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Utilization of biodegradable calcium phosphate nanocarriers for the purpose of delivering drugs to tumors

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Abstract

Calcium phosphate (CaP) is an inorganic mineral found in complex tissues, including bone and teeth. CaP has been widely used in dental and orthopedic implants and bone tissue engineering due to its biocompatibility and biodegradability, closely resembling real bone. Calcium phosphate Nanoparticles (CaP-NP) may be used as efficient delivery carriers for transporting therapeutic substances, including nucleic acids, medicines, proteins, and enzymes, into tumor cells when formulated as nanoparticles. Recently, many methodologies have been devised to fabricate CaP Nanocarriers (CaP-NC) with the ability to adjust their size, maintain stability, and exhibit multiple functionalities. Additionally, the surfaces of these nanocarriers have been modified with targeting moieties to facilitate active targeting. The use of CaP-NC has been seen in loading probes, nucleic acids, anti-cancer medicines, and photosensitizers for cancer imaging, treatment, and theranostics. In this paper it has been conducted a comprehensive examination and methodologies used for the synthesis of biodegradable CaP-NC using co-precipitation method. The co-precipitation method is a highly regulated synthesis approach used for producing biodegradable CaP-NC, making it a viable technology in DD applications. The standalone application of biodegradable CaP-NC exhibits a modest inhibitory impact on the proliferation of tumors, resulting in a volume of 1000 mm3 by the fifth day. However, the utilization of biodegradable CaP-NC in conjunction with the incorporation of Doxorubicin (DOX) and the application of laser therapy yields a noteworthy decrease in tumor size, resulting in a final volume of 600 mm3. This outcome underscores the promising prospects of employing this particular DD system as a productive approach to cancer treatment. The findings of this study highlight the enhanced anti-tumor effectiveness of the combination of biodegradable CaP-NC, DOX, and laser treatment, indicating its potential as a viable strategy for reducing tumor volume.

Key Words: biodegradable, calcium phosphate nanoparticles, tumor diagnostics, Nanocarriers, drug administration.

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INTRODUCTION

The use of biomaterials in contemporary medicine is continuously evolving alongside the development of novel materials. Biomaterials find various clinical applications, such as their utilization in the fabrication of sophisticated surgical tools for plastic surgery procedures, modification of anomalies, production of scaffolds (porous constructions employed as guiding substrates for tissue regeneration) for regenerative therapies, as well as their implementation in structural functions [1]. Polymeric, metallic, and ceramic materials are often used as biomaterials. Furthermore, it is essential to emphasize that in the context of clinical medicine, using a specific biomaterial necessitates the assurance of its biological compatibility.

Biocompatibility, as defined by D. F. Williams, refers to the capacity of a substance to elicit an acceptable host reaction in a certain application, ensuring its safety and suitability for usage. Hydroxyapatite (HAp) is a prominent ceramic biological material used in therapeutic settings. HAp is a CaP mineral that naturally occurs in bones and teeth. It is extensively used in the manufacturing of macroporous scaffolds [2]. One of the primary uses of HAp in medicine is its utilization in bone grafts and implants due to its remarkable osteointegration characteristic. Additionally, HAp is used as a carrier for bioactive molecules, such as medicines and growth factors. Bioceramics have extensive use in several domains, including regeneration of bones and cancer nanomedicine [3].

According to the National Cancer Institute (INCA) in Brazil, cancer is characterized as a collection of over 100 disorders sharing the common feature of aberrant cellular proliferation, which can infiltrate tissues and organs [4]. Currently, there has been a significant surge in the prevalence of this particular phenomenon, making it the second most prominent cause of mortality on

a worldwide scale. Osteosarcoma, a malignant neoplasm impacting the connective tissue, has a notably high incidence rate among individuals in the pediatric and teenage age group (0-19 years). Typically, the standard therapeutic approach for osteosarcoma is the surgical removal of the main tumor and bone metastases in conjunction with chemotherapy. The bone deficiency that arises from tumor removal is often addressed using bone grafts to prevent fractures and deformities. The removal of tumor tissues is a difficult process, sometimes necessitating the subsequent administration of chemotherapy or radiation treatment [5].

Nevertheless, chemotherapy infusion is accompanied by the drawback of promptly releasing a significant portion of the anti-tumor medication, resulting in a quick attainment of maximum concentration shortly after treatment initiation, followed by a swift drop. This pattern of drug release is undesirable for effective treatment. In the present situation, endeavors have been undertaken to acquire alternate therapy modalities, with two areas of study emerging as the most promising. One potential use is the utilization of hydroxyapatite (HAp) scaffolds as Drug Delivery (DD) composites. The gradual release of anti-tumor drugs, such as Doxorubicin (DOX), cisplatin, and methotrexate [6], is ensured, facilitating targeted delivery and maintaining optimal drug concentration at the desired site for extended durations, thereby minimizing unwanted side effects [7]. The second area of study is to integrate HAp with Magnetic Nanoparticles (MNPs) to ensure their biological compatibility. Introducing nanoparticles into the human body, then raising the temperature in the surrounding area by using low-intensity exterior magnetic fields to heat the MNPs is often referred to as local Magnetic Hyperthermia (MH).

Cancer continues to pose significant worldwide health challenges, characterized by a rising incidence and considerable fatality rates. The prioritization of medical research has historically focused on the discovery of effective treatments for cancer treatment. A notable challenge in cancer therapy is the targeted delivery of therapeutic drugs to the tumor location while minimizing damage to adjacent healthy tissues. In response to this difficulty, scholars have redirected their focus toward the field of nanotechnology, which has prospects for the implementation of tailored medication administration. Biodegradable CaP-NC has recently emerged as a state-of-the-art strategy promising for transforming anti-cancer treatment.

LITERATURE SURVEY

Pursuing enhanced and precise cancer therapies has prompted significant research attention toward developing novel DD methods. Within this selection, it is evident that biodegradable CaP-NC has emerged as a promising platform for the targeted delivery of medications to tumor sites. The distinctive characteristics of CaP-NP, such as their biocompatibility, ability to regulate drug release, and potential for employment in imaging and theranostics, provide them a promising avenue of exploration within the realm of cancer. This literature review aims to provide a comprehensive summary of current scholarly investigations on the use of nanocarriers in targeted DD for tumors. In this study, we will examine a range of research papers that investigate nanocarriers' production, loading, and therapeutic capabilities.

Gang et al. (2021) conducted a study whereby they synthesized and evaluated drug carriers composed of hyaluronic acid-modified amorphous CaP. The fluorescent drug carriers they have developed show significant promise in tumor-targeted medication delivery [8]. The research successfully demonstrates the attainment of desirable drug release kinetics, characterized by a prolonged release of about 75% of the loaded medication throughout 72 hours. The present methodology capitalizes on the benefits of hyaluronic acid and CaP in the context of tumor targeting. However, it is important to acknowledge that this strategy is constrained by scaling limits and possible concerns about long-term stability.

The study conducted by Qiu et al. (2022) centers on synthesizing and using CaP-NC for medication delivery [9]. The work illustrates the adaptability of these nanocarriers in various pharmacological applications, exhibiting drug-loading capabilities ranging from 20% to 50%. The advantageous aspect of the nanocarriers for DD lies in their scalability, while the issue

of producing continuous drug release persists. Furthermore, it is essential to do additional research on their efficacy in in vivo settings.

The present study by Mesas C. et al. (2022) examined the potential of CaP-NP, that are loaded with bioactive chemicals derived from Euphorbia lathyris, for colon cancer treatment [10]. The research effectively demonstrates the capacity of these nanoparticles to suppress the proliferation of cancer cells, as shown by their inhibitory effects in both laboratory settings (in vitro) and living organisms (in vivo). Significantly, they demonstrate a remarkable 70% decrease in tumor volume in an in vivo setting. Nevertheless, the research shows a deficiency in doing a thorough evaluation of toxicity and should delve into the examination of any unintended consequences.

In their recent publication, Yang et al. (2021) introduced an innovative methodology aimed at addressing the issue of bone metastases in patients with prostate cancer. Using CaP-polymer hybrid nanoparticles with bone-targeting properties to simultaneously administer zoledronate and docetaxel has considerable potential. The findings demonstrate successful localization of the treatment to the bone, resulting in a notable decrease of 50% in tumor dimensions [11]. Further research is required to examine possible systemic toxicity, particularly concerning the administration of zoledronate.

In their study, Liu et al. (2019) investigated the use of degradable CaP-coated upconversion nanoparticles for chemo-photodynamic treatment. The nanoparticles demonstrate effective kinetics for drug release and possess potential for photodynamic treatment [12]. The findings indicate a significant reduction in the size of the tumor. However, more research is necessary to explore the extended safety and biocompatibility of the upconversion nanoparticles.

In their study, Fu et al. (2019) introduced a novel approach, including using biodegradable manganese-doped CaP nanotheranostics to improve the efficacy of anti-tumor treatment [13]. The nanotheranostics demonstrate efficient execution of traceable cascade events, resulting in a notable 60% decrease in tumor dimensions. Although this strategy displays innovation, further research is required to investigate its long-term safety and potential systemic toxicity thoroughly. The study by Huang et al. (2019) primarily examines the use of CaP-NC in the context of tumor DD. The publication comprehensively examines several aspects, including imaging, treatment, and theranostics [14].

In their study, Khalifehzadeh and Arami (2020) investigated the potential of biodegradable CaP-NP in cancer treatment. The article examines the potential use of nanoparticles in medication delivery, offering valuable insights into their degradation patterns and release kinetics [15]. The work provides valuable insights into the biodegradability of CaP-NP. However, doing more research to assess their safety and explore their possible therapeutic uses is essential.

Given the intricate and demanding nature of cancer therapy, biodegradable CaP-NC has shown significant promise as a viable approach for DD. The literature survey examined many publications that jointly emphasize the adaptability and efficacy of nanocarriers in tumor targeting and therapeutic DD. Nanocarriers provide a multimodal approach to cancer treatment, including tumor-specific medication release, better therapeutic results, and diagnostic capabilities.

UTILIZATION OF BIODEGRADABLE CAP-NC FOR DD TO TUMORS

Within DD systems' dynamic and changing realm, nanocarriers have emerged as promising entities for targeted and controlled drug release. Biodegradable CaP-NC have garnered significant interest owing to their distinctive characteristics, which provide several benefits for medicinal purposes. This work comprehensively examines the synthesis, characteristics, and prospective uses in DD of biodegradable CaP-NC. The focus is on providing an overview of the development and characterization of these materials.

Preparation and characterization of CaP-NC

The process of synthesizing biodegradable CaP-NC encompasses a range of methodologies, each tailored to attain

distinct attributes and drug-loading capabilities. The co-precipitation approach is a frequently used technique in which calcium and phosphate precursors undergo a process to generate nanoparticles. The ability to exert meticulous control over reaction conditions, including factors such as temperature, pH, and the selection of precursors, facilitates the customization of nanocarrier characteristics such as size, morphology, and surface charge. Furthermore, using surfactants, polymers, or organic modifiers during manufacturing might augment drug encapsulation's stability and efficacy in these nanocarriers.

Various techniques were devised to synthesize CaP-NP with varying characteristics such as size, shape, and content. The methods described in this study are primarily concerned with synthesizing CaP particles at the nanoscale level. Various forms of CaP, such as HAp with a calcium-to-phosphorus ratio of 1.7, Tri-Calcium Phosphate (TCaP) with a ratio of 1.5, brushite with a ratio of 1, and Amorphous CaP (ACaP) with a ratio of 1.5, among others, are prepared using different material ratios. The present CaP co-precipitation synthesis methodologies often use the utilization of NaH2PO4, Na2HPO4, Na3PO4, or a mixture thereof as phosphate salts. The reaction is given as follows:

$$10CaCl2 + 6Na3PO4 + NaOH = Ca(9+x/2)(PO4)6(OH)2 + (18+x)NaCl + (1-x/2)CaCl2 \quad (1)$$

The value of x in the equation maybe 0, 1, or 2. Several factors, including the quantity of calcium and phosphate ions and the pH and temperature of the solution, influence the saturation levels of various CaP phases in a solution. These constituents are categorized based on their Ca/P atomic ratio; pH stability range in aqueous solutions at a temperature of 24°C, and density.

The following steps have been used in the synthesis of biodegradable CaP using the co-precipitation method (as shown in Fig 1):

Step 1: Preparation of the calcium precursor. Utilize an analytical balance to measure a precise quantity of calcium nitrate tetrahydrate ($Ca(NO3)2 \cdot 4H2O$). The required quantity will depend on the targeted Ca/P ratio inside the ultimate nanocarriers. The calcium nitrate should be dissolved in a beaker holding a predetermined quantity of distilled water. Agitate the solution with a glass rod until the salt achieves full dissolution.

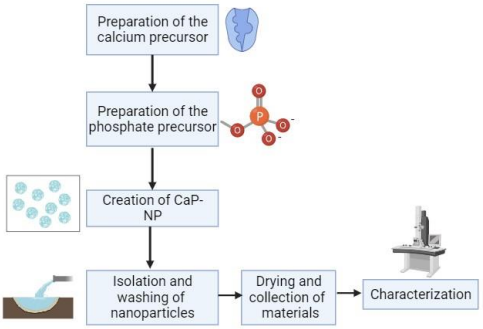

Fig.1. Synthesis of biodegradable CaP using co-precipitation method.

Step 2: Synthesis of Phosphate Precursor

In an independent container, measure the necessary quantity of dibasic ammonium phosphate ($(NH4)2HPO4$) using a weighing instrument. The ammonium phosphate should be dissolved in a separate beaker containing purified water. Agitate the mixture until it achieves full dissolution.

Step 3: Creation of CaP-NP

The calcium precursor solution (Step 1) should be carefully poured into the phosphate precursor (Step 3) while continuously stirring with a magnetic stirrer. This process will result in the simultaneous precipitation of calcium and phosphate ions, resulting in the formation of nanoparticles composed of amorphous calcium phosphate.

The pH of the reaction mixture may be modified by adding ammonia solution ($NH4OH$). It is necessary to regulate the pH level within a specified range, often between 9 and 10. The manipulation of pH levels significantly impacts both the size and content of nanoparticles. Proceed with the agitation of the mixture for a designated duration, often spanning a few hours, to facilitate the growth of the nanoparticles. The adjustment of reaction temperature is contingent upon the specific features needed for the nanocarriers.

Step 4: Isolation and washing of nanoparticles

Following the completion of the reaction, it is recommended to cease stirring and provide sufficient time for the nanoparticles to undergo sedimentation. The combination should be centrifugated to separate the nanoparticles from the solution. The supernatant should be discarded, and the nanoparticles should be washed often using

deionized water to eliminate any remaining unreacted precursors and contaminants.
Step 5: Drying and collection of the materials
The cleaned nanoparticles should be placed in a drying oven at a carefully regulated temperature to eliminate residual moisture. The selection of drying temperature and duration will be contingent upon the particular specifications of the experiment. After the whole drying process, the biodegradable calcium phosphate nanocarriers should be gathered.
Step 6: Characterization
The produced nanocarriers were subjected to several characterization methods, including Scanning Electron Microscopy (SEM), X-ray diffraction (XRD), Dynamic Light Scattering (DLS), and Fourier-Transform Infrared spectroscopy (FTIR). These techniques were used to validate and ascertain the nanocarriers' size, shape, crystallinity, and chemical composition.
The co-precipitation method is a highly regulated synthesis approach used for producing biodegradable CaP-NC, hence making it a viable technology in the field of DD applications. The attainment of desired features of nanocarriers requires careful regulation of reactant concentrations, pH levels, and reaction circumstances. The obtained nanocarriers may be further modified or filled with pharmaceutical substances to cater to particular therapeutic purposes.
It is important to emphasize that calcium phosphate is not a singular compound but a diverse group of compounds. This diversity arises from the many protonation states of the phosphate anion and the capacity of CaP to undergo anion and cation substitution with other ions. The investigation and identification of the crystalline phase found in CaP materials are often omitted or unknown in different papers. Consequently, these materials are commonly referred to simply as "CaP." Therefore, it is common for CaP-NP to consist of a combination of several phases of calcium phosphate. Considering the acid solubility of calcium and phosphate ions, it is important to highlight that this characteristic significantly impacts the biomedical application.
The degradability of various CaP phases in acidic buffers varies and may be categorized as follows (indicated by "≫" to signify significantly larger solubility): ACP is greater than α-TCP, which is greater than ß-TCP, followed by calcium-deficient hydroxyapatite (CDHAp), HAp, and fluorapatite. Moreover, HAp is considered the most prevalent kind of CaP among them. The formation of HAp occurs in a solution with a neutral to basic pH. This process involves the interaction between calcium ions and phosphate ions, forming a precursor amorphous phase known as Aqueous Calcium Phosphate (ACP) with a Ca/P ratio of 1.5. The ACP consists of $Ca_3(PO_4)_2{\cdot}xH_2O$. Subsequently, the ACP transforms into spherical clusters called Posner's Clusters (PCs) composed of $Ca_9(PO_4)_6$. These PCs densely accumulate and bind to water in the surrounding environment, forming larger spherical particles. Nevertheless, HAp is considered one of the most stable phases that may be synthesized under physiological settings. Therefore, it has become the prevailing technology often used for medication administration.

Biodegradable CaP-NC for DD to tumors

Biodegradable CaP-NC, sometimes referred to as biodegradable nanoparticles, have been designed to encapsulate therapeutic medications and facilitate their targeted delivery to specific tumor sites. The nanoparticles are constructed using CaP components that are biocompatible and biodegradable, guaranteeing compatibility with the human body's physiological processes. These entities exhibit several notable characteristics, making them very suitable contenders for targeted DD:
Precise targeting refers to the ability to accurately identify and focus on certain individuals, groups, or segments within a larger population. One of the primary benefits inherent in these nanocarriers is their capacity to selectively target tumor locations with a notable degree of selectivity. By modifying their surface with ligands capable of specifically recognizing distinct markers on cancer cells, these carriers may effectively target medication delivery to the most critical sites.
Biodegradability: It refers to the ability of a substance to undergo decomposition. The name "biodegradable" connotes the characteristic of these carriers to undergo decomposition over a while, resulting in the

slow release of the encapsulated medicine. This characteristic guarantees the maintenance of therapeutic medication concentrations at the specific location of the tumor, hence enhancing the overall efficacy of the therapy.

The augmentation of drug solubility: A significant limitation in the effectiveness of several anti-cancer medications arises from their inadequate solubility. Using CaP-NC can potentially enhance medication solubility, augmenting the drug's bioavailability and efficacy in targeting cancerous cells.

Safeguarding drug payloads: The nanocarrier functions as a protective barrier, shielding the medicine from premature breakdown until it reaches the tumor site. This mechanism guarantees a higher proportion of the therapeutic payload is successfully transported to the cancer cells without degradation.

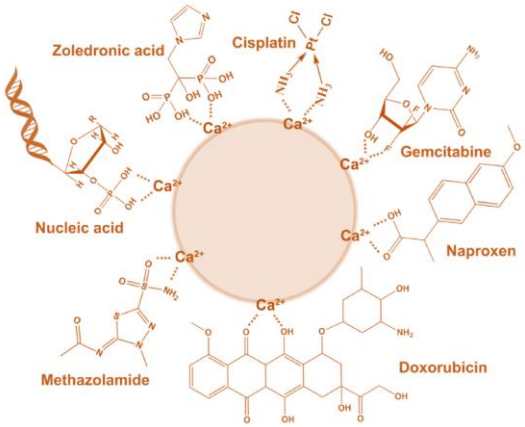

Fig.2. A schematic representation of the interaction between a collection of typical molecules and the Ca2+ ions inside CaP-NC

The process by which CaP-NC captures drugs involves the interplay between calcium ions and the functional groups in the drug molecules. As depicted in Fig. 2, the functional groups encompass various chemical moieties, including the phosphate group (-PO3H) found in nucleic acids such as DNA, siRNA, and microRNA, as well as other small molecule compounds like zoledronic acid. Additionally, the carboxyl group (-COOH) is present in substances like naproxen, while the sulfonic group (-SO3H) can be found in compounds such as methazolamide. Furthermore, the amino group (-NHn) is observed in cisplatin, and the hydroxyl or fluorine group (-OH or –F) is present in compounds like gemcitabine and DOX. Lastly, the sulfhydryl group (-SH) is another functional interest group. In theory, CaP-NC has the potential to carry small molecule chemical medications or macromolecular biological pharmaceuticals that include the functional groups indicated before, hence enabling a wide range of medicinal uses. It should be noted that the stability of CaP-NPs is intricately linked to the concentration of ions present in the surrounding medium.

The introduction of changed molecules disrupts this delicate equilibrium, forming unstable agglomerates or the dissolution of CaP-NP. Therefore, it is important to exercise control over the synthesis of CaP-NP from several viewpoints, including the technique used (such as material dose, pH, temperature, electrolyte, and feeding sequence). In addition, it is imperative to perform surface functionalization of therapeutic CaP-NP to extend their duration in the bloodstream. This can be achieved by incorporating targeting molecules such as peptides and antibodies onto the surface of the nanoparticles. This modification often facilitates the Enhanced Permeation and Retention (EPR) of CaP-NP at the site of interest, resulting in improved therapeutic effectiveness while requiring a lower dosage of the given nanoparticles. Various techniques have been used to modify the surface of CaP materials, including the attachment of macromolecules such as lipids, polymers, peptides, and nucleic acids by covalent or non-covalent (electrostatic) conjugation. To be considered a certified CaP-NP, the particle must maintain its structural stability at the nanoscale while also possessing distinct functionalities.

The use of biodegradable CaP-NC presents a paradigm-shifting strategy in cancer therapy. The precise delivery of medications to tumor locations significantly transformed the approach to cancer treatment, presenting the potential for enhanced efficacy and reduced adverse effects in therapeutic interventions. The current epoch of cancer treatment, characterized by customized and targeted approaches, is on the verge of emerging. Biodegradable CaP-NC has emerged as a prominent player in driving this paradigm shift.

RESULTS AND DISCUSSION

The produced nanocarriers were subjected to several characterization methods, including Transmission Electron Microscopy (TEM), used to validate and ascertain the nanocarriers' size, shape, crystallinity, and chemical composition.

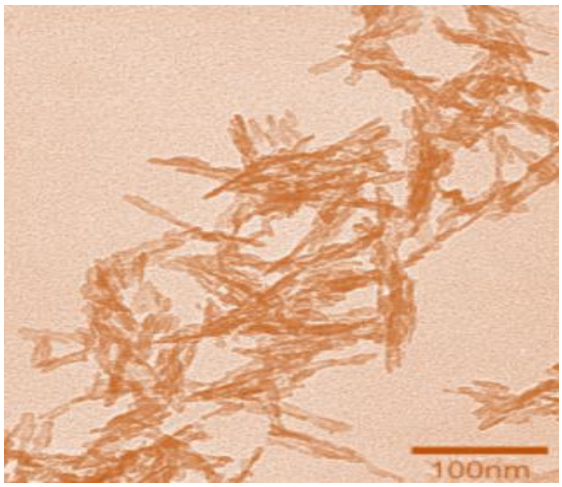

Fig.3. TEM image of biodegradable CaP-NP

The shape of biodegradable CaP-NP generated via the co-precipitation process is seen in Fig. 3. The provided picture showcases nanoparticles that exhibit a homogeneous and spherical morphology characterized by a relatively limited range of sizes. This observation serves to emphasize the efficacy of the synthesis procedure used. The size and shape of nanoparticles play a crucial role in determining their behavior in DD applications. A uniform and precisely specified size is necessary for reliable drug loading and release characteristics. The TEM image in this study indicates that the co-precipitation process has successfully produced nanoparticles well-suited for effective drug encapsulation. This finding has significant potential for developing tailored DD systems, particularly in the field of cancer treatment.

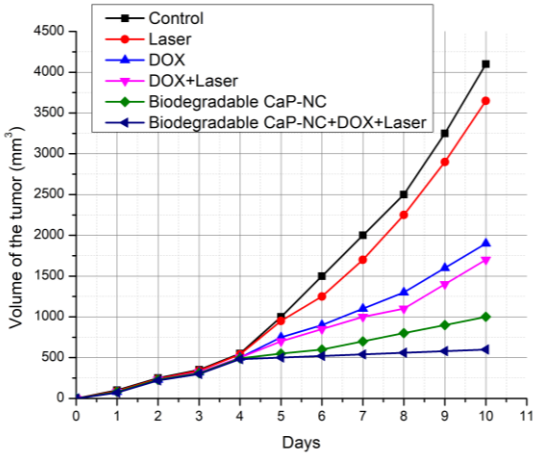

Fig.4. Tumor volume graph

Fig. 4 presents a thorough depiction of tumor progression over ten days under different treatment conditions. The data presented in the study provide evidence of the efficacy of various treatment modalities in managing tumor volume. Within the control group, the tumor volume exhibits a consistent upward trend, ultimately reaching a measurement of 4100 mm3 on the tenth day. The isolation laser therapy demonstrates a degree of decrease, resulting in a final volume of 3650 mm3. The DOX chemotherapy treatment demonstrates a significant decrease, resulting in a final volume of 1900 mm3. However, when DOX is coupled with laser therapy, the therapeutic impact is further augmented, reducing the volume to 1700 mm^3.
The standalone application of Biodegradable CaP-NC has a modest inhibitory impact on the proliferation of tumors, resulting in a volume of 1000 mm3 by the fifth day. Nevertheless, using Biodegradable CaP-NC in conjunction with Doxorubicin (DOX) administration and laser therapy results in a noteworthy decrease in tumor size, ultimately reaching a volume of 600 mm3. This outcome underscores the promising prospects of using this particular DD system in cancer treatment, as it demonstrates its efficacy. The findings of this study highlight the enhanced anti-tumor effectiveness of the combination of CaP-NC, DOX, and laser treatment, indicating its potential as a viable strategy for reducing tumor volume.

CONCLUSION

This work presents a complete analysis of the approaches employed in producing

biodegradable CaP-NC by the co-precipitation process. The co-precipitation method is a well-controlled synthesis technique employed for the fabrication of biodegradable CaP-NC, therefore establishing its suitability as a promising technology in DD applications. Using biodegradable CaP-NC as a single treatment has a moderate inhibitory effect on tumor multiplication, leading to a final volume of 1000 mm3 by the fifth day. However, the use of biodegradable CaP-NC in combination with the integration of DOX and the implementation of laser treatment leads to a significant reduction in tumor size, ultimately culminating in a final volume of 600 mm3. As mentioned above, the result highlights the potential benefits of utilizing this specific drug delivery technology as an effective strategy for cancer therapy. The results of this study emphasize the augmented anti-cancer efficacy achieved by the utilization of a composite consisting of biodegradable CaP-NC, DOX, and laser therapy. These findings suggest that this combination has promise as a feasible approach for diminishing tumor size.

REFERENCES

1. Chen Y, Yu J, Ke Q, Gao Y, Zhang C, Guo Y. Bioinspired fabrication of carbonated hydroxyapatite/chitosan nanohybrid scaffolds loaded with TWS119 for bone regeneration. *Chem Eng J*. 2018;341:112-125. Google Scholar Crossref
2. Chen S, Shi Y, Luo Y, Ma J. Layer-by-layer coated porous 3D printed hydroxyapatite composite scaffolds for controlled drug delivery. *Colloids Surf B Biointerfaces*. 2019;179:121-127. Google Scholar Crossref
3. Park K, editor. *Biomaterials for Cancer Therapeutics: Evolution and Innovation*. Woodhead Publishing; 2020. Google Scholar Crossref
4. Moura SF, de Mello MRSP, Muzi CD, Guimarães RM. Padrão Sintomatológico em Pacientes do Câncer Colorretal de acordo com a Idade. *Rev Bras Cancerol*. 2020;66(1). Google Scholar Crossref
5. Zhou ZF, Sun TW, Chen F, Zuo DQ, Wang HS, Hua YQ, et al. Calcium phosphate-phosphorylated adenosine hybrid microspheres for anti-osteosarcoma drug delivery and osteogenic differentiation. *Biomaterials*. 2017;121:1-14. Google Scholar Crossref
6. dos Apostolos RC, Andrade GF, da Silva WM, de Assis Gomes D, de Miranda MC, de Sousa EM. Hybrid polymeric systems of mesoporous silica/hydroxyapatite nanoparticles applied as anti-tumor drug delivery platform. *Int J Appl Ceram Technol*. 2019;16(5):1836-1849. Google Scholar Crossref
7. Zhang Y, Fang F, Li L, Zhang J. Self-assembled organic nanomaterials for drug delivery, bioimaging, and cancer therapy. *ACS Biomater Sci Eng*. 2020;6(9):4816-4833. Google Scholar Crossref
8. Gang X, Wang L, Jia J, Wang H, Lian X, Gao X, et al. Synthesis and biological evaluation of fluorescent hyaluronic acid modified amorphous calcium phosphate drug carriers for tumor-targeting. *Int J Biol Macromol*. 2021;182:1445-1454. Google Scholar Crossref
9. Qiu C, Wu Y, Guo Q, Shi Q, Zhang J, Meng Y, et al. Preparation and application of calcium phosphate nanocarriers in drug delivery. *Mater Today Bio*. 2022;100501. Google Scholar Crossref
10. Mesas C, Garcés V, Martínez R, Ortiz R, Doello K, Dominguez-Vera JM, et al. Colon cancer therapy with calcium phosphate nanoparticles loading bioactive compounds from Euphorbia lathyris: In vitro and in vivo assay. *Biomed Pharmacother*. 2022;155:113723. Google Scholar Crossref
11. Yang Q, Liu DZ, Liu M, Ji QF, Mei QB, Cheng Y, et al. Bone-targeted calcium phosphate-polymer hybrid nanoparticle co-deliver zoledronate and docetaxel to treat bone metastasis of prostate cancer. *J Pharm Sci*. 2021;110(2):876-887. Google Scholar Crossref
12. Liu S, Li W, Dong S, Gai S, Dong Y, Yang D, et al. Degradable calcium phosphate-coated upconversion nanoparticles for highly efficient chemo-photodynamic therapy. *ACS Appl Mater Interfaces*. 2019;11(51):47659-47670. Google Scholar Crossref
13. Fu LH, Hu YR, Qi C, He T, Jiang S, Jiang C, et al. Biodegradable manganese-doped calcium phosphate nanotheranostics for traceable cascade reaction-enhanced anti-tumor therapy. *ACS Nano*. 2019;13(12):13985-13994. Google Scholar Crossref
14. Huang D, He B, Mi P. Calcium phosphate nanocarriers for drug delivery to tumors: imaging, therapy and theranostics. *Biomaterials Sci*. 2019;7(10):3942-3960. Google Scholar Crossref
15. Khalifehzadeh R, Arami H. Biodegradable calcium phosphate nanoparticles for cancer therapy. *Adv Colloid Interface Sci*. 2020;279:102157. Google Scholar Crossref