IN VITRO AND IN VIVO EVALUATION OF SOME NOVEL HERBAL COMPOSITION FOR TREATMENTS OF DIABETES BY USING CURCUMIN AND CINNAMON EXTRACT

Arjun Singh[1], Anubi Badhani[2], Nidhi Nitin Chauhan[3*], Anu Sharma[4], Ashok Kumar[5], E. Siva Rami Reddy[6], Ujash kumar Shah[7], Rajeev Ranjan[8]

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Abstract:

Introduction: Diabetes mellitus is an increasingly prevalent chronic metabolic disease characterized by prolonged hyperglycaemia that leads to long-term health consequences.Currently, close to 500 million people are estimated to be suffering from diabetes mellitus (DM), with a predicted startling increase in the upcoming years.Curcumin, the active ingredient of the *Curcuma longa* plant, has received great attention over the past two decades as an antioxidant, anti-inflammatory, anti-diabetic anticancer agent.cinnamon has been used as a spice and as traditional herbal medicine for anti-inflammatory, antimicrobial, antioxidant, antitumor, cardiovascular, cholesterol-lowering, and immunomodulatory effects

Objectives: This currentresearch aims to formulate Some Novel Herbal Composition (Transdermal patch) using Curcumin and Cinnamon Extracts, Various evaluation parameters of transdermal patches like Weight variation test, Folding endurance, Thickness, Drug content study, Drug polymer interaction studies,were performedinvitro drug release studies were performed by using Franz diffusion cell. In vivo studies were performed by using Wistar albino ratsby inducing the diabetics using alloxan monohydrate

Conclusion: Transdermal patch using curcumin and extracts of cinnamon were successfully prepared suggesting a comparatively suitable option for treatment of diabetics. Based on the results it can be concluded that curcumin and cinnamon exhibited better in vivo performance in rats and further study on higher animals and on clinical research is required.

Keywords: Diabetics, Curcumin, Transdermal patch, Cinnamon,in vivo studies.

[1]Principal, MMT. Chhatrapati Shahuji Maharaj Group Of Institutions Faculty of B.Pharmacy, Rewa Road, Iradatganj, Ghoorpur, Prayagraj, Uttar Pradesh. 212111

[2]Assistant professor, Shri Guru Ram Rai University, Dehradun, Uttarakhand. 248001

[3*]Professor, HOD in the Department of Pharmacognosy, Laxminarayandev College of Pharmacy, Bholav, Bharuch, Gujarat. 392001

[4]Associate professor, Shanti Niketan College of Pharmacy, Mandi Himanchal Pradesh. 175008

[5]Associate Professor, Faculty of Pharmaceutical Sciences, The ICFAI University, Baddi, Himachal Pradesh 174103

[6]Professor, Department of Practice of Medicine, MNR Homoeopathic Medical College, MNR nagar, Fasalwadi, Sangareddy, Telangana. 502294

[7]Professor and Head, Faculty of Pharmacy, Nootan Pharmacy College, SK campus, Sankalchand Patel University, Visnagar, Mehsana, Gujarat. 384315.

[8]Assistant Professor, Department of Chemistry, DSPM University, Morhabadi, Ranchi, Jharkhand. 834008

[*]Corresponding Author
Nidhi Nitin Chauhan[3*]
[3*]Professor , HOD in the Department of Pharmacognosy, Laxminarayandev College of Pharmacy, Bholav, Bharuch, Gujarat. 392001

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1. Introduction

Diabetes mellitus is an increasingly prevalent chronic metabolic disease characterized by prolonged hyperglycaemia that leads to long-term health consequences diabetes mellitus is taken from the Greek word diabetes, meaning siphon - to pass through and the Latin word mellitus meaning sweet, Currently, close to 500 million people are estimated to be suffering from diabetes mellitus (DM), with a predicted startling increase in the upcoming years [1].In the US alone, over $300 billion is spent annually on both medical costs.[2].Mering and Minkowski, in 1889, discovered the role of the pancreas in the pathogenesis of diabetes. In 1922 Banting, Best, and Collip purified the hormone insulin from the pancreas of cows at the University of Toronto, leading to the availability of an effective treatment for diabetes[3]. Diabetes mellitus (DM) is a metabolic disease, involving inappropriately elevated blood glucose levels. DM has several categories, including

- Type 1 diabetes,
- Type 2 diabetes,
- Maturity-onset diabetes of the young (MODY),
- Gestational diabetes,
- Neonatal diabetes,

and secondary causes due to endocrinopathies, steroid use, etc [4]..

The main subtypes of DM are Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM), which classically result from defective insulin secretion (T1DM) and/or action (T2DM) [5]. T1DM presents in children or adolescents, while T2DM is thought to affect middle-aged and older adults who have prolonged hyperglycaemia due to poor lifestyle and dietary choices[6].The diagnosis of T1DM is usually through a characteristic history supported by elevated serum glucose levels (fasting glucose greater than 126 mg/dL, random glucose over 200 mg/dL, or haemoglobin A1C (HbA1c exceeding 6.5%) with or without antibodies to glutamic acid decarboxylase (GAD) and insulin. [7].The physiology and treatment of diabetes are complex and require a multitude of interventions for successful disease management,Regular screenings are necessary since microvascular complications are a feared complication of diabetes [8]. Therefore, the quest for more efficient and less toxic diabetic treatment strategies is still at the forefront of current research

Curcumin

Curcumin is obtained from the rhizomes of *Curcuma longa L.* (turmeric), Turmeric is extensively used as a spice, food preservative and colouring material in India [9], China and South East Asia.it belongs to the family Zingiberaceae and distributed throughout tropic and subtropical region of the world [10].The plant is cultivated in all parts of Indiathe plant grows up to 3-5 ft tall and dull yellow flowers as shown in **Figure1.** The rhizome is an underground stem that is thick and fleshy ringed with the bases of old leaves is part of turmeric which possess a potential medicinal property [11].

Figure 1 Plant of Turmeric (*Curcuma longa L*)

Curcumin and its derivatives have received immense attention in the past two decades due to their bifunctional properties such as anti-tumour, antioxidant, and anti-inflammatory activities [12]it was extracted from turmeric plant in a pure crystalline form for the first time in 1870,These properties are attributed due to the key elements in the curcumin structure as shown in the Figure 2.

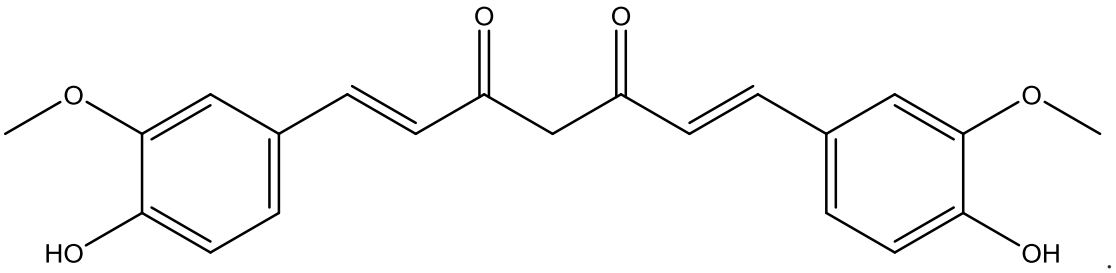

Figure2 Structure of curcumin

It consists of two phenyl rings substituted with hydroxyl and methoxyl groups and connected via a seven carbon keto-enol linker [13] While curcumin is naturally derived, its derivatives are generally produced by a chemical reaction between aryl-aldehydes and acetylacetone. This assembly method can yield multiple chemical analogues.Curcumin is also a powerful antioxidant. Antioxidants scavenge molecules in the body known as free radicals, which damage cell membranes, tamper with DNA, and even cause cell death it can fight free radicals and may reduce or even help prevent some of the damage they cause [14]. In addition, curcumin lowers the levels of two enzymes in the body that cause inflammation. It also stops platelets from clumping together to form blood clots [15].

Cinnamon

Cinnamon is one of the most important spices used daily by people all over the world, Cinnamon (*Cinnamomum zeylanicum, and Cinnamon cassia*), belongs to thefamily Lauraceae[16].

There are mainly four types of cinnamon:

- True cinnamon or Ceylon cinnamon or Mexican cinnamon (*Cinnamomum zeylanicum*)
- Indonesian cinnamon (*Cinnamomum burmanni*)
- Vietnamese cinnamon (*Cinnamomum loureiroi*)
- Cassia cinnamon or Chinese cinnamon (*Cinnamomum aromaticum*).

The English word "cinnamon", attested in English since the 15th century, deriving from the ancient Greek [17]. The tree characterized by oval-shaped leaves, thick bark and a berry fruit as shown in the figure 3. When harvesting the spice, the bark and leaves are the primary parts of the plant used [18]. It is used as an antioxidant, anti-inflammatory, antidiabetic, antimicrobial, anticancer, lipid-lowering, and cardiovascular-disease-lowering compound, cinnamon has also been reported to have activities against neurological disorders, such as Parkinson's and Alzheimer's diseases [19].

Figure. 3. Plant of cinnamon (*Cinnamomum zeylanicum*)

Cinnamon consists of a variety of resinous compounds, including cinnamaldehyde, cinnamate, cinnamic acid, and numerous essential oils as shown in Figure 4 it is reported that the spicy taste and fragrance are due to the presence of cinnamaldehyde and occur due to the absorption of oxygen [20]. As cinnamon ages, it darkens in colour, improving the resinous compounds.

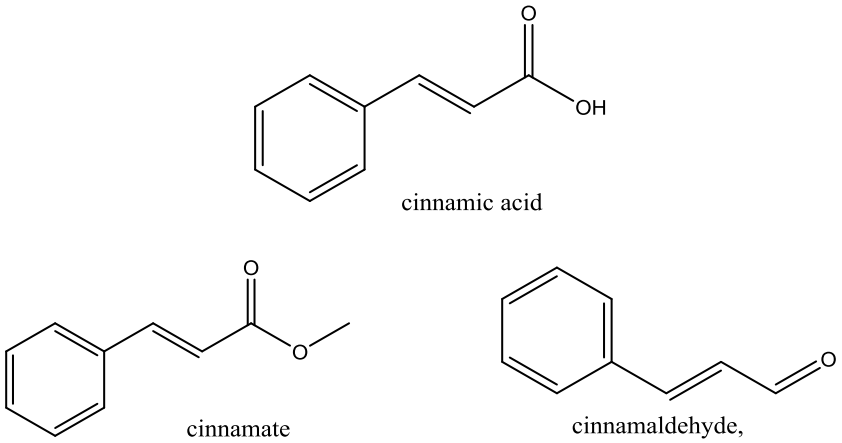

Figure. 4. Various chemical constituents present in cinnamon.

This article presents a comprehensive methodology for the development of Transdermal patch using Curcumin and Cinnamon Extracts, Various evaluation parameters of transdermal patches, in vitro and in vivo studies.

2. Methodology

2.1 Materials

Curcumin and crude cinnamon bark were purchased from Amsar Private Ltd, Hydroxy propyl methyl cellulose K100M (HPMC), Polyethylene glycol (PEG) were brought from Research Lab Fine Chem, Alloxan monohydrate was procured from Sigma Aldrich Co., Glipizide, a standard anti-diabetic drug was purchased from Franco-Indian remedies, Glucose; triglyceride and cholesterol kitswere procured from Bio Lab Diagnostics Pvt. LtdAll the chemicals and reagents of analytical grade and were purchased from Hexon Labs.

2.2 Animals

Wistar albino rats of either sex weighing 160-200 g were maintained under standard environmental laboratory conditions and fed with laboratory diet and water ad libitum

2.2 Preparation of Cinnamon extract

The cinnamon extract was obtained from Draco Natural Products, which contained 5% cinnamonaldehyde. Cinnamon (1 kg) was extracted with 640 ml of water for 16 h at 90 °C, two times. The water extract was lyophilized and stored at room temperature until use. Dry yield was 8% (w/w) [21].

2.3 Preparation of Transdermal patch

Transdermal patches were prepared by solvent evaporation technique [22]. The polymer (HPMC) and curcumin, cinnamon extract was weighed PEG, which acts as a plasticizer and permeation enhancer, was used in the concentration of 30 % v/v. Ethanol was used as a solvent. PEG 400 (30% weight of polymer) was dissolved in ethanol with stirring, which serve the purpose of plasticizer as well as penetration enhancer and then calculated amount of HPMC (500 mg) was dispersed in solvent ethanol, curcumin (150mg) and cinnamon extract (150mg) were dissolved in ethanol this solution was then added to polymer base and stirred continuously to get uniform solution. The final volume was made up using water. The above solution was then poured into Petri plate coated with liquid paraffin and then dried at room temperature. After drying, patches were removed and cut into 2 cm2 area and wrapped with aluminium foil and kept in desiccators until they were used for further study [23].

2.5Various Evaluation parameters of Transdermal patches of Curcumin and Cinnamon extract

2.5.1.Weight variation test

The weight of each patch was taken using analytical weighing balance (Shimadzu). The mean weight of the film as well as deviation from the mean was obtained and the data was recorded.

2.5.2 Folding endurance

The folding endurance was measured manually for the prepared patches. The patches were repeatedly folded at the same place till it broke. The number of

times the patches could be folded at the same place without breaking gives the accurate value of folding endurance.

2.5.3Thickness
The thickness of patches was determined using digital vernier calliper.The mean thickness was measured at five different points of film.

2.5.4Drug content study
Transdermal patches were taken (2 cm2 area) individually, crushed, and taken in a 100-ml volumetric flask (pH 7.4 phosphate buffer). The medium was stirred with a Teflon-coated magnetic bed for 2 h. The contents were filtered using Whatman filter paper and the suitable dilutions of the filtrate were prepared by using phosphate buffer pH 7.4. Absorbance of dilutions were was measured by using UV- Vis spectrophotometer (Shimadzu) 1701, at 276.5 nm against phosphate buffer pH 7.4 as a blank [24].

2.5.5Moisture vapour transmission
MVT is defined as the quantity of moisture transmitted through unit area of film in unit time. Glass cells were filled with 2 g ofanhydrous calcium chloride and a film of specified area was affixed onto the cell rim. The assembly was accurately weighed and placed in a humidity chamber (80 ± 5% RH)at 27 ± 2 °C for 24 h.

2.5.6 Drug polymer interaction studies
Drug-polymer interaction was investigated using Fourier Transform Infrared (FTIR). FTIR of curcumin and cinnamon extract, polymer (HPMC) and mixture of drug and polymer were taken using Shimadzu 8400S FTIR spectrophotometer with KBr pellets.

2.5.6 Invitro release studies
In vitro drug absorption and permeability analysis was performed by using Franz diffusion cell with pretreated dialysis membrane (Sigma9777)(receptor compartment capacity: 20 ml).Full thickness skin from dorsal region of Wistar rat, whose hair had been removed on the previous day with hair removal cream, was used as membrane. The rats were sacrificed by cervical dislocation and the fatty material was removed from dissected skin and skin was washed with phosphate buffer used immediately. The receiver compartment was filled with 20 ml of 10 % hydroalcoholic phosphate buffer, pH 7.4. The transdermal patch was firmly pressed onto the centre of the rat skin and then the skin was mounted on the donor compartment. The donor compartment was then placed in position such that the surface of dermis side skin just touches the receptor fluid surface. The whole assembly was kept on a thermostatically controlled magnetic stirrer set at 37 ± 20 C and the content in the receiver compartment was continuously stirred at a constant speed (100 rpm) using a magnetic bead.The samples (2 ml) were withdrawn at the intervals of half hour up to 6 hr. and replaced with same amount (2 ml) of 10% hydroalcoholic phosphate buffer to maintain the sink condition. The samples were analysed for drug content using UV- Visspectrophotometer (Shimadzu 1701) at 276.5 nm.The cumulative % drug release from the transdermal patch was then calculated by using PCP DISSO software

3. IN VIVO EVALUATION OF TRANSDERMAL PATCHES

3.1 Skin irritation study
The rats whose hair were removed on previous day, were divided into three groups (n = 6) and treated as follows. Group I – Normal control group, animals in group II were treated with formalin solution (a standard irritant; 0.8% v/v) up to 7 days, animals in group III were treated with transdermal patches of curcumin and cinnamon extract (2 cm2, 10 mg/patch) by using USP adhesive tape for 7 days.
The animals were treated daily with formalin solution and new transdermal patches up to 7 days by using USP adhesive tape. After 7 days animals were sacrificed and treated skin samples were processed for histological examination.

3.2Antihyperglycemic activity in diabetic rats
Diabetes was induced by of alloxan monohydrate (120 mg/kg, i.p) in saline solution. The diabetic state was confirmed 48 hr after alloxan injection by hyperglycaemia. Surviving rats with fasting blood glucose level higher than 250 mg/dl were included in the study.

3.3. Acute study
The hairs on the backside of the rat were removed with a hair removal cream on the previous day of the experiment. Following an overnight fast, rats were divided into four groups (n = 6).

The rats were treated as following:
- Group I (NC) received 0.9% w/v saline (1 ml/kg, p.o.),
- Group II (DC) received 0.9% w/v saline (1ml/kg, p.o.),
- Group III (STD) received Glipizide (5 mg/kg, p.o),
- Group IV (HT) received herbal tablet (89 mg/kg, p.o).
- Animals in group IV (TEST) were treated with new transdermal patch(2 cm^2; 10 mg/kg) by

using USP adhesive tape as shown in the **Figure 5.**

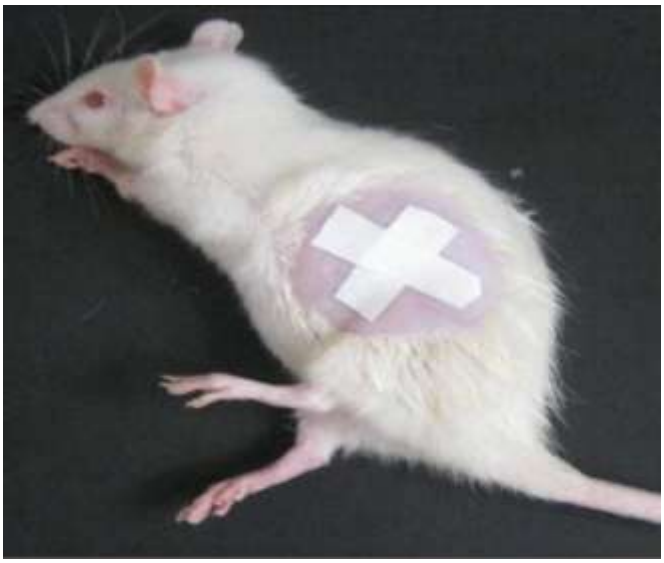

Figure 5 Application of patch to rat ski

At 0 min, 30 min, 1 hr, 2hr, 6 hr, and 24 hr after drug administration and patch application, blood was collected by puncturing tail vein under light ether anaesthesia by using fine syringe in Eppendroff. Plasma glucose levels were estimated by the GOD/POD method

3.4Sub-acute study

The hairs on the backside of the rat were removed with a hair removal cream on the previous day of the experiment. Following an overnight fast, rats were divided into four groups (n = 6). The rats were treated as following:

- Group I (NC) received 0.9% w/v saline (1 ml/kg/day, p.o.) for 14 days,
- Group II (DC) received 0.9% w/v saline (1ml/ kg/day, p.o.) for 14 days,
- Group III (STD) received Glipizide (5mg/ kg/day, p.o) for 14 days.
- Group IV (HT) received herbal tablet (89 mg/kg/day, p.o) for 14 days.
- Animals in group IV (TEST) were treated daily with new transdermal patch (2 cm^2 ; 10 mg/kg) upto 14 days by using USP adhesive tape.

At day 1, day 8, and day 14 after drug administration and patch application, blood was collected by puncturing retro-orbital plexus under light ether anaesthesia by using fine glass capillary in Eppendroff. Plasma glucose levels were estimated by the GOD/ POD method. At day 14, blood was collected from animals of all groups and serum was separated off. TC, TG, HDL-C measured by using enzymatic kit of Bio Lab Diagnostics Pvt. Ltd. Company. According to that result LDL-C, VLDL-C and atherogenic index were calculated

3.5 Biochemical evaluation

At the end of each week of treatment, all the animals were anesthetized with anaesthetic ether and blood was withdrawn by puncturing retro-orbital plexus by using fine glass capillary and collected in Eppendroff tubes and used for estimation of plasma glucose (GOD/POD method). Likewise at the end of 7thand 14th day of treatment blood was withdrawn by puncturing retro-orbital plexus by using fine glass capillary and collected in Eppendroff tube. The serum was used for estimation of total cholesterol (COD/POD method), triglyceride (GPO/POD method), HDL-C, LDL-C, and VLDL-C.

3.6 Statistical analysis

Data are expressed as mean ± SEM and statistically analysed by ANOVA followed by Dunnett test

4. Results

4.1 Physicochemical parameters of transdermal patch

In the present study, transdermal patches of Curcumin and cinnamon extract were prepared using HPMC K100M. PEG was used as plasticizer as well as penetration enhancer. The films were evaluated for their physical characteristics, such as weight variation, folding endurance, thickness, drug content study, and release characteristics. The physicochemical properties viz. weight variation test, folding endurance, thickness, and drug content of transdermal patches were within the limits as shown in the Table 1

Parameters	**Transdermal patches (2 cm^2, 10 mg/patch)**
Weight variation test	00.03 ± 0.00 gm
Folding endurance	340 ± 08.70
Thickness	00.05 ± 0.00 mm
Drug content	96%

4.2 Drug polymer interaction studies

From the FTIR spectra, it was clear that there were no interactions of the drug with the polymer as shown in **Figure 6(a,b).** The main peaks in the curcumin and cinnamon do not show anysubstantial difference when fraction was combined with polymer

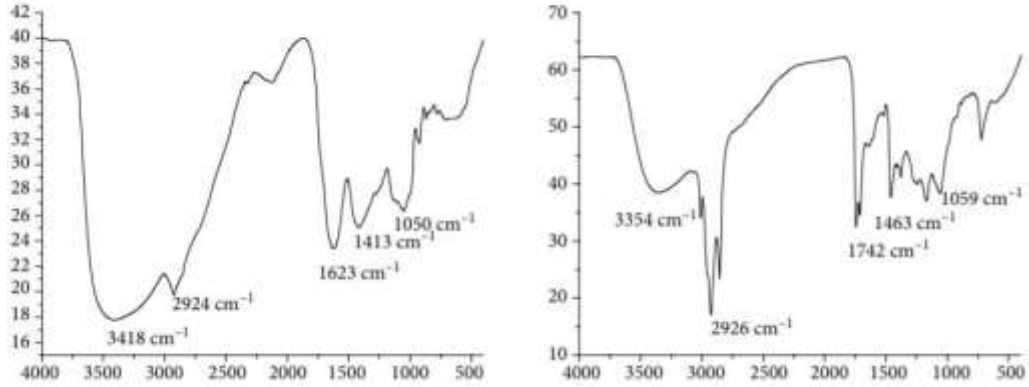

Figure 6.a FTIR Spectra of Curcumin and cinnamon

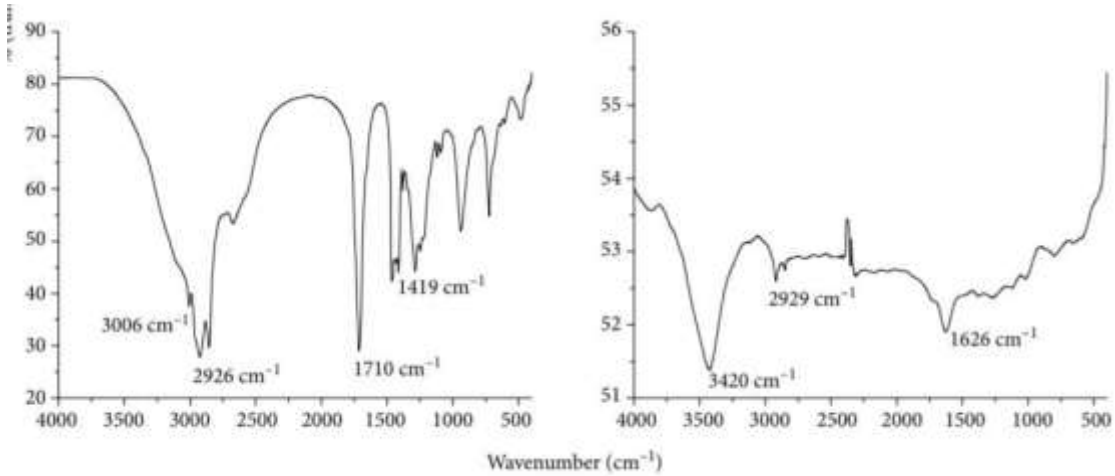

Figure 6.b FTIR spectra of Transdermal patch polymer

4.3Invitro release studies

Transdermal patches (2 cm^2 area; 10 mg/patch) showed good release characteristics in hydroalcoholic phosphate buffer medium than in phosphate buffer solution. In vitro release profile of transdermal patches of curcumin and cinnamon extract (2 cm^2; 10 mg/ patch) showed 47.59% drug release in six hours as shown in **Figure 7.**

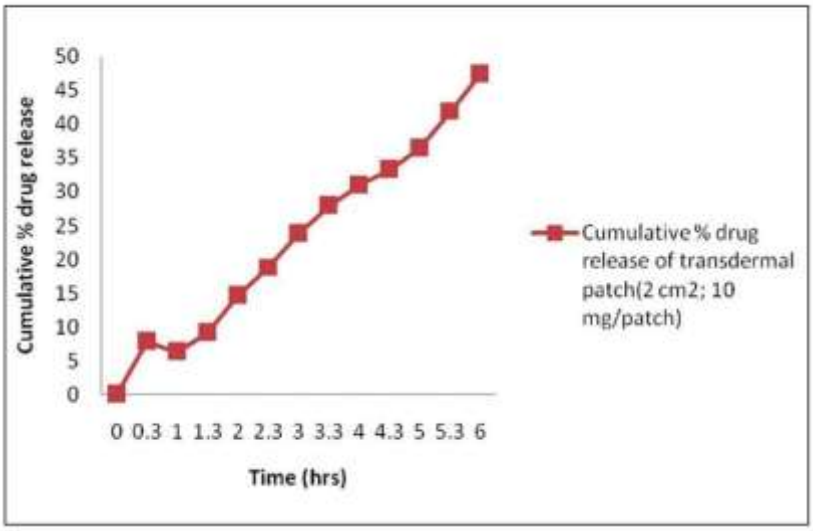

Figure. .7. Cumulative % drug release from transdermal patches

4.4Skin irritation test

The histopathological examination of the skin indicates that prepared systems produced mild inflammation. Formalin produced high grade of irritation, indicated by severe inflammation

4.5Anti-hyperglycaemic activity in diabetic rats

Acute study

Group treated with Glipizide showed significant decrease in plasma glucose level at 1 hr, 2 hr, and 6 hr when compared with diabetic control group. Group treated with HT, TEST groupshowed significant decrease ($P < 0.01$) in plasma glucose level at 2 hr and 6 hr when compared with diabetic control group as mentioned in **Table 2.**

Gr.	0 min	30 min	1 hr	2 hr	6 hr	24 hr
NC	75.79±02.50	78.46±01.77	80.20±01.90	79.43±02.00	77.23±01.77	77.32±01.78
DC	268.00±02.05	288.54±02.07	281.78±01.43	293.24±01.56	282.12±01.42	290.19±02.86
STD	250.93±02.02	279.77±01.52	240.70±03.01	180.62±01.18	144.54±02.03	274.88±01.86
HT	280.24±02.02	282.00±02.02	286.61±02.25	287.01±02.686	269.71±01.71	267.51±01.36
TEST	289.69±01.89	279.79±01.64	288.54±01.03	286.22±02.36	280.42±01.72	276.63±01.85

Results are presented as mean ± SEM. (n = 6)

Table. 2. Effect of transdermal patches on plasma glucose level in diabetic rats (acute study)

Sub-acute study

The transdermal patches produced significant decrease in blood glucose levels up to 14 days indicating that these devices provide optimum Anti-hyperglycemic effects upon long-term application also. Groups treated with Glipizide showed significant decrease ($P < 0.01$) in plasma glucose level on day 8 and onwards, this significant anti-diabetic activity remains also at the end of treatment schedule (on day 14). also groups treated with HT, TEST showed significant decrease ($P < 0.01$) in plasma glucose level at the end of treatment schedule (on day 14) as show in **Table.3**

Results are presented as mean ± SEM. (n = 6)

Groups	Day 1	Day 2	Day 3
NC	79.58 ± 02.10	80.28 ± 01.95	78.46 ± 01.97
DC	290.13 ± 01.96	295.15 ± 01.33	283.56 ± 01.70
STD	290.82 ± 02.05	223.78 ± 04.85	160.96 ± 02.75
HT	290.02 ± 02.08	210.94 ± 01.90	290.02 ± 02.08
TEST	289.89 ± 01.47	278.67 ± 01.45	250.22 ± 01.37

Table.3 Effect of transdermal patches on plasma glucose level in diabetic rats (subacute study)

Biochemical parameters

The elevated lipid profile levels (total cholesterol, triglycerides, low density lipoprotein-cholesterol and very low-density lipoprotein-cholesterol) were significantly decreased with transdermal patches at the end of day 14 treatment compared to diabetic control group. Whereas high density lipoproteincholesterol level was significantly increased with transdermal patches at day 14 of treatment as shown in the **Table 4.**

Gr.	Total cholesterol (mg/dl)	HDL-C (mg/dl)	Triglyceride (mg/dl)	VLDL-C (mg/dl)	LDL-C (mg/dl)
NC	83.6 ± 01.4	38.29± 01.87	43±02.19	13.88± 00.43	29.43± 02.55
DC	129.9 ± 02.72	26.54 ± 02.00	149.01± 02.07	29 ± 00.41	73.43 ± 02.57
STD	85.3 ± 01.53	36.38 ± 02.12	51±01.00	11.2 ± 00.20	26.76 ± 03.35
HT	122.16±01.76	33.35±0 1.29	107.81± 01.64	21.56±00.32	67.24 ± 01.97
TEST	124.1 ± 01.53	31.71 ± 01.09	124.02±01.96	22.8 ± 00.39	69.58 ± 01.93

Table .4. Effect of transdermal patches on lipid profile in diabetic rats

5. CONCLUSION

In this study, transdermal patches of Curcumin and Cinnamon extract (2 cm^2; 10 mg/kg), produced a significant fall in blood glucose of diabetic rats, hence the transdermal patches have anti hyperglycaemic activity. The blood glucose lowering effects of transdermal patches in diabetic rats was higher at 6 hr. Its preparations are reported to increase glucose utilization by liver and increase cellular uptake of glucose, promote, insulin release and potentiate its effect, which is probably responsible for the anti-diabetic effect.

A variety of orally active hypoglycaemic agents are frequently used to help to manage the glucose intolerance of NIDDM patients. But the effectiveness of these drugs is limited and suffers from a variety of side effects including hypoglycaemia.Many patients develop failure to oral anti-hyperglycaemic agents. All these factors together reduce compliance. On the other hand, plant extracts evaluated in this study are commonly used as spice in Indiais commonly employed as a household remedy for diabetes. In conclusion, this experimentation is one of the few attempts to utilize herbal drugs through transdermal drug delivery system. Above study demonstrates that transdermal patches of curcumin and cinnamon extracts exhibited better in vivo performance in rats and further study on higher animals and on human beings are required.

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