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# Preparation and Evaluation of Solid Lipid Nanoparticles for Tavaborole Transdermal Gel

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**ABSTRACT**
*Solid lipid nanoparticles (SLNs) are very potential formulations for the topical delivery of antifungal drugs. Hence, the purpose of this research was to formulate the novel antifungal agent Tavaborole-loaded SLNs topical gel to improve its efficiency in the treatment of Fungal infection (Toenail onychomycoses). Tavaborole-loaded SLNs were prepared by modified high shear homogenization and ultrasonication method using different concentrations of solid lipid (Compritol 888 ATO, Cholesterol) and stabilizers (Tween 80 or Span20) The physicochemical properties and the in vitro release study for all Tavaborole -loaded SLNs were investigated. Furthermore, the optimized Tavaborole loaded -SLN formula was incorporated into the gel using Carpobol 934. The results showed that Tavaborole-loaded -SLNs were almost spherical having colloidal sizes with no aggregation. The drug entrapment efficiency ranged from 89% to nearly 100%. The zeta potential values lie between -10 and -30 mV presenting good stability. From the results, F4 is considered an optimized formulation. Tavaborole showed prolonged in vitro release from SLNs dispersion and its Carbopol gel following the Peppas release equation. The findings of the study suggest that the developed Tavaborole-loaded SLNs topical gels have a superior significant fast therapeutic index in the treatment of fungal infection (Toenail onychomycoses).*
***Key words:*** *Tavaborole, SLN topical gel*

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## INTRODUCTION

Tavaborole, a cyclized boronic acid complex (5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxazole), is an FDA-approved (in 2014) a topical antifungal for the treatment of mild-to-moderate toenail onychomycosis [1, 2].This novel, low-molecular-weight (152 Da) compound demonstrates potent antifungal activity against dermatophytes with minimum inhibitory concentration values in the low microgram per milliliter range [3]. Tavaborole inhibits protein synthesis by inhibition of an aminoacyl-transfer ribonucleic acid (tRNA) synthetase (AARS) [4]. It is slowing the disease progression and prevents adverse reactions. The requirement for designing a topical drug delivery system of tavaborole, which could not only increase the presence of the drug locally and for a prolonged period but also reduce the risk of systemic toxicity [5]. Colloidal particles ranging in size between 10 and 1000 nm are known as nanoparticles. They are manufactured from synthetic/natural polymers and are ideally suited to optimize drug delivery and reduce toxicity. Over the years, they have emerged as a variable substitute for liposomes as drug carriers. The successful implementation of nanoparticles for drug delivery depends on their ability to penetrate through several anatomical barriers, sustained release of their contents, and their stability in the nanometer size [6, 7].

Solid lipid nanoparticles (SLN) introduced in 1991 represent an alternative carrier system to traditional colloidal carriers such as emulsions, liposomes, and polymeric micro and nanoparticles. Nanoparticles made from solid lipids are attracting major attention as novel colloidal drug carriers for intravenous applications as they have been proposed as an alternative particulate carrier system. SLN are sub-micron colloidal carriers ranging from 50 to 1000 nm, which are composed of physiological lipids, dispersed in water or an aqueous surfactant solution. SLN offers unique properties such as small size, large surface area, high drug loading, and the interaction of phases at the interface and is attractive for their potential to improve the performance of pharmaceuticals [8, 9].

## MATERIAL AND METHODS

Tavaborole was Procured From Symed labs Ltd, Provided by Sura Labs, Dilsukhnagar, Hyderabad. Compritol 888 ATO was procured from Gattefosse Pvt. Ltd, Mumbai. Cholesterol and Triethanolamine procured from Purchased from Merck Limited, Mumbai. Tween 80, Ethanol, Carbopol 934, and Propylene glycol were Purchased from SD Fine- Chem Limited, Mumbai. Span 60 procured from Purchased from Loba Chemie Pvt Ltd, Mumbai.

## PREPARATION OF SLN GEL

### Preparation of Tavaborole-loaded solid lipid nanoparticles

Drug-loaded solid lipid particles were prepared by hot homogenizing followed by the ultrasonication method. Tavaborole was dispersed during about 10 g of mixed lipid phase (consisting of Compritol 888 ATO and Cholesterol) maintained at around 5$^{o}$C above the melting temperature of mixed lipid and dissolved in a mixture of ethanol. Organic solvents were completely removed employing a rotary flash evaporator. An aqueous phase was prepared by dissolving the stabilizers (Tween 80 or Span 20) in distilled water (sufficient to supply 30 mL) and heating to an equivalent temperature of the oil phase. The hot aqueous phase was added to the oil phase and homogenization was performed (at 2500 rpm and 70 $^{o}$C) employing a mechanical stirrer for 25 minutes. Tavaborole-loaded SLN was finally obtained by allowing the recent nano-emulsion to chill at temperature and was stored at 4 $^{o}$C within the refrigerator [10].

**Table 1: Composition of solid lipid nanoparticles formulations (F1 to F9)**

| Excipients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| Tavaborole (mg) | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Compritol 888 ATO (mg) | 1 | 1.5 | 2 | 2.5 | 3 | 1.5 | 2 | 2.5 | 1.5 |
| Cholesterol(mg) | 0.5 | 0.7 | 0.5 | 0.7 | 0.5 | 0.7 | 0.5 | 0.7 | 0.5 |
| Tween 80(mL) | 0.1 | 0.5 | 0.7 | 0.8 | - | - | - | - | 1 |
| Span 60 (mL) | - | - | - | - | 0.5 | 1 | 1.2 | 0.5 | 1 |
| Distilled water (mL) | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s |
| Ethanol(mL) | 2 | 2.5 | 2 | 2.5 | 2 | 2.5 | 2 | 2.5 | 2 |
| Total amount(mg) | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

### Characterization of preparing solid lipid nanoparticles:

### Particle Sizes, Zeta Potential:

Samples had been diluted with distilled water before measurement and measured at a hard and fast angle of 165$^{0}$c for the particle size and polydispersity index (PDI) analysis. For the Zeta ability measurement, Samples have been diluted at 1:40 ratios with filtered water (v/v) before analysis. Average particle size, PDI, and zeta potential have been then measured in zeta Sizer Nano ZS (Malvern Instruments, UK) [11, 12].

### Drug content:

Solid lipid nanoparticles (100 mg) were dissolved in 10mL methanol by shaking the mixture for 5 mins. One mL of the resultant solution was taken and diluted to 10 mL with methanol [13]. Then, aliquots were withdrawn and absorbance was recorded at 283 nm using a UV-visible spectrophotometer (Lab India 3200).

### The yield of solid lipid nanoparticles:

After complete drying, the solid lipid nanoparticle powders were collected and weighed accurately. The yield of solid lipid nanoparticles was calculated using the formula[13]

$$Percentage\ yield = \frac{\text{Total weight of proliposomes}}{\text{Total weight of drug} + \text{weight of added materials}} \times 100$$

### Entrapment Efficiency:

The nanoparticles had been centrifuged during a high-space cooling Centrifuge (C-24.Remi) the usage of nano step centrifuge tubes with ultra-filter out having a relative molecular mass cutoff 100KD (Pall existence sciences-India) at 5000rpm for 15min at 4$^{o}$c, and therefore the supernatant was separated. The amount of Tavaborole inside the supernatant changed into determining the usage of a UV-Visible spectrophotometer (U-1800, Hitachi) at lambda max 283 nm after suitable dilution.

The percent entrapment efficiency (%) changed into calculated utilizing the usage of the subsequent formula [14]:

$$\%EE = \frac{\text{Total drug content-Free drug x100}}{\text{Total drug content}}$$

***In vitro* drug release studies:**
Franz diffusion cell was used for the *in vitro* drug release studies. The semi-permeable membrane was placed between the donor and receptor chamber of the diffusion cell. The receptor chamber was filled with freshly prepared 30 mL 5.5 PH phosphate buffer. SLN gel equivalent to 1gm was placed on a semi-permeable membrane. The Franz diffusion cell was placed over a magnetic stirrer (REMI 1ML) with 500rpm and the temperature was maintained at 37±1$^0$C. 5mL of samples were withdrawn periodically and replaced with fresh buffer[14]. The withdrawn samples were periodically diluted and analyzed for drug content using a UV visible spectrophotometer (Lab India 3200) at 283 nm.

**Preparation of carbopol gel base:**
1gm of carbopol 934 was weighed and dispersed in distilled water. Then, propylene glycol was added and the mixture was neutralized by the dropwise addition of 1% triethanolamine. Mixing was continued until the transparent gel was obtained and allowed to swell for 24 hours. Similarly, 2% and 3% carbopol gels were prepared [15].

**Preparation of solid lipid nanoparticles containing transdermal gels:**
solid lipid nanoparticles containing Tavaborole (separated from the unentrapped drug) were mixed into the 1% carbopol gel by using mortar and pestle, the concentration of solid lipid nanoparticles in the gel being 1%. All optimized formulation was incorporated into different carbopol gels[16] (1%, 2%, and 3%).

**Physical appearance: [17-20]**
All prepared gel formulations have been observed for their visual appearances, such as transparency, color, texture, grittiness, greasiness, stickiness, smoothness, stiffness, and tackiness. The prepared gels were also evaluated for the presence of any particles. Smears of gels were prepared on a glass slide and observed under the microscope for the presence of any particles or grittiness.

**pH of formulation:**
pH measurement of the gel was carried out of the formulation was measured by using a digital pH meter (Lab India SAB 5000) [21].

**Rheological properties:**
The rheological properties of prepared gels were estimated using a Brookfield viscometer pro-D II apparatus, equipped with standard spindle LV1 with 61 markings. The sample holder of the Brookfield viscometer was filled with the gel sample, and then the spindle was inserted into the sample holder. The spindle was rotated at 100 rpm.
All the rheological studies were carried out at room temperature. A viscosity measurement was done in triplicate. The viscosity of 1, 2, and 3% carbopol gel was determined and select the optimized formulation [22].

**Drug Content**
For determination of drug content, an accurately weighed quantity (1 gm) of gel equivalent to 10 mg of Tavaborole was dissolved in phosphate buffer (PH 5.5) and analyzed by UV-Vis Spectrophotometer [23] (Lab India 3200) at 283 nm for drug content.

***Ex vivo* permeation studies:** The amount of drug released from rat skin was determined by using a Franz diffusion cell. The dorsal skin of the Wistar rat (4-6 weeks old) was placed between the donor and receptor compartments of the diffusion cell with the stratum corneum side facing upwards. The receptor chamber was filled with 30mL 5.5 PH phosphate buffer. SLN gel equivalent to 1gm was applied onto the surface of the skin evenly. The receptor chamber was stirred by a magnetic stirrer rotating at 500rpm and kept at 37±1$^0$C. The samples (1.5mL) were collected at a suitable time interval. Samples were analyzed for Tavaborole content by UV visible spectrophotometer (Lab India 3200) at 283 nm after making proper dilutions. Data obtained from *in vitro* release studies were fitted to various kinetic equations to find out the mechanism of Tavaborole release from SLN gel [24].

**Application of Release Rate Kinetics to Dissolution Data:**
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 Korsmeyer-Peppas release models [23-25].

## RESULTS AND DISCUSSION

**Characterization of solid lipid nanoparticles:**

**Particle Sizes, Zeta Potential:**
The particle size of all formulations was observed in the range of 314.3 to 1165.2. The less particle size, PDI observed in the F4 formulation i.e., 314.3 nm, 0.168 respectively. The Zeta potential range from -10.80 mV to -28.25 mV for all the formulations. The negative charge on the surface of the nanoparticle is believed to facilitate uptake from the intestine by the Payers patch, leading to lymphatic circulation, also

it is believed to prevent the entangling of the nanoparticles in the negatively charged mucous owing to the repulsion of like charges [26].

**Table 2:** Particle Sizes, PDI, and Zeta Potential of all solid lipid nanoparticles formulations

| FORMULATION | Particle Size(nm) | PDI | Zeta Potential (mV) |
|---|---|---|---|
| F1 | 1165.2 | 0.668 | -26.12 |
| F2 | 925.8 | 1.268 | -24.81 |
| F3 | 632.6 | 1.153 | -23.52 |
| F4 | **314.3** | **0.168** | **-28.25** |
| F5 | 804.1 | 0.277 | -16.55 |
| F6 | 387.3 | 0.309 | -20.83 |
| F7 | 329.8 | 0.698 | -22.59 |
| F8 | 505.4 | 0.385 | -12.11 |
| F9 | 602.5 | 0.481 | -10.80 |

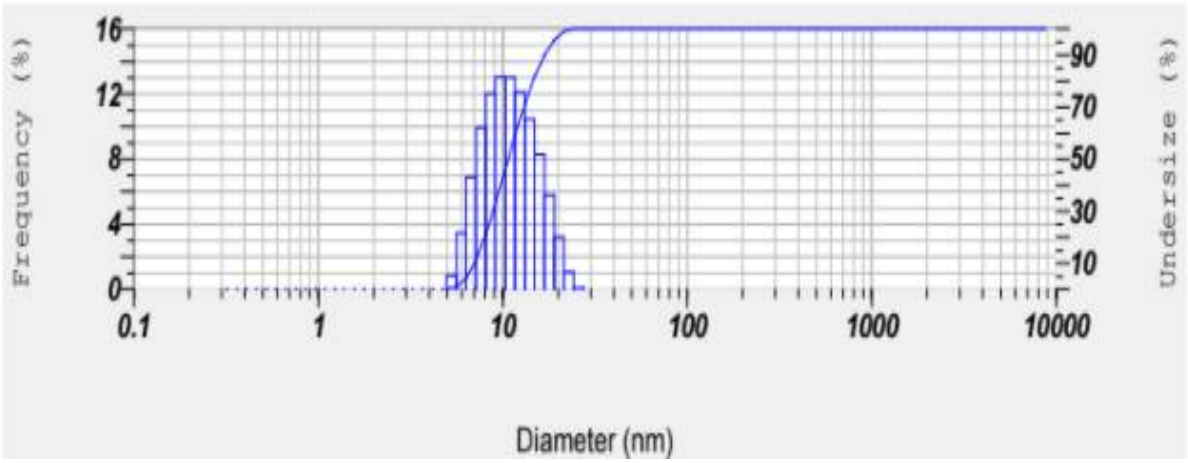


**Figure 1: Particle size of F4 Formulation**

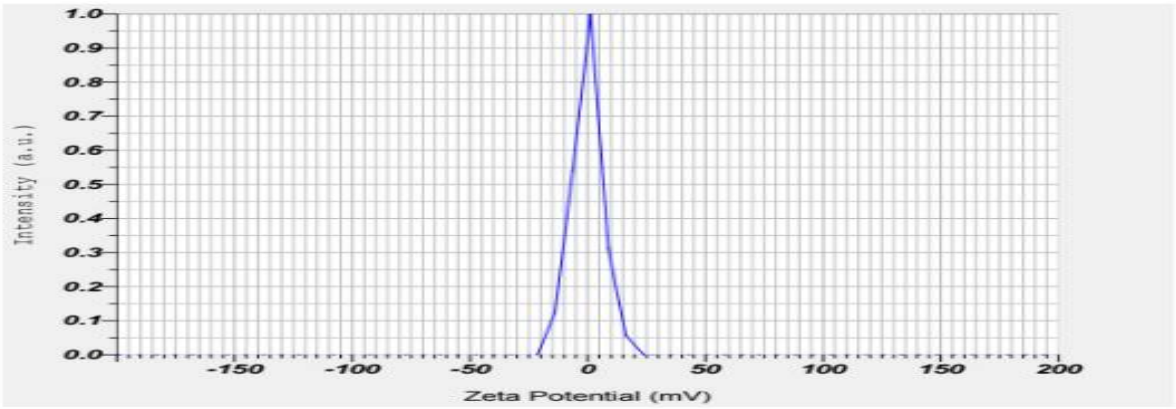


**Figure 2: Zeta Potential of F4 Formulation**

**Drug content, Yield, Entrapment Efficiency**

The percentage yield of formulations F1 to F9 by varying drug-to-lipid ratio was determined and is presented in Table 3. The highest drug content, Highest Entrapment efficiency was observed for F4 formulation. The EE% of the Tavaborole in the SLNs showed an increase in the quantity of Tavaborole entrapped with increasing Compritol 888 ATO concentration. The lipid matrices incorporating 2.5 mg of Compritol 888 ATO in Tavaborole formulation (F4) had the highest percentage entrapped, while those containing 3 mg of Compritol 888 ATO in Tavaborole formulation (F5) had the least percentage entrapped [27].

**Table 3:** Percentage yield, Drug Content, and Entrapment Efficiency of all solid lipid nanoparticles formulations

| FORMULATION | Percentage yield | Drug Content | Entrapment Efficiency |
|---|---|---|---|
| F1 | 90.36 | 97.20 | 95.91 |
| F2 | 93.51 | 98.01 | 97.35 |
| F3 | 95.28 | 98.89 | 97.17 |
| F4 | **97.10** | **99.66** | **99.76** |
| F5 | 87.35 | 90.03 | 98.42 |
| F6 | 90.51 | 97.14 | 97.30 |
| F7 | 93.62 | 98.65 | 92.91 |
| F8 | 92.02 | 99.17 | 96.35 |
| F9 | 96.96 | 97.35 | 90.17 |

***In vitro* drug release studies:**

*In vitro* drug release study of the selected SLNs (F1, F2, F3, F4, F5, F6, F7, F8, and F9) was carried out. The SLNs exhibited 48 hours sustained release pattern. Fifty percent of the incorporated amount of drugs was found to be released during the first 2 hours, followed by a slowed release of 99.34% of the drug up to 48 hours. The Tavaborole-loaded SLN F4 showed a better release profile of 99.34% by 48 hours. The prolonged release at 48 hours can be attributed to the slow diffusion of the drug from the lipid matrix. The results of *in vitro* drug release are depicted above in Table 4. The drug release study of batch F4 was carried out as it showed the maximum Entrapment efficiency. The dissolution profile showed biphasic behavior consisting of an initial burst release followed by a slow release phase. The initial burst release can be attributed to the presence of the free drug in the external phase and the drug absorbed on the surface of particles while the slow release was due to the drug encapsulated within a lipid matrix [28].

**Table 4:** *In vitro* dissolution studies of F1-F9 SLN formulations in percentage

| Time (hour) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 15.21 | 32.91 | 28.06 | 36.84 | 18.65 | 32.21 | 41.34 | 13.23 | 25.45 |
| 2 | 30.69 | 44.83 | 35.80 | 50.38 | 30.76 | 45.98 | 46.15 | 25.67 | 37.98 |
| 4 | 42.30 | 52.14 | 46.96 | 58.67 | 36.78 | 53.12 | 55.45 | 32.34 | 44.82 |
| 6 | 50.93 | 61.50 | 53.62 | 65.26 | 43.23 | 60.78 | 60.12 | 39.23 | 50.87 |
| 8 | 55.48 | 65.41 | 59.09 | 70.93 | 50.25 | 68.45 | 68.11 | 45.89 | 57.34 |
| 10 | 65.59 | 73.86 | 65.18 | 76.64 | 55.56 | 76.78 | 74.47 | 51.67 | 64.87 |
| 12 | 70.15 | 79.48 | 68.33 | 81.14 | 61.67 | 80.65 | 80.78 | 59.23 | 68.34 |
| 18 | 77.26 | 82.08 | 76.12 | 86.20 | 68.98 | 85.86 | 88.34 | 67.56 | 72.56 |
| 24 | 86.10 | 90.52 | 87.86 | 93.16 | 82.34 | 90.22 | 93.12 | 80.23 | 83.67 |
| 48 | 91.43 | 96.28 | 96.14 | 99.34 | 87.19 | 95.67 | 97.01 | 89.89 | 86.35 |

**GEL EVALUATION PARAMETERS**

Immediately after the formulations were prepared their physical characteristics of formulations were studied and the data was shown in Table 5. Thus all the formulations exhibited good characteristics like homogeneity in color, and appearance.

Three topical gel formulations were prepared by varying the concentration of the polymer. From the results, it was found that the pH of all gel formulations was in the range of 6 to 7 which lies in the skin's normal pH range. The minimum pH of the gels should be less than neutral [29] i.e., 7.0.

The viscosity of the prepared gels showed a direct proportion with the concentration of polymer [30]. The order of viscosity of the formulations indicates the higher the concentration of carbopol agent higher will be viscosity. The results were shown in Table 5. The viscosity of Optimized formulation (F2) 2% carbopol 72204 cps increased viscosity.

The percentage drug content was found to be between 80% and 100% Tavaborole indicating good content uniformity in all the formulations means the drug was uniformly distributed throughout the gel.

**Table 5: Gel Evaluation Parameters**

| Formulation | pH | Viscosity (cp) | Clarity | Drug Content |
|---|---|---|---|---|
| F4 optimized 1% carbopol gel | 6.91 | 67790 | + | 97.92 |
| F4 optimized 2% carbopol gel | 6.27 | 72204 | ++ | 98.56 |
| F4 optimized 3% carbopol gel | 6.12 | 74567 | + | 97.13 |

***Ex vivo* permeation studies of SLN nanoparticles gel:**

The results of *ex vivo* skin permeation study [Figure 3]. F4 optimized 2% carbopol gel's highest drug release (96.85% for 48 hours), good Homogeneity, highest drug content, and Proper viscosity. Hence it was considered an optimized formulation. These results suggest that SLN nanoparticles gel has the capability to enhance the penetration of drug across the skin and hence is expected to enhance the bioavailability [31].

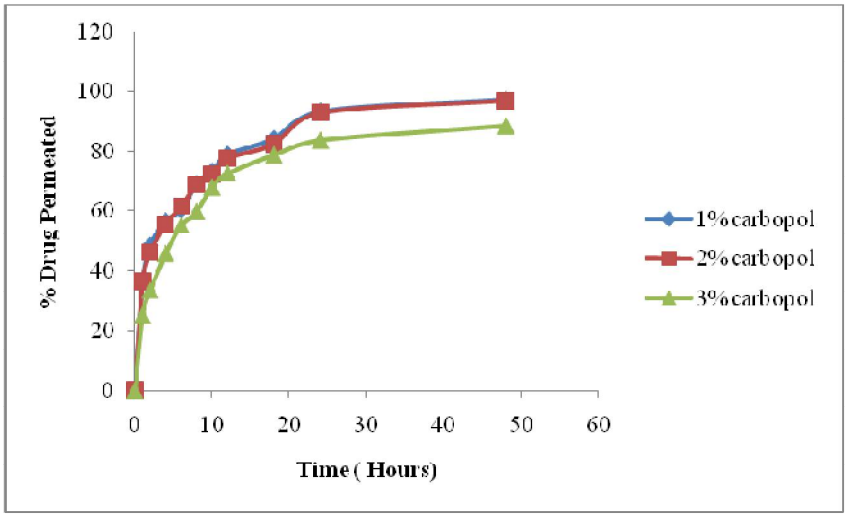


**Figure 3: *Ex vivo* permeation studies of SLN nanoparticles gel**

**Release Kinetics**

The prepared F4-optimized 2% carbopol SLN transdermal gel was subjected to the drug release kinetics and release mechanism. The formulations were studied by fitting the drug release time profile with various equations such as Zero order, First order, Higuchi, and Korsmeyer Pappas. The data revealed a better fit to the Peppas model with n value less than 0.26 i.e. Fickian diffusion for F4 optimized 2% carbopol SLN transdermal gel batch formulation and the drug release was dependent on time. The best correlation coefficient value (0.979) indicates the best release mechanism (peppas).

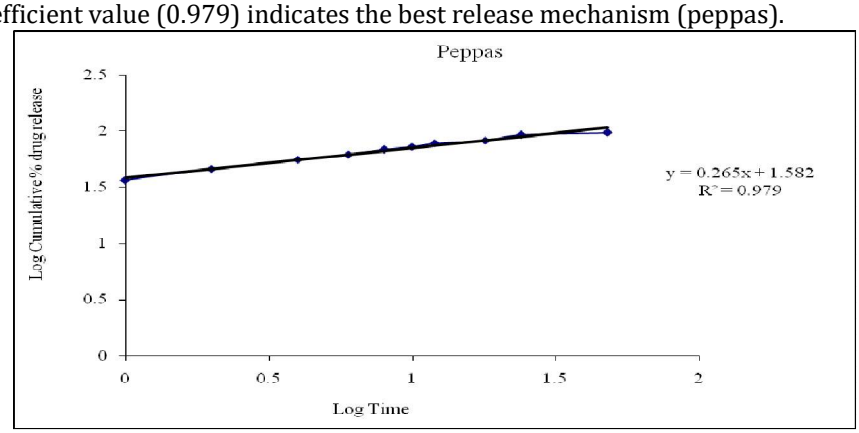


**Figure 4:** Peppas release kinetics

## CONCLUSION

The present study is to make the most benefits of solid lipid nanoparticles as a drug delivery system by developing Tavaborole loaded Solid lipid nanoparticles (SLNs) then formulated as transdermal gels.
Among all the formulations F4 is considered the best formulation. Among all the formulations F4 with Compritol 888 ATO (2.5 mg), and Cholesterol (0.7 mg) showed a drug release of 99.34% in 48 hours and was selected as the ideal formulation. The less particle size, PDI observed in the F4 formulation i.e., 314.3 nm, 0.168 respectively. It had the highest zeta potential value and hence stable formulation. The optimized Tavaborole-loaded SLN F4 formulation was introduced to formulate the 1%, 2%, and 3% carbopol transdermal gel preparations. From the percent cumulative amount release data, it was observed that about 96.85% of the drug was released from the optimized Tavaborole-loaded solid lipid nanoparticles. Among all 2% optimized formulations. The data revealed a better fit to the Peppas model with an n value less than 0.26 i.e. Fickian diffusion.

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