NANOBIOTECHNOLOGY FOR IMPROVING TRANSDERMAL DRUG DELIVERY

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Abstract: Skin delivery of certain medical products during treatment of local skin disease is one of the oldest ways to administer medicine, but skin delivery of medical products for transdermal carriers is relatively new and often used.
The rapid development of transdermal carriers in the past several years is due to the advantages of transdermic administration over the classic oral administration. The difficulty in transdermic administration is represented by skin penetration of the products, because skin, through it's nature, acts as a barrier in controlling the loss of water, electrolytes and other substances and also in preventing the penetration of medical substances from the outside environment. In order to enhance skin permeability for transdermal portage of medical substances, several methods, both passive and active, have been developed.
This review aims to examine classic and novel modalities for skin delivery of drugs, including the development of dermal/transdermal nanocarriers.

Keywords: skin delivery, nanocarriers, transdermal carriers, liposomes, deformable vesicles, penetration enhancer, nanobiotechnologies, unique medicine

Introduction

Topical medical substances have been used for hundreds of years in the treatment of local skin disease, but using transdermal carriers for systemic release of medicine, hormones and even nutritional factors is relatively new and more often used. The transdermal delivery of medical substances for a reflex action (with global welfare results) or general delivery have several advantages the oral way : avoiding the factors that influence gastro-intestinal absorption (the pH variations along the gastro-intestinal duct, food ingestion, intestinal movements) as well as the limits imposed by the first hepatic passage. Systemic therapy through topical adminis-tration can lead to controlled plasma levels of the medical substances with low halving time, avoiding the harmful effects of oral administration, minimal trauma, infection or lesions to the tissue risks, constant dosage, avoiding fluctuations that may appear while using traditional ways of administrating medicine. It has also been demonstrated that, sometimes, bio-availability can be highly improved through transdermal delivery.
Transdermal therapy also has it's limitations. The highest inconvenience is that the skin acts as a barrier in controlling the loss of water, electrolytes and other substances and also in preventing the penetration of medical substances from the outside environment.

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Transdermal passage is possible only if the medicine has the ability to penetrate the skin and get into the blood flow in the right therapeutic dosage. The pores in the skin are very narrow, so it is only permitted the passage of entities which are smaller than a million of a millimeter.

2. PROBLEM FORMULATION

In order to improve skin permeability for transdermal carriers of medical substances, a series of methods have been developed. The methods are both passive: penetration enhancers, saturated solutions, vesicles, and active: iontophoresis, elec-troporation, sonophoresis, microneedles, jetin-jectors etc.

2.1. Optimizing the release of medical substances through human skin

Optimizing the passage of medicine through skin is of high importance to modern therapy. Therefore, several methods to improve transdermal medicine flow have been researched and used. The increase of cutaneous absorption can be achieved through passive means in ointments, cream, gels and transdermal patches (penetration enhancers, oversaturated systems, hyaluronic acid; to modify the stratum corneum through hydration or using penetration enhancers for it's ablation; to pass through the cornous layer using microneedles; Transpho-llicular release; using vesicles such as liposomes, niosomes, transfersomes, etosomes or high speed particles) od active means (electrical methods such as: iontophoresis, electroporation, sonophoresis, microneedles, jetinjectors

2.2. Passive means used to improve skin absorption.

2.2.1.Penetration carriers

Chemical penetration carriers are all phamaco-logical inactive chemical substances that can hydrate the cornous layer.

In order for the substances to penetrate the skin through penetration enhancers, several action mechanisms are needed: disturbing the lipids in the cornous layer so that it becomes permeable; interacting with keratin and unfolding the complex structure of proteins in the cornous layer; portioning the medical substances with solvents such as ethanol, nitroglycerin, estradiol, oleic acid.

2.2.2. High speed particles

Using the PowerJect device we can uncharged small solid particles in the stratum corneum to the lower layers of the skin, using a helium supersonic gas shock wave.

The advantages of this system are: painless transfer of medicine trough the skin (the particles are to small to activate the skin receptors); aiming at a certain tissue; precise dosage; overcoming the patient's needle phobia; avoiding skin lesions of infections.

The device can be used to deliver local anesthetics, proteins, vaccines (hepatitis B).

2.3. Vesicular structures as skin delivery systems

Vesicular systems used in transdermal transport are nanosystems with dimensions between 25 nm and over 100 nm.

In the last years, the nanovesicular systems have been promoted as a mean of sustained or controlled release of drugs, because of their certain advantages, e.g. lack of toxicity, biodegradation, capacity of encapsulating both hydrophilic and lipophilic molecules, capacity of prolonging the existence of the drug in the systemic circulation by encapsulation in vesicular structures, capacity of targeting the organs and tissues, capacity of reducing the drug toxicity and increasing its bioavailability [5, 14, 15, 16, 20, 23, 24].

Vesicles are water-filled colloidal particles. The walls of these capsules consist of amphiphilic molecules (lipids and surfactants) in a bilayer conformation. In an excess of water these amphiphilic molecules can form one (unilamellar vesicles) or more (multilamellar vesicles) concentric bilayers. Hydrophilic drugs can be entrapped into the internal aqueous compartment, whereas amphiphilic, lipophilic and charged hydrophilic drugs can be associated with the vesicle bilayer by hydrophobic and/or electrostatic interactions. Most commonly, the vesicles are composed of phospholipids or nonionic surfactants. The reason for using vesicles in transdermal drug delivery is based on the fact that they act as drug carriers to deliver entrapped drug molecules across the skin, as

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well as penetration enhancers because of their composition. In addition, these vesicles serve as a depot for the sustained release of active compounds in the case of topical formulations, as well as rate-limiting membrane barrier for the modulation of systemic absorption in the case of transdermal formulations [14].
Liposomal formulations can be classified in two categories: rigid vesicles: liposomes and niosomes, and elastic or ultradeformable vesicles, transferosomes, pharmacosomes and ethosomes.

2.3.1. Liposomes

Liposomes are small spherical vesicles mainly composed by one or more lipidic bilayers, separated by aqueous compartments; they represent the most studied nano- and microparticulate systems for pharmaceutical applications. Liposomes are amphiphilic so effectively encapsulates both hydrophilic and lipophilic drugs.

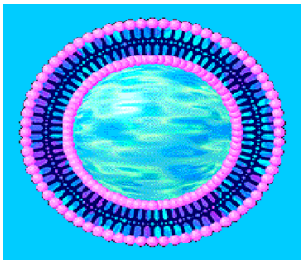

Fig. 1- Liposome structures: overall view (15)

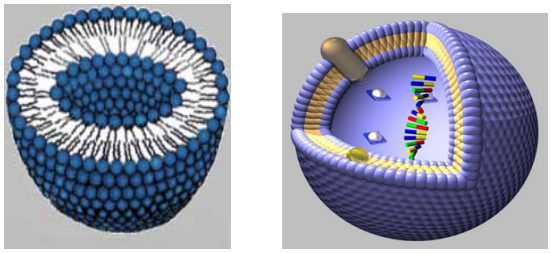

Fig. 2- Liposome structures: section view (15)

Mezei and Gulasekharam reported for the first time the effectiveness of vesicles for skin delivery, suggesting that the lipid formulations can enhance the topical release of drugs [5, 15, 20]. Despite all the efforts devoted by several researchers, it was impossible to formulate a liposomal compound that permits the systemic release of a drug (because the dimension of the liposomes does not allow them to penetrate the *stratum corneum*) [7, 23, 24].

2.3.2. Niosomes

Niosomes are vesicles composed of nonionic surfactants. They were first proposed by Handjani-Vila et al. [16] as systems to improve accumulation of the active molecule within the skin and thus benefit cosmetic products.
The niosomes have been mainly studied because of their advantages compared with the liposomes: they are quite stable structures and require no special conditions for preparation and storage, they have no purity problems and the manufacturing costs are low [6, 14, 15]. Unfortunately, the performed studies showed that, like liposomes, niosomes are not suitable for transdermal delivery, because they cannot reach the deeper layers of the skin, being trapped in the superior layers of *stratum corneum*. To overcome this problem, the carried out researches introduced a novel generation of vesicular elastic systems: transferosomes (ultradeformable vesicles consisting of phosphatidylcholine and an edge activator) and ethosomes (ultradeformable vesicles with high alcohol content) [6, 26].
The main advantage of these ultradeformable vesicular systems is the elasticity of the bilayer, given by the surfactant molecules in the case of transferosomes and ethanol in the case of ethosomes; this elasticity allows them to squeeze through channels in the *stratum corneum* that are less than one-tenth the diameter of the vesicles.
Niosomes improve the therapeutic performance of drug molecules by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to targetcells.

2.3.3. Transfersomes

The concept of transfersomes was introduced in 1992 by Cevc and coworkers.
Transfersomes are a special type of liposomes, consisting of phospholipids (soya-phosphatidyl-choline, eggphosphatidylcholine, dipalmityl-phosphatidylcholine, etc) and an edge activator (sodium cholate, sodium deoxycholate, span 80, and Tween 80, etc). These vesicular transfersomes are several orders of magnitude more elastic than the standard liposomes and thus well suited for the skin penetration [6, 8].

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Transfersomes overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipids of *stratum corneum*. At present, the mechanism of enhancing the delivery of active substances in and across the skin is not very well known. Two mechanisms of action have been proposed [6, 18, 19, 20, 21]: 1. Transfersomes act as drug vectors, remaining intact after entering the skin; 2. Transfersomes act as penetration enhancers, disrupting the highly organized intercellular lipids from *stratum corneum*, and therefore facilitating the drug molecules penetration in and across the *stratum corneum*. Cevc and coworkers proposed the first mechanism, suggesting that deformable liposomes penetrate the *stratum corneum* because of the transdermal hydration gradient, normally existing in the skin, and then, crossing the *epidermis*, enter in the systemic circulation.
The recent studies propose that the penetration and permeation of the vesicles across the skin are due to the combination of the two mechanisms. Depending on the nature of the active substance (lipophilic or hydrophilic) and the composition of the trans-fersomes, one of the two mechanisms prevails.

2.3.4. Pharmacosomes

The limitations of transfersomes can be overcome by the pharmacosome approach. The prodrug conjoins hydrophilic and lipophilic properties, and therefore acquires amphiphilic characters, and similar to other vesicle forming components, was found to reduce interfacial tension, and at higher concentrations exhibits mesomorphic behavior. These are defined as colloidal dispersions of drugs covalently bound to lipids, and may exist as ultrafine vesicular, micellar, or hexagonal aggregates, depending on the chemical structure of drug-lipid complex.
Pharmacosomes are amphiphilic lipid vesicular systems that have shown their potential in improving the bioavailability of poorly water soluble as well as poorly lipophilic drugs.
Pharmacosomes impart better biopharmaceu-tical properties to the drug, resulting in improved bio-availability. Developing the pharmacosomes of the drugs has been found to improve the absorption and minimize the gastrointestinal toxicity.

2.3.5. Ethosomes

Ethosomes are deformable liposomes with high alcohol content (up to 45%). It is proposed that the alcohol fluidizes the ethosomal lipids and *stratum corneum* bilayer lipids thus allowing the soft, malleable ethosomes to penetrate [1, 4]. They have been introduced for the first time by Touitou in 1996. The ethanol from ethosomes composition plays the same role as the surfactant from the transferosomes, namely disorganizing the lipid bilayer, conferring a ten times higher deformability to the particles [12, 17]. The size of ethosomes can be modulated from tens of nanometers to microns. Ethosomes have been found to be much more efficient at delivering drug to the skin, than either liposomes or hydroalcoholic solution.
The mechanism of penetration of the ethosomes in and through the skin is not yet completely elu-cidated. Two simultaneous mechanisms of action have been proposed: ethanol has a fluidization effect on the ethosomal lipids and ethanol has a flui-dization effect on the *stratum corneum* lipids. Because of the use of ethanol in the preparation of the ethosomes, the defor-mability of the prepared vesicles is increasing. Besides, the high alcohol content is expected to partially extract the *stratum corneum* lipids. These processes are responsible for increasing inter and intracellular permeability of ethosomes [16, 25]. The ultradeformable vesicles can forge paths in the disordered *stratum corneum* and finally release drug in the deeper layers of the skin. Therefore, a path through the skin can be expected to result, permitting the fusion of ethosomes with the cells from the deepest skin layers [25, 26].

3. PROBLEM SOLUTION

3.1. Iontophoresis

Iontophresis is an electrochemical method used to improve transportation of certain chemical com-pounds with electric charge, with the help of an electrical field which induces high migration of ionic substances in the skin. The negative ions in medical substances are released to the cathode and the positive ones to the anode.

3.2. Electroporation

Electroporation is a process of short time exposal to electrical impulses of high intensity (100-1000 V/cm^2). This process increases skin permeability by producing aqueous pores in the lipid bilayers of the stratum corneum and improving the flow of medical substances through the skin 1000 times. Electro-poration can be associated with iontophoresis in order to increase permeability to peptides (vasopressin, calcitonin, LHRH hormone).

3.3. Sonophoresis

This technique is frequently used in physiotherapy and medical gymnastics and involves using a topical substance as a coupling agent (gel, cream or ointment) on the treatment surface and massaging the area with an ultrasound source in order to achieve high concentration of the medical substance in the selected skin area.

Low-frequency ultrasound (approximately 20kHz) disturbes the lipids within the intracellular spaces in the stratum corneum following an increase in temperature and the apparition of cavitation phenomenons, therefore improving penetrationg of the medicine in the tissue.

Medical substances delivered thrugh sano-phoresis: hydrocortisone, lidocaine, salicylic acid.

This method is important for transdermal release of larger polar molecules such as insulin and erythro-poetine.

Conclusions

1. The use of the transdermal route has been well established in the past, and, because the inherent advantages of administration of this route, new methods for transdermal delivery are countinuously developed.
2. The introduction of ultradeformable vesicles was an important step in relaunching the researches regarding the use of vesicles as transdermal drug delivery systems.
3. In comparison to other transdermal delivery systems, the use of elastic vesicles has certain advantages: they are enhanced permeation of drug through skin; their composition is safe and the components are approved for pharma-ceutical and cosmetic use; they can increase the transdermal flux, prolonging the release and improving the site-specificity of bioactive molecules; they can accommodate drug molecules with a wide range of solubility.
4. The high tolerability and efficiency of vesicular systems, open vast potential thera-peutic uses. These nanocarriers might offer advanced local and systemic new therapies with agents that are unable to efficiently penetrate the stratum corneum via passive diffusion.
5. Although each vesicle type has its own characteristics, their common feature is their ability to improve the delivery of drugs across the skin barrier.

Acknowledgments

The problem regarding nanobiotechnologies needs to be approached through an unique medicine. In the attention of the post-doctoral school, this subject will represent a modern issue for inter-disciplinary approaches.

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Reference:

[1]. Barry B., *Transdermal Drug Delivery, in Pharmaceutics: The Science of Dosage Form Design,* ed. Aulton E. M., Churchill Livingstone, 2002, 499 – 528.

[2]. Mezei, M., Gulasekharam, V.: *Liposomes a selective drug delivery system for the topical route of administration.* Lotion dosage form. Life Sci. 26, 1980, 1473–1477.

[3]. Lodzki M, Godin B, Rakou L, Mechoulam R, Gallily R, and Touitou E, *Cannabidol transdermal delivery and anti-inflammatory*

effect in a marine model, J. Control. Release, 2003; 93: 379-389.
[3]. Ossama Y. Abdallah, Viviane F. Naggar, Nawal M. Khalafallah. *Lipid vesicles for skin delivery of drugs*: Reviewing three decades of research, International Journal of Pharm. 332, 2007, 1–16.
[4]. Mezei, M.: *Liposomes as a skin drug delivery system.* In: Breimer, D.D., Speiser, P. (Eds.), Topics in Pharmaceutical Sciences. Elsevier, Amsterdam, 1985, pp. 345–358.
[5]. Godin B., Touitou E.: Ethosomes: *New prospects in transdermal delivery,* Ther. Drug Carriers Systems, 2003, 20: 63-102.
[6]. Jain S., Mishra D., Kuksal A., Tiwary A., K., Jain N., K.: *Vesicular approach for drug delivery into or across the skin: current status and future prospects*, www.Pharmainfo.net.
[7]. Touitou E, *Drug delivery across the skin*, Expert Opin. Biol. Ther., 2002; 2:723-733.
[8]. Steve*, "Lipophilic Drug Derivatives For Use In Liposomes*," US Patent 5534499 (1996).
[9]. Touitou E., Godin B., Weiss C.: *Enhanced Delivery of Drug Into and Across the Skin by Ethosomal Carriers*, Drug Develop. Res., 2002, 50: 406-415.
[10]. Choi, M.J., Maibach, H.I.: *Liposomes and niosomes as topical drug delivery systems*. Skin Pharmacol. Physiol. 18, 2005, 209–219.
[11]. Honeywell-Nguyen P. L., Bouwstra J. A.: *Vesicles as a Tool for Transdermal and Dermal Delivery*, Drug discovery Today: Technologies, 2005, 2: 67-74.
[12]. Jadoul A., Preat V.*: Electrically-enhanced transdermal delivery of domperidone*, Int. J. Pharm., 1997, 154:229 – 234.
[13]. Prausnitz MR: *Microneedles for transdermal drug delivery. Adv Drug Deliv Rev 2004;FK: Dermal and transdermal drug delivery systems: current and future prospects*. Drug Deliv 2006; 13: 175–187.
[14]. W.W. Ting, D. Courtney, R. Sontheimer: *Review of traditional and novel modalities that enhance the permeability of local therapeutics across the stratum corneum*, Int. J. of Dermatology, 2004, 43.538-547.
[15]. Cevc, G., Schatzlein, A., Richardsen, H.: *Ultradeformable lipid vesicles can penetrate the skin and other semi-permeable barriers unfragmented. Evidence from double label CLSM experiments and direct size measurements.* Biochim. Biophys. Acta 2002, 1564, 21–30.
[16]. Mezei, M., Gulasekharam, V.: *Liposomes a selective drug delivery system for the topical route of administration: gel dosage form.* J. Pharm. Pharmacol. 1982, 34, 473–474.
[17]. Barry B. : Breaching the skin' barrier to drugs, Nature Biotechnology, 2004, 22: 165-167.
[18]. Cevc G., Blume G.: Lipid vesicles penetrate into intact skin owing to the transdermal osmotic gradients and hydration force, Biochim Biophys Acta, 1992, 1104: 226–232.
[19]. Nelson A Ochekpe, Patrick Olorunfemi and Ndidi Cgwuluka: Nanotechnology and Drug Delivery Part 2: Nanostructures for Drug Delivery, Tropical Journal of Pharmaceutical Research, June 2009, 8 (3), 275-287.
[20]. Barry BW :Is transdermal drug delivery research still important today? Drug Discovery Today, 2001; 6 (19): 967-971.
[21]. Sinico C, Manconi M, Peppi M, Lai F, Valenti D, Fadda AM.Liposomes as carriers for dermal delivery of tretinoin: in vitro evaluation of drug permeation and vesicle-skin interaction. J Control Release 2005, 103 (1), 123-36
[22]. Hofland H.E.J., Bouwstra J.A.,Spies F., Gooris G., Nagelkerke J.F.: Interaction of Liposomes and Niosomes with Human Skin, J. Pharm. Sci., 1994, 83:1192-1196.
[23]. Patel S.S., Mukesh S.P., Natvarlal M.P.: Ethosomes: A Promising Tool For Transdermal Delivery of Drug, Pharmaceutical Reviews, 2007, 5 (2), www.Pharmainfo.net
[24]. Juanjuan Liu, Gan Hu: Advances in studies of phospholipids as carriers in skin topical application Journal of Nanjing Medical University 2007, 21 (6), 349-353.
[25]. Trotta M, Peira E, Carlotti ME, Gallarate M. Deformable liposomes for dermal administration of methotrexate. Int J Pharm, 2004, 270 (1-2): 119-25.
[26]. Handy RD, Shaw BJ. :Toxic effects of nanoparticles and nanomaterials: implications for public health, risk assessment and the public perception of nanotechnology. Health, Risk and Society, 2007; 9 (2): 125-144.