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FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF METFORMIN HYDROCHLORIDE

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ABSTRACT

The aim of present research work was to prepare and evaluate transdermal drug delivery (TDDS) of metformin hydrochloride (MFH). MFH is an agonist at a2 adrenergic receptor sites. The drug undergoes rapid first pass metabolism (approximately 95% of dose) which necessitates its frequent Dosing by oral route. Transdermal drug delivery system of MFH was prepared using combinations of polyvinyl pyrrolidone K 30 and Hydroxypropylmethylcellulose E50 in different ratios by solvent evaporation technique. Polyvinyl alcohol was used to prepare the backing membrane and dibutyl phthalate as plasticizer. The prepared polymeric Films were characterized for various physiochemical parameters like film thickness, folding endurance, Moisture content, weight variation, drug content, moisture uptake. Permeation studies were carried out for patches through cellophane membrane using Franz diffusion cell. Formulation F7 showed 99.1% drug release from the patch within 12 h and drug release data of selected Patch showed good fit into Higuchi equation.

Keywords: Metformin Hydrochloride, Permeation Studies, Franz Diffusion Cell.

INTRODUCTION

A transdermal patch is used to deliver a specific dose of medication through the skin and into bloodstream. Transdermal patches products were first approved in 1981 by FDA. Transdermal delivery provides controlled, constant administration of the drug, and allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation. TDDS offers many advantages over conventional injection and oral methods. It reduces the load that the oral route commonly places on the digestive tract and liver. It enhances patient compliance and minimizes harmful side effects of a drug caused from temporary overdose. It is convenient, especially notable in patches which require only once weekly application. Such a simple dosing regimen aids in patient adherence to drug therapy[1].Transdermal delivery systems are currently available containing scopolamine (hyoscine) for motion sickness, clonidine and nitroglycerin for cardiovascular disease, fentanyl for chronic pain, nicotine to aid smoking cessation.[1]

ADVANTAGES

1. It is convenient method and requires only once weekly application. Such a simple dosing regimen can aid patient adherence to drug therapy.

2. It is of great advantage in patients who are nauseated or unconscious.

3. Drugs that cause gastrointestinal upset can be good candidates for transdermal delivery because this method avoids direct effects on the stomach and intestine.

4. First pass metabolism, an additional limitation to oral drug delivery, can be avoided with transdermal administration.

5. Drugs that require relatively consistent plasma levels are very good candidates for transdermal drug delivery[2].

Fig. 1: Transverse section of skin showing routes of penetration (Copy right figures need prior permission)

MATERIALS

Metformin Hydrochloride obtained as a gift sample from hetero labs Hyderabad.HPMC E 50 ,Poly vinyl pyrolidine K 30, Dichloromethane, Dibutyl phthalate ,Methanol , Potassium dihydrogenpthalate and Sodium hydroxide purchased from sd fine chemicals mumbia.

METHODOLOGY

Construction of Standard Graph of Metformin hydrochloride:-

Accurately weighed amount of 100 mg Metformin hydrochloride was transferred into a 100ml volumetric flask. 20 mL of distilled water was added to dissolve the drug and volume was made up to 100 mL with the same distilled water. The resulted solution had the concentration of 1mg/ml which was labeled as 'stock'. From this stock solution 10ml was taken and diluted to 100 mL with distilled water which has given the solution having the concentration of 100 mcg/mL. Necessary dilutions were made by using this second solution to give the different concentrations of metformin hydrochloride (1 to 10 mcg/mL) solutions[3-5].

The absorbances of above solutions were recorded at λ_{max} (233 nm) of the drug using double beam UV-Visible spectrophotometer. Standard graph was plotted between the concentration (on X-axis) and absorbance (on Y-axis).

Similarly, standard graph was plotted with 7.4 pH phosphate buffer.

Preparation of pH 7.4 phosphate buffer: Accurately measured 50 mL of 0.2 M potassium dihydrogen orthophosphate was transferred to a 200mL volumetric flask and 39.1 mL of 0.2 M sodium hydroxide was added to it. Volume was made up to 200 mL with distilled water, mixed and pH was adjusted to 7.4 with 0.2 M sodium hydroxide or 0.2 M othophosphoric acid.

Preparation of 0.2 M potassium dihydrogen phosphate solution: Accurately weighed 27.218 g of monobasic potassium dihydrogen phosphate was dissolved in 1000 mL of distilled water and mixed.

Preparation of 0.2 M sodium hydroxide solution: Accurately weighed 8 g of sodium hydroxide pellets were dissolved in 1000 mL of distilled water and mixed.

Preparation Of Metformin Hydrochloride Transdermal Patches

Transdermal patches of MFH were prepared using different proportion of polymers like PVP K30 and HPMC E50 by solvent evaporation technique in cylindrical both side opened glass moulds. The bottom of the mould was wrapped with aluminum foil on which the backing membrane was cast by pouring 4% (w/v) PVA solution followed by drying at 60°C for 6 h in an oven. The two polymers were weighed in requisite ratio and they were then dissolved in methanol:dichloromethane (1:1) as a solvent. Dibutyl phthalate was used as a plasticizer. The drug was dissolved in solvent mixture then added to the polymer solution, by slow stirring with a magnetic stirrer. The uniform dispersion (2 ml each) was casted on the PVA backing membrane casted earlier and dried at 40°C for 6 h. After drying patches were removed from the mold, wrapped with aluminum foil and kept in desiccators until they were used for further study[6-9].

Formulations of transdermal patches:

Calculation of drug dose for preparing transdermal patch

Area of mould= 3.14*5*5=78.5 cm^2

For 4 cm^2 =10mg

78.5 $cm^{2=?}$

=196mg.

Table 1. Composition of transdermal patches

F code	HPMC E 50:PVP K 30	MET HCL (mg)	HPMC E 50 (mg)	PVP K30 (mg)	DMC:M	DBP(ml)
F1	1:1:1.5	10	117.6	78.4	1:1	0.5
F2	1:1:2	10	130.7	65.3	1:1	0.5
F3	1:1:2.5	10	140	56	1:1	0.5
F4	1:1:3	10	147	49	1:1	0.5
F5	1.5:1	10	78.4	117.6	1:1	0.5
F6	2:1	10	65.3	130.7	1:1	0.5
F7	2.5:1	10	56	140	1:1	0.5
F8	3:1	10	49	147	1:1	0.5

In the formulations prepared, the release retardants included was hydroxypropylmethylcellulose E50 (HPMCE50) and Polyvinyl pyrolidone K30 (PVP K30) was used as a polymer. Dichloromethane and methanol was used as solvents. Dibutyl phthalate was used as plasticizer.

EVALUATION PARAMETERS

THICKNESS OF THE PATCH:

The thickness of the drug loaded patch is measured in different points by using screw gauge or Vernier Callipers at different points of the film[10-14.]

WEIGHT VARIATION:

The prepared patches are dried at 60°c for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights[15-18.]

FOLDING ENDURANCE:

A strip of specific area is to be cut evenly and repeatedly folded at the same place till it breaks. The number of times the film could be folded at the same place without breaking gives the value of the folding endurance [19-22.]

PERCENTAGE MOISTURE CONTENT:

The prepared films are to be weighed individually and to be kept in a desiccators containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula [23]

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

CONTENT UNIFORMITY TEST:

10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115%, of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity.

MOISTURE UPTAKE:

Weighed films are kept in desiccators at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in desiccators until a constant weight is achieved. % moisture uptake is calculated as given below[23.]

$$\% \text{ moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

DRUG CONTENT:

A specified area of patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyze the drug contain with the suitable method (UV technique). Each value represents average of three different samples [24.]

IN VITRO SKIN PERMEATION STUDIES:

An in vitro permeation study can be carried out by using diffusion cell.The cellophane membrane is to be mounted between the compartments of the diffusion cell, with the half portion facing upward into the donor compartment. sample volume of definite volume is to be removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is to be replaced. Samples are to be filtered through filtering medium and can be analyzed by uv spectrophotometer at 233nm. Flux can be determined directly as the slope of the curve between the steady-state values of the amount of drug permeated (mg cm-2) vs. time in hours and permeability coefficients were deduced by dividing the flux by the initial drug load (mg cm-2)[24].

Kinetic Analysis of Data:

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration .The first order Eq. (2) describes the release from system where release rate is concentration dependent. Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3)[24,25].

$$C = K_0 t \quad (1)$$

where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$LogC = LogC_0 - K_1 t / 2.303 \quad (2)$$

where, C_0 is the initial concentration of drug and K_1 is first order constant.

$$Q = K_H t^{1/2} \quad (3)$$

where, K_H is the constant reflecting the design variables of the system.

The following plots were made using the in-vitro drug release data

Cumulative % drug release vs. time (Zero order kinetic model);
Log cumulative of % drug remaining vs. time (First order kinetic model);
Cumulative % drug release vs. square root of time (Higuchi model);

Mechanism of drug release

Korsmeyer derived a simple relationship which described drug release from a polymeric system Eq. (5). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model.

$$M_t / M_\infty = Kt^n \quad (5)$$

where $M_t / M\infty$ is fraction of drug released at time t, K is the release rate constant incorporating structural and geometric characteristics of the tablet, and n is the release exponent. The n value is used to characterize different release mechanisms.

A plot of log cumulative % drug release vs. log time was made. Slope of the line was n. The n value is used to characterize different release mechanisms as given in Table 2 , for the

cylindrical shaped matrices. Case-II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release[24-26].

Table 2. Diffusion Exponent and Solute Release Mechanism for Cylindrical Shape

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

RESULTS AND DISCUSSION

Standard Curve Of Metformin Hydrochloride:

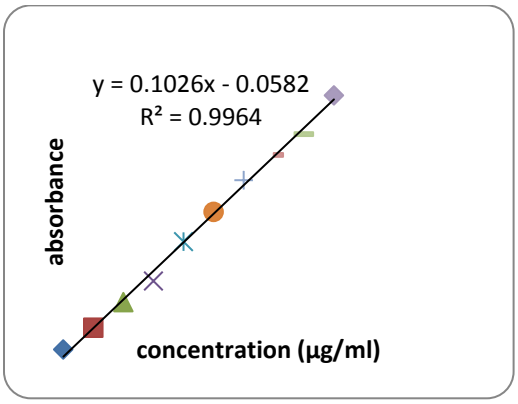

Fig .2: standard curve of metformin hydrochloride in distilled water

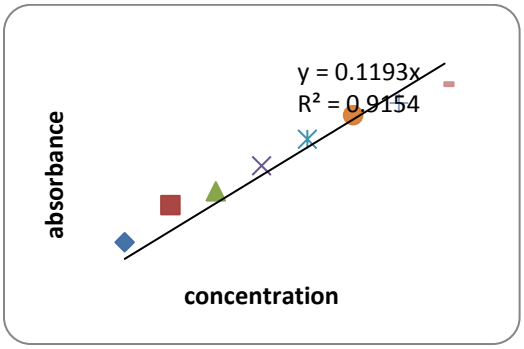

Fig .3: standard curve of metformin hydrochloride in pH 7.4 phosphate buffer

Physical Evaluation of transdermal patches of metformin hydrochloride:

Solvent evaporation technique was used to prepare the transdermal patches of MFH using hydrophilic polymer like HPMC E50 and hydrophobic polymer like PVP K 30. The study was targeted to prepare once a day delivery systems of MFH by using different combination of the above mentioned polymers and the concentration of drug kept constant for every formulation.

Evaluation of eight sets of transdermal patches viz. folding endurance, uniformity of thickness, moisture content and moisture uptake, weight variation study, %drug content study, and in vitro permeation study were done accordingly.

Weight variation data of all the patches shown that there were no significant differences among the patches in individual set and the deviation was within the limits. The thicknesses of the prepared films were found to 19 to 21.8.mm as describe in the Table 8. As there was increasing in HPMC E50 there is consistent decrease in thickness. So it is evident from the data that PVP help in increasing in thickness of the film.

Table 3: Physical Evaluation of transdermal patches of metformin hydrochloride:

FORMULATION CODE	THICKNESS (mm)	WT.VARIATION (mg)	% DRUG CONTENT
F1	19.8±0.74	0.385±0.38	92.2
F2	19.6±0.45	0.386±0.36	92.5
F3	19.7±0.27	0.387±0.34	93.6
F4	19.0±0.03	0.388±0.33	94.3
F5	21.2±0.31	0.387±0.38	94.5
F6	21.3±0.33	0.388±0.35	95.3
F7	21.8±0.88	0.391±0.33	97.2
F8	21.5±0.30	0.389±0.31	96.5

Folding endurance of all the formulations were found to be varied in between 51 to 106 as shown in Table 4. It was found that the film containing higher proportion of PVP K30 shown reduction in endurance. It can be claimed that higher the HPMC E50 more the endurance. The moisture content and moisture uptake of all the formulations was shown in Table 9.

The moisture content is increased as hydrophilic polymer concentration increased and similarly decreased as hydrophobic concentration increased. Among all the patches F7 was found to lowest moisture content.

Table 4: Physical Evaluation of transdermal patches of metformin hydrochloride:

FORMULATION CODE	FOLDING ENDURANCE	MOISTURE UPTAKE	% MOISTURE CONTENT
F1	51±0.74	0.589	0.543
F2	62±0.64	0.742	0.609
F3	68±0.55	0.778	0.712
F4	72±0.58	0.836	0.923
F5	76±0.54	1.273	1.555
F6	81±0.65	1.443	1.628
F7	106±0.78	1.623	1.889
F8	102±0.54	1.421	1.623

INVITRO DRUG RELEASE STUDIES

Table 5: Invitro Drug release Studies Of Metformin Hydrochloride Transdermal Patches:

TIME (HOURS)	CUMULATIVE % DRUG RELEASE			
	F1	**F2**	**F3**	**F4**
0	0	0	0	0
1	21.5±0.77	20.5±0.65	19.07±0.71	17.63±0.58
2	44.2±0.55	34.2±0.58	32.3±0.68	30.24±0.56
4	63.1±0.64	58.4±0.56	56.2±0.57	52.69±0.45
6	70.4±0.54	68.4±0.58	65.5±0.55	61.96±0.24
8	73.1±0.56	71.7±0.55	70.68±0.51	69.32±0.55
10	79.3±0.58	72.4±0.52	72.65±0.50	71.15±0.46
12	83.6±0.55	82.6±0.50	75.17±0.49	73.27±0.41

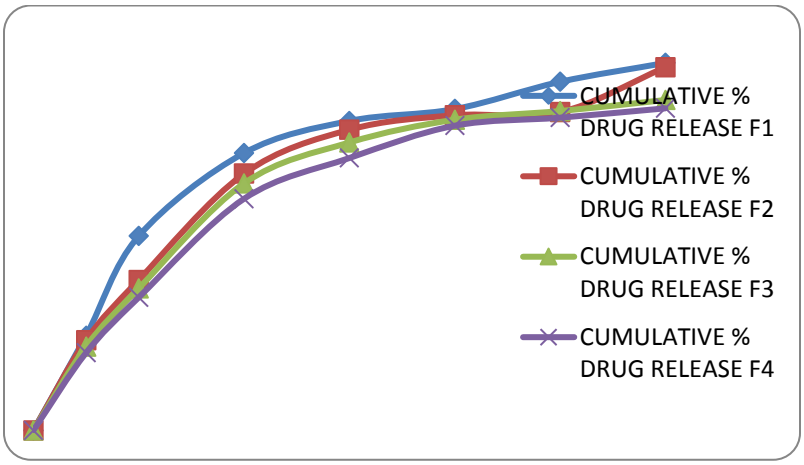

Fig.4: **Invitro Drug release Studies Of Metformin Hydrochloride Transdermal Patches**

Table 6: Invitro Drug release Studies Of Metformin Hydrochloride Transdermal Patches:

TIME (HOURS)	CUMULATIVE % DRUG RELEASE			
	F5	**F6**	**F7**	**F8**
0	0	0	0	0
1	23.04±0.73	25.1±0.65	28.3±0.66	32.7±0.54
2	47.38±0.71	48.5±0.55	48.7±0.44	57.28±0.44
4	60.62±0.69	61.1±0.51	61.1±0.41	63.42±0.58
6	65.22±0.61	70.1±0.45	71.5±0.42	70.09±0.54
8	78.45±0.59	80.5±0.69	84.2±0.54	78.56±0.56
10	80.25±0.55	89.4±0.65	94.1±0.42	91.05±0.45
12	85.44±0.54	95.7±0.57	99.1±0.52	98.68±0.58

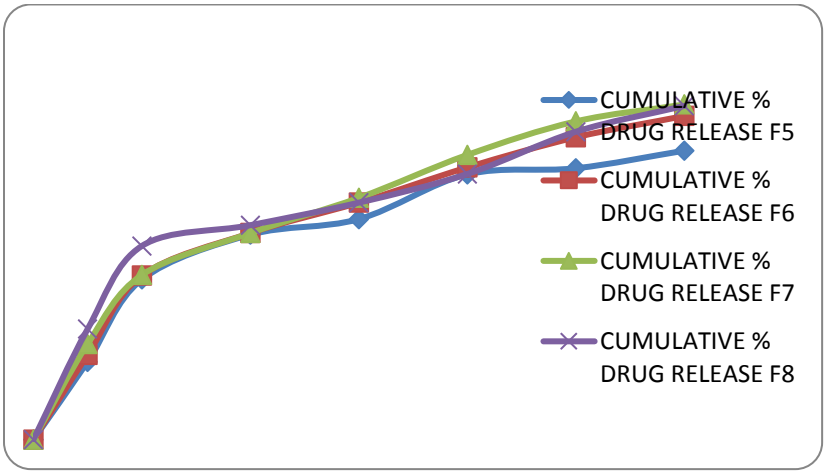

Fig.5: **Invitro Drug release Studies Of Metformin Hydrochloride Transdermal Patches**

FLUX=slope/area
=28.81/4
=7.21 mg.hrs^{-1}cm^{-2}
PERMEABILITY COEFFICIENT= flux/dose
= 7.21/2.5
=2.88 cm/h

Kinetic analysis of dissolution data

The release rate kinetic data for the F7 is shown in Table 7 respectively. As shown in Figures, drug release data was best explained by Higuchi's equation (r^2 = 0.992). As the drug release was best fitted in Higuchi's kinetics explains why the drug diffuses at a comparatively slower rate as the distance for diffusion increases.

Mechanism of drug release

The corresponding plot (log cumulative percent drug release vs time) for the Korsmeyer-Peppas equation indicated a good linearity (r^2 = 0.979). The diffusion exponent n was 0.48, which appears to indicating a coupling of the diffusion and erosion mechanism (Anomalous diffusion) and may indicate that the drug release was controlled by more than one process.

The kinetic analysis of F7 Formulation:

Zero order profile:

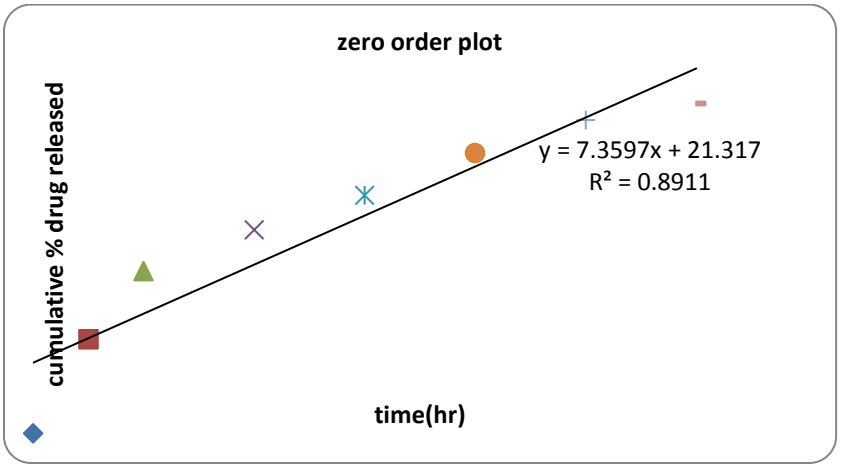

Fig.6: Zero order profile

First order profile:

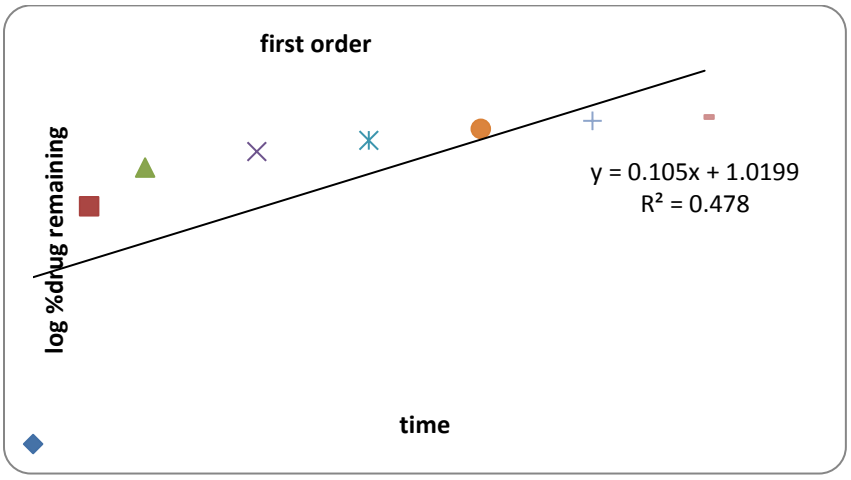

Fig.7 First order profile

Higuchi plot:

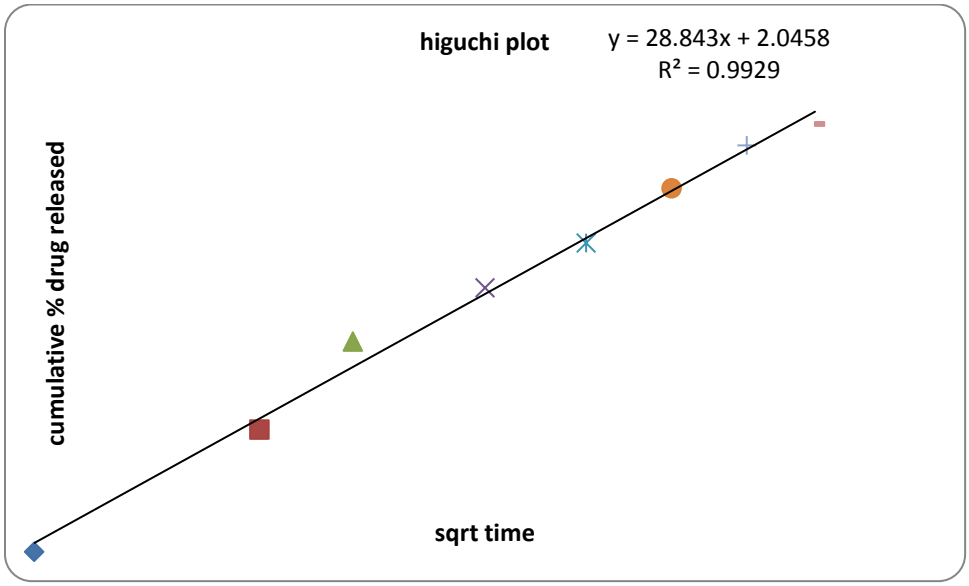

Fig.8 Higuchi plot

Korsemeyer peppas plot:

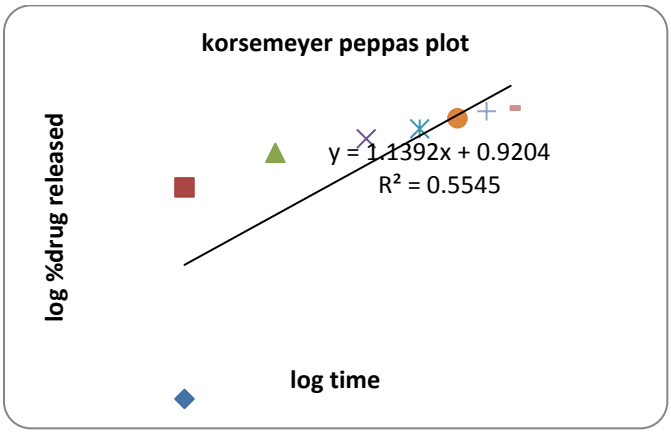

Fig.9 korsemeyer peppas plot

Table 7.Drug Release Kinetics of Batch (F7)

Zero order	First order	Higuchi	Korsmeyer-Peppas	
r^2	r^2	r^2	r^2	*N*
0.891	0.842	0.992	0.979	0.48

* r^2 = Correlation coefficient ; n= Diffusional exponent.

CONCLUSION

From the above discussion it can be concluded that Metformin hydrochloride that released from the transdermal patches of F7 (PVP K30- HPMC E50 2.5:1) are best suited for once a day drug delivery[34]. The higher proportion of PVP K30 is responsible for the controlling the drug release and suitable for a prolonged regimen of drug delivery through transdermal route. The research work gives a rational guideline for formulating a transdermal delivery system of Metformin hydrochloride for effective therapy of hyperglycemia.

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