Comparative Evaluation of Topical Pentoxifylline Cream and Zinc Oxide Nanoparticle-Loaded Pentoxifylline Cream for The Management of Intermittent Claudication

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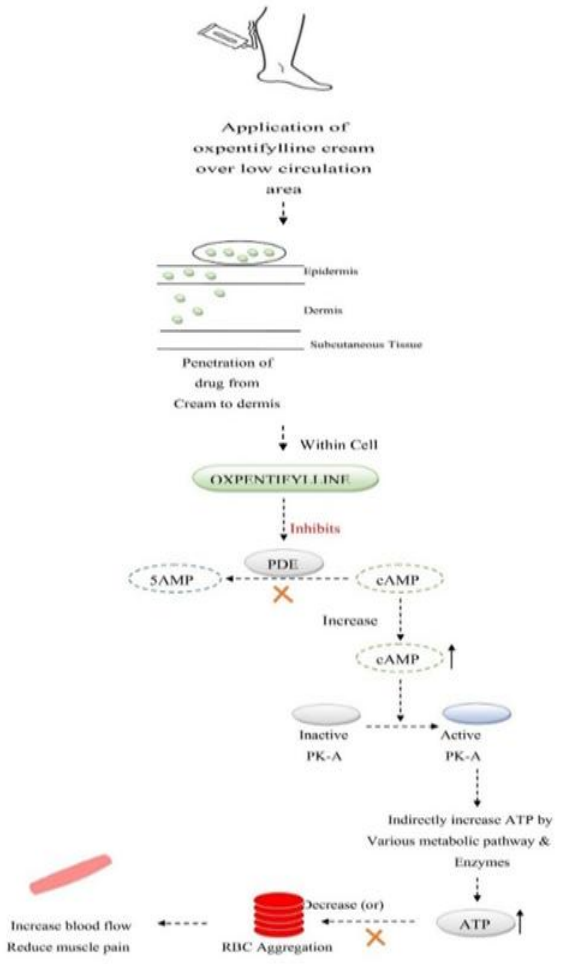
***Abstract*—Intermittent claudication is a peripheral arterial disease characterized by reduced blood flow to the lower limbs, resulting in pain and discomfort during physical activity. The present study aimed to formulate and evaluate topical Pentoxifylline cream and zinc oxide nanoparticle-loaded Pentoxifylline cream for improved topical drug delivery and sustained release. Zinc oxide nanoparticles were prepared by the surfactant-assisted sol-gel method and characterized using particle size and zeta potential analysis [2,14]. Six different cream formulations containing various polymers such as HPMC, Chitosan, and Eudragit were prepared and evaluated for physicochemical parameters including pH, viscosity, spreadability, drug content, and in-vitro drug release studies [11,13]. Among all formulations, F4 containing HPMC and zinc oxide nanoparticles showed optimum pH, better spreadability, acceptable viscosity, highest drug content (98.00%), and superior sustained drug release (85%) over an 8-hour period. FTIR studies confirmed the compatibility between Pentoxifylline and excipients without significant drug–excipient interactions [14]. The study demonstrated that zinc oxide nanoparticle-loaded formulations enhanced the controlled release behaviour and topical delivery Pentoxifylline. Therefore, nanoparticle-based topical formulations may provide a promising approach for the effective management of intermittent claudication with improved patient compliance and reduced systemic side effects.**

***Index Terms*—Intermittent claudication, topical cream, Pentoxifylline, drug delivery, zinc oxide nanoparticles.**

I. INTRODUCTION

Peripheral Arterial Disease (PAD) is a cardiovascular ailment defined by obstruction or narrowing of the peripheral arteries leading to reduced blood circulation to the legs. Primarily occurring due to atherosclerosis, PAD affects many people around the world, particularly among the older population. Intermittent Claudication is one of the common symptoms experienced by individuals suffering from PAD; it involves pain or muscle cramps in the legs when walking or climbing upstairs, relieved by resting. Oxpentifylline (Pentoxifylline), a methylxanthine derivative, is commonly employed in treating intermittent claudication. The drug enhances erythrocyte flexibility and reduces blood viscosity, thereby improving microvascular blood flow and tissue oxygenation [4,5]. These effects are associated with symptom reduction and increased walking distance in PAD patients. However, traditional systemic administration may result in limited drug concentration at the target site and potential systemic adverse effects, necessitating alternative drug delivery routes. The potential of topical drug delivery systems to produce prolonged drug release [6–8], improve patient compliance, lower systemic adverse effects, and provide localized therapeutic effects has been thoroughly studied. Topical formulations can be made even more effective by using medication delivery technologies based on nanotechnology. Nanoparticles offer advantages such as improved skin permeation [1,3] controlled drug release, enhanced drug stability, and increased bioavailability. Zinc oxide (ZnO) nanoparticles, among various nanomaterials studied for pharmaceutical applications, have garnered significant attention [1,2,14], due to their excellent biocompatibility, chemical stability, large surface area, and ability to penetrate the skin. Topical formulations have extensively explored ZnO nanoparticles as drug carriers due to their enhanced drug delivery [3,8] and sustained therapeutic effects. They are promising candidates for improving the efficacy of topical

vascular therapeutics due to their unique physicochemical properties. Although Pentoxifylline has therapeutic potential and ZnO nanoparticles offer beneficial effects, few studies have evaluated the efficacy of ZnO nanoparticle-loaded Pentoxifylline cream for treating intermittent claudication. This study aimed to develop and evaluate conventional Pentoxifylline cream and Zinc Oxide nanoparticle-loaded Pentoxifylline cream, comparing their physicochemical properties, drug content, spread ability, viscosity, pH, and in vitro drug release profiles to identify the most effective formulation for the topical management of intermittent claudication.



II. MATERIALS AND METHODS

Materials/Equipment:

Chitosan (Modern Scientific Laboratories) Hydroxypropyl Methylcellulose (HPMC) (Yarrow Chem Pvt. Ltd.) Eudragit (Yarrow Chem Pvt. Ltd.) Carbopol 940 (Loba Chemical Pvt. Ltd.) Cetostearyl Alcohol (Modern Scientific Laboratories) Stearic Acid (Modern Scientific Laboratories) Glycerin (Modern Scientific Laboratories) Propylene Glycol (Loba Chemical Pvt. Ltd.) Tween 80 (Modern Scientific Laboratories) Span 80 (Modern Scientific Laboratories) Dimethyl Sulfoxide - DMSO (Modern Scientific Laboratories) Triethanolamine - TEA (Loba Chemical Pvt. Ltd.) Methylparaben (Modern Scientific Laboratories) Propylparaben (Modern Scientific Laboratories) Distilled Water (Modern Scientific Laboratories)

Equipment:

Balance, weighing (Shimadzu) Magnetic Stirrer Heating Plate (Hover Labs). pH Meter (Elico pH Meter). UV-Vis Spectrometer (Shimadzu UV-1800) Fourier Transform – Infrared Spectroscopy (Shimadzu). Brookfield Viscometer (Shimadzu). Probe Sonicator (Microsil, India). Roche India Muffle Furnace.

Method

Preparation of Zinc-Oxide Nanoparticles (by solgel method)

To prepare the solution, 3.66 g of zinc acetate dihydrate was dissolved in 100 mL of ethanol and stirred for 1 hour at 50 °C. In a separate procedure, 0.5 g of Polyvinyl Alcohol (PVA) was mixed with 35 mL of cold water and gently heated until a homogeneous solution was achieved. Additionally, 5.90 g of sodium hydroxide granules were dissolved in ethanol and stirred for 1 h at 50 °C. Upon completion of all solutions, the PVA solution was combined with the zinc acetate solution, and the sodium hydroxide solution was gradually introduced to facilitate the formation of zinc hydroxide [2,14], resulting in a white gel precipitate. The mixture was subsequently dried in a hot air oven at 90 °C for 2 hours. Following this, the dried powder underwent calcination at 400 °C for 2 hours to yield zinc oxide. The size of the synthesized ZnO nanoparticles was further reduced using a probe sonicator.

Preparation of Pentoxifylline Cream

The aqueous phase was formulated by dissolving 1.5 g of HPMC in 20 mL of distilled water, followed by stirring at a temperature range of 50-60°C. Subsequently, 0.5 g of Carbopol 940 was incorporated, and the mixture was stirred until complete hydration

was achieved. The pH was then adjusted to a range of 5.5-6.5 using Triethanolamine (TEA).

The formulation process involves several steps. Initially, Methylparaben (0.1 g) and Propylparaben (0.05 g) are utilized. For the preparation of the oil phase, 3 g of Cetostearyl Alcohol and 2.5 g of Stearic Acid are accurately weighed and melted at 70 °C. Subsequently, 4 g of Glycerin and 3 g of Propylene Glycol are incorporated to ensure thorough mixing. This procedure is conducted concurrently. 400 mg of Pentoxifylline was dissolved in 2 2g (DMSO) to enhance absorption [5]. A homogeneous dispersion is achieved using a high shear homogenizer by gradually adding the oil phase to the aqueous phase while agitating at 2000-3000 rpm. The emulsion is then allowed to stabilize at room temperature with gentle stirring, and pH adjustments are performed as necessary to maintain a pH range of 5.5-6.5. The final cream is stored in a secure container at room temperature.

Pentoxifylline Cream with Zinc Oxide

Initially, a uniform dispersion was achieved by dispersing 5 g of Zinc Oxide Nanoparticles in 10 mL of distilled water using a probe sonicator. To prevent nanoparticle aggregation, 1.5 g of Tween 80 and 1.5 g of Span 80 were incorporated. The aqueous phase was prepared by dissolving 1.5 g of HPMC in 20 mL of distilled water under agitation at a temperature of 50-60 °C. Subsequently, 0.5 g of Carbopol 940 was added and stirred until fully hydrated. The pH was adjusted to a range of 5.5 to 6.5 using triethanolamine (TEA). Methylparaben (0.1 g) and Propylparaben (0.05 g) were included as preservatives. Concurrently, the oil phase was prepared by melting 3 g of Cetostearyl Alcohol and 2.5 g of Stearic Acid at 70 °C. Following this, 4 g of Glycerin and 3 g of Propylene Glycol were added and mixed thoroughly. The active ingredient, 400 mg of Pentoxifylline, was dissolved in 2 g of Dimethyl Sulfoxide (DMSO) to enhance absorption. Subsequently, the Zinc Oxide Nanoparticle suspension was gradually introduced into the oil phase. The oil phase was then added dropwise to the aqueous phase while stirring at 2000–3000 rpm. A uniform dispersion was achieved using a high shear homogenizer. The mixture was cooled to room temperature with gentle stirring, and the pH was adjusted to 5.5-6.5 if necessary. The resulting cream was stored in a closed container at ambient temperature.

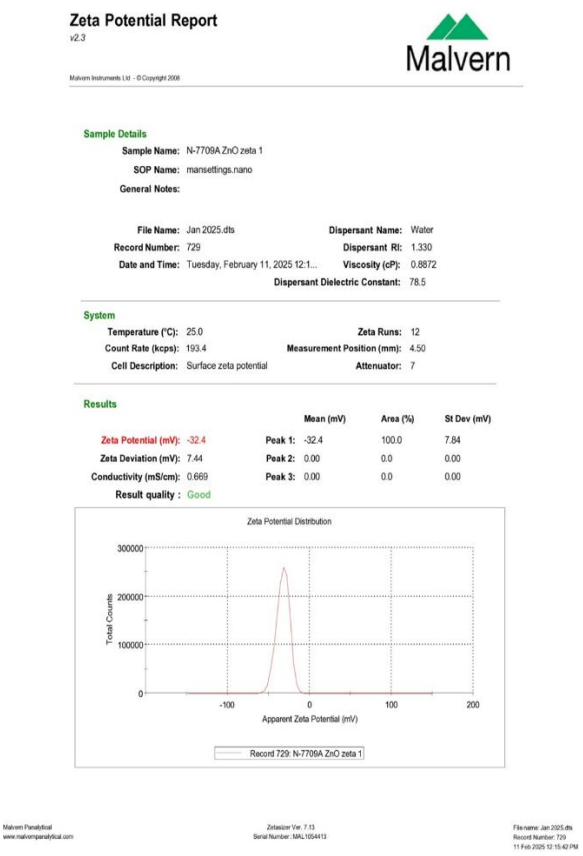
TABLE 1: FORMULATION OF PENTOXIFYLLINE CREAM

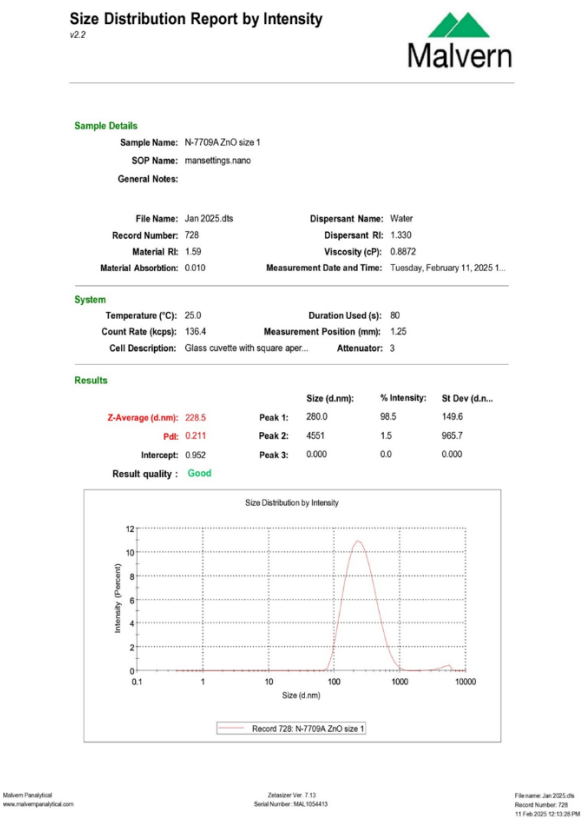
Ingredient	F1	F2	F3	F4	F5	F6
Pentoxifylline (mg)	400	400	400	400	400	400
Zinc Oxide Nanoparticles (g)	–	–	–	5	5	5
Chitosan (g)	–	1.5	–	–	1.5	–
HPMC (Hydroxypropyl Methylcellulose) (g)	1.5	–	–	1.5	–	–
Eudragit (g)	–	–	1.5	–	–	1.5
Carbopol 940 (g)	0.5	0.5	0.5	0.5	0.5	0.5
Cetostearyl Alcohol (g)	3	3	3	3	3	3
Stearic Acid (g)	2.5	2.5	2.5	2.5	2.5	2.5
Glycerin (g)	4	4	4	4	4	4
Propylene Glycol (g)	3	3	3	3	3	3
Tween 80 (g)	1.5	1.5	1.5	1.5	1.5	1.5
Span 80 (g)	1.5	1.5	1.5	1.5	1.5	1.5
Dimethyl Sulfoxide (DMSO) (g)	2	2	2	2	2	2
Triethanolamine (TEA) (pH 5.5–6.5) (g)	q.s	q.s	q.s	q.s	q.s	q.s
Methylparaben (g)	0.1	0.1	0.1	0.1	0.1	0.1
Propylparaben (g)	0.05	0.05	0.05	0.05	0.05	0.05
Distilled Water (mL)	Up to 100	Up to 100	Up to 100	Up to 100	Up to 100	Up to 100

TABLE 2: ZnO CHARACTERIZATION [14,15]

CHARACTERIZATION OF ZINC OXIDE NANOPARTICLES:

Property	Zinc Oxide Nanoparticle with Surfactant	Zinc Oxide Nanoparticle without Surfactant
Particle Size	228 nm	835 nm
Zeta Potential	-32.4 mV	-34 mV
Poly-dispersity Index	0.21	0.533
SEM	Rod shape	Rod shape





III. EVALUATION:

Fourier Transform Infrared Spectroscopy (FTIR):

FTIR analysis was carried out to study the compatibility between Pentoxifylline, zinc oxide nanoparticles, and the excipients used in the formulation. The FTIR spectra of pure drug, zinc oxide nanoparticles, and the optimized formulation were recorded using a Shimadzu FTIR spectrophotometer. The spectra were compared to identify any changes in the characteristic peaks of the drug. The characteristic peaks of Pentoxifylline were retained in the optimized formulation, indicating good compatibility between the drug and the excipients used. [14,15]

pH determination:

The formulations were weighed out to approximately 20 g each, transferred into a beaker and the pH was measured with a digital pH meter. The pH of the formulated preparations was measured using a calibrated digital pH meter.

Viscosity:

Viscosity was determined using a Brookfield viscometer at 25°C (Brookfield DV-II+Pro-10). The Brookfield viscometer's sample cup was filled with about 25 g of cream. Viscosity was measured at different rates of rotation and a rheogram was plotted to correlate the shear rate to shear stress.

Evaluation of spreadability:

Spreadability of the semisolid formulations is important parameter. The spread ability of the formulation is also very important for the therapeutic efficacy of the formulation. The spread ability of the cream was determined by placing 5 g of the cream in a circle of one-centimetre diameter at the centre of the glass plate. It was estimated that one kilogram of weight was held for five minutes on the top glass plate. The change in diameter was measured and recorded after 5 min.

Determination of Drug Content [11]:

Take 1 g of cream and dissolve it in a suitable solvent. Filter the solution to obtain a clear liquid. Its absorbance is determined using a UV spectrophotometer. A graph of a typical drug is plotted in the same solvent. The concentration and drug content can be determined by substituting the absorbance value into the standard plot equation.

In-vitro Drug Diffusion Study [13,16]:

The prepared cream was subjected to in-vitro diffusion studies using the above method. The preparation of the donor compartment was done by using an open-ended tube, one end of which was sealed with a gelatin membrane pre-soaked in phosphate buffer. 10ml of water was added in the donor compartment and 300mg of prepared cream was added. Subsequently, the cream was introduced into the container holding 100 ml of water and mixed using a magnetic stirrer set to 50 rpm. The drug release was studied by taking out 1 ml samples from the recipient compartment and replacing with the same volume of fresh medium. Samples were collected at various time intervals, specifically at 30 min, 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 7 h, and 8 h. The drug content was subsequently determined using a UV spectrophotometer set at 275 nm, following appropriate dilutions.

IV. RESULTS AND DISCUSSION

FTIR Analysis

The FTIR spectra of pure Pentoxifylline, zinc oxide nanoparticles, and the optimized formulation showed the characteristic absorption peaks of the drug and ZnO nanoparticles. The ZnO stretching vibration was observed below 600 cm^{-1}, while the characteristic peaks of Pentoxifylline were retained in the optimized formulation. No significant disappearance or shift of the characteristic peaks was observed, indicating that there was no interaction between Pentoxifylline and the excipients. These findings confirm the compatibility of the drug with zinc oxide nanoparticles and the selected polymers used in the formulation [14,15]as shown in the Figure2.

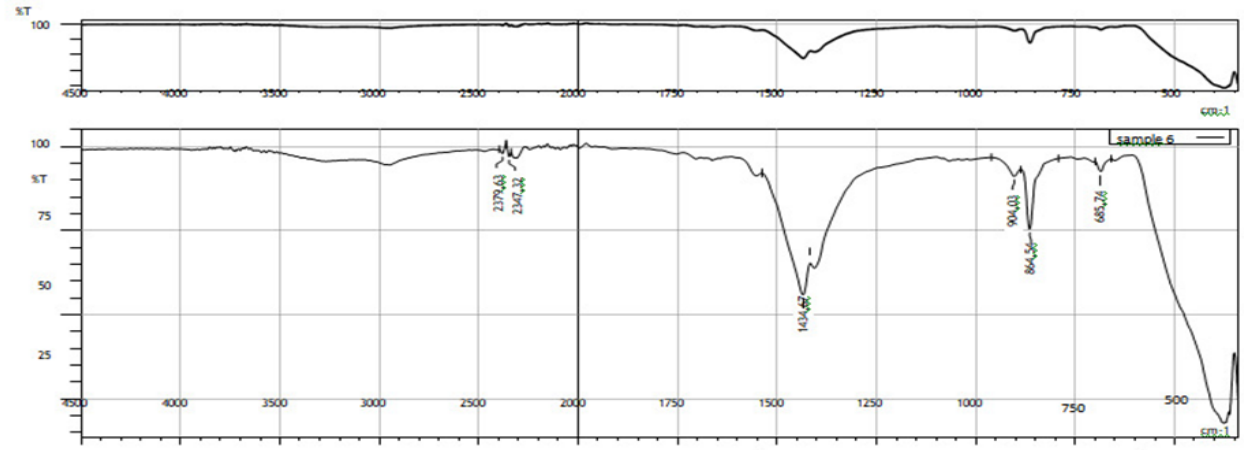


Figure1: FTIR Spectrum of Pentoxifylline

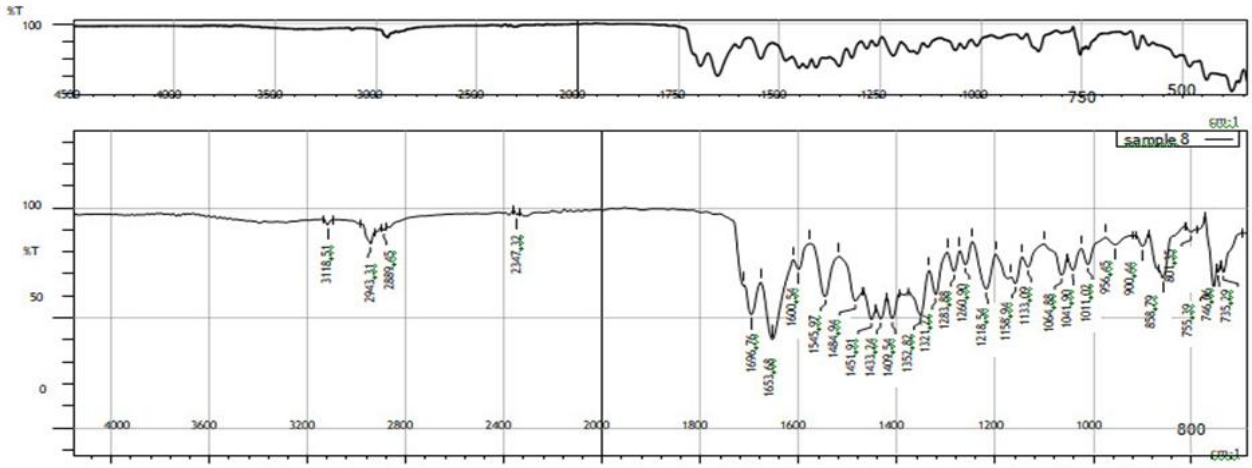


Figure2: FTIR Spectrum of Pentoxifylline + Zinc Oxide

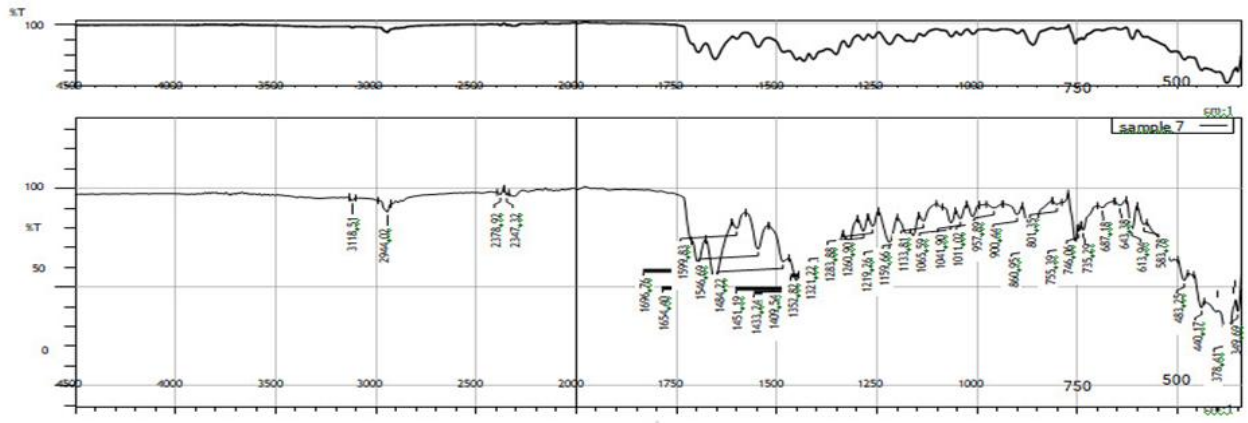


Figure3: FTIR Spectrum of Pentoxifylline + Zinc Oxide + Chitosan

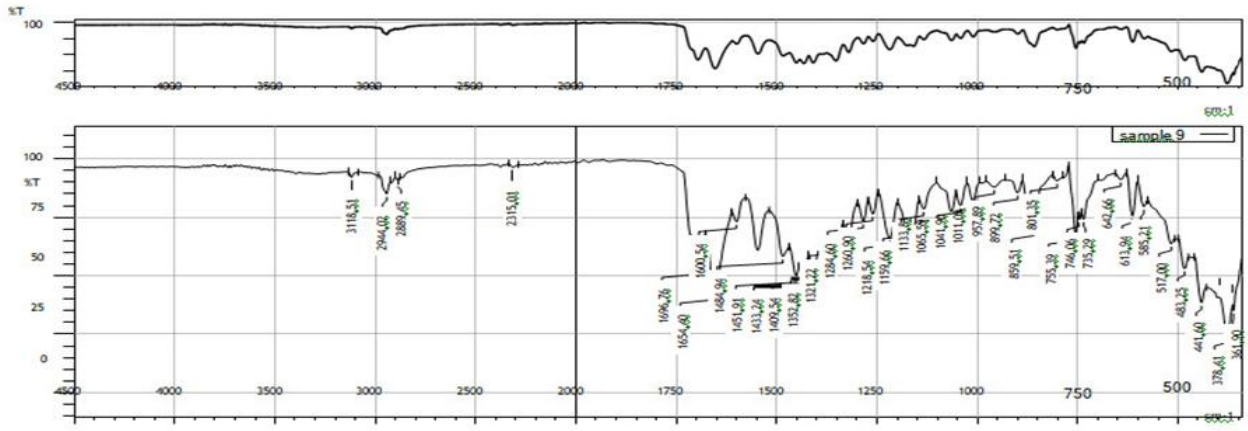


Figure4: FTIR Spectrum of Pentoxifylline + Zinc Oxide + HPMC

Viscosity:

Formulation F5 and F6 exhibited higher viscosity values of 3,200 mPa·s compared to other formulations.

pH:

The pH of the 6 formulations was measured with and without zinc oxide nanoparticles. The optimum pH of formulation 4 was 7.

Spreadability:

The spreadability of the formulations was evaluated to determine their ease of application on the skin. Among all formulations, F4 showed the highest spreadability value of 6 cm^2/s, indicating better consistency and ease of spreading. In contrast, formulation F5 (Chitosan + ZnO nanoparticles) exhibited the lowest spreadability value of 4.5 cm^2/s due to its higher viscosity. The incorporation of zinc oxide nanoparticles influenced the spreadability of the formulations by altering their rheological properties. An optimum spreadability is important for uniform topical application and effective drug release.

TABLE 3: RESULT OF CREAM EVALUATION

Formulation	pH Value	Spreadability (cm^2/s)	Viscosity (mPa·s)
F1: Pentoxifylline + HPMC	6.5	5.0	2,000
F2: Pentoxifylline + Chitosan	6.0	5.5	2,800
F3: Pentoxifylline + Eudragit	6.5	5.8	2,500
F4 Pentoxifylline + HPMC + ZnO NPs	7.0	6.0	2,800
F5: Pentoxifylline + Chitosan + ZnO NPs	6.5	4.5	3,200
F6: Pentoxifylline + Eudragit + ZnO NPs	7.0	5.2	3,200

Quantification of Drugs Content

To calculate the 1 % of drug content from the standard plot equation obtained from your UV spectrophotometric calibration curve. A typical example is Beer's Law: $A = \varepsilon \cdot c \cdot l$

Let us suppose now that the path length (l) is 1cm.

$A = 0.010 \times C$ Where A = absorbance and C = concentration in µg/mL.

TABLE 4: DRUG CONTENT DETERMINATION [18]

Formulation	Absorbance (A)	Calculated Conc. (µg/mL)	% Drug Content
F1	0.910	91.0	91.00%
F2	0.945	94.5	94.50%
F3	0.965	96.5	96.50%
F4	0.980	98.0	98.00%
F5	0.955	95.5	95.50%
F6	0.970	97.0	97.00%

In-vitro drug release studies:

In-vitro drug release studies were performed to evaluate the release profile of Pentoxifylline from six different cream formulations over an 8h period [13]. The study mainly focused on assessing the sustained release characteristics of the prepared formulation

TABLE 5: DRUG RELEASE STUDY OF PENTOXIFYLLINE CREAM

Time (h)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)
0.5	5	4	6	3	5	4
1	10	9	12	8	10	9
2	18	15	20	13	17	14
3	30	27	32	25	28	26
4	40	38	45	35	40	38
5	50	48	55	45	50	47
6	60	58	65	55	60	57
7	70	68	75	65	70	67
8	80	78	75	85	80	77

V. CONCLUSION

The zinc oxide nanoparticle-loaded Pentoxifylline cream formulations exhibited better physicochemical properties, sustained drug release, and improved stability compared to conventional formulations [1,3,13]. Among all formulations, F4 showed optimum pH, viscosity, spreadability, and highest drug content, indicating superior topical delivery characteristics. The incorporation of ZnO nanoparticles enhanced the controlled release behaviour and therapeutic potential of Pentoxifylline cream for intermittent claudication [1,14]. Topical nanoparticle-based formulations may improve patient compliance and reduce systemic side effects associated with oral therapy [6,8].

Conflict of Interest

The authors declare no conflict of interest.

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