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Review Article

A REVIEW ON APPLICATIONS OF DENDRIMERS IN TRANSDERMAL DRUG DELIVERY

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ABSTRACT
Dendrimers formulations were significantly explored over the last decade for the transdermal drug delivery applications. The ability of transdermal drug delivery systems (TDDS) to deliver and maintain a constant therapeutic concentration of drug offers a significant potential for safe administration of therapeutic agents. The higher level of control possible over the architectural design of dendrimers; their size, shape, branching length/density, and their surface functionality clearly distinguish it as unique and optimum carriers in TDDS applications. In this paper we have attempted to summarize the applications of dendrimers in the field of transdermal drug delivery by citing numerous investigators over the last decade.
Keywords: Dendrimers; transdermal drug delivery; therapeutic effect; application.

INTRODUCTION

Today about 74% of drugs are taken orally and are found not to be as effective as desired to improve such characters transdermal drug delivery system was emerged. Drug delivery through the skin to achieve a systemic effect of a drug is commonly known as transdermal drug delivery. Transdermal drug delivery systems (TDDS) are dosage forms involves drug transport to viable epidermal and or dermal tissues of the skin for local therapeutic effect while a very major fraction of drug is transported into the systemic blood circulation. The adhesive of the transdermal drug delivery system is critical to the safety, efficacy and quality of the product. Several important advantages of transdermal drug delivery are enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug. Transdermal drug delivery (TDD), a noninvasive method of penetrating therapeutic agents through the skin, has already revolutionized the pharmaceutical industry. The ability of transdermal drug delivery systems (TDDS) to deliver and maintain a constant therapeutic concentration of drug offers a significant potential for safe administration of therapeutic agents. TDDS can provide a steady drug blood concentration and thus avoid peaks and valleys in the drug plasma levels, which occur with traditional dosing, such as oral administration and intravenous administration. Also, sustained/prolonged delivery of therapeutic agents in TDDS can simplify the dosing schedule and minimize the pain during traditional drug administration[1]. Besides, TDDS can improve patient compliance and eliminate the hepatic first-pass effect and chemical degradation in the gastrointestinal tract[2]. Additionally, patients can choose elsewhere on the skin to conduct the TDDS according to their need because skin is the largest and most easily accessible organ in the body[3]. However, transdermal delivery of drugs is limited due to the slow rate of transdermal delivery, chiefly attributable to the barrier functions of the skin. The outer layer of the skin which is served as the first line of defense is composed of closely packed dead cells formed by epidermal differentiation and cornification[3]. It imposes a significant role on the diffusion path across the membrane. This major challenge in TDDS prevents this promising technology from clinical practice.

Only small drug molecules (<500 Da) with optimal physicochemical properties (log *P*- 13) can be passively transported through SC. As a result, various chemical and physical enhancement strategies have evolved to expand the number of drugs delivered through skin[4]. In this regard, several chemical penetration enhancers have been widely investigated[5]. A large number of these chemical enhancers are small molecules that penetrate the skin in significant amounts and cause skin irritation or irreversibly alter the skin barrier. On the other hand, polymeric enhancers due to their large molecular size cannot penetrate deep into the skin and hence do not cause skin irritation[6] tested a series of linear polymeric enhancers and found them to be non-irritating to the skin. The present study focuses on evaluating branched PAMAM dendrimer polymers as skin penetration enhancers. Over the last decade, numerous drug delivery systems have been explored to overcome the limitation of conventional dosage forms. Novel formulations such as nanoparticles, liposomes, dendrimers, and niosomes were developed to enhance drug bioavailability and to minimize adverse effects[4,5]. Among them dendrimers formulations were widely explored in the last decade for drug delivery applications.

Dendrimer chemistry was first introduced in 1978 by Fritz Vogtle and coworkers[7]. In 1985, Donald A.Tomalia, synthesized the first family of dendrimers[8]. Dendrimers are hyperbranched and monodisperse three-dimensional macromolecules. Macromolecular architecture and 3D structure provides a high degree of surface functionality and versatility. The word dendrimer comes from the Greek word dendron, meaning ‘tree’, and meros meaning ‘part’. The other synonyms terms used for dendrimer are ‘arborols’ and ‘cascade molecules’, but ‘dendrimer’ is the best establised one. Dendrimers are widely used in drug delivery system due to its narrow polydispersity and nanometer size range. Dendrimer are large and complex molecules having very well defined chemical structures.

Dendrimers possess three distinguished architectural components, namely a central core which is either a single atom or an atomic group, generation in which branching emanating from the core composed of repeating units, which is radially in position and many terminal functional group generally located in the exterior of the macromolecule.(Figure-1)

The structural advantages allow dendrimers to play an important role in the fields of nanotechnology, pharmaceutical and medicinal chemistry particularly

attractive[9]. Dendrimers possess empty internal cavities and open conformations (for low-generation dendrimers), which helps in make encapsulation of hydrophobic drug molecules. The higher level of control possible over the architectural design of dendrimers; their size, shape, branching length/density, and their surface functionality clearly distinguish these structures as unique and optimum carriers in those applications. Recently, more research focused on the application of dendimers in biomedical fields.

There are many other approaches to enhance the drug solubility and drug delivery but they are associated with some other limitations i.e. colloidal and surfactant based system (micelles, emulsion and liquid crystal) have draw back related to incomplete and premature release of drug because of disruption of micellular structure on dilution with body fluid below critical micelles concentration[10]. Parenteral administrations of β-cyclodextrin produce nephrotoxicity because of formation of β-cyclodextrin- cholesterol complex, which precipitate in kidney. CDS may also cause sharp change and haemolysis of human erythrocytes. Currently the most commonly drug delivery system liposomes have limited application due to poor stability and difficulty in targeting to specific tissue. Dendrimers with hydrophobic core and hydrophilic periphery have shown to exhibit unimolecular micellar type behavior and have container properties in solution.

APPLICATIONS OF DENDRIMERS IN TRANSDERMAL DRUG DELIVERY SYSTEM

Dendrimers in Transdermal Drug Delivery (TDD), a noninvasive method of penetrating therapeutic agents through the skin, has already revolutionized the pharmaceutical industry. The ability of transdermal drug delivery system (TDDS) to deliver and maintain a constant therapeutic concentration of drug offers a significant potential for safe administration of therapeutic agents. TDDS can provide a steady drug blood concentration and thus avoid peaks and valleys in the drug plasma levels, which occurs with traditional dosing, such as oral administration and intravenous administration. Also, sustained / prolonged delivery of therapeutic agents in TDDS can simplify the dosing schedule and minimize the pain during traditional drug administration. TDDS can improve patient compliance and eliminating the hepatic first-pass and chemical degradation in the gastrointestinal tract. Patients can choose elsewhere on the skin to conduct the TDDS according to their need because skin is the largest and most easily accessible organ in the body. However, Transdermal delivery of drug is limited due to the slow rate of transdermal act as effective penetration enhancers. The most common method to improve drug penetration through the skin is to use transdermal enhancers. Various transdermal enhancers, such as organic solvents, are effective because they can directly react with the skin, and thus transiently increase their permeability but induce immune responses in the skin. Therefore, polymeric enhancers with hydrophilic and hydrophobic properties have attracted increasing interest. PAMAM dendrimers can improve either the water solubility or stability of hydrophobic drugs. These materials with hydrophilic outer shells and hydrophobic interiors, which accord with structural requirement of polymeric transdermal enhancer, are expected to act as effective penetration enhancers. Recently, several researches have investigated the potential of dendrimers in the transdermal route of drug administration[11].

The transdermal ability of three types of PAMAM dendrimers (G 4-NH2, G 4 OH, and G 4.5 COOH dendrimers) had been studied[12]. Indomethacin was used as the model drug. The result showed that the steady-state flux of indomethacin increased linearly with the concentrationof all the three PAMAM dendrimers and was the highest with cationic G4 PAMAM dendrimers at 0.2% w/v concentration by in vitro permeation studies. During conducting the in vivo pharmacokinitcs and pharmacodynamic studies, indomethacin and dendrimers formulations were applied to the shaved abdominal skin of wistar rats, and the blood from the tail vein was collected at the scheduled time after dendrimers/drug administration. The maximum indomethacin concentration in the blood was significantly higher with PAMAM dendrimers when compared to pure drug suspension[11].

Dendrimers have ideal properties which are useful in targeted drug-delivery system. One of the most effective cell-specific targeting agents delivered by dendrimers is folic acid PAMAM dendrimers modified with carboxymethyl PEG5000 surface chains revealed reasonable drug loading, a reduced release rate and reduced haemolytic toxicity compared with the non-PEGylated dendrimer. A third-generation dendritic unimolecular micelle with indomethacin entrapped as model drug gives slow and sustained in vitro release, as compared to cellulose membrane control[39].Controlled release of the Flurbiprofen could be achieved by formation of complex with amine terminated generation 4 (G4) PAMAM Dendrimers[13].The results found that PEG-dendrimers conjugated with encapsulated drug and sustained release of methotrexate as compare to unencapsulated drug.

Dendrimers have found recent applications in novel topical and transdermal, providing benefits such as improved drug solubilization, controlled release, and drug-polymer conjugates (pro-drugs). The viscosity- generation-number property of a dendrimers solution allows for ease of handling of highly concentrated dendrimers formulations for these applications. Dendrimers have been shows to be useful as transdermal and topical drug delivery systems for nonsteroidal anti-inflammatory drugs ($NSAID_S$), antiviral, antimicrobial, anticancer, or antihypertensive drugs. PAMAM dendrimers have been studied as carrier transdermal systems for the model NSAID. It was found that the PAMAM dendrimers-drug formulation showed increased transdermal drug delivery compared with formulations lacking dendrimers.

DENDRIMERS IN INTRAVENOUS/INTRAPERITONEAL/ INTRATUMORAL DRUG DELIVERY

The intravenous route is the rapidest and simplest method for delivering a drug into the systemic circulation (Figure-2). However, poor water solubility of many drugs, especially anti-cancer drugs, limits the application of intravenous administration route in clinical trials. Intravenous administration of these drugs results in several side effects, such as hemolysis and phlebitis. Much effort has been made to develop new formulations that are suitable for the intravenous route, among which dendrimer-drug formulation is attracting increasing interests as one of the emerging delivery systems. It should be indicated here that both intraperitoneal and intratumoral administration of anti-cancer drugs can increase the exposure of cancer cells within the peritoneal cavity or directly to the drug and minimize potential toxic effects to internal organs. Dendrimers have also proved themselves suitable for these unconventional administration routes. Before the proposed application of

dendrimers in the intravenous route, it is worth considering their biodistribution in the body and takes care that these artificial materials will not induce unacceptable toxicity or immunogenicity because most dendrimers are not intended for pharmaceutical use[11].

DENDRIMERS IN ORAL DRUG DELIVERY

Oral delivery system has been the dominant route for many years because of its significant advantages. It is by far the most convenient administration route with good patient compliance, especially in the patient opinions. In spite of these benefits, defects of oral delivery route are also obvious. Oral delivery usually associates with immediate release of the drug and hence causes toxicity in practice. In addition, orally administrated drugs may display low solubility in the aqueous solutions and low penetration across intestinal membranes. Current strategies to overcome these issues focus on several systems in which drugs are loaded into oral drug carriers. As the absorption and distribution of drugs in such systems mainly depended on the properties of these macromolecular carriers, minimization of the side effects can be achieved by modification of the macromolecules structure**.** An ideal macromolecular carrier for orally administrated drugs should have the ability to protect the drugs from degrading. They might reduce nonspecific interactions with food proteins and allow enhanced absorption across the intestinal epithelium. Dendrimers with featured properties may act as potential candidates for orally controlled release systems by conjugating/encapsulating drug molecules in them. They allow the maintenance of drug concentrations within the therapeutic range at the injured regions, and hence can simplify dosing schedules. In addition, dendrimers can significantly increase the solubility of these orally administrated drugs and even the stability of drugs in biological environments. These macromolecules with bioadhesive properties have strong affinity for mucosa and can prolong the residence time of the orally administrated drug in contact with the intestinal epithelium. Furthermore, dendrimers themselves can easily penetrate through intestinal membranes, and thus can enhance the oral absorption of low-penetration drugs. These properties make dendrimers suitable carriers for the development of oral drug delivery systems.

It was suggested that colloidal drug carriers such as dendrimers could be absorbed by way of the Payer's patches, which is a route to enhance the oral absorption of encapsulated drug molecules and to minimize enzymatic degradation in the intestine tissue. Experimental results showed a preferential uptake of dendrimers through the lymphoid tissue in the small intestine but not in the large intestine. These results indicated that dendrimers were capable to enhance the absorption of low-penetration drugs in the small intestine tissues.

Oral drug delivery studies using the human colon adenocarcinoma cell line, Caco-2, have indicated that low-generation PAMAM dendrimers cross cell membranes, presumably through a combination of two processes, i.e. paracellular transport and adsorptive endocytosis. Remarkably, the P- gp efflux transporter does not appear to affect dendrimers, therefore drug dendrimer complexes are able to bypass the efflux transporter[14]. As increase in the concentration and generation, there was and methotrexate. PAMAM dendrimers conjugated with the folic acid and fluorescein isothiocyanate for targeting the tumor cells and imaging respectively. DNA-assembled dendrimer conjugates may allow the combination of different drugs with different targeting and imaging agents so it is easy to develop combinatorial therapeutics[15].

Studies on Caco-2 monolayers, as models of intestinal epithelial barrier, show that by engineering surface chemistry of PAMAM dendrimers, it is possible to minimize toxicity while maximizing transepithelial transport[16].

Duncan and her research group systematically investigated the effect of dendrimer size, charge, and concentration on uptake by the adult rat intestine and studied the absorption mechanisms of dendrimers in intestine tissues so as to develop PAMAM dendrimers as potential oral drug carriers. It was suggested that dendrimer size was a key factor on determining overall uptake. Macromolecules with diameters up to 3 nm may penetrate through the intestinal membranes via either the transcellular or paracellular pathway. Therefore, G 2.5 and G 3.5 PAMAM dendrimers could transport across the intestine via these ways. On the other hand, G 4 and higher generation PAMAM dendrimers could attach to the invigilating plasma membrane, and enter cells by specific or nonspecific adsorptive endocytosis. G 2.5 and G 3.5 PAMAM dendrimers showed particularly low tissue uptake ability, while G5.5 PAMAM dendrimers displayed a higher tissue accumulation than G 2.5 and G 3.5 dendrimers. Moreover cationic dendrimers showed a different pattern of accumulation from anionic dendrimers. The negatively charged cell membrane could interact strongly with cationic molecules, and hence led to higher tissue association and lower transport rate of these dendrimers. These results indicated that dendrimers exhibited a size/conformation/charge sensitivity of the transport mechanism across the intestine[11].

DENDRIMERS IN OCULAR DRUG DELIVERY

Ideal ocular drug-delivery systems should be nonirritating, sterile, isotonic, and biocompatible, does not run out from the eye and biodegradable[17].The main challenge in ocular drug delivery is to increase the drug bioavailability and prolong the residence time of the drug on the cornea, conjunctival, and corneal epithelia. Up to now, different polymeric formulations, such as natural polymers, bioadhesive polymers, and colloidal formulations have been used as potential ophthalmic drug carriers. These polymeric formulations with perfect viscosity can prolong the drugs residence time on the cornea and increase their bioavailability. However, most of these formulations give rise to unwanted side effects. Polymeric nanoparticles tend to be removed by lachrymal drainage whereas micro particulates of larger sizes are less tolerable because they may cause eye irritation and tend to be eliminated by the flow of tears. These surface-modified dendrimers were predicted to enhance pilocarpine bioavailability[17, 18]. Additionally, administration of these polymers to the cornea may lead to blurred vision resulting from infiltration of the lachrymal gland with round cells and reduced secretion of lachrymal fluid. Overall, development of new functional materials to avoid these problems still holds the key for the future ocular drug delivery. Recently, dendrimers with distinct properties from traditional polymers were suggested to act as ophthalmic vehicles in ocular delivery systems. These dendritic polymers might dissolve hydrophobic drugs.

DENDRIMERS IN GENE TRANSFECTION

The use of dendrimers as gene transfection agents and drug delivery devices has been thoroughly reviewed very recently[19, 20-22]. Therefore, only a few highlights are summarized together with additional recent studies. Dendrimers are very actively under investigation for the

delivery of DNA and small organic molecule drugs, especially for cancer therapy.

Numerous reports have been published describing theuse of amino-terminated PAMAM or PPI dendrimers as non-viral gene transfer agents, enhancing the transfection of DNA by endocytosis and, ultimately, into the cell nucleus[23,24-33]. It should be noted that dendrimers of high structural flexibility and partially degraded high-generation dendrimers (i.e., hyperbranched architectures) appear to be better suited for certain gene delivery operations than intact high-generation symmetrical dendrimers. Perhaps this is due to their enhanced flexibility, which allows the formation of more compact complexes with DNA[34, 35]. Furthermore, it has been found that maximum transfection efficiency is obtained with a net positive charge on the complexes (i.e., an excess of primary amines over DNA phosphates).

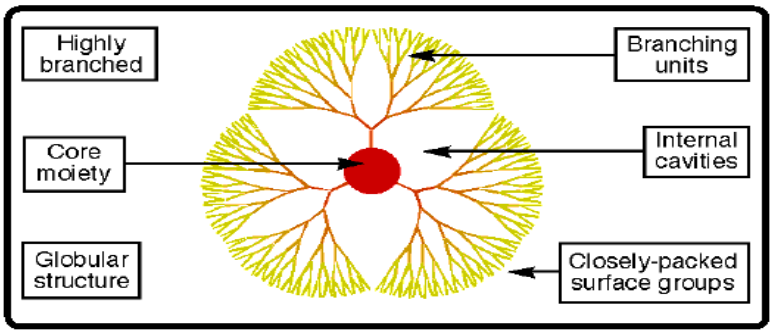

Figure 1: Structure of dendrimers

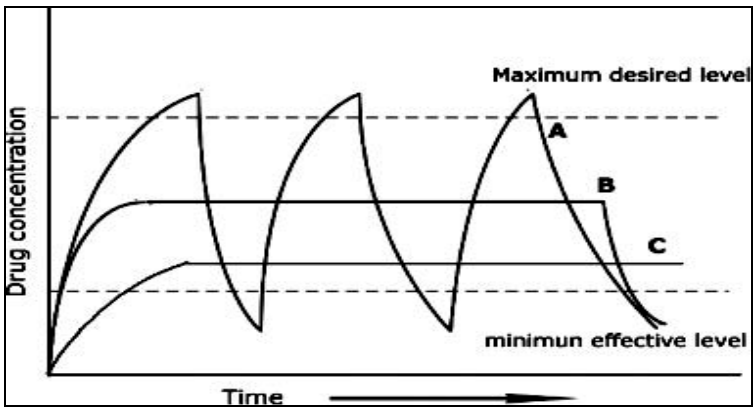

Figure 2: Potential pharmacokinetics of (A) Traditional dosing, (B) Formulations of drug/dendrimer complexes, and (C) Drug–dendrimer conjugates.

CONCLUSION

Numerous applications of dendrimer in transdermal drug delivery were extensively studied. These carriers have successfully improved the drug bioavailability by controlled and targeted delivery. The high level of control over the architecture of dendrimer, their shape, branching length and density, and their surface functionality, makes dendrimer ideal carriers for the various applications like drug delivery, therapeutic and diagnostic agent. So all this studies at last concluded that dendrimers is successfully used in application of transdermal drug delivery system.

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