Journal of Comprehensive Pharmacy

Research Article

Available Online at: www.jcponline.in

ISSN NO: 2349-5669

Design and characterization of unidirectional drug release of *Metformin hydrochloride* using transdermal drug delivery system

Sowjanya Battu,^{a*} Uma Maheshwar R Vatikuti^b

^aDepartment of Pharmaceutics, CMR College of Pharmacy, Medchal Road, Hyderabad-501401, Andhra Pradesh, India

^bDepartment of Pharmacognosy, CMR College of Pharmacy, Medchal Road, Hyderabad-501401, Andhra Pradesh, India

ARTICLE INFO

Article history:

Received 1 April 2014

Accepted 15 July 2014

Available online 21 August 2014

*Corresponding author:

Sowjanya Battu

E-mail:

sowjanyabattumpharmacy@gmail.com

Tel.: +91-9703239351

ABSTRACT

Aim The objective of the current research work was to develop Metformin loaded transdermal patch for prolonged & controlled drug release and minimize the dose and dosing frequency, thereby overcome the drawbacks of a conventional dosage form like frequent dosing and tolerability and improve patient compliance.

Method Transdermal patches of Metformin hydrochloride were prepared by the Solvent evaporation technique using spherical bangles of known volume. The backing membrane used was Aluminium foil. The drug reservoir was prepared by dissolving HPMC K15, HPMC K4 and Carbopol 940 polymers and evaluated for various characters such as thickness, uniformity of weight, drug content, partition coefficient of drug, folding endurance, moisture uptake, moisture content, *In – Vitro* drug release studies and release Kinetics.

Results All the physico-chemical evaluation tests of formulations from TP 1 to TP 12 are found within the Standard conditions. The formulations from TP 1 to TP 12 have Good % cumulative drug release wherein TP 12 was found to be best formulation containing low (80.5 %) drug release even at 12th hour and expected to show even for 2 more hours. Higuchi and Peppas's results for TP1 to TP12 formulations follows Non- Fickian type of diffusion.

Conclusion From the above observed and calculated evaluation tests for formulations TPI-TP12, the formulation code bearing TP-12 with drug(100mg) and 2% Carbopol-940+2%HPMC k15 was observed to be the best combination(proportion) to improve the bioavailability their by prolonged drug release by minimizing the dose and dosing interval hence reducing the side effects.

KEYWORDS

Transdermal drug delivery system, Metformin, controlled release, characterization studies, release kinetics.

INTRODUCTION

Transdermal drug delivery is the non-invasive delivery of medications from the surface of skin-the largest and most accessible organ of human body through its layers, to the circulatory system. 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 [1]. It enhances patient compliance and minimizes harmful side effects of a drug caused from temporary overdose. Another advantage is convenience,

especially notable in patches that require only once weekly application. Such a simple dosing regimen can aid in patient adherence to drug therapy. Transdermal patches have been developed to improve clinical efficacy of the drug and to enhance patient compliance by delivering smaller amount of drug at a predetermined rate. This makes evaluation studies even more important in order to ensure their desired performance and reproducibility under the specified environmental conditions.

Diabetes mellitus type-2 formerly non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset

diabetes is a metabolic disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency [2]. The classic symptoms are excess thirst frequent urination, and constant hunger. Type 2 diabetes makes up about 90% of cases of diabetes with the other 10% due primarily to diabetes mellitus type 1 and gestational diabetes. Obesity is thought to be the primary cause of type 2 diabetes in people who are genetically predisposed to the disease. If blood glucose levels are not adequately lowered by these measures, medications such as metformin or insulin may be needed. In those on insulin there is typically the requirement to routinely check blood sugar levels.

Metformin is an oral antidiabetic drug in the biguanide class. It is the first-line drug of choice for the treatment of type 2 diabetes, in particular, in overweight and obese people and those with normal kidney function [3]. Its use in gestational diabetes has been limited by safety concerns. It is also used in the treatment of polycystic ovary syndrome, and has been investigated for other diseases where insulin resistance may be an important factor. Metformin works by suppressing glucose production by the liver. Metformin is the only antidiabetic drug that has been conclusively shown to prevent the cardiovascular complications of diabetes. It helps reduce LDL cholesterol and triglyceride levels, and is not associated with weight gain.

MATERIALS

Metformin is a drug of choice and is obtained from Dr. Reddy's laboratories, HPMC K4, HPMC K15, Carbopol-940 are Polymers purchased from Tirumala glassware and chemical stores, Hyderabad, Glycerol was used as Anti-adherent and is obtained from Tirumala glassware and chemical stores, Poly ethylene glycol a Plasticizer from Tirumala stores.

METHODS

Drug partition coefficient study:

The partition coefficient study was performed using *n*-octanol as the oil phase and phosphate buffer pH 7.4 as the aqueous phase [4]. The two phases were mixed in equal quantities and were saturated with each other on a mechanical water bath shaker at 37 °C for 24 h. The saturated phases were separated by centrifugation at 2000 rpm. Standard plots of the drug were prepared from both phosphate buffer pH 7.4 and *n*-octanol. Equal volumes (10 mL) of the two phases were placed in triplicate in conical flasks and, to each, 100 mg of drug was added. The flasks were shaken at 37 °C for 6 h to achieve complete partitioning at 100 rpm. The two phases were separated by centrifugation at 1000 rpm for 5 min and concentration of drug in each phase was determined spectrophotometrically by measuring absorbance at 245 nm. The partition coefficient (Kp)

was calculated from the equation.

$$\text{Partition coefficient (Kp)} = \frac{\text{Concentration of drug in organic phase}}{\text{Concentration of drug in aqueous phase}} \quad (1)$$

Preparation of Transdermal Patch of Metformin HCl by Solvent evaporation technique

Transdermal patches of Metformin hydrochloride were prepared by the Solvent evaporation technique using spherical bangles of known volume [5]. The backing membrane used was Aluminium foil. The drug reservoir was prepared by dissolving HPMC K15, HPMC K4 and Carbopol 940 polymers. The ratio of polymers was varied as mentioned in formulation table I, keeping the total volume of all the formulations fixed. Propylene glycol was added as a plasticizer as well as permeation enhancer. The drug Metformin was added in to the homogenous dispersion of polymer under slow stirring with magnetic stirrer. The uniform dispersion was then casted on an Aluminium foil (acts as backing membrane) of bangle size, previously attached on a petridish and dried at room temperature. The films were kept in desiccators for further study.

Table I: Formulation Table

F.Code	Carbopol - 940	HPMC K4	HPMC K15	Propylene Glycol (PG)
TP 1	1 %	-	-	4-5 drops
TP 2	-	1 %	-	
TP 3	-	-	1 %	
TP 4	1 %	1 %	-	
TP 5	-	1 %	1 %	
TP 6	1 %	-	1 %	
TP 7	2 %	-	-	
TP 8	-	2 %	-	
TP 9	-	-	2 %	
TP 10	2 %	2 %	-	
TP 11	-	2 %	2 %	
TP 12	2 %	-	2 %	

F.Code = Formulation Code

CHARACTERIZATION STUDIES

1. Physicochemical evaluation

Thickness

The thickness of transdermal film is determined by traveling microscope [6], dial gauge, screw gauge or micrometer at different points of the film.

Uniformity of weight

Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight [7]. The individual weight should not deviate significantly from the average weight.

Folding Endurance

Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding [8]. Folding endurance is determined by repeatedly folding the film at the same place until it break. The number of times the films could be folded at the same place without breaking is folding endurance value.

Drug content determination

An accurately weighed portion of film (about 100 mg) is dissolved in 100 mL of suitable buffer solution and the solution is shaken continuously for 24 h in shaker incubator [10]. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilutions.

Moisture content

The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h [11]. The films are weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using following formula.

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

Moisture Uptake

Weighed films are kept in a desiccator at room temperature for 24 h [11]. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in a desiccator until a constant weight is achieved. % moisture uptake is calculated as given below.

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

2. In vitro drug/ Permeation or release studies

Diffusion Cells e.g. Franz Diffusion Cell and its modification Keshary- Chien Cell

In this method transdermal system is placed in between receptor and donor compartment of the diffusion cell [11]. The transdermal system faces the receptor compartment in which receptor fluid *i.e.*, buffer is placed. The agitation speed and temperature are kept constant. The whole assembly is kept on magnetic stirrer and solution in the receiver compartment is constantly and continuously stirred throughout the experiment using magnetic beads. At predetermined time intervals, the receptor fluid is removed for analysis and is replaced with an equal volume of fresh receptor fluid. The concentration of drug is determined spectrophotometrically.

The pH of the dissolution medium ideally should be adjusted to pH 5 to 6, reflecting physiological skin conditions. For the same reason, the test temperature is typically set at 32°C (even though the temperature may be higher when skin is covered). Ph Eur considers 100 rpm a typical agitation rate and also allows for testing an aliquot patch section. The latter may be an appropriate means of attaining sink conditions, provided that cutting a piece of the patch is validated to have no impact on the release mechanism. The dissolution data obtained is fitted to mathematical models in order to ascertain the release mechanism [12].

RESULTS

The results for the required characterization studies that were performed for the current formulations are clearly noted in Table No's: II to V.

Table II: Ideal properties complied for Metformin to design TDDS

Parameter	Fullfilled value
Dose	100 mg
Half life in hr	1.5 to 4 h
Molecular weight	165.6 daltons
Partition coefficient*	Log P (octanol-water) between -2.64
Skin permeability coefficient*	5.5×10^{-6} cm/s at pH 7.4
Skin reaction	Non irritating and non sensitizer

DISCUSSION

Physico-chemical properties:

All the physic-chemical evaluation tests like thickness, weight variation, folding endurance, drug content, Moisture content, moisture uptake and partition coefficient results for above formulations from TP 1 to TP 12 are found within the Standard conditions wherein TP 12 was found to have least moisture content and excellent drug content, less weight variation and good folding endurance were observed for TP 12 than other formulations as mentioned in Table No: III.

In-Vitro drug release

The formulations from TP 1 to TP 12 have Good % cumulative drug release wherein TP 12 was found to be best formulation containing low (80.5 %) drug release even at 12th hour and expected to show even for 2 more hours, there by complying with the aim of controlled

Table III: Results for evaluated physic chemical parameters

Time (Hrs)	% CUMULATIVE DRUG RELEASE											
	TP 1	TP 2	TP 3	TP 4	TP 5	TP 6	TP 7	TP 8	TP 9	TP 10	TP 11	TP 12
1	18.2	17.2	22.2	17.2	18.3	17.3	16.3	18.3	18.7	16.9	15.3	10.5
2	28.2	25.3	28.2	29.6	25.3	26.5	24.3	24.2	21.3	20.2	21.2	21.2
3	35.2	35.6	38.2	40.2	38.2	32.1	38.2	36.2	31.2	24.2	28.2	30.2
4	47.2	44.3	47.2	44.2	40.2	40.6	40.2	43.2	41.2	32.2	32.3	38.2
5	51.2	56.2	57.2	50.3	46.2	46.1	48.3	52.2	52.2	38.9	38.2	44.2
6	63.2	66.5	67.2	62.2	54.2	50.3	53.1	61.2	58.2	42.5	42.5	52.6
7	69.3	70.3	75.2	74.3	60.2	55.6	59.1	66.0	66.2	48.2	50.5	64.2
8	74.3	76.8	84.3	78.2	70.5	73.2	65.1	72.2	69.3	52.2	58.2	68.5
9	80.2	84.2	86.2	80.3	76.1	89.2	73.2	81.2	72.2	68.2	66.2	72.5
10	90.2	88.3	92.2	84.2	82.2	91.6	79.3	85.2	80.0	72.2	75.5	78.6
11	97.2	96.2	96.6	88.2	87.3	92.6	82.0	86.8	84.2	85.1	82.2	79.0
12	99.1	99.5	98.2	92.2	91.6	96.2	87.3	88.7	89.3	90.3	87.5	80.5

Table IV: Results for *In – Vitro* Drug release studies

F.Code	Thickness (mm) ± S.D	Weight Variation (mg) ± S.D	Folding Endurance (times)	Drug Content (%)	Moisture Content (%)	Moisture Uptake	Partition Coefficient value for Metformin
TP1	1 ± 0.01	0.20 ± 0.01	110	96.5	1.04	1.05	- 2.64
TP2	1 ± 0.01	0.19 ± 0.005	128	96.8	4.76	5	
TP3	1 ± 0.01	0.60 ± 0.01	136	97.1	6.73	7.2	
TP4	1 ± 0.01	0.56 ± 0.11	142	98.4	1.05	1.06	
TP5	1 ± 0.01	0.18 ± 0.005	108	97.6	1.02	1.03	
TP6	1 ± 0.01	0.18 ± 0.005	119	97.8	1.51	1.53	
TP7	1 ± 0.01	0.18 ± 0.01	151	98.5	1.06	1.08	
TP8	1 ± 0.01	0.19 ± 0.01	148	98.7	4.76	5	
TP9	1 ± 0.01	0.18 ± 0.005	156	96.9	1	1.01	
TP10	1 ± 0.01	0.18 ± 0.005	98	98.1	1.08	1.09	
TP11	1 ± 0.01	0.17 ± 0.01	124	99.1	1.09	1.1	
TP12	1 ± 0.01	0.18 ± 0.005	160	99.3	1.47	1.5	

and prolonged drug release of drug from the patch. The results for *In-vitro* release are mentioned in Table No.- IV and Fig 1.

Mechanism of drug release

The Higuchi and Peppas's results for TP1 to TP12 formulations shows that all the formulations are under

Non- Fickian type of diffusion along with TP12 which is considered as best formulation based on the physico-chemical evaluation tests and *In-vitro* drug release studies as shown in Fig 2.

Table V: Results for Mechanism of drug release

F. Code	Higuchi's value	Peppas's value
TP1	0.931	0.701
TP2	0.929	0.739
TP3	0.946	0.660
TP4	0.949	0.678
TP5	0.930	0.668
TP6	0.861	0.726
TP7	0.946	0.672
TP8	0.944	0.687
TP9	0.933	0.695
TP10	0.823	0.714
TP11	0.858	0.734
TP12	0.998	0.828

Fig 1: Graph showing the *In-vitro* drug release studies for all formulations

Fig 2: Graph showing mechanism of drug release for best formulation

CONCLUSION

The current project transdermal patches was performed using Metformin, an anti diabetic drug to treat type-2diabetis mellitus using different polymers such as Carbopol, HPMC K4, K15 by solvent evaporation technique and formulated 12 different formulations and performed different physico-chemical evaluation tests such as thickness, Uniformity of weight, Drug content determination, Moisture content, Moisture Uptake, Folding Endurance, *In-vitro* evaluation using Franz Diffusion Cell. In vitro drug release studies were performed for 12 hours and release kinetics were calculated based on Higuchis and Peppas plots to confirm the best formulation from the 12 different formulations and noted the type of drug release kinetics.

From the above observed and calculated evaluation tests for formulations TPI-TP12 ,the formulation code bearing TP-12 with drug(100mg) and 2% Carbapol-940+2%HPMC k15 was observed to be the best combination(proportion) to improve the bioavailability their by prolonged drug release by minimizing the dose and dosing interval hence reducing the side effects.

AKNOWLEDGEMENT

Auhtor's wish to thank management CMR College of Pharmacy for providing all necessary assistance required for this study.

Conflict of Interest: None

REFERENCES

1. Kandavilli S, Nair V, Panchagnula R. Polymers in transdermal drug delivery systems, *Pharmaceutical Technology* 2002;62-78. Available from: www.pharmtech.com. Accessed on 15 Jan, 2008.
2. Guy RH. Current status and future prospects of transdermal drug delivery. *Pharm Res* 1996;13(12):1765-1769.
3. Guy RH, Hadgraft J, Bucks DA. Transdermal drug delivery and cutaneous metabolism. *Xenobiotica* 1987;17(3):325-343.
4. Singh UV, Pandey S and Udupa N, Preparation and evaluation of flurbiprofen and diclofenac sodium transdermal films, *Indian J. Pharm. Sci* 1993;54(4):145-147.
5. Chein YW. *Transdermal Controlled Systemic Medication*. New York and Basel, Marcel Dekker Inc. 1987;159-176.
6. Amnuaikit C, Ikeuchi I, Ogawara K, Higaki K, Kimura T, Skin permeation of propranolol from polymeric film containing terpene enhancers for transdermal use. *Int. J. Pharm* 2005;289(1-2):167-178.
7. Verma PR, Iyer SS, Transdermal delivery of propranolol using mixed grades of Eudragit: Design and in vitro and in vivo evaluation. *Drug Dev Ind Pharm* 2000;26(4):471-476.
8. Kusum Devi V, Saisivam S, Maria GR, Deepti PU, Design and evaluation of matrix diffusion controlled transdermal patches of verapamil hydrochloride. *Drug Dev Ind Pharm* 2003;29(5):495-503.
9. Saxena M, Mutalik S, Reddy MS, Formulation and evaluation of transdermal patches of Metoclopramide Hydrochloride, *Indian Drug* 2006;43(9):740-745.
10. Keshary PR, Chien YW, Mechanisms of transdermal nitroglycerin administration (I): development of finite-dosing skin permeation system, *Drug Dev Ind Pharm* 1984;883-913.
11. Panner Selvam R, Anoop Kumar Singh, Sivakumar T, Transdermal drug delivery systems for antihypertensive drugs – A review. *Int J Pharm. Biomed Res* 2010;1(1):1-8.

Cite this Article as: Battu S, Vatikutti UMR, Design and characterization of unidirectional drug release of *Metformin hydrochloride* using transdermal drug delivery system. *J Compr Phar* 2014;1(2):41-46.