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Research Article

Transdermal delivery of Non-Steroid Anti-Inflammatory Drugs (NSAIDs): a mini review

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ABSTRACT

The transdermal route has several advantages over the oral route, especially for the drugs which significantly experience first-pass effect in the liver. Another advantage of drug administration via the transdermal route is its non-invasive nature and can be used by patients themselves. In addition, it also allows long-term use, thereby increasing patient compliance and is generally inexpensive . The development of transdermal preparations itself is not easy because the permeability factor of drug ingredients through the skin is relatively low compared to the gastrointestinal route or mucous membrane because the skin is part of the body's defense system and prevents foreign materials from entering the body . The biggest challenge for drug administration via the transdermal route is the limitations of drugs that can be administered through this route. NSAIDs are drugs that are widely used in chronic conditions and can cause serious gastrointestinal side effects, therefore the transdermal route is expected to be a promising alternative in the future. The drug-loaded nanoparticles delivered using iontophoresis method can improve the bioavailability of NSAID drugs via the transdermal route.

INTRODUCTION

The drug delivery system via the transdermal administration is an interesting alternative compared to the per-oral and hypodermic injection that has been widely used. The transdermal route has several advantages over the oral route, especially if there is a significant first-pass effect in the liver. Compared with administering drugs with hypodermic needles that cause pain, produce dangerous medical waste, and transmission of disease due to repeated use of needles that occur in developing countries. Another advantage of drug administration via the transdermal route is its non-invasive nature and can be used by patients themselves. In addition, it also allows long-term use, thereby increasing patient compliance and is generally inexpensive (Prausnitz & Robert., 2008). These

characters attract many researchers in the field of Drug Delivery System to develop transdermal preparations for systemic therapy.

The development of transdermal preparations itself is not easy because the permeability factor of drug ingredients through the skin is relatively low compared to the gastrointestinal route or mucous membrane because the skin is part of the body's defense system and prevents foreign material from entering the body (Tomoda et al., 2011). Anatomically, the barrier to the penetration of medicinal substances through the skin is mainly caused by the stratum corneum which is the outer thin layer of the epidermis. In contrast to other body tissues, the stratum corneum consists of corneosytes (mainly formed by aggregation of keratin filaments) which are surrounded by extracellular lipids which are arranged as multiple lamellar lipid bilayers forming a structure often called brick and mortar. Naturally, the function of this lipid layer is to prevent excessive loss of water from the body. This layer will also prevent the entry of drugs that are used topically except for drug ingredients that are soluble in lipids and have a low molecular weight (Prausnitz et al., 2012). Drug molecules can penetrate the stratum corneum by going through three main routes including transccellular pathway which means to penetrate cells, Intercellular pathway that passes through the gaps between cells, and transacessory/ transappendageal pathway through skin accessories such as hair follicles.

The biggest challenge for drug administration via the transdermal route is the limitations of drugs that can be administered through this route. The administration of drugs via the transdermal route is still limited to drugs with the following characteristics: Molecular weights are limited to several hundred daltons, the octanol partition coefficient of water (log P) must be high enough - lipophilic in nature, and the dose needed in a day is not too high. So far, it is still difficult to develop drugs that are hydrophilic for the transdermal route although it does not rule out the possibility of further development, transdermal delivery systems are used for macromolecular such as proteins and genes (Prausnitz & Robert., 2008).

Among the efforts to increase the permeability of drug molecules to the stratum corneum is to create an occlusive layer (occlusive dressing) that will hydrate the stratum corneum by preventing evaporation from the surface and increasing the penetration of drug ingredients compared to dry conditions (Florence & Attwood, 2006). Formula modification can also be done by adding chemical penetration enhancers such as sulfoxide with examples of dimethylsulfoxide (DMSO), Pyrrolidone represented by N-methyl-2-pyrrolidone (NMP), fatty acids such as oleic acid, some types of alcohol and glycols such as ethanol and propylenglycol, terpenes and terpenoids are represented by menthol, limonone, and 1,8-sineol. Physical modification can be done with ionthophoresis techniques that increase permeability using electropotential energy, electroporation which makes small pores on the surface of the stratum corneum by providing certain voltages, sonophoresis using the effects of ultrasonic wave cavitation, and microneedles that create new permeation pathways. The use of chemical and physical enhancers has the risk of irritation, causing damage, and decreasing the function of skin barriers.

NANOPARTICULATE DELIVERY SYSTEM FOR ANTI-INFLAMMATORY DRUG

Efforts to deliver drug molecules or therapeutic agents through the stratum corneum while maintaining normal conditions are certainly preferred. For the purpose of the delivery of drugs with nanoparticles containing drugs (drug loaded nanoparticles) get more attention from researchers (Tomoda et al., 2011). In addition, nanoparticles too has other advantages over chemical enhancers because of its ability to sustain release drug at a certain time as well as a protective function against chemical degradation for encapsulated drugs. In order to deliver the drug optimally, then the drug must be released from its carrier and absorbed through the structure of the skin. The nanoparticulate alert system through the skin has been successfully developed including liposomes along with other vesicle systems, as well nanosized drug carrier system Carrier) a kind of Solid Lipid Nanoparticle (SLN), nanostructured Lipid carrier Carrier), polymer-based nanoparticles Nanoparticles), as well as magnetic nanoparticles. Evidence from recent research shows that in part large nanoparticle system - without regard material used - not across the stratum corneum, but predominantly it is through the route trans-appendageal for skin entry (Desai, Patlolla & Singh, 2010).

Only polymeric nanoparticles can do penetration to the surface of the stratum corneum, from there the encapsulated drug will be released to deeper parts of the skin. In addition to, Polymeric nanoparticles can accumulate in hair follicles, creating local

concentrations which is tall and can diffuse even further into parts Viable skin (Desai et al., 2010). Release of molecules drug from a polymeric nanoparticle system occurs through a controlled diffusion process or erosion from the core pass through the polymeric membrane or matrix. The membrane layer functions as a release barrier, because of the solubility and diffusivity of the drug ingredients inside the polymer is the determining factor for release. For developing a successful nanoparticle system, both the release and biodegradation of the polymer is an important factor that must be be considered. In general, the rate of drug release in the nanoparticle system depends on solubility of drug ingredients, desorption on surface / drug adsorption, diffusion of drugs through the matrix nanoparticles, matrix degradation of nanoparticles, and a combination of diffusion and erosion processes (Mudshinge, Deore, Patil & Bhalgat., 2011)

Generally delivery of drugs by mediation nanoparticles leading to the dermis and epidermis without barrier modification (stratum corneum) has levels small success. If this barrier problem can be overcome, then the penetration of particles also has the potential increased (Prow et al., 2011). That's why, in a study conducted by the Tomoda et al. Group combination of nanoparticles was also carried out ionthoporesis. Iontophoresis facilitates the movement of charged drug molecules towards the network is enhanced by the use of current electricity (Florence & Attwood, 2015). Iontophoresis increase the delivery of drugs through the skin with two principle mechanisms: electro-repulsion and electroosmosis. Electro-repulsion is a direct effect due to the application of an electric field to charged material which will carry on force generated by style reject the same charge. Second mechanism is electro -osmosis which is a displacement solvents due to differences in electric charge. At pH physiologically, the skin will be negatively charged (Dhote, Bhatnagar, Mishra, Mahajan & Mishra., 2012).

TRANSDERMAL DELIVERY OF INDOMETHACIN: Study by Tomoda, et al.

Indomethacin (IM) is a potent nonsteroidal anti-inflammatory as well as a strong analgesic, commonly used in conditions as diverse as rheumatoid arthritis, spondylosis deformans, and acute gout syndrome. However, the severe gastrointestinal side effects they cause limit the use of indomethacin in therapy. In addition, low solubility in water requires special formulation techniques. Indomethacin transdermal delivery has been extensively studied to avoid side effects on GIT and the central nervous system (El-Leithy, Ibrahim & Sorour, 2013). Physically, indomethacin has water solubility of 0.937 mg/L and octanol-water partition coefficient (log P) of 4.27 (Fini, Fazio & Feroci, 1995). In the division of Bioharmaceutical Classification System (BCS), indomethacin is included in class II which means it has low solubility but high permeability (Benet, Broccatelli & Oprea, 2011). So that the solubility of the active ingredient is a limitation in the absorption process.

Colloidal particles have been developed as a form of drug delivery system, including liposomes, micelles, SLN, inorganic nanoparticles and polymeric nanoparticles. The advantages of this form of colloidal delivery are the protection of less/unstable materials against degradation, as well as regulating the release of active ingredients from its carrier. Drugs should be released from their carriers in a constant ratio over a period of time. This is important because there are some drugs that are irritating to the skin at high concentrations (Tomoda et al., 2011). Poly (lactic-co-glycolic acid) or commonly referred to as PLGA is one of the most successful biodegradable polymers because hydrolysis of this polymer will produce lactic acid and glycolic acid monomers that are naturally present in the body and can be easily metabolized through the Krebs cycle, in addition to the systemic toxicity is also minimal (Danhier et al., 2012)

The effect of iontophoresis and nanoparticle systems is performed to determine changes in plasma levels of indomethacin. Systemic blood sampling from the heart as much as 1 mL in syringe with heparin is done at a certain time. Measurement of IM levels in plasma was carried out by HPLC ODS column at a wavelength of 254 nm. In addition, the skin part where the sample was applied was excised for observing the transdermal delivery route with the confocal laser scanning microscope at the excitation wavelength of 488 nm and the emission wavelength of 519 nm (Tomoda et al., 2011).

The test results showed that in the first 60 minutes, the concentration of IM increased due to the application of iontophoresis. After that the levels decrease gradually, while the IM levels in the muscles have increased up to 6 hours of use. Plasma IM levels shown in figure C show the initial increase in the first 60 minutes to 6 hours. From these results it appears that IM can be delivered efficiently to systemic circulation. When iontophoresis is not

applied, IM is detected in the skin, muscles, and plasma after 6 hours of testing, slower than iontophoresis. Therefore, researchers conclude that the combination of iontophoresis and nanoparticles can increase the delivery of IM through the skin (Tomoda et al., 2012). The combination of nanoparticles containing drugs with iontophoresis has more advantages because the charged na nanoparticles will be delivered by this technique. Not only are charged drug ingredients that can be delivered if the drug is encapsulated in charged nanoparticles, neutral drug ingredients can also be delivered through this technique (Tomoda et al., 2011).

As explained earlier, the route of penetration of a material on and through the skin consists of intracellular, intercellular, and transaccessory or transappendageal routes. In a previous study, Tomoda et al. reported that gold nanoparticles with a diameter of 100 nm can easily penetrate the skin and accumulate in deep skin parts (Tomoda et al., 2011). Particles smaller than 3 microns are reported to penetrate the skin through the transacessory pathway. In this paper, the researchers stated that coumarin-6 was chosen as a marker for nanoparticles because of its nature that is difficult to remove, so that the nanoparticle's footprint and the route taken through the skin can be properly tracked through its luminescence (Tomoda et al., 2012).

After two hours of permeation studies of PLGA-IM nanoparticles with tophoresis ions, a picture was obtained showing that nanoparticles were detected in the follicle and epidermis, and luminescence was difficult to detect in the dermis. on the other hand, when PLGA-IM nanopaticles are not used in combination with iontophoresis, almost no fluorescence is detected. This is also supported by measurements of IM levels in the skin which are twice as high as iontophoresis. Coumarin-6 is more hydrophobic than IM, therefore the interaction between coumarin-6 and PLGA nanoparticles is higher than IM and PLGA, so that luminescence can be interpreted as the location of the nanoparticles. From this it appears that nanoparticles accumulate in the epidermis, then IM is released into the muscles and blood circulation. The dominant pathway in the permeation of PLGA-IM nanoparticles is through the follicle (Tomoda et al., 2012).

CONCLUSION

The combination of drug-loaded nanoparticles with iontophoresis can provide better benefits. Charged nanoparticles can be delivered through iontophoresis. The fact that IM can be delivered effectively to the systemic circulation shows that this technique can be applied to delivery through the skin.

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