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Review Article

An Overview of Current Developments in Possible Vesicular Carriers Models for Transdermal Delivery Using Ethosomes

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Abstract

The ethosomal systems gained a great attention for the researchers to overcome problems associated with liposomal vesicles. These systems are best alternative for conventional oral and parenteral dosage forms. These systems are very successful in crossing the barrier and overcoming the problems associated with stratum corneum by encapsulating the drugs in these vesicles, ethosomes are noninvasive drug delivery vesicle carriers where these enable drugs to penetrate or permeate in to deeper layers of skin or into systemic circulation. The preparation is very easy, convenient and one of the most gullible methods for drug transport across the skin use of vesicle formulations as drug delivery systems. As the formulation application mode itself saying that which is very suitable for the drugs which are unfavorable to administer orally, as well as these formulations are suitable for the drugs which are having gastrointestinal toxicity and pain free administration is added advantage. The mini-review aims to reveal the different noteworthy drugs which are formulated form year 2000 to mid 2024, what are the different kinds of methods adopted in preparing the ethosomes and future prospects.

Key words: Vesicles; transdermal; skin; formulation; ethosomes; permeation; drug delivery; bioorganic chemistry

Introduction

The human body is covered by a layer which is known as skin. It receives about one third blood that circulates throughout the body. The drug absorption is higher as the surface of the skin contains sweat pores and hair follicles per each centimeter square, by mean of this components more surface area is possible, which enables grater rate of drug absorption [1-3]. Transdermal formulation have gained the great importance over conventional dosage forms in recent few years such as, circumvention of fluctuation which appears at gastrointestinal absorption, improving the bioavailability of drug by transporting them via systemic circulation by neglecting the hepatic metabolism [4-5]. In order to enhance the permeation of molecules when administered as transdermal applications various passive and active approaches are proposed like penetration enhancers, supersaturated systems, iontophoresis, phonophoresis, use of micro needles and jet injections, among all these techniques penetration enhancement is concentrated mostly [6-8]. Only few bioactive agents are administered transdermally in current scenario [9-12]. Drug delivery research entered a new era with the discovery of liposomes, and since then, numerous vesicular systems have been developed [13]. A liposome is a tiny synthetic vesicle with at least one lipid bilayer that is spherical in shape [14]. Liposomal delivery vehicles for the administration of pharmaceutical medications and nutrients, such as lipid nanoparticles in mRNA vaccines and DNA vaccines, can be employed as drug delivery vehicles due to their hydrophobicity and/or hydrophilicity, biocompatibility, particle size, and many other features [15].

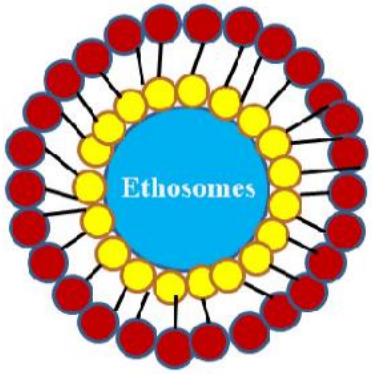

Figure 1: Ethosomes

In 1992, Cevc and Blume also developed transferosomes, which are elastic or pliable liposomes [16]. After transferosomes, Touitou et al.'s groundbreaking research led to the identification of ethosomes, a distinct kind of lipid vesicular system [17]. Because of their smaller size, reduced entrapment effectiveness, and negative zeta potential, modified liposomes were developed. Ethosomes are novel modified lipid carriers composed of phospholipids, water, and ethanol [18-20]. Ethosomes include relatively large concentrations of ethanol in addition to phospholipids and water, which have been proposed to have enhanced vesicular characteristics and skin penetration [21-23] (Figure 1). Ethosomes have rapidly become a distinctive drug delivery mechanism. They are classified as binary, classical, and transethosomes depending on their contents, such as alcohol [24-26]. The mini review contains the information of different drugs which were designed as ethosomes and types/ methods adopted to process them.

2. Vesicle Carrier In Drug Delivery

Due to the requirement of controlled or sustained delivery of molecules vesicular systems had been adopted from past few years [27]. Vesicles are nothing but a colloidal moieties which is composed of aqueous core where it is bounded by amphiphilic bodies in a dual layer pattern, single layered (unilamellar) or multilayered (multilamellar) concentric are possible in case of overindulgence of water [28-29]. The behaviour of vesicle is directed by physicochemical properties such as charge, size, lamellarity and thermodynamic phase and bilayer elasticity and the following are influenced by formulation considerations and vesicles play several roles in dermal and transdermal options [30]. It was evidenced from the past recent research reports not the how effectively vesicles work and focused on the development from conventional studies in 1980s to mid 2024 [31-36].

2.1. Composition of ethosomes

The ethosomal vesicles are comprised in a way such alcohol content is grater and the different ingredients employed in manufacturing the ethosomes in general they are likely vesicle forming agents, penetration enhancers, stabilizer, gel formers, and dyes and few examples are in below Table 1.

Ingredients	Functions	Examples
Phospholipid	Works as vesicle formers	Soya phosphatidylcholine, Egg phosphatidylcholine, Dipalmitylphosphatidylcholine Distearylphosphatidylcholine.
Polyglycol	Works as Penetration enhancer	Propylene Glycol, Transcutol
Cholesterol	Stabilizer	Cholesterol
Alcohol	Which promotes the smoothness to membrane of vesicle	Ethanol, Isopropyl alcohol

Table 1: Formulation considerations

2.2. Methods employed to prepare ethosomes of various drugs

There are different methods to process the ethosomal preparations as enlisted in below Table 2.

S.No	Drug	Method	Year	Ref.
1	Flubiprofen	Cold method	2019	37
2	Repaglinide	Thin film hydration	2021	38
3	1-Palmitoyl-2-{12-[(7-nitro-2–1,3-benzoxadiazol-4-yl)amino]dodecanoyl}-sn-glycero-3-phosphocholine (NBD-PC)	Ethanol Injection	2019	39
4	Lamivudine	Cold method	2020	40
5	Indomethacin	Thin film hydration	2019	41
6	Vitamin E, and caffeine	Cold method	2015	42
7	Mycophenolic Acid	Thin film hydration	2012	43
8	Tocopherol-succinate	Cold method	2022	44

9	Rutin	Cold method	2019	45
10	Alfuzosin hydrochloride	Cold method	2012	46
11	Curcumin	Thin film hydration	2018	47
12	Apigenin	Cold method	2013	48
13	Thymosinβ-4	Ethanol infusion	2019	49
14	Griseofulvin	Cold method	2016	50
15	Aceclofenac	Cold method	2010	51
16	Methotrexate (MTX)	Thin film hydration	2007	52
17	Zidovudine	Cold & hot method	2020	53
18	Stavudine	Cold method	2010	54
19	Isotretinoin	Hot method	2013	55
20	Nefidipine	Hot method	2023	56
21	Tazarotene	Hot method	2019	57
22	Lamivudine	Cold method	2007	58
23	Tretinoin	Hot method	2018	59
24	Gliclazide	Cold method	2015	60
25	Atorvastatin	Cold method	2020	61
26	Lidocaine	Injection sonication method	2013	62
30	Fluconazole	Hot method	2009	63
31	Methoxsalen	Cold method	2015	64
32	Cromolyn Sodium	Hot method/ Cold method	2012	65
33	Salbutamol sulfate	Classic Mechanical dispersion method	2007	66
34	Minoxidil	Classic Mechanical dispersion method	2005	67
35	Bacitracin	Classic dispersion method	2003	68
36	Testosterone	Cold method	2000	18
37	Ethanolicneem extract, Luliconazole	Cold method	2020	69
39	Ropivacaine	Thin film hydration	2015	70
40	Carvedilol	Thin film hydration	2019	71
41	α-Phellandrene	Cold method	2021	72
42	Matrine	Injection sonication method	2009	73
43	Ligustarzine	Injection sonication method	2011	74
44	Atorvastatin	Cold method	2020	75
45	Febuxostat	Cold method	2019	76
46	Diclofenac Sodium	Ethanol injection method	2013	77
47	Eberconazole nitrate	Cold method	2024	78
48	Indomethacin	Cold method	2019	79
49	Raloxifiene HCl	Rotary evaporation method	2018	80
50	Glimiperide	Cold method	2016	81

Table 2: Ethosomal preparation methods

2.3. Description of different methods to prepare ethosomal vesicles

2.3.1. Thin film hydration

Thin film hydration was employed in the ethosomal research bench as procedural technique to carry drug molecules, however evaporation is required in this method. The ethosomes can be achieved by mixing of drug with soy lecithin, phosphatidylcholine, cholesterol in methanol at required concentrations. The organic layer can be evaporated by using rotary evaporation method under lipid transition temperature under the subjection of vacuum [41, 43, 47, 52].

2.3.2. Cold method

Firstly the drug is dispersed in ethanol followed by solubilizing the soylecithins, phospholipids either both are any one of the excipients under magnetic stirring. A small quantity propylene glycol can be added for promoting the sooth penetration. The formed solution is covered to prevent the evaporation of ethanol from the ethosomal formulation, stirring should be continued for 30 minutes at room temperature. The final preparation should undergo centrifugation under 20x103 revolutions per minute for not less than three hours. The formulation can be considered for further investigations if phase separation was not found after centrifugation because the step reveals the stability of the product. Refrigeration recommended to store the vesicles [18, 37, 40, 42, 44-46, 48, 50-51, 53-54, 58, 60-61, 64-65, 69, 72, 75-76, 78-79, 81].

2.3.3. Hot method

This method follows as such lecithin, cholesterol solubilized in ethanol with drug under mixing with help of magnetic stirrer for 30 minutes by maintaining 40 oC heat to boil the lipid mixture the opening of the round bottomed flask should be closed in order to retain ethanol content water for injection (distilled water) can be added slowly on maintain continuous stirring which results the colloidal ethosomal suspension. The obtained suspension can be sonicated for size reduction [53, 55-57, 59, 63, 65].

2.3.4. Ethanol injection/sonication method

In the method, organic media which holds solubilized phospholipid in ethanol where it should be injected into aqueous media by employing a syringe system under the flow rate of 200 µL/min, can be sonicated using probe sonicator for homogenizing the mixture [39, 49, 62, 73-74, 77].

2.3.5. Trans menbrane pH-gradient method

The process is done two steps: which involves in making binary ethosomes and active loading of drug. Initially, the phospholipid dissolved in alcoholic phase which comprises both ethanol and propylene glycol. Upon constant stirring under 700 rpm slowly a citrate buffer solution can be added and system is approximately maintained 30±10C while running this process later on cooled at room temperature then blank binary ethosomes are formed. Upon formation blank binary ethosomes drug loading can done actively into ethosomes under 700 rpm constatnt stirring to obtain effective dispersion drug can be solubilized. The pH gradient alkaline layer (external) and the in the internal layer (acid) of ethosomal system can be attained by addition 0.5 molar sodium hydroxide solution to adjust external pH. Later on the system is incubated under suitable temperature for a certain time period. Where this facilitates unionized drug can pass actively via ethosomal lipid bilayer and gets entrapped or encapsulates into vesicles [82].

3. Characterization of ethosomal vesicles

This phase is very important for any type of pharmaceutical formulation and there are various parameters which are implemented on ethosomal systems to optimize them to provide a safe and effective formulation. The various parameters are explained below.

Morphology

The morphology is majorly considered in the field of nanomaterials and vesicular drug delivery systems. This parameter can be assessed by employing the microscopic techniques like scanning electron and transmission electron microscopic studies are useful in determining the architecture of the vesicles. The mean size of the vesicle can be determined by adopting photon correlation spectroscopy [9, 77]. Dynamic light scattering would be an added advantage on applying this technique in morphological studies which results about the size and zeta potential of the vesicle [40].

4. Entrapment efficiency

Dialysis method can be employed for determining the entrapment efficiency. In this method cellulose acetate membrane plays a major role in this procedure so it should be soaked in suitable solution to moisten the membrane. The required sample should be taken in dialysis bag furtherly the bag is transferred in to the receiver media on magnetic stirrer. Then sample to be withdrawn at respective time points and replace the same media (suitable buffer). Upon the separation of free drug lysing agent triton X can be added in the required amount (for example 0.1% v/v) and then subject it for drug content analysis [40]. The entrapment efficiency reveals about the amount of drug entrapped in to the vesicles and it can be calculated by applying the following equation which is written below [55].

$$\% \text{ Entrapment efficency} = \frac{\text{Total amount of drug added} - \text{amount free drug}}{\text{Total amout of drug added}} \times 100$$

5. Permeation Studies

In vitro permeation study using synthetic membranes and skin

The study can be carried out by using Franz diffusion cell apparatus with synthetic membranes. The prepared formulation can be placed on the superior portion on donor compartment and as well as by maintaining the temperature 370 ± 2 0C. Samples should be collected at appropriate time interval meanwhile, the same amount dissolution solution to be replaced freshly prepared receptor media. Then collected sample should undergo further analysis [51]. The synthetic membranes are replaced skin of any experimental subjects for conducting the permeation analysis of drug which permeated through skin or natural membranes by maintaining all the above conditions [76].

Ex vivo permeation study

The studies can conducted by using animals skin (Wister rats, Guinea pig, Goat, and Rabbit) can be used in while conducting experimental studies. The transdermal preparations like patch or gels can be conducted by assessing in between control formulation and optimized formulation, finding can be finalized upon acquired data of steady state flux (Jss), Permeability coefficient (P) diffusion coefficient (D) and further it is important find out whether it follows fickian or non fickian release [81].

Confocal laser microscopic studies

The confocal laser microscopic technique can be employed to study the penetration ethosomal drug formulations. During the permeation analysis any type of dyes can be entrapped into the ethosomal vesicles. The dye which is present in the deeper layers of the skin signifies the extent of distribution of drug. This technique helps a researcher to find about penetration capacity of drug for proving the ethosomal vesicles might be best due high penetration of drug which is possible due to ethanol which is affecting the intracellular portion of stratum corneum [80].

Conclusion

The stratum coreneum does not permit most drug and other therapeutic moieties to pass through. The ethosomal vesicles are specially designed with high amount of ethanol which hammers, the strong lipid layer of stratum corneum which can escape the damage of the vesicles finally which attains the delivery of drug in to deeper layers of the skin. Along with the non-invasive drug delivery of small and larger drug molcules it also provide good patient compliance and cost effective acyclovir ethosmal formulation supports and bench marks this statement.

However ethosomes need more concentration in preventing the evaporation by describing closure techniques clearly, reporting the skin irritation studies of the formulation is required, the proper stability assessment is recommended to be carried out for the drug which are used in the treatment of hair transplantation therapy like finasteride this technique might give commercial importance over problems associated with marketed finasteride formulation. This topic has enormous scope for the young researchers to design and apply new strategies for effective drug delivery.

Ethics Approval and Consent to Participate: Not applicable

Consent For Publication: Yes

Conflict of Interest: None

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