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OPPORTUNITIES AND CHALLENGES TO DEVELOP TRANSDERMAL PATCH WITH NANOCARRIER

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ABSTRACT

The aim of the present study was to review the opportunity and challenges for development of transdermal patch with nanocarrier system. Nanocarriers are colloidal systems, in this particle or droplet size should be smaller than 500 nm. Nanocarriers are non-invasive delivery carriers that enable drugs to reach the hypodermic layer of skin layers and/or the systemic circulation. Effective targeting of drugs can be achieved by using suitable hosting molecules on their surface, which is govern for recognizing and binding to specific receptors on the target molecules**.** Enhanced delivery of potent drugs through the skin and cellular membranes by means of a nanocarrier opens numerous challenges and opportunities for the research and future development of novel improved therapies. Transdermal patch can be developed by new nanocarriers such as nanoemulsions, vesicular (liposomes, ethosomes etc.), nanoparticles etc. This review article is focused on the potentials of nanocarrier for dermal and transdermal drug delivery.

KEYWORDS: Nanocarrier, Transdermal patch, Vesicular system, Skin.

INTRODUCTION

Drug delivery through the skin to the systemic circulation is convenient for a number of clinical conditions due to which there has been a considerable interest in this area.[1,2] Transdermal drug delivery offers many benefits over other traditional routes of administration including non-invasiveness, accessibility, avoidance of first-pass metabolism, compliance, ease of drug input termination in problematic cases and controllable drug delivery rates.[3,4] The fate of effectiveness of TDD system lies on the drug's ability to invade

the skin barrier and how its reaches the targeted site.[5] Recent technologies which are currently under investigation, ranging from chemical enhancers which either increase the diffusivity across the skin or increase the drug solubility in the skin[6] to newer innovative approaches which involve the extension of this concept to the design of super loaded formulations, micro emulsion[7] and vesicular systems. The vesicular system are liposomes, dendrimers and micro emulsions have also been used as chemical enhancers with supramolecular structure that can not only increase skin permeability, but also increase drug solubilisation in the formulation and drug partitioning into the skin.[8,9]

Opportunity with nanocarrier loaded transdermal patch

Ming-Jun Tsai et al has proved that nanocarrier is good carrier vehicle of hydrophilic drug for transdermal delivery. A study[8] pointed out that, small droplet size provides a better chance for adherence to biological membranes transporting therapeutic compounds in a controlled manner. Hence, nano- or micro- carriers such as ethosomes, nanoemulsions, liposomes and polymeric nanoparticles have been widely used to improve permeability of therapeutic agents through skin in recent years.[3,10,12]

Different nanocarrier systems

Nanoemulsions

Nanoemulsions are a unique class of emulsions with a droplet size in the colloidal range. Like micro-emulsions, they may be characterized by having optical transparency and high kinetic stability.[13] Nanoemulsions showed a variety of applications in pharmaceutical formulation, cosmetics and others.[14,15] It improves the bioavailability of drugs.[16,17] The main components of nanoemulsion are oil, emulsifying agents and aqueous phases.[18,20]

Dendrimers

Dendrimers are three dimensional, highly branched mono dispersed macromolecules, which are obtained by an iterative sequence of reaction steps producing a precise, unique branching structure.[21] Unique structures of dendrimers include highly branched and well-defined globular structures with controlled surface functionality, adding to their potential as new scaffolds for drug delivery.[22] Dendrimers cores consist by a host, capacity for guests (that is, drug molecules); in this way they have been reported to release drug in a controlled manner.[23,24] Dendrimers is used as host for both hydrophilic and hydrophobic drugs, thus demonstrating their versatility. The nanoscopic particle size of dendrimers (ranging from 1-100 nm) makes them less susceptible to uptake by the reticuloendothelial system. Because of

their nanoscopic sizes dendrimers have already been reported to transfect cells.[25,27] Wang *et al*[28] have reported that dendrimers can be used to enhance penetration of drug in transdermal drug delivery system. Chauhan *et al*[29] also proved that, dendrimers are good carrier to deliver drug transdermally.

Liposome

In the past two decades, colloidal lipid aggregates called liposomes and developed as vesicular drug carrier systems. Liposome consist of lipids, typically cholesterol and phospholipids, but also other amphiphilic components are possible.[30] Liposomes can exert different functions after topical application.[31] There are three characteristics retained for a good skin penetration is a size around 100 nm[32], a negative zeta potential[33] and also ultra-deformability properties.[34] The penetration enhancer association is also wanted for promoting skin penetration.[35]

Niosome

Niosomes are uni or multilamellar spheroid structures composed of amphiphilic molecules assembled into bi-layers. Niosomes area very useful drug delivery system with numerous applications as described below.[36,40] Non-ionic surfactants can improve the solubility of some poorly soluble drugs.[41] Formulation in Niosomes can also improve their bioavailability as shown for acyclovir and griseofulvin.[42,43] The stability of peptide drugs can be significantly increased by encapsulation in Niosomes.[44] For instance, insulin loaded Niosomes have high resistance to proteolytic enzymes and exhibit good stability in the presence of sodium deoxycholate.[45] Transdermal delivery of various drugs such as minoxidil, enoxacin, aceclofenac and estradiol are enhanced by encapsulation in Niosomes.[46,49] Finally, encapsulation in niosomes can provide sustained release of drugs to prolong their duration of action.

Ethosome

Ethosomes are novel carrier system used for delivery of drugs having low penetration through the biological membrane mainly skin. Ethosomes are lipid vesicles containing phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively high concentration and water.[50] Ethosomes are soft vesicles made of phospholipids and ethanol (in higher quantity) and water. The size range of ethosomes may vary from tens of nano meters to microns (μ).[51] In the ethosome, ethanol is very helpful for enhancement of cell membrane and skin permeability. Therefore, ethosome permeate easily in deeper layer of the skin.

Challenges with nanocarrier-loaded transdermal patch

There are various challenges, associate to develop transdermal patch with nanocarrier system, such as skin irritation, drug loading, skin permeability etc. Since only potent drugs are suitable candidate because of low permeability of skin. Cellular uptake decreases with large surface area and negative surface charge of drug. Various another problems associated with skin delivery such as molecular weight of drug, presystemic metabolism of drug by skin enzymes, pH of formulation etc. When we use nanocarrier then we face many problems such as vehicle-skin interactions, size reduction of drug and drug loading.

Cutaneous irritation

Delivery of drugs by transdermal routes adds the potential for side effects in the form of skin irritation at the delivery site. Skin irritation reactions include dermatitis, inflammation and allergy. There are various factors responsible for skin irritation like changes in the physiological pH of the skin, disruption of the stratum corneum layer (i.e., changes in protein- lipid layer, hydration and change in stratum corneum lipid packing), immunological and physiological reactions, microorganism proliferation at the delivery site and chemical/pharmacological property of the drug or vehicle. Some property of topical and transdermal systems contribute to skin irritation including the active pharmaceutical ingredient (API), formulation (including nanocarrier, skin permeation enhancers and additives), invasion of the skin and the type of delivery system used.

Drug loading problems

Only small dose of drug can deliver with nanocarrier system by transdermal route. It is potential drawback of this type of system. Loading of large dose in a nanocarrier drug delivery system is very difficult. Such as high drug, loading nanoparticles are a potential strategy for circumventing many of the issues that plague nanotherapeutics. Since most nanocarriers have low drug loading capacity, a large amount of nanoparticles is needed to deliver a clinically relevant dose of a therapeutic, leading to the use of a large amount of excipients, which may cause undesirable side effects and drive up the cost of a nanotherapeutic.[52,53] Commonly less than 10 mg dose can be delivered through nanocarrier system via transdermal route. This system is useful for potent drugs only.

Skin permeation challenge

Skin permeation problem is vital challenge for transdermal drug delivery system. When we use nanocarrier to increase skin permeation then we face some other problems such as drug

partitioning, solubility, change in pH of formulation etc. The mathematical model development and prediction of skin permeability is very complex process for transdermal drug delivery system. In the permeation study when we select individual chemical enhancers then it, show limited success, so combinations of chemical enhancers are necessary in transdermal formulations. Although, the rational model of enhancer combinations is limited due to the lack of mechanistic data on the interactions between individual chemical enhancers and the stratum corneum.

Therapeutic limitations

When we want to look ahead to develop transdermal patch with nanocarrier for successful delivery of therapeutic agent across the skin depends on various parameters, such as molecular mass (<500 Da), therapeutic efficacy of drug (below to 25 mg systemic dose/day) and partition coefficient (1-3). Although when we deal with these parameters range, then limited choices are available for therapeutic agent selection. The concentration of drug in nanocarrier loaded dosage form and the area of skin to which it is applied are important parameters that affect the permeation rate.

Other limitations

Factors such as skin temperature and skin hydration level, which can not be altered by formulation designing. Metabolism of drug in nanocarrier with skin enzymes (by oxidation, reduction and hydrolysis) is major problem to develop transdermal drug delivery system. Many other factors, such as disease state, gender, age etc. show limitations for therapeutic transdermal drug delivery systems.

CONCLUSION

The nanocarrier-loaded transdermal patch in this review could well translate into significant variation in drug delivery via the transdermal route. Because of this study, the present scenario of transdermal delivery system can be enhanced by considering all opportunity and challenges. Most challenging issues with nanocarrier-loaded transdermal patch are follicular drug administration as well as concerning deposition of these systems in the hair follicles. The efficient delivery of drug depends upon loaded drug in nanocarrier, types of patch and therapeutic efficacy of drugs. Many researchers have developed transdermal patch with nanocarrier system successfully. It is the future need for develop transdermal patch with nano-medicine for many curable disease.

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