International Journal of Multidisciplinary Research And Studies

Available online at www.ijmras.com
INTERNATIONAL JOURNAL OF MULTIDISCIPLINARY RESEARCH AND STUDIES

E ISSN: 2640 -7272
Volume:07; Issue:11 (2024)

Page no. 1-12

Development and evaluation of sustain release matrix tablet of metformin by using different polymer and comparison with marketed formulation

SHASHI KALA MEENA*[1], SATKAR PRASAD[2], REENA YADAV[3]

[1,2,3]RKDF School of Pharmaceutical science, Bhabha University, Bhopal, (Madhya Pradesh)

*Corresponding author Email: shashimeena0106@gmail.com

ABSTRACT

This study was to develop and evaluate of sustain release matrix tablet of metformin by using different polymer and comparison with marked formulation. Sustained release dosage forms are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. Sustained release dosage forms are prepared by coating the tablets so that the rate of solubility is controlled or individually encapsulating micro particles of varying sizes so that the rate of dissolution can be controlled. The release rate of Metformin from tablets was determined using USP Dissolution Testing Apparatus II and the data was analyzed using zero order graph of F3 formulation showed the constant drug release from the formulation. The Higuchi model is used to describe the limits for transport and drug release. Matrix tablets of Metformin were prepared by direct compression technique using varying proportions of polymers in combination with HPMC K-100, Eudragit RLPO and other excipients like MCC, PVP, Talc and Mg stearate. All the prepared tablets were evaluated for the test like hardness, friability, weight variation, disintegration time, drug content and dissolution studies. Sustained release tablets of Metformin have been successfully formulated using HPMC and Eudragit RLPO as drug release modifiers.

Keywords: Metformin, Eudragit RLPO, Sustain release, HPMC

1. INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administered among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. Oral sustained drug delivery system is complicated by limited gastric residence times (GRTs). Tablets are the most accepted drug delivery systems for oral administration. Sustained release (SR) drug delivery systems are developed to modulate the release of drug, in order to achieve specific clinical objectives that cannot be attained with conventional dosage forms. Conventional oral drug products, such as tablets and capsules release the active drug for oral administration to obtain rapid and complete

systemic drug absorption. However, fluctuations in plasma concentration below MEC lead to loss of therapeutic activity **(Ratnaparkhi *et al.*, 2013).** Sustained release dosage forms are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. Sustained release dosage forms are prepared by coating the tablets so that the rate of solubility is controlled or individually encapsulating micro particles of varying sizes so that the rate of dissolution can be controlled.

Metformin is an oral anti-hyperglycemic agent, shows incomplete absorption from the gastrointestinal tract and the absolute bioavailability is 50 – 60 % with relatively short plasma half-life of 1.5 - 4.5 h **(Roselet *et al.*, 2020).** Oral absorption of metformin is confined to the upper part of the intestine, i.e., the duodenum, jejunum and, to a lesser extent, ileum. Metformin controlled release may be by preparing formulations able to initiate release in the stomach and complete it in the jejunum, thus realizing a correspondence between time required for complete release and time of transit of delivery system across the upper part of the gastrointestinal (GI) tract, where drug absorption occurs and where are located sites of metformin glucose-lowering action that contribute to the overall pharmacodynamic effect **(Glossmann *et al.*, 2019).**
Matrix tablets can be defined as the oral solid dosage forms in which the drug is homogeneously dispersed or dissolved within the hydrophilic or hydrophobic polymeric matrices. Amongst the available matrix forming polymers, methacrylic resins (Eudragit®) appear particularly attractive due to high chemical stability, compact ability and variability in physicochemical characteristic. The preparation of sustained release matrix tablets involves the direct compression of blend powder mixture of drug, retardant material and other additives to formulate a tablet in which the drug is dispersed in a matrix of the retardant **(Alhalmi *et al.*, 2018).** Alternatively, drug, retardant blend and other additives may be granulated prior to compression. These systems release the drug in a continuous manner by dissolution-controlled and diffusion-controlled mechanisms**.** Commercial tablet formulation is compressed using excessive speed rotary pill presses and as a result it's far necessary that cloth fed in these pill presses ought to have some special characteristic, not most effective to keep away from segregation, but additionally to guarantee homogeneous filling of the dies for retaining weight homogeneity **(Chavan *et al.*, 2020).** To put together tablet with acceptable characteristics, granulation technologies is maximum broadly used. Many exclusive granulation technologies are available, ranging from dry granulation and moist granulation strategies which encompass two-step granulation (granulating acid and alkali phase one by one) to one-step granulation using water or organic solvents (**Biswas *et al.*, 2017**). Manufacturing solid dosage forms such as tablets and capsules involves several powder handling steps, including blending, transfer, storage, and feeding to a press or a dosator. The inability to achieve reliable powder flow during these steps can have a significant adverse effect on the manufacture and release of a product to market. The bulk density, tap density and compressibility index can be helpful in estimation of flow ability of powder/granules and thus the problems related to flow properties can be avoided by taking the measures of prevention **(Shanta, 2016).**

2. MATERIAL AND METHOD

2 |12: * **SHASHI KALA MEENA**, RKDF School of Pharmaceutical science, Bhabha University, Bhopal, (Madhya Pradesh)

2.1 Pre formulation Study

The preliminary analysis in pre formulation research determines the substance's color, flavor, and odor. The appearance's color, uniformity, and transparency were examined visually. The appearance's color, uniformity, and transparency were examined visually.

2.1.1 Organoleptic parameters

It is the initial evaluation during Pre-formulation studies which assess the colour, odour and appearance of the drug.

2.1.2 Solubility study

Solubility is an important physicochemical property of drug substance, which determines its systemic absorption and in turns its therapeutic efficacy. Solubility of drug was determined in different solvents **(Jain and Verma 2020)**.

2.1.3 Melting Point

Melting point was analysed by open Capillary method using Thiele's tube. Few quantity of the Metformin was placed in a thin walled capillary tube 10-15 mm long, about 1mm inside diameter, and closed at one end. Liquid paraffin oil was filled in the thieles tube and placed in the contact of flame. The capillary was suspended into the thiele's tube and heat the sample slowly; thermometer was attached to check the temperature. The temperature at which the sample starts to melt was taken as the melting point of the sample **(Chowk, M. I. 2020).**

2.1.4 Determination of Lambda max and calibration curve

- **Lambda (λ) max**

A stock standard solution containing 1 mg/mL of Metformin was prepared in 80% methanol. Working standard solution equivalent to 100 µg/mL of Metformin was prepared by appropriate dilution of stock solution with the same solvent. The solution was scanned in the range of 200 – 400 nm UV spectrum using shimadzu 1700 double beam spectrophotometer (**Kumbhar and Salunkhe 2013)**.

Standard calibration curve

10 mg of Metformin was accurately weighted into 10 ml volumetric flask, dissolved in 80% Methanol and volume was made up with same solvent. Pipette 1ml of this solution into another 10 ml volumetric flask and the volume was made with Methanol as Stock. The resultant solution is scanned in the range of (200-400 nm) by UV Spectrophotometer to get absorption maximum (λ max).

Preparation of calibration curve

The prepared stock solution was further diluted with solvent to get working standard solution of 10, 20, 30, 40 and 50µg/ml of Metformin to construct Beer's law plot for the pure drug, the absorbance was measured, against solvent as blank. The standard graph was plotted by taking concentration of drug on X-axis and absorbance on Y-axis in the concentration range of 10-50µg/ml (**Behera*et al.*, 2012).**

2.1.5 Fourier transmission Infra-Red Spectroscopy

FT-IR spectrum of Drug was recorded over the range of 4000 to 400 cm−1 by KBr pellet method using a FT-IR spectrophotometer. The KBr disc was prepared using 1 mg of each Drug in 100 mg of spectroscopic grade KBr which has been dried using IR lamp. Both KBr and drug was mixed and subjected to hydraulic pressure to form disc. This disc was placed in FT-IR chamber. Infrared spectrum was recorded in the 4000 - 400 cm-1 region **(Mishra et al., 2024).**

2.2 Powder Property

Flow property (Angle of repose)

Angle of repose was determined by using funnel method. Powder was poured from a funnel that can be raised vertically until a maximum cone height h, was obtained. Diameter of heap D, was measured. The angle of repose, Ɵ, was calculated by formula

tan Ɵ = h / r

Ɵ=tan-1(h/r)

Where, Ɵ is the angle of repose, h is the height in cm and r is the radius.

Bulk density

A funnel was used to gently add a precisely weighed sample of granulation to the measurement cylinder. The volume was then noted. A graded cylinder fixed on a mechanical tapping device served as the apparatus's means of measuring the packing's volume.

Apparent bulk density was determined by the following formula: -

BU =M/Vu

Where M=Mass of granulation Vu=volume of granulation (Initial untapped volume).

Tapped density

The above procedure was followed. The final volume was tapped till no further eduction in volume was noted. Packed bulk density was determined by the following formula.

DB=m/Vb

Where m = mass of granulation in gmVb = volume of granulation (Final tapped volume).

Carr's Index

It is expressed in percentage and is expressed by:

I=Dt-Db/Dt

Where, Dt is the tapped density of the powder and Db is the bulk density of the powder.

Housner Ratio

It is expressed in percentage and is expressed by:

H= Dt/Db

Where, Dt is the tapped density of the powder and Db is the bulk density of the powder. Lower Haunser ratio (< 1.25) indicates better flow properties than higher ones 6 (>1.25).

2.3 Development of Metformin matrix tablet

Matrix tablets of Metformin were prepared by direct compression technique using varying proportions of polymers in combination. All the ingredients were individually passed through a 60-mesh sieve, except glidant and lubricant. For each formulation required quantities of Metformin, polymer (HPMC K-100 and Eudragit RLPO), were accurately weighed according to the composition and mixed in a polybag for about 30 to 45 minutes. The obtained blend was lubricated with talc and magnesium stearate for another 5 minutes. The appropriate amount of the mixture was weighed and then compressed using 8 station rotary tablet press (CEMACH machineries ltd Ahmedabad, India) equipped with flat faced punches at a constant compression force required to produce hardness of tablets kg/ cm2. All the tablets were stored in airtight containers for further use.

Table 1: Compositions of Metformin matrix tablet

S. No.	Ingredients(mg)	Formulations					
		F1	**F2**	**F3**	**F4**	**F5**	**F6**
1	Metformin	500	500	500	500	500	500
2	HPMC K-100	25	50	75	….	……	…….
4	Eudragit RLPO	……	……	……	25	50	75
5	PVP	15	15	15	15	15	15
7	Magnesium stearate	5	5	5	5	5	5
8	MCC	10	10	10	10	10	10
6	Talc	q.s	q.s	q.s	q.s	q.s	q.s

2.4 Evaluation parameter of sustained release tablet formulation

2.4.1 Hardness

Monsanto hardness tester was used to evaluate hardness of tablet.

2.4.2 Friability

Friability of the tablets was determined using friabilator (Erweka, TAP, and Germany). It subjected the tablets to the combined abrasion and shock in a plastic chamber revolving at 25 rpm for 4 minutes and dropping a tablet at height of 6 inches in each revolution.

2.4.3 Weight variation

Twenty tablets were randomly selected and weighed individually and the weights of tablets were compared with the calculated mean weight.

2.4.4 Drug Content

10 tablets were selected randomly. Each tablet was transferred into a 50mL volumetric flask, dissolved and diluted to 50 mL with phosphate buffer pH 6.8. One ml of this solution was diluted to 100 ml with phosphate buffer pH 6.8.

2.4.5 *In-vitro* dissolution rate

The release rate of Metformin from tablets was determined using USP Dissolution Testing Apparatus II. The dissolution medium used was900 ml of phosphate buffer pH 6.8 which was maintained at 37±0.5^{0}C. The paddle speed was kept at 50 rpm throughout the study. Five ml of samples was withdrawn at every 5 minutes 'interval and diluted to 10ml then 5ml of fresh dissolution media maintained at the same temperature was replaniced. The samples were analyzed spectrophotometrically at 237.0 nm using phosphate buffer pH 6.8 as blank. The raw dissolution data was analyzed for calculating the amount of drug released and percentage cumulative drug released at different time intervals.

3. RESULTS AND DISCUSSION

3.1 Pre formulation studies

Pre formulation studies were performed. The result is given below.

3.1.1 Organoleptic evaluation

In organoleptic evaluation of drug, colour, odour and appearance were evaluated.

Table 2: Organoleptic Evaluation of Metformin

S. No.	Parameter	Inference
1	Appearance	Crystalline powder
2	Color	White to off white
3	Odour	Odour less

From the above table it is depicted that the drug Metformin is White to off white in colour, odourless and crystalline appearance.

3.1.2 Solubility study

Results of the solubility studies are given below.

Table 3: **Solubility profile of Metformin in different solvents**

S.NO.	Solvents	Category
1.	Water	Soluble
2.	Methanol	Freely soluble
3.	Ethanol	Sparingly soluble
4.	Chloroform	Insoluble
5.	DMSO	Freely soluble

Metformin was found to be freely soluble in methanol and DMSO, soluble in water and insoluble in chloroform.

3.1.3 Melting point determination

Table 4: Melting point of Metformin

S. No.	Drug	Specification	Inference
1	Metformin	222ºC-226ºC	224ºC

Melting point of Metforminwas found to be 224ºC.

3.1.4 Determination of λ max

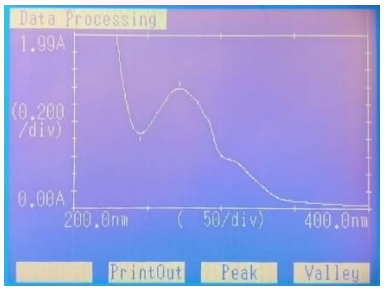


Figure 1: λ max of Metformin

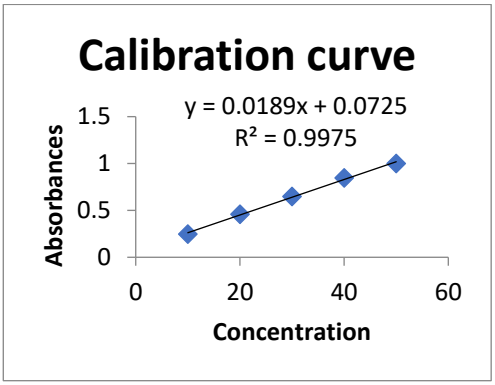
Standard Calibration Curve of Metformin

All dilutions and measurements were made in phosphate buffer and the absorbance was taken at λ max 237.0 nm against a methanol solvent blank. The standard curve was plotted between absorbance and concentrations.

Calibration curve:

Table 5: Calibration curve of Metformin

Concentration (µg/ml)	Absorbance
10	0.248
20	0.459
30	0.648
40	0.846
50	1.001
Mean	0.6404
SD	0.299685335
%RSD	46.71



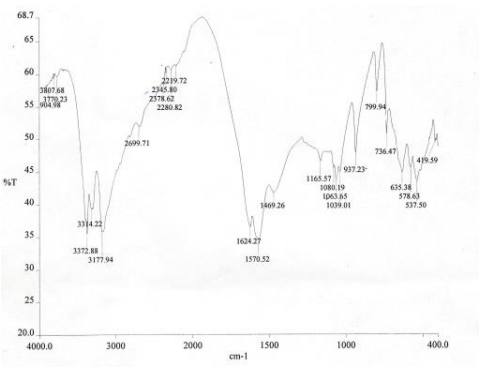


Figure 2: Calibration curve of Metformin **Figure 3: FTIR graph of Metformin**

3.2 Powder Property

Table 6: Flow ability properties of granules

Formulation	Angle of repose	Bulk Density	Tapped density	Carr's index ratio	Hausner's ratio	Loss on drying
F 1	29.42±0.56	0.412±0.01	0.460±0.01	10.43±0.18	1.11±0.013	0.86
F 2	24.11±0.55	0.312±0.03	0.363±0.03	14.04±0.23	1.16±0.008	0.99
F 3	28.63±0.76	0.269±0.08	0.322±0.05	16.45±0.52	1.19±0.006	0.93
F 4	22.63±0.13	0.318±0.04	0.326±0.08	2.45±0.18	1.02±0.007	1.05
F 5	21.52±0.44	0.309±0.06	0.349±0.07	11.46±0.55	1.12±0.005	0.85
F 6	24.36±0.24	0.325±0.01	0.376±0.07	13.56±0.28	1.15±0.012	0.67

3.3 Evaluation parameters

Table 7: Evaluation of tablets

S. No	Formulation	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation (%)	Drug content (%)
1	F 1	5.8±0.01	4.1±0.12	0.46±0.03	650±0.88	96.23
2	F 2	5.7±0.03	3.9±0.05	0.56±0.05	650±1.54	97.26
3	F 3	6.1±0.03	4.2±0.06	0.56±0.07	648±1.29	98.86
4	F 4	6.0±0.04	4.3±0.06	0.23±0.08	649±1.57	96.38
5	F 5	6.0±0.08	4.3±0.09	0.78±0.09	650±1.87	96.11
6	F 6	5.8±0.07	4.4±0.03	0.88±0.03	654±1.97	97.56

3.3.1 *In-vitro* drug release

Table 8: Release study of all formulations (F1 to F6)

Time	F1	F2	F3	F4	F5	F6	Marketed formulation
0	0	0	0	0	0	0	0
1	29.63	16.02	23.11	31.23	33.47	28.36	21.08
2	41.53	38.56	36.1	48.27	46.78	39.63	44.28
4	53.11	46.63	43.13	55.96	57.63	47.86	55.78
6	69.13	58.55	57.59	71.28	76.34	65.56	67.33
8	85.22	67.22	66.83	87.13	86.13	79.35	77.53
10	95.03	89.56	77.17	98.33	97.58	88.23	90.19
12	98.25	97.36	82.41	98.34	98.35	93.66	98.73
13	---	----	98.69	---	98.35	98.04	---

: * **SHASHI KALA MEENA**, RKDF School of Pharmaceutical science, Bhabha University, Bhopal, (Madhya Pradesh)

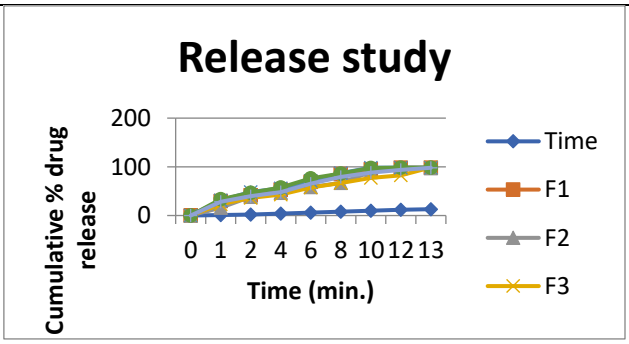


Figure 4: Release study

Table 9: Release kinetics study of tablet formulation (F3 formulation)

Time (Hr)	cumulative % drug released	% drug remaining	Square root time	log Cumu % drug remaining	log time	log Cumu % drug released
0	0	100	0.000	2.000	0.000	0.000
1	23.11	76.89	1.000	1.886	0.000	1.364
2	36.1	63.9	1.414	1.806	0.301	1.558
4	43.13	56.87	2.000	1.755	0.602	1.635
6	57.59	42.41	2.449	1.627	0.778	1.760
8	66.83	33.17	2.828	1.521	0.903	1.825
10	77.17	22.83	3.162	1.359	1.000	1.887
12	82.41	17.59	3.464	1.245	1.079	1.916
13	98.69	2.86	3.606	0.456	1.114	1.987

Table 10: Correlation value (R^2 value)

Formulation	Model	Kinetic parameter values
Tablet Formulation	Zero Order	$R^2 = 0.948$
	First Order	$R^2 = 0.812$
	Higuchi	$R^2 = 0.983$
	Korsmeyerpeppas	$R^2 = 0.609$

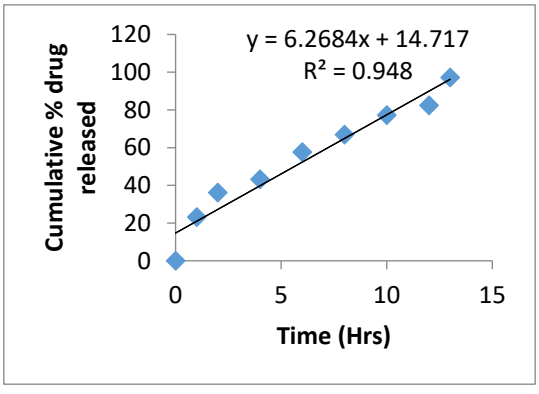


Figure 5: Zero order kinetic model

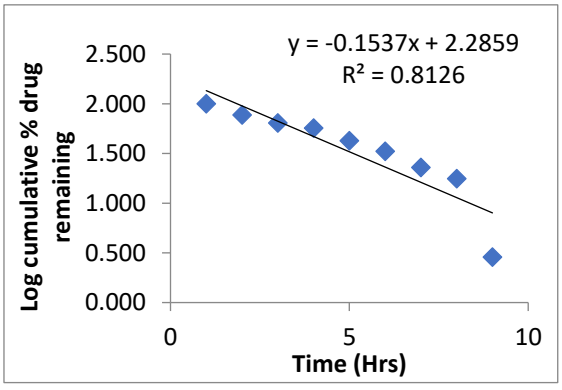


Figure 6: First Order kinetic model

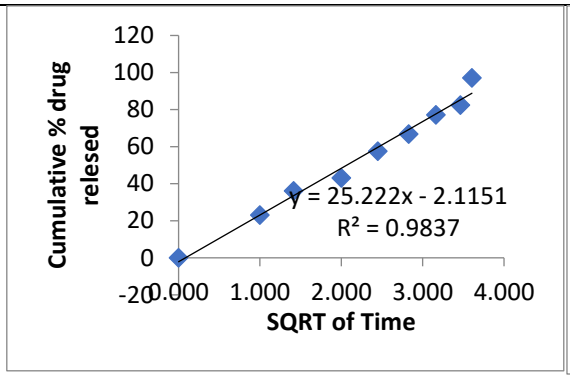


Figure 7: Higuchi model

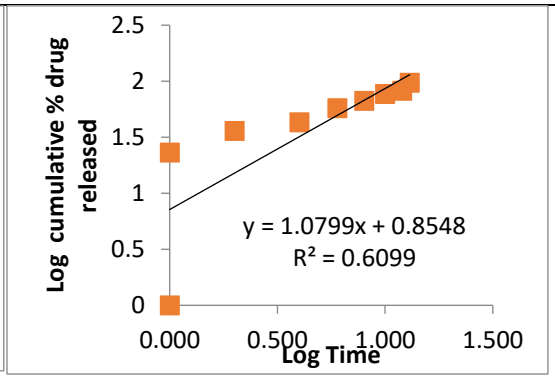


Figure 8: Korsmeyerpeppas

4. DISCUSSION

Matrix tablets of Metformin were prepared by direct compression technique using varying proportions of polymers in combination with HPMC K-100, Eudragit RLPO and other excipents like MCC, PVP, Talc and Mg stearate.

Pre formulation study colour and odourless. The solubility of the drug was found to be freely soluble in methanol and DMSO, soluble in water and insoluble in chloroform. The melting point of Metformin was found to be 224ºC. The UV absorbance's of Metformin standard solution was found to be 237.0 nm. A granule prepared by wet granulation was subjected to the evaluation of their flow property like angle of repose, bulk density, tapped density, carr's index and hausner's ratio. The results were found to be in the limits. After mixing the powder with appropriate characteristics and flow property, tablets were made by direct compression method in a single punch machine. All the prepared tablets were evaluated for the test like hardness, friability, weight variation, disintegration time, drug content and dissolution studies. Hardness friability was found to be in limits. In-vitro drug release studies were evaluated for drug release by using USP dissolution test apparatus, F3 formulation showed 98.69% drug release among all the formulations within 13 hours. It concluded that F3 formulation showed good in-vitro dissolution as well as disintegration. This study confirms that Metformin can be successfully prepared in the form of sustained release tablets by compressing granules that were prepared by direct compression technique with excipients.

The data of percentage drug release formulation were shown in Figure. 1 to 8. For kinetic study following plots were made: cumulative % drug release vs. time (zero order kinetic models); log cumulative % drug remaining vs time (first order kinetic model); cumulative % drug release vs square root of time (Higuchi model); log cumulative % drug release vs log time (Korsmeyer–Peppas model). All Plots are shown in Figure. 1 to 8 and results are summarized in Table 8. Zero order kinetic models refer to the process of constant drug release from a drug delivery device independent of the concentration. The zero order graph of F3 formulation showed the constant drug release from the formulation, the results of the zero order model was found to be y = 56.2684x + 14.717 R^2 = 0.948. The first order kinetic model describes the release from system where release rate is concentration dependent. The results of first order kinetic model was found to be y = -0.1537x + 2.2859 R^2 = 0.812. The Higuchi model is used to describe the limits for transport and drug release. The Higuchi model of formulation was found to be, y= 25.222x - 2.1151 R^2 = 0.983. And the results of Korsmeyerpeppas kinetic model

was found to be y = 1.0799x + 0.8548 R^2 = 0.609. *In-vitro* drug diffusion studies were carried out using Dissolution apparatus method. In the above table R2 is correlation value. On the basis of best fit with the highest correlation (R2) value it is concluded that in the optimized formulation of F3 follow the Higuchi kinetic model.

5. CONCLUSION

Sustained release matrix tablets of Metformin formulation system include the drug delivery system that achieves slow and extended release of the drug over an extended period of time. Sustained release tablets of Metformin have been successfully formulated using HPMC and Eudragit RLPO as drug release modifiers. The findings of the present study demonstrate that the hydrophilic matrix of Metformin alone could not control the release effectively for 13 h, whereas, when combined with HPMC, it could slow down the release of the drug from their matrices and can therefore be successfully employed for formulating SR matrix tablets. Diffusion coupled with erosion might be the mechanism for the drug release, which can be expected to reduce the frequency of administration and decrease the dose-dependent side-effects associated with repeated administration of conventional Metformin tablets.

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