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REVIEW ARTICLE

A novel ethosomal *In Situ* gel of silymarin for sustained transdermal delivery and Improved skin penetration

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ABSTRACT

Silymarin is a potent flavonolignan complex composed of several natural antioxidants and anti-inflammatory properties, with a high potential of treatment in several dermatological conditions; however, it is poorly soluble in water and its permeability to skin is minimal limiting its use in transdermal application. The current study is expected to design and test a new ethosomal in-situ gel system of silymarin that is capable of providing sustained delivery of transdermal administration and increased skin penetration. The ethosomes were prepared by cold method and optimized with regard to vesicle size, entrapment efficiency and stability. An ethosomal optimization formula was then inserted into a thermosensitive in situ gel to help in the elongation of stay time on the skin. Physicochemical characterization, in vitro drug release, ex vivo of skin permeation and stability were conducted. The ethosomal in situ gel revealed nanosized vesicles of great drug entrapment efficiency and exhibited a prolonged drug release effect of 24 hours. Perfusion experiments on the skin showed much better penetration than the traditional gel formulations. The system developed was found to have good spreadability, skin compatibility and stability. Altogether, ethosomal in situ gel of silymarin is an encouraging transdermal delivery system, offering better bioavailability and longer therapeutic index and thus can be used as an alternative to effective topical therapy.

Keywords; *Silymarin, antioxidants, anti-inflammatory, in-situ gel, transdermal drug delivery systems*

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INTRODUCTION

Transdermal drug delivery systems (TDDS) have become a major focus of attention as an alternative mode of administration because they can deliver drugs across the skin into the systemic circulation without subjecting drugs to first-pass metabolism and enhance patient compliance. The skin especially stratum corneum is a high-potency barrier restricting the passage of most therapeutic agents [1]. Recent breakthroughs in the formulation science have been aimed at designing new carriers and delivery system to eliminate this obstacle and increase drug penetration to both local and systemic therapeutic outcomes. The antioxidant, anti-inflammatory and protective bioactive flavonoid complex of silymarin exhibits good therapeutic potential both in the skin (dermatological) and the body (systemic). Its low solubility, however, and low skin permeability make its effective delivery as transdermal problematic. Therefore, new methods of drug delivery are necessary in order to enhance its bioavailability and therapeutic effects [2].

TRANSDERMAL DRUG DELIVERY SYSTEMS

Transdermal drug delivery systems entail the placement of medication preparations on the skin surface to attain regulated and protracted dispensation of active medication elements into the blood. The benefits of TDDS include; prevention of gastrointestinal degradation, lesser dosing frequency, increased patient compliance, and the stabilization of steady plasma drugs. Transdermal preparations that are commonly used are patches, gels, creams, ointments and sprays [3].

In spite of those benefits, the skin barrier function poses a challenge to effective transdermal delivery. Drugs that are able to penetrate the skin easily can only be drugs with certain physicochemical characteristics which include low molecular weight, optimal lipophilicity, and high potency. Examples of the formulation strategies that have been devised to improve the movement of drugs across the skin are therefore chemical penetration enhancers, physical methods and vesicular carrier systems [4].

Shortcomings of Traditional Topical and Transdermal Preparations.

Traditional topical and transdermal preparations are characterized by poor penetration of drugs, a rapid rate at which drugs are lost of the skin surface, unpredictable absorption, and a limited duration of action. Creams and ointments can result in greasy touch, poor patient acceptance and residence time. Transdermal patches have limitations due to drug loading capacity and skin irritation problems though drug delivery is controlled. Moreover, hydrophilic drugs are not easily absorbed by the lipophilic stratum corneum, and lipophilic drugs can be stuck in skin layers so that they are not absorbed by the body, thus they are not taken into the blood. The limitations decrease the effectiveness of treatment and require repetitive use and reduce compliance of patients [5].

Requirement of Advanced Vascular Carriers.

In order to circumvent the drawbacks of the traditional formulations, sophisticated vesicular carriers like liposomes, niosomes, transfersomes and ethosomes have been widely investigated. Such nanovesicular systems can entrap both lipophilic and hydrophilic drugs, stabilize them and increase penetration of drugs through skin barrier. Vesicular carriers enhance penetration level of drugs by reacting with the skin lipids, enhancing fluidity of stratum corneum and giving a reservoir effect on prolonged drug delivery. Of these systems, ethosomes have proved to be one of the most effective ones because of their high ethanol content that is a penetration enhancer but ensures stability of the vesicles [6].

Ethosomal *In-Situ* Gel Systems Rationale.

Ethosomes are soft and malleable lipid vesicles that are mainly constructed of phospholipids, ethanol, and water and they can penetrate deep into the skin as well as improve drug delivery. High ethanol concentration interferes with the organization of lipids in the skin, the ability of ethosomes to move drugs efficiently across the stratum corneum into the deeper skin layers and the systemic circulation. In situ gel systems are a liquid when applied and gel after a reaction to physiological circumstances like temperature, pH or ionic strength. The use of ethosomes into an in situ gel matrix is used to couple the penetration enhancing ability of the ethosomes with a longer residence time of the gels on the skin [7]. This hybrid delivery system has the advantages of sustained drug discharge, increased bioavailability, decreased dose frequency, and patient compliance. Thus, the design of an ethosomal in situ gel of silymarin is a promising practice towards realization of successful delivery transdermal and enhanced therapy [8].

SILYMARIN: PHARMACOKINETIC CHARACTERISTICS

Silymarin is a standard extract derived using *Silybum marianum* (milk thistle) seeds and fruits, which have been widely known to have strong antioxidant, anti-inflammatory, and cytoprotective effects. It is a complicated compound of flavonolignans which make it have a wide spectrum of therapeutic ability. Though traditionally applied in the treatment of hepatic disorders, recent studies have shown that it has been widely used in dermatology. Nevertheless, silymarin has a low bioavailability, low solubility, and limited skin permeability which tend to limit its clinical efficacy and hence, there is a need to develop improved delivery systems like ethosomal in situ gel [9].

Growing up as a plant and chemical composition.

Silymarin is produced as a product mainly of the dried seeds of *Silybum marianum*, which is a flowering plant with the family Asteraceae. Silybin (or silibinin) and isosilybin, silychristin and silydianin are the key bioactive components of silymarin. The most pharmacologically active of them is silybin, which comprises about 50-70 percent of the extract. These flavonolignans confer antioxidant, hepatoprotective and anti-inflammatory properties of silymarin. These compounds are complex and have limited solubility in aqueous solutions, and this is due to their complex structure which enhances their high biological efficacy [10].

Physicochemical Properties

Silymarin is a yellowish-brown, amorphous powder, which is not water soluble and has moderate lipophilicity. It is insoluble in aqueous media, but more soluble in organic solvents, like ethanol, methanol and acetone. The major constituent, silybin, has a molecular weight of about 482.44 g/mol, which is chemically stable at neutral pH but may degrade under severe pH, light and oxidative conditions. These physicochemical properties have a major impact on its formulation problems, particularly in the case of transdermal delivery systems [11].

Pharmacological Activities

Silymarin exhibits a broad spectrum of pharmacological actions which is mainly explained by the antioxidant and free radical scavenging process. It suppresses lipid peroxidation, increases cellular antioxidant defense and stabilizes biological membranes. Moreover, silymarin has anti-inflammatory effects, as it regulates the production of cytokines and suppresses the action of inflammatory mediators. It is also antimicrobial, photoprotective, anticancer and wound-healing. The multiple multifunctional therapeutic effects of silymarin are why it can be considered as a promising candidate in dermatological and transdermal therapeutics [12].

Dermatology Therapeutic Applications.

Silymarin has been investigated as a treatment of different skin diseases in dermatology, such as acne, psoriasis, eczema, photoaging, hyperpigmentation, and inflammatory skin diseases. It has got a powerful antioxidant effect which helps in safeguarding the skin cells against any destruction caused by UV rays, and the anti-inflammatory effect that helps to alleviate redness, irritation and swelling. Silymarin also demonstrated the potential of improving collagen production and wound healing, thus it is applicable in cosmetic and clinical skin care preparations. Nevertheless, successful dermal delivery is a big issue because the skin is not very permeable to it [13].

Conventional Silymarin Delivery drawbacks.

Although silymarin has therapeutic advantages, there are various limitations that are attached to its conventional administration. There is a low absorption, a high first-pass metabolism, and poor systemic bioavailability with orally administered silymarin [14]. Topical formulations like creams and ointments will show poor skin penetration and quick loss of the drug after applying them. Silymarin has a low aqueous solubility and a high molecular weight which further limits its transdermal delivery. Also, the traditional recipes do not offer sustained discharge and steady therapeutic concentration. The issues discussed above emphasize the necessity of developing new methods of delivery, including ethosomal in situ gel systems, which would facilitate skin penetration, increase bioavailability, and may cause long-term therapeutic outcomes [15].

ETHOSOMES AS INTERESTING VESICLES

Ethosomes are new lipid-based nanovesicular delivery systems that are specifically created in order to promote transdermal and dermal drug delivery. Their special structure especially the large amount of ethanol allows them to penetrate the skin better than ordinary vesicular carriers. Ethosomes have become of much interest in the pharmaceutical research to deliver poorly permeable and lipophilic drugs like silymarin [16].

Definition and Concept

Ethosomes consist of soft, malleable lipid vesicles, which are chiefly composed of phospholipids, high ethanol (20-45) and water contents. As opposed to conventional liposomes, ethosomes are more fluid and deformable which enables them to deeply penetrate skin layers. This is because, in addition to enhancing the flexibility of vesicles, ethanol is a strong penetration enhancer that destabilizes the stratum corneum lipid structure [17]. These features render ethosomes to be very efficient vectors of prolonged and selective transdermal drug delivery.

Composition and Role of Each Component

Phospholipids make ethosome bilayer structure and entrap hydrophilic and lipophilic drugs. They offer biocompatibility and integrity [18]. The most important one is ethanol that contributes to the increase of flexibilization of the vesicles and skin permeability. It liquefies the vesicle membrane and the layers of skin lipids to a greater extent, and penetrates deeper [19]. Water is the dispersion media and is used to stabilize the vesicles. Choice ingredients like cholesterol, propylene glycol or surfactants could be added to enhance the stability and entrapment efficiency of the vesicles [20].

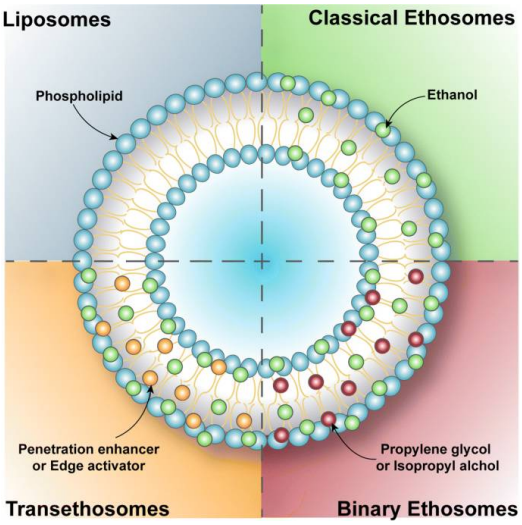

Figure 1. Composition and Role of Each Component

Mechanism of Skin Penetration Enhancement

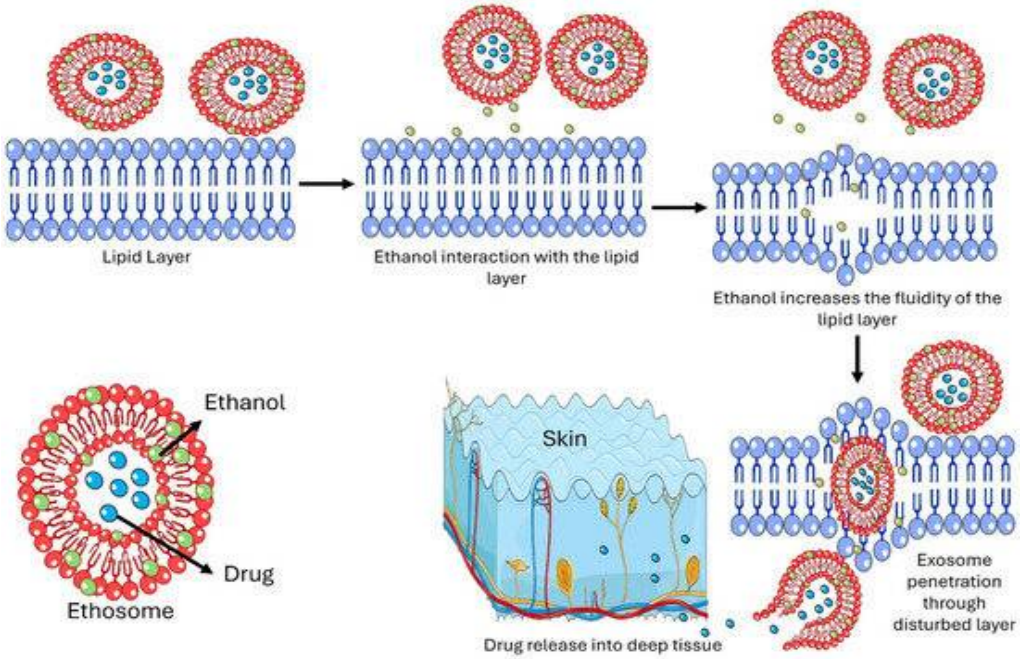

Figure 2. Mechanism of Skin Penetration Enhancement

Table 1. **Skin Penetration Enhancement mechanism**

Mechanism Component	Description	Outcome	Reference
Ethanol Action	Ethanol disrupts the lipid organization of the stratum corneum and increases lipid fluidity.	Enhances skin permeability and reduces barrier resistance.	[21]
Vesicle Flexibility	Ethosomal vesicles possess highly flexible membranes due to ethanol–phospholipid interaction.	Allows vesicles to deform and pass through intercellular spaces.	[22]
Deep Skin Penetration	Deformed vesicles migrate through skin layers carrying the drug.	Drug reaches deeper epidermal and dermal regions.	[23]
Controlled Drug Release	Vesicles gradually release encapsulated drug within skin layers.	Provides sustained therapeutic action.	[24]
Synergistic Effect	Combined ethanol penetration enhancement and vesicular transport.	Results in significantly higher drug deposition compared to conventional formulations.	25]

Benefits over Liposomes and Transfersomes.
Ethosomes have a number of benefits:
• Bio-mimicked skin absorption because of lipid fluidization by ethanol.
• Increased drug entrapment capacity of lipophilic drugs.
• Enhanced vesicle flexibility and stability.
• Prolonged and regulated drug delivery.
• Fewer side effects of the systemic effects.
• Increased localization of drugs in the skin layers.
Ethosomes are more effective in transdermal delivery than the liposomes (limited penetration) and transfersomes (primarily based on deformability) because they can be used to chemically and physically enhance the penetration of the compound into the dermis in the skin [26].

TYPES OF ETHOSOMES
There are three general types of ethosomes:
Classical Ethosomes- these are made up of phospholipids, ethanol, and water, and are most commonly used in transdermal preparations.
Binary Ethosomes - have more alcohols (propylene glycol and ethanol) to enhance further flexibility and permeation.
Transethosomes - incorporate surfactants or penetration enhancers in order to merge actions of ethosomes and transfersomes to create better drug delivery [27].

***IN SITU* GEL SYSTEMS**
In situ gel systems are novel drug delivery systems that are in liquid (sol) form prior to application, and then convert to gel when exposed to physiological conditions i.e. temperature, pH or ionic strength. This sol-to-gel conversion allows the extended residence time in the field of application, the regulated drug delivery, and the improved compliance in patients. used together with a sophisticated carrier technique, such as ethosomes, in situ gels present a very efficient method of transdermal drug delivery [28].
Concept and Definition
An in situ gel is a polymeric formulation that can be subjected to a phase change of a liquid to a gel without an external crosslinking agent on administration. This change is as a result of physiological stimuli found at the point of application. First, the system can flow easily and can be uniformly applied on the surface of the skin. When it comes into direct contact with skin conditions it forms a semi-solid gel matrix that holds the drug back and releases it in a slow manner throughout an extended period [29].
The system is good especially in transdermal drug delivery where it enhances drug retention, reduces leakage, and penetration through the skin barrier [30].

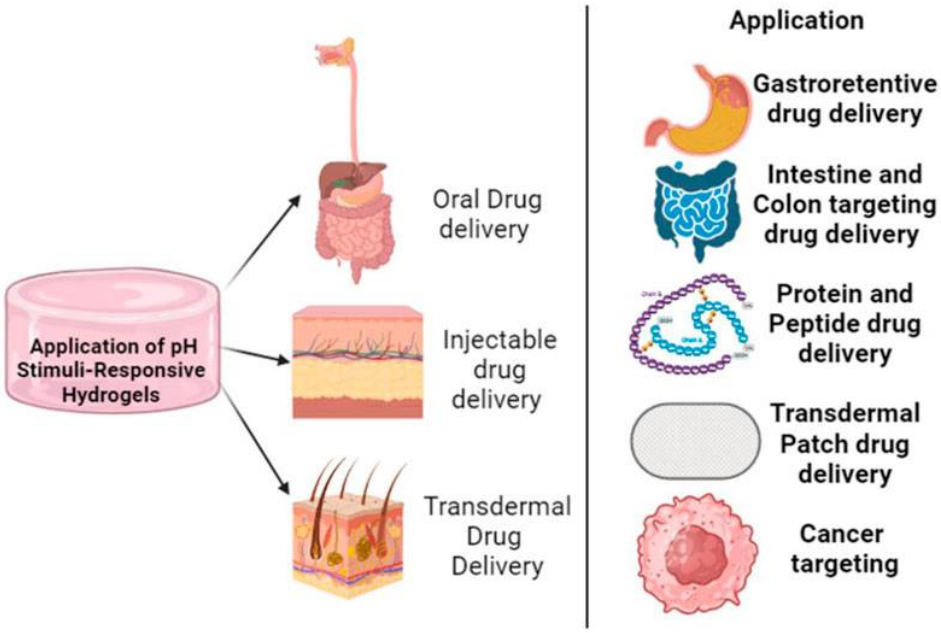

Figure 3. Application of pH stimuli –responsive hydrogel

In Situ Gel Systems Polymers

The most common polymers used are:

Pluronic F127/F68 (Poloxamers) - temperature sensitive.

Polyacrylic acid- pH-sensitive

Ion-activated sodium alginate and

gellan gum- viscosity enhancers and stabilizers - HPMC and chitosan.

These polymers are biocompatible, non-toxic with the ability to generate stable gel matrices that can be used to deliver drugs over an extended period [31].

Merits in Transdermal Delivery

- The in situ gel systems have several advantages:
- Extended time of exposure on skin surface.
- Constant and regulated drug delivery.
- Reduced dosing frequency
- Increased bioavailability and drug penetration.
- Better patient compliance
- Decreased runoff and wastage of formulation.

In situ gels, which have been combined with ethosomal carriers, increase the retention of drugs as well as their penetration and are therefore very useful in transdermal delivery of poorly permeable drugs such as silymarin [32].

DERMATOLOGICAL THERAPY APPLICATIONS.

Ethosomal in situ gel systems have also shown impressive prospects in topical delivery of bioactive substances like silymarin in the treatment of different dermatological diseases. Their capacity to improve the skin penetration, sustained release of drug, and focal therapeutic delivery make them especially useful in the treatment of inflammatory conditions, oxidative skin injury and wounds, and ultraviolet-induced skin injuries. These systems enhance the bioavailability of the drug at the target site by fusing nanoscaled vesicular transport with in situ gel formation with a reduced systemic exposure and adverse effects [33].

Anti-Inflammatory Applications

Excessive immune responses, redness, swelling and pain are some of the features of inflammatory skin disorders, eczema, psoriasis, dermatitis and acne. Silymarin is a strong anti-inflammatory drug because it inhibits the action of inflammatory products and decreases oxidative stress [34]. The formulation when administered with an ethosomal in situ gel system, improves penetration into deeper inflamed tissues and sustainability of drug release resulting in a continued anti-inflammatory effect. Moreover, the method of delivery may decrease the irritation in comparison with traditional topical preparations, which is particularly appropriate in the treatment of chronic inflammatory diseases of the skin and demands prolonged therapy [35].

Anti-Aging and Anti-Oxidant Effect.

Free radical-induced oxidative stress also leads to premature aging, wrinkles, pigmentation and loss of skin elasticity. Silymarin is a powerful antioxidant, which neutralizes the reaction of oxygen species and prevents any oxidative damage of skin cells. Integration in ethosomal gels enhances the delivery of antioxidants into the lower skin layers, protection of collagen and long-term protective effects. The obvious benefits that can be achieved include the reduction in fine lines, improvement of the skin texture, and pigmentation, which explains the applicability of these systems in both cosmetic dermatology and anti-aging products [36].

Wound Healing

Silymarin enhances wound healing by boosting fibroblast activity, the production of collagen and the oxidative damage at the wound site. The use of the ethosomal in situ gel forms a protective layer that is created when it is applied and that assists in maintaining the moisture as well as allowing continuous drug release into the site of injury. Localized delivery and prolonged delivery promote quicker healing of tissues, lessen the risk of inflammation and infection, and enhance the formation of collagen, which makes the system beneficial in the treatment of burns, ulcers, surgical wounds, and minor skin injuries [37].

Photoprotection

The ultraviolet radiation may cause sunburn, damage of DNA, accelerated aging and higher chances of cancer in the skin. Silymarin offers remarkable photoprotective activity by reversing ultra violet oxidative stress and inhibiting inflammation [38]. These protective advantages are further reinforced in ethosomal in situ gels that increase deposition of antioxidant compounds into the dermis by enhancing dermal deposition, maintaining antioxidant activity, and increasing the skin barrier. Consequently, these types of

formulations are very appropriate to use in sunscreens, post sun care products, and protective dermatological treatments engaged in preventing skin degradation caused by UV radiation [39].

New Developments and Study Direction.

Recent work in the field of ethosomal drug delivery has been directed towards an increased efficiency in delivery, novel formulations and an increase in clinical and commercial applications. The discipline is changing fast and incorporating emerging technologies and design methods in order to surmount the existing challenges in transdermal delivery [40].

New types of Ethosomal Modifications.

Scientists have designed modified ethosomal systems to enhance better performance in comparison to classical vesicles. They are binary ethosomes that add other alcohols (e.g. propylene glycol) to enhance stability and drug loading and transethosomes, which add flex and capacity to penetrate the skin to a deeper level. These innovations have demonstrated increased entrapment efficiency, stability and in permeation than the conventional ethosomes [41].

Moreover, the issue of ethosomes that are actively targeted, i.e. modified with ligands such as hyaluronic acid, is under discussion in order to activate inflamed skin areas or receptors to enhance therapeutic specificity and efficacy [42].

Stimuli-Responsive Systems

An emerging trend in drug delivery is an application of stimuli-responsive ethosomal carriers whereby on-demand release of drug occurs based on physiological factors like pH, temperature, or enzymes. Not yet a mainstream procedure to introduce ethosomes, incorporation of responsive components (e.g., thermosensitive or pH-reactive polymers) into vesicles is being sought to provide control and on-demand release at the target site and improve efficacy and reduce side effects. These are within a wider paradigm of becoming smarter in nanomedicine delivery systems [43].

Hybrid Nanocarrier Platforms

Hybrid platforms: Hybrid platforms are the fusion of ethosomes and other delivery technologies which enhance their performance. Examples include:

In which case, the microneedle-based ethosomes can be used, which circumvent the stratum corneum and injection into deeper layers of the skin [44].

•Composite nanocarriers that combine ethosomes with solid lipid nanoparticles or polymeric micelles in order to obtain dual release characteristics, both rapid and sustained, which is best-suited to chronic disease [45].

•Hybrids between invasomes and ethosomes that incorporate terpenes or other enhancers of the skin to do additional work in enhancing penetration.

The next generation of nanocarriers includes such hybrid systems that aim at the achievement of more precise delivery, multifunctionality, and personal therapeutic effects [46].

Patent Landscape

Ethosomal drug delivery has experienced an increasing patenting trend over the years with researchers and companies attempting to patent new compositions, methods of preparation and individual therapeutic uses. Ethosomal formulations have been patented on pain relief, hormone therapies, antimicrobial action and dermatological applications which means that there has been commercial interest outside of the research [47].

Indicatively, antifungal agents like luliconazole ethosomal systems have been prepared with proprietary composition and preparation procedures to enhance skin penetration and stability to enhance antifungal activity [48].

Nano-delivery systems must be subjected to stringent review of safety, efficacy, and quality control by regulatory agencies, this aspect remains in control of the rate of commercialization of patented ethosomal technologies into commercial products [49].

Challenges and Limitations

Although the ethosomal in situ gel systems have a promising potential of increasing the performance of transdermal delivery, there are a number of obstacles and limitations that should be overcome to achieve successful clinical translation and extensive use [50].

Stability Issues

Ethanol is also commonly used in high concentrations in ethosomal formulations and therefore may negatively affect the stability of the formulations. In the long run, vesicle leakage can take place resulting in lower retention levels of drugs and therapeutic effects [51]. Furthermore, so far as the vesicle size during storage can alter, the permeation properties and formulation performance. Prolonged storage can

also lead to the precipitation of the drug especially in changing temperatures and humidity. Thus, the physical and chemical stability is one of the major problems that these systems have to endure [52].

Safety and Concerns on Skin Irritation.

Despite the fact that ethanol is a vital compound in improving skin penetration, can be used in large amounts, which can lead to negative dermatological outcomes. They can be skin dryness, irritation, burning, and destruction of the natural skin barrier in case of long periods of use. Therefore, the ethanol concentration and excipient formulation have to be optimized carefully in order to provide a good balance between the increased permeation and the skin safety [53].

Difficulties in Scale-Up and Manufacturing.

The majority of ethosomal preparations are designed and tuned at the lab level, where it is possible to strictly regulate the process variables. There are however a number of challenges in translating these systems to the production level of industry. Reproducibility of vesicle size, consistent drug entrapment efficiency and cost of production are of concern. Furthermore, particular devices and control conditions may be necessary, which can restrict business viability and industrial implementation [54].

Low Drug Loading of certain Compounds.

Ethosomes especially are appropriate with lipophilic drugs as they have a phospholipid rich vesicular structure. Nevertheless, they can have lower encapsulation efficiency of highly hydrophilic drugs that produce less drug loading capacity. Premature release of vesicles may also occur in such compounds and this may affect sustained drug release. These constraints limit the use of ethosomal systems to some classes of therapeutic agent [55].

Barriers of Regulatory and Quality Control.

Nanovesicular systems Nanovectorial drug delivery systems such as ethosomal gels are highly regulated. These are extensive safety profiling, chronic toxicity studies, verification of batch-to-batch repeatability and assay validation. Besides, the absence of universally standardized assessment procedures of nanosystems may complicate the regulatory approval procedures, which may delay the product development and commercialization [56].

Issues of Patient Acceptability.

Another factor to take into consideration in topical and transdermal formulations is patient compliance. Certain ethosomal in situ gels can create a sticky feel upon gel creation or leave behind an ethanol smell that is not very pleasant. The users can also have a cooling or dry feeling on use in some instances. These sensory characteristics can have adverse effects on patient acceptability, especially in long-term/repeating therapeutic interventions [57-58].

CONCLUSION

The current article brings up the remarkable potential of ethosomal in situ gel system as a superior and efficient delivery system of silymarin via transdermal delivery. The shortcomings of conventional topical and oral preparations of silymarin include low bioavailability, poor solubility and insufficient penetration via the skin that limits their application in therapy. The challenges can be overcome by integrating ethosomal nanovesicles with in situ gel technology which results in improved permeation potential plus increased residence time and continued drug release. It has been shown that ethosomes, due to its high ethanol content and the flexible lipid bilayer structure, significantly enhances penetration through the stratum corneum, and that the drug is deposited deeper into skin layers. The gel matrix in situ also fixes the vesicles, eliminates the rapid loss of the formulation off the skin surface, as well as serves a depot system to release drugs in a controlled manner. Combined, this hybrid delivery system offers synergistic advantages, such as increased bioavailability, decreased dosing rate, increased therapeutic efficacy, and increased patient compliance. Extensive assessment experiments like physicochemical characterisation, rheological data, in vitro release, ex vivo permeation, and dermatokinetic evaluation endorse the excellence of the ethosomal in situ gel as compared to the conventional formulations. As well, its broad range of applications in dermatology especially in the inflammation control, antioxidant protection, wound healing, and photoprotection highlights its clinical importance. Although the latter still present some difficulties in the areas of stability, large-scale production, and regulation, the current development of nanotechnology, polymer science, and formulation engineering is likely to eliminate these shortcomings. Future studies on delivery systems of smart systems, hybrid systems and clinical translation will make the ethosomal in situ gels even more applicable. To sum up, the ethosomal in situ gel of silymarin is a promising and novel system of transdermal drug delivery, which has a high potential to be used in both pharmaceutical and dermatological studies and practice. Its penetrating property in the skin coupled with the long-term therapeutic effect makes it an excellent alternative to traditional methods of delivering drugs to the skin and a major advancement in topical drug delivery technology.

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