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Original Article

GLIBENCLAMIDE TRANSETHOSOME PATCH FOR TRANSDERMAL DELIVERY: FORMULATION AND EVALUATIONS

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ABSTRACT

Objective: The glibenclamide transethosome patch is a patch containing glibenclamide encapsulated in nanoparticle-based vesicles that can improve the penetration of the compound into the skin. The research work aims to evaluate glibenclamide transethosome patches using HPMC and PVP as matrix polymers and glibenclamide as a drug model.

Methods: Glibenclamide transethosome patches were prepared using a solvent evaporation technique. Evaluations that have been carried out to assess the stability of the patch include weight variation, folding endurance, thickness, moisture absorption, moisture content, drug content, and drug release *in vitro* glibenclamide transethosome was carried out using Franz diffusion cell.

Results: The results of the evaluation of the glibenclamide transethosome patch showed a patch weight uniformity between 0.051-0.063 g and a CV (Coefficient of Variation) value of less than 5%. The resulting folding resistance of the patch can withstand without tearing over 200 folds. The thickness of the glibenclamide transethosome patch is between 0.14-0.24 cm. The moisture absorption capacity of the patch is between 2.1-23.5%. The moisture content of the patch is between 4.7-7.4%. The drug content of the patch is between 6.7–12.7 g/cm^2. Drug release from the patch was between 45.9-82.1% after 480 min. Overall, in the moisture absorption test (F3; F4; F5), moisture content, drug content, and drug release (F1) gave significantly different results ($p<0.05$).

Conclusion: The glibenclamide transethosome patch showed evaluation results that met the requirements and were stable during the stability test. The polymer combinations also significantly influence drug release during stability tests.

Keywords: Glibenclamide, Transethosome patch, HPMC, PVP K30

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INTRODUCTION

Transdermal delivery refers to the process of administering drugs through the skin. This technique offers a different, more versatile method for delivering medications into the body. Transdermal drug delivery has various benefits, including fewer side effects, more patient compliance, avoidance of first-pass effects, slower drug delivery, and the ability to quit therapy [1-6]. The semipermeable characteristic of the skin barrier must be reduced without creating negative side effects, especially local irritation, which is a major difficulty in developing transdermal delivery systems [7-10].

In patients with hyperglycemia, glibenclamide a second-generation sulfonylurea compound, increases endogenous insulin secretion and lowers serum glycogen levels. Glibenclamide is categorized as class II by the Biopharmaceutical Classification System (BCS) and has good permeability and low water solubility. According to Mutalik S. and Udupa N. in 2004, glibenclamide has a plasma half-life ($t_{1/2}$) of 4-6 h and a first-pass hepatic metabolism of 50% [11]. The long-term use of glibenclamide necessitates careful consideration of patient compliance. Following oral medication, glibenclamide has result occasionally in severe hypoglycemia and stomach disturbances like nausea, vomiting, anorexia, and increased appetite [12, 13]. This is an alternative reason for percutaneous (transdermal) delivery. However, due to the presence of a barrier layer that limits the number of compounds that cross the stratum corneum, it is necessary to develop a formula to increase the penetration of glibenclamide.

The permeability of substances into the skin has been increased through several methods, including penetration enhancers such as fatty acids and organic solvents. However, these methods have drawbacks [14]. One method for attaining effective transdermal medication administration is the vesicular system. Transethosomes may improve therapeutic effectiveness and skin penetration [5, 15-17). Transethosomes are a vesicular drug delivery system made up of phospholipids, surfactants, ethanol, and water to enhance transdermal administration [12].

Excellent film-forming capabilities are possessed by PVP [18, 19]. PVP-based films have primarily been made until this point via solution casting, followed by solvent evaporation. Transdermal patches are most frequently created using PVP-based films. PVP has good film-forming capabilities and can be used with various polymers. PVP-based thin films can be used topically or transdermally. However, the high moisture absorption caused by PVP's high hydrophilicity and hygroscopicity can be a significant issue. Microbial contamination can result from high water absorption. In this situation, research on polymer blends is required to enhance the films' mechanical properties [20]. The cellulose ester derivative hydroxypropyl methylcellulose (HPMC K 100 M) is biodegradable, biocompatible, and non-toxic. HPMC is helpful in regulated or prolonged drug distribution because of its swelling, gelling, and thickening qualities [21].

In this study, transethosome patches were created utilizing HPMC and PVP K30 polymers. The medication glibenclamide is used as an example. The impact of the HPMC/PVP K30 ratio comparison and the inclusion of glibenclamide transethosome was evaluated on the physicochemical characteristics and drug release.

MATERIALS AND METHODS

Materials

Glibenclamide transethosome was procured from Padjadjaran University, Indonesia. Aquadest, phosphate buffer, and ethanol 70% were purchased from Multi Usaha Mandiri, Indonesia. HPMC, potassium chloride, propylene glycol, and PVP K30 were purchased

from Quadrant, Indonesia. Methanol was purchased from Merck, India.

Glibenclamide transethosome patch formulation

Glibenclamide transethosome patch patches were designed in a formula with various polymer concentrations.

Preparation of glibenclamide transethosome patches

The glibenclamide transethosome patch was prepared by solvent evaporation technique in a mold with a cylindrical shape on both sides. The polymers (HPMC and PVP K30) were dispersed separately into the water using a magnetic stirrer speed of 200 rpm at 25 °C. After being homogeneous, the two mixtures were put together and homogenized again. The mixtures were Added propylene glycol and glibenclamide transethosome. The homogeneous mixture was then poured into molds and dried in an oven at 40 °C for 9 h. After drying, the patch is removed from the mold, wrapped in aluminum foil, and stored in a desiccator [21].

Evaluation of glibenclamide transethosome patch

Weight variation

The patch weights were weighed using an analytical balance, every 3 patches were weighed and then the average weight, standard deviation, and percentage of CV (Coefficient of Variation) were determined. The patch weight is said to be uniform if the CV value is ≤ 5%

Table 1: The composition of the glibenclamide transethosome patch formulation

Formula	Total of polimer (2%)		Plasticizer
	HPMC	PVP K30	Propylene glycol
F1	90	10	2%
F2	85	15	2%
F3	80	20	2%
F4	75	25	2%
F5	70	30	2%

Each formulation contains glibenclamide transethosome, equivalent to 3 mg of glibenclamide in a patch weighing 1 g and measuring 2.25 cm^2 in total area.

Folding endurance

The test is carried out by folding the patch many times in the same position until the patch breaks. The value of folding resistance is the number of folds in the same place without breaking [22, 23].

Thickness

The thickness of the resulting patch was measured using a micrometer with a screw micrometer accuracy of 0.01 mm. Measurements were made at 3 points [13, 24].

Moisture absorption

The patch is weighed and stored in a desiccator containing a saturated potassium chloride solution for 24 h. The patch was weighed again, and the percentage of moisture content was determined using the formula [22].

$$\text{Moisture absorption (\%)} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Final weight}} \times 100 \ldots\ldots [1]$$

Moisture content

The patch was weighed and stored in a silica desiccator for 24 h. After 24 h, the patch was re-weighed, and the percentage of moisture content was determined [25]

$$\text{Moisture content (\%)} = \frac{\text{Initian weight} - \text{Final weight}}{\text{Initian weight}} \times 100 \ldots\ldots [2]$$

Drug content

The levels of 3 patches were measured by dissolving in methanol, then sonicated for 15 min and filtered. Glibenclamide levels were measured using a UV spectrophotometer [22].

Drug release study

On the patch formulations for glibenclamide transethosome, drug release studies were conducted. Male Wistar rat's shaved back skin was utilized as the membrane, which was then cleaned with distilled water, bathed in saline for five minutes, and kept at-18 °C until needed [26]. The receptor compartment contained phosphate buffer (pH 7.4), the membrane's surface area was 1.5 cm^2, and it was agitated at 100 rpm at 37±0.5 °C. The sample is a transethosome patch for glibenclamide that is 3 mg in strength. At 5, 10, 15, 30, 60, 90, 120, 180, 240, 270, 300, 360, 420, and 480 min, sampling was done using a syringe to extract 3 ml of the receptor compartment [27-29]. All animal experiments were approved by the Research Ethics Committee at Padjadjaran University Bandung and were carried out according to scientific procedures 208/UN6. KEP/EC/2022 for animal experiments.

Table 2: Data of glibenclamide transethosome patch weight variation

Formula		Cycles					
		0	1	2	3	4	5
F1	Average (g)	0.063±0.01	0.05±0.003	0.049±0.002	0.049±0.002	0.047±0.002	0.047±0.002
	CV (%)	0.021	0.053	0.035	0.039	0.036	0.036
F2	Average (g)	0.051±0.004	0.047±0.003	0.047±0.026	0.047±0.026	0.045±0.002	0.044±0.001
	CV (%)	0.081	0.066	0.554	0.562	0.046	0.019
F3	Average (g)	0.058±0.002	0.054±0.001	0.052±0.001	0.051±0.026	0.05±0.002	0.049±0.002
	CV (%)	0.036	0.022	0.022	0.513	0.046	0.042
F4	Average (g)	0.052±0.002	0.045±0.002	0.044±0.001	0.044±0.001	0.043±0.001	0.043±0.002
	CV (%)	0.045	0.038	0.013	0.016	0.031	0.038
F5	Average (g)	0.061±0.003	0.051±0.003	0.048±0.001	0.047±0.001	0.046±0.001	0.045±0.001
	CV (%)	0.05	0.066	0.012	0.024	0.025	0.024

Data are expressed as mean±SD, n=3

Statistical analysis

In this study, all results were presented as means±standard deviation. Statistical analysis using SPSS software was carried out using one-way ANOVA and post hoc using LSD (Least Significant Difference). Analysis was carried out to assess the differences in results between formulas and the differences in results before and after stability tests in evaluating weight variation, folding endurance,

thickness, moisture absorption, moisture content, drug content, and drug release. The significance level was determined at $p<0.05$.

RESULTS

Weight variation

The weight variation test seeks to ascertain the consistency of the manufacturing process in producing a uniform product, in this case regarding uniform drug dose in each dosage unit, and is designed to assess the similarity of the weight of each patch. In medication preparations, where patch weights must be uniform and CV values 5%, dose consistency is crucial.

Based on table 2, it can be concluded that the CV value of the weight variations produced by all formulas meets the requirements, namely not more than 5% both before and after the stability test. A good weight variation parameter can be seen from the CV value, namely if the CV value is less than or equal to 5%. The results of the weight variation test performed on each formula showed that the glibenclamide transethosome patch had good weight variation.

Based on fig. 1, the patch weights from F1 to F5 before the stability test ranged from 0.051-0.063 g, overall, there was no significant difference between the patch weights between formulas ($p>0.05$). After the stability test for 5 cycles, the overall patch weight of the formula decreased F1 (0.063 to 0.047 g); F2 (0.051 to 0.044 g); F3 (0.058 to 0.049 g); F4 (0.052 to 0.043 g); and F5 (0.061 to 0.045 g). Based on statistical analysis, there was no significant difference before and after the stability test for each formula ($p>0.05$).

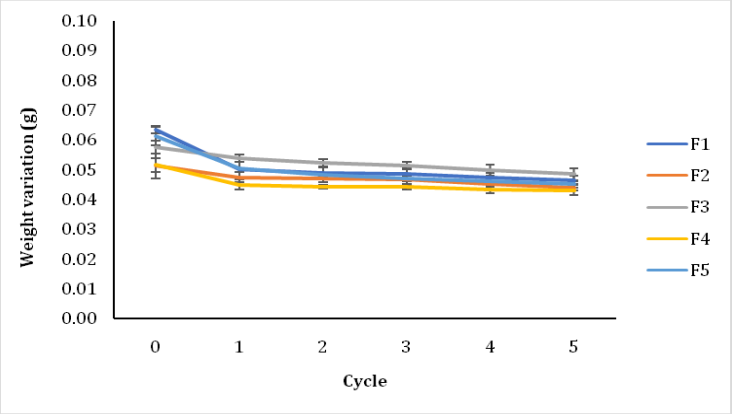

Fig. 1: **Graph of glibenclamide transethosome patch weight variation stability (n=3)**

Folding endurance

The folding endurance test aims to determine the flexibility and elasticity of the patch after it is folded at the same angle. A good patch must have strong but elastic properties. The integrity of the patch when applied to the skin is shown by its good folding durability so that it is not easily broken or torn during stability tests [30, 31]. Patches that tear easily show their fragile nature.

Table 3: Fold endurance stability of glibenclamide transethosome patches (n=3)

Cycles	Folding endurance														
	F1			F2			F3			F4			F5		
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
0	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200
1	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200
2	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200
3	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200
4	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200
5	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200

Based on table 3, the five glibenclamide transethosome patch formulas were able to survive without tearing above 200 folds. A good patch can fold more than 200 times without tearing. The glibenclamide transethosome patch also did not change after 5 cycles of the stability test.

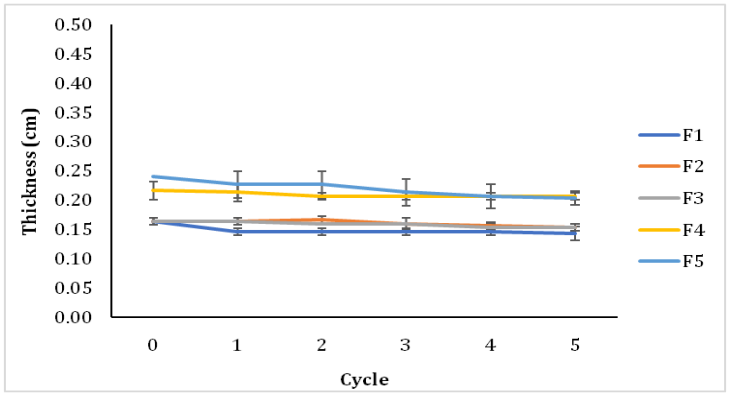

Fig. 2: Graph of glibenclamide transethosome patch thickness stability (n=3)

Thickness

The thickness test on the glibenclamide transethosome transdermal patch aims to determine the uniformity of the resulting patch thickness, indicating the uniformity of the patch solution poured into the mold.

Based on fig. 2, the thickness of glibenclamide transethosome patches are between 0.14 and 0.24 cm. The patch with the highest thickness was F5 (0.24 cm), and the patch with the lowest thickness was F1, F2, and F3 (0.163 cm). Overall there was no significant difference in patch thickness between formulas ($p>0.05$). After the stability test for 5 cycles, the overall patch thickness of the formula decreased F1 (0.163 to 0.143 cm); F2 (0.163 to 0.153 cm); F3 (0.163 to 0.153 cm); F4 (0.217 to 0.207 cm); and F5 (0.240 to 0.203 cm). Based on statistical analysis, there was no significant difference before and after the stability test for each formula ($p>0.05$).

Moisture absorption

The moisture absorption test aims to evaluate the degree of water absorption of glibenclamide transethosome patches that have been conditioned for 24 h in a desiccator with a saturated potassium chloride solution. The glibenclamide transethosome patch's capacity to absorb moisture reveals how much water is absorbed by the patch when it is applied to the skin [22].

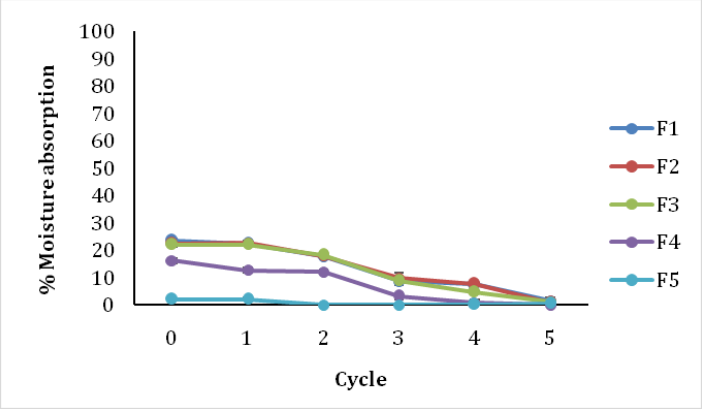

Fig. 3: Graph of glibenclamide transethosome moisture absorption stability (n=3)

Based on fig. 3, the moisture absorption of the glibenclamide transethosome patch is between 2.1-23.5%. The patch with the highest moisture absorption was F1 (23.5%), and the patch with the lowest moisture absorption was F5 (2.1%). Based on statistical analysis, F1 and F2 did not have a significant difference ($p>0.05$), while F3; F4, and F5 differed significantly ($p<0.05$). The patch with the highest HPMC content and the lowest PVP K30 has the highest percentage of moisture absorption. After the stability test for 5 cycles, the overall moisture absorption capacity of the formula decreased to F1 (23.5 to 1.5%); F2 (22.3 to 0.845%); F3 (22.0 to 1.1%); F4 (16.1 to 0%); and F5 (2.1 to 0.5%). Based on statistical analysis, there was a significant difference before and after the stability test for each formula ($p>0.05$).

Moisture content

The moisture content test aims to ascertain how moist the manufactured patch matrix is. By dividing the starting weight by the final patch weight after being kept in a desiccator for 24 h, this number is given as a percentage of the initial weight difference. A proper solvent evaporation process is indicated by low moisture content. Additionally, the patch may remain more stable, flexible, and not brittle due to the low moisture content.

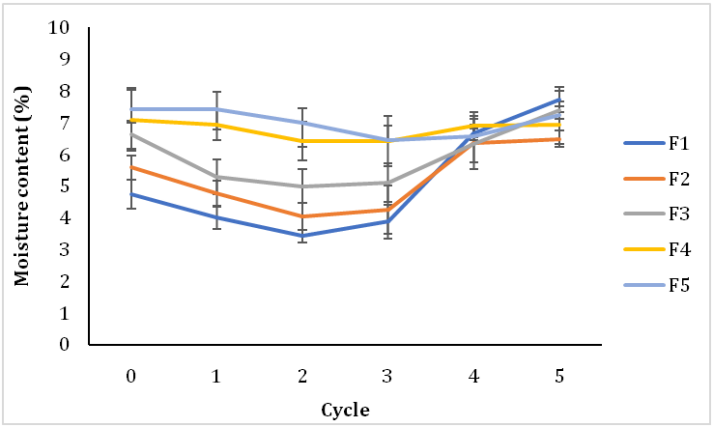

Fig. 4: Graph of glibenclamide transethosome moisture content stability (n=3)

Based on fig. 4, the moisture content of the glibenclamide transethosome patch is between 4.7-7.4%. The patch with the highest moisture content was formula 5 (7.4%), and the patch with the lowest moisture content was F1 (4.7%). Overall there was a significant difference in moisture content between the formulas ($p>0.05$). This percentage met the requirements for the moisture content of the patch (1-10%). After the stability test for 5 cycles, the moisture content of F1 (4.7 to 7.7%); F2 (5.6 to 6.5%); F3 (6.6 to 7.4%); F4 (7.1 to 6.9%); and F5 (7.4 to 7.2%). Based on statistical analysis, there was no significant difference before and after the

stability test was carried out for each formula ($p>0.05$) except F1 which was significantly different ($p<0.05$).

Drug content

The glibenclamide transethosome patch's level of homogeneity will be assessed using the drug content test. One can suppose that the uniformity of drug levels corresponds to the patch's active ingredient consistency. Due to the potential impact on the therapeutic outcome, the patch's weight must be uniform.

Based on fig. 5, the drug content of the glibenclamide transethosome patch ranged from 6.7–12.7 g/cm². The highest patch drug content was F5 (12.7 g/cm²) and the lowest patch drug content was formula 1 (6.7 g/cm²). Based on statistical analysis, all formulas were significantly different ($p<0.05$) except for F4 and F5, which were not significantly different ($p>0.05$). After the stability test for 5 cycles, drug content F1 (6.7 to 5.4 g/cm²); F2 (7.6 to 9.7 g/cm²); F3 (8 to 11.2 g/cm²); F4 (12.4 to 15.2 g/cm²); and F5 (12.7 to 16.8 g/cm²). Based on statistical analysis, there was no significant difference before and after the stability test was carried out for each formula ($p>0.05$) except F1, which was significantly different ($p<0.05$).

Drug release study of glibenclamide transethosome patches

The ability of the medication to enter the skin from the patch matrix was tested using a drug release method. Because it provides an *in vitro* picture of the amount of medication in the patch that penetrates the systemic circulation, this test is an essential metric in patch development.

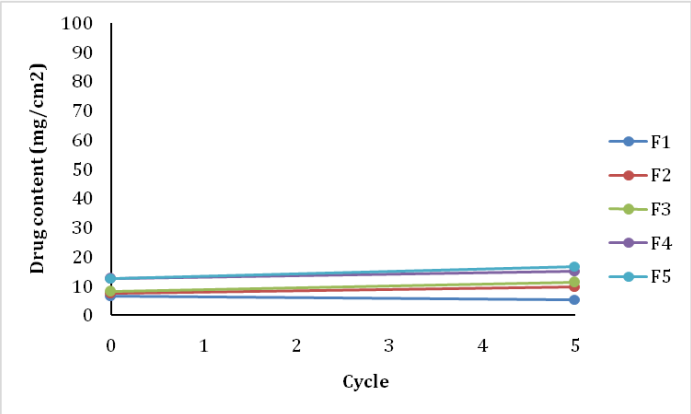

Fig. 5: Graph of glibenclamide transethosome drug content stability (n=3)

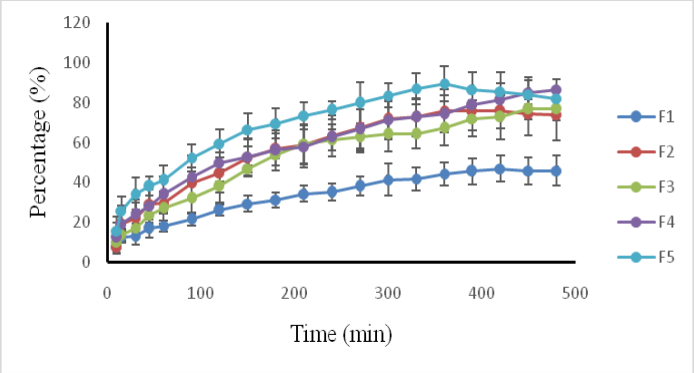

Fig. 6: Graph of glibenclamide transethosome drug release stability in cycle 0 (n=3)

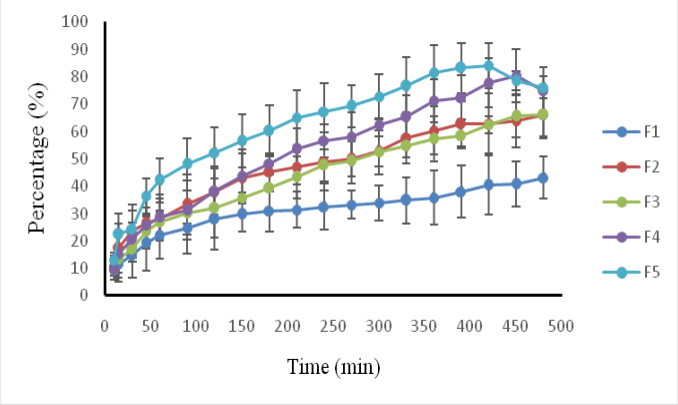

Fig. 7: Graph of glibenclamide transethosome drug release stability in cycle 3 (n=3)

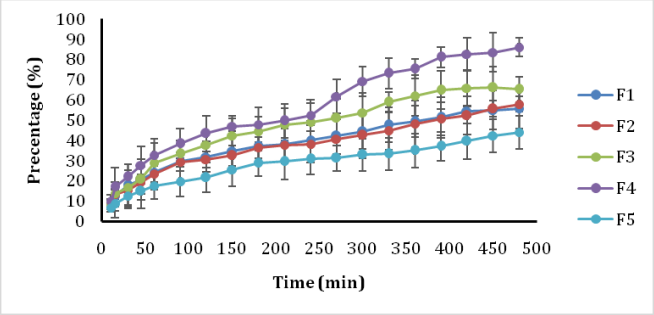

Fig. 8: Graph of glibenclamide transethosome drug release stability in cycle 5 (n=3)

Based on fig. 6, drug release from the glibenclamide transethosome patches ranged from 45.9–82.1% after 480 min. The highest drug release in the patch was formula 5 (82.1%) and the lowest patch drug release was formula 1 (45.9%). Based on statistical analysis, F2; F3; F4; F5 did not have a significant difference ($p>0.05$), while F1 had a significant difference ($p<0.05$) with the other formulas.

Based on fig. 6-8, there was a change in the percentage of drug release after the stability test. After stability test for 5 cycles, drug release at F1 (45.9 to 55.7%); F2 (74 to 58%); F3 (76.7 to 65.2%); F4 (86.4 to 86.1%); and F5 (82.1 to 44%). Based on statistical analysis, there was no significant difference before and after the stability test was carried out for each formula ($p>0.05$, except for F5, which was significantly different after the stability test ($p<0.05$).

DISCUSSION

In this research, glibenclamide transethosome patches were made using the patch matrix type. In this type of system, the drug is dispersed homogeneously into a hydrophilic or lipophilic polymer matrix, while the advantage of this type is that it will form a thin and elegant patch preparation so that it is comfortable to use. HPMC and PVP-K30 are the two polymers used. Because PVP-K30 can form pores, which aid in releasing the active ingredients from the base and has good film-forming properties, these two polymers are combined. The resulting patch is rather soft, so it can easily release the active substance, whereas HPMC can be used as a good release stabilizer so that drug release can be controlled, and the resulting patch is rather hard, so it can release. To manage the release of drugs, HPMC is crucial as a water-soluble polymer carrier [21, 32].

The weight of the patch affects how comfortable it is to wear; the lighter and thinner the patch, the more pleasant it will be. The patch would yield more weight the higher the polymer concentration was employed. The CV value of the weight variation produced by the patch with HPMC and PVP K30 polymer variations has met the requirements, namely, not more than 5%. A good patch must have strong but elastic properties. The integrity of the patch when applied to the skin is shown by its good folding durability so that it is not easily broken or torn during stability tests. Patches that tear easily show their fragile nature. The folding resistance ability produced by the glibenclamide transethosome patch with various HPMC and PVP K30 polymers has met the requirements above 200 folds. So it can be concluded that the different combinations of HPMC and PVP K30 polymer concentrations contained in the patch matrix did not affect the folding resistance of the glibenclamide transethosome patch. Thickness has a role in the physical properties of the patch; a thin patch will be easily accepted in use. Weight uniformity is related to patch thickness results. The patch's thickness can rise with a larger PVP K30 polymer concentration [33]. PVP K30 is a hydrophilic polymer because it can expand and will create a gel layer, increasing the patch's thickness [20]. Increasing the composition of PVP K30 in the patch caused a decrease in moisture absorption. The glibenclamide transethosome patch's capacity to absorb moisture reveals how much water the patch absorbs when it is applied to the skin. A patch's quality will be impacted by excessive moisture absorption, which may reduce the patch's elasticity and make it more likely to break. Patches with good solvent evaporation processes are indicated by low moisture content. In addition, the patch can remain more stable, flexible, and less brittle due to the low moisture content. The patch with the highest PVP K30 content is the patch with the highest moisture content percentage. The results of the drug content study indicate minimal batch variability. The patch with the lowest HPMC content and the highest PVP K30 was the patch with the highest drug content [11]. The glibenclamide transethosome drug content test results showed that variations in polymer combinations significantly affected the uniformity of drug levels. However, it does not have a significant effect during the stability test. PVP K30 is a hydrophilic polymer because it stretches and generates a gel layer that regulates drug release [20]. The PVP K30 polymer with higher composition will boost the hydration of the polymer matrix, which will improve the swelling process [34].

The best swelling technique will facilitate drug dissolution in the matrix, resulting in increased drug release from the matrix. The glibenclamide release rate increases with increasing PVP K30 concentration in the patch [11]. As the concentration of PVP K30 in the patch rises, the rate at which glibenclamide is released also rises. Due to the hydrophilicity and hygroscopicity of PVP K30, polymer-solvent interactions frequently outweigh polymer-polymer forces. In a nutshell, the solvent is swiftly absorbed into the polymer matrix, and the polymer swells, allowing for the quick release of drug molecules. Drugs with HPMC demonstrated longer drug release, but PVP K30 showed faster drug deposition and a significant drop in drug dissolution rate quickly. HPMC is a water-soluble polymer carrier with swelling characteristics that can control drug release [21].

CONCLUSION

In the present study, glibenclamide transethosome patch with the polymer component HPMC: PVP K30 (75:25) is a patch with physicochemical properties that fulfill the stability requirements in terms of physicochemical properties and is capable of being responsible for controlling drug release making it suitable for drug delivery regimens that are prolonged via the transdermal route. The glibenclamide transethosome patch is capable of better and more controlled drug release for treating hyperglycemia compared to oral dosage forms and glibenclamide patches.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest.

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