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Review Article

Nanotechnology-based Doxorubicin delivery for the treatment of skin cancer: A comprehensive review

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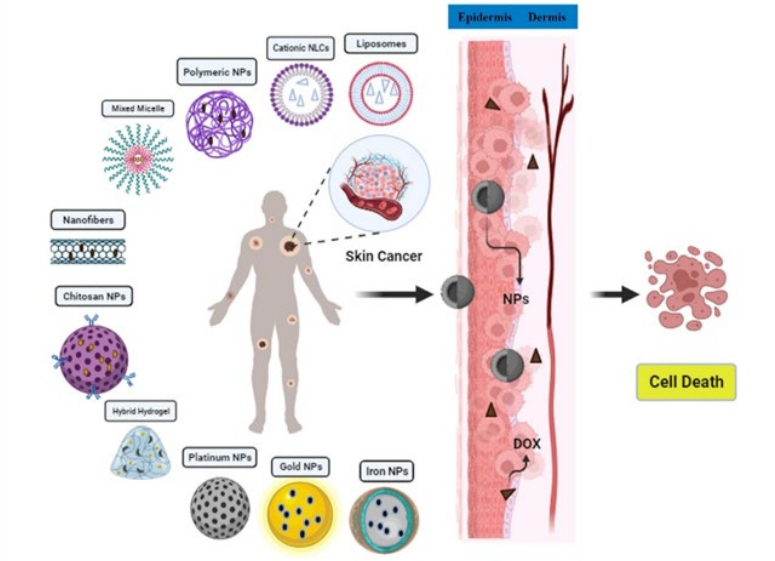
ABSTRACT

Skin cancer is becoming more prevalent, with a rapid increase in incidence, posing a substantial public health problem. Doxorubicin, an anticancer agent, recognized as one of the most potent medications, is frequently employed in the treatment of skin cancer. Nevertheless, its application is constrained by challenges such as restricted penetration, dose-dependent toxicity, the development of multidrug resistance, and its limited specificity for cancer cells. The utilization of nanoparticles (NPs) emerges as a promising strategy to effectively address the myriad challenges encountered in the skin cancer treatment of doxorubicin (DOX). The inherent characteristics and components of NPs provide a range of advantageous properties, including enhanced permeation, sustained release, biocompatibility, low immunogenicity, and reduced toxicity. Notably, the specificity and selectivity of NPs for tumor tissues contribute to a reduction in DOX doses, thereby minimizing side effects in healthy tissues. Furthermore, NPs enhance the cytotoxicity of DOX, often leading to a decreased requirement for drug amounts to achieve the desired effect. The adaptable chemical formulation of NPs allows for easy modifications, expanding their applications, including incorporating materials with cytotoxic properties that synergize with DOX. Additionally, NPs exhibit an affinity for compounds secreted by tumor cells and bind to specific receptors on these cells, effectively overcoming barriers associated with multidrug resistance (MDR). In light of these advancements, this review underscores the considerable progress achieved in the realm of skin cancer chemotherapy through the implementation of doxorubicin nanoplatform-based delivery systems.

Keywords: Doxorubicin; skin cancer; nanoparticles



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INTRODUCTION

Globally, Skin cancer stands out as the most prominent cancer, with the United States taking the lead. Estimates suggest that around 1 in 5 Americans will confront skin cancer during their lifespan. Human skin, composed of the epidermis, dermis, and connective tissue, serves as an essential protective barrier in mammals. The dermis is a rich connective tissue matrix that houses nerves, blood vessels, and lymphatic vasculature. Skin cancer develops when normal skin cells deviate from their normal function and proliferate abnormally. The three primary types of skin cancer are basal cell carcinomas (BCCs), squamous cell carcinomas (SCCs) or non-melanocytic skin carcinoma, and cutaneous malignant melanomas (CMs), also known as skin malignant melanoma or melanoma as depicted in [Figure 2] [1,2].

Basal cell carcinoma is the most common human cancer originating from keratinized epithelial cells and is often termed keratinocyte carcinoma. Despite growing awareness of the deleterious effects of sun exposure, their incidence continues to spike. Basal-cell carcinoma alone is experiencing a 10% annual increase worldwide, suggesting it may soon surpass the combined prevalence of all other cancers. These tumors are typically slow-growing and locally invasive. Squamous cell carcinoma, the second most common non-melanomatous skin cancer, constitutes 20% to 30% of cases. Their less lethal nature compared to melanoma is attributed to their tendency to remain confined to their primary site, simplifying management.

Melanoma, arising from epidermal melanocytes, represents about 2% of malignant skin cancer cases but is responsible for the majority of deaths, particularly among the younger population. In 2010, over 2 million cases of skin cancer were diagnosed in the United States. Cutaneous malignant melanoma, marked by treatment resistance and a propensity for metastasis, has shown a steady and significant increase over the past few decades according to research by Linares et al. and Madan et al [3].

Skin cancer treatment options encompass chemotherapy, surgery, and radiotherapy depending on the patient's condition and the specific type of skin cancer. chemotherapy is the most prominent option utilized in case of skin cancers. Doxorubicin (DOX), an anthracycline antibiotic, has emerged as a primary therapeutic choice for skin cancer management due to its unique structure. Comprising a water-soluble sugar called daunosamine and a water-insoluble tetracyclic aglycone (adrimycinone). It belongs to BCS III and only available in IV formulation as shown in [Figure 3] [4]. DOX operates through mechanisms like DNA intercalation and free radical generation [5].

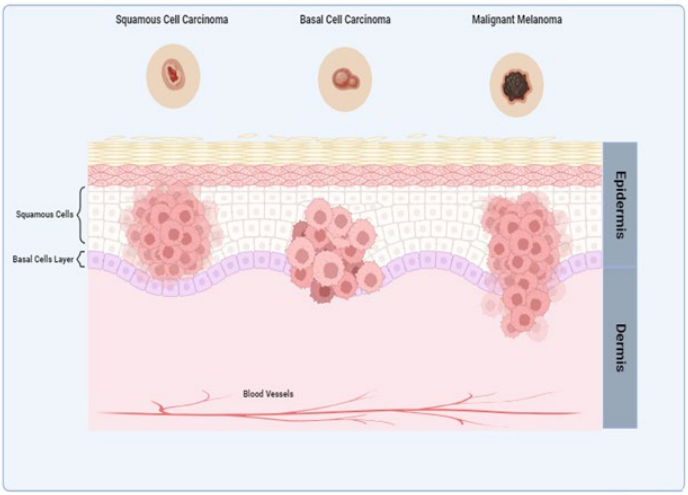

Figure 2. Types of skin cancer.

The two eminent pathways for DOX activity are the DNA strands intercalation and generation of free radicals as shown in [Figure 4] [6]. Owing to the drug's low efficacy and poor penetration into the stratum corneum or lesions, higher doses of DOX are required, which limits the effectiveness of skin cancer therapy. Furthermore, it has a non-specific biodistribution, a shorter plasma half-life, and severe adverse effects as myelosuppression and cardiotoxicity. To overcome these issues, nanocarriers have been employed in anti-cancer drug delivery systems due to various advantages as shown in [Figure 5]. The current landscape explores nanotechnology-based therapies as promising solutions for more efficient and targeted drug delivery in skin cancer treatment [7,8].

DOXORUBICIN LOADED NANOPARTICLES BASED THERAPIES FOR SKIN CANCER

Liposomes

Liposomes consist of single or multiple concentric lipid bilayers enclosing an aqueous compartment [9]. Phospholipids, a diverse group of biological membrane lipids that naturally form bilayers in water, play a pivotal role in liposome structure [10, 11].

The key feature for effective stratum corneum penetration is the liquid crystal phase of liposomes [12, 13]. This state allows liposomes to interact with both the lipid and aqueous components of the stratum corneum simultaneously, facilitating the delivery of

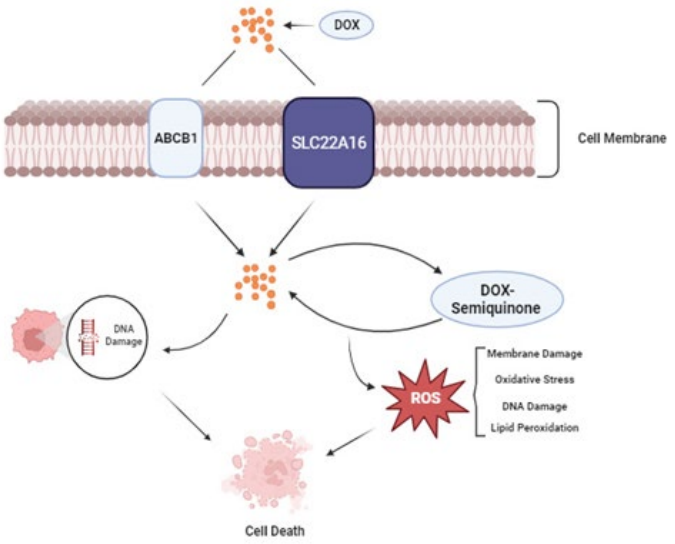

Figure3 Physicochemical properties of doxorubicin.

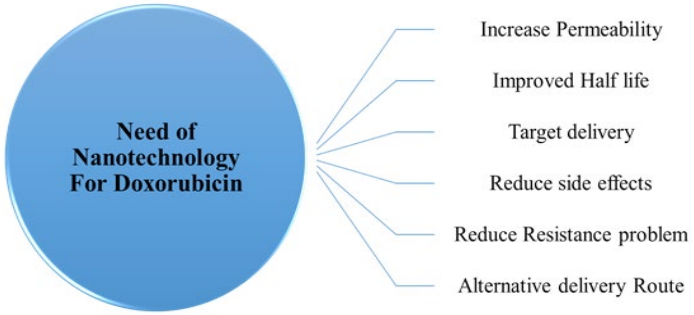

Figure 4: Mechanism of action of doxorubicin.

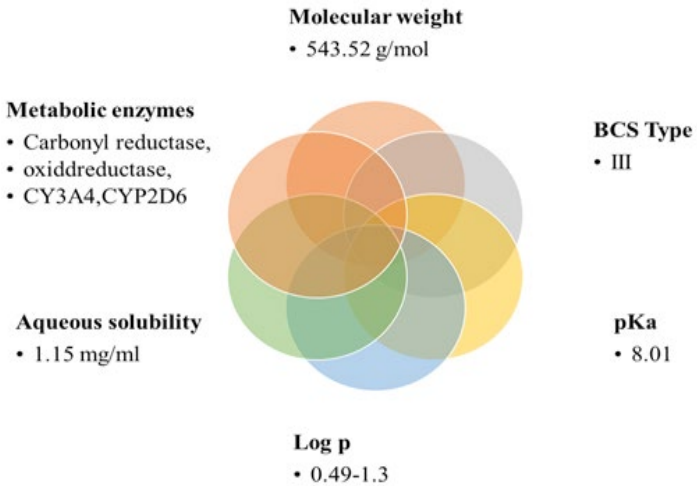

Figure5. Advantages of nanotechnology in drug delivery of Doxorubicin.

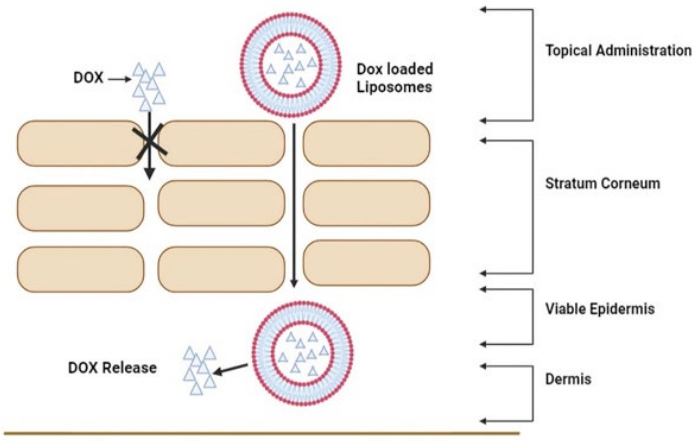

Figure 6. Liposomal Drug Delivery of Doxorubicin in Skin Cancer.

encapsulated drugs into the skin [14, 15, 16].

Liposomes, when topically applied, serve various functions. They enhance drug deposition within the skin, to minimize systemic absorption and reduce potential side effects, thus exhibiting a localizing effect [17]. Additionally, they have the capability to provide targeted delivery to skin appendages, expanding their potential for transdermal delivery and increasing systemic absorption as depicted in [Figure 6] [18].

Despite liposomes being theoretically thermodynamically stable, tackling the storage stability problem is a key difficulty in the real world. Liposome instability can lead to drug leakage from vesicles, as well as aggregation and/or fusion to form larger vesicles. Following aggregation, ultimate nano-sized vesicles may not demonstrate their benefits [19]. Liposome stability can be increased by introducing hydrogels, sugars, polymers, or collagen [20,21]. The development and evaluation of novel stabilizers will become increasingly important in the future. The high cost of components like phospholipids has long impeded product development for industrial and therapeutic uses [22].

The initial indication of altered drug deposition through topical application of liposomal encapsulated drugs was reported at the FIP 1979 congress. This report suggested that the encapsulation of a drug in liposomes increased its deposition in the skin while reducing absorption into the central blood supply. In particular, a 5-day topical treatment of liposomal triamcinolone acetonide resulted in a high drug concentration in the epidermis and dermis when compared to a control ointment. consequently, these data revealed that liposomes could be useful for increasing local activity while decreasing percutaneous absorption of drug [23].

Patel proposed the use of liposomes for the sustained release of topically applied drugs into the epidermis. For instance, the liposomal encapsulation significantly reduced percutaneous drug absorption, as indicated by decreased radiolabel amounts in the blood topically on the skin of nude mice, Moreover, the retention of methotrexate in the skin with liposomal formulation compared to the free form suggested a localized and sustained release methotrexate from liposomes [24,25].

Doxil™, an FDA-approved liposomal doxorubicin variant, involves coating doxorubicin-loaded liposomes with polyethylene glycol for treating various skin cancers. The findings indicate that pegylated-liposomal doxorubicin shows efficacy in treating sarcomas with a poor prognosis, and the associated toxicity is relatively modest [26]. Based on another study, Doxil doesn't exhibit significant effectiveness in treating metastatic melanoma, suggesting that further exploration of its use in this context may not be warranted [27]. In a similar study, liposomes loaded with a combination of doxorubicin and celecoxib in a ratio metric manner were successfully created. These liposomes, carrying both drugs, demonstrated the ability to inhibit cancer cell viability by more than 99%, even at lower concentrations where each drug alone was ineffective [28]. Co-administering hispolon with doxorubicin has the potential to reduce chemotherapy toxicity, enabling the use of lower doxorubicin doses as reported by Al Saqr et al. This data indicated that incorporating hispolon into a liposome formulation enhanced the synergistic performance of doxorubicin liposomes [29].

Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) represent a novel drug carrier system characterized by a solid lipid matrix, featuring a mean particle size (PS) ranging from 50 to 1000 nm. SLNs have emerged as an attractive alternative to traditional carriers such as polymeric nanoparticles, emulsions, and liposomes [30,31]. SLNs are becoming more recognized as a new colloidal drug carrier for topical usage, presenting advantages such as minimal skin irritation, controlled release and active ingredient protection. Because of their non-irritating and non-toxic lipid content, SLNs are suited for use on inflamed and injured skin. SLNs also have strong occlusive characteristics, creating an intact layer on the skin's surface after drying. This film substantially lowers transepidermal water loss while also increasing medication penetration via the stratum corneum [32,33]. Numerous researchers have been assessing the impact of solid lipid nanoparticles (SLNs) on the topical penetration of doxorubicin hydrochloride (DOX) with the aim of achieving localized treatment for skin tumors while minimizing side effects as shown in [Figure 7] [34].

Based on aforementioned reasons, Subedi et al. successfully crafted and characterized doxorubicin loaded SLNs, utilizing glyceryl caprate and curdlan as core and shell materials. They fine-tuned various formulation parameters, including lipid phase, surfactant concentration, aqueous phase volume, and drug/lipid matrix ratio, resulting in high-quality nanoparticles. The SLNs demonstrated a small particle size, high entrapment efficiency, and a relatively robust drug loading capacity. Furthermore, stability studies revealed that lyophilized SLNs maintained effectiveness even after one year of storage at 4°C. These findings indicate the potential of

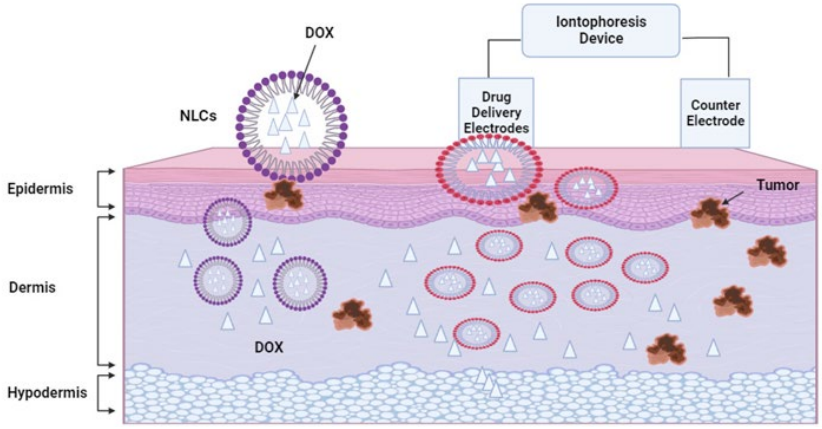

Figure7. Nano-lipid Carrier based delivery of Doxorubicin in Skin Cancer.

the developed SLN formulation for drug delivery, particularly in the targeted delivery of doxorubicin [35].

In another study Mussi et al. reconnoitred an innovative approach to improving the encapsulation and anticancer activity of doxorubicin within solid lipid nanoparticles (SLNs). Their research found that integrating docosahexaenoic acid (DHA) into doxorubicin-loaded SLNs considerably improved drug encapsulation efficiency and increased the anticancer efficacy of the nanoparticles. The resulting SLNs, which were loaded with both doxorubicin and DHA, had a tiny particle size, good drug encapsulation efficiency, and better release in low pH settings, making them a viable cancer treatment option. *In vitro* experiments on the human lung carcinoma cell line (A549) revealed that doxorubicin-DHA-loaded SLNs had more cytotoxicity than free doxorubicin and DHA, with improved cellular uptake contributing to this result. These data imply that the DHA-doxorubicin-loaded SLN formulation shows promise as a cancer therapeutic alternative [36].

Taveira et al. also evaluated the influence of iontophoresis on the penetration of doxorubicin (DOX) delivered in solid lipid nanoparticles (SLNs) as well as the cytotoxicity of DOX-SLNs against skin cancer cells. Their specific objectives included defining the role of electroosmotic flow in DOX transport, evaluating DOX accumulation in the stratum corneum and viable epidermis, and evaluating the efficacy of DOX-SLNs in targeting and killing skin cancer cells. DOX-SLN iontophoresis increased DOX distribution to the viable epidermis significantly, with 56% of all DOX reaching this skin layer and only 26% staying in the stratum corneum. This suggests that DOX-SLN iontophoresis could be employed as a topical treatment for skin cancer. DOX-SLNs improved DOX cytotoxicity against melanoma cells by 50%, demonstrating their ability to target skin cancer cells. Importantly, the study found that at the concentrations studied, DOX-loaded SLNs did not have enough cytotoxicity against squamous or melanoma cells. These findings emphasize the potential of combining iontophoresis with solid lipid nanoparticles for enhanced topical administration of anticancer medicines, resulting in superior skin cancer treatment outcomes when compared to DOX-water iontophoresis [37]. The possibility of using anodic iontophoresis to improve the distribution and tumor penetration of cationic solid lipid nanoparticles loaded with doxorubicin (DOX-SLN) was studied in another piece of research by Huber et al. They designed and characterized a double-labeled cationic DOX-SLN formulation with stearic acid, monoolein lipids, and a new BODIPY dye. In vitro skin distribution and penetration of DOX were assessed using confocal microscopy and vertical diffusion cells. The anticancer capability of DOX-SLN has been studied in vivo using anodic iontophoresis in squamous cell carcinoma in nude BALB/c mice. DOX encapsulation increased the DOX partition coefficient considerably, Enhancing its distribution in the stratum corneum (SC) lipid matrix. Iontophoresis, in combination with DOX-SLN, established high-concentration drug reservoirs in skin follicles. While iontophoresis of a DOX solution increased DOX penetration in the viable epidermis fourfold, cationic DOX-SLN iontophoresis increased DOX penetration fiftyfold. DOX-SLN iontophoretic therapy successfully suppressed tumor cell survival and proliferation in vivo, resulting in enhanced keratinization and cell death. These findings emphasize iontophoresis's powerful and synergistic effect with DOX-SLN, providing a potential technique for skin cancer treatment [38].

The findings of another study by Tupal et al. explored that the SLN suspension enhanced the permeability of doxorubicin, facilitating increased penetration through the skin to reach tumor cells. The study also demonstrated that SLNs effectively reduced cell viability in tumor cells, showcasing their efficacy in cancer cell destruction. Furthermore, SLNs were found to restrict tumor tissue growth, presenting a positive outcome for cancer treatment. This innovative approach holds promise for enhancing doxorubicin delivery and improving treatment outcomes for skin cancer. However, further research is essential to ascertain the long-term stability of SLNs and their potential toxicity on other organs [5].

In a similar research study, Taveira et al. successfully formulated cationic solid lipid nanoparticles incorporating doxorubicin, demonstrating encouraging outcomes in enhancing the drug's cellular uptake and cytotoxicity in melanoma B16F10 cells. Employing the 3^2 full factorial design enabled the optimization of nanoparticle formulation, highlighting the essential role of a cationic co-surfactant, CPC, in imparting a positive charge to the particles. In summary, the study suggests that these cationic SLNs hold promise in topical chemotherapy application [39].

pH-sensitive polymeric nanoparticle

Polymeric nanoparticles with pH sensitive properties are ideal for delivery of drug owing to their biodegradability and biocompatibility. These nanoparticles exhibit core-shell structures and are composed of amphiphilic polymers, including copolymers of di-block, di-triblock, star, and graft copolymers [40]. The physical characteristics of these polymeric particles are influenced by the proportion of hydrophilic and hydrophobic components within the individual block copolymer. Drug loading onto these nanoparticles

follows two principles: conjugation to monomeric polymers or encapsulation. Attaching hydrophobic active pharmaceutical ingredients to polar block polymers through biodegradable linkers emerges as a viable approach for achieving targeted drug release and enhancing the pharmaceutical profile [41,42].

As cytoplasmic endosomes or lysosomes has weak acidic pH, the pH sensitivity of polymeric nanoparticles can cause significant drug release in antitumor therapy. This mechanism not only minimizes cytotoxicity but also improves chemotherapeutic efficacy [43]. Polymeric nanoparticles offer additional advantages such as easy handling without compromising their physical, chemical, or biological properties, precise size control, and uncomplicated methods for incorporating and modifying biological payloads. To enhance efficacy and minimize toxicity resulting from off-target exposure of doxorubicin, the use of stimulus-responsive nano-carriers is considered [44]. [Figure 8] shows the mechanism of drug delivery of DOX utilizing polymeric nanoparticles.

A Recent study demonstrated that nanoparticles loaded with DOX utilizing PEG-poly(l-histidine)-poly(l-lactic acid) (PEG45 PHis45-PLLA82) swelled and improved DOX release at pH 5.0 in their investigation. This response was due to imidazole groups protonation in the PHis block, which resulted in a significant anticancer impact in HepG2 cells [45].

Qiu et al. found that pH responsive DOX micelles based on polyphosphazene-containing diisopropylamino (DPA) side groups have identical anticancer activity to free DOX against MCF-7 cells in a similar study. Furthermore, when tested against drug-resistant MCF-7 cells (MCF-7/ADR), the IC50 of these micelles was 10-20 times lower than that of free DOX [46]. The potent anticancer activity was attributed to pH-induced DOX release as well as increased endosomal escape through the 'proton sponge effect' of DPA moieties. Huo et al. discovered that doxorubicin (DOX) was released in a pH-dependent way by N-deoxycholic acid O, N-hydroxyethylation chitosan micelles modified with octreotide-PEG-deoxycholic acid. These micelles were effectively taken up by MCF-7 cells (which overexpress somatostatin receptors) using receptor-mediated endocytosis, leading to improved anticancer activity in nude mice bearing MCF-7 cancer xenografts compared to non-targeting N-deoxycholic acid-O, N-hydroxyethylation chitosan micelles [47].

In another study, Bhattacharya et al. synthesized a copolymer, PEG-SS-PCL-DOXI, as a proficient nanosystem for the controlled release of DOX. The copolymer demonstrates pH-responsive drug release in acidic conditions, and its biodegradability facilitates effective internalization into tumor cells. The study implies that this copolymer holds promise as an efficient nanocarrier for treatment of cancer [48].

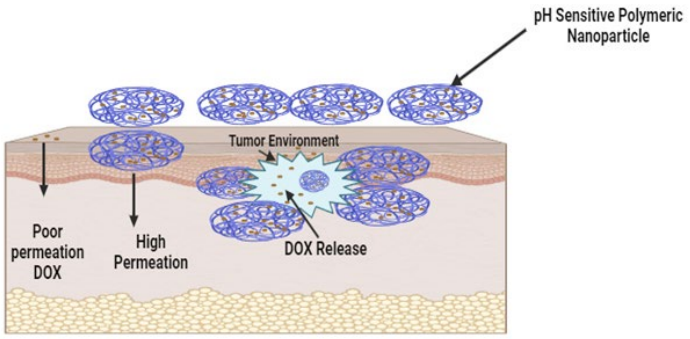

Figure 8. Doxorubicin delivery utilizing Polymeric Nanoparticles.

Nano fibrous membranes

Electrospun nanofibrous nonwoven membranes, serving as drug delivery systems, have demonstrated significant potential and consequently garnered considerable attention [49,50]. This simple, versatile, and valuable approach produces ultrafine Fibers with diameters ranging from nano to sub-micrometers from polymer solutions, as shown in [Figure 9].

Consequently, it allows for the preparation unique nanofibrous structured membranes with porous nature that exhibit favorable properties for topical delivery.

These properties include permeability, ability to maintain a moist environment, protection against microorganisms, and the potential to leave no scar [51]. This delivery system holds a distinct advantage in its ability to deliver controlled and consistent doses of bioactive agents to the target site, owing to its unique properties. These include the exceptionally high surface area, facilitating the rapid release of the entrapped active moieties. Furthermore, these membranes are highly porous, allowing the medication to reside in electro-spun nanofibers as amorphous or in nanocrystals form. This characteristic aids in the solubility and dissolving rate of drugs that are poorly water soluble [52,53].

Based on such unique properties Guo et al. engineered an nanofibrous membrane implant designed for effective and safe skin cancer therapy. They developed a core-shell nanofiber with a core of poly(lactic-co-glycolic acid) (PLGA), poly(-caprolactone) (PCL), DOX and a gelatin shell crosslinked with genipin using coaxial electrospinning. Electrospun fibers are recognized for their exceptional drug-carrying capabilities, offering a large surface area and high entrappment efficiency. Additionally, they can act as implantable devices at the tumor's edge or during surgical resection of solid tumors. Using core-shell electrospun nanofibrous membranes for local drug administration appears to be an intriguing approach for achieving excellent anti-tumor efficacy with minimum side effects. Following surgery, the fibers can encircle the remnant tumor. Guo et al. predict that as the fibers degrade, DOX will be gradually released and accumulate at the tumor site, resulting in higher efficacy and decreased toxicity without increasing treatment costs [54].

Mixed micelles

Drug delivery nanocarriers, commonly in the form of mixed micelles, are typically crafted from block copolymers as shown in [Figure 10]. These copolymers can be a combination of different types, a blend of block copolymers with amphiphilic molecules,

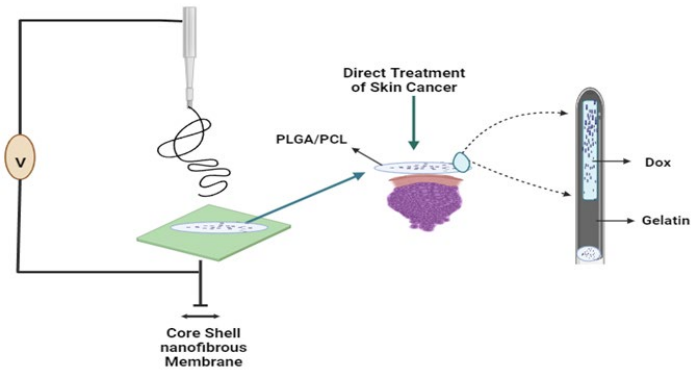

Figure 9. Nano-fibrous membranes preparation and it use for delivery of Doxorubicin.

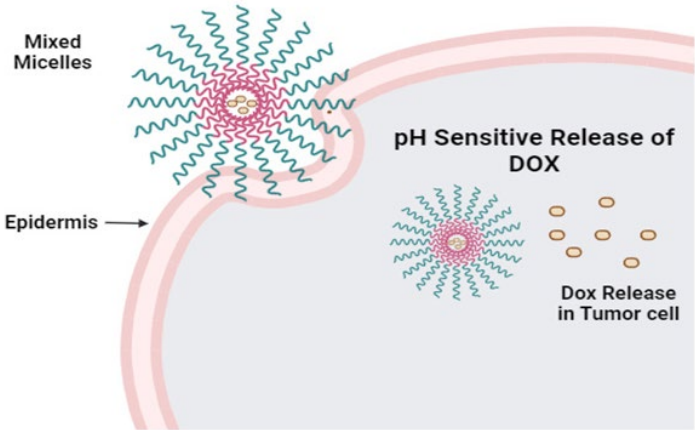

Figure 10. Doxorubicin Delivery in Skin Cancer using Mixed Micelle.

or a mixture of block copolymers with traditional anionic or cationic surfactants [55]. In contrast to single polymeric micelles (PMs), mixed micellar systems offer several advantages, including enhanced thermodynamic stability (lower CMC), improved kinetic stability, increased drug loading capacity, precise size control, and simplified methods for incorporating various modifications [56,57].

Recently, Thotakura et al. utilized a solvent dispersion technique to fabricate polymeric micellar systems with the goal of enhancing the safety and bioavailability of doxorubicin. They designed a mixed micellar system based on phospholipids, resulting in nanometric and symmetrical carriers. These carriers not only allowed for significant drug loading, but also controlled and maintained drug release over long periods of time. The pH-sensitive drug release demonstrated by these mixed micelles allowed for targeted spatial distribution to the specified spot, decreasing medication wastage via systemic circulation. The developed system's efficacy was proved by cancer cell toxicity tests and in vivo anti-tumor studies, emphasizing its exceptional performance. Blood profile investigations and biochemical calculations validated the combined micelles' safety. Biodistribution studies revealed that there was less medication available for microsomal breakdown. In summary, these findings provide evidence for the more efficient and safer administration of doxorubicin for the treatment of skin cancer using simple excipients such as phospholipids [58].

Chitosan based nanoparticle

Chitosan, a naturally derived polysaccharide from crustaceans, is extensively utilized in nanoparticle synthesis due to its exceptional biocompatibility and biodegradability. Commercially accessible chitosan typically exhibits a degree of deacetylation ranging from 60 to 100%, with a molecular weight spanning 3800 to 20,000 Da. Significantly, it undergoes facile in vivo degradation and subsequent elimination through renal pathways [59]. Chitosan formulations possessing elevated degrees of deacetylation are favored in drug delivery systems due to the accelerated breakdown rates associated with this characteristic. It is a non-toxic substance approved by the US Food and Drug Administration for application in wound dressings [60,61]. Additionally, under acidic conditions, chitosan behaves as a cationic polyelectrolyte, simplifying its binding with negatively charged cross-linking agents such as sodium tripolyphosphate (TPP) [62]. In contrast to alternative nanoparticle production techniques like emulsion-solvent extraction, spray drying, or micelle generation, the ionic gelation process offers distinct advantages. The cross-linking agent TPP exhibits non-toxic properties and remarkable gelling capacity. The manufacturing process is straightforward and devoid of toxic substances, allowing for easy modulation of particle size and zeta potential by adjusting the quantities of chitosan and TPP [63]. Additionally, chitosan nanoparticles (Chi-NPs) possess improved permeability, rendering them valuable as carriers for transdermal drug delivery [64].

In a study conducted by Janes et al. chitosan nanoparticles were evaluated as carriers for the drug doxorubicin (DOX). The primary challenge was to encapsulate the cationic and hydrophilic DOX within the nanoparticles formed through the ionic gelation of chitosan. The study revealed that the complexation of DOX with dextran sulfate not only doubled the encapsulation efficiency but also facilitated real loadings of up to 4.0 wt.% DOX. In vitro studies demonstrated that DOX-loaded nanoparticles with dextran sulfate maintained cytotoxic activity comparable to free DOX, whereas DOX complexed to chitosan before nanoparticle formation exhibited slightly decreased activity. Additionally, the bioactivity of DOX remained intact when encapsulated in these nanoparticles, indicating their potential for achieving controlled release over extended periods [65].

Soares et al. conducted a similar study, using chitosan and O-HTCC (ammonium-quaternary derivative of chitosan) nanoparticles as drug delivery vehicles for encapsulating doxorubicin. The findings indicated that the release of doxorubicin from the nanoparticles was unaffected by molecular weight and exhibited higher rates at acidic pH (4.5) compared to physiological pH. The nanoparticles demonstrated an average hydrodynamic diameter below 200 nm and achieved encapsulation efficiencies of up to 70% and 50% for doxorubicin in chitosan and O-HTCC nanoparticles, respectively. The release mechanism was identified as anomalous or mixed, featuring an initial burst effect within the initial hours and reaching a plateau after 24 hours. This study suggests that both chitosan and O-HTCC nanoparticles hold promise as effective drug delivery systems, showcasing high encapsulation efficiencies and controlled release potential for doxorubicin [66].

Doxorubicin-loaded chitosan nanoparticles elicit a cytotoxic response in A549 cells in vitro, albeit weaker compared to the free form of doxorubicin. The nanoparticles exhibit a delayed release of the drug to the cell, leading to a postponed cellular response. The study underscores the potential of mathematical modeling in gaining a deeper understanding of intracellular mechanisms involving nanoparticles and active pharmaceutical ingredients. Further investigations are required to explore the implications of these findings in an in vivo system and to assess the potential benefits of delayed drug release in cancer treatment [67]. An alternative study conducted a thorough examination of the physicochemical, photophysical, and morphological attributes of chlorin e6 (Ce6)-decorated doxorubicin (DOX)-encapsulated chitosan (CS)-tripolyphosphate (TPP) nanoparticles. Through dynamic light scattering (DLS) analysis, the nanoparticle size distribution was assessed, disclosing a span of 80-130 nm and an average size of 100 nm. The nanoparticles displayed a negative surface charge attributed to the presence of protonated amine groups. Scanning electron microscopy (SEM) and atomic force microscopy (AFM) revealed the spherical morphology of the nanoparticles, exhibiting homogeneous distribution and smooth surfaces. The physical loading efficiency of Ce6 in the nanoparticles was quantified using UV-Vis absorbance and emission spectra. The study demonstrated the nanoparticles' capability to generate singlet oxygen and their photostability. Overall, this investigation provided valuable insights

into the Ce6-decorated DOX-encapsulated CS nanoparticles' physical, chemical, and photophysical properties [68].

Iontophoresis, especially when using a chitosan gel, holds promise for augmenting the cutaneous penetration of doxorubicin (DOX) in the skin, thereby enhancing chemotherapy for skin cancer while minimizing systemic toxicity. The study demonstrated a substantial increase in the permeation and retention of DOX in the skin with iontophoresis. DOX incorporation into a non-ionic gel and iontophoresis with a chitosan gel resulted in decreased electroosmotic flow, showing DOX interaction with negative charges in the skin and better diffusion of DOX to deeper skin layers assisted by chitosan. Furthermore, the researchers discovered that directly applying a low electrical current to melanoma cells boosted DOX cytotoxicity. Overall, these findings indicate that iontophoresis, particularly with a chitosan gel, has the potential to improve cutaneous penetration of DOX, hence increasing treatment for skin cancer while reducing systemic toxicity [69].

In a separate investigation, the research delved into the development of doxorubicin (DOX) loaded chitosan (CS) nanoparticles using an innovative technique known as electrospray ionization, stabilized with tri-polyphosphate (TPP) for drug delivery. This study systematically optimized critical parameters, including needle gauge, electrospraying voltage, flow rate, working distance, and DOX to CS molar ratio. The result was the formation of nanoparticles within a size range of 300 – 570 nm (dry particles) and 530 – 870 nm (hydrated particles), as determined by scanning electron microscopy (SEM) and particle size analyzer. The encapsulation efficiency (EE) of DOX in the nanoparticles varied from 63.4% to 67.9% at DOX loadings of 1% to 0.25%. Furthermore, in vitro DOX release exhibited a sustained pattern for more than 7 hours at a concentration of 100 µg/mL equivalent of DOX. The study concludes that electrospray ionization proves to be a straightforward and efficient method for producing DOX-CS nanoparticles, with TPP emerging as a viable alternative to other chemically cross-linking agents. These DOX-CS nanoparticles hold potential applications in mitigating the side effects of cancer drugs during systemic administration and extending their therapeutic efficacy [70]. Souto et al. investigated the cytotoxicity profile and intracellular localization of doxorubicin-loaded chitosan nanoparticles for possible cancer drug delivery. The encapsulation of doxorubicin within nanoparticles led to a deferred release of the drug to the cell, consequently causing a delayed cellular response. The study employed mathematical modeling in conjunction with intracellular imaging techniques to visualize and comprehend the intracellular mechanisms of action of the nanoparticles. Emphasizing the significance of numerical simulations and in vitro models in assessing the toxicological effects of nanomaterials, establishing specific threshold effects in cells, and comprehending drug delivery processes, the study successfully demonstrated the cytotoxicity and internalization profiles of doxorubicin-loaded chitosan nanoparticles in A549 cells. Employing various assays, including the AlamarBlue® and MTT assays, the study evaluated cellular responses to free doxorubicin and doxorubicin-loaded nanoparticles, revealing a delayed response to the latter. This indicates a reduced rate of intracellular delivery for the chemotherapeutic agent encapsulated in the nano drug delivery vehicle. Moreover, insights into the cytotoxic mechanisms of doxorubicin-loaded chitosan nanoparticles within cells were gained through numerical simulations using a rate equation model. In essence, the study's results enhance our comprehension of the nanoparticles' behavior and their potential roles in cancer therapy [67].

Another study focused into the formulation and evaluation of chitosan nanospheres containing Doxorubicin hydrochloride for targeted drug delivery systems. This study revealed the self-assembly of chitosan into nanoparticles enables the encapsulation of drugs for specific site delivery. It also investigated the incorporation of Doxorubicin into nanoparticles and assessed its anticancer activity, with the goal of reducing side effects through targeted drug delivery. Analytical methods such as HPLC were employed to quantify drug loading, and in vitro drug release studies revealed a zero-order kinetic drug release. The article underscores the significance of nanotechnology in drug delivery for achieving controlled drug targeting and release [71].

Nonetheless, modifications in aforementioned chitosan result in N-palmitoyl-N-monomethyl-N,N-dimethyl-N,N,N-trimethyl-6-O-glycolchitosan derivatives (GCPQ), that could self-assemble into stable nanoparticles in aqueous conditions. GCPQ, as a safe carrier that forms nanometer-sized particles, raises the possibility of tumor targeting via passive diffusion generated by the EPR effect. As consequently, the use of GCPQ polymers offers an opportunity to establish a solid foundation for an effective anticancer drug delivery approach [72,73]. Recent in vitro investigations with GCPQ micelles as nanocarriers for selumetinib (AZD6244), an organic kinase inhibitor and anticancer medication, yielded excellent results. Despite their limited diffusion across tumoroid tissue, GCPQ-based nanoparticles outperformed the free drug in monolayer cell culture assays and tumoroids [74]. Moreover, etoposide, a lipophilic anticancer drug, was successfully encapsulated in GCPQ micelles, resulting in increased cellular absorption in breast cancer cells. Biodistribution studies in A431 xenografted mice confirmed the efficient transport of loaded GCPQ polymers to the solid tumor [75] [Figure11].

In a study designed by Kanwal et al. targeted drug delivery doxorubicin-loaded quaternary ammonium palmitoyl glycol chitosan (DOX-GCPQ) nanoformulation. The nanoformulation exhibited a sustained release pattern, higher uptake in cancer cells, and significant cytotoxicity against tumors in vitro. In xenografts, optical imaging demonstrated enhanced accumulation in the tumor, indicating its potential for targeted delivery and reduced systemic exposure [76].

Metal based nanoparticles

Metallic nanoparticles (MNPs) play a crucial role in biomedical applications, offering various possibilities for uses like enhancing radiotherapy and diagnostic assays [77]. MNPs are highly regarded due to their strong surface electromagnetic field, straightforward synthesis methods, and ease of surface functionalization [78]. Nanoparticle-based drug delivery systems exhibit greater efficacy

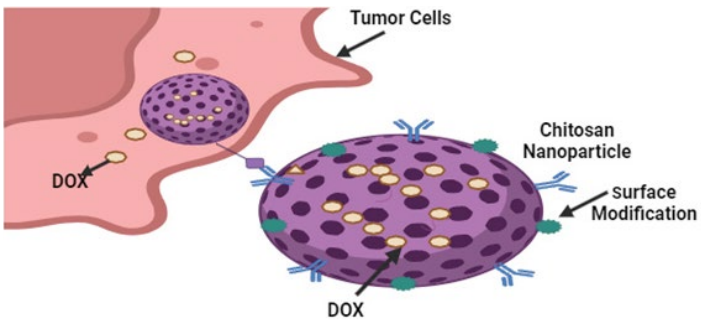

Figure 11. Chitosan based Nanoparticles in skin cancer therapy.

compared to conventional therapies, providing desirable pharmacokinetics, enhanced tumor cell targeting, reduced side effects, and mitigated drug resistance MNPs, either alone or in conjunction with polymers, peptides, DNA/RNA, lipids, and antibodies, can be used to target various tumor cells [79]. MNPs have grown in prominence in targeted drug delivery systems, where they are used in both active and passive targeting techniques, including tumor imaging. The inclusion of appropriate functional groups gives these particles unique characteristics [80].

Recently, the potential anticancer capabilities of nanoparticulate forms of various metals such as silver, gold, and copper have been widely identified as depicted in [Figure 12] [81, 82, 83].

Metallic nanoparticles have demonstrated the ability to accumulate either on the skin's surface or within it, depending on the surface properties of the material. Enhancing these technologies with skin-penetrating proteins could provide an additional advantage [79].

Based on aforementioned properties Mukherjee et al. conducted a study on PEGylated platinum nanoparticles (PtNPs) for melanoma drug delivery, offering valuable insights into advanced drug delivery systems for cancer therapy. The in vitro anticancer activity was confirmed through viability, cell cycle, and apoptosis assays. Cellular internalization studies using TEM and EDAX analysis demonstrated PtNPs and PtNPs-DOX internalization, indicating the potential effectiveness of the drug delivery system. In vivo experiments in a melanoma tumor model in mice showed promising results in tumor volume reduction and histopathological changes in treated groups. Platinum biodistribution in organs and tumors was analyzed using ICP-OES in mice treated with PtNPs-DOX. The study recognizes the support from individuals and organizations and suggests that the PEGylated platinum nanoparticles-based drug delivery system holds promise for effective melanoma treatment. It highlights the vital role of effective drug delivery in contemporary cancer therapy, providing a hopeful path for the advancement of drug delivery systems in the treatment of cancer [84].

In a similar study Chen et al. found improved therapeutic effects using DOX loaded porous Pt nanoparticles loaded for synergistic Chemo-/Electrodynamic Therapy. The study highlighted that the DOX@pPt-PEG NPs, along with square-wave AC treatment, caused severe damage to cancer cells and resulted in minimal cell proliferation. Moreover, the combination therapy demonstrated an impressive tumor growth inhibition rate of 95.5%, showcasing the most significant suppression of tumor growth compared to other group. These results indicate that this strategy shows potential for a more efficacious cancer treatment [85].

Recently, Kankala et al. has developed a versatile nanoformulation by efficiently incorporating ultrasmall platinum (Pt) nanoparticles into chitosan-wrapped zinc-doped mesoporous silica nanocarriers (Zn-MSNs). This novel approach shows promise in effectively addressing cancer multidrug resistance (MDR). The nanocomposites, featuring platinum nanoparticles dispersed on zinc-doped mesoporous silica nanocarriers, exhibit enhanced tumor penetration and synergistic therapeutic effects. The platinum nanoparticles aid in the nanocomposites' penetration into tumor tissues, contributing to tumor ablation. Moreover, these nanoparticles demonstrate high activity against MDR cells in conjunction with the chemotherapeutic agent doxorubicin (Dox), generating reactive free radical species. The nanocomposites display pH-responsive release of Dox, improving its delivery in the acidic tumor environment. In vivo investigations validate the tumor ablation effects of the designed nanocomposites. In conclusion, the study suggests that incorporating ultrasmall platinum nanoparticles into nanocomposites holds promise for effectively overcoming cancer multidrug resistance [86]. In another study, Gu et al. created nanocomposites based on mesoporous silica, decorated with platinum nanoparticles (PtNPs), and loaded with the anticancer drug doxorubicin (DOX), exhibiting promise for synergistic electrodynamic-chemotherapy. These nanocomposites showcase proficiency in effectively eliminating tumor cells by inducing the generation of reactive oxygen species (ROS) under the influence of an electric field. The integration of electrodynamic therapy (EDT) and chemotherapy within this nanoplatform introduces a novel strategy for treating large-sized tumors while minimizing side effects [87].

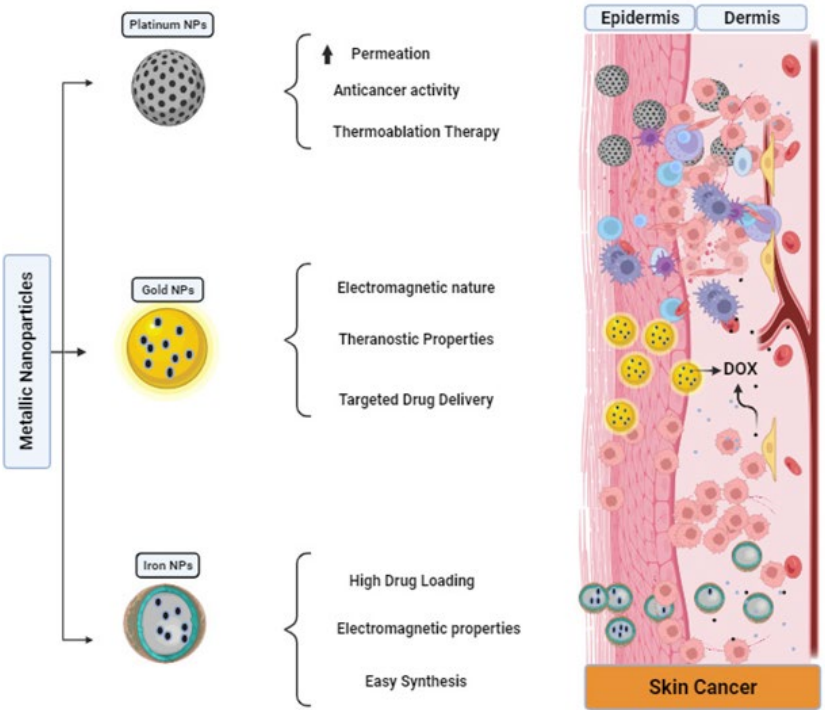

Figure 12. Doxurubicin loaded Metallic Nanoparticles for skin cancer treatment.

A similar study was conducted by Du et al. on gold nanoparticles (Au-Dox) synthesis with varying PEG and doxorubicin loadings. The study revealed intersting result displaying notably lower plasma levels of doxorubicin in a treated mice compared to those treated with an equivalent amount of free Doxorubicin, indicating the construct's stability in physiological conditions. Histopathological examination revealed no discernible differences between mice treated with Au-Dox and saline, while mice receiving an equivalent doxorubicin dose exhibited significant histopathological lesions [88].

In another study, Elbialy et al. synthesized nanoconjugates incorporating doxorubicin-loaded magnetic gold nanoparticles (MGNPs-DOX) and administered them into the bloodstream of mice with tumors, utilizing an external magnetic field for targeted delivery. The study assessed the therapeutic efficacy of the formulated nanoparticles, measured the biodistribution of doxorubicin in different organs, and conducted various biochemical analyses. Significantly, an external strong magnet with a surface strength of the magnetic field at 1.14 Tesla was employed to ensure extensive penetration of the magnetic field lines throughout the body [89]. Similarly, the potential of gold nanoparticles functionalized with doxorubicin (D-GNPs) for targeted treatment of chemically induced fibrosarcoma in mice was explored. Utilizing green chemistry methods, the carrier GNPs were synthesized and loaded with doxorubicin through an incubation process. D-GNPs have demonstrated to be cell-compatible and non-toxic when tested on normal mouse fibroblasts (L929). Passive targeting was evaluated by comparing antitumor activity against chemically produced fibrosarcoma to free Dox at different dosages (2.5, 2, and 1.5 mg/kg comparable to Dox). D-GNPs demonstrated notably elevated therapeutic anticancer effectiveness, accomplishing approximately 81% tumor suppression at a dosage equivalent to 2.5 mg/kg of Dox. In comparison, free doxorubicin achieved around 48% tumor suppression at the identical dosage. The safety and targeting efficiency of the formulated treatment were validated through the evaluation of cardiac and blood markers [90].

To prevent reoccurrence and development of tolerance Preet et al. explored the therapeutic potential of gold nanoparticles (GNPs) in co-delivering nisin and doxorubicin, individually or in combination, against DMBA-induced murine skin cancer. The observed efficacy was likely a result of apoptosis induction mediated by reactive oxygen species (ROS) and immunomodulation, either independently or through synergistic effects [91]. Mirza & Shamshad showcased the functionalization of gold nanoparticles (Au NPs) with the antitumor drug doxorubicin. The attachment of doxorubicin to gold was accomplished through amino group interaction, occurring under mild acidic conditions. In an alkaline solution, Au NPs couldn't adsorb doxorubicin due to the non-protonated state of the amino group. Nevertheless, in acidic conditions, protonation occurred, leading to the formation of a positively charged amino group, which facilitated easier adsorption. The presumed interaction between Au colloids and doxorubicin was primarily electrostatic in nature. High-resolution transmission electron microscopy (TEM) was employed to visualize the nanoparticles, confirming their consistent size and shape. This approach lays the foundation for creating hybrid nanoparticles labeled with multiple drugs and receptors, offering a promising alternative for nanosized drug-delivery systems [92].

Due to unique properties like superparamagnetic nature and anticancer activity, iron oxide nanoparticles (IO-NPs) is vastly used carriers in treatment of various cancers. For instance, Li et al. utilized IONPs for transporting Ce6 and doxorubicin (DOX) to melanoma cells by enhancing affinity to the cell membrane and improving cellular uptake. The hydrophobic nature of DOX induced IO-NP aggregation, forming nanoclusters. Ultimately, the IO@PG@DOX NPs were recognized as a simple and safe delivery platform, efficiently promoting the tumor enrichment of Ce6 and thereby enhancing antimelanoma photodynamic therapy (PDT) [93]. In a similar study, Kievit et al. showcase the potential of doxorubicin-loaded iron oxide nanoparticles in overcoming multidrug resistance in cancer cells. These nanoparticles were engineered to be pH-sensitive and resistant to drug efflux, leading to enhanced retention and efficacy compared to the free drug. This groundbreaking approach presents a promising strategy for enhancing cancer chemotherapy outcomes and holds significant implications for the treatment of diverse human tumors [94]. Kayal & Ramanujan conducted a study involving the coupling of doxorubicin (DOX) with iron oxide nanoparticles coated with varying concentrations of polyvinyl alcohol (PVA). The iron oxide nanoparticles were synthesized using the coprecipitation technique and coated with different weight percentages of PVA solution. Characterization techniques such as X-ray diffraction (XRD), transmission electron microscopy (TEM), thermogravimetric analysis (TGA), Fourier-transform infrared spectroscopy (FTIR), and vibrating sample magnetometry (VSM) were employed. The findings indicated that, within 80 hours, up to 45% of the adsorbed drug was released. FTIR analysis confirmed the conjugation of DOX to PVA-coated iron oxide nanoparticles. The functionalization of magnetic iron oxide nanoparticles with PVA, subsequent DOX conjugation, and the observed drug release collectively suggest the potential application of DOX-loaded PVA-coated iron oxide nanoparticles in magnetically targeted drug delivery [95].

Hydride hydrogel system

Hybrid hydrogel systems are intricately designed structures that incorporate polymer–drug conjugates with nanoparticles, providing versatile applications that include both antitumoral and antimicrobial activities [96, 97] [Figure13].

The potential is rooted in the integration of various therapeutic options, for instance chemotherapy, magnetic hyper-thermotherapy, and photo-thermotherapy, offering a range of options for multimodal treatment approaches [98,99]. However, achieving this goal is still a work in progress, and there is a distance to cover before it becomes a reality.

Capanema et al. pioneered a new class of hybrid hydrogels

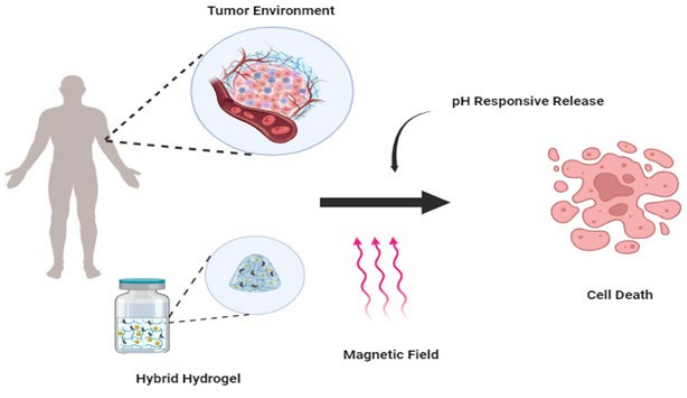

Figure 13. Use of Hybrid Hydrogel for Doxorubicin delivery in Skin Cancer.

incorporating Carboxymethylcellulose‐Silver Nanoparticles, showcasing dual functionality with both anticancer and antibacterial activities. Specifically tailored for topical delivery of drug in treatment of melanoma skin cancer, the environmentally friendly synthesis process involved utilizing carboxymethyl cellulose (CMC). CMC act both as a reducing agent and a polymer ligand. The colloidal silver nanoparticles (CMC@AgNPs) were intricately complexed with doxorubicin (CMC@AgNP-DOX) in aqueous dispersions, forming nanosized supramolecular structures. These nanoparticulate complexes were cross-linked through citric acid mediated covalent bonds, resulting in the creation of engineered hybrid hydrogel structures (CMC@AgNP-DOX-CA). In vitro studies showcased sustained release profiles of Doxorubicin against melanoma cells, coupled with antibacterial growth inhibition activity. This breakthrough opens new avenues for the application of these hybrid hydrogels in cancer nanomedicine [100].

Shahzadi et al. recently developed a MgO-doped CNC-g-PAA hydrogel by grafting poly(acrylic acid) (PAA) onto cellulose nanocrystals (CNC) and doping with magnesium oxide (MgO) at pH 7.0 and 12.0. The aim was to create a versatile nanocomposite hydrogel with both antibacterial and anti-cancer capabilities. Thorough characterization affirmed the formation of a well-connected porous structure in the synthesized nanocomposite hydrogels. Notably, MgO/CNC-g-PAA (pH = 12.0) displayed heightened bactericidal activity against both gram negative and gram positive bacteria, corroborated through in-silico molecular docking and assessments of produced reactive oxygen species. Furthermore, the nanocomposites efficiently loaded Doxorubicin (DOX), an anticancer drug, through electrostatic interactions, with a pH-triggered release of over 53.7% within 24 hours. In vitro cytotoxicity studies confirmed the enhanced antitumor efficacy of the nanocomposite hydrogels [101].

These research findings hold substantial implications for advancing the development of novel materials in medical applications, particularly in the domain of cancer therapy. The multifunctional attributes of the MgO-doped CNC-g-PAA hydrogel make it a promising candidate for further exploration and potential implementation in medical treatments.

CONCLUSION AND FUTURE PERSPECTIVES

Every year, skin cancer affects millions of individuals, and despite considerable research progress, it remains a formidable and often fatal disease. Doxorubicin is one of the most used chemotherapeutic agents for management of various cancers with special focus on skin cancer. But due to certain physiochemical properties its use is limited in case of skin cancers. These limitations of existing therapies with Doxorubicin underscore the pressing need for novel treatments. Numerous investigations are underway to address the challenges associated with Doxorubicin. Diverse nanocarriers are being explored to improve efficiency, enhance permeation, and mitigate side effects. Further research is required to elucidate the impact of alternative nanocarriers on doxorubicin for skin cancer with focus on ultra deformable nanocarriers like transferosomes and trans-ethosomes etc.

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