Formulation and In-Vitro Evaluation of Matrix Type Transdermal Patches of Glibenclamide Using Various Penetration Enhancers

Fatin Nabila Md Ami[1], Mohammed Kaleemullah[2], Jiyauddin Khan[3], Samer Al-Dhalli[4], Sakina Ruhi[5], Mohamed Rasny[6], Shariq Baber[7], Santosh Fattepur[8], Kiran Nilugal[9], Chean Hui Ng[10], Gamal O. E[11], Ibrahim Abdullah[12]

[1,2,3,4,6,7,8,9,10,12] School of Pharmacy, Management & Science University,40100 Shah Alam, Selangor Darul Ehsan, Malaysia
[5] International Medical School, Management & Science University,40100 Shah Alam, Selangor Darul Ehsan, Malaysia
[11] Department of Pharmaceutics, Unaizah College of Pharmacy, Qassim University, KSA
[2]mohd_kaleemullah@msu.edu.my

Abstract**: Background and aim: Transdermal medication conveyance is one of the sort of organization which has been catching eye over the previous years concerning its potential in ailment treatment. The utilized of entrance enhancers which may improve the bioavailability and broaden the scope of medications are concentrated in the organization of transdermal course. Its utilization in this field might be helpful in reversibly lessen the hindrance capacity of the layer corneum, the furthest layer of the skin. For this analysis, the definition and assessment of transdermal patches of Glibenclamide towards improving saturation through the skin and keeping up the plasma focus utilizing different infiltration enhancers have been researched. Materials and methods: The transdermal were set up by the dissolvable throwing strategy utilizing HPMC and PVA as the polymers notwithstanding the dibutylphthalate as a plasticizer. The infiltration enhancers utilized are oleic corrosive, DMSO, D-limonene, and Sodium Lauryl Sulfate. The transdermal patches have been assessed by their physicochemical properties and in-vitro drug release. Results: The transdermal patches appearance were straightforward and smooth surface, no huge varieties of thickness, weight varieties and collapsing perseverance. Among the definitions considered, F4 which has D-limonene as infiltration enhancers demonstrated great attributes with low dampness misfortune and dampness take-up, most extreme medication arrival of 99.713% and medication content with 92.588% ± 0.8541. Conclusion: The current examinations demonstrated the necessary penetration pace of the medications might be accomplished with the guide of enhancers either physical or substance.

Keywords: Transdermal drug delivery, penetration enhancers, stratum corneum, glibenclamide

1. INTRODUCTION:

Diabetes mellitus is an incessant metabolic issue portrayed by high blood glucose obsession hyperglycemia realized by insulin need, consistently got together with insulin block (Etemad *et al.*, 2012). Glibenclamide, a noteworthy medicine of sulfonylurea class, is correct now open for compensating hyperglycemia in Non-Insulin Dependent Diabetes Mellitus (NIDDM); anyway has been connected with genuine and to a great extent deadly hypoglycemia and gastric agitating impacts like disorder, spewing, heartburn, anorexia and

extended longing for after oral treatment (Davis *et al,* 1996). Antidiabetic ordinarily taken for a long time period thusly steady consistence are central to restrict risk of side effects and improve individual fulfillment. Such standard structures of medication which require multi divide treatment have different issues and most starting late, there is an extending affirmation that the skin can fill in as the port give tenacious transdermal medicine imbuement into the basic spread (Reddy *et.al*, 2003).

Transdermal therapeutic systems have been proposed to give constant movement of prescriptions through the skin in a controlled rate to the essential scattering in express proportion of time (Yamamoto, 1990). Moreover, it over comes various indications like unbearable transport of the drugs, GI disturbance, low decay, the chief pass processing of the prescription occurred by various strategies for steady movement systems, short half-life requiring relentless dosing and the improvement of metabolites that cause responses (Al-Khamis *et. al*, 1986). Application and ejection of transdermal patches produce the perfect progression of pharmacological effect whereby the prescription data can be stopped whenever of time by emptying the transdermal fixes as a result of possible results of self-association (Guy *et. al*, 1987). Used of enhancers have been widely known in pharmaceutical industries in increasing the rate of penetration of medications into the skin. Studies has shown by using enhancers, it may alter the lipid bilayer, or increase the diffusion rate of the drug into the skin and increase the interaction between protein receptor in the skin which may enhance the amount of drug entering the circulation. Thus, in this experiment various types of chemical enhancers were used in developing the transdermal patches as well as enhance the efficacy of the formulation.

2. MATERIALS AND METHOD

a) Materials and Apparatus

i) Materials

Glibenclamide powder, Hydroxypropyl Methyl Cellulose, Poly Vinyl Alcohol, Dibutyl phthalate, Dimethyl Sulfoxide, Oleic, Sodium Lauryl Sulphate, D-limonene, water, ethanol, phosphate buffer, saturated aluminium chloride and anhydrous calcium chloride, Glycerin, PEG-400, dialysis membrane

ii) Apparatus

Petri dish, hot air oven, surgical blade, beaker, digital micrometer, weighing balance, glass rod, spatula, pipette, UV spectrophotometer, desiccator, aluminium foil, magnetic stirrer, Franz diffusion cell and tweezers.

b) Procedure

i) Development of Transdermal Patches

The patches were set up by solvent casting technique. The polymers (all out weight: 600mg) and drug (50mg) were weighed with 150mg of Poly Vinyl Alcohol (PVA) and 450mg Hydroxypropyl Methyl Cellulose (HPMC) and disintegrated in reasonable solvent. Dibutyl phthalate was utilized as plasticizer that are 30% from polymer). 5 definitions was led utilizing diverse infiltration enhancers where one plan go about as control and the others are Dimethyl Sulfoxide, Eugenol, Sodium Lauryl Sulfate and D-limonene as enhancers. The proportion of 1:1 water: ethanol were utilized as dissolvable for the medication. The fixed volume of polymeric arrangement with medication and plasticizer were combined and blended utilizing attractive stirrer until uniform. At that point the medication was included last. The blend arrangement was poured in to glass petri dish greased up with glycerin and afterward dried in stove at 45°C for 24 hours. The recorded were expelled by utilizing sharp

cutting edge by embeddings alone the edges of the film (Shankar *et al.,* 2015). The formulations are presented in Table.1.

Table 1: Transdermal Patches Formulations

Formulation code	Polymer		Plasticizer (DBT) % of polymer	Drug (mg)	Enhancer (5% of polymer)	Solvent, Water : Ethanol (1:1)
	HPMC	PVA				
F1	240 mg	360 mg	30%	50	None	10 ml : 10 ml
F2	240 mg	360 mg	30%	50	SLS	10 ml : 10 ml
F3	240 mg	360 mg	30%	50	Oleic acid	10 ml : 10 ml
F4	240 mg	360 mg	30%	50	D-limonene	10 ml : 10 ml
F5	240 mg	360 mg	30%	50	DMSO	10 ml : 10 ml

**Total weight of polymer: 600 mg*

ii) Physico-Chemical Evaluation test

- Physical appearance

All transdermal patches were visually inspected for color, clarity, flexibility and smoothness (Shankar *et al.,* 2015).

- Thickness of the patch

The thicknesses of the drug-loaded polymeric films were measured at five different points using a digital micrometer. The average and standard deviation of five reading were calculated for each film (Shankar *et al.,* 2015).

- Weight variation

The films of different batches were dried at 60°C for 4 hours before testing. Five patches from each batch were accurately weighed in a digital balance. The average weight and the standard deviation values were calculated from the individual weights (Shankar *et al.,* 2015).

- Folding endurance

The folding endurance measured manually for the prepared film. A strip of film is cut evenly (2cm x 2cm) and folded at the identical place till it breaks. The amount of times the film may well be folded at the identical place without breaking gives the precise value of folding endurance (Girani *et al*., 2016).

- Percentage of Moisture uptake

The films were weighed accurately and kept in a desiccators containing 100ml of saturated solution of aluminium chloride, after 3 days, the films were taken out and weighed (Shankar *et al.,* 2015).

$$\left(\%\ \text{Moisture uptake:}\ \frac{\text{Initial weight-Final weight}}{\text{Initial weight}}\ \text{x}\ 100\% \right)$$

- Percentage of Moisture Loss (Shankar et al., 2015).

The films were carefully weighed and stored in a desiccator containing anhydrous calcium chloride. The films were taken out and weighed after 3 days. The loss of moisture was measured using formula:

$$\left(\%\ \text{Moisture loss:}\ \frac{\text{Initial weight-Final weight}}{\text{Initial weight}}\ \text{x}\ 100\% \right)$$

- Swelling index

Weighed pieces 2 cm x 2 cm of film were immersed in distilled 7.4 phosphate buffer, at 5, 10, 30, 60 minutes. Soaked film was removed from the medium at predetermined time, blotted to remove excess liquid and weighed immediately (Guy *et al.,* 1987). The swelling index was calculated as follow:

$$\left(\text{Swelling index: } \frac{\text{Weight after immersion-weight before immersion}}{\text{Weight before immersion}}\right)$$

- Drug content

The fabricated film was cut into small pieces and placed in a pH 7.4 solution of 100 ml of phosphate buffer. Then stir in a mechanical stirrer to obtain a homogeneous solution and filter it. The fluid of 1 ml was excluded and made up to 100 ml, again pipette out of this 1 ml of solution and made up to 10 ml of buffer of 7.4 pH. The drug content was analyzed by UV - vis spectrophotometer at 229 nm. (Shankar *et al.,* 2015).

- *In-vitro* Drug Penetration Studies

Drug penetration studies have been conducted for the prepared formulation using the Franz Diffusion Cell. The equipment was maintained at a constant temperature of 37°C through thermostatic circulation of the bath, while the receptor medium was consistently stirred at 350 rpm during the experiments. The patches were stuck to the dialysis membrane, which was slightly larger than the patch, fixed using a water impermeable adhesive to ensure that the receptor fluid did not touch the sides of the film. The faces with lower concentration was placed in contact with 7.4 pH phosphate buffer with 20% w/v PEG-400 to maintain sink condition. The mouth was coated with silicon grease to avoid any leakage before placing the patch fixed on aluminium foil. 1ml of the solution was withdrawn at an interval of 1 hour up to 12 hours. Then fresh 1ml of buffer solution was added to replace the old one. The removed solution was analyzed spectrophotometrically at λmax 228 nm and concentration was observed from calibration curve (Gupta *et al.,* 2009).

3. RESULTS AND DISCUSSION

Transdermal medication conveyance framework is a most reasonable framework for a drawn out treatment or for a multi – portion treatment and this framework likewise builds the bioavailability of medication by maintaining a strategic distance from the primary pass digestion and expands the restorative adequacy of medication by venturing into the systemic circulation. Polymers HPMC and PVA were chosen based on their following property and non- harmfulness (Burdock, 2007; Chiellini *et al.,* 2003). The consequence of the finding demonstrated incredible following property and controlled discharge. In the present study, different types of penetration enhancers were used in the formulation in addition of dibutylphthalate as plasticizer by solving casting method (Cherukuri *et al.,* 2017).

The formulations were subjected to certain evaluation to ensure the quality of the products. All formulations were shown acceptable appearance with good smoothness, opaque, good flexibility and clear. Thickness and weight differences considered acceptable. Value of folding endurance results showed the products can withstand pressure and does not break easily when applied.

Table 2: Physico-chemical test results

Parameters	Formulations				
	F1	F2	F3	F4	F5
Thickness	0.139 ± 0.070	0.124 ± 0.041	0.130 ± 0.003	0.121 ± 0.016	0.125 ± 0.003
Weight variations	39.3 ± 1.0200	35.26 ± 3.078	34.30 ± 1.618	33.14 ± 2.671	33.28 ±1.849
Folding endurance	256 ± 11.53	260 ±8.89	267 ± 3.00	251 ± 3.61	271 ± 8.89
Moisture uptake	8.749 ± 0.290	7.104 ± 0.047	7.514 ±0.258	6.594 ± 0.386	6.890 ± 2.548
Moisture loss	5.778 ± 0.642	5.254 ± 0.257	5.587 ± 0.266	4.23 ± 0.213	5.476 ±0.693
Swelling index	35.012 ± 0.122	38.521 ± 0.541	36.124 ± 0.588	45.561 ± 0.877	42.569 ± 0.235
Drug content	90.451± 0.4572	89.255± 0.2251	90.854± 0.7558	92.588± 0.8541	90.867± 0.0059

Low moisture content was detected in all the formulation with less than 10%, are suitable to prevent from microbial contamination and not being too dry and brittle. Less moisture loss is preferable to maintain a stable product for a long-time storage (Singh & Bali. 2016). The results indicated great uniformity of drug content which varies from 89 % to 92% and minimal significant variations. Furthermore, *In-vitro* drug release studies were conducted for 12 hours throughout the experiments. The drug release of F1 were shown to be lowest out of all formulations due to absence enhancers (Jafri *et al.,* 2019). F4 showed highest value of drug release where D-limonene as enhancers. Studies have proven the interaction of D-limonene and ethanol solvent may have synergetic effects in penetration rate (Shirakura *et al.,* 1995).

Table 3: *In-Vitro* Drug Release Studies for formulations F1 to F5.

Time (Hrs.)	*In Vitro* Drug Release (Mean)				
	F1	F2	F3	F4	F5
1	9.018	10.253	9.145	13.015	58.47
2	11.887	19.257	12.854	23.565	22.098
3	14.920	25.864	22.156	32.053	33.451
4	18.149	33.877	31.561	40.396	41.122
5	23.014	41.855	40.524	49.000	50.761
6	27.973	49.822	46.522	57.642	58.451
7	32.215	52.691	51.862	65.359	67.908
8	36.277	58.719	62.857	73.601	74.132
9	44.293	64.235	68.577	81.954	82.166
10	48.916	69.511	72.861	88.275	88.910
11	52.164	73.102	76.321	94.012	93.450
12	58.523	77.462	79.292	99.713	98.450

Statistical analysis with one-way ANOVA was conducted to compare the effect of drug release between five formulations (El-Nabarawi *et al.,* 2013) Based on the analysis a significant difference between the formulations was statistically proven which can be seen in the appendices. Between F2 to F5 formulations slightly significant differences were shown between F4 and F5 whereas with F1 and F2 there is statistically significant differences. Based on the drug release profile F4 has shown highest drug release compared to all formulations followed by F5. This behavior can be seen as there is slightly differences of significant differences between them. Furthermore, comparing of two formulations are being done with Independent T-Test between F3, F4 and F4, F5 (Zhan *et al.,* 2015). There are slightly significant differences in statistical analysis between F3 and F4. The performance of F4 is better drug release compared to F3 with mean values. After 12 hours the in vitro performance of F4 and F5 were observed with statistical analysis. Based on the release there were no

slightly differences are shown and statistical analysis has been prove the above results. Both were similar and having higher drug release compared to others.

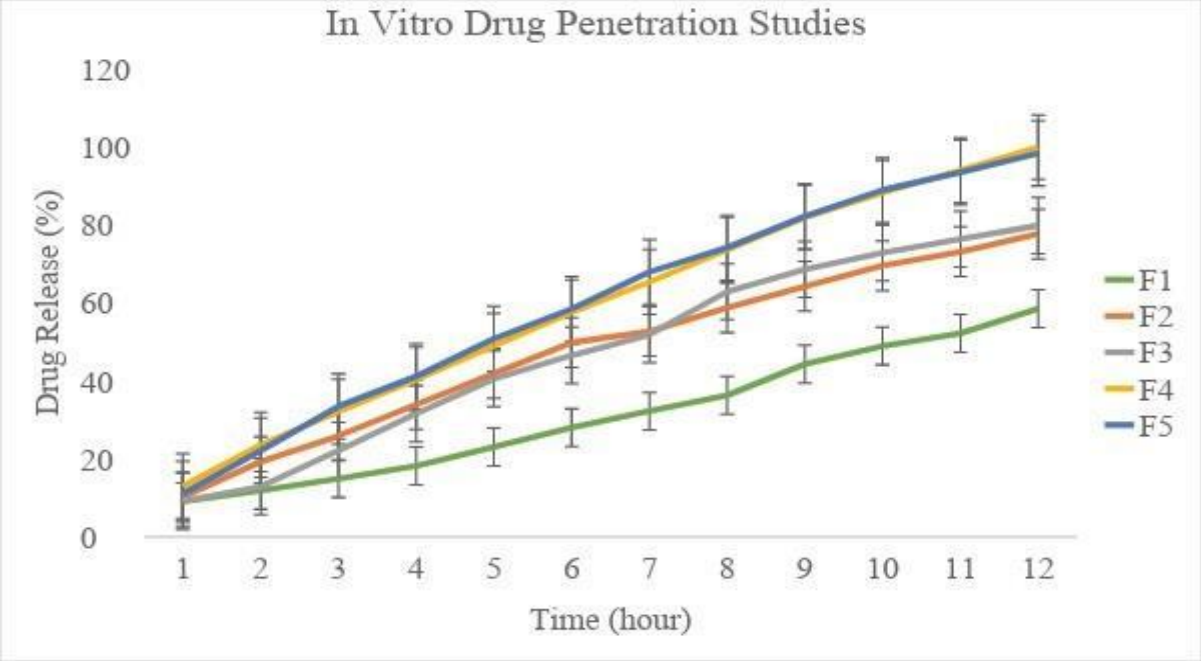

Figure 1: *In-Vitro* Drug Release for formulations F1 to F5.

Further stability studies need to be done to ensure the longevity and effectiveness of the drug for a long term. It is important to evaluate the stability of active component whether it can be maintained for a long time. It is advisable to be carried out the test in two different temperature like 25-30℃ and 45-50℃ with minimum of 60 days (Saroha *et al.*, 2011). From here the loss of drug content and other parameters can monitored with time intervals of 0, 15, 30, 45 and 60 days (Shah *et al.*, 2014). Any physical changes also can be observed throughout the studies. Stability testing is essential in providing evidence on the quality of a drug substance or its product over time due to effect on environmental factors such as temperature, humidity and light. Establishment of storage conditions, shelf-lives are recommended to be achieved within this test.

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5. CONCLUSION

In conclusion, F4, which utilised D-limonene as the enhancers, showed the best formulation with good physicochemical properties of all the penetration enhancers used. The *in vitro* release data showed that drug release from the patch has been affected by the different types of enhancers and the interactions of enhancers with the polymers. These studies indicated different types of enhancers give a different range of drug penetration. Recommendation of stability testing for further investigations is important to ensure the product last for a long time. Nonetheless, the aid of enhancers may increase the drug penetration into the body.

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