NANOCARRIERS FOR ANTITUMORAL DRUG DELIVERY IN SKIN CANCER THERAPY

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Abstract. *Nanomedicine represents one of the most active research areas of nanotechnology. Nanotechnology has found applicability in nanomedicine for diagnosis, prevention and treatment of various diseases, in particular cancer. Over the last few years, researchers have agreed with the incorporation/association with markers or antitumoral drugs into/with nanoparticles, with the aim to detect, prevent and treat cancer. The multiple advantages of nanoparticulated drug carrying systems consist in reducing drugs metabolism, improving bioavailability and diminishing immunogenicity. Within the present work, we have presented the most recent discoveries in the utilization of various types of nanoparticles for the treatment of skin cancer. The advances in the nanocarriers treatment of basal cell carcinoma, squamous cell carcinoma and melanoma have been reported.*

Keywords: antitumoral drugs, melanoma, nanocarries, nanoparticles skin cancer**.**

Introduction

One of the leading causes of death worldwide remains cancer (Aruna et al., 2013). Over the past several decades a significant progress has been made in the fundamental knowledge of cancer biology, diagnostic and treatment methods (Ruoslahti et al., 2010). Skin cancer is one of the most common of all cancer types and if it is detected early it can be treated effectively. Each year in the United States of America more than 3.5 million cases of non-melanoma skin cancer are diagnosed and this year, 2015, more than 73.000 cases of melanoma (ACS, 2014a) are expected to be diagnosed. At the same time, in Europe, malignant melanoma is also the most common cause of cancer death, with almost 22.200 deaths in 2012. Norway and Slovenia have the highest mortality rates in men, respectively women, while Albania and Malta have the lowest death rates for men and restively women (Ferlay et al., 2013).

The terminology of skin cancers is in accordance with the cells they arise from and their clinical behaviour. There are three general types: basal cell carcinomas (BCCs), squamous cell carcinomas (SCCs), both referred as non-melanocytic skin cancer-NMSC, and cutaneous malignant melanomas (CMs), the latter known as

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malignant melanoma of the skin or melanoma. From all skin cancer cases, melanoma accounts for less than 2% and the incidence rates have been increasing in the last 30 years, particularly in the white population (ACS, 2014b). The incidence of cutaneous malignancies has been growing and, in this way, we can explain the need for multiple treatment options (Simoes et al., 2015).

In 2010, in the US, 2.8 million cases of BCC were diagnosed, and this number has continued to augment. Actually, BCC is the most frequently occurring form of all types of cancers. Statistics showed that more than one out of every three new cancers is in fact a skin cancer, and the majority are BCCs. Every year, almost 700.000 cases of SCC are diagnosed in the US, and numbers show that an estimated 3900 and 8800 people died because of this disease in 2012 in America. The incidence of SCC has increased up to 200 percent over the last three decades in the US. Melanoma is the most dangerous form of skin cancer. At this moment, more than 135.000 new cases of melanoma are diagnosed in America (SCF, 2015).

Skin structure

The integument or skin is the largest organ of the human body, forming up to 16% of the body weight, with a surface area of 1.8 m^2. It has different functions, the most important being to form a physical barrier to the environment, allowing and limiting the inward and outward passage of water, electrolytes and various substances while providing protection against microorganisms, ultraviolet radiation, toxic agents and mechanical injuries. The epidermis, the dermis and subcutis are the three structural layers of the skin. Hair, nails, sebaceous, sweat and apocrine glands are regarded as derivatives of skin (Fig.1).

Skin is a dynamic organ in constant state of change, as cells of the outer layers are continuously shed and replaced by inner cells moving up to the surface. Although structurally consistent throughout the body, skin varies in thickness according to the anatomical site and age of the individual. The epidermis is the outer layer, serving as the physical and chemical barrier between the interior body and exterior environment; the dermis is the deeper layer providing the structural support of the skin, below which there is a loose connective tissue layer, the subcutis or hypodermis which is an important depot of fat (Table 1) (Ro and Dawson, 2005).

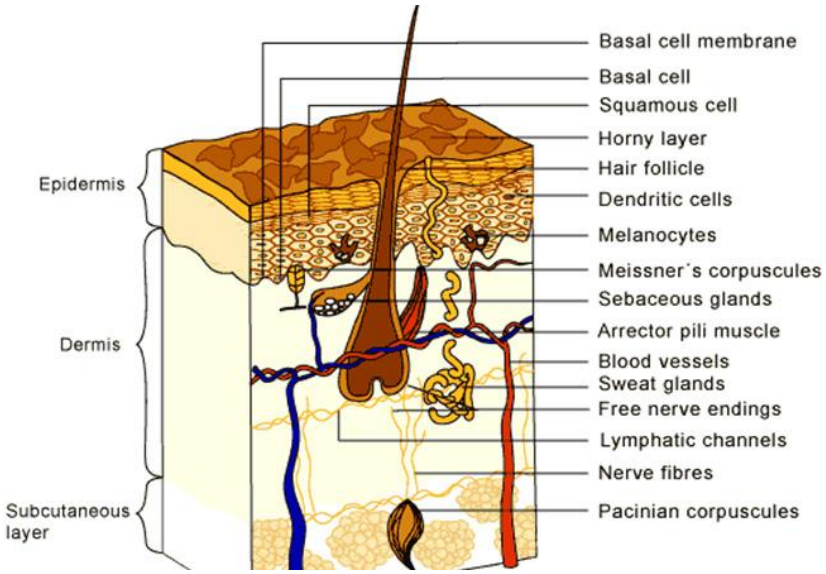


Fig. 1. Skin structure

Table 1. Skin structure

Skin layer	***Description***
Epidermis	The external layer mainly composed of layers of keratinocytes and also containing melanocytes, Langerhans cells and Merkel cells.
Basement membrane	The multilayered structure forming the dermo-epidermal junction.
Dermis	The area of supportive connective tissue between the epidermis and the underlying subcutis: contains sweat glands, hair roots, nervous cells and fibres, blood and lymph vessels.
Subcutis	The layer of loose connective tissue and fat beneath the dermis.

Risk factors generating skin cancer incidence

The incidence of skin cancer has grown so dramatically over the last years and the scientists have no explanation for this. Yet we can enumerate the environment, hereditary risk factors, the earlier diagnosis and the increased ultraviolet exposure as risk factors. In recent studies, researchers suggested that the epidermal cells can develop into malignant tumours, not only one pathway. They explain the fact that

there are more ways of transformation, such as the molecular profiles, anatomical distributions and the risk factor profiles for subgroups of skin malignancies. In addition, in melanoma prognosis, in several studies gender differences have been reported that indicate an increased survival proportion in women compared with men (http://www.skincancer.org/). However, the most important risk factors for melanoma are clinically or dysplastic nevi and freckling, fair pigmentation, multiple nevi and poor tanning ability (Alexis et al., 2008; Bharali et al., 2011; Dinzani et al., 2014; Nie et al., 2011; Niemeyer, 2001).

It is well-known that the sun may cause skin cancer. This may be due to long term exposure, or short periods of intense sun exposure and burning. The ultraviolet light in sunlight damages the deoxyribonucleic acid (DNA) in the skin cells. This damage can occur years before a cancer develops. The sun's rays contain 3 types of ultraviolet (UV) light, classified according to their wavelength. At the same time, the rays differ in their biological activity and in the way they penetrate the skin. If the wavelength is shorter, UV radiation will be more harmful and less able to penetrate the skin. The most damaging type of UV radiation is UVC, short-wavelength, which is completely filtered by the atmosphere and does not touch the earth's surface. UVB, a medium-wavelength, is very biologically active and cannot penetrate the superficial skin layers. UVB is responsible for delayed tanning and burning, for skin ageing, and for promoting the development of skin cancer. Most solar UVB are filtered by the atmosphere. However, the long-wavelength UVA accounts for almost 95% of the UV radiation getting to the Earth's surface. UVA can infiltrate into the deeper stratum of the skin and is liable for the immediate tanning effect. At the same time, it can contribute to skin ageing and wrinkling (SCF, 2015).

While physicians have always thought that UVB represents the main risk for skin cancer, sunbeds/tanning beds produce mostly UVA but also some UVB. UVA damages the skin and it is now also linked to skin cancer. We know that the use of sunbeds causes melanoma, and there is now evidence that sunbeds may increase the risk of non-melanoma skin cancer. The evidence is strongest for a link between sunbeds and SCC. Basal cell and squamous cell skin cancers develop very slowly. As you get older you have more time to build up sun damage to your skin. So the older you are, the more likely you are to get a non-melanoma skin cancer. However, skin cancers can develop in younger people too. Both long-term sun exposure over your lifetime and occasional extended, intense exposure (typically leading to sunburn) combine to cause damage that can lead to BCC (www.cancer.org). UV has effects via direct and indirect mechanisms, for example gene mutations, formation of cyclobutane pyrimidine dimmers, immune-suppression and oxidative stress (Simoes et al., 2015).

In spite of these causative factors, there are also additional risk factors that have been studied in literature: patients with HIV or patients that have received organ transplant, patients with radiation therapy, phototherapy, psoralen and long-wave ultraviolet radiation can develop skin cancer.

The treatment of skin cancer

New treatments for skin cancer have appeared and evolved rapidly in recent years, because of the growing incidence of these cutaneous malignancies. The option of treatment depends on the dimensions, location, margins and progression degree of the tumour (Martinez and Otley, 2001). Surgery is the most used method for skin cancer treatment (Clarke, 2012; Galiczynski and Vidimos, 2011; Lazareth, 2013). The treatment takes into account the complete eradication of the cancer, the preservation of the normal function and cosmetics. Still, one surgical technique has stood the test of time. Created by Dr. Frederick Mohs, in the 1930s, Mohs micrographic surgery has with a few refinements come to be embraced over the past decade by an increasing number of surgeons for an ever-widening variety of skin cancers.

Now, Mohs surgery has come to be accepted as the single most effective technique for removing Basal Cell Carcinoma and Squamous Cell Carcinoma (BCCs and SCCs), the two most common skin cancers. It accomplishes the nifty trick of sparing the greatest amount of healthy tissue while also most completely expunging cancer cells; cure rates for BCC and SCC are of an unparalleled 98 percent or higher with Mohs, significantly better than the rates for standard excision or any other accepted method (Li et al., 2015).

Physicians suggest that personalised cancer therapy will be the future of skin cancer treatment. There can be no doubt that we have advanced into the era of changes.

Utilisation of nanocarries as drug delivery in skin cancers

In the 21st century, the nanotechnology has had a revolutionary impact on many aspects and at the same time it has provided a real opportunity to explore new ways that usual technologies were unable to have an impact on diagnosis, prevention, and also the therapy of different diseases, in particular cancer (Mehnert and Mäder, 2001). The study of the control of matter on an atomic and molecular scale that involves creating materials or devices on nanometer structures is typically known as nanotechnology (Mosallaei et al., 2013). Behind nanotechnology there is a central idea which says that a metal, a semiconductor and polymeric nanoparticles must have new electronic, optical, magnetic and structural properties that usually are not available from single molecules and bulk solids (Minelli et al., 2012).

Of late years, nanotechnology has been implemented in various areas of cancer management and therapeutics, having the hope that it will improve the diagnosis and the treatment of this disease (Zhang and Zhang, 2013).

Additionally, in literature, the investigators have reported specific drug-nanoparticles formulations for the treatment of the three types of skin cancer: basal cell carcinoma, squamous cell carcinoma and melanoma. Many of these studies have investigated the development of nanocarrier drug delivery systems, like bacterial nanoparticles, carbon-based nanoparticles, dendrimers, hybrid nano-particles, inorganic/metallic nanoparticles, liposomes, magnetic particles, micelles, nanoshells, polymeric nanoparticles, polymersomes and protein-based nanoparticles for the treatment of skin cancers, in particular for melanoma treatment. A schematic presentation of several types of nanocarriers is shown in Fig. 2. The gold standard treatment of the basal cell carcinoma and of the squamous cell carcinoma is excision. But for the metastasized skin cancers, nanocarriers supply a drug delivery system, permitting anticancer drugs to target the cancer site (Yano et al., 2004).

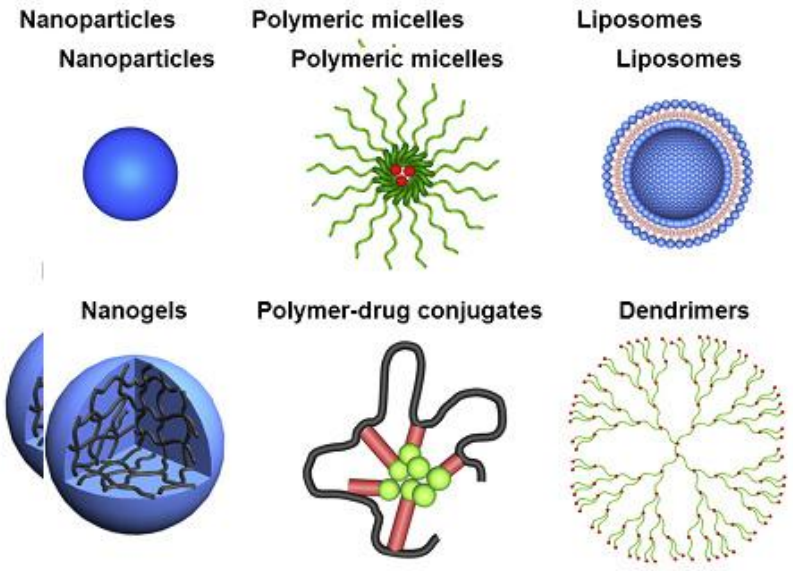


Fig 2. Types of nanocarriers for drug delivery (Slingerland et al., 2012)

In the next paragraphs, the characteristics of the most common nanocarries used in skin cancer treatment are presented.

Solid Lipid Nanoparticles (SLNs)

We can imagine a lipid nanoparticle as a solid lipophilic matrix in which active substances can be incorporated. The dimensions are for the most part between 150 and 300 nm, including <100 nm or larger sizes up to 1000 nm (Müller et al., 2011).

They can be derived from oil-in-water nanoemulsions, where the liquid lipid of the oil droplets is substituted by a solid lipid. For that reason, lipid nanoparticles stay solid after administration. This indicates that they may ensure a matrix for modified release of the active substances. Simultaneously, chemically labile active molecules can be secured by the matrix. We can differentiate two generations of lipid nanoparticles: solid lipid nanoparticles-first generation (these are made from solid lipid only) and nanostructured lipid carriers-second generation (these represent a blend of solid and liquid lipids (Muchow et al., 2008; Müller et al., 2002; Müller et al., 2007; Severino et al., 2012).

These nanoparticles were introduced and presented a long time ago (beginning of the 1990s) as a real alternative delivery system to emulsion, liposomes and polymeric nanoparticles, because they are biodegradable and biocompatible. At the same time, they have a high physical stability, low toxicity and can protect the drug against degradation. For the preparation of SLNs it is not necessary to use organic solvents (Muthu and Feng, 2013).

Some authors reported that the production and the sterilisation on a large scale are rather easy (Soenena et al., 2008). In the case of malignant melanoma (A-375), if SLNs are containing docetaxel, this will improve the efficacy of the chemotherapeutic agent (Hunag, 2008). Other researchers showed that cholesteryl butyrate solid lipid nanoparticles inhibit human umbilical vein endothelial cell adhesiveness to cancer cell lines derived from melanoma (Allen and Cullis, 2013).

Liposomes

Liposomes are phospholipid vesicles (with dimensions between 50–100 nm and even larger) that are characterised by bi-layered membrane structure, identical to that of biological membranes, together with an internal aqueous phase. According to the size and number of the layers they can be multi-, oligo-, or unilamellar. Liposomes present diffusion properties, excellent circulation and penetration (Parhi and Suresh, 2012).

Early studies showed that liposomes can remain in the tumour interstitial fluid just near the tumour vessels (Senior, 1987). In the mid 90s several liposomal formulations used in the clinical practice which contained various drugs for the treatment of different types of cancer, including melanoma were reported in literature (Woodle, 1995). Other liposomal chemotherapeutic drugs are still at the

different stages of clinical trials. Some authors proposed new opportunities developing theranostic liposomes. Another interesting idea is that liposomes can also be modified to integrate a magnetic element in order to monitore their movement within the body using Magnetic Resonance Image or to entrap gases and drugs for ultrasound-controlled drug delivery (Antonio et al., 2014; Janknegt et al; 1992; Weiss and Aplin, 2010).

Other studies related to the treatment of skin cancer are the encapsulation of the UV-DNA repair enzyme T4N5 (Ceccoli et al., 1989; Yarosh et al., 2001), aloe-emodin liposomes for the treatment of non-melanoma skin cancer or ultra-deformable liposomes including bleomycin as squamous skin cancer therapy (Lau et al., 2005).

Nanosuspensions and nanoemulsions

Nanosuspensions contain colloidal particles composed of only a drug and an emulsifier. Nanoemulsions (composed of oil-in-water (O/W) or water-in-oil (W/O)) are lipid droplets with a drug and an emulsifier. For the lipid phase fatty oils or middle chain triglycerides are used, which amounts to typically 10–20% of the emulsion. Systems based on nanosuspensions/nanoemulsions are employed as drug carriers for lipophilic drugs and several formulations are commercialised so far. Actually, compared with solubilisation based formulations of the same drug, a decrease of side effects was found using these systems (Jumaa and Müller, 2000; Loo et al., 2004). There is the possibility of controlled drug release, but it is limited because of to the small dimension and the liquid state of the carrier.

Lipid nanoemulsions and nanoparticles applied onto the skin supply benefits due to their small size and consequent high surface area managing to a bioadhesiveness and formation of a film that intensifies drugs penetration owing to occlusive and hydrating properties. Nanoemulsions and nanoparticles increase skin hydration and skin elasticity, assure protection (mechanical, microbiological, thermal, and chemical irritation), lubrication and emolliency (smoothing and substitution of surface lipids). It has been shown that these carriers are able to encapsulate chemotherapeutic drugs improving their residence time and minimising acute toxicity of irritating drugs at high concentrations (Goenka et al., 2014; Gupta et al., 2013; Hainfeld et al., 2004; Jain et al., 2012; de Jong et al., 2008; Tran et al., 2009).

Caffeine has been examined as a potential drug against skin cancer (Shakeel and Ramadan, 2010). Various water/oil nanoemulsions of caffeine were prepared by the oil phase titration method and the *in vitro* skin permeation profile of optimised formulation was compared with aqueous solution of caffeine. Studies showed that

microemulsions are able to efficiently protect curcumin and penetrate skin layers for the treatment and prevention of skin cancers (Severino et al., 2013).

Nanoemulsions loaded with dacarbazine, which is an anticancer drug used for different types of skin cancer, showed to be efficient in the reduction of tumour size in an apidermoid carcinoma in rats (Kakumanu et al., 2011).

Carbon-based nanoparticles (CNPs)

Carbon-based nanoparticles were first made in 1985 and are known as fullerenes, being an arrangement of 60 carbon atoms. In 1991, a carbon nanotube was obtained (Anilkumar et al., 2011).

For different applications in optoelectronics, tissue and biomedical engineering, sensors, medical implants and medical devices carbon-based materials like graphite, fullerenes, diamond, nanowires, nanotubes, nanoribbons and grapheme have been used (Zavaleta et al., 2009).

Nanowires consist of a nanostructure characterised by cylindrical cross-sections of less than 100 nm, but of possibly hundreds of microns long, and include the well-described carbon nanotubes (CNTs). One of the most important roles of CNTs is their capacity to deliver active substances directly into cancer cells, their shape allowing an easy penetration into the cell barrier; recently there have been several *in vitro* and *in vivo* studies using antibody-functionalised CNTs loaded with antineoplastic agents. At this moment, CNTs and fullerenes still need further investigation for application in skin treatments (Lu et al., 2010).

Latterly, nanodiamonds were used to deliver drugs against melanoma [60]. Carbon-based nanoparticles have indicated an increase of the efficacy of chemotherapy in melanoma cells (Bei et al., 2010; Chaudhuri et al., 2010). Chaudhuri et al. (2010) showed that a single walled carbon nanotube loaded with doxorubicine (Dox) induced *in vitro* melanoma cell death in a dose-dependent fashion and limited tumour growth in a xenograft melanoma model.

Gold nanoparticles (GNPs)

Due to their exclusive characteristics, the utilisation of gold nanoparticles (GNPs) is a promising solution for skin cancer therapy.

Gold nanoparticles (GNPs) are being studied since the 19th century. Although common oxidation states of gold include +1 and +3, GNPs exist in a non-oxidized state (Au [0]) (Baroli et al., 2007). Gold nanoparticles are metallic nanoparticles. Other examples of metallic nanoparticles include Ag, Ni, Pt, and TiO_2. Gold nanoparticles (1–150 nm) can be prepared with different geometries, such as nanospheres, nanoshells, nanorods, or nanocages (Lu et al., 2007).

For clinical use, they are studied as carriers for the delivery of drugs, imaging molecules, genes and for the development of new cancer therapy products (Desai et al., 2010; Misak et al., 2010; Wadajkar et al., 2012). These nanoparticles possess several characteristics that are useful for cancer therapy. Besides being small, they can penetrate the body, accumulating in tumours. As regards skin cancer, a highly efficient drug vector for PDT drug delivery was developed through the synthesis of PEG-ylated GNPs, which act as a water-soluble and biocompatible "cage" that allows delivery of a hydrophobic drug to its local of action.

Furthermore, they are not toxic and biocompatible. In fact, they do not elicit any allergic or immune responses.

These particles exhibit a combination of electronic, chemical, physical, and optical properties different from other biomedical nanotechnologies and offer a highly multifunctional platform for biochemical applications in the delivery of gene, imaging agents, and drugs (Rao et al., 2014; Slowing et al., 2007). The advantages of gold nanoparticles are their easy preparation in a range of sizes, good biocompatibility, ease of functionality, and their ability to conjugate with other biomolecules without altering their biological properties.

Besides, their non-ionizing radiation absorption characteristics and particular surface plasmon resonance allow them to be used in radiotherapy and photodermal therapy.

Magnetic nanoparticles (MNPs)

Magnetic/metallic NPs are small, which can be important for aspects of cell targeting (Slowing et al., 2008). MNPs composed of iron derivatives (magnetic, paramagnetic or superparamagnetic) have potential application for drug delivery to skin, as they can be easily targeted after administration, especially by injection using an external magnetic field.

Some studies showed that rigid MNPs, smaller than 10 nm, can pass through the skin, reaching the *stratum granulosum* (Slowing et al., 2006; Torney et al., 2007).

A magnetic-based core–shell particle (MBCSP) drug delivery system was successfully developed to target skin cancer cells. In another study, albumin/5-FU loaded magnetic nanocomposite spheres were produced and tested on a skin cancer mouse mode (Cauda et al., 2009). The results clearly indicated that the magnetic targeted nanoparticles exhibited significantly superior efficacy (Tsai et al., 2009). Functionalised superparamagnetic iron-oxide nanoparticles were also developed, using magnetism for the targeted transdermal chemotherapy of skin tumours with epirubicin (Wang and Chen, 2011).

Silica nanoparticles (SiNPs)

In recent years, silica nanoparticles have attracted a growing interest as an efficient drug delivery system (Alivisatos, 1996; Huang et al., 2011; Medintz et al., 2005). Compared with conventional organic nanocarriers, SiNs have unique properties including tuneable particle size and morphology, tailored mesoporous structure, uniform and tuneable pore size, high chemical and mechanical stability, high surface area and pore volume, high drug-loading capacity, and easy surface functionalization (LaRocque et al., 2009; Ruoslahti et al., 2010).

Researchers believe that if they modify the surface of SiNPs with antibodies specific to CM cells, this will lead to improved diagnosis and targeted treatment of melanoma (Caracò et al., 2013).

Quantum Dots (QDs)

Quantum dots are colloidal fluorescent semiconductor nanocrystals (2–10 nm) that possess a broad absorption band and a symmetric, narrow emission band, typically in the visible to near infrared spectral range (Sahu et al., 2013).

Usually, the central core of quantum dots is composed of combinations of elements from groups II–VI of the periodic system (such as zinc, cadmium, selenium, and tellurium) or III–V (like arsenic and phosphorus), which are "overcoated" with a layer of ZnS (Mangalathillam et al., 2012). They present size- and composition-tuneable emission spectra and high quantum yield. Quantum dots are photostable; therefore, the optical properties of QDs make them suitable for highly sensitive, long term, and multi target bioimaging application (Puga et al., 2013; Sabitha et al., 2013). Yet the application to cancer detection lies in the ability to select a specific colour of light emission of QDs (Svenson, 2009). Indeed, in order for QDs to be used for melanoma detection, the surface must be first treated to increase hydrophilicity and the desired tumour-targeting ligand must be attached. Possible ligands include antibodies, peptides, and small-molecule drugs/inhibitors (Pehamberger, 2002).

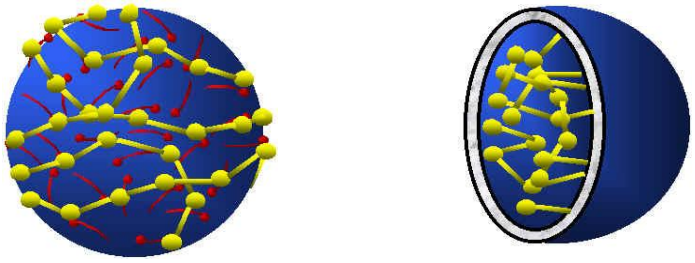
Recent studies reported that the addition of a silica coating or a biocompatible polymer coating, have further increased the biocompatibility and reduced their toxicity.

QDs preferentially are collected in the upper layers of the *stratum corneum* and in hair follicles, penetrating throughout the skin by getting through intracellular lipid lamellae along the edges of differentiated corneocytes. In addition, QDs skin penetration and toxicity depend on physicochemical properties as particle size, shape, chemical structure of the core/ shell and surface coating, charge and pH of the applied vehicle (Di Trolio et al., 2012).

Although further research is still required, derivatised QDs have improved tumour localisation and can enhance skin cancer monitoring and chemotherapy (Byers and Hitchman, 2011; Tholouli et al., 2008; Wang and Chen, 2011).

Polymeric nanoparticles (PNs)

Nanoparticles as drug carriers can be formed from both biodegradable polymers and non-biodegradable polymers. In recent years, biodegradable polymeric nanoparticles have attracted considerable attention as potential drug delivery devices in view of their applications to the controlled release of drugs, in targeting particular organs/tissues, as carriers of DNA in gene therapy, and in their ability to deliver proteins, peptides and genes. The term of polymeric nanoparticles is used for two types of formulations: nanopsheres and nanocapsules (presented in Fig. 3). The term of sphere describes a spherical polymer particle having the active principle dispersed within the continuous polymer matrix. The term of capsule refers to the usually spherical polymer particle that incorporates within its inner volume one or more solid or liquid substances. These make *the core* of the capsule, while the polymer matrix forms *the shell/the wall* of the particle. Although they are more difficult to obtain, nanocapsules are preferred, due to their capacity to include high amounts of drugs (Letchford and Burt, 2007).



a. nanospheres ***b.*** nanocapsules

Fig. 3. Types of nanoparticles and ways of incorporating drugs:
(a) nanospheres; **(b)** nanocapsules

The morphology of drug carrying nanoparticles has a great influence on *in vitro* or *in vivo* drug release profile. Different types of morphology are illustrated in Fig. 4.

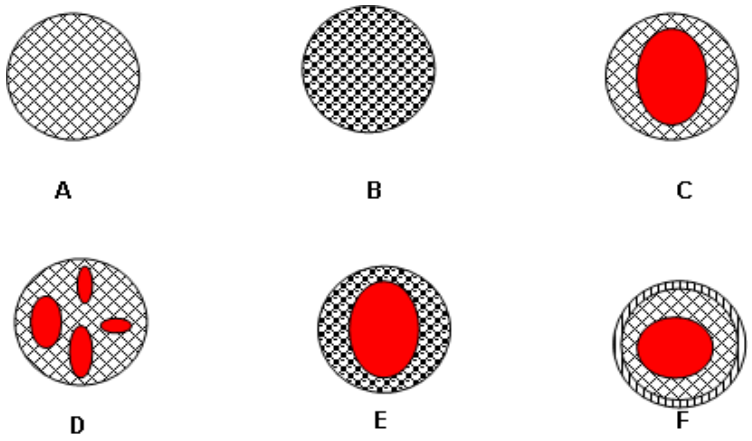


Fig. 4. Different types of polymer particles morphology: **A**-the typical case of nanosphere in which the drug is totally dissolved or molecularly dispersed into the polymer matrix; **B**- polymer matrix in which the drug is uniformly dispersed; **C**-typical case of drug continuous phase-*core* surrounded by polymer shell; **D**-polynuclear nanocapsule, containing more drug cores surrounded by polymer membrane; **E**-nanocapsules having drug core and also drug partially dispersed into the polymer shell; **F**- nanocapsules will double polymer shell

Various studies have been performed employing polymers and polymeric nanoparticles for the treatment of skin malignancies. A study of Zhang et al., (2013) describes the release and retention of quercetin (a herbal lipophilic drug with anticancer properties) from ethylcellulose nanoparticles, given topically, intended for skin cancer; the authors concluded that the drug being lipophilic could be engaged in the skin for longer periods, reducing the dose and frequency of drug administration (Hosino et al., 2012). Nanoparticles based on low molecular weight poly(ethylene imine) have been bound to β-cyclodextrin conjugated with folic acid and later mixed with IL-2 plasmid and they have been found to inhibit tumour growth and prolong life expectancy in melanoma bearing mice (Yao et al., 2011). Biodegradable polymer, poly(polycaprolactone), was prepared in order to obtain a nanoporous miniature device for local delivery of cytokine IFN-alpha and showed constant slow release of IFN-alpha (He et al., 2011). 5-FU-loaded chitosan micro and nanogels were also obtained in 2013 (Mora-Huertas et al., 2010; Zhu et al., 2014). In addition, several commercial anticancer drugs have also been successfully associated with dendrimers such as poly(amidoamine), either through physical interactions or chemical bonding (Parthasarathy et al., 1994). PEG-ylated IFN (PEG-IFN), already available on the pharmaceutical market, is a form of recombinant human IFN that has been chemically modified by the covalent attachment of a branched metoxpolyethylene

glycol moiety, with great results in the treatment of skin malignancies (Elkeeb et al., 2010; Kuchler et al., 2009).

Conclusions and Perspectives

Skin cancer affects millions of people yearly. Limitations in the current therapies signal the necessity of new treatments. Among several therapy approaches, nanotechnology, even as a quite young research area, offers a real opportunity on the molecular scale through specific interaction with cancer cells and inhibition of their function.

However, the large and various choice of already developed nanoparticles makes their toxicity values vary from inert to extreme toxic, limiting their use and determining research to focus its attention on the safety of these products used in biomedical applications. In order to put them into clinical practice, some other aspects need to be considered, such as biodistribution farmaco-kinetics, biodegradability, biocompatibility, metabolisation.

Therefore, the importance of melanoma targeting with the aid of nanoparticles for a better therapeutic efficacy, even if extremely promising, is just one side of the coin.

In conclusion, we can say that nanotechnology combined with multifunctional nanocarriers with the tumour-specific ability of carrying one or multiple natural products and antitumoral drugs has the potential of being within reach in order to treat and cure cancer in the near future.

Notations and/or **Abbreviations**
Basal cell carcinomas (BCCs)
Squamous cell carcinomas (SCCs)
Non-melanocytic skin cancer-NMSC
Cutaneous malignant melanomas (CMs),
Solid Lipid Nanoparticles (SLNs)
Oil-in-water (O/ W)
Water-in-oil (W/O)
Carbon nanotubes (CNTs).
Gold nanoparticles (GNPs)
Magnetic nanoparticles (MNPs)
Magnetic-based core–shell particle (MBCSP)
Nanoparticles (NPs)
Silica nanoparticles (SiNPs)
Quantum Dots (QDs)
Photodermal therapy (PDT)

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