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TRANSDERMAL CONTROLLED DRUG DELIVERY OF THREE SELECTED ANTI DIABETIC DRUG

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Abstract:
Transdermal therapy systems are described as "self-contained" discrete dose forms that, when applied to undamaged skin, transport the drug(s) via the skin at a regulated pace to the systemic circulation." By putting a medication formulation to sound, unbroken skin, it provides a painless technique of systemic drug delivery. A collection of illnesses known as Diabetes Mellitus alter how your body utilises blood sugar (glucose). Because it serves as a significant source of energy for the cells that make up your muscles and tissues, glucose is essential to your health. It also serves as the primary fuel for your brain. Diabetes has a variety of underlying causes. However, diabetes may result in too much blood sugar, irrespective of the kind you have. Serious health issues might result from an excessive blood sugar level. Because it was necessary to keep the blood glucose level stable, three medicines were chosen as candidates for constructing a TDDS. The main objective is to study the in vitro diffusion analysis andstability analysis of drug delivery through male wister rat skin. The Sitagliptin phosphate, Glimepiride, and Gliclazide drugs were chosen as candidates for developing TDDS because of their short biological half-lives due to extensive hepatic first pass metabolism, which also eliminates pulsed entry into systemic circulation, which frequently results in undesirable side effects. Additionally, in order to lessen the adverse effects like GI tract infection, peptic ulceration, hepatic impairment, fatigue, and diarrhoea associated with long-term oral administration in humans

Keywords: *Diabetes, Transdermal drug delivery system,Sitagliptin phosphate, Glimepiride, and Gliclazide*

Introduction

Transdermal drug delivery systems (TDDS), commonly referred to as "patches," are medication dosage forms intended to disperse a therapeutically adequate dose of medication over the skin of a patient (Bose et al., 2021). The safety, effectiveness, and quality of the transdermal medication delivery system depend greatly on the adhesive. This offers a foundation for more debate and research to enhance the efficacy of transdermal adhesives (Wokovich et al., 2006). When compared to oral dose forms, it provides better drug concentration consistency in the plasma level during the course of

administration. Transdermal medication administration techniques to prevent hepatic first pass metabolism and increase patient compliance (Veerapaneni, 2021). This is especially helpful for the preventative treatment or for maintenance therapy in chronic disorders like hypertension, hyperglycemia, and other cardiac ailments when the patient would otherwise need to become used to traditional oral medications and remember to take them multiple times a day (Urutia et al., 2021). Although there are a number of long-acting, controlled-release, and extended-release formulations for the treatment of these disorders that have shown promise, they must be administered at least once daily in contrast to transdermal patches that prolong drug release for up to seven days (Sarhan et al., 2012).The study of cutaneous biology of the skin has sparked a great deal of interest from many researchers (Akhtar et al., 2020).

Diabetes Mellitus (NIDDM), however, has been linked to severe and sometimes deadly hypoglycemia as well as stomach disturbances such as nausea, vomiting, heartburn, anorexia, and increased hunger following oral medication (Grover et al., 2014). Patient compliance is crucial as well since these medications are often meant to be used for a long time. However, diabetes may result in too much blood sugar, irrespective of the kind you have (Harshitha et al., 2015). As a result, a new medication delivery method is urgently needed, one that would result in better drug release over a longer course of treatment and a smaller dosage (Ng and Gupta, 2020; Mishra et al., 2009). The desirable qualities mentioned above are present in transdermal drug delivery system (TDDS) (Amjadi et al., 2018).

Sitagliptin phosphate, Glimepiride, and Gliclazide are the pharmaceuticals that have been chosen for this study project. It is widely known how effective these medications are (Shinde et al., 2010). According to research, these medications enhance pancreatic function while lowering blood glucose levels, the risk of hospitalisation and death, and the combined risk of these events. Because it was necessary to keep the blood glucose level stable, three medicines were chosen as candidates for constructing a TDDS (Rani et al., 2019). Additionally, in order to lessen the adverse effects like GI tract infection, peptic ulceration, hepatic impairment, fatigue, and diarrhoea associated with long-term oral administration in humans

Material and method

Research design and strategies

The conceptual framework provides the framework for data collection, measurement, and analysis. After collecting the data, we will investigate and conduct a descriptive research.

Calibration of modified Franz diffusion cell and selection of elution fluid

The borosilicate glass was used to create the modified Franz diffusion cell, which has a receptor compartment capacity of 15 ml and a skin exposure area of 1 cm2. A Teflon-coated magnetic bead and a water jacket were used to stir the receptor chamber. Warm water was pumped through the jacket to keep the assembly's temperature at 37°C.

Permeability studies

The male wistar rat skin was used for the drug permeability investigations, and a modified Franz diffusion cell was used. The quantity of medication diffused was measured UV/Spectr of luorometrically from samples that were taken every hour for up to 12 hours.

Calculating of loading dose for transdermal patches

The aim was to incorporate a dose of 1 mg per cm2 of the patch in case of STP, GLP and GLZ. The amount of drug incorporated for an area of 23.55 cm2 was calculated and the same is represented in Table 13

S.No	Drug	Dose/cm2*	Quantity taken
1	Sitagliptin Phosphate	1 mg	24.55 mg
2	Glimepiride	1 mg	24.55 mg
3	Gliclazide	1 mg	24.55 mg

***In vitro* diffusion studies**

The *in vitro* diffusion from prepared polymeric films across male wistar rat skin barrier was studied in a **modified Franz diffusion cell**.

Statistical analysis

The statistical analysis was conducted using a Windows-based version of SPSS, and the data were entered into an Excel spreadsheet (version 22.0). The variables were explained by means of descriptive statistics such as mean, standard deviation, and percentages. Also employed as a definition of statistical significance was a p value of 0.05. Excel displays analysis using, among other things, charts, graphs, and bar diagrams. The data are always provided as the mean standard deviation.

Result and Discussion

***In vitro* diffusion studies**

Table 1. The *In-vitro* Diffusion Studies (Drug Release) of STP through male wistarrat skin with PVP vs. PVA

S. No	Time in hrs	Cumulative	Percentage	Different	Ratio Drug	Diffused	In mcg/cm²
1		**STP-1 (1:2)**	**STP- 2 (2:1)**	**STP-3 (2:3)**	**STP-4 (3:2)**	**STP-5 (1:4)**	**STP-6 (4:1)**
2	10 min	27.47±0.45	15.46±0.67	10.35±0.20	11.84±0.36	12.75±0.66	20.35±0.45
3	30 min	33.05±0.29	18.59±0.66	19.26±0.25	13.13±0.09	15.01±0.15	28.72±0.48
4	1 hr	48.10±0.67	22.87±0.66	29.70±0.56	17.68±0.39	19.87±0.61	39.85±0.68
5	2 hr	54.15±0.76	29.67±0.62	36.01±0.65	25.13±0.41	25.21±0.36	45.87±0.70
6	4 hr	61.20±0.55	34.31±0.44	40.84±0.44	33.99±0.93	30.86±0.94	50.81±0.75
7	8 hr	76.25±0.33	40.42±0.73	44.86±0.68	42.18±0.58	36.21±0.53	56.93±0.60
8	12 hr	81.33±0.23	45.39±0.94	47.71±0.57	47.82±0.48	41.51±0.32	61.41±0.55
9	24 hr	98.42±0.52	56.84±0.34	62.06±0.56	56.06±0.65	48.21±0.35	72.85±0.45

Table 1 displays the in vitro diffusion results for several batches of drug-loaded PVP:PVA films. Studies revealed that there was some selection of an optimum formula. In terms of physicochemical

characteristics and diffusion parameters, the STP patch formula utilising the PVP: PVA combination in the ratio of 1:2 was shown to be better to the other formulations.

Stability studies

According to ICH requirements, stability tests for the improved formulation were conducted for six months at 40°C and 75 percent relative humidity. The final evaluation of the formulation looked at its thickness, drug content, moisture content, moisture absorption, appearance, and diffusion research. the outcome shown in Table 2.

Table 2. Evaluated data of optimized formula after 6 months

S.No	Parameter	0 week	6 months
	Thickness	0.22 mm	0.24
	Weight	23 mg/cm2	22.5 mg/cm2
	Moisture content	2.70	2.75
	Moisture uptake	5.75 (75% RH)	5.85 (75% RH)
	Drug content	98.60%	96.5%

Table 3. The *In-vitro* Diffusion Studies (Drug Release) of GLP through male wistar rat skin with PVP vs. PVA

S. No	Time in hrs	Cumulative	Percentage	Different	Ratio Drug	Diffused	In mcg/cm²
1		**GLP-1 (1:2)**	**GLP - 2 (2:1)**	**GLP -3 (2:3)**	**GLP -4 (3:2)**	**GLP -5 (1:4)**	**GLP -6 (4:1)**
2	10 min	21.47±0.45	21.46±0.67	20.35±0.20	18.84±0.36	15.75±0.66	15.35±0.45
3	30 min	34.05±0.29	27.59±0.66	29.26±0.25	23.13±0.09	19.01±0.15	20.72±0.48
4	1 hr	42.10±0.67	36.87±0.66	31.70±0.56	27.68±0.39	25.87±0.61	25.85±0.68
5	2 hr	46.15±0.76	40.67±0.62	39.01±0.65	32.13±0.41	29.21±0.36	32.87±0.70
6	4 hr	51.20±0.55	44.31±0.44	45.84±0.44	41.99±0.93	35.86±0.94	40.81±0.75
7	8 hr	56.25±0.33	47.42±0.73	49.86±0.68	45.18±0.58	41.21±0.53	46.93±0.60
8	12 hr	61.33±0.23	54.39±0.94	54.71±0.57	53.82±0.48	52.51±0.32	51.41±0.55
9	24 hr	78.42±0.52	71.84±0.34	68.06±0.56	68.06±0.65	61.21±0.35	62.85±0.45

Table 3 displays the in vitro diffusion results for several batches of drug-loaded PVP:PVA films. The investigations revealed that there was a selection of an optimum formula. With regard to physicochemical characteristics and diffusion parameters, the GLP patch formula utilising the PVP: PVA combination in the ratio of 1:2 was determined to be better to the other formulations. The ingredients of the optimised batch GLP 1 are listed in Table 3.

Stability studies

According to ICH requirements, stability tests for the improved formulation were conducted for six months at 40°C and 75 percent relative humidity. The final evaluation of the formulation looked at its thickness, drug content, moisture content, moisture absorption, appearance, and diffusion research. the outcome shown in Table 4.

Table 4. Evaluated data of optimized formula after 6 months

S.No	Parameter	0 week	6 months
1	Thickness	0.22 mm	0.24
2	Weight	23 mg/cm2	22.5 mg/cm2
3	Moisture content	2.70	2.75
4	Moisture uptake	5.75 (75% RH)	5.85 (75% RH)
5	Drug content	98.60%	96.5%

***In vitro* diffusion studies**

Table 5. The *In-vitro* Diffusion Studies (Drug Release) of GLZ through male wistar rat skin with PVP vs. PVA

S. No	Time in hrs	Cumulative	Percentage	Different	Ratio Drug	Diffused	In mcg/cm²
		GLZ-1 (1:2)	GLZ - 2 (2:1)	GLZ -3 (2:3)	GLZ -4 (3:2)	GLZ -5 (1:4)	GLZ -6 (4:1)
1	10 min	24.47±0.45	19.46±0.67	20.35±0.20	20.84±0.36	15.75±0.66	14.35±0.45
2	30 min	30.05±0.29	25.59±0.66	25.26±0.25	21.13±0.09	21.01±0.15	17.72±0.48
3	1 hr	34.10±0.67	31.87±0.66	32.70±0.56	32.68±0.39	30.87±0.61	26.85±0.68
4	2 hr	35.15±0.76	40.67±0.62	45.01±0.65	48.13±0.41	39.21±0.36	35.87±0.70
5	4 hr	59.20±0.55	40.31±0.44	45.84±0.44	51.99±0.93	45.86±0.94	46.81±0.75
6	8 hr	56.25±0.33	48.42±0.73	50.86±0.68	55.18±0.58	51.21±0.53	53.93±0.60
7	12 hr	65.33±0.23	54.39±0.94	57.71±0.57	63.82±0.48	58.51±0.32	61.41±0.55
8	24 hr	79.42±0.52	61.84±0.34	69.06±0.56	78.06±0.65	69.21±0.35	72.85±0.45

The in vitro diffusion statistics of several batches of drug-loaded PVP:PVA films were shown

Stability studies

According to ICH requirements, stability tests for the improved formulation were conducted for six months at 40°C and 75 percent relative humidity. The final evaluation of the formulation looked at its thickness, drug content, moisture content, moisture absorption, appearance, and diffusion research. the outcome shown in Table 5.

Table 6. Evaluated data of optimized formula after 6 months

S.No	Parameter	0 week	6 months
1	Thickness	0.22 mm	0.24
2	Weight	23 mg/cm2	22.5 mg/cm2
3	Moisture content	2.70	2.75
4	Moisture uptake	5.75 (75% RH)	5.85 (75% RH)
5	Drug content	98.60%	96.5%

According to the investigations, there was some selection of an optimum recipe. Regarding physicochemical characteristics and diffusion parameters, it was discovered that the GLZ patch formula utilising a PVP: PVA combination at a ratio of 1:2 was better to the other formulations. The make-up of the optimised batch GLP 1 is presented in Table 6.

When the body does not react properly to insulin, the pancreas may not generate any insulin, or produces very little insulin. an issue known as "insulin resistance." Diabetes is a chronic condition (Ng and Gupta, 2020). Additionally, relationships with hypertension, obesity, a family history of diabetes, and low levels of education. A group of risk variables analysed together (dyslipidemia, waist-to-hip ratio, and family history of diabetes) exhibited excellent predictive value, according to multivariate analysis adjusted for age and sex (Urutia et al., 2021).

Conclusion:

Drug administration by non-oral methods is often justified for strong reasons. Transdermal delivery has drawn more attention in the past ten years due to a growing understanding that drugs given orally are frequently overly toxic and occasionally inactive because they are injected into the body as pulses, causing significant fluctuations in drug concentration in the blood and tissues, which in turn cause undesirable patterns of efficacy and toxicity. The formulator received significant assistance from fundamental research on skin physiology, structure, and immunological qualities in order to overcome the skin's very excellent barrier capabilities, which are ascribed to the stratum corneum, the skin's outermost layer.

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