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Review

Lecithin-based nanostructured gels for skin delivery: An update on state of art and recent applications

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ABSTRACT

Conventional carriers for skin delivery encounter obstacles of drug leakage, scanty permeation and low entrapment efficiency. Phospholipid nanogels have recently been recognized as prominent delivery systems to circumvent such obstacles and impart easier application. The current review provides an overview on different types of lecithin nanostructured gels, with particular emphasis on liposomal versus microemulsion gelled systems. Liposomal gels investigated encompassed classic liposomal hydrogel, modified liposomal gels (e.g. Transferosomal, Ethosomal, Pro-liposomal and Phytosomal gels), Microgel in liposomes (M-i-L) and Vesicular phospholipid gel (VPG). Microemulsion gelled systems encompassed Lecithin microemulsion-based organogels (LMBGs), Pluronic lecithin organogels (PLOs) and Lecithin-stabilized microemulsion-based hydrogels. All systems were reviewed regarding matrix composition, state of art, characterization and updated applications. Different classes of lecithin nanogels exhibited crucial impact on transdermal delivery regarding drug permeation, drug loading and stability aspects. Future perspectives of this theme issue are discussed based on current laboratory studies.

Contents

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1. Introduction

In the last decade, drug delivery via the skin has captured higher attention in order to minimize and avoid the limitations of traditional routes of administration. The major challenge in designing dermal or transdermal drug delivery systems is to overcome the natural transport barrier of the skin represented by the stratum corneum. To passively diffuse through the skin, drugs should have specific physicochemical properties. Although their boundaries are not well defined it is generally accepted that the best drug candidates for passive transdermal diffusion should be nonionic, of molecular weight less than 400 or 500 Da, have adequate solubility in oil and water, partition co-efficient (log $P_{o/w}$) in the range of 1 to 3 or 4, a melting point less than 200 °C, and are of small dose (less than 50 mg per day, and ideally less than 10 mg per day) [1,2]. Other factors that must be also well considered include skin irritancy, short drug half life, and insufficient bioavailability as they may hinder the development of transdermal delivery. Therefore, the transdermal route of administration cannot be employed for a large number of drugs and there is a need for using carriers that deliver the drug through the skin irrespective of its physicochemical characteristics. Accordingly, various delivery systems and strategies have been developed. Most promising are the lipid based systems including, vesicular systems [3], lipid microspheres [4], lipid nanoparticles [5], and microemulsions [6].

Among different types of lipid based systems, phospholipid (Lecithin) based nanocarriers were found intriguing. Phospholipids (PL) are natural, biocompatible molecules. In presence of water, they can form different supramolecular structures that can be modified sometimes by using some polymeric substances and solvents or by applying other methods to modulate topical drug delivery [7]. Owing to their similarity to biomembrane composition (Fig. 1), phospholipids are recognized as non-allergic, bio-friendly permeation enhancers. The amphiphilic nature of PL gathers the benefits of aqueous and fatty vehicles in skin delivery while circumventing drawbacks against both. The most common phospholipid based nanoplatforms in this area are liposomes [8,9] and more recently lecithin microemulsions [10].

Liposomes – the traditional phospholipid-based vesicles – have been widely used as safe and effective drug vehicles in topical treatment of diseases, especially in dermatology, due to their proved potential in improving skin penetration and clinical efficacy of several drugs [11,12]. They are able to incorporate a variety of hydrophilic and hydrophobic drugs, enhance the accumulation of the drug at the administration site and reduce side effects. Modified liposomes such as transfersomes and ethosomes have also been utilized to impart deeper permeation compared to traditional liposomes [13]. On the other hand, Lecithin microemulsions were found to have some advantages over liposomes, such as easier and lower cost preparation, absence of organic solvents and intensive sonication, and higher storage stability. These advantages may be due to the thermodynamic stability of microemulsions, thus they can spontaneously be formed by mixing an aqueous phase and a lipophilic phase together with a surfactant/cosurfactant mixture [14].

Nevertheless, topical application of lecithin based nanocarriers is hampered by their liquid status. They suffer from low contact time with the skin in addition to drug leakage upon application and storage [15,16]. Incorporation of such nanocarriers into gel matrices is then anticipated to circumvent drawbacks of liquid status upon skin application [16–18]. Moreover, entrapment of such systems inside polymer matrices offers an opportunity to additionally modify the drug release kinetics. Additionally, for liposomal dispersions – that are well known to be unstable and aggregated by time – gelling of the system will improve their stability [19]. Recent years of research have witnessed the emergence of various types and generations of lecithin based nanostructured gels. The large diversity in matrix composition, technologies, developing materials and mechanisms of these systems highlighted the need for a comprehensive overview about them. This review is the first one to focus on gelation of lecithin based nanocarriers compared to their liquid state and conventional topical vehicles. An emphasis on different types of liposomal gels in contrast to lecithin microemulsion gels would be addressed. Differences would be highlighted in view of state of art, matrix composition, morphology, preparation methods, applications and assessment. Future perspectives of these vehicles would be discussed as well.

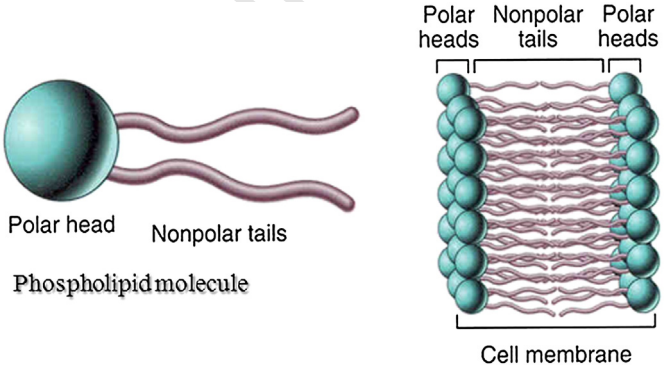

Fig. 1. Chemical structure of phospholipid molecules.

2. Liposomal gel

Topical application of conventional liposomes suffers from rapid drug leakage upon administration and accordingly a short residence time on the skin. In addition, the drug may leak from the prepared liposomes during storage by diffusion and erosion into the surrounding dispersion buffer [15]. Great efforts have been exerted in order to incorporate these liposomes into a gel structure to avoid their shortcomings [17,18,20,21]. Liposomes were found to be compatible with polymeric gelling agents derived from cross linked poly acrylic acid such as carbopol, hydroxyethyl-cellulose, and methyl cellulose [22,23]. Most commonly used as gellator is carbopol with concentrations ranging from 1 to 2% [20,21,24,25].

Many researchers have evaluated the prepared liposomal gels by comparing them to conventional gels or creams (containing the free drug) and neglected their comparison to the liquid state liposomes. They found that liposomal gels enhanced the skin retention of drugs, however, they did not enhance their systemic absorption [26–28]. These studies did not consider the effect of the gel matrix, but attributed the results to the liposome effect that is well known to provide a localized and controlled drug delivery when topically applied [17,28,29]. Recently, the release rates of lidocaine HCl [20] and diclofenac sodium [30] from liposome gel systems were evaluated compared to the aqueous liposomal dispersion The results revealed that incorporation of liposomes into gel form retarded the drug release compared to liposomal suspensions. Thus, it was concluded that the gel matrix viscosity may be responsible for the lower release rate from liposome gels and slower drug penetration [30].

Surveying the literature, different types of liposomal gels were observed. They can be classified according to their composition and

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