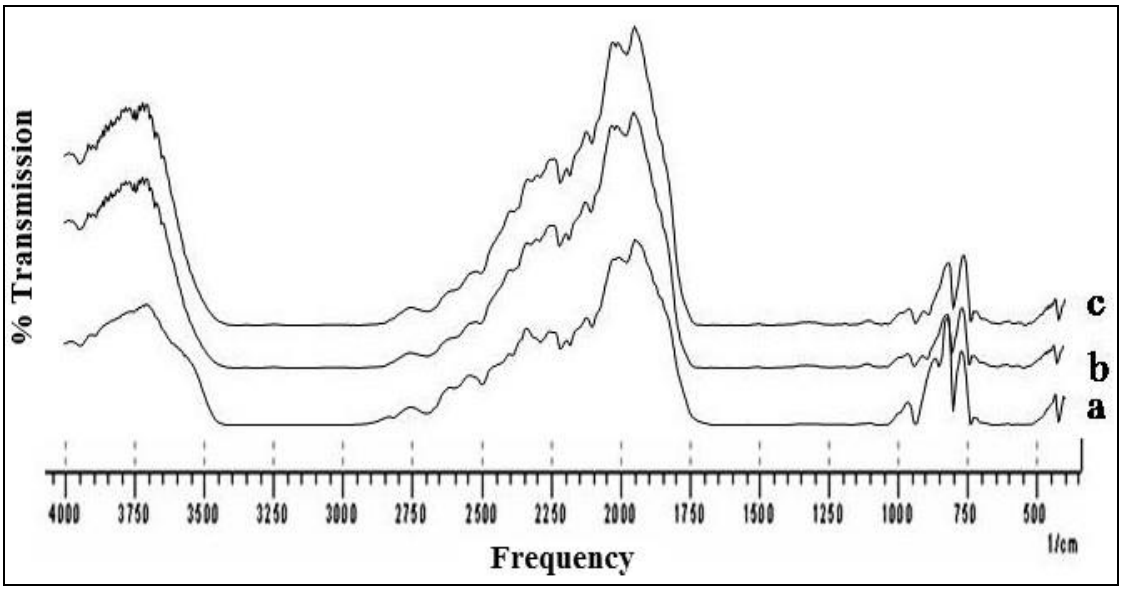

Figure 2: FT-IR Spectra of (A) drug (metformin HCl) (B) drug +HPMC K100M (C) Drug+HPMC K100M+xanthan gum+carbopol 971+carbopol 71G

Micromeritic Properties

Table 2: Micromeritic properties of drug and powder blend

Drug & Formulation Blend	bulk density, gm/cc*	Tapped Density, gm/cc*	Angle of Repose, θ	Compressibility, %*
Drug	0.660± 0.04	0.744± 1.0	32± 0.25	11.29± 0.06
F01	0.591± 0.02	0.722± 0.04	20.26± 0.9	18.14± 0.5
F02	0.583± 0.01	0.718± 0.03	21.00± 1.0	18.80± 0.85
F03	0.573± 0.015	0.715± 0.034	20.55± 1.25	19.86± 0.6
F04	0.591± 0.01	0.722± 0.04	20.26± 0.9	18.14± 0.5
F05	0.583±0.015	0.718± 0.05	21.00± 0.5	18.80± 0.5
F06	0.573± 0.02	0.715± 0.04	20.55± 0.55	19.86± 0.5
F07	0.591± 0.25	0.722± 0.25	20.26± 0.7	18.14± 0.15
F08	0.583± 0.2	0.718± 0.35	21.00± 1	18.80± 0.25
F09	0.573± 0.2	0.715± 0.4	20.55± 0.55	19.86± 0.2
F10	0.583± 0.025	0.710± 0.03	22.28± 0.5	17.88± 1
F11	0.585± 0.04	0.712± 0.04	24.00± 0.1	18.39± 0.9
F12	0.581± 0.05	0.708± 0.06	23.51± 0.2	17.37± 1

Evaluation Parameters

The Metformin HCl matrix tablets were uniform in weight (750±5 to 750 ±13 mg) and the thickness (5.9 mm), width (8.0 mm) & Length (16.4 mm) of the tablets were uniform. The hardness of tablets was found to be between 8 to 9 kg/cm^2, while the friability of tablets was ranged between 0.14% to 0.46%. The tablets had enough hardness to withstand stress during transport & handling. The drug content in various formulations varied between 96.7 % to 101.1%. (Table 3)

Table 3: Post Compression Studies

Formu-lation	Uniformity of Weight, mg*	Thickness, mm*	Width, mm*	Length, mm*	Hardness, kg/cm^2*	Friability, %	Drug content , %w/w
F01	750±7	5.9±0.15	8.0 ±0.15	16.4±0.09	8 ±0.2	0.31±0.02	98.3±0.2
F02	750±11	5.9±0.25	8.0 ±0.1	16.4±0.1	8 ±0.2	0.4±0.025	101.1±0.1
F03	750±10	5.9±0.2	8.0 ±0.01	16.4 ±0.2	8 ±0.2	0.4±0.015	98.7±0.5
F04	750±11	5.9±0.3	8.0 ±0.15	16.4 ±0.15	9 ±0.2	0.22±0.01	99.4±0.54
F05	750±6	5.9±0.2	8.0 ±0.25	16.4±0.2	9 ±0.2	0.27±0.01	98.1±0.1
F06	750±10	5.9±0.25	8.0 ±0.1	16.4 ±0.25	9 ±0.2	0.14±0.01	97.4±0.15
F07	750±11	5.9±0.25	8.0 ±0.2	16.4 ±0.3	9 ±0.3	0.22±0.02	99.2±0.55
F08	750±6	5.9±0.5	8.0 ±0.15	16.4±0.2	9 ±0.5	0.27±0.025	98.1±0.45
F09	750±10	5.9±0.35	8.0 ±0.10	16.4 ±0.7	9 ±0.8	0.14±0.03	97.8±0.25
F10	750±5	5.9±0.2	8.0 ±0.1	16.4 ±0.1	8 ±0.2	0.46±0.02	96.7±0.5
F11	750±11	5.9±0.2	8.0 ±0.1	16.4 ±0.1	8 ±0.2	0.46±0.02	100.5±0.1
F12	750±13	5.9±0.2	8.0 ±0.1	16.4 ±0.1	8 ±0.2	0.46±0.02	99.5±0.5

* Mean of 3 readings.

Uniformity of Drug content

All the formulations exhibited uniformity of drug content.

In-vitro release study

From the results of in-vitro release of SR matrix tablet of Metformin HCl, The formulation F12 containing 20% of HPMC K100M has controlled release of drug for 12 hours (Figure 3).

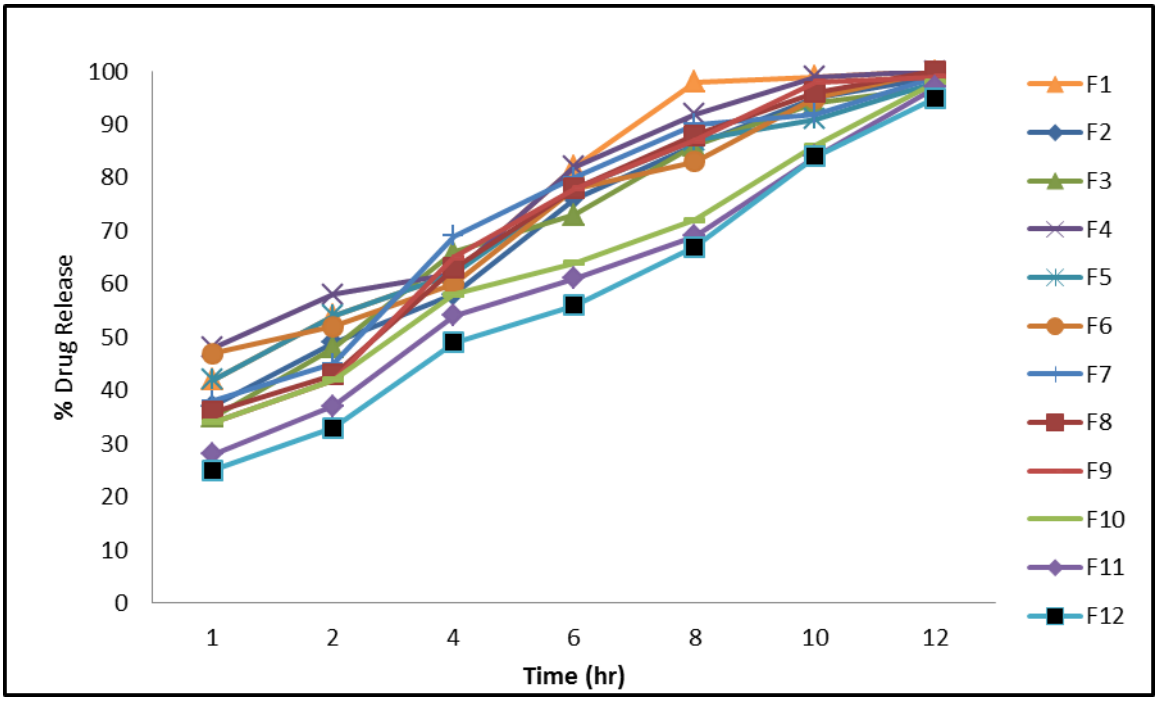

Figure 3: In-Vitro Release Study of Metformin HCl Matrix Tablets

It was also observed that as the amount of polymer increases from 10% to 20% in the formulation there was decline in drug release rate. This may be due to the drug entrapped in hydro gel by forming hydrophilic polymers. The swelling degree is less because of high concentration of polymers.

In case of Xanthan Gum, Carbopol 71, & Carbopol 971 there was no significant difference between the release rates. But the drug release profile of HPMC K100M showed lesser release compare to other formulation. As the concentration of HPMC increased, the release rate of Metformin HCl was decreased. This again, is due to the drug entrapped in hydro gel by forming hydrophilic polymers around the matrix formulation and retarded drug release from the matrix.

From all F12 formulations prepared with different polymers in different concentration, batch F12 (HPMC K100 M 20% of tablet weight) showed desired drug release profile Therefore, batch F12 was considered as optimized formula for preparation of metformin HCl sustained release matrix tablet using wet granulation method.

Effect of pH of dissolution medium on drug release

The Effect of pH of dissolution medium on drug release was shown in figure 4. The result showed that the pH of release medium did not have significant effect on drug release. Thus the fluid in different parts of gastrointestinal tract will scarcely affect the drug release.

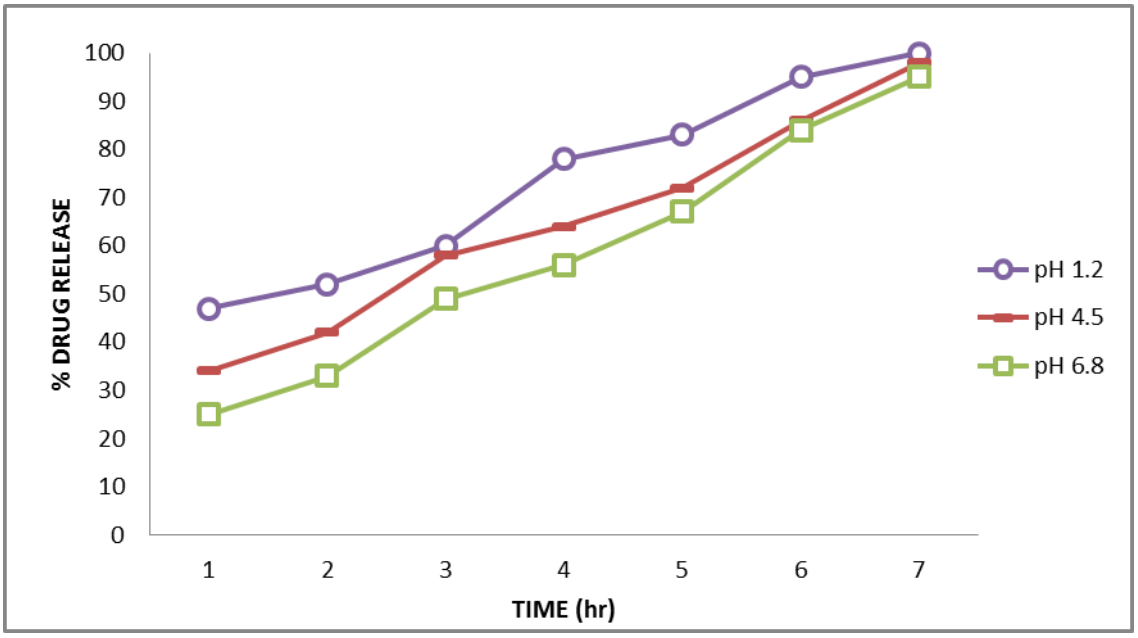

Figure 4: Effect of pH on drug release

Effect of agitation intensity on drug release

The effect of agitation intensity on drug release was shown in figure 5. The speed of rotation have much effect on drug release in terms of increasing agitation makes decrease in drug release. Therefore it can be expected that as the rotational speed of the apparatus was increased, the integrity of the gel layer was decreased, and the release of drug was increased. Hence, it can be expected that the release from the developed formulations may be dependent of the hydrodynamic conditions of the GIT.

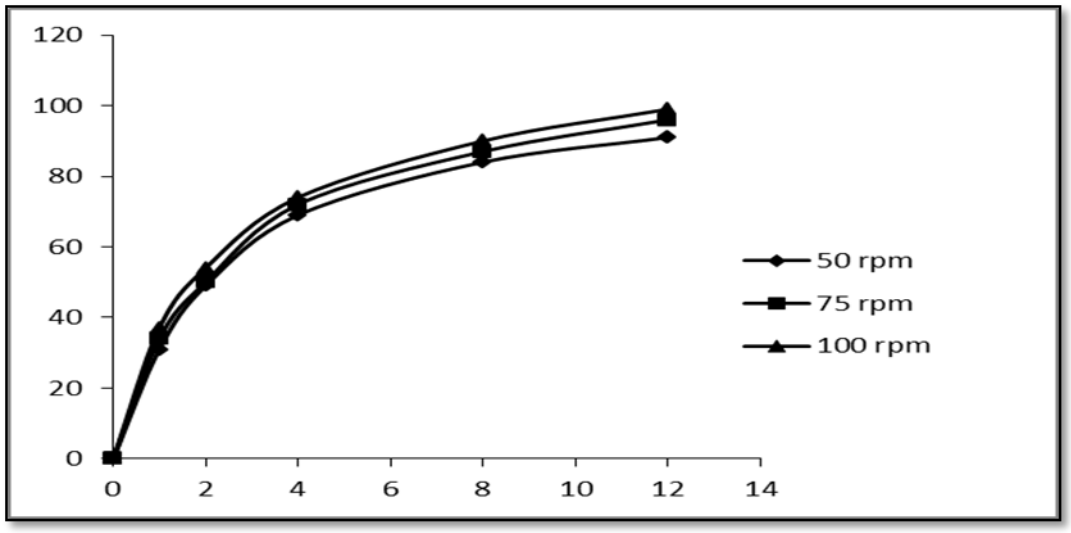

Figure 5: Effect of agitation intensity on drug release at different rpm

Accelerated Stability Study

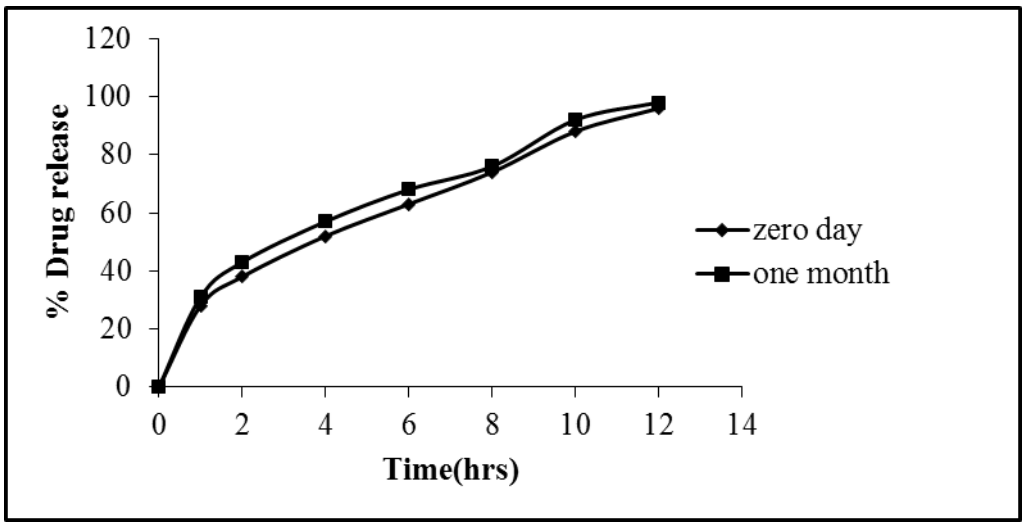

Figure 6: In vitro release of F12 matrix tablets on zero days and after one month

The matrix tablets (F12) were stored at 40°C/75% RH for a month, there was no change either in physical appearance or in drug content. In-vitro drug release profile showed that there was no significant change in the formulation after 1 month of accelerated stability study. It indicated that prepared formulation F12 was found to be stable.

Release Kinetics of the Optimized Formulation

The R^2 values were found to be 0.9109 for zero order release model & 0.9388 for first order release model. The release followed first order kinetics. (Figure 7 & 8)

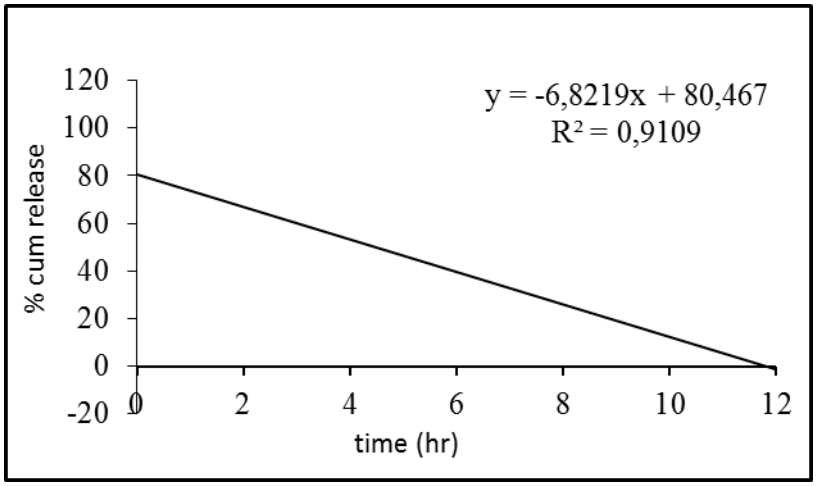

Figure 7: A plot of Zero order Kinetics

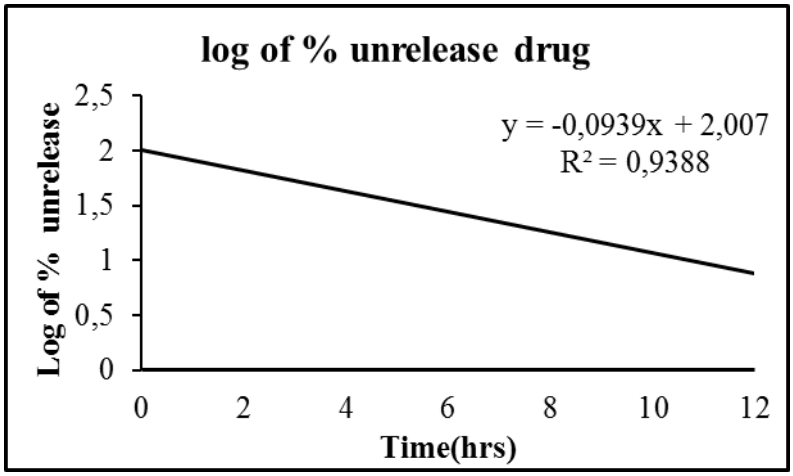

Figure 8: A plot of First order Kinetics

CONCLUSION

Matrix tablets of Metformin HCl were successfully prepared using Carbopol 71, Carbopol 971, Xanthan gum, HPMC K100M, MCC as excipients by Wet granulation method. Of the several formulations investigated, the formulation F12 containing hydrophilic matrix of HPMC K100M (20% w/w) was a better system for once-daily sustained release of a water-soluble drug like Metformin HCl which effectively release more than 90% for 12 hrs. Metformin release from the matrix tablet was inversely proportional to the agitation intensity of the dissolution medium, confirms hydrodynamic conditions of GIT is the major mechanism for drug release. Drug release from the developed formulation followed first order kinetics.

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