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Original Article

DEVELOPMENT AND CHARACTERIZATION OF METFORMIN HCL SUSTAINED RELEASE MATRIX TABLETS BY USING WET GRANULATION METHOD

Dr. Vijaya Kuchana[1], Pradip Das[1]*, S. Visaka[1], Bathula. Bharathi.[2]
[1]Department of Pharmaceutics, Teegala Krishna Reddy College of Pharmacy, Medbowl, Meerpet, Saroornagar, Hyderabad-500079, Telangana, India.
[2]Syncorp Clincare Technologies Pvt. Ltd, Hyderabad, India
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Abstract

The main objective of the present study was development and characterization of metformin Hcl matrix tablets. These matrix tablets prepared by using wet granulation method and by using synthetic polymers such as HPMC and carbopol 934. Metformin drug as short plasma half life it is used to treatment of type 2 diabetes. The prepared tablets were evaluated for hardness, thickness, disintegration time and drug release studies. Optimized formulation of drug release was 99.73% in 12 hours along with satisfactory results. It was concluded that F3 formulation as best formulation compared with the other formulations based on the Drug release studies and physical parameters.

Key words: Metformin, HPMC, carbopol 934, wet granulation, In vitro drug release studies.

***Correspondence Address:**
Pradip Das, Department of Pharmaceutics**,** Teegala Krishna Reddy College of Pharmacy, Medbowl, Meerpet, Saroornagar, Hyderabad-500079, Telangana, India.
E-mail- visaka.satti@gmail.com

1. INTRODUCTION

Oral drug delivery is the most widely utilized routes for administration of drugs, which has been explored for systemic delivery via various pharmaceutical products as different dosage form.[1] In long-term therapy for the treatment of chronic disorders, conventional formulations are required to be administered frequently in multiple dosage regimens, and therefore have several undesirable effects. Hence, in order to reduce the drawback associated with multiple dosing, controlled or sustained release solid unit dosage forms as tablets were developed. They often produce better patient compliance, maintain uniform drug therapeutic level, are cost-effective, have broad regulatory acceptance, reduce dose as well as side-effects, and increase the safety margin for high-potency therapeutic agents.[2] Diabetes mellitus, simply referred to as diabetes, is a group of metabolic diseases in which a person has high level of blood sugar. The possible causative reason maybe that the body does not produce enough insulin, or cells do not respond to the insulin that is produced by the pancreatic cells[3]. Metformin hydrochloride is an orally administered biguanide, which is widely used in the management of type-II diabetes, a common disease that combines defects of both insulin secretion and insulin action. It is a hydrophilic drug and is slowly and incompletely absorbed from the gastrointestinal tract, and the absolute bioavailability is reported to be

of 50-60 %. The compound has relatively short plasma half-life of 1.5-4.5 h and the low absolute bioavailability of 50-60 %.[4] Side effects, short half lives, low bioavailability and the need for the administration two to three times a day when larger doses are required can decrease patient compliance. Sustained release products are needed for metformin to prolong its duration of action and to improve patient compliances. Sustained drug contains loading dose and maintaince dose. In that loading dose is quickly released to form speed drug on site if action and maintaince dose is released at a sustained release rate so that the plasma concentration persist continual above minimum effective concentration.[5,6]

2. MATERIALS AND METHOD

Metformin HCl was obtained from Hetero laboratories, India. HPMC k 4M, Carbopol 934, microcrystalline cellulose, Povidone, Isopropyl alcohol, Magnesium stearate and talc were purchased from S. D. Fine Chem. Labs. (Mumbai, India) All other ingredients used throughout the study were of analytical grade and were used as received.

Preparation of tablets (F1-F3): To weigh accurate quantity of HPMC K4M in first trail. And in second trail carbopol, In third trail eudragit is taken same quantity that is 100mg. All powders were passed through 100-mesh sieve.

The microcrystalline and the polymer were mixed uniformly. Drug was added to the polymers and blended for 20 min. After that PVP K30 solution was added to the above mixture it form a dump mass. These Dump mass was transferred through sieve no.40 and these granules kept under hot air oven. After that dried the granules for 2 hrs at 50^{o} c. In this granules add magnesium stearate and talc in polyethylene bag for 10 min. The lubricated granules were compressed using 10mm punch (single punch tablet machine) in to tablets

Preparation of tablets (F4-F6): To weigh accurate quantity of combinational polymers such as in F4 trail HPMC K4M and carbopol 934 same. In same way in F5 Trail the HPMC K4M and eudragit. In F6 Trail carbopol and eudragit. All powders were passed through 100-mesh sieve.

The microcrystalline and the polymer were mixed uniformly. Drug was added to the polymers and blended for 20 min. After that PVP K30 solution was added to the above mixture it form a dump mass. These Dump mass was transferred through sieve no.40 and these granules kept under hot air oven. After that dried the granules for 2 hrs at 50^{o} c. In this granules add magnesium stearate and talc in polyethylene bag for 10 min. The lubricated granules were compressed using 10mm punch (single punch tablet machine) in to tablets.[7]

Table-1: Formulation of sustained release tablets of Metformin

Ingredients (mg)	M1	M2	M3	M4	M5	M6
Metformin	100	100	100	100	100	100
HPMC K_4M	100	-	-	50	50	-
Carbopol 934	-	100	-	50	-	50
Eudragit	-	-	100		50	50
Povidone	10	10	10	10	10	10
Microcrystalline cellulose	235	235	235	235	235	235
Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s
Talc	2	2	2	2	2	2
Magnesium Stearate	3	3	3	3	3	3

Total wt	450	450	450	450	450	450

3. EVALUATION PARAMETERS

Drug excipient compatibility studies

Drug excipients compatibility studies were performed to know the compatibility of excipient with drug at accelerated conditions. The study was conducted by preparing homogenous mixture of excipients with drug and filled in HDPE bags and LDPE bags. Glass vials were exposed to 600 C and 400C/75 %RH for 4 weeks and LDPE bags were exposed to 400C±75 %RH for 4 weeks. Samples were observed periodically for any physical change.[9]

I. Pre compression parameters[10, 11]

A. Angle of repose

Weigh accurately of the powder was passed through a funnel. In this funnel put at a height 2 cm from the base. Then the powder is passed till it forms a heap and touches the tip of the funnel. The radius the base of the conical pile, and the height of pile were measured and the angle of repose was calculated using the formula.

$$\tan^{-} = h/r$$

Where,

h=height of the pile

r=radius of the base of the conical pile

θ=angle of repose

B. Bulk density and Tapped density

Weighed quantity of the Metformin was poured into 100 ml measuring cylinder. The volume occupied by the drug was measured, and then subjected to 500, 750, 1250 taps in the tap density tester (electro lab USP II), the blend was subjected to 500, 750.taps respectively then the percentage variation in volume was calculated, if it is more than 2 then the blend has to be subjected for 1250 taps and the percentage variation in volume has to be calculated.

Bulk density is denoted by (ρ_i)

$\rho_i = m/v_i$

Tapped density is denoted by (ρ_t)

$\rho_t = m/v_t$

m=mass of the blend

V_i = initial volume

V_t =tapped volume

C. Compressibility index (CI)

The compressibility index was expressed in percentage calculated using the formula

$$CI = \frac{TD - BD}{TD} \times 100$$

D. Hausner's ratio

It is determined by the ratio of tapped density and bulk density.

$$\text{Hausner's ratio} = \left(\frac{v_i}{v_i}\right) \text{or} \frac{TD}{BD_S}$$

II. Post compression parameters[12, 13, 14, 15]

A. Weight variation

Take prepared 20 tablets were unsystematic selected form each batch and separately weighed. After that average weight of tablets was calculated.

B. **Thickness**

Ten tablets were unsystematically selected form single batch and these 10 tablets thickness was measured by using vernier caliper. Thickness of three tablets from each batch was measured and mean was calculated.

C. **Hardness**

The hardness of the tablets was determined using Pfizer hardness tester. It is expressed in kg/cm. Take 3 tablets were unsystematically choose and hardness of the tablets were determined.

D. **Friability**

It is the disposition for a tablet to chip, break following compression. This tendency is normally restricted to uncoated tablets during handling and storage. Ten tablets were weighed and placed in the Roche friabilator, which was then operated for 25 rpm for 4 min. After revolution Tablets were de-dusted and reweighed. Compressed tablets should not lose more than 1% of their weight.

$$\% F = \{1-(Wo/W)\} \times 100$$

Where,

% F = friability in percentage

Wo = Initial weight of tablet

W = weight of tablets after revolution**.**

E. Content Uniformity

Twenty tablets from each batch were powdered and weighed accurately equivalent to 100 mg Metformin. Required amount of tablet powder transferred into 100 ml of 6.8 phosphate buffer solution by stirring it for 15 min. 1 ml of solution was pipette out into 10 ml volumetric flask and make up the volume with distilled water. After that sample solution analyze the drug by taking absorbance at 235 nm using reagent blank.

F. *In- Vitro* Release study

In-Vitro drug release studies were carried out using Tablet dissolution test apparatus USP II at 100 rpm. The dissolution bowls 900 ml of Standard buffer 0.1 N Hcl for 2 hr and followed by pH 6.8 period of time. And the Temperature maintained at 37±5. The sample of 1ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. From that 1 ml sample, 1 ml sample was withdrawn and placed in a 10 ml volumetric flask, and make the volume with buffer. The diluted samples were assayed at 235 nm against reagent blank.

G. Stability studies

The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile

Metformin tablets were placed on desiccant and stored at ambient conditions such as 37 ^{o}c and 40±2^{o}c and refrigerator 2-8^{o}c for a period of 3 months.

4. RESULTS & DISCUSSION

Table-2: Calibration curve of Metformin in 0.1 N Hcl

Sample No.	Concentration («g/ml)	Absorbance
1	0	0.000
2	1	0.145
3	2	0.252
4	3	0.367
5	4	0.472
6	5	0.589

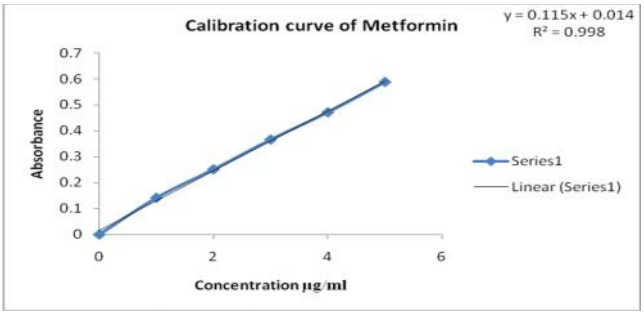

Figure-1: Calibration curve of Metformin

Standard curve of Metformin in 6.8 phosphate buffer

Table-3: Calibration curve of Metformin in 6.8 phosphate buffer

Sample no.	Concentration («g/ml)	Absorbance
1	0	0.000
2	1	0.145
3	2	0.256
4	3	0.363
5	4	0.472
6	5	0.581

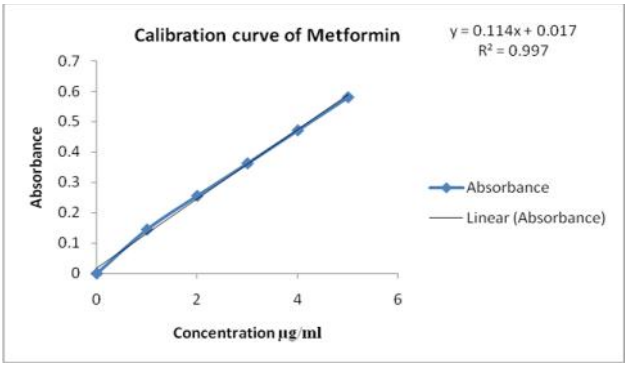

Figure-2: Calibration curve of Metformin in 6.8 phosphate buffer

FTIR Studies

Compatibility studies were performed using IR spectrophotometer. It determines the pure drug and excipient compatibility studies. The characteristic absorption peaks of Metformin were obtained at 3500cm^{-1}, 1084 cm^{-1}, 3095 cm^{-1}, 1745 cm^{-1}, 1105 cm^{-1}, 1599 cm^{-1}. The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum.

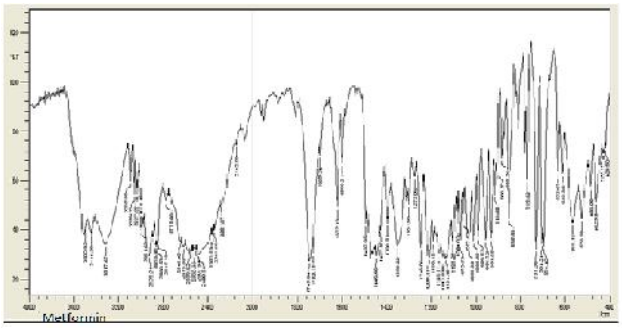

Figure-3: FTIR Spectra of Metformin

Table-4: Characteristic Peaks and frequency of Metformin

S. No.	Characteristic Peaks	Frequency (cm-1)
1	OH stretching	3500.92
2	OH Bending	1084.03
3	C-H stretching	3095.95
4	C-N stretching	1105.25
5	C=O stretching	1745.61
6	C=C	1599.04
7	C=C	1492.95

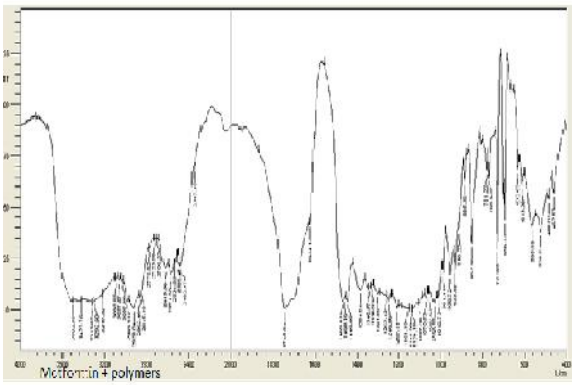

Figure-4: FTIR Spectra of Optimized formulation

Table-5: Characteristic Peaks and frequency of Optimized formulation

S.No.	Characteristic Peaks	Frequency (cm-1)
1	OH stretching	3462
2	OH Bending	1068.03
3	C-H stretching	3112
4	C-N stretching	1278.2
5	C=O stretching	1723
6	C=C	1478
7	C=C	1678

Evaluation parameters

Pre compression Parameters

a) Bulk Density: The bulk density for the formulated blend was carried out for all formulation and found in the range of 0.294-0.333.

b) Tapped density

The tapped density for the formulated blend was carried out for all formulation and found in the range of 0.357-0.4.

c) Angle of repose

The angle of repose for the formulated blend was carried out and the results were shown in Table No 6. It concludes that all the formulations blend was found to be in the range of 290 to35^0

d) Compressibility index

Compressibility index was carried out, it was found in between 10% to 18.10% indicating the powder blend have the required flow property for compression.

Table-6: Results of Pre compression parameters

S. No	Bulk density	Tapped density	Compressibility index	Hausner ratio	Angle of repose (0)
M1	0.322	0.384	16.14	1.17	30^0
M2	0.333	0.370	10	1.11	31^0
M3	0.312	0.370	15.67	1.18	32^0
M4	0.333	0.4	16.75	1.20	35^0
M5	0.294	0.344	14.53	1.17	30^0

M6	0.303	0.370	18.10	1.22	31^0

Post compression

Weight variation

All the formulated (M1 to M6) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight.

Thickness:

The thickness determined for formulated tablets were tabulated in Table No 7. Tablets mean thickness (n=3) were uniform in M1 to M6 formulations and were found to be in the range of 2.43mm to 2.56 mm.

Hardness

The measured hardness of tablets of each batch ranged between 6.5 to 7 kg/cm^2

Friability

The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity

The percentage of drug content for M1 to M6 was found to be between 96.72% and 98.92% of Metformin it complies with official specifications.

Table-7: Results of Post compression parameters

B. no.	Weight variation (mg)*	Thickness (mm)*	Hardness (kg/cm^2)*	Friability (%)	Drug Content (%)
M1	203 ±2.75	2.46 ±0.05	6.83 ±0.28	0.56	96.89
M2	201 ±2.33	2.43 ±0.05	6.66 ±0.28	0.54	98.42
M3	202 ±2.24	2.46 ±0.05	6.93 ±0.11	0.61	96.80
M4	202 ±1.78	2.53 ±0.06	6.76 ±0.25	0.59	97.22
M5	201 ±1.59	2.56 ±0.05	6.6 ±0.17	0.62	98.77
M6	202 ±1.93	2.5 ±0.05	6.66 ±0.28	0.64	96.83

Drug release studies

The formulated metformin tablets were subjected to in vitro drug release using 0.1 N Hcl and 6.8 phosphate buffer as a dissolussion medium. The amount of metformin drug release was estimated spectrophotometrically at 255nm. The percentage amount of free drug released was 99.73% within 12

Table-8: Dissolution Profile of batch no. M1 to M6

B. NO.	Drug release studies (Time)					
	1	**2**	**3**	**4**	**5**	**6**
M1	12.79	29.36	43.58	58.54	64.28	77.62
M2	17.51	31.59	39.14	51.16	63.21	71.79
M3	17.5	31.31	41.58	53.62	66.49	72.59
M4	12.21	25.58	33.42	43.29	49.16	56.72
M5	34.02	53.23	66.32	74.15	86.82	94.38
M6	43.05	57.62	63.38	72.28	79.15	80.7
B. No.	**7**	**8**	**9**	**10**	**11**	**12**
M1	86.32	97.64				
M2	82.51	96.65				
M3	84.65	92.19	94.2	95.52	96.19	99.73
M4	62.52	67.48	76.12	81.26	85.23	89.6

M5						
M6	82.15	88.54	96.42			

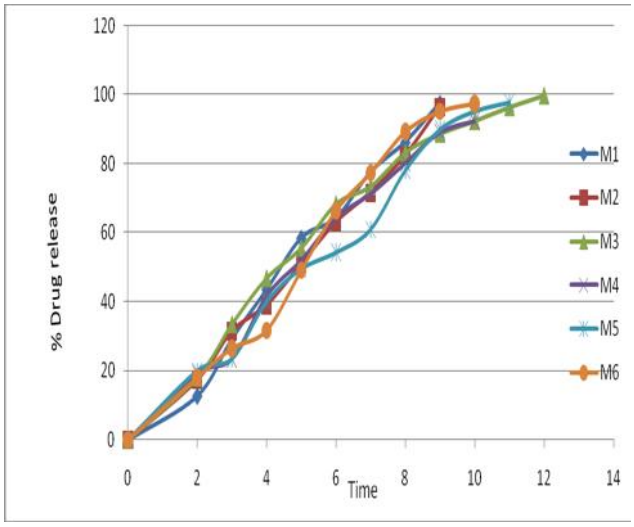

Figure-4 : Percentage Drug release studies

8	2.8284	0.9030	74.80	25.20	1.8739	1.4013	2.931
9	3	0.9542	80.00	20.00	1.9030	1.301	2.714
10	3.1622	1	89.07	10.93	1.9497	1.0384	2.219
11	3.3166	1.0413	93.37	6.63	1.9701	0.8217	1.878
12	3.4641	1.0791	97.46	2.54	1.9888	0.4054	1.364

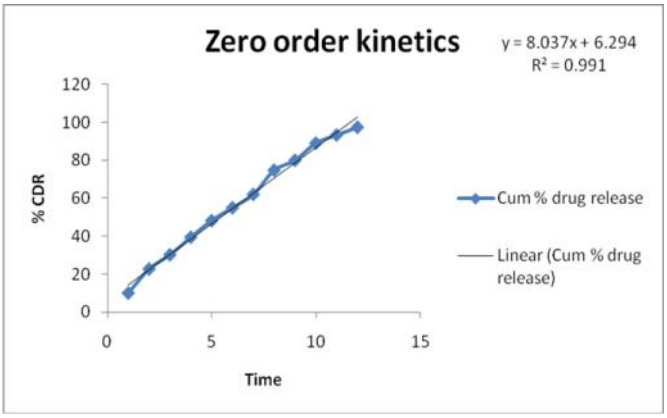

Figure-5 : Drug release of Zero order kinetics

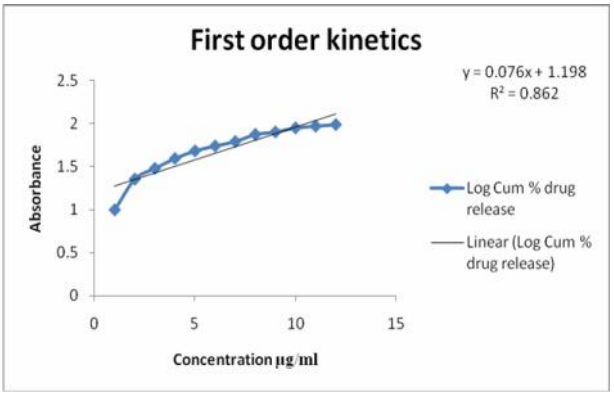

Figure-6: Drug release of First order kinetics

Drug release kinetics

Table-9: In vitro release profile of Metformin sustained release matrix tablet of optimized formulation

Time (hrs)	Root T	Log T	Cum % drug release	Cum % drug retained	Log Cum % drug release	Log Cum % drug retained	(% retained)$^{1\backslash3}$
1	1	0	10.03	89.97	1.0012	1.9540	4.48
2	1.4142	0.3010	22.75	77.25	1.3570	1.8878	4.258
3	1.7320	0.4771	30.24	69.76	1.4806	1.8435	4.116
4	2	0.6020	39.44	60.56	1.5959	1.7821	3.927
5	2.2360	0.6989	48.24	51.76	1.6834	1.7139	3.726
6	2.4494	0.7781	55.02	44.98	1.7405	1.6530	3.556
7	2.6457	0.8450	62.00	38.00	1.7923	1.5797	3.361

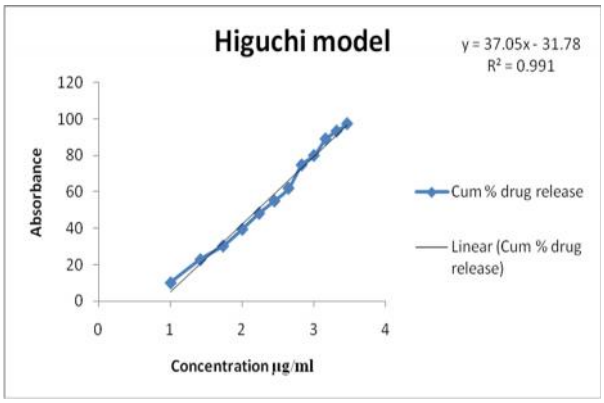

Figure-7: Drug release of Higuchi model

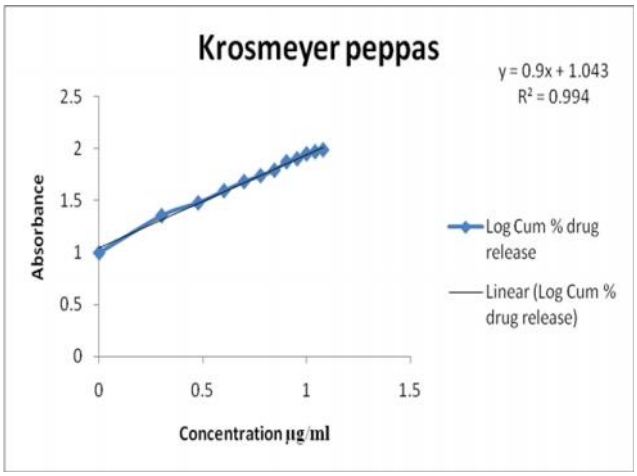

Figure-8: Drug release of Krossmayer peppas

Table-10: Drug release kinetics

S.no	Kinetic model	R^2 value
1	Zero order kinetics	0.991
2	First order kinetics	0.862
3	Higuchi model	0.990
4	Krossmayer peppas	0.988

Stability Studies

The results revealed that no important changes in appearance, drug content, hardness, friability, and invitro release for M3 formulation. When it was stored at the three storage conditions. However there was slight variation in invitro release when it is stored at 2-8^{o}c, there was no change when it is stored at 40^{o}c and room temperature

Table-11: Stability Studies of Optimized Formulation

S.NO	Time in days	Physical changes	Mean % drug content ± SD	Mean % drug content ± SD	Mean % drug content ± SD
			METFORMIN	METFORMIN	METFORMIN
			25^{0}C/60 %	30^{0}C/75 %	40^{0}C/75%
1.	01	No Change	99.73 ±0.49	99.68 ±0.49	99.68 ±0.49
3.	30	No Change	99.52± 0.39	99.47± 0.42	99.46± 0.83
5.	60	No Change	99.45± 0.81	99.32 ±0.80	99.55 ±0.45
7.	90	No Change	99.22 ±0.43	98.94 ±0.73	99.71 ±0.19

5. CONCLUSION

In the present work, attempts were made to development and characterization of sustained release Metformin matrix tablets. Metformin was subjected to preformulation studies; based on the results obtained Metformin sustained release tablets were successfully formulated.

Formulations prepared by direct compression technique using HPMC, Carbopol 934, eudragit as polymers showed desired in vitro release.

Set of trials were formulated for which physical parameters (bulk density, tapped density, compressibility index, hausner's ratio, weight, thickness, hardness) were found to lie within the specifications

Dissolution study was performed in USP type II apparatus at 100 RPM in 0.1 HCL for 2 hours followed by pH 6.8 phosphate buffer and pH 7.4 phosphate buffer up to 12 hr.

From the results of the in vitro study it appears that the release of the Metformin was significantly influenced by the characteristics of the polymer used.

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