

PREPARATION AND EVALUATION OF TAVABOROLE SOLID LIPID NANO PARTICLES TOPICAL GEL

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Abstract: Aims: The work is aimed to formulate nanodispersion of tavorole solid lipid nanoparticles (SLNs) gel by using a high shear homogenization technique using ultrasonication method. Which is preferably utilized in case of anti-fungal nail infection (onychomycosis) as an effective drug. (1) The nine different formulations of Tavorole SLNs (SLN1-SLN9) were prepared using solid and liquid lipid with Compritol 888 ATO (2) and cholesterol in several Concentration by the ultrasonication method. (3) The formulations were also characterized for particle size, entrapment efficiency, drug loading and depression in freezing point. **The results:** The DSC, FTIR analyses were performed to characterize the state of drug and lipid modification. Shape and surface morphology were determined by SEM which showed spherical shapes of the formulations. Further the formulation was evaluated for in vitro drug permeability Study, rheological properties, skin irritation, pharmacodynamic and stability studies. (4)

Keywords: Tavorole, Solid Lipid Nanoparticles, Toe-nail infection, High shear homogenization, Topical gel

I. INTRODUCTION

Solid lipid (SLNs) added in 1991 constitute an opportunity carrier gadget to the way of life colloidal carried alongside emulsion, liposome, and polymeric micro and nanoparticles¹. It's made up of robust lipids that are attracting major interest as a totally unique colloidal pharmaceutical company for intravenous utility as they were proposed as a chance particulate provider tool. SLN may be a sub-micron colloidal service ranging from 50 to 1000 NM, which may be composed of physiological lipids, dispersed in water, or aqueous surfactant solution. (1) SLN gives precise properties alongside small size, huge ground area, excessive drug loading, and therefore the interaction of stages at the interface and are appealing for his or her capability to reinforce the performance of pharmaceuticals. (2) to overcome the disadvantage partner with the liquid of the oil droplets, the liquid lipid emerges as replaced with the help of a stable lipid, which sooner or later converted into stable lipid nanoparticles. (2) The motives In the growing interest inside the lipid-based gadget is a lousy lot fold and include lipid beautify oral bio-availability and reduce plasma profile variability, better characterization of lipid excipients, and improved capability to affect the key problems with era transfer and manufacture scale-up. (2) Solid lipid nanoparticles are one among the novel capability colloidal provider structures As opportunity materials for polymers which are just like oil in water emulsion for parenteral nutrition, however, the liquid lipid of the emulsion has been changed by employing a strong lipid as proven in fig-1. (3) they need blessings which include particular bio-compatibility, low toxicity, and Philippine capsules are better added by using strong lipid Nanoparticles and therefore the tool is bodily stable. 3 this is often one among the foremost famous processes to beautify the oral bioavailability of poorly water-soluble pills. Sons are the sub-micron size tiers of 50-1000 mm and is compared to physiologically tolerate lipid components which may be in the strong-state at a temperature. (4) Onychomycosis may be a common mix of the nail unit, primarily thanks to the dermatophytes *Trichophyton rubrum* and *Trichophyton mentagrophytes*, which will motive sublingual hyperkeratosis, nail plate thickening and detachment of the nail plate from the nail bed (Onycholysis). (4)

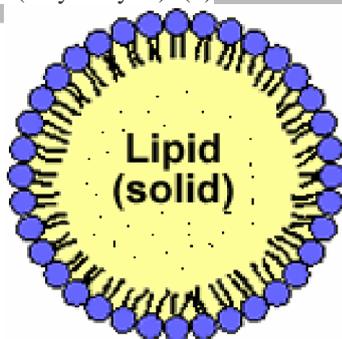


Fig. 1: Structure of solid lipid nanoparticle (SLN)

II. MATERIALS AND METHODS:

2.1 MATERIALS:-

Tavorole was purchased from Anacor Pharmaceuticals, Inc, Palo Alto, (Canada) (4). Compritol 888 ATO (glyceryl behenate) by Gattefosc India Pvt. Ltd., (5) PEG-8 Miglyol 812 by Subhash chemicals. Ethanol and other required chemicals are purchased from Loba chemise. (6) The water used for all experiments was double water and filtered before use through a nylon paper.

2.2 Preparation of Tavaborole solid lipid nanoparticles:

Blank and drug-loaded solid lipid particleboard were prepared by hot homogenizing followed by the ultrasonication method. (6) Tavaborole was dispersed during about 10g of mixed lipid phase (consisted of Compritol 888 ATO and PEG-8 Miglyol 812) maintained at around 50c above the melting temperature of mixed lipid and dissolved in a mixture of ethanol And chloroform (1:1). Organic solvents were completely removed employing a rotary flash evaporator. (5) An aqueous phase was prepared by dissolving the stabilizers (Tween 80 or Span20) in distilled water (sufficient to supply 30ml) 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 2500rpm and 70oc) 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 4oc within the refrigerator. (6)

TABLE:1:-Composition of solid lipid nanoparticles

Excipients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Pure drug(mg)	50	50	50	50	50	50	50	50	50
Compritol888ATO	75	80	90	100	85	95	100	95	100
Cholesterol(mg)	100	120	130	140	100	120	130	140	150
Tween 80(ml)	1.2	1.5	1.7	1.8	-	-	-	-	1
Span 60(ml)	-	-	-	-	1.6	2	2.2	2.1	1
Chloroform(ml)	15	15	15	15	15	15	15	15	15
Ethanol(ml)	15	15	15	15	15	15	15	15	15

2.3 Preparation of tavaborole loaded SLNs gel: -

Tavaborole loaded SLN gel turned into organized by using using 1gm of carbopol 940 changed into weighed and dispersed in water. (7) Then propylene glycol changed into introduced and the combination was neutralized by using dropwise addition of 1% Triethanolamine. Mixing was continued till the obvious gel changed into acquired and allowed to swell for 24hours. Similarly, 2% and three of carbopol Gels have been organized. (7)

2.4 Preparation of Proliposomal gel: -

SLNs containing pure capsules separated from the untrapped drug became mixed into the 1%carbopol gels by way of the usage of mortar and pestles, the awareness of SLNs in the gels being 1%. All optimized formula became integrated into exclusive carbopol gels (1%, 2percentand3%). (7)

III.Characterization of preparing solid lipid nanoparticles:

3.1 Particle Sizes, PDI, Zeta Potential:

The mean particle length and polydispersity index (PDI), that's a degree of the distribution of nanoparticles population, was decided the usage of dynamic light scattering (Delta Nano C, Beckman counter), and Zeta capability becomes anticipated on the premise of electrophoretic mobility under an electric powered field, the use of zeta Sizer Nano ZS (Malvern Instruments, UK). Samples had been diluted with the distilled water before measurement and measure at a hard and fast angle of 165⁰c for the particle size and polydispersity index (PDI) analysis. For the Zeta ability measurement, Samples have been diluted as 1:40ratio with filtered water (v/v) before analysis. Average particle size, PDI, and zeta potential have been then measured in triplicate.

3.2 Entrapment Efficiency:

Entrapment Efficiency (EE) of the RL-HCL loaded SLNs changed into determined by measuring the awareness of uninterrupted drug in an aqueous medium by centrifugation method. 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 4oc, and therefore the supernatant was separated. The amount of RL-HCL inside the supernatant changed into determining the usage of a UV-Visible spectrophotometer (U-1800, Hitachi) at lambda max 238nm after suitable dilution.

The percent entrapment efficiency (%) changed into calculated by means of the usage of the subsequent formula:

$$\%EE = \frac{\text{Total drug content} - \text{Free drug}}{\text{Total drug content}} \times 100$$

3.3 Scanning electron micro-graphic studies:

The shape and surface characteristics of SLNs were determined by SEM using gold sputter technique (ZEISS EV40, Carl Zeiss NTS, North America). Samples of SLNs were dusted onto a double-sided tape on an aluminum stub. The stuns containing the sample were coated with gold employing a cool sputter coated (Polaran E 5100) to a thickness of 400oA. Photomicrographs were taken at the accelerated voltage of 20KV chamber pressure of 0.6mmHg.

3.4 In Vitro Drug Release studies:

In vitro release studies were performed employing a modified Franz diffusion cell. The release studies were performed using pH 6.8 Phosphate buffer containing 0. 5% v/v polysorbate 80 using dialysis membrane having pore size 2.4mm and relative molecular mass cutoff between 12,000-14,000 Daltons was used. The membrane was soaked in double-distilled water for 12h before

Mounting during a Franz diffusion cell. SLNs dispersion like 0.4mg of the drug was filled into a donor compartment and tied at both the ends and placed during a beaker containing 100 ml of diffusion medium; temperature and speed were maintained at $37\pm 5^\circ\text{C}$ and stirred at 100rpm using Teflon-coated magnetic stirrer bars (Chen et al, 2012). 5ml of Sample were withdrawn at Predetermined time intervals from the receiver compartment through a side tube, and therefore the same volume was replaced with the fresh buffer to take care of the sink condition. Samples were analyzed using UV spectrophotometrically at 280nm. The cumulative percentage release was then calculated from the quantity of drug release. The discharge kinetics were determined by following kinetic equation like zero-order(cumulative % drug release versus time), First order ($\log\%$ drug remaining versus time), Higuchi's model cumulative preferred drug release versus root of your time, and Korsmeyer-Peppas model \log drug release versus \log time, values were calculated from the linear curve obtained by multivariate analysis of the plots. 'n' the worth was calculated.

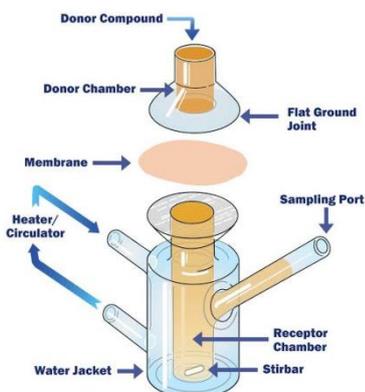


FIG:3:-FRANZ DIFFUSION CELL

3.5 Ex Vivo Permeation studies:

The optimized formulation and therefore the formulation giving better in vitro drug diffusion rate were selected for the ex vivo skin permeation studies. In vitro permeation of SLNs based gel and marketed formulation Flucos Gel, Cosme Pharma Ltd, India was performed using excised full-thickness hairless abdominal skin of rats Male albino rats, Sprague Dawley; weight average 100-150g. After ether anesthesia in the rats, the abdominal skin was surgically far away from the animal, and adhering subcutaneous fat was carefully cleaned. The skin samples were mounted on modified Franz diffusion cells. Crown Glass Co., NJ with a surface of three. 14 cm^2 and a receptor volume of 10ml such the dermal side of the skin was exposed to the receptor. Fluid (Ethanol: PBS (pH 6.8) I.E., 30:70) ratio and therefore the corneum remained in touch with the content of donor compartment. The formulation was placed within the donor compartment enabling one to hide the whole skin surface evenly. The temperature was maintained at $37\pm 1^\circ\text{C}$ serial sample 0.5 ml was performed at specific time intervals and replaced it with the fresh medium. The sample was analyzed employing a UV visible spectrophotometer at 224nm and therefore the % cumulative was calculated.

3.6 Fourier Transform Infrared studies:

The interaction between drug and lipid was identified from the Fourier transform infrared (FTIR-8400S, Shimadzu) studies. The FTIR spectra were measured over the range of $4000\text{-}400\text{ cm}^{-1}$ with a resolution of 4 cm^{-1} for 50 scans.

3.7 Differential Scanning Calorimetry (DSC) Analysis:

Differential Scanning Calorimetry (DSC) is widely utilized in the thermal analysis of endothermic processes (melting, solid-solid phase transitions, and chemical degradation) also as exothermic processes (crystallization and oxidative decomposition). For DSC measurement, 10mg of the sample was put in an open aluminum pan, then heated at the scanning rate of $10^\circ\text{C}/\text{min}$ between 0 and 400°C temperature Ranges (Zhao et., al., 2010).

IV.Characterization of the gel:

Determination of drug content, Spreadability, and pH:

4.1 Drug Content

500 mg of the gel was weighed during a 100 ml volumetric flask and dissolved in 50ml of phosphate buffer of pH 6.8. The Volumetric flask was kept for 2h and shaken well during a shaker to combine it properly. It had been diluted appropriately and analyzed on a UV Spectrophotometer at a λ_{max} of 280 NM.

4.2 Spreadability:

The spreadability of the gel decided to use the subsequent technique: 0.5g of the gel was placed within a circle of 1 cm diameter pre- marked on a glass plate over which a second glass plate was placed. A weight of 500g was allowed to rest on the upper glass plate. The rise within the diameter thanks to the spreading of the gels was noted.

4.3 PH determination:

The pH of the gel decided by employing a digital pH meter Model EQ610, standardized using pH 4.0 and 7.0 standard buffers before use, one gram of gel was dissolved in 100ml of water and stored for 2h. The results of the characterization of gel are noted.

4.4 Rheological studies:

on the gel Brookfield Synchro-Lectric Viscometer (Model RVT) with a helipad stand was used for Rheological studies. The sample (30g) was placed in a beaker and was allowed to equilibrate for 5min before measuring the dial reading T-C spindle at 0.5,1,2.5, and 5rpm. At each speed, the corresponding dial reading was successively lower and therefore the corresponding dial reading was noted. The measurements were carried out in duplicate at ambient temperature. Direct multiplication of the dial readings with factors given within the Brooke field Viscometer catalog gave the viscosity in centipoises (Joshi and Patravale, 2006). The consistency index and therefore the flow index were calculated from the power-law equation;

4.5 SKin Irritation test:-

The developed formulation was tested for primary skin irritation on albino mice of either sex weighing 20-22gm. The hair was far away from the mice 3 days before the experiments. The animal was divided into two batches each batch was used on the test animal. A bit of cotton soaked during a saturated drug solution was placed on the rear of albino mice taken as controls. The animals were treated daily up to 7 days and eventually The treated skin was examined visually for erythema and edema.

4.6 Stability Studies:

In the stability study, after every 30 days samples were withdrawn and retested for viscosity (cps) and total drug content. The formulation did not show any significant changes in both the parameters, It indicates that this formulation was able to retain its stability up to 3 months

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