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FORMULATION AND EVALUATION OF LINEZOLID LOADED SOLID LIPID NANOPARTICLES AS TOPICAL GEL

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Keywords:

SLN, Linezolid, Lipoids, Surfactants, Taguchi L9 orthogonal design of experiment, Higuchi release

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ABSTRACT: Linezolid loaded Solid Lipid Nanoparticles (SLN) were prepared and then incorporated in a topical gel as a carrier. The formulation was prepared by solvent injection method followed by probe sonication for reducing particle size. Excipients like lipids (Phospholipon 90H, Lipoid S-100, and Lipoid S-75) and emulsifier (Tween-80, Span-20, and poloxamer-407) were optimized using Taguchi L9 orthogonal design of an experiment. The optimized formulations were based on entrapment efficiency and were further evaluated for particle size, polydispersity index, zeta potential, *in-vitro* and *ex-vivo* studies. SLN4, SLN5, and SLN6 were optimized as their entrapment was more compared to other formulations. The results obtained were 93.05 nm of particle size, 0.252 is PDI, and -13.0 mV of zeta potential. From the *in-vitro* studies, it has been found that SLN5 with 2% of lipid is showing sustained-release followed by SLN4 (1.5%) and SLN6 (1%), and hence SLN5 was selected for evaluations like *ex-vivo* studies, and stability studies of gel. *Ex-vivo* permeation studies have shown sustained release of drugs with a flux of 11.22 ± 0.10 µg/cm^2 /hr. Skin retention was found to be 88.93 ± 0.6%. Stability studies were performed for one month at 4 °C ± 2 °C and evaluated for entrapment efficiency (%), drug content (%), appearance, and pH. Stability results suggested that the formulation was stable for one month. Linezolid loaded SLN for topical use was prepared successfully, and from the results, it was concluded that the prepared formulation can be used for localized bacterial infections, showing sustained drug release.

INTRODUCTION: Topical drug administration is a localized drug delivery system anyplace within the body through ophthalmic, rectal, vaginal, and skin as topical routes. Patients tend to like those ways be painless and straightforward, which is why many pharmaceuticals come in the form of topical and enteral methods which can be taken by mouth or applied directly to the skin [1].

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Various skin diseases can be treated by formulating them as SLN due to localized action and minimized systemic side effects provided by the formulation [2]. Linezolid is a synthetic antibacterial agent of a new class of antibiotics, the oxazolidinones, which has clinical utility in the treatment of infections caused by aerobic gram-positive bacteria.

The drug inhibits bacterial protein synthesis through a mechanism of action different from that of other antibacterial agents; therefore, cross-resistance between linezolid and other classes of antibiotics is unlikely [3]. Formulating Linezolid as SLN will provide sustained release, which will aid in a longer duration of action and longer availability of the drug at the site of application.

In this present study, an attempt is made for delivering Linezolid through topical route in order to get the response at the site of application, and doing this will minimize the unwanted side effects, which are seen through the administration of linezolid by enteral and parenteral routes.

By topical administration of linezolid there is a chance for delivering the drug at the site of infection, thereby enhancing drug concentration and improving therapeutic action.

MATERIALS AND METHODS:

Materials: Active entity, Linezolid was obtained as a gift sample from Optimus drugs Pvt. Ltd. Lipid, Stearic acid was purchased from Finar chemicals, hyd. Phospholipon 90H, Lipoid S-75, and Lipoid S-100 were purchased from Lipoid, Germany. Surfactant, Tween-80, and Span-20 were purchased from SD fine chem. Limited. Poloxamer-407 was purchased from Yarrow, Mumbai. All reagents were of analytical grade.

Methods:

Analytical Screening: Drug and excipient compatibility were studied by FTIR.

Preparation of SLN: SLN of Linezolid was prepared by the solvent injection method. In this method, the lipid phase was prepared by melting lipid, stearic acid (70 °C) and lipophilic surfactant, Phospholipon 90H, or Lipoid S75 or Lipoid S100 together. Then the drug, linezolid, was dissolved in ethanol, which was then added to the melted lipid phase. This solution was taken in a syringe and was injected rapidly into the aqueous phase containing hydrophilic surfactant, Tween-80, or Span-20 or Poloxamer-407 to get pre-emulsion. Then the formulation is sonicated using probe sonicator to get nano-particulate semi-solid formulation. While doing sonication, the temperature was maintained at 4 °C to avoid lipid degradation due to heat produced by the sonicator4. All the formulations were prepared as per the combinations given by Taguchi design **Table 2**.

Experimental Design:

Selection of Method and Screening of Excipients: Screening for a method of preparation was done from the literature survey, and it was found that there are many methods of preparation for SLN. However, various methods were screened based on the feasibility of preparation at lab scale. Screening of excipients like lipids and surfactants was done based on vesicle formation, then lipophilic and hydrophilic excipients were selected.

Optimization of Linezolid Loaded SLN Gel using Taguchi OA L9 Design Experiment: Taguchi experimental design was used to study the effect of different lipids like Phospholipon 90H, Lipoid S-100 and Lipoid S-75 at three levels of 1 %, 1.5%, and 2% and effect of different surfactants like Tween-80, Span - 20 and Poloxamer-407 at three levels of 1%, 2.5% and 5% **Table 1**.

TABLE 1: DEPENDENT AND INDEPENDENT FACTORS FOR TAGUCHI DESIGN

Independent variables	Level A	Level B	Level C
Factor A (type of lipid)	Phospholipon 90H	Lipoid S-75	Lipoid S-100
Factor B (type of surfactant)	Tween-80	Span-20	Poloxomer-407
Factor C (% of lipid)	1 %	1.5 %	2 %
Factor D (% of surfactant)	1 %	2.5 %	5 %

TABLE 2: FORMULATION TABLE BY TAGUCHI PERMUTATION COMBINATIONS

Material (% w/v)	SLN1	SLN2	SLN3	SLN4	SLN5	SLN6	SLN7	SLN8	SLN9
Linezolid (mg)	60	60	60	60	60	60	60	60	60
Stearic acid	2	2	2	2	2	2	2	2	2
Phospholipon 90H	0.1	0.15	0.2	-	-	-	-	-	-
Lipoid S-100	-	-	-	0.15	0.2	0.1	-	-	-
Lipoid S-75	-	-	-	-	-	-	0.2	0.1	0.15
Tween-80	0.1	-	-	0.5	-	-	0.25	-	-
Span-20	-	0.25	-	-	0.1	-	-	0.5	-
Poloxamer-407	-	-	0.5	-	-	0.25	-	-	0.1
Ethanol	3 ml								
Distilled water	Up to 10 ml								

Four factors (independent variables) such as type of lipid, type of surfactant, the concentration of lipid, and concentration of surfactant, were studied at all three levels. Entrapment efficiency was taken as the response (dependent variable). An L9 orthogonal array was used for choosing the best and optimized formulation. The software used was Minitab-18 English. The resultant formulations were studied for drug content, pH, *in-vitro* dissolution study, *ex-vivo* studies [5].

Physicochemical Evaluation of Linezolid Loaded SLN Gel: Physicochemical evaluations that were performed on linezolid loaded SLN gel were drug content, pH, spreadability, extrudability, viscosity, homogeneity.

A. Estimation of Drug Content: One gram of optimized Linezolid SLN gel was taken into a 10 ml standard volumetric flask and mixed with methanol. Dilutions were done with 7.4 pH PBS6. The amount of drug per 1 g of gel was determined spectrophotometrically at 252 nm after filtration [7].

Drug loading (%) = Amount of drug present / Total amount of drug taken × 100

B. Visual Appearance and pH: Visual appearance and clarity of prepared Linezolid loaded SLN gel was observed and checked for clarity. The pH of each gel batch was determined using a pH meter (JENWAY 350, UK). One gram of each formulated gel was dispersed in 30 ml of distilled water, then the pH was measured, which was noted by bringing the electrode near the surface of the formulations and allowing it to equilibrate for 1 min [6].

C. Spreadability: The spreadability of the formulation was measured by taking 0.25 g of the gel on the glass plate, and then a second glass plate was kept upon it. 250 g of weight was permitted to rest on the upper glass plate for 2.5 min. (150 sec.) [6]. Then spreadability is calculated using the formula, Where s = Spreadability, m = weight on the upper slide, l = length of the formulation after a certain time, t = time

$$\text{Spreadability (s)} = m \times lt$$

D. Extrudability: A closed aluminium collapsible tube was taken and filled with 20 g of gel. It was pressed firmly at the crimped end, and a clamp was applied to prevent any rollback of gel. The cap was removed, and the gel was extruded. The percentage of gel extruded **Fig. 3** Spreadability procedure was observed and grades were allotted [6] (+++ Good; ++ Fair; + Poor).

E. Determination of Viscosity: Viscosity of prepared gels was determined by Brookfield viscometer (model LVDV-II+PRO). The spindle number 64 was rotated at 15 rpm. The determination of viscosity for each formulation was done in triplicate and average of it was calculated6.

F. Percentage Yield: After preparation, the formulation of drug-loaded SLN was accurately weighed. The % yield of SLN was calculated by the formula.

Percentage yield = Practical yield / Theoretical yield × 100

Evaluation of Linezolid Loaded SLN Gel:

A. Measurement of Particle Size and Polydispersity Index: the mean particle size, particle size distribution and polydispersity index of the prepared formulations were measured using Photon Correlation Spectroscopy (Malvern Instruments, UK). The sample was diluted with distilled water (1: 100), and the measurements were done at 25 °C at an angle of detection of 90° 8,9.

B. Zeta Potential: Zeta potential was determined by measuring the electrophoretic mobility using Malvern Zetasizer Nano ZS 90 (Malvern Instruments, UK). The field strength applied was 20 V cm^{-1}. Prior to the measurement, all samples were diluted in distilled water10.

C. Surface Morphology: The morphological characteristic of SLN was determined by scanning electron microscope (JEOL-JSM-6360 JAPAN). One drop of the sample was placed on a slide, and excess water was left to dry at room temperature. Then the slide was attached to the specimen holder using a double-coated adhesive tape and gold-coated under vacuum using a sputter coater (Model JFC-1100, Jeol, JAPAN) for 10 min. and investigated at 20 kV8.

D. Entrapment Efficiency: 5 mg equivalent formulation was taken in a volumetric flask and diluted up to 10 ml with buffer. The diluted formulation was taken in Eppendorf tubes and ultra-centrifuged at 10,000 rpm for 2 h at 4 °C. The

supernatant was collected carefully and filtered. The filtered sample was analyzed by UV at 252 nm to get the drug present in supernatant [10].

E.E (%) = (Total amount of drug in the formulation - Drug in supernatant) / Total amount of drug in fromulation × 100

***In-vitro* Drug Release Studies:** Diffusion studies were performed using Franz diffusion cell. The cell was locally fabricated, and the volume of receptor compartment was 50 ml, which is filled with buffer. The dialysis membrane used for diffusion studies was placed between donor and receptor compartment. Optimized Linezolid loaded SLN formulations are uniformly applied on membrane and clamped together. The receptor compartment was filled with pH 7.4 phosphate buffer saline and maintained by continuous stirring at 50 rpm with a magnetic bead and maintained at 37 °C.

At predetermined time intervals, 5 ml samples were withdrawn and replaced with an equal volume of buffer. The samples were analyzed after appropriate dilution at λ_{max} of 252 nm using UV spectrophotometer. The release rate was calculated by plot the amount of drug permeated versus square time. The slope is the release rate (µg/cm²/√hr.) [6].

***Ex-vivo* Studies of Optimised Formulation:** The *ex-vivo* permeation studies of optimized formulation and placebo gel were determined using Franz diffusion cell. The male Wister rat skin was mounted on the receptor compartment with the stratum corneum side upwards into the donor compartment.

The effective surface area of the cell was 2.0 cm^2 and had a receptor volume of 20 ml. The donor compartment was applied to the formulation. 20 ml of pH 7.4 phosphate buffer saline was used as a receptor medium to maintain the sink condition. The receptor compartment was maintained at 37 °C and stirred by a magnetic bead. At appropriate intervals, 1 ml of aliquot was withdrawn and replaced by fresh media [11]. The samples were analyzed by UV spectrophotometry at 252 nm.

A. Calculation of Permeability Parameters:

I. Steady State Flux (µg/cm²/hr.): Steady state flux (Jss) is defined as the rate of diffusion or transport of a substance through a permeable membrane.

The steady-state flux can be obtained by plotting the cumulative amount of drug permeated in micrograms per square centimeter versus time in hours, and the slope is the flux. Lag time is X intercept of this graph.

II. Permeability Coefficient (cm/hr.): The permeability coefficient (Kp) was calculated with the following equation:

$$Kp = Jss/CV$$

Where, CV is the total donor concentration of the formulation.

B. Calculation of Release Kinetics for Prepared Formulation: Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first-order, Higuchi and Korsemeyer-Peppas release model, to study the drug release from the dosage form.

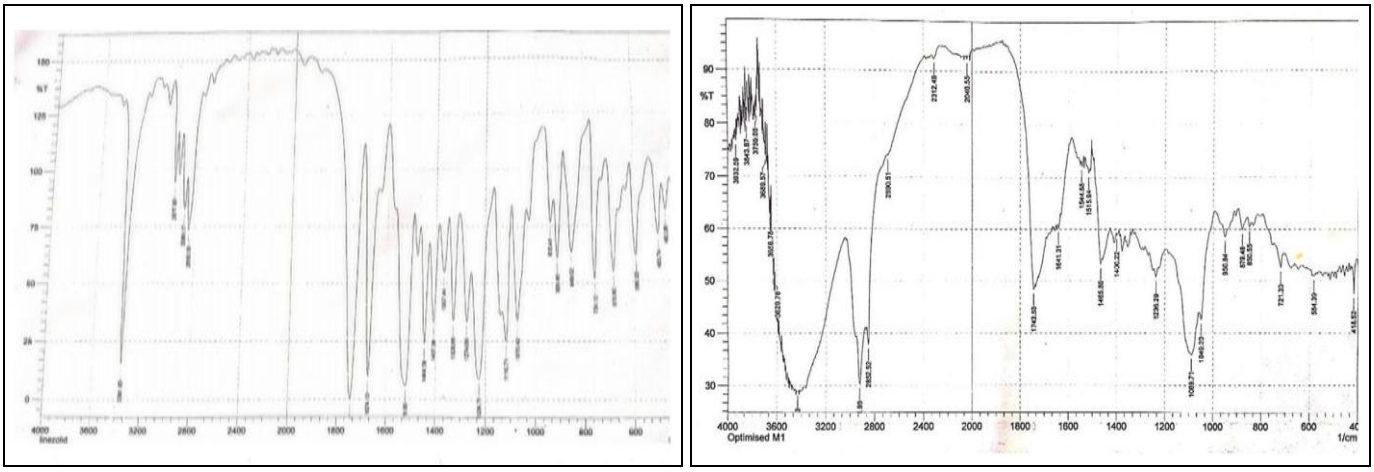
C. Skin Retention Studies: After *ex-vivo* diffusion studies, the diffusion cell was dismantled, and rat skin was removed carefully. Then the skin was soaked in methanol overnight to remove formulation attaching to the skin. The skin was cut into small pieces, homogenized and drug present in the skin was extracted in buffer under sonication, after filtration through Whatman filter membrane and a sample was analyzed by UV spectroscopy and % drug deposited in the skin was calculated [12].

D. Skin Irritation Study: It was performed by using control gel and test formulation. After the removal of hair from the left dorsal surface of rabbit skin, gel was applied, and applied areas were examined for 8 h. The presence of erythema and edema were evaluated, and the score was given according to the Primary Dermal Irritation Index classification (PDDI) [12].

Stability Studies: Stability studies were carried out by keeping optimized formulations in glass containers with polypropylene closure for one month at freezer temperature, as lipids are not stable at room temperature. Known amount of SLN gel was taken out at different time intervals like 0, 1st, 2nd, 4th week and was analyzed for entrapment efficiency, appearance, pH, and drug content [12].

RESULTS AND DISCUSSION:

Analytical Screening: Drug excipients compatibility studies were done by FTIR. Peaks present in the optimized formulations were the peaks present in the individual components used and no new peak was observe indicating there exist no incompatibility between the drug and other components employed for formulation **Picture 1**.



PICTURE 1: FTIR SPECTRUM OF LINEZOLID AND FTIR SPECTRUM OF OPTIMIZED FORMULATION

Preparation of SLN: Formulations were prepared based on the experimental run's formula from Taguchi design (**Table 2**). The solvent injection method was successfully employed to prepare SLN.

Experimental Design:

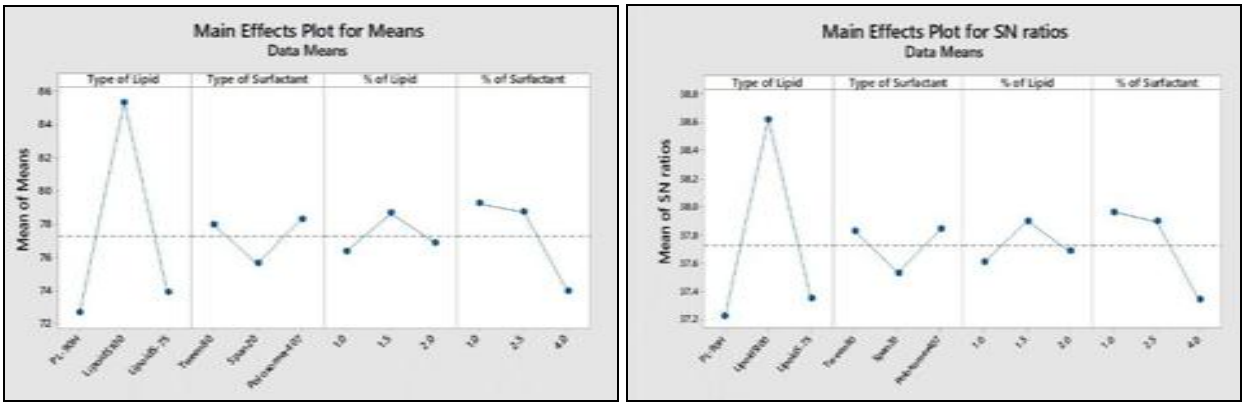
A. Screening of Method of Preparation: During screening for various methods of preparation, solvent injection followed by probe sonication is found to be a feasible and effective way of preparation of SLN [4]. Formulations were successfully prepared with the screened method of preparation, solvent injection followed by probe sonication

Screening of Lipids and Surfactants: Vesicles were observed for formulations employing lipids like Phospholipon 90H, Lipoid S75, and Lipoid S100 and the hydrophilic surfactants were Tween-80 Span-20 and Poloxamer-407

B. Statistical Analysis of Taguchi Designs: One-way ANOVA was used in the analysis of the Taguchi design of the experiment. ANOVA is used to determine whether the factors are significantly related to response [5].

TABLE 3: ANOVA TABLE

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Type of Lipid	2	293.53	146.76	12.22	0.008
Type of Surfactant	2	12.85	6.427	0.11	0.898
% of Lipid	2	8.704	4.352	0.07	0.930
% of Surfactant	2	50.49	25.25	0.48	0.640



PICTURE 2: MAIN EFFECT PLOTS FOR MEANS AND SN RATIO

ANOVA **Table 3** shows that the type of lipid has a significant effect on the entrapment efficiency as the 'P' value is 0.008 at 95% confidence interval. The type of surfactant, the concentration of lipid and concentration of surfactant does not have a significant effect on the entrapment efficiency, 'P' value is 0.898, 0.930 and 0.640 at 95% confidence interval respectively which implies the factors are statistically insignificant, In **Picture 2**, the intervals for any two means or SN ratio are not overlapping, suggesting that the population means are different.

Physicochemical Evaluation of Gel Formulations:

A. Drug Content: The percentage drug content for optimized formulations and control gel was found in between 95% - 98%. Indicating efficient drug loading.

B. Visual Appearance pH: All the prepared gels of selected SLN formulations were spreadable, white, smooth, and homogenous with semisolid consistency. The pH of all prepared SLN gels was found in the range of 7.02 - 7.12.

C. Spreadability: Spreadability of all the formulations was found to be between 2.4 to 3.0 g.cm/sec.

D. Extrudability: Extrudability of optimized formulations was excellent.

E. Viscosity: Viscosities for all the formulations were found in the range of 180 - 260 cps.

F. Percentage Yield: Percentage yield for all the formulations was found to be in the range of 90-95 %.

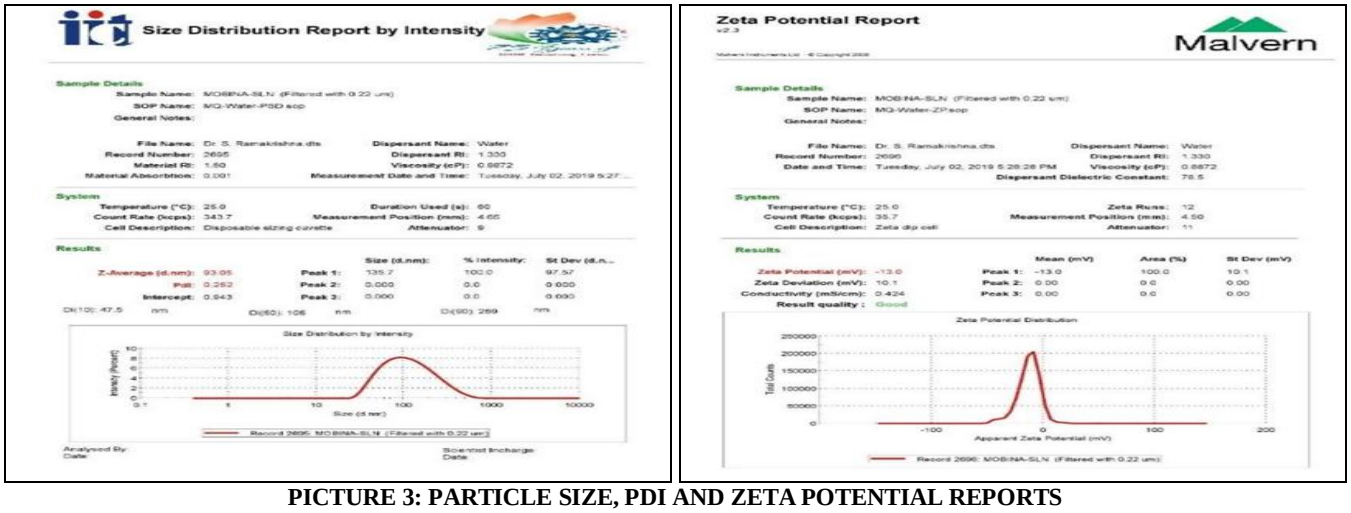
Evaluation of Linezolid Loaded SLN Gel:

A. Particle Size and Polydispersity Index: The Z-avg value of optimized formulation SLN5 was found to be 93.05 nm **Picture 3**.

Smaller size particles are obtained by solvent injection method, and the decrease in size was due to presence of lipophilic surfactant in higher concentration (Lipoid S100 - 0.2 %) in combination with hydrophilic surfactant (Span 20 - 0.1%), presence of surfactant leads to decrease in surface tension between the aqueous phase and lipid phase thereby aiding in the formation of smaller size particles.

Polydispersibility index (PDI) is a measure of particle size distribution and will define the correctness of the method of preparation used.

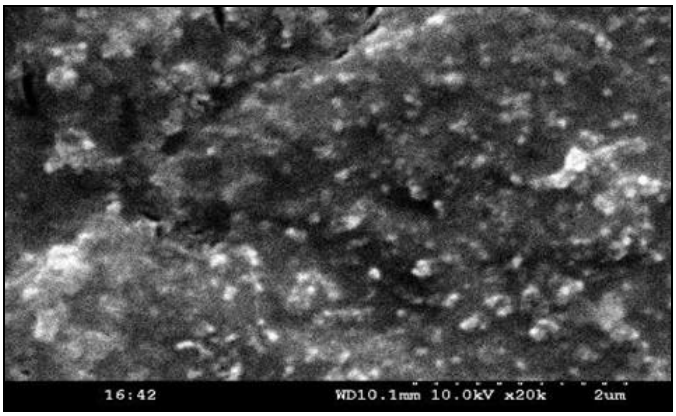
PDI of optimized SLN5 formulation was found to be 0.252 **Picture 3,** which is less than 0.5 and is acceptable, indicating narrow particle size distribution. The method chosen was appropriate as the PDI is less 10.



PICTURE 3: PARTICLE SIZE, PDI AND ZETA POTENTIAL REPORTS

B. Zeta Potential: Zeta potential is an important parameter for deciding the stability of the formulation. Optimal zeta potential value should be ± 30 mV, as a higher charge on the particles indicates more repulsive forces hence decreasing particle aggregation and increasing the stability of the formulation. For optimized formulation, -13.0 mV **Picture 3** of zeta potential was observed, and this might be due to the present of Span 20, which will impart a negative charge to the formulation [10].

C. Surface Morphology: SEM images of optimized formulation **Picture 4** reveals that the smaller particles possess round shape.



PICTURE 4: SEM IMAGE OF OPTIMIZED FORMULATION

D. % Entrapment efficiency (% EE): Influence of various variables like type of lipid, type of surfactant, the concentration of lipid and concentration of surfactant were studied on % EE. From the DOE it was found that type of lipid has a greater influence on % EE than other variables **Table 3**. The % EE was found in the range of 67.90 % - 86.80 %, of all the formulations SLN4, SLN5 and SLN6 showed higher entrapment due to the presence of Lipoid S-100. As the concentration of lipid was increased, more space was provided by the lipid for entrapment of drug so EE increased from SLN4-SLN6 [10].

TABLE 4: RESPONSE TABLE FOR ENTRAPMENT EFFICIENCY

Formulation code	Entrapment efficiency (%)
SLN1	74.32
SLN2	73.75
SLN3	69.91
SLN4	84.03
SLN5	85.16
SLN6	86.80
SLN7	75.54
SLN8	67.90
SLN9	78.144

***In-vitro* Diffusion Studies:** From the % entrapment efficiency data higher incorporation was found in SLN4, SLN5 and SLN6, so this formulation was selected for diffusion studies.

From diffusion data, SLN4 showed 87.71% release after 8 h, SLN5 showed 72.88% release after 8hrs and SLN6 showed 79.23% release after 8 h. Of the above formulations SLN5 showed sustained release **Fig. 1** due to the presence of Lipoid S100 - 0.2% compared to other formulations like SLN4 with Lipoid S100 - 0.15% and SLN6 with Lipoid S100 - 0.1%. The sustained release of the formulation is due to the lipid matrix, and an increase in lipid concentration leads to a decrease in drug release either by decreasing the partitioning of the drug from lipid matrix into the receiver medium or by increasing the thickness of lipid barrier and increasing the length of diffusion. This result followed the results reported by Khalil *et al.*, (2014) [13] and Pandita *et al.*, (2009) [14]. Initial burst release followed by sustained release was observed with the formulations **Fig. 1**. This mechanism is useful in dermal applications as the burst release will provide faster onset of action and aids in penetration, whereas the sustained release provides action for a longer duration of time [15]. For getting a sustained release, SLN5 can be considered, and for better release, SLN4 and SLN6 can be considered depending on the action needed.

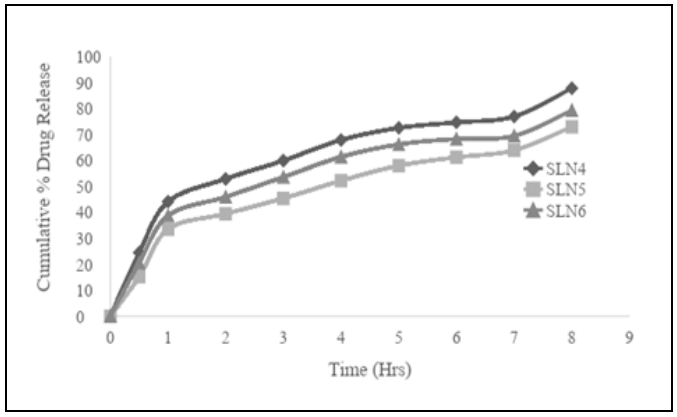


FIG. 1: *IN-VITRO* DRUG RELEASE OF OPTIMIZED FORMULATIONS

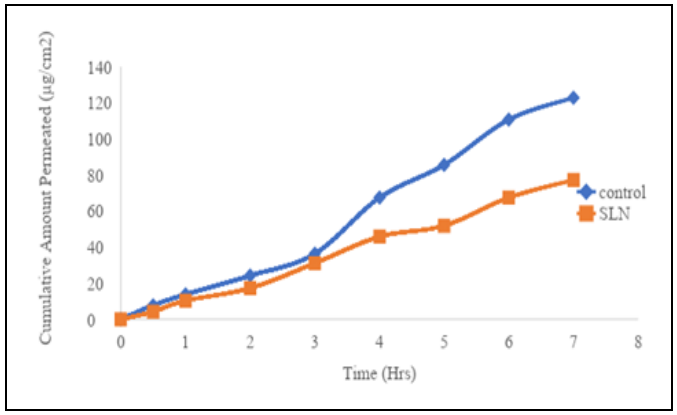


FIG. 2: *EX-VIVO* STUDIES OF OPTIMIZED AND CONTROL FORMULATION

***Ex-vivo* Studies of Optimized Formulation:** *Ex-vivo* diffusion studies were performed for the formulation of SLN5 and compared with pure drug

formulation **Fig. 2**. SLN formulation showed sustained slower release than control gel, indicating sustained release can be achieved by preparing SLN.

A. Calculation of Permeability Parameters:

I. Flux: Flux for the prepared formulation was sustained when compared with that of pure drug formulation **Table 5** this might be due to the presence of lipid matrix, which will control drug release from the formulation [10]. Lesser flux was observed due to ionization of drug in the medium as the pka of the drug was 1.4, and pH of the buffer was 7.4, and due to less log P value of drug, 0.9, the permeation was less through the skin [16]. When compared to *in-vitro* diffusion studies, the drug permeation results in ex-vivo were less; this might be due to multilayered rat skin compared to single-layer dialysis membrane [17].

II. Permeability Coefficient (Kp): Kp of optimized formulation was found to be more compared with pure drug **Table 5;** this might be due to the presence of emulsifiers in the SLN, which will decrease the interfacial tension and increase the contact duration with skin [17].

TABLE 5: PERMEABILITY PARAMETERS

Formulation Code	Flux (µg/cm^2/hr)	Permeability coefficient (cm/hr)	Lag time (hr.)	Tissue deposition (%)
Control gel	18.24 ± 0.08	6.08×10^{-3}	0.15	4.3
SLN5	11.22 ± 0.10	3.74×10^{-3}	2	16.93

B. Calculation of Release Kinetics for Prepared Formulation: The *ex-vivo* diffusion data were fitted into the model-dependent kinetic plots to determine the order and mechanism of release, and the results are shown in **Table 6**. It was found that the formulation follows the first-order release with case-2 transport mechanism [10].

TABLE 6: DRUG RELEASE KINETICS

Formulation code	r^2				n	Drug transport mechanism
	Zero	First	Higuchi	Peppas		
SLN5	0.982	0.993	0.904	0.994	1.08	Case-II transport

C. Skin Retention Studies: From **Table 5** we can say more skin deposition is observed with SLN formulation when compared to that of control gel; this might be due to two reasons.

One is due to the presence of a lipid matrix, which will provide fluidization of stratum corneum and hence more penetration, and the second reason is because of nanosized of the particles adhesive surface is provided due to which an occlusive layer is formed, and we can achieve retention in skin [18].

PICTURE 5: SKIN IRRITATION STUDIES

D. Skin Irritation Studies: The skin irritation studies results were based on visual observation of erythema (redness) and edema (swelling). The use of both the gels showed no skin irritancy (score = 0) on rabbit skin **Picture 5**. This result suggests that the SLN gel exhibits no irritation, hence, improving patient acceptability and skin suitability. Linezolid loaded SLN gel was found to be safe for topical application [12].

Stability Studies: Stability studies were done on SLN5 formulation at freezer temperature, and there was no significant change observed in various parameters [12].

SUMMARY AND CONCLUSION: Linezolid loaded solid lipid nanoparticles were successfully formulated and loaded in a topical gel. Drug and excipient compatibility were studied by FTIR, and no incompatibility was observed. Optimization of phospholipids and surfactants at three different concentration levels was performed by Taguchi L9 orthogonal array (34, *i.e.*, four factors, type of lipid, type of surfactant, the concentration of lipid and

concentration of surfactant at three different levels) design using Minitab-18 English software. Using Taguchi design, in the present study, it has been found that the type of lipid is having more influence on entrapment efficiency when compared with other parameters (type of surfactant, % of lipid, % of surfactant) based on probability values. From the selected lipids (Phospholipon 90H, Lipoid S-75, Lipoid S-100) Lipoid S-100 in the concentration range of 1-2% is showing better EE. They contain surfactants like Tween-80, Span-20 and polo-xomer-304 in the concentration of 0.4, 0.1 and 0.25, respectively.

From the Taguchi experimental formulas SLN4, SLN5 & SLN6 were optimized to evaluate parameters like particle size, *in-vitro* and *ex-vivo* studies *etc*. The average size, PDI for the optimized formulation, was found to be 93.05 nm, 0.252, respectively, with a zeta potential of -13.0 mV all the values were within limits, which indicate that formulation is physically stable.

From the *in-vitro* studies, it has been found that SLN5 with 2% of lipid is showing sustained-release followed by SLN4 with 1.5% and SLN6 with 1%. *Ex-vivo* permeation studies for optimized formulation SLN5 have shown sustained release of drugs with a flux of 11.22 ± 0.10 µg/cm^2/hr.

The release date was in favor of the Higuchi diffusion model, which will define drug diffusion from transdermal matrix preparations. Skin retention for optimized formulation SLN5 was found to be 16.93%, which is greater when compared with that of control gel, which shows 4.3% of retention; therefore, the formulation will show sustained release at the applied area.

Skin irritation studies were performed, and no redness or swelling is observed; hence the formulation is safe for application. Stability studies were performed for 1 month at refrigeration condition (4 °C), and various parameters were evaluated at regular time intervals. All the values were within limits indicating the stability of the formulation.

FUTURE SCOPE: Efficacy of the formulation must be proved by preclinical and clinical studies, once proved can be used for the treatment of cellulitis, which is caused by gram-positive bacteria and need a higher class of antibiotics like linezolid.

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CONFLICTS OF INTEREST: The authors declare that there is no conflict of interest.

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