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Biocompatible polymer-based drug carrier nanoparticles containing chemotherapeutics

PH.D. THESIS

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Introduction and Aim of Research

The traditional chemotherapy treatment of malignant tumors can be accompanied by severe side effects, and resistance to the anticancer agent can develop in the tumor cells. To overcome this, chemotherapy drugs can be encapsulated into nanoparticles and used as drug delivery systems to specifically target the tumor tissue. The release of the active ingredient can be controlled and designed, allowing for its actualization in the target tissue. Significant dose reduction can be achieved compared to conventional systemic administration, thus greatly reducing unwanted side effects. The lack of resistance development is expected through the combined application of multiple agents with different mechanisms of action.

Nanoparticles were prepared using various biodegradable polymers, such as poly(lactic-co-glycolic acid) (PLGA), polyhydroxyalkanoate (PHB) derivatives, and poly(vinyl alcohol) (PVA). The chemotherapy agents doxorubicin and sorafenib were encapsulated into these nanoparticles. To achieve greater stability, selective targeting, and an extended circulation half-life, the surface of the nanoparticles was modified with different materials (secondary bonds: poloxamers, polyvinyl alcohol; covalent bonding: polyethylene glycol, tumor-penetrating peptide). The physical and chemical properties of the produced nanoparticles, including size and composition, were analyzed using techniques such as dynamic light scattering, UV-visible spectroscopy, and liquid chromatography.

The rate of drug release from the microencapsulated drugs in the form of nanoparticles was investigated, as well as the efficacy of the drug delivery system on live cell cultures. The uptake of nanoparticles by cancer cells (HT-29 and HepG2 cell lines) was measured before and after surface modification, and the cytotoxic effects of the chemotherapeutic drugs released from the nanoparticles were compared to the equivalent amount of free drug compound.

Experimental work

During my research, the aim was to overcome the side effects of chemotherapeutic agents and the development of resistance in tumor cells against individual drugs by utilizing various polymers to create biocompatible and biodegradable drug delivery nanocarriers. The goal was to develop drug delivery systems with personalized therapy requirements, using different materials, particle sizes, and varying drug contents. Nanocarriers were fabricated to meet the demands of personalized therapy, incorporating different materials and varying particle sizes and drug loadings. The objective was to create drug delivery systems that are biocompatible, biodegradable, and tailored to the specific needs of individual patients.

By utilizing these nanocarriers, it was aimed to enhance the therapeutic efficacy while minimizing the adverse effects of chemotherapy, as well as to address drug resistance issues commonly observed in tumor cells. The development of these versatile drug delivery systems offered the potential for targeted and controlled drug release, allowing for improved treatment outcomes and increased patient well-being.The sorafenib drug was efficiently encapsulated with high drug loading into water-insoluble PVA polymers with well-defined structures synthesized using metathesis, demonstrating a favorable result in the uptake of these nanocarriers by tumor cells. In cytotoxicity tests, the encapsulated drug showed similar efficacy to the pure, unencapsulated drug. Polymer nanocarriers containing a combination of sorafenib and doxorubicin were first prepared using traditional PLGA and PEG-modified PLGA polymers. The release of drug content occurred at the desired rate for doxorubicin, while for sorafenib, the carrier matrix only modestly slowed down drug release in plasma medium. Studies conducted on the HT-29 cell line demonstrated that PEG-modified PLGA-based carriers were significantly taken up by tumor cells to a greater extent. Based on the cytotoxicity tests, both types of drug delivery systems exhibited concentration-dependent effects, but the PEG-modified version displayed a significantly more pronounced effect. The surface of PEG-modified PLGA-based nanocarriers was modified with iRGD tumor-penetrating peptide, and the changes in their physicochemical parameters and biological effects were investigated. The size of the nanocarriers increased as expected, and the modified nanocarriers were taken up by tumor cells to a greater extent, 22% higher compared to the unmodified nanocarriers. Nanocarriers containing both doxorubicin and sorafenib with high drug content were prepared from PHB-based polymers. The drug release profile was described using a kinetic process.

The PHB-based nanocarriers were modified with PEG, and the physical, chemical, and biological effects of the surface modification were examined. Although the size of the nanocarriers slightly increased, their drug release was slowed down. The PEG-modified nanocarriers exhibited increased cytotoxicity compared to the traditional version.

New scientific results: thesis statements of the doctoral dissertation

1. The sorafenib drug was efficiently encapsulated with high encapsulation efficiency (93.6%) and drug loading (12.0%) into well-defined, metathesis-synthesized, water-insoluble polyvinyl alcohol polymer microcapsules. The resulting nanocarriers were effectively taken up by cancer cells and exhibited concentration-dependent cytotoxicity on HT-29 adenocarcinoma cells. (S2)
2. Polymer nanocarriers containing both sorafenib and doxorubicin were first prepared using biodegradable poly(lactic-co-glycolic acid) (PLGA) and PEG-modified PLGA polymers. The nanocarriers exhibited sustained drug release of doxorubicin in plasma for up to one week, while rapid drug release was observed under acidic pH conditions characteristic of the tumor microenvironment. Sorafenib was quickly released from PLGA nanocarriers in plasma, whereas PEG-modified PLGA slowed down its release. In acidic conditions, both types of polymer carriers exhibited a slower release of sorafenib. HT-29 adenocarcinoma cells took up a significantly higher amount of PEG-PLGA nanocarriers compared to PLGA nanocarriers. This explains the observation that although both carriers exhibited concentration-dependent cytotoxicity, the PEG-PLGA drug delivery nanocarriers proved to be more effective in the cytotoxicity evaluation on HT-29 adenocarcinoma cells. (S1)
3. The successful surface modification of PEG-modified PLGA drug delivery nanocarriers with iRGD tumor-penetrating peptide was confirmed by dynamic light scattering analysis, which showed an increase in the average hydrodynamic diameter of the particles from 197.4 nm to 225.2 nm. The iRGD-modified particles were taken up by HCT-116 colorectal cancer cells in 22% higher proportions compared to the unmodified nanocarriers. (S1)
4. Monodisperse drug delivery nanocarriers containing both sorafenib and doxorubicin, were first prepared using polyhydroxybutyrate (PHB) as the carrier polymer, with high encapsulation efficiency. The release of doxorubicin was described by a three-phase kinetic process, consisting of an initial burst release, followed by polymer degradation, and finally, slow diffusion. Sorafenib exhibited a faster two-phase release process from the polymer, with an initial burst release followed by polymer degradation. (S3)
5. PEGylation of PHB nanocarriers containing sorafenib and doxorubicin resulted in the production of monodisperse drug delivery nanostructures that were less recognizable by macrophages in the living organism. The release of doxorubicin from the nanocarriers followed a three-phase kinetic profile, but exhibited a higher release rate in both plasma and acidic tumor microenvironment compared to PHB-based nanocarriers. Sorafenib rapidly released from PHB nanocarriers, while PEGylation of the nanocarriers slowed down the release. PEGylated PHB nanocarriers demonstrated enhanced cytotoxicity against HCT-116 colon cancer cell line. (S3)

Core publications from the PhD thesis work

S1. Babos. G.. Biró. E.. Meiczinger. M.. Feczkó. T. (2018). Dual Drug Delivery of Sorafenib and Doxorubicin from PLGA and PEG-PLGA Polymeric Nanoparticles. Polymers. 10(8). 895. Q1 (IF: 3,672)

S2. Feczkó T. Merza G. Babos G. et al. Preparation of cubic-shaped sorafenib-loaded nanocomposite using well-defined poly(vinyl alcohol alt-propenylene) copolymer. International Journal of Pharmaceutics. 2019;562:333-341. D1 (IF: 4,793)

S3. György Babos, Joanna Rydz, Michal Kawalec, Magdalena Klim, Andrea Fodor-Kardos, László Trif, Tivadar Feczkó: Poly(3-Hydroxybutyrate)-Based Nanoparticles for Sorafenib and Doxorubicin Anticancer Drug. International Journal of Molecular Science, 2020; 21 (19), 7312 D1 (IF: 5,819)

Other scientific publications:

S4. Izolda Kántor, Diana Aparaschivei, Anamaria Todea, Emese Biró, György Babos, Dóra Szerényi, Balázs Kakasi, Francisc Péter, Eugen Şişu, Tivadar Feczkó: Biocatalytic synthesis of poly [ε-caprolactone-co-(12-hydroxystearate)] copolymer for sorafenib nanoformulation useful in drug delivery, Catalysis Today, 2021, 366, 195-201. Q1, (IF: 6,565)

S5. Izolda Kántor, Diana Dreavă, Anamaria Todea, Francisc Péter, Zoltán May, Emese Biró, György Babos, Tivadar Feczkó: Co-Entrapment of Sorafenib and Cisplatin Drugs and iRGD Tumour Homing Peptide by Poly [ε-caprolactone-co-(12-hydroxystearate)] Copolymer. Biomedicines, 2022, 10, 43. Q1, (IF: 4,757)

S6. Miklós Jakab, Margit Enisz-Bódogh, Kristóf Kovács, Eszter Keil, György Babos, Tivadar Feczkó: Structure and properties of bovine bone-glass ceramic composite scaffolds. Processing and Application of Ceramics 15 [4] (2021). Q3 (IF: 1,51)

S7. Iulia Păușescu, Izolda Kántor, György Babos, Zoltán May, Andrea Fodor-Kardos, Zsombor Miskolczy, László Biczók, Francisc Péter, Mihai Medeleanu, Tivadar Feczkó: Halochromic behavior and anticancer effect of new synthetic anthocyanidins complexed with β-cyclodextrin derivatives. International Journal of Molecular Sciences 2022, 23, 8103. D1 (IF: 6,208)