Section A-Research paper
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Exploring the Influence of Permeation Enhancer (Cinnamon Bark Extracts) on the Bioavailability of Fenofibrate Formulated Transdermal Patches

Ashish Kandalkar[1], Somkant Jawarkar[2], Rakesh Dhole[3], Vinod Tiwari[4], Nilesh Chachda[5], Pankaj Chaudhary[6], Neha Patil[3], Geeta Darekar[8]

1. Vidyaniketan College of Pharmacy, Maharashtra, India
2. Dr. S.D. Patil Institute of Pharmacy, Islampur, Maharashtra, India
3. Ahinsa Institute of Pharmacy, Dhule Road, Dondaicha, Maharashtra, India
4. Dr. Mahendra Kumar Chhote Lal Bind College of Pharmacy, Handia, Prayagraj (Allahabad) U.P. India
5. Shri Chhatrapati Shahumaharaj Shikshan Santha's Institute of Pharmacy, Maregaon, Maregaon , Yavatmal, Maharashtra, India
6. P.R. Pote College of Pharmacy, Amravati, Maharashtra, India
7. Srinath college of Pharmacy Aurangabad, Maharashtra, India

Corresponding author: drashishkandalkar@gmail.com

Abstract:

In the pursuit of knowledge, this study endeavours to extract the intricate phytochemical constituents residing within the confines of Cinnamon Bark. Simultaneously, it aspires to orchestrate the conception and formulation of a transdermal patch, amalgamating the essence of the herbal remedy and the contemporary elixir, Fenofibrate. The solvent casting method takes center stage in this endeavour, acting as the alchemical conduit to orchestrate a reduction in requisite dosages, thus harmonizing pharmacological effects while simultaneously diluting the Specter of toxicity.

Methods: Through the artistry of solvent casting, Fenofibrate Transdermal patches were formulated, their seamless synergy with the patch base confirmed through Infrared Spectroscopy (FTIR). Meticulously crafted, these patches underwent a comprehensive assessment, unveiling attributes from weight and plumpness to moisture embrace. The grand performance unfolded ex vivo, showcasing both drug release and absorption, a testament to their harmonious integration of innovation and precision.

Results: Utilizing the tools of the Franz diffusion cell and the everted gut sac method, the realm of diffusion was explored. Among the formulations, F5 emerged triumphant, boasting a slender thickness of 0.220±0.007mm, a weight uniformity of 0.147±0.015gm, and a moisture uptake of 6.220±1.00%, a testament to its exceptional attributes along with moisture content at 4.025±0.114%, drug content at 84.80±0.071%, and folding endurance standing at 28±5.30. Among these, the standout performer, Formulation F5, takes the stage, showcasing a

remarkable % cumulative drug release of 75.47±1.14% over 8 hours, accompanied by the highest % drug absorption at 4.987±0.41within 120 minutes.

Conclusion: In summation, the evidence points towards Formulation F5 as the harbinger of heightened bio-enhancement, surpassing its peers within the realm of Fenofibrate-laden patches infused with the ethanolic essence of Cinnamon bark.

Key words: *Fenofibrate, Extract, Cinnamon bark, Moisture content, Ex vivo, drug absorption.*

Introduction:

Bioavailability refers to the extent and degree to which a therapeutically active substance enters systemic circulation and becomes accessible at the primary site of action. Intravenous administration achieves optimal bioavailability, while oral intake exhibits diminished rates due to partial drug absorption and first-pass metabolism.[1] The biopharmaceutics classification system (BCS) evaluates key factors like solubility, dissolution, and intestinal permeability that influence oral drug absorption, classifying drugs into four types: Type I (high solubility, high permeability), Type II (low solubility, high permeability), Type III (high solubility, low permeability), and Type IV (low solubility, low permeability). Certain commonly used antibiotics fall under Class III and Class IV categories according to this system.[2,3]

Hyperlipidaemia is recognized as a contributing factor to the onset of coronary heart diseases., prompts the use of potent antilipidemic agents such as Fenofibrate, often administered orally for hyperlipidaemia treatment. Transdermal drug delivery systems offer advantages over traditional administration methods, facilitating drug absorption. A consistent, prolonged concentration of medication can be achieved through transdermal drug delivery.[3,4]

In 1982, the US FDA approved the Scopolamine transdermal film for motion sickness, marking a significant milestone. The USA has sanctioned over 35 transdermal delivery products for various pathophysiological conditions.[5] Transdermal drug delivery surpasses conventional dosage forms and oral controlled release systems, notably by evading hepatic first-pass metabolism, reducing administration frequency, minimizing gastrointestinal effects, and enhancing patient compliance.[6,7]

Presently, research in transdermal drug delivery has witnessed remarkable growth over the past few years. This expansion is driven by the increasing number of drugs that can attain clinically effective concentrations in the systemic circulation through the skin portal. These achievements owe credit to drug technologists who have not only established transdermal delivery as a premier non-oral systemic drug delivery method but have also transformed its production into a highly efficient commercial venture.[8.9]

Transdermal administration emerges as the optimal approach for sustained and frequent drug usage to maintain plasma concentration over extended periods.[10]

Materials and Method:

Fenofibrate was acquired as a complimentary sample, while the remaining ingredients were sourced from the Research Lab. Every ingredient procured held the distinction of being of analytical grade. The Cinnamon bark, a crucial component, was procured from the local market, meticulously examined for impurities and extraneous matter, subsequently

authenticated by a botanist. This particular Cinnamon Bark hails from the inner layers of Cinnamomum zeylanicum Nees, nestled within the embrace of the Lauraceae family. Within the annals of its composition, Cinnamon Bark unveils its treasures a volatile oil content ranging from 0.5 to 1.0%, accompanied by tannis mucilage at 1.2%, calcium oxalate, starch, and the sweet essence known as mannitol. Revered for its therapeutic attributes, this bark serves as a remedy for gastric distress, alleviates loose motions, and combats flatulence. Moreover, it stands as an appetite enhancer, bearing antibacterial and anti-parasitic prowess.[11,12]

Successive Solvent Extraction:

Cinnamon Bark underwent a meticulous extraction process utilizing the successive hot extraction method, employing the revered Soxhlet apparatus. The objective: to ascertain the extract that exhibits supreme bio enhancing potential. The extraction unfolded as follows:

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

With methodical precision, all plant materials underwent gentle air dehydration in the comforting shade to attain uniform weight. Subsequently, the dehydrated plant samples metamorphosed into a coarse powder. The journey continued as fifty grams of this bark's raw essence nestled within the heart of the Soxhlet apparatus. A succession of extractions ensued, each with its distinct solvent (Chloroform, Butanol, Methanol, Ethanol, and Aqueous), a symphony of transformative forces at play.

The extracts were meticulously filtered through the eloquent embrace of funnel and Whatman No. 1 filter paper. Each remaining residue embarked on a voyage to aridity under reduced pressure at 40°C, elegantly orchestrated by an evaporator. The extracts were then serenely stored at 4°C, a sanctuary for further scholarly exploration and inquiry.[13,14]

Pre formulation Studies

he compatibility of the drug, extract, and polymer trio underwent scrutiny through Fourier-transform infrared spectroscopy (FTIR), employing the KBr pellet technique. This analysis encompassed the unadulterated Fenofibrate, as well as its amalgamation with HPMC, PG, PEG 400, Glycerine, and ascorbic acid. The spectral investigation spanned the range of 4000 – 650 cm^{-1}. To establish the foundation for quantification, the standard curve of Fenofibrate was meticulously erected. The process involved crafting a stock solution by dissolving 100 mg of Fenofibrate in 100 ml of a standard volumetric flask. This solution, immersed in phosphate buffer 7.4, led to a concentration of 1000 µg/ml. Subsequent dilutions across the concentration range of 5-50 µg/ml were devised using the mobile phase. The resultant standard solutions constructed the calibration curve, a map of concentration against response, for the ensuing analysis.[15] The formulation and evolution of transdermal patches were carried out through the dissolvable solvent casting method. Precisely weighed HPMC was introduced to 3 ml of distilled water, invoking 15 minutes of magnetic stirring to initiate polymer swelling. Propylene glycol followed suit, becoming a part of the polymer solution. Fenofibrate, quantified at 100 mg, dissolved in 2 ml of distilled water, and this drug solution

mingled with the polymer dispersion. The harmonious fusion incorporated Citric acid, facilitated by magnetic stirring, followed by a 20-minute respite to eliminate air bubbles. The resulting blend was uniformly poured into Petri dishes, ushered into a 24-hour drying period at room temperature. Subsequently, the parched patches were extracted from their Petri confines, metamorphosed into square dimensions of 2×2 cm. Encased within aluminium foil and nestled within an airtight vessel, the patches found sanctuary, safeguarding their structural integrity and flexibility. The compositions of various Fenofibrate and extract formulations find their exposition in Tables 1 and 2.[16,17]

Evaluation of Transdermal Delivery Patches

1. Thickness of Patch: The measurement of patch thickness was conducted using a screw gauge at five distinct locations across the film, and the resulting mean value was determined.[18]
2. Weight Uniformity: Transdermal film segments with a 2 cm radius (4 cm diameter) were excised. The masses of five individual films were measured, and the differences in weight were calculated.[19]
3. Folding Endurance: A transdermal film with a 2 cm radius (4 cm diameter) was uniformly cut and repeatedly folded at the same location until it ruptured. The count of folding at the same spot without breakage provided the folding endurance value.[20]
4. Percentage Moisture Content: Formulated patches underwent individual weighing and were placed within a desiccator containing anhydrous calcium chloride, left at room temperature for 24 hours. After this duration, the patches were weighed again, and the percentage moisture content was deduced using a formula.[21]
5. Percentage Moisture Uptake: Weighed patches were subjected to a 24-hour period within a desiccator at room temperature, housing a saturated potassium chloride solution to maintain an 84% relative humidity. Following this, the patches were reweighed, and the percentage moisture uptake was calculated using a formula.[22]
6. Drug Content: A specific area of the film was dissolved within a phosphate buffer solution. Stirring facilitated the dissolution of the transdermal patch, after which the solution was transferred to a volumetric flask. The solution's absorbance was measured, enabling the determination of the drug content.[23]

The meticulous evaluation of these parameters offers a comprehensive understanding of the physicochemical attributes inherent to the transdermal patches under scrutiny.

Bio enhancing Activity:

A) Ex Vivo Permeation Study: Goat skin, procured from the local market and duly treated, formed the basis for ex vivo permeation studies. Employing Franz diffusion cells featuring a 3.14 cm2 effective sectional area and a 15 ml capacity receiver chamber, the treated goat skin was tailored to fit between the receptor and donor compartments of the diffusion cell. The transdermal patch, adorning the membrane, adorned the setup. The donor compartment was harmoniously united with the receptor compartment, cradling phosphate buffer at a pH of 7.4, all while being maintained at a steadfast 37 ± 0.5°C. The symphonic arrangement rested upon a magnetic stirrer, and the receiver compartment solution experienced ceaseless agitation through magnetic beads. Monitoring the elixir's journey, discrete samples were extracted at predefined intervals, promptly replaced with equal volumes of phosphate buffer. The

spectrophotometer's discerning gaze measured the samples' absorbance, culminating in a symphony of data capture.[24,25,26]

B) Everted Gut Sac Model: The goat's small intestine, sourced from local slaughterhouses, embarked on a transformative journey. Immersed within buffer solution, it emerged in two fragments, each spanning 15 cm, their diameter estimated at 0.7 cm. Through a choreography guided by a glass rod, one end surrendered to being tied, while the other embraced eversion, culminating in the formation of a pouch. A trickle of drug-free buffer solution coursed through the cannula, sustaining the vivacity of the tissue through a continuous dance with oxygen facilitated by an oxygen pump. This orchestration played out against the backdrop of a steadfast 37 ± 0.5°C temperature. As the everted transformation unfolded, the mucosal facet unveiled itself, while the serosal counterpart remained concealed. Aligning in symphony, the skin's stratum corneum interface made intimate contact with the transdermal patch's release surface. At predetermined junctures, a glimpse into the sac rendered samples, their drug concentration quantified under the discerning gaze of a spectrophotometer. Thus, a ballet of absorbance against time came to fruition, elucidating the narrative of drug interaction and absorption.[27,28]

Result:

All the meticulously formulated patches demonstrated successful performance in diffusion studies, validated through the reliable methodologies of the Franz diffusion cell method and the everted gut sac model. At predefined intervals, samples were meticulously collected, their essence quantified through spectrophotometric absorbance readings to discern the percentage of drug content released. The culmination of these efforts is eloquently portrayed in the graphical representation of results, where time graces the X-axis and cumulative percentage release or absorbance dances upon the Y-axis.

Amidst this exploration, a revelation emerged - the potential symbiosis of natural bioenhancers, exemplified by cinnamon bark extract, and contemporary pharmaceutical marvels such as Fenofibrate, within the realm of transdermal drug delivery. Through a harmonious fusion, the bioavailability of the drug found avenues of expansion.

The compatibility of drug-extract and drug-polymers harmoniously unveiled itself through the medium of FTIR studies, fostering confidence in the formulation's integrity. Essential physicochemical parameters, encompassing % moisture content, thickness, and weight variation, gracefully resided within the confines of acceptable limits, as detailed in Table 3.

The culmination of the ex vivo permeability studies and everted gut sac investigations is enshrined within Tables 4 and 5, respectively, shedding light on the outcome of these meticulous examinations. Amidst the array of extracts, the ethanolic extract (F5) emerged as a protagonist, boasting a significant increase in both cumulative drug release (CDR) at 75.47±1.14% and drug absorbance at 4.987±0.41%.

Within the confines of these comprehensive studies, a hierarchy of permeation enhancement revealed itself: Franz Diffusion cell studies heralded F5>F3>F4>F2>F6>F1, while the panorama of % drug absorption in the Everted Gut Sac model unfolded as F5>F4>F3>F2>F6>F1. Collectively, these insights unveiled the profound potential of cinnamon bark extract to synergize with modern medicine, thereby elevating bioavailability to levels beyond the grasp of Fenofibrate alone.

Conclusion:

The transdermal drug delivery system presents a solution for prolonged and multidrug treatments, enhancing drug bioavailability by bypassing first-pass metabolism. Fenofibrate, a potent antilipidemic drug, often faces diminished therapeutic efficacy due to this metabolism. Polymers like HPMC and PEG were chosen for patch construction due to their adhesive properties and structural integrity. The use of phosphate buffer with pH 7.4 aided in determining drug solubility and concentration. FTIR analysis ensured compatibility, while formulation F5 emerged as a standout, significantly boosting Fenofibrate's bioavailability compared to other extracts. This study highlights the promise of transdermal delivery and herbal extracts in augmenting drug efficacy.

Tables

Table 1: Composition of patches formulation code.

Formulation Code	Content
F1	Fenofibrate
F2	Fenofibrate + Cinnamon Chloroform Extract
F3	Fenofibrate + Cinnamon Butanolic Extract
F5	Fenofibrate + Cinnamon Methanolic Extract
F5	Fenofibrate + Cinnamon Ethanolic Extract
F6	Fenofibrate + Cinnamon Aqueous Extract
F7	Fenofibrate + HPMC+PG+ PEG 400+ Glycerine+ citric Acid

Table 2: Optimized formulation design for cinnamon bark extracts with Fenofibrate

	Formulation Codes					
Ingredients	F1	F2	F3	F4	F5	F6
Fenofibrate	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	-----	-----	50 mg	-----	-----	-----
Methanolic Extract	-----	-----	-----	50 mg	-----	-----
Ethanolic Extract	-----	-----	-----	-----	50 mg	-----
Aqueous Extract	-----	-----	-----	-----	-----	50 mg

Table: 3 Formulation Characterization for Thickness, Weight Uniformity, Moisture, and Drug Content

	Formulation Code					
Parameters	F1	F2	F3	F4	F5	F6
Thickness (mm)	0.220±0.007	0.218±0.009	0.214±0.006	0.234±0.003	0.220±0.007	0.228±0.103
Weight uniformity (gm)	0.147±0.015	0.176±0.006	0.170±0.005	0.177±0.003	0.147±0.015	0.172±0.033
% Moisture uptake	6.220±1.009	7.224±0.009	6.321±1.09	6.169±2.01	6.220±1.009	6.502±1.29
% Moisture content	4.025±0.114	4.12±0.926	4.55±0.636	4.434±0.207	4.025±0.114	6.045±0.214
% Drug content	84.80±0.071	72.84±0.084	74.89±0.34	82.74±0.02	84.80±0.071	80.92±0.45
Folding Endurance	20±2.63	22±2.80	19±302	25±3.33	20±2.63	23±3.39

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

Table 4: Release kinetic of formulation from studies Franz Diffusion cell

	Formulation Code					
Time in hr	F1	F2	F3	F4	F5	F6
0.5	2.12±0.11	2.40±0.13	3.22±0.78	5.82±0.55	9.10±0.45	2.42±0.23
1.0	4.19 ±0.33	4.78±0.43	5.24±0.77	7.28±0.86	10.55±0.78	4.39±1.04
1.5	6.06±1.01	7.14±0.29	7.12±0.23	9.19±0.47	11.12±0.56	6.45±1.04
2.0	7.90±1.13	8.76±0.89	10.53±0.34	12.53±0.48	17.24±0.25	8.87±1.98
2.5	9.01±1.12	9.89±0.19	14.25±0.44	17.23±0.34	22.19±0.13	9.87±0.59
3.0	10.06±1.20	12.67±0.19	20.77±0.60	22.43±0.67	26.21±0.41	11.71±1.25
4.0	13.22±1.37	14.75±0.87	26.17±0.17	30.09±1.12	34.11±0.90	13.98±1.74
5.0	24.03±0.90	24.88±0.38	31.32±0.23	36.23±1.12	41.74±1.12	25.11±1.04
6.0	34.90±1.55	36.55±0.74	40.09±0.98	45.09±1.07	58.10±1.25	35.98±1.12
8.0	53.11±1.11	54.45±0.98	60.90±0.87	59.90±1.23	75.47±1.14	53.74±1.18

Table 5: Gut sac model of formulation

	Formulation Code					
Time in Min.	F1	F2	F3	F4	F5	F6
10	0.510±0.24	0.590±0.41	0.601±0.11	0.611±0.14	0.745±0.23	0.552±0.71
20	0.978±0.12	1.121±0.21	1.171±0.19	1.245±0.17	1.425±0.45	0.987±0.84
30	1.124±0.85	1.277±0.39	1.348±0.22	1.554±0.12	1.997±0.14	1.235±0.14
60	1.010±0.78	1.782±0.12	1.975±0.14	2.810±0.32	3.224±0.78	1.611±0.19
90	1.752±0.17	2.273±0.17	2.694±0.52	3.481±0.25	3.985±0.48	1.851±0.29
120	2.001±0.41	2.643±0.56	3.217±0.71	4.101±0.21	4.987±0.41	2.114±0.72

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

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29