"Transdermal Telmisartan Patch Development With Natural Permeation Enhancers: Ex Vivo Release Comparison"

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ABSTRACT:

The aim of this research was to develop and evaluate matrix-type transdermal patches containing Telmisartan using various polymers and to investigate the impact of Cumin seed extract on the bioavailability of Telmisartan. We conducted Fourier Transform Infrared (FTIR) Spectroscopy analysis to examine the physicochemical compatibility between the drug and the polymers. Our findings indicated that there were no significant physicochemical differences between the drug and the polymers. To assess the quality of the formulated transdermal patches, we conducted various tests, including weight variation, thickness, folding endurance, moisture loss, moisture absorption, ex-vivo drug release, and ex-vivo drug absorption. For the best formulation, F41, we observed the following characteristics: a thickness of 0.298±0.012mm, weight uniformity of 0.291±0.021gm, moisture uptake of 7.434±2.435%, moisture content of 8.341±0.671%, drug content of 80.32±0.619%, and folding endurance of 29±3.61. Notably, formulation F41 exhibited the highest cumulative drug release of 68.25±1.14% within 8 hours and the highest drug absorption rate of 2.994±0.73% within 120 minutes.

Keywords: Telmisartan, moisture content, FTIR, folding endurance, ex vivo.

INTRODUCTION:

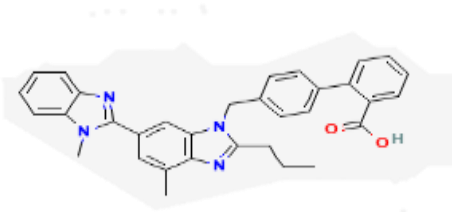

Figure 1 1chemical structure of Telmisartan

Bioavailability refers to the rate and extent at which a therapeutically active substance enters the bloodstream and becomes available at the target site. Intravenous drugs achieve the highest bioavailability, while oral administration results in a lower rate due to incomplete drug absorption and first-pass metabolism.[1]

Telmisartan is a commonly prescribed medication for treating high blood pressure (hypertension) and belongs to the class of drugs known as angiotensin II receptor blockers (ARBs). It works by relaxing blood vessels and lowering blood pressure.[2] Telmisartan is also used to manage certain heart conditions, including the prevention of stroke, heart attacks, and kidney problems in individuals with diabetes.[3] This medication is typically available in tablet form and is usually taken once daily. It can be used alone or in combination with other drugs to effectively manage hypertension and related cardiovascular conditions.[4]

The biopharmaceutics classification system (BCS) evaluates three key factors—solubility, dissolution, and intestinal permeability—that influence the absorption of oral medications. It classifies drugs into four categories: Class I (high solubility, high permeability), Class II (low solubility, high permeability), Class III (high solubility, low permeability), and Class IV (low solubility, low permeability). Some antibiotics, such as Telmisartan, fall into Class III and Class IV, indicating poor oral absorption due to ionization in

the gastrointestinal tract and low lipid solubility, leading to low bioavailability.[5]

Transdermal drug delivery systems (TDDS) offer a consistent and long-term concentration of medication in the bloodstream. In 1982, the US FDA approved the Scopolamine transdermal film for motion sickness, developed by GlaxoSmithKline.[6] The USA has approved more than 35 transdermal delivery products for a wide range of medical conditions.[7] TDDS provides several advantages over conventional dosage forms and oral controlled delivery systems, including the avoidance of first-pass metabolism in the liver, reduced administration frequency, fewer gastrointestinal side effects, and improved patient compliance.[8]

In recent years, research into transdermal drug delivery has significantly increased, driven by the growing number of drugs that can be effectively delivered to the bloodstream through the skin.[9] This success is attributed to advancements made by drug technologists who have not only established transdermal delivery as an optimal non-oral systemic drug delivery method but have also streamlined its manufacturing processes.[10] Transdermal administration is considered the preferred route for long-term and frequent drug use to maintain a consistent plasma concentration.[11]

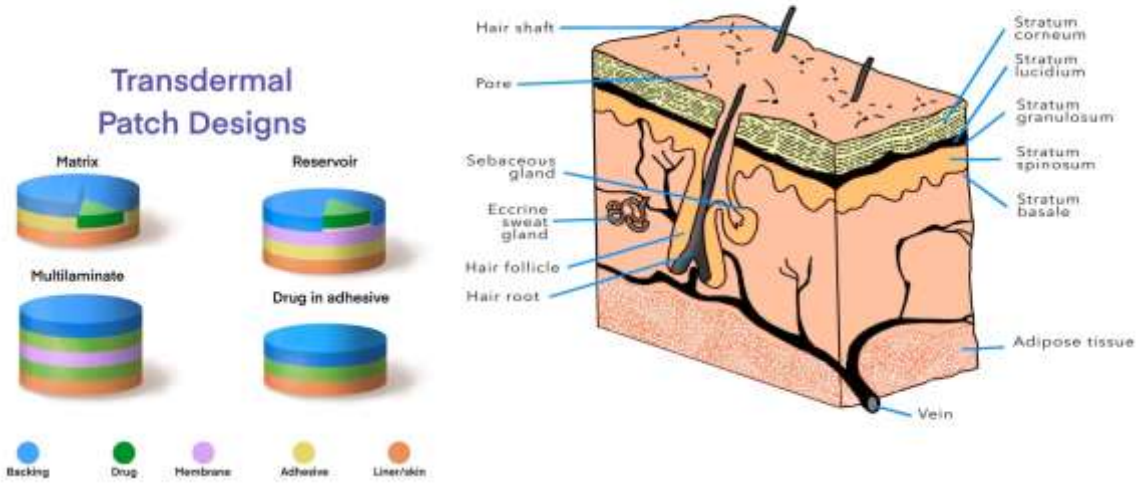

Figure 2 Transdermal patches design and structure of skin

OBJECTIVE:

The main objective of this study is to isolate phytochemical compounds from three specific herbs. Subsequently, we intend to develop a transdermal patch that incorporates a herbal medicine along with the modern medication Telmisartan. Our approach involves employing the solvent casting method with the goal of reducing the required dosage while maintaining the same pharmacological impact. Furthermore, our aim is to minimize the potential toxicity linked to the drug's usage.

MATERIALS AND METHOD:

Materials:

Drug & Chemical

Telmisartan was obtained as a gift sample from Unique Pharmaceutical Laboratories, Daman (Gujrat) and other ingredients were obtained from Research lab Mumbai.

Plant Material Used

We sourced Black Cumin Seeds from the local market, where we carefully examined them to ensure they were free from impurities and foreign materials. These seeds were subsequently authenticated by a qualified botanist to confirm their identity and quality.

PLANT PROFILE

a) Black Cumin Seeds:[12]

Figure 3 Black Cumin Seeds

Synonyms Black Cumin Seed Synonyms: black caraway, nutmeg flower, Roman coriander, nigella

Biological Source: It consists of dried seeds of Nigella sativa belonging to family Ranunculaceae.

Chemical Constituents: Carvone, Alpha Pinene, p-cymene, oleic acid.

Taxonomical Classification:

• Kingdom: Plantae –Vegetal, plants, Planta

• Subkingdom : Viridiplantae – green plants

• Infrakingdom : Streptophyta – land plants

• Superdivisio : Embryophyta

• Division : Tracheophyta – vascular plants, tracheophytes

• Subdivision :Spermatophytina – spermatophytes, seed plants, phanérogames

• Class : Magnoliopsida

• Superorder : Ranunculanae

• Order :Ranunculales

• Family : Ranunculaceae

• Genus : Nigella L.

• Species : Nigella sativa L. – black cumin

Ethno medicinal use:

Black cumin seeds have been found to possess a diverse range of health-promoting properties, including antihypertensive (blood pressure-lowering), antidiabetic (blood sugar-regulating), diuretic (promoting urine production), anticancer (cancer-fighting), analgesic (pain-relieving), anthelmintic (worm-expelling), antimicrobial (fighting against microorganisms), spasmolytic (muscle-relaxing), anti-inflammatory (inflammation-reducing), bronchodilator (expanding airways), gastroprotective (protecting the digestive tract), hepatoprotective (liver-protecting), renal protective (kidney-protecting), and antioxidant (free radical-fighting) characteristics.

These versatile N. sativa seeds find application in traditional medicine for addressing a wide array of health concerns, including

asthma, bronchitis, rheumatism, diarrhea, and skin conditions. They are also utilized as a liver tonic, digestive aid, anti-diarrheal remedy, appetite stimulant, and to support lactating mothers in enhancing milk production.

SUCCESSIVE SOLVENT EXTRACTION[13,14]

Black Cumin seeds were subjected to extraction using the successive hot extraction method with a Soxhlet apparatus. The objective was to determine which extract exhibited the highest bio enhancing activity. The extraction process was carried out using the following solvents:

1. Chloroform 2. Butanol 3. Methanol 4. Ethanol 5. Aqueous

To ensure consistency in weight, all plant materials were air-dried at room temperature. Subsequently, the dried samples of the plant material were ground into coarse powder. For each extraction, 50 grams of the crude powder was placed in the Soxhlet apparatus. Sequential extraction with the various solvents (Chloroform, Butanol, Methanol, Ethanol, and Aqueous) was performed. The resulting extracts were then filtered using a funnel and Whatman No. 1 filter paper.

Each filtrate was concentrated to dryness under reduced pressure at a temperature of 40°C using an evaporator. The concentrated extracts were stored at 4°C for further analysis and research.

PREFORMULAION STUDIES

Melting point: Melting point of drug was found to be 200°C and normal range is 197-204°C

DRUG, EXTRACT AND POLYMER INTARACTION

Fourier-change infrared spectroscopy (FTIR) was utilized to examine the unadulterated medication Telmisartan, actual blend of Telmisartan, and HPMC, PG, PEG 400, Glycerine, and ascorbic acid for any medication polymer interaction by KBr pellets technique. All samples were examined at Range: 4000 – 650

STANDARD CURVE OF TELMISARTAN[15]:

To prepare a stock solution of Telmisartan, 100 mg of Telmisartan was dissolved in a 100 ml standard volumetric flask. This flask initially contained 50 ml of phosphate buffer 7.4. The solution was then filled up to the mark with phosphate buffer 7.4, resulting in

a final concentration of 1000 µg/ml. Subsequent dilutions of this stock solution were made using the mobile phase, creating a concentration range spanning from 5 to 50 µg/ml. These standard solutions, prepared as described above, were employed to construct a calibration curve, which would later be used to determine the unknown concentration of Telmisartan in further experiments.

FORMULATION AND DEVELOPMENT OF TRANSDERMAL PATCHES[16,17]

Transdermal patches were prepared using the solvent casting method. Hydroxypropyl methylcellulose (HPMC) was accurately weighed and placed in a beaker with 3 ml of purified water. The mixture was stirred on a magnetic stirrer for 15 minutes to allow the polymer to swell. Following this, Propylene glycol was added to the polymer solution. Next, 100 mg of Telmisartan was precisely weighed and dissolved in 2 ml of distilled water. This drug solution was added to the polymer dispersion, and Citric acid was thoroughly mixed in using a magnetic stirrer. After complete mixing, the solution was left to stand for 20 minutes to ensure the removal of any air bubbles. Subsequently, the solution was poured evenly into Petri dishes and left to dry at room temperature for 24 hours. After the drying period, the patches were carefully removed from the Petri dishes and cut into square pieces measuring 2x2 cm. These patches were then packaged in aluminium foil and stored in an airtight container to maintain their integrity and flexibility. The compositions of the different formulations of Telmisartan and extracts are detailed in Table No. 3 for reference.

EVALUATION OF TRANSDERMAL DELIVERY PATCHES:

The Physicochemical evaluation of transdermal patches are based on following parameters

Thickness of patch[18]

The thickness of each patch was measured by using screw gauge at five different positions of the patch and the mean value were calculated

Weight uniformity[19]

Patches sizes of 2cm radius (4cm diameter) was cut. The weights of five patches were taken and the weight variation was calculated.

Folding endurance[20]

A patch of 2cm radius (4cm diameter) cut evenly and repeatedly folded at the same place till it brakes. The numbers of times the film were folded at the same place without breaking given the value of the folding endurance

Percentage moisture content[21]

The prepared films were weighed individually and kept in a desiccators containing fuse calcium chloride at room temperature for 24h. After 24h, the films were weighed and determined the percentage moisture content from the mentioned formula.

Percentage moisture uptake[22]

The weighed films were kept in desiccators at room temperature for 24h containing saturated solution of potassium chloride in order to maintain 84% RH. After 24h, the films will be reweighed and determined the percentage moisture uptake from the below mentioned formula.

Drug content[23]

A specified area of patch was dissolved in a phosphate buffer solution. The content was stirred to dissolve the film. The content was transfer to a volumetric flask. The absorbance of the solution were measured and content of drug was determined

BIOENHANCING ACTIVITY MODEL:

Preparation of phosphate buffered saline pH 7.4 [7]

0.19 g of potassium dihydrogen phosphate, 2.38 g of disodium hydrogen orthophosphate, and 8.0 g of NaCl was dissolved in distilled water, and the volume was made up to 1000 ml with distilled water. The pH of the buffer was adjusted to 7.4

A) Ex-vivo Permeation Study[24,25,26]

We procured goat skin from the local market and subjected it to proper treatment. Ex vivo permeation studies were conducted using Franz diffusion cells with an effective cross-sectional area of 3.14 cm^2 and a receiver chamber capacity of 15 ml. The treated goat skin was cut into the desired size and positioned between the donor and receptor compartments of the diffusion cell. The transdermal patch was then placed over the membrane. The donor compartment was aligned with the receptor compartment, both containing phosphate buffer with a pH of 7.4, and maintained at a temperature of 37 ± 0.5°C. A clamp was used to secure the entire assembly, which was then placed on a magnetic

stirrer. To ensure continuous mixing, magnetic beads were employed to stir the solution in the receiver compartment. The quantity of the drug passing through the membrane was determined by withdrawing specific samples at predefined time intervals and replacing them with an equal volume of phosphate buffer. The absorbance of these samples was measured at a wavelength of 239.00 nm, with phosphate buffer serving as the blank. The drug's absorbance was determined using a standard curve for Telmisartan in phosphate buffer at pH 7.4. The amount of drug permeated during each time interval was calculated based on this calibration curve. Subsequently, the mean cumulative percentage of drug permeation across the total patch area was plotted against time

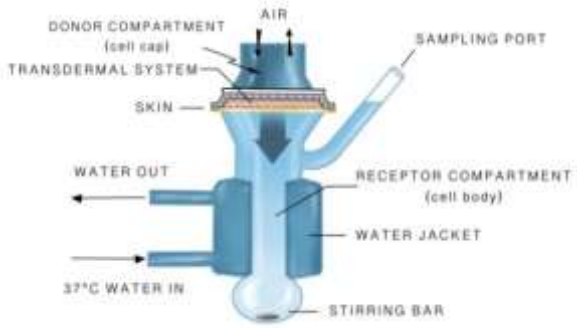

Figure 4 Franz Diffusion Cell

B) Everted Gut Sac Model[27,28]:

We obtained goat small intestine from a local slaughterhouse, which was then transported in a buffer solution. The intestine was cut into two pieces, each approximately 15 cm long, with an approximate diameter of 0.7 cm. One end of the intestine was securely tied, and the other end was connected to a cannula to create a pouch. We added a small volume of drug-free buffer solution to the pouch. To ensure the tissue remained viable, we provided a continuous supply of oxygen using an aerator, and the tissue was kept at a constant temperature of 37 ± 0.5ºC throughout the entire procedure. When the intestine was everted, the mucosal side was exposed, while the serosal side remained inside. The stratum corneum side of the skin was placed in close contact with the release surface of the transdermal patch. At predetermined intervals, samples were collected from the pouch, and the drug concentration in the serosal fluid was determined

using a spectrophotometer. Finally, the percentage of absorbance was calculated over time.

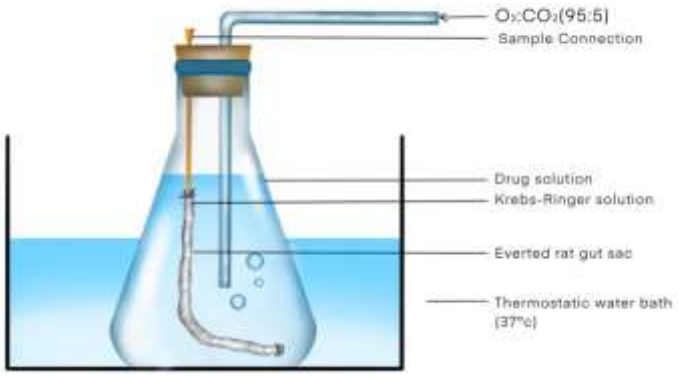

Figure 5 Everted Gut Sac Model

LIST OF TABLES

Table 1 Formulation code table (Telmisartan +Black Cumin seeds Extracts)

Formulation code	Content
F39	Telmisartan + Black Cumin Seeds Chloroform Extract
F40	Telmisartan + Black Cumin Seeds Butanolic Extract
F41	Telmisartan + Black Cumin Seeds Methanolic Extract
F42	Telmisartan + Black Cumin Seeds Ethanolic Extract
F43	Telmisartan + Black Cumin Seeds Aqueous Extract`
F33	Telmisartan + HPMC+PG+ PEG 400+ Glycerine +Citric Acid

Table-2 Standard curve of Telmisartan

S. N	Concentration(µg/ml)	Absorbance
1	5	0.213
2	10	0.423
3	15	0.646
4	20	0.866
5	25	1.076
6	30	1.276

Table 3 Formulation Design for Black Cumin Seed Extract + Telmisartan

Ingredients	FORMULATION CODE					
	F33	**F40**	**F41**	**F42**	**F43**	**F44**
Telmisartan	100mg	100mg	100mg	100mg	100mg	100 mg
HPMC	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg
PG	0.4ml	0.4ml	0.4ml	0.4ml	0.4ml	0.4ml
PEG-400	0.4ml	0.4ml	0.4ml	0.4ml	0.4ml	0.4ml
Citric Acid	10mg	10mg	10mg	10mg	10mg	10mg
Water	Up to 5ml	Up to 5ml	Up to 5ml	Up to 5ml	Up to 5ml	Up to 5ml
Chloroform extract	-----	50mg	-----	-----	-----	-----
Butanolic Extract	-----	-----	50mg	-----	-----	-----
Methanolic Extract	-----	-----	-----	50mg	-----	-----
Ethanolic Extract	-----	-----	-----	-----	50mg	-----
Aqueous extract	-----	-----	-----	-----	-----	50mg

Table 4 Evaluation of patches of Black Cumin Seed Extract + Telmisartan

Parameters	FORMULATION CODE					
	F33	F39	F40	F41	F42	F43
Thickness (mm)	0.233± 0.013	0.234± 0.0126	0.233± 0.201	0.298± 0.012	0.356± 0.104	0.356± 0.113
Weight uniformity (gm)	0.321± 0.016	0.312± 0.116	0.296± 0.121	0.291± 0.021	0.212± 0.346	0.241± 0.127
% Moisture uptake	9.112± 2.12	9.342± 3.343	8.231± 1.231	7.434± 2.435	9.561± 2.451	9.331± 2.671
% Moisture content	4.342± 0.766	8.112± 0.451	6.342± 0.435	8.341± 0.671	8.231± 0.341	6.115± 0.651
% Drug content(mg)	79.1± 0.23	82.12± 0.651	78.55± 0.582	80.32± 0.619	79.63± 0.654	80.12± 0.912
Folding Endurance	25±2.67	30±5.21	30±3,69	29±3.61	31±2.241	29±3.32

*All data are presented in Average ± SD, n=3

Table 5 %CDR of Black Cumin Seed Extract + Telmisartan patches

Time in hrs.	FORMULATION CODE					
	F33	F34	F35	F36	F37	F38
0.5	1.13 ±0.67	2.23 ±0.36	3.11 ±0.43	4.44 ±0.31	5.90 ±0.33	1.40 ±0.50
1.0	2.45 ±0.43	2.98 ±0.56	3.98 ±0.33	4.65 ±0.32	7.54 ±0.45	2.46 ±0.26
1.5	4.54 ±1.56	4.87 ±0.45	4.98 ±0.12	5.58 ±0.55	8.56 ±1.67	4.60 ±0.45
2.0	6.34 ±1.41	8.67 ±1.67	10.78 ±0.34	11.11 ±1.27	13.12 ±1.23	6.67 ±1.76
2.5	8.23 ±0.57	11.34 ±1.35	13.22 ±1.39	15.54 ±1.76	18.45 ±0.56	8.45 ±1.57
3.0	9.67 ±1.52	14.66 ±1.34	18.67 ±1.54	21.23 ±1.65	23.12 ±0.55	9.88 ±1.65
4.0	11.56 ±1.67	20.88 ±0.45	24.56 ±1.56	27.47 ±0.37	31.34 ±1.56	11.78 ±1.56
5.0	19.91 ±1.23	28.32 ±0.44	32.45 ±1.87	35.43 ±1.87	37.45 ±1.02	20.22 ±1.25
6.0	30.25 ±0.62	39.26 ±0.71	45.12 ±0.47	49.12 ±1.45	52.11 ±1.23	30.56 ±0.56

8.0	48.20 ±1.67	49.42 ±1.47	54.67 ±0.15	61.56 ±0.56	64.13 ±1.11	48.89 ±1.66

*All data are presented in Average ± SD, n=3

Table 6 %Drug absorbed of Black Cumin Seed Extract + Telmisartan bulk drug

Time in Min.	**FORMULATION CODE**					
	F33	**F39**	**F40**	**F41**	**F42**	**F43**
10	0.352±0.21	0.474±0.47	0.612±0.45	0.991±0.54	0.804±0.45	0.360±0.78
20	0.698±0.42	0.945±0.65	1.101±0.61	1.433±0.61	1.211±0.62	0.701±0.37
30	0.944±0.92	1.225±0.56	1.574±0.71	1.937±0.24	1.741±0.42	1.100±0.43
60	1.212±0.32	1.454±0.41	1.987±0.25	2.305±0.35	2.107±0.37	1.220±0.55
90	1.542±1.12	1.817±1.02	2.541±0.16	2.779±0.61	2.451±0.62	1.548±0.19
120	1.974±0.17	2.238±1.14	2.705±0.32	2.994±0.73	2.714±0.49	1.982±0.73

*All data are presented in Average ± SD, n=3s

LIST OF ADDITIONAL FIGURES

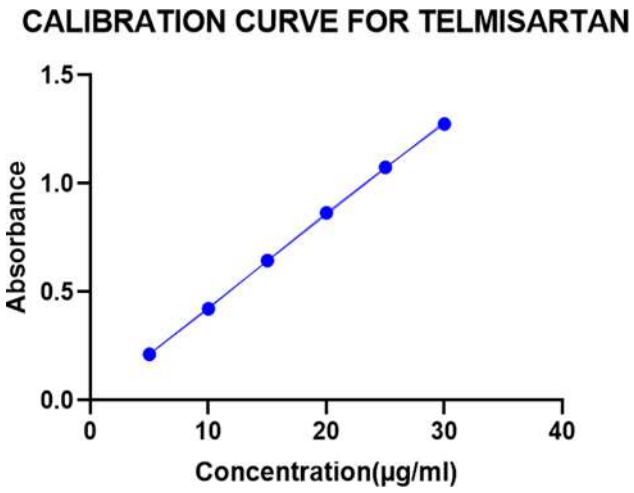

Figure 6 calibration curve of Telmisartan

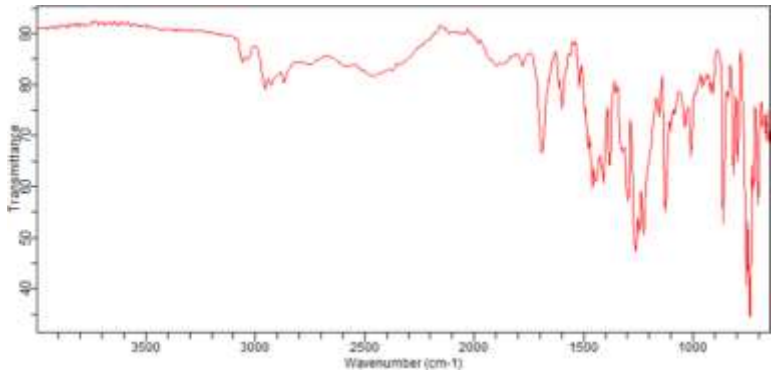

Figure 7 IR Spectra of F33 Formulation

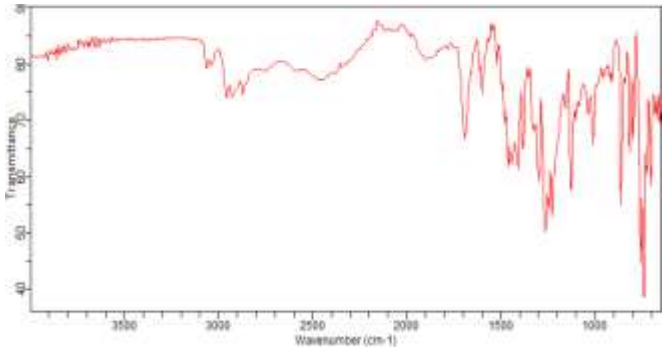

Figure 8 IR Spectra of F39 Formulation

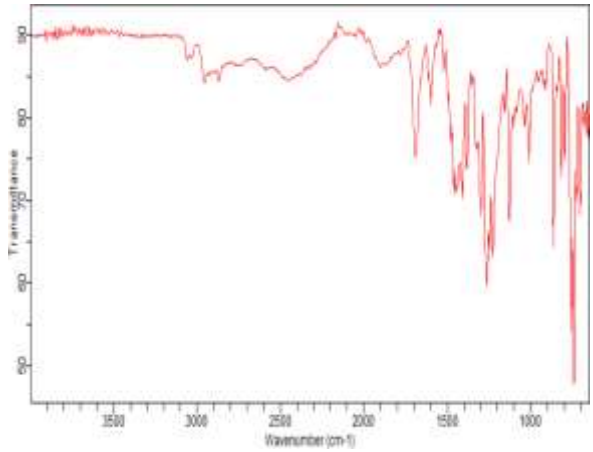

Figure 9 IR Spectra of F40 Formulation

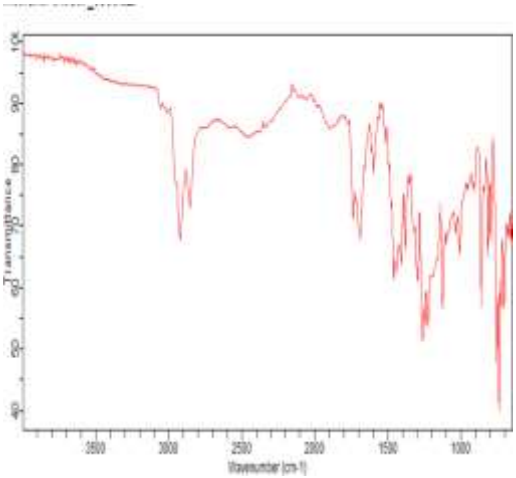

Figure 10 IR Spectra of F41 Formulation

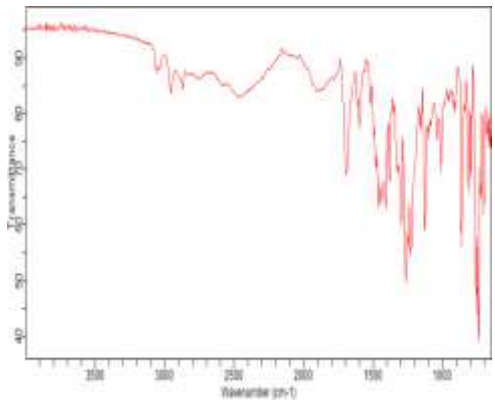

Figure 11 IR Spectra of F42 Formulation

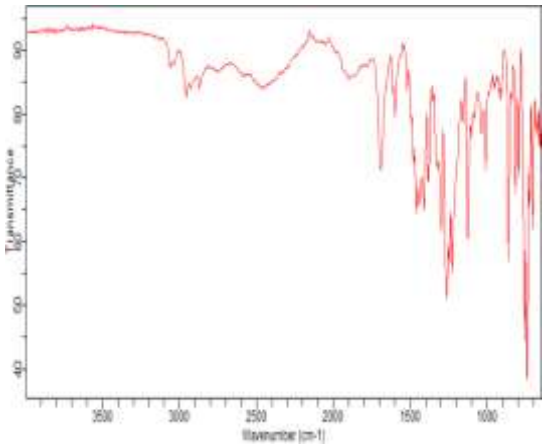

Figure 12IR Spectra of F43 Formulation

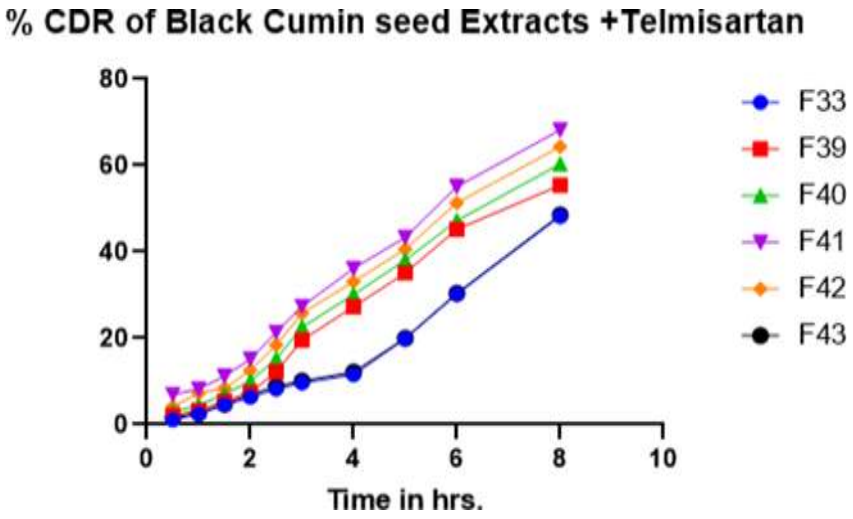

Figure 13 % CDR of Black Cumin Seeds Extract and Telmisartan

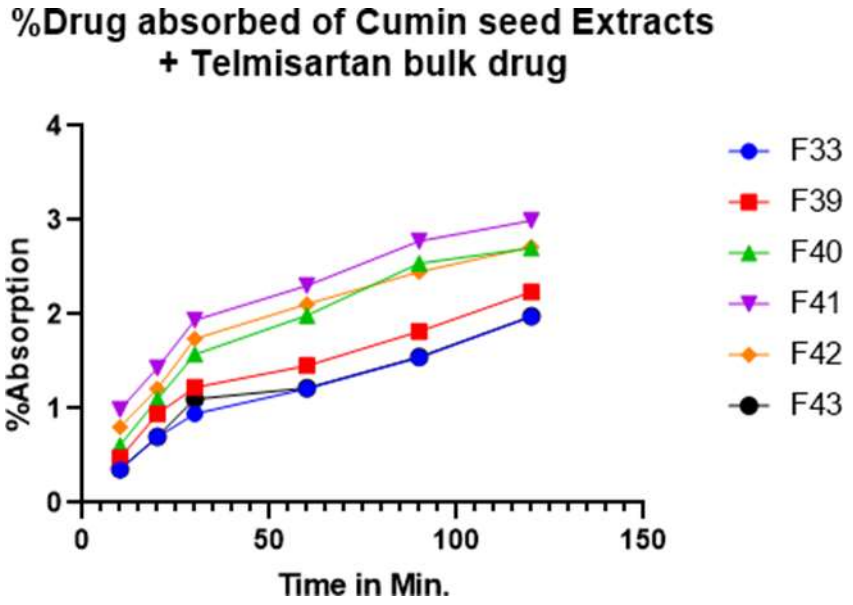

Figure 14 % Drug Absorbed of Black Cumin Seed Extract and Telmisartan

RESULT AND DISCUSSION:

The production of all patches was successfully completed, and these patches were subsequently subjected to diffusion studies. These studies were conducted using both the Franz diffusion cell method and the Everted Gut Sac model. At predefined time intervals, we collected samples and measured the absorbance of each sample using a spectrophotometer to determine the percentage of drug content. The results of the diffusion studies were analyzed and presented graphically. The X-axis represented time, while the Y-axis displayed cumulative percentage release. In the case of the Everted Gut Sac model, the graph depicted the percentage absorbance against time. Through this study, it

was discovered that natural bioenhancers, such as Black Cumin seed extract, can be effectively utilized in combination with modern medicines like Telmisartan to enhance the bioavailability of the drug. Notably, in the combination of Cumin seed extract with Telmisartan, the Methanolic extract demonstrated a significant increase in the percentage of cumulative drug release (% CDR).

1. Compatibility studies of drug and extract as well as drug and polymers were studied with the help of FTIR shows no drug extract and drug polymer interaction, result of which shown in **Figure 7-12**
2. Physicochemical parameters like % moisture content, thickness, weight variation etc. are within limit shown in **table 4**
3. Ex vivo permeability studies are mention in **table 5 and Figure 13**
4. Everted Gut Sac studies are mention in **table 6 and Figure 14**
   Amongst all the extract Methanolic extract of Black Cumin Seed F41 showed significant increase in % CDR as well as in drug absorbance.

As an extension to this work In-vivo studies and clinical research on human being can be carried out in future.

CONCLUSION: It can be concluded that herbal drugs in the form of extract can also be used in formulating transdermal patches due to opportunity of release of drug formulation which is very novel approach.

The Telmisartan n patches made by solvent evaporation technique comprising of different extract of Black cumin seed, with Telmisartan were formulated. The drug was found compatible different extracts and the polymers. All extracts show to some extent bio enhancing effect compared to individual Telmisartan patch. Amongst all the formulations F41 showed significant increase in drug release and drug absorption.

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CONFLICTS OF INTEREST: Authors have no conflict of interest regarding this research work.

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