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NANOTECNOLIGIA EM DERMATOLOGIA

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RESUMO – Os últimos avanços em nanotecnologia revolucionaram os conceitos de prevenção e tratamento de algumas afeções cutâneas. O uso de nanopartículas e micropartículas em cosmética e terapêutica preventiva é cada vez mais utilizado.
Menos conhecida mas muito investigada e utilizada é a aplicação de nano e micropartículas em materiais que contactam a pele, tais como vestuário, papel, equipamentos diversos, peles de animais, betão, vernizes, tintas, etc.,.
PALAVRAS-CHAVE – Infeções bacterianas; Nanopartículas; Nanotecnologia; Pé diabético; Pérnio; Repelentes de insetos.

NANOTECHNOLOGY APPLIED TO DERMATOLOGY

ABSTRACT – *The use of the latest advances in nanotechnology has revolutionized the way towards prevention and treatment of some skin affections. The use of nanoparticles and microparticles in dermatology with a cosmetic, preventive and therapeutic aim is becoming increasingly common.*
Less known but also thoroughly researched and used is the application of several active nano and microparticles in materials that are in contact with the skin, such as clothing, paper, various types of equipment used in everyday life, furniture, concrete, varnishes paints and so on.
KEY-WORDS – *Bacterial infections; Chilblains; Diabetic foot; Nanoparticles; Nanotechnology; Insect repellents; Diabetic foot.*

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INTRODUCTION

In nanotechnology, particles are classified according to their diameter. The term microparticles is applied when they comprise sizes between 100 and 2500 nanometers. For dimensions inferior to 100 nanometers the term nanoparticles is used.

The use of the latest advances in nanotechnology has revolutionized the way towards prevention and treatment of some skin affections. The use of nano and microparticles in dermatology with a cosmetic and therapeutic aim is becoming increasingly common.

Less known but also thoroughly researched and used is the application of several of these active principles in materials that are in contact with the skin, such as clothing, paper, various types of equipment used in everyday life, furniture, concrete, varnishes and paints for example.

Clearly, once the active principles are in contact with the skin, they must combine excellent efficacy with good tolerability. Moreover, they must be eco friendly, hence, non toxic to the environment once degraded and eliminated for the ground and the water courses.[1] Finally, they must be resistant to washing.

Obviously, the effectiveness and tolerance of the products used must be appropriately guaranteed by internationally accredited institutions.

The use of microcapsules for this purpose is not a good solution, since they do not resist or withstand manual washing, neither machine washing due to friction and consequent

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rupture of the capsules. The capsules will break and the product is released rapidly. Consequently, its action time is very short, normally less than 50% of initial efficacy concentration after five washings.

The ideal vehicle are solid particles, which maintain the active principle fixed to the surface being slowly released, so that effective concentrations are maintained after one hundred washes.

It is usual to compare the microcapsules to a ping-pong ball in which the active ingredient is contained inside acting only when the container is broken, and to compare the microparticles to a golf ball where the active principle fixed in the irregularities of the surface is released slowly and not in its entirety at once.

Our technology is very affordable and easy to use.

We use over the counter natural and synthetic chemicals. Our advantage is in the way we place them in the finished products making them resistant to some ten washes without loss of efficacy.

In the case of fabrics, the silica particles to which the active principle is added are applied during the manufacture in padding, in the form of solution in the finishing stage. It can also be used in industrial washing machines or tumblers, in the spray-drying stage.

Impregnation can also be carried out in household laundry washing machines or even in a plastic bucket. However, in the latter case, the active principle is kept with high efficacy to twenty washes.

In solid surfaces, like walls and desks, we can apply bactericides and/or insect repellents as paint or varnish, maintaining its efficacy over a minimum period of four years.

For medical supplies such as computers, stethoscopes, sphygmomanometers and devices used for diagnosis and treatment in healthcare, the application is made in the form of spray. However, in this method, the durability of the effect lasts four to five hours with high efficacy and reloading will be necessary.

This report will not consider the applications in cosmetic and therapeutic nanotechnology but rather the use of active principles in materials in contact with the skin.

All the ingredients cited in this report were tested in thirty volunteers by a internationally accredited pharmaceutical research group in order to detect an eventual irritant or allergic skin reaction (*Inovapotek*, Portugal).

Let us look at some potential applications.

ANTISEPTICS

Antibiotic resistance is a big problem nowadays.[1-3] The use of nanoparticles is being studied as a potential alternative to antibiotics as the microorganisms are unable to develop resistance against nanoparticles.[1]

Nanoparticles bind to bacterial cell walls causing membrane disruption through direct damage or through free radical productions.[1] In the interior of the cells they bind with mitochondrial DNA, enzymes that control respiration and other fundamental functions or with membrane receptors and cause cell death.[4]

Some bacteria produce biofilms that protect them against antibiotics. This antibiotic-resistance can be solved with nano and micromaterials that cross the biofilm and the bacterial membrane and generate reactive oxygen species that kill the bacteria.[1,4-7]

Various chemical, physical and natural nanoparticles and microparticles have been studied for improving bacteria and biofilm penetration.

Antiseptics which have a large antimicrobial spectrum and are very well tolerated can be fixed in fabrics like bed clothing, pajamas, t-shirts, shorts, stockings, diapers, towels, mattresses, drapes, turbans, paints and so on. In materials that are rarely washed like mattresses, the antimicrobial effect keeps for a few years.

Several antimicrobial chemical finishes grasped the attention of health professional and textile manufacturers, but there are some environmental concerns regarding antimicrobial finishing of textiles.[8-10]

Silver, for example, has an excellent antibacterial spectrum. Continued exposure to the silver nanoparticles, even in low concentrations, interferes with the microsomal function on producing energy to the cell and causes cellular death.[9,10]

Nevertheless, silver is not an eco friendly substance, especially for the marine fauna and flora.[13,14] Effectively we must consider that all the products applied in fabrics are spread in the environment through washing water, contaminating the land and the water courses.

Ammonium quaternary compounds are another excellent solution.[15-18] Nevertheless it is not easy to incorporate them in fabrics with our technology. We are still doing new tests and so far, it has been possible to maintain an efficacy of 72% after more than fifty washes.

Zinc oxide and titanium dioxide are being used worldwide in consumer product applications. The toxicity of zinc oxide and of other metal oxides towards human beings has not been observed in low concentrations.[4] This product is easily applied in a lot of materials and has the advantage of being very cheap. *In vitro* studies, confirm the efficacy of zinc oxide and titanium dioxide against *Pseudomonas aeruginosa* and *methicilin-resistant Staphylococcus aureus*.[3] Our testing with zinc oxide microparticles proved an efficacy of 99% on *Staphylococcus aureus* and 100% on *Klebsiella pneumonia* (*Citeve*, Portugal).

Infectious conditions like pyodermatitis, miliaria rubra and papulo-pustulous acne of the dorsum, can be prevented and

even improved by incorporating zinc oxide microparticles in clothes.

Atopic dermatitis can also benefit from reducing skin bacterial colonization by *Staphylococcus aureus*.[19-21]

Diaper dermatitis follows skin barrier damage by urine and fecal bile salts which create humidity and ammonium hydroxide, raising the pH level. Elevated pH and mechanical friction from the movement increase the skin irritation and alkaline and wet skin is easily colonized by microorganisms. *Candida species, Bacillus faecalis, Proteus spp, Pseudomonas spp, Staphylococcus aureus* and *Streptococcus spp* are the habitual contaminants. Powders, oils and ointments can be irritants and worsen the diaper rash.

In our experience, diapers treated with zinc oxide microparticles prevent the diaper rash and the odors from the perspiration in old people who are bedridden over a long of time.

Bad odor, which is related the chemical degradation of the sweet components by bacteria present in the skin, can be eliminated with a t-shirt containing zinc oxide microparticles. If the bad odor occurs in the interior of a labor glove in people suffering from excessive perspiration, we can control that. In fact labor gloves are rarely washed and if an antiseptic is incorporated in the lining, it will persist over a long period of time limiting the degradation of the sweet components.

Nosocomial infections can be more easily to control with biocides used in healthcare environment, mainly for the sterilization of surfaces, water, equipment and sterilization of medical devices.[1,4,22]

When used on hospital walls as paint and on medical devices, beds, litters and tables as spray, these antimicrobials can reduce nosoconial infections.[1,20] We can improve the efficacy of the paint with the association of zinc oxide with an antifungal product.

The development of nano and microparticles covering the surfaces of ambulatory and other medical devices, capable of penetrating the bacterial biofilm and the bacterial membrane, would provide an excellent alternative to decrease the microorganism colonization and device-associated infection, including methicillin-resistant *Staphylococcus aureus*. These can be obtained with some physical, chemical and natural ingredients.[1,4-7,11-15,18,19]

Ventilated associated pneumonia, central venous catheter infections and catheter-associated urinary tract infections could be controlled by this way.[1,4] Some studies prove that the application of zinc oxide polymer composites may improve biomaterial effectiveness for endotracheal tubes, catheter and implanted devices, which are prone to bacterial infection.[1,4]

In our experience, when zinc oxide is incorporated in paints with our technology and applied on walls, the antiseptic efficacy is kept for more than five years.

Some natural products have an important antimicrobial effect.[23-26] Antibacterial efficacy of these ingredients can be improved through the combination of the bactericidal ingredient with natural products, like tea tree oil which have a broad-spectrum antibacterial, antifungal, antiviral and anti-inflammatory proprieties.[27,28]

MOSQUITOES AND BED BUGS REPELLENTS

Some of the agents of several deadly diseases, including malaria, dengue fever, yellow fever, chikungunya and encephalitis are carried by mosquitoes.

The use of pesticides to control mosquitos is not a good solution because they can disrupt the fauna and flora balance, so they are not eco friends.[29,30] Recent reports in the media refer to honeybees abandoning their hives and dying due to the use of insecticide. Moreover pesticides can induce serious adverse effects in human beings. Recently some studies have found increased prevalence of cognitive, behavioral and psychomotor dysfunction in individuals chronically exposed to pesticides.[31]

Neem oil for example, reduces insect feeding and acts as a repellent but also interferes with insect hormone systems making it harder for insects to grow and lay eggs. By this fact it is a pesticide and its use is not forbidden in CEE (Directive 91/414 CEE).

Numerous essential oils were found to possess repelling properties but only five products were approved by the Environmental Protection Agency (EPA) and the Center for Disease Control and Prevention (CDC) as having low toxicity and safe protection.[32,33]

One of the more common synthetic active on the market is N,N-diethyl-m-methylbenzamida (DEET) because of their long-lasting protection. DEET has been implicated as a factor in neurotoxicity illness due to a large absorption of the chemical through the skin.[4,34-39]

Another chemical is picaridin that is slightly toxic by ye, dermal and oral mucosa absorption.[4,35-37]

IR3535, also considered a synthetic active, is not insecticide and shows no harmful toxicity when ingested, inhaled or used on the skin and mucosa.[4,38,39]

Citronella is a natural chemical that shows little toxicity but may cause skin irritation and citriodiol, a para-menthane-3.8--diol (PMD), can cause eye irritation.[4]

The big problem is that almost all of the cited products can be insecticides, disrupt the natural insect fauna and can enhance skin cancer.

The ideal repellent must be efficient, well tolerated when in contact with the skin and when inhaled and it must not inflict environmental toxicity. Moreover, it must not have an insecticidal effect so as not to cause ecological imbalances.

Insect repellents can be incorporated in clothes, swimsuits, bracelets, hats, bath towels, picnic utensils, sun umbrellas,

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veils, turbans, drapes, sofas and so on.

When applied in fabrics in industrial phase with our technology by padding (immersion) the repellence maintains for more than an hundred washings. The repellent can also be incorporated in new and used fabrics on a tumbler (pulverization and drying) with the same durability.

The product can also be incorporated in paints and varnishes. Once dried, it remains effective for over a period of at least 4 years. The same happens when it is incorporated in decorative ceramic materials and others, perfect to keep insects away in socializing environments.

In home environments, the repellent can be applied by dipping the fabric into a basin containing the product dissolved in water for one minute or by using it in the washing machine. Once dried, clothes remain repellent to mosquitoes after twenty washes. In a spray form repellency lasts until clothes are washed again. In bracelets that can be worn on the wrists or ankles repellency lasts two weeks and in paper wipes it lasts five hours.

Our insect repellent has shown 98% mosquito repellency against *Aedes egypti* (*Siri Life Sciences*, Bangalore, India).

Bed bugs (*Cimex lectularius*) infestations are rapidly increasing worldwide. They can be potential disease vectors and have been implicated in cutaneous and systemic reactions.[38,39] Cutaneous reactions can start out as small macular lesions that develop into wheals and occasionally bullous eruptions, which are accompanied by intense itching. Widespread urticaria and erythematous rashs can be seen.[38,39]

These products can also exercise repellence against bed bugs and other arthropods implicated in dermatoses like prurigo simplex and prurigo nodularis. So, it is possible to prevent to some degree the incidence and the intensity of the hives when used for example in pajamas.

Our testing evaluating repellency by counting the number of bed bugs on treated heat packs versus non-treated heat packs has shown good repellency effect (*Siri Life Sciences*, Bangalore, India).

We have also tested the repellence against termites in paints and varnish treated with our repellent with excellent results: 90-99%.

MITE REPELLENTS

Mites are microscopic insects invisible to the naked eye belonging to the *Arachnida* family, found in large quantities in bed clothing.

People who are allergic to mites and especially to their carcasses and droppings can suffer reactions via inhalation, such as allergic rhinitis and asthma, and by direct contact, such as allergic conjunctivitis and atopic dermatitis.

Acaricides do not prevent the accumulation of carcasses of mites or their droppings which are the main cause of intolerance reactions, so they are a deceitful solution. Furthermore, since they are usually in spray form, they should be applied with caution as they are toxic and potentially harmful to the human body. This means that it is necessary to air out the rooms for a few hours after the application in order to avoid adverse reactions when applied frequently and in great quantities in bedrooms.

The best solution is to incorporate a mite repellent in the bed clothing, pajamas and mattresses which does not kill the mites but simply keeps them away, thus making exposure to their antigens truly reduced.

Tests were performed with material gathered in different divisions of a house and in fabrics impregnated with a synthetic ingredient to evaluate the repellency effect on two species of dust mites, *Dermatophagoides pteronyssinus* and *Dermatophagoides farina*. The results showed a repellency effect of 92.25% for the first and 85.8% for the second (Insect Research Development, Cambridge, England). In the non-impregnated fabric the repellency was null. Furthermore, the product showed a large antifungal activity and good insect repellence for bed bugs (Instituto de Higiene e Medicina Tropical, Portugal). This mite repellent bound to bed clothing, pajamas, shorts, diapers and t-shirts resists at least an hundred washings with our technology

Other applications of these repellents are on carpets and furniture. Carpeting provides a perfect environment for dust mites. Fig. 1 reproduces the presence of nanoparticles in samples removed from carpets pulverized with our mite repellent showing good concentration of nanoparticles.

Our experiences confirm the efficacy of these repellent in the prevention and reduction of hives in atopic patients.

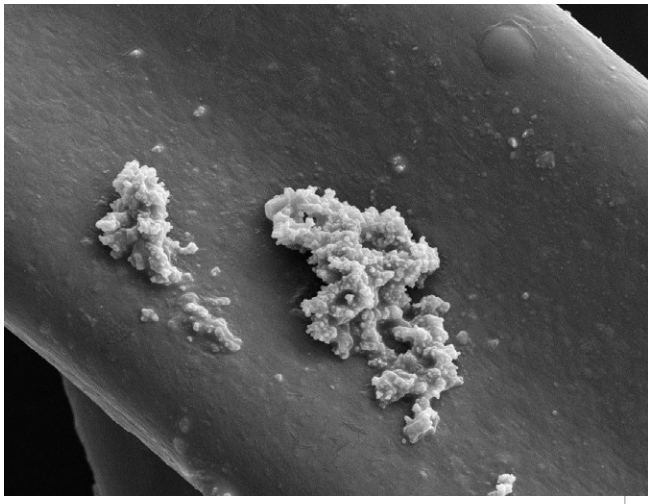

Fig 1 - Nanoparticles in samples removed from carpets pulverized with mite repellent.

TINEA CRURIS AND TINEA PEDIS

Products with antifungal activity can be incorporated in shorts and stockings in patients suffering from recurring fungal infections, as a preventive measure.

Some physical, chemical and natural products have antifungal proprieties. When our nanotechnology is applied in shorts and stocks the product maintains its antifungal efficacy for about fifty washes.

Our antifungal ingredient is also an excellent antimicrobial and can prevent secondary bacterial infection.

PERNIOSIS (CHILBLAINS)

Chilblains occur in predisposed individuals exposed to cold and humidity. This causes skin damage and the occurrence of redness, itching and blisters in the extremities.[42,43]

The best solution is the use of gloves and/or socks impregnated with one or more products with vasodilators and anti-inflammatory properties, without inducing skin irritation. This goal can be reached with some natural ingredients that increase the local blood efflux and have anti-inflammatory effects.[44-54] Furthermore, some of these natural ingredients have an antiseptic and antifungal activity.

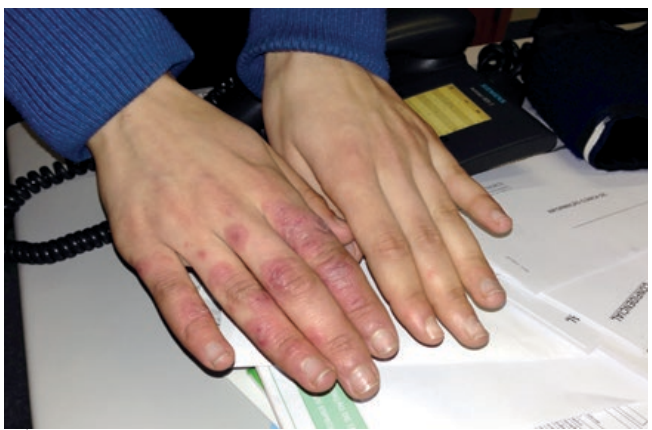

Fig 2 - *Patient suffering from chilblains one week after using a glove impregnated with a vasodilator and anti-inflammatory natural ingredient (left hand).*

In Fig. 2 we can see the hands of a patient suffering from chilblains one week after using a glove impregnated with a vasodilator and anti-inflammatory natural ingredient only in the left hand. The difference between the two hands is evident. This efficacy resists about fifty washings.

DIABETIC FOOT PREVENTION

Diabetes *mellitus* is a serious problem at a global level. It is the sixth leading cause of death in the United States of America. The number of affected people is constantly increasing.

There are several factors involved in the genesis of pathological changes occurring in the diabetic foot. The most important one is vascular insufficiency with decreased blood flow to the tissues due to thickening and narrowing of the arterial vessels.[55-57] Also, at least half of the patients with diabetes develop some type of neuropathy.

Neuropathy responsible for the decreased cutaneous sensitivity is largely the result of poor nutrition of the nerve endings, but also degenerative alterations pertaining to the condition. Finally, deficient inflammatory reaction due to the partial or complete blockage of the influx of repairing immune cells to tissues increases susceptibility to infection.[58]

Hyposensitivity due to the neuropathy allows patients to injure themselves without realizing it. The changes in sensitivity lead to deformations and calluses in the feet and result in poor distribution of body weight on plantar regions. These calluses precede the onset of ulcers which are then infected almost always by several microorganisms. The reduced defense ability of the ischemic skin allows the infection to perpetuate itself.

Several biochemical abnormalities can induce and accelerate vascular and neurological changes in the diabetic foot. One of the most important is hyperglycemia which damages the endothelium of blood vessels and inhibits the production and activation of nitric oxide synthase, a crucial element in the mechanism of arterial vasodilation. Dyslipidemia, insulin resistance and oxidative stress are other crucial elements in the genesis of endothelial dysfunction and cell damage.[53]

Some natural ingredients have a strong vasodilator and thrombolytic effect therefore contributing to removing of the obstruction of small subcutaneous vessels.[44-54,72] Some of them can even enhance angiogenesis.[54,59]

Furthermore, they prevent damaging of mitochondrial material of the endothelial cells by oxidative stress, avoiding damage and subsequent cell death after oxygen glucose deprivation.[50]

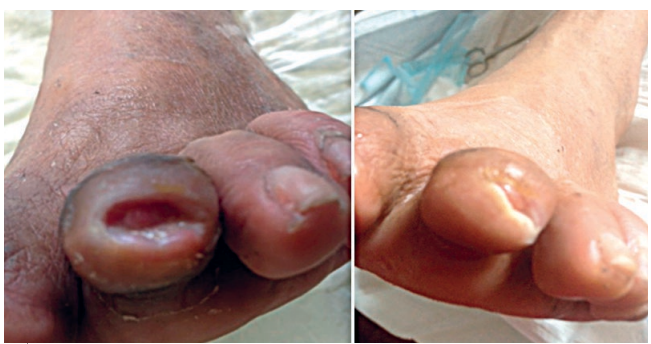

Fig 3 - *The foot of a patient suffering from diabetic ulceration before and one month after using a sock impregnated with a vasodilator and anti-inflammatory natural ingredient.*

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These ingredients have also a delaying or even repairing effect on the occurrence of neuropathy, as a result of the improvement of the vascular support and by direct action on the nerve endings. Effectively some natural ingredients protects the neurons from oxidative stress and reduce the ischemic damage by multiple mechanisms, inhibiting apoptosis.[60-72]

These natural ingredients also contribute to decrease local glycemic levels and have a potent antioxidant effect and, by consequence, anti-inflammatory properties.[73]

Lastly, some of them have an antibacterial effect over *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and other bacteria, contributing towards the prevention of secondary infections on the diabetic foot. They also have some activity against fungus.

With our technology the product remains effective after fifty washes.

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