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# Formulation and evaluation of different topical dosage forms for wound healing properties

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ABSTRACT

The aim of the present work was to compare the wound healing efficacy of different topical dosage forms such as $\beta$ cyclodextrin complex gel, liposomal gel, and ointment on the rat model. Simvastatin was used as a drug, $\beta$ cyclodextrin was used as a complexing agent to enhance solubility, L $\alpha$ Phosphatidylcholine as a phospholipid, and cholesterol as a stabilizing agent. Liposomes were prepared by thin-film hydration method, $\beta$ cyclodextrin complexes of simvastatin were prepared by spray drying technique, and the ointment was prepared in simple method. Beta cyclodextrin gels and liposomal gels were prepared by direct incorporation of spray-dried products and lyophilized liposomes into Carbopol gel. The gel was evaluated for drug content, particle size, viscosity, spreadability, surface morphology, *in-vitro* drug release studies, skin irritation study, and wound healing activity studies. FTIR and DSC studies showed no chemical interaction between the drug and excipients. The particle size of $\beta$ cyclodextrin complexes was in the range of 0.5 $\mu$m to 2.5 $\mu$m and for liposomes 163 nm to 725 nm. The *in-vitro* drug release was 96.7 % at the end of the sixth hour for $\beta$ cyclodextrin gel, 29.7 % at the end of the sixth hour for liposomal gel, and 96.2 % at the end of 3 hours for ointment. Wound healing activity studies were carried out for 21 days on albino wrister rats, a period of epithelization, and rate of wound contraction was measured on 4, 8, 14, 16, and 21 days. Simvastatin ointment showed a significant effect on wound healing in the rat model compared to $\beta$-cyclodextrin gel and liposomal gel. Hence, Simvastatin ointment could be a potential dosage form for clinical utility on wound healing.

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## INTRODUCTION

A wound may be characterized as a disturbance of normal skin tissue structure due to physical or thermal damage or due to the existence of an underlying medical or physical condition and function and maybe classified by etiology, position or length (Dhivya *et al.*, 2015). Wound healing includes a series of well-orchestrated biochemical and cellular events leading to clear growth and regeneration of wounded tissue, including coagulation, inflammation, the formation of granulated tissue, epithelization, collagen synthesis, and tissue remodeling (Gonzalez, 2016).

There are several topical solutions available to treat

surface wounds which apply directly to damaged tissue. For example, the medium used in formulating determines the product's consistency, dense and greasy or thin or watery, and whether the active ingredient stays on the surface or penetrates into the body. The given drug is also loaded in jelly, cream, lotion, powder, solution, ointment, oil, or paste, depending on the vehicle used. Therefore, there are many preparations available at various concentrations. Vehicle choice depends on where to use the drug, aesthetic value, and ease of use.

Creams, the most commonly used formulations, are liquid-type oil emulsions, while in case of ointments, certain aqueous solvents are often combined with oily solutions. Creams are easy for application and, when rubbed into the hair, tend to disappear. They're very annoying. Lotions are cream-like, but they contain more liquid. In fact, they are suspensions in a base of water or oil and water of finely dispersed, powdered material. These are less effective in distributing drugs than ointments, gels, and creams, and are considered to be of lesser power for a given concentration of drugs. Lotions, however, possess several useful effects. They can easily be applied to rough skin, deliver cooling effect, and also treat dried, inflamed skin as well as oozing lesions caused by contact dermatitis, athlete's foot (*Tinea pedis*), or jock itch caused by *Tinea cruris* (Madaan, 2014).

Gels are liquids which do not require oil or fat for thickening rather depend on alcoholic or aqueous solvents. The skin is not absorbing gels as well as absorbing oil or fat preparations. These are, therefore, often the most active for conditions requiring slow absorption, such as acne, rosacea, and scalp psoriasis (Purnamawati, 2017).

Liposomes are innovative devices for distributing skin drugs and preserving damaged skin, providing many benefits over conventional dosage forms of topical delivery such as ointment, oil, cream, foam, lotion, solution, dust, or gel. Liposomes offers a great benefit in the terms of penetration and stability by overcoming the skin's major barrier properties. The use of formulation made up of lipid vesicles such as transdermal drug delivery systems to facilitate the passage of drugs across the skin barrier is one of the most contentious advances, with particular focus on the efficiency of these liposomes as topical drug delivery systems (Hussain, 2017).

Ointments are native to the topical delivery of many drugs, especially for lipophilic drugs such as statins, and due to their other properties, such as spreadability, the study also centered on evaluating the efficacy of simvastatin ointment on wound healing.

Simvastatin, a drug that lowers lipids, has a wound-healing effect by increasing angiogenesis and angiogenesis of lymph in healthy wounds and diabetic wounds. Right wound healing process was not well investigated. Because of the pleotropic properties of simvastatin, scientists were interested in working on the efficacy of wound healing statins (Raposio, 2015).

Simvastatin is a hypolipidemic drug categorized as a Class II biopharmaceutical classification system (BCS) compound of low aqueous solubility (2.24 $\mu$g / ml) and reasonable bio-membrane permeability. The goal of the study is to find the efficacy of simvastatin by enhancing drug solubility in $\beta$-cyclodextrin complexation. Beta cyclodextrin is a hydrophilic polymer, and Biodegradable nature increases product solubility by complexation and spray drying technique (Medarević, 2015).

## MATERIALS AND METHODS

Simvastatin is collected from Biocon Pvt Ltd, Bangalore. L-$\alpha$ Phosphatidylcholine and Cholesterol from sigma Aldrich. Vitamin E and $\beta$-cyclodextrin were purchased from Himedia Laboratories Pvt.Ltd, Mumbai. Isopropyl Alcohol, Glycerine, Butylated Hydroxyl Toulene, Propyl paraben, Triethanolamine, and Menthol from Merck, Mumbai. White petroleum Jelly, Carbopol 934, Chloroform, Sodium Hydroxide and Potassium dihydrogen phosphate from Loba Chemie Pvt.Ltd.

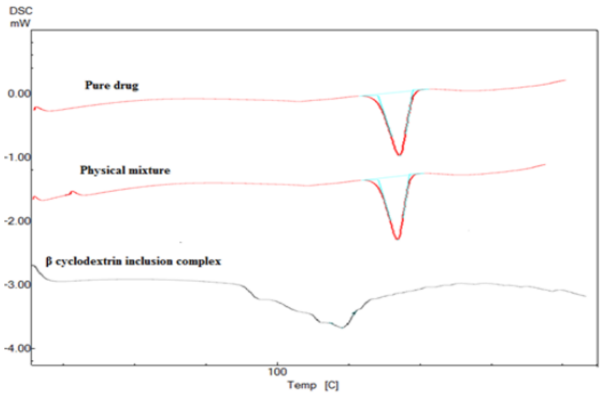


**Figure 1: DSC thermogram of SIM, physical mixture and $\beta$- cyclodextrin Inclusion complex**

### Preparation of cyclodextrin inclusion complexe with simvastatin

Medarević (2015) Spray drying method was used to prepare cyclodextrin complexes containing simvastatin. Dissolved in isopropyl alcohol (IPA), the drug and $\beta$-CD was taken in the ratio (1:1), and with the help of magnetic stirrer, distilled water is added. All solutions have been combined on a magnetic stirrer

**Table 1: List of Equipment's**

| Sl. No. | Name of the equipment | Model/manufacturer |
|---|---|---|
| 1 | UV-Visible spectrophotometer, UV-1800 | Shimadzu 1800, Japan |
| 2 | Digital balance | Shinko Sansui, Shimadzu, Japan |
| 3 | Magnetic stirrer | Remi equipments, India |
| 4 | Digital pH meter | Elico-LI120 pH (type003), Hyderabad, India |
| 5 | Freeze dryer | Ilshin lab co, Mumbai |
| 6 | FT-IR spectrophotometer 8400S | Shimadzu-8400 S, Japan |
| 7 | KBr Press | Techno search instruments, India |
| 8 | Differential scanning calorimeter (DSC)-60 | DSC 60, Shimadzu, Japan |
| 9 | Rotary Evaporator | REMI, Mumbai |
| 10 | Diffusion cell apparatus | Electrolab EDC 216 |
| 11 | Stability chamber | Thermolabs |
| 12 | Cooling Centrifuge | C24 BL-Remi, India |
| 13 | Particle size analyzer | Malvern Zeta sizer, UK |
| 14 | Zeta potential | Malvern Zeta sizer, UK |
| 15 | X-Ray Diffractometer | D2 Phaser XRD, Bruker AXS GMBH, Germany |
| 16 | Scanning electron microscope (SEM) | Joel SEM analysis Instrument, Model JSM 840A, Japan |
| 17 | Spray dryer | JISL LSD-48, India |
| 18 | Visco lab 4000 viscometer | PAC Labs, china. |

**Table 2: Formulation of Simvastatin liposomes**

| Formulation | L $\alpha$ Phosphatidyl-choline (mg) | Cholesterol (mg) | Chloroform (mg) | Menthol (mg) |
|---|---|---|---|---|
| F1 | 500 | 100 | 37.5 | 12.5 |
| F2 | 750 | 100 | 37.5 | 12.5 |
| F3 | 1000 | 100 | 37.5 | 12.5 |
| F4 | 250 | 1000 | 37.5 | 12.5 |
| F5 | 1000 | 200 | 37.5 | 12.5 |
| F6 | 1000 | 400 | 37.5 | 12.5 |
| F7 | 1000 | 600 | 37.5 | 12.5 |
| F8 | 1000 | 800 | 37.5 | 12.5 |

**Table 3: Formulation of liposomal gel of Simvastatin**

| Si.No. | Ingredients | Quantity |
|---|---|---|
| 1. | Liposome suspension | 20ml |
| 2. | Gelling agent | Carbopol – 1% |
| 3. | Glycerol | 10gm |
| 4. | Distilled water | Upto 50ml |
| 5. | Triethanolamine (TEA) | QS |
| 6. | Methyl paraben | QS |
| 7. | Propyl paraben | QS |

**Table 4: Types of gels based on spreadability 51**

| Type of gel | Measurements (in cm) |
|---|---|
| Fluid gel | More than 2.5 |
| Semi fluid gel | 1.90-2.5 |
| Semi stiff gel | 1.9-1.7 |
| Stiff gel | 1.6-1.45 |
| Very stiff gel | Less than 1.4 |

**Table 5: *In vitro* drug release from $\beta$ cyclodextrin gel**

| Time (in hrs) | Cumulative % Drug release |
|---|---|
| 0.5 | $23.2 \pm 5.21$ |
| 1 | $32.6 \pm 5.34$ |
| 2 | $44.9 \pm 3.1$ |
| 3 | $63.4 \pm 4.08$ |
| 4 | $71.6 \pm 3.13$ |
| 5 | $82.7 \pm 4.97$ |
| 6 | $96.7 \pm 2.79$ |

Standard deviation, n=3

**Table 6: *In vitro* release kinetics data of the prepared formulation**

| Release Model | R2 Values |
|---|---|
| Zero-order | 0.962450841 |
| First-order | 0.866901005 |
| Peppas | 0.991768142 |
| Higuchi | 0.987514304 |
| Hixson Crowell | 0.867686361 |
| Best fit model | Peppas |

**Table 7: Stability studies data of $\beta$ cyclodextrin complex gel (1:1)**

| Stability Condition | Sampling (in days) | % Drug content |
|---|---|---|
| 25ºC/60% RH | 0 | $98.72 \pm 0.269$ |
| | 15 | $97.63 \pm 0.654$ |
| | 30 | $96.12 \pm 0.482$ |
| | 60 | $95.45 \pm 0.325$ |
| | 90 | $95.16 \pm 0.332$ |
| 40ºC/75% RH | 0 | $99.54 \pm 0.423$ |
| | 15 | $98.37 \pm 0.892$ |
| | 30 | $98.02 \pm 0.621$ |
| | 60 | $97.28 \pm 0.872$ |
| | 90 | $96.33 \pm 0.954$ |

**Table 8: % Entrapment efficiency of liposomes**

| Formulation | % drug entrapment efficiency | Particle size (nm) | Zeta-potential (mV) *SD ± |
|---|---|---|---|
| F1 | 45.54 ± 0.162 | 342.8 ± 0.032 | -25.4 ± 4.00 |
| F2 | 46.26 ± 0.151 | 561.2 ± 0.237 | -29.1 ± 5.59 |
| F3 | 54.23 ± 0.074 | 252.6 ± 0.256 | -31.2 ± 3.52 |
| F4 | 44.14 ± 0.069 | 725.7 ± 0.642 | -23.2 ± 6.56 |
| F5 | 51.23 ± 0.094 | 163.1 ± 0.125 | -42.2 ± 2.56 |
| F6 | 49.12 ± 0.036 | 185.0 ± 0.345 | -36.5 ± 9.42 |
| F7 | 48.74 ± 0.078 | 200.6 ± 0.265 | -41.4 ± 4.42 |
| F8 | 47.87 ± 0.081 | 315.2 ± 0.331 | -37.5 ± 3.59 |

*Standard deviation (n=3)

**Table 9: DSC thermograms data for SIM, physical mixture & F 3**

| Type | Temperature onset (°c) | Tm (°c) | Tc (°c) | ΔH (J/g) | Melting range (°c) |
|---|---|---|---|---|---|
| Pure SIM | 134.12 | 138.41 | 140.18 | 31.72 | 6.06 |
| Physical mixture | 135.14 | 138.42 | 143.92 | 48.58 | 8.78 |
| Formulation | 126.31 | 138.44 | 140.49 | 18.31 | 5.18 |

**Table 10: Viscosity values of different formulations**

| Formulation | Viscosity values (cps) | Avg ± S.D* (in cm) | pH of gel |
|---|---|---|---|
| F1 | 31047 | 1.2 ± 0.0816 | 6.8 |
| F2 | 25846 | 1.2 ± 0.0816 | 7.4 |
| F3 | 26228 | 1.3 ± 0.0816 | 7.1 |
| F4 | 26817 | 1.3 ± 0.0816 | 6.9 |
| F5 | 32451 | 1.5 ± 0.0816 | 7.0 |
| F6 | 22749 | 1.4 ± 0.1632 | 7.3 |
| F7 | 20401 | 1.4 ± 0.0816 | 6.5 |
| F8 | 24343 | 1.4 ± 0.0816 | 7.2 |

Standard deviation, n=3

**Table 11: Cumulative % drug release from liposomal gel formulations F1-F8**

| Time (h) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|---|
| 0.5 | 2.3 ± 1.62 | 3.01±3.62 | 5.3 ± 4.17 | 4.2 ±2.76 | 3.1± 4.25 | 5.7 ±4.1 | 5.8 ±5.31 | 7.6 ±3.15 |
| 1 | 8.6 ± 3.21 | 9.6 4 ±.13 | 10.6 ±6.46 | 7.4 ±2.04 | 8.3± 3.14 | 7.0 ±6.23 | 9.3± 3.76 | 9.3± 3.18 |
| 2 | 11.6± 3.63 | 12.5 ±5.11 | 13.9 ±5.01 | 9.8± 5.24 | 11.1± 3.61 | 8.3 ±5.16 | 14.5± 5.14 | 12.7± 5.46 |
| 3 | 13.8± 4.05 | 13.06 ±4.26 | 15.6 ±6.02 | 12.8± 3.61 | 13.5± 4.74 | 10.4 ±5.05 | 16.8± 6.03 | 15.9± 4.35 |
| 4 | 15.1± 3.21 | 17.2 ± 4.18 | 18.8 5.32 | 13.4± 4.06 | 14.6± 5.53 | 15.2 ±2.68 | 19.4 ±3.71 | 19.8± 3.23 |
| 5 | 21.4 ±2.59 | 23.4 ± 3.12 | 26.7± 4.74 | 14.4± 3.15 | 15.7± 6.04 | 18.2 ±3.27 | 20.5± 4.53 | 24.4 ±3.06 |
| 6 | 23.0 ± 2.64 | 25.1 ± 3.16 | 29.7 ±3.35 | 16.6± 4.63 | 17.2± 3.62 | 21.2 ±4.69 | 23.2± 5.42 | 26.1± 4.15 |

**Table 12: Cumulative percentage drug release from SIM liposomes formulations F1-F8**

| Time (h) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|---|
| 0.5 | 9.3 ± 3.87 | 8.01 ± 4.62 | 8.3 ± 5.71 | 4.2 ± 3.67 | 3.1 ± 3.72 | 5.7 ± 5.1 | 5.8 ± 4.69 | 7.6 ± 4.13 |
| 1 | 25.6 ± 4.26 | 17.6 ± 5.01 | 27.6 ± 5.64 | 7.4 ± 3.04 | 10.3 ± 4.11 | 12.0 ± 5.23 | 15.3 ± 3.67 | 19.3 ± 4.01 |
| 2 | 34.6 ± 3.98 | 30.5 ± 4.1 | 35.9 ± 4.1 | 15.8 ± 4.25 | 13.1 ± 4.26 | 21.0 ± 4.36 | 26.5 ± 4.16 | 33.7 ± 4.68 |
| 3 | 38.8 ± 4.11 | 41.0 ± 3.83 | 43.6 ± 5.02 | 22.8 ± 2.69 | 26.5 ± 2.89 | 33.4 ± 4.05 | 35.8 ± 5.03 | 39.9 ± 3.71 |
| 4 | 45.1 ± 3.58 | 48.2 ± 3.04 | 48.8 ± 4.23 | 35.4 ± 5.06 | 37.6 ± 3.67 | 40.2 ± 3.89 | 42.4 ± 2.79 | 46.8 ± 2.14 |
| 5 | 51.4 ± 2.79 | 53.4 ± 2.15 | 56.7 ± 3.97 | 42.4 ± 4.15 | 44.7 ± 5.04 | 48.2 ± 4.72 | 50.5 ± 3.58 | 54.4 ± 2.01 |
| 6 | 53.0 ± 2.87 | 55.1 ± 2.36 | 59.7 ± 2.79 | 46.6 ± 3.76 | 47.2 ± 2.97 | 51.2 ± 2.96 | 53.2 ± 4.24 | 56.1 ± 2.67 |

**Table 13: *In vitro* release kinetics data of the prepared formulations**

| Release model | | Formulations | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
| Zero order | R2 | 0.9158 | 0.9191 | 0.9410 | 0.9081 | 0.8633 | 0.9610 | 0.9307 | 0.9475 |
| First order | R2 | 0.9223 | 0.9220 | 0.9350 | 0.9153 | 0.8765 | 0.9554 | 0.9411 | 0.9805 |
| Peppas | R2 | 0.8921 | 0.8990 | 0.9507 | 0.9701 | 0.9028 | 0.8986 | 0.9853 | 0.9591 |
| Higuchi | R2 | 0.9416 | 0.9341 | 0.9485 | 0.9854 | 0.9684 | 0.9416 | 0.9919 | 0.9734 |
| Hixson Crow-ell | R2 | 0.8711 | 0.8874 | 0.9347 | 0.8801 | 0.8129 | 0.9742 | 0.9042 | 0.9055 |
| | | Higuchi | Higuchi | Peppas | Higuchi | First-order | Hixson Crowell | Higuchi | First-order |

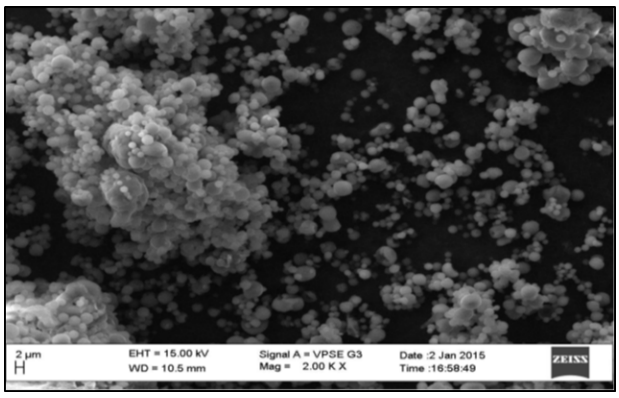


**Figure 2: SEM Photographs of Spray-dried product of SIM and $\beta$ cyclodextrin inclusion complex (1:1)**

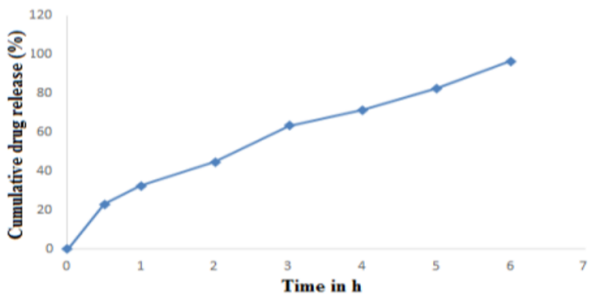


**Figure 3: *In vitro* drug release from $\beta$ cyclodextrin gel**

for 30 min gradually fall wise. The solution has been fed into the mini spray dryer (JISL LSD-48, India) and Sprayed in a chamber from a 0.7 mm diameter nozzle under a 1.5 kg / cm2 atomization pressure with a feed rate of 3.0 ml/min and the temperature was adjusted at 80 ° C and the temperature of the outlet at 60 ° C ± 2 ° C. The unit vacuum was 588.3

**Table 14: Stability studies data of liposomal gel formulation F3**

| Stability Condition | Sampling (in days) | Physical appearance | % Drug content | Report |
|---|---|---|---|---|
| 25ºC/60% RH | 0 | No change | 98.32 ± 0.157 | Complies |
| | 15 | No change | 91.33 ± 0.243 | Complies |
| | 30 | No change | 81.12 ±0.452 | Complies |
| | 60 | No change | 72.03 ± 0.525 | Complies |
| | 90 | No change | 69.16 ± 0.332 | Complies |
| 40ºC/75% RH | 0 | No change | 98.54 ± 0.423 | Complies |
| | 15 | No change | 89.37 ± 0.692 | Complies |
| | 30 | No change | 78.24 ± 0.821 | Complies |
| | 60 | No change | 56.05 ± 0.972 | Complies |
| | 90 | No change | 51.04 ± 0.954 | Complies |
| 4°C | 0 | No change | 97.64± 0.885 | Complies |
| | 15 | No change | 97.53 ± 0.842 | Complies |
| | 30 | No change | 97.48 ± 0.917 | Complies |
| | 60 | No change | 97.41 ± 0.934 | Complies |
| | 90 | No change | 97.32 ± 0.967 | Complies |

**Table 15: Cumulative % drug release of simple ointment**

| Time (in h) | Percentage of drug release |
|---|---|
| 0.5 | 33.5 ± 5.21 |
| 1 | 42.4± 5.34 |
| 1.5 | 59.6 ± 3.1 |
| 2 | 76.4 ±4.08 |
| 2.5 | 89.3 ±3.13 |
| 3 | 96.2 ±3.57 |

Standard deviation n=3,

**Table 16: *In vitro* release kinetics data of the prepared ointment**

| Release Model | R2 Value |
|---|---|
| Zero-order | 0.936837977 |
| First-order | 0.949225178 |
| Peppas | 0.971419706 |
| Higuchi | 0.978411663 |
| Hixson Crowell | 0.848835173 |
| Best fit model | Higuchi |

pascal and 45 percent aspirator. The resulting material was wrapped in an aluminum foil and kept at room temperature.

**Formulation of cyclodextrin functionalized gel of simvastatin**

Simões (2015)The required polymer quantity (Carbopol 934) was weighed (1 g) and dispersed with a magnetic stirrer in distilled water. Then 10gm of glycerol was added for full polymer hydration and held overnight. With the vigorous stirring, thickening of the preparation is formed and then neutralized until transparent gel appeared by adding dropwise triethanolamine (TEA). Methyl Paraben and propyl paraben were added as a preservative. The prepared complex of cyclodextrin were injected directly into the gel when stirring for 2 min at 25 rpm. Care was taken to stop moisture from being mixed into the solution. The pH was adjusted in the range of 6.9-7.3 for each formulation.

**Method of preparation of simvastatin liposomes**

**Table 17: Stability studies data of Simple Ointment formulation**

| Stability Condition | Sampling (in days) | Physical appearance | % Drug content | Report |
|---|---|---|---|---|
| 25ºC/60% RH | 0 | No change | 98.32 ± 0.269 | Complies |
| | 15 | No change | 98.21 ± 0.654 | Complies |
| | 30 | No change | 98.12 ±0.482 | Complies |
| | 60 | No change | 97.86 ± 0.325 | Complies |
| | 90 | No change | 97.16 ± 0.332 | complies |
| 40ºC/75% RH | 0 | No change | 98.74 ± 0.423 | Complies |
| | 15 | No change | 98.57 ± 0.892 | Complies |
| | 30 | No change | 98.24 ± 0.621 | Complies |
| | 60 | No change | 97.65 ± 0.872 | Complies |
| | 90 | No change | 97.04 ± 0.954 | Complies |

**Table 18: Effect of topical dosage forms of SIM on a percentage (%) wound closure**

| Groups | Treatment | percentage (%) wound closure | | | | | | Period of epithelization (no of days) |
|---|---|---|---|---|---|---|---|---|
| | | $4^{th}$day | $6^{th}$day | $8^{th}$ day | $11^{th}$ day | $14^{th}$ day | $16^{th}$ day | |
| I | Untreated | 22.52± 1.21 | 35.72± 1.58 | 51.92± 1.71 | 68.28± 2.23 | 76.24± 1.18 | 81.56± 1.03 | 23.16± 0.71 |
| II | Cyclodextrin gel | 28.88± 1.95 | 45.34± 1.86 | 65.28± 2.83 | 77.25± 1.31 | 90.42± 1.71 | 93.7± 1.22 | 18.5± 0.77 |
| III | Liposomal gel | 24.15± 1.75 | 38.73± 2.16 | 57.70± 3.25 | 71.58± 1.88 | 80.69± 1.22 | 85.88± 2.01 | 20.5± 1.33 |
| IV | ointment | 29.23± 1.65 | 51.01± 2.01 | 79.78± 1.91 | 86.37± 1.01 | 97.76± 2.22 | 100± 00 | 16.23± 0.98 |

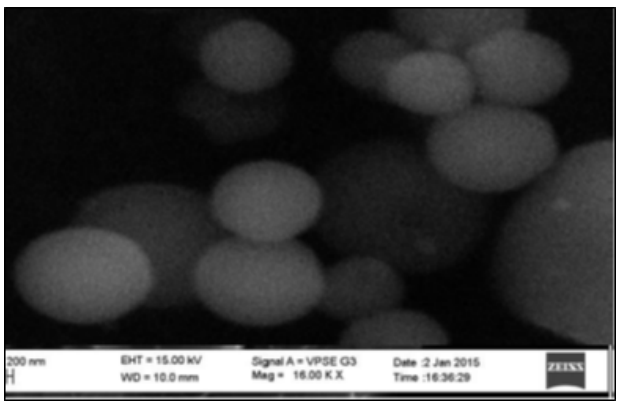


**Figure 4: SEM Photographs of liposomes F3 formulation**

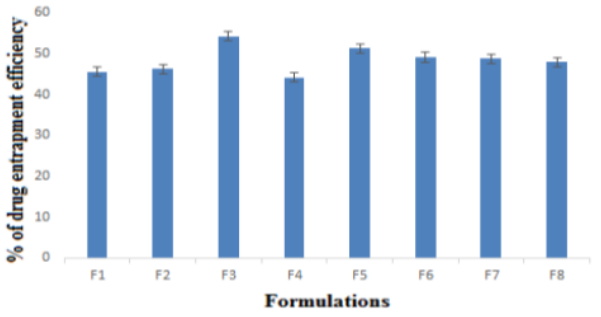


**Figure 5: Bar graph showing % drug entrapment efficiency of for mulations**

Matusewicz *et al.* (2018) Using the thin film hydration technique, with the different molar proportions, liposomal formulations was prepared, which is SIM multilamellar in its structure. The lipid portion (L-$\alpha$ Phosphotidylcholine) was mixed in chloroform with different cholesterol molar ratio (Tables 1 and 2): methanol mixture (3:1, percent v / v) in a round flask. Using a rotary evaporator (REMI, MUMBAI), the organic solvents are slowly removed at 45 ° C above the gel-liquid crystal transition tem-

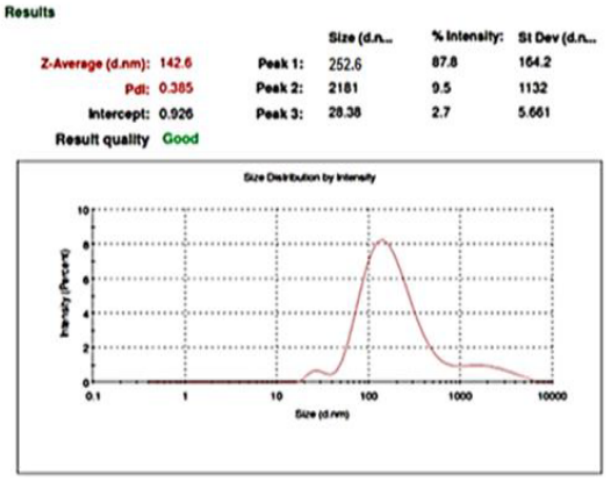


**Figure 6: Particle size distribution of formulation F3**

perature (Tc) of phospholipids, thus creating a dry truculent film of dry lipid inside the surface of the flask. The film was gradually hydrated with 20.0 ml of phosphate-buffered saline (PBS) (pH 7.4), which contains SIM in a rotary evaporator for 3h, resulting in multi lamellar liposomes being produced. To increasing the liposome length, the resulting suspension was sonicated for 10 min.

### Formulation of lyophilized liposomal gel of simvastatin

Matusewicz *et al.* (2018)The required polymer quantity (Carbopol 934) was weighed (1 g) and dispersed with a magnetic stirrer in distilled water. Then 10 g of glycerol was applied and held for maximum polymer hydration overnight (Table 3). Stirring is carried out till thickening was formed, and the gel is neutralized when triethanolamine (TEA) is added by dropwise till clear gel is formed. As a preservative, methyl paraben and propyl paraben have been added. Care was taken to stop moisture from being mixed into the solution. Before that, by using a magnetic stirrer set at 25 rpm for 2 min, Liposome containing drug was mixed in to 1 percent Carbopol gel.

### Preparation of simple ointment

Usha and Ashish (2015)Simple Ointment was prepared using 89.9% petroleum jell, 10.0% mineralized oil, propylparaben (0.1%)and 0.5% butylated hydroxytoluene, mixed at 75 ° C for at least 15 minutes before uniform mixing was achieved, then held at room temperature for about 1 hour. SIM has been added to the ointment at 35 ° C (2% w / w).

### Evaluation of prepared formulations

### $\beta$- Cyclodextrin complex

### Drug content

In a 100 ml volumetric flask, $\beta$-CD inclusion complex (2 mg) was taken, methanol was added to make up the volume. The drug concentration was calculated by using a UV-Vis spectrophotometer to calculate the solution absorbance at 237.7 nm (Shimadzu 1800, Japan) (Kutty *et al.*, 2012).

### Percentage yield

The percentage yield was determined to determine the method's performance. Complex inclusion was collected and weighed to determine the practical yield of the following equation (Shekh, 2011).

% Yield=

$$\frac{Weight\ of\ \beta\ cyclodextrin\ inclusion\ complex}{Weight\ of\ drug + Weight\ of\ polymer} \times 100$$

### Scanning electron microscopy (SEM)

SEM is applied to determine the surface morphology of formulation. The prepared samples were mounted on an aluminium support using the dual-sided adhesive tape and spluttered under vacuum with Au and scanned before observation at a voltage accelerating about 25 KV (Yang, 2015).

### Liposomes

### Entrapment efficiency

In Cooling Centrifuge (C-24 BL-Remi, India), phosphate buffer solution liposomes are centrifuged at 10 ° C for 30 min at 15,000 rpm to isolate untrapped SIM from liposomally trapped material. The supernatant was isolated after centrifugation and further diluted with methanol to assess SIM content using a 237 nm UV spectrophotometer (Patel, 2011).

### Scanning electron microscopy (SEM)

SEM is applied to determine the surface morphology of formulation. The prepared Samples were mounted on an aluminium support using the dual-sided adhesive tape and spluttered under vacuum with Au and scanned before observation at a voltage accelerating about 25 KV (Yang, 2015)

### Analysis of Particle size and zeta potential of the liposomes

Extreme light scattering was used to assess the PDI (poly dispersity index) and loading capacity of the resultant liposomes by the use of an instrument, Malvern Zetasizer, supplied by Malvern Instruments Ltd. The United Kingdom, (MAL1045544, Zetasizer of version 6.34 Sl.no). The analysis was conducted using a transparent zeta cell, a dispersant liquid with a 1.330 refractive indexes (RI), and 0.88 viscosity (cP). At a constant temperature of 25 ° C remained constant. Three times the test was evaluated to eliminate the error (Nguyen *et al.*, 2017).

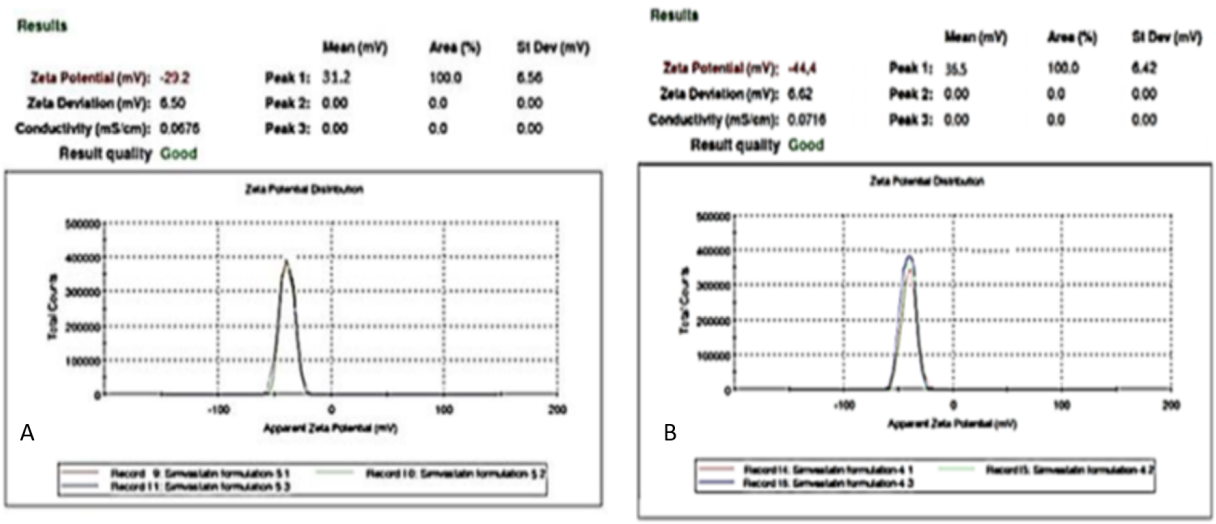


**Figure 7: Zeta potential A- formulation F3; B - formulation F6**

### X-ray diffraction (XRD)

Sample patterns for XRD are reported by the use of D2 Phaser XRD, Bruker AXS GMBH, Germany. As an analyzer, Miniflex 2 was used. X-ray Filtered radiation diffractometer (Cu Target) is used. Samples have been scanned in the 5-40o range of 2 theta. The recording scanning rate was 5 ° /min, and the stage size was 0.02 ° (Filipe *et al.*, 2010).

### Gels/ointment

### Viscosity

A viscometer (Viscolabs 4000) was used to assess the viscosity of formulations such as $\beta$ cyclodextrin gel / liposomal gel/ointment, and viscosity was calculated in cps. Measurement of each formulation in triplicate and estimation of average values (Sabale and Vora, 2012).

### Spreadability

It has been determined the spreadability of formulations like $\beta$ cyclodextrin gel / liposomal gel/ointment formulation. Another glass plate (125 g) has been placed on it for one minute, gel/ointment diameter has been measured in triplicates, and average values are calculated (Basha *et al.*, 2019).

### Measurement of pH

Pre-calibrated digital pH meter (ELICO, LI120) helps in the determination of pH of the prepared formulations such as $\beta$ cyclodextrin gel / liposomal gel/ointment. One gram of gel/ointment was dissolved and deposited for two hours in 100 ml of distilled water. Measurement of each formulation in triplicate and estimation of average values (Karri *et al.*, 2014).

### *In vitro* drug diffusion studies

Studies of drug diffusion are performed using diffusion cell instruments (EDC-07 model, Electrolab model). Using Franz diffusion cell, $\beta$ cyclodextrin gel / liposomal gel/ointment was subjected to in vitro diffusion via the dialysis membrane (0.65 $\mu$m). The receptor chamber was filled with Phosphate buffer solution (12 ml) 7.4 pH and held at 32 $\pm$ .5 ° C and placed on a magnetic stirrer for constant stirring. One gram of gel formulation has been put in the donor compartment on the dialysis membrane. Samples are removed from the receiver chamber at a specific time period and replenished with a fresh PBS (Sink condition) solution. The experiment was conducted with three formulations in three individual cells, respectively. Spectrophotometrically, the specimens were analyzed at 237 nm. Studies of *In vitro* release have been conducted for six hours. The triplicate studies were performed (Salamanca, 2018).

### Mathematical model fitting

Using BCP Software, the data for the release of drugs in vitro were incorporated into different mathematical models. Technology from Disso-V2.08 to know the best match design and release process. Parameters such as "n" the exponent of diffusion and "R2" the coefficient of regression were determined. The mathematical model with the highest degree of a correlation coefficient or determination coefficient (R2) was considered the best fit model (Manda *et al.*, 2019).

### *In vivo* studies

The study was carried out after receiving permission from the JSS College of Pharmacy's Institutional Animal Ethics Committee, Mysore. In the study, males and females of 200-250 g Albino wrister rats were used. The animals are housed on a normal diet

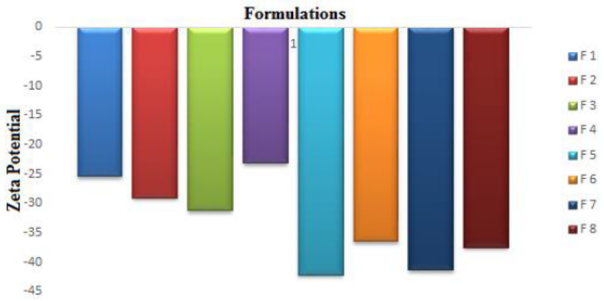


**Figure 8: Bar graph showing zeta-potential for formulations**

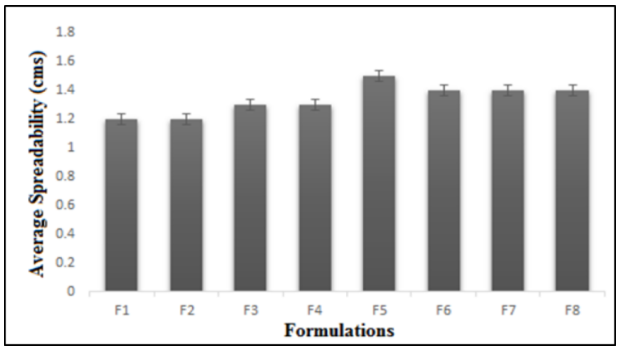


**Figure 12: Spreadability studies of different formulations**

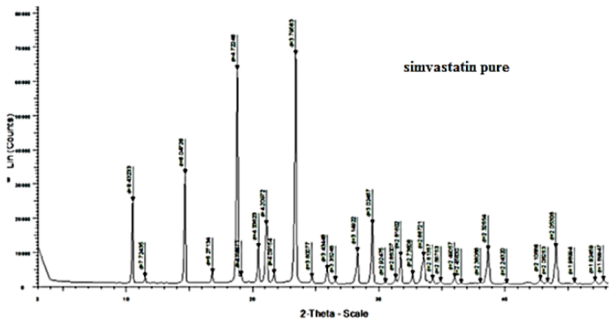


**Figure 9: XRD of the SIM**

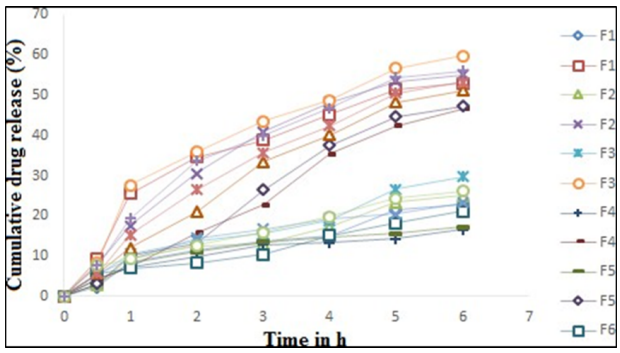


**Figure 13: *In vitro* drug release studies of SIM liposomes and liposomal gels F1 to F8**

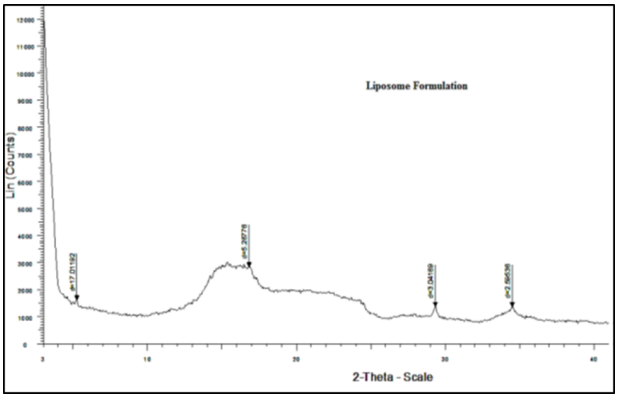


**Figure 10: XRD of the F3 formulation**

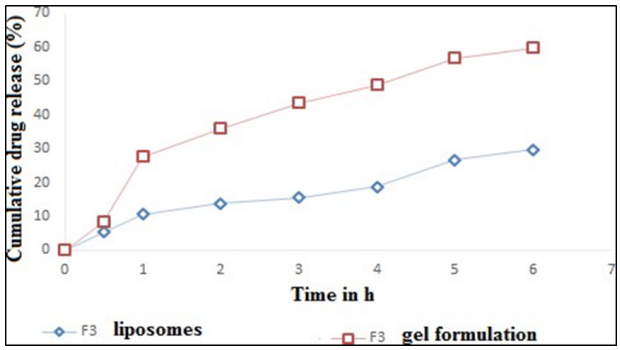


**Figure 14: *In vitro* drug release studies of optimized formulation F3**

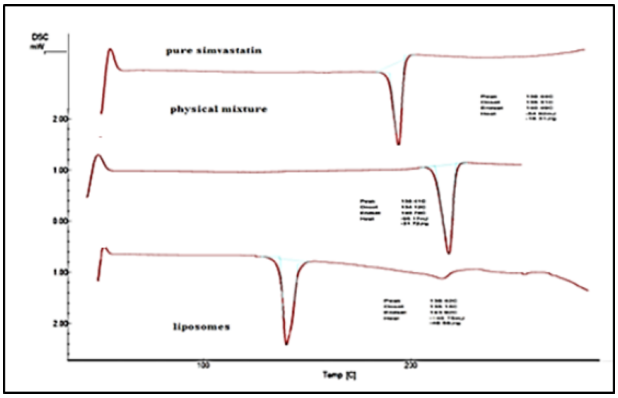


**Figure 11: DSC thermogram of SIM, physical mixture and formulation F3**

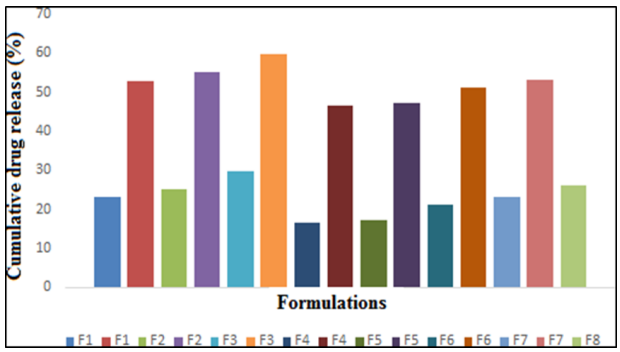


**Figure 15: Percentage drug release of liposomes and liposomal gels F1 to F8 at the end of 6 h**

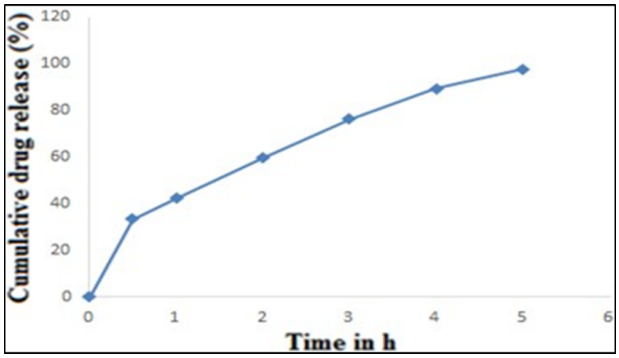


**Figure 16: *In vitro* drug release of simple ointment of SIM**

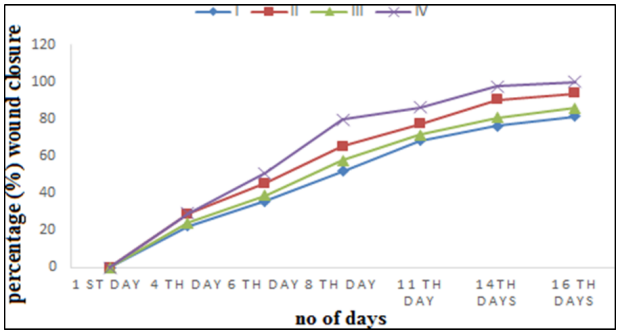


**Figure 17: Rate of wound contraction**

in well-spaced ventilated cages. The animals were divided into four classes, anesthetizing the rats at a dosage of 40 mg/kg body weight by intraperitoneal injection of ketamine. The animals ' skin was rasped and disinfected, with 70% (v / v) ethanol. Using a punch-biopsy needle and a depth of about 1 mm on the dorsal aspect of the rats ' thoracolumbar region, skin excision wounds of 1 cm x 1 cm were created. The first team was treated with normal saline and remained exposed throughout the study. Wounds were treated in the 2nd, 3rd, and 4th groups by applying 1 cm2 of $\beta$ cyclodextrin gel, liposomal gel, and simvastatin ointment, respectively. For every 12 hours, the dressings are changed.

The wounds have been tracked, and the wound area has been assessed. The wound closure is measured by the use of transparent paper, and the wound on 4, 6, 8, 10, 12, and 16 days of post-wounding was recorded using a permanent marker. A chart paper was used to calculate the wound regions. The time of epithelization was provided by the number of days needed to drop the eschar regardless of residual raw wound.

The proportion of contraction of a wound is determined as follows.

% of wound contraction=

$$\frac{wound\ area\ on\ day\ (zero) - wound\ area\ on\ day\ (a)}{wound\ area\ on\ day\ (zero)} \times 100$$

### Stability Studies

Accelerated stability studies seek to predict a product's shelf life, i.e., the rate of decomposition is accelerated by elevating the relative humidity (RH) and temperature (Bajaj *et al.*, 2012).

A drug formulation is said to be stable if it contains at least 90% of the stated active ingredient, an effective concentration of the added preservatives, and does not exhibit discoloration or precipitation, nor produce a foul odor.

For stability tests, a freeze-dried optimized formulation of the liposomal gel has been chosen. In a screw-capped container, the formulation was packed, and short-term stability tests were performed at 4oC, 25±2oC/60±5 percent Related humidity and 40±2oC/75±5 percent Related humidity for a span of 90 days. Samples were extracted on the 0th, 15, 30, 60, & 90th day, and spectrophotometrically analyzed at 237.7 nm for drug material.

## RESULTS AND DISCUSSION

### sim - $\beta$ cyclodextrin complex gel – results of evaluation parameters

### Differential scanning calorimetry

Differential scanning calorimetry thermograms of the physical mixture of drugs and excipients indicate the presence of SIM's endothermic level, suggesting the absence of drug-excipient contact. The inclusion complex formulation DSC thermogram indicates the disappearance at 137.17 ° C of the SIM endothermic peak. This can be due to an amorphous solid and molecular dispersion (Figure 1).

### Drug content

For product material, the formulation was analyzed. It was found that the drug content was 95.26 ± 0.025 percent in SIM's prepared $\beta$-CD inclusion complex (1:1). The results show that the medication was administered evenly in the formulations.

### Percentage yield

The yield was about 97.45 ± 0.032%. Suggesting that the method of spray drying is the optimal way to prepare complexes for inclusion.

### pH measurement

The pH of the prepared gel was pH 7.1, within the acceptable pH range.

### Viscosity

The $\beta$-CD complex gel viscosity was measured using the 4000 viscometer viscolab. The sample's viscosity was measured at various temperatures. For

higher temperatures, viscosity decreases. The prepared $\beta$-CD complex gel's viscosity was 11,392 cps. The prepared gel had a good texture to be applied to the skin.

**Spreadability**

Prepared gel Spreadability using 1% SIM Carbopol and $\beta$-CD complex (1:1) was 1.233$\pm$ 0.05 cms. The gel was in a very specific class (Table 4).

**Scanning electron microscopy**

To test the surface morphology, scanning electron microscopy for the pure material, spray-dried inclusion complex was performed. The $\beta$-CD complex SEM photographs (Figure 2) showed that the particles are almost spherical with a relatively uniform diameter of about 2 $\mu$m, and no drug crystals are found.

***In vitro* drug diffusion studies**

The rate of cumulative drug release of SIM from the $\beta$ cyclodextrin complex gel formulation (1:1) in in vitro drug diffusion studies was 96.7 $\pm$ 2.79% at the sixth hour (Table 5) and (Figure 3).

Within six hours, the total concentration of drugs in the release mechanism is reached. The drug release of $\beta$ cyclodextrin gel obeyed the kinetic model of Korsmeyer-Peppas (Table 6). Korsmeyer-Peppas kinetic model describes the release mechanism based on the n value if n < 5 indicating the release of the drug through Fickian diffusion (n < 0.5), matrix erosion or combination of both mechanisms and (n > 0.5) indicates the release mechanism due to non-Fickian transport product release of $\beta$ cyclodextrin gel was 0.57, suggesting the release mechanism accompanied by non-Fickian transport.

**Skin irritation test**

The study of skin irritation showed that during the time of research, neither the polymer nor the drug caused visible discomfort or inflammation on or around the area applied.

**Stability studies**

The findings of the stability test of formulated formulations (Table 7) have been analyzed and tested at regular intervals for changes in product content and physical appearance. There was no significant change in the physical appearance of the product at the end of 90 days. During storage, the drug content of all formulations stored at 25oC/60% Relative humidity and 40oC/75% Relative humidity remains unchanged.

**Liposomal gel**

**Determination of percentage Entrapment efficiency**

The efficacy of encapsulation depended on the cholesterol used in the formulation of the phospholipid. The formulations ' encapsulation performance ranged from 44.14 $\pm$ 0.069 to 54.23 $\pm$ 0.074% (Table 8 andFigure 5). As the rigidity of the liposomal membrane increases, cholesterol and phospholipids are known to increase the effectiveness of trapment. An additional increase in cholesterol content resulted in a decrease in the efficiency of trapping, as higher amounts of cholesterol growing compete within the bilayer with the drug for packing room. The decrease in the efficiency of entrapment with an increased cholesterol ratio above a certain limit may also be due to the fact that that cholesterol above a certain concentration may interfere with the normal linear structure of vesicular membranes. Results indicated that low drug levels were caught up in the lipophilic nature of the drug.

**Scanning electron microscopy (SEM)**

Scanning electron microscopy for the liposomal formulation was carried out to check the surface morphology, and the SEM photographs are shown in (Figure 4). It indicated that the liposomes are in a spherical shape with a relatively uniform size of about 200 nm in diameter, and no drug crystals were observed.

**Particle size analysis**

Liposome particle size rose from 163 nm to 725 nm with cholesterol rise from 0.1% to 1% w / w. The mean vesicle length of the drug packed with F1-F8 liposomal formulations was 163.1 nm–725.7 nm (Table 8 and Figure 6).

**Zeta-potential**

The zeta potential gives the prepared product stability. A zeta potential value of $\pm$ 30 mV is important for successful stability and aggregation inhibition. The zeta potential values of all formulations of liposomes were between-23.2 and-42.2 mV (Table 8 and Figure 7). The Zeta potential of all formulations graphically represented in Figure 8. The Zeta potential of all graphically depicted formulations in Figure 8. Zeta potential of liposome formulation F3, F6, has been observed to have enough charge to prevent vesicle aggregation. The presence of a charge along a bilayer surface meant that the various liposome lamellae were repulsed.

**X-Ray Diffraction studies**

XRD analysis was done to evaluate the crystallinity of the drug in the formulation. XRD of SIM liposomal formulations (F3) is shown in Figure 9. All major characteristics of crystalline peaks are diffused were of low intensity in F3 liposomes. The SIM peaks in the liposomes appear to be of reduced peak area and

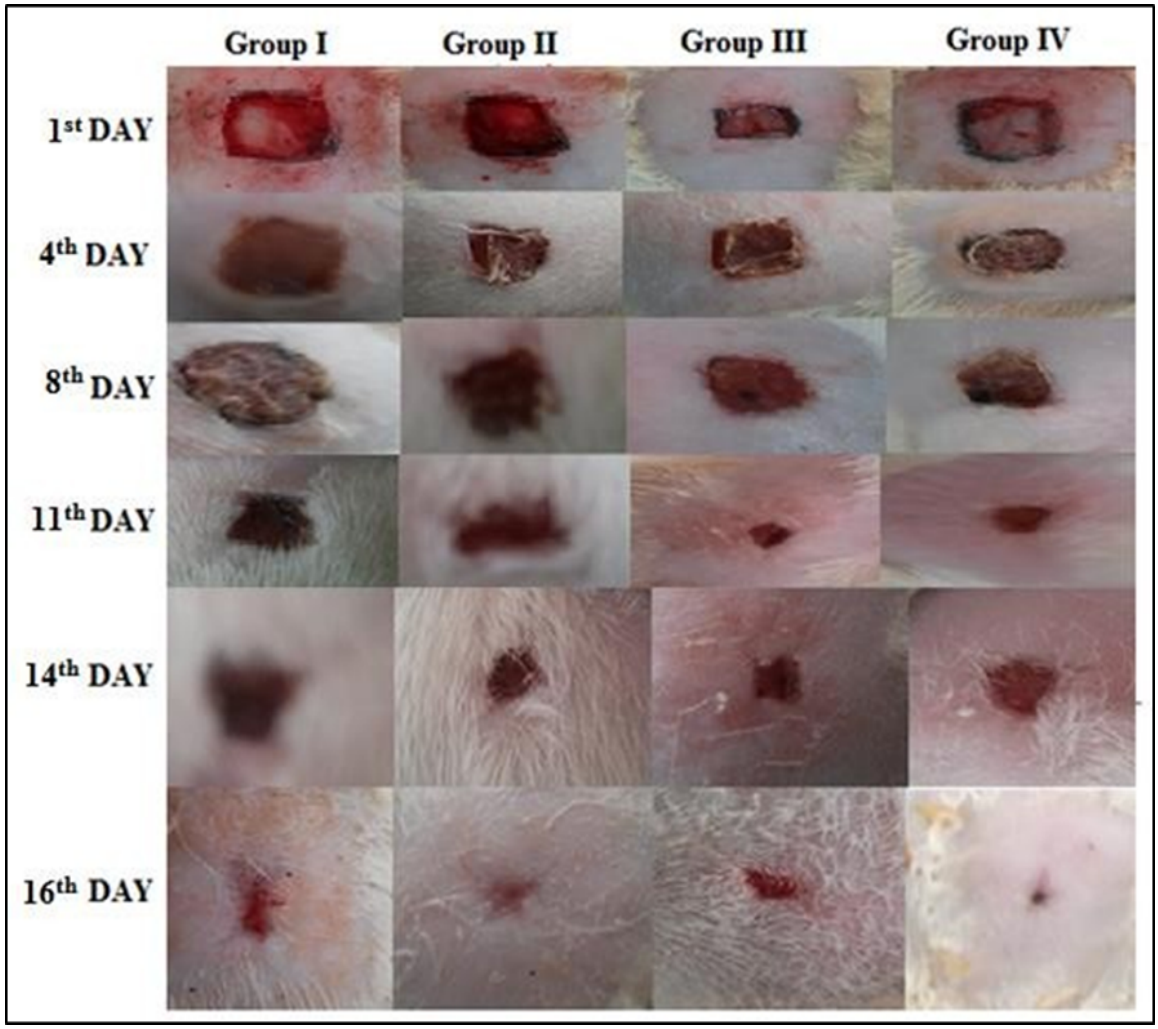


**Figure 18: Wound healing effect of SIM on a rat model Group I: Untreatedrats (control). Group III: Ratstreated with liposomal gel. Group II: Ratstreated with $\beta$-Cyclodextrin gel. Group IV: Ratstreated with ointment**

peak height. F3 has the most diffused peak compared to all liposomes formulations. This proves a decrease in the crystallinity of SIM as some of the crystals of drugs converted into an amorphous form in liposomes (Figure 9 and Figure 10).

**Differential scanning calorimetry**

The DSC thermogram exhibited a sharp endothermic peak at 137.17°C (Figure 11). DSC thermograms of the medication and excipient physical mixture revealed the presence of the endothermic level of SIM, suggesting the lack of drug-excipient contact. The liposomal formulation F3 DSC thermogram showed that the SIM endothermic peak disappeared at 137.17 ° C. This could be attributed to an amorphous solid being formed. Table 9 shows a comparison of the thermogram value of drugs with a physical mixture of excipients.

**Viscosity**

The viscosity of the liposomal gels are shown in Table 10. The viscosities of liposomal gels prepared using 1% carbopol was measured by using viscolab 4000 viscometer. The viscosity of the samples was measured at different temperatures it indicates viscosity decreases with higher temperatures. All liposomal gel formulations from F1-F8 showed the viscosity in the range of 20401-32451 cps, which was acceptable.

**Spreadability**

The spreadability of the prepared SIM liposomal gels are shown in Table 10 and Figure 12. It was observed that F1 – F8 formulations prepared using carbopol belonged to very stiff gels category and showed good spreadability. Lesser values of spreadability (< 1.4) having high viscosity or stiff gels shows good efficacy and retention time on the skin layer.

**pH measurements**

As the physiological pH range of the open wounds is 7.1 to 7.3, it is required that the pH value of preparation should remain in this range. pH of formulations F2, F3, F5, F6, F8 were found within the physiological range for the required topical application. The pH values of the prepared liposomal gels are shown in Table 10.

***In vitro* drug diffusion studies**

The *in vitro* drug diffusion of SIM from the liposomal gel formulations (F1 to F8) are shown in Table 11 and in Figure 13.

The *in vitro* drug diffusion of SIM liposomes formulations (F1 to F8) are shown in Table 12 and their profile in Figure 13.

The *in-vitro* permeation of SIM using the dialysis membrane 135 from liposomal gel containing SIM was studied. SIM is a lipophilic drug which is entrapped into the phospholipid membranes of liposomes. Due to the partition coefficient of the drug, slow movement of the drug was observed through the carbopol matrix layers into the dissolution media, indicating a sustained drug release from the gel. The drug release from the optimized liposomal gel (F3) (Figure 14) (Figure 15) was 29.7 $\pm$ 2.79 % at the end of 6th h, but drug release from the liposomes showed 59.7 % at the end of six hours. The cumulative release values were more for freeze-dried product than the liposomes in a gel formulation. This suggests that the release rate depends primarily on the gelling agent (carbopol) in a hydrogel. The presence of carbopol in gels retarded the release of the drug compared to the freeze-dried product. This retarding effect could be explained by the slower diffusion of drug through the carbopol matrix layer. Swollen carbopol controlled the drug diffusion and consequently, its release. Slower drug diffusion was observed in liposomal gel comparative with $\beta$-CD gel formulations and ointment.

**Mathematical model fitting**

Drug release was managed primarily by diffusion. The rate of release was inversely proportional to the thickness of the wall. The profile of the in vitro drug release suggested release from liposomal gel delayed by integration into the gel network. The drug release from all formulations obeyed Higuchi kinetic equation except for formulations F3, F6 obeyed Peppas, Hixson crowell kinetics and F5, F8 followed First-order kinetics, all the formulations released the drug by diffusion following non-Fickian (n>0.5) transport mechanism except for formulations F4, F6 and F7 which followed Fickian (n<0.5) transport mechanism (Table 13).

**Stability studies**

Optimized gel F3 has been processed for 90 days at 25oC/60% RH, 40oC/75% RH and 4 ° C (Table 14). There was no significant change in the product's physical appearance. The drug content of all formulations are stored at 25 ° C and 40 ° C significantly decreased, which could be attributable to lipid product degradation, while the drug content remained unchanged at 4 ° C. This indicates that the language should be kept at 4 ° C

**Ointment -evaluation parameters**

**pH -** The pH of ointment was found to be 7.1.

**Spreadability**

The spreadability of the prepared ointment was 1.6 $\pm$ 0.023 cm. It indicates ointment belonged to a stiff gel category.

**Viscosity of ointment**

The viscosity of prepared ointment with a 2 % drug was measured by using viscolab 4000 viscometer. The viscosity of the ointment was measured at different temperatures. It does not affect significantly at higher temperatures. The viscosity of ointment formulation was 299.78 cps.

***In vitro* drug diffusion studies**

At the end of the third hour, the release of SIM across the dialysis membrane from ointment was only 96.2$\pm$3.57, while the release of $\beta$-CD gel and the liposomal gel was 96.7% and 29.7% at the end of 6 hours. More drug was released from the ointment because of the ointment bases used in the formulation that allowed the drug to spread from the base to the dissolution media. In *in vitro*, drug release is shown in Table 15 and Figure 16.

The maximum drug concentration in release mechanism is achieved in three hours. The drug release from the ointment obeyed Higuchi kinetic model (Table 16). Higuchi kinetic model describes the release mechanism follows diffusion controlled.

**Skin irritation test**

The study of skin irritation showed that simple ointment formulation during the study period did not show any visible irritation or inflammation on or around the applied region.

**Stability studies**

There was no significant change in the product's physical appearance (Table 17). During the study period, the ointment's drug content ranged from 97.04 percent to 100 percent. The substance was stable at the base of the ointment.

***In-Vivo* Evaluation of wound healing activity Excision Wound Model**

The wound healing properties of prepared topical dosage forms such as $\beta$ cyclodextrin gel, liposomal gel, and ointment was studied by using the excision wound model. Group I was maintained as a control (untreated). Group III animals were tested for wound healing activity of liposomal gel, and results showed that 85.88 % of wound contraction on the 16 th day and period of epithelization was 20 days, which is similar to the control group. This indicates the poor wound healing efficacy of liposomal gel and is due to slow drug release from liposomes in gel and low entrapment of drugs. Group II animals were tested for wound healing activity of $\beta$ cyclodextrin gel, and results showed that 93.7 % wound contraction on 16 th day and period of epithelization was 18 days. The higher wound healing efficacy may be attributed to enhanced solubility of SIM. Group IV animals were tested for wound healing activity of ointment, and results showed that 100 % of wound contraction after 16 days (period of epithelization) significant wound contraction was observed with ointment due to the ointment base which offers a lipophilic pathway for the movement of a drug to the wound site. The results of the percentage wound healing and the rate of contraction are shown in Table 18 and Figure 17 andFigure 18.

The objective of the present work was to formulate and evaluate the different topical dosage forms such as $\beta$- cyclodextrin gel, liposomal gel, and ointment containing simvastatin. The following conclusions could be drawn from the results obtained,

### $\beta$- Cyclodextrin gel

The drug was compatible with excipients used for the study. $\beta$- Cyclodextrin inclusion complex was successfully prepared by using a spray drying method. The solubility of simvastatin is less in distilled water (02.23 $\pm$ 0.027) $\mu$g/ml. Drug required solubility enhancement technique. Scanning electron micrographs of cyclodextrin complexes shows that particles are spherical and free from aggregation. The inclusion complex of $\beta$ cyclodextrin with simvastatin is stable at 25ºC/60% RH and 40ºC/75% RH. Cyclodextrin gel showed more efficacy in wound healing than liposomal gel which may be attributed to inclusion complex of SIM with $\beta$ cyclodextrin that offers the hydrophilic property to inclusion complex which helps the drug to diffuse faster through matrix layers thereby releasing a higher amount of drug through the carbopol matrix to the wound site.

### Liposomal gel

Liposomes could be prepared by thin-film hydration method by using rotary evaporator, L-$\alpha$ Phosphatidylcholine, cholesterol, chloroform, and methanol are suitable excipients for liposomes. A higher concentration of phospholipid showed greater entrapment efficiency and sustained drug release. The drug was compatible with excipients used for the study. The thermal curve of SIM loaded liposomes showed a peak at 126.44 °C with fusion enthalpy of -18.31 J/g corresponding to its melting point. The decreasing fusion enthalpy indicates the drug may be dispersed in the form of the amorphous state. Based on entrapment efficiency, F3 was considered as optimum formulation and used for *in vivo* study. Drug release from F3 followed Peppa's model and followed the non- fickian transport mechanism. The liposomal gel was not stable at 25°C/60 % RH, 40°C/75 % RH, but stable at 4°C due to the degradation of the drug in lipids. Wound healing efficacy of liposomal gel was poor compared to $\beta$ cyclodextrin gel and ointment, due to low drug entrapment in phospholipid membranes of liposomes which has lipophilic nature.

### Ointment

The simple ointment was prepared by using white petroleum jelly. The ointment was stable at 25°C/60 % RH, 40°C/75 % RH during the period of study. An ointment has high efficacy for the wound healing properties when compared to prepared liposomal gel and $\beta$-CD. Drug release in an ointment was found to be highest due to high spreadability and viscosity. pH of ointment did not exhibit any skin irritation. Invivo release studies on Albino Wister rats was done, and prepared SIM ointment showed marked wound healing activity.

## CONCLUSIONS

This work results reveals that the preparation of simple ointment prepared showed enhanced wound healing activity when compared to $\beta$- Cyclodextrin gel and Liposomal gel. The study showed marked enhancement in wound healing activity because of its viscosity and spreadability. To conclude, the prepared gels and ointment had a promising effect on wound healing activity with higher solubilization and prolonged release of a drug. Wound healing activity exhibits higher residence of time and greater potential to the wound in Wistar rats.

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