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FORMULATION AND KINETIC *IN VITRO* EVALUATION OF METFORMIN HYDROCHLORIDE CONTROLLED RELEASE TABLETS

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ABSTRACT

Controlled release formulation offers a number of advantages in therapeutics. Metformin Hcl is an anti diabetic drug used in treatment of Type-2 Diabetics Mellitus was used as a model drug to develop a Controlled release formulation. The objective of the present work was to formulate Controlled release tablet formulation containing Metformin Hcl in order to provide a prolonged effect and relatively constant effective levels of these drugs in the treatment of Type-2 Diabetics Mellitus. In this present study Controlled release tablet of Metformin Hcl was prepared by using wet granulation method and using different Hydrophilic polymer. The Fourier Transform Infrared Spectroscopy study reveals that there is no interaction between the polymer and drug. The prepared tablets evaluated in terms of their pre-compression parameters, post-compression parameters, *in vitro* release and Kinetic release study. The results conclude that FMST-6 (91.433%) can be considered as a optimized formula for Controlled release of drug, when it is compared with Marketed product (Metformin Hcl 500mg CR tablets (GLYCIPHAGE SR) (89.433%)) for 8hours. Kinetic treatment to the *in vitro* release data revealed that the drug release followed zero order non - fickian diffusion, It means the release of drug from tablet dissolution and diffusion both mechanisms are used.

Key Words:- Metformin Hydrochloride, HPMC K4M, Carbopol 934-P and Xanthan gum, Wet granulation method, *In vitro* and Kinetic release study.

INTRODUCTION

Introduction of matrix tablet as controlled release (CR) has given a new breakthrough for Novel Drug Delivery System (NDDS) in the field of Pharmaceutical Technology (Uttam M *et al*., 2007) Controlled release dosage forms are having various advantages compared to the conventional release dosage forms such as increased therapeutic efficacy, decreased frequency of dosing, reduced adverse effect and improve patient compliance.

Metformin Hcl is an oral anti diabetic drug in the biguanide class. It is the first line drug of choice for the treatment of type-2 diabetes particularly in over weight and obese people and those with normal kidney function. Metformin Hcl improves hyperglycemia primarily through its suppression of hepatic glucose production (hepatic gluconeogenesis).

Metformin Hcl is an anti diabetic drug used in treatment of Type-2 Diabetics Mellitus was used as a model drug to develop a Controlled release formulation.

MATERIALS AND METHODS

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Metformin Hydrochloride was a Gift sample from Medley pharmaceuticals, Gujarat. HPMC K4M, Carbopol 934-P and Xanthangum was a Gift sample from Apex Laboratories Pvt.Ltd, Chennai. Polyvinyl pyrrolidone K30, Talc and Isopropyl alcohol was a Gift sample from Loba chemistry, Mumbai. Magnesium stearate was a Gift sample from Molychem, Mumbai. All other chemicals and ingredients were used for study are of Analytical grade.

Method of Preparation (Raju DB *et al.*, 2010)
Preparation of Metformin Hydrochloride Controlled release tablets

Tablets were prepared by wet granulation method. Metformin Hydrochloride (500 mg) was mixed with required amount of polymers and other excipients (Table 5). All the excipients were passed through sieve no.40, the drug, polymer and other excipients mixed and granulated with 10% solution of PVP K-30 in isopropyl alcohol. The wet mass was passed through sieve no.16 and dried at 45°C for 2h. Dried granules were passed through sieve no. 20 and mixed with magnesium stearate and talc.

Preformulation Studies

Preformulation testing is an investigation of physical and chemical properties of drug substances alone and when combined with pharmaceutical excipients. It is the first step in the rational development of dosage form.

Compatability studies (Fourier Transform Infrared Spectroscopic studies)

One of the requirement for the selection of suitable excipients or carrier for the pharmaceutical formulation is its compatability. Therefore in the present work a study was carried out by using FT-IR spectrophotometer to find out if there is any possible chemical interaction of Metformin Hcl with HPMC K_4M; Carbopol 934 P; Xanthan Gum.

Procedure

To study the compatability of various formulation excipients with Metformin Hcl, solid admixtures were prepared by mixing the drug with each formulation excipients separately in the ratio of 1:1 and stored in air tight containers at 30+20c/65+5% RH. The solid admixtures were characterized using Fourier Trans form Infrared Spectroscopy (FT-IR).

EVALUATION PARAMETERS (Raju D.B *et al.*, 2010; **Mohamed Raffick M *et al.*, 2012;** Lachman L *et al.*, 2009)

Precompression studies of Metformin Hcl **Controlled release tablet Bulk density**

3gm of Metformin Hcl granules were weighed separately and transferred into 100ml measuring cylinder, initial volume was measured and calculated according to the formula

Bulk density = Mass / Volume

Tapped density

Tapped density is determined by placing a graduated cylinder containing a known mass of granules and mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the granules in the cylinder and this minimum volume, the tapped density may be computed.

Tapped density = Weight of granules/ Tapped volume of granules

Angle of Repose

The manner in which stresses are transmitted through a bead and the beads response to applied stress are reflected in the various angles of friction and response. The most commonly used of this in angle of repose, which may be determined experimentally by number of methods. The method used to find the angle of repose is to pour the powder a conical on a level, flat surface and measure the included angle with the horizontal.

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

Where,

θ **= Angle of repose,**
h = Height of the powder cone,
r = Radius of the powder cone.

Compressibility Index or Carr's Index

Carr's Index is measured using the values of bulk density and tapped density.
The following equation is used to find the Carr's Index,

$$CI = \frac{(TD-BD)}{TD} \times 100$$

Where, TD = Tapped density
BD = Bulk density

Hausner's Ratio

It indicates the flow properties of the powder and ratio of Tapped density to the Bulk density of the powder or granules.

Hausner's Ratio = Tapped density/Bulk density
Postcompression studies of Metformin Hcl **Controlled release tablets**
Hardness or Crushing strength Test

Hardness of the tablet was determined using the Monsanto hardness tester (The lower plunger was placed

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in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force (The Anonymous, 2008).

The force required to break the tablet is measured in kilograms and a crushing strength of 4Kg is usually considered to be the minimum for satisfactory tablets. Oral tablets normally have a hardness of 4 to 10kg ; however, hypodermic and chewable tablets are usually much softer (3 kg) and some Controlled release tablets are much harder (10 -20 kg).

Thickness Test

The thickness of the tablet is mostly related to the tablet hardness can be uses as initial control parameter. Ten tablets were randomly selected from each tablet thickness was determined using a Vernier calliper and the reading was recorded in millimeters.

Friability Test

The pre-weighed tablets were placed in the friabilator (EF-2, Electro lab, Mumbai) which was then operated for 100rpm, then dusted and reweighed. The Conventional compressed tablets that lose less than 0.5-1.0% of their weight are generally considered acceptable.

$$\text{Friability index} = \frac{I - F}{I} \times 100$$

Where,

    I - Initial weight
    F - Final weight

Weight variation test

Weights of 20 individual tablets were noted and their mean weight also calculated. The percentage deviation was calculated by using the following formula,

$$\text{Percentage deviation} = [X - X^* / X] \times 100$$

    X - Actual weight of the tablet
    X*- Average weight of the tablet

Estimation of Drug Content

Ten tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 100 mg of drug was transferred into 250 ml volumetric flask, it was shaken with 150 of distilled water and volume was adjusted to 250ml with water. The solution was filtered, suitable dilutions were made and absorbance was recorded by using U.V. spectrophotometer (Labindia, Hyderabad) at 233nm.The experiment was repeated three times. Calculation

The amount of Metformin present in tablet can be calculated using the formula

$$A_t / As \times S_w / 100 \times 100$$

Where, A_t = Absorbance of sample preparation

    A_s = Absorbance of Standard preparation

    S_w = weight at Metformin working standard (mg)

***Invitro* drug release study**

Invitro release studies were carried out by using USP paddle dissolution test apparatus. 900ml of 0.1 N Hcl (pH1.2) was taken in the dissolution vessel and the temperature of the medium were maintained at 37 ± 0.5^oC. 100rpm was maintained, 1 ml of sample was withdrawn at predetermined time intervals for 2 hours and the same volume of the fresh medium was replaced. After 2 hrs in same dissolution vessel 900ml of phosphate buffer (pH 7.4) was taken and the temperature of the medium were maintained at 37 ± 0.5^oC. 100rpm was maintained, 1 ml of sample was withdrawn at predetermined time intervals for remaining 6 hours and the same volume of the fresh medium was replaced. The samples were analysed at 233nm by using a UV spectrophotometer (Labindia, Hyderabad). The dissolution data obtained were plotted as percentage drug release versus time.

Bioequivalence studies

The bioequivalence study was carried out for 8 hours were using USP paddle type dissolution apparatus from that 2 hrs in 0.1N Hcl (pH 1.2) and 6 hrs in phosphate buffer (pH 7.4) at 100 rpms maintaining temperature at 37 ± 0.5^0c. A 1ml samples were collected from each vessel at 0, 1, 2, 3, 4, 5, 6, 7 and 8 hours and analyzed by UV spectrophotometer at 275 nm. The withdrawn sample was immediately replaced by equal volume of fresh buffer. The dissolution data obtained were plotted as percentage drug release versus time.

Kinetic Characteristics of the Drug Release (Korseyer R W *et al*., 1983; Higuchi T *et al*., 1963)

To know the mechanism of the drug release from the batches, the results obtained from the *In-vitro* dissolution process were fitted into different kinetic equations as follows:

Zero order kinetics

Zero order release would be predicted by the following equation:-

$$A_t = A_0 - K_0 t$$

Where, A_t = Drug release at time 't'.

    A_0 = Initial drug concentration.

    K_0 = Zero - order rate constant (hr^{-1}).

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When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys Zero – order equal to K_0.

First Order Kinetics

First – order release would be predicted by the following equation:-

$$Log\ C = log\ C_0 – Kt / 2.303$$

Where,

C = Amount of drug remained at time 't'.

C_0 = Initial amount of drug.

K = First – order rate constant (hr^{-1}).

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line, indicating that the release follow first order kinetics. The constant 'K' can be obtained by multiplying 2.303 with the slope values.

Higuchi's model

Drug release from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation: -

$$Q = [D\varepsilon / \tau (2\ A - \varepsilon Cs)\ Cst]^{½}$$

Where,

Q = Amount of drug released at time 't'.

D = Diffusion coefficient of the drug in the matrix.

A = Total amount of drug in unit volume of matrix.

Cs = the solubility of the drug in the matrix.

ε = Porosity of the matrix.

τ = Tortuosity.

t = Time (hrs) at which 'q' amount of drug is released.

Above equation may be simplified if one assumes that 'D', 'Cs' and 'A' are constant. Then equation becomes:-

$$Q = Kt^{1/2}$$

When the data is plotted according to equation i.e. cumulative drug release versus square root of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K'.

Korsemeyer equation / Peppa's model

To study the mechanism of drug release from the transdermal patches, the release data were also fitted to the well-known exponential equation (Korsemeyer equation/ Peppa's law equation), which is often used to describe the drug release behavior from polymeric systems.

$$M_t / M_\alpha = Kt^n$$

Where,

M_t / M_α = the fraction of drug released at time 't'.

K = Constant incorporating the structural and geometrical characteristics of the drug / polymer system.

n = Diffusion exponent related to the mechanism of the release.

Above equation can be simplified by applying log on both sides,

$$Log\ M_t / M_\alpha = Log\ K + n\ Log\ t$$

When the data is plotted as log of drug released versus log time, yields a straight line with a slope equal to 'n' and the 'K' can be obtained from y – intercept. For Fickian release 'n' <0.5 while for anomalous (non - Fickian) transport 'n' ranges between 0.5 and 1.0.

'n' values can be used to characterize diffusion release mechanism as:

n < 0.5	Fickian diffusion
n >0.5 < 1	Non-fickian diffusion
n > 1	Class – II transport

Table 1. Formulation of different batches of Metformin Hydrochloride Controlled Release Tablets (mg/tab)

S.No	Formulations	Drug (Metformin Hcl)	Polymers			Lactose	PVP K$_{30}$	Magnesium stearate	Talc
			HPMC K$_4$M	Carpobol – 934 P	Xanthan gum				
1	FMCT-1	500	180	-	-	25	15	20	10
2	FMCT-2	500	-	180	-	25	15	20	10
3	FMCT-3	500	-	-	180	25	15	20	10
4	FMCT-4	500	90	90	-	25	15	20	10
5	FMCT-5	500	-	90	90	25	15	20	10
6	FMCT-6	500	90	-	90	25	15	20	10
7	FMCT-7	500	60	60	60	25	15	20	10

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Table 2. Precompression studies of Controlled Release tablet granules

S.No	Formulations	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Angle of Repose (θ)	Carr's Index (%)	Hausner's Ratio
1	FMCT-1	0.378	0.400	33.82	5.550	1.058
2	FMCT-2	0.364	0.384	34.29	5.208	1.054
3	FMCT-3	0.337	0.354	33.82	4.802	1.050
4	FMCT-4	0.345	0.369	34.29	5.865	1.062
5	FMCT-5	0.333	0.358	35.07	6.504	1.069
6	FMCT-6	0.392	0.434	35.07	4.147	1.043
7	FMCT-7	0.363	0.374	33.48	3.940	1.030

Table 3. Precompression studies of Metformin Hydrochloride Controlled Release Tablets

S.No	Formulations	Hardness Test (kg/cm)	Thickness Test (cm)	Friability Test (%)	% of Weight variation test	Estimation of Drug Content
1	FMCT-1	14.45	0.47	0.134	100.0	97.12
2	FMCT-2	11.34	0.47	0.428	99.2	95.23
3	FMCT-3	13.42	0.47	0.236	99.8	96.51
4	FMCT-4	14.12	0.47	0.287	99.9	96.47
5	FMCT-5	12.65	0.47	0.324	99.9	95.78
6	FMCT-6	14.23	0.47	0.194	99.9	97.32
7	FMCT-7	12.86	0.47	0.253	99.6	95.84

Table 4. Comparative dissolution study of different formulations with various ratios of polymers

S.No	Time (hrs)	% of drug release (FMCT-1)	% of drug release (FMCT-2)	% of drug release (FMCT-3)	% of drug release (FMCT-4)	% of drug release (FMCT-5)	% of drug release (FMCT-6)	% of drug release (FMCT-7)
1	0	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2	1	3.21	2.211	2.880	2.417	1.954	3.394	1.954
3	2	5.55	3.960	4.782	4.320	3.651	6.068	3.651
4	3	13.20	9.732	12.466	10.700	10.066	13.900	10.066
5	4	25.76	19.460	25.400	21.733	20.766	25.766	20.766
6	5	41.63	27.498	40.533	39.133	38.533	44.132	38.532
7	6	57.43	40.231	56.100	48.933	47.466	62.166	47.466
8	7	72.80	49.766	68.466	59.466	57.700	77.065	57.700
9	8	88.40	61.730	87.566	71.600	69.100	91.433	69.100

BIOEQUIVALENCE STUDIES
Table 5. Comparative dissolution study of formulation-6 (FMCT-6) and Marketed sample (GLYCIPHAGE SR)

S.No	Time (hrs)	% of drug release (FMCT-6)	% of drug release Marketed sample
1	0	0.000	0.000
2	1	3.394	3.034
3	2	6.068	5.374
4	3	13.900	12.898
5	4	25.766	25.133
6	5	44.132	43.600
7	6	62.166	61.433
8	7	77.065	76.166
9	8	91.433	89.433

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Kinetic Characteristics of the Drug Release
Table 6. Zero - order drug release

S.No	Time (hrs)	% of drug release (FMCT-6)
1	0	0.000
2	1	3.394
3	2	6.068
4	3	13.900
5	4	25.766
6	5	44.132
7	6	62.166
8	7	77.065
9	8	91.433

RESULTS AND DISCUSSIONS
Preformulation studies
Compatability studies (Fourier Transform Infrared Spectroscopic studies)

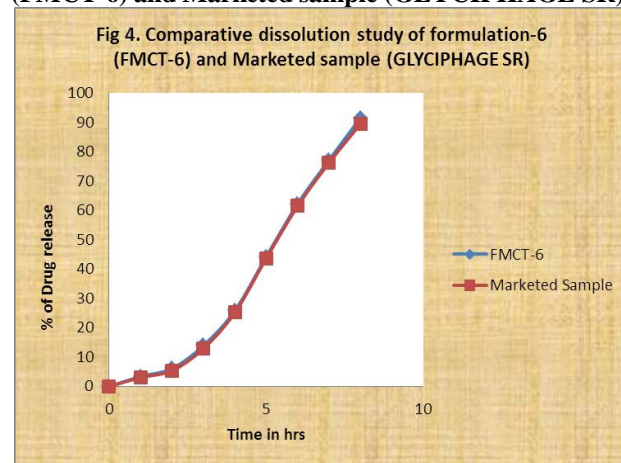**Fig 1. FTIR spectrum of Pure Drug (Metformin Hcl)**
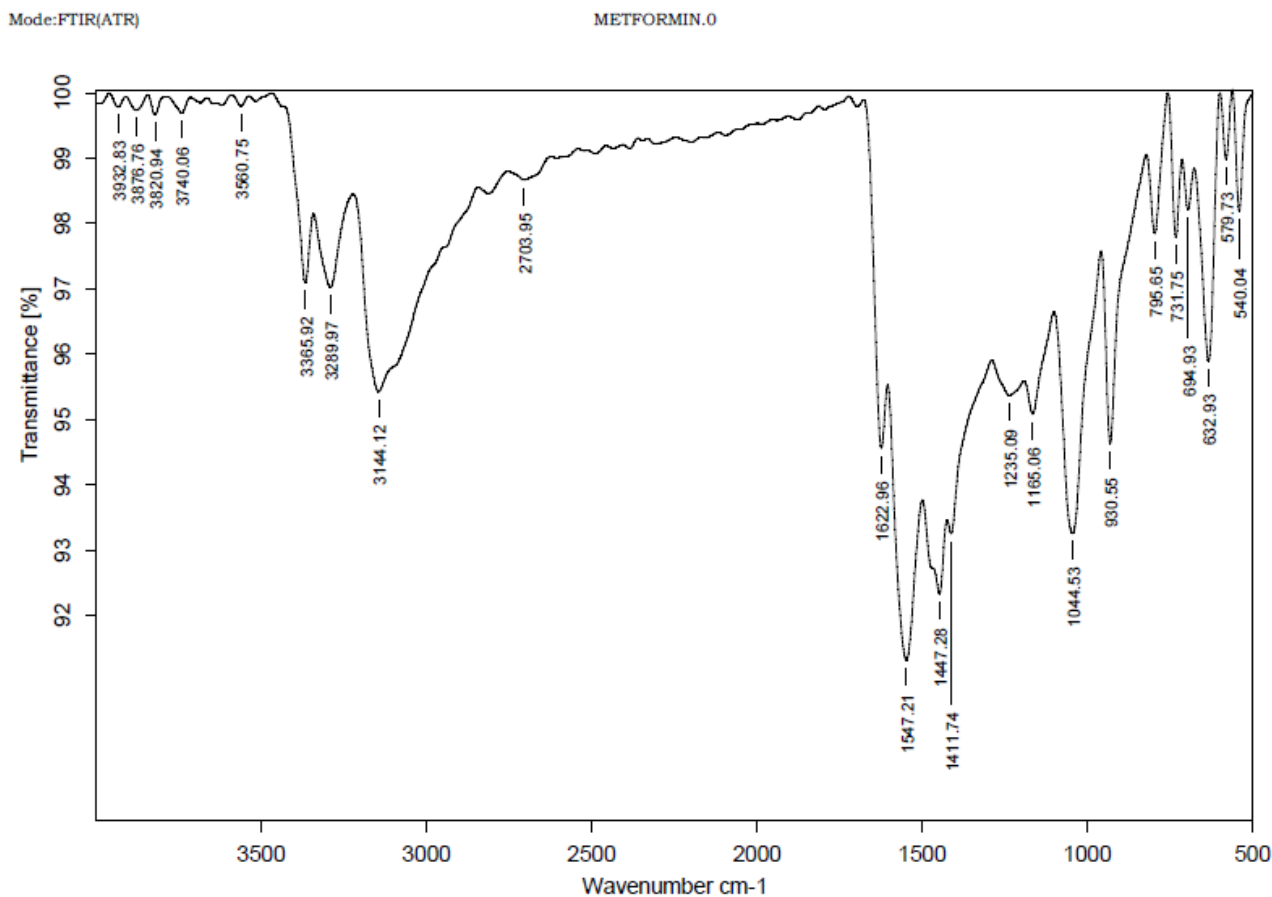
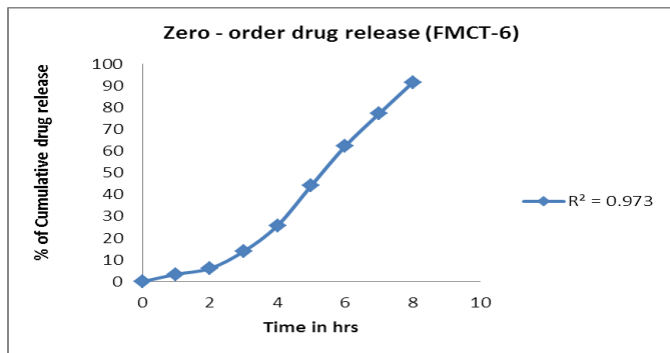**Fig 2. FTIR spectrum of Metformin HCL, HPMC K4M and Xanthan Gum**
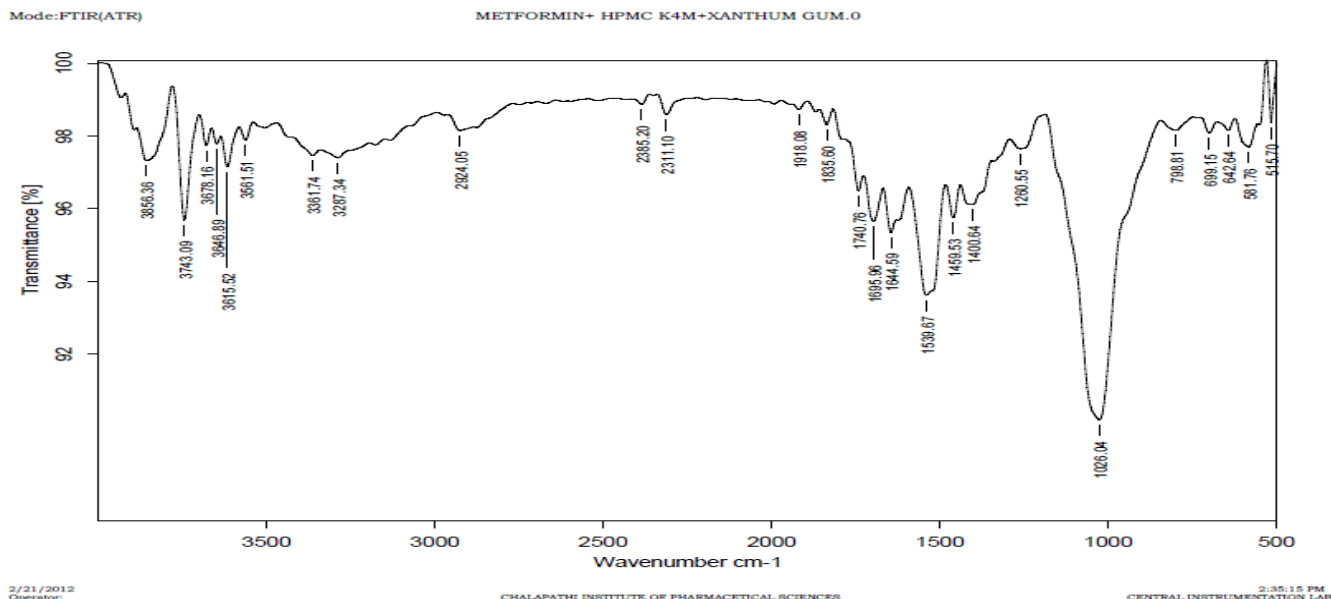
Fig 3. Comparative dissolution study of different formulations with various ratios of polymers
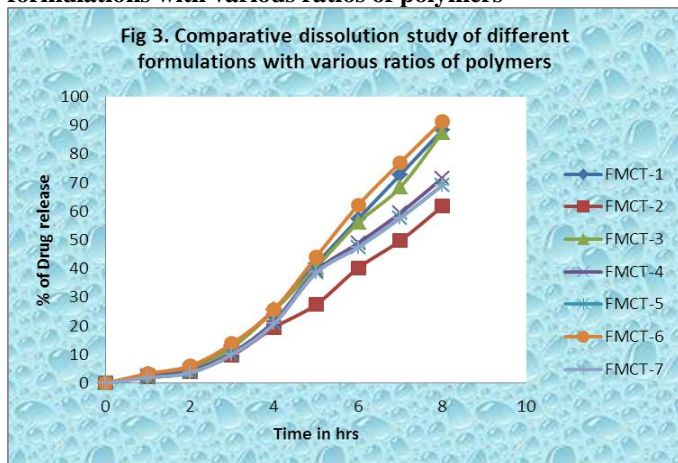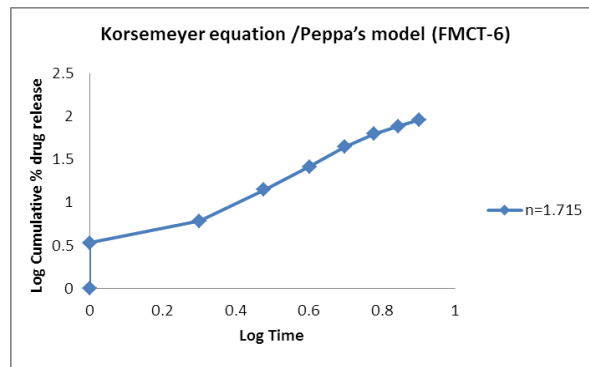

Fig 4. Comparative dissolution study of formulation-6 (FMCT-6) and Marketed sample (GLYCIPHAGE SR)

Fig 5. Zero - order drug release

Fig 6. Peppa's Korsemeyer Exponential equation

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DISCUSSION

Controlled release tablets of Metformin Hcl were prepared by wet granulation method. The prepared Controlled release tablets are round in shape. Microscopic examination of tablets from each formulation batch showed circular shape with no cracks. The fourier transform infra-red analysis was conducted for the surface structure characterization. FTIR spectrum of the formulated Controlled release tablets, pure drug and polymers was recorded. The Fourier Transform Infrared Spectroscopy study reveals that there is no interaction between the polymer and drug. Standard calibration curve of Metformin Hcl obeys the Beer's law in the range between 5-30µg/ml.

Bulk density (0.337 to 0.416 gm/cm^3) and Tapped density (0.354 to 0.434 gm/cm^3) values are within the limits, indicating that the powder blends have the required flow property for wet compression. The values obtained for angle of repose for all formulations are tabulated in table the values were found to be in the range from 33.48-35.07^0. This indicates good flow property of the powder blend. Compressibility index (3.94 to 6.504) and Hausner's ratio (1.030 to 1.069) values are within the limits, indicating that the powder blends have the required flow property for wet compression.

The hardness of the Controlled release tablet various batches were determined. The various batches of the Controlled release tablets of hardness values are found within limits and it indicates good strength of the Controlled release tablets. Tablet mean thicknesses were almost uniform in the all formulations and were found to be in the range of 0.47mm. Friability values are found to be less than 1% in all cases and considered to be satisfactory. All this tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits. Drug content of all the batches are within the acceptable range which shows the proper mixing of the drug with the excipients.

The invitro drug release profile of tablets from each batch (FMCT-1 to FMCT-7) was carried in 0.1N Hcl for 2 hours and phosphate buffer (pH 7.4) for 6 hours by using paddle type device. From the invitro dissolution data, FMCT-6 formulation was found that the drug release is best (formulation containing HPMC K$_4$M: Xanthan gum) and the cumulative % of drug release was 91.433 % respectively. The promising formulation FMCT-6 was found by evaluation studies were compared with Marketed product (Metformin Hcl 500mg SR tablets (GLYCIPHAGE SR)), the FMCT-6 formulation gave 91.433 % of the drug release and the Marketed product gave 89.433 % of drug release in 12 hours of dissolution study. The formula FMCT-6 with 91.433 % of drug release has better control over release of drug is compared to marketed product.

Kinetic treatment to the *in vitro* release for FMCT-6, revealed that the drug release followed zero order Cass II transport, It means the release of drug from tablet dissolution and diffusion both mechanisms are used.

CONCLUSION

The main objective of the present study was to develop Controlled release tablet formulation containing 500mg of Metformin Hcl for the treatment of Type-2 Diabetics Mellitus. In the present work it has been observed that using of Metformin Hcl, HPMC K4M and Xanthan gum combination (FMCT-6) retarded the drug release upto 8 hrs satisfactorily when compared with other formulations. When it is compared with marketed product. The formulations FMCT-6 was sufficiently Controlled the release of the drug and anomalous Cass II transport from zero order release from the formulation was observed.

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