Available online at www.icjpir.com ISSN: 2349-5448

INTERCONTINENTAL JOURNAL OF PHARMACEUTICAL INVESTIGATIONS AND RESEARCH

ICJPIR |Volume 3 | Issue 2 | April - June- 2016

Research Article

Development and evaluation of a novel twice daily cup core metformin hydrochloride tablet formulation

Sravanthi Todasam and Nagarajan Srinivasan

Srisarada College of pharmacy. (Jntuh)Anantharam, Bhongir, Nalgonda, Telangana, India.

Corresponding Author: Sravanthi Todasam

ABSTRACT

The study was undertaken with an aim to formulate develop and evaluation of a novel twice daily core cup of Metformin hydrochloride(Antidiabetic drug) tablets using different grades and weight of HPMC polymers as release retarding agent. Granules were evaluated for tests Bulk density, tapped density, Hausner ratio before being punched as tablets. Tablets were tested for weight variation, thickness, hardness and friability as per official procedure. F-2 was found to be 73.90. From the above results and discussion it is concluded that formulation of Cup core tablet of containing Metformin hydrochloride HPMC K 4M & 215: 230 (in mg) can be taken as an ideal or optimized formulation of sustained release tablets for 12hour release as it fulfills all the requirements for sustained release tablet and our study encourages for the further clinical trials on this formulation. The core in cup tablets of Metformin hydrochloride were prepared by wet granulation method, they were evaluated for weight variation, friability, hardness, and thickness for all batches (F1 – F9). No significant difference was observed in the weight of individual tablets from the average weight. The weight variation tests were performed according to the procedure given in the pharmacopoeia. In a weight variation test, pharmacopoeial limit of tablet for percentage deviation is 5%. The average percentage deviation of all tablet formulation was found to be within the pharmacopoeial limit and hence all formulation passed the test for uniformity of weight.

Keywords: Metformin, HPMC, Diabetes.

INTRODUCTION

Diabetes, often referred to by doctors as diabetes mellitus, describes a group of metabolic diseases in which the person has high blood glucose (blood sugar), either because insulin production is inadequate, or because the body's cells do not respond properly to insulin, or both.[1, 2]

The present study was undertaken with an aim to formulate develop and evaluation of Metformin hydrochloride. Sustained release oral tablets using different grades of polymer (HPMC) as release retarding agent.[3, 4, 5]

Oral drug delivery is the most preferred and convenient option as the oral route provides maximum active surface area among all drug

delivery system for administration of various drugs.[6,7] The attractiveness of these dosage forms is due to awareness to toxicity and ineffectiveness of drugs when administered by oral conventional method in the form of tablets and capsules. Usually conventional dosage form produces wide range of fluctuation in drug concentration in the bloodstream and tissues with consequent undesirable toxicity and poor efficiency.[8] The maintenance of concentration of drug in plasma within therapeutic index is very critical for effective treatment.[9] These factors as well as factors such as repetitive dosing and unpredictable absorption lead to the concept of oral Sustained release drug delivery systems.[10, 11]

METHODOLOGY

Methods of preparation of cup core tablets

TABLE NO: 1 MATERIAL USED IN FORMULATION

S.NO	MATERIALS USED	GRADE	COMPANY
1	Metformin hydrochloride		Essel fine chem, Mumbai
2	Hydroxy propyl methyl cellulose(Hpmc k4M)	LR	Essel fine chem, Mumbai
3	Hydroxy propyl methyl cellulose (Hpmc k15M)	LR	Essel fine chem, Mumbai
4	Hydroxy propyl methyl cellulose(Hpmc k100M)	LR	Essel fine chem, Mumbai
5	Microcrystalline cellulose		Essel fine chem, Mumbai
6	Magnesium Stearate	LR	S.D.Fine chemicals,mumbai
7	Talcum powder		S.D.Fine chemicals,mumbai

PREPARATION OF METFORMIN HYDROCHLORIDE CUP CORE TABLET FORMULATION

Preparation of core tablet formulation

The core tablets of Metformin hydrochloride were prepared by wet granulation technique. Metformin hydrochloride, SSG, Microcrystalline cellulose, Talc, Magnesium Stearate, were mixed with each other according to the geometric method same for all the formulations (**TABLE NO 1)** And granules are prepared by adding 5%Starch paste. The granules were dried in a Hot air oven (**B.T.I. Instruments**)

For sufficient time. The dried granules were passed through sieve no. 22 to form granules of uniform size. Rapid release core tablets composed of the active ingredient were prepared by compressing the granules using 5 mm flat faced punch and die cavity on a punching machine (**IP machineries' Pvt. Ltd, Ahmadabad).**

Table No: 2 Composition of core tablet :(70 mg)

S.NO	MATERIALS USED	CONCENTRATION
1.	Metformin hydrochloride	6.75mg
2.	SSG	4%(2.8mg)
3.	MCC	Q.S(59.05mg)
4.	Talc	1%(0.7mg)
5.	Mg Stearate	1%(0.7mg)
6.	5% Starch paste	

Preparation of cup granules

The core tablets were compression coated with different weight ratios (w/w) of HPMCK4M, HPMCK15M, HPMC K100 M mixtures. Weighed quantities of Metformin hydrochloride, SSG, Microcrystalline cellulose, Talc, Magnesium Stearate, were mixed with each other according to the geometric method. For each formulation **(TABLE NO: 2**) and granules are prepared by adding 5%Starch paste. The granules were dried in a Hot air oven (**B.T.I. Instruments**) for sufficient time. The dried granules were passed through sieve no. 22 to form granules of uniform size.

Compression of Cup core Tablets

Rapid release core tablets composed of the active ingredient were manually placed in the centre of 9mm die cavity on a punching machine (**IP machineries' pvt.ltd, Ahmadabad),** before the addition of the cup material and the machine was run until the lower punch moved down slightly. Weighed quantity of the blend for the cup was manually poured into the die cavity using a spatula, and finally compressed.

TABLE NO: 3 COMPOSITION OF CUP USED IN FORMULATION

S.No	Material Name	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Metformin Hcl	215mg	215mg	215mg	215mg	215mg	215mg	215mg	215mg	215mg
2	Hpmc k4m	170mg	200	230	---	---	---	---	---	---
3	Hpmc k15m	----	----	----	170	200	230	----	----	----
4	Hpmc k100m	----	----	-----	---	----	----	170	200	230
5	Mg St	1%	1%	1%	1%	1%	1%	1%	1%	1%
6	Talc	1%	1%	1%	1%	1%	1%	1%	1%	1%
7	Mcc	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
8	Pvp k30	5%	5%	5%	5%	5%	5%	5%	5%	5%

EVALUATION OF METFORMIN HYDROCHLORIDE CUP CORE TABLETS

Thickness

The thickness of the tablets was determined using vernier calipers. Five tablets were used from each batch. Thickness of the core tablets was noted prior to compression of the cup. Finally the thickness of core-in-cup tablets was determined.

Hardness

The hardness of the tablets was determined by Monsanto hardness tester. Five core tablets were taken and hardness was tested before compression of the cup and finally five core-in-cup tablets were taken and hardness was tested.

WeightVariationTest

Twenty core and coated tablets with coat were selected at random and individually weighed in a single pan electronic balance (Labinda analytical instruments pvt ltd, Mumbai) and the average weight was calculated. The uniformity of weight was determined according to official compendia. The weight variation of the tablets was determined and reported. The individual weight variation of twenty tablets was calculated. All the batches of tablets complied with the weight variation limits as per Indian Pharmacopoeia i.e., The percentage weight variation of the individual tablets remained within 5% and not more than 2 tablets in a batch of 20 deviated from ±5% weight variation. All the formulations passed the test for weight variation.

FriabilityTest

This was measured using a friability apparatus where the tablets were subjected to the combined effect of abrasion and shock by utilizing a plastic chamber of Roche friabilator (Labinda analytical instruments pvt ltd, Mumbai) that revolves at 25 rpm dropping the tablets from a distance of 6

inches with each revolution. Preweighed samples of 20 tablets were placed in the friabilator, which is then operated for 100 revolutions. The friability test of all batches of tablets was done.

In-vitro Dissolution Studies

Release rate of all designed formulations were studied up to 12 h. The in-vitro dissolution studies of the tablets were carried out by using USP-dissolution apparatus type-II, paddle method (Labinda analytical instruments pvt ltd, Mumbai.) using 900 ml of phosphate buffer pH 6.8 as medium maintained at 37 ± 5° C at 100 rpm for 12 hour. Samples of 5 ml volume were withdrawn at specified time points (30min, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 h) predetermined time intervals, with the replacement of fresh dissolution medium for 12 h. The samples were passed through cotton and diluted to a suitable concentration with phosphate buffer. The absorbance of these solutions was measured at 234 nm using a UV/Vis double-beam spectrophotometer. (Labinda analytical instruments pvt ltd Mumbai). An equal volume of fresh medium was immediately replaced to maintain the dissolution volume constant. The amount of Metformin hydrochloride release at each time interval was calculated from the absorbance of the samples.

RESULTS

The core in cup tablets of Metformin hydrochloride were prepared by wet granulation method, they were evaluated for weight variation, friability, hardness, and thickness for all batches (F1 – F9). No significant difference was observed in the weight of individual tablets from the average weight. The weight variation tests were performed according to the procedure given in the pharmacopoeia. In a weight variation test, pharmacopoeial limit of tablet for percentage deviation is 5%. The average percentage deviation of all tablet formulation was found to be within the pharmacopoeial limit and hence all formulation passed the test for uniformity of weight.

All the formulation showed % friability less than 1% that indicates ability of tablets to withstand shocks, which may encounter. The friability of all formulation was below the 1% limit shown in the pharmacopoeia indicating that the friability is within the standard limit.

The hardness of tablets of all batches is in acceptable limits, as shows in the literature. The thickness of tablet was carried out for all batches were found consistent.

TABLE NO: 4 PREFORMULATION RESULTS

Formulation code	Angle of repose (2)	Bulk density(gm/cc)	Tapped density(gm/cc)	Carr s index (%)	Hausners ratio
F1	27.36± 0.61	0.445 0.005	0.529± 0.03	16.00 0.03	1.17 ±0.23
F2	27.12± 0.35	0.448 ±0.002	0.539± 0.02	15.60± 0.18	1.18± 0.004
F3	26.72± 0.19	0.490 ±0.006	0.575± 0.002	14.80± 0.02	1.18± 0.002
F4	27.91± 0.15	0.470 ±0.004	0.550± 0.01	14.60±0.13	1.17 ±0.02
F5	25.9± 0.20	0.496± 0.003	0.601± 0.002	17.60± 0.11	1.16 ±0.01
F6	25.38± 0.34	0.456± 0.007	0.539± 0.002	15.40± 0.04	1.18 ±0.02
F7	25.38± 0.34	0.462± 0.003	0.537± 0.003	14.00 ±0.07	1.16± 0.02
F8	27.54± 0.37	0.442 ±0.006	0.527± 0.02	16.20 ±0.06	1.18± 0.04

Table: 5 Evaluation parameters

Formulation	Average Weight variation(mg)	Average Hardness(Kg/inch²)	Average Thickness(mm)	Average %of friability
F1	568±1.98	4.2±0.2	4.5±0.002	0.32±0.27
F2	565±1.67	4.2±0.1	4.4±0.003	0.23±0.12
F3	569±3.05	4.3±0.4	4.3±0.003	0.34±0.23
F4	566±3.02	4.2±0.5	4.5±0.004	0.23±0.15

F5	568±3.56	4.3±0.3	4.2±0.004	0.21±0.25
F6	569±1.45	4.5±0.2	4.3±0.001	0.25±0.15
F7	565±2.78	4.1±0.4	4.3±0.004	0.26±0.19
F8	567±3.98	4.1±0.4	4.3±0.001	0.32±0.24
F9	568±2.65	4.2±0.2	4.2±0.002	0.34±0.26

Invitro dissolution studies of the formulations

TABLE NO: 6 (FORMULATION 1)-Drug: Hpmck4M, 215:170.

S.NO	TIME	ABS	D.F	CONC	AMT	%OF D.R
1	30min	0.187	50	78.30821	70.47739	33.78018
2	1hr	0.278	50	116.4154	104.7739	48.73203
3	2hr	0.389	50	162.8978	146.608	68.18979
4	3hr	0.589	50	246.6499	221.9849	103.2488
5	4hr	0.59	50	247.0687	222.3618	103.4241

TABLE NO: 7 (FORMULTION 2) -Drug: Hpmck4M, 215:200.

S.NO	TIME	ABS	D.F	CONC	AMT	%OF D.R
1	30min	o.336	20	56.28141	50.65237	23.55966
2	1hr	0.448	20	75.04188	67.53769	31.41288
3	2hr	0.551	20	92.29481	83.06533	38.63504
4	3hr	0.785	20	131.4908	118.3417	55.04266
5	4hr	0.985	20	164.9916	148.4942	69.06626
6	5hr	0.498	50	208.5427	187.6884	87.29695
7	6hr	0.523	50	219.0117	197.1106	91.67933
8	7hr	0.612	50	256.2814	230.6533	107.2806

TABLE NO: 8 (FORMULATION 3) -Drug: Hpmck4M, 215:230.

S.NO	TIME	ABS	D.F	CONC	AMT	% OF D.R
1	30min	0.148	20	24.79062	22.31156	10.37747
2	1hr	0.202	20	33.83585	30.45226	14.16384
3	2hr	0.298	20	49.91625	44.92462	20.89517
4	3hr	0.385	20	64.48911	58.0402	26.99544
5	4hr	0.432	20	72.36181	65.12563	30.29099
6	5hr	0.521	20	87.26968	78.54271	36.53149
7	6hr	0.733	20	122.7806	110.5025	51.39652
8	7hr	0.845	20	141.541	127.3869	59.24974
9	8hr	0.989	20	165.6616	149.0955	69.34673
10	9hr	0.426	50	178.392	160.5528	74.6757
11	10hr	0.489	50	204.7739	184.2965	85.71929
12	11hr	0.565	50	236.5997	212.9397	99.04172
13	12hr	0.569	50	238.2747	214.4472	99.7429

TABLE NO: 9 (FORMULATION 4) -Drug: Hpmck15M, 215:170.

S.NO	TIME	ABS	D.F	CONC	AMT	%OF D.R
1	30min	0.135	20	22.61307	20.35176	*9.465934*
2	1hr	0.169	20	28.30821	25.47739	*11.84995*
3	2hr	0.215	20	36.0134	32.41206	*15.07538*
4	3hr	0.299	20	50.08375	45.07538	20.96529

5	4hr	0.345	20	57.78894	52.01005	24.19072
6	5hr	0.401	20	67.16918	60.45226	28.11733
7	6hr	0.469	20	78.55946	70.70352	32.88536
8	7hr	0.51	20	85.42714	76.88442	35.7602
9	8hr	0.538	20	90.11725	81.10553	37.7235
10	9hr	0.598	20	100.1675	90.15075	*41.93058*
11	10hr	0.645	20	108.0402	97.23618	*45.93*
12	11hr	0.789	20	132.1608	118.9447	*55.32*
13	12hr	0.874	20	146.3987	131.7588	*61.28*

TABLE NO: 10 (FORMULATION 5) -Drug: Hpmck15M, 215:200.

S.NO	TIME	D.F	ABS	CONC	AMT	% OF D.R
1	30min	20	0.104	17.42044	15.67839	7.292275
2	1hr	20	0.125	20.93802	18.84422	8.764754
3	2hr	20	0.168	28.1407	25.32663	11.77983
4	3hr	20	0.199	33.33333	30	13.95349
5	4hr	20	0.22	36.85092	33.16583	15.42597
6	5hr	20	0.261	43.71859	39.34673	18.30081
7	6hr	20	0.286	47.9062	43.11558	20.05376
8	7hr	20	0.358	59.9665	53.96985	25.10226
9	8hr	20	0.42	70.35176	63.31658	29.44957
10	9hr	20	0.478	80.067	72.0603	33.51642
11	10hr	20	0.532	89.11223	80.20101	37.30279
12	11hr	20	0.548	91.79229	82.61307	38.42468
13	12hr	20	0.602	100.8375	90.75377	42.21106

TABLE NO: 11 (FORMULATION 6) -Drug: Hpmck15M, 215:230.

S.NO	TIME	ABS	D.F	CONC	AMT	% OF D.R
1	30min	0.099	20	16.58291	14.92462	6.941685
2	1hr	0.115	20	19.26298	17.33668	8.063574
3	2hr	0.135	20	22.61307	20.35176	9.465934
4	3hr	0.169	20	28.30821	25.47739	11.84995
5	4hr	0.202	20	33.83585	30.45226	14.16384
6	5hr	0.245	20	41.03853	36.93467	17.17892
7	6hr	0.288	20	48.24121	43.41709	20.19399
8	7hr	0.32	20	53.60134	48.24121	22.43777
9	8hr	0.354	20	59.29648	53.36683	24.82178
10	9hr	0.403	20	67.50419	60.75377	28.25757
11	10hr	0.439	20	73.53434	66.1809	30.78182
12	11hr	0.489	20	81.90955	73.71859	34.28772
13	12hr	0.52	20	87.10218	78.39196	36.46138

TABLE NO: 12 (FORMULATION 7) -Drug: Hpmck100M, 215:170.

S.NO	TIME	ABS	D.F	CONC	AMT	%D.R
1	30min	0.128	20	21.44054	19.29648	8.975108
2	1hr	0.165	20	27.63819	24.87437	11.56948
3	2hr	0.186	20	31.15578	28.0402	13.04195
4	3hr	0.231	20	38.69347	34.82412	16.19727

5	4hr	0.259	20	43.38358	39.04523	18.16057
6	5hr	031	20	51.9263	46.73367	21.73659
7	6hr	0.385	20	64.48911	58.0402	26.99544
8	7hr	0.426	20	71.35678	64.22111	29.87028
9	8hr	0.478	20	80.067	72.0603	33.51642
10	9hr	0.51	20	85.42714	76.88442	35.7602
11	10hr	0.545	20	91.28978	82.1608	38.21433
12	11hr	0.601	20	100.67	90.60302	42.14094
13	12hr	0.687	20	115.0754	103.5678	48.17109

TABLE NO: 13 (FORMULATION 8) -Drug: Hpmck100M, 215:200.

S.NO	TIME	ABS	D.F	CONC	AMT	%D.R
1	30min	0.084	20	14.07035	12.66332	5.889915
2	1hr	0.103	20	17.25293	15.52764	7.222157
3	2hr	0.135	20	22.61307	20.35176	9.465934
4	3hr	0.184	20	30.82077	27.73869	12.90172
5	4hr	0.213	20	35.67839	32.11055	14.93514
6	5hr	0.245	20	41.03853	36.93467	17.17892
7	6hr	0.284	20	47.57119	42.81407	19.91352
8	7hr	0.305	20	51.08878	45.9799	21.386
9	8hr	0.336	20	56.28141	50.65327	23.55966
10	9hr	0.389	20	65.15913	58.64322	27.27591
11	10hr	0.42	20	70.35176	63.31658	29.44957
12	11hr	0.465	20	77.88945	70.1005	32.60488
13	12hr	0.52	20	87.10218	78.39196	36.46138

TABLE NO: 14 (FORMULATION 9) -Drug: Hpmck100M, 215:230.

S.N0	TIME	ABS	D.F	CONC	AMT	% D.R
1	30min	0.045	20	7.537688	6.78392	3.15
2	1hr	0.085	20	14.23786	12.81407	5.96
3	2hr	0.108	20	18.09045	16.28141	7.57
4	3hr	0.132	20	22.11055	19.8995	9.25
5	4hr	0.179	20	29.98325	26.98492	12.55
6	5hr	0.205	20	34.33836	30.90452	14.37
7	6hr	0.235	20	39.36348	35.42714	16.47
8	7hr	0.287	20	48.0737	43.26633	20.12
9	8hr	0.301	20	50.41876	45.37688	21.10
10	9hr	0.335	20	56.1139	50.50251	23.48
11	10	0.365	20	61.13903	55.02513	25.59
12	11	0.394	20	65.99665	59.39698	27.62
13	12	0.432	20	72.36181	65.12563	30.29

TABLE NO: 15 % of drug release in 12hours of all the 9 formulations.

S.No	Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	30min	33.78	23.55	10.37	9.46	7.29	6.94	8.97	]5.88	3.15
2	1hr	48.73	31.41	14.16	11.84	8.76	8.06	11.56	7.22	5.96
3	2hr	68.18	38.63	20.89	15.07	11.77	9.46	13.04	9.46	7.57

4	3hr	103,24	55.04	26.99	20.96	13.95	11.84	16.19	12.90	9.25
5	4hr	103.42	69.06	30.29	24.19	15.42	14.16	18.16	14.93	12.55
6	5hr		87.29	36.53	28.11	18.30	17.17	21.73	17.17	14.37
7	6hr		91.67	51.39	32.88	20.05	20.19	26.99	19.91	16.47
8	7hr		107.28	59.24	35.76	25.10	22.43	29.87	21.38	20.12
9	8hr			69.34	37.72	29.44	2.82	33.51	23.55	21.10
10	9hr			74.67	41.93	33.51	28.25	35.76	27.27	23.48
11	10hr			85.71	45.22	37.30	30.78	38.21	29.44	25.59
12	11hr			99.74	55.32	38.42	34.28	42.14	32.60	27.62
13	12hr			99.04	61.28	42.21	36.46	48.17	36.46	30.29

% of drug release Vs Time (hour) of all the 9 formulations.

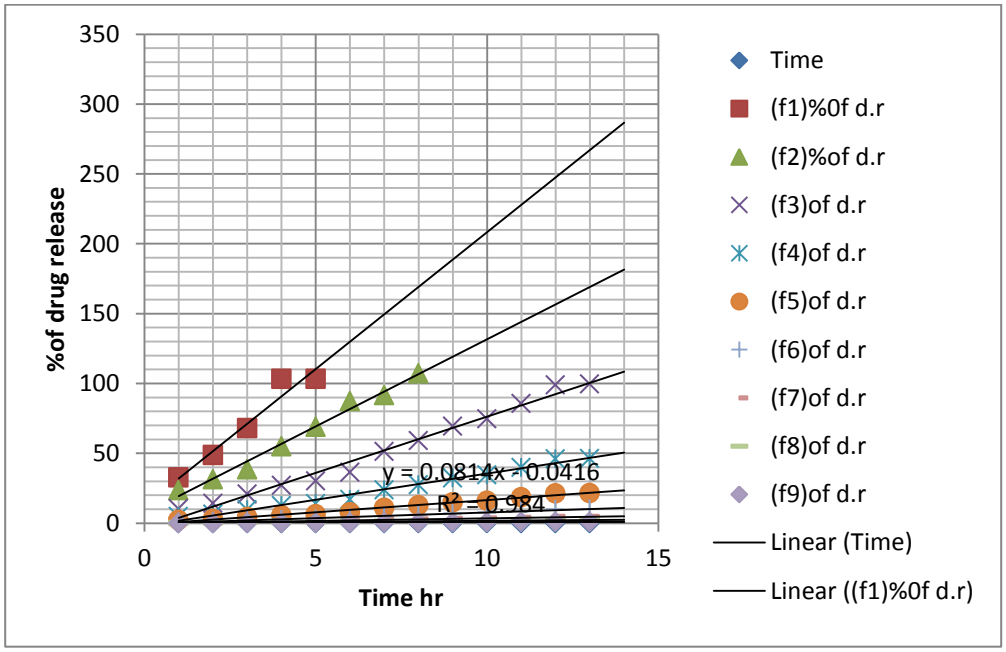

Figure 1

TABLE NO: 16 Optimized formulations (F3)

S.NO	TIME	ABS	D.F	CONCN	AMT	% OF D.R
1	30min	0.148	20	24.79062	22.31156	10.37747
2	1hr	0.202	20	33.83585	30.45226	14.16384
3	2hr	0.298	20	49.91625	44.92462	20.89517
4	3hr	0.385	20	64.48911	58.0402	26.99544
5	4hr	0.432	20	72.36181	65.12563	30.29099
6	5hr	0.521	20	87.26968	78.54271	36.53149
7	6hr	0.733	20	122.7806	110.5025	51.39652

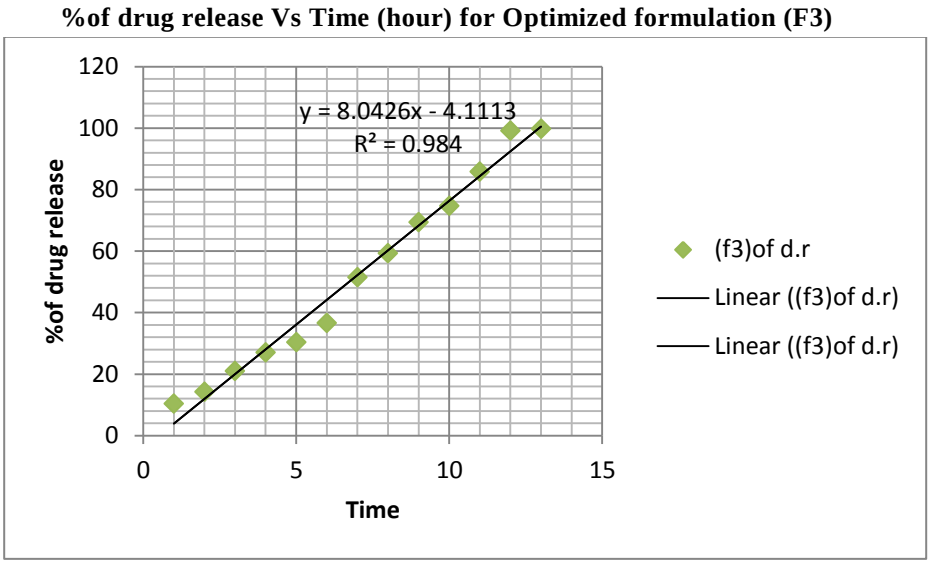

Figure: 2

DISCUSSION

Standard calibration curve of Metformin hydrochloride was prepared in phosphate buffer medium 6.8pH.Correlation coefficient values indicate the linear correlation between concentration and absorbance and following lamberts beers law. The release of Metformin hydrochloride from sustained release tablet of various formulations varied according to the ratio and degree of the polymer.

In case of tablets of F1 containing drug & HPMCK4M (quantity in mg). 215: 170. The release profile was showing the release 103.4241% in 4hours (TABLE NO: 6). In case of tablets of F2 containing drug and HPMC K4M (in mg). 215:200 it was showing 107.2806% release in 7 hours (TABLE NO: 7). In case of tablets of F3 containing drug polymer (HPMCK4M in mg) 215: 230: but it was showing 99.7429% up to 12 hour (TABLE NO: 8). In case of tablets F4 containing drug and HPMC K15M (in mg) 215:170 the release profile was showing drug release61.28316 % 0nly up to 12hours(TABLE NO: 9). In case of tablets of F5 containing drug and HPMC K15M (in mg) 215:200.But it also showing the drug release 42.2116% in12hours (TABLE NO: 10). In case of tablets of F6 containing drug and HPMC K 15M (in Mg) 215: 230. It was seen the release of drug shown 36.46138% in 12hours (TABLE NO: 11). In case of tablets F7, containing drug. HPMCK100M (in mg) 215:170 the release profile was showing drug release 48.1712% in 12hours (TABLE NO: 12). In case of Tablets F8 containing drug. HPMCK100M (in mg) 215: 200. The release profile was showing drug release 36.46138% in 12 hours (TABLE NO: 13). In case of tablets F9, containing drug. HPMCK100M (in mg) 215:230. The release profile was showing drug release 30.29099% in 12hours (TABLE NO: 16, with very slower release than all formulations).

SUMMARY AND CONCLUSION

The study was undertaken with an aim to formulate develop and evaluation of a novel twice daily core cup of Metformin hydrochloride(Antidiabetic drug) tablets using different grades and weight of Hpmc polymers as release retarding agent. Granules were evaluated for tests Bulk density, tapped density, Hausner ratio before being punched as tablets. Tablets were tested for weight variation, thickness, hardness and friability as per official procedure. F-2 was found to be 73.90. From the above results and discussion it is concluded that formulation of Cup core tablet of containing Metformin hydrochloride HPMC K 4M & 215: 230 (in mg) can be taken as an ideal or optimized formulation of sustained release tablets for 12hour release as it fulfills all the requirements for sustained release tablet and our study encourages for the further clinical trials on this formulation.

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