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Design, Evaluation and Optimization of Sustained Release Metformin HCl Matrix Tablet

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ABSTRACT

The sustained release system includes any drug delivery system that achieves slow and extended release of drug over an extended period of time. The present study was carried out to develop and evaluate the matrix tablets of Metformin HCl 500 mg strength containing cellulose derivatives as release modifying polymer. The matrix tablets of 500 mg strength were prepared by direct compression. The data generated from *in-vitro* studies showed, the drug release from matrices containing HPMCK100M was based on diffusion and erosion. Therefore, HPMCK100M can be used to modify release rate of Metformin HCl in matrix tablets. The results of *in-vitro* drug release studies in simulated GI fluids was showed that matrix tablets containing HPMC K100M in (F-5) batch in direct compression are able to control the release of water-soluble Metformin HCl. Therefore it was concluded that HPMCK100M is suitable for the formulating matrix system of Metformin HCl. Metformin HCL was stable in the designed matrices.

KEYWORDS: Metformin HCl, matrix tablet, extended release, HPMC, **Sustained Release**

INTRODUCTION

In Pharmaceutical practice several approaches exist for administration of drugs to the patients. If the drug is given in conventional dosage form, it has to be administered several times a day, to produce the desired therapeutic effect. Because of frequent dosing, fluctuations in plasma drug level occur. The pronounced fluctuations resulting from the conventional drug administration are likely to yield period of therapeutic effects, when the drug concentration falls below the minimum therapeutic level. Drug concentration can be controlled within the narrow therapeutic range by the use of sustained release systems, which will minimize the severity of side effects. Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basel and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Elimination half life of metformin HCl is 6.2 hrs, so need of another dose. Frequency is reduced by the making sustained release formulation metformin HCl 500mg and 1000mg matrix sustained release formulation.

Development of a metformin HCl sustained release matrix tablet formulation would be a significant advantage for patient compliance accompanied by minimization of the drug side effects as a result of reduction in the drug blood concentration fluctuations, especially in long-term therapy. To formulate the sustained release dosage form of metformin HCl, To study the effect of polymer concentration on tablet characteristic. To study the effect of combination and composition of various polymer materials on tablet characteristic, to study the effect of temperature and relative humidity on tablet characteristic.

The aim of present investigation is formulation development and evaluation of matrix sustained release tablets of metformin hydrochloride and dissolution profile of formulated product.

MATERIAL AND METHOD

Metformin HCl was obtained from Amari Bombay as gift. Methocel(HPMC-K100M)and Methocel(HPMC-K4M) were purchased from Rutai Chemicals China. Micro crystalline cellulose, Magnesium Stearate and talc were purchased from Vijalak Pharma, Bombay. All other used chemical and reagent were belongs to L.R. Grade.

Identification of Drug

Organoleptic characteristics: Melting points, FT-IR analysis, UV analysis, Solubility of drug were determined.

Drug-Excipient compatibility study: excipients weight according to mention ratio and shifted through BSS #36 and blended together. Mixture placed in 2 vials. A set of vial are stored at 4^0C.

Table No. 1: Drug –excipients ratio for compatibility study

S. No.	Ingredients	Ratio (drug 200 ≤ 500 mg)
1	Metformin HCl + Methocel (HPMC- K 100M)	1:0.5
2	Metformin HCl + Methocel (HPMC- K 4M)	1:0.5
3	Metformin HCl + Microcrystalline cellulose	1:0.5
6	Metformin HCl + Magnesium Stearate	1:0.05
7	Metformin HCl + Colloidal silicon dioxide (aerosol)	1:0.05
8	Metformin HCl + Talc	1:0.05
9	Metformin + Lactose	1:2

Formulation of matrix tablet containing Metformin HCl

Table No. 2: Quantitative formula of the following table

S. No.	Ingredients (mg)	F-1	F-2	F-3	F-4	F-5	F-6	F-7
1	Metformin HCl	500	500	500	500	500	500	500
2	HPMC K100 M	-	-	245	-	480	385	480
3	Methocel (HPMC-K4M)	-	240	240	485	-	-	-
4	Micro crystalline cellulose	480	245	-	-	-	100	-
5	Colloidal silicon dioxide (aerosol)	15	10	10	10	15	10	15
6	Magnesium Stearate	5	5	5	5	5	5	5
7	Purified water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
8	Total Wt. (mg.)	1000	1000	1000	1000	1000	1000	1000

Methods: Preparation of metformin HCL matrix tablet 500 mg by direct compression methodmethod Mill the metformin hydrochloride through 1 mm multi mill and pass through40 meshes. Pass hydroxy propyl methyl cellulose K100M (245mg, 480mg, 385mg,480mg, inF-3, F-5, F-6, F-7 formulations respectively), Hydroxy propyl methylcellulose K4M (240mg, 240mg, 485mg, in F-2, F-3, F-4, formulations respectively)Microcrystalline cellulose (480mg, 245mg, 100mg, in F-1, F-2, F-6, formulations respectively), Colloidal Anhydrous Silica and magnesium Stearate through 40 mesh. These mix well with metformin hydrochloride. Remove 20% blend form mixture and Compress the slug tablets of remaining 80% mixture. By using 13.5 mm round shape punch at 900 mg per tablets weight. Tablet hardness at NLT 8.0 Kg. Pass slug through 2mm screen using multi mill with and pass thru 16 meshes. Mix the granules with remaining mixture and compress on 13.5mm round biconvex punch at average weight1000 mg per tablets.

Evaluation of blend mixture:

The angle of repose was determined by fixed funnel method. The bulk density, Tapped density, Compressibility index and Hausner's ratio were determined.

Evaluation of tablet: All the prepared Sustained release tablets were evaluated for following official and unofficial parameters e.g. Weight variation, Friability test, Hardness, Thickness and Diameter, Uniformity of Drug content and *In-Vitro* Dissolution Studies.

Dissolution Profile: Metformin Hydrochloride showed good solubility in 0.1N HCl, pH 4.5 and pH 6.8 phosphate buffers. Therefore any of the above buffers should be regarded as a suitable dissolution media for Metformin Tablets. Since Metformin SR Tablets 500mg are sustained release tablets, pH 6.8 phosphate buffers was selected as the dissolution medium of choice for the initial dissolution profiling, because tablets are design for sustained release. Metformin Hydrochloride from tablets up to 12 hrs and after ingestion tablets would be first exposed to acidic condition in the stomach only for about 2 Hrs (gastric emptying time) however after two hours tablets exposed almost alkaline condition (pH around 6.8) throughout G.I. tract therefore.

RESULT AND DISCUSSION

Preformulation Study

Organoleptic Propertie: The Organoleptic properties of drug are shown in table below. These were observed by visual observation, which are similar with the given specifications.

Table No. 3: Organoleptic properties of Drug

Test	Specification/limits	Observations
Color	White crystalline powder	White crystalline powder
Taste	Slightly bitter taste	Slightly bitter taste
Odor	Odorless	Odorless
Appearance	Crystalline powder	Crystalline powder

Melting Point: The Melting point of drug is shown in table below. It was observed by capillary method. Result of n = 3 times observation, founds within the limit.

Table No. 4: Melting point of Drug

Material	Specification	Observation
Metformin HCl	222^0– 224^0Ċ	222^0-226^0Ċ

Confirmation of λmax: The Wavelength of maximum absorbance (λmax) in distilled water was observed. By using 2µg/ml concentration of drug, distilled water used as blankfor base line correction. The λmax observed between ranges of 200 nm – 400nm.The λ_{max} was found to be 233 nm. The graph is shown in figure below.

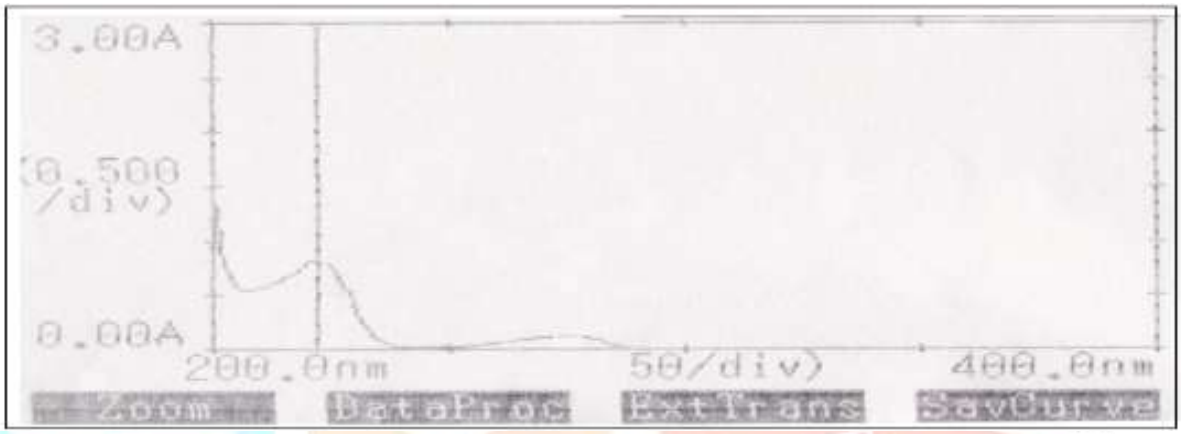

Figure No. 1: Wavelength of Maximum Absorbance (λmax) of Metformin HCl

Solubility: The solubility of drug as qualitatively by visual observation in different solvents is shown in table 6.3. This solubility carried out for to dissolution media selection. The drug was found freely soluble in distilled water, 0.1NHCl, pH6.8 Phosphate Buffer, pH 4.5 Phosphate Buffer.

Table No. 5: Solubility profile of Dug

S. No.	Solvents	Solubility
1.	Distilled water	Freely soluble
2.	0.1N HCl	Freely soluble
3.	pH 6.8 Phosphate Buffer	Freely soluble
4.	pH 4.5 Phosphate Buffer	Freely soluble

Flow property: The obtainedvalues of Angle of repose, Bulk density, Tapped density, Compressibility index, and Hausner's ratio is shown in table below:

Table No 6: Flow Property of Metformin HCl (API)

S. No.	Parameters	Obtained value
1.	Angleof Repose	$30^0 54'' \pm 1^0 00''$
2.	BulkDensity (g/cm^3)	0.511 ± 0.004
3.	TappedDensity(g/cm^3)	0.621 ± .009
4.	Compressibilityindex(%)	17.74 ± 0.78
5.	Hausner'sRatio	1.21± 0.01

Note: ± value for 'n' = three times.

FT-IR analysis of Drug: The IR spectrum of sample drug (Metformin HCl) shows the peak values, which are characteristics of the drug and the graph was shown in figure below:

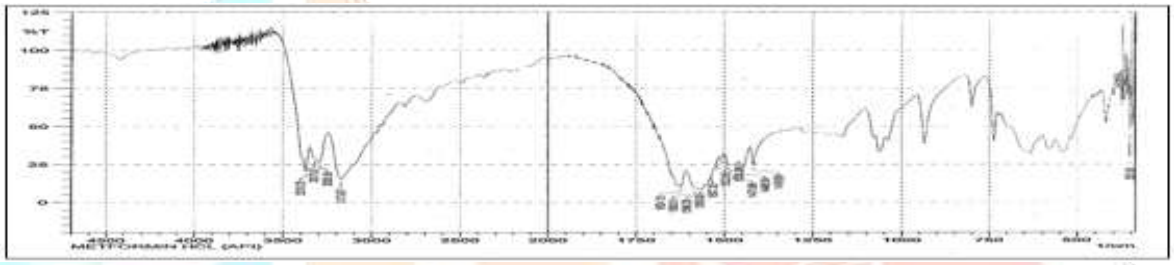

Figure No. 2: FT-IR spectrum of pure drug Metformin HCl

Calibration of Metformin HCl in pH 6.8 phosphate buffer

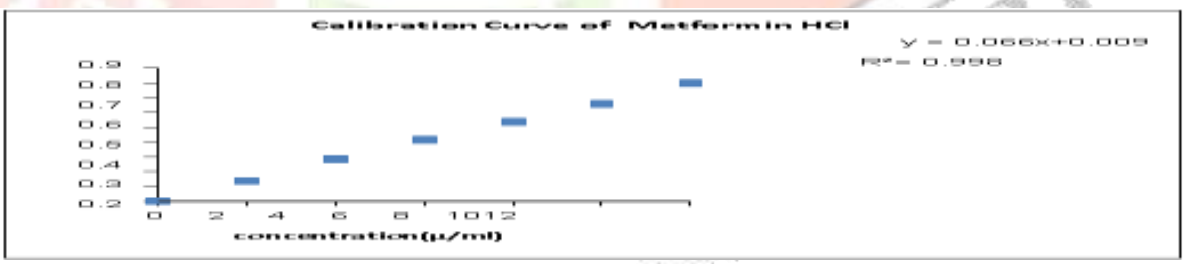

Figure No. 3: Calibration curve of Metformin HCl in pH 6.8 phosphate buffer

Drug-excipient Incompatibility study: Incompatibility studies of Metformin HCl with different excipients for one month.

Table No. 7: Drug-excipient in compatibility study

Ingredients	Ratio (drug 200- ≤ 500 mg)	Ratio (drug >500mg)	Initial	After 01 Week 40^0C/75 %RH	After 02 Week 40^0C /75%RH	After 03 Week 40^0C/75 %RH	After 04 Week 40^0C/75 %RH
Metformin HCL + Methocel (HPMC-K100M)	1:0.5	1:0.25	White powder	NC	NC	NC	NC
Metformin HCL + Methocel (HPMC-K4M)	1:0.5	1:0.25	White powder	NC	NC	NC	NC
Metformin HCL + Microcrystalline cellulose	1:0.5	1:0.25	White powder	NC	NC	NC	NC
Metformin HCL + Dibasic calcium phosphate (DCP)	1:0.5	1:0.25	White powder	NC	NC	NC	NC
Metformin HCL + PVP-K30	1:0.25	1:0.1	White powder	NC	NC	NC	NC
Metformin HCL + Magnesium Stearate	1:0.05	1:0.05	White powder	NC	NC	NC	NC
Metformin HCL + Colloidal silicondioxide (aerosol)	1:0.05	1:0.05	White powder	NC	NC	NC	NC
Metformin HCl + Talc	1:0.05	1:0.05	White powder	NC	NC	NC	NC
Metformin + Lactose	1:2	1:2	White powder	Slight color change	Slight color change	Slight color change	Slight color change

Drug-Excipients Compatibility Study by FT-IR

Infra-red spectra of drug and excipients are shown in figure below, this result observed that there is no interaction between drug and polymers.

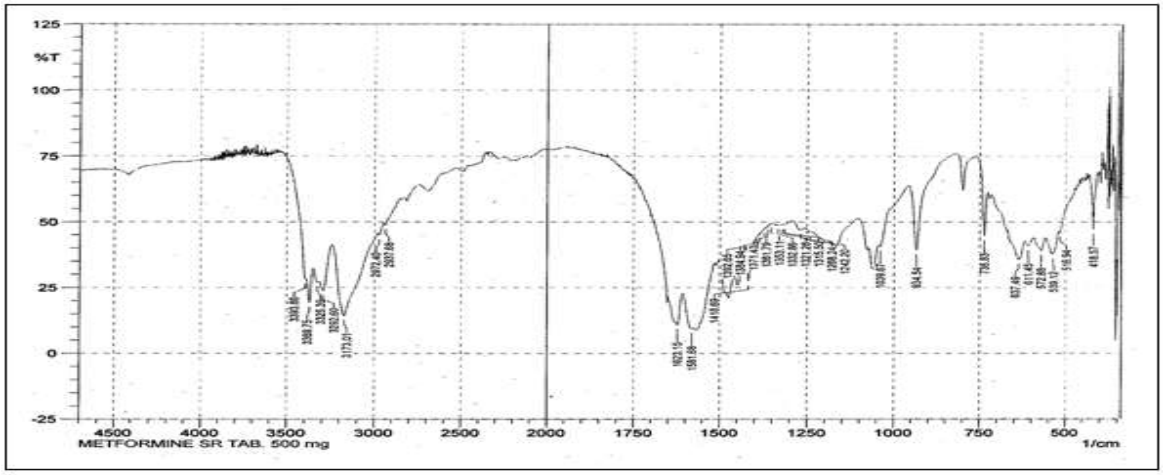

Figure No. 4: FT-IR spectrum of Metformin HCl 500 mg matrix tablet

Characteristics of blend for all formulation and tablet characteristic

The matrix tablets were prepared by. The various parameters of blending like angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio were determined before punching the tablets. The flow ability of granules was found fair to good with anangle of repose 25.3°-32.5°. The results of bulk density, tapped density, Hausner's ratio and compressibility index were found satisfactorily within acceptable limits and mentioned in table

Table No. 8: Result of blend for Metformin HCl 500 mg tablet formulation

Formulations	Angle of repose (θ)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr's index	Hausner's ratio
F-1	$32^0 6"$	0.452	0.510	10.00	1.128
F-2	$31^0 6"$	0.395	0.450	12.22	1.139
F-3	$31^0 1"$	0.412	0.463	11.01	1.123
F-4	$29^0 8"$	0.460	0.512	10.10	1.113
F-5	$28^0 2"$	0.449	0.510	11.90	1.135
F-6	$30^0 5"$	0.381	0.432	11.62	1.113
F-7	$28^0 5"$	0.432	0.489	11.60	1.131

The compressibility Indices (Carr's index values) were indicated a good flow potential for all granulated excipients. The results of compressibility index of various formulations were found between 8.22-12.85 %, which is below 15% indicating good flow properties. The tablets were evaluated for physical characteristics and *in- vitro* drug release study. All matrix optimized formulations both strength were evaluated on the basis

of various parameters and results obtained were within the range Weight variation was found within the limit of ± 5 % hardness, thickness and % friability was found within specified limit.

Table No. 9: Evaluation data for Metformin HCl matrix tablets 500mg

Batch	Thickness (mm)	Hardness (Kg/cm2)	Friability (%)	Weight variation
F-1	7.55	11.5	0.768	Pass
F-2	7.56	11.5	0.779	Pass
F-3	7.60	11.5	0.785	Pass
F-4	7.57	11.5	0.764	Pass
F-5	7.59	11.5	0.783	Pass
F-6	7.57	11.5	0.764	Pass
F-7	7.55	11.5	0.768	Pass

Thickness and diameter of tablets was found fixed as per punch size and thickness was controlled as well to an average of 7.20 to 7.7 mm. By holding the tablet weight and thickness constant, the surface area and volume were essentially fixed.

***In-Vitro* Dissolution studies Metformin HCl 500 mg tablet in pH 6.8 phosphate buffer**

During the studyofdrugreleasefor12hoursitwasassuredthatthereleaseofthedrug is slow enough and the polymer concentration is high enough to sustain their lease of the drug. For a freely soluble drug like Metformin HCl

Table No. 10: *In-vitro* release studies for Metformin HCl 500 mg tablet Formulation trials

Time (hrs)	F-1	F-2	F-3	F-4	F-5	F-6	F-7
0	0	0	0	0	0	0	0
1	15.32	11.27	24.92	36.48	31.92	18.57	32.9
2	30.46	40.15	35.46	52.7	41.51	26.5	40.8
3	45.21	59.28	55.78	69.12	50.93	33.48	51.1
4	65.13	80.79	76.29	82.43	59.42	37.54	58.6
6	80.84	98.54	89.95	98.2	72.19	49.6	73.2
8	95.39	-	98.86	-	84.86	63.87	85.1
10	100.12	-	-	-	91.75	76.25	90.2
12	-	-	-	-	98.84	89.49	97.9
F2	**59**	**43**	**59**	**39**	**76**	**52**	**74**

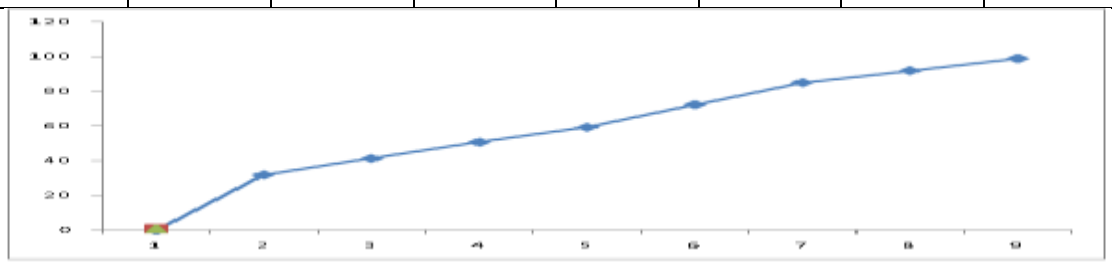

Figure No. 5: Dissolution profile of Metformin HCl 500mg with Optimized batch

Kinetic Study of *In-vitro* Drug Release Profile for Metformin500mg tablet

Table No. 11: *In-vitro* release profiles of matrix tablet of F-5 formulation

Time (hrs)	% Cumulative drug released	Log % cumulative drug released	%cum drug remaining (x)	Log % cum drug remaining	Log T	√T	(x)⅓
0	0	-	100	2	-	0	4.641
1	31.92	1.504	68.08	1.833	0	1	4.083
2	41.51	1.618	58.49	1.767	0.301	1.414	3.881
3	50.93	1.706	49.07	1.690	0.477	1.732	3.661
4	59.42	1.773	40.58	1.608	0.602	2	3.436
6	72.19	1.858	27.81	1.444	0.778	2.449	3.029
8	84.86	1.928	15.14	1.180	0.903	2.828	2.473
10	91.75	1.962	8.25	0.916	1	3.162	2.020
12	98.84	1.994	1.16	0.064	1.079	3.464	1.050

Drug Release Kinetics for Metformin HCl 500mg Tablet (Trial and Optimized Batch)

To analyze the Metformin HCL release mechanism as well as to select the optimized formulation, the *in-vitro* release data were fitted into various release equations and kinetic models Zero order, First order, Higuchi and Korsmeyer and Peppas.

Table No. 12: Zero order kinetic treatment on Metformin HCl 500mg tablet

Formulation code	Equation of the line	Correlation coefficient (R^2)
F-1	Y =10.52x +10.13	0.969
F-2	Y=17.55x +1.70	0.983
F-3	Y =12.40x +11.98	0.963
F-4	Y=15.64x +14.85	0.953
F-5	Y =7.42x +22.10	0.948
F-6	Y=6.82x +9.11	0.990
F-7	Y=7.15x +22.37	0.956

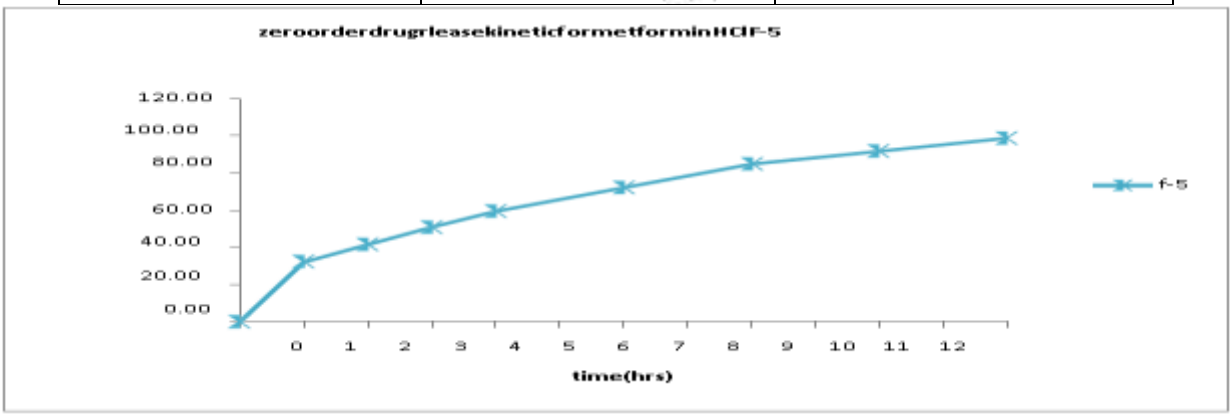

Figure 6: Cumulative % drug release v/s time for formulation (F-5) of Metformin HCl matrix tablets [zero order rate]

Table No. 13: First order kinetic treatment on Metformin HCl 500 mg tablet

Formulation code	Equation of the line	Correlation coefficient (R^2)
F-1	Y=-0.161X+2.12	0.971
F-2	Y=-0.298X+2.26	0.938
F-3	Y=-0.230X+2.24	0.863
F-4	Y=-0.270X+2.15	0.857
F-5	Y=-0.136X+2.08	0.850
F-6	Y=-0.071X+2.03	0.965
F-7	Y=-0.120X+2.04	0.868

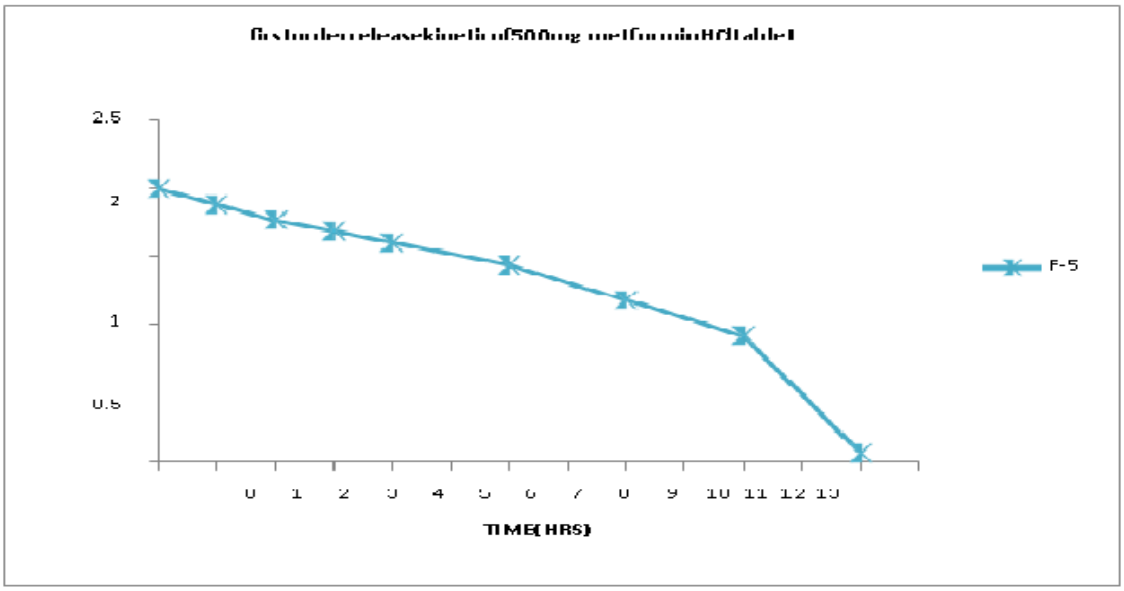

Figure 7: Log Cumulative % drug unreleased v/s time for formulation (F-5) Metformin HCl matrix tablets [first order rate kinetics]

Table No. 14: Higuchi's square root kinetic treatment on dissolution data Metformin HCl 500 mg tablet

Formulation code	Equation of the line	Correlation coefficient (R^2)
F-1	Y=35.55x -10.69	0.979
F-2	Y =42.87x – 12.90	0.954
F-3	Y=37.73 x– 7.06	0.981
F-4	Y =40.82x -2.05	0.997
F-5	Y=28.73 x+1.52	0.999
F-6	Y =25.50x – 7.16	0.983
F-7	Y=28.44x+1.28	0.998

Higuchi's plot of F-5 was showed the R^2=0.999 which indicating the drug release was followed by diffusion.

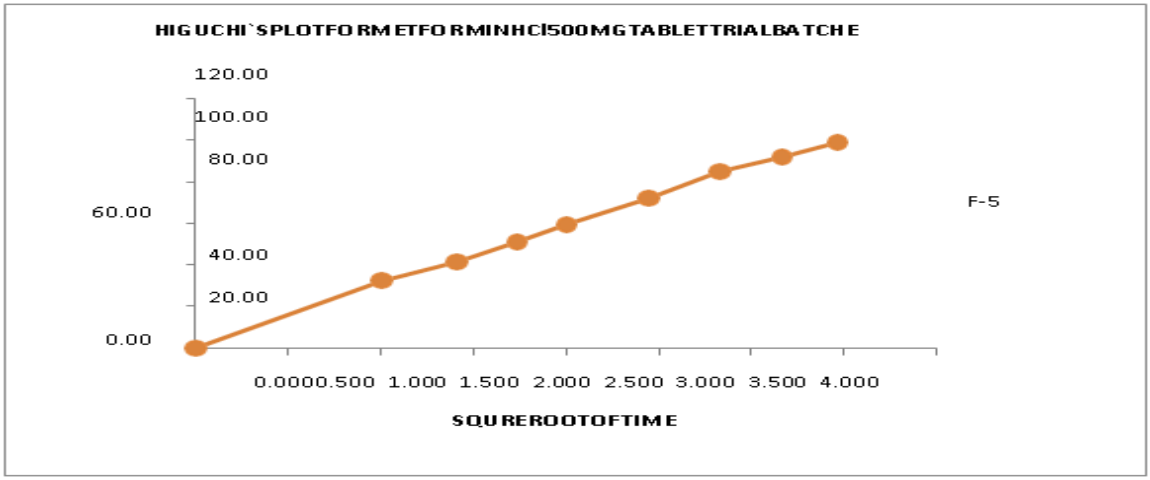

Figure 8: Cumulative % drug released v/s root time for formulation (F-5) Metformin HCl matrix tablets [higuchi classical diffusion equation]

Mechanism of Drug Release:

To explore the release pattern, by incorporating the first 60% of release data mechanism of release can be indicated according to Korsmeyer where n is the release exponent, indicative of mechanism of drug release. Fickian diffusional release and acase-II relaxational release are the limits of this phenomenon. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. Case-II relaxational release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers which swell in water or biological fluids. This term also includes polymer disentanglement and erosion.

The value of the release exponent for F-5 was obtained 0.473 which indicating release governed by non-Fickian diffusion i.e. diffusion coupled with other mechanism. Fitting the data to Korsmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release. The results of the present study were showed sustained release up to 12 hrs. It was achieved when HPMC K100M alone, the release of Metformin HCl from matrix tablets followed nearly Higuchi kinetics, via non-Fickian diffusion controlled mechanism. Drug release mechanism as per 'n' value of Korsmeyer & Peppas (Power law) cannot be predicted clearly as it appears to be a complex mechanism of swelling, diffusion and erosion.

Table No. 15: Korsmeyer and Peppas equation kinetic treatment on 500 mg Metformin HCl dissolution data

Formulation code	Equation of the line	Correlation coefficient (R^2)
F-1	Y=0.836X+1.232	0.986
F-2	Y=1.223X+1.137	0.972
F-3	Y=0.731X+1.389	0.984
F-4	Y=0.567X+1.561	0.991
F-5	Y=0.473X+1.491	0.998

F-6	Y=0.630X+1.225	0.993
F-7	Y=0.461X+1.497	0.997

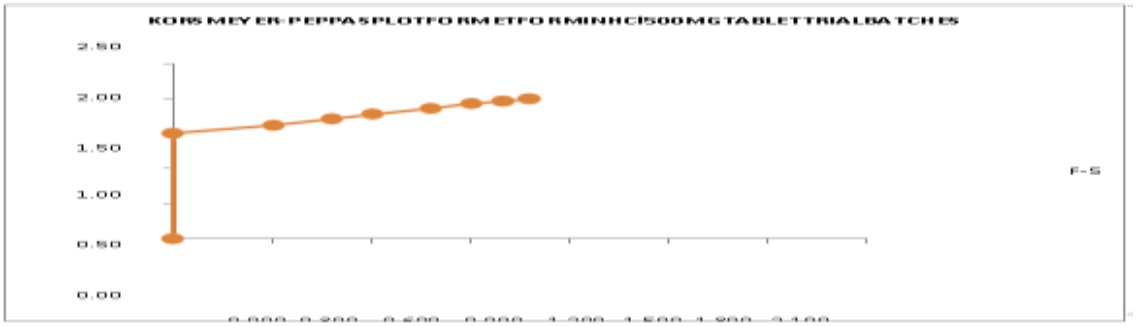

Figure 9: Log cumulative % drug released v/s log time for formulation (F-5 of Metformin HCl matrix tablets [Peppas exponential equation]

The F-5 was selected for optimized formulaon the basis of *in-vitro* dissolution studies, which indicates maximum sustained release till 12 hrs and comparatively similar with innovator. It was showed more linearity than other formulations; it was indicated by the highest value of the correlation coefficient R^2 in the Higuchi model. The R^2 value was obtained 0.999 in Higuchi plot and that 0.850 in first order describing the drug release rate independent with concentration of drug, also in formula optimization batches. I observed effect of polymer on release of drug. Concentration of polymer was slightly changed due to this reason observed no significant affect on release kinetic of drug. But release of drug affected and primary aim of project was achieved.

CONCLUSION

The sustained release system includes any drug delivery system that achieves slow and extended release of drug over an extended period of time. The present study was carried out to develop and evaluate the matrix tablets of Metformin HCl 500 mg strength containing cellulose derivatives as release modifying polymer. The physicochemical compatibility of the drug with polymers was established through IR spectroscopy. The study was indicated that the drug have good compatibility with polymers. The formulation procedure is simple and does not involve lengthy procedures and use of several pharmaceutically excipients. Metformin HCl sustained release matrix tablets were prepared successfully by direct compression using HPMCK100M respectively, as polymers in different proportion, to retard the release and achieve required dissolution profile. The matrix tablets of 500 mg strength were prepared by direct compression. Various parameters of blends like angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio were determined before punching as tablets and the results were found within the range. All matrix formulations were evaluated for physical characteristics on the basis of various parameters and results obtained were within the range. Data generated from *in-vitro* studies showed, the drug release from matrices containing HPMCK100M was based on diffusion and erosion. Therefore, HPMCK100M can be used to modify release rate of Metformin HCl in matrix tablets. The results of *in-vitro* drug release studies in simulated GI fluids was showed that matrix

tablets containing HPMC K100M in (F-5) batch in direct compression are able to control the release of water-soluble Metformin HCl. Therefore it was concluded that HPMCK100M is suitable for the formulating matrix system of Metformin HCl. Drug release kinetics of F-5 formulation correspond best to Higuchi model and drug release mechanism as per n-value of Korsmeyer & Peppas (Power law) followed non-Fickian diffusion, that means water diffusion and polymer rearrangement had an essential role in the drug release. No significant difference was observed in the release and release kinetic profile of optimized matrix formulation. Also release kinetics unaltered on storage and there were no changes in tablets characteristics, suggesting that Metformin HCL was stable in designed matrices.

Thus, results of the current study were indicated, a promising potential of the Metformin HCL matrix system as an alternative to the conventional dosage form. Since the polymer and the drugs were found to be compatible and the release mechanism was characterized, there is a great scope for the formulation of this antidibetic drug as a matrix system.

CONFLICTS OF INTERESTS

There are no conflicts of interests

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