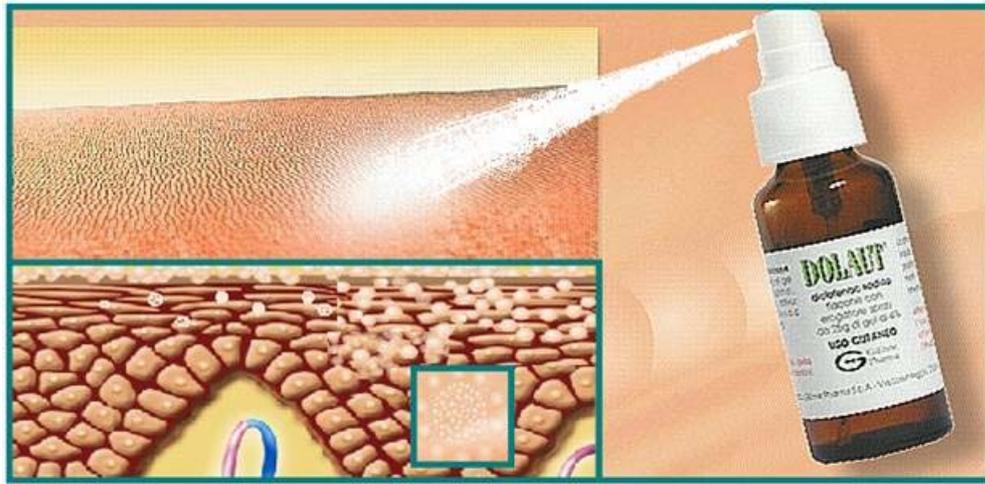


Noninvasive Transdermal and Transmucosal Drug Delivery Technologies

Introduction

Systemic therapy with pharmaceutical actives often causes severe side-effects, e.g. gastrointestinal bleedings in case of the most prominent representatives of non-steroidal anti-inflammatory drugs (NSAIDs) million fold used every day in the treatment of pain and inflammation.

Therefore a local administration of e.g. NSAIDs is advantageous for the treatment of local pain or inflammation processes. However, the main hurdle to be overcome with such a local administration is penetration by the drug of the skin barrier.



Mechanism of skin penetration

The skin has an extremely good barrier function, and to improve topical bioavailability it is usually necessary to employ enhancement strategies.

Based on the current scientific knowledge, it appears very likely that drug penetration into and through the skin involves a most complex interaction of various mechanisms and factors, such as diffusion processes of the active along chemical and/or electro-chemical gradients and sophisticated interactions of certain formulation ingredients with special components and structures of the skin.

Safety aspects of drug delivery systems

Overcoming the barrier function of the skin already poses a great challenge to modern drug delivery systems, but no less important are safety and tolerability aspects. In the past, many common drug penetration enhancement strategies turned out to destroy the natural barrier function of the skin and cause irritations and other partially severe side-effects. Therefore, right from the beginning MIKA Pharma GmbH (www.mika-pharma.de) has focused on the development of primarily safe and efficient drug delivery technologies.

The safety of MIKA's drug delivery technologies was assessed in a large number of preclinical and clinical trials, as well as during routine use over a period of more than 6 years, covering treatment in more than 3 million patients in various countries for 30 million days. Only a handful of non-serious adverse drug reactions were observed.

Up to 20fold improved skin penetration rates

With respect to drug transportation, MIKA's drug delivery technologies proved to exhibit up to 20fold increased penetration rates compared to worldwide leading conventional topical ointments and gels.

Regulatory demands and production costs

However, even proven and superior efficacy and safety do not make a successful international drug delivery technology. New products developed on the basis of MIKA's technologies comply with all international regulatory demands and allow production at competitive costs in comparison to even conventional ointments and gels.

MIKA Pharma GmbH - together with experienced and reliable contract manufacturers, producing under international GLP and GMP conditions (incl. FDA compliance) - has established production facilities guaranteeing production capacities for the world market.

Experience and Reliability

MIKA Pharma GmbH started its research on transcutaneous delivery in the 1990s and was the first company worldwide to develop a stable topical liposomal product in the pharmaceutical field (the liposomal MIKA-heparin-spray). Further extensive investigations led MIKA Pharma GmbH to develop even more favorable drug delivery systems on the basis of highly innovative proprietary and special microemulsions, and later even brand new nanoemulsions.

Major licensing deals have been successfully completed with top 10 intl. pharmaceutical companies (human as well as animal health sector).

MIKA™-liposome spray technology

Since their discovery by Sir Alec D. Bangham in 1961, liposomes and their potential use as drug delivery vehicles have been investigated by almost all scientific groups in industry and academia. Nevertheless, until today only a few pharmaceutical liposomal products have been approved and marketed. Lack of stability and extraordinary high production costs have turned out to be the main obstacles for these promising new drug carriers.

In 1995 MIKA Pharma GmbH was the first company worldwide to introduce a stable topical liposomal product to the pharmaceutical market (the liposomal MIKA-heparin-spray) and to manufacture it on an industrial scale with competitive production costs.

Based on the MIKA™-liposome spray technology, this technology has proved capable of transporting even a macromolecule like heparin through the skin barrier.

MIKA™-spraygel technology (aqueous nano/microemulsion spray)

Microemulsions are clear, stable, isotropic liquid mixtures of oil, water and surfactant, frequently in combination with a cosurfactant. Microemulsions are highly dynamic systems in which contained substructures are subject to permanent destruction and rebuilding. Structures, as for instance detected by electron microscopy, thus simply reflect a momentary condition or structure. Over the last few years there has been a steadily increasing interest in the pharmaceutical use of microemulsions as drug delivery systems. MIKA™-spraygel technology is based on a very special type of microemulsion and offers the potential to create emulsions on the nanometer scale far below 20 nm.

As a drug delivery system it offers the following features:

- much enhanced penetration and permeation of pharmaceutically active substances through the skin barrier
- creation of a drug depot guaranteeing a long-term effect at the target site and thus reducing the frequency of dosing and the total treatment time
- improved benefit/risk ratio (reduction in side-effects by prevention of toxic plasma concentrations)
- higher product safety by more accurate dosage, due to the more exact spray system

- rapid penetration of the whole formulation into the skin without leaving a residual fatty surface film (making surgical dressing unnecessary)
- no need for additional gelling substances, known to inhibit drug penetration
- no need for additional preserving substances, causing further problems in patients with allergies
- no gastro-intestinal or hepatic first-pass effects
- minimal risk of gastro-intestinal side-effects

MIKA™-SILEC technology (non aqueous reversed micellae spray)

The non-aqueous and non-greasy MIKA™-SILEC technology offers the potential to formulate, for instance, pharmaceutical actives known to be sensitive to chemical degradation in aqueous solutions. So far such actives have been offered with either very greasy or fatty ointments or in solutions or gels with a very high alcohol content (irritation potential). The MIKA™-SILEC technology is a very elegant and cosmetically attractive reversed micellae spray technology employed so far in various projects within the dermatological field (corticosteroids, antimycotics and biologicals). In two cases its good drug transportation capabilities have allowed the concentration of the contained corticosteroids to be significantly reduced.

Noninvasive rapid systemic drug delivery

Over the last ten years there has been a particular interest in delivering drugs via the buccal/transmucosal route. This route offers

- a very fast and direct systemic bioavailability
- thus avoiding the hepatic first-pass effect and degradation in the gastrointestinal tract,
- a relatively permeable mucosa with a rich blood supply,
- ease of administration,
- high patient acceptance for administration into the oral cavity,
- and safe administration since the virtual lack of Langerhans cells makes the oral mucosa tolerant to potential allergens.

With the development of this new drug delivery technology (MIKA™-RAPOSAL technology), MIKA Pharma GmbH has gained many additional strategic opportunities to develop innovative products, such as fast-acting pain relievers.

MIKA-diclofenac-spraygel

Diclofenac is one of the most prominent representatives of non-steroidal anti-inflammatory drugs (NSAIDs) used in the treatment of rheumatic disorders and other pain and inflammation-related conditions. NSAIDs exhibit antipyretic, analgesic, central antinociceptive effects and anti-inflammatory properties by efficiently inhibiting cyclooxygenase activity in a reversible manner and thus decreasing prostaglandin synthesis.

Systemic therapy with non-steroidal anti-inflammatory drugs often causes gastrointestinal and other severe side-effects.

In September 1999, MIKA-diclofenac-spraygel was brought onto the Italian market (under the tradename DOLAUT by GiEnne Pharma S.p.a., Milan) with great success and rapidly increasing sales figures. The product had been authorized for indications involving painful, inflammatory, rheumatic or traumatic complaints in the muscles, joints or tendons. Already, preclinical tests have shown up to 10fold increased penetration rates compared to worldwide leading topical NSAID ointments and gels (ex-vivo skin permeation study with human abdominal skin - see figure) and outstanding tolerability. In 6 phase I trials the safety and high and long-term tolerability were investigated, later confirmed by more than a million patients. Furthermore, a clinical phase III, multicenter placebo-controlled, randomized, double-blind study (n = 230) has successfully been completed, showing significant reduction in pain and swelling under treatment with verum in comparison to placebo.

MIKA-ketoprofen-spray

Ketoprofen is a highly potent and safe nonsteroidal antiinflammatory drug (NSAID) of the propionic acid derivative group with analgesic and antipyretic effects. Ketoprofen has a short half-life, a simple metabolism, and a broad therapeutic window. These features contribute to a rapid onset of action, flexible dosing, and a reliable tolerance profile. The pharmacodynamic and pharmacokinetic properties of ketoprofen clearly distinguish it from other non-steroidal anti-inflammatory agents.

The mechanisms of action for the nonsteroidal anti-inflammatory drugs (NSAIDs) have not been completely illuminated. The primary mechanism of action for ketoprofen is considered to be inhibition of the cyclooxygenase pathway of arachidonic acid metabolism, leading to decreased production of prostaglandins.

Based on in vitro experiments, ketoprofen is considered one of the more potent inhibitors of prostaglandin synthesis.

MIKA-ketoprofen-spray is based on one of MIKA's innovative drug delivery systems guaranteeing a fast and efficient transdermal delivery of the active to the target tissue.

During the development of MIKA-ketoprofen-spray the safety aspect was also analyzed first. A dermal tolerability study of MIKA-ketoprofen-spray in piglets of domestic swine confirmed the category non-irritable on the base of clinical and histological examinations. In phototoxicity- and photosensitization studies with MIKA-ketoprofen-spray in guinea pigs, neither verum nor placebo revealed any phototoxic- and photosensitization properties. While the clinical program is still on-going, first marketing authorizations have been obtained in 6 countries and in the meantime the product is launched in 4 countries already.

MIKA-heparin-spray

Heparin modifies the physiological processes of blood clotting by influencing various aspects of enzymatically catalyzed reactions involved in the coagulation cascade.

Results obtained with topically administered heparin demonstrated markedly increased thrombolysis (Tauschel et al, 1984). Kuglmeier (1990) concluded from his experiments with topically applied heparin a significantly increased reabsorption of induced hematomas, and thus healing of subcutaneous wounds accompanied by hematomas may be greatly accelerated by intensive topical application of heparin ointments.

In summary, the therapeutic efficacy of many heparin preparations following topical application has been investigated in numerous valid clinical trials; the results demonstrate that the tested preparations are effective in the adjuvant therapy of:

- acute swellings following contusion traumas (preparations containing at least 30,000 IU/100g superficial thrombophlebitis
- in as far as the disorder cannot be treated using compressions (preparations containing at least 60,000 IU/100 g)

The administered heparin (pig mucosa) is effective in deeper skin areas where injured tissue is regenerated. Improved microcirculation within the treated area is indication of bioavailability and efficacy as well as the increased rate of regeneration (see following figure). Within this 5-day treatment Artmann et al. (1995) demonstrated an improvement in microcirculation of 220% as compared to placebo and untreated cases. In comparison to conventional gels the microcirculation was improved by a factor of 4.

For more information please visit
www.mika-pharma.eu