

UNIVERSIDADE FEDERAL DE CIÊNCIAS DA SAÚDE DE PORTO ALEGRE
QUÍMICA MEDICINAL

JOÃO VÍTOR RAUPP DE OLIVEIRA

**AVALIAÇÃO DE NANOPARTÍCULAS DE SÍLICA COMO SISTEMAS DE *DRUG*
DELIVERY PARA O SISTEMA NERVOSO CENTRAL**

PORTO ALEGRE

2022

JOÃO VÍTOR RAUPP DE OLIVEIRA

**AVALIAÇÃO DE NANOPARTÍCULAS DE SÍLICA COMO SISTEMAS DE *DRUG*
DELIVERY PARA O SISTEMA NERVOSO CENTRAL**

Trabalho de Conclusão de Curso de graduação apresentado ao curso de Química Medicinal da Fundação Universidade Federal de Ciências da Saúde de Porto Alegre, como requisito parcial para a obtenção do grau de Bacharel em Química Medicinal.

Orientadora: Prof^ª. Dr^ª. Tanira A. S. Aguirre
Co-orientadora: Dr^ª. Jussânia de A. Gnoatto

PORTO ALEGRE

2022

CIP - Catalogação na Publicação

de Oliveira, João Vitor Raupp

Avaliação de nanopartículas de sílica como sistemas de drug delivery para o sistema nervoso central / João Vitor Raupp de Oliveira. -- 2022.

40 f.

Orientador: Dra. Tanira Alessandra Silveira Aguirre.

Coorientador: Dra. Jussânia de Almeida Gnoatto.

Trabalho de conclusão de curso (Graduação) --
Fundação Universidade Federal de Ciências da Saúde de
Porto Alegre, Bacharelado em Química Medicinal, Porto
Alegre, BR-RS, 2022.

1. Nanopartículas de sílica. 2. Entrega controlada de fármacos 3. Sistema nervoso central. 4. Distúrbios neurológicos. I. Aguirre, Tanira Alessandra Silveira, orient. II. Gnoatto, Jussânia de Almeida, coorient. III. Título.

UNIVERSIDADE FEDERAL DE CIÊNCIAS DA SAÚDE DE PORTO ALEGRE
QUÍMICA MEDICINAL

FOLHA DE APROVAÇÃO

JOÃO VÍTOR RAUPP DE OLIVEIRA

**AVALIAÇÃO DE NANOPARTÍCULAS DE SÍLICA COMO SISTEMAS DE *DRUG*
DELIVERY PARA O SISTEMA NERVOSO CENTRAL**

Trabalho de Conclusão de Curso de graduação apresentado ao curso de Química Medicinal da Fundação Universidade Federal de Ciências da Saúde de Porto Alegre, como requisito parcial para a obtenção do grau de Bacharel em Química Medicinal.

Aprovado em 11 de fevereiro de 2022.

Banca Examinadora

Prof^ª. Dr^ª. Tanira Alessandra Silveira Aguirre

Prof^ª. Dr^ª. Monique Deon

Prof^ª. Dr^ª. Helena Maria Tannhauser Barros

PREÂMBULO

O presente trabalho de conclusão de curso será apresentado no formato de artigo científico. A apresentação neste formato está prevista no Art. 4º da Resolução Nº 11/2020/CONSEPE, de 23 de janeiro de 2020, que regulamenta os trabalhos de conclusão do curso de Bacharelado em Química Medicinal. Segundo o Art. 4º, “Os resultados oriundos da pesquisa do TCC serão escritos na forma de artigo científico ou monografia, à critério do professor orientador do TCC.”.

RESUMO

Nos últimos anos, as nanopartículas de sílica (NPSiO₂) têm sido amplamente estudadas como sistema de liberação de fármacos devido às suas propriedades favoráveis para aplicação na nanomedicina. Nesse contexto, o desenvolvimento de sistemas baseados em sílica específicos para entrega de fármacos para o sistema nervoso central tem sido investigado objetivando tratamento de distúrbios associados ao sistema nervoso central, tais como os tumores cerebrais, referidos glioma, neuroblastoma e glioblastoma, além das doenças de Alzheimer e Parkinson, dentre outros. A partir dessa perspectiva, o presente trabalho de revisão buscou avaliar as características químicas e físicas, como funcionalização da superfície e tamanho e carga superficial, das NPSiO₂ empregadas para o tratamento dos distúrbios neurológicos e associar com as propriedades biológicas observadas, bem como sumarizar os principais aspectos relacionados à produção e caracterização das NPSiO₂.

Palavras-chave: nanopartículas de sílica; entrega controlada de fármacos; sistema nervoso central; distúrbios neurológicos.

ABSTRACT

In recent years, silica nanoparticles (NPSiO₂) have been extensively studied as a drug delivery system due to their favorable properties for application in nanomedicine. In this context, the development of silica-based systems for drug delivery to the central nervous system has been investigated to treat disorders associated with the central nervous system, such as brain tumors including gliomas, neuroblastomas, and glioblastomas, as well as Alzheimer's and Parkinson's diseases, among others. From this perspective, the present review aimed to evaluate the chemical and physical characteristics of NPSiO₂, such as surface functionalization, size, and surface charge, used for the treatment of neurological disorders and to associate them with biological outcomes. Additionally, this review aimed to summarize the main aspects related to the production and characterization of NPSiO₂.

Keywords: silica nanoparticles; drug delivery; central nervous system; neurological disorders.

SUMÁRIO

1. APRESENTAÇÃO.....	9
2. ARTIGO DE REVISÃO.....	10
3. REFERÊNCIAS.....	50

1. APRESENTAÇÃO

O manuscrito do referido trabalho de conclusão de curso foi publicado na revista científica Química Nova sob o título “NANOPARTÍCULAS DE SÍLICA (NPSiO₂) UTILIZADAS PARA O TRATAMENTO DE DISTÚRBIOS ASSOCIADOS AO SISTEMA NERVOSO CENTRAL (SNC)”, sendo os direitos de reprodução reservados ao periódico. Por este motivo, as páginas 10 a 49 foram suprimidas desta versão. O trabalho completo pode ser acessado através do DOI: <http://dx.doi.org/10.21577/0100-4042.20230015>.

3. REFERÊNCIAS

AHLKOG, J. E. Common Myths and Misconceptions That Sidetrack Parkinson Disease Treatment, to the Detriment of Patients. **Mayo Clinic Proceedings**, v. 95, n. 10, p. 2225–2234, 2020.

AMIN, M. U. *et al.* Enhanced efficacy and drug delivery with lipid coated mesoporous silica nanoparticles in cancer therapy. **European Journal of Pharmaceutics and Biopharmaceutics**, v. 165, n. April, p. 31–40, 2021.

APOLINÁRIO, A. C. *et al.* Opening the pandora's box of nanomedicine: There is needed plenty of room at the bottom. **Química Nova**, v. 43, n. 2, p. 212–225, 2020.

BAGHIROV, H. *et al.* Feasibility study of the permeability and uptake of mesoporous silica nanoparticles across the blood-brain barrier. **PLoS ONE**, v. 11, n. 8, p. 1–22, 2016.

BALDASSARRE, F.; CACCIOLA, M.; CICCARELLA, G. A predictive model of iron oxide nanoparticles flocculation tuning Z-potential in aqueous environment for biological application. **Journal of Nanoparticle Research**, v. 17, n. 9, p. 1–21, 2015.

BAYDA, S. *et al.* The history of nanoscience and nanotechnology: From chemical-physical applications to nanomedicine. **Molecules**, v. 25, n. 1, p. 1–15, 2020.

BENVENUTTI, E. V. *et al.* Materiais híbridos à base de sílica obtidos pelo método sol-gel. **Química Nova**, v. 32, n. 7, p. 1926–1933, 2009.

BERTUCCI, A. *et al.* Combined Delivery of Temozolomide and Anti-miR221 PNA Using Mesoporous Silica Nanoparticles Induces Apoptosis in Resistant Glioma Cells. **Small**, v. 11, n. 42, p. 5687–5695, 2015.

BIRBECK, G. L.; MEYER, A. C.; OGUNNIYI, A. Nervous system disorders across the life course in resource-limited settings. **Nature**, v. 527, n. 7578, p. S167–S171, 2015.

BREZÁNIOVÁ, I. *et al.* Silica-based nanoparticles are efficient delivery systems for temoporfin. Photodiagnosis and Photodynamic **Therapy**, v. 21, n. December 2017, p. 275–284, 2018.

BREZNAN, D. *et al.* Physicochemical Properties Can Be Key Determinants of Mesoporous Silica Nanoparticle Potency in Vitro. **ACS Nano**, v. 12, n. 12, p. 12062–12079, 2018.

BRODUSCH, N. *et al.* Scanning Electron Microscopy versus Transmission Electron Microscopy for Material Characterization: A Comparative Study on High-Strength Steels. **Scanning**, v. 2021, 2021.

BROS, M. *et al.* The protein corona as a confounding variable of nanoparticle-mediated targeted vaccine delivery. **Frontiers in Immunology**, v. 9, n. AUG, p. 1–10, 2018.

BRUINSMANN, F. A. *et al.* Nasal drug delivery of anticancer drugs for the treatment of glioblastoma: Preclinical and clinical trials. **Molecules**, v. 24, n. 23, 2019.

CARISSIMI, G. *et al.* Direct quantification of drug loading content in polymeric nanoparticles by infrared spectroscopy. **Pharmaceutics**, v. 12, n. 10, p. 1–15, 2020.

COUNTY, C. *et al.* Wildlife Management Plan for the Blue-Spotted Salamander , Blanding ' s Turtle , and Common Garter Snake at Neithercut. **Current**, n. 10, p. 4247–4256, 2005.

DA SILVA, G. H. *et al.* Recent Advances in Immunosafety and Nanoinformatics of Two-Dimensional Materials Applied to Nano-imaging. **Frontiers in Immunology**, v. 12, n. June, p. 1–20, 2021.

DENGLER, E. C. *et al.* Mesoporous silica-supported lipid bilayers (protocells) for DNA cargo delivery to the spinal cord. **Journal of Controlled Release**, v. 168, n. 2, p. 209–224, 2013.

FAHMY, H. M. *et al.* Targeting of Thymoquinone-loaded mesoporous silica nanoparticles to different brain areas: In vivo study. **Life Sciences**, v. 222, n. October 2018, p. 94–102, 2019.

FEIGIN, V. L. *et al.* Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. **The Lancet Neurology**, v. 18, n. 5, p. 459–480, 2019.

FRICKENSTEIN, A. N. *et al.* Mesoporous silica nanoparticles: Properties and strategies for enhancing clinical effect. **Pharmaceutics**, v. 13, n. 4, p. 1–27, 2021.

GHIMIRE, P. P.; JARONIEC, M. Renaissance of Stöber method for synthesis of colloidal particles: New developments and opportunities. **Journal of Colloid and Interface Science**, v. 584, p. 838–865, 2021.

GNOATTO, J. A. *et al.* Hybrid nanosilicas produced by the Stöber sol-gel process: In vitro evaluation in MRC-5 cells. **Journal of Non-Crystalline Solids**, v. 542, n. May, p. 120152, 2020.

GNOATTO, J. A. *et al.* PEGylated and zwitterated silica nanoparticles as doxorubicin carriers applied in a breast cancer cell line: Effects on protein corona formation. **Journal of Drug Delivery Science and Technology**, v. 71, n. March, 2022.

GONÇALVES, M. C. Sol-gel silica nanoparticles in medicine: A natural choice. design, synthesis and products. **Molecules**, v. 23, n. 8, p. 1–26, 2018.

HU, J. *et al.* Asn-Gly-Arg-modified polydopamine-coated nanoparticles for dual-targeting therapy of brain glioma in rats. **Oncotarget**, v. 7, n. 45, p. 73681–73696, 2016.

ISA, E. D. M. *et al.* Progress in mesoporous silica nanoparticles as drug delivery agents for cancer treatment. **Pharmaceutics**, v. 13, n. 2, p. 1–33, 2021.

JAMBHRUNKAR, S. *et al.* Modulating in vitro release and solubility of griseofulvin using functionalized mesoporous silica nanoparticles. **Journal of Colloid and Interface Science**, v. 434, p. 218–225, 2014.

JAMPILEK, J. *et al.* Preparation of silica nanoparticles loaded with nootropics and their in vivo permeation through blood-brain barrier. **BioMed Research International**, v. 2015, 2015.

JITKANG, L. *et al.* Characterization of magnetic nanoparticle by dynamic light scattering. **Nanoscale Research Letters**, v. 8, n. 1, p. 308–381, 2013.

JOSÉ, N. M.; SANCHEZ DE ALMEIDA PRADO, L. A. Hybrid organic-inorganic materials: Preparation and some applications. **Química Nova**, v. 28, n. 2, p. 281–288, 2005.

KARANDE, S. D. *et al.* Green and sustainable synthesis of silica nanoparticles. **Nanotechnology for Environmental Engineering**, v. 6, n. 2, p. 1–14, 2021.

KIM, C.; YOON, S.; LEE, J. H. Facile large-scale synthesis of mesoporous silica nanoparticles at room temperature in a monophasic system with fine size control. **Microporous and Mesoporous Materials**, v. 288, n. July, p. 109595, 2019.

KUNC, F. *et al.* Quantification of surface functional groups on silica nanoparticles: Comparison of thermogravimetric analysis and quantitative NMR. **Analyst**, v. 144, n. 18, p. 5589–5599, 2019.

LABAUVE, A. E. *et al.* Lipid-Coated Mesoporous Silica Nanoparticles for the Delivery of the ML336 Antiviral to Inhibit Encephalitic Alphavirus Infection. **Scientific Reports**, v. 8, n. 1, p. 1–13, 2018.

LEE, C. M. *et al.* Optical imaging of absorption and distribution of RITC-SiO₂ nanoparticles after oral administration. **International Journal of Nanomedicine**, v. 9, p. 243–250, 2014.

LI, H. *et al.* Biomimetic synthesis and evaluation of histidine-derivative templated chiral mesoporous silica for improved oral delivery of the poorly water-soluble drug, nimodipine. **European Journal of Pharmaceutical Sciences**, v. 117, n. December 2017, p. 321–330, 2018.

LI, H. *et al.* Biomimetic synthesis of proline-derivative templated mesoporous silica for increasing the brain distribution of diazepam and improving the pharmacodynamics of nimesulide. **Drug Delivery**, v. 24, n. 1, p. 1086–1098, 2017.

LI, H. *et al.* Evaluation of biomimetically synthesized mesoporous silica nanoparticles as drug carriers: Structure, wettability, degradation, biocompatibility and brain distribution. **Materials Science and Engineering C**, v. 94, n. February 2018, p. 453–464, 2019.

LI, Z.; ZHANG, Y.; FENG, N. Mesoporous silica nanoparticles: synthesis, classification, drug loading, pharmacokinetics, biocompatibility, and application in drug delivery. **Expert Opinion on Drug Delivery**, v. 16, n. 3, p. 219–237, 2019.

LIMA, T. *et al.* Understanding the Lipid and Protein Corona Formation on Different Sized Polymeric Nanoparticles. **Scientific Reports**, v. 10, n. 1, p. 1–9, 2020.

LIU, D. *et al.* In vitro and in vivo studies on the transport of PEGylated silica nanoparticles across the blood-brain barrier. **ACS Applied Materials and Interfaces**, v. 6, n. 3, p. 2131–2136, 2014.

LIU, Y. *et al.* Large-scale synthesis of fractal silica nanoparticles: understanding the impact of solvents. **Microporous and Mesoporous Materials**, v. 316, n. February, p. 110976, 2021.

LONE, M. S. *et al.* Temperature- and composition-induced multiarchitectural transitions in the cationic system of a conventional surfactant and a surface-active ionic liquid. **ACS Omega**, v. 6, n. 18, p. 11974–11987, 2021.

LUNGARE, S.; HALLAM, K.; BADHAN, R. K. S. Phytochemical-loaded mesoporous silica nanoparticles for nose-to-brain olfactory drug delivery. **International Journal of Pharmaceutics**, v. 513, n. 1–2, p. 280–293, 2016.

MEBERT, A. M. *et al.* Nanoengineered silica: Properties, applications and toxicity. **Food and Chemical Toxicology**, v. 109, p. 753–770, 2017.

MENDIRATTA, S. *et al.* Multidisciplinary Role of Mesoporous Silica Nanoparticles in Brain Regeneration and Cancers: From Crossing the Blood–Brain Barrier to Treatment. **Particle and Particle Systems Characterization**, v. 36, n. 9, 2019.

MINTZER, J. *et al.* Lifestyle Choices and Brain Health. **Frontiers in Medicine**, v. 6, n. October, p. 1–11, 2019.

MORA-HUERTAS, C. E.; FESSI, H.; ELAISSARI, A. Polymer-based nanocapsules for drug delivery. **International Journal of Pharmaceutics**, 2010.

MORALES, V. *et al.* L-Dopa release from mesoporous silica nanoparticles engineered through the concept of drug-structure-directing agents for Parkinson's disease. **Journal of Materials Chemistry B**, v. 9, n. 20, p. 4178–4189, 2021.

MOURDIKOU DIS, S.; PALLARES, R. M.; THANH, N. T. K. Characterization techniques for nanoparticles: Comparison and complementarity upon studying nanoparticle properties. **Nanoscale**, v. 10, n. 27, p. 12871–12934, 2018.

NARAYAN, R. *et al.* Mesoporous silica nanoparticles: A comprehensive review on synthesis and recent advances. **Pharmaceutics**, v. 10, n. 3, p. 1–49, 2018.

NDAY, C. M. *et al.* Quercetin encapsulation in modified silica nanoparticles: potential use against Cu(II)-induced oxidative stress in neurodegeneration. **Journal of Inorganic Biochemistry**, v. 145, p. 51–64, 2015.

ORLANDO, A. *et al.* Mesoporous silica nanoparticles trigger mitophagy in endothelial cells and perturb neuronal network activity in a size- and time-dependent manner. **International Journal of Nanomedicine**, v. 12, p. 3547–3559, 2017.

- ORTIZ-ISLAS, E. *et al.* Preparation and characterisation of silica-based nanoparticles for cisplatin release on cancer brain cells. **IET Nanobiotechnology**, v. 14, n. 3, p. 191–197, 2020.
- PANDEY, P. K. *et al.* MCM-41 Nanoparticles for Brain Delivery: Better Choline-Esterase and Amyloid Formation Inhibition with Improved Kinetics. **ACS Biomaterials Science and Engineering**, v. 4, n. 8, p. 2860–2869, 2018.
- PARDRIDGE, W. M. The blood-brain barrier: Bottleneck in brain drug development. **Neurotherapeutics**, v. 2, n. 1, p. 3–14, 2005.
- PARK, J. *et al.* Alternative Activation of Macrophages through Interleukin-13-Loaded Extra-Large-Pore Mesoporous Silica Nanoparticles Suppresses Experimental Autoimmune Encephalomyelitis. **ACS Biomaterials Science and Engineering**, v. 7, n. 9, p. 4446–4453, 2021.
- PARK, K. Controlled drug delivery systems: Past forward and future back. **Journal of Controlled Release**, v. 190, p. 3–8, 2014.
- PAULA, A. J. *et al.* Suppression of the hemolytic effect of mesoporous silica nanoparticles after protein corona interaction: Independence of the surface microchemical environment. **Journal of the Brazilian Chemical Society**, v. 23, n. 10, p. 1807–1814, 2012.
- PETERS, R. Ageing and the brain. **Postgraduate Medical Journal**, v. 82, n. 964, p. 84–88, 2006.
- PHILLIPS, E. *et al.* Clinical translation of an ultras-small inorganic optical-PET imaging nanoparticle probe. **Science Translational Medicine**, v. 6, n. 260, p. 1–10, 2014.
- QIAO, Z. A. *et al.* Synthesis of mesoporous silica nanoparticles via controlled hydrolysis and condensation of silicon alkoxide. **Chemistry of Materials**, v. 21, n. 16, p. 3823–3829, 2009.
- RAHMAN, I. A.; PADAVETTAN, V. Synthesis of Silica nanoparticles by Sol-Gel: Size-dependent properties, surface modification, and applications in silica-polymer nanocomposites a review. **Journal of Nanomaterials**, v. 2012, 2012.
- RASTEGARI, E. *et al.* An update on mesoporous silica nanoparticle applications in nanomedicine. **Pharmaceutics**, v. 13, n. 7, p. 1–56, 2021.

RAZINK, J. J.; SCHLOTTER, N. E. Correction to “Preparation of monodisperse silica particles: Control of size and mass fraction” by G.H. Bogush, M.A. Tracy and C.F. Zukoski IV, *Journal of Non-Crystalline Solids* 104 (1988) 95-106. **Journal of Non-Crystalline Solids**, v. 353, n. 30–31, p. 2932–2933, 2007.

SHAHEIN, S. A. *et al.* Targeted anticancer potential against glioma cells of thymoquinone delivered by mesoporous silica core-shell nanoformulations with pH-dependent release. **International Journal of Nanomedicine**, v. 14, p. 5503–5526, 2019.

SHEN, S. *et al.* High drug-loading nanomedicines: progress, current status, and prospects. **International Journal of Nanomedicine**, v. Volume 12, p. 4085–4109, maio 2017.

SHEN, Y. *et al.* ROS responsive resveratrol delivery from LDLR peptide conjugated PLA-coated mesoporous silica nanoparticles across the blood-brain barrier. **Journal of Nanobiotechnology**, v. 16, n. 1, p. 1–17, 2018.

SHI, B. *et al.* Multifunctional Hybrid Nanoparticles for Traceable Drug Delivery and Intracellular Microenvironment-Controlled Multistage Drug-Release in Neurons. **Small**, v. 13, n. 20, p. 1–10, 31 maio 2017.

SINGH, A. K. *et al.* Lipid-Coated MCM-41 Mesoporous Silica Nanoparticles Loaded with Berberine Improved Inhibition of Acetylcholine Esterase and Amyloid Formation. **ACS Biomaterials Science and Engineering**, v. 7, n. 8, p. 3737–3753, 2021.

SUKHANOVA, A. *et al.* Dependence of Nanoparticle Toxicity on Their Physical and Chemical Properties. **Nanoscale Research Letters**, v. 13, 2018.

SWAR, S.; MÁKOVÁ, V.; STIBOR, I. Effectiveness of Diverse Mesoporous Silica Nanoparticles as Potent Vehicles for the Drug L-DOPA. **Materials**, v. 12, n. 19, p. 3202, 30 set. 2019.

SWINDELL, E. P. *et al.* Anticancer activity of small-molecule and nanoparticulate arsenic(III) complexes. **Inorganic Chemistry**, v. 52, n. 21, p. 12292–12304, 2013.

TAKEUCHI, Y. Sagittal plane spinal mobility is associated with dynamic balance ability of community-dwelling elderly people. **Journal of Physical Therapy Science**, v. 29, n. 1, p. 112–114, 2017.

TAN, Y. H. *et al.* Surface area and pore size characteristics of nanoporous gold subjected to thermal, mechanical, or surface modification studied using gas adsorption isotherms, cyclic voltammetry, thermogravimetric analysis, and scanning electron microscopy. **Journal of Materials Chemistry**, v. 22, n. 14, p. 6733–6745, 2012.

TIWARI, G. *et al.* Drug delivery systems: An updated review. **International Journal of Pharmaceutical Investigation**, v. 2, n. 1, p. 2, 2012.

TREWYN, B. G. *et al.* Synthesis and functionalization of a mesoporous silica nanoparticle based on the sol-gel process and applications in controlled release. **Accounts of Chemical Research**, v. 40, n. 9, p. 846–853, 2007.

TRZECIAK, K. *et al.* Mesoporous silica particles as drug delivery systems—the state of the art in loading methods and the recent progress in analytical techniques for monitoring these processes. **Pharmaceutics**, v. 13, n. 7, 2021.

TURAN, O. *et al.* Delivery of drugs into brain tumors using multicomponent silica nanoparticles. **Nanoscale**, v. 11, n. 24, p. 11910–11921, 2019.

WU, J. *et al.* Neurotoxicity of silica nanoparticles: Brain localization and dopaminergic neurons damage pathways. **ACS Nano**, v. 5, n. 6, p. 4476–4489, 2011.

WU, W. *et al.* Glioblastoma multiforme (GBM): An overview of current therapies and mechanisms of resistance. **Pharmacological Research**, v. 171, n. July, p. 105780, 2021.

XING, R.; RANKIN, S. E. Reactive pore expansion during ammonia vapor post-treatment of ordered mesoporous silica prepared with mixed glucopyranoside and cationic surfactants. **Microporous and Mesoporous Materials**, v. 108, n. 1–3, p. 65–76, 2008.

YAMADA, H. *et al.* Preparation of aqueous colloidal mesostructured and mesoporous silica nanoparticles with controlled particle size in a very wide range from 20 nm to 700 nm. **Nanoscale**, v. 5, n. 13, p. 6145–6153, 2013.

YILDIRIM, A.; OZGUR, E.; BAYINDIR, M. Impact of mesoporous silica nanoparticle surface functionality on hemolytic activity, thrombogenicity and non-specific protein adsorption. **Journal of Materials Chemistry B**, v. 1, n. 14, p. 1909–1920, 2013.

YOO, J. *et al.* Active targeting strategies using biological ligands for nanoparticle drug delivery systems. **Cancers**, v. 11, n. 5, 2019.

YU, T.; MALUGIN, A.; GHANDEHARI, H. Impact of silica nanoparticle design on cellular toxicity and hemolytic activity. **ACS Nano**, v. 5, n. 7, p. 5717–5728, 2011.

ZANONI, D. K. *et al.* Use of Ultrasmall Core-Shell Fluorescent Silica Nanoparticles for Image-Guided Sentinel Lymph Node Biopsy in Head and Neck Melanoma: A Nonrandomized Clinical Trial. **JAMA Network Open**, v. 4, n. 3, p. 1–14, 2021.

ZEIN, R.; SHARROUF, W.; SELTING, K. Physical Properties of Nanoparticles That Result in Improved Cancer Targeting. **Journal of Oncology**, v. 2020, 2020.

ZHOU, Y. *et al.* A New Method for Evaluating Actual Drug Release Kinetics of Nanoparticles inside Dialysis Devices via Numerical Deconvolution. **Journal of Controlled Release**, v. 243, p. 11–20, 2016.

ZHU, J. *et al.* Angiopep-2 modified lipid-coated mesoporous silica nanoparticles for glioma targeting therapy overcoming BBB. **Biochemical and Biophysical Research Communications**, v. 534, p. 902–907, 2021.

ZHU, R. *et al.* Efficient VEGF targeting delivery of DOX using Bevacizumab conjugated SiO₂@LDH for anti-neuroblastoma therapy. **Acta Biomaterialia**, v. 63, p. 163–180, 2017.