FORMULATION, CHARACTERIZATION AND EVALUATION OF MATRIX TYPE TRANSDERMAL PATCH CONTAINING GLIBENCLAMIDE

Rajratna D. Gaikwad[1]*, Vijaya U. Barge[2], Amit J. Kasbe[3], Pallavi S. Borse[1], Kamlesh R. Deshmane[1], Pratiksha B. Avhad[1], Harshal M. Shinde[4]

[1] Research Scholar, Department of Pharmaceutical Quality Assurance, PDEAs Shankarrao Ursal College of Pharmaceutical Sciences and Research Centre, Kharadi, Pune-14, Maharashtra, India.
[2]Vice Principal,Professor, Department of Pharmaceutical Quality Assurance, PDEAs Shankarrao Ursal College of Pharmaceutical Sciences and Research Centre, Kharadi, Pune-14, Maharashtra, India.
[3]Assistant Professor, Department of Pharmaceutical Quality Assurance, PDEAs Shankarrao Ursal College of Pharmaceutical Sciences and Research Centre, Kharadi, Pune-14, Maharashtra, India.
[4] Research Scholar, Department of Pharmaceutics, PDEAs Shankarrao Ursal College of Pharmaceutical Sciences and Research Centre, Kharadi, Pune-14, Maharashtra, India.
*Corresponding author Email: rajratnagaikwad15@gmail.com

Article History: **Received:** 18.04.2023 **Revised:**07.05.2023 **Accepted:** 16.06.2023

Abstract: *Transdermal patches have been one of the effective tools in the delivery of active pharmaceutical ingredients parenterally with greater patient compliance and ease of use with minimum side effects. In the present research matrix type transdermal patches containing Glibenclamide were prepared using different ratios of hydrophilic polymer HPMC and hydrophobic polymer ethyl celluloseby solvent evaporation technique for its sustained release effect and increased bioavailability as compared to oral dosage form. The mixture of methanol and chloroform was used as a solvent and 30%w/w polyethylene glycol 400 (PEG 400) was used as a plasticizer with Dimethyl sulfoxide (DMSO) as a permeation and solubility enhancer. The possible drug and polymer interaction was studied by FTIR spectroscopy. All the prepared patches were subjected to physicochemical studies (Folding Endurance, Thickness, Weight variation, Drug content, Moisture content and Moisture uptake), in vitro permeation studies were done through a cellulose membrane having 45µ pore size.Short term stability studies were carried out to check the shelf life of formulation. The results suggested that there was no interaction between the drug and polymers. Variations in permeation profiles among the Batches were observed. Based on physicochemical and in vitro permeation studies, the formulated Batch 4 with 94.46% drug diffusion met most of the required ideal specifications and was considered an optimized batch. the formulated patches were good in physical strength as well as stable and effective with uniform drug content.Transdermal patches of Glibenclamide are likely to enhance the patient compliance as it would eliminate the need of repeated dosing, enhance the bioavailability and sustain the action of the drug.*

Keywords: *Transdermal Patch, Antidiabetic, Hypoglycaemic, Glibenclamide, HPMC, Ethyl Cellulose, Matrix Type.*

DOI: 10.48047/ecb/2023.12.Si8.577

INTRODUCTION

Diabetes is one of the largest global health emergencies of this century, ranking among the 10 leading causes of mortality together with cardiovascular disease (CVD), respiratory disease, and cancer[1]. Once known as ‘Honey urine’, diabetes was first discovered in 1500 BCE and has been recognized as a calamitous and lethal disease for about 2000 years [2-4]. Despite of availability of various formulations for the treatment of diabetes like Insulin, Tablets, Ayurvedic Syrups, etc. the management of diabetes has been a challenging task. Various approaches for the development of Novel Drug Delivery System have been made and development of such NDDS has been a necessity for the better, easy treatment for the treatment of Diabetes.

Transdermal drug delivery mechanism is most promising one. It has been demonstrated that medicines administered by this method has improved bioavailability with less side effects. It ensures controlled release of drug and deliver it directly to blood circulation. At the same time, the side effects are considerably reduced. As drug does not come in contact with stomach surface, there is no gastrointestinal irritation and side effects thus increasing drug compliance. The process is painless, drug does not go through usual metabolism in liver thus no adverse effects on liver. Most important impact is long availability of required serum levels which may result in decrease frequency of medicine. As a result of all above, TDD is becoming famous method of drug administration for increasing number of medicines [5,6].

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 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. 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 [7,8].

Glibenclamide is a secondgeneration sulphonyl urea oral hypoglycaemic agent, chemically it is 5-chloro-N-[2-[4-(cyclohexylcarbamoylsulfamoyl)phenyl]ethyl]-2methoxybenzamide. It is more potent than first generation sulphonylurea. Glibenclamide is also called as glyburide and its formula is $C_{23}H_{28}CIN_3O_5S$[9]. Plasma ½ life of Glibenclamideis about 3-5 h. Which enhance therapeutic effectiveness and keep steady plasma level. Transdermal application of Glibenclamidecan avoid the hypoglycaemic episode which are concomitant by oral Glibenclamide administration[10]. Glibenclamide has shown several adverse and potential side effect related to hypoglycemia with inaccurate dosing. It is demonstrated that Glibenclamide can cause gastrointestinal side effects including nausea, vomiting, anorexia, and heart burn and increase appetite. It can cause severe hypoglycemia through direct effect on the pancreatic cells of islets to inhibit production of glucagon and increased release of somatostatin[11,12]. The administration of Glibenclamide through Transdermal patch can avoid the above mentioned side effects and can also lead to increased Bioavailability and sustained release effect with better patients compliance.

In the present study and attempt to formulate matrix type transdermal patch was made for Glibenclamide drug by using hydrophilic polymer HPMC and hydrophobic polymer ethyl cellulose with help of plasticizer and permeation enhancer and using a combination of methanol and chloroform as volatile solvents. The possible drug and excipients interaction were checked by FTIR and formulated transdermal patches were thoroughly evaluated on physical and chemical parameters such as appearance,folding endurance,thickness,weight variation,percentage moisture content,percent moisture uptake and *in-vitro* diffusion studies. Short term stability studies were carried out to check the shelf life of formulation. The purpose of this study was to provide the delivery of drug across the skin into the systemic circulation in controlled rate to obtain sustained release effect with reduced side effects and reduced frequency of dosing with enhanced bioavailability as compared to oral dosage form with greater patient compliance.

MATERIALS AND METHODS

Materials

Glibenclamide was procured from Yarrow Chem Pvt. Ltd, Mumbai, India.Hydrophilic polymer HPMC was obtained as gift sample from Ashland, Netherlands. Co. Hydrophobic polymer Ethyl cellulose, Chloroform was used as solvent, Polyethylene Glycol 400 was used as plasticizer was obtained from Research-Lab Fine Chem Industries, Mumbai. Other chemicals such as Dimethyl sulfoxide(DMSO)

which was used as permeation enhancer and solubility enhancer, methanol was used as solvent were procured from COSCO CHEM, Pune.

Drug and excipients compatibility study

The possible Drug and Excipients interaction was checked by FTIR (Shimadzu 8400s)Spectrophotometer. The drug was placed in the sample holder using IR grade potassium bromide as a blank and scanned between the ranges 400–4000 cm^{-1} to determine the characteristic peaks of the drug[13].

The drug and all the Excipients were mixed in 1:1 ratio uniformly and kept for 1 month at room temperature. This mixture of drug and excipients was analysed on FTIR (Shimadzu 8400s) Spectrophotometer.The mixture was placed in the sample holder using IR grade potassium bromide as a blank and scanned between the ranges 400–4000 cm^{-1} to determine the characteristic peaks of the mixture. The obtained spectra of Drug and Mixture was compared for their characteristics peak and checked if any shift in characteristic peak can be seen[14].

Method of Preparation of Transdermal Patch of Glibenclamide

The Matrix type Transdermal Patch containing Glibenclamide was prepared by Solvent evaporation technique. Different concentration of HPMC and Ethyl cellulose were taken keeping total polymer weight 900mg and dissolved in mixture of Methanol and Chloroform (3:2) ratio respectively keeping total volume 30ml. In the above polymeric solution drug was added in small parts for uniform dispersion of drug and subsequent dissolution in polymeric solution. DMSO was added in dropwise manner as solubility enhancer as well as permeation enhancer. It was followed by addition of PEG 400 as plasticizer. The stirring was continued for 1 hour and the polymeric solution containing drug and excipient was poured into petri plate avoiding formation of bubbles and kept for drying for 24hrs. After 24 hours, the petri dish was kept in hot air oven at 50-60^{0}C for half hour to remove excess solvents. Further patch was removed from petri plate and cut into desired size and shape and further evaluated for various physicochemical parameters[15-19].

Table 1: Formulation Table of Transdermal Patch of Glibenclamide

Ingredients	**F1**	**F2**	**F3**	**F4**
Glibenclamide (mg)	125	125	125	125
HPMC K35M (mg)	150	225	300	375
Ethyl Cellulose (mg)	750	675	600	525
PEG 400 (% W/W)	30	30	30	30
Methanol:Chloroform (3:2) (ml)	30	30	30	30
Dimethyl Sulfoxide (DMSO) (ml)	0.6	0.6	0.6	0.6

{*Note: - 1. The total polymer weight was kept 900mg, 2. The total solvent volume was kept 30ml, 3. By above formulation table Patch of 44.15625cm^2area was obtained from which circular patches of 1.76625cm^2 area were cut with each patch containing 5 mg drug}

Evaluation of prepared transdermal patch of Glibenclamide

The formulated Transdermal Patch was evaluated on the basis of various physicochemical parameters such as physical appearance, folding endurance, thickness, weight variation, percentage moisture content, percentage moisture uptake, in-vitro drug diffusion study. Short term stability studies were carried out to check the stability of formulated transdermal patch over time and to check shelf life of the formulation.

Physical Appearance

The prepared transdermal patch was inspected visually for its colour, shape,flexibility, smoothness any possibility of crystal formation of drug[20].

Folding endurance
The transdermal patches were evaluated for mechanical strength by determining the folding endurance. Transdermal patch of 2x2cm size was cut and repeatedly folded at same point until it breaks and the folds were measured. The number of times the patches had to be folded until it breaks was observed is considered as folding endurance[21,22].

Thickness
The thickness of patches was measured by using digital calliper.The mean values and standard deviation were calculated for individual batches[23].

Weight variation
Prepared circular patches of 1.76625cm^2 areawascut and weight of each patch was determined by using digital balance. The average weight of each patch and standard deviation was calculated for individual batches[24].

Percentage moisture content
The prepared films were weighed individually and kept in a desiccator containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films were reweighed and the percentage moisture content was determined by using the given formula [25,26].
Percentage moisture content = (Initial weight- Final weight/Final weight) x 100

Percentage moisture uptake
The weighed films were kept in a desiccator at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the films were reweighed and the percentage moisture uptake was determined by using the given formula[27,28].
Percentage moisture uptake = (Final weight- Initial weight/ Initial weight) x 100

Drug Content
5 Patches were selected randomly and was completely dissolved in methanol. The solution was filtered through filter paper and amount of drug present in the filtrate was determined by using UV spectrophotometer at 228nm. absorbance was taken on UV Spectrophotometer and the drug content was estimated from the standard graph [29,30].

in-vitro drug diffusion
The *in vitro* Diffusion Study was performed using Franz Diffusion having receptor compartment quantity of 50ml using cellulose membrane of 45µ pore size. The patch of predefined size was selected randomly and placed on membrane facing donor compartment and the receptor compartment was filled using phosphate buffer solution (pH 7.4). And the whole assembly was maintained at 37 ± 2 ^{0}C. For diffusion studies cellulose membrane was soaked in the same buffer solution for 12 hrs. before mounting on diffusion cell. The samples were withdrawn after predefined time interval and sink condition was maintained by replacing same amount of phosphate buffer (pH 7.4). Glibenclamide concentration was assayed using UV spectrophotometer for noting absorbance at the lambda max that is 228nm[27-34].

Short term stability studies
To assess the stability the randomly selected patches were kept at room temperature over a period of 45 days. Patches were evaluated at 15th, 30th, 45th day for their physicochemical properties and Drug content[16].

RESULTS AND DISCUSSION

Drug and excipients compatibility study

Drug and excipient interactions play a vital role with respect to release of drug from the formulation amongst others. FTIR techniques have been used here to study the physical and chemical interaction between drug and excipients used.The IR spectral analysis of Glibenclamide (Figure 1) alone showed that the principal peaks were observed at wave numbers of 3357.84cm^{-1}(N-H Stretching), 2931.60cm^{-1} (C-H Stretching), 744.47cm^{-1} (C-Cl stretching), 1712.67cm^{-1} (C=O stretching), 1606.59cm^{-1}(C=O stretching), 1230.50cm^{-1}(C-O-C stretching), 1334.65 cm^{-1}(O=S=O stretching) confirming the purity of the drug as per established standards. In the IR spectra of the physical mixture of Glibenclamide, HPMC and Ethyl cellulose(Figure 2) the major peaks of Glibenclamide were 3357.84cm^{-1} (N-H Stretching), 2935.46cm^{-1}(C-H Stretching), 742.54cm^{-1}(C-Cl stretching), 1701.10cm^{-1} (C=O stretching),1606.59cm^{-1}(C=O stretching), 1228.57cm^{-1}(C-O-C stretching), 1325.01cm^{-1} (O=S=O stretching). However, some additional peaks were observed with physical mixtures, which could be due to the presence of polymers.there were no remarkable changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers.

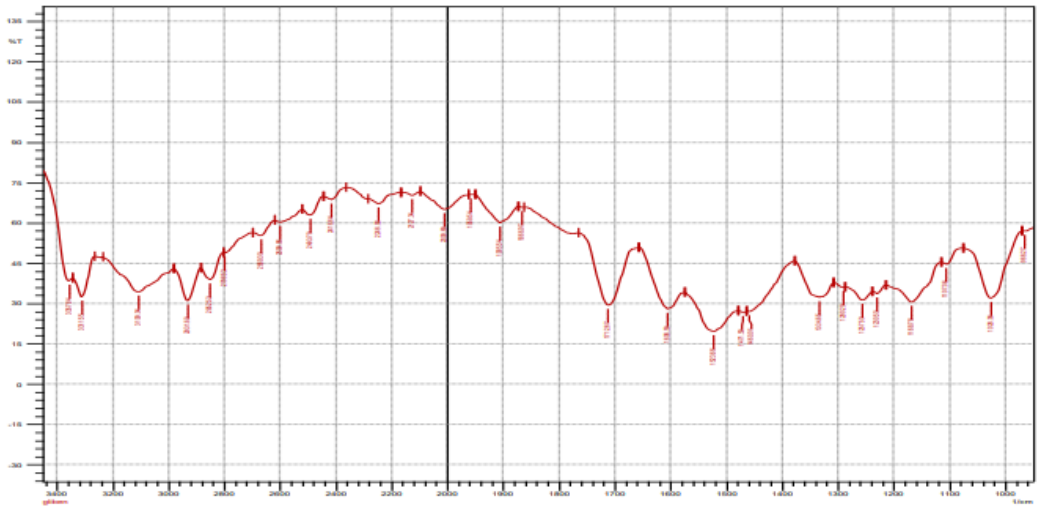

Figure 1: FTIR spectra of pure drug Glibenclamide

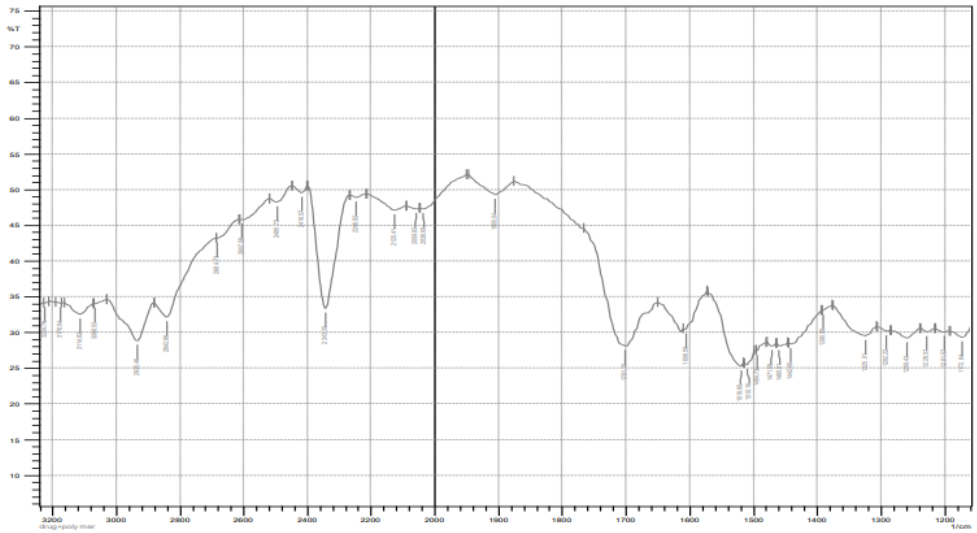

Figure 2: FTIR spectra of Drug and Excipients

Evaluation of prepared transdermal patch of Glibenclamide: -

Physical Appearance

The prepared transdermal patch was inspected visually for its colour, shape,flexibility, smoothness any possibility of crystal formation of drug. All the prepared patches were Uniformly circular, White in colour, Flexible, Translucent and there was no formation of any drug crystals was observed.

Folding endurance

The folding endurance indicated the mechanical strength of transdermal patches. The folding endurance was found to be in the range of 180,193,204,218 folds from batch 1 to 4 Respectively as shown in (Table 2) suggesting that the films produced were found to possess enough mechanical strength.The increased concentration of hydrophilic polymer in the formulation greatly affected the folding endurance as it provided better elasticity.The high value of folding endurance implies that the patch fabricated would maintain its integrity without appearance of any cracks on application of the surface of the skin.

Table 2: Folding Endurance of Formulated Transdermal Patches

Batch No.	Batch 1	Batch 2	Batch 3	Batch 4
Folding Endurance (Folds)	180	193	204	218

Thickness

The thickness of patches was measured by using digital calliper.The thickness ranged between 38 ±2 µm, 36 ±2 µm, 37±2 µm and36±2 µm, from batch 1 to 4 respectively as shown in (Table 3). which indicate that the prepared patches were uniform in thickness.

Table 3: Thickness of formulated patches and standard deviation

Batch No.	Batch 1	Batch 2	Batch 3	Batch 4
Thicknessµm	38 ±2	36 ±2	37±2	36±2

Weight variation

The average weight of patches was found to be in the range of 73 ±5mg, 74 ±5mg, 75 ±5mg, 75 ±5mg for the batches 1 to 4 respectively as shown in (Table 4)which shows the uniformity of weight throughout the formulated transdermal patches.The uniformity of weight indicates that the polymer solution of the drug is well dispersed on a flat surface. However, a little variation in average weight among the formulatedbatch 1 to batch 4 was observed in the range of 73–75 mg which may attribute to the variation in polymeric content. The increase in concentration of Hydrophilic polymer HPMC results into holding of more amount of moisture hence slight increase in weight can be observed.

Table 4: Average weight of Formulated transdermal patches with standard deviation

Batch No.	Batch 1	Batch 2	Batch 3	Batch 4
Average Weight (mg)	73 ±5	74 ±5	75 ±5	75 ±5

Percentage moisture content

Moisture content can influence the mechanical strength and drug release behavior of the transdermal therapeutic systems. Small moisture content in formulation helps them to remain stable and prevent from being completely dry and brittle. The percentage moisture content was found to be 8.96%, 9.26%, 8.34%, 7.28% from batches 1 to 4 respectively as shown in (Table 5). It shows that the concentration of hydrophilic polymer influences the moisture content in the patches. The more concentration of

hydrophilic polymer HPMC in batch 4 holds more amount of moisture and shows less loss in moisture as compared to other batches.

Table 5: Percentage moisture content of formulated transdermal patches

Batch No.	Batch 1	Batch 2	Batch 3	Batch 4
Moisture content %	8.96	9.26	8.34	7.28

Percentage moisture uptake

The absorption of moisture is an imperative aspect which influences the drug diffusion as it extends into the water uptake of the patch from the body tissues as well as from the environment during the application period. It is a vital parameter which helps to maintain the mechanical integrity. The percentage moisture uptake from formulated transdermal patches was reported to be 3.07%, 3.40%, 3.49%, 3.81% from batches 1 to 4 respectively as shown in (Table 6). The formulations with high concentration of hydrophobic polymer Ethyl cellulose displayed the lowest moisture absorption attributes as a result of the decrease in water permeability of the polymer ethyl cellulose. Low moisture uptake prevent formulation from microbial contamination and prevents the bulkiness of the patch.

Table 6: Percentage moisture uptake of formulated transdermal patches

Batch No.	Batch 1	Batch 2	Batch 3	Batch 4
Moisture uptake %	3.07	3.40	3.49	3.81

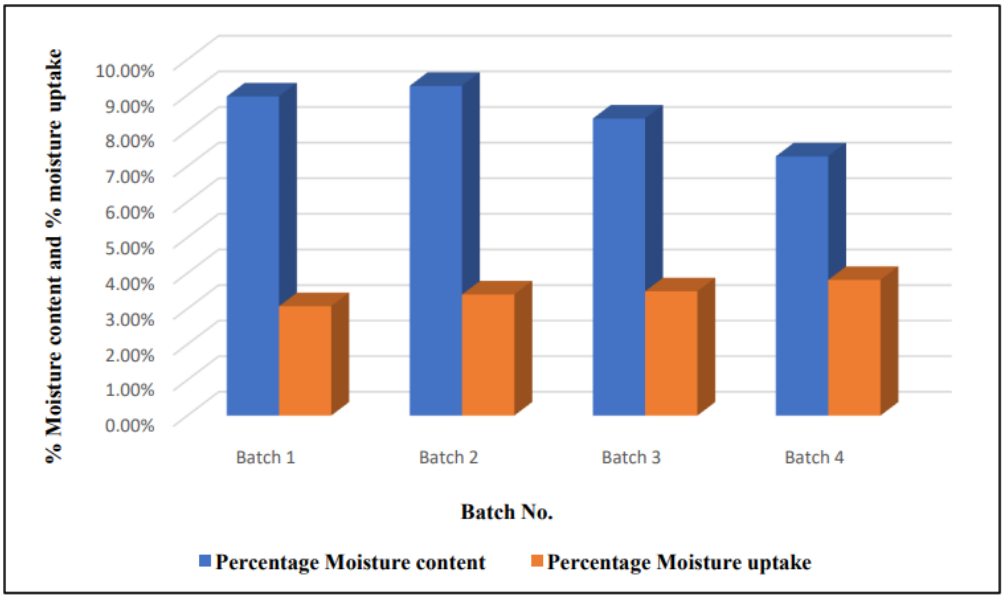

Figure 3: % Moisture Content and % Moisture Uptake

Drug Content

The formulated Transdermal patches were analysed for their drug content and the average drug content from 5 patches of each batch was noted. patches shown drug content from 99.03%, 100.08%, 98.8%, 101.2% from Batch 1 to 4 respectively as shown in (Table 7). The results complies with IP standards which are from 95% to 105%.By this study we conclude that uniform distribution of drug occurred in Formulated Transdermal patches and the expected dose in individual patches that is 5mg was successfully achieved.

Table 7: Percentage drug content in formulated transdermal patches in-vitro drug diffusion

Batch No.	Batch 1	Batch 2	Batch 3	Batch 4
Drug Content %	99.03	100.08	98.8	101.2

The percent drug release in all the 4 batches showed significant difference in pattern of diffusion.The combination of high concentration of Hydrophilic polymer HPMC and low concentration of hydrophobic polymer Ethyl cellulose in Batch 4 gives more Sustained drug release effect as compared to High concentration of Hydrophobic Polymer Ethyl Celluloseand low concentration of Hydrophilic polymer HPMC in Batch1.In thisexperiment, as the concentration of hydrophilic polymer was increased, the amount of drug permeated was increased. This may be a result of the initial rapid dissolution of the hydrophilic polymers when the patch is in contact with the hydrated skin, which results in accumulation of high amounts of drug on the skin surface and thus leads to the saturation of the skin with drug molecules at all times. The rapid dissolution of the aqueous soluble fraction of the film also leads to the formation of pores, and hence, higher release rates[36].The *in vitro* study results showed that with an increase in the concentration of polymers especially hydrophilic, the total amount of drug release increased with increase in sustained release effect. Thus, formulation F4 was considered the best formulation which released 94.46% of total drug in our 24h study.The results obtained are depicted in Figure 4.

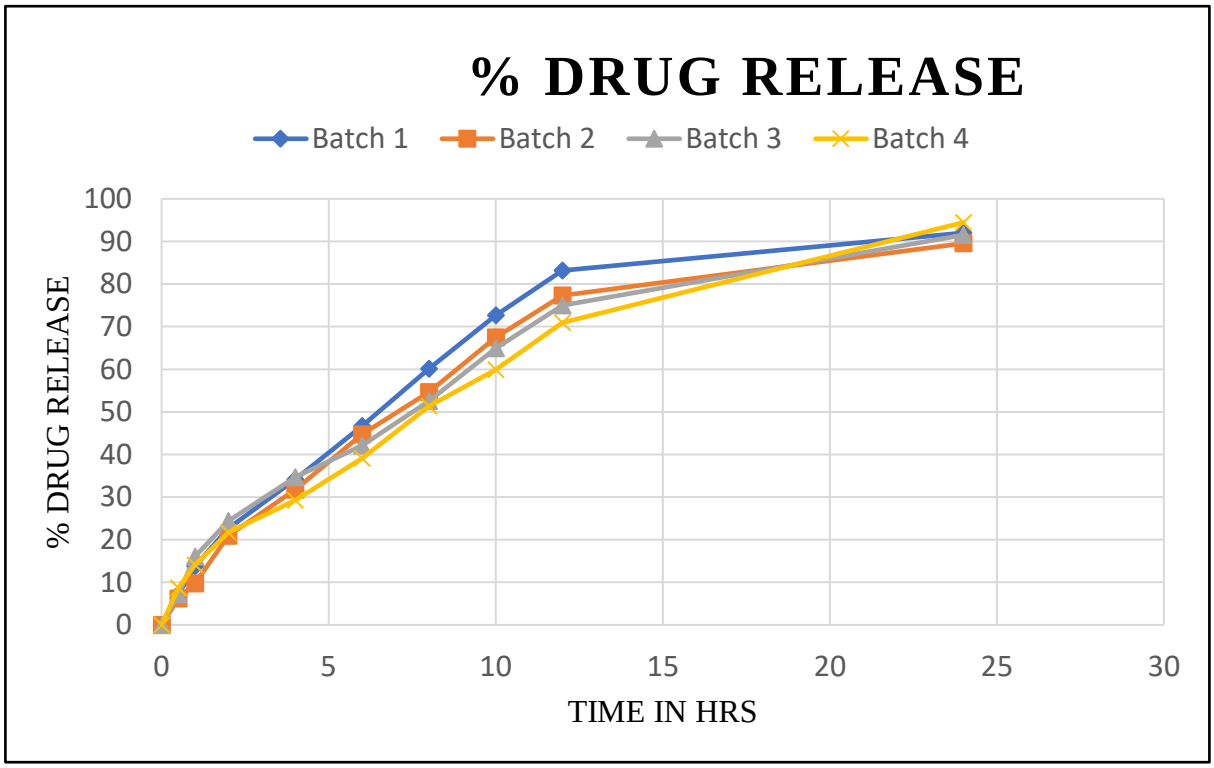

Figure 4: % Drug release VS Time

Short term stability studies

In order to assess the stability of optimized formulation of Batch 4 was subjected to short term stability studies. There was no remarkable change in its colour, shape,flexibility, smoothness any possibility of crystal formation of drug. The patches were analysed for drug content and showed 100.4% average drug

content which was significantly similar to previous drug content. The stability studies results signified that the formulated patches possess adequate shelf life till 45 days.

CONCLUSION

The purpose of the study was to develop,characterize and evaluate the transdermal patch containing Glibenclamide for the treatment of diabetes and the objectives were met. Four batches of Transdermal patch containing Glibenclamide was prepared and evaluated on various physicochemical parameters. Based on the findings of Preformulation studies that is from FTIR studies it was concluded that there is no any interaction between drug and excipients. The uniformity of weight, thickness and drug content between the patches indicates the suitability of procedure for development of transdermal patches.The high value of folding endurance shows thestrength and flexibility of patch to withstand mechanical pressure. The behaviour of patches towards moisture shown that formulated patches were found to contain adequate amount of moisture and significant amount of moisture uptake which will potentially help them for their effectiveness.By the *in vitro* diffusion studies the drug release in optimised formulation that is batch 4 was more sustained as compared to other formulation with maximum drug diffusion of 94.46% across the membrane. The optimised batch also showed satisfactory folding endurance, moisture content as well as drug content with good physical strength. The stability studies results signified that the formulated patches possess adequate shelf life till 45 days.

The objective behind the present work of formulation and evaluation of transdermal patch containing Glibenclamide for treatment of diabetes was achieved and found that the formulated patches were good in physical strength as well as stable and effective.Transdermal patches of Glibenclamide are likely to enhance the patient compliance as it would eliminate the need of repeated dosing, enhance the bioavailability and sustain the action of the drug.

ACKNOWLEDGEMENT

The authors are very much thankful to PDEAs Shankarrao Ursal College of Pharmaceutical Sciences and Research Centre, Pune, Maharashtra, India, all teaching and non-teaching staff for providing the necessary support to complete this Research work successfully.

CONFLICT OF INTEREST

All authors declared no conflicts of interest

REFERENCES

1. Rajratna Gaikwad, Dr. Vijaya Barge "A Review on Continuous Glucose Monitoring System: A Competent Technique in Monitoring and Management of Blood Glucose Levels" International Journal of Trend in Scientific Research and Development, Volume-7 , Issue-2, April 2023,
2. Sattley M. The history of diabetes: diabetes health; 2015. Available from: https://www.diabeteshealth.com/thehistory-of-diabetes/.
3. Lakhtakia R. The history of diabetes mellitus. SQUMJ 2013;13(3):368–70.
4. Ng LC, Gupta M. Transdermal drug delivery systems in diabetes management: A review. Asian journal of pharmaceutical sciences. 2020 Jan 1;15(1):13-25.
5. Ghosh TK, Pfister WR, Yum SI. Transdermal and topical drug delivery systems. Informa Health Care; 2004.
6. Hadgraft J, Guy R. In; Transdermal drug delivery, marcel dekker, Inc, New York and Basel; 1989. p. 1-17
7. Dhiman S, Singh TG, Rehni AK. Transdermal patches: a recent approach to new drug delivery system. Int J Pharm Pharm Sci. 2011;3(5):26-34.

8. Gaur PK, Mishra S, Purohit S, Dave K. Transdermal drug delivery system- A review. Asian Journal of Pharmaceutical and Clinical Research. 2009; 2:14-20.
9. Tengli AR, Gurupadayya BM, Soni N, Vishwanathan B. Method development and validation of metformine, pioglitazone and glibenclamide in tablet dosage form by using RP-HPLC. Biochem Anal Biochem 2003;2:130.
10. Yamamoto T, Okumura M, Washiyama A. Re: topical application of glibenclamide lowers blood glucose levels in rats. Diabetes Res Clin 1990;1:19-22.
11. Mutalik S, Udupa N, Kumar S, Agarwal S, Subramanian G, Ranjith AK. Glipizide matrix transdermal systems for diabetes mellitus: preparation, *in vitro* and preclinical studies. Life Sci 2006;16:1568-77
12. Anwar N, Jan Su, Gul R. Formulation and Evaluation of Glibenclamide Gel for Transdermal Drug Delivery. International Journal of Current Pharmaceutical Research. 2020 Sep 15:35-9.
13. Garg AK, Kumar A, Rani S, Singh M, Sharma A, Kumar R. Formulation and evaluation of chronotherapeutic pulsatile drug delivery system containing rabeprazole sodium. J Appl Pharm Sci 2017;7:93-100.
14. Soral M, Nanjappa SH, Alayadan P. Formulation and evaluation of transdermal patch of rabeprazole sodium. J Rep Pharm Sci 2021;10:240-6
15. Arora P, Mukherjee P. Design, development, physicochemical, and invitro and in-vivo evaluation of transdermal patches containing diclofenac diethylammonium salt. J Pharm Sci. 2002; 91: 2076-2089.
16. Patel RP, Patel G, Patel H, Baria A. Formulation and evaluation of transdermal patch of aceclofenac. Research Journal of Pharmaceutical Dosage Forms and Technology. 2009;1(2):108-15.
17. Mutalik S, Udupa N. Glibenclamide transdermal patches: physicochemical, pharmacodynamic, and pharmacokinetic evaluations. Journal of pharmaceutical sciences. 2004 Jun 1;93(6):1577-94.
18. Nair RS, Ling TN, Shukkoor MS, Manickam B. Matrix type transdermal patches of captopril: ex vivo permeation studies through excised rat skin. Journal of Pharmacy Research. 2013 Jul 1;6(7):774-9.
19. Gungor S, Bektas A, Alp FI, et al. Matrix-type transdermal patches of verapamil hydrochloride: *in vitro* permeation studies through excised rat skin and pharmacodynamic evaluation in rats. Pharm Dev Technol. 2008;4:283e289.
20. Xi H, Yang Y, Zhao D, et al. Transdermal patches for site-specific delivery of anastrozole: *in vitro* and local tissue disposition evaluation. Int J Pharm. 2010;1e2:73e78.
21. Kumria R, Nair AB, Al-Dhubiab BE. Loratidine buccal films for allergic rhinitis: Development and evaluation. Drug Dev Ind Pharm 2014;40:625-31.
22. 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;1e2:167e178
23. Rhee YS, Nguyen T, Park ES, Chi SC. Formulation and biopharmaceutical evaluation of a transdermal patch containing aceclofenac. Arch Pharm Res. 2013;5:602e607.
24. Aggarwal G, Dhawan S, Hari Kumar SL. Formulation, *in vitro* and in vivo evaluation of transdermal patches containing risperidone. Drug Dev Ind Pharm. 2013;1:39e50.
25. Kumar JA, Pullakandan N, Prabhu SL, Gopal V. Transdermal drug delivery system: an overview. International Journal of Pharmaceutical Sciences Review and Research. 2010; 3(2): 49-54.
26. Gupta R, Mukherjee B. 2003. Development and *in vitro* evaluation of diltiazem hydrochloride transdermal patches based on povidone-ethyl cellulose matrices. Drug Dev Ind Pharm 1:1–7.
27. Kumar PD, Kavitha K. Development of transdermal patch of nircardipine hydrochloride: an attempt to improve bioavailability. International Journal of Research in Pharmaceutical and Biomedical Sciences. 2011; 2(1): 285-293.
28. Devi K, Saisivam S, Maria GR, Deepti PU. 2003. Design and evaluation of matrix diffusion controlled transdermal patches of verapamil hydrochloride. Drug Dev Ind Pharm 5:495–503.
29. Mutalik S, Udupa N. 2002. Transdermal delivery of glibenclamide and glipizide: *In vitro* permeation studies through mouse skin. Pharmazie 12:838– 841.

30. Yadav V, Sipai A, Mamatha Y, Prasantha V. Trandermal drug delivery: A technical writeup. Journal of Pharmaceutical and Scientific Innovation. 2012; 1(1): 5-12.
31. Shivaraj A, Selvam RP, Mani T, Sivakumar T. Design and evaluation of transdermal drug delivery of ketotifen fumarate. International Journal of Pharmaceutical and Biomedical Research. 2010; 1(2): 42-47
32. Aggarwal G, Dhawan S, Hari Kumar SL. Formulation, *in vitro* and in vivo evaluation of transdermal patches containing risperidone. Drug Dev Ind Pharm 2013;39:39-50.
33. Jafri I, Shoaib MH, Yousuf RI, Ali FR. Effect of permeation enhancers on *in vitro* release and transdermal delivery of lamotrigine from Eudragit® RS100 polymer matrix-type drug in adhesive patches. Progress in biomaterials. 2019 Jun;8:91-100.
34. Jayaprakash S, Halith SM, Firthouse PM, Yasmin, Nagarajan M. Preparation and evaluation of celecoxib transdermal patches. Pakistan J Pharm Sci. 2010;3:279e283.
35. Patel RP, Patel G, Patel H, Baria A. Formulation and evaluation of transdermal patch of aceclofenac. Research Journal of Pharmaceutical Dosage Forms and Technology. 2009;1(2):108-15.
36. Rama Rao P, Diwan PV. 1998. Formulation and *in vitro* evaluation of polymeric films of diltiazem hydrochloride and indomethacin for transdermal administration. Drug Dev Ind Pharm 4:327–336.