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Transdermal Drug Delivery: An Overview of the Evolving Field

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The skin acts as a barrier against infections and external agents. The transdermal drug delivery system (TDDS) is an innovative technological method to deliver drug molecules through the skin into the systemic circulation at an effective and protected rate. Although topical therapy plays an important role in the treatment of skin diseases, TDDSs differ in that they deliver drugs into the systemic circulation through the skin at a predetermined and controlled rate. Therefore, TDDSs are among the most suitable new drug delivery systems. It has many advantages over oral and parenteral drug delivery systems.[1-4] The main ones are: increased patient compliance, avoidance of the first-pass effect in the liver, ease of administration, minimal systemic exposure, potential to reduce the frequency of administration, no need for specialized personnel, and painlessness.[1,2,4-6] This technology has also been used to deliver both hydrophilic and hydrophobic drugs. Because of these advantages, pharmaceutical researchers have frequently focused on the development of TDDSs and increasing skin permeability via modification of the stratum corneum.[5] The disadvantages associated with TDDS are limited drug permeability, skin irritation, sensitization, and allergic reactions, inability to administer high doses of drugs, delayed effect, risk of dislodging the patches with water/sweat, and the risk of needle breakage in microneedle patches.[1,7-9]

TDDSs are rapidly developing technological systems. The first transdermal system containing scopolamine was approved in the USA in 1979, followed by the approval of nicotine patches by the US Food and Drug Administration in 1984.[9] Apart from nicotine and scopolamine, many drugs can be administered via TDDS, and these drugs have been approved for use in the USA and Europe. Nitroglycerin, estradiol, clonidine, fentanyl, asenapine, donepezil, testosterone, methylphenidate, selegiline, rotigotine, rivastigmine, and buprenorphine are examples of these drugs. This list is constantly expanding with the advances in technology.[1,2,5,6,8]

During the development of TDDSs, novel designs for transdermal patches to enhance drug penetration have been the subject of numerous studies. Depending on the different designs, TDDSs can also be classified in various ways. Developmentally, TDDSs have been classified as first-generation, second-generation, third-generation, and fourth-generation.[4] First-generation: diffusion-based transdermal drug delivery; these are systems based on natural drug diffusion through the skin, including the first transdermal patches. Most drugs of this generation are highly lipophilic. Research on first-generation TDDSs has focused on tailoring the physicochemical properties of chemical drugs. Second-generation: actuated non-invasive transdermal drug delivery; are systems that aim to increase the permeability of the skin to the drug using chemical enhancers or external energy sources. Chemical enhancers increase the penetration of the drug into the skin by interacting with proteins in the skin and increasing the solubility of the drug. Terpenes, fatty acids, surfactants, urea, sulfoxides, and alcohols are some examples of chemical enhancers. Chemical enhancers should be non-allergenic and non-irritant, provide rapid and consistent onset of action, and be biocompatible with the drug and excipients. Light, mechanical force, and magnetic fields are examples of external stimuli that can increase drug absorption. External devices in wearable forms can be integrated with drug-loaded patches.[10-12]

The action of most therapeutic agents is limited by the stratum corneum; therefore, few molecules can reach the site of action. Third-generation: minimally invasive TTDS provide more efficient delivery of hydrophilic drugs and macromolecules to the skin by controlling the destruction of the stratum corneum. The main technologies used in third-generation TTDS are microneedles and high-power energy modalities (radiofrequency, ultrasound, laser). Microneedle drug delivery systems have been developed with the problem of transdermal patching in mind and are considered to be a hybrid of both. The microneedle device consists of micron-sized needles placed on a small patch. Although microneedles can be of varying sizes, they are mostly 150-1500 microns in length, 50-250 microns in width and 1-25 microns in tip thickness. Microneedles can be triangular, pentagonal, cylindrical, etc. in shape and solid, coated, dissolving, hollow, and hydrogel-type. This technology exhibits positive features, such as faster onset of action, better patient compliance, and increased permeability. Because the needle size is very small, breakage of the microneedle tips can occur very rarely; however, this problem can be overcome with the selection of advanced materials. It can cause skin irritation and allergic reactions in sensitive skin. Fourth generation: controlled and feedback-driven TTDS that use smart technologies

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such as sensors and microcontrollers to monitor and control drug delivery in real time. Recently, wearable devices have recently made rapid advances. These advances enable personalized treatment based on the patient's physiological parameters.[2,4,7,13-15]

In conclusion, although TDDSs are very useful, there is a need to plan new research that focuses on solving shortcomings that have not yet been solved. In the future, the integration of smart technologies into personalized drug delivery is expected to increase the use of nanostructured carriers, such as lipid nanoparticles. With new developments in TDDSs, better dosing and increased patient compliance will be achieved, making it easier for healthcare professionals to treat diseases. The existence of around 900 trials using TTDSs on clinicaltrials.gov suggests that the number of drugs that can be used in this way will gradually increase.

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