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RESEARCH PAPER

Formulation and Evaluation of Extended Release Tablets of Metformin HCl

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The present study was aimed to develop metformin hydrochloride extended release tablets for the treatment of non-insulin-dependent diabetes mellitus (NIDDM), particularly those with refractory obesity. Metformin HCl extended release tablets reduce the dosage frequency, enhance patient compliance and maintain the therapeutic effect of the drug throughout the day. A total of nine formulations were developed using varying proportions of hydroxy propyl methyl cellulose K100M as release retardant polymers and PVP K 90 as binder by wet granulation method. FT-IR studies revealed that there was no interaction between drug and polymer. Before compression, the granules were evaluated for pre compression parameters. After compression, evaluation tests of tablets such as general appearance, hardness, thickness, weight variation, friability, content uniformity, in vitro release studies and stability studies were performed. Out of nine formulations, the drug release was found to be within the limit as per USP in formulation F9. The stability study of formulation F9 revealed there was no significant change in physical and chemical properties of drug stored at 40±2°C/75±5% RH for three months.

Key Words : extended release tablets, pre compression parameters, hardness, weight variation, friability, stability studies , content uniformity

INTRODUCTION

Over the past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems. Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency[1-3]. This factors as well as factors such as repetitive dosing and unpredictable absorption lead to sustained or controlled drug delivery systems. The goal in Designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery[4-5].

Metformin is used in patients with type 2 diabetes (non-insulin dependent diabetes). Controlling high blood sugar helps prevent kidney damage, blindness, nerve problems, loss of limbs, and sexual function problems. Proper control of diabetes may also lessen the risk of a heart attack or stroke. The biological half life of metformin HCl is 1.5-4.5hrs. So conventional metformin HCl tablets should be administered 2-3 times a day to maintain the therapeutic effect of the drug throughout the day. Metformin HCl extended release tablets reduces the dosage frequency and enhance the patient compliance. A total of nine formulations were developed using varying

proportions of hydroxy propyl methyl cellulose K100M and PVP K 90 as release retardant polymers by wet granulation method[6-11].

Materials and Methods

Metformin hydrochloride was obtained from Smruthi Organics, Mumbai. Microcrystalline Cellulose was procured from Patel Industries, Ahmedabad. PVP K 90 was obtained from Nanhang Industries, Quzhou, Zhejiang, China. HPMC K100M was obtained from Coloron Asia Pvt Ltd., Mumbai. Magnesium Stearate was procured from Donglian Aromatic Chemicals Development Co. Ltd. (China). Isopropyl Alcohol was obtained from Exxon Mobile Chemical Company (USA) and Colloidal Silicon Dioxide was procured from Signet Chemical, Mumbai.

Precompression Parameters

General appearance:

Drug was observed for its color, odor and taste and obtained results are described in table

Identification of drug:

Identification of metformin HCl was carried out by Infra Red Absorption Spectrophotometer.

Selection of solvent:

The phosphate buffer pH 6.8 was selected as dissolution media because it represents the pH of gastrointestinal fluid and it is recommended for metformin HCl tablets by USFDA.

Solubility studies:

The solubility of drug in various solvent was determined by using shake flask method. Excess amount of drug that can be dissolved was added to 250 mL conical flask containing 100 mL of dissolution media. The shaking process was carried for 24 hrs by keeping the conical flask on rotary shaker at 200 rpm. A portion of drug dissolved in distilled water, alcohol, acetone, methylene dichloride, chloroform and phosphate buffer pH 6.8 was filtered through membrane filter (0.45µm) and concentration of drug in the filtrate was determined at 233nm by UV Spectrophotometer.

Melting point:

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

Bulk density:

The bulk density of the ingredients was evaluated using a graduate cylinder.

Tapped density:

It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in gram/mL.

Compressibility and Hauser's ratio: Compressibility and Hauser's ratio were determined by using formula.

Angle of repose

This is the maximum angle possible between the surface of a pile of powder and the horizontal plane. Sufficient quantities of Metformin HCl granules were passed through a funnel from a particular height onto a flat surface until it formed a pile, which touched the tip of the funnel. The height and radius of the pile were measured. The angle of repose was calculated using the formula-

$$\tan \theta = h/r$$

$$\theta = \tan^{-1} (h/r)$$

UV Spectroscopy:

Determination of λmax:

Accurately weighed 100 mg of drug was dissolved in 100 mL of phosphate buffer pH 6.8 in 100 mL volumetric flask. This solution was labeled as Stock-1. From the Stock-1, 10 mL of solution was withdrawn and diluted up to 100 mL in 100 mL volumetric flask and labeled as Stock-2. From Stock-2, 1mL of solution was withdrawn and diluted up to 10 mL in 10mL volumetric flask. The spectrum of this solution was run in 200-400 nm range in UV spectrometer. The spectrum peak point in graph of absorbance of metformin HCl versus wavelength was shown in figure and it shows the absorbance maxima 232nm in phosphate buffer pH 6.8.

Standard calibration curve:

The main Stock solution was prepared by dissolving 100 mg of drug in 100 mL of phosphate buffer pH 6.8 in 100 mL volumetric flasks. This solution was labeled as Stock -1. From the Stock -1, 10 mL of solution was withdrawn and diluted up to 100 mL in 100 mL volumetric flask. This solution was labeled as Stock-2. From the Stock-2; 1mL, 2mL, 3mL up to 10 mL of solutions were withdrawn and diluted up to 100mL in 100mL volumetric flask with same media. The absorbance of each solution was measured at 232 nm using phosphate buffer pH 6.8 as a blank in UV spectrometer. The absorbance versus concentration curve was plotted.

Manufacturing Procedure

Different metformin HCl formulations were prepared by Wet granulations technique (F-1 to F-9). Firstly metformin HCl pure drug was weighed accurately and shifted through 40# mesh. Then PVP K-30 was dissolved completely in sufficient quantity of water and IPA.

Wet granulation was done in Rapid Mixing Granulator (RMG). In the rapid mixing granulator, metformin HCl pure drug, the PVP K-30 solution was added with slow speed of rapid mixing granulator. Then 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 dried in air dryer without giving temperature for 20 min. Then these semidried granules subjected for final drying in FBD at inlet temperature of 40°C and again after air dried without heating, granules were further dried by same process to obtained dried granules. Then these granules passed through 16 # mesh. In polymerisation step the polymers HPMC K 100CR was 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 metformin HCl was mixed with polymer for 5 min. Then lubricating agent magnesium stearate was mixed in to first mixture for 2 min. Finally these granules are ready for compression. Then these granules are compressed by using punch size of length 19.2mm and 9.05(D-tooling) maintaining humidity below 50%RH. Different metformin HCl formulations were prepared by wet granulations technique (F-1 to F-9).

Table1: Different Formulations of Metformin HCl

S.No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Metformin HCl	500	500	500	500	500	500	500	500	500
2.	HPMC K100M	175	175	195	210	220	200	250	245	225
3.	MCC	185	180	157	145	135	155	105	110	130
4.	PVP K 90	20	30	30	27	27	27	27	27	27
5.	IPA:Water(1:1)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
6.	Magnesium Stearate	10	8	9	9	9	9	9	9	9
7.	Aerosil	10	7	9	9	9	9	9	9	9

Evaluation of Tablets:

Appearance:

The general appearance and elegance of tablet was identified visually, which include tablet size, shape, presence or absence of an odor, surface texture etc.

Weight variation:

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance, average weights was calculated, individual tablet weights were compared with the average weight and the maximum percent difference allowed is 5%.

Thickness:

The results of thickness for formulated tablets were determined using calibrated Vernier callipers and results are shown in Table. Tablet thickness was almost uniform in all the tablets and values were controlled within a ± 0.5% variation of standard value.

Hardness:

The hardness of the tablets was determined using hardness tester. It was expressed in kg/cm^2. Ten tablets were selected and hardness of the tablets was measured.

Friability:

Friability was determined by Roché friabilator. The friabilator was operated at 25 rpm for four minutes (100 revolutions) then remove any loose dust from them and weigh them accurately. A maximum loss of weight not greater than 1.0 percent is acceptable for most tablets (Table). The percent friability was calculated using equation

$$\%F = 1 - \frac{W_0}{W} \times 100$$

Where, %F = friability in percentage

W = Initial weight of tablet

W_0 = weight of tablets after revolution

Assay:

Twenty tablets were weighed and powdered. A quantity of powder containing about 0.1gm of metformin hydrochloride was weighed. The weighed quantity was shaken with 70mL of water for 15min. This was diluted to 100mL with water and filtered. 10mL of the solution was diluted to 100mL and 10 mL of the solution was diluted to 100mL. The absorbance

of the resulting solution was observed at 232nm.

Dissolution studies:

In vitro dissolution study was carried out for different formulation of metformin HCl in phosphate buffer pH 6.8 and analyzed at 232 nm by UV spectrophotometer and plotted graph as shown in Figure 6.6 and 6.7.

Drug release studies were conducted using USP-22 dissolution apparatus-2, paddle type at a rotational speed of 50 rpm at 37±0.5 ºC. The dissolution media used were 900 mL of pH 6.8 phosphate buffer solutions for 12h. Sink condition was maintained for the whole experiment. Samples (10 mL) were withdrawn at regular intervals and the same volume of pre warmed (37±0.5 ºC) fresh dissolution medium was replaced to maintain the volume constant. The samples withdrawn were filtered through a 0.45 µ membrane filter and the drug content in each sample was analyzed after suitable dilution with a UV spectrophotometer (Shimadzu UV-1700) at 233 nm. The dissolution test was performed in triplicate. Drug dissolved at specified time periods was plotted as cumulative percent release versus time (h) curve.

Stability studies:

The best formulation of Metformin hydrochloride extended release tablets was subjected to stability studies by storing at 40C±2°C /75±5% RH for 3 months. At every month interval, the tablets were visually examined for any physical change and evaluated for the drug content and in vitro drug release.

Results

Preformulation Parameters:

- **Solubility:**

Solubility of drug determined in different media is obtained and given in Table 2:

Table2: Solubility determination of metformin HCl

Sr. No.	Solvent	Solubility (gm/mL)	Solubility profile
1	Distilled Water	0.2	Freely soluble
2	pH 6.8	0.15	Freely soluble
3	Ethanol	0.01	Slightly soluble

- **Melting point determination:**

Melting point of metformin HCl was performed by open capillary method and the melting point was found to be 222-224ºCand given in above Table 3

Table3: Melting point determination

Reported Melting Point	Observed Melting Point
222-226° C	222-224° C

- **Identification of Pure Drug:**

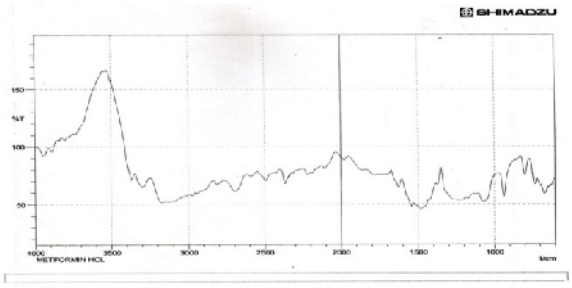

Fig.1: FTIR spectrum of pure drug

Table 4: Identification of drug was carried out by FTIR.

Peak (cm^{-1})	Functional group
2814.6	CH Stretching
1420.32	CN Stretching
1455.99	NH Deformation
937	CH Deformation
3374	NH Stretching
638.32	NH Deformation
3199	NH_2

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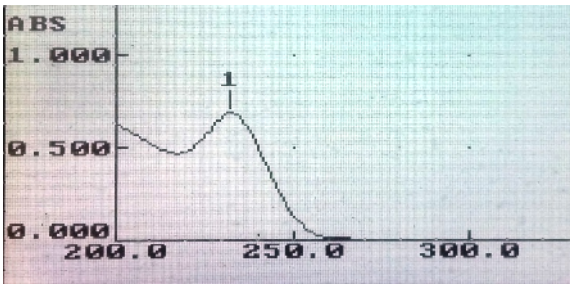


Fig.2: Spectrum of drug in phosphate buffer pH6.8

- **Standard curve of drug:**

Table 5: Standard curve of the drug in phosphate buffer ph 6.8

S.No.	Concentration	Absorbance
1	2	0.268
2	4	0.504
3	6	0.701
4	8	0.921
5	10	1.078

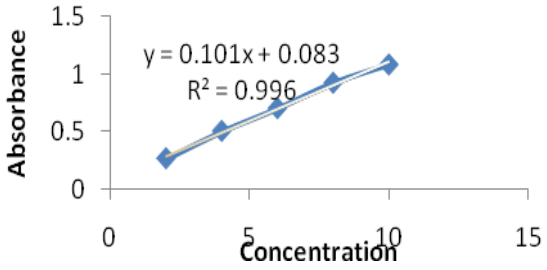


Fig.3: Calibration curve of metformin HCl in phosphate buffer pH 6.8

Result of Linearity test shows that the absorbance of the drug in phosphate buffer pH 6.8 at 232 nm is linear (R^2=0.996) with concentration range of 1 µg/ mL to 10 µg/mL.

- **Density and flow properties**

Table 6: Observation of density and flow properties for Metformin HCl

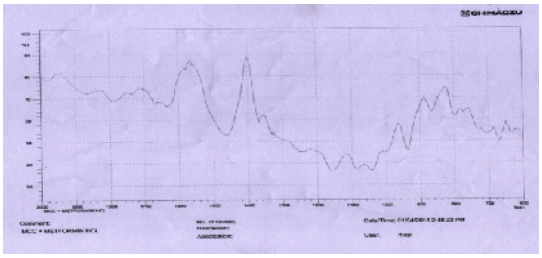
S.No.	Parameters	Drug
1	Bulk density(gm/cm³)	0.42
2	Tapped density(gm/cm³)	0.62
3	Compressibility index (%)	32.25
4	Hausner's Ratio	1.47
5	Angle of repose	42.27

The results of angle of repose (<30) indicate fair flow properties of the powder. This was further supported by lower compressibility index values. Generally, compressibility index values upto15% results in good to excellent flow properties.

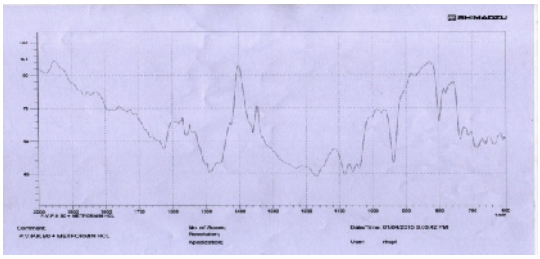
Drug Excipient compatibility study:

A) Physical compatibility: Given in Table 7

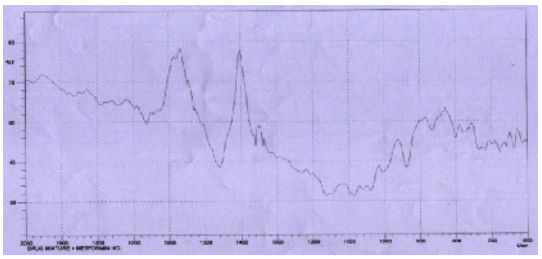
B) Drug- excipient compatibility studies by FTIR: 1. Compatibility study of drug with MCC



2. Compatibility study of drug with PVP K 90



3. Compatibility study of drug with all excipient



4. Compatibility study of drug with Aerosil

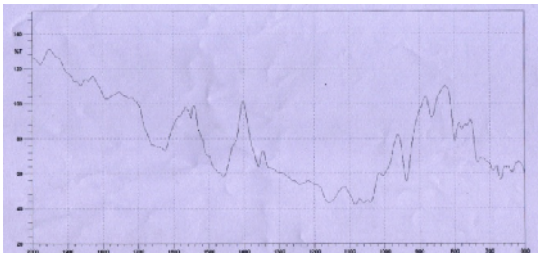


Fig.4.1-4.4: Drug- excipient compatibility studies by FTIR in different excipients

Table7: Result of physical compatibility of Metformin HCl

Drug+Excipients	Ratio	Observations on appearance	
		Initial (Color)	At 40°C±2°C 75%RH±5% for 1 Month
Drug	1	White	No Change
Microcrystalline cellulose	1:1	White	No Change
HPMC K 100M	1:1	White	No Change
PVP K90	1:1	White	No Change
Magnesium Stearate	1:1	White	No Change
Aerosil	1:1	White	No Change
Drug+MCC+PVPK90+ HPMC K 100M +Aerosil+Magnesium stearate	Proportional Mixture	White	No Change
Drug+MCC+PVPK90+ HPMC K 100M +Aerosil+ Magnesium stearate + Coating Material	Proportional Mixture	White	No Change

Evaluation of Pre-compression In the below Table 8 characteristics of the granules from F-1 to F-9 is given. From the values of angle of repose, Hauser's ratio and Carr's Index it can conclude that granules have good flow properties

Table8: Pre-compression parameters

Tablet	Weight(mg)	Hardness (Kg/cm^2)	Thickness	Friability (%)	% Assay
F1	900	6±0.28	5.63±0.05	0.22±0.01	98.3±0.2
F2	900	7±0.25	5.85±0.05	0.12±0.05	101.1±0.1
F3	900	8±0.28	6.15±0.05	0.01±0.04	99.4±0.54
F4	900	7±0.25	5.70±0.1	0.15±0.03	98.1±0.1
F5	900	8±0.11	5.630±0.10	0.05±0.01	97.4±0.15
F6	900	8±0.22	6.00±0.07	0.08±0.05	99.2+0.55
F7	900	7±0.5	6.05±0.02	0.20±0.02	100.5+0.1
F8	900	6±0.20	5.95±0.07	0.18±0.09	97.8+0.25

Evaluation of Post-compression Parameters

Table 9: Post-compression parameters

S. No.	Formulation Code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Angle of Repose (°)	Carr's Index (%)	Hauser's Ratio (HR)
1	F1	0.45	0.55	36.52	22.2	1.22
2	F2	0.54	0.63	29.74	14.28	1.16
3	F3	0.49	0.59	32.41	16.95	1.20
4	F4	0.56	0.64	33.69	16.66	1.14
5	F5	0.45	0.56	25.30	20.00	1.18
6	F6	0.44	0.57	27.30	18.22	1.17
7	F7	0.52	0.59	26.87	11.86	1.13
8	F8	0.51	0.62	28.12	16.94	1.20
9	F9	0.53	0.61	29.91	16.52	1.23

Discussion

The thickness of the tablets was found to be in the range of 5.63±0.05 to 6.15±0.02mm. The results showed that the thickness of all formulated tablets is found to be uniform. The hardness of all tablet formulations was found to be in the range of 6±0.28 to 8±0.28 kg/cm^2. It indicates all the tablets have adequate mechanical strength. The accepted percentage deviation was ±5% for more than 324 mg weight tablets. In friability test the maximum weight loss should be not more than 1%. The results revealed that the tablets passed the friability test.

***In vitro* dissolution profile:**

Medium: pH 6.8 phosphate buffer

Apparatus: Apparatus 2 (Paddle)

Speed: 50 rpm

Temperature: 37±0.5°C

Table10: % Cumulative drug release data from batch F1-F5

Time in min	% Cumulative drug released				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
15	2.27	3	2.95	3	2
30	5.4	6	4.93	6	5
60	11	12	7.89	10	8
120	19.08	20	13.21	18	13
180	23.45	25	20.46	23	20
240	40.31	33	26.22	30	26
300	47	45	39.45	40	33
360	58	57	45	53	40.84
420	64	62	55.76	59.5	48.28
480	70	71	63	64	56
540	74	74	70	69	62
600	70	82	76	72.63	69
660	78	83.85	79.5	78.4	76
720	82	88	86	84	82

Discussion:

The trial batches F_1 to F_5 were formulated using PVP K_{90} as binder with water and IPA.

Trial F1 was compressed using SC punch, which showed the problem of capping in the tablets, and also during coating of the tablets, the coating was not uniform and the movement of the tablets during pan coating was not good and also the edges broke during the rotation.

Trial F2 was compressed after increasing the concentration of binder. But in this trial also capping was observed.

Trial F3 was compressed with an increase in the binder concentration. In this trial no capping was observed. Broken edges were also disappeared during coating. But dissolution profile was not as per required so, further trials were taken.

Trial F4 and F5 were compressed with less binder concentration. In this trial capping was not observed with suitable dissolution profile but very less as compared to the reference product. So, further trials were taken by increasing concentration of polymer.

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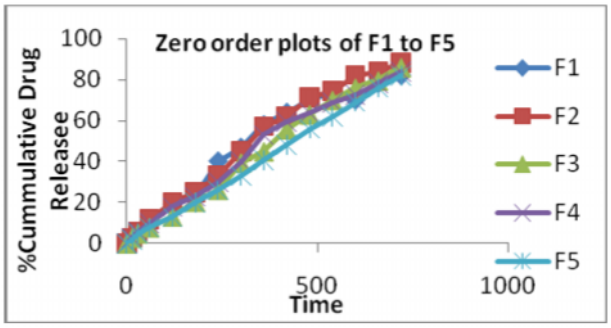
Table11: % Cumulative drug release data from batch F6-F9:

Time in min	% Cumulative drug released			
	F6	F7	F8	F9
0	0	0	0	0
15	2.88	2	2.75	3.88
30	4.89	4.11	4.77	6.01
60	8	7	8	9
120	12	11	13	14.32
180	21.66	19	19	21.33
240	25	22	27	26
300	31	29.64	35	37.57
360	42	37	40	46.53
420	51	45	49	56.41
480	60	54	56	64
540	69	60.48	63	73.59
600	75	66.24	73	81
660	79	75.88	80	91.79
720	82	84	89	98.86

Release kinetics: Different kinetic equations (zero-order, first-order, Higuchi's equation and Korsemeyer-Peppas model) were applied to interpret the release rate of the drug from drug delivery systems**.** Following graphs were obtained:



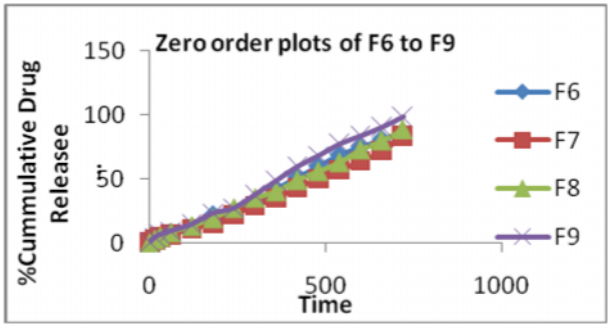
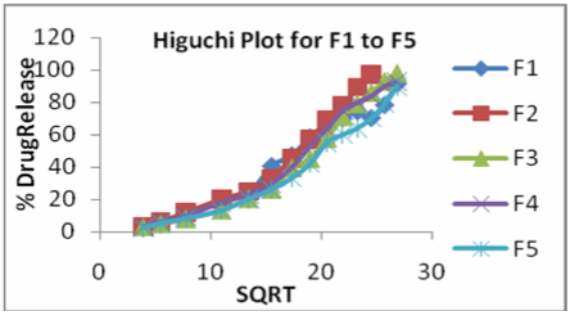


Fig.5: Cumulative plots for zero order model for F1-F9



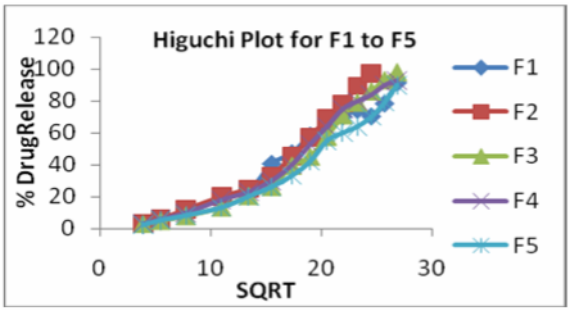
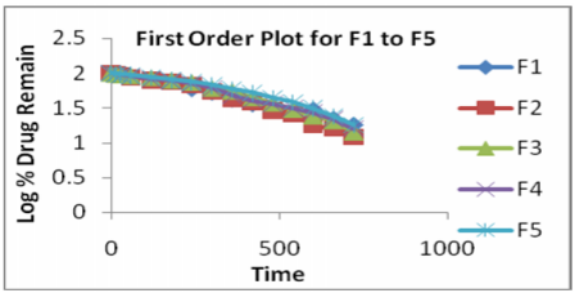


Fig.6: Cumulative plots for Higuchi model for F1-F9



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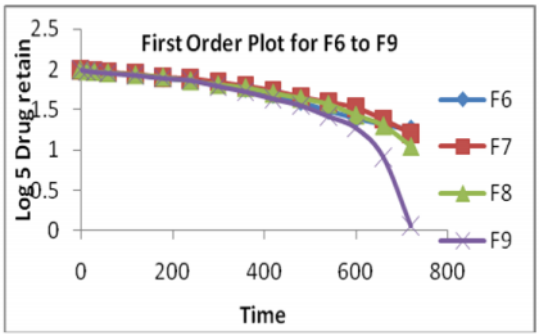


Fig.7: Cumulative plots for first order model for F1-F9

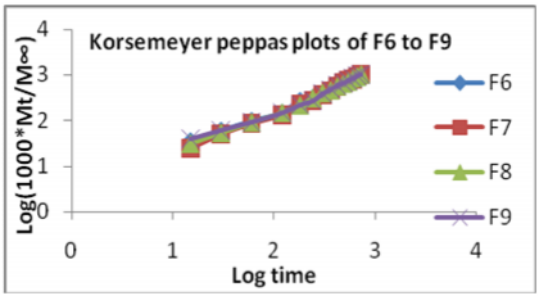
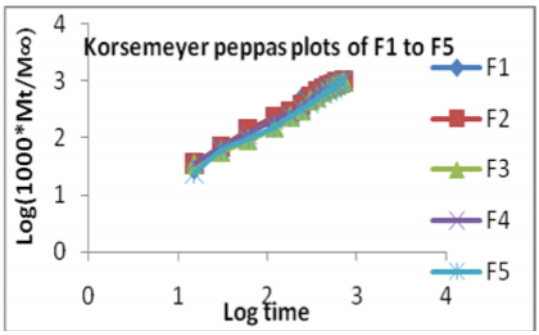


Fig.8: Cumulative plots for Korsemeyer-Peppas model for F1-F9



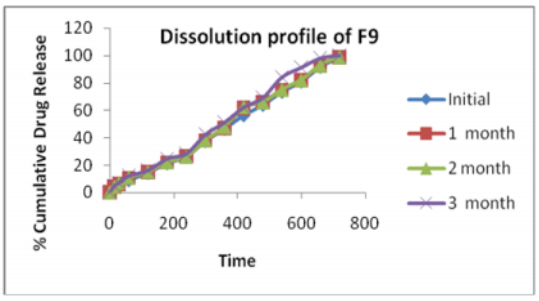


Fig.9: *In vitro* release profile for F9 after different time period

Table12: *In vitro* release kinetic data for F1 to F9

Formulation	Zero-order kinetics data	First-order kinetics data	Higuchi matrix kinetic data	Korsemeyer Peppas data
	Regression coefficient (r^2)	Regression coefficient (r^2)	Regression coefficient (r^2)	Regression coefficient (r^2)
F1	0.955	0.949	0.958	0.988
F2	0.983	0.975	0.954	0.995
F3	0.994	0.978	0.926	0.989
F4	0.986	0.958	0.951	0.995
F5	0.999	0.949	0.929	0.994
F6	0.991	0.954	0.941	0.986
F7	0.994	0.913	0.921	0.991
F8	0.996	0.893	0.937	0.991
F9	**0.995**	**0.731**	**0.930**	**0.978**

Stability Data:

Batch F9 was put on stability as below mentioned condition

Table13: Stability Study:

Pack	Alu – Alu Blister				
Condition	40°C/75%RH				
Batch No.	F09				
Appearance	No Change				
Test Parameters	**Specification**	**Initial**	**1 month**	**2 Month**	**3 Month**
Drug Content (%)	95-105	100.58	100.27	99.89	99.71

Table14: First, Second and Third months stability data of tablets at the condition 40°C/ 75±5% RH

Time	Initial Release	1 month	2 months	3 months
0	0	0	0	0
15	3.88	4.01	4.28	4.86
30	6.01	6.24	7.02	7
60	9	10.67	11	12
120	14.32	14.87	15.12	16
180	21.33	21.95	22.19	24.57
240	26	26.78	26.03	28.14
300	37.57	38.01	38.21	42.1
360	46.53	47.14	47.89	51
420	56.41	62.05	62.59	62
480	64	65.87	65.94	69
540	73.59	74.96	75.12	84
600	81	81.94	82.06	91
660	91.79	92.32	93	97.86
720	98.86	98.99	99.04	99.87

From the above stability data at 40°C/ 75±5% RH, it reveals that the product is stable in above conditions for three months.

CONCLUSION

The present study concludes that combination of hydroxy propyl methyl cellulose and binder PVP K90 can be utilized for designing and development of controlled release solid dosage form. The best formulation F9 has shown a drug release NLT 60-80 % in 18hr was in accordance with the USP dissolution criteria for extended release metformin HCl formulation. In the present research, extended release tablet formulations of metformin HCl were successfully prepared for a once daily administration.

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