WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 18, 1460-1477. Research Article ISSN 2277– 7105

FORMULATION AND EVALUATION OF METFORMIN TRANSCUTANEOUS PATCHES

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Article Received on
17 Sept. 2018,
Revised on 08 Oct. 2018,
Accepted on 29 Oct. 2018
DOI: 10.20959/wjpr201818-13678

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ABSTRACT

The aim of the work was to develop a sustained release transcutaneous patch of metformin hydrochloride using natural and synthetic polymers like HPMC and PEG. Transcutaneous drug delivery can be efficiently used for the drugs which cause severe gastritis and undergo rapid first pass effect; hence the transcutaneous patches of metformin hydrochloride were prepared by using combination of PEG and HPMC along with GLYCERINE as a plasticizer. The prepared formulations were evaluated for thickness, weight variation, drug content, folding endurance, moisture content, in vitro permeation studies. The patches showed best tensile strength, folding endurance. In vitro dissolution test was carried for 24 hours and formulation F7 showed 95.89% drug release at the end of 24 hours. Release kinetics studies revealed that the drug release from formulation F7 followed zero order kinetics with release exponent value n=0.997, which shows that release pattern of patches follows Non - fiction diffusion mechanism. It was observed that the system with PEG: HPMC in the ratio 75:25 along with plasticizer was very promising in controlling release of Metformin via transcutaneous drug delivery system.

KEYWORDS: Formulation, Evaluation, Metformin, Transcutaneous, Patches.

1. INTRODUCTION

In the field[1] of the dermal or transcutaneous drug delivery the skin represent the application site and sometimes also the target. Skin until the early 1990s, it was believed to be an impervious barrier designed protects the body from foreign microorganism, including chemical and drugs. This view changed with a serendipitous finding that polar compound, such as dimethyl sulpha oxide, are rapidly absorbed into the blood stream after its exposure to skin. This discover led to active research to develop transcutaneous methods for systematic

drug administration. Today[2], there are a host of drug for combating virtually every disease or condition known to man and verity of means by which this drug delivered to the human body for therapy such as tablets, capsule, injections, aerosols, creams, ointment, liquid etc. Often refer to as conventional drug formulations. Therapy with such formulation involves attainment and maintenance of drug concentration in the body with in a therapeutically effective range by introduction of fixed dosage of the drug, at regular intervals, in to the body after the administration of one dose, the drug concentration raises to high level, system wide, at least initially with passage of time, the concentration diminishes owing to natural metabolic process and second dose must be administered to prevent the concentration from dropping below the minimum effective level The disadvantages these kind of therapy are.

1. Drug concentration in the body follow a peak and through profile leading to greater chance of adverse effect for therapeutically failure.
2. Therapy is inefficient and costly since large amount of drug are lost in vicinity of the target organ and close attention is required to monitor therapy to avoid over dosing.

It is recognized that continuous intra venous (IV) Infusion is a superior mode of drug administration as compared to the oral route not only to bypass hepatic ‘’first-pass’ ’metabolism. A closely monitored iv infusion can provide the duel advantage of direct entry of drug in systemic circulation and the control of circulating drug level. However, such mode of administration involved certain risk with necessities hospitalization of the patient for close medical supervision of drug administration.

It was realize[3] and later demonstrated that the benefits of IV infusion could be closely duplicated without its hassles by using the skin as the port of entry of drug. This is known as transcutaneous administration and the drug delivery system are known as transcutaneous therapeutic system or transcutaneous drug delivery system or popularly as transcutaneous patches. Transcutaneous therapeutic system are defined self-contained, discrete dosage form which, when applied to the intact skin, deliver the drug(s), through the skin, at a controlled rate to the systemic circulation. Table describes various transcutaneous drug delivery systems available commercially.

Table 1: various transcutaneous systems available commercially.

Sl.no	Therapeutic Agent	TTDS	Design
1	Clonidine	Catapres-TTS	Four-layer patch
2	Estradiol	Estraderm(Novartis)	Four-layer patch
3	Estradiol	Vivelle(Novartis)	Three-layer patch
4	Fentanyl	Duragesi (Janssen)	Three-layer patch
5	Nicotine	Prosstep(Lederic)	Multilayer
6	Testosterone	Testoderm(Alza)	Three-layer patch
7	Nitroglycerine	Transderm-Nitro(Novertis)	Four-layer patch
8	Scopalamine	Transderm-Scop	Four-layer patch
9	Nicotine	Habitrol(Novartis consumer)	Multilayer-round patch
10	Nicotine	Nicoderm CQ(Smithline Beecham)	Multilayer-round patch
11	Nitroglycerine	Deponit(Schwarz-pharma)	Three-layer patch
12	Testosterone	Ansroderm(Smithline Beecham)	Five layer patch
13	Estradiol	Climara(Novartis)	Three-layer patch

ADVANTAGES OF TRANSCUTANEOUS DRUG DELIVERY SYSTEM OVER OTHER ROUTES.

- Avoid gastrointestinal drug absorption difficulties caused by gastro intestinal pH, enzymatic activity and drug interactions with food, drink or other orally administered drugs.
- Avoid the first-pass effect that is initial pass of drug substances through the systemic and portal circulation fallowing gastro intestinal absorption; they are by digestive and liver enzymes.
- The system or non-invasive avoiding the convenience of parenteral therapy.
- They provide extended therapy with single application, Thereby improving patient compliance over other dosage forms requiring. More frequent dose administration.
- Drug input can be stopped simply by removal of the patch.

DISADVATAGES OF TRANSCUTANEOUS DRUG DELIVEY SYSTEM OVER OTHER ROUTES

1. Only relatively potent drugs are suitable candidates for transcutaneous delivery

2. Same patients may develop contact dermatitis at the site of application due to one or more of the system component.

The main components to a Transcutaneous drug delivery system

1) Release liner[4]

Release liner protect the patch during storage .The liner is removed prior to use.

2) Drug reservoirs

The most important part of TDDS is drug reservoir .It consists of drug particles dissolved or dispersed in the matrix.

3) Adhesive

Adhesive serve to adhere the component of the patch together along with adhering the patch to the skin. The adhesive must possess sufficient adhesion property so that the TDDS should remain in place per a long time. Pressure sensitive adhesive are commonly used for Trans dermal patch to hold the skin. Commonly used adhesive are silica adhesive, poly isobutylene adhesive, and poly acrylate –based adhesive**.**

4) Membrane

Membrane control serve to release of the drug from the reservoir and multi-layer patches It may or may not be spite or crack on bending or stretching .Some of rate controlling membrane or polyethylene sheets, Ethylene vinyl acetate co polymer, and cellulose acetate.

5) Backing

Backing protects the patch from the outer environment. The backing layer should be in permeable to drug and penetration enhancer. It serves a function of holding the entire system and protect drug reservoir from atmosphere. The commonly used backing material is polyester, aluminized polyethylene.

Fig 1: Transcutaneous patches.

The technologies can be classified in four basic approaches

1) Membrane permeation controlled system.
2) Adhesive dispersion type system.

3) Matrix diffusion controlled systems.
4) Micro reservoir type or micro sealed dissolution controlled system.

Mechanism of action: drug's mechanisms of action differ from other classes of oral anti hyperglycemic agents. It reduces blood glucose levels by reducing hepatic glucose production, decreasing intestinal absorption of glucose, and increasing insulin sensitivity by increasing peripheral glucose uptake and utilization. These effects are mediated by the initial activation of drug by AMP activated protein kinase (AMPK), a liver enzyme that plays an important role in insulin signaling, whole body energy balance, and the metabolism of glucose and fats. Activation of AMPK is required for drug's inhibitory effect on the production of glucose by liver cells. High levels of peripheral utilization of glucose may be due to improved insulin binding to insulin receptors. drug administration also increases AMPK activity in skeletal muscle. AMPK is known to cause GLUT4 deployment to the plasma membrane, resulting in insulin independent glucose uptake. The rare side effect, lactic acidosis, is thought to be caused by reduced liver uptake of serum lactate, one of the substrates of gluconeogenesis. In those with healthy renal function, the slight excess is simply cleared. However, those with severe renal impairment may accumulate clinically significant serum lactic acid levels. Other conditions that may precipitate lactic acidosis include severe hepatic disease and acute decompensated heart failure.

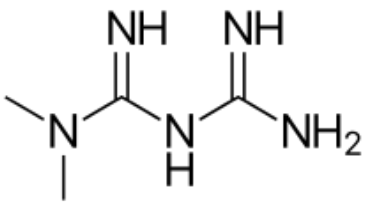
MATERIALS

METFORMIN

Molecular Formula: C4H11N5

Molecular mass: 129 g/ mole.

Graphic formula



Chemical Name: N, N-Dimethylimidodicarbonimidic diamide.

Nature: White granular powder

Solubility: highly soluble in water, slightly dissolvable in alcohol, practically insoluble in acetone and methylene chloride

Molecular mass: 129 g/ mole.

Protein Binding: minimal.

Half Life: 4-8.7 hrs.

Excretion: Not by liver.

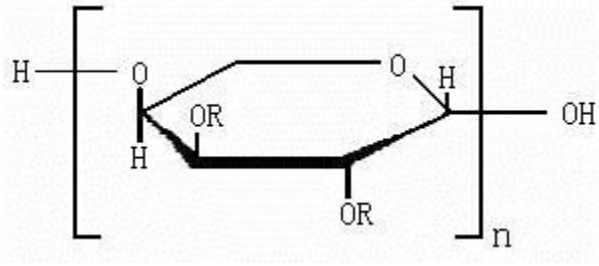
Routes: Oral and Parenteral.

Category: Biguanides,

Melting Point: 222 ºC - 226 ºC.

Doses: Each tablet of oral administration is contains 20mg, 40mg, and 80mg of Metformin.

HYDROXY PROPYL METHYL CELLULOSE (HPMC)



IUPAC: 2-[6-[4,5-bis(2-hydroxypropoxy)-2-(2-hydroxypropoxymethyl)-6-methoxyoxan-3-yl]oxy-4,5-dimethoxy-2-(methoxymethyl)oxan-3-yl]oxy-6-(hydroxymethyl)-5-methoxyoxane-3,4-diol.

Synonyms: HPMC, E464, MHPC, Hydroxypropyl methylcellulose, Hydroxypropyl methyl cellulose.

Functional category: Coating agents, film-former, rate-controlling polymer for sustained release stabilizing agent, tablet binder, viscosity-increasing agent.

Description: Methocel is an odorless and tasteless, white or creamy-white fibrous or granular powder.

Solubility: Soluble in water, suitable proportion of ethanol/ water, propanol/water.

Viscosity: 50,000-2,00,000mPa.

Applications

Use concentration (w/w %)

Binder 2-5

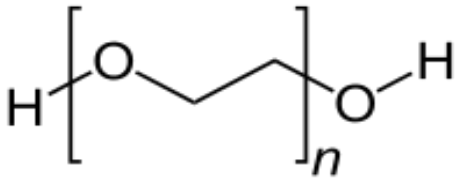
film-forming agent 2-20

Rate controlling polymer 10-80

Apparent density: 0.42-0.51 g/mL (usually about 0.5 g/mL), specific density 1.26-1.31mL.

Surface tension: 42-56 dyne/cm (2% aqueous solution with 25 ℃).

POLY ETHYLENE GLYCOL(PEG)



Name: POLY ETHYLENE GLYCOL

Molecular weight: 3,500-4000

Synonyms: Poly Ethylene Glycol; Carbowax; Polyglycol; Polyethylene glycol 200, 300, 400, 600, 1000, 1450, 3350, 4000, 6000, 8000 and20000.

Functional category: Poly ethers

Solubility: Dissolves slowly in cold water. Insoluble in hot water.

Applications: A lubricating coating for various surfaces

- In Many Pharmaceutical Products PEG is used as an excipient
- For lubricating eye drops PEG is used
- A binder in the preparation of technical ceramics.

Uses of PEG: polyethylene glycol and added electrolytes is used for bowel preparation before surgery or colonoscopy.

4. METHODOLOGY

Instrumentation.

5. MATERIALS

Table 2: List of materials& Name of the Manufacturer.

MATERIALS	NAME OF MANUFACTARURE
Metformin	Maven life sciences
HPMC	LOBA CHEMIE PVT.LTD
PEG	Oxford Laboratory
Glycerine	Finer chemicals Ltd
Hydro alcoholic solution	Made in chaina changshu Yangyuan chemicals

ESTIMATION OF METFORMIN

Determination of UV absorption maxima for Metformin.

Solution of Metformin was prepared in phosphate buffer7.4 and was scanned for absorbance between 200-400nm using double beam UV/VIS spectrophotometer (Shimadzu, UV-1700, Japan) Metformin exhibited maximum absorption at 234.The output from the equipment is shown in figures.

Preparation of calibration curve in phosphate buffer pH 7.4

Preparation of standard solution

100mg of Metformin was dissolved in 100ml of phosphate buffer pH 7.4, 10ml of solution was withdrawn and volume was made up to 100ml with buffer. From the stock solution aliquot of 5,10,15,20,25,30µg/ml. The volume was made up to the mark with phosphate buffer pH 7.4 Absorbance of each solution was measured 234nm using UV/VIS Spectrophotometer against phosphate buffer pH 7.4 as blank.

1. Standard calibration curve yield straight with R^2=0.9975, indicating that the drug obeys Beer's Law in the concentration range of 5-30 mcg/ml.

5.1.2 Preparation of TDDS

Matrix type transcutaneous patches containing Metformin were prepared using HPMC & PEG by solvent evoparation technique in petri dish. The polymer was weighed and dissolved in Hydro alcoholic solution(70;30) solvent system then add then add Glycerine used plasticizer The resultant homogenous solution was poured into a petri dish .Controlled solvent evoparation was achieved by investing funnel over the petri dish for 24 hr The dry film were wrapped in aluminum foil and kept in desiccator until used The composition of different patches is given in table:3.

Table 3: The composition of different Transcutaneous patches.

Ingredients(gr)	F1	F2	F3	F4	F5	F6	F7
Metformin	0.1	0.1	0.1	0.1	0.1	0.1	0.1
HPMC	0.5	1	1.5	2	0.25	0.29	0.375
PEG	_	_	_	_	0.25	0.21	0.125
Glycerin	1ml	1ml	1ml	1ml	1ml	1ml	1ml
Hydro alcoholic solution (70:30)	10ml	10ml	10ml	10ml	10ml	10ml 10 ml	10ml

Figure 2: various transcutaneous patches.

Solubility study

The solubility studies were performed in the phosphate solution 7.4 by adding excess amount of drug in each case keeping on water bath shaker for 24 hrs at 32°C after 24 hr, solution was analyzed spectrophotometerically at 234 nm.

Physicochemical properties of the film

The film were evaluated for the following.

Thickness

The thickness of patch was determined using a micro meter (Mitoyo, Japan).

Films was measured at three different places of each patch and mean value was calculated.

Determination of drug content in film

The uniformity of drug distribution was determined by taking known weight of the films a different places of patches the patch were dissolved in 2 ml of alcohol and subsequently diluted with phosphate buffer pH7.4. Appropraite dilution, Solutions were analyzed spectrophotometerically for Metformin at 234nm.

Folding Endurance

This was evaluated by folding the film several times at the same place until it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance**.**

In vitro permeation study

Egg membrane

The natural membrane was presoaked in phosphate buffer pH7.4 for 45min before experiment.

Procedure

Permeation studies were performed for different formulations across egg membrane using phosphate buffer pH7.4 as in vitro fluid in receptor compartment of modified diffusion cell at 32°C. This whole assembly was kept on magnetic stirrer and the solution was stirred continuously using a magnetic bead. The sample was withdrawn at different time intervals and replaced with equal volume of diffusion media. Samples were analyzed in UV spectrophotometer at 234nm.

6. RESULTS AND DISCUSSION

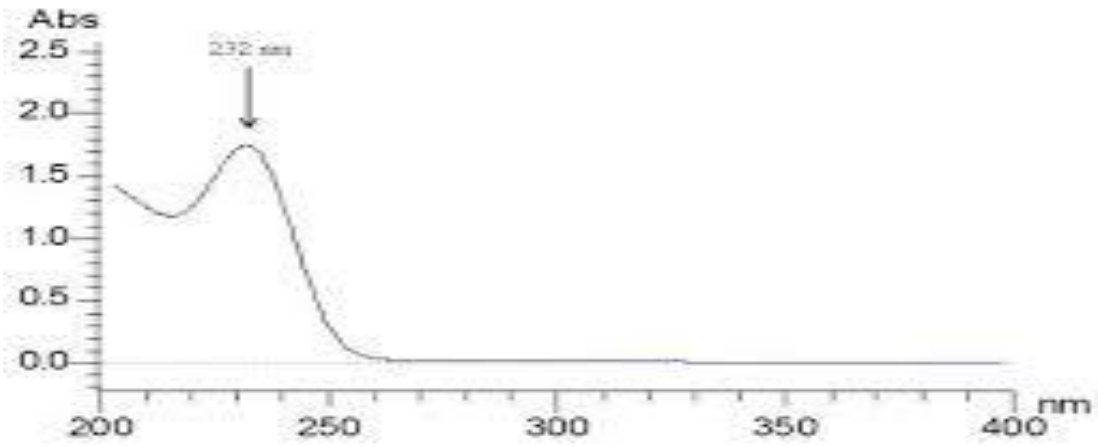


Figure 3: UV Absorption maxima of Metformin.

Table 4: Calibration curve data for Metformin in phosphate buffer 7.4.

S.No	Concentration(mcg/ml)	Absorbance Mean(±SD)
1	5	0.134
2	10	0.312
3	15	0.45
4	20	0.593
5	25	0.794
6	30	0.941

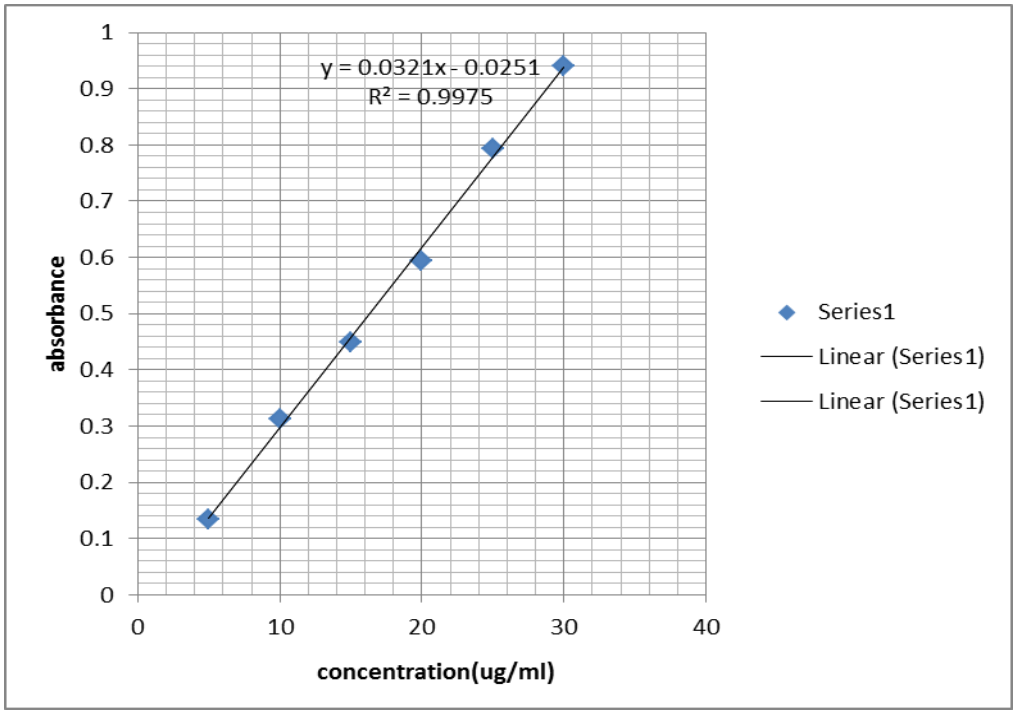


Figure 4: Calibration curve for Metformin in phosphate buffer 7.4.

Physicochemical parameters

The film were evaluated for the following.

Thickness of patches

Table shows thickness of various patches. Thickness of various patches varied (from0.012-0.062mm) Films were measured at four different places of each patch and mean value was calculated.

Folding endurance

The folding endurance of formulations is shown in the table no: 3 the folding endurance was found to be higher in formulation F1 and F2 than other formulations the folding endurance in the formulations was found in the following order.

F1>F2>F3>F7>F4>F6>F7.

Table 5: 1Evaluation parameters of transcutaneous patches,

Formulation	Drug content (%) SD, n=4	Thickness(mm)± SD, n=6	Folding endurance (No of folds), n=6
F1	31.25	0.012	50
F2	51.95	0.039	34
F3	18.25	0.046	9
F4	69	0.062	5
F5	61.9	0.012	1
F6	67.13	0.022	5
F7	82.85	0.025	8

F1 FORMULATION

Table 6: In-vitro diffusion studies of formulation F1.

Time(hr)	Absorbance	Concentration	con×DF ×100	Amnt of release	% drug release	Cumulative % release
1	0.119	4.25	4250	4.25	10.62	10.17
2	0.126	4.5	4500	4.5	11.25	10.93
4	0.132	4.71	4714	4.71	11.78	11.51
6	0.150	5.35	5357	5.35	13.39	12.58
8	0.171	6.1	6107	6.1	15.26	14.3
10	0.171	6.1	6107	6.1	15.26	14.3
12	0.175	6.25	6250	6.25	15.62	15.44
24	0.35	12.5	12500	12.5	31.25	23.34

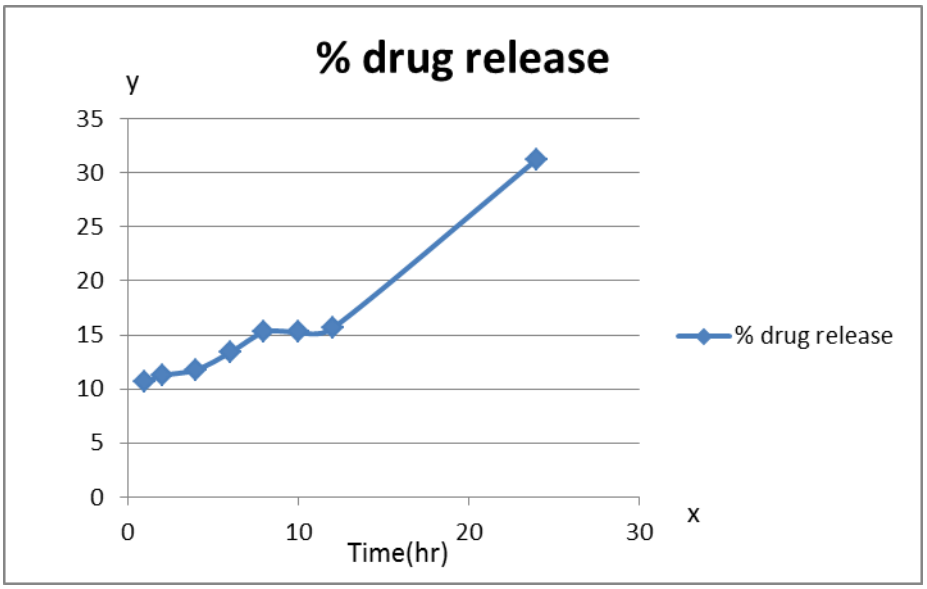


Figure 5: Graphical representation of time vs. % drug release.

F2 FORMULATION

Table 7: In-vitro diffusion studies of formulation F2.

Time(hr)	Absorbance	Concentration	Con ×DF ×100	Amt of release	% drug release	Cumulative % release
1	0.06	2.14	2142	2.14	5.35	5.35
2	0.07	2.5	2500	2.5	6.25	5.8
4	0.115	4.10	4107	4.1	10.26	8.25
6	0.212	7.57	7571	7.57	18.92	14.59
8	0.249	8.89	8892	8.89	22.23	20.57
10	0.249	8.89	8892	8.89	22.23	20.57
12	0.291	10.39	10392	1.39	22.98	24.10
24	0.582	20.78	20780	20.78	51.95	38.02

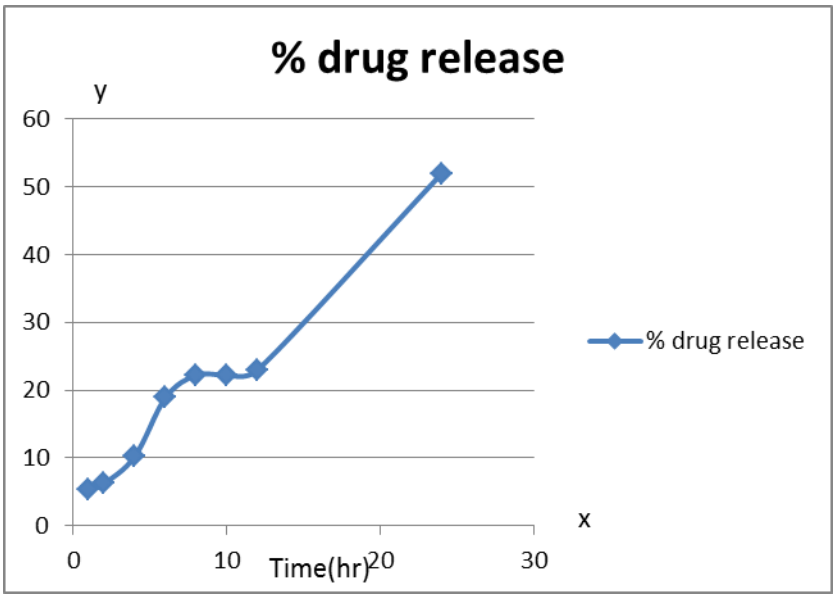


Figure 6: A Graphical representation of time vs. % drug release.

F3 FORMULATION

Table 8: In-vitro diffusion studies of formulation F3.

Time(hr)	Absorbance	Concentration	con×DF ×100	Amnt of release	% drug release	Cumulative % release
1	0.10	3.57	3571	3.57	7.14	7.14
2	0.11	3.92	3928	3.92	7.85	7.49
4	0.11	3.92	3928	3.92	7.85	7.85
6	0.112	4.01	4010	4.01	8.02	7.93
8	0.117	4.195	4195	4.195	8.39	8.20
10	0.117	4.195	4195	4.195	8.39	8.39
12	0.128	4.57	4571	4.57	9.14	8.76
24	0.256	9.14	9140	9.147	18.25	13.69

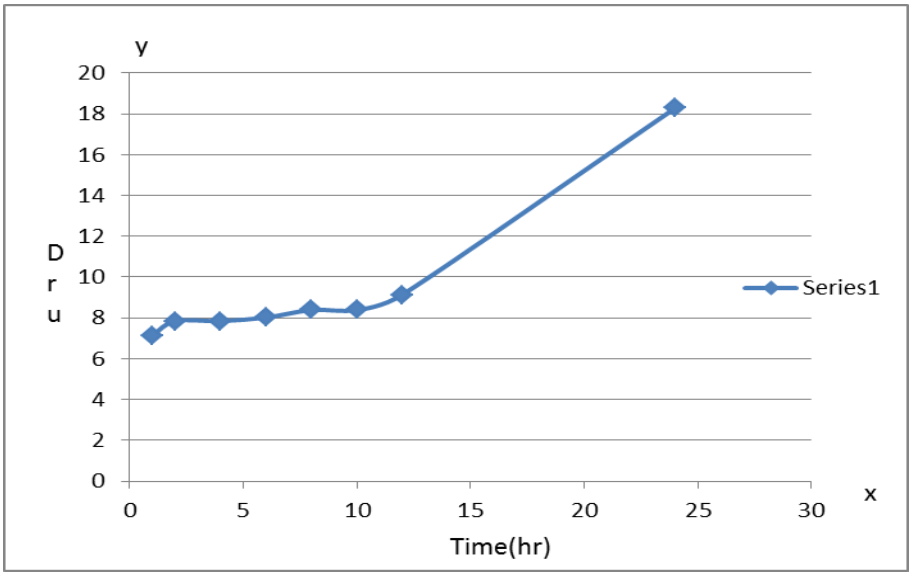


Figure 7: A Graphical representation of time vs. % drug release,

F4 FORMULATION

Table 9: In-vitro diffusion studies of formulation F4.

Time(hr)	Absorbance	Concentration	Con×DF ×100	Amnt of release	% drug release	Cumulative % release
1	0.145	5.17	5178	5.17	51.78	51.78
2	0.19	6.78	6785	6.78	67.85	59.81
4	0.17	6.07	6071	6.07	60.71	64.28
6	0.171	6.13	6130	6.13	61.3	61.0
8	0.175	6.28	6280	6.28	62.8	62.05
10	0.175	6.28	6280	6.28	62.8	62.8
12	0.175	6.28	6280	6.28	62.8	62.8
24	0.193	6.9	6900	6.9	69	65.9

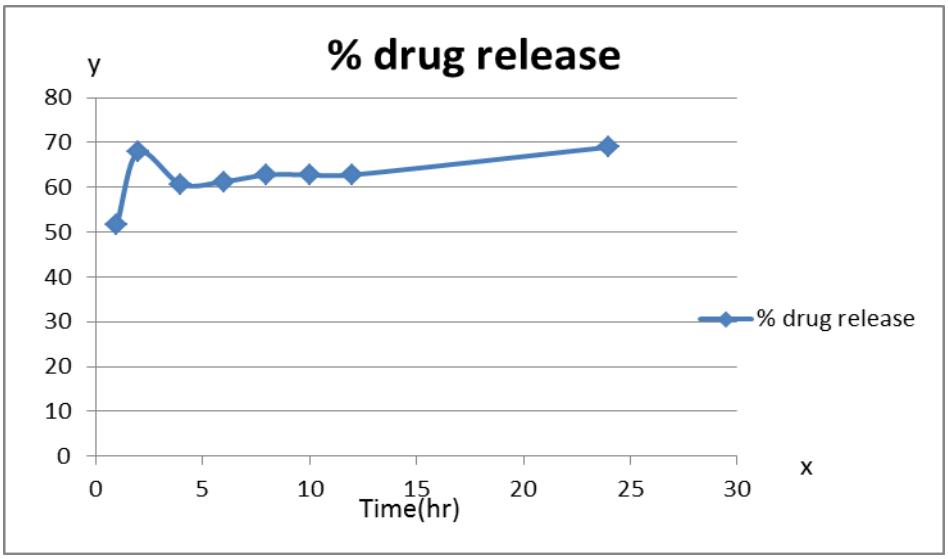


Figure 8: Graphical representation of time vs. % drug release.

F5 FORMULATION

Table 10: In-vitro diffusion studies of formulation F5.

Time(hr)	Absorbance	Concentration	Con ×DF ×100	Amt of release	% drug release	Cumulative % release
1	0.14	5.07	5071	5.07	10.14	10.14
2	0.272	9.71	9714	9.71	19.42	14.78
4	0.387	13.82	13821	13.8	27.64	23.53
6	0.550	19.65	19650	19.65	39.3	33.47
8	0.578	20.65	20650	20.65	41.3	40.8
10	0.578	20.65	20650	20.65	41.3	41.3
12	0.578	20.65	20650	20.65	41.3	41.3
24	0.854	30.5	30500	30.5	61	51.15

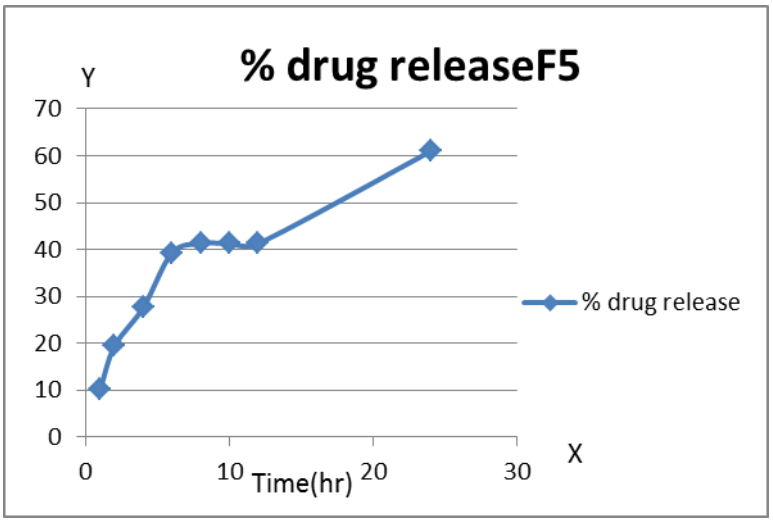


Figure 9: A Graphical representation of time vs. % drug release.

F6 FORMULATION

Table 11: In-vitro diffusion studies of formulation F6,

Time(hr)	Absorbance	Concentration	con×DF ×100	Amnt of release	% drug release	Cumulative % release
1	0.125	4.46	4464	4.46	14.88	14.88
2	0.252	9	900	9	30	22.4
4	0.262	9.3	9357	9.35	31.19	30.59
6	0.27	9.64	9642	9.64	32.13	31.36
8	0.27	9.64	9642	9.64	32.13	31.36
10	0.282	10.07	10071	10.07	33.57	32.85
12	0.282	10.07	10071	10.07	33.57	33.57
24	0.564	20.14	20140	20.14	67.13	50.35

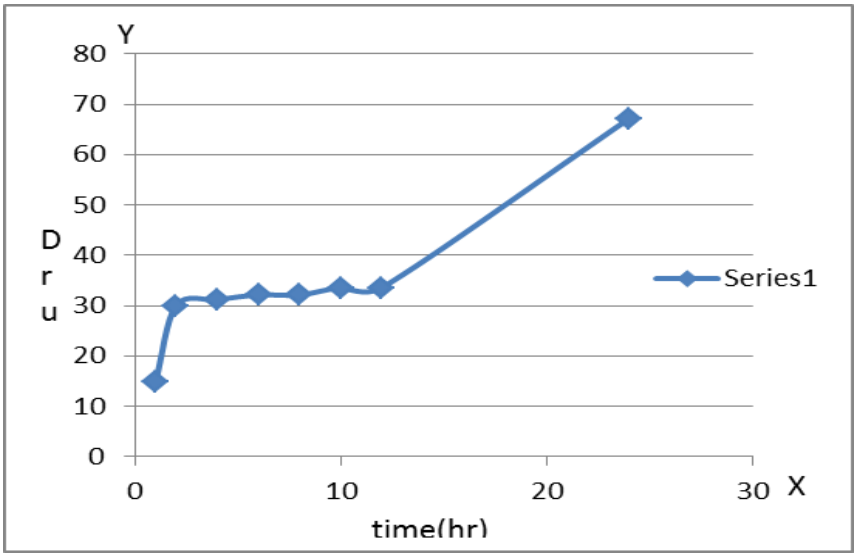


Figure 10: A Graphical representation of time vs. % drug release.

F7 FORMULATIONS

Table 12: In-vitro diffusion studies of formulation F7.

Time(hr)	Absorbance	Concentration	con×DF ×100	Amnt of release	% drug release	Cumulative % release
1	0.061	2.92	2928	2.92	14.64	14.64
2	0.082	3.03	3035	3.03	15.17	14.90
4	0.272	9.71	9714	9.71	48.57	31.87
6	0.272	9.71	9714	9.71	48.57	48.57
8	0.272	9.71	9714	9.71	48.57	48.57
10	0.272	9.71	9714	9.71	48.57	48.57
12	0.373	13.32	13321	13.32	66.60	57.58
24	0.6	16.57	26571	16.57	82.85	74.72

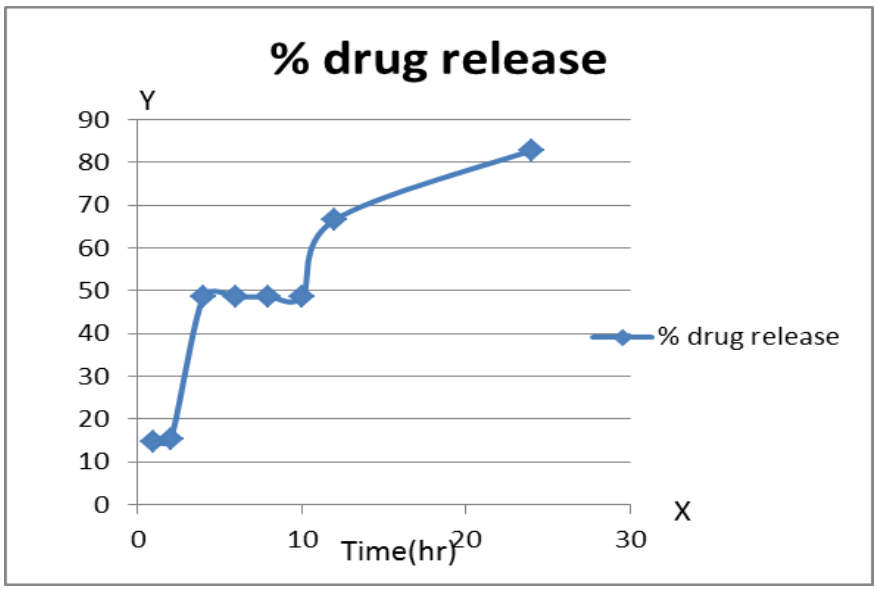


Figure 11: A Graphical representation of time vs. % drug release.

Table 13: In-Vitro Diffusion Studies (24 Hr) of All Formulations.

Formulation code	Absorbance	Concentration	con×DF ×100	Amnt of release	% drug release	Cumulative % release
F1	0.35	12.5	12,500	12.5	31.25	31.25%
F2	0.582	20.78	20,780	20.780	51.95	41.6%
F3	0.256	9.74	9,140	9.14	18.28	35.11%
F4	0.193	6.9	6900	6.9	69	43.64%
F5	0.854	30.05	30,500	30.50	61	65%
F6	0.564	20.14	20,140	20.14	69.13	65.06%
F7	0.6	16.57	26571	16.57	82.85	75.99%

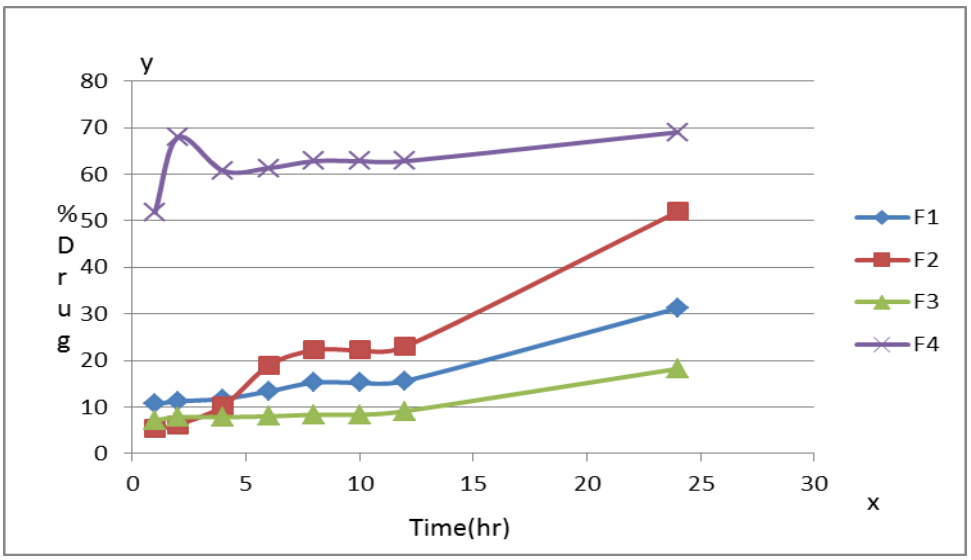


Figure 12: % Drug release of HPMC Pure patches.

From the above four pure HPMC formulations F1, F2, F3&F4. F4 Formulation showed high release of 69% in 24 hrs.

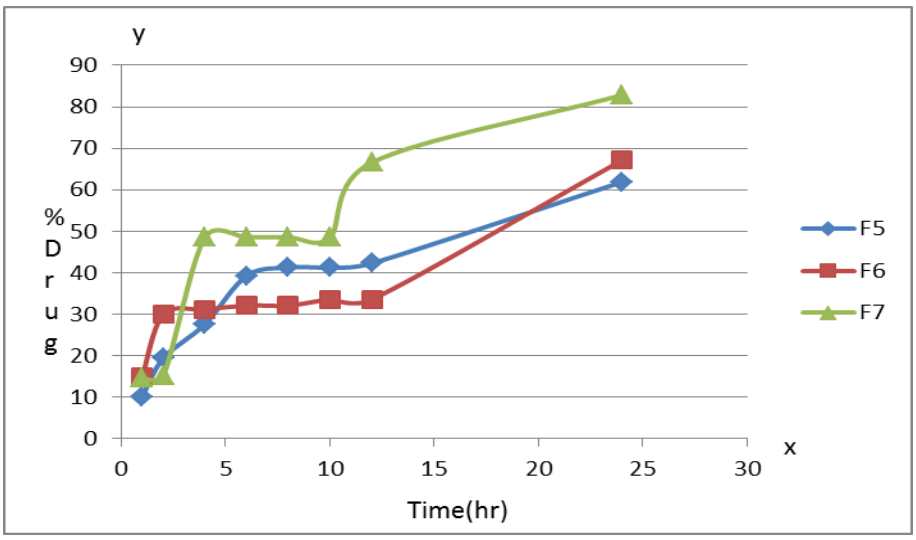


Figure no: 13 % Drug release of (HPMC+PEG) Hybrid Patches.

From the above three Hybrid formulations F5, F6 & F7 The F7 Formulation showed high release of 82.85% in 24 hrs.

7. SUMMARY AND CONCLUSION

The patches were prepared by solvent evaporation method. The standard curve was plotted by using U.V spectroscopy. Patches were evaluated for physico chemical parameters such as Thickness, Drug content, folding endurance. Thickness of patches varied with HPMC Pure and Hybrid patches. Drug content was found to be high and uniform. Folding endurance found to be greater in 5%Pure HPMC patch F1.

Permeation studies were carried out using Egg membrane. As the concentration of polymer increases thickness of patches were increase in Pure HPMC patches. But in the hybrid patches thickness did not increased.

Various concentrations of natural and synthetic hydrophilic polymers on *in vitro* release rate from the prepared Metformin Transcutaneous patches. Combinations of natural and synthetic polymers in the ratio of 75:25 were showing good release rate as compared to pure polymer and other hybrid formulation.

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