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Tirzepatide Transdermal Patches for Diabetes management: Formulation and evaluation:A Research

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Abstract

The transdermal drug delivery system (TDDS) was created with the main goals of achieving extended pharmaceutical release, increasing bioavailability, and enhancing patient adherence. The matrix dispersion transdermal patch works by dispersing the drug and polymers in a solvent, which is then evaporated to leave a homogenous drug-polymer matrix. The goals of the present study were on designing and formulating TDDS for tirzepatide and afterwards assessing their in vitro performance characteristics. In diabetes mellitus, the pancreas either produces inadequate amounts of insulin or the body is unable to properly use the insulin that is generated. More than 415 million people worldwide have diabetes, and it is anticipated that by 2040, that number would reach 642 million. By 2030, diabetes will surpass heart disease as the seventh largest cause of death, according to the WHO.

Keyword: Compliance, Dispersion, Homogeneous, Bioavailability, matrix.

Introduction

Diabetes, once known as "honey urine," was originally identified around 1500 BCE and has been acknowledged as a fatal and catastrophic condition for over 2000 years [1,2]. Chronic hyperglycemia is the hallmark of a set of metabolic illnesses collectively referred to as diabetes mellitus. Diabetes pathophysiology is brought on by either impaired insulin action, faulty insulin secretion, or both. Diabetes may be classified into a variety of groups depending on the pathophysiology and clinical symptoms at the time of diagnosis.

The loss of insulin-producing beta cells in the islets of Langerhans is the root cause of type 1 diabetes mellitus (T1DM), which leads in a complete absence of insulin. Type 1A diabetes mellitus, sometimes referred to as insulin-dependent diabetes, is an immune-mediated form of the disease in which beta cells are destroyed by the immune system at varied rates in various patient groups. On the other hand, Type 1B diabetes mellitus, sometimes referred to as idiopathic diabetes, is described as having no recognized cause of insulin insufficiency and no known autoimmune mechanism causing beta-cell death. Type 2 diabetes mellitus (T2DM), previously known as non-insulin-dependent diabetes mellitus, is the most common form of diabetes (between 90% and 95%). Relative insulin insufficiency and insulin resistance brought on by hereditary or environmental causes are seen in this kind of diabetes. T2DM and obesity are often linked, and many people spend years without receiving a diagnosis[3].

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Until the late 20th century, the biggest organ in our body, the skin, which gets about one-third of the total blood flow, was not recognised as a route for systemic drug administration [4-7]. Transdermal medication administration has attracted more interest recently because to its specific benefits over regular oral dosage types. Transdermal drug delivery is expected to grow and reach a market size of around $95.57 billion by 2025. [8].

The possibility of overdose is one of the primary issues with conventional oral and parenteral administration, mostly due of variations in peak plasma concentration. With regard to measuring effective plasma concentration, this presents a considerable issue. Since they enable medications to avoid the hepatic first-pass metabolism and factors that might alter the gastrointestinal tract's pharmacokinetics, transdermal drug delivery methods have a number of advantages. This greatly improves systemic bioavailability while lowering the chance of adverse effects brought on by variations in concentration. Additionally, since it is straightforward and comfortable to use, requiring less frequent dosage because the medicine is delivered over a long period of time at a predefined pace, this method frequently increases patient compliance. [6].

Since the skin has a dead layer (stratum corneum) and live layers (dermis and papillary layer), most molecules reach the microcirculation immediately after exiting the epidermis. Catechol-o-methyl transferase metabolizes medicines in live tissue. A drug species' cutaneous aqueous phase resistance time may last only a few seconds [11-14].

Material and Methods

Chemical Used:tirzepatide, oleic acid, tween 80, ethyl acetate, ethanol, hydrochloric acid, n-hexane, acetonitrile, HPMC, PVP-K30, PEG-40, Propylene glycol.

Equipmentrequired:Homogenizer, Centrifuge, Sonicator, UV-Visible Spectrophotometer, FT-IR Spectrophotometer, Melting Point, pH meter, Rotary Vacuum Evaporator.

The analytical reagent grade (AR grade) was employed for all compounds and reagents used in the current investigation [15-17].S.S

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Drug Profile:

Tirzepatide: Tirzepatide, a both GIP and GLP-1 receptor agonist, is used in addition to diet and exercise to treat type II diabetes in adults.

Bioavailability: 80%

half-life: five days

Mechanism of action : Increase glucose-dependent first and second-phase production of insulin and decrease glucagon levels.

Preformulation studies:

Preformulation experiments were carried out to determine the trizipatide medication's physicochemical characteristics and compatibility with different excipients before it is made into a transdermal patch (dosage form).

The parent compound, trizipatide, had already been preformulated. The purity and authenticity of the tirzepatide were determined using preformulation tests, which also looked at the potential for interactions between the tirzepatide and the polymeric carrier[17].

Formulation of Transdermal Patch:

For the synthesis of the transdermal patches, the nano precipitation method was adopted. When making the TP, different concentrations of lipids were employed, which you can see here.

Table 1: The formula for preparation of TP

Ingredients	TPC1	TPC2	TPC3	TPC4
Trizipatide (mg)	200	200	200	200
Oleic acid (mmol)	0.1 **S**	0.12	0.14	0.16
Tween 80 (%)	5	5	5	5

Determination of drug compatibility

Organoleptic characterization:

On some butter paper, a small amount of pure tirzepatide powder was deposited, and the color, taste, and odor of the powder were analyzed.

Solubility:

An analysis was done to determine whether or not tirzepatide is soluble in water, methanol, or ethanol. Shaking very small amounts of tirzepatide in test tubes that were filled with the solvent and looking for any undissolved particles was done.

Melting Point:

The melting point of tirzepatide was determined by utilizing a technique known as open capillary, which involves placing the drug inside of a capillary tube that is then sealed.

Drug excipient compatibility Study:

Component and mixture IR spectra, FT-IR spectrophotometer, as well as lipids and medications. In the spectra of both the medication and the lipid, there were found to be distinct physical and chemical variances.

Calibration curve of Tirzepatide:

After making tirzepatide stock solutions in methanol with a concentration of up to 100 g/ml, aliquots were transferred to a series of 10 mL volumetric flasks with varying capacity in order to make standard dilutions of the compound with concentrations ranging from 5 to 25 g/ml. After being scanned with a UV-Visible spectrophotometer from 1100 to 200 nanometers, the greatest wavelength at which the solution absorbs light, represented by the absorption coefficient (max), was measured to be 286 nanometers. This value was determined after the absorption coefficient was calculated. In order to produce a calibration curve that plots absorbance versus concentration, the absorbance of the standard dilutions was measured at a wavelength of 286 nm. The linearity equation, denoted by the notation y =mx + c, was developed and applied in the process of determining the amount of trizipatide present in formulations.

Characterization of TP:

Particle size and zeta potential:

Particle size was determined using a particle size analyzer while the zeta potential was determined using a zeta sizer.

Entrapment Efficiency:

After centrifuging the drug-loaded at 15,000 rpm for 15 minutes, the supernatant was collected and used to calculate the drug incorporation % during nanoparticle manufacturing. Absorbance at 286 nm was measured using a UV-visible spectrophotometer to determine how much of the medication was present after the pellet was washed twice with water and dissolved in acetonitrile.

In-vitro drug release:

It was used as part of an in vitro study to determine how much trizipatide was released from the TP. The dialysis bags, each of which held one milliliter of trizipatide-loaded TP, were dropped into beakers that contained the dissolving medium. The dissolving medium was a simulation of stomach fluid made of phosphate buffer saline with the pH adjusted to 2.0 with hydrochloric acid. The medium was kept at 37°C and agitated at 100 rpm. The sample, which was 1 mL in volume, was collected using a pipette, and at regular intervals, the collected volume was replaced with newly produced medium. Calculating the amount of tirzepatide that was present required first centrifuging the samples at 10000 rpm for 5 minutes, then diluting the supernatant, and finally using a UV-visible spectrophotometer to detect the absorbance at 286

Evaluation of Transdermal Patches:

Uniformity of weight test:

For the purpose of introducing mass variance, patches were chosen at random and weighed many times (44.15 cm2). Each mixture was examined and evaluated thrice to guarantee its precision.

Thickness:

We were able to determine the average thickness of each patch by using a vernier caliper to measure the patch at a number of different locations.

Folding endurance:

The folding endurance of a patch was measured by repeatedly cracking it as it was being folded. The ability of the film to withstand folding was evaluated by folding it in half using the same place until it either cracked or broke.

Drug content test:

By slicing off distinct regions from each patch, we were able to collect three 4 cm2 patches in total. These fragments were placed in a vial that held 10 milliliters of ethanol, and the vial was subsequently shaken in a vortex for sixty minutes in order to completely dissolve the patches. Following the use of Whatman paper to filter the solutions, 0.1 milliliter was extracted and diluted to a total amount of 10 milliliters in a separate volumetric flask. A UV-Visible spectrophotometer was used to measure the absorbance of this solution at 286 nm in order to

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calculate the amount of the active component that was present in the mixture.

Percent moisture content:

Desiccators made of fused calcium chloride were employed in order to store transdermal films for 24 hours at room temperature. After waiting for twenty-four hours, we reweighed the films in order to get a better reading of their relative humidity.

$$\text{Percentage of moisture content} = \frac{\text{Initial weight} - \text{Final weight x 100}}{\text{Initial weight}}$$

In-vitro permeation study:

For the transdermal patch penetration testing, Franz diffusion cells that had a capacity of thirty milliliters for each receptor compartment were utilized. Following the insertion of the dialysis membrane that was placed between the donor compartment and the receptor compartment, the 4 cm2 patch was applied. Phosphate buffer saline with a pH level of 7.4 was used to fill the compartment of the diffusion cell receptor. The solution in the receptor compartment was stirred at a rate of 50 revolutions per minute, and the temperature was maintained at 37 degrees Celsius plus 0.5 degrees Celsius. The drug concentration was measured by ultraviolet light at a wavelength of 286 nm after aliquots of 1 milliliter had been diluted with ethanol at 0, 1, 2, 3, 4, 6, and 12 hours. We took samples at regular intervals and added phosphate buffer to the receptor stage in order to quantify the amount of medication that was absorbed per square centimeter over the course of time at 37 degrees Celsius.

Table 2: Ingredients used for tirzepatide loaded Transdermal patch

Ingredients	TPP1	TPP2	TPP3	TPP4
TPC (mg)	45	45	45	45
HPMC (mg)	100	100	100	100
PVP K30 (mg)	0.1	1	1.5	2
PEG-400	30	30	30	30
Propylene Glycol	15	15	15	15

Results and Discussion

To provide a regulated release, increase the bioavailability of the therapeutic medication, and lower the toxicity, transdermal patches containing tirzepatide were created using a matrix type solvent casting approach. This is the first study on the transdermal drug administration of tirzepatide, and it has been proven to be more successful than other reported tirzepatide dosage forms [17].

Preformulation studies

FTIR tests, or preformulation studies, showed that excipients and polymers were compatible with tirzepatide. Microscopic images of formulations using various polymers were examined, and a calibration curve for tirzepatide was developed and shown to be linear.

Evaluation parameter

Table 3: Physiochemical features of Transdermal Patches

Formulation	Thickness (mm)	Average weight (mg)	Moisture content (%)	Drug content (%)	Folding Endurance
TPP1	0.3123	162	6.517	98.163	68
TPP2	0.3012	164	6.374	99.012	77
TPP3	0.2754	152	6.245	99.226	86
TPP4	0.2611	145	6.032	99.247	95

Organoleptic properties of Tirzepatide

Test	Specification	Observation
Color	Orange- yellow needles	Pale Yellow
Odour	Characteristic	Characteristic
Taste	Bitter	Bitter
Melting Point	183°C	181-185°C
Solubility	Water	Insoluble
	Methanol	Soluble
	Ethanol	Freely Soluble

FT-IR study:

The FT-IR spectrum of Tirzepatide and a physical mixture of Tirzepatide and oleic acid were obtained and analysed for any deletion of the pure drug's peaks.

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S. No	Functional group	Observed range (cm^{-1})
1	(OH stretching)	3341 cm^{-1}
2	(CH aromatic stretching)	3056 cm^{-1}
3	(CH_2 stretching)	2923 cm^{-1}
4	(C=O stretching)	1647 cm^{-1}
5	(C=C aromatic stretching)	1574 cm^{-1}
6	(CH_2 bending)	1441 cm^{-1}
7	(C-O stretching)	1146 cm^{-1}

All peaks in the physical combination indicated component compatibility.

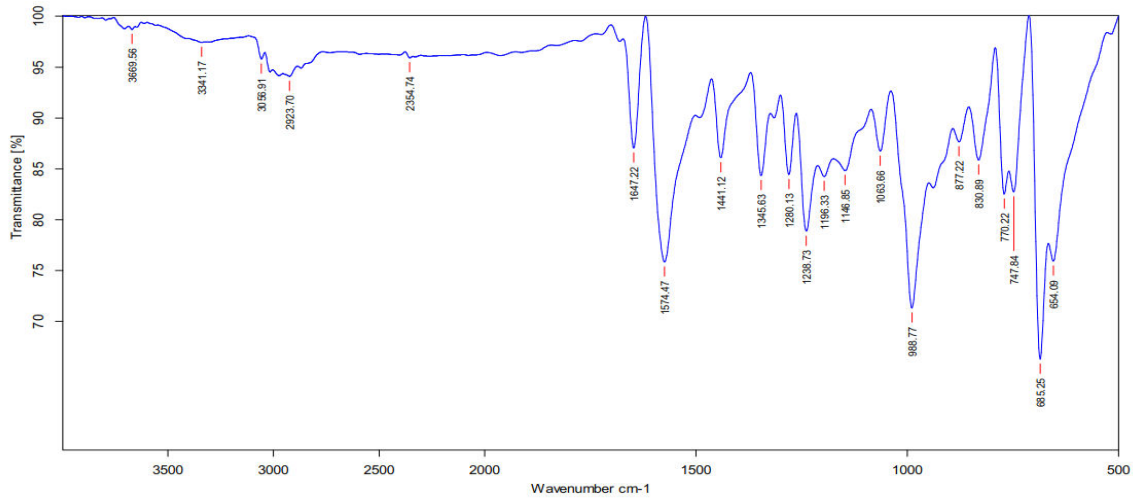

Fig. FT-IR of Tirzepatide

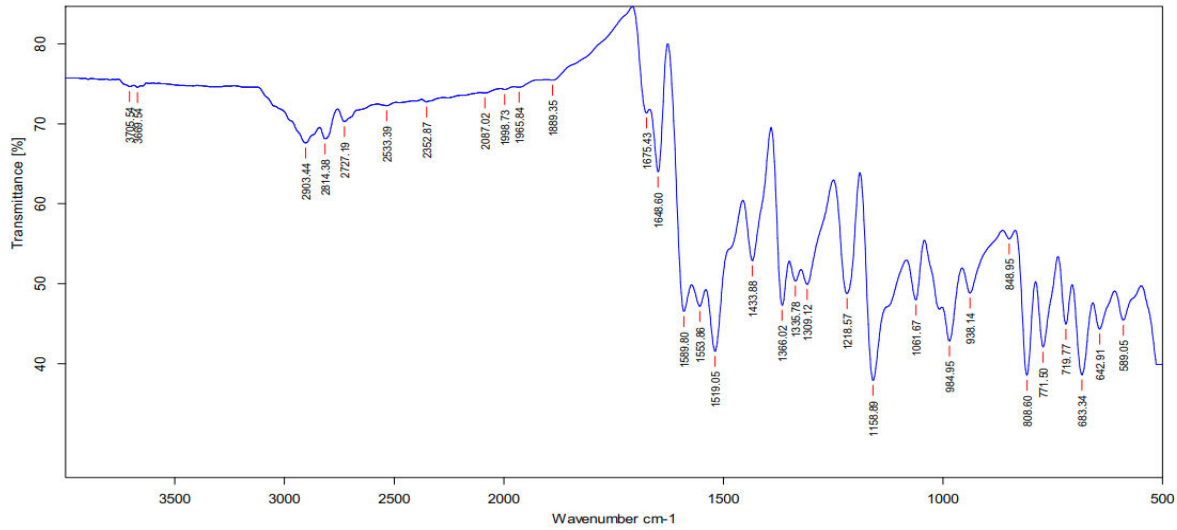

Fig. FT-IR of mixture of oleic acid and trizipatide

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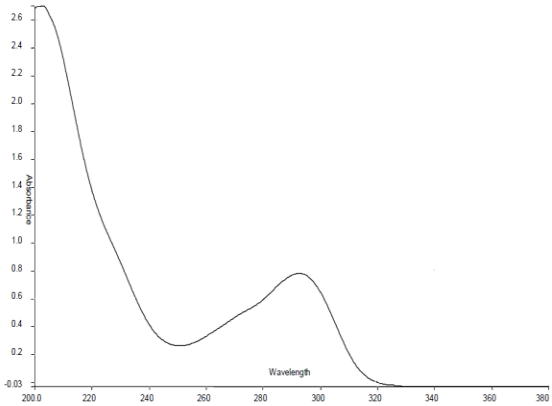
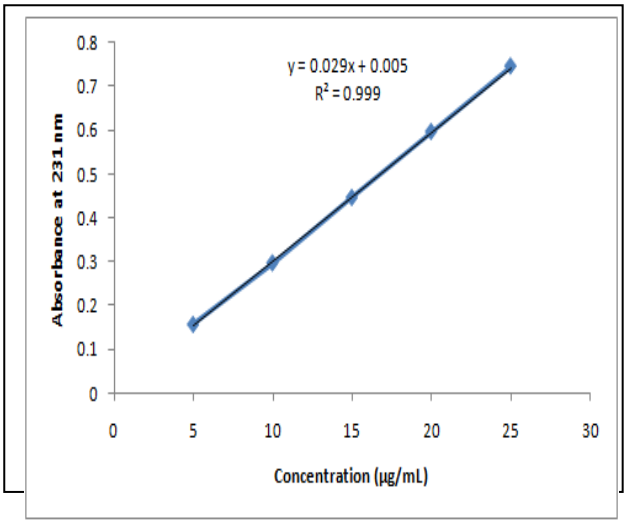
Calibration curve:



The above mention graph shows in methanol, the calibration curve for trizipatide was constructed by using a UV-Visible spectrophotometer at 286 nm and plotting the absorbance vs concentration. The linearity equation was determined to be as follows: The regression coefficient, R2, was determined to be 0.999 for the absorbance (y) = 0.029 and the concentration (x) +0.005. The concentration of trizipatide was determined throughout the study by applying this equation to the appropriate data.

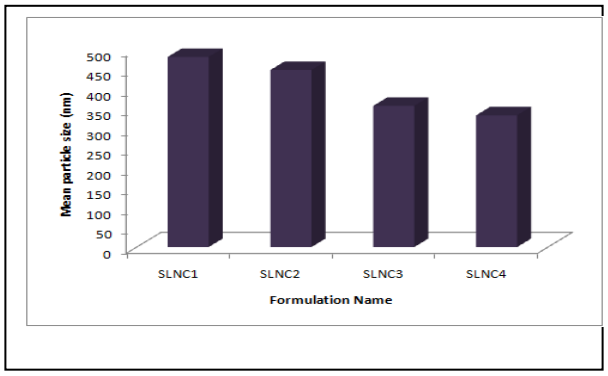
Absorbance of Tirzepatide at 286 nm

Concentration (µg/ml)	Absorbance
5	0.156 ± 0.00057
10	0.295 ± 0.00173
15	0.466 ± 0.004
20	0.590 ± 0.00152
25	0.743 ± 0.00251



Particle size and zeta potential of TP

FC	Particle Size	Zeta Potential
TPC1	482 ± 201	-19.8 ± 1.4
TPC2	449 ± 112	-17.2 ± 2.8
TPC3	358 ± 590	-18.5 ± 5.6
TPC4	334 ± 117	-15.2 ± 3.9



According to the particle size test results, the smallest particles were formed when 0.16 mmol of lipid was in solution, but a lower ratio resulted in an increase in the particle size of the TP.

Table 4: Entrapment of Tirzepatide in TP

Formulation	Entrapment Efficiency
TPC1	54.5 ± 7.31
TPC2	56.2 ± 2.34
TPC3	61.1 ± 1.25
TPC4	66.7 ± 11.18

Table 5: In vitro release of Tirzepatide from TP

Formulation	% Release of Tirzepatide					
	0	1	2	4	8	24
TP1	0	17.1	21.4	31.5	49.8	70.2
TP2	0	14.9	16.2	26.1	39.1	62.8
TP3	0	14.1	14.8	20.6	37.2	56.9
TP4	0	13.4	14.3	19.8	32.7	51.4

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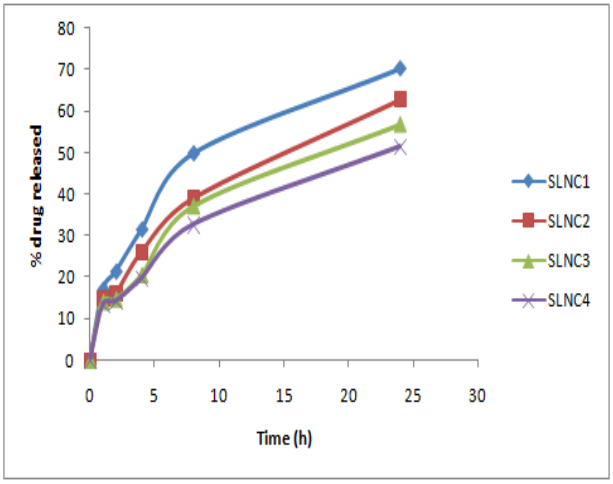

Fig 3: Release of Tirzepatide form TP

After reviewing all of the data, it was discovered that TPC-1 was the most stable of all of the TP; thus, this material was chosen to be used in the formulation of the transdermal patches.

Table 6: Release date of Tirzepatide from TP loaded patch

Time (h)	1	2	3	4	6	12
TPP1	2.941	10.588	18.342	38.817	54.112	59.74
TPP2	4.864	12.183	17.687	40.583	61.046	63.68
TPP3	4.332	11.458	19.183	43.855	58.962	65.12
TPP4	5.087	14.074	20.580	41.162	64.254	67.33

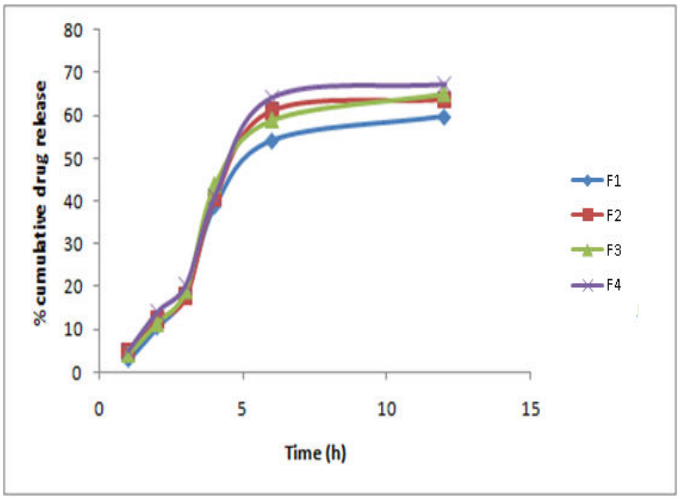

Fig 4: Zero-order release of Tirzepatide from TP from patches

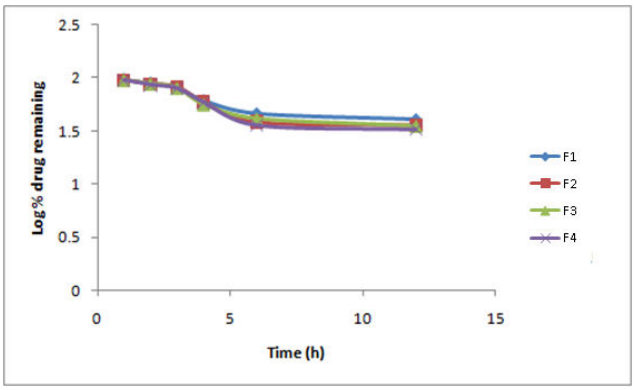

Fig 5: First order release of Tirzepatide from TP from patches

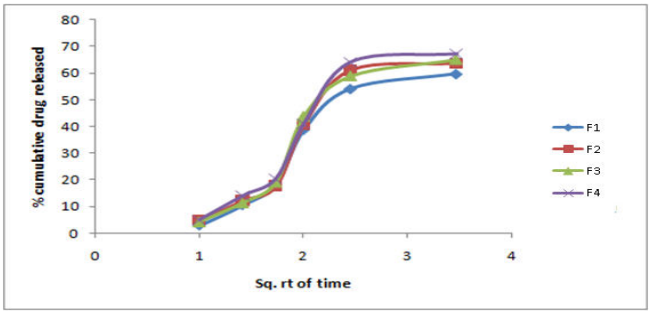

Fig 6: Higuchi release of Tirzepatide from TP from patches

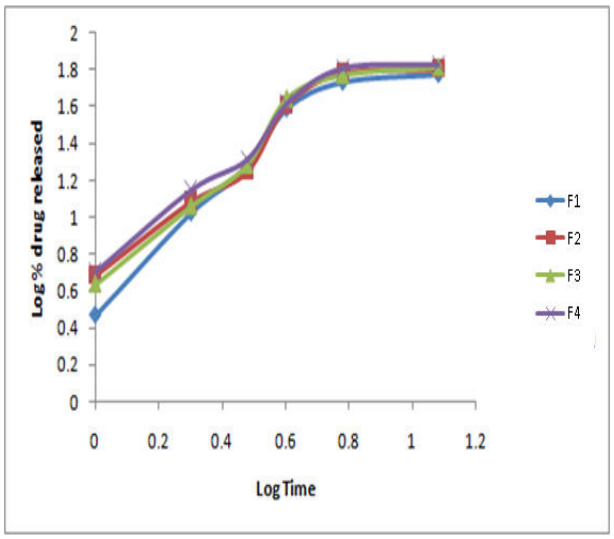

Fig 7: Korsmeyer-Peppas release of Tirzepatide from TP from patches

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Table 7: Statistical data of kinetic modeling of drug release from the patch

	Zero Oder		First Oder		Higuchi		Korsemeyer Peppas	
FC	**Slope**	**R^2**	**Slope**	**R^2**	**Slope**	**R^2**	**Slope**	**R^2**
TPP1	5.225	0.774	-0.036	0.83	25.48	0.877	1.271	0.898
TPP2	5.558	0.756	-0.04	0.793	27.08	0.851	1.125	0.909
TPP3	5.652	0.760	-0.042	0.83	27.55	0.866	1.175	0.905
TPP4	5.814	0.779	-0.045	0.81	28.31	0.866	1.11	0.915

Tirzepatide release from TP-loaded transdermal patches is able to be represented by the Korsmeyer-Peppas model, as shown by the regression coefficients of the visual representation of the models based on mathematics. Diffusion of the rug through the matrix of the patch accounts for most of the control over how much drug is released.

Scanning Electron Microscopy:

It was determined that there were no drug particles on the surface of the sample patch; however, the morphology of the vehicle and the bioadhesive transdermal patch looked to be same, which suggests that a homogeneous mixture of polymers with drug and natural agents was used. The scanning electron micrographs of HPMC and EC, as well as their intraped forms, demonstrate that.

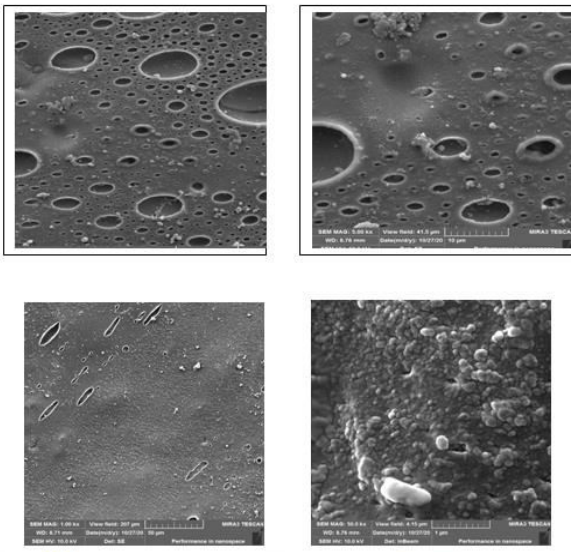

Fig. 8 SEM image of patch at magnification 50000X and 1000X

Conclusion

Transdermal patches of Tirzepatide were made utilising a solvent casting approach with a mixture of oleic acid, Tween 80, PG, in various ratios, with ethylcellulose, PVP, eudragit L 100, CAP, and carbopol acting as plasticizers and permeation boosters. All formulations had exceptional physicochemical characteristics, such as thickness, weight fluctuation, medicine content, and folding durability. The in vitro release of data revealed that the kind and concentration of the polymer had an effect on drug release from the patch. Using this information, optimised formulations were assessed. Ex vivo permeation tests were used to evaluate the impact on optimum formulations of penetration-enhancing substances like Tween 80 and oleic acid. These investigations found that formulations containing permeation enhancers had greater drug diffusion rates than formulations without them. The aforementioned formulas gave the greatest medication penetration over 12 hours. Among the prepared patches, these formulas were deemed the best.

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