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FORMULATION AND EVALUATION OF A UNIQUE TRANSDERMAL PATCH COMPRISING OF TELMISARTAN FOR HYPERTENSION THERAPY

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ABSTRACT

The Aim of this study was to design and develop Transdermal patches of Telmisartan and Telmisartan plus various extract of Cinnamon bark to find out the bioenhancing effect of various extract of Cinnamon bark. The transdermal patches were formulated using solvent casting technique with the help of various polymers. The Telmisartan drug is used widely for the treatment of hypertension but loses its potential due to less bioavailability. Its bioavailability might be improved by combining bioenhancers like Cinnamon bark. The present study deals with the use of Cinnamon bark extracts for increasing bioavailability of Telmisartan. The absorption of Telmisartan improved by addition of Cinnamon bark extract for formulating the Transdermal patches, this combination may reduce the dose of the drug, patient compliance as well as toxicity of the drug can be reduced to a greater extent. Drug extract and polymer compatibility studied with the help of Fourier Transform infrared Spectroscopy (FTIR).The diffusion examines were performed by utilizing the Franz Diffusion cell and Everted gut Sac method. The best formulation F37 showed thickness 0.322±0.134mm, Weight uniformity 0.129±0.245gm, % Moisture uptake 9.121±2.454 Moisture content 8.116±0.212, % Drug content 80.65±0.678, Folding endurance 32±2.34. Formulation F537 exhibits the highest % cumulative drug release 64.13±1.11% in 8hrs and highest %Drug absorbed 2.994±0.28 in 120 min. Formulation no. F37 shows maximum bioenhancing action compared to all other patches which contains Telmisartan along with the Ethanolic extract of the Cinnamon bark.

Keywords: Cinnamon bark, Telmisartan, Cinnamon bark, FTIR, Bioavailability

1. INTRODUCTION

Bioavailability is the beat and level to which a restoratively unique substance enters essential dispersal and gets accessible at the fundamental site of movement. Intravenous prescriptions accomplish the best bioavailability, while it was seen that oral association yields a lessened rate in view of inadequate drug absorption due to first-pass metabolism **[1]**. Transdermal medication transportation system is the conveyance of medications through the skin has been consistently a testing area for specialists, because of obstruction properties produced by the peripheral layer of skin corneum. Exceptionally in the most recent twenty years, the transdermal medication conveyance framework has become a seriously centring innovation that offers huge clinical advantages over other drug delivery mechanisms **[2]**.

It is assessed that up to 40% of new chemical entities under development might be arranged as inadequately dissolvable entities **[3]**.

Three essential focuses specifically dissolvability, disintegration, and intestinal permeability, affecting oral drug absorption can be surveyed using the biopharmaceutics portrayal system (BCS). It masterminds the medicine into four classes: Class I (high dissolvability, high vulnerability), Class II (low dissolvability, high permeability), Class III (high dissolvability, low permeability), and Class IV (low dissolvability, low vulnerability). A part of the conventionally used enemy of contamination specialists falls into Class III and Class IV order according to this system **[4]**. Consistent and future concentration of drug will be achieved by transdermal drug delivery **[5]**. In 1982 North America was the only country whose Food and Drug Administration approved hyoscine transdermal film for motion sickness developed by Glaxo Smith Kline **[6]**. USA has approved quite thirty five transcutaneous delivery product for large choice of pathophysiological condition **[7]**. TDDS provide varied advantages over the regular dose structures and oral controlled delivery conveyance frameworks, strikingly escape of internal organ first-pass metabolism, the decline in repetition of organization, decrease in duct results and improves patient consistence **[8]**. These days, examination into transdermal medication conveyance has terribly dilated within the course of recent years, one in every of the most impetuses for this development is that the increasing range of medicines which will be sent to the basic flow in clinically successful fixation by suggests that of the skin access. This has been conceivable visible of the superb accomplishments of drug technologists who

haven't simply created the transcutaneous conveyance framework because the best non-oral foundational drug conveyance framework nevertheless additionally created its collection a deeply effective advertisement adventure **[9]**. Transdermal patches are the drug of choice for long term and frequent drug administration for steady plasma concentration **[10]**.

2. MATERIALS AND METHODS

2.1. Drug & Chemical

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

2.2. Plant Material Used

Materials Cinnamon bark, was obtained from native market, impurities and foreign material was inspected then removed and authenticated from plant scientist.

Cinnamon Bark [11, 12]

Biological Source: It consists of dehydrated bark inside bark of *Cinnamomum zeylanicumnees*, belonging to family Lauraceae.

Chemical Constituents: 0.5 to 1.0% of volatile oil, 1.2 % of tannis mucilage, calcium oxalate, starch and a sweet substance is known as mannitol

Uses: Cinnamon bark is used for gastric suffering, loose motion, and has anti flatulence. It is also used appetizer; it is having antibacterial and anti-parasitic activity.

2.3 Successive Solvent Extraction

Cinnamon Bark was extracted by means of serial hot extraction methodology by using Soxhlet equipment so as to seek out that extract shows the utmost Bio enhancing activity. Extraction was done in following manner

1) Chloroform, 2) Butanol, 3) methanol, 4) ethyl alcohol 5) aqueous

Preparation of all extracts by serial extraction methodology all stuff were air dehydrated in shade so as to induce consistent weight. The dehydrated samples of all stuff were ground later to rough powder. Fifty grams of crude powder of bark were taken in Soxhlet equipment. serial extraction with completely different solvents (Chloroform, Butanol, Methanol, Ethanol, and Aqueous) was dole out. Extracts were being sifted using funnel and Whatman No. 1 paper every remainder are going to be combined to aridness under condensed pressure at 40°C through evaporator and hold on at 4°C for further studies **[13, 14]**.

2.4. Preformulaion Studies

Drug, Extract and Polymer compatibility:

Fourier-change infrared spectroscopy (FTIR) was utilized to examine the medication Telmisartan, herbal drug extract and polymer compatibility.

2.5 Standard Curve of Telmisartan [15]

Stock solution of Telmisartan prepared in phosphate buffer and calibration curve was obtained after further dilutions.

2.6 Formulation and Development Of Transdermal Patches

Transdermal patches were set up by soluble solvent casting technique. HPMC was weighed exactly and enclosed three ml of distil water. The substance within the beaker was intermingled on magnetic stirrer for 15 min for swelling of the compound. At that time propylene glycol was additional to the compound resolution. 100mg Telmisartan was weighed and dissolved in two ml of Water. The medication arrangement was additional to the compound dispersion and citric acid was intermingled altogether with the help of magnetic stirrer. At that time once complete compounding resolution was unable to square for 20 minute to make sure the removal of air bubbles. Subsequently it had been poured systematically in Petri dishes and was left for 24hours at room temperature for drying. After drying after 24hrs patches were taken out by stripping from the Petri dishes at that time delve a square component of 2× 2 cm. Patches were stuffed in foil and place away in a very water/air proof holder to stay up their trustworthiness and flexibility. The compositions of the assorted formulations of Telmisartan and extracts area unit listed in tables **[16, 17]**.

2.7 Evaluation of Transdermal Delivery Patches:

The Physicochemical evaluations of transdermal patches were performed including following parameters.

a. Drug content: A particular region of the movie changed into dissolved in a phosphate buffer solution. The content changed into stirred to dissolve the transdermal patch. The content material becomes relocated to a volumetric flask. The absorbance of the solution changed into measured and the content material of the drug become determined **[18]**.

b. Percentage moisture content material: The formulated patches were weighed separately and reserved in a desiccator containing fuse calcium chloride at room temperature for 24h. After 24h, the patches had been weighed, and decided the fraction moisture content material from the formulation **[19]**.

c. Folding endurance: A film cut uniformly and more than once folded at a similar point till it brakes. The quantities of times the film were distorted at a similar spot without breaking given the estimate of the folding endurance **[20]**.

d. Weight uniformity: Film sizes of 2cm radius (4cm diameter) were cut. The masses of five films were taken and the weight difference was intended **[21]**.

e. Percentage moisture uptake: The weighed patches had been reserved in desiccators at room temperature for 24h comprising saturated answer of potassium chloride to be able to maintain84% RH. After 24h, the patches had been reweighed and determined the percentage moisture uptake from the formula **[22]**.

f. Thickness of patch: The thickness of each transdermal patch was assessed by utilizing screw gauze at five different places of the film and the mean value was determined **[23]**.

Bioenhancing Activity Model:

a) Ex-vivo permeation study: Goatskin obtained was preserve properly in phosphate buffer. Ex vivo permeation research was carried out with the help of Franz diffusion cells with an effective sectional place of 3. 14 cm2 and 15 ml of receiver chamber potential. The treated goatskin becomes reduce to the preferred size and positioned among the receptor and donor compartments of the diffusion cell. The patch becomes placed over the membrane. The donor compartment becomes placed on the receptor compartment containing phosphate buffer ph 7. 4 maintained at 37± 0. 5^{o}C and the clamp were located in between the donor compartment and receptor compartment for fixing them together the whole assembly became put on a magnetic stirrer. The amount in the receiver compartment was uninterruptedly stirred with magnetic beads. The quantity of the drug-infused through the membrane turned determined via chickening out the unique quantity of the pattern at programmed time intermission and substituting them with an equal extent of phosphate buffer. The absorbance of the samples becomes fascinated about the assist of a spectrophotometer **[24, 25, 26]**.

b) Everted gut sac model: Goat's small gut was acquired from slaughtering homes from the local marketplace. The intestine changed into transported in buffer solution and acquired into two pieces of 15cm every; the predicted diameter of the intestine changed into 0. 7 cm. One-stop of the gut was tied up and everted with the help of a tumbler rod; the cannula became related to another cease of the intestine so one can shape the pouch and delivered a small extent of drug-free buffer solution. Continuous delivery of oxygen changed into supplied to the tissue in order to preserve it alive with the assist of an oxygen pump and phosphate buffer solution; the temperature changed into persisted at 37± 0. 5ºc during the entire manner. After eversion, the mucosal side got here out and the serosal facet was present inside. The stratum corneum side of the skin changed into kept in near contact with the release surface of the transdermal patch. At a predetermined time the pattern

from the sac becomes removed and the attention of the drug in a serosal fluid turned into determined with the assist of a spectrophotometer. Finally, % of absorbance becomes calculated in opposition to time **[27, 28]**.

3. RESULT AND DISCUSSION

All of the formulated patches correctly worked subjected to diffusion have a look at that's supported out with the help of the Franz diffusion cellular approach and everted intestine sac Samples had been collected at a predetermined time and the absorbance of every sample changed into measured with the help of a spectrophotometer with the purpose to find out the % of drug content. The end result of the diffusion research has been discussed in the graph via plotting time in the x-axis and cumulative % release in the y-axis in addition to % absorbance in opposition to time in the case of everted intestine sac model. All through this examine it's been determined that natural bio-enhancers like cinnamon bark extract can be used along with a modern-day medicinal drug-like Telmisartan so that you can amplify the bioavailability of drug through transdermal drug delivery gadget.

Compatibility studies of drug and extract, as well as drug and polymers, had been studied with the help of FTIR shows no drug extract and drug-polymer interaction, end result of which proven in determine vii-xiii.

Physicochemical parameters like % moisture content, thickness, weight version and so on. Are within the limit shown in **Table 4** ex vivo permeability studies are point out in desk 5and **Figure 14** everted intestine sac studies are mention in **Table 6 and Figure 15** among all of the extracts, ethanolic extract (F37) showed a vast increase in % CDR 67. 90, as well as in drug absorbance 4. 26. Order of permeation enhancing effect Franz diffusion cell research

Order of % drug absorption in case of everted intestine sac model

F37>F36>F35>F34>F38>F33

Order of % drug absorption in case of Everted Gut Sac model

F37>F36>F35>F34>F38>F33

Lengthy-term remedy and multidrug therapy may be triumph over through the usage of the transdermal drug delivery machine which in turn will increase the bioavailability of the drug by means of avoiding the first-pass metabolism which destroys the maximum quantity of the drug. The drug without delay reaches the systemic flow and will increase the healing efficacy. Telmisartan is a strong ant diabetic drug used extensively for the treatment of type-ii diabetes. However, due to the primary-skip metabolism, it indicates less healing effect. Polymers along with

HPMC, peg decided on because it confirmed right adhesive activity and higher skeleton formation which is the bottom of transdermal patches. Phosphate buffer with pH 7, 4 turned into used to discover the solubility of the drug and also to find out the unknown attention of the drug. Fair turned into achieved to find out the drug-polymer and drug-herbal extracts compatibility. FTIR studies were executed on the natural bulk drug in addition to on extract and polymer with the intention to get a stable formulation. The formulated patches were subjected to various physical and chemical evaluation parameters a good way to standardize the formulation. All the evaluated parameters for various components come underneath restriction. Out of all of the components, system quantity F37 showed advanced bioavailability of Telmisartan in comparison to relaxation of the extracts.

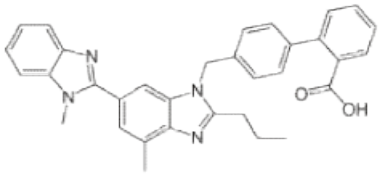


Figure-1 Telmisartan
2-(4-{[4-Methyl-6-(1-methyl-1*H*-1,3-benzodiazol-2-yl)-2-propyl-1*H*-1,3-benzodiazol-1-yl]methyl}phenyl)benzoic acid

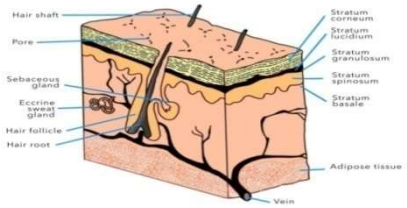


Figure 2: Transdermal patches design and structure of skin

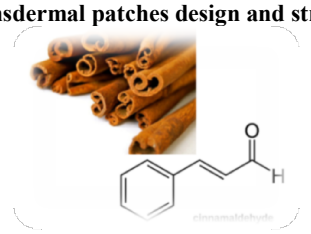
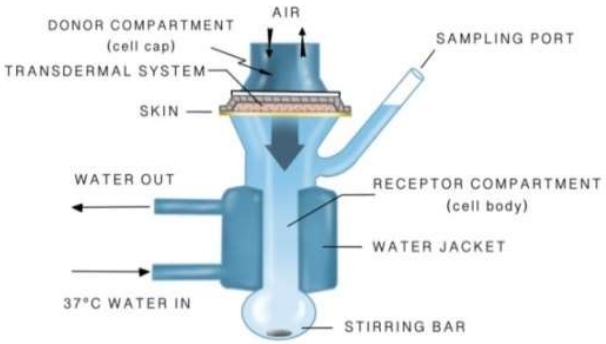


Figure: 3 Cinnamon bark



"Figure 4: Franz Diffusion Cell"

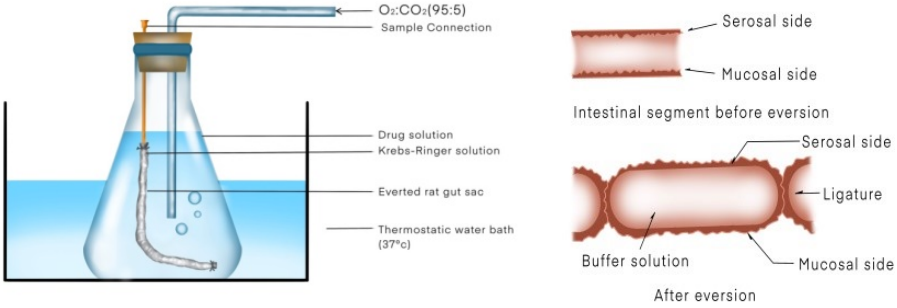


Figure 5: Everted Gut Sac Model

Table 1: Formulation code

Formulation code	Content
F33	Telmisartan
F34	Telmisartan+ Cinnamon Chloroform Extract
F35	Telmisartan + Cinnamon Butanolic Extract
F36	Telmisartan + Cinnamon Methanolic Extract
F37	Telmisartan + Cinnamon Ethanolic Extract
F38	Telmisartan + Cinnamon Aqueous Extract
F51	Telmisartan +HPMC+PG+ PEG 400+ Citric Acid

Table 2: Standard curve of Telmisartan

S. No.	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 Cinnamon Bark Extracts + Telmisartan

Ingredients	FORMULATION CODE					
	F33	F34	F35	F36	F37	F38
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

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

Table 4: Evaluation of patches of Cinnamon Bark Extracts + Telmisartan

Parameters	FORMULATION CODE					
	F33	F34	F35	F36	F37	F38
Thickness (mm)	0.233±0.013	0.216±0.016	0.220±0.231	0.311±0.009	0.322±0.134	0.346±0.156
Weight uniformity (gm)	0.321±0.016	0.213±0.112	0.245±0.017	0.231±0.013	0.129±0.245	0.121±0.167
% Moisture uptake	9.112±2.12	8.123±3.004	9.121±1.112	8.134±2.212	9.121±2.454	8.212±2.321
% Moisture content	4.342±0.766	7.128±0.673	6.121±0.342	6.126±0.673	8.116±0.212	6.221±0.876
% Drug content(mg)	79.1±0.23	87.45±0.563	77.45±0.459	79.33±0.243	80.65±0.678	82.11±0.891
Folding Endurance	25±2.67	33±5.23	27±4.56	31±3.65	32±2.34	31±4.67

***All data are presented in Average ± SD, n=3; *Ex-vivo* drug release studies Franz Diffusion cell**

Table 5: %CDR of Cinnamon Bark Extracts + 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 Cinnamon Bark Extract Telmisartan bulk drug

Time in Min.	FORMULATION CODE					
	F33	F34	F35	F36	F37	F38
10	0.352±0.21	0.400±0.71	0.610±0.14	0.642±0.45	0.947±0.77	0.360±0.47
20	0.698±0.42	0.748±0.23	0.814±0.25	0.954±0.21	1.324±0.51	0.700±0.61
30	0.944±0.92	1.012±0.37	1.102±1.14	1.341±0.37	1.721±0.34	1.012±0.32
60	1.212±0.32	1.287±0.45	1.405±1.21	1.778±0.29	2.105±0.43	1.220±0.47
90	1.542±1.12	1.620±0.55	1.887±1.45	2.250±0.84	2.541±0.61	1.549±0.39
120	1.974±0.17	2.104±0.41	2.210±0.74	2.720±0.91	2.994±0.28	1.982±0.51

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

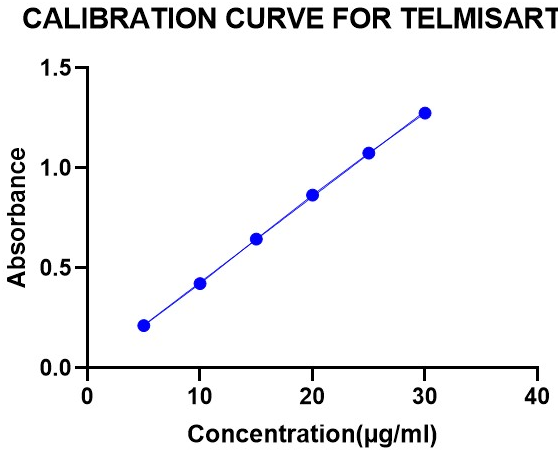


Figure 6: Calibration curve of Telmisartan

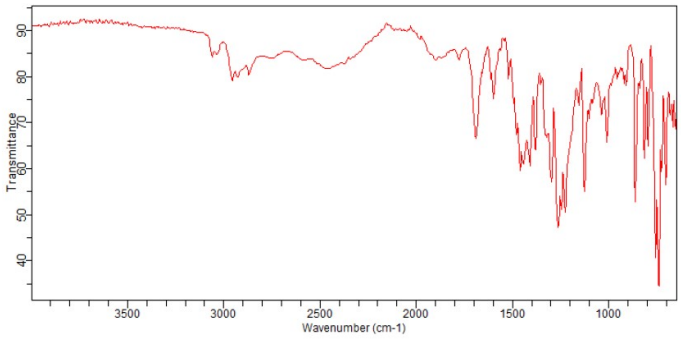


Figure 7: FTIR Telmisartan F33

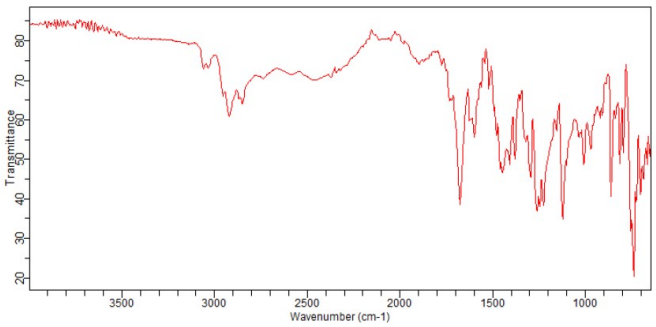


Figure 8: FTIR Telmisartan+ Cinnamon Chloroform Extract F34

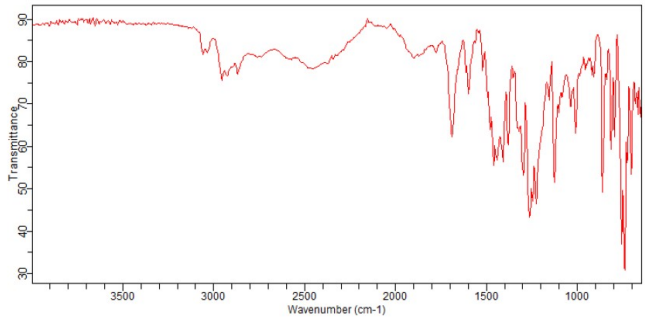


Figure 9: FTIR Telmisartan + Cinnamon Butanolic Extract F35

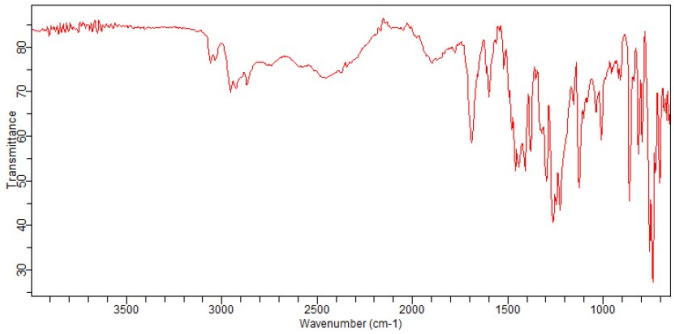


Figure 10: FTIR Telmisartan + Cinnamon Methanolic Extract F36

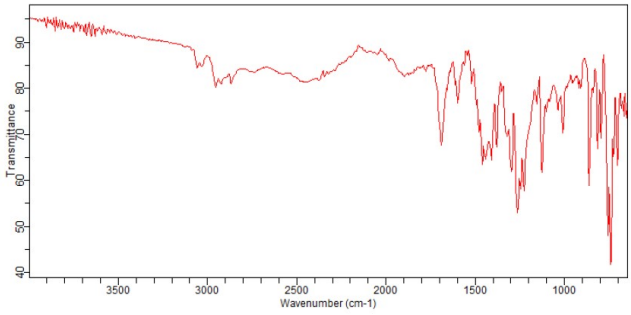


Figure 11: FTIR Telmisartan + Cinnamon Ethanolic Extract F37

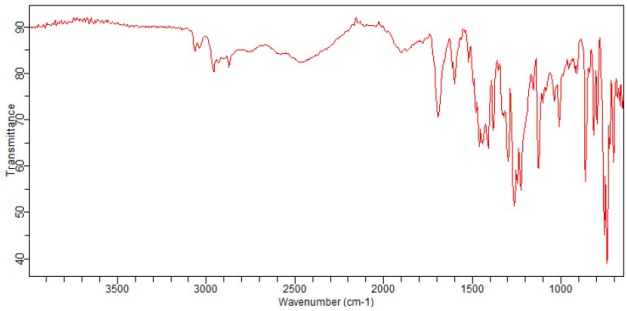


Figure 12: FTIR Telmisartan + Cinnamon Aqueous ExtractF38

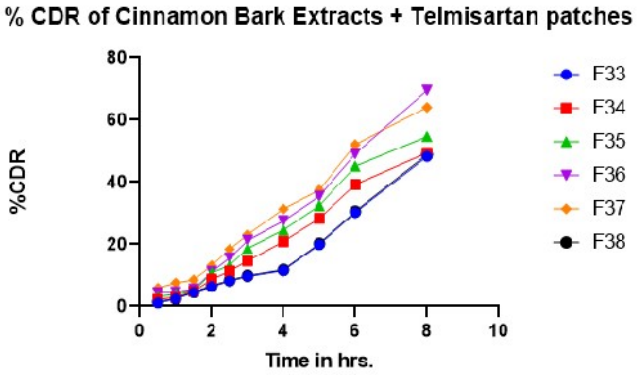


Figure 13: %CDR of Cinnamon Bark Extracts + Telmisartan patches

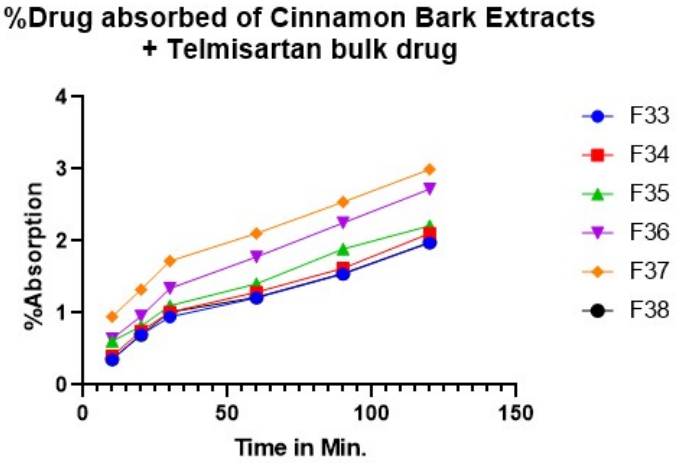


Figure 14: % Drug absorbed of Cinnamon Bark Extracts + Telmisartan bulk drug

4. CONCLUSION

It is able to be concluded that herbal drugs in the shape of the extract can also be used in formulating transdermal patches because of the opportunity of the launch of drug formulation which may be a very novel approach. The Telmisartan patches made with the aid of solvent evaporation approach comprising of various extract of cinnamon bark along with Telmisartan were formulated. The drug changed into determined well suited with specific extracts and the Telmisartan patches. Amongst all of the formulations, f5 indicates a tremendous increase in drug launch and drug absorption. As an extension to this study, in-vivo research and clinical research on human beings can be achieved in destiny.

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