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Original Research Article

Formulation and evaluation of posaconazole loaded nanostructured lipid carriers for topical drug delivery system

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ABSTRACT

The aim of the present study was to formulate and evaluate Posaconazole loaded NLCs gel using solid lipid as GMS, liquid lipid as oleic acid and surfactants as tween 80 and span 80, with the help of high-speed homogenization followed by sonication technique to improve the bioavailability, to avoid the oral side effects, to achieve the site-specific delivery and to improve the patient compliance. NLCs of Posaconazole was prepared with different drug: carrier ratios using high speed homogenization followed by sonication technique. % entrapment efficiency for F3 batch of NLC was found to be more than 95%. SEM studies were carried out and depending on it F3 batch was found to have particle size range 200nm which was selected as optimized NLCs batch. IR, XRD and DSC were performed to identify the physicochemical interaction between drug and optimized formulation. The optimized NLCs was then incorporated into gel base to form Posaconazole loaded NLCs gel. The prepared NLCs gel were evaluated for viscosity, pH, spread-ability, extrudability and in-vitro drug release studies. It was found to be 34666 cps, 5.7, 12.22 ±0.8 cm, 85.34% and drug release of NLCs gel within 6hrs was 98.62% respectively. The obtained data for in-vitro drug release was putted in various mathematical kinetic models. Hence, F3 batch was selected as optimized batch.

1. Introduction

Currently, a large number of new therapeutic compounds are being produced, however chemical screening has revealed roughly 40% of new drug candidates as having low water solubility and bioavailability.[1,2] It is necessary to create drug delivery systems that address these issues. Lipid nanoparticles (SLN) and nanostructured lipid carriers are alternatives to emulsions, liposomes, and polymeric micro particulate systems.[3,4]

Nanostructured lipid carriers are a novel colloidal system that consists of submicron particles that are spherical in shape and have an average diameter of 50-500 nm. Physical stability, bioavailability, biocompatibility, and controlled drug release are just a few of the advantages they offer as a drug delivery vehicle,[5–10] Nanostructured lipid carriers are a promising system in many applications due to their adaptability.[11]

Nanocarriers have been utilized to deliver drugs for a long time. A number of polymeric nanoparticles have been developed for use in a variety of medications. However, despite substantial study, polymeric nanoparticle-based solutions have yet to gain traction in the marketplace due to a lack of pilot plant scale-up methodologies.[12–15] To address this issue, solid lipid nanoparticles (Solid Lipid Nanoparticles) were developed. Solid Lipid Nanoparticles has several advantages over polymeric nanoparticles, including biodegradability, biocompatibility, and large-

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scale manufacture.[16–20] However, they had drawbacks such as limited drug loading and drug expulsion, which prompted researchers to develop a novel lipid carrier, the nanostructured lipid carrier (NLC), with regulated nano-stability.[21]

Nanostructured Lipid Carriers are created by combining solid and liquid lipids, resulting in spherical nanostructures with better therapeutic loading, drug release profile change, and stability[22] Nanostructured Lipid Carrier is a potential Drug Administration System that can prolong the delivery of liposoluble drugs, increase their stability, and reduce their systemic toxicity.[23–25]

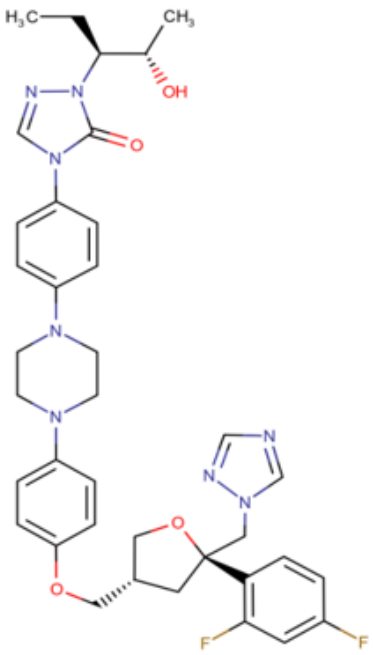

Fig. 1: Structure of Posaconazole.

Posaconazole is a structurally related antifungal drug to itraconazole. Posaconazole is a triazole antifungal drug that works by attaching to the heme cofactor on the cytochrome p-450 dependent enzyme sterol 14-demethylase in fungus. This causes the synthesis of ergosterol, a critical component of the fungal cell membrane, to be inhibited, as well as the accumulation of methylated sterol precursors. Posaconazole is very lipophilic (log P 5.5) in nature and has a low water solubility. Posaconazole is effective against a wide variety of fungus and moulds in-vitro, including Aspergillus, Candida, Cryptococcus, filamentous fungi, and endemic mycoses such as coccidioidomycosis, histoplasmosis, and blastomycosis. Importantly, Posaconazole is far more effective against numerous Mucorales species than other azoles, and combining Posaconazole with other antifungal medicines may be beneficial. Hence, Posaconazole is a potential candidate as a single or combination agent to treat fungal infections.[26–28]

Posaconazole is a BCS Class-II medication with a high lipid solubility and low water solubility. Posaconazole is an antifungal medication that comes in a variety of forms, including injections, oral suspensions, and delayed-release tablets. When taken orally, these formulations can cause patient incompliance, bioavailability, site specific administration, poorer stability, constipation, and stomach pain. Hence, preparing Posaconazole loaded nanostructured lipid carriers gel for topical delivery to avoid such side effects of drugs and to improve the bioavailability, patient compliance for different topical fungal infections.[29,30]

The goal of this study was to create Posaconazole-loaded NLCs utilizing a high homogenization approach followed by sonication. Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and X-ray diffraction (XRD) examinations were used to characterize NLCs. Diluted NLCs were submitted to SEM analysis in order to determine their shape. The improved NLCs were subsequently entrapped in a gel using Carbopol and studied for in-vitro drug release.[31,32]

2. Materials and Methods

2.1. Materials

Posaconazole was provided by Glenmark Pharma in Goa, India as a free gift sample. From lab grade, glyceryl monostearate and oleic acid were employed. The reagents employed in research were analytical reagent grade Span 80, Tween 80, and other compounds.

2.2. Methods[33–35]

2.3. Preparation of posaconazole loaded NLCs

The batches of Nanostructed NLCs were prepared by using High-speed homogenization followed by sonication were used to create NLCs containing Posaconazole. Posaconazole was added to melted lipid phases after they were heated to a temperature 10-15 ∘C above their melting point. Surfactants were heated to the same temperature at the same time. The primary emulsion was then created by dispersing the heated lipids phase into the Surfactants mixture using continuous stirring at 4000 rpm for 1 hour. The pre-emulsion was then thoroughly homogenized and sonicated for 45 minutes. In a refrigerator, the synthesized NLCs formulations were kept at 4°C.'

2.4. Preparation of standard curve of posaconazole[36–40]

10 mg of Posaconazole was dissolved in 10 ml of phosphate buffer pH 6.8 with 0.5% w/v SLS, until the drug dissolves completely then make up the volume up to 100 ml with phosphate buffer pH 6.8 with 0.5% w/v SLS to give a concentration of 100 μg/ml. From the prepared stock solution aliquots of 0.5, 1, 1.5, 2 and 2.5 ml were taken

Table 1: Formulation table for Posaconazole loaded NLCs

Ingredient's	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Posaconazole	1	1	1	1	1	1	1	1	1	1
GMS	3	3	3	3	3	7	7	7	7	7
Oleic acid	7	7	7	7	7	3	3	3	3	3
Tween 80	4	3	2	1	0	4	3	2	1	0
Span 80	0	1	2	3	4	0	1	2	3	4

in 10 ml of volumetric flask and the volume was made up to the mark with phosphate buffer pH 6.8 with 0.5%w/v SLS to prepare concentration of 5, 10, 15, 20 and 25 μg/ml respectively. The prepared stock solution was scanned in the UV range i.e from 200 nm to 800 nm. λ max was found to be 255 nm for Posaconazole in phosphate buffer pH 6.8 with 0.5%w/v SLS as a blank. The absorbance of each concentration was measured using UV visible spectrophotometer at 255 nm.

2.5. Solubility studies of Posaconazole and excipients[41]

The solubility of Posaconazole in pH 6.8 phosphate buffer + 0.5% w/v SLS was carried out.

Screening of liquid lipids and surfactants: Posaconazole's solubility in various lipids and surfactants will be evaluated by pouring excess oil into tiny vials containing 3ml of oil. The vials are tightly sealed and continually agitated for 72 hours at 25°C in a mechanical shaker to achieve equilibrium. The mixes are then centrifuged for 30 minutes at 37°C. The supernatant was separated, dissolved in methanol, and the solubility was measured at 255nm with a UV spectrophotometer.

Screening of solid lipids: Posaconazole solubility in various solid lipids is determined by adding 1mg increments of Posaconazole until it fails to dissolve further in the molten solid lipid.

Selection of binary lipid phase: To determine the miscibility of the two lipids, the solid and liquid lipids with the best-solubilizing potential for Posaconazole were mixed in various ratios, including 95:5, 90:10, 85:15, 80:20, 70:30, and 60:40. A magnetic stirrer was used to agitate lipid mixtures at 200 rpm for 1 hour at 85 ∘C. (Remi instruments Ltd., Mumbai, India). The miscibility of the two components was tested by distributing a cooled sample of the solid combination onto filter paper and visually inspecting the filter paper for the presence of any liquid oil droplets. For the creation of Posaconazole loaded nanostructured lipid carriers, a binary combination with a melting temperature over 40 ∘C was used that did not disclose the presence of oil droplets on the filter paper.

3. Evaluation of Posaconazole Loaded NLCS

3.1. Percent entrapment efficiency[43] *(%)*

For determination of entrapment efficiency, the Posaconazole loaded NLCs dispersion was centrifuged at 15000 rpm for 45 min. at 25 °C. Supernatant were separated and determined by spectrophotometrically at 255 nm. Entrapment efficiency were determined by using following equation.

% entrapment efficiency= [Posaconazole] total-[Posaconazole]supernatant / [Posaconazole]total ×100

Where, [Posaconazole] total is the total weight of the drug incorporated and [Posaconazole] supernatant is the

weight of the drug analyzed in supernatant.

3.2. Fourier transform infrared spectroscopy study[42]

The FTIR Spectrophotometer was used to record the FTIR research of the drug (Posaconazole) and the physical mixture (PerkinElmer Company). The samples were made utilizing press pellet procedures with KBr pellets, and the spectra were scanned in the 400- 4000 cm-1 range.

3.3. Scanning electron microscopy[43] (SEM)

SEM was used to determine the form and surface features of NLCs using the gold sputter technique (ZEISS EV40, Carl Zeiss NTS, North America). NLC samples were dusted onto an aluminium stub with double-sided tape. A cool sputter coater (Polaran E 5100) was used to coat the sample stubs with gold to a thickness of 400 A∘. At an accelerated voltage of 5.21 kV and a chamber pressure of 3.6 mmHg, photomicrographs were taken.

3.4. Differential scanning calorimetry[44] (DSC)

The amorphous nature of the drug distributed in the lipid was determined using differential scanning calorimetry tests. The Mettler Toledo DSC 8220 instrument was used to conduct DSC analysis of Posaconazole and created Posaconazole loaded NLCs. To ensure an inert atmosphere, samples were weighed in an aluminium pan and regulated at temperatures ranging from 0 to 800 °C at a scanning rate of 10 °C/min.

3.5. X-ray diffraction XRD[45]

Using an X-ray diffractometer (Bruker D 8 ADVANCE, Bruker, USA) and Cu as a radiation source, the XRD pattern of the drug and the formulated NLC were obtained. The scan range employed was 0–50 degrees of diffraction angle 2h. A voltage of 40 kV and a current of 30 mA were used to measure the XRD pattern. In the XRD experiment, equal amounts of samples were employed.

3.6. Zeta potential[46,47]

Using the Malvern Zeta-sizer, the zeta potential of formed NLCs was determined (Malvern Instruments, Worcestershire, UK). After appropriate dilutions with deionized water, the analysis was conducted in triplicates.

3.7. Preparation of posaconazole loaded NLC'S GEL

The gel was prepared by dispersing 1% w/w Carbopol 940 in the selected NLC formulations and subsequently neutralizing the Carbopol dispersion using triethanolamine (TEA). The final concentrations of Posaconazole in the NLCs gel coded as optimized NLCs.

3.8. Evaluation of optimized NLC'S GEL[38–40]

3.8.1. Viscosity[13,48]

The viscosity of the optimized NLC sample was obtained by Brookfield viscometer (Brookfield engineering laboratories, Inc., MA, USA) with spindle No. 6 at 10 rpm at temperature of 37 ± 0.5 C.

3.8.2. Measurement of pH[12,49]

pH measurement was carried out by using pH meter.

3.8.3. Spreadability[18,50]

The spread-ability was assayed, by measuring the spreading diameter of 1g of sample gel between two horizontal glass plates after 1minute. The standard weight 100g placed on upper glass plate.

The spread-ability was calculated by using following formula.

1. S= m. L/t Where,
2. S= Spread-ability
3. m= weight tied to upper slide (15g)
4. L= length of the glass slide (cm)
5. t = time taken in seconds

3.8.4. Extrudability[38]

Extrudability was based upon the quantity in percentage of gel extruded from tube on application of certain load. The formulation under study was filled in a clean, aluminum collapsible one-ounce tube with a nasal tip. It was then placed in between two glass slides and clamped. Extrudability was determined by weighing the amount of gels extruded through the tip when a constant load of 1 Kg was placed on the slides and gels extruded was collected and weighed. The percentage of NLCs gel extruded was calculated.

3.8.5. In-vitro drug release study

In-vitro drug release of NLCs gel was executed using Franz diffusion cells. The activated dialysis membrane was placed between the compartments of diffusion cell. An accurately weighed amount of samples were placed on the donor compartment. The receptor medium contains phosphate buffer (pH 6.8) with 0.5% w/v SLS. The medium of receptor compartment were maintained at 37 °C ± 1°C with continuous stirring at 500 rpm. At fixed time interval aliquots of 2 ml were withdrawn and recovered with equal volume of fresh phosphate buffer (pH 6.8) with 0.5%w/v SLS. The withdrawn samples were evaluated by using UV-spectrophotometer at a wavelength of 255nm.

To illustrate the kinetics of the drug release from the NLC gel, the obtained results from in-vitro release studies was fitted to various kinetic mathematical models such as First-order, Higuchi and Krosmeyer Peppas model. The criterion for selecting the most appropriate model was based on a

goodness-of-fit test.

4. Result and Discussion

4.1. Standard curve of Posaconazole

The ƛmax of Posaconazole was determined by scanning 100 µg/ml solution of drug using UV spectrophotometer and was found to be 255 nm. The absorbance of the solution to 25ug/ml was measured in UV- spectrophotometer at 255nm (Table 2). The linear correlation was found to be 0.9963 it is shown in (Figure 2)

Table 2: Standard calibration graph values of Posaconazole in phosphate buffer pH 6.8 + 0.5% w/v SLS.

Concentration (ug/ml)	Absorbance
0	0
5	0.1491
10	0.3775
15	0.5516
20	0.7438
25	0.9872

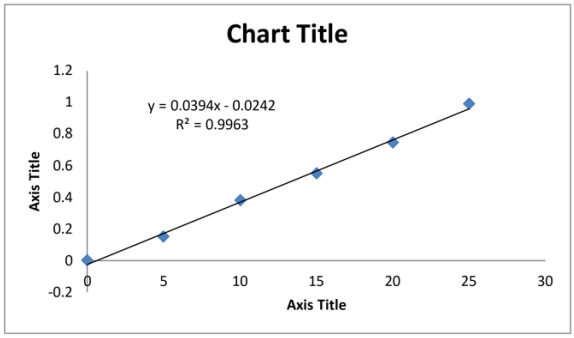

Fig. 2: Calibration curve of Posaconazole.

It was observed that solutions of Posaconazole in Phosphate buffer shows linearity (R2= 0.9963) in absorbance at concentration of 5-25ug/ml and obeys Beer's Lamberts Law.

4.2. Solubility studies of Posaconazole and excipients

Solubility was carried out by using pH 6.8 phosphate buffer + 0.5% w/v SLS. Posaconazole shows 675mg/ml solubility in pH 6.8 phosphate buffer+ 0.5 % w/v SLS. Solubility studies of excipients was shown in Figure 3.

The criteria for the selection of excipients for developing Posaconazole loaded NLCs includes pharmaceutical acceptability, non-irritant and non-sensitizing to skin and that they fall under GRDS (generally regarded as safe) category. The solubility of various solid lipids, liquid lipids and surfactants in Posaconazole is given in the Figure 3. As per the results of solubility studies, Posaconazole exhibited maximum solubility in Glyceryl monostearate (GMS)

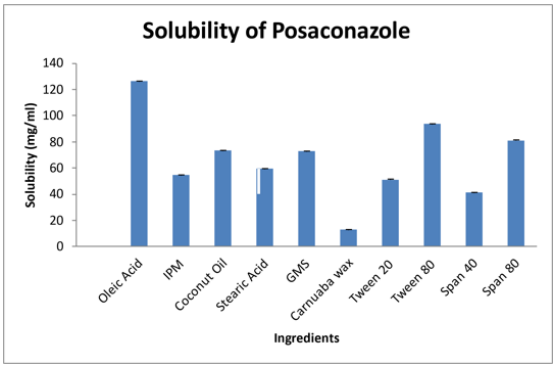

Fig. 3: Solubility of ingredients

(72.84 ± 0.10) as solid lipid, oleic acid (126.46 ± 0.13) as liquid lipid, tween 80 (93.63 ± 0.14) and span 80 (81.17 ± 0.08) as surfactants. Hence, Posaconazole loaded NLCs was prepared by using these excipients as GMS, oleic acid, tween 80 and span 80. Based on the visual observation, binary lipid phase was selected in ratio 7:3 w/w (solid: liquid lipid) ratio for designing NLC.

4.3. Percent (%) entrapment efficiency

The percentage of entrapped drug was determined spectrophotometrically. The % EE of F3 batch was found to be 96.64%.

4.4. Fourier transform infra-red spectroscopy (FTIR) result

The FTIR analysis was implemented to assume the compatibility of assorted excipient blend with the pure drug. Spectral examination was executed using FTIR to explore the generation of new compound or any chemical change in the functional portion of the admixtures among the blends. Infrared spectroscopy was utilized in pharmaceutical investigation for its authentication and structure elucidation of drug. The peaks given in the Figure 4 could be considered as the characteristic peaks of Posaconazole.

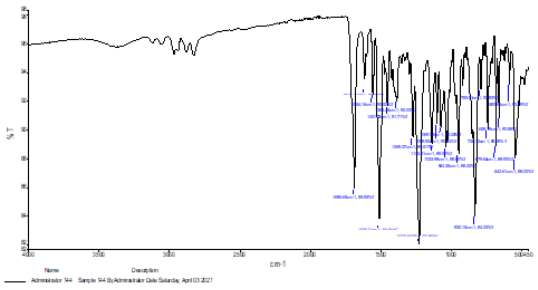

Fig. 4: FTIR spectrum of Posaconazole.

Various absorption peak of functional group at Carbonyl group stretching, Furan ring stretching, C-H bend alkane, C-O-C stretch asymmetrical aryl alkyl ether, C-F aryl halide and C-H aromatic (out of plane) bending was found to be 1710.23 cm-1, 1412.61 cm-1, 1392.48 cm-1, 1243.57 cm-1, 1106.97 cm-1 and 718.27 cm-1 respectively. Hence, Posaconazole loaded NLCs showed similar absorption peaks which indicates its good compatibility with polymers. This declared that there was no remarkable chemical interaction between excipients or drug or confirms that the drug is in the stable nature during the formulation process. The FTIR spectrum for optimized (F3) batch of NLCs was shown in Figure 5.

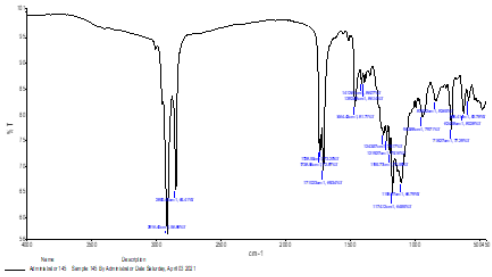

Fig. 5: FTIR spectrum of F3 batch (Optimized NLCs)

4.5. *SEM (Scanning Electron Microscopy) studies*

The surface morphology of NLCs was investigated by scanning electron microscopy. The scanning electron microscopy for F3 batch of Posaconazole loaded NLCs were carried out. It shows particle size range of 200 nm. From this image, it was observed that NLCs were spherical in shape, porous in nature and spongy. The irregularity in the shape may be due to the existence of lipid. It was shown in Figure 6.

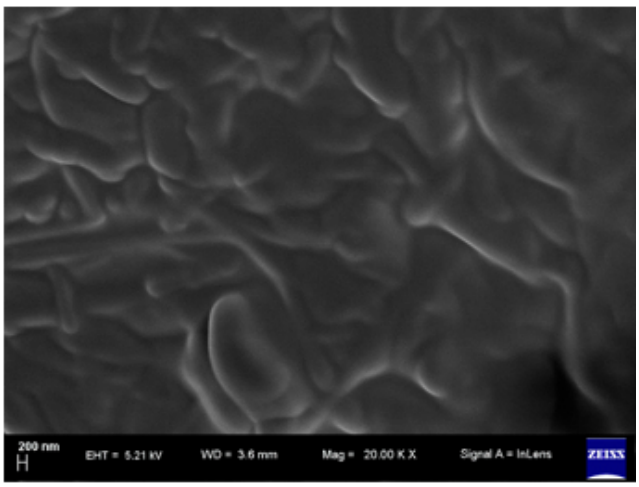

Fig. 6: SEM image of F3 batch

4.6. *Zeta potential*

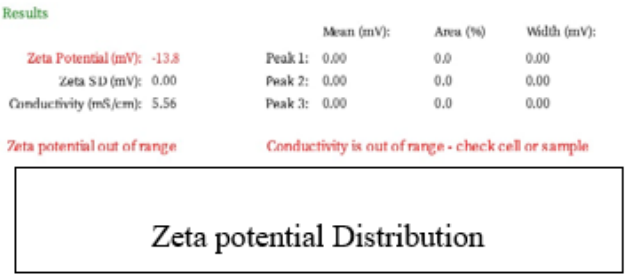

Fig. 7: Zeta potential for F3 batch.

4.7. *DSC (Differential Scanning Calorimentry)*

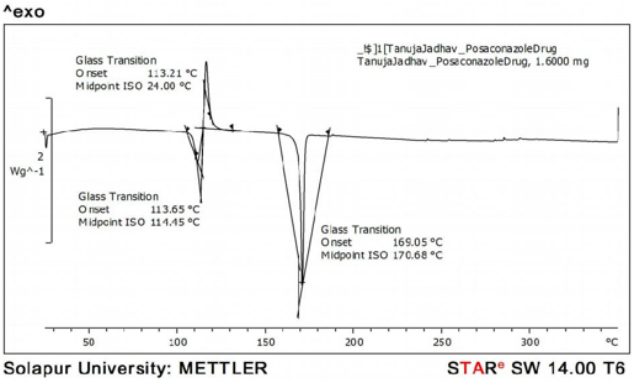

Fig. 8: DSC Thermogram of Posaconazole.

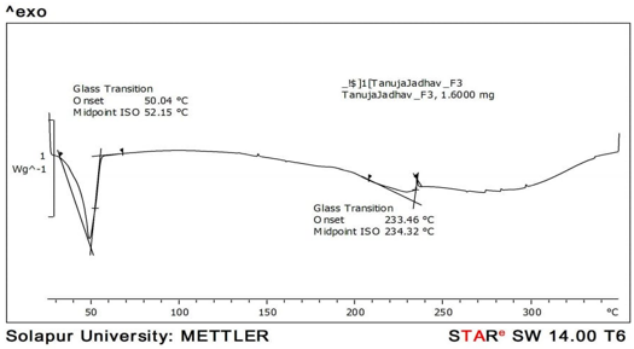

Fig. 9: DSC Thermogram of F3 batch.

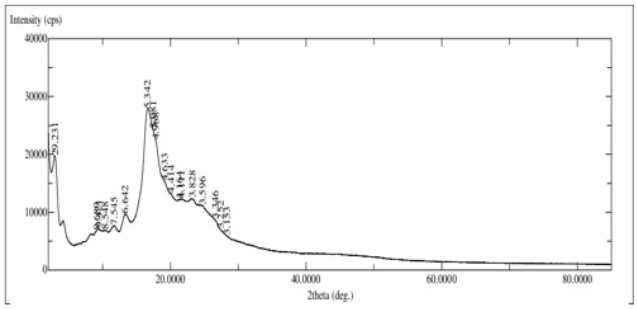

Fig. 10: XRD results for Posaconazole.

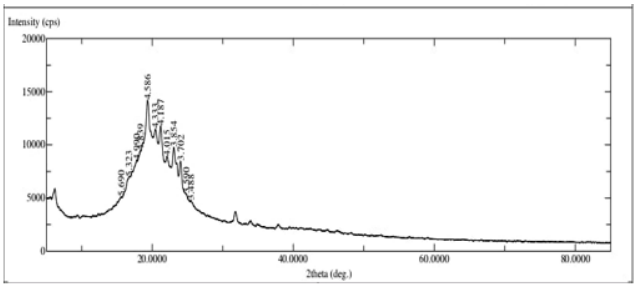

Fig. 11: XRD results for F3 batch.

Table 3: Formulation table for preparation of Posaconazole loaded NLC's gel.

Sr. no.	Ingredients	Qty (%)	Qty (gm)
1	NLC's	15	7.5
2	Propylene Glycol	10	5
3	Water (q.s)	73.4	36.7
4	Carbopol 980	1.5	0.75
5	Triethanolamine	0.1	0.05
Total		100	50

4.8. X-ray diffraction (XRD) studies

4.9. Preparation of posaconazole loaded NLCS

5. Evaluation of Posaconazole Loaded NLCS

5.1. Viscosity

The viscosity of the optimized gel F3 batch was determined using Brookfield viscometer and found to be 34666 cps. It was carried out in triplicate manner.

5.2. pH measurement

pH was measured using pH meter and it was found to be 5.7 for the optimized NLCs gel.

5.3. Spread-ability

The spread-ability of the optimized NLCs gel was found to be 12.22 ± 0.8 cm. The obtained value indicated good spread-ability of the gel preparations. Spread-ability is an essential property from the point of view of the patient compliance whereas it's also important if applied gel on the inflamed skin or damaged skin would more comfortable if it can spread easily.

5.4. Extrudability

The extrudability of the optimized gel F3 batch was found to be 85.34% and it can be said that it shows acceptance property.

5.5. In-vitro drug release studies

The in-vitro release profile of Posaconazole loaded NLCs gel was obtained by using Franz diffusion cell. From the results, it was observed that 57.89% drug released in 2hrs from the optimized NLCs gel, whereas in 6hrs 98.62% drug released which revealed that the formulation is effective for topical delivery of drug. The results are presented Figure 12.

The in-vitro drug release data from optimized NLCs gel was then fitted to various models. The results are presented Figures 13, 14 and 15.

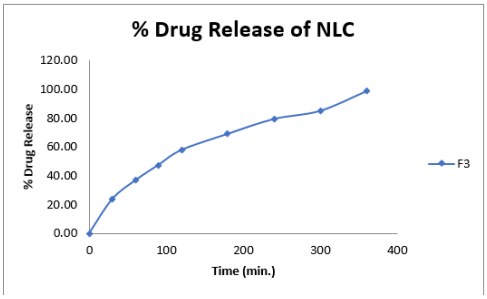

Fig. 12: % drug release graph for optimized Posaconazole loaded NLC's gel.

5.6. Mathematical kinetic models

Fig. 13: First order model.

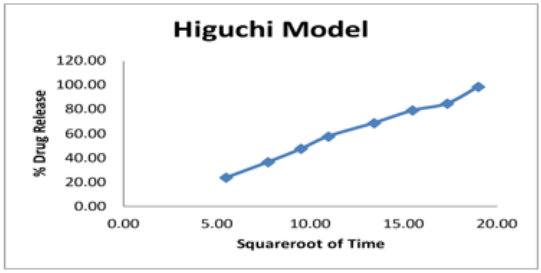

Fig. 14: Higuchi model.

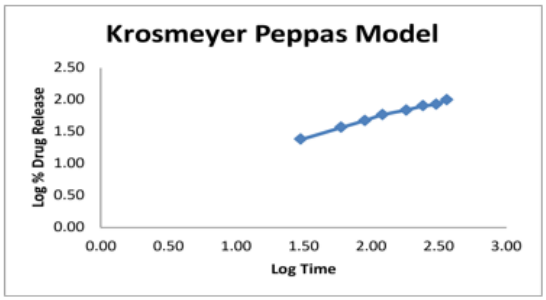

Fig. 15: Krosmeyer peppas model.

6. Summery and Conclusion

The main goal of the research work was to prepare Posaconazole loaded nanostructured lipid carriers (NLC's) for improving the solubility, drug release profile and patient compliance. It was proved by FTIR studies that there were no chemical interaction between the drug and excipients. Solid lipid as GMS, liquid lipid as oleic acid and surfactants tween 80, span 80 was used for formulation which was carried out by using high speed homogenization followed by sonication technique. The % entrapment efficiency of F3 batch was found to be more than 95%. Scanning-electron microscopy was done by using ZEISS instrument. The average particle size range for F3 batch was found to be 200nm whereas, NLC's showed spherical surface of particles and irregularity in the shape which is due to the availability of lipids. DSC studies were carried out which shows physical compatibility of excipients. XRD studies were carried out which shows conversion of amorphous form to crystalline form. Zeta potential were carried out which shows incipient instability but F3 batch shows good stability compared to other batches. Solubility studies of Posaconazole and excipients was measured using pH 6.8 phosphate buffer with 0.5% w/v SLS. Increase in solubility was observed. The in-vitro drug release for optimized batch of gel was found to be 98.62% in 6hrs. The obtained drug release data was put in various kinetic mathematical models.

It was concluded that Posaconazole loaded NLC's were produced by high-speed homogenization followed by sonication technique. Depending upon drug content, % EE, SEM, DSC, XRD, FTIR and zeta potential F3 batch containing GMS, oleic acid 3:7 and span 80, tween 80 2:2 was considered as optimized batch. The results of above study shows that research work was satisfactory for improved solubility, drug release profile, patient compliance for the topical delivery of the drug.

7. Source of Funding

None.

8. Conflict of Interest

None.

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