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Formulation and Evaluation of Extended Release Tablets containing Metformin HCl

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ABSTRACT: Extended release dosage forms cover a wide range of prolonged action preparations that provide continuous release of their active ingredients for a specific period of time.Metformin Hcl is antihyperglycemic agent used in the treatment of type 2 Non Insulin Dependent Diabetes Mellitus. The extended release formulation of Metformin Hcl (MER), prolongs drug absorption in the upper gastrointestinal tract and permits once daily dosing in patient with Type 2 Diabetes Mellitus .This newer formulation may enhance patient compliance with oral therapy compared to conventional immediate release (MIR) Metformin Hcl in Type 2 Diabetes Mellitus Extended release formulation of Metformin Hcl presents significant challenges due to its poor inherent compressibility, high dose and high water solubility. Extended release matrix tablet of Metformin Hcl were formulated different combinations of polymers in Hydroxyl propyl methyl cellulose (HPMC K 100M CR) and Carbopol 71 G by wet granulation method. The formulated granules blends were evaluated for compatibility, Angle of repose, True density, Bulk density, Compressibility index. The formulated tablets were subjected to Thickness, Weight variation test, Hardness test, Friability test and Drug content. Invitro dissolution studies carried out in 6.8 phosphate buffer using the apparatus Type 2 paddle type as described in the USP dissolution monograph. Formulations F1, F2 and F5 showed sudden drug release which might be due to low level of the polymer in the tablets. Formulations F7, F9 and F10 containing HPMC K 100 M CR and Carbopol 71G in different concentration shows the extended drug release for up to 10 hrs, among these formulation, F10 is considered as optimized formulation because it shows similar drug release pattern with that of innovator. There was no significant change in physical and chemical properties of the tablets of formulation F10 after 3 Months, parameters like % drug release and assay values at various conditions as per ICH guidelines.
Key words- Metformin Hcl, Extended release Tablets, Invitro dissolution studies, Carbopol 71G.

INTRODUCTION

Oral drug delivery is the largest and oldest segment of the total drug delivery market. It is the fastest growing and most preferred route for drug administration. Use of hydrophilic matrices for oral extended release of drugs is common practice in the pharmaceutical industry. However, also drugs with long half-life qualify if a reduction in steady state fluctuation is desired. With many drugs, the basic goal of therapy is to achieve a steady-state blood level or tissue level that is therapeutically effective and non toxic for an extended period of time[2]. To achieve better therapeutic action various types of drug delivery systems are available, out of which extended release systems are gaining much importance because of there wide advantages over others like ease of administration, convenience and non-invasiveness. The maximum recommended daily dose of Metformin Hcl in the United States is 2.5 g given in three doses with meals. Metformin Hcl acts by decreasing hepatic glucose

production and improves insulin sensitivity by increasing peripheral glucose uptake. Because of its shorter and variable biological half-life of 1.5—4.5 hr, it should be repeatedly administered (500 mg thrice a day) to maintain effective plasma concentration. In spite of its favorable clinical response and lack of significant draw backs, chronic therapy with Metformin Hcl suffers from certain problems of which the most prominent is the high dose (1.5 – 2.0 g/day) low bio-availability (60%) and high incidence of gastrointestinal tract (GIT) side effect (30% case). Therefore, there were continued efforts to improve the pharmaceutical formulation of metformin hydrochloride in order to achieve an optimal therapy. These efforts mainly focus on extended release of drug.Administration of a extended release, once-a-day Metformin Hcl dosage form could reduce the dosing frequency and improve patient compliance.

PREPARATION OF MATRIX TABLETS[2,3]

Different Metformin Hcl formulations were prepared by Wet granulations technique (F-1 to F-10). Firstly metformine hcl pure drug was weighed accurately and shifted through 10# mesh. Then PVP K-30 was dissolved completely in half quantity of water. Wet granulations was done in Rapid Mixing Granulator (RMG). In the rapid mixing granulator, metformine hcl pure drug, the PVP K-30 solution was added slowly in 1stminute with slow speed of rapid mixing granulator. On 2nd minute remaining water was added with same speed of rapid mixing granulator. Then on 3rd minute the rapid mixing granulator operated at high speed. Then again sufficient water was added if necessary. Then lastly for two minutes the rapid mixing granulator operated on slow speed to form granules. In drying, the granules were semidried in air dryer without giving temperature for 20 min. Then semidried granules passed through sieve 12 # mesh. Then these semidried granules subjected for final drying for sufficient time in air dryer with temperature 60^{0}C to obtain dried granules. Then these granules passed through 16 # mesh. In polymerisation step the polymers HPMC K 100CR and Carbopol 71Gwas accurately weighed and shifted through 40 # mesh, the lubricating agent magnesium stearate weighed accurately and shifted through 40 # mesh. In final Mixing step, in double cone blender firstly dried granules of Metformine Hcl was mixed with both polymers for 5 minutes. Then lubricating agent magnesium stearate was mixed in to first mixture for 2 minute. Finally these granules are ready for compression. Then these granules are compressed by using punch size of length 19.7mm & 7.3 mm width maintaining humidity below 50%RH. Different metformine hcl formulations were prepared by wet granulations technique (F-1 to F-10). As shown in Table 1.

Table 1: FORMULATION SERIES MATRIX TABLETS METFORMINE HCL

INGREDIENTS	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10
Metformin HCL	500	500	500	500	500	500	500	500	500	500
PVP K-30	18	16	12	13	13	13	13	13	16	17
IPA	45	45	50	55	-	-	-	-	-	-
Water	-	-	-	-	35	35	30	30	30	30
HPMC K 100M CR	300	200	250	300	240	260	280	260	260	280
Carbopol 71 G	90	190	190	190	190	190	170	160	170	142
Magnesium stearate	8	8	8	8	8	8	8	8	8	8

RESULT AND DISCUSSION

PREFORMULATION STUDY: [1,2,4]

A. Colour, odor, taste and appearance:

The drug sample was evaluated for its colour and odor. The results are shown in Table 2.

B. Melting point determination:

Melting point of the drug sample was determined by capillary method by using melting point apparatus. The reported and observed melting point is shown in Table 3.

C. Determination of solubility

The solubility of the Metformin HCl was determined by adding excess amount of drug in the solvent and equilibrium solubility was determined by taking supernatant and analyzing it on Shimadzu UV 2501 PC, double beam spectrophotometer. The solubility studies have suggested the values as in the Table 4.

The solubility of the Metformin Hcl was found to be slightly soluble in water and freely soluble in acetone.

Evaluation of Blend:

Angle of Repose: - The angle of repose is the constant, three dimensional angle (relative to horizontal base) assumed by a cone like pile of material formed by any of several different methods. When the angle of repose exceeds 50 degrees, the flow is rarely acceptable for manufacturing purposes

Table 2: Results of identification tests of drug

Sr.No	Parameter	Drug
1	Colour	White or colorless
2	Odour	Odourless
3	Taste	Tasteless
4	Appearance	Crystalline powder

Melting point determination: Drug: Metformin Hcl

Table 3: Results of Melting point determination test of drug

Reported Melting Point	Observed Melting Point
222 -226^0 C	**222^0 – 224^0 C**

Table 4: Solubility of Metformin Hcl in different solvents

Medium Used	% Found	mg/100 ml
Water	99.58 %	99.58
0.1N HCl	100.10 %	100.10
Acetate Buffer pH 4.5	99.19 %	99.19
Phosphate Buffer pH 6.8	99.65 %	99.65

Table-5 Evaluation of Blend:

BATCH NO.	BULK DENSITY	TAPPED DENSITY	COMPRSIBILITY (%)	HOUSNER RATIO	ANGLE OF REPOSE (°)
F1	0.614	0.789	22.2	1.28	25.0
F2	0.668	0.726	15.4	1.08	21.0
F3	0.699	0.776	9.92	1.11	20.0
F4	0.621	0.712	12.78	1.14	23.0
F5	0.656	0.722	9.14	1.10	22.0
F6	0.677	0.778	12.98	1.14	21.0
F7	0.624	0.723	13.69	1.15	23.0
F8	0.621	0.744	16.53	1.19	22.0
F9	0.658	0.734	10.34	1.11	20.0
F10	0.719	0.854	15.80	1.18	25.0

D. Evaluation of Tablets: [5,6]

1.Thickness: The thickness of the tablets was determined using a Vernier Caliper. Five tablets from each batch were used, The results are shown in Table 6.

2.Weight Variation: To study weight variation, 20 tablets of each formulation were weighed using an electronic balance, average weights was calculated, indivisual tablet weights were compared with the average weight. Not more than two individual weights deviate from the average weight by more than the percentage shown in following Table 10 and the results are shown in Table 6 .

$$\% \text{ Deviation} = \frac{\text{Average weight} - \text{Tablet weight}}{\text{Average weight}} \times 100$$

3.Hardness:
For each formulation, the hardness of five tablets was checked using the Erweka hardness tester, average values are shown in Table.6

4.Friability:
For each formulation, twenty tablets were selected randomly and weighed. Tablets were then placed in friability testing apparatus (Electrolab, Mumbai, India), which was rotated at a speed of 25 rpm for 4 minutes. Tablets were then weighed and friability values were determined and are reported in Table 6 .

5.Content Uniformity Test:

Assay Preparation:

The Metformin Hcl content in tablets were determined by powdering 10 tablets in each batch. Powder equivalent 500 mg of Metformin Hcl was dissolved in 450ml of 10%. Acetonitrile while stirring in suitable homogenizer at 4000 rpm for 5min and stock for 2 min. Repeat the same procedure further 2 times, wash the beaker and the stirrer transfer the washing and the sample solution in 500ml volumetric flask. Sonicate the sample with intermittent vigorous shaking for 10 minutes. Then soak for 1 hr and make up the volume up to mark mix centrifuge the sample for 10 min at 3000 rpm. The further dilute 25 to 200ml with water. filter with 0.45m nylon filter paper. Evaluation of system suitability and record the chromatograms. Resolution between peaks due to Metformin related compounds and Metformin is not less than 1.5. The tailing factor is not less than 0.8 and not more than 2.0, the relative standard deviation for six replicate injections of standard solution is not more than 1.5 % and NTM 10 % for Metformin related compounds.

Table 6: Evaluation of Tablet.

FORMULATION CODE	WEIGHT VARIATION	HARDNESS Kg/cm^2	THICKNESS Mm	FRIABILITY	CONTENT UNIFORMITY
F-1	Passes	160-180N	6.20-6.30N	0.82	99.18
F-2	Passes	160-180N	6.20-6.30N	0.87	99.78
F-3	Passes	160-180N	6.20-6.30N	0.80	98.12
F-4	Passes	160-180N	6.20-6.30N	0.93	99.19
F-5	Passes	200-240N	6.55-6.70N	0.86	98.68
F-6	Passes	200-220N	6.50-6.60N	0.78	99.18
F-7	Passes	180-200N	6.60-6.70N	0.81	99.36
F-8	Passes	180-200N	6.45-6.55N	0.72	98.23
F-9	Passes	180-200N	6.45-6.55N	0.49	98.95
F-10	Passes	180-200N	6.45-6.55N	0.53	99.20

E. Dissolution studies:
The in-vitro release of Metformin HCl from formulated tablets was carried out for 10 hours in 6.8 phosphate buffer. The studies were performed in USP dissolution apparatus II (Electrolab, Mumbai, India) at 37 ± 0.5° C and 100 rpm speed. Samples were taken at 1, 3, 5, 7 & 10hours and diluted to suitable concentration and analyzed for Metformin hcl content at 233.0 nm by using UV–visible spectrophotometer.

Dissolution in Multimedia:
The optimized batch then evaluated for multimedia dissolution study. The 4.5 Phosphate buffer and 0.1N Hcl are used as dissolution medium. Then the drug release is compared with Innovator drug release respectively. The values for 4.5 Phosphate buffer and 0.1N Hcl are shown in Table 6 and 7 and plots for the same are shown in Figure 3 and 4 respectively.

6. Drug release kinetics:
Dissolution data of above two methods was fitted in Zero order, First order and Higuchi equations. The mechanism of drug release was determined by using Higuchi equation.

Zero-Order Kinetics:
Zero order as cumulative amount of drug released vs time,

$$\mathbf{C = K_0 t}$$

Where K_0 is the zero-order rate constant expressed in units of concentration/time and t is the time in hours. A graph of concentration vs time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.

First order kinetics:
First order as log cumulative percentage of drug remaining vs time,

$$\mathbf{Log\ C = Log\ C_o - k\ t / 2.303}$$

Where C_0 is the initial concentration of drug, k is the first order constant, and t is the time.

Higuchi Model:
Higuchi's model as cumulative percentage of drug released vs square root of time

$$\mathbf{Q = K\ t^{1/2}}$$

Where K is the constant reflecting the design variables of the system and t is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.

Korsmayer Peppas equations:
To evaluate the mechanism of drug release from Disulfiram implant, data for the first 60% of drug release were plotted in Korsmeyer et al's equation log cumulative percentage of drug released vs log time, and the exponent n was calculated through the slope of the straight line.

$$\mathbf{M\ t / M \infty = K\ t\ n}$$

where M_t/M_∞ is the fractional solute release, t is the release time, K is a kinetic constant characteristic of the drug/polymer system, and n is an exponent that characterizes the mechanism of release of tracers. For cylindrical matrix tablets, if the exponent $n = 0.45$, then the drug release mechanism is Fickian diffusion, and if $0.45 < n < 0.89$, then it is non-Fickian or anomalous diffusion. An exponent value of 0.89 is indicative of Case-II Transport or typical zero-order release.

7. Stability studies:
Selected Formulation was subjected to stability studies as per ICH guidelines.
Following conditions were used for Stability Testing.
25^0C/60% RH analyzed every month for period of three months.
30^0C/75% RH analyzed every month for period of three months.
40^0C/75% RH analyzed every month for period of three months.
The results are shown in table 11.
The optimized formulation F10 and Innovator sample are also kept for stability at room temperature for 2 months. Then comparative dissolution study of Optimized formulation F10 with Innovator sample of 1 month and 2 month is taken. The results ff dissolutions with Innovator are shown in table 11 and plots for the same are shown in Figure . 8

In vitro drug release study Paddle method
Dissolution Data of Matrix tablets formulations of Metformin HCL by Paddle method (USP II) are reported in Table.7.

Table 7: Cumulative % drug released of formulations of Metformin HCl tablets.

Sr.No	TIME (hrs)	Innovator	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
	1	28.3	37.9	35.0	27.7	24.6	37.2	32.1	35.3	33.7	25.2	29.6
	3	51.2	60.6	58.9	48.7	50.3	64.6	55.1	49.1	53.0	44.2	53.1
	5	68.0	72.6	73.5	62.9	62.6	77.4	68.5	62.2	66.0	62.1	71.3
	7	79.0	78.0	82.2	74.3	74.1	87.1	78.1	72.0	76.1	72.6	81.3
	10	88.0	91.4	90.8	83.4	82.2	100.4	88.6	81.0	85.6	81.9	89.4

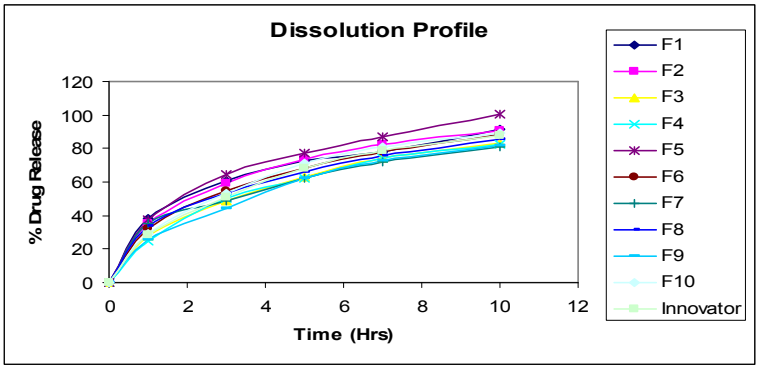

Figure 1: Dissolution profile of formulations F1 to F10 with Innovator.

Dissolution Study in Multimedia solution of Optimum batch F10:
4.5 Phosphate Buffer

Table 8: Comparison of cumulative % drug released from Metformin HCl Matrix tablets in 4.5 Phosphate Buffer with Innovator

Sr.No	TIME	F-10	Innovator
	1 hr	29.2	28.5
	3 he	53.7	54.7
	5 hr	70.2	73.6
	7 hr	82.1	85.3
	10 hr	89.8	94.1

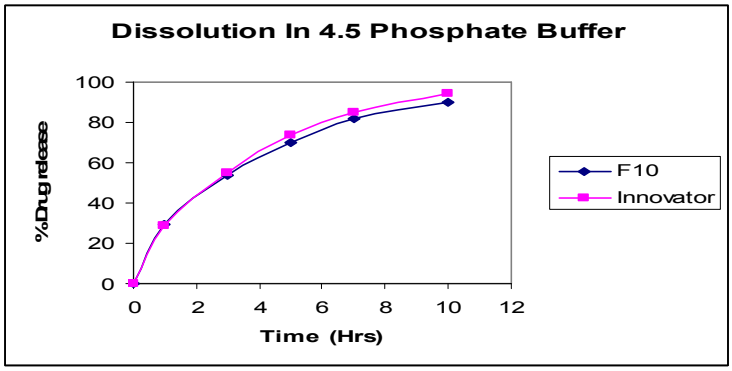

Figure 2: Dissolution profile of optimized formulations F10 compared with Innovator in 4.5 Phosphate Buffer.

Dissolution Study in Multimedia solution of Optimum batch F10 0.1(N) Hcl

Table 9: Comparison of cumulative % drug released from Metformin HCl Matrix tablets in 0.1 N HCL with Innovator

Sr.No	TIME	F-10	Innovator
	1 hr	30.2	33.6
	3 he	57.2	57.0
	5 hr	75.1	72.8
	7 hr	87.7	85.2
	10 hr	95.4	91.0

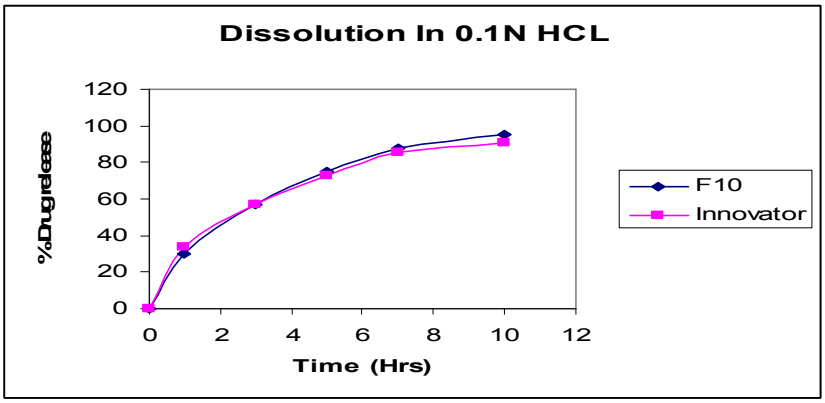

Figure 3: Dissolution profile of optimized formulations F10 compared with Innovator in 0.1 N HCL.

Kinetic Models:

Table 10 : Zero order kinetic treatment of the formulations.

Formulation code	Equation of line	Determination of coefficient (R^2)
Innovator	y = 14.72x + 18.74	R2 = 0.9633
F1	y = 12.44x + 30.78	R2 = 0.9497
F2	y = 13.49x + 27.61	R2 = 0.9461
F3	y = 13.7x + 18.3	R2 = 0.9727
F4	y = 13.9x + 17.06	R2 = 0.9481
F5	y = 14.89x + 28.67	R2 = 0.9554
F6	y = 13.6x + 23.68	R2 = 0.9634
F7	y = 11.43x + 25.63	R2 = 0.9907
F8	y = 12.69x + 24.81	R2 = 0.9761
F9	y = 14.18x + 14.66	R2 = 0.9741
F10	y = 14.78x + 20.6	R2 = 0.9516

Figure 4: Zero order kinetic treatment plot for dissolution of F1 to F10 with Innovator.

Table 11 : Higuchi's treatment of formulations

Formulation code	Equation of line	Determination of coefficient (R^2)
Innovator	y = 28.292x + 1.9239	R2 = 0.9875
F1	y = 24.053x + 16.26	R2 = 0.9853
F2	y = 26.071x + 11.892	R2 = 0.9805
F3	y = 26.274x + 2.7726	R2 = 0.9928
F4	y = 26.841x + 0.9106	R2 = 0.981
F5	y = 28.749x + 11.379	R2 = 0.9884
F6	y = 26.189x + 8.0374	R2 = 0.9913
F7	y = 21.752x + 13.04	R2 = 0.9956
F8	y = 24.328x + 10.448	R2 = 0.9955
F9	y = 27.133x - 1.2785	R2 = 0.9897
F10	y = 28.472x + 3.5763	R2 = 0.980

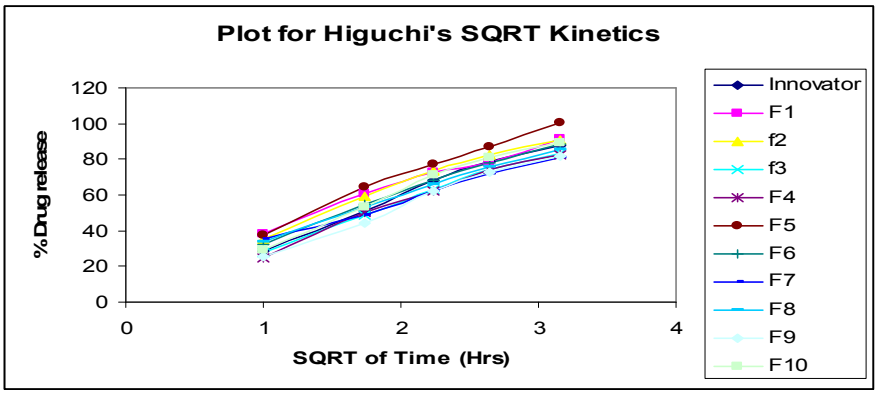

Figure 5: Higuchi's square root kinetic treatment plot for dissolution of F1 to F10 with Innovator.

Stability Study[6]

There was no significant change in physical and chemical properties of the tablets of formulation F10 after 3 Months. Parameters quantified at various time intervals were shown in Table 11.

Table 12: Results of stability studies of optimized formulation F10

Formulation code	Parameters	Initial	1 Month	2 Month	3 Month	Limits as per Specifications
F10	**25^{0}C/60% RH % Release**	89.4	85.2	89.9	89.2	Not less than 85 %
F10	**30^{0}C/75% RH % Release**	89.4	89.2	88.9	89.1	Not less than 85 %
F10	**40^{0}C/75% RH % Release**	89.4	88.6	87.1	87.9	Not less than 85 %
F10	**25^{0}C/60% RH Assay Value**	99.45	99.2	08.49	98.7	Not less than 90 % Not more than 110 %
F10	**30^{0}C/75% RH Assay Value**	99.45	99.51	99.12	98.91	Not less than 90 % Not more than 110 %
F10	**40^{0}C/75% RH Assay Value**	99.45	99.5	99.78	97.78	Not less than 90 % Not more than 110 %

Table 13: Stability dissolution profile of F10 for 1 month & 2 month with Innovator

Sr.No	Innovator	TIME	F-10 1M	F-10 2M
	28.3	1 hr	27.4	27.0
	51.2	3 he	52.1	54.1
	68.0	5 hr	67.6	70.9
	79.0	7 hr	76.6	82.3
	88.0	10 hr	85.2	89.9

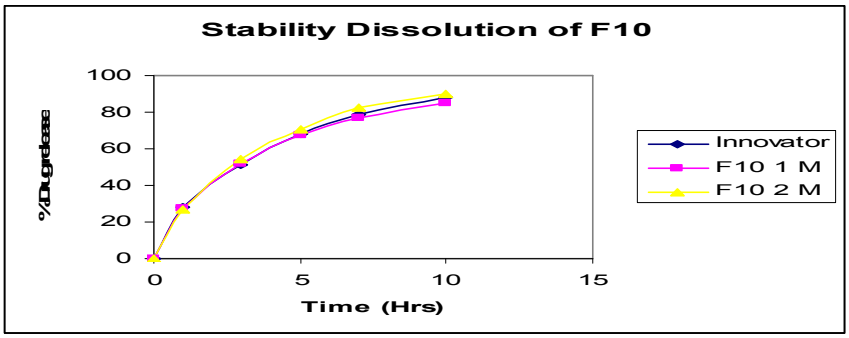

Figure 6: Dissolution profile of optimized formulations F10 compared with Innovator of stability 1 month & 2 month.

SUMMARY AND CONCLUSION

Metformin Hcl is antihyperglycemic agent, metformin is absorbed mainly from the small intestine. Extended release tablets of Metformin Hcl were prepared using HPMC K 100 CR and Carbopol 71 G as retardant polymers. Various evaluation parameters like thickness, hardness, friability weight variation and drug content of the formulations were found to be satisfactory. among all formulations prepared and evaluated F6 F8 and F10 appeared to have desired release pattern than others. But the formulation F10 nearly matches release pattern with that of Innovator release at each hour release. Formulations F1, F2 and F5 showed sudden drug release which might be due to low level of the polymer in the tablets.The Polymers HPMC K 100 CR and Carbopol 71 G and partical size were important factor affecting drug release profile. The viscosity of the polymer was found to affect the drug release and inverse relationship appeared to exit between polymer viscosity and drug release thus, higher the viscosity of the polymer, lower the drug release. The polymer used Carbopol 71 G is granular in nature and hence improves the flow properties of the blend. Also it is concluded that it improves the drug release at 10^{th} hour.The kinetic treatment of the drug release data of the prepared formulations followed zero order drug release the prepared formulations followed Higuchi profile. It indicated that drug release was diffusion controlled and directly proportional to square root of time. On compairing equation of line and regression coefficient (R^2) with Innovator, the formulation F10 shows similarity of results with innovator, hence F10 was considered as formulation extending 89.4% of drug was released at the end of 10 hrs. The stability studies were carried out for period of 3 months as per ICH guidelines, there is no significant change in dissolution profile and other parameters of the optimized formulation F10 were in acceptable limits.

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