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REVIEW PAPER

Smart terbinafine recent nano-advances in delivery of terbinafine

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ABSTRACT

Terbinafine (TBF) is a drug with well-known antifungal properties effective against skin dermatophyte infections and nail particularly in treatment of pityriasis (tinea) vesicolor due to Malassezia furfur. Terbinafine topical administration is often recommended because commercial conventional terbinafine hydrochloride tablets are more expensive and have potential for significant adverse effects. Only less than 5% of terbinafine is absorbed in conventional topical forms. Novel nano-formulation approaches would be an efficient way to enhance penetration and abortion of topical drugs and eliminate limitations of conventional drug delivery systems. As conclusion, we believe that administering the Terbinafine in nano-formulations, according to different studies, could increases penetration of TBF through stratum corneum and viable epidermis and light the path of nano-structural delivery system in clinical application. Present overview aims to evaluate nano-strategies applied to improve permeation profile and terbinafine skin delivery.

Keywords: *Drug delivery, Nanoparticle; Percutaneous penetration; Terbinafine*

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INTRODUCTION

Fungal infections are the well-known skin infection in developing and under developed countries that affecting more than 40 million people all around the world and the superficial fungal infection is counted as the most common infection in clinical scales [1]. Different type of fungal organism capable to produce superficial infections including dermatophytes , Tinea pedis and yeasts [2]. The severity of the fungal infections is variable depend on the site of infection, type of fungi that cause the infection and the personal health care behavior of the affecting person [3]. Many antifungal compounds have been generated in last three decades and are classified into different categories but the major topical groups include Azole with Imidazole functional group and Allylamine with amine functional groups [1].

The most characterized member of Allylamine group is Terbinafine hydrochloride (TBF) also known as Lamisil®, is a leading antifungal agent for topical treatment of fungal infections. Fig 1. represents the chemical structure of terbinafine. TBF, a white fine crystalline powder is an allylamine agent developed by Novartis and highly hydrophobic in nature, freely soluble in methanol, ethanol, and dichloromethane and sparingly soluble in water. Terbinafine was approved by the US Food and Drug Administration in 1993 and is utilized in cream, gel, solution and spray forms to treat fungal infection such as ringworm of the body (tinea corporis), foot contamination (interdigital and plantar tineapedis; athlete's foot); groin (tinea cruris; jock itch); tinea versicolor (sometimes

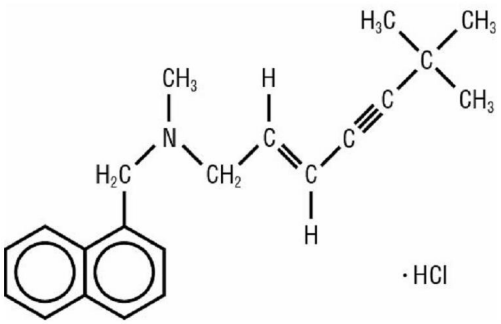

Fig 1. Chemical structure of Terbinafine

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called “sun fungus”); and skin yeast infections (cutaneous candidiasis) [4].

Terbinafine inhibits the action of enzymes that are involved in cell membrane synthesis pathway such as squalene epoxidase. This process eliminate ergo sterol synthesis and by accumulation of intracellular squalene lead to fungal cell lysis [5].

Anti-fungal topical therapy is an attractive choice for treatment of cutaneous infections that not only reduce systemic side effect risks such as hepatotoxicity and nephrotoxicity, but also targeting delivery to the infection’s site. On the other hand, the efficiency of topical therapy relies on two main parameters; penetration of the substrate through different layers of skin base on hydrophobicity and hydrophilicity properties and size of therapeutic components and amount of drug depot in the action site. One general approach, is applying nanostructures that would increase drugs penetration by changing their solubility and promote drug diffusion through stratum corneum (SC) to viable epidermis and dermis by manipulating their size [6, 7].

NPs-based delivery systems are able to overcome many unfavorable drug properties to enhance drug targeting and delivering wile limit unwanted interaction between drugs and surrounding medium to maximize treatment results. The role of NPs-based delivery system has been shown schematically in Fig 2. Nanoparticles in this system generally are colloidal particles ranging from 10 to 1000 nm that are classified based on their composition and structure. They might be different types of vesicles such as liposomes and niosomes, polymeric NPs, dendrimer, nano-emulsion and solid lipid [8, 9].

Active principles (drug or biologically active material) can be dissolved, entrapped, adsorbed or attached to the nanoparticles and offer numerous advantages such as sustained drug release, less frequency of administration, reduced toxicity, and protection of the associated drug against enzymatic dissociation and *in vivo* chemical degradation. They can also resolve problems of long treatment durations of the antifungal agent [10–12]. Present overview focuses on new alternative formulation approaches using nanoparticles to improve terbinafine skin penetration.

Nano-carriers in skin delivery system

The major facing trouble for treatment of fungal infections is the poor penetration of drugs into different layers of the skin. To solve this problem, a drug delivery system needs to be designed to provide efficient and sustained delivery in localized area of the infection and diminished percutaneous unwanted absorption of the drugs. Several researchers have explained that drug penetration into skin is affected by the physico-chemical properties of nanoparticles such as particle size, surface charge, surface area, solubility, effect of solvents, salt form of the drug and chemical composition [13–16]. Furthermore, the most important strategy in tropical therapy is liquid crystal (LC)dosage form. This system also is called “mesophase” in which both solid and liquid form of drug and carrier are packed together. Size of carrier in this system is around 200nm but depend on row materials and their combination ratio can reach to around 1 mm. Owing to similarity of LC and stratum corneum, LC system not only enhance drug localization and penetration to decrease toxicity and promote local delivery, but also promote the hydration of stratum corneum due to membrane-like structure of LC and its connection to lipid microstructure of stratum corneum [17, 18].

Mainly, LC system is consisting of three types collecting systems; Lamellar, hexagonal, and cubic forms. Since the basic substance of mesophase is water, hydrophobic and hydrophilic properties of participant materials lead to final

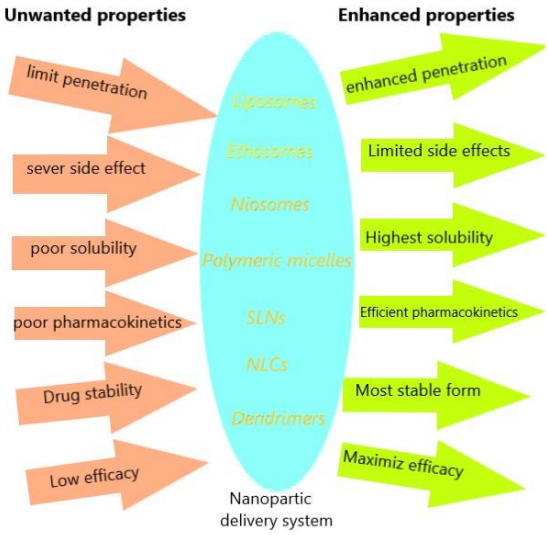

Fig 2. schematic effect on nanoparticles effects on drug delivery system. SLNs; Solid Lipid nanoparticles, NLCs; Nanostructure carriers

form construction. In the lamellar form, water as solvent fill the space between hydrophobic parts, where the hydrophilic head is toward the water and hydrophobic parts bend inward. The hexagonal form is construct by seven rod-like micelles that form a three dimensional cylinder that drug based on its properties can be loaded inside or outside of this cylinder. In the cubic form of LC micelles are distributed into a cubic format that according to their arrangement in side of cube, generate different structure mainly; biocontinous (with infinitive periodic minimal surface pattern) and discontinuous (micelles are arranged in cubic lattice) [19–21]. Moreover, different phase of mesophase contain different value of viscosity; generally cubic forms are most viscous while lamellar forma are least viscous and when the system is exposed to eques media viscousity increase due to water absorbance [22].

Vesicles in mesophase are made by nonionic surfactant, consist of polar and nonpolar components that when interact with water to form different bilayer structures. The formation of structures is control by some parameters called critical packing parameters(CPP). The first parameter in CPP is the ratio of hydrophobic-hydrophilic balance (HLB) of surfactant which determine solubility of yielded in water and lipid phases. HLB is ranged between 0-18; when a material has HLB>10 is water soluble and HLB <10 is lipid soluble [23]. On the other hand, entrapment efficiency (EE) indicate the entrapment of drug into the carrier compare to total added drug added to system. These two parameters represent efficiency of whole system; if HLB increase, EE will decrease and vice versa [24]. Furthermore, CPP indicate the final format of vesicle structure by calculate the value of hydrophobic tail (V). the accupied area by hydrophilic head (a) and the length hydrophilic tail (l);

$$\mathbf{CPP} = \frac{V}{a + l}$$

If CPP value be >1, we can see invers micelle whereas 1>CPP>0.5 system forms lamellar formation and in the case of ½>CPP>1/3, cylinder micelle are made and if CPP< 1/3, spherical micelle will be shaped [25, 26].

Nanoparticles possess several advantages in drug delivery systems. They are synthesized in particular size and their surface can be modified with different functional groups that enhance targeted delivery. They particularly increase therapeutic efficiency by sustained delivery of the drugs and significantly control the side effect of the drug. Furthermore water-lees soluble drugs can be loaded into nanocarrier without any extra interaction that not only allows the drugs to circulate into the body's fluids, but also protect the drug from the degradation by numerous enzymes in the body [27, 28].

In this regards many nano-based carrier have been developed by nanotechnology techniques with ranging size from 10 to 1000 nm that capable several drug to be dissolved, attached and encapsulated into the nanocarrier to promote their penetration in various tissues and organs [29]. Particle size is the most important property which influences skin penetration. Analysing nanoparticles at different sizes consisting of diverse materials with various surface properties has revealed that smaller size of nanoparticles is more likely to penetrate to skin compared with lager size. In addition, hair follicles are considered as an important shunt route for nanoparticles. Particles of approximately 300–600 nm in size exhibit the deepest penetration into hair follicles [30] where they were stored significantly longer than in the stratum corneum [31].

Drug penetration can also be affected by the surface charge of nanoparticles. The results in the literature are contradictory. While some experiments report higher skin penetration potential of the positively charged submicron emulsions, other experiments show more skin penetration by negatively charged nano compounds. Positively charged submicron emulsions exhibit more efficacies in promoting drug bioavailability due to droplets higher binding affinity to skin. Since the skin's epithelial cells carry a negative charge on their surface and the presence of protein residues on the outer membrane of cells creates a negative charge on the surface of epithelial cells in various tissues including skin [32–34]. Using the salt forms of drugs is one of the important ways for improving percutaneous absorption when the physic-chemical characteristics of the parent drug molecule are unsuitable. A large number of drugs which are being used for local applications are weak acid or bases and ionize under normal physiological conditions. Ionized molecules cannot well absorb by biologic membranes. Increased

absorption followed by drug ion pairing and salt formation can be related to electrical neutrality and increased drug lipophilicity. Using different salt counter ions makes significant changes in drug solubility, dissolution rate, and other pharmaceutically important properties which are essential for drug absorption [35].

Further interesting point that might influence the selection of a nanoparticle in some drug delivery systems is their penetration mechanism. Polymeric nanoparticles are able to reach to the upper layer of stratum corneum and transfer therapeutic cargo into the deeper skin's layers. Moreover, since polymeric nanoparticles are able to be accumulated in hair follicles, they are preferred for hair root treatment [36]. Solid lipid nanoparticles can influence the drug penetration through interaction with skin surface due to its lipoid nature [37]. Indeed, this carrier increase the cargo connection with the corneocytes layer of the skin and in this way might be more applicable in the cream production. Nanostructured lipid carriers have a high potential ability to adhere into stratum corneum and are appropriate for transferring drug into viable skin cells. This carrier, owing to its inherent ability to occlude skin pores, can conserve the water in the applying site and thereby promote the drug penetration [38].

On the other hand, vesicle based nanocarriers transfer the loading cargo in a different way; Transferosome, due to its flexible surface, attach to the skin pore and via a hydrotaxis process is absorbed into the skin. This carrier is able to cross entire stratum corneum under a suitable condition which is dehydration of skin surface [39]. Ethosome disrupt lipid bilayer of the membrane and promote the drug penetration [40] and invasomes disorganized the intercellular lipid lamina and construct a channel through the skin and thereby enhance the penetration [41].

Methods of nanoparticles preparation

In drug delivery systems, mechanism of therapeutic agent release plays an essential role to control drug retention at required level in target tissue. Therefore, mathematical tools would be necessary to design a proper pharmaceutical formulation to optimize delivery system. On the other hand, therapeutic agents are released under influence of extra conditions such as medium inherence, diffusion and dissolution rate, osmosis, system swelling and carrier erosion, for instance, a hydrophilic agent easily distribute in an aquatic medium via diffusion process whereas a hydrophobic material distribution depends on matrix swelling and carrier erosion. So we can see why the therapeutic movement behavior is change when they are applied in a polymeric matrix [42].

However, many statistical methods have been invented to help scientists to have better realization of drug release mechanisms *in vitro* and in vivo conditions and facilitate evaluation and monitoring the delivery systems. When an active agent is administrated through rapid-release dosage form, a rapid absorption and elimination take place, as a result, frequent repetitive dosing is required to maintain desired drug levels. Now, if therapeutic system be design to release drug at a constant rate in a particular period of time, the release mechanism will depend on diffusion rate similar to osmosis and this process can be calculated by Zero-order Kinetic method. In this method, drug is released at a constant rate to reach to saturate level and then remain at that level till its break-point time [42]. Furthermore, First-Order Kinetic method is applied to explain drug distribution only based on drug concentration in target tissue, although, none of these methods describe drug release in a matrix system. In 1961, Higuchi report a new mathematical method to represent release behavior in polymeric and complex medium such as an ointment [43]. The efforts of Higuchi enable theoretical tools to represent release procedure of soluble and semi-soluble material in solid and semi solid [43–45]. {333} which is basic method in nanotechnology to study delivery system and optimize their efficiency. Table 1 shows different mathematical method and their formulation which are used in study of drug delivery systems.

Preparation on nano-carriers in nanotechnology systems basically rely on two main mechanisms; Bottom-up and Top-down manipulation of components. In bottom-up methods the nano-carriers are constructed via molecule-by-molecules re-arrange based on thermodynamic properties of the reacting materials. This technique is applied by controlling the chemical interaction in different phase that led to the production of highly stable nanostructure [46, 47]. On the other hand, in Top-Down technique, nanomaterials are generated by grinding and etching of large mass precursors in which the additional chemical reagents might facilitate the preparation mechanism. This technique is partially unsuitable due to its time consuming process and variation in particle size

Table 1. some mathematical models in drug delivery system42

Kinetic model	Formulation		Applied system
Zero-order kinetics	$f_i=K_0t$	K_0: constant of dissolution t: time	• Simple diffusion, • osmosis • transdermal system
First-order kinetics	$logQ_1 = logQ_0 + \frac{k1t}{2.303}$	Q_1: amount of drug on time t Q_0: initial amount of drug K_1: first order constant t: time	• Only based on concentration in many delivery systems & porous matrix
Higuchi model	$Q = K_H\sqrt{t}$	K_H: constant of Higuchi t: time	• Matrix systems • Nano-carrier • ointments
Hixson–Crowell model	$\sqrt[3]{W_0} = \sqrt[3]{W_i} + K_{HC}t$	W_0: initial amont of drug W_i: amount of drug remaining in the system K_{HC}: constant of Hixson-crowell t: time	• Spherical particles • tablets
Ritger–Peppas and Korsmeyer–Peppas model (Power law)	$\frac{M_i}{M_\infty} = Kt^n + b$	Mi: amount of drug release over the time M∞: amount of drug at equilibrium state K: constant of system t: time n: exponent of release b: burst effect	• Polymeric system • When more than one type phenomenon involve • Hydrogel
Brazel and Peppas model	$S_W = \frac{\gamma\delta_r}{D_{3,21}}$	υ: movement of vitreous/rubbery border of polymer δ: thickness of swollen gel $D_{3,21}$:diffusion coefficient of drug in polymer	• Swelling system • Polymer/solvent system
Baker and Lonsdale model	$\varepsilon = \varepsilon_0 + KC_0$	ε_0: initial porosity C0: initial drug concentration K: constant of system	• Spherical matrices
Hopfenberg model	$\frac{M_t}{M_\infty} = 1 - \left[1 - \frac{K_0t}{C_0a_0}\right]$	M_t: drug release at time t M_∞: total amount of release K_0: erosion grade constant C_0: initial con. A0:initial release of sphere or cylender	• Erodible polymers • Various geometrical forms • Planar, spherical or cylindrical film

that have been produced [48]. In the following parts we are trying to briefly introduce some of the major methods using in nanoparticle preparation

Complex co-acervation method

This method is a basic technique for preparation of colloidal particles through the phase separation of two liquids that colloidal nanomaterial are generated in micro and nano scale according to the substrate's physic-chemical properties such as ionic strength, pH and polyelectrolyte concentration. However, this method requires more modification and cross-linking due to drawback of low stability and inefficient cargo loading [49]. Fig 3. represents the fundamental step in this process. The complex co-acevation technique later has been developed to produce cross-shell particles and represent a reliable method for loading the water insoluble therapeutic compounds which is called co-precipitation [50]. Evaporative precipitation in liquid phase is another derivative of co-acervation method in which a hydrophilic stabilizer

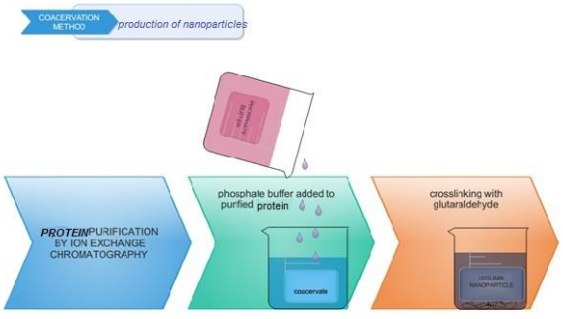

Fig 3. Basic steps of coacervation method for nanoparticle preparation

incorporates between the aqueous solution and hydrophobic encapsulated material to reduce the particle size and eliminate the cargo crystallization during the deposit time [51].

High- pressure homogenization

This is a promising and powerful method for preparation of lipid-based nanomaterial such as solid lipid nanoparticles, parenteral emulsions and nanostructure lipid carriers in large scale of production. This method is based on mechanical disruption of lipid through high pressure and high shear stress. The homogenization of lipid and cargo take place in two categories; cold homogenization and hot homogenization. Cold homogenization is a preferable process for heat labile compounds. In this method dispersed drug and melted lipid are mixed at 5-10° C above the melting point of lipid platform and then resulting solution is transferred into liquid nitrogen to generate solid lipid nanoparticles. In contrast, Hot homogenization is performed by adding melted lipids and loading drugs into hot surfactant solution and subsequently homogenized under high pressure that lead to the formation of oil in water nano-emulsion, then the resulting solution is allowed to be crystallized in room temperature and solid lipid nanoparticles being formed [52, 53].

Salting-Out method

The salting-out method is the interesting method of nanoparticle production in the industrial pharmacology due to high yield of production and easy handling processes as well as purity of products. Moreover, this method is very suitable for thermo labeling material owing to no requirement of heat treatment [54]. This technique is based on altering the solubility of nonelectronic components in aquatic phase by adding a saturated solution of electrolytes. To this aim, a viscous gel is prepared by dispersion of stabilizing polymer into a very high concentrated solution of electrolytes such as magnesium chloride. Then both drug and viscose gel containing polymer are solved in organic solvent such as acetone separately. The nanoparticles, then, are synthesized by adding the viscous gel into the organic solvent and ultimately cross-flow filtration removes the electrolytes and organic [55, 56].

Other nanoparticle preparation methods

The solvent Displacement method works by displacement of water-soluble polymer' functional groups with semi polar solvent from a lipophilic mixture and the interfacial deposition of polymer take place due to the rapid diffusion of solvent into a water-based solution [57]. Solvent Emulsification-diffusion method is a common method for preparation of polymeric nanoparticles in which polymers and oil are dissolved in a liquid phase and organic solvent respectively, and under high shear mixing process and the presence of stabilizer and water the nanoparticles are formed [58]. The basics of these processes are represented in Fig 4.

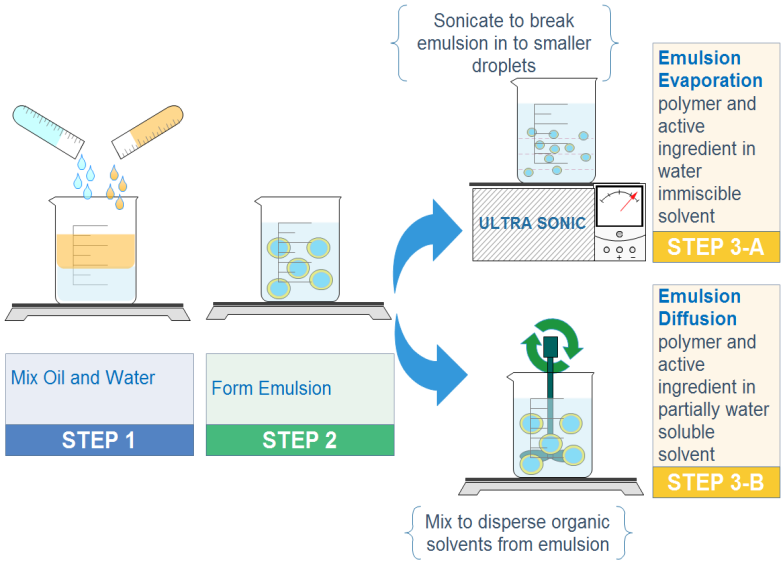

Fig 4. Emulsification method for preparation of nanoparticles

In supercritical fluid methods, the thermodynamic critical point of liquid and gas materials is used to produce nanoparticles [59]. This method can be classified into two main categories; Rapid Expansion of supercritical solution which is a suitable method for thermo labile material [60] and Supercritical anti-solvent precipitation that is used for preparation of nanoparticles from biological molecules such as antibodies [61].

Apart from all above mentioned methods, disordered molecules and polymers that are participating in the structure of nanoparticles can spontaneously bind together through a physico-chemical interaction and without any external forces generate a regulated nano-sized structure. This process of formation is called self-assembly method. Nature dynamic structure of biological membrane is a good example this process in which hydrophobic fatty acid and hydrophilic phosphate groups form a bilayer membrane. In nano biotechnolgy this method is mainly used for production of micelles and vesicles [62].

Nano-terbinafine delivery systems under current development

As it was discussed above, the most important step in the treatment of fungal infection is efficient delivery of a proper antifungal compound into a desire site of action. Therefore, knowing the properties of Terbinafine would be the best guideline to select and compose an efficient carrier. As we mentioned, Terbinafine is a hydrophobic and lipophilic compound thereby the best carrier might be lipid based nanostructured material that increase its penetration and water solubility. On the other hand, the action site of Terbinafine is in the stratum corneum and from there, it influence fungal infection. As a result, we most design a delivery system somehow to carry our drug into this part. By this view, nanostructured lipid carriers are seemed to be more suitable for topical administration of Terbinafine. In the following parts we have reviewed the latest and advanced carrier system in delivery of terbinafine. Fig 4. showed the major liposome-derived nanocarrier

Nanoparticulate carriers

Nanostructured lipid carrier

NLCs are the newest, most applicable lipid based carriers which have been produced to overcome the drawbacks of SLNs and other nanocarriers. This nanostructure is generated by the interaction of individual lipids from distinct phases; solid lipid and liquid oil [63]. Lipids are exclusive structures that provide a promising platform to develop drugs' conjugation. The loaded drugs disperse into the body by degradation of the NLC compartments. The main reasons for NLC generation were improvement of drug loading and elimination of drug leakage in deposition time [64]. NLCs are produced in three major types, including imperfect-type NLCs in which some spatially different lipids are combining together and owing to spatial differences, the final formed crystalline structure contains gaps that can be accumulated by guest molecules. In this type, if tow lipids be taken from different phase the size of gape will be larger, multiple-type NLCs which is similar to water-oil, water emulsion, but the solid phase possess the drawback of drug leakage and amorphous-type NLC that the crystallization process is prevented by exposing to additional special lipids such as hydroxyl octacosanyl and isopropyl myristate [65].

Compare to other carriers, NLC showed significant advantages such as developed stability, more efficient drug entrapment and reduced drug leakage [66], but they are not proper for industrial scale up [67]. Gaba et al [68]. Used Glyceryl Monostearate (GMS) as solid phase and mixed it with lubrasol as liquid phase in the presence of pluronic F-127 as a stabilizer. These materials have been combined via high pressure homogenization technique and nanocarrier was obtained with 128+ 4.5 nm diameter and 92.60 % drug releasing rate in *in vitro* which is 10% higher than marketed available formula. Furthermore, both permeability and therapeutic efficiency of the treatment with this carrier have been particularly increased.

Solid Lipid Nanoparticles (SLN)

Recently, increasing attention has been focused on SLNs as colloidal drug carriers. SLNs, composed of physiological and biodegradable lipids are generally inert and GRAS listed or have a regulatory accepted. They offer lower toxicity, as compared with polymeric systems and can be produced in large scale and have importance in new product commercialization. SLN specific characteristics make it an interesting carrier system for optimized topical drug delivery. The small size of the lipid particles ensures close contact to the stratum corneum and can enhance

the drug amount penetrating into the skin and it allows controlled drug release [64, 69,70]. The basic structure of SLN is depicted and compared to emulsion in Fig 5.

Chen et al. [71] tailored SLN-TBF by a microemul¬sion technique in which glyceryl monostearate (GMS), glyceryl behenate (Compritol® 888; Gattefossé), and glyceryl palmitostearate (Precirol® ATO 5; Gattefossé) were used as solid lipid phase, Tween® and Cremophor® series as surfactants, and propylene glycol as co-surfactant. The opti¬mal SLN system contained < 5% lipid phase and > 50% water phase. Terbinafine penetration profile in new formulations and in commercial products (Lamisil®Once™; Novartis Pharmaceuticals) was measured and compared in the stratum corneum, viable epidermis, and dermis of nude mouse skin. Combination of GMS and Compritol® 888 increased terbinafine penetration amount. For ACP1-GM1 (4% lipid phase; Compritol®888/GMS: 1/1), terbinafine penetrated SC was similar to that of Lamisil® OnceTM, whereas the TB amount in the dermis was higher than Lamisil® OnceTM at 12 hours similar to Lamisil® OnceTM at 24 hours. ACP1-GM1 application for 12 hours exhibited an efficacy comparable to Lamisil® OnceTM for 24 hours. Presented formulation might resolve the practical problems of longer administration period necessary for Lamisil® OnceTM. Wavikar and Vavia [72] fabricated a novel topical terbinafine-nanolipid gel (NLH) and evaluated its skin deposition and antifungal activity. TBF-SLNs were formulated by high-pressure homogenization technique (HPH) in which TBF-SLN was incorporated into Carbopol 980 NF 1%. Optimized TBF-SLN had a particle size and zeta potential value of 148.6±0.305 nm and −20.4±1.2 mV, respectively. TBF-NLH indicated good theological and texture properties which facilitated its topical application. TBF-NLH demonstrated 3-fold increased TBF skin deposition over plain and 2-fold over marketed TBF formulation. TBF-NLH was non-irritant to rabbit skin and exhibited efficient occlusion properties and significantly enhanced antifungal activity against Candida albicans. [73] et al. loaded TBF to SLNs by high pressure homogenization (HPH) technique in which glyceryl monostearate, compritol 888ATO and co-processed lipid were used as lipid matrix, poloxamer 188 as stabilizer and distilled water as dispersion medium. Drug loading percentage was higher with co-processed lipid. Terbinafine released from SLNs dispersion and SLNs based gel showed sustained release over prolonged period of time. SLNs was stable under accelerated storage conditions. TBF-SLN based gel exhibited better activity against Candida albicans.

Colloidal carriers

Nanoemulsions (NE)

Nano emulsions are a type of fine transparent or translucent emulsions with lipid droplets

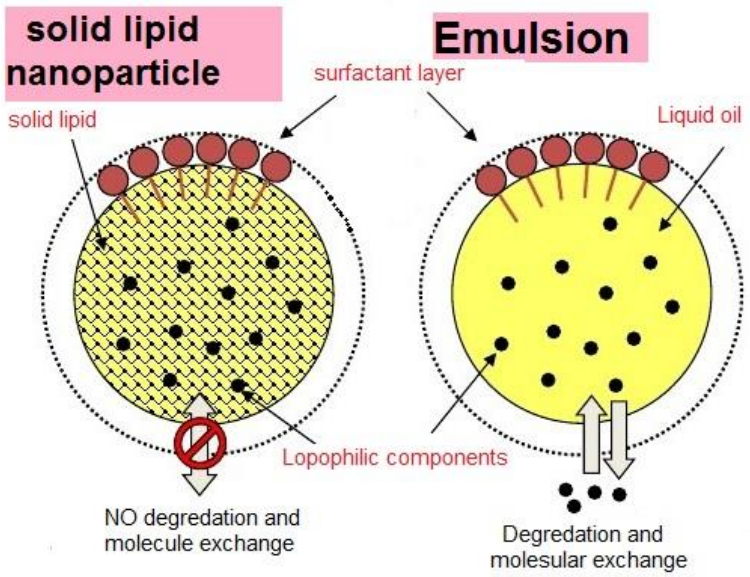

Fig 5. Basic structure of Solid lipid nanoparticle and emulsion

diameter between 20-200 nm, non-toxic and metastable systems, whose structure depends on synthesizing method. They can be produced in large quantities by mixing a water-immiscible oil phase into an aqueous phase with a high-stress, mechanical extrusion process. They exhibit high drug loading capacity and can be tolerated on the skin and mucous membranes with low skin irritation and are considered as potential tools for skin hydration and drug permeation enhancement [74, 75].

Reddy Karry et al. [6] designed and developed a topical based terbinafine. Nano emulsions were incorporated into carbomer gel. NEs were synthesized by two methods viz. high pressure homogenization (HPH) and high speed homogenization (HSH) and designated as Gel-P and Gel-S respectively. Size of developed gels by high pressure homogenization was less than 2 nm and that by high speed homogenization was less than 10 nm. Gel-P showed high spreading coefficient 40.00 as compared to Gel-S, 30.30 and M.C, 28.57. Higher spread ability of Gel-P than Gel-S and M.C (control) was attributed to NE-P less viscosity (obtained by HPH method) compared to that of NE-S (produced by HSH, Gel-P). NE-P exhibited more stability and therefore more efficacy than Gel-S and M.C. *In vitro* permeation studies demonstrated higher permeation of Gel-P (51.2 ± 0.8%) as compared to Gel-S (31.7 ± 1.1%) and marketed cream (19.8 ± 1.0%). *In vivo* antifungal studies in Wistar rats infected with Trichophyton mentagrophytes revealed cure within 3 days by Gel-S and Gel-P compared to 14 days for marketed cream (M.C). In conclusion, nano emulsion gels improved permeation followed by increasing cure rates in animal model, therefore can be considered as topical application carriers to overcome drug permeability and stability problems.

Dendrimers

Dendrimers are artificial hyperbranched and monodisperse three-dimensional molecules possessing defined molecular weights and host–guest entrapment properties [76]. Potential of different generations of PAMAM and PPI for enhancement of terbinafine antifungal activity was investigated by Khairnar et al. PAMAM and PPI dendrimers increased TBF antifungal activity against Candida albicans, Aspergillusniger and Sachromyces cerevasae as compared to pure TBF dissolved in DMSO [48].

Chitosan

Chitosan nanoparticles have received attention for topical drug delivery because of their biodegradability, biocompatibility, non- toxicity, and controlled drug release capability [77, 78].

Özcan et al., 2009, prepared topical terbinafine gel formulations based chitosan using different molecular weights of chitosan: G1:150–400; G2: 50,000–90,000; G3: 90,000–190,000; G4:190,000–310,000. Viscosity of G1 to G4 changed from 300 to 19800, terbinafine content for G1 to G4 changed from 88.9 to 92.4 %. The lowest molecular weight of chitosan (Protasan UP CL 213) exhibited higher drug release and highest inhibition zone compared with other chitosan gels and marketed product. New topical formulation indicated higher topical antifungal therapy against Candida species and filamentous fungi [79].

In another study, potential of chitosan-tripolyphosphate (TPP) nanoparticles was studied for enhancing terbinafine bioavailability and decreasing effects. Chitosan–TPP loaded with TBF was synthesized by ionotropic gelation method. Particles ranged from 139-200 nm had a positive zeta potential of +13.6 mV and an encapsulation efficiency of 77.8%. Variations in chitosan to TBF ratio changed the nanoparticles physicochemical properties. By increasing terbinafine concentration, particles size increased while zeta potential decreased. Terbinafine loaded to chitosan-TPP appears as a promising system in antifungal treatment [80].

Vesicular carriers

Niosomes

Niosomes are microscopic lamellar structures formed on admixture of cholesterol and single alkyl chain non-ionic surfactant with subsequent hydration in aqueous media. They are gaining popularity in the field of topical and transdermal drug delivery because of their special characteristic features like increasing penetration of drugs, acting as local depot to provide sustained release and serving as a solubilizing matrix for hydrophilic and lipophilic drugs [81–83]. Fig 6. showed the basic structure of the Niosome and other vesicular-based carriers.

Terbinafine loaded niosomes were formulated by Sathal and Rajalakshmi 2010. TBF-niosomes were prepared by thin film hydration method using different ratios of non-ionic surfactant (tween 20, 40, 60, and 80) and cholesterol with a

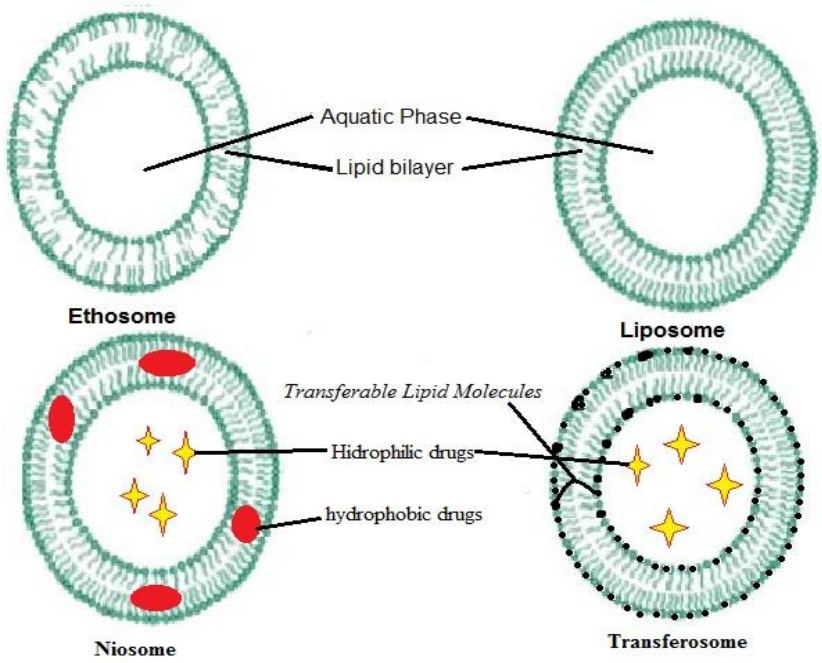

Fig 6. Basic structure of vesicular nano-carrier

constant TBF concentration. Prepared niosomes were discrete in size (20-60 nm) and shape. As the concentration of surfactant increased, entrapment efficiency augmented up to 85%. By increasing the concentration of cholesterol, entrapment efficiency decreased and a short time was required to release drug. The best entrapment efficiency was found at surfactant/cholesterol (2:1). Results of *in vitro* antifungal activity using the strain Aspergillusniger showed controlled release of medicament due to gradual increase in zone of inhibition. Incorporation of best formulation (tween 40 nisomes) into gel (sodium carboxy methylcellulose) indicated maximum zone of inhibition values, with an initial burst release at 1.5 hour followed by sustained drug release. By increasing the concentration of surfactant, enhanced antifungal activities can be obtained as compared with conventional topical dosage form. They concluded that transdermal gel formulations (containing total niosomes) increased penetration of drug into skin and enhanced antifungal activity. As a result, niosomes can be considered as an efficient carrier for improved TBF transdermal delivery [84].

Ethosomes

Ethosomes, novel carriers for enhanced skin delivery are phospholipid-based elastic nanovesicles containing a high ethanol content (20–45%). They have exhibited more efficiency at delivering drug to skin in terms of quantity and depth, than either liposomes or hydroalcoholic solution and have recently examined for antifungal drug delivery [85–87].

Recently, ethosomes containing TBF were synthesized by HOT technique following by sonication and unsonication. ET1 to ET8 formulations contained phospholipid 0.5% w/v; propylene glycol 10% w/v; drug 1.0% w/v with 20, 30, 40% w/v ethanol in ET1, ET2, ET3 (sonicated) and ET6, ET7, ET8 (unsonicated), respectively. Different shapes and sizes of ethosomes were attained by sonication and unsonication. Average size of unsonicated ethosomes was 333 nm while that of sonicated ethosomes was 76 nm. Sonicated ethosomes were smaller and more uniform in vesicular size and shape than unsonicated ethosomes. Optimal localized concentration and higher entrapment efficiency was observed for sonicated ethosomes which was assigned to their smaller size. Terbinafine skin deposition by sonicated ethosomal formulation was 19% as compared to 2% by unsonicated formulation. Sonicated ethosomes caused greater accumulation in deep skin strata indicating higher

drug localizeation. Both sonicated and unsonicated ethosomes were stable at refrigeration and room temperature [88].

Pratik and Tushar 2014 prepared terbinafine ethosomal vesicles through cold method under stirring and sonication and get them into carbapol gel. Ethosomal vesicles were prepared by different formulations: E1-E9: phospholipids 30, 60, 90 mg; ethanol 2, 3, 4 ml. The best formulation; E5 was incorporated into gel concentrations (Carbapol in G1, G2, G3; 1, 1.5, 2%, respectively). Drug content and entrapment efficiency of ethosomal formulations were high and exhibited controlled release behavior. Topical penetration of TBF-ethosomal gels enhanced significantly as 1.5-fold compared to terbinafine marketed cream (Terbicip Cream). G1, G2 and G3 showed 10.6 ± 2.0, 6.33 ± 0.47, 3 ± 0.8 mm inhibition fungal growth, respectively. G1 formulation (ethosomal suspension 10 ml; carbapol gel 1%; and triethanolamine 0.5%) showed % drug diffuse values significantly higher than other batches and Terbicip and presented the most efficient antifungal activity. TBF loaded ethosomal gels didnt cause skin irritation for up to 7 days [89].

Zhang et al. 2011 compared skin permeation of ethosomes, binary ethosomes and transfersomes of TBF under non-occlusive conditions. Drug quantity in skin from ethosomes, binary ethosomes (ethanol/propylene glycol: 7/3 w/w), and transfersomes was 1.2, 1.5 (P<0.05), 1.5 (P<0.01) times higher than that of TBF from traditional liposomes (control). Skin deposition of TBF from ethosomes, binary ethosomes, and transfersomes was 3.3 (P< 0.05), 9.9 (P< 0.01), 2.5 times higher than that of TBF from control. Significant penetration depth and fluorescence intensity of rhodamine B from binary ethosomes (ethanol-PG=7:3, w/w) demonstrated most effective penetration through skin, while transfersomes made easiest drug accumulation. Ethosomes promoted drug delivery with greater improvement in permeation than improvement in deposition [90].

Transferosomes

Transferosome, a novel vesicular drug carrier is composed of phospholipid, surfactant, and contains membrane softeners, like Tween 80, to make it ultra-deformable. This feature makes them more efficient at delivering low and high molecular weights of drugs to skin in terms of quantity and depth. Transferosomes can increase transdermal flux, prolong release, and improve site specificity of bioactive molecules [91, 92]. TDT 067, is a novel terbinafine formulation in Transferosome (1.5% terbinafine) which has been synthesized for topical delivery of terbinafine to nail, nail bed, and surrounding tissue for treatment of onychomycosis. TDT 067 demonstrated inhibitory and cidal activity against dermatophyte and nondermatophyte pathogens of onychomycosis, with higher activity than conventional terbinafine preparations. Transfersome facilitated terbinafine entry into fungal cells and improved its fungicidal effects. Clinical studies of TDT 067 showed high rates of mycological cure 90%, after only 12 weeks [93].

A Phase II, open-label study was conducted in participants with mycologically confirmed bilateral onychomycosis of the great toe nail. Participants applied TDT-067 to nails and surrounding skin twice daily for 12 weeks. Cure rate at week 48 was 38%. In addition, 9% of participants achieved ≥ 5 mm of clear nail growth and 24% achieved ≥ 2 mm clear nail growth [94].

CONCLUSION

Clinical efficacy of an antifungal agent depends on several factors in topical formulations, including drug physicochemical properties, concentration in targeted skin tissues, duration of contact with skin, and ability of the compound to penetrate tissues. Formulation of a topical application is a useful mean for achieving therapeutic levels. Recently, nano-strategies have been widely employed for improving efficacy of antifungal drugs. Solid lipid nanoparticles, liposome, niosome, ethosome, nanoemulsion, transferosome, dendrimer, chitosan are the nanoparticles which have been examined for increasing the efficacy of terbinafine. They have presented improved permeability, increasing efficacy and have been considered as a potential tool for high level terbinafine permeation with controlled drug delivery. However, many of these experiments are limited to *in vitro* or animal studies. Advantage of a nano-formulation has not been definitely proven. Further research is needed to translate these findings into clinical arena in order to benefit patients at risk for or suffering from fungal infections. Nano-formulations can find a place in clinical use after clinical evaluation.

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