Available online on 15.09.2022 at ijmspr.com

International Journal of Medical Sciences and Pharma Research

Open Access to Medical and Research

Open Access **Research Article**

Formulation, Development and Characterization of Transdermal Patches of Glipizide

Shubham Shivhare[1] Ashutosh Pal Jain[1], Teena Jain[1], Rinki Vishwakarma[1], Pinki Vishwakarma[3], Rubeena Khan[2], Shalini Prajapati[1], Anushree Jain[2]*

[1] *Bhagyoday Tirth Pharmacy College, Khurai Road, Achrya Vidhya Sagar Marg, Sagar, MP 470002*

[2] *Adina College of Pharmacy, ADINA Campus Rd, Lahdara, Sagar, MP, 470001*

[3] *People's College of Pharmaceutical Sciences & Research, Peoples University Campus, Bhanpur, Bhopal, MP, 462037*

Article Info:

Article History:

Received 08 July 2022
Reviewed 27 Aug 2022
Accepted 04 Sep 2022
Published 15 Sep 2022

Cite this article as:

Shivhare S, Jain AP, Jain T, Vishwakarma R, Vishwakarma P, Khan R, Prajapati S, Jain A, Formulation, Development and Characterization of Transdermal Patches of Glipizide, International Journal of Medical Sciences & Pharma Research, 2022; 8(3):1-7

DOI: http://dx.doi.org/10.22270/ijmspr.v8i3.47

*Address for Correspondence:

Ms. Anushree Jain, Adina College of Pharmacy, ADINA Campus Rd, Lahdara, Sagar, MP, 470001

Email: anushree1595@gmail.com

Abstract

Transdermal patches are innovative drug delivery systems and can be used for achieving efficient systemic effect by passing hepatic first pass metabolism and increasing the fraction absorbed. Like other drugs among the second-generation sulfonylureas, glipizide (GLP) acts by stimulating insulin secretion from pancreatic beta-cells as well as modifying the responsiveness of insulin-sensitive tissues. GLP belongs to biopharmaceutical classification system (BCS) class II and has a low solubility and high permeability. The aim of the current research was to formulate GLP transdermal patches utilizing various polymers combinations. HPMC, ethyl cellulose, eudragit RLPO, eudragit RSPO and permeation enhancer were mixed in different ratios, in presence of polyethylene glycol 400 as plasticizer by the solvent casting evaporation technique. The physicochemical parameters such as flexibility, thickness, smoothness, weight variation, moisture content, hardness, folding endurance and tensile strength were evaluated for the prepared patches. The formulation exhibited flexibility, uniform thickness and weight, smoothness, good drug content (98.65±0.26 to 99.45±0.65%) and little moisture content. The *in vitro* diffusion studies were carried out using modified Franz diffusion cell using egg membrane as the diffusion membrane and the formulation followed the zero order diffusion mechanism. The formulation containing HPMC: Eudragit as polymers showed faster release rate compared to ethyl cellulose: eudragit. The stability studies indicated that all the patches maintained good physicochemical properties and drug content after storing the patches in different storage conditions. Compatibility studies indicated that there was no interaction between the drug and polymers. The results revealed that, GLP transdermal patch could be considered as promising drug delivery system for diabetic patients.

Keywords: Transdermal patches, Glipizide, Sulfonylureas, Physicochemical parameters, *In vivo* diffusion study

INTRODUCTION

Transdermal drug delivery system (TDDS) has been an increased interest in the drug administration via the skin for both local therapeutic effects on diseased skin (topical delivery) as well as for systemic delivery of drugs. The skin as a site of drug delivery has a number of significant advantages over many other routes of drug administration, including the ability to avoid problems of gastric irritation, pH and emptying rate effects, avoid hepatic first-pass metabolism thereby increasing the bioavailability of drug, reduce the risk of systemic side effects by minimizing plasma concentrations compared to oral therapy, provide a sustained release of drug at the site of application; rapid termination of therapy by removal of the device or formulation, the reduction of fluctuations in plasma levels of drugs, and avoid pain associated with injections. The transdermal delivery can also eliminate pulsed entry into the systemic circulation, which might often cause undesirable side effects[1]. Diabetes mellitus is a major and growing health problem worldwide and an important cause of prolonged ill health and early death. It is a chronic metabolic disorder characterized by a high blood glucose concentration (hyperglycemia) caused by insulin deficiency, and it is often combined with insulin resistance[2,3]. Like other drugs among the second-generation sulfonylureas, glipizide (GLP) acts by stimulating insulin secretion from pancreatic beta-cells as well as modifying the responsiveness of insulin-sensitive tissues[4]. GLP belongs to biopharmaceutical classification system (BCS) class II and has a low solubility and high permeability. One of the properties limiting the oral use of GLP is its short elimination half-life of about 2-4 hr and incompliance problems can arise[5]. In addition, severe and sometimes fatal hypoglycemia and gastric disturbances are side effects of GLP oral therapy[6]. Poorly water-soluble compounds such as GLP have solubility- and dissolution-related bioavailability problems. Several attempts have been made to improve the bioavailability of oral GLP and hence patient compliance. A sustained-release system is one of the approaches used in several studies. It is likely that transdermal patches are efficient for treating chronic disorders such as diabetes mellitus because they can successfully manage blood sugar with minimal side effects of

oral delivery. This system may be particularly useful to control the blood glucose level and sustain the drug release. The administration of GLP by the transdermal route could overcome the problems associated with its oral route resulting in improved bioavailability[4,7] . To the best of our knowledge, only limited attempts have been made to facilitate the transdermal delivery of GLP. It has been reported that the solubility and permeation of GLP may hamper its application for transdermal delivery. However, the highly organized structure of stratum corneum forms an effective barrier to the permeation of drugs, which must be modified if poorly penetrating drugs are to be administered. The use of chemical penetration enhancers would significantly increase the number of drug molecules suitable for transdermal delivery[8]. Transdermal patch or skin patch is a medicated adhesive patch which is placed on the skin to deliver a specific dose of medication through the skin and in to the blood stream. Transdermal patches of drugs with polymers were prepared by solvent casting technique[9,10] . However, from a drug delivery sand point, it's far better that rate control resides with in the delivery devise in order to attain uniform input rates and reduce inter individual variability[11,12]. The objective of present research was development of matrix type transdermal patches of GLP and to evaluate physicochemical, mechanical properties, *in vitro* drug release, *in vitro* permeation.

MATERIAL AND METHODS

Materials

Glipizide was received from Bioplus Life Science, Bangalore, India, as a gift sample. Propylene glycol, HPMC, ethyl cellulose and eudragit RLPO purchased from Himedia Laboratory, Mumbai. Methanol, chloroform was purchased from CDH chemical Pvt. Ltd. New Delhi. Dialysis membrane of Mol Wt cutoff 1200 was purchased from Himedia Laboratory, Mumbai. All other chemicals and reagents used were of analytical reagent grade.

Preformulation studies

Determination of UV-visible absorption maxima of GLP

10mg of GLP was engaged in 10ml volumetric flask and dissolved up to 10ml with phosphate buffer pH 7.2, to contribute the concentration of 1000 µg/ml. 1ml of beyond was diluted to 10ml with phosphate buffer pH 7.2 to give concentration of 100 µg/ml. From the beyond stock solution, aliquots of 0.5, 1.0, 1.5, 2.0 and 2.5 ml were shifted to 10 ml volumetric flasks and made up to the mark with phosphate buffer pH 7.2. This solution was perused in UV-Visible Spectrophotometer. The absorbance of these solutions was restrained at 224nm and a graph of concentration versus absorbance was plotted.

FTIR spectroscopy of GLP

An FTIR spectrum of pure drugs was recorded on KBr disk method using Brukers Alpha Spectrophotometer with IR solution software to confirm the purity of drug. Sample powder was thoroughly mixed by triturating with potassium bromide in a glass mortar with pestle and compressed into disks in a hydraulic press (Techno search Instruments, India). FTIR spectra of the samples were recorded over a spectral region from 4700 to 400 cm-1 using 20 scans with 4 cm-1 resolution.

Preparation of matrix type transdermal patches

GLP containing transdermal patch was prepared utilizing method with slight modification[13]. The casting solution was prepared by dissolving weighed quantities of HPMC (350, 400 and 450mg) and ethyl cellulose, eudragit RLPO (50, 100 and 150mg), eudragit RSPO (50, 100 and 150mg) in 10 ml of methanol and chloroform and water mixture in ratio 1:1. To the resulting solution, 0.5% w/w of propylene glycol as plasticizers and 10% w/w penetration enhancer was added in this solution. Then drug (60 mg) was added and mixed thoroughly to form a homogeneous mixture. The casting solution was then poured into glass mould/Petri dish specially designed to seize the contents. The glass mould containing the casting solution was dried at room temperature for 24 hours in vacuum oven. The patch was removed by peeling and cut into round shape of 1 cm^2. These patches were kept in desiccators for 2 days for further drying and enclose in aluminum foil and then packed in self-sealing cover. Compositions of different formulations are shown in Table 1.

Table 1 Preparation of matrix type transdermal patches

Formulation Code	Drug (mg)	HPMC (mg)	Eudragit RSPO (mg)	Ethyl cellulose (mg)	Eudragit RSPO (mg)	Total polymer weight (mg)	Propylene glycol (Plasticizer) % w/w	Permeation Enhancer % w/w
F1	60	350	-	150	-	500	0.5	10
F2	60	400	-	100	-	500	0.5	10
F3	60	450	-	50	-	500	0.5	10
F4	60	350	150	-	-	500	0.5	10
F5	60	400	100	-	-	500	0.5	10
F6	60	450	50	-	-	500	0.5	10
F7	60	350	-	-	150	500	0.5	10
F8	60	400	-	-	100	500	0.5	10
F9	60	450	-	-	50	500	0.5	10

Dose calculations

- Width of the plate = 5cm
- Length of the plate = 12cm
- No. of 2.5 x 2.5cm^2 patch present whole plate = 12
- Each patch contains 5mg of drug.
- 12 no. of patch contains mg of drug? = 5×12 = 60mg
- The amount of drug added in each plate was approximately equal to 60 mg.

Characterization of transdermal patches

The prepared transdermal patches were evaluated for the following parameters[14-18].

Physical appearance

All the transdermal patches were visually inspected for color, flexibility, homogeneity and smoothness.

Thickness

The thickness of patch was measured by Vernier callipers.The thickness of patches were measured at three different places and average of three readings was taken with standard deviation.

Folding endurance

This was determined by repeatedly folding one patch at the same place until it broken. The number of times the patch could be folded at the same place without breaking / cracking gave the value of folding endurance.

Tensile strength

The tensile strength of the patch was evaluated by using the tensiometer (Erection and instrumentation, Ahmedabad). It consists of two load cell grips. The lower one was fixed and upper one was movable. Film strips with dimensions of 2×2cm were fixed between these cell grips, and force was gradually applied till the film broke. The tensile strength was taken directly from the dial reading in kg.

$$Tensile\ strength\ (s) = \frac{Applied\ Force\ (m * g)}{Cross\ section\ area\ (b * t)}$$

Where, S = tensile stress in 980 dynes/cm2

m = mass in grams

g = acceleration due to gravity (980 dynes/cm2)

b = breadth of strip in centimeters

t = thickness of strip in centimeters

Percentage of moisture content

The prepared patches were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. Individual patches were weighed. The percentage of moisture content was calculated as the difference between final and initial weight with respect to initial weight.

Percentage of moisture uptake

Firstly weighed the patches and then kept in a desiccators at room temperature for 24 hrs and then it's exposed to 84% RH (A saturated solution of potassium chloride) in a desiccators. The % of moisture uptake was calculated by difference between final and initial weight with respect to initial weight.

Drug content analysis

The patches (2.5*2.5 cm (Equivalent to 6.25 mg of drug) were taken into a three separate 10 ml volumetric flask and dissolved in methanol (10ml) with the help of shaker. The solution was centrifuged to separate out any particulate matter. 1mL of sample was withdrawn and transferred in volumetric flask (10 ml of capacity). The sample was dilute up to the mark with distilled water and analyzed by UV spectrophotometer at 224.0 nm.

***In vitro* skin permeation study**

The in vitro skin permeation study was done by using a Franz diffusion cell (receptor compartment capacity: 80 ml: surface area: 3.14 cm^2. The egg membrane was separated and used for in vitro study. The receiver compartment was filled with 40 ml of phosphate buffer, pH 7.4. The Transdermal patch was firmly pressed onto the centre of the egg membrane and then the membrane was mounted on the donor compartment. The donor compartment was then placed in position such that the surface of membrane just touches the receptor fluid surface. The whole assembly was kept on a magnetic stirrer with suitable rpm throughout the experiment using magnetic beads. The temperature of receptor compartment was maintained at 37± 0.5ºC.

Drug release kinetic data analysis

Several kinetic models have been proposed to describe the release characteristics of a drug from matrix. The following three equations are commonly used, because of their simplicity and applicability. Equation 1, the zero-order model equation (Plotted as cumulative percentage of drug released vs time); Equation 2, Higuchi's square-root equation (Plotted as cumulative percentage of drug released vs square root of time); and Equation 3, the Korsemeyer-Peppas equation (Plotted as Log cumulative percentage of drug released vs Log time) [19-21].

RESULT AND DISCUSSION

Solubility of GLP was found, soluble in ethanol, chloroform and 0.1 N NaOH, slightly soluble in distilled water, 0.1 N HCl and soluble in phosphate buffer pH 7.2 and freely soluble in methanol. Loss on drying and melting point of GLP was found to be1.56±0.26 % and 210-212°C respectively. The λ_{max} of GLP was found to be 224nm by using U.V. spectrophotometer (Labindia-3000+) in linearity range 5-25µg/ml Figure 1& 2. The calibration curve of the drug displayed a high linearity with an r^2 value of 0.999 where a linear relationship was observed within the concentration range. Identification of GLP was done by FTIR spectroscopy with respect to marker compound. It was identified from the result of IR spectrum as per specification Figure 3. All the patches prepared with different polymer concentration were found to be flexible, smooth, opaque, non-sticky and homogeneous in nature. This may be due to the presence of plasticizer. Marginal difference in thickness was observed among each group indicated that more the amount of polymer higher the thickness values. All the nine patches have showed good folding endurance and indicated that the patches have good flexibility Table 2. The maximum folding endurance was found 236±3 in formulation F7. All the formulation show lowest moisture content i.e. less than 4%. Moisture in this value is required to provide strength and flexibility to the patches. In all formulations formulation F7 contain minimum moisture contain 2.47±0.25% and moisture uptake was less in F7 as compared to other formulation Table 3. The effect of concentration of polymers was observed on the percentage elongation and tensile strength. It was found that as the concentration of polymers increased, the percentage elongation and tensile strength were also increased within the patches. There was no significant difference in the drug content among the patches indicated content uniformity. The maximum drug content was found in formulation F7, 99.45±0.65% Table 4. The drug

release from optimized transdermal patches was found to be 98.74% at the end of 12 h for F7 Table 5. The *In vitro* drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order, first order and peppas plots kinetic equation, in order to determine the mechanism of drug release. When the regression coefficient values were compared, it was observed that an 'r' value of transdermal patches was maximum zero order i.e 0.983 hence indicating drug releases from formulations was found to follow zero order for transdermal patches Table 6 Figure 4-6. Stability studies showed that, there is no significant change in physical characteristics and drug content. Based on these results it was concluded that the formulated transdermal patches were found to be physically and chemically stable during the study period (60 days).

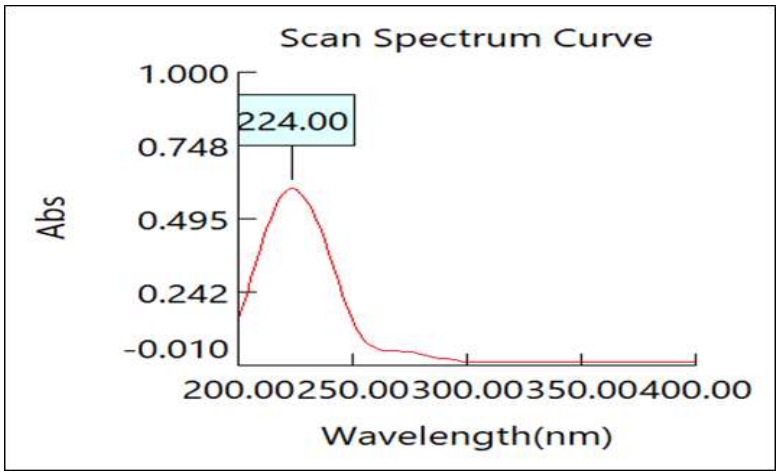

Figure 1 Determination of λ_{max} of glipizide

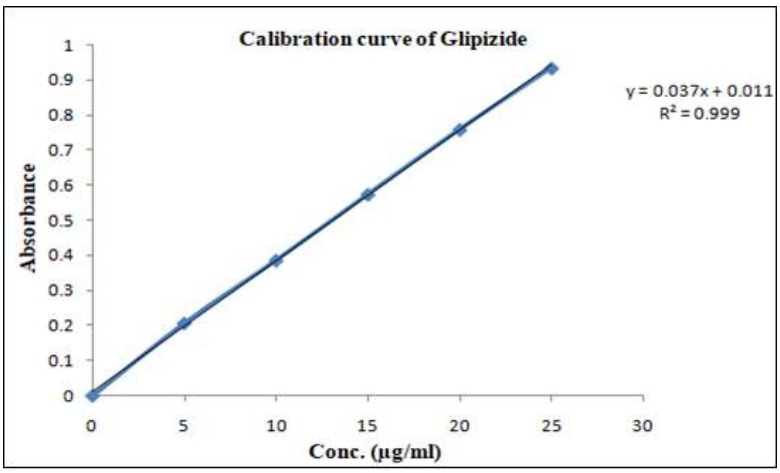

Figure 2 Calibration curve of glipizide

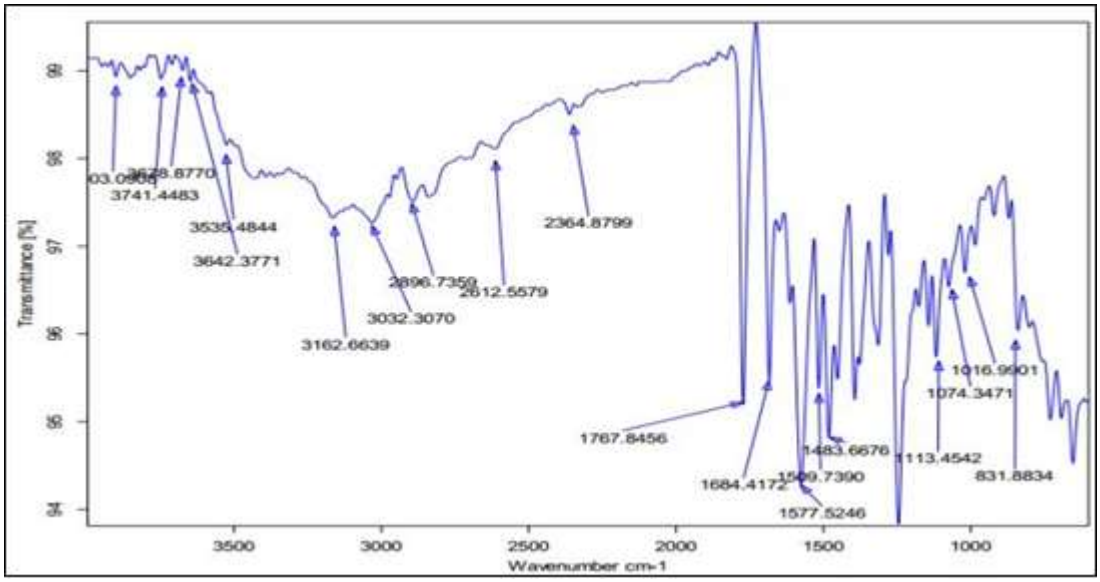

Figure 3 FTIR spectra of glipizide

Table 2 Thicknesses and folding endurance of different formulations

S. No.	Formulation Code	Thickness* (µm)	Folding Endurance* (Times)
1.	F1	65±3	185±54
2.	F2	71±5	198±6
3.	F3	65±4	205±5
4.	F4	69±5	195±8
5.	F5	63±6	210±4
6.	F6	68±5	216±2
7.	F7	61±2	236±3
8.	F8	63±3	185±8
9.	F9	65±6	193±4

*Average of Three determinations (n=3, Mean ± S.D.)

Table 3 % Moisture content and moisture uptake of different formulations

S. No.	Formulation Code	% Moisture Content	% Moisture Uptake
1.	F1	3.14±0.32	3.56±0.25
2.	F2	3.45±0.25	3.74±0.32
3.	F3	3.65±0.14	3.85±0.25
4.	F4	3.25±0.26	3.74±0.26
5.	F5	3.22±0.30	3.62±0.34
6.	F6	3.45±0.14	3.74±0.21
7.	F7	2.47±0.25	2.85±0.15
8.	F8	2.98±0.21	3.12±0.23
9.	F9	2.96±0.15	3.65±0.36

Table 4 Tensile strength and percentage drug content of different formulation

S. No.	Formulation code	Tensile strength (kg/cm²)	% Drug content
1	F1	0.95±0.04	98.87±0.15
2	F2	0.75±0.05	98.65±0.26
3	F3	0.65±0.06	98.74±0.32
4	F4	0.74±0.02	98.65±0.25
5	F5	0.65±0.04	99.05±0.14
6	F6	0.73±0.02	98.85±0.48
7	F7	0.62±0.05	99.45±0.65
8	F8	0.68±0.03	98.65±0.51
9	F9	0.73±0.04	99.08±0.42

*Average of Three determinations (n=3, Mean ± S.D.)

Table 5 *In-vitro* drug release data for optimized formulation F7

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	16.65	1.221	83.35	1.921
1	1	0	28.85	1.460	71.15	1.852
2	1.414	0.301	36.65	1.564	63.35	1.802
4	2	0.602	48.95	1.690	51.05	1.708
6	2.449	0.778	59.98	1.778	40.02	1.602
8	2.828	0.903	67.45	1.829	32.55	1.513
10	3.162	1	86.65	1.938	13.35	1.125
12	3.464	1.079	98.74	1.994	1.26	0.100

Table 6 Regression analysis data of formulation F7 transdermal patches

Formulation	Zero order	First order	Pappas plot
F7	R^2 = 0.983	R^2 = 0.765	R^2 = 0.982

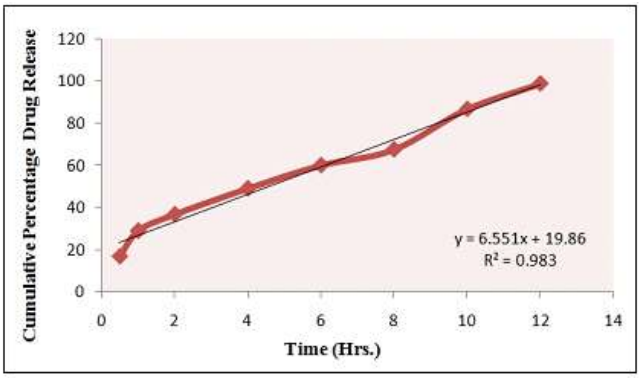

Figure 4 Cumulative percent drug released vs time (Zero Order Plots)

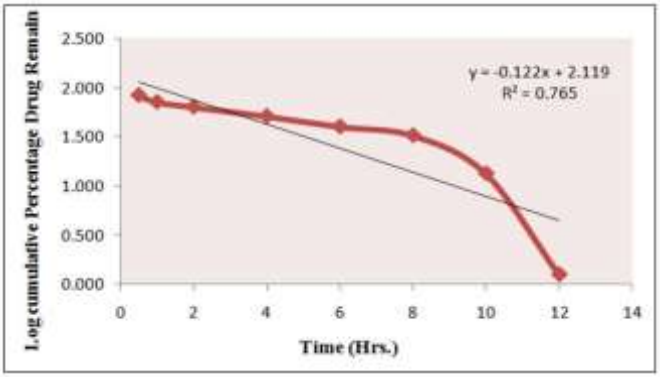

Figure 5 Log Cumulative percent drug remaining vs time (First Order Plots)

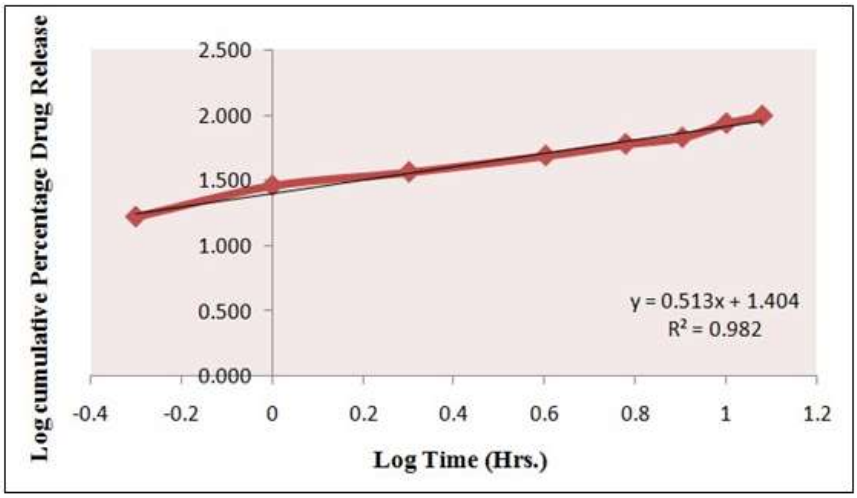

Figure 6 Log cumulative percent drug released vs log time (Peppas Plots)

CONCLUSION

The transdermal patches of GLP prepared by solvent casting method using a combination of HPMC, ethyl cellulose, eudragit RLPO, eudragit RSPO and in various ratios of plasticizers and permeation enhancers were studied. All the formulations showed good physicochemical properties such as thickness, weight variation, drug content and folding endurance. The *in vitro* release data showed that drug release from the patch has been affected by the type and concentration of the polymer. From this data, optimized formulations were screened. Formulation F7 were considered as the best formulations. Based on the encouraging results, the GLP transdermal patch can be used as a controlled drug delivery system and frequency of administration can be minimized. Though the efforts were made for the development of GLP transdermal patch, long-term pharmacokinetic and pharmacodynamic studies are needed to undertake the establishment of the usefulness of these patches. Further, these findings may help the industry to scale up for commercial production. Transdermal dosage form of GLP may provide clinicians an opportunity to offer more therapeutic options to their patients to optimize their care.

REFERENCES

1. Garala KC, Shinde AJ, Shah PH. Formulation and in-vitro characterization of monolithic matrix transdermal systems using HPMC/Eudragit S 100 polymer blends. International J Pharm Pharma Sci., 2009; 1(1):108-120.
2. Ghosal K, Rajan R, Nanda A. Effects of chemical enhancers on the release of glipizide through matrix patch. Int J ChemTech Res., 2009; 1(4):1128-1130.
3. Nagar H, Jain DK, Soni RS, Chandel HS. Potentiation of anti-diabetic effect of metformin and sitagliptin with ofloxacin in alloxan induced diabetic rabbits Pharmacologyonline 2011; 2:563-567.
4. Goyal S, Rai JK, Narang R, Rajesh K. Sulfonyl ureas for antidiabetic therapy, an overview for glipizide. Int J Pharm Pharm Sci., 2010; 2:1-6.
5. Emami J, Boucher MS, Varshosaz J. Preparation, characterization and optimization of glipizide controlled release nanoparticles. Res Pharm Sci., 2014; 9: 301-314.
6. Sun P, Li P, Li YM, Wei Q, Tian LH. A pH-sensitive chitosan-tripolyphosphate hydrogel beads for controlled glipizide delivery. J Biomed Mater Res B Appl Biomater., 2011; 97:175-183. https://doi.org/10.1002/jbm.b.31801
7. Behin SR, Punitha IS, Saju F. Development of matrix dispersion transdermal therapeutic system containing glipizide. Der Pharma Lett., 2013, 5:278-286.
8. Kanikannan N, Andega S, Burton S, Babu RJ and Singh M. Formulation and in vitro evaluation of transdermal patches of melatonin. Drug Dev Ind Pharm., 2004; 30:205-12. https://doi.org/10.1081/DDC-120028716
9. Kumar A, Transferosome: A recent approach for transdermal drug delivery, Journal of Drug Delivery and Therapeutics. 2018; 8(5-s):100-104 https://doi.org/10.22270/jddt.v8i5-s.1981
10. Lec ST, Yak SH, Kim SW and Berner B. One way membrane for transdermal drug delivery systems/system optimization. Int J Pharm., 1991; 77:231-7. https://doi.org/10.1016/0378-5173(91)90321-E
11. Nair SS, Chitosan-based transdermal drug delivery systems to overcome skin barrier functions, Journal of Drug Delivery and Therapeutics 2019; 9(1):266-270 https://doi.org/10.22270/jddt.v9i1.2180
12. Carslaw HS and Jaeger JC. Conduction of Heat in Solids, Oxford University Press. Oxford, edn. 1986.
13. Manvi FV, Dandagi PM, Gadad AP, Mastiholimath VS, Jagadeesh T. Formulation of a Transdermal Drug Delivery System of Ketotien Fumarate. Indian J Pharm Sci., 2003; 65(3):239-243
14. Rao RP, Divan PV. Influence of casting solvent on permeability of ethyl cellulose free films for transdermal use. East Pharma., 1997; 40:135-7.
15. Kusum DV, Saisivam S, Maria GR, Deepti PU. Design and evaluation of matrix diffusion controlled transdermal patches of verapamil hydrochloride. Drug Devel Indust Pharm., 2003; 29:495-503. https://doi.org/10.1081/DDC-120018638
16. Pandit V, Khanum A, Bhaskaran S, Banu V. Formulation and evaluation of transdermal films for the treatment of overactive bladder. Int J Pharm Tech Res., 2009; 1:799-804
17. Sankar V, Johnson DB, Sivanad V, Ravichadran V, Raghuram S. Design and evaluation of nifedipine transdermal patches. Indian J Pharm Sci., 2003; 65:510-5.
18. Rao RP, Divan PV. Influence of casting solvent on permeability of ethyl cellulose free films for transdermal use. East Pharma., 1997; 40: 135-7
19. Brahamankar DM, Jaiswal SB. Biopharmaceutics and pharmacokinetics e a treatise, pharmacokinetics: basic consideration. 2nd ed. Vallabh Prakashan; 2009. pp. 240e3.
20. Higuchi T. Mechanism of sustained action medication, theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci., 1963; 52:1145e9. https://doi.org/10.1002/jps.2600521210
21. Korsmeyer RW, Gumy R, Doelker E, Buri P, Peppas NA. Mechanism of solute release from porous hydrophilic polymer. Int J Pharm., 1983; 15:25e35. https://doi.org/10.1016/0378-5173(83)90064-9