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DEVELOPMENT AND ASSESSMENT OF A GUAVA-BASED TRANSDERMAL SYSTEM FOR ANTIDIABETIC THERAPY

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ABSTRACT

The study focuses on the development and evaluation of a transdermal drug delivery system (TDDS) incorporating guava (Psidium guajava) extract, targeting enhanced management of diabetes mellitus. Guava, known for its antidiabetic properties due to the presence of bioactive compounds such as flavonoids and polyphenols, offers a natural therapeutic alternative with minimal side effects.

The TDDS was formulated using a polymer-based matrix system to ensure controlled and sustained release of the guava extract. Characterization techniques such as Fourier-transform infrared spectroscopy (FTIR) and scanning electron microscopy (SEM) confirmed the compatibility and uniform distribution of the extract within the polymer matrix. The patches were evaluated for physical properties, including thickness, tensile strength, folding endurance, and moisture absorption, ensuring optimal application feasibility.

In vitro drug release studies demonstrated a sustained release profile, with a significant percentage of guava extract permeating over 24 hours. Ex vivo skin permeation studies using animal skin models validated the system's ability to deliver bioactive compounds through the dermal layers effectively. Further, in vivo antidiabetic activity was assessed in diabetic rat models, showing significant reductions in fasting blood glucose levels and improved glycemic control.

The developed guava-based TDDS exhibited favorable physicochemical properties, effective drug release, and potent antidiabetic activity, making it a promising alternative to oral therapies. This innovative approach highlights the potential of natural phytochemicals in advanced drug delivery systems, offering a sustainable and patient-friendly solution for managing diabetes.

I. INTRODUCTION:

Diabetes mellitus, a chronic metabolic disorder characterized by persistent hyperglycemia, remains a significant global health challenge due to its increasing prevalence and associated complications. Conventional treatments, including oral hypoglycemic agents and insulin therapy, often face challenges such as poor patient compliance, adverse side effects, and fluctuations in drug plasma levels. These limitations underscore the need for alternative delivery methods and natural therapeutic agents that can provide effective, sustained glycemic control.

Psidium guajava (guava) has emerged as a promising natural source for antidiabetic therapy due to its rich phytochemical composition, including flavonoids, tannins, and polyphenols. These compounds exhibit potent hypoglycemic and antioxidant properties by enhancing insulin sensitivity, reducing oxidative stress, and regulating glucose metabolism. However, the bioavailability of guava's active constituents is often limited when administered orally due to extensive first-pass metabolism and poor gastrointestinal absorption.

Transdermal drug delivery systems (TDDS) offer a novel approach to address these challenges. By bypassing the gastrointestinal tract and providing controlled and sustained drug release, TDDS improves the therapeutic efficacy and patient adherence. This study focuses on the formulation and evaluation of a guava-based TDDS to harness its antidiabetic potential in a more efficient and patient-friendly manner.

This research aims to develop a transdermal patch loaded with guava extract, evaluate its physicochemical properties, and assess its efficacy through in vitro and in vivo studies. By exploring the integration of natural antidiabetic agents into advanced drug delivery systems, this study contributes to the growing field of plant-based pharmaceuticals and innovative diabetes management strategies.

II. LITERATURE SURVEY

The development of transdermal drug delivery systems (TDDS) for the management of diabetes mellitus has gained significant attention in recent years. This literature survey explores key research studies and findings related to the use of Psidium guajava (guava) and the advancements in TDDS.

Antidiabetic Potential of Psidium guajava

Flavonoids and Polyphenols: Studies highlight the presence of bioactive compounds such as quercetin, catechin, and gallic acid in guava, which contribute to its hypoglycemic effects by improving insulin sensitivity and regulating glucose metabolism.

Mechanisms of Action: Guava leaf extract has been shown to inhibit alpha-glucosidase and reduce postprandial glucose spikes, as demonstrated in various in vivo and clinical studies (Shen et al., 2012).

Transdermal Drug Delivery Systems

Advantages of TDDS: Unlike oral administration, TDDS bypasses first-pass metabolism, enhances bioavailability, and provides a controlled release of the drug over an extended period. Studies indicate better patient compliance and reduced side effects (Prausnitz & Langer, 2008).

Polymers in TDDS: The use of biocompatible polymers such as hydroxypropyl methylcellulose (HPMC)

and ethyl cellulose for sustained drug release is well-documented (Ghosh et al., 2013).

Transdermal Delivery of Natural Extracts

Research on incorporating plant extracts into transdermal systems has demonstrated improved therapeutic efficacy. For instance, aloe vera gel and turmeric-based patches have shown success in delivering bioactive compounds transdermally (Singh et al., 2017).

Skin Permeation Studies

In vitro and Ex vivo Methods: Studies emphasize the importance of permeation enhancers like ethanol and propylene glycol in facilitating the delivery of natural compounds through the skin barrier (Barry, 2001).

Evaluation Metrics: Parameters such as cumulative drug permeation, flux, and lag time are critical in assessing the performance of transdermal systems.

Guava-Based Therapeutics

Recent studies have explored guava leaf and fruit extracts in various formulations, including capsules, tablets, and ointments. However, limited work has been done on transdermal systems, presenting a gap in the literature.

In Vivo Antidiabetic Models

Animal models such as alloxan- or streptozotocin-induced diabetic rats are widely used to evaluate the efficacy of antidiabetic formulations. Studies confirm the effectiveness of guava extract in reducing fasting blood glucose levels and improving lipid profiles (Liu et al., 2014).

This literature survey highlights the potential of guava as a natural antidiabetic agent and the advantages of TDDS in drug delivery. The integration of guava extract into a transdermal system addresses existing gaps in diabetes management strategies and provides a promising area for future research.

III. MATERIALS AND METHODS

Table 2: Materials used for formulation development of transdermal patch

Sr. No.	Chemicals	Supplier
1.	Canagliflozin	(Gift sample from Bioplus Life Science, Bangalore)
2.	HPMC	Ozone international, Mumbai
3.	RLPO	Evonic industries
4.	RSPO	Evonic industries
5.	PEG	Thomas beker (chemical)
6.	Disodium Hydrogen Phosphate	S. D. Fine Chem. Ltd., Mumbai
7.	Sodium Chloride	S. D. Fine Chem. Ltd., Mumbai
8.	Methanol	Qualigens Fine Chemicals, Mumbai
9.	Ethanol	Qualigens Fine Chemicals, Mumbai
10.	Chloroform	Qualigens Fine Chemicals, Mumbai

3.1 Preformulation characteristics:

The following properties of active pharmaceutical ingredients (API) wereinvestigated;

- Organoleptic properties
- Solubility Analysis
- Loss on drying
- Melting point
- UV Spectrophotometric analysis
- FTIR spectroscopy

3.1.1 Organoleptic properties:

Organoleptic properties of the drug substance are very important for designing thedosage form. The colour, odour and tests of the drug are characterized.

3.2.2 Solubility Analysis:

An important Physical-chemical property of a drug substance is solubility, especially aqueous solubility [8] . A drug must possess some aqueous solubility for therapeutic efficacy in the physiological pH range of 1 to 8.

Table 2.1:IP Index

Descriptive term	Parts of solvent required for Parts of soluble
Very soluble	Less than 1
Freely soluble	From 1to 10
Soluble	From 10 to 30
Sparingly soluble	From 30to 100
slightly soluble	From 100 to1000
Very slightly soluble	From 1000 to 10000
Practically insoluble	10000 or more

For the determination of solubility of Canagliflozin in various solvents that were methanol, ethanol, chloroform and distilled water etc. 5mg of Canagliflozin was added to 10 ml of each solvent in a test tube and shaken for few minutes at room temperature (21.0 ± 1.5°C).

3.2.3 Loss on drying (%)

The weight loss due to water and any volatile materials that can be driven off under certain conditions is known as loss on drying, and it is stated as a percentage of weight [9].

IR moisture balance was used to evaluate drying loss directly. After first calibrating the device using the knob, five grammes of powder were added, and the temperature was maintained at 100°C to 105°C for fifteen minutes while the reading remained constant. The knob was then fixed, and the moisture percentage was checked.

$$\text{Loss on drying (\%)} = \frac{\text{initial weight of sample - weight of sample after drying x 100}}{\text{Initial weight of sample}}$$

3.2.4 Melting point

Canagliflozin's melting point was ascertained using melting point equipment utilising the open capillary technique. A glass capillary tube was filled with the drug's fine powder and sealed at one end. After tying the capillary tube to the thermometer and keeping it in the Ilil tube equipment, the temperature of the apparatus was gradually raised, and the temperature at which the drug melted entirely was noted [10]. The drug's measured melting point and the melting point reported in the literature were compared.

3.2.5 Determination of UV-visible absorption maxima of Canagliflozin: Preparation of standard solutions

Ten milligrammes (mg) of the standard canagliflozin (weighed precisely) were dissolved in ten millilitres of methanol to create a standard stock solution. To get working standard solutions of 10µg/ml, this stock solution was further diluted. A succession of 10 ml volumetric flasks were filled with aliquots (0.05, 0.1, 0.15, 0.2, and 0.25 ml) of the working standard solution in order to get the required concentration range for the calibration curve. The volumes were prepared using a pH 7.4 phosphate buffer.

3.2.6 FTIR spectroscopy of Canagliflozin:

I.R. assessed the pure drug's purity. In an agatte mortar, 100 mg of dry potassium bromide (KBr) and around 10 mg of canagliflozin were triturated. The KBr press pellet technique [81] was used to prepare the pellet. With background correction, the pellet was scanned in the 400–2000 cm-1 range. After recording the spectra, the main peaks were identified.

3.3 Development of transdermal patches

A) Preparation of blank patches:

Accurately weighed polymers taken in combination and dissolved in respective solvent (chloroform and methanol in the ratio of 1:1 v/v) then poured in petridish with glycerin on plain surface. Then film was dry over night at room temperature.

B) Preparation of rate controlling membrane

Eudragit RLPO and RSPO were used for the preparation of rate controlling

membranes. Polymers were dissolved in chloroform and methanol with PEG 600 as plasticizer. Then solution was then poured into a glass Petri dish. The solvent was allowed to evaporate under room temperature for 24 hrs[11] .

C) Preparation of matrix type transdermal patches

Transdermal patches composed of different polymers HPMC, Ethyl Cellulose, Eudragit RLPO and Eudragit RSPO [12] . The polymers were dissolved in chloroform and methanol along with plasticizer. Then the solution was poured into a glass Petri dish containing Glycerin. The solvent was allowed to evaporate under room temperature for 24 hrs. The polymers (total weight: 500 mg) and drug (20 mg) were weighed in requisite ratios and dissolved in 10 ml of chloroform and methanol and PEG 400. After vortex then the solution was poured on glycerin placed in a glass Petri dish and driedat room temperature for 24 hrs[13] .

IV. RESULTS AND DISCUSSION

4.1 Preformulation study

4.1.1 Organoleptic properties:

Table 3: Organoleptic characteristics of Canagliflozin

S. No.	Properties studied	Results
1.	Colour	White
2.	Odour	Odorless
3.	Taste	Bitter
4.	Appearance/Morphology	Fine powder

4.1.2 Solubility analysis:

Table 3.1: Solubility determination of Canagliflozin in various solvent

Solvents	Results of Solubility
Methanol	Soluble
Ethanol	Soluble
Chloroform	Sparingly soluble
Distilled water	Sparingly soluble
Phosphate buffer 7.4 pH	Sparingly soluble
0.1 N HCl	Sparingly soluble
0.1 N NaOH	Sparingly soluble

It was found that Canagliflozin was soluble in ethanol and methanol, sparingly soluble in phosphate buffer 7.4 pH, 0.1 N HCl, distilled water, chloroform and 0.1 NNaOH.

4.1.3 Results of loss on drying

Results:

Results of loss on drying of Canagliflozin was found 0.147±0.004%. 3.1.3

Melting point Results:

The melting point of Canagliflozin was found to be 70-72°C.

4.1.4 Determination of UV-visible absorption maxima of Canagliflozin

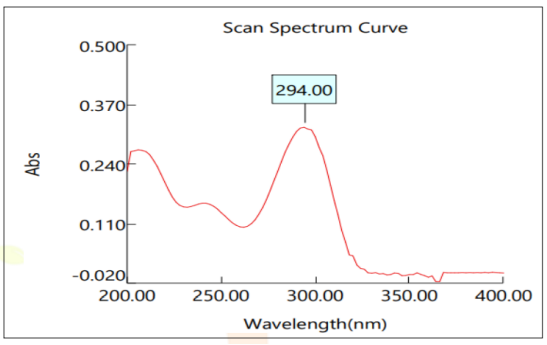


Figure 3: Determination of λmax of Canagliflozin

Table 7.3: Calibration curve of Canagliflozin

S. No.	Concentration (µg/ml)	Mean Absorbance
1	0	0
2	5	0.151±0.005
3	10	0.321±0.003
4	15	0.474±0.001
5	20	0.632±0.002
6	25	0.778±0.004

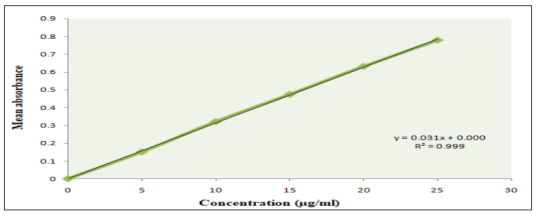


Figure 3.1: Calibration curve of Canagliflozin

4.1.5 FTIR spectroscopy of Canagliflozin

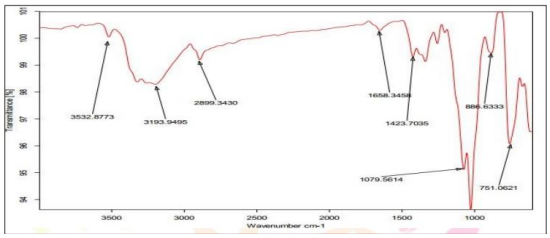


Figure 3.2: IR spectra of Sample Canagliflozin

4.2 Evaluation of Formulated Patch

4.2.1 Thickness:

The thickness of the films varied from 85±5 to 96±3 mm. The values obtained for allthe formulations are given in the table 3

4.2.2 Folding Endurance:

The folding endurance was measured in triplicate, according to procedure given in table 5.5 and the folding endurance was found to be in the range. The thickness was approximately close to every formulation. It depends on polymer ratio. All the patches showed satisfactory folding endurance properties. Folding endurance values of all formulation more than 185 indicating good elasticity and strength.

Table 3 : Thicknesses and folding endurance of different formulations

S. No.	Formulation Code	Thickness* (µm)	Folding Endurance* (Times)
1.	F1	98±5	168±5
2.	F2	100±7	175±7
3.	F3	102±9	205±6
4.	F4	95±8	185±8
5.	F5	98±4	174±4
6.	F6	110±6	165±3

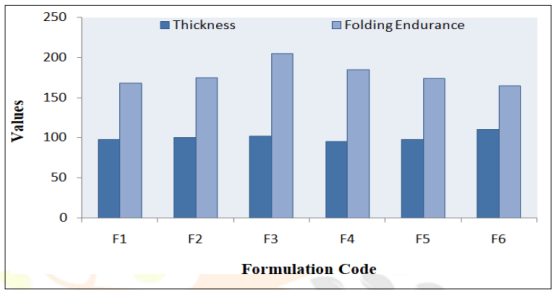


Figure 3.3: Graph of thickness and folding endurance

4.2.3 Moisture Content:

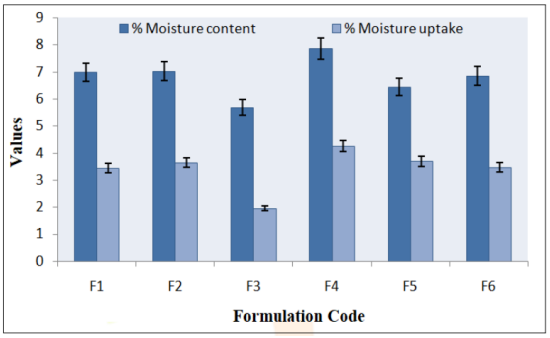
By storing patches in desiccators with activated silica, the moisture content was ascertained. The difference between the beginning and final weights in relation to the final weight was used to compute the % moisture absorption. Table 3.1 displays the findings of the moisture content analyses for the various formulations.

4.2.4 Moisture Uptake:

The difference between the beginning and final weights in relation to the initial weight was used to compute the % moisture absorption. Table 3.1 displays the findings of experiments on moisture absorption for various formulations. Compared to other formulations, formulation F3 has the lowest moisture content and moisture absorption. The ratio of polymers, such as ethylene cellulose, is to blame for this. Reduced moisture content in transdermal patches helps to preserve formulation stability and avoid brittleness with 100% dryness. Higher moisture content in the formulation may result in microbial contamination while the patches are being stored.

Table 3.1: % Moisture content and moisture uptake of different formulation

S. No.	Formulation Code	% Moisture content*	% Moisture uptake*
1.	F1	6.98±0.25	3.45±0.33
2.	F2	7.02±0.35	3.65±0.65
3.	F3	5.68±0.24	1.95±0.25
4.	F4	7.85±0.15	4.25±0.14
5.	F5	6.45±0.32	3.69±0.25
6.	F6	6.85±0.14	3.47±0.21



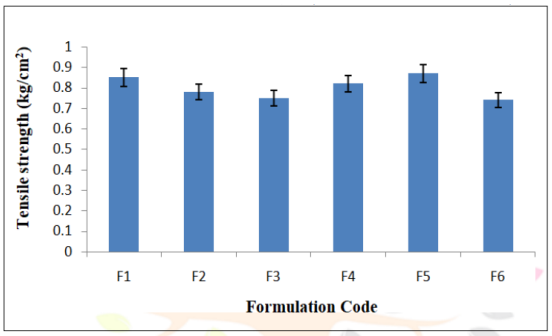


Figure 3.5: Graph of Tensile strength of different formulation

The prepared patch showed good tensile strength and there was no cracking sign inpatch. There was an increase in tensile strength with an increase in Eudragit RLPOin polymers ratio.

4.2.5 Drug Content Analysis:

The drug content analysis of different formulations was done. The drug content ranged between 98.45±0.65 and 99.45±032. The percentage drug content of all formulations is shown in Table 3.3.

Table 3.3: Percentage drug content of all the formulations

S. No	Formulation Code	% Drug content
1	F1	97.78±0.45
2	F2	96.85±0.25
3	F3	99.12±0.36
4	F4	97.78±0.21
5	F5	98.85±0.18
6	F6	98.47±0.25

*Average of Three determinations (n=3, Mean ± S.D.)

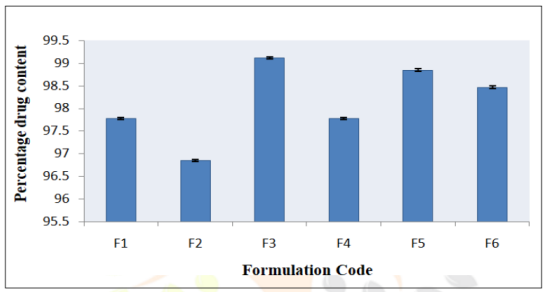


Figure 3.6: Graph of percentage drug content of formulation F1 to F6

This test is essential to check the uniformity of drug content in different patches from a single batch. The drug content analysis of patch show that the process employed to prepared patch was capable of giving uniformity drug content and minimum batch variability. F3 is optimized formulation that shows the good result.

4.2.1 In-vitro permeation studies:

The in vitro permeation studies are prediction of in vivo performance of a drug. These studies were performed for different formulations across egg membrane usingphosphate buffer, pH 7.4 as an in vitro study fluid in the receptor compartment of Franz diffusion cell. The results of these studies are given in Tables 3.4-3.6 and Fig. 3.7-3.9.

Table 3.4: In Vitro % permeation profile of Canagliflozin in formulation F1-F6

Time	% of Drug Release						
(hr)	F1	F2	F3	F4	F5	F6	Pure Drug
0.5	43.25	35.65	28.85	38.85	35.45	30.25	55.85
1	55.65	48.85	36.65	49.98	45.65	42.25	78.85
2	69.98	59.98	48.89	62.23	59.98	55.65	98.78
4	78.85	69.98	65.56	78.85	74.45	69.98	-
6	89.98	79.98	73.32	85.45	82.23	79.85	-
8	99.45	93.32	82.23	92.23	95.65	88.85	-
10	99.85	98.85	93.36	98.85	98.78	98.85	-
12	99.92	99.12	99.74	99.05	99.12	99.15	-

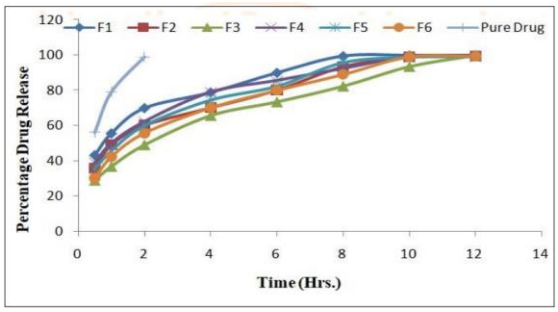


Figure 3.7: % of Drug release of Canagliflozin transdermal patches

4.2.1.1 Release kinetics of Canagliflozin Transdermal patches

Table 3.5: In-vitro drug release data for optimized formulation F3

Time (h)	Square Root Time (h) $^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0. 5	0. 707	-0. 301	28. 85	1. 460	71. 15	1. 852
1	1	0	36. 65	1. 564	63. 35	1. 802
2	1. 414	0. 301	48. 89	1. 689	51. 11	1. 709
4	2	0. 602	65. 56	1. 817	34. 44	1. 537
6	2. 449	0. 778	73. 32	1. 865	26. 68	1. 426
8	2. 828	0. 903	82. 23	1. 915	17. 77	1. 250
10	3. 162	1	93. 36	1. 970	6. 64	0. 822
12	3. 464	1. 079	99. 74	1. 999	0. 26	-0. 585

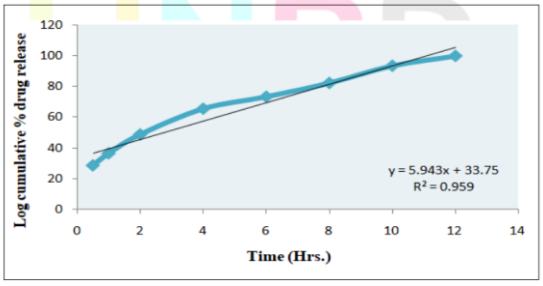


Figure 3.8: Cumulative % drug released Vs Time

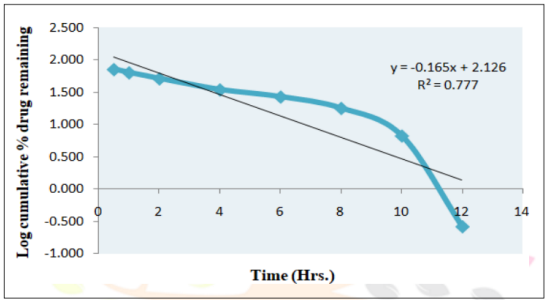


Figure 3.9: Log cumulative % drug remaining Vs Time

Table 3.6: Regression analysis data of Canagliflozin transdermal patches

Batch	Zero Order	First Order
	R^2	
F3	0. 959	0. 777

The Franz diffusion cell was used in the in-vitro permeation study to observe the impact of polymers from patches containing Eudragit RLPO, RSPO, HPMC, and EC at various concentrations to optimise the formulation for the in-vitro investigation. To understand the diffusion process and pattern, every formulation was examined, and all data was fitted on a Zero Order and First Order basis.

The percentage of cumulative drug release was computed for the 0–12 hour trial period.The formulation adhered to zero order release kinetics, according to data analysis for order of release kinetics. It was proven by the in-vitro permeation investigation that formulation F3 had a greater release than the other formulations (F1, F2, F4, F5, F6).

V. SUMMARY AND CONCLUSION:

Transdermal route has gained accolade as it has several advantages over conventional forms such as, avoids first pass metabolism and lowers gastrointestinal irritation that are associated with oral administration. Easy termination of therapy enables a constant plasma level profile that results in decreased side effects are some other advantages. The release of the drugs from topical preparations depends on the physicochemical properties of the drug and gels employed. Gels for dermatological use have many advantageous properties such as thixotropic, emollient, greaseless, easily spreadable, and easily removable. Gelling agents when mixed with appropriate solvent entangle to form a

three-dimensional colloidal network that limits fluid flow by entrapment and immobilization of the solvent molecules. One more advantage of network structure of gels is their resistance to deformation and hence its viscoelastic properties.

In the current research was planned to formulate and evaluate transdermal patch containing Canagliflozin using HPMC, RLPO, RSPO, EC and PEG. The prepared gels were evaluated for clarity, viscosity, drug content and in vitro permeation studies.

The thickness of the films varied from 98±5 to 110±6mm. The thickness was approximately close to every formulation. It depends on polymer ratio. All the patches showed satisfactory folding endurance properties. Folding endurance values of all formulation more than 205±6 indicating good elasticity and strength.

The moisture content was determined by keeping patches in a desiccators containing activated silica. The percentage moisture uptake was calculated as the difference between initial and final weight with respect to final weight.

The formulation F3 show lowest moisture content and moisture uptake than other formulation. This is due to because of polymer ratio (like Ethyl Cellulose). If lower moisture content in transdermal patch it be good to prevent the brittleness with 100% dryness and also maintain the stability of formulation. If formulation content higher moisture it can lead the microbial contamination during the storage of patchs.The tensile strength was found to be in the range of 0.74±0.02 to 0.87±0.03. The formulation Canagliflozin F3 showed the best tensile strength.

The prepared patch showed good tensile strength and there was no cracking sign inpatch. There was an increase in tensile strength with an increase in Eudragit RLPO in polymers ratio. The drug content ranged between 97.78±0.45 and 99.12±0.36.

This test is essential to check the uniformity of drug content in different patchesfrom a single batch. The drug content analysis of patch show that the processemployed to prepared patch was capable of giving uniformity drug content and minimum batch variability. F3 is optimized formulation that shows the good result. The In-vitro permeation study was done to see the effect of polymers through theFranz diffusion cell from patch having Eudragit RLPO, RSPO, HPMC, EC indifferent conc. to optimized formulation for in-vitro study. All the formulation wasstudied and all data fitted on Zero Order, First Order to explain the diffusion mechanism and pattern.

The % cumulative drug release was calculated over the study time range in 0-12 hrs.Data analysis for order of release kinetics the formulation followed zero order release kinetics. From the in-vitro permeation study it was confirmed that the releaseof formulation F3 was to be found higher as compared to other formulation (F1, F2, F4, F5, F6).

5.1 CONCLUSION:

The development of a guava-based transdermal drug delivery system (TDDS) offers a novel and effective approach for the management of diabetes mellitus. Guava, enriched with bioactive compounds such as flavonoids and polyphenols, demonstrates significant antidiabetic potential by enhancing insulin sensitivity, reducing oxidative stress, and regulating glucose metabolism.

The formulated transdermal patches were found to possess desirable physicochemical properties, including uniform thickness, tensile strength, and folding endurance. In vitro drug release studies indicated a sustained and controlled release profile, while ex vivo skin permeation studies confirmed the system's ability to deliver guava's bioactive constituents effectively through dermal layers. Furthermore, in vivo antidiabetic activity validated the therapeutic efficacy of the guava-based TDDS, showing significant reductions in blood glucose levels and improved glycemic control in diabetic models.

This study underscores the potential of natural phytochemicals, like guava extract, in advanced drug delivery systems, offering several advantages such as bypassing first-pass metabolism, enhancing bioavailability, and improving patient compliance. The successful integration of guava extract into a TDDS highlights its potential as a safe, efficient, and patient-friendly alternative to conventional diabetes therapies. Future research could focus on scaling up production, exploring additional natural compounds, and conducting clinical trials to establish its efficacy and safety in human populations.

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