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Research Article

Formulation and Evaluation of Metformin Hcl by CR-Matrix Tablets, in Vitro dissolution Tests and its Stability Studies

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ABSTRACT

Sustained release products are needed for metformin to prolong its duration of action and to improve patient compliances. The overall objective of this study was to develop an oral sustained release metformin hydrochloride tablet by using hydrophilic The *in vitro* dissolution study was carried out using USP 22 apparatus I, paddle method and the data was analysed using zero order, first order, Higuchi, Korsmeyer and Hixson-Crowell equations. Kinetic modeling of *in vitro* dissolution profiles revealed the drug release mechanism ranges from diffusion controlled or Fickian transport to anomalous type or non-Fickian transport. Fitting the *in vitro* drug release data to Korsmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release.

Keywords: metformin hcl tablet, gum copal, gum damar, matrix tablets, release kinetics.

INTRODUCTION:

Dissolution controlled systems can be made either by rate controlling coats or by administering the drug as a group of beads that have coating of different thickness. In first case if the outer layer is a quickly releasing bolus dose of drug, initial levels of drug in the body can be quickly established with pulsed intervals. In second case since the beads have different coating thickness; their release will occur in a progressive manner. Those with the thinnest layer will provide the initial dose and the maintenance of drug levels at later times will be achieved from those with thicker coating. This dissolution process at steady state is described by the Noyes-Whitney equation.

$$\frac{dc}{dt} = \frac{K_D A (C_s - C)}{h} = \frac{D A (C_s - C)}{h}$$

Where,
dc/dt = dissolution rate.
K_D= dissolution rate constant D = Diffusion coefficient
C_s= saturation solubility of the solid
C= concentration of solute in the bulk solution.
The above equation predicts that the rate of release can be constant only if the following parameters are constant.

a) Surface area
b) Diffusion coefficient
c) Diffusion layer thickness
d) Concentration difference.

But these parameters are not easily maintained constant, especially surface area. For spherical particles, the

change in surface area can be related to the weight of the particle that is under assumption of sink conditions, above equation can be rewritten as the cube root dissolution equation.

$W^{1/3} - W^{1/3} = K_D t$

Where,

K_D = Cube root dissolution rate constant W_o =Initial weight

W =Weight of the amount remaining at time t.

METHODOLOGY:

IN- VITRO DRUG RELEASE STUDY:

In Vitro dissolution study was carried out using USP II (Paddle) apparatus in 900ml 0.1 N HCl for first two hours. Then the dissolution was carried in 900 mL of P^H 6.8 phosphate buffer for 10 hours. The temperature of the dissolution medium was kept at 37± 0.5˚C and the basket was set at 100 rpm. 5 ml of sample solution was withdrawn at specified interval of time and filtered through 0.45 µm Whatmann filters. The absorbance of the withdrawn samples was measured at λmax 271 nm using UV visible spectrophotometer. The concentration was determined from the standard curve of Metformin HCl drug prepared in P^H 6.8 phosphate buffer at λ max 271 nm.

Dissolution:

Medium: P^H 6.8 phosphate buffer, 0.1 N HCl Volume: 900 mL
Apparatus: USP II (Paddle type) Rotation: 100
Time: 12 hrs. (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12)
Detection: UV, 233 nm.

Preparation of Phosphate buffer P^H 6.8

Take 250 ml of (0.2 N) KH_2PO_4 in 1000 ml volumetric flask and add 112 ml of (0.2 N) NaOH and make up to the mark with distilled water.

Preparation of 0.1N HCl

Dissolve 8.4 ml HCl in 1000ml volumetric flask and make up volume upto 1000 ml with distilled water.

Table No. 8: USP limits of controlled release tablets of Metformin

Time (Hrs)	% Drug release
1	Less than 10%
3	10-35%
6	35-65%
12	65-90%
24	More than 75%

Each formula (F1, F2, F3,F4,F5) was carried out *in-vitro* for five batches each and the average values were taken.

RELEASE KINETICS OF *IN VITRO* DISSOLUTION:

All the three formulations of prepared matrix tablets of Metformin HCl were subjected to *in-vitro* release studies these studies were carried out using dissolution apparatus. The dissolution medium consisted of 900 mL PH 6.8 phosphate buffer & 0.1 N HCl.

The results obtaining in vitro release studies were plotted in different model of data Treatment as follows:

1. Cumulative % drug release vs. time (zero order rate kinetics).
2. Log % drug retained vs. time (First Order rate Kinetics).
3. Cumulative % drug release vs. square root of time (Higuchi's plot).
4. Log cumulative % drug release Vs log time (Peppas plot).

STABILITY STUDIES:

Definition:

Stability is defined as "the capacity of the drug product to remain within Specifications established to ensure its identity, strength, quality and purity" (FDA 1987).In other words the stability of a drug is its ability to resist detoriation.

-Controlled release matrix tablets of Metformin HCl formulated in the present study were subjected to accelerated stability studies.

-Stability studies of the optimum formulation were performed at ambient humidity conditions, at room temperature, at 40°c ± 2°C, 75% RH and 2-8°c for a period up to 3 Months.

-The samples were withdrawn after periods of 1month,2 month and 3 month and were analyzed for its

appearance, hardness, friability, drug content and in vitro drug release.

Need for stability studies: Objective and Purpose:

It is important that the point of view of the safety of patients, it is important that the patient receive a uniform dose of a drug throughout the whole of shelf-life. Consideration must be taken to the relevant legal requirements concerned with the identity, strength, purity, and quality of the drug. .Such a study is important to prevent economic repercussion of marketing an unstable product Detoriation of drug may take several forms arising from changes in the chemical, physical, and microbiological properties .These changes may affect therapeutic value ofa dosage form or increases toxicity.

Procedure:

-Controlled release matrix tablets of Metformin HCl formulated in the present study were subjected to accelerated stability studies.-Stability studies of the optimum formulation were performed at ambient humidity conditions, at room temperature, at 40°c ± 2°C, 75% RH and 2-8°c for a period up to 3 months.
-The samples were withdrawn after periods of 1st month, 2nd month and 3rd month and were analyzed for its appearance, hardness, friability, drug content and *in vitro* drug release.

RESULTS AND DISCUSSIONS: DRUG-EXCIPIENT COMPATIBILITY STUDIES:

Compatibility of the drug with recipients was determined by FT-IR spectral analysis, this study was carried out to detect any changes on chemical constitution of the drug after combined it with the excipients. The samples were taken for FT-IR study.

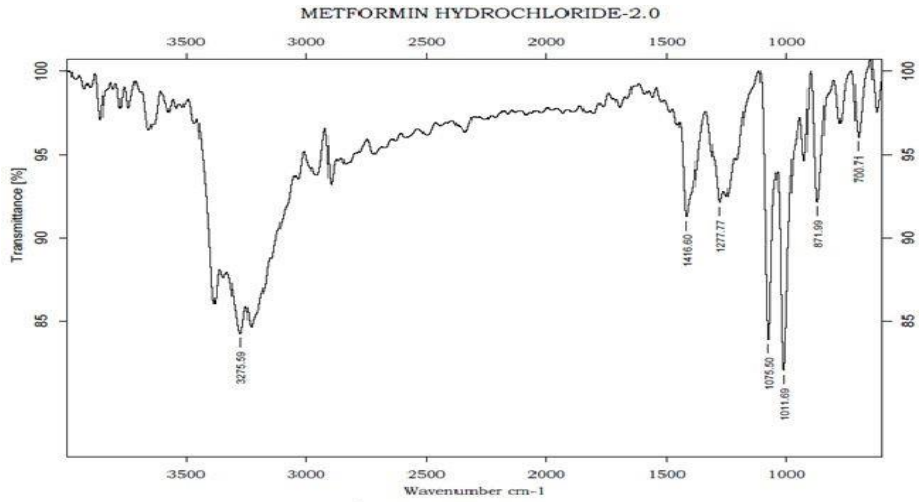

Figure No. 6: FTIR Spectrum Of Metformin Hydrochloride

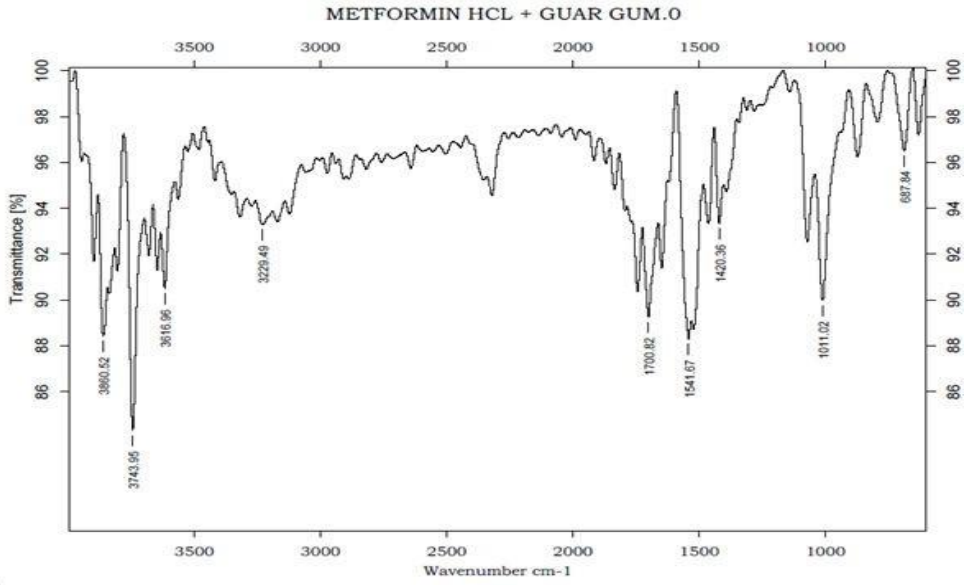

Figure No. 7: FTIR Spectrum Of Metformin Hydrochloride And Guar Gum

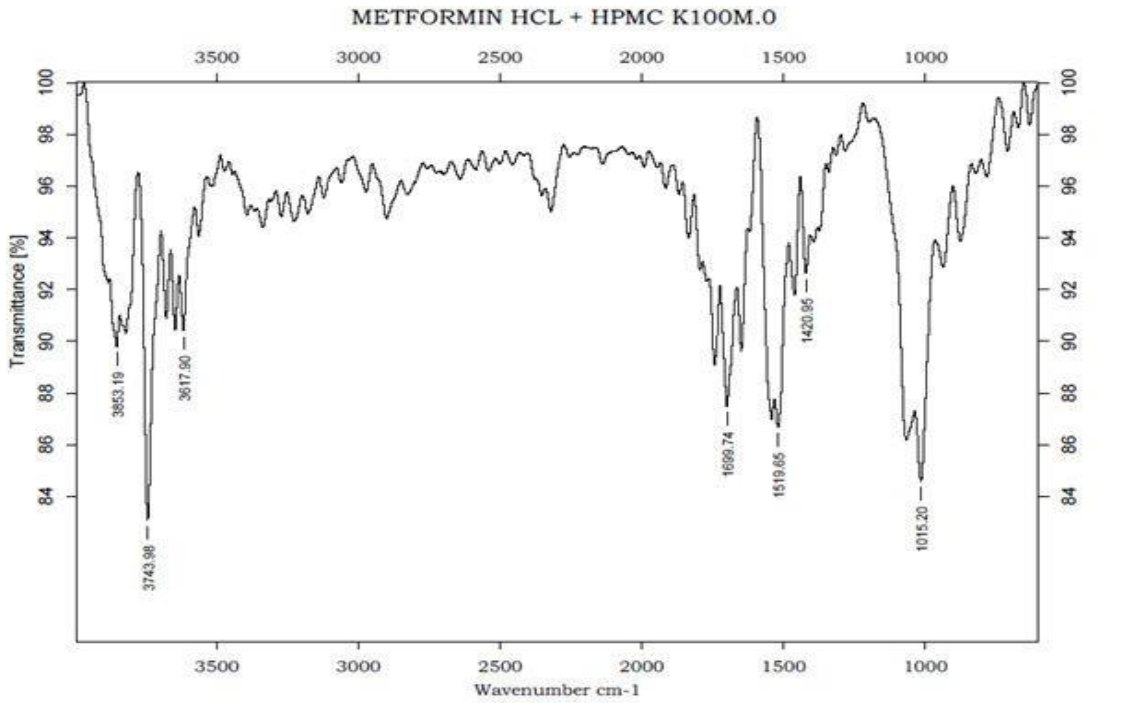

Figure No. 8: FTIR Spectrum Of Metformin Hydrochloride And HPMC K100M

Discussion: From the FTIR spectra it is clearly evident that there were no interactions of the drug and the polymer. This confirms the undisturbed structure of the drug in the formulation. This proves the fact that there is no potential incompatibility of the drug with the carriers used in the formulation.Organoleptic Evaluation Of The Drug:
Visual inspection of drug was done for the candidate drug.

Table No. 9: Organoleptic Evaluation Of The Drug Metformin Hydrodhloride.

Parameter	Observation
Color	White
Odour	No characteristic odour
Taste	Tasteless
Appearance	Crystalline powder

Melting point :
It was found to be in the range of **222°C to 226°C. Calibration curve of Metformin Hydrochloride :**
The Standard calibration curve of Metformin HCl was obtained by plotting Absorbance Vs concentration. Table No.10 shows the absorbance values of Metformin HCl. It was found that the estimation of Metformin HCl by spectrometric method at 233 nm shown in figure No.6 has a good reproducibility .The standard calibration curve shows the slope of
0.081 and correlation coefficient of 0.999.The curve was found to be linear in the concentration range of 10-150µg/ml(Beer's range) at 233nm. The calculations of drug content, in-vitro release and stability studies are based on this calibration curve.

Table No. 10: Standard Calibration Curve Of Metformin Hydrochloride.

Conc.(Mcg/ml)	Absorbance
0	0
1	0.081
2	0.163
3	0.243
4	0.325
5	0.406
6	0.482
7	0.565
8	0.648
9	0.731
10	0.815

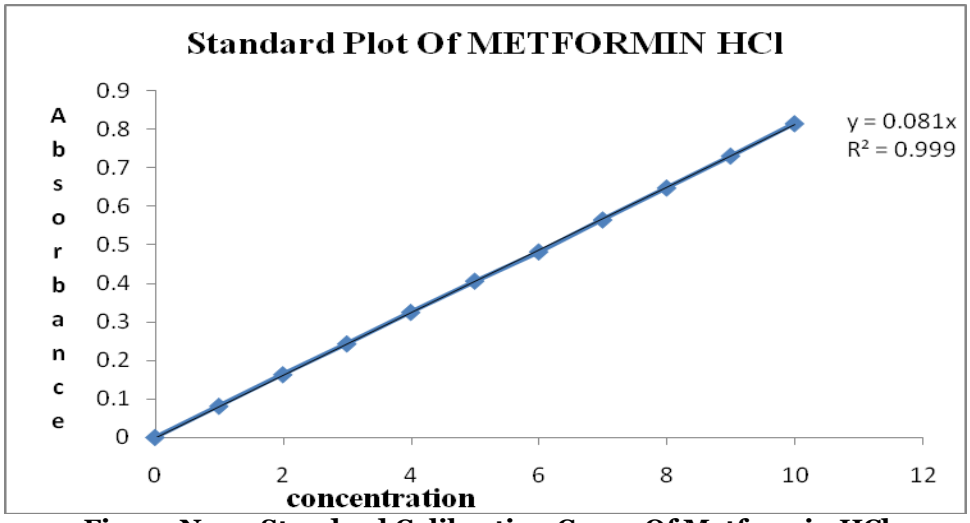

Figure No.9: Standard Calibration Curve Of Metformin HCl

IN-VITRO DISSOLUTION STUDY AND KINETIC MODELLING OF DRUG:

Table No. 17: Dissolution data of all the batches

Time (hr)	% cumulative drug release (F1)	% cumulative drug release (F2)	% cumulative drug release (F3)	% cumulative drug release (F4)	% cumulative drug release (F5)
0	0	0	0	0	0
1	10.05	3.26	6.3	3.12	1.11
2	21.6	15.25	16.2	19.6	9.9
3	36	25.2	24.3	23.7	21
4	49.5	32.3	37.8	39.0	34.2
5	54.0	42.5	55.8	45.5	42.3
6	67.5	53.05	65.7	58.6	55.8
7	77.6	63	78.3	69.2	64.8
8	84.5	78	89	75.1	77.4
9	93.6	84	92.7	86.8	84.6
10	....	96.9	....	97.2	86.4
11	....	....	....	....	90.9
12	....	....	....	....	98.6

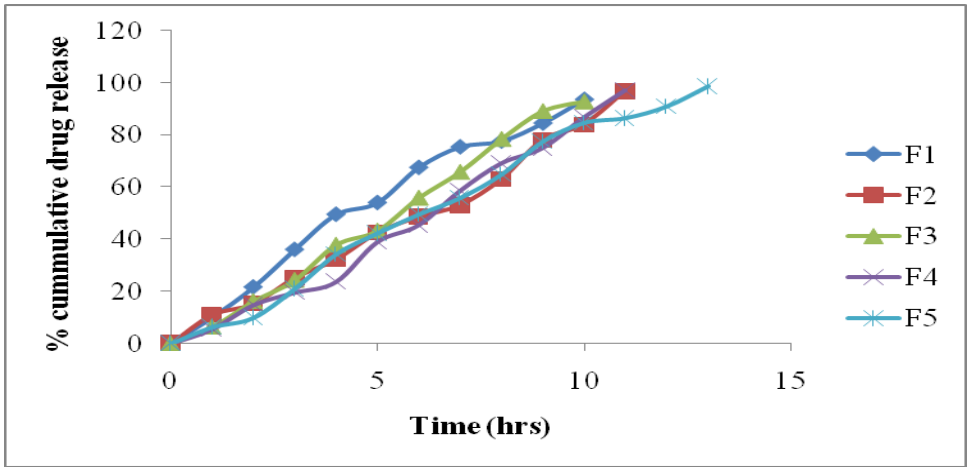

Figure No. 10: Comparitive Dissolution Profile Of Formulations F1 To F5.

Table No. 18: R^2 values for release kinetics of F1 to F4

	ZERO	FIRST	HIGUCHI	PEPPAS
	R Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
F1	0.992	0.866	0.935	0.787
F2	0.992	0.778	0.889	0.811
F3	0.992	0.893	0.896	0.877
F4	0.986	0.770	0.891	0.879

Inference: All the batches follow zero order kinetics and Higuchi model drug release.

Dissolution profile of optimized formula(F5):

Table No. 19: Dissolution Data Of Optimized Formula F5

Time(hrs)	% drug released	Log time	uare root of time	% drug unreleased	Log % released	Log % unreleased
0	0	0	0	100	0	2
1	1.11	0	1	98.89	0.045	1.99
2	9.9	0.301	1.414	90.1	0.99	1.95
3	21	0.47	1.732	79	1.32	1.89
4	34.2	0.602	2	65.8	1.53	1.81
5	42.3	0.69	2.23	57.7	1.62	1.76
6	55.8	0.84	2.44	44.2	1.74	1.64
7	64.8	0.90	2.64	35.2	1.81	1.54
8	77.4	0.95	2.82	22.6	1.88	1.35
9	84.6	1	3	15.4	1.92	1.18
10	86.4	1.04	3.16	13.6	1.93	1.13
11	90.9	1.07	3.31	9.1	1.95	0.95
12	98.6	1.11	3.46	1.4	1.99	0.146

Figure No. 11: zero order plot of optimized formula F5

Figure No. 12: First order plot of optimized formula F5

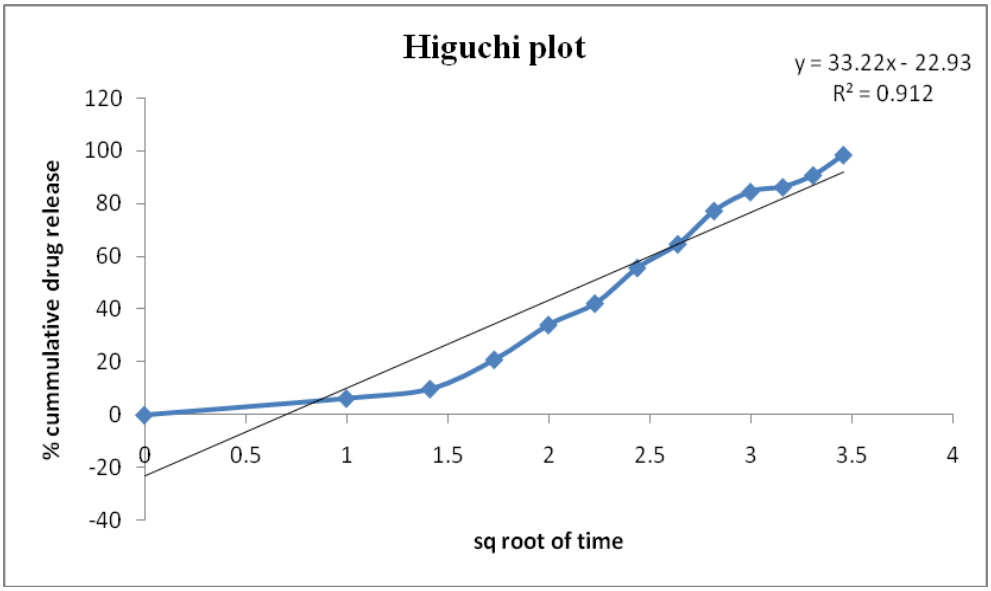

Figure No.13: Higuchi plot of optimized formula F5

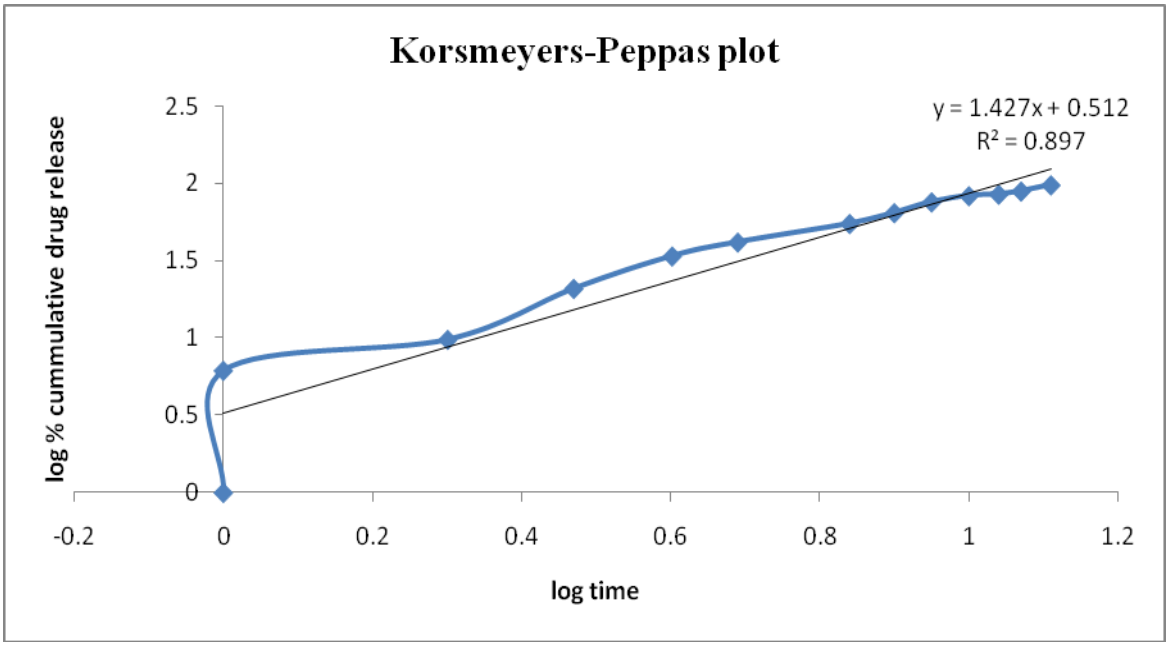

Figure No. 14: korsmeyers-peppas plot of optimized formula F5

Inference: From the drug kinetics of F-5, it follows zero order release and higuchi diffusion pattern.

Stability studies:

Table No. 20:Optimised Formula F5 at temp. (40°C ± 2°C & 75% R.H)

Formulation	Tested after time(months) ± SD	Hardness Kg/cm²) ±SD	Friability (%)) ±SD	Drug content (%) ± SD	% drug released) ±SD
F5	1	7.00±0.1	0.28±0.5	99.49	98.6±0.2
F5	2	6.5±0.28	0.31±0.20	99.15±0.43	98.2±0.2
F5	3	6.3±0.31	0.33±0.14	99.00±0.25	98.0±0.42

Each value represents the mean ± standard deviation (n=3)

Inference:

-The samples were withdrawn after periods of 15 days, and 30 days and were analyzed for its appearance, hardness, friability, drug content and in vitro drug release.

-The results obtained were shown in Table No 20.

The results revealed that no significant changes were seen in appearance, drug - content, hardness, friability, and in vitro release for F5formulation.

CONCLUSION

Formulation of controlled release matrix tablets of Metformin HCL thus helped to decrease dosing frequency , reduces local adverse effects, and extends release of drug from the matrix to a prolong period of time, thus improves patient compliance. This may also extends biological half-life of existing drug.

- The result generated in this study showed that the profile and kinetics of drug release were the functions of polymer type, polymer grade (viscosity) and polymer concentration.

HPMC K-100M + Guargum > Guargum > HPMC K-100M

- The present study showed that the release of Metformin HCL depended on the ratio of polymers used. Thus we can infer that drug release rate **decreases** With **increase** in polymer level in the formulations.
- Data generated in this study also shows that anomalous mechanism (non-fickian) of drug release is predominant for all batches of matrices.

Release was found to follow; Zero order, and Higuchi kinetics model.

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