Original Article

FORMULATION OF METFORMIN HYDROCHLORIDE CONTROLLED RELEASE MATRIX TABLETS, AND ANALYTICAL METHOD USED IN THE DETERMINATION OF METFORMIN HCL

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ABSTRACT

Metformin hydrochloride has relatively short plasma half-life, low absolute bioavailability. The need for the administration two to three times a day when larger doses are required can decrease patient compliance. Sustained release formulation that would maintain plasma level for 8-12 h might be sufficient for daily dosing of metformin. 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

Oral drug delivery system has been known for decades as the most widely utilized route for drug administration among all the routes that have been explored for the systemic delivery of drugs via pharmaceutical products of different dosage forms.[1] Oral route is the most convenient and extensively used route for drug administration. More than 50% of drug delivery systems available in the market are oral drug delivery system. Conventional oral drug delivery system achieves as well as maintains the drug concentration within the therapeutically effective range needed for treatment only when taken several times a day. Compared to other oral dosage forms, tablets are the manufacturer's dosage form of choice because of their relatively low cost of manufacture, package and shipment; increased stability and virtual tamper resistance.[2] Tablets represent unit dosage forms in which one usual dose of the drug has been accurately placed.[3,4]

TABLETS

Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared either by compression or moulding methods.[5]

Advantages of tablets[4]

Tablets are unit dosage forms and they offer the greatest capabilities of all oral dosage forms for the greatest dose precision and the least content variability.
1. Cost is lowest of all oral dosage forms.
2. They are the lightest and most compact of all oral dosage forms.
3. They are in general the easiest and cheapest to package and ship of all oral dosage forms.
4. Product identification is potentially the simplest and cheapest, requiring no additional processing steps when employing an embossed or monogrammed punch face.

METHODOLOGY
Preformulation Studies[57,58]

DRUG-EXCIPENTS COMPATIBILITY STUDY
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.

ANALYTICAL METHOD USED IN THE DETERMINATION OF METFORMIN HCL
U.V/VIS Spectroscopy
Stock solution of concentrations of 1-10 µg /ml was prepared and appropriately diluted with respective dissolution medium and the series of solutions were subjected to U.V Spectroscopy and recorded at 233nm.

Organoleptic Evaluation
The Organoleptic evaluation refers to the evaluation of color, odour, shape, taste and special features which include touch and texture. The majority of information on the identity, purity and quality of the material can be drawn from these observations.

Melting point
Melting point of drug was determined by capillary method in triplicate.

PRE-COMPRESSIVE EVALUATION
Preparation of matrix tablets of Metformin Hydrochloride
All ingredients were sieved through an ASTM #60 sieve (250µm size), and then weighed quantity of drug was physically mixed with all auxiliary excipients by geometric addition using a glass mortar and pestle for about 10 min.

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Then magnesium stearate and talc were added as the lubricant/ glidant and thoroughly mixed for 5min.

↓

This was the Powder blend Ready for Compression.

↓

From the Powder blend, the homogeneous powder mixture for a single matrix was weighed, fed manually into the die of an eight station automatic rotary tablet machine equipped with biconcave die-punch set of 8mm diameter and compressed to a target weight of 400mg and an average hardness of 7–8 kg/cm^{2}for all tablets.

PROCEDURE
Matrix tablets containing400mg of Metformin hydrochloride along with various amounts of polymers such as HPMC, guar gum, and other excipients (such as magnesium Stearate, talc and MCC) were used and tablets were prepared by direct compression technique. In the first step, the drug and ingredients with the exception of magnesium Stearate were blended in mortar for 5 minutes. Then magnesium Stearate was added and formulation was mixed for an additional 2 minutes. Desired amount of blend was directly compressed into tablets using rotary tablet compression machine (RIMEC, MINI PRESS-1). Before compression, the surfaces of the die and punch were lubricated with magnesium stearate. All the preparations were stored in airtight containers at room temperature for further studies.

Table No. 6: Composition of matrix tablets of Metformin hydrochloride.

Sl no:	Ingredients	Formula F1	Formula F2	Formula F3	Formula F4	Formula F5
1	Metformin HCL	100mg	100mg	100mg	100mg	100mg
2	HPMC K 100M	-	-	50mg	100mg	50mg
3	Guar gum	50mg	100mg	-	-	50mg
4	Micro crystalline cellulose	240mg	190mg	240mg	190mg	190mg
5	Talc	4mg	4mg	4mg	4mg	4mg
6	Magnesium Stearate	6mg	6mg	6mg	6mg	6mg

All ingredients were sieved through an ASTM #60 sieve (250µm size), and then weighed quantity of drug was physically mixed with all auxiliary excipients by geometric addition using a glass mortar and pestle for about 10 min. Then magnesium Stearate and talc were added as the lubricant/ glidant and thoroughly mixed (zip bag) for 5min. This was the powder blend Ready for Compression. From the powder blend, the homogeneous powder mixture for a single matrix was weighed, fed manually into the die of an eight station automatic rotary tablet machine equipped with biconcave die-punch set of 8mm diameter and compressed to a target weight of 400mg and an average hardness of 7–8 kg/cm^2 for all tablets. The obtained matrices were subjected to various Pharmacopoeial and physical properties evaluation like weight variation, thickness, hardness, Friability, drug content and in vitro drug release of the matrix tablets.

Total weight of the tablet is 400mg.

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
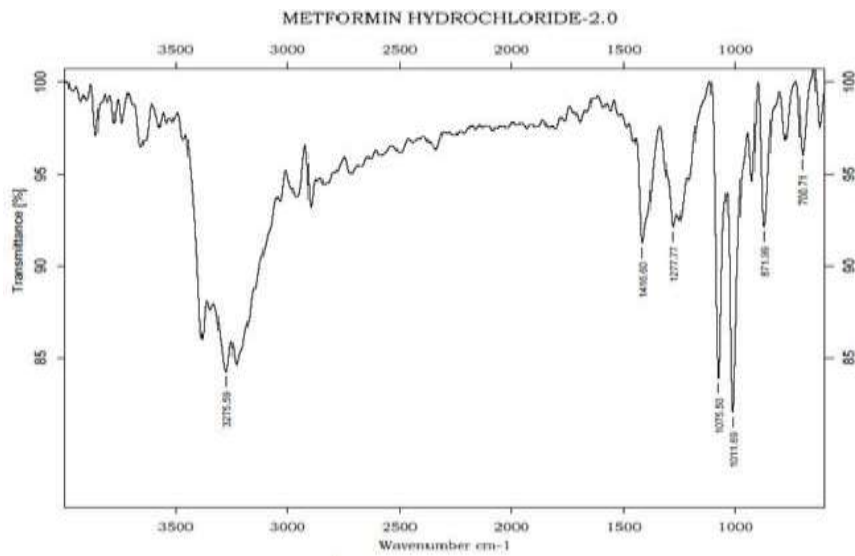
taken for FT-IR study.

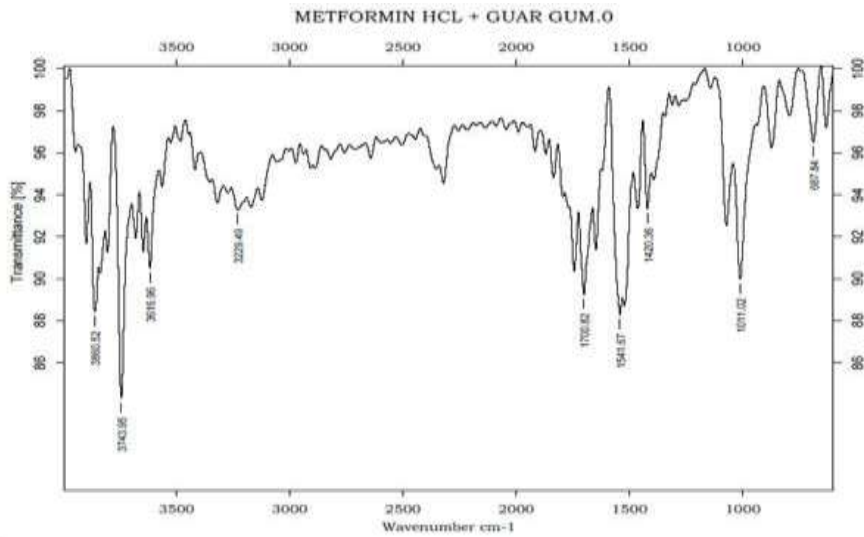**Figure No. 6: FTIR Spectrum of Metformin Hydrochloride.**

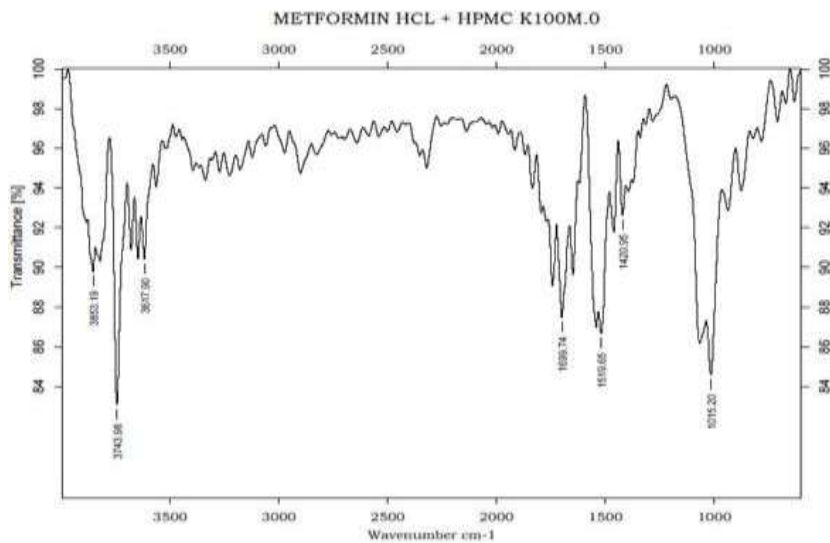**Figure No. 7: FTIR Spectrum of Metformin Hydrochloride and Guar Gum.**

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.

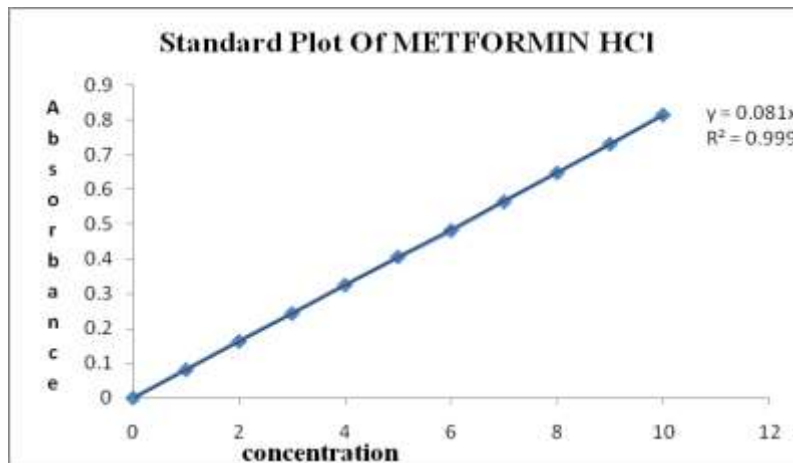| Conc.(Mcg/ml)	Absorbance
0	0
1	0.081
2	0.163
3	0.243
4	0.325
5	0.406
6	0.482
7	0.565
8	0.648
9	0.731
10	0.815

Figure No. 9: Standard Calibration Curve Of Metformin HCl.

PREFORMULATION STUDY
BULK DENSITY (g/ml)
Table No. 11: Blend characteristics (Bulk Density).

S.NO	Formulation Code	Bulk Density (g/ml)±sd
1	F1	0.34 ± 0.01
2	F2	0.39 ± 0.02
3	F3	0.34 ± 0.01
4	F4	0.32 ± 0.01
5	F5	0.38 ± 0.02

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

Inference: The performed trial batches from formulae 1to5. The Bulk Density was found to be 0.32 to 0.38 g/ml.

TAPPED DENSITY (g/ml)
Table No. 12: Blend characteristics (Tapped Density).

S.NO	Formulation Code	Tapped Density (g/ml) ±SD
1	F1	0.47 ± 0.02
2	F2	0.56 ± 0.02
3	F3	0.46 ± 0.02
4	F4	0.47 ± 0.01
5	F5	0.47 ± 0.02

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

Inference: The performed trial batches from formulae 1to5. The Tapped Density was found to be 0.46 to 0.56 g/ml.

CARR'S INDEX (%)
Table No. 13: Blend characteristics (Compressibility Index).

S.NO	Formulation Code	Carr's Index (%)±SD
1	F1	27.6 ± 0.53
2	F2	30.3 ± 0.59
3	F3	26.0 ± 0.81
4	F4	31.9 ± 0.73
5	F5	19.1 ± 0.77

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

Inference: The performed trial batches from formulae 1to5. The Compressibility Index (%) was found to be 19.1 to 31.9. The flow rate for the optimized formula of F5 was found to be fair.

HAUSNER RATIO
Table No. 14: Blend characteristics (Hausner's Ratio).

S.NO	Formulation Code	Hausner Ratio±Sd
1	F1	1.38 ± 0.17
2	F2	1.43 ± 0.03
3	F3	1.35 ± 0.12
4	F4	1.46 ± 00.03
5	F5	1.23 ± 0.12

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

Inference: The performed trial batches from formulae 1 to 5. The Hausner's Ratio was found to be 1.23 to 1.46. The flow rate for the optimized formula of F5 was found to be fair.

ANGLE OF REPOSE (^{0})
Table No. 15: Blend characteristics (Angle of Repose).

S.NO	Formulation Code	Angle of Repose (^{0})
1	F1	39
2	F2	38.5
3	F3	38.1
4	F4	39.9
5	F5	40

Inference: The performed trial batches from formulae 1 to 5. Angle of Repose (°) was found to be 38.1 to 40. The flow rate for the optimized formula of F5 was found to be passable.

EVALUATION OF TABLETS
Table No. 16: physical parameters of tablets of each batch.

S.no	Weight Variation (mg) ± SD	Thickness (mm) ± SD	Hardness (Kg/cm²)	Friability (%) ± SD	Drug content ± SD
F1	400.67±1.53	4.6±0.02	8.5±0.12	0.42±0.01	99.45±1.53
F2	399.00±2.00	4.2±0.01	7.0±0.17	0.37±0.01	98.87±2.55
F3	401.33±1.53	4.2±0.01	7.5±0.21	0.33±0.009	100.05±0.01
F4	398.00±2.55	4.1±0.02	6.5±0.35	0.22±0.015	98.56±0.15
F5	399.25±1.50	4.5±0.01	7.00±0.15	0.28±0.01	99.49±0.5

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

Inference: All the batches were within the limits.

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.

SUMMARY
The objective of present study was directed towards fabrication and characterization of controlled release matrix tablets of Metformin HCL by using some selected polymers to achieve controlled release of drug from the matrix systems.

Metformin HCL was used as a model drug and release was controlled by inclusion of some selected polymers of various types.

Controlled release matrix tablets of Metformin HCL were successfully prepared using some selected polymers as the release controlling matrices and by employing direct compression method.

- All the prepared formulations were evaluated for both pre-compressive and post- compressive parameters such as tablet thickness, hardness, friability, weight variation and drug content uniformity, the values obtained were found to be satisfactory and they complies with pharmacopoeial standards.

All the parameters were under acceptable ranges. The polymer with HPMC+guargum ratios greatly retarded the release of drug from the polymeric matrix. The

retardation of drug release was greatly influenced when the concentration of polymer was increased.

Respectively after a study of 12 hours. The drug release followed zero order and Higuchi kinetic model. Thus this polymer can be successfully employable to formulate controlled release tablets for existing drug.

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.

BIBLIOGRAPHY

1. "Controlled and Modulated Release Drug Delivery Systems", in Encyclopedia of Pharmaceutical Technology, (J. Swarbrick and J.C. Boylan, eds.) Chein Yie W. [3rd] Ed Marcel Dekker, New York, 1990; 280-313.
2. "Modern pharmaceutics", Gilbert S Banker, Christopher T Rhodes, [4th] Ed. New York: Marcel Dekker Inc, 2002; 291: 333.
3. "The theory and Practice of Industrial Pharmacy", Leon Lachman, Herbert A Liberman. Special Indian [3rd] Ed. New Delhi: CBS Publishers, 2009; 67, 183, 293-302, 318-319, 329-335.
4. "Remington's pharmaceutical sciences", Alfonso R. Gennaro. [18th] Ed. Pennsylvania: Mack publishing company, 1990; 1633.
5. Pharmaceutical Dosage Forms. Herbert A. Liberman, Leon Lachman, Joseph B. Schwartz. [2nd] Ed. Vol-I. New York Marcel Dekker Inc., 1989; 195-197: 285-286.
6. Remington's "The science and practice of pharmacy", Alfonso. R. [20th] edition, 2002; 903-929.
7. Pharmaceutical dosage forms and drug delivery systems, Howard Ansel, Loyd V. Aller, Jr. Nicholas G. Popovich, [8th] Ed., 2005; 260-275.
8. Theory and practice of industrial pharmacy. Leon Lachman, Herbert A Libermann, Joseph L. Kanig. 3rd edition, 1998; 431-439.
9. Controlled drug delivery fundamentals and applications. Joseph R Robinson, Vincent H. L. Lee, [2nd] edition Marcel Dekker Inc, New York., 2005; 29: 5-36.
10. Biopharmaceutics and Pharmacokinetics- A Treatise, Brahmankar, D. M., Sunil, B. Jaiswal. Vallabh Prakashan, New Delhi. [1st] Ed., 1995; 347-354.
11. "Theory and Practice of Contemporary Pharmaceutics", Tapesh, S., Ghosh, K. and Bhaskara R. Jasti. [2nd] ed., CRC Press, New Delhi, 2005; 333-357.
12. Modern Pharmaceutics. Gilbert S. Banker, Christopher T. Rhodes. [4th] e.d., Marcel Dekker Inc, New York, 2005; 121: 501-514.
13. "Remington's pharmaceutical sciences" Longer M.A., Robinson J.R. 18th edition, Mac Publishing Company, 1990; 1675-1684.