**RESEARCH PAPER**

# DESIGN, DEVELOPMENT, OPTIMIZATION AND CHARACTERIZATION OF LINEZOLID MICRONEEDLE PATCH USING DESIGN EXPERT SOFTWARE FOR ACCELERATED WOUND HEALING PROCESS

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**ABSTRACT:**

Microneedles represent a promising advancement in wound healing treatment, combining precision drug delivery with minimally invasive techniques to enhance therapeutic outcomes. The study on the development of microneedle patches for the transdermal delivery of Linezolid aimed at improving localized drug therapy, especially for wound healing. The study's objective was to create and evaluate dissolving microneedle patches for the treatment of wound healing that are composed of polymers and Linezolid. Microneedle patches were developed by Solvent Casting and Micro molding technique. Linezolid was used as active constituent, and polymers like Hydroxyethyl Cellulose, Polyvinyl Alcohol and glycerol were used for the development of microneedle patches. Four formulations were created by altering the concentration of various polymers while maintaining a constant drug ratio. The optimization was performed by Design Expert software (DoE) using $2^2$ full factorial design by taking 2 independent variable as factors and 2 dependent variables *in-vitro* Drug release(Y1) and Drug content(Y2). FTIR, as well as other metrics like drug content, moisture loss %, folding endurance, SEM analysis, in-vitro drug release, in-vitro release kinetics, and stability tests, were used to examine the produced Microneedle patches for the interaction study. Franz diffusion cell was used to conduct ex-vivo investigations on the optimal formulation F3, which was chosen based on the in-vitro release research and drug content. After eight hours, the created Microneedle patch displayed 97.51% drug release. FTIR, as well as other metrics like drug content, moisture loss %, folding endurance, SEM analysis, in-vitro drug release, in-vitro release kinetics, and stability tests, were used to examine the produced Microneedle patches for the interaction study. The optimized formulation F3 was chosen based on the in-vitro release research and drug content, and it was used in ex-vivo experiments. The patches exhibited anomalous transport mechanisms as suggested by the 'R2' values from various mathematical models, indicating diffusion-based drug release. Stability testing of formulation F3 was carried under accelerated conditions, demonstrated no appreciable alterations in the drug concentration, organoleptic characteristics, or physical texture in accordance with ICH criteria, indicating the stability of the manufactured microneedle patch. Thus, it was determined that the research could have a transdermal use. when compared to the conventional therapy for the treatment of accelerated wound healing.

**Keywords:** Linezolid, Microneedle patches, polyvinyl alcohol, Hydroxyethyl cellulose, DoE.

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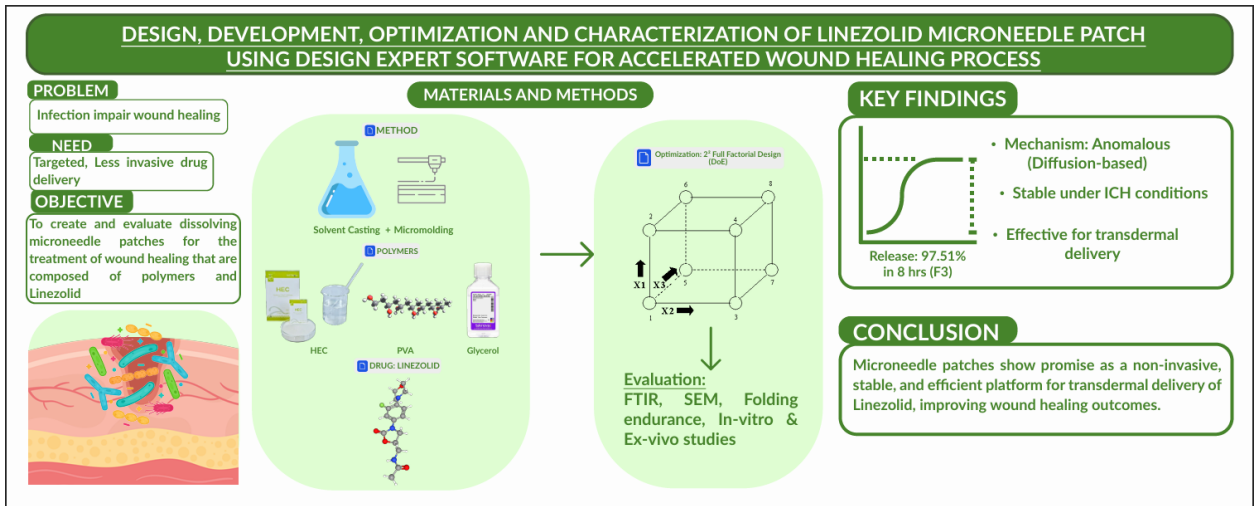



## INTRODUCTION:

Transdermal drug delivery systems (TDDS), or transdermal patches, are gadgets intended for use in medicine administration through the skin into the bloodstream. The skin's outermost layer, the stratum corneum, acts as the primary barrier to drug absorption, requiring drugs to be formulated to be both lipid-soluble and water-soluble to effectively cross this barrier.

Transdermal patches adjust the speed at which the liquid medication enters the bloodstream and passes through the skin by using a specific membrane. Certain medications need to be mixed with things like alcohol in order to make them more soluble in the skin. Thus, the limited capabilities of these systems to administer specific medications resulted in the development of cavitation ultrasound, electroporation, thermal ablation, microdermabrasion, and microneedle (MN)-based methods. Microneedles represent a minimally invasive approach to drug delivery, skincare, and biomedical research. These tiny needles, ranging from tens to hundreds of micrometers in length, puncture the skin's outer layer to facilitate various applications, including enhancing the absorption of therapeutic compounds, enabling painless cosmetic procedures, and serving as platforms for biosensing. Patients often accept this method well since, for certain conditions, "putting on a patch" is more convenient and effective than "popping a pill." Microneedle patches (MNPs) have been shown to deliver drugs more efficiently compared to topical or oral intake, reaching peak concentrations faster (as fast as 20 minutes) and achieving higher maximum concentrations (up to six times higher) than oral intake. This makes MNPs a potential alternative to direct injection, especially for people with needle phobia. Hence aim was focused to develop microneedle patch using Linezolid and suitable polymers like PVA & HEC for the treatment of wound healing.

## MATERIALS AND METHODOLOGY:

### MATERIALS:

**Linezolid** was acquired from NTK PHARMA PVT., Ltd; **Polyvinyl Alcohol** from Thermo Fischer Scientific India PVT., Ltd; **Hydroxyethyl** Cellulose from Carbanio.com; **Glycerol** from Jiangyin Tenghua Import & Export Co., Ltd; **Polyvinyl Pyrrolidone** from Prakash Chemicals Pvt., Ltd, India. All reagents were used exactly as supplied and were of analytical quality.

### METHODOLOGY:

**Preformulation studies**

Before the formulation of a drug substance into a dosage form, it must be chemically and physically characterized. Pre-formulation studies give the information needed to define the nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipients in the fabrication of a dosage form.

**Identification Studies**

**Organoleptic properties of Drug**

The drug sample was noted for its Organoleptic properties such as Color, odor, Taste, and appearance.

**Determination of melting point**

The melting point of the sample was determined by the open capillary tube small amount of powdered drug was filled inside the thin capillary tube and sealed from one side by melting. The capillary was placed into the melting point apparatus. After some time at a specific temperature drugs were melted was the melting point of the drug.

**Determination of solubility**

About 5mg of linezolid was added to 10 ml of various solvents and sonicated for 10 minutes and inspected visually for solubility and compared with standard.

**Determination of Wave Length (λ max)**

Wavelength maxima (λ max) of Linezolid were determined as follows.

**Preparation of standard stock solution:**

The stock solution was prepared by dissolving 100mg Linezolid in 100ml of phosphate buffer pH 7.4 in a volumetric flask by shaking manually for 10 min. The volume was adjusted with the same up to the mark to give the final strength, i.e. 100mg/ml.

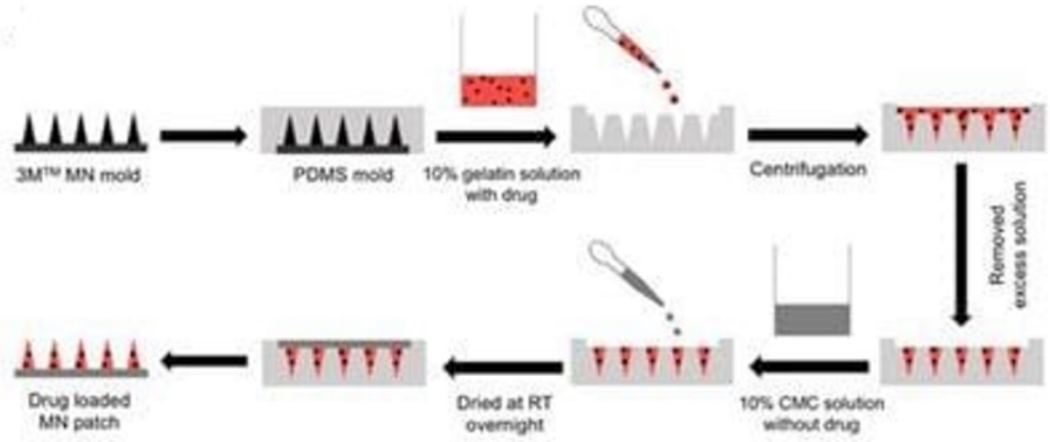



**Figure 1:** Fabrication of Microneedle

**Preparation of Calibration curve**

The solution which was prepared at the concentration of 2, 6, 10, 14, and 20µg/ml, respectively, were scanned on a spectrophotometer in the UV range of 200-400 nm. The spectrum was recorded at 280 nm. The calibration curve was plotted as concentration vs. absorbance.

**Optimization of Linezolid Microneedle Patches Using $2^2$ Full Factorial Design**

Optimization of Linezolid-loaded microneedle patches was performed using a $2^2$ full factorial design with the aid of Design-Expert® software. This experimental design was employed to evaluate the individual and interactive effects of two independent formulation variables on the critical quality attributes of the microneedle patches. Polyvinyl alcohol (PVA) concentration ($X_1$) and hydroxyethyl cellulose (HEC) concentration ($X_2$) were selected as independent variables, each studied at two levels. Drug content and cumulative drug release were considered as dependent responses. A total of four experimental formulations were generated according to the design matrix and prepared using the solvent casting method. The obtained responses were statistically analyzed using analysis of variance (ANOVA), and polynomial equations were generated to describe the relationship between the formulation variables and the responses. Response optimization was carried out to identify the formulation exhibiting the desired characteristics, and the optimized formulation was selected based on maximum drug content and drug release.

**Preparation of Linezolid-Loaded Microneedle Patches by Solvent Casting Method**

Linezolid-loaded microneedle patches were prepared by the solvent casting method using polyvinyl alcohol (PVA) and hydroxyethyl cellulose (HEC) as matrix-forming polymers and glycerol as a plasticizer. Briefly, PVA was dissolved in distilled water by heating at 70–80°C under continuous magnetic stirring until a clear solution was obtained. Separately, HEC was dispersed in distilled water and mixed with glycerol to form a homogeneous solution. The HEC-glycerol solution was then added gradually to the cooled PVA solution under continuous stirring to obtain a uniform polymeric solution.

Linezolid was dissolved in distilled water and incorporated into the polymeric solution with continuous stirring to ensure uniform drug distribution. The resulting formulation was stirred further to remove entrapped air bubbles. The drug-loaded polymeric solution was carefully poured into microneedle molds, and the molds were gently tapped to ensure complete filling of the cavities. The filled molds were dried in a hot air oven at 40°C for 3 h. After complete drying, the microneedle patches were carefully removed from the molds and stored in a desiccator until further characterization and evaluation.

**EVALUATION PARAMETERS OF MICRONEEDLE PATCHES:**

**Drug content uniformity:**

A 4 $cm^2$ film was sliced into tiny pieces and added to a 100ml phosphate buffer with a pH of 7.4. To obtain a homogenous solution, the setup was agitated for thirty minutes and then filtered. After an appropriate dilution, the drug content was measured spectrophotometrically at 251 nm. [15],[16]

**Moisture loss percentage:**

The integrity of the film under dry conditions was evaluated using the percentage moisture loss. The patch was weighed and then stored in a hot air oven. The patches were removed after three days, the weight was collected again, and the percentage of moisture loss was calculated using the formula. [15]

The percentage of moisture loss was computed using

$$\textbf{Moisture loss} = \frac{\textit{Initial weight} - \textit{final weight}}{\textit{Initial weight}} \times 100$$

**Endurance of Folding:**

In order to determine the film's folding endurance, it was folded repeatedly in the same location until it broke or folded in a way that was judged sufficient to reveal good film attributes. This test was applied to every movie. [15], [24]

**SEM Analysis:**

Using a Hitachi SU 8030, Japan (1.0kV) low-speed acceleration voltage SEM (scanning electron microscopy), the morphology of microneedle patches was examined to evaluate the size, shape, and other physical characteristics of the needles. The transcutaneous penetration of Linezolid scanning electron was examined using dissolving microneedles in order to assess the needle's sharpness and array formation. [16]

***In vitro* release studies:**

A Franz diffusion cell with a receptor compartment was used for *in vitro* drug release experiments. After the Microneedle film was made, it was sandwiched between the donor compartment and the receptor and wrapped in aluminum foil. Phosphate buffer pH 6.8 was put into the diffusion cell's receptor compartment. Since skin temperature normally ranges from 320 to 32±0.50C, the entire assembly was mounted on a hot plate magnetic stirrer, and the solution in the receptor compartment was continually stirred using magnetic beads. Samples were taken out at various intervals and subjected to a drug content spectrophotometer analysis at 251 nm. After every sample withdrawal, the receptor phase was refilled with the same volume of phosphate buffer. [17],[18],[19]

***Ex vivo* Permeation studies:**

An *in vitro* permeation study was carried out using a Franz diffusion cell. The rat skin, weighing 200–250 g, was utilized. An electric clipper was used to delicately cut off the hair, and distilled water was used to remove any blood vessels or sticking tissues from the dermal side of the skin. The skin was given an hour to acclimate in phosphate buffer pH 7.4 before to the start of the experiment. To make sure the diffusant was evenly dispersed, it was then put on a magnetic stirrer equipped with a tiny magnetic needle. The cell's temperature was kept at 32±0.5°C via thermostatically controlled heating. The isolated goat skin sample was placed between the diffusion cell's compartments with its epidermis facing upward into the donor compartment. A 5 mL sample volume 49 was removed from the receptor compartment on a regular basis and replaced with an equivalent volume of new medium. The samples were assessed using the UV 1800 double-beam spectrophotometer (Shimadzu, Kyoto, Japan). The flow was directly measured as the slope of the curve between the steady-state values of the amount of drug penetrated (mg/cm2) vs time in hours, and the permeability coefficient was computed by dividing the flux by the initial drug load (mg/cm2). [18]

***In vitro* release kinetics:**

The following data treatment modes were used to illustrate the results of the in-vitro release profiles for each formulation. Drug release percentage cumulative over time (zero order kinetic model) First order kinetic model: log cumulative proportion of medication remaining vs time Drug release cumulative percentage vs time squared (Higuchi's model) Logarithmic total percentage Log time versus drug release (Korsmeyers model) Medication release kinetics: fitting the dissolution model Information The proper dissolving of the medicine must always be ensured when developing or producing a novel solid dosage form. Kinetic models have been used to describe drug dissolution from solid dosage forms. In these models, the dissolved drug amount (Q) is a function of the test time, t, or O = f(t) The Q (t) function is typically defined analytically using the following definitions: zero order, first order, Higuchi, Korsmeyer-Peppas models, and Hixson-Crowell model. [20],[21],[24]

**STABILITY STUDIES:**

The formulation's stability was investigated at 40°C±2 °C/75%RH±5%RH. The samples for stability analysis must be subjected for three months to an ambient of 40°C±2°C and 75%RH±5% RH, per ICHQIA norms. The samples must be tested at time intervals of 0, 1, 2, and 3 months in accordance with the standard protocol. For a duration of three months, accelerated stability experiments were conducted for the final optimized Microneedle patch. Samples were reported after analysis. [22],[24]

**RESULTS AND DISCUSSION:**

The present work aimed to achieve optimized formulation for Linezolid and Polymer based microneedle patches by determining effects of some

important factors and their interactions during the process of preparation of microneedle patches.

**OPTIMIZATION STUDIES OF LINEZOLID MICRONEEDLE PATCHES:**

Optimization was carried out by Designs Expert Software (DoE) using $2^2$ full factorial designs by taking two independent variables as factors and two dependent variables *In vitro* Drug release (Y1) and Drug content (Y2) as factors.

**DESIGN OF EXPERIMENTS [DoE]:**

**Table 2:** Independent and Dependent Variables Used in the Design

| **Independent variables** | **Levels (-1 to +1)** | |
|---|---|---|
| PVA(mg) | -1 | +1 |
| HEC(mg) | -1 | +1 |
| Linezolid(mg) | -1 | +1 |
| **Dependent variables** | Y1= In Vitro Drug Content<br>Y2= Drug Release | |

**Impact of Independent Variables on Drug Release *In-Vitro* (Y1):**

ANOVA test for the observed data, According to In Vitro Drug Release, the 2-level factorial model was important with F value 53.27 and P value < 0.0500 are fitting for the data.

**The resulting equation with coded values is as follows:**

$Log_{10}$ (In vitro drug release) = +97.03+2.44A, From the equation, it was observed that the PVA and HEC reacts and releases the drug slowly. From the contour plot we can observe that 97.51% drug released from the formulation by 8th hour. The model suggests that the polymers PVA and HEC are more effective in the In vitro drug release.

The model's F-value of 53.27 indicates that it is significant. Only 1.83 percent noise could produce such a large F-value. When P-values are less than 0.0500, model terms are deemed significant. In this case, A is an important model word. If the value exceeds 0.1000, the model terms are not significant. If your model contains a lot of unnecessary model terms (apart from those required to maintain hierarchy), model reduction may improve it.

The following table and figure depict the optimized value for the in vitro drug release.

**ANOVA for Linear Model (Aliased)**

**Response 1: Drug Release**

**Table 3:** Response of drug release

| **Source** | **Sum of Squares** | **df** | **Mean Square** | **F-value** | **p-value** | |
|---|---|---|---|---|---|---|
| **Model** | 15.31 | 1 | 53.31 | 53.27 | 0.0183 | significant |
| A-PVA | 15.31 | 1 | 53.51 | 53.27 | 0.0183 | |
| B-HEC | 0.0000 | 0 | | | | |
| **Residual** | 0.5749 | 2 | 0.2874 | | | |
| **Cor Total** | 15.89 | 3 | | | | |

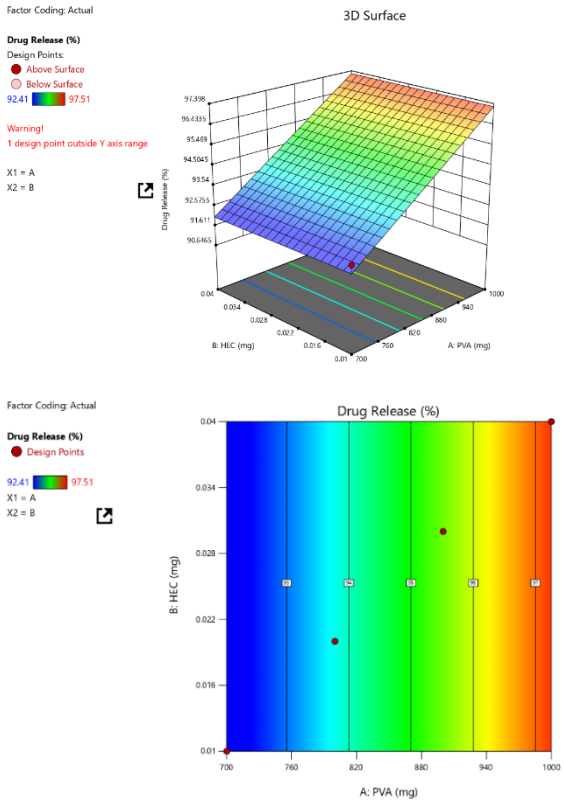



**Figure 2:** 3D Surface and Contour graph

**Effect of Independent Variables on Drug Content (Y2):**

ANOVA test for the observed data of Drug Release in Vitro Suggested that the 2-level factorial model was significant with F value 72.77 and P value > 0.1000 are fitting for the data. The resulting equation with coded values is as follows:

Drug Content= +1.23+1.09A

The PVA is primarily in charge of the medication content of the patches, according to the equation. The contour map shows that the F3 Formulation has the highest drug concentration of 96%. According to the model, the medication content and its therapeutic effect depend on the polymer PVA. The model's F-value of 7.38 indicates that it is significant. There is only a 3.48% chance that an F-value this high may be the product of noise. When P-values are less than 0.0500, model terms are deemed significant. In this case, A is an important model word. If the value exceeds 0.1000, the model terms are not significant.Model reduction may help our model if there are a lot of unimportant model terms (apart from those needed to maintain hierarchy).
The following table and figure depict the optimized value for the in vitro drug release:

**ANOVA for Linear Model**

**Response 2: Drug Content**

| Source | Sum of Squares | df | Mean Square | F-value | p-value | |
|---|---|---|---|---|---|---|
| **Model** | 2.64 | 1 | 2.64 | 72.77 | 0.0135 | significant |
| A-PVA | 2.64 | 1 | 2.64 | 72.77 | 0.0135 | |
| B-HEC | 0.0000 | 0 | | | | |
| **Residual** | 0.0726 | 2 | 0.0363 | | | |
| **Cor Total** | 2.72 | 3 | | | | |

**Table 4:** Response of drug content

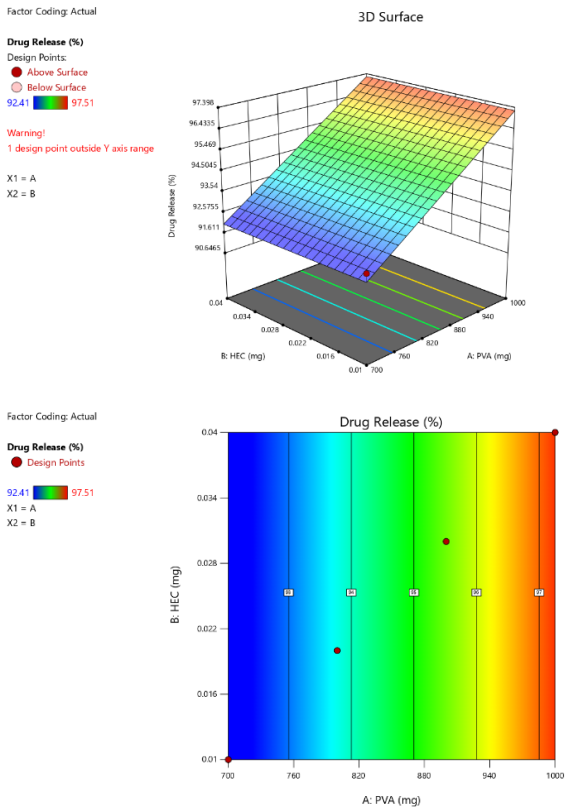



**Figure 3:** 3D surface and contour graph

**FORMULATION CHART OF LINEZOLID MICRONEEDLE PATCHES:**

**Table 9:** Formulation chart

| INGREDIENTS | FORMULATION CODE | | | |
|---|---|---|---|---|
| | $F_1$ | $F_2$ | $F_3$ | $F_4$ |
| **LINEZOLID(mg)** | 1000 | 1000 | 1000 | 1000 |
| **PVA(mg)** | 700 | 800 | 900 | 1000 |
| **HEC(mg)** | 100 | 200 | 300 | 400 |
| **GLYCEROL(ml)** | 0.5 | 0.5 | 0.5 | 0.5 |
| **WATER** | Quantity sufficient to 100ml | | | |

**FORMULATION OF LINEZOLID MICRONEEDLE PATCHES**

The prepared microneedle patch by micro molding technique using resin and hardener was found to be hardened over a period of time. Hence, an alternative approach of preparation of microneedle patch by solid casting technique was employed.

The Linezolid Microneedle patches were prepared using Micro molding technique as mentioned earlier in the experimental methodology, the results of the formulation from F1 to F4 was shown in the below.

**Figure 8:** Microneedle patches prepared using solvent casting method

**DRUG CONTENT UNIFORMITY:**

**Table 10:** Content uniformity of the Linezolid

| Formulation code | Trial I | Trial II | Trial III | Average (%) |
|---|---|---|---|---|
| F1 | 91.32 | 91.42 | 91.52 | 91.42 |
| F2 | 93.3 | 95.3 | 94.1 | 94.23 |
| F3 | 98.70 | 97.72 | 99.71 | 98.71 |
| F4 | 97.85 | 96.33 | 98.4 | 97.52 |

n = 3

To make sure the medication was dispersed evenly throughout the formulation, the content uniformity test was run.

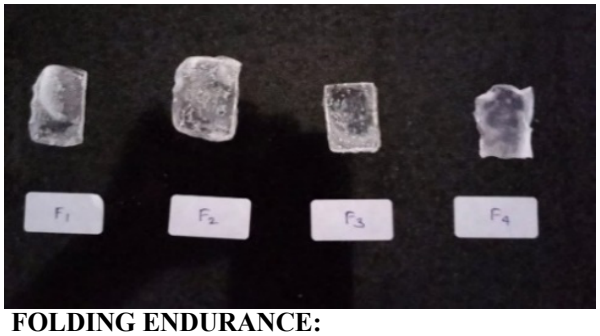
**PERCENTAGE MOISTURE LOSS:**

**Table 11:** % Moisture loss of the Linezolid patches

| Formulation code | Trial I (%) | Trial II (%) | Trial III (%) | Average |
|---|---|---|---|---|
| F1 | 5.78 | 5.65 | 5.55 | 5.65 |
| F2 | 5.75 | 5.65 | 5.45 | 5.61 |
| F3 | 5.01 | 5.23 | 5.65 | 5.29 |
| F4 | 5.43 | 5.21 | 5.34 | 5.36 |

n = 3

As per the result, F3 has the lowest moisture loss while F1 has the highest moisture loss. The amount of moisture lost reduces as the polymer content rises.




**FOLDING ENDURANCE:**

**Table 12:** Folding endurance of Linezolid Microneedle patch.

| Formulation code | Trial I | Trial II | Trial III | Average |
|---|---|---|---|---|
| F1 | 203 | 213 | 219 | 211 |
| F2 | 217 | 210 | 214 | 213 |
| F3 | 219 | 223 | 233 | 225 |
| F4 | 212 | 219 | 220 | 217 |

n = 3

Drug loaded Microneedle patch were tested for folding endurance. According to the results, the F3 formulation has the highest folding endurance since it includes the largest concentration of polymer, while the F1 formulation has the least folding endurance.

**SCANNING ELECTRON MICROSCOPY ANALYSIS:**

Dissolving Microneedle were utilized to study the transcutaneous penetration of Linezolid scanning electron microscopy of dissolving Microneedle were shown in Figure 6, the results demonstrated that the developed Linezolid Microneedle was sharp and arrays were well formed.

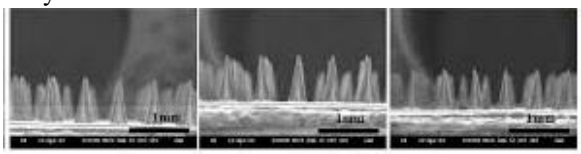


**Figure 9:** scanning electron microscopy analysis

***IN VITRO* RELEASE STUDIES:**

Every formulation was examined. In vitro release utilizing a Franz diffusion cell equipment with cellophane paper serving as the dialysis membrane and phosphate buffer pH 7.4. The in vitro release pattern data were displayed in Figure 7.

For all the developed microneedle patches. Among all the four formulations, F3 showed 97.51% of drug release at 8 hours of study.

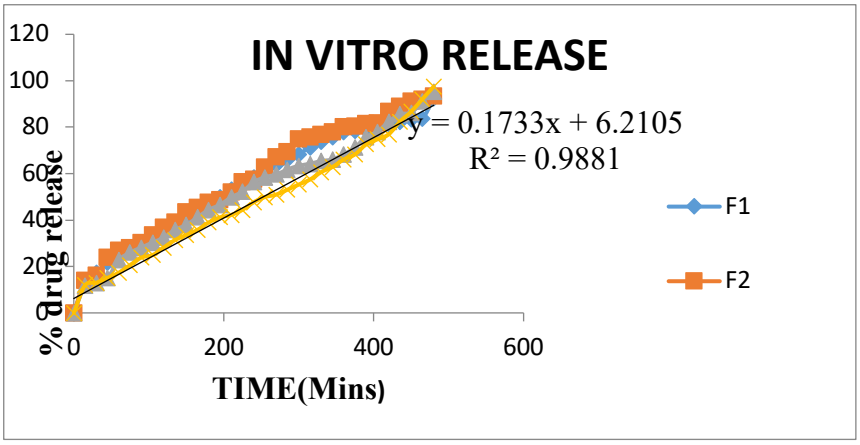



**Figure 10:** Pattern of in vitro drug release of all developed microneedle patches.

***IN VITRO* RELEASE KINETICS:**

Several kinetic models were fitted to the Microneedle patch's in vitro drug release data. The investigations showed that the improved formulation F3 complied with korsemeyers Peppas model with (R2 value = 0.9979) as mentioned in below table.

**Table 13:** Release kinetics of in vitro drug release

| KINETIC OUTLINE | $F_1$ | $F_2$ | $F_3$ | $F_4$ |
|---|---|---|---|---|
| Zero order release kinetics | 0.9716 | 0.9684 | 0.9644 | 0.9541 |
| Higuchi model | 0.9138 | 0.9082 | 0.9024 | 0.9866 |
| First order release kinetics | 0.9674 | 0.9637 | 0.9642 | 0.9492 |
| Peppas model | 0.9413 | 0.9584 | 0.9979 | 0.9526 |
| Hixson crowell model | 0.9689 | 0.9653 | 0.9643 | 0.9508 |

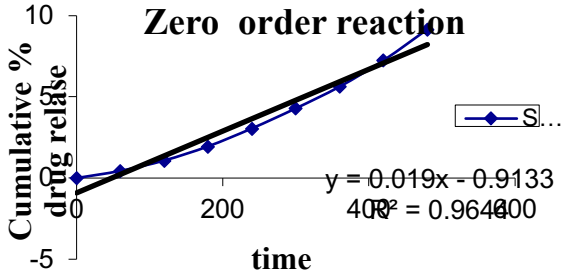



***Figure 11:*** Zero order reaction for formulation F3

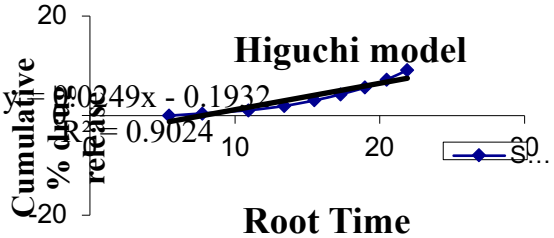


***Figure 12:*** Higuchi model for formulation F3

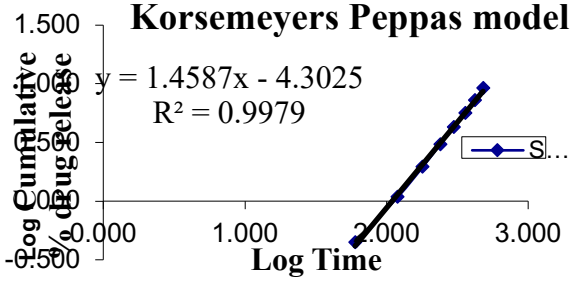



***Figure 13:*** Peppas model for formulation F3

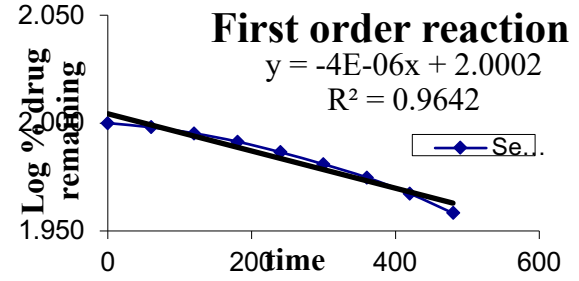



***Figure 14:*** First order reaction for formulation F3

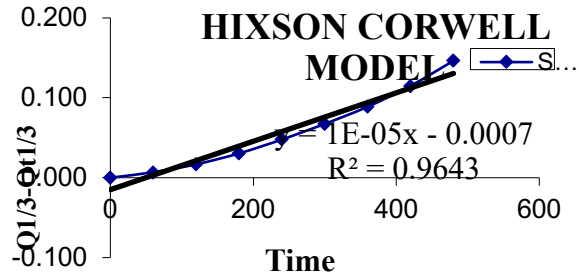



***Figure 15:*** Hixson crowell model for formulation F3

***Ex VIVO* KINETICS:**

According to the results of the characterization and in vitro release investigations, the F3 formulation was deemed to be optimal. Hence the Optimized formulation F3 were studied further for *Ex-vivo* release with goat skin using pH 6.8 phosphate buffer.

***Figure 16:*** *Ex vivo release pattern of optimized patch (F3)*

**STABILITY STUDIES**

**Test Results for Accelerated Stability Study:**

According to modified ICH recommendations, the stability experiments of Microneedle patches were conducted for three months at 40°C ± 2° C / 75 ± 5% RH Relative Humidity (RH). For three months, the improved formulation F3 was visually inspected every thirty days to assess the medication content, microbiological growth, color of the patch, and overall look. It was noted that the formulation's physical appearance remained unchanged.

**Table 14:** Test Results for Accelerated Stability Study

| | | |
|---|---|---|
| **1.** | Colour of the patch | Creamy white and transparent |
| **2.** | Visual appearance | No visual change |
| **3.** | Microbial growth | None |
| **4.** | Odor | Odorless |

The table below shows the comparison of the parameters prior to and following stability studies: **Parameter comparison prior to and following stability studies:**

**Table 15:** Before and after stability studies

| PARAMETERS | BEFORE STABILITY STUDIES | AFTER STABILITY STUDIES |
|---|---|---|
| **APPEARANCE** | Creamy white MICRONEEDLE patches | Creamy white MICRONEEDLE patches |
| **DRUG CONTENT** | 96.61 | 94.23 |

**CONCLUSION:**

**Conclusion**

The present study successfully developed and optimized Linezolid-loaded dissolving microneedle patches using a **2² full factorial Design of Experiments (DoE)**. Among the formulations, **F3** exhibited the best performance, with high drug content (98.71%), excellent mechanical properties, well-defined microneedle morphology, and **97.51% cumulative drug release within 8 hours**. The optimized formulation followed the **Korsmeyer–Peppas release model**, indicating an anomalous diffusion-controlled drug release mechanism, and demonstrated effective *ex vivo* skin permeation and good stability under accelerated storage conditions. Overall, the developed Linezolid microneedle patch represents a promising transdermal drug delivery system for localized wound management, offering sustained drug release, improved patient compliance, and the potential to enhance wound healing. Further *in vivo* and clinical studies are warranted to establish its therapeutic efficacy and clinical applicability.

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**CONFLICT OF INTEREST:**

The authors declare that there are no conflicts of interest.

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