EXPERT OPINION

A feasible way to use carbon nanotubes to deliver drug molecules: transdermal application

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Introduction: Nanotechnology has gained increasing importance in the pharmaceutical and medical fields, beyond its importance in physics and technology. Targeting of the drug or active molecules can be achieved rather easily with some nanocarriers because of their unique properties; to program or control of delivery can also be possible. One of the smart nanosystems is carbon nanotubes (CNTs) because they are elecroconductive and they have very big surface area to deliver active molecules. There have been many drug delivery systems proposed to the scientific world using CNTs. One administration way which appears to be the most appropriate for drug delivery is transdermal application.
Areas covered: Performed experiments and proposed techniques with the use of CNTs are scrutinized and discussed in this review.
Expert opinion: In the light of current knowledge, a feasible way to use CNTs to deliver drug molecules is transdermally.

Keywords: carbon nanotube membrane, carbon nanotubes, iontophoresis, transdermal

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1. General overview on nanotechnology and nanoaparticles in drug delivery

The word 'nano' is derived from the Latin word, which means dwarf [1]. Nano size refers to one thousand millionth of a particular unit, thus nanometer is one thousand millionth of a meter (i.e., 1 nm = 10^{-9} m). Nanotechnology concerns materials or processes that occur at a molecular level and of a size preferably between 100 and 10 nm. Nanotechnology is a rapidly growing area among almost every scientific discipline but when the term 'Nanotechnology' is used in the area of pharmacy it is termed 'Pharmaceutical nanotechnology' [2]. Nanotechnology is, in fact, a multidisciplinary field which has had a powerful impact in various fields of medicine and pharmacy. Pharmaceutical nanotechnology provides many complicated systems, devices, drug delivery systems and materials for better pharmaceutical applications and effective therapies. It also describes and proposes applications of nanoscience to pharmacy as nanomaterials and devices like drug delivery systems, diagnostic or imaging formulations and biosensors.

Pharmaceutical nanotechnology provides nanotools or nanomaterials and nanodevices, which play a key role in the area of pharmaceutical sciences and related fields. Nanomaterials can include some biomaterials, for example, in orthopedic or dental applications they can be implants or scaffolds for tissue-engineering products. Their surface modifications or coatings have been claimed to enhance their biocompatibilities by favoring the interaction of living cells with these biomaterials. These materials can be sub-classified into nanocrystalline and nanostructured materials.

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Article highlights.

- The main problem of CNTs for drug delivery is the bio-incompatibility.
- CNTs have quite high surface area available for drug molecules for adsorption and subsequent desorption may release the drug.
- Transdermal route appears to be the most appropriate way for drug carrying CNTs.
- The application of iontophoresis is possible when CNT membrane is used.

This box summarizes key points contained in the article.

Nanocrystalline materials are manufactured materials and can substitute poorer performing bulk materials. These raw nanomaterials can be used for drug encapsulations, bone replacements, different kind of prostheses and implants.

Nanostructured materials are sometime processed forms of raw nanomaterials that provide special shapes or functions, for example, quantum dots, dendrimers, fullerenes and carbon nanotubes (CNTs).

Nanodevices are miniature devices in nanoscale which include nano- and microelectromechanical systems (so called NEMS/MEMS), microfluidics which try to control and manipulation of micro- or nanoliters of fluids in biological systems, various microarrays and their various applications. Examples of biosensors and detectors to detect bacteria, airborne pathogens, biological hazards and some intelligent machines have been proposed and developed.

The various types of nanosystems have been given in the literature [2].

Conventional therapy options generally face some hurdles such as bioavailability issues, hepatic first-pass effects related to route of administration and precise targeting. All of these obstacles cannot be overcome in each given instance [3-7]. The blood–brain barrier is almost impermeable for most drug molecules [8,9] and many times effective concentration of anticancer drug cannot be achieved at the tumor site [10].

A vehicle for ideal drug delivery would be capable of finding every single diseased cell in the body and destroying itself by discharging active molecules. Pharmaceutical nanotechnology offers some new and developed technology to overcome all these difficulties. For instance, many developed nanoparticles and developed systems are able to avoid hepatic first-pass effect by passing the liver and escaping phagocytic cells by means of modified surfaces (PEGylated liposomes, quantum dots, etc.) [11]. In such cases, the attachment of some big and branched molecules like polyethylene glycol (PEG) to the surface of nanoparticles makes them unrecognizable by phagocytic cells [12]. Therefore, such nanoparticles are able to navigate themselves in the blood stream for longer periods without being destroyed and therefore have more opportunity to reach the site of action.

The other advantages of nanosized drug delivery systems include leaving the vasculature through leaky angiogenic vessels and the ability to accumulate in tumor interstitia (as illustrated by its use in targeted drug delivery and for imaging). The enhanced permeability and retention (EPR) effect also provides active molecule to reach effective concentration in the tumor tissues [12-14].

Transdermal administration appears to be the most suitable non-invasive way to administer drug molecules and other substances such as vaccines. Transdermal administration offers a variety of advantages with the major challenge being the possibility of an efficient and easy delivery of drug molecules through the skin. In particular, the stratum corneum (SC) and the epidermis are the major challenges in transdermal drug delivery. Although the SC is only 10 – 15 μm thick, while epidermis is 50 – 100 μm thick and the dermis layer is about 2 – 3 mm, usually a drug, even with a vehicle, cannot easily pass through the SC [15-19].

Some new approaches aimed at targeting the sweat glands and hair follicles show a better delivery when compared with overall skin flux, which is claimed to work by means of shunt routes [20].

Microneedles, which are in the size-range of a micrometer, are capable of delivering drug molecules when inserted into the skin. Drugs made of nanoparticles are efficiently delivered directly into the epidermis via this method [21]. This method shows that microneedles can transfer the drug effectively and the possibility of using nanoneedles appears to be the most suitable approach. Some nanotubes, such as CNTs, have been also proposed to be useful for this application [22]. However, this is still an invasive method and poses the risk of inserting microorganisms that live naturally on the skin into the deeper layers of the skin, which is problematic as it may cause unexpected infections.

2. Use of CNTs to deliver drug molecules and their role in anticancer therapy

CNTs can be subclassified as fullerenes, magnetic CNTs and CNTs. Fullerenes are from carbon allotrope family and named after the US architect Richard Buckminster Fuller (1895 – 1983) because of the resemblance of the structure to the geodesic dome, which Fuller invented. Fullerenes are shaped like a ball and not water soluble [23,24]. Fullerenes have been used to increase quality of underground water and used for fuel cells and some studies have been performed to deliver active molecules into the skin in cosmetics [25]. The smallest fullerene has 60 carbon atoms and they are electroconductive in nature and thermo-resistant [26]. In an interesting study, fullerenes were decorated with amino acids and it has been successfully targeted to human keratinocytes in cultured cells [27]. This study shows surface modifications and functionalization can enhance the penetration ability of CNTs. Functionalization of CNTs has been proposed to be easily manipulated and modified by encapsulation with biopolymers or by covalent linking of solubilizing groups to the external walls and tips. Recent advances in the development of CNT technology and functionalizations of CNTs for the delivery of some drugs, antigens and genes have

been reviewed [28] and the use of CNTs for combating infectious diseases have also been proposed and discussed [29]. All systems use CNTs as an individual material to deliver active substance. In other words, CNTs also incorporate the penetration of, absorption into or taking up by living cells.

CNTs can be magnetized by adhering metal nanoparticles on the surface. This has been shown for multi-walled CNT (MWCNT) [30]. Magnetized by ferric oxide, herceptin-conjugated MWCNT has been used to diagnose cancer and to detect cancer cells when investigated under magnetic resonance [31]. In another study, magnetized MWCNT has been used to deliver 5-fluorouracil and cisplatin to lymphatic cells. Therapeutic agents were attached to the MWCNT by nano-precipitation and surfaces have been modified by PEG, phospholipids and folic acid. The effective targeting of anti-cancer drugs has been shown to be possible by these kinds of modifications [32].

In fact, CNTs are 10,000 times smaller than hair follicles and were first discovered and proposed to the scientific world by Sumiyo Lijima in 1991 [33]. Their radiuses are 2 – 100 nm and they are 5 – 500 nm in length [34]. Despite many pharmaceutical applications and investigations, CNTs have been widely studied mainly for the development of microelectronic devices. CNTs have some unique and extraordinary physicochemical properties that enable them to be efficiently taken up by cells, to present high stability and to be incorporated in many composite materials, mainly on the basis of their tremendous mechanical strength, light weight, high aspect ratio and thermal insulator properties [35-37]. Such properties, together with electronic approaches ranging from metallic to semiconducting [35-37], have increased the interest from scientists in electronics [38,39] and material sciences [40]. Moreover, CNTs have been recently investigated as drug delivery systems [41] used in cancer therapy. CNTs proposed to offer the advantage of entering the cells by piercing the cell membrane-like nanoneedles [42]. Moreover, they present a hollow space at the interior, where drugs can be confined and thus prevented from interactions with the surrounding milieu, which often causes deactivation [43].

Despite the eminence of CNTs in nanotechnology, exploration of their pharmaceutical applications still remains at a very early stage [44]. It has been shown that single-walled CNTs (SWCNTs) and MWCNTs can be internalized by living cells and pass across the biological membranes in cell culture studies. The internalization of CNTs by corneocytes has been shown [45] in the literature but their drug-carrying properties through the skin have not been fully evaluated. The application of iontophoresis using CNTs electrode having adsorb drug molecules on their surface has been shown and molecules found to be successfully transferred through deeper skin layers [46].

In cancer treatment, to deliver active molecules to the site of action at effective concentration is the most important concern and a need [47]. Cancer cells are sometime more resistant to anti-cancer drugs while normal cells are quite sensitive. Therefore, the aim in research has been to obtain drugs that selectively target the cancer cells and that can overcome resistance. Another aim has been to reduce cellular toxicity by using nanoparticulate systems [48]. In recent years, the use of non-steroidal anti-inflammatory drugs (NSAIDs) has been suggested to reduce solid tumor mass [49]. NSAIDs inhibit cyclooxygenase-2, but some NSAIDs also inhibit proliferation of cancer cells and induce apoptosis. Although several mechanisms have been suggested, the p75 neurotrophin receptor (p75NTR) has been identified as a tumor and metastasis suppressor. Treatment with NSAIDs causes high expression of p75NTR protein. A delay in tumor growth initiation and attenuation of metastatic growth has been shown with the use of indomethacin (IND) in cell lines and in mice [50]. In another study, the transdermal drug carrier properties and penetration enhancement effect of CNTs have been demonstrated. MWCNT and double-walled CNTs (DWCNTs) have been used [46]. Penetration enhancement into the skin following passive diffusion and iontophoresis were determined. Doxorubicin and IND were used as anticancer drug. Besides providing the first results and usage of CNTs for delivering drug molecules through skin by adsorption and subsequent desorption, this study also underscores the valuable information that can be useful to understand the complex skin penetration processes of molecules and these results highlight some important parameters. The electroconductive nature of CNTs allows easy application of iontophoresis with the additional advantage of using them as drug-containing electrodes. This study gives first information about the usage and application of new type of electrode having adsorbed drug on for further iontophoresis applications [46].

3. Problems and positive perspectives on CNTs

The main problems with CNTs are biocompatibility and water insolubility. Functionalization of CNTs, coating, radius, length and agglomeration issues affect toxicity, absorption, distribution, metabolism and elimination of CNTs [51]. Unexpected residues such as ferric or acidic residues, metal ions and aluminum or silica particles can be present in or on the CNTs. Such residues can be responsible for toxic effects. Initially, lung toxicities of CNTs and related concerns were investigated because of their long and asbestos-like shapes [52]. Lung toxicities of MWCNTs and SWCNTs have been investigated and biocompatibilities and cellular toxicities have been put forward [53-55]. On the other hand, their toxicities are decreased by surface modifications and functionalization. Enhanced biocompatibilities have been reported [56]. It has also been reported that oral and dermal toxicities of CNTs are quite lower than lung conditions after exposure [57]. The biocompatibility and solubility of CNTs can be increased by functionalization and adding hydrophilic moieties [58-60]. Specifically, CNTs have been functionalized with biotin and subsequently complexed with a fluorescent streptavidin. These functionalized CNTs were found to be taken up by endosomes following incubation in cultured cells [61]. The mechanism of penetration is not yet completely explained but two possible routes of internalization have been proposed. It has been shown that functionalized CNTs can penetrate through

cells following passive diffusion across the lipid bilayer. This has been attributed to their 'nanoneedle' shape which allows them to perforate the cell membrane without causing cell death [62-64]. Both SWCNTs and MWCNTs can be internalized by cells and made to pass across biological membranes [65]. The internalization of CNTs by skin cells, namely corneocytes, has also been shown [66]; however, their drug-carrying properties through the full thickness of skin have not been tested and evaluated.

Some studies have shown cellular toxicity when immortalized non-tumorigenic human epidermal cells were exposed to CNTs [67]; however, inflammatory markers were not fully evaluated. The reported toxicity was considered to be a result of impurities present on the CNTs. Gene expression profiling studies on human epidermal keratinocytes exposed to SWCNTs have shown similar properties to that of α-quartz or silica, which is known to be the main cause of silicosis in humans [68] and accordingly, exposure to CNTs has been considered to be dangerous. On the other hand, recent reports show no hazardous effects with CNTs. Human volunteers and albino rabbits were exposed to high amounts of CNTs [69]. In this trial, aqueous suspensions of CNTs were applied to filter papers and patch tests were carried out. Albino rabbits received ocular instillation of CNT suspensions and modified Draize rabbit eye tests were performed. These trials did not show any sign of hazardous effects to the skin or any allergic reactions [69]. Similarly, intratracheal administration of CNTs did not cause or induce any abnormalities of pulmonary functions or measurable inflammation and it was concluded that working with CNT is unlikely to be associated with any health risks [69].

After all these considerations, it appears that administering CNTs through parenteral or enteral (through gastrointestinal tract) route, nasal, ocular, aural way may not be very promising. All these ways include material internalization which may not be very feasible for CNTs being not biocompatible and water-soluble material.

Functionalized MWCNTs containing amphotericin B have been incubated with human Jurkat lymphoma cells and it has been reported that MWCNTs can selectively pass through biological membranes and they are capable to deliver active substance effectively to the infected cells [70]. Several attempts have been made to show that functionalized CNTs are not very toxic for the living cells. Functionalized CNTs have been used to investigate toxic effects on macrophages, T and B type of lymphocytes. The degree of functionalization has been found to be directly related with cytotoxicity [71]. Functionalized CNTs were incubated with the cells for 22 – 24 h and more soluble CNTs were found to be not effective on the immunoregulator cell activity where less soluble ones induced cytokine release from macrophages [71].

In another study, it has been shown that functionalized MWCNTs with glucosamine were not toxic in mice [72]. Te^{99m}-labeled MWCNTs functionalized with glucosamine were administered to mice intraperitoneally with no acute toxicity observed. MWCNTs were found to be distributed very fast to the tissues and eliminated mainly through urine and feces. The half-life in blood has been determined as 5.5 h [72].

SWCNTs have also been used for imaging. Photoacoustic analysis has been performed and compared with optic techniques. SWCMTs have been conjugated with cyclic peptide (Arg-Gly-Asp; RGD) and used as contrast agent [73]. Conjugated SWCNTs were found to be accumulated in the tumor and this approach has been proposed as good and promising method [73]. Other study has been performed using radiolabeled and functionalized CNTs with chelating agent DOTA and it has been shown that these CNTs can be used for positron emission tomography imaging [74].

4. A feasible administration way to overcome the problems of CNTs

One of the feasible ways for drug administration using CNTs appears to be the transdermal way. Transdermal administration has got some advantages when considering the biocompatibility concerns encountered with CNTs, as mentioned earlier. CNTs can be internalized by living cells and they can even reach the nucleus of the cell but they cannot come back; they are very strong and stable for quite a long time even in many strong acids. The issue is to understand that, is it possible for them to be internalized by skin cells? Skin is the biggest organ in the body. The ultra-structure of the skin and the epidermis is different at molecular level according to body site, gender and species which makes molecular diffusion different. The tortuous epidermal lipid layers limit drug permeation (the size limitation is reported to be 50.4 nm [75]). The skin is practically impermeable to typical particles or even to colloidal components with the exception of major opening namely pores, shunts or lesions on the skin and of some hydrophilic pathways in the stratum corneum. The radius of negatively charged hydrophilic transepidermal pores has been calculated with the range of 13 – 27 nm [76]. Obviously, skin pores wider than 30 nm are not compatible with the protection role of the skin; because of rapid evaporation or losing water which would present a dramatic problem in skin with pores that are large. However, the transepidermal pathway and pores with their distributions depend on the size and shape of the clusters in the stratum corneum. In some places, a narrow average opening (50.4 nm water evaporation pathways) exists but in other places much wider pores (100 nm inter corneocyte pathways) claim to exist [77]. A few micrometer wide follicular shunts on clean human skin are open all the time. Depilation increases the openings to 50 – 100 mm and to depths below the SC which can exist for several days [78]. The hydrophilic path between the skin cell clusters can act as a transcutaneous shunt, which is typically wider than 30 nm and almost permanently open. Transepidermal shunts thus cover a broad spectrum of widths, encompassing anything between a relatively

wide intercluster gap (width 5 μm), a hair follicle (width 5 μm) and a cutaneous gland (width 50 μm; [77]). Penetration of nano-sized materials through the skin layers can be achieved by several complex mechanisms [16-19,78]. They can enter through the pores or through the lipid bilayers or they can alter the barrier function of the lipids in the membrane (the fluidity of the membrane can be altered or molecules may remain among the lipids in the membrane bilayer and they can alter the composition of the membrane) or penetrant can be bound to the material of interest and these can then penetrate together. The hydrogen bonding acceptor or donor ability plays an important role [79]. The size of the CNTs used is about 100 – 200 nm in length and 2 nm in diameter; therefore, the CNTs cannot penetrate through the skin but they may have some positive effects on skin penetration of compounds. It has been shown in the literature that CNTs are suitable for drug transport since they consist of an adsorptive material with a high surface area [46,80]. The CNTs investigated so far did not penetrate through the skin layers, and their penetration enhancement is via adsorption and subsequent desorption (i.e., depot effect) [46] or may be due to an alteration of thermodynamic activity of the molecule. CNTs have reported to be useful in increasing transdermal penetration especially for hydrophobic drugs. The application of iontophoresis has been reported to be possible using CNTs as adsorptive electrodes and they can be used for both water-soluble and -insoluble compounds [46].

5. More about CNTs, their drug-carrier abilities for transdermal applications

The physical appearance of CNTs has been widely investigated using various techniques such as transmission electron microscopy (TEM), energy filtered TEM (EFTEM), high angle angular dark field scanning TEM (HAADF-STEM), etc. [81] and their TEM images have been compared with AFM images in the literature [82-88]. Generally, there is no extra process needed for TEM or AFM analysis where a smooth surface of mica has been used for observations [89]. CNTs are observed as tubular structured materials under TEM and AFM. The main problem with CNTs has been addressed as poor water solubility and dispersibility. PEGylation of CNTs materials has been proposed to improve their water dispersibility [90,91] and related biocompatibility issues have also been thought to be decreased. It has been shown that CNTs have available surfaces to adsorb drug molecules. The CNTs were also investigated after PEGylation using AFM and there was a noticeable change observed in their appearance following PEGylation [46,91]. PEG molecules were shown to be attached to the CNTs surface and they were observed at side of CNTs when smooth surface of non-PEGylated CNTs were clearly seen. Functionalizations could be made through side –COOH groups of CNTs and PEG molecules were found to be bound to surface by chemical bonds. These molecules on the surface of CNTs increase the diameter of CNTs and are also claimed to enhance their water dispersibility [46,91]. PEGylated CNTs were shown to be dispersed very well and found to be stable for more than a month in water [46]. The surface of CNTs became an important parameter for the adsorption. The surface areas of the CNTs were found to be different according to their type. SWCNTs (≈ 600 m^2/g) were reported to have quite high surface area then MWCNTs (≈ 240 – 300 m^2/g) [91,92]. Interestingly, surface areas were also reported to be decreased by PEGylation.

The differential scanning calorimetry (DSC) of the material can show the strongness of the crystalline structure and it can also be an indicator of transdermal penetration behavior of a drug molecule [17-19,93]. When the DSC scans of compounds were subjected to the analysis with the presence of MWCNTs after complete adsorption, the melting points were reported to disappear [80,91]. This interesting finding suggest that when the material adsorbed by CNTs, molecules cannot create any bonds and cannot go back to the crystalline state because of strong interaction with the carbon molecules. This disappearance can be seen if the compound actually goes and stays inside the CNTs.

Many modifications and improvements have been done with CNTs and some covalent and non-covalent functionalizations of their external walls have been performed. So far, some investigations showed that using CNTs to encapsulate molecules may be valuable in drug delivery [94]. The interior part of the CNTs has been reported to have higher binding energy toward molecule adsorptions than the exterior walls [95]. Although it seems not to be suitable for all molecules, it may encapsulate some molecules. In 2003, Yudasaka *et al.* introduced two different methods to load molecules in the inner cavity of CNTs [96]. These two strategies have been defined as nanoextraction and nanocondensation, respectively, and they both allowed incorporating the fullerene (C60) molecule into CNTs in liquid phases. Therefore, CNTs may offer an inner hollow space for molecule loading, provided that their extremities are opened in order to make this cavity accessible to the drug but it is not possible for all molecules to go inside spontaneously, this process needs specific conditions. After all, it can be accepted that CNTs cannot encapsulate drug molecules if specific/necessary environmental conditions are maintained.

In the literature, a membrane made by CNTs has been prepared successfully [97,98]. Electroconductive carbon stickers [99] were also used to fix drug-adsorbed CNT membrane [46]. This preparation has been adopted to prepare an electroconductive [46,91] and drug absorbable [80] MWCNT membrane. This membrane has been proposed and used for *in vitro* experiments [46] and to treat experimentally developed cancers in mice [91] by applying small electrical current.

CNT membranes were also employed as an active element of a switchable transdermal drug delivery device that can facilitate more effective treatments of drug abuse and addiction [100]. Due to the dramatically fast flow through CNT cores, high charge density and small pore dimensions, highly efficient electrophoretic pumping through functionalized

CNT membrane has been reported to be achieved [100]. These membranes integrated with a nicotine formulation to obtain switchable transdermal nicotine delivery. The transdermal nicotine delivery device has been found to be able to successfully switch between high and low fluxes that coincide with therapeutic demand levels for nicotine cessation treatment [92].

6. Conclusion

All these data and results represented and discussed here show that CNTs can be used to deliver active drug molecules through skin successfully. Moreover, although all these are at the development stage, CNTs can also be used as it is. CNTs have quite large surface area to adsorb drug molecules and subsequently they can release the drug. Functionalization of CNTs and more developments are still available to apply. These applications will develop these systems and more opportunities for different applications will also be possible. CNTs are found to be suitable for drug transport being an adsorptive material and having high surface area. The CNTs investigated in the literature did not found to be penetrated through the skin but they have been reported to enhance skin penetration. The application of iontophoresis is also possible using a membrane made by CNTs.

7. Expert opinion

CNTs are unique materials being an electroconductive and adsorptive material. The electroconductivity provides an opportunity to make some electronical measurements possible and makes these materials interesting for especially biosensor applications and for the development. It also opens a door for us to make a smart device or delivery systems by controlling the drug release with electrical current applications namely iontophoresis. It has been shown that preparation of a membrane using MWCNTs is possible [80,91,97,98] and the mobility of ions within such CNTs membranes were found to be much higher than the bulk mobility [101,102]. Moreover, the induced electro-osmotic velocities are many orders of magnitude faster than those measured in conventional porous materials. It has been also shown that a nanotube membrane can function as a rectifying diode due to ionic steric effects within the nanotubes. All these positive information make CNTs very attractive but the main problem with the CNTs is biocompatibility and water solubility. It has been reported for them rather easier to be penetrated through biological membranes or to be taken up by endocytosis when living cells were exposed. We understand that PEGylation or adding water-soluble substrates make them water soluble and rather less toxic but some of the surface areas occupied with this molecules and available surface area will be decreased. Using CNTs appears to be the most logical approach at the beginning of the development stage. The way of administration is coming out as an important issue to decide. All experiments have been performed and current knowledge show us that the transdermal application will be the best approach because the outmost layer of the skin (stratum corneum) is already constituted from dead cells which are not capable to actively internalize any molecule, active endocytosis is not possible. Even if we think that any CNT has been taken up by any skin cell or penetrated through, the way of skin cell production is from inside to outside. Therefore, any internalized CNT will come out any way after a time. Therefore, CNTs will not be a big problem when used transdermally.

Finally, it can be said that CNTs are suitable for drug transport through, especially, the skin since they consist of an adsorptive material with a high surface area. The CNTs investigated so far did not penetrate through the skin layers, and their penetration enhancement can be possible via adsorption and subsequent desorption (i.e., depot effect). The application of iontophoresis is also possible using CNTs as adsorptive electrodes and they can be used for both water-soluble and -insoluble compounds. The feasible way to use CNTs to deliver drug molecules appeared to be transdermal way. More electronic development can still be applicable to these systems and it is believed that such development will be made in near future.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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