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Research Article

Development And Evaluation Luliconazole Embedded Transungual (Nail) Patches for the Treatment of Onychomycosis

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ABSTRACT

Transungual drug delivery is involves the administering of medicament through nail plate for treatment of infected nail disorders like onychomycosis and nail psoriasis. Luliconazole (LCZ) is novel imidazole antifungal drug used to treat against a variety of fungal infections and belongs to BCS class II drug having poor aqueous solubility and high permeability. In the present research work was to develop and evaluate of LCZ nail patches by solvent evaporation technique using different concentration of HPMC K-4M and Eudragit RS PO. Nail patches were characterized by drug content, weight uniformity, thickness, folding endurance and In-vitro drug diffusion studies. No drug and excipients interactions in the formulation analyzed by FTIR. Formulated patches (F1-F6) were smooth, flexible and uniform in transparency. Drug content of the formulation batches F1-F6 were observed in the range of 88.91 ± 1.12 to 98.85 ± 0.75w/w. Thicknesses of nail patches were found to be in the range of 0.18 ± 0.10 to 0.26 ± 0.08mm. The folding endurance was found to be >100 reveals that the patches were having a excellent flexibility. Drug release from the patches were found to be in the range of 79.41 to 66.38%w/w at the end of 6 hrs. In the present investigation, conclude that the formulated LCZ nail patches by solvent evaporation technique shows excellent physical properties and release the drug in sustained manner for the therapy of Onychomycosis.

INTRODUCTION

Transungual drug delivery "Trans" means "through" and "unguis" means "nails" involves delivering drugs through the nail plate to treat nail disorders such as onychomycosis and nail psoriasis associated with symptoms like discoloration, deformation, hyperkeratotic, separation from nail bed, brittle nails etc.[1] Several oral and topical medicaments are used for the treatment of nail disorders especially in the conditions of onychomycosis leads to dose related side effects followed by poor patient compliance

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[2]. Transungual drug delivery is a successful therapy for offering a targeted approach with effective therapeutic effects and minimizes systemic side effects compared to oral and other topical medications [3]. The keratin and water, along with certain minerals and fates are involve in nail health and growth. The components of nail unit are nail bed, nail plate and nail matrix, are also protects base of the nail from external environment. Nail infection is caused by entry of fungi, bacteria or viruses through nail bed or skin around nail plate can leads to conditions like onychomycosis and nail psoriasis symptoms such as redness, swelling, discoloration, loose keratinization. The main component of human nails is keratin, a hard protein that acts as a strong barrier to significant challenge for drug penetration and absorption [4]. Topical treatments are the primary approach for managing nail conditions like onychomycosis and nail psoriasis, as they deliver medication locally, minimize systemic side effects, improve patient adherence, and reduce overall treatment expenses.[5] Traditional topical therapy is difficult to deliver the medication through nail due to the dense, keratinized structure of the nail plate presents that acts as a significant barrier to drug permeation.[6] The fungal infection of the nails is may be treated with topical antifungal agents such as miconazole nitrate, clotrimazole, terbinafine hydrochloride, butenafine hydrochloride, itraconazole in the form of lotions, aerosol foams and sprays, powders, creams, ointments, pastes, jellies. These dosage forms having lack of potential bioavailability drawbacks such as less residential time, poor permeability and absorption shows poor patient compliance.[7]. Therefore, drug penetration enhancement techniques are need to modification of nail barrier functions to improve permeation of drug in to deeper layer of nail plate. These techniques include mechanical methods for filing or abrading the nail to thin the nail plate, chemical methods for keratolytic agents (salicylic acid or urea) to make the nail softer, and physical methods including photodynamic therapy and iontophoresis (which uses electrical currents) to improve drug delivery[8] .In order to enhance residential time, drug permeation and reduce adverse effects, recent advanced nano sized drug delivery systems such as liposome's, transferosomes, and nanoparticles, nano emulsions in the formulations such as nail lacquers, adhesive medicated patches to enhance penetration through the nail plate and release the medicament gradually over long period of time.[9].

Luliconazole (LCZ) is a novel imidazole antifungal drug with broad-spectrum activity against various fungal species. LCZ exhibits antifungal effects by inhibiting the enzyme lanosterol 14-α-demethylase (a cytochrome P450 dependent enzyme).[10] This inhibition disrupts the biosynthesis of ergosterol leads to increased membrane permeability and ultimately results in fungal cell death. LCZ was first developed and approved in Japan in 2005 as a topical antifungal for the treatment of skin fungal infections. It was subsequently approved by the Food and Drug Administration (FDA) in 2013 for the treatment of tinea corporis, tinea pedis, and tinea cruris and launched in India by Ranbaxy Laboratories Ltd [11]. LCZ having a high level of efficacy against dermatophytes and certain non-dermatophyte fungi, available in various formulation types like cream, gel, lotion, powder, and soaps. LCZ is available as a very fine yellowish powder and high lipophilic nature which facilitates rapid and deep penetration into the stratum corneum and dermis [12]. Therefore, LCZ is a very good drug candidate for the topical lipid-based formulations.

The present research work was planned to formulation of nail patches by using HPMC K4M, Eudragit RS PO, Ethyl cellulose as drug release

modifiers, Oleic acid as penetration enhancer and polyethylene glycol as plasticizer and LCZ antifungal drug.

2. MATERIALS AND METHODS

Luliconazole (LCZ) was obtained as a gift sample from KIMA Bioscience Ltd, Mumbai. HPMC K4M gift sample from Colorcon, Asia Pvt. Ltd. Eudragit RS PO, Ethyle cellulose, Oleic acid, polyethylene glycol was purchased from SD Fine Chemicals, Bengaluru. All other reagents and solvents used were of analytical grade satisfying pharmacopoeias specifications.

2.1. Melting point of LCZ:

The melting point of LCZ was determined using a capillary tube method. Fine powder drug is filled in capillary tube sealed at one end, tied to thermometer and placed in a paraffin filled melting point apparatus. The temperature range at that the drug melted was recorded.

2.2 . Determination absorption maxima (λ max)

The primary standard stock solution was prepared by dissolving 10 mg of LCZ in 10 ml methanol to get concentration of 1mg/ml (1000µg/ml). Secondary stock solution was obtained by diluting 1ml of the primary stock solution with 10 ml methanol to get concentration of 0.1mg/ml (100µg/ml). The solution was subjected to scanning between 200-400nm in a UV-Visible spectrophotometer (Shimadzu 1800, Japan) [13]. The wavelength at which LCZ shows maximum absorbance is recorded.

2.3. Construction of standard calibration curve at pH7.4PBS

From the secondary standard LCZ stock solution, 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0ml aliquots were diluted with 10ml with pH7.4 PBS to obtain working solutions in ranging from 5-30 µg/mL. The obtained concentration of serial aliquots was measured at 299nm by using UV-Visible spectrophotometer. (Shimadzu 1800, Japan) [14]. A standard calibration curve was constructed by taking the absorbance vs concentration(µg/ml).

2.4 Solubility of LCZ in different solubility:

Excess amount of LCZ was dissolved in a measured amount of acetone, methanol, ethanol, pH 1.2 acidic buffer solution, pH 4.8, pH7.4 phosphate buffer solution (PBS) and distilled water in a volumetric flask, stirred by mechanical shaker for 24hrs. After the solutions were filter through Whatman filter paper (0.45 µ) and content of LCZ in filtrate was estimated by using UV-visible spectrophotometry at 299nm (Shimadzu 1800 Japan) [15]. Solubility behaviour of LCZ in each specific solvent was observed and recorded.

2.5 Fourier Transform Infrared Spectroscopy (FTIR)

Potassium bromide (KBr) press pellet technique was used to carried out FTIR analysis of pure drug, individual polymer and physical mixture of formulation. The pellet was scanned from 4000 to 450cm^{-1} in FTIR Spectrophotometer (Shimadzu 1700S), taking air as the reference and compared to study any spectral interference [16]

2.6 Differential scanning calorimetry (DSC): DSC was performed using DSC-60 (Shimadzu, Tokyo, Japan) calorimeter to study the thermal behaviors of drug alone and physical mixture of drug and excipients. The analysis was performed at temperature 40-400ºC at the rate of 10ºC/min. Nitrogen gas was introduced at a pressure of 2 bars and a flow rate of 20ml/min and the data was analyzed by using TA-60 collector software.

2.7 Preparation of LCZ nail patches

Six batches of LCZ nail patches were formulated by solvent evaporation technique. HPMC K4M, Eudragit RS PO are dissolved in acetone in a separate beaker by using magnetic stirrer at 50rpm, maintain temperature 45^0C. LCZ drug, polyethylene glycol and oleic acid are added into polymeric solution with continuous stirring for 15min to form homogeneous dispersion. Taking clean glass petridish, lubricating the inner bottom surface with cotton wool, immediately pour drug-polymeric dispersion allowed to disperse uniformly. Glass funnel was kept inverted for controlled solvent evaporation for 24hr with continuous air circulation. Then, dried films were peeled from the petridish, cut into preferred size (2 x 2cm^2) and shape (oval), sealed in aluminium foil, kept in a desiccator with control humidity and temperature conditions until further studies[17]. The detail composition of different formulation patches was mentioned in Table 1.

Table 1: Detail composition of Luliconazole nail patches

Ingredients	F 1	F 2	F3	F4	F5	F6
Luliconazole (mg)	250	250	250	250	250	250
HPMC-K 4M (gm)	0.4	0.6	0.8			
Eudragit RS PO (gm)				0.4	0.6	0.8
Propylene glycol (ml)	0.5	1	1.5	0.5	1.0	1.5
Oleic acid (ml)	1.0	1.0	1.0	1.0	1.0	1.0
Acetone (ml)	5.0	5.0	5.0	5.0	5.0	5.0

3. Evaluation Of Luliconazole Loaded Nail Patches

3.1 Physical appearance:

All the formulated nail patches were visually examined under the electronic microscope for its colour, transparency, clarity and smoothness.

3.2 Thickness uniformity:

The thickness of the formulated patches was performed by using digital screw gauge. From each batch three patches were randomly selected and measured the thickness at different points. The average thickness value of each patch was recorded.

3.3 Weight uniformity:

The three randomly selected patches (2 x 2cm^2) from each formulated batches and subjected to weigh in electronic balance. Calculating the mean average wight of all the formulated patches and percentage of deviation was recorded. The individual weight from each patch should not be deviated significantly form average weight[18]. Each measurement was carried out in triplicate (n=3).

3.4 Percentage moisture absorption and Loss

Accurately weighed patches (2 x 2cm^2) were placed in a desiccator containing anhydrous calcium chloride as desiccating agent, after three days the desiccated patches were taken out and subjected to weighing. Each measurement was carried out in triplicate (n=3). The percentage moisture absorption and loss were calculated using the formula:

$$\text{Percentage Moisture Absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \text{x} 100$$

3.5. Folding Endurance:

The folding endurance was measured by taking uniform size (2 x 2cm^2) of formulated patch and subjected to folding repeatedly at the same place (single point) till it broken. The number of times that the patch could be repeated folding at the same place without cracking/breaking indicates the folding endurance value[19]. Each measurement was carried out in triplicate (n=3).

3.6. Drug content

A strip of each patch 1.6cm^2, weighed accurately (equivalent to 5mg of drug) and dissolved in 100ml pH7.4PBS. The contents were stirred on magnetic stirrer at 100rpm for 24 hrs, maintain the temperature at 45^{0}C. The solution was then filtered through Whatman filter paper (0.45 µ) and diluted suitably with pH 7.4PBS. LCZ content in the solution was analysed at 299 nm using placebo patch as blank by using UV-visible spectrophotometer (Shimadzu 1800, Japan) [20]

3.7. In-vitro diffusion studies

Franz diffusion cell was used to determine the *In-vitro* diffusion of LCZ from various formulated nail patches. Diffusion cell composed of two compartments i.e., donor and receptor. The receptor compartment comprises 25ml capacity of volume and filled with pH7.4PBS. A suitable thickness of pre-treated cellophane membrane was fixed between donor and receptor compartment of the diffusion cell that acts as semipermeable membrane. The fabricated drug embedded patches were cut into 2 x2 cm^2 and placed on cellophane membrane facing towards the donor compartment. The whole assembly maintained constant temperature 37± 5^{0}C, stirred magnetically at 50rpm. At predetermined time intervals the sample is withdrawn and equal volume of fresh PBS replaced each time in order to maintain sink condition. After appropriate dilution, the samples were analysed by using UV-visible spectrophotometer (Shimadzu 1800, Japan) at 299nm [21]. The concentration, amount of drug released and the percentage of drug release from the patches were calculated by using PCP-Disso-V2 software.

3.8. Kinetic drug release: In order to understand the mechanism kinetics of drug release and best fit model for the formulations by using PCP-Disso-V2 software. The drug release data of the *Invitro* diffusion study was analyzed with various kinetic equations like zero-order (% release v/s time), first-order (Log % retained v/s time), and Korsmeyer and Peppas equations ($Mt/M\infty = Ktn$). Where Mt is the amount of drug released at time t, $M\infty$ is the amount of drug released at infinite time, K is the kinetic constant incorporating the structural and geometric characteristics of the gel, and n is the diffusional exponent indicative of the release mechanism. Where n = 0.5 represents Fickian diffusion, <1.0 represents non-Fickian diffusion, n = 1.0 case-II transport, and n> 1.0 super case-II transport [22].

3.9. Stability studies: The most satisfactory formulated patch was subjected to accelerated stability studies according to the International Conference on Harmonization guidelines [21]. The patch was sealed in aluminium foil and stored at 25 ± 2°C/45RH,45± 2°C/75RH for 60 days. Every 15 days interval the physical appearance, drug content was estimated and recorded,

4. RESULTS AND DICUSSION:

Traditional topical antifungal therapy is difficult to deliver the medication through nail due to the dense, keratinized structure of the nail plate presents a significant barrier to drug permeation. The importance of nail permeability to topical therapeutics has been realized, primarily in the treatment of onychomycosis. Permeability of nail plate is necessary to be altering by using novel

lipid-based matrix drug reservoir systems are developed through patch delivery to enhances the diffusion of drug and improve therapy [23]. In the present research work, nail patches of LCZ were prepared by solvent evaporation technique, using different concentration of film forming polymers combination with penetration enhancer and plasticizers. This is the first investigated report of LCZ nail patches are to achieve a modification of nail plate permeability and therapeutic effectiveness to better patient acceptance and compatibility compared to previous research report of LCZ.

4.1 Melting point of LCZ: The melting point (MP) determination is a key tool used in the formulation research and development as well as in quality control in various industry segments to identify and check the purity and thermal behaviour of the active drug. In the present investigation the M.P of LCZ was found to be 152^0C. There are no changes in melting range of the drug as mentioned in standard drug specifications. Therefore, the drug LCZ is in pure form and suitable in the manufacturing of nail patches.

4.2 Determination absorption maxima (λ max): The absorption maxima of LCZ were subjected to scanning in the range of 200-400nm using double beam UV-Visible spectrophotometer (ShimazduUV-1800). The characteristic sharp absorption peak LCZ was obtained at 299nm. Thus, regression analysis for the linearity showed very good correlation between absorbance and concentration at 299nm.

4.3 Construction of standard calibration curve: The linear regression equation was generated in pH7.4 PBS (y=0.0528x+0.0095, R2=0.9946). Standard curve was plotting concentration vs absorbance to obtain a straight line, which indicated that the present analytical method obeyed Beer-Lambert's law in the concentration range of 5-50 µg/ml (Figure2). The selected method was found to be sensitive, accurate, precise and reproducible and used for the estimation of LCZ in the formulation.

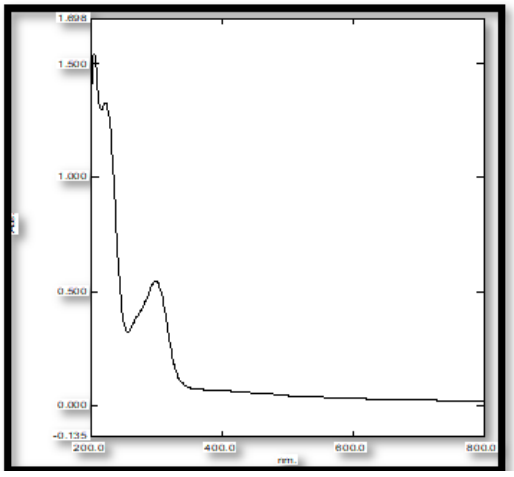

Figure 1: Absorption maxima of pure LCZ

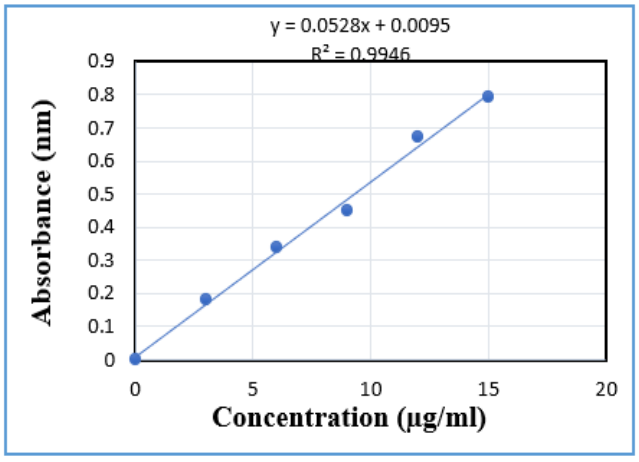

Figure 2: Standard calibration curve of LCZ in pH7.4 PBS

4.4 Solubility of LCZ: The available data on solubility profile of LCZ indicated that the drug is freely soluble in methanol, ethanol, acetone and practically insoluble in water. The solubility of LCZ in different solvents were analysed by using UV-visible spectrophotometry at 299nm (Shimadzu 1800 Japan). LCZ shows higher solubility in acetone and pH7.4PBS than other solvents (Table 2), based on the evidence pH 7.4PBS is used as major buffer medium for

quantification of LCZ in the formulation and acetone used as vehicle to solubilize LCZ, other excipients in the preparation of nail patches.

4.5 FTIR Analysis: The molecular interactions of LCZ with other excipients used in the formulation were investigated using FTIR spectroscopy (Shimadzu 1700S). The major characteristic absorption peaks of LCZ that corresponds to chemical structure at 2979 cm-1for C-H stretching, 2200cm^{-1}, C≡N (nitrile) stretching, 1471.88 cm^{-1} for C=C aromatic ring stretching and 720.33 and 1101.29 cm^{-1} for C-Cl stretching (Figure 3a). FTIR spectra shows at 2933.63cm^{-1}C-H stretching, 1119.77cm^{-1} and 1067.61cm^{-1} C–O–C stretching, C–O stretching respectively (Figure 3b). The major peaks of Eudragit RS PO were observed at 2989.83cm^{-1} C-H stretching, 1732.73cm^{-1}, 1242.48cm^{-1} C=O stretching, C–O stretching respectively (Figure3c). All the exhibited sharp peak bands of pure LCZ are also present in the formulation batches F2 and F5 (Figure 3d, e), confirm that the drug was molecularly dispersed and there are no significant chemical or physical interactions occurred during the formulation process.

Table 2: Saturation solubility of LCZ in different solvents

Vehicles	Solubility of LCZ (mg/ml)
Distilled water	024.55 ± 0.05
Ethanol	155.65 ± 0.07
Methanol	165.55 ± 0.23
Acetone	184.66 ± 1.25
pH1.2 buffer solution	122.54 ± 0.88
pH4.8 buffer solution	137.25 ± 1.35
pH 7.4 phosphate buffer solution	168.45 ± 0.55

Data are the mean ± S.D. n=3

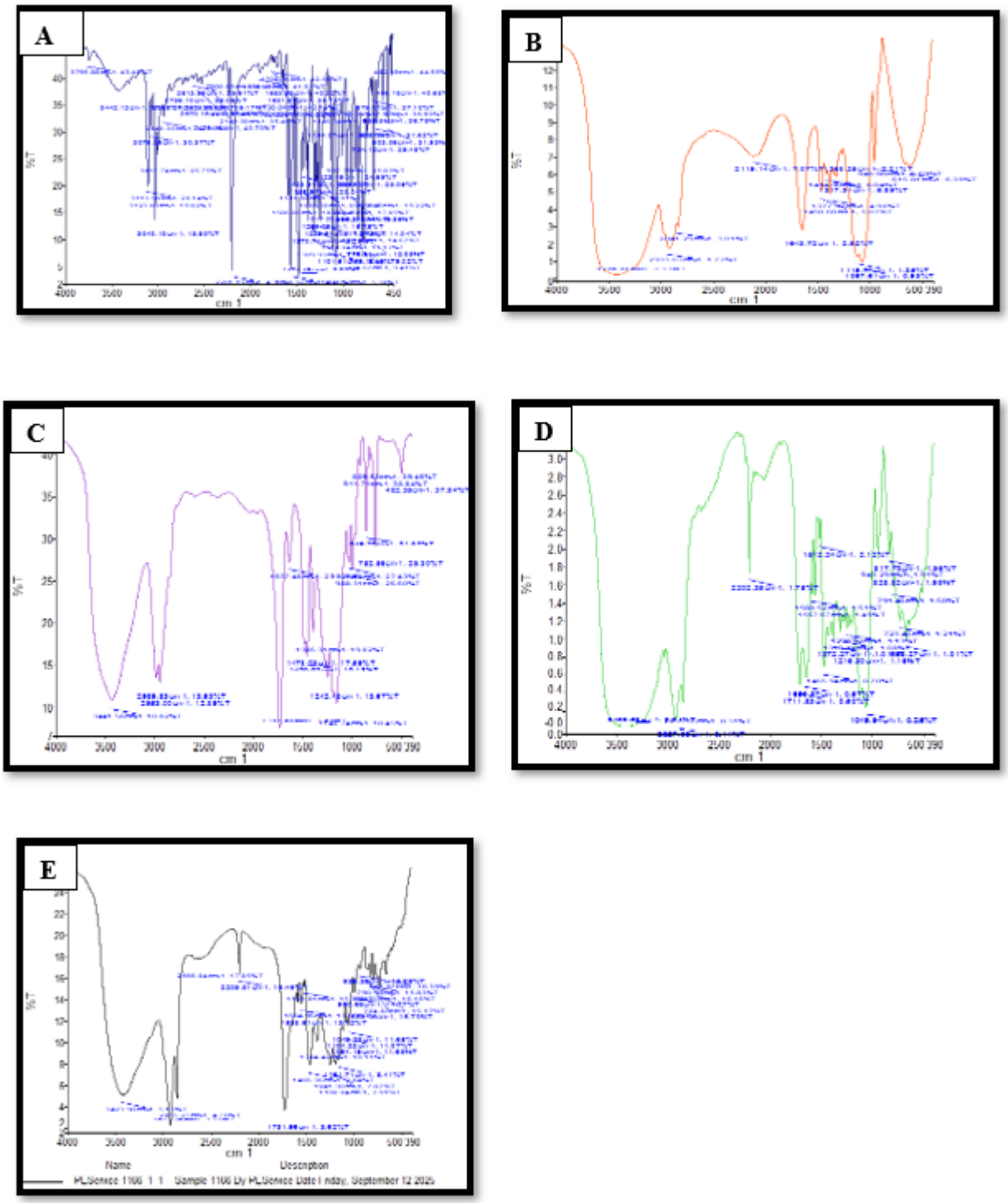

Figure 3: FT-IR Spectra of (A) Pure Luliconazole (B) HPMC K4M (C) Eudragit RS P.O (D) Formulation F2 (E) Formulation F5

4.6 DSC analysis: The analytical technique of DSC was frequently used to study melting behavior, thermal stability, crystallization, solid-state polymorphic transitions and chemical interactions of the drug during manufacturing process. The DSC thermogram of pure LCZ showed a sharp endothermic peak at 156.50^{0}C, the formulation F2 and F5 showed a sharp endothermic peak at 149.14^{0}C. and 161.94^{0}C

respectively (Figure 4). By observing the thermograms of pure drug and physical mixture of formulation were suggest that there is no thermal transition or interaction during in the manufacturing process.

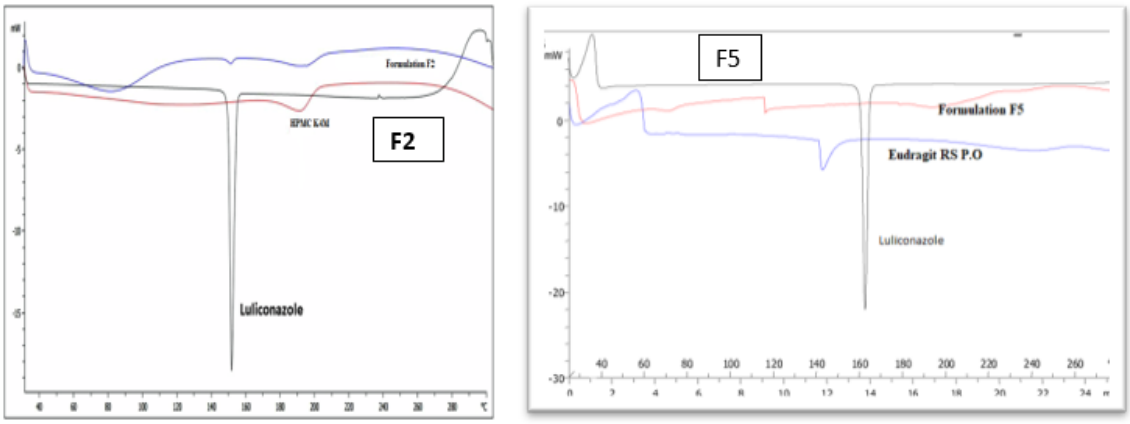

Figure: 4: DSC Thermograms pure LCZ in Formulation F2 and F5.

4.7. Physical appearance: By observing the physical appearance of all the formulated Nail patches are thin, transparent, flexible, smooth and uniform transparency. There are any cracks, pin holes; surface tackiness and dullness were not observed (Figure5)

Figure.5: Physical appearance of Nail patches (F1, F2, F3)

4.8. Thickness: The uniformity of thickness is a crucial role to maintain the dimensional shape, size, flexibility, softness, brittleness and consistent drug release of the patches. The optimization of thickness of films is a very challenge to manufacturers. A formulated patches are too low thickness it becomes brittle, highest thickness to feel rigid, prone to be cracking. Thicknesses of nail patches were found to be in the range of 0.18mm to 0.26mm (Table3). Investigated results are acceptable range, indicates that the drug was uniformly distributed in the formulated patches.

4.9. Weight variation: The weight variation test is a critical quality control parameter in the development of nail patches. While increasing in the polymer concentration, percentage of weight deviation of the patches was slightly increased. Percentage of weight variation F1-F3 is obtained in the range of 0.074 ± 0.11 to 0.128 ± 0.01w/w, F4-F6 is in the range of 0.056 ± 0.22 to 0.126 ±

0.18w/w (Table3). The higher percentage weight variation was observed from the formulation containing HPMC K4M batches (F1-F3) comparing to Eudragit RS PO (F4-F6) because hydrophilic nature of HPMC K4M may be produces higher thickness of patches.

4.10. Moisture gains and loss: Moisture gain and loss tests are a critical measure for ensuring that patches remain effective, safe, and stable throughout their shelf-life. Moisture gain of batches (F1-F3) was showed in the range 2.30 ± 0.42 to 2.80 ± 1.31%w/w, batches of (F4-F6) is in the range of 2.19 ± 0.88 to 2.28 ± 0.56%w/w. (Table 3). The results reveals that the higher level of HPMC K4M could be linearly increases moisture level in the patches due its hydrophilic nature. Formulation batches F4- F5 were exhibiting optimized moisture level than other batches. Patches exhibit the lower moisture content suggests better stability and minimize the development of microbial growth. Moisture losses from nail patches (F1-F6) shows an acceptable range of 1.10 ± 0.55 to 1.56 ± 0.15 w/w (Table 3). Moreover, a patch loses too much moisture, it can become hard, brittle, and inflexible. This can cause the patch to crack or break with movement, effects on therapeutic efficacy.

4.11. Folding Endurance: The folding endurance measurement is an important parameter to accesses the mechanical strength and flexibility of nail patches. Folding Endurance of nail patches from F1 to F6 was found in the acceptable range of 125 ± 0.10 to 110 ± 0.27number of times to fold. (Table 3), The result reveals that the formulated batches (F1-F3) using HPMC K4M were shows lower number of folding endurances. The patches formulated with Eudragit RS P.O (F4-F6) were exhibiting higher number folding endurance and becomes more flexible that can be withstand repeated bending without cracking or breaking. Moreover, a too thin patch exhibits more flexible and higher number of folding endurances.

Table 3: Various physicochemical properties of LCZ loaded nail patches

Batch Code	Thickness (mm)	Weight variation (%w/w)	Moisture gain (%w/w)	Moisture loss (%w/w)	Folding Endurance	Drug content (%w/w)
F1	0.21 ± 0.04	0.074 ± 0.11	2.30 ± 0.42	1.10 ± 0.55	125 ± 0.10	88.91 ± 1.12
F2	0.24 ± 0.13	0.123 ± 0.05	2.60 ± 1.12	1.20 ± 0.24	115 ± 0.14	92.86 ± 1.55
F3	0.26 ± 0.08	0.128 ± 0.01	2.80 ± 1.31	1.46 ± 0.26	101 ± 0.23	97.21 ± 0.95
F4	0.18 ± 0.10	0.056 ± 0.22	2.19 ± 0.88	1.32 ± 0.71	135 ± 0.17	85.98 ± 0.87
F5	0.19 ± 0.22	0.112 ± 0.85	2.21 ± 0.35	1.36 ± 0.65	122 ± 0.15	98.85 ± 0.75
F6	0.21 ± 0.13	0.126 ± 0.18	2.28 ± 0.56	1.56 ± 0.15	110 ± 0.27	97.42 ± 1.14

Data are the mean ± S.D. n=3

4.12. Drug content: The content of LCZ from the formulated nail patches were estimated, obtained in the range of 88.91 ± 1.12 to 98.85 ± 0.75%w/w (Table 3) Investigated results reveals that the concentration of polymer increases the drug content was significantly increases due the formation thick polymeric matrix. The formulation with Eudragit RS P.O (F5) was showed highest drug content (98.85 ± 0.75) due to uniform dispersion of drug in polymer matrix.

4.13. *In-vitro* diffusion: *Invitro* drug release of the formulated patches were conducted by using Franz diffusion cell in pH 7.4PBS as dissolution medium. Drug release from LCZ loaded patches F1–F-3 were found to be in the range of 79.65 to 69.54 (Figure 6) and F-4 to F-6 is 82.92 to 71.15%w/w (Figure 7) at the end of 6hrs. Nail

patches fabricated by using HPMC K4M (F1-F3) were gives the percentage of drug release in a sustained manner may be due to formation thick drug containing matrix reservoir which take longer period of time to diffuses the drug from the polymeric film surface.[24]. Thinner matrix drug reservoir formed with Eudragit RS P.O patches(F4-F5) were showing faster drug release.

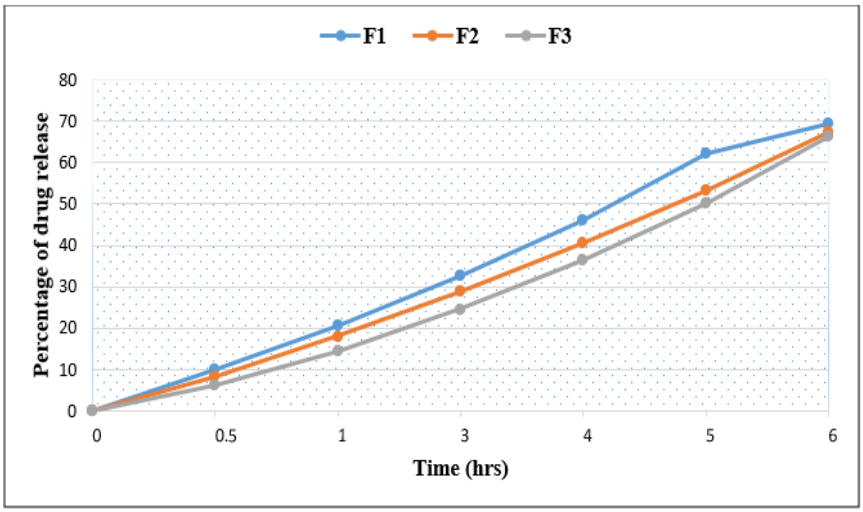

Figure 6: In-vitro drug release of LCZ loaded nail patches in pH7.4 PBS

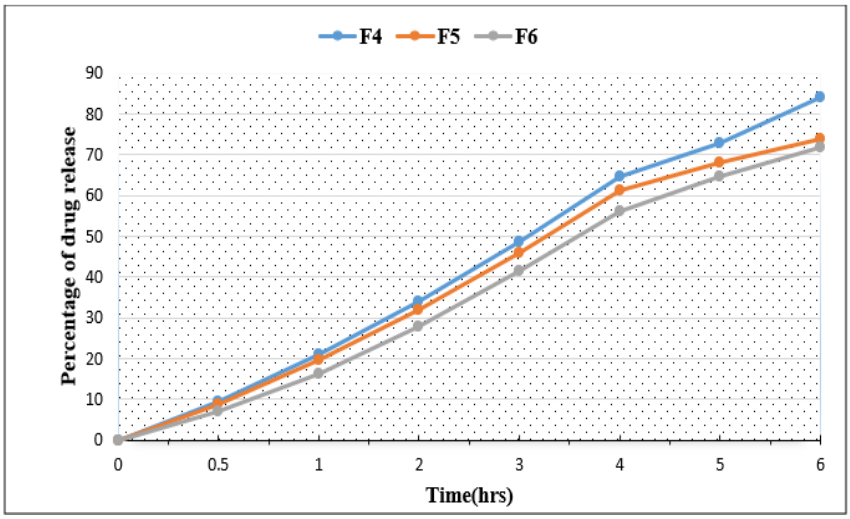

Figure 7: In-vitro drug release of LCZ loaded nail patches in pH7.4 PBS

4.14. Kinetic drug release studies: The data obtained from the *In-vitro* diffusion studies was subjected to kinetic treatment to obtain the order of release and best fit model for the formulations by using PCP-Disso-V2 software. Drug release from the formulated nail patches were closely followed to Higuchi matrix model with highest coefficient value (R^2) values (Table 4). The Korsmeyer–Peppas model was applied to release profiles to determine the diffusion types. The optimized batch(F5) was showed diffusion exponent (n) values around 0.42, followed to the Peppas model which indicates that the drug release from the patches exhibiting a Fickian diffusion mechanism.

Table 4: Various kinetic drug release profiles of LCZ nail patches

Formulation Code	Zero order	First order	Higuchi	Korsmeyer-Peppas	
	R^2	R^2	R^2	n-value	R^2
F1	0.9473	0.9774	0.9719	0.4890	0.9852
F2	0.9547	0.9549	0.9788	0.4382	0.9852
F3	0.9338	0.9540	0.9808	0.4977	0.9850
F4	0.9221	0.9224	0.9772	0.4242	0.9921
F5	0.9608	0.9611	0.9799	0.4201	0.9932
F6	0.9502	0.9505	0.9816	0.4631	0.9952

4.15. Stability studies: The optimized formulation F5 LCZ loaded nail patches were subjected to conduct short term stability studies according to the ICH for zone IV in the desiccators with saturated salt solution. The physicochemical parameters, drug content was determined after 15, 30-, 45- and 60-days period and there are no significant changes in the physical appearance and drug content. Therefore, the formulated LCZ nail patches have good stability at mentioned humidity and temperature conditions (Table 5).

Table: 5. Stability of optimized formulation of LCZ loaded nail patches (F5)

Sampling interval	Drug Content (%w/w)		Physical appearance		
Days	**25^0C/60%RH**	**45^0C/75%RH**	**Color**	**Transparency**	**Flexibility**
0	98.85 ± 0.75	98.85 ± 0.75	White off	Uniform transparency	Good
15	98.55 ± 0.35	97.85 ± 0.25	No Changes	No Changes	No Changes
30	98.45 ± 0.85	97.75 ± 0.15	No Changes	No Changes	No Changes
45	97.65 ± 0.15	96.95 ± 0.05	No Changes	No Changes	No Changes
60	97.95 ± 0.55	96.25 ± 0.35	No Changes	Dull surface	Changes

Data are the mean ± S.D. n=3

5. CONCLUSION: In the present research work, LCZ embedded nail patches were successfully manufacturing by solvent evaporation technique. Six formulations (F1- F6) were prepared by using two polymers HPMC K-4M and Eudragit RS PO and investigated for various physicochemical properties, including thickness, weight variation, folding endurance, moisture gain, moisture loss, drug content uniformity and *in vitro* drug diffusion studies. Formulated LCZ nail patches were exhibiting acceptable physicochemical properties with uniformity in thickness, high folding endurance (>100), minimal weight variation. The LCZ content from nail patches were increasing with higher level of polymer used in formulation followed to release the drug in sustained manner for prolonged period of time. The optimized formulation batch (F5) prepared by using 0.6G of Eudragit RS PO was exhibiting good mechanical properties, flexibility and stability and consistent drug release with good correlation diffusion exponent (n) values around 0.42, followed to the Peppas model which indicates that the drug release from the patches exhibiting a Fickian diffusion mechanism. Therefore, the Eudragit RS PO is a promising polymeric material which improves the absorption of LCZ nail patches at the site of

application and patient compliance for the treatment of nail disorders.

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