REVIEW ON TREATMENT OF DIABETIC WOUND HEALING USING STATINS AS AN ETHOSOMAL CARRIER

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Abstract

Diabetes mellitus is an increasingly prevalent chronic metabolic disease characterized by prolonged high blood sugar levels, which can lead to long-term health issues. The high blood sugar environment promotes the formation of biofilms and makes diabetic wounds difficult to treat. Diabetic wounds are a major public health issue caused by inadequate blood supply, bacterial infection, high levels of oxidative stress, and abnormalities in antioxidative defenses, and there is currently no effective treatment. Nanoparticles have shown promise in addressing these challenges due to their small size, ability to be taken up by cells, low toxicity, antibacterial properties, good compatibility, and biodegradability. Ethosomes, which are ethanolic phospholipid vesicles used as nanovesicles for transdermal drug delivery, have shown higher skin penetration rates compared to other nanovesicles, likely due to their ethanolic content. This paper reviews the therapeutic potential and further perspectives of nanovessicle in the treatment of diabetic wound healing, demonstrating the promise of these nanoparticulate carriers for dermal and transdermal delivery. Data derived from both animal and human studies showed that statins especially atorvastatin, simvastatin and pravastatin can accelerate the wound-healing process

Keyword: *- Nanovessicles, Ethosomes, Statin, Diabetic wound healing.*

Introduction

"Nanotechnology is a prominent term in this millennium that has revolutionized research in science and technology. It is extensively used in various advanced fields such as electronics, petrochemicals, food, pharmaceuticals, and the biomedical industry. The application of nanotechnology in the pharmaceutical field has given rise to the concept of nanomedicines. According to the European Science Foundation, nanomedicine is the science and technology of diagnosing, treating, and preventing diseases and traumatic injuries, relieving pain, and utilizing molecular knowledge of the human body. Nanovesicles are tiny, membrane-enclosed structures used to deliver molecules such as drugs, RNA, and DNA to specific cells or tissues. They are typically between 10 and 1000 nanometers in size.[1]

Transdermal drug delivery systems (TDDS) have shown promising results compared to oral drug delivery systems because they bypass gastrointestinal interference and first-pass metabolism. However, TDDS faces a drawback in that it encounters the barrier properties of the Stratum Corneum, allowing only lipophilic drugs with a molecular weight

of less than 500 Da to pass through it [2,3]. Various mechanisms, such as the use of chemical or physical enhancers like iontophoresis and sonophoresis, have been investigated to improve the permeation of drugs through the skin. Additionally, vesicles can control the release rate of drugs over an extended period, keeping the drug shielded from the immune response or other removal systems, thereby releasing the right amount of drug and maintaining constant concentration for longer periods. A significant advancement in vesicle research was the discovery of a vesicle derivative known as Ethosomes.[4]

Classification of nanovessicles: -

1. **Niosomes and proniosomes.**

Niosomes and proniosomes are lipid-based nanostructures known for their unique ability to enhance the bioavailability of poorly soluble drugs. Unlike liposomes, they are composed of nonionic surfactants and can form multilamellar and unilamellar vesicles. [5]

Proniosomes are nonionic dehydrated structured vesicles in powdered form or in gel states. Provesicles are water-soluble, dry, free-flowing granular products that can be immediately rehydrated before use, avoiding many issues related to aqueous vesicular dispersions. Proniosomes and Niosomes can be produced using cholesterol, non-ionic surfactants (Tween 20, 40, 80, Span 20, 40, 60, 80, 85), solvents such as chloroform, and methyl and ethyl alcohols, and lecithin.[6]

Niosomes are similar to liposomes but they are cheaper, exhibits a higher stability, encapsulation efficiency and permeability for small molecules, it avoids degradation of phospholipids by oxidation and easier to store and handle. Indeed, niosomes have some disadvantage such as aggregation, fusion, and leakage of drugs, while proniosomes can overcome these issues contrasting leakage, aggregation, or hydrolysis of drugs while optimizing their storage and biodistribution, adding the possibility of sterilization, room temperature storage, and being rehydrated instantly to create niosomes .[7]

2.Ethosomes

Ethosomes were designed and developed in 2000 by Touitou et al [8]as an advanced noninvasive passive lipid-based delivery system. As represented in Figure 3, these carriers are lipid bilayers composed of phospholipids, water, and high concentrations of ethanol which gives them remarkable transdermal permeability skills. Ethosomes are the novel carrier system used for delivery of drugs having low penetration through the biological membrane mainly skin. Ethosomes are the modification of well-established drug carrier Liposomes. The size range of ethosomes varies from tens of nanometer to microns (µ).[9]

. Ethanol and lipid molecules act in the polar head group region increasing membrane fluidity and permeability. Ethosomes have significantly improved skin delivery, carrying the active compounds in the deeper layers of the skin in occlusive and non-occlusive conditions. In addition, they display high deformability, encapsulation efficiency, stability, biocompatibility, and a

negative charge due to ethanol that leads to small vesicles size, enhancing the bioavailability of the compounds.[10]

3.Transferosomes

From the other nanovessicles transfersomes offers various many advantanges i.e capacity of escaping presystemic metabolism, tune drug releases reducing variation in drug levels, enhancing pharmacological response. Compared to the other transdermal delivery methods including chemical permeation enhancers, sonophoresis, microneedles, lipid vesicles thanks to their distinctive composition can transport both hydrophilic and lipophilic drugs.[11]

Transfersomes was firstly proposed in the early 1990s , are the ultra-deformable elastic vesicles successfully employed as a non – occluded methods able to permeate skin through the stratum corneum reaching dermis and blood circulation .[12] As in figure 4 they are firstly characteristic by an aqueous core enclosed by a lipid bilayer of Amphipathic constituents as phosphatidylcholine, lecithin or a mixture of lipids . it consist very low concentration (3-10 %) of alcohol, they are made with 10 – 25 % of bilayer –softening complexes, surfactants, or edges activators as Tweens , Spans , sodium , cholates, and deoxycholate. The appropriate phospholipids /surfactants ratio tunes transferosomes' membrane elasticity reducing vesicles' rupture chances through the skin [13,14]. due to enhanced skin penetration abilities, transfersomes molecules delivery releasing low, as well as high, molecular weight drugs as antioxidants , chemotherapy, Anti-inflammatory and Cortocosteroids . [14]

4.Pharmacosomes

The name pharmacosomes refers to the amphiphilic, zwitterionic, stoichiometric complexes of polyphenolic compounds with phospholipids, as schematized in Figure 5. The success in the use of pharmacosomes is explained by the surface and bulk interactions of lipids with drugs since the latter possess an active hydrogen atom as –OH, -COOH, -NH2, which can be esterified to the lipid causing an amphiphilic compound. [15,16] The use of pharmacosomes in drug delivery has several advantages over that of other vesicles such as niosomes, transferosomes, and liposomes. More in detail, any active molecules in which a carboxyl group is present can be esterified without a spacer chain as opposed to those characterized by the presence of amino or hydroxyl groups which, in order to be esterified, require spacer groups. Pharmacosomes design is based on the phospholipids/water superficial and bulk interaction; the drug molecule and the connected lipid molecule, respectively, behave like the polar head group and the lipidic chain giving the molecule an amphipathic character. Due to these hydrophilic and lipophilic properties advantages, these lipid LNV improve drugs' dissolution in gastrointestinal fluid, increasing the bioavailability of low soluble treatments, avoiding leak and rupture release [17,18]. Pharmacosomes' in vivo pharmacokinetic performances are conditioned by vesicles' dimension, by the drug molecule's functional groups, by the lipids' fatty acid chain length, and, last but

not least, by the spacer groups' availability.[19]

5. Ufasomes

Ufasomes are the Unsaturated fatty acid vesicles preparation, was first reported in 1973 by Gebicki and Hicks.[20] In a controlled pH range, from 7 to 9, they are a closed lipid bilayered suspension, made from unsaturated fats and their ionized species. In detail, fatty acid molecules' hydrocarbon tails are directed toward the deeper membrane layer while the carboxyl heads are in contact with water [21] as shown in Figure 6. Oleic and linoleic acid (cis, is-9,12-octadecadienoic acid), the major ufasomes' constituents, confer to these nanovesicles a more versatile nature than that of the other LNV, by ranking them between different nanosystems formed from double-chain amphiphiles and from single-chain surfactants micelles. Their biochemical composition makes them easily to assemble and real biocompatible [22,23]. By enhancing ufasomes stability with the identification of the appropriate fatty acid, pH range, and lipoxygenase amount, increasingly targeted and effective drug delivery solutions are being developed.

6. Phytosomes

Phytosomes have many structural and functional aspects in common with liposomes and tranferosomes such as the capability to improve the solubility of weakly soluble polyphenolic phytochemicals. Otherwise, phytosomes and transferosomes are more stable than liposomes in 4 ◦C and 25 ◦C aqueous media up to three months since liposomes should be freeze dried to preserve their stability. Phytosomes, as well as transferosomes, exhibit superior dermal penetration properties leading noticeable accumulation in the epidermis and dermis. Since the phytosomes configuration is grounded on the H-bond interaction between the phospholipid molecules' polar moiety and the phytoconstituents, the laded compounds permanence is higher than in other lipid nanovesicles [24] . It should be magnified how phyto active constituents as phenolics, flavonoids, and terpeniods .[25]

7. Catonionic Vesicles

An innovative class of biocompatible and biodegradable drugs lipidic nanovehicle is represented by the catanionic vesicles for their capability to improve the stability and cellular uptake of a wide range of active molecules [26] . These hybrid nanovesicles spontaneously form when unequal amounts of cationic and anionic single-tailed surfactants are dispersed in water [27]. These nanovesicles are produced by using easily accessible cheap surfactants and, in comparison with phospholipid vesicles, are thermodynamically advantaged in terms of colloidal stability. Alkyl ammonium bromide and Gemini surfactants such as bis-quaternary ammonium salts have been used for catanionic vesicles production; however, since they are cytotoxic and not biodegradable, the conjugation with safer molecules is being successfully considered [28]. Their low production costs, higher stability and drug loading capability, together with the fact that they suffer less from ruptures and pressure drops make them excellent drug delivery vehicles for vaccination and anti-microbial, cancer, and

inflammatory applications. Thus, although catanionic vesicles have a huge applicability in biomedicine, they can suffer safety problems due to their eventual low bio- and eco compatibility. Numerous ongoing researches point to the optimization of their morphology, hydrophobicity, and ionic charge by carefully choosing the proper surfactant and by tuning the anionic/cationic surfactant ratio eventually adding some suited additive. [29]

Ethosomes

Ethosomes were designed and developed in 2000 by Touitou et al. And as an advanced noninvasive passive lipid-based delivery system. As represented in Figure 3, these carriers are lipid bilayers composed of phospholipids, water, and high concentrations of ethanol which gives them remarkable transdermal permeability skills.[8]

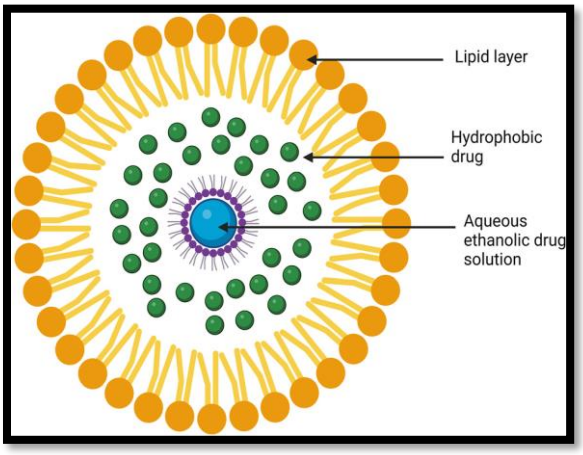


Figure No1: Schematic structure of ethosomes [30]

Ethosomes are mainly used for the delivery of drugs through transdermal route. The transdermal delivery is one of the most important routes of the drug administration. The limitation of transdermal route for drug delivery is the permeation of the drugs through the skin. Lipophilic drugs can pass through the skin but the drugs which are hydrophilic in nature can't pass through. Water soluble drugs either show very less or no premeation. To improve the permeation of drugs through the skin various mechanism has been investigated including use of chemical or physical enhancers such as iontophoresis, sonophoreisis. Liposomes, niosomes, transferosomes, and ethosomes also have been reported to enhance permeability of drugs through the stratum corneum barrier. Permeation enchaners increase the permeability of the skin, so that the drugs can cross through the skin easily [31,32]. Ethosomes can entrap drugs molecules with various physicochemical characteristic i.e of hydrophilic, lipophilic or amphiphilic [33,34]. The high concentration of ethanol makes the ethosomes unique. the ethanol in ethosomes cause disturbance of skin lipid bilayer organization, hence when incorporated into vesicle membrane, it enhances the vesicles' ability to penetrate the stratum corneum. [35]

Ethanol is an established efficient permeation enhancer and is present in quite high concentration (20-50%) in ethosomes. However, due to the interdigitating effect of ethanol on lipid bilayers, it was commonly believed that vesicles could not co-exist with high concentration of ethanol. Touitou discovered and investigated that lipid vesicular systems representing ethanol in relatively high concentration and named them ethosomes. The basic difference between liposomes and ethosomes lies in

their composition. The synergistic effect of combination of relatively high concentration of ethanol (20- 50%) in vesicular form in ethosomes was suggested to be the main reason for their better skin permeation ability. The high concentration of ethanol (20-50%) in ethosomal formulation could disturb the skin lipid bilayer organization. Therefore, when integrated into a vesicle membrane, it could give an ability to the vesicles to penetrate the Stratum corneum. Furthermore, due to high ethanol concentration the ethosomal lipid membrane was packed less tightly than conventional vesicles but possessed equivalent stability [36].

Characteristic of ethosomes:-(37-43)

S. No	Parameter	Importance	Method
1	Size and shape	Determine skin penetration	SEM, TEM, DLS
2	Zeta potential	Stability of vesicles	Zeta Meter
3	Entrapment efficiency	Suitability of method	Ultracentrifugation
4	. Drug content	Important in deciding the amount of vesicle	preparation to be used UV, HPLC
5	Stability studies	To determine the shelf life of vesicle formulation	SEM, TEM, HPLC
6	In vitro dissolution	Determine the drug release rate from vesicle	Franz diffusion cell.
7	Skin permeation.	Determines rate of drug transport through skin	CLMS

Advantages of Ethosomes: - [44,45]

1. Ethosomes enhance permeation of drugs through skin for dermal, transdermal and intracellular delivery.
2. Deliver various molecules with different physicochemical properties, hydrophilic and lipophilic molecules, peptides, proteins and other macromolecules.
3. Ethosomes components are recognized as safe, non-toxic and approval for pharmaceutical and cosmetic use.
4. The ethosomal system is passive and non-invasive and is suitable for immediate marketing.

5. The high patient's adherence: the ethosomal drug is delivered in a semi solid form (gel or cream).
6. Cost of manufacturing is very cheap.
7. Ethosomal drug delivery system can be widely used in pharmaceutical, biotechnology, Veterinary, Cosmetic and nutraceutical field
8. High entrapment efficiencies of drugs when compared to liposomes.
9. Excellent stability over long periods can be observed.
10. Alcohol in the ethosomes acts as a natural preservative, hence there is no necessity to add any other preservatives. (44,45)
11. Delivery of large molecules (peptides, protein molecules) is possible.[46]

Disadvantages of Ethosomes: -

1. Allergic reaction can be identified if the patients are allergic to ethanol or any of ethosomal components.
2. Ethosomal carrier are important for transdermal route only.
3. Due to the fact that ethanol is inflammable, sufficient care should ba taken during planning, application, transport and storage.
4. Very poor yield so may not be economical.
5. Loss of product during transfer from organic to water media.
6. Ethosomal is intended to provide steady, continuous drug delivery.
7. Skin irritation or dermatitis due to excipients and penetration enhancers of drug delivery systems. [44,45]

Ethosomal System types

1. **Classical Ethosomes: -**
   They are the Variation of classical liposomes consist of phospholipids, high ethanol concentrations of up to 45 % w\w and water. Classical liposomes are stated as superior for the transdermal drug delivery because they were smaller and had negative efficiency without clogging. It improves skin penetration and stability profile.
2. **Binary Ethosomes**: -
   Binary ethosomes were introduced by Zhou et al. we were created essentially by adding a different form of alcohol to classical liposomes. Propylene glycol and isopropyl alcohol are the most widely used Ethosomes in binary Ethosomes.
3. **Transethosomes**
   These are the newest generation of ethosomal system and were first recorded in 2012 by Song et al. It consists of basic components of classical ethosomes and in addition compound such as a penetration enhancer or surfactants in its formula .it combine the advantage of classical ethosomes with deformable liposomes (transfersomes) in one formula to generate transethosomes these novel vesicles are formed. [47]

Material And Methods

Ethosomes preparation method:

Hot Method

This method phospholipid is dispersed in water by heating in a water bath at 400C until a colloidal solution is obtained. In a separate vessel ethanol and propylene glycol are mixed together and heated to 400C. Once both mixtures reach 400C, the organic phase is added to the aqueous one. The drug is dissolved in water or ethanol depending on its hydrophilic/ hydrophobic properties. The vesicle size of ethosomal formulation can be

decreased to the desire extent using probe sonication or extrusion method [64].

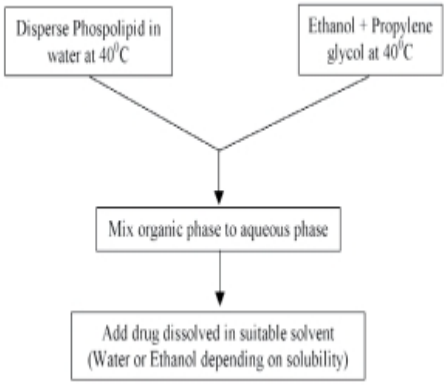


Fig no 3. Hot method for the preparation of ethosomes

Cold method

This is the most common method used for the preparation of ethosomal formulation. In this method phospholipid, drug and other lipid materials are dissolved in ethanol in a covered vessel at room temperature by vigorous stirring with the use of mixer. During stirring propylene glycol or other polyol is added to it. This mixture is heated up to 300C in a water bath. The water heated to 300C in a separate vessel is added to the mixture, which is then stirred for 5 min in a covered vessel. The vesicle size of ethosomal formulation can be decreased to desire extend using sonication method or extrusion method. Finally, the formulation is stored under refrigeration [65].

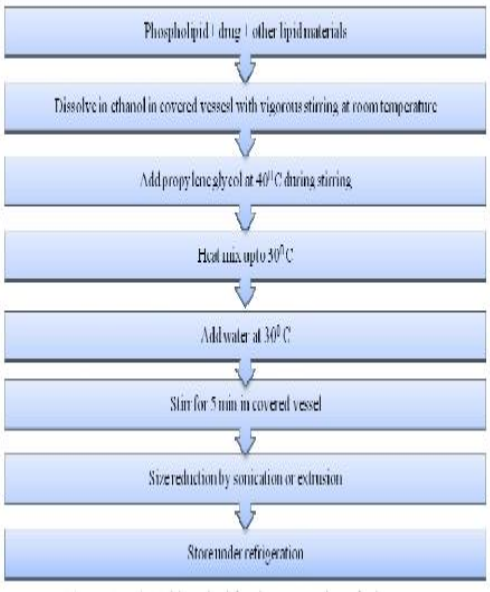


Fig no 4. Cold method for the preparation of ethosomes

Application of ethosomes: -

Ethosomes can be used for many purposes in drug delivery. Ethosomes are mainly used as replacement of liposomes. Mostly the transdermal route for transdermal delivery of hydrophilic and impermeable drug through the skin. [48]

- 1.Pilosebaceous targeting
- 2.Transcellular Delivery
- 3.Delivery of problematic drug molecules
- 4.In the treatment herpetic infection
- 5.Transdermal Delivery of Hormones
- 6.Cosmaceutical Applications of Ethosomes

Mechanism of drug penetration [49]

Over liposomes the major advantage of ethosomes is the increased permeation of the drug.

It acts as a penetration enhancer through the skin. Ethanol penetrates intracellular lipids and increases the fluidity of cell membrane lipids and decreases the density of lipid multilayer of cell membrane.

Skin permeability can be increased due to increased cell membrane lipid fluidity so it can be penetrated very easily inside skin layer and mixed with skin lipid and releases drug.

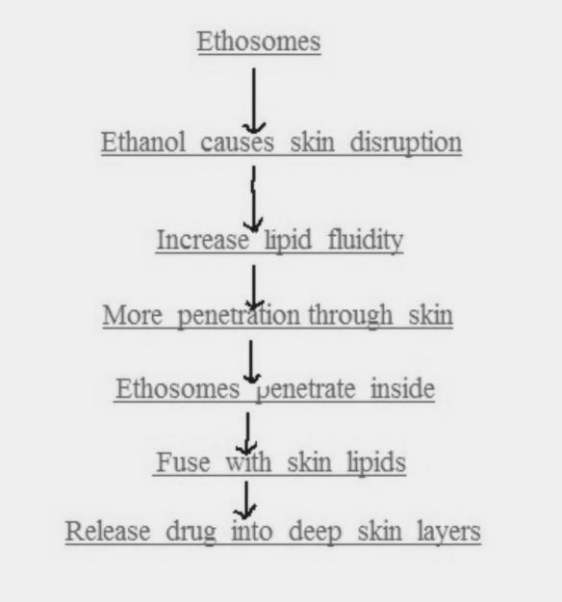
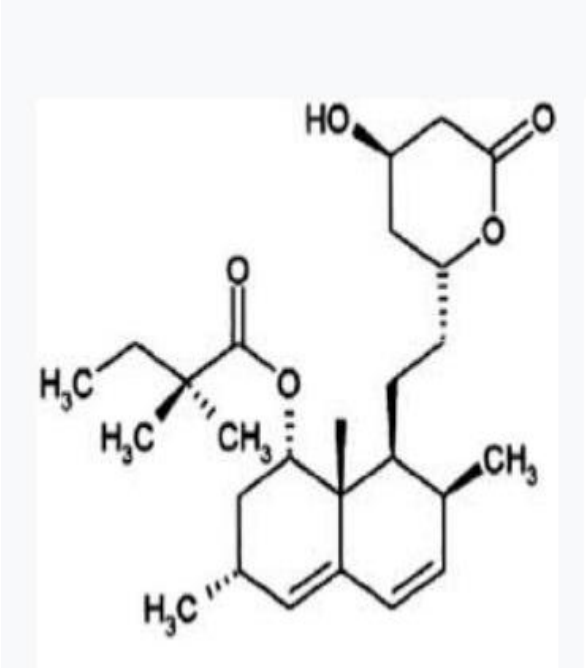


Fig no 2. Mechanism of action of ethosome [50]

Simvastatin drug profile

IUPAC: - 3-hydroxy-3methylglutarate coenzyme A
Common brand name: - Flolipid , Zocor
Common generic name: - Simvastatin
Drug class: - HMG- CoA redustase inhibitor, lipid lowering agents, statin.
Availability: - Prescription only, generic available for some forms
Used: - In liquid and tablet forms**.**



Simvastatin is a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor. It has been shown to be especially effective in reducing low-density lipoprotein cholesterol (LDL) and improving other conditions that are infl uenced by lipid levels, including coronary artery diseases [51]. Simvastatin has a high degree of selectivity in liver after oral administration. Almost 95% of simvastatin is metabolized by the liver and excreted from bile. Less than 5% of the active structures were found in the blood circulation after oral administration [52]. Existing simvastatin formulations include tablets, capsules, dry suspension, orally disintegrating tablets, and particles without lubricant. They have low bioavailability after oral administration but cause a huge burden on the liver. The ethosomal system is a vesicular system composed of phospholipids, ethanol, and water. Its difference from liposome is that it contains a large amount of ethanol, which

give it a good transdermal property [53,54]. We prepared a transdermal formation, simvastatin ethosome, which can penetrate through the skin and into the blood circulation to avoid the first pass effect of the liver. Therefore, the transdermal administration of simvastatin ethosome could be expected to relieve the burden of the liver and a lesser dosage of simvastatin ethosome could be bioequivalent to the oral administration in which the bioactivity is 5%.

Effect of statin on diabetic wound healing Diabetes mellitus and its complications are common problems throughout the world (55) Healing defects of diabetic wounds is prevalent among these patients and result in a high economic burden for healthcare organizations. Several interventions have been initiated to improve wound healing in diabetic patients such as wound dressing (56). Based on the available evidence that showed the beneficial effects of statins on wound healing (57,58), it was proposed that statins may have beneficial effects on managing diabetic foot wounds (57,58).

A (HMG-CoA) reductase inhibitors are commonly used in lowering total cholesterol and lowdensity lipoprotein (LDL) levels [59]. Furthermore, it has been reported that statins can prevent ischemic damage-induced angiogenesis in animals that are neuro cholesterolemic [60].Simvastatin, a white crystalline powder[61], is a lipophilic drug with a log P of 4.46 [62]. In addition to its hypocholesterolemic effect, it has been reported that simvastatin can enhance vascular endothelial growth factor synthesis and release at the wound site, which is a vital stage in the wound healing process.[63]

Literature review: -

1. **Pratiksha K Jadhav, Kundan A Kapadnis, Dattatraya M Shinkar , Vasim T Pathan, Anil G Jadhav Int. J. Pharm. Sci. Rev. Res., 62(1), May - June 2020; Article No. 29, Pages: 173-182**

   Oral route is the normal route of drug delivery, which has many benefits such as easy delivery but has many drawbacks such as low bioavailability and propensity, reqirement of high dose, and repeating dosing. with all these disadvantages in mind there is need for novel drug delivery system with increased therapeutic efficacy and safety with controlled delivery to minimum the size and number of doses.

2. **N.B.MAHALE*, S.A. KHAIRNAR, R.N.KANAWADE, K.K.WALE, D.D. NAVANDAR S.R.CHAUDHARI. Indo American Journal of Pharmaceutical Research. 2011;1(5):469-475. ISSN NO: 2231-6876**

   One of the major advances in vesicle research was the finding a vesicle derivative, known as an ethosomes. Ethosomes are modified lipid carriers that enable drugs to reach into deeper skin layers and/or systemic circulation, and represent a lipid vesicular carrier system embodying ethanol in relatively high concentration and are very effective in delivering drugs into and across the skin.

3. **Shadi Farsaei, Hossein Khalili, Effat Sadat FarboudFarsaei S, Khalili H, Farboud ES. Potential role of statins on wound healing: review of the literature. Int Wound J 2012; 9:238–247**

Diabetic wounds are one of the most challenging public health issues of 21th century due to their inadequate vascular supply, bacterial infection, high levels of oxidative stress and abnormalities in antioxidant defenses whereas there is no effective treatment of diabetic wound healing. due to distinct property of nanoparticles such as their small particles size, elevate cellular uptake, low cytotoxicity , antibacterial activity , good biocompatibility , and biodegradable.

4. **AlamZeb , Sadia Tabassam Arif , Maimoona Malik, Fawad Ali Shah , Fakhar Ud Din, omer Salman Qureshi.1 August 2018 / Accepted: 30 October 2018 / Published online: 4 December 2018**
© The Author(s) 2018, corrected publication 2019
This review focus on nanoparticles carrier including conventional liposomes, deformable liposomes, ethosomes, niosomes, and lipid nanoparticles developed for topical and transdermal drug delivery. Skin as a delivery route for drugs has attracted a great attention as it avoids many of the limitation of oral and parentral administration.

5. **Dibyalochan Mohanty1, A.Mounika2, Vasudha Bakshi3, M. Akiful Haque4, Chinmaya Keshari Sahoo5*CODEN (USA): IJCRGG, ISSN: 0974-4290,** ISSN(Online):2455-9555 Vol.11 No.08, pp 219-226, 2018
Transdermal drug delivery technology generated tremendous excitement and interest amongst major pharmaceutical companies in the 1980s and 90s. Ethosomes are the ethanolic phospholipid vesicles which are used mainly for transdermal delivery of drugs. Ethosomes have higher penetration rate through the skin as compared to liposomes hence these can be used widely in place of liposomes.

Conclusion

There are clear benefits of statins as a class effect in patients with diabetes. In primary prevention, guidelines maintain that diabetes is often a CHD risk equivalent, and this strategy guides a generally aggressive approach to statin therapy. The benefits of statin therapy among individuals with diabetesrisk are clearly established. Importantly, not all patients with diabetes have an identically elevated risk. Thus, additional risk stratification is an option to ensure identification of the highest-risk individuals who would benefit most from an aggressive primary prevention strategy. By using Ethosomes as a carrier it is effective way to treat diabetic wound, it contain ethanol which penetrate into the skin. Whether statins are effective for improving wound healing in clinical setting, and whether long-term statin therapy is appropriate for delaying or prevention of wound exacerbation,
As a main role of statin during wound-healing process independently of their well-known lipid-lowering action.

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