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COMPARATIVE STUDY OF SITAGLIPTIN PHOSPHATE, GLIMEPIRIDE AND GLICLAZIDE FOR THEIR SAFETY AND EFFICACY IN DIABETES

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Abstract
A transdermal drug delivery system (TDDS), often known as a transdermal patch, is a flexible, multilaminated pharmaceutical preparation of variable sizes containing one or more pharmacological substances that are placed to the intact skin for systemic circulation to maintain the plasma level.Normally, this is made using pressure-sensitive adhesive, which ensures that the skin preparation will adhere to it. Very few commercially marketed transdermal patches exist at the moment.Research on transdermal technology has grown significantly in the past 20 years, both academically and commercially. Even though there are currently few acceptable medication candidates for this method of administration, it continues to be a topic of intense attention across the globe. An in-depth research has been conducted and produced in order to concentrate these advancements.In order to determine the safety, effectiveness, and tolerability of Sitagliptin phosphate, Gliclazide, and Glimepiride in the treatment of type 2 Diabetes Mellitus, the current research was conducted. Physicochemical, pharmacokinetics parameters were evaluated. Comparative pharmacokinetic parameters of oral tablets and transdermalpatches of Sitagliptin phosphate, Glimepiride and Gliclazide were evaluated. In the current research, Sitagliptin phosphate patches performed more safely and effectively than Gliclazide and Glimepiride patches. This finding is consistent with a prior study in which STP, GLZ, and GLP users reported 50% fewer hypoglycemia episodes. In the current investigation, it was discovered that sitagliptin phosphate was more effective.transdermal medication administration has shown to be a practical substitute for pharmaceuticals that would otherwise need to be circulated throughout the body. The chosen antihyperglycemic medicines' matrix-type transdermal drug delivery methods have shown to be successful in managing diabetics and show promise for future clinical application.
Keywords: *Transdermal patches, Diabetes Sitagliptin phosphate, Glimepiride and Gliclazide*

Introduction:
Introduction must include background, LR and aim + hypothesis
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 (Akhtar et al., 2019). The safety, effectiveness, and quality of the transdermal medication delivery system depend greatly on the adhesive (Rani et al., 2019). By preventing "first pass metabolism," medicines' bioavailability and effectiveness may be increased. reduce oral administration-related variations in absorption and metabolism. Utilizing medications allows for continuous delivery with a low therapeutic index and short biological half-life. Due to the removal of medications, dose regimens may be lowered and patient compliance can improve. Simple drug delivery termination in case of toxicity, if the course of therapy may be maintained or stopped whenever required. Impaired fasting and impaired glucose tolerance are risk factors for developing diabetes and cardiovascular disease in the future (Mishra et al., 2009). In addition to being the main cause of renal failure, it also

raises the risk of TB, vision impairment, and lower limb amputations.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. A collection of illnesses known as Diabetes Mellitus alter how your body utilises blood sugar (glucose)(Urutia et al., 2019). Skin-based medicine administration, however, did not become commonplace until the 20th century. In fact, Marian Webster gives the phrase "transdermal" a 1944 birthdate, demonstrating that it is a relatively new idea in medical and pharmaceutical practise (Ellen et al 2011). In place of more conventional delivery methods including intravenous, intramuscular, subcutaneous, and transmucosal, TDDS uses the skin to administer medications (Bose et al., 2019). A transdermal drug delivery system (TDDS), often known as a transdermal patch, is a flexible, multilaminated pharmaceutical preparation of variable sizes containing one or more pharmacological substances that are placed to the intact skin for systemic circulation to maintain the plasma level.

Normally, this is made using pressure-sensitive adhesive, which ensures that the skin preparation will adhere to it (Amjadi et al., 2018). Very few commercially marketed transdermal patches exist at the moment (Veerapaneni, 2019). Under typical diffusion circumstances, the skin readily permits medications with an average molecular weight (MW) of 500 Da. Inversely proportional to molecular size is transdermal penetration (Akhtar et al., 2019).

Material and method

Drug brands of Sitagliptin phosphate, Gliclazide and glimepiride used in the study

1. STPM
2. GLPM
3. GLZM

Comparative parameters

Description

STP - White fine powder, GLP - Crystalline powder, physical state is solid nature, powder form and GLZ - White, off-white powder, physical state is solid nature, powder form.

Odor

STP - odorless, GLP - odorless or practically odorless and GLZ- odorless.

Solubility

STP - Soluble in water, GLP - Soluble in methanol and GLZ - Soluble in methanol.

Physicochemical evaluation

STP, GLP and GLZ - Transparent, clear, smooth and flexible in nature

Surface morphology by SEM

Uniformly distribution of drug (STP, GLP and GLZ) in the polymer matrix.

Thickness test

STP - Ranges between 0.18 to 0.23mm, GLP - Ranges between 0.17 to 0.21mm and GLZ - Ranges between 0.16 to 0.22mm.

Flatness Test

STP, GLP and GLZ - The patches were found to exhibit 100% flatness.

Uniformity of weight Test

STP, GLP and GLZ – The patches were found to be in the ranges of 17 to 22mg.

Percentage of elongation Test

STP, GLP and GLZ - All the films were found to exhibit 100 % elongation

Result and Discussion

Drug Content and content uniformity Test

STP, GLP and GLZ - Ranges between 95.44 to 98.66 %

Moisture content

STP, GLP and GLZ - Ranges between 2.1018 to 4.9229 % for loaded films

Moisture uptake Test

STP, GLP and GLZ - 5.696 to 11.772 (at 70 %), 11.472 to 23.644 (at 90 %)

STP, GLP and GLZ patches using PVP: PVA combination in the ratio of 1:2 was found to be superior compared to the other formulations in terms of physicochemical properties and diffusion parameters.

Table 1. Optimized formulation of STP

S.No.	Ingredients	Quantity/cm2
1	Sitagliptin phosphate (mg)	1.00
2	PVP: PVA	1:2
3	Dibutyl phthalate	30% w/w
4	DMSO	1% w/w
5	Water	q.s

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. The batch STP 1 optimization's makeup is shown in Table 54.

Table 2. Optimized formulation of GLP

S.No.	Ingredients	Quantity/cm2
1	Glimepiride (mg)	1.00
2	PVP: PVA	1:2
3	Dibutyl phthalate	30% w/w
4	DMSO	1% w/w
5	Methanol	q.s

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 1.

Table 3. Optimized formulation of GLZ

S.No.	Ingredients	Quantity/cm2
1	Gliclazide (mg)	1.00
2	PVP: PVA	1:2
3	Dibutyl phthalate	30% w/w
4	DMSO	1% w/w
5	Methanol	q.s

Regarding physicochemical characteristics and diffusion factors, it was discovered that GLZ patches made with a 1:2 ratio of PVP and PVA were better to those made with other formulations. The makeup of the optimised batch GLP 1 is shown in Table 2.
STP, GLP, and GLZ's transdermal drug delivery systems were created using the solvent casting (evaporation) technology.
Thus, we are able to produce films that are both cost-effective and of high quality in terms of their physical and chemical characteristics. According to research on permeability, diffusion, and the physicochemical properties of film formulation, DMSO is an effective enhancer for transdermal drug delivery systems. Therefore, the formulation of STP, GLP, and GLZ transdermal drug delivery systems using the aforementioned polymer with enhancer may be employed to get the ideal release kinetics. The in vitro drug diffusion investigation of the STP4, GLP10, and GLZ16 (1:2) optimised formulation was 98.420.52 percent. In this formulation, the maximal impact was therefore achieved. To prevent the danger and inconvenience of intravenous treatment, the developed optimal formulation and the marketed formulation (oral tablet and intravenous therapy) were evaluated.

Table 4Comparative pharmacokinetic parameters of oral tablets and transdermal patches of Sitagliptin phosphate, Glimepiride and Gliclazide

S.No	Parameter	ORL STP	ORL GLP	ORL GLZ	TDP STP	TDP GLP	TDP GLZ
1	Cmax (ng/ml)	208	210	200	215	205	209
2	Tmax (h)	21-2	1-2	1-2	8-12	8-16	8-24
3	AUC →24h or 0→ 12h (ngh/ml)	- 87.403	- 45.135	- 235.3	-- 3094.117***	-- 1565.07***	840.81*** --
4	AUC 0→∞ (ngh/ml)	654.407	134.7	500.845	2431.55***	5473.124***	3425.09***
5	K(h-1)	0.179	0.245	0.147	0.098***	0.079***	0.045***

The transdermal patches containing Sitagliptin phosphate, Glimepiride, and Gliclazide were discovered to be whole, leak-free, and to have acceptable content consistency.
The drug-spiked plasma and the plasma obtained after oral administration or transdermal application both exhibited identical HPLC retention times with respect to the drugs, demonstrating that the components of plasma did not affect the estimation of sitagliptin phosphate, glimepiride, and gliclazide in plasma.
Following the use of transdermal patches and oral administration of tablet dosage forms, the mean plasma concentrations of various medications at various time intervals are shown in Table 4.
After oral administration, the peak plasma concentration (Cmax) of the medications Sitagliptin phosphate, Glimepiride, and Gliclazide tablets was 200, 208, and 210 ng/ml, respectively. The time to maximum effect (tmax) for all the drugs was predicted to be

between 1-2 hours. Sitagliptin phosphate, glimepiride, and gliclazide all had peak plasma concentrations (Cmax) of 215, 209, and 205 ng/ml after being applied transdermally through matrix patches, and the three medicines' tmaxes were discovered to be between 8 and 12 hours for all three.

Wagner and Nelson's approach was used to determine each and every pharmacokinetic parameter (Modern Bio-pharmaceutics V6 demo version software). In Tables 48 and 49, respectively, the values of log Cp and AUC for the three medicines' transdermal patches and oral tablets are shown.

Sitagliptin phosphate, glimepiride, and gliclazide were taken orally, with the AUC (012 h) being 87.403, 45.135, and 235.3 mmol/l and the AUC (0) being 654.407, 500.845, and 134.7 mmol/l, respectively (Table 4).

Transdermal patches containing Sitagliptin phosphate, Glimepiride, and Gliclazide had AUCs (024 h) of 840.81, 3094.117, and 1565.07 mmol/l, respectively, whereas their AUCs (0) were 2431.55, 5473.124, and 3425.09 mmol/l, respectively (Table 4).

This research offers fresh perspectives on treatment approaches using sulphonylureas and the dipeptidyl peptidase IV inhibitor trizolopyrazine (SU). In comparison to Gliclazide and Glimepiride patches (Shinde et al., 2010), it demonstrates that Sitagliptin phosphate patches were at least as effective. Comparing Sitagliptin phosphate patches to Gliclazide and Glimepiride patches, the safety of the former showed a significant improvement, with almost 50% fewer verified hypoglycemia episodes (Harshitha et al.,2015).

In the current research, Sitagliptin phosphate patches performed more safely and effectively than Gliclazide and Glimepiride patches. This finding is consistent with a prior study in which STP, GLZ, and GLP users reported 50% fewer hypoglycemia episodes. In the current investigation, it was discovered that sitagliptin phosphate was more effective. Throughout the trial, it was discovered that all of the medications were well tolerated by the individuals.

In terms of safety and effectiveness, a patch formulation of sitagliptin phosphate (STP GLZ GLP) was shown to be better. As a result, the study's findings suggest that Sitagliptin phosphate patches are preferable to Gliclazide and Glimepiride patches for the treatmentof diabetes.

Conclusion: According to the current investigation, transdermal patches applied to animals' skin resulted in steady-state plasma concentrations of sitagliptin phosphate, glimepiride, and gliclazide. In hyperglycemic rats, the medications also demonstrated a consistent and persistent drop in blood glucose levels from 2nd hour to 24th hour. The findings of the pharmacokinetic and pharmacodynamic tests of the aforementioned medications call for more research in healthy human volunteers and patients to investigate the feasibility of a commercially viable, therapeutically effective, and safe delivery method.

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