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Formulation, Characterization And Evaluation Of Topical Biodegradable Film Loaded With Levofloxacin Solid-Lipid Nano Carriers

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Abstract: The major goal of this research was to develop a levofloxacin loaded solid lipid nanoparticles and formulate the topical biodegradable film of that nanoparticles and assess its prospects as a topical drug delivery system. The films were created utilising a solvent casting method using varied quantities of ethyl cellulose, hydroxypropyl methylcellulose K4M, hydroxypropyl methylcellulose, eudragit L-100, and Chitosan coalescence, as well as dibutyl phthalate as a plasticizer. The films were assessed for weight variation, thickness, percent moisture absorption, percentage moisture loss, folding endurance, percentage swelling index, percentage elongation, as well as an in vitro drug release study and an ex-vivo permeation investigation. The F5 formulation was discovered to be superior in terms of film. As a result, it was investigated as an optimum formulation. When compared to another formulation, the in-vitro drug release analysis shows that the F5 formulation had the highest drug release (91.34 percent) at the end of 8 hours.

Keywords: Biodegradable film, solvent casting, Levofloxacin, solid-lipid nanoparticles, and so on.

INTRODUCTION

The oral cavity is a suitable place for medication delivery because of its ease of administration and the delay of possible drug degradation through the gastrointestinal tract and first-pass metabolism. During colonisation by a wide variety of microorganisms, the mouth cavity provides a diverse environment [1]. Skin is the substantial organ of human body, purpose as a crucial obstruction assist among physiological, astounding and preventive potential. Delinquent to its revelation to the superficial environment skin is exposed to a variation of utmost element that outcome in several kinds of skin destruction and injury [2].

Surface charges of nanoparticles possess incredible effect on interactivity among cells and additionally on their intake. Definitely charged nanoparticles appear to permit aerial area of allocation seemingly

as a outcome of the ionic interactivity accepted all over positively charged particles and negatively charged laminate [3].

Solid lipid nanoparticles (SLNs) possess enticed enhancing recognition throughout current years in topical drug delivery. These are nanospheres or nanoplatelets made up of a solid lipid matrix made up of solid lipids that are solid at room and body temperatures, with a mean particle size ranging from 50 to 1000 nanometers. Solid lipid nanoparticles have various properties that make them useful for topical drug delivery since they are made of physiological and biodegradable lipids that have been shown to be safe during topical administration and to have less cytotoxicity [4-6].

The portable size of soli-lipid nanoparticles secure near proximity to the stratum corneum and may improve bioadhesive and occlusive properties, both of that are required in topical implementation. Because solid-lipid nanoparticles improved the deliver and perforation of vital pharmacological drugs, especially lipophilic compounds, the concentration of these lipophilic chemicals in the skin increased. Because of their solid lipid grid, these carriers can also deliver a regulated release. Solid-lipid nanoparticles have occlusive qualities that minimise transdermal water loss as a result of film development on the skin. Furthermore, to achieve a semisolid consistency suitable for topical treatment, solid lipid nanoparticle dispersion can be mixed into dermal carriers such as gels and hydrogels [7].

Levofloxacin is a third-generation fluoroquinolone broad range antimicrobial factor manifest superior action opposed to pathogens such an ultimate usually accountable during severe bacterial meningitis and moreover further sporadic factor of central nervous system (CNS) infections like Streptococcus agalactiae [8]. Levofloxacin is promptly and nearly entirely engrossed behind oral doses among apex plasma concentrations happening inside 1 to 2 hours and elimination half-life of 6 to 8 hours. It is broadly dispensed towards body tissues involving the bronchial mucosa and lungs however penetration towards cerebrospinal fluid is moderately poor.

Levofloxacin, antibacterial activity of a third-generation fluoroquinolone against gramme positive and gramme negative bacteria is wide [9]. The majority of fluoroquinolone derivatives are used to treat infections in the urinary system, respiratory tract, skin, and soft tissues. After oral treatment, levofloxacin hemihydrate is promptly and completely absorbed. After a single or repeated dosages administered orally or intravenously, levofloxacin has a terminal plasma elimination half-life of approximately 6 to 8 hours [10]. It requires repeated dosages to maintain therapeutic activity because to its short biological half-life and constantly variable pharmacological concentrations in blood. As a result, using Levofloxacin-loaded nanoparticles as a controlled-release drug delivery strategy to achieve longer blood circulation than the half-life, improve bioavailability, and reduce dose frequency could be a good idea [11].

Considering the present scenario, Levofloxacin was select due to a broad-spectrum fluoroquinolone antibiotic among vigorous bactericidal action opposed to a wide compass of medicinally suitable pathogens such is generally utilized during the therapy of a diversity of bacterial infections [12]. Although, Levofloxacin is correlated among aqueous solubility and flexible bioavailability, that assembled the delineation and dosage of pharmaceutical preparation onerous [13]. The effectiveness of oral Levofloxacin preparation is disposed to two time a day administration during successive days or weeks among conventional and immediate-release tablets. Furthermore, Levofloxacin administration over a lengthy period of time may result in unfavourable effects on the neurological and gastrointestinal systems [14-16].

Solid lipid nanoparticle was evolved in the early '90s as potential substitute drug delivery systems among enhanced characteristics and numerous benefits contrasts to the traditional colloidal carriers [17]. Solid lipid nanoparticles provide distinctive properties and various benefits above another traditional drug porter are superior biocompatibility, less cytotoxicity, drug targeting, regulating drug release and the probability of fabrication on an enormous industrial scale [18,19]. Although, the solid lipid nanoparticles are examining a glamorous nanocarrier.

Pruritus (additionally mention as itch) is a disagreeable sensation differing in an intensity diverge from lenient to crucify, that desire the person to engrave the skin to momentarily reduced pruritus. It is the most common symptom in skin illnesses, with a wide range of causes [20].

MATERIAL AND METHOD

Material: Levofloxacin, Stearic acid, Tween 80, Poloxamer 188, Ethylcellulose, hydroxypropyl methylcellulose, eudragit L100 and chitosan etc. The manufacturer in the college provided the laboratory supplies and chemicals used in the formulation and development study.

Method

Drug and Excipient compatibility study

Fourier Transform Infrared Spectroscopy (FTIR)

The physical mixture of drug and excipients were used for similarity experiment. FTIR spectroscopy was used to conduct a compatibility evaluation. The samples of pure drug and excipients and physical brew of drug and excipients were scan with solid state KBr dispersion medium and the scanning range remain from 4000 to 400 cm−1.

Differential Scanning Calorimetry (DSC)

At a heating rate of 10°C/min, a differential scanning calorimeter (Mettler Toledo) was utilised to measure the thermal behaviour of a pure drug, optimised SLN batch. The experiments were conducted at temperatures ranging from 30 to 400 degrees Celsius in nitrogen atmospheres.

Method of Preparation of Solid lipid nanoparticles

Selection of lipid, surfactant and co-surfactant

Based on the values in Table 1 for solubility. As a lipid, surfactant, and co-surfactant, stearic acid, Tween 80, and poloxamer 188 were used.

The microemulsion process was used to make solid lipid nanoparticles.

1. Liquify the lipid above its melting point of 10 °C to make the oil phase.
2. Levofloxacin should be dissolved in the melting lipid.
3. Mix the surfactant, co-surfactant, and water to make the aqueous phase.
4. Maintain the temperature of both phases at or above the lipid's melting point, which is 80°C.
5. Use a vortex to mix the oil and aqueous phases to form a microemulsion at this temperature.
6. Dilute this warm microemulsion in cold water (2-3°C) while mechanically stirring to make SLN dispersion.

Table 1: Formulation Table of different batches of SLNs

Sr No.	Ingredients (g)	Batches		
		F1	F2	F3
1	Levofloxacin (Drug)	0.375	0.375	0.375
2	Stearic acid (Lipid)	0.500	0.750	1.00
3	Tween 80 (Surfactant)	0.500	0.500	0.500
4	Poloxamer 188 (Co-surfactant)	0.100	0.100	0.100

Preparation of Levofloxacin loaded solid-lipid nanoparticles film

Solvent casting was used to make levofloxacin-loaded solid-lipid nanoparticle films. During the casting of the films, glass moulds were employed. Ethylcellulose, hydroxypropyl methylcellulose, eudragit L100, and chitosan were utilised in various ratios. They were dissolved in a beaker with a magnetic stirrer in a mixture of chloroform and ethanol, as well as dibutyl phthalate as a plasticizer, to obtain varied quantities of polymeric solution. A spatula was utilized to grab the required amount of levofloxacin-loaded solid lipid nanoparticles and dissolve them in enough water. Mercury was carefully stream in the form of a layer towards clean, labelled glass moulds coated in aluminium foil. Behind absolute blending, the solution was flow towards these moulds and set on a horizontal plane. By upending a container, the solvent was allowed to slowly evaporate.

Evaluation parameters of Film

The preliminary evaluation experiments were performed on levofloxacin-loaded solid-lipid nanoparticle films. Films with flaws, such as entrapped air or differences in thickness, weight, or content consistency, were ruled out of future research. The thickness, weight uniformity, and % moisture loss of the manufactured Levofloxacin loaded solid-lipid nanoparticles films were measured, as well as folding endurance, surface pH, swelling index, and drug content uniformity.

Assessment of percentage moisture loss

The films were weighed precisely and then held in desiccators for three days before being reweighed. The formula was used to calculate the % moisture loss.

Moisture loss =

(Initial weight – final weight/initial weight) ×100

Thickness uniformity

The thickness of the film was measured with a screw gauge at various locations on the film, and the average was calculated.

Folding endurance

The folding endurance value for levofloxacin-loaded solid lipid nanoparticle films was greater than 200, indicating that the formulations had absolute film characteristics.

Uniformity of weight

Levofloxacin-loaded solid-lipid nanoparticle film sections (with a diameter of 74 mm) were obtained from various regions of the film. Every film's weight dissimilarity was determined.

Drug content uniformity

Individual films from the batch were taken and dissolved in 5 ml of pH 6.6 phosphate buffer in a beaker to determine the drug concentration of the produced film. The distribution was kept in a dark place overnight. On the dispersion, filtering was done. 0.1 ml of the filtered solution was diluted to 10 ml with pH 6.6 phosphate buffer in a 10 ml volumetric flask. Three readings were taken with a UV visible spectrophotometer set to 288 nm to determine medication concentrations.

Tensile strength

The designed apparatus determined the tensile strength. A sharp blade was used to cut a little film (744 mm) on a glass plate. A horizontal wooden platform with a fixed scale and attachments for two clips that held periodontal film under evaluation comprised the apparatus. One clip was fixed and the other could be moved. One end of the pulley was attached to a movable clip, while the other end was suspended with weights. The wooden platform was built in such a way that it did not dislocate throughout the test. The film was pulled through a pulley system to evaluate elongation and tensile strength. To boost the pulling force, weights were gradually placed to the pan.

Surface pH

The pH of the surfaces of the formulations was determined. All of the formulations were determined to have a pH of between 6 and 7. This means that the formed films will not alter the pH of the gingival fluid in the periodontal pocket, causing the gums to irritate.

Swelling index

The swelling index of drug-loaded films was calculated by placing the film (area 744 mm) in a Petri dish containing around 10.0 ml of phosphate buffer pH 6.6, calculating the film's initial weight before placing it in the Petri dish, and weighing the film at predetermined time intervals to determine the increase in weight due to swelling.

In vitro drug release studies

Because the pH of gingival fluid ranges between 6.5 and 6.8, the phosphate buffer pH 6.6 was used as the simulated gingival fluid. To assess drug release in vitro, a keshary–Chien (K-C) diffusion cell was used. Phosphate buffer pH 6.6 was used as a dissolving medium and as a receptor solution. The diffusion cell was 10 mL in size. The prepared film (74 mm) was firmly pushed into the core of the semipermeable laminate, which was then placed in the donor compartment. The donor compartment was then placed so that the donor compartment's laminate surface just touched the receptor fluid surface. The complete collection was placed on a hot plate magnetic stirrer, and the solution in the receptor compartment was agitated at 100 rpm with magnetic beads at 371°C. To prolong the sink condition, 1 ml of receptor fluid was withdrawn at regular intervals and quickly replaced in the same volume of fresh dissolving media. The samples were analysed at 288 nm using an ultraviolet (UV) visual spectrophotometer after suitable dilution with diffusion fluids.

RESULT AND DISCUSSION

To ensure the identification, purity, and stability of pharmaceuticals for formulation, as well as to establish a pharmacological profile, preformulation investigations were conducted.
The UV visible spectroscopic technique was used to identify levofloxacin. The highest absorption of levofloxacin was established at 288 nanometers, appropriately. The standard curves of levofloxacin were produced in pH 6.6 phosphate buffer.

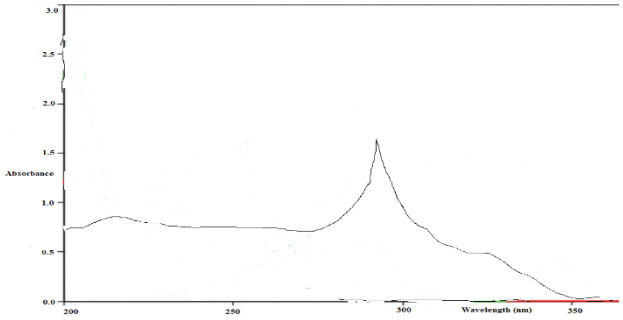

Fig. 1: UV spectra of Levofloxacin

Drug-excipients interaction study

The research of drug-excipient interactions is critical for the release of a medication from a formulation. The pure Levofloxacin and its mixture with eudragit L100 and chitosan were assorted individually in IR grade KBr and scanned with an FTIR instrument across a range of 400–4500 cm-1. Because of the existence of groups like C=C stretching, C=O, N-H, and C-H stretching, the drug reveals a peak. In the IR spectra of a blend of medicine and polymers, no changes in these primary peaks were found. As shown in the accompanying figures, there are no physical or chemical interactions between Levofloxacin and eudragit, ethyl cellulose, or chitosan in the FTIR analysis.

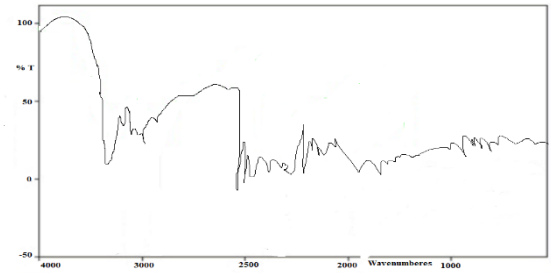

Fig.2: FTIR Spectra of Levofloxacin

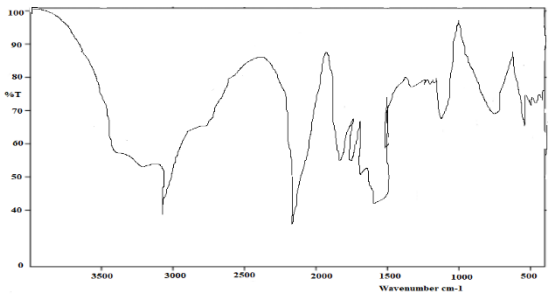

Fig. 3: FTIR Spectra of Eudragit L100

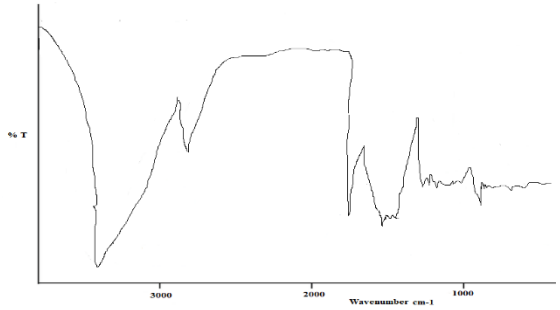

Fig. 4: FTIR Spectra of Chitosan

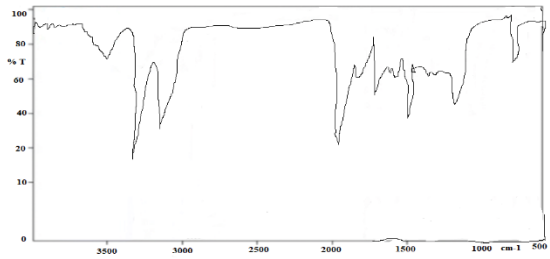

Fig. 5: FTIR Spectra of Physical mixture

Physical investigation of Film

All the prepared levofloxacin loaded solid lipid nanoparticles film were characterized visibly during emergence in selection of aspect smoothness, transparency, stickiness, flexibility, and equaling aspect.

Thickness of the films

The thickness of each film was measured in numerous places, and the average thickness was computed using a standard deviation. The data on film thickness demonstrated that the formulas' thicknesses did not differ much. The thickness varies from 0.400.56 and 0.570.12 millimetres.

Tensile strength

A film's tensile strength was reported in a table. A considerable influence of the concentration on the mechanical properties of the films was noticed. Tensile strength was observed to enhance among increased in the polymer content in the films. It was described that the tensile strength ranged from 25.23 ± 1.03 N/mm^2 to 58.24 ± 1.09 N/mm^2. The enhancement in tensile strength of the transdermal films might be ascribed to the high-appearance ratio and inflexibility that consequence from the sturdy affection through the polymer.

Moisture absorption and moisture content studies

The effect of moisture content and moisture absorption studies were indicated in table 2. The moisture content in the preparation differs from 11.45 % to 23.34 %. The moisture absorption in the preparation was from 18.06% to 28.67%. The outcomes disclosed that the moisture absorption and moisture content was initiate to enhanced among polymer concentration proportion. The less moisture content in the formulation assists impudent to abide immovable and not existence a totally dried and breakable film. Once more, less moisture absorption maintains the film from microbial impair.

Table 3: Moisture studies of transdermal patches

Batch	Moisture content (%)	Moisture absorbed (%)
F1	13.94 %	14.76 %
F2	15.08 %	16.98 %
F3	16.32 %	17.09 %
F4	17.12 %	19.45 %
F5	19.04 %	21.65 %

Swelling index

Swelling indexes for all films were determined, and they ranged from 11.310.06 to 29.140.007. The swelling property of a preparation containing ethyl cellulose and hydroxypropyl methylcellulose K4M is greater than that of the other films. The swelling index increased as the polymer content increased. Before the medicine can be liberated from the dosage form, it must first swell. Table 3 displays the swelling index.

Surface pH

Every preparation's surface pH was calculated as described in the methods chapter. The pH of all formulations was found to be in the range of 6 to 7. As a result, the produced films did not change the pH of the gingival fluid, and hence did not irritate the gums.

Drug content uniformity

Table 3 shows the percentage drug content of Levofloxacin in numerous formulations, which vary from 82.87 percent to 91.45 percent. There was no notable dissimilarity in the homogeneity of the medication content, as evidenced by the drug content information. Despite the fact that the computed drug content was slightly lower in drugs as compared to the theoretical drug content. It's possible that this is because of drug deprivation throughout the filming process.

Weight uniformity test

The consistency of weight of drug-loaded films (744 mm) was examined, and the findings of weight consistency are shown in Table 3. The films' weight was uniform, as evidenced by lower standard deviation readings. The weight difference ranges from 12.340.13 to 14.760.119 mg.

Table 3: Several physicochemical properties of Film

Film code variables	F1	F2	F3	F4	F5
Thickness (mm)	0.40±0.56	0.41±0.98	0.43±0.67	0.47±0.23	0.57±0.12
Weight variation (mg)	12.34±0.13	12.87±0.78	13.34±0.45	13.98±0.88	14.76±0.119
Folding endurance	159	167	173	185	191
% Swelling index	11.31±0.06	14.54±0.05	17.87±0.02	23.43±0.08	29.40±0.07
Tensile strength	25.23±1.03	32.56±0.09	48.09±1.02	51.23±0.05	58.24±1.09
% Elongation	5.23±0.04	6.98±0.34	8.56±0.98	9.12±0.02	9.98±0.08

In- vitro drug release studies

The drug liberating account of prepared transdermal films is constituted in Figure 6 and Table 4. The result of released studies indicate that F5 batch preparation has greater drug release 91.34 % in 8 hrs. variance to the further batches. Along with a result and graphs it is definite that the drug release was depending upon numerous polymer proportion and permeation enhancer content.

Table 4: In-vitro drug release study

Time	F1	F2	F3	F4	F5
0	0	0	0	0	0
0.5	30.23 %	35.76%	38.56%	39.49%	40.30%
1	32.34%	36.98%	39.76%	40.12%	41.76%
2	34.91%	38.46%	41.43%	42.88%	44.82%
4	36.45%	39.23%	42.76%	43.56%	46.78%
6	42.75%	73.56%	75.09%	76.84%	77.12%
8	43.87%	84.83%	88.34%	90.22%	91.34%

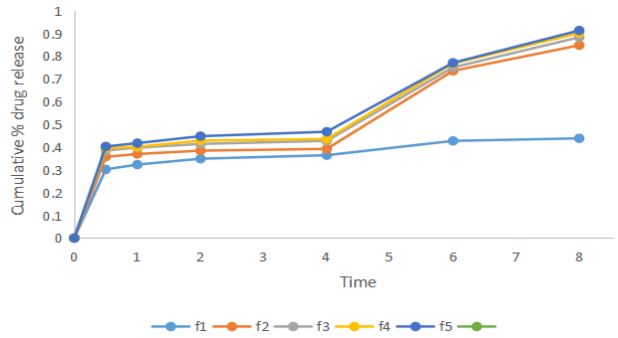

Fig. 6: In-vitro drug release studies of transdermal film

Ex- vivo permeability study

For F1, F2, F3, F4 and F5 formulation ex -vivo permeation studies were achieved. The successful outcomes indicate in Figure 7 and Table 5 disclosed that F5 formulation has drug permeation 16.76898 µg/cm² in 8 hrs. Accordingly, throughout the use of permeation enhancer indicate a greater result in enhanced drug permeation. Plotting the correct amount of medicine permeated between square centimeters of patches on the rat stomach skin versus time in minutes.

Table 5: Ex-vivo skin permeation study

Time	F1	F2	F3	F4	F5
0	0	0	0	0	0
0.5	2.476858	2.567893	2.649876	2.874536	2.914567
1	4.356478	4.397663	4.451233	4.567744	4.679944
2	6.897653	6.917545	6.928756	6.94659	6.984433
4	10.456893	10.654933	10.783356	10.829763	10.97234
6	13.482457	13.543982	13.612356	13.739245	13.823946
8	16.348753	16.478652	16.573426	16.649873	16.76898

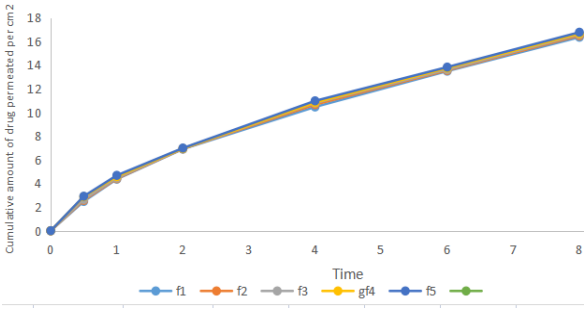

Fig. 7: Ex- vivo permeation studies of transdermal film

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