Nanospheres: A Revolutionary Approach in Drug Delivery Systems

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Abstract:

Nanospheres, as an advanced drug delivery system, have transformed therapeutic approaches across various medical fields by improving drug bioavailability, controlling release rates, and enhancing targeted delivery. This review explores the structure, composition, and versatile applications of nanospheres, highlighting their significance in oral, parenteral, pulmonary, transdermal, and ocular drug delivery systems. The use of various polymers, along with surface modifications, has further optimized therapeutic outcomes by enhancing drug stability, improving bioavailability, and enabling controlled release. This review highlights the versatility and potential of nanospheres in revolutionizing treatments for a wide range of diseases, including chronic and life-threatening conditions. By providing more precise drug targeting and minimizing systemic side effects, nanospheres are proving to be a pivotal innovation in modern drug delivery systems, with promising applications in diverse therapeutic areas.

Keywords: Nanotechnology, Nanoparticles, Drug delivery systems, Solubility enhancement, targeted drug delivery.

1. Introduction:

In the evolving landscape of pharmaceutical sciences, nanotechnology has emerged as a pivotal player in addressing many of the limitations of conventional drug delivery systems [1]. With the increasing complexity of diseases and the growing demand for more effective, personalized treatments, nanotechnology offers a promising platform for enhancing the therapeutic efficacy of drugs. Specifically, nanospheres have revolutionized drug delivery by offering controlled and targeted release, improved drug bioavailability, and reduced systemic toxicity. The nanoscale size of these carriers allows them to penetrate biological barriers and deliver drugs to specific tissues or cells, an essential feature for the treatment of conditions such as cancer, infectious diseases, and chronic illnesses [3]. Moreover, their customizable surface properties facilitate targeted delivery and prolonged circulation, significantly improving the pharmacokinetics and biodistribution of drugs that are otherwise limited by poor solubility, instability, or rapid clearance from the body.

The need for nanotechnology in drug delivery has never been more critical than in the present scenario, where the pharmaceutical industry is grappling with challenges such as the increasing prevalence of drug-resistant infections, cancer treatment failures, and the rise of personalized medicine [1]. Traditional drug delivery methods often fail to provide the precise control over drug release and distribution needed for optimal therapeutic outcomes, leading to off-target effects and undesirable side effects. Nanospheres address these challenges by enabling the encapsulation of drugs within a protective polymer matrix, shielding them from degradation and facilitating their release at a controlled rate [4]. This is particularly important for delivering drugs to hard-to-reach areas such as the brain, where the blood-brain barrier restricts the entry of many therapeutic agents [5]. In addition, nanospheres enhance the solubility of poorly water-soluble drugs, increasing their bioavailability and therapeutic potential. The ability to engineer nanospheres for specific applications, from cancer therapies to gene delivery, underscores their transformative potential in the future of drug delivery systems [6]. This review explores the structure, preparation methods, and diverse applications of nanospheres in various drug delivery.

2. Structure and Composition of Nanospheres

Nanospheres, as solid colloidal particles ranging between 10 to 1000 nm in size, represent a key advancement in nanotechnology-based drug delivery systems due to their ability to encapsulate or adsorb drugs either within their matrix or on their surface [3]. Their unique structure facilitates improved bioavailability and controlled drug release, overcoming many of the limitations faced by traditional drug delivery methods. The drug is distributed homogeneously within the nanosphere’s polymeric matrix or adhered to the surface, offering versatility for both hydrophilic and hydrophobic drug molecules. This flexibility, along with their minute size, allows nanospheres to penetrate cellular barriers and target specific tissues, a significant advantage when addressing complex therapeutic needs, such as cancer and neurological disorders [7].

The noteworthy aspect of nanospheres’ structure is their ability to carry hydrophobic drugs, which are often difficult to formulate using traditional delivery systems due to their poor solubility. The hydrophobic core of nanospheres can effectively encapsulate such drugs,

protecting them from degradation and enhancing their solubility and stability in the bloodstream. This not only improves drug bioavailability but also allows for the delivery of higher concentrations of the therapeutic agent to the target site, improving treatment outcomes. For example, many anticancer drugs, which are typically hydrophobic, can be successfully delivered using nanospheres, thus enhancing their therapeutic efficacy while minimizing side effects [7].

The selection of polymers is critical in designing nanospheres, influencing not only the structural integrity but also the release kinetics, biocompatibility, and biodegradability of the delivery system. Polymers used in nanosphere formulation can be classified into three major categories: synthetic, semi-synthetic, and natural polymers. Synthetic polymers, such as poly(lactic-co-glycolic acid) (PLGA), poly(lactic acid) (PLA), and polycaprolactone (PCL), are well-studied due to their tunable physicochemical properties, controlled degradation, and FDA approval for pharmaceutical use. They are extensively employed in nanosphere formulation due to their biocompatibility and ability to degrade into non-toxic byproducts like lactic acid and glycolic acid. These degradation products are naturally metabolized by the body, making them ideal for sustained and controlled drug delivery applications. Moreover, these polymers offer flexibility in tailoring the degradation rate to suit specific therapeutic needs by adjusting their molecular weight or copolymer composition, thereby controlling the duration of drug release from days to months. Semi-synthetic polymers, like cellulose derivatives, combine natural polymer backbones with synthetic modifications, offering enhanced mechanical properties and drug encapsulation efficiency. However, in recent years, the focus has shifted significantly towards the exploration of natural polymers, particularly due to their biodegradability, low toxicity, and environmental sustainability [8-11].

Natural polymers such as chitosan, alginate, and gums (e.g., gum arabic, guar gum) have shown tremendous potential in nanosphere formulations. These biopolymers are inherently biocompatible, which minimizes the risk of adverse reactions and allows for safe delivery of therapeutic agents. Their biodegradability further reduces the burden of long-term accumulation in tissues, addressing a critical limitation of many synthetic polymers. Additionally, natural polymers possess unique functional groups that facilitate drug conjugation and encapsulation, making them ideal candidates for controlled and targeted drug delivery systems. For instance, chitosan, derived from chitin, has been widely utilized due to its mucoadhesive properties, which enhance drug absorption across biological membranes, including the gastrointestinal and nasal mucosa. Studies have demonstrated that chitosan-based nanospheres can improve the bioavailability of poorly soluble drugs, making it a versatile carrier for oral, nasal, and transdermal drug delivery systems .

Gum-based nanospheres, derived from plant exudates such as gum arabic, guar gum, and xanthan gum, represent a newer area of exploration with promising results in drug delivery [12]. Gum Arabic, a natural polysaccharide, has been employed to create nanospheres capable of encapsulating hydrophobic drugs. Its amphiphilic nature allows it to stabilize drug-loaded nanospheres in aqueous environments, facilitating their distribution in biological systems [13]. A study by Ziyang *et al.* (2024) reported that gum arabic nanospheres significantly enhanced the bioavailability of curcumin, a hydrophobic compound with poor solubility, by providing sustained release and protecting the drug from degradation in the gastrointestinal tract [14]. Similarly, guar gum, known for its swelling and gel-forming properties, has been used to

develop nanospheres for colon-targeted drug delivery. These nanospheres degrade specifically in the colon, releasing the drug at the desired site, which is particularly advantageous for treating conditions such as colon cancer and inflammatory bowel disease (IBD) [15].

Another example of natural polymers in nanosphere systems is alginate, extracted from brown seaweed, which forms gels in the presence of divalent cations like calcium. Alginate nanospheres have been successfully used for the controlled release of proteins and peptides, which are otherwise unstable in physiological conditions. The biocompatibility and non-toxicity of alginate make it an excellent candidate for parenteral drug delivery. For instance, a study demonstrated the use of alginate nanospheres to deliver insulin, showing enhanced stability and prolonged release, making them a viable option for diabetes management [16]. Natural polymers such as xanthan gum, tragacanth, and pectin have also been explored for their ability to create nanospheres with specific targeting abilities. Xanthan gum, known for its high viscosity and stability, has been employed in the formulation of nanospheres for sustained drug release in ocular and oral delivery systems [17]. These gums are biodegradable, ensuring that after the drug is released, the polymer matrix is broken down and safely excreted from the body.

The use of natural polymers for nanosphere formation offers several advantages, including biocompatibility, the ability to encapsulate both hydrophilic and hydrophobic drugs, and versatility in formulating nanospheres for different routes of administration. Although synthetic polymers provide more control over degradation rates and mechanical strength, natural polymers excel in their inherent compatibility with biological systems, making them suitable for sensitive and long-term therapies [17]. As research continues to advance, the incorporation of natural gums and other natural polymers in nanosphere drug delivery systems promises to revolutionize how drugs are administered, particularly in achieving sustained and targeted delivery with minimal side effects.

3. Surface modification of nanospheres for better therapeutic performance:

The surface of nanospheres can be engineered to enhance their therapeutic performance. One of the most effective strategies involves surface modification with polyethylene glycol (PEG), a process known as PEGylation. PEGylation plays a critical role in increasing the nanospheres' circulation time within the bloodstream by reducing opsonization, the process by which particles are marked for clearance by the immune system. By coating the nanospheres with PEG, they acquire a hydrophilic layer that prevents protein adsorption and reduces recognition by the reticuloendothelial system (RES). As a result, PEGylated nanospheres evade rapid clearance by macrophages, prolonging their presence in the bloodstream and enhancing their ability to reach target tissues. This feature is especially crucial for delivering drugs to tumors or other disease sites that may require longer systemic exposure to achieve optimal therapeutic outcomes.

The incorporation of PEG also facilitates passive targeting through the enhanced permeability and retention (EPR) effect, where the leaky vasculature surrounding tumors or inflamed tissues allows nanoparticles like PEGylated nanospheres to accumulate more readily than in normal tissues. This selective accumulation in diseased tissues helps reduce off-target effects and enhances the overall efficacy of the treatment.

Moreover, nanospheres can be further functionalized with ligands, such as antibodies, peptides, or small molecules, that enable active targeting to specific receptors on the surface of diseased cells. This active targeting approach can improve the specificity of drug delivery, ensuring that the therapeutic agent is delivered directly to the intended site of action, thereby minimizing systemic toxicity and increasing the therapeutic index [18, 19].

The structure and composition of nanospheres offer tremendous flexibility in drug delivery, allowing for controlled and sustained release, enhanced drug stability, and targeted delivery. The use of biodegradable polymers and surface modifications such as PEGylation are critical innovations that enable nanospheres to improve therapeutic outcomes, reduce systemic toxicity, and address the limitations of conventional drug delivery systems. As research in nanotechnology advances, nanospheres will continue to play a pivotal role in developing next-generation therapeutics for a wide range of diseases.

4. Preparation Methods of Nanospheres

Several techniques are employed in the preparation of nanospheres, each with its own advantages and limitations. The most common methods include solvent evaporation, nanoprecipitation, emulsion polymerization, and ionic gelation.

4.1. Solvent Evaporation

In this method, the drug and polymer are dissolved in an organic solvent, which is then emulsified in an aqueous phase containing a stabilizer. The organic solvent is subsequently evaporated, leading to the formation of nanospheres. This technique is widely used due to its simplicity and ability to produce particles with a narrow size distribution [20].

4.2. Nanoprecipitation

Nanoprecipitation involves the precipitation of the polymer from an organic solution to an aqueous solution, where the drug and polymer co-precipitate to form nanospheres. This method is particularly useful for hydrophobic drugs and allows for the production of nanoparticles with a controlled size and high drug loading efficiency [21].

4.3. Emulsion Polymerization

In emulsion polymerization, monomers are polymerized in an emulsion system to form nanospheres. The polymerization can be initiated by heat, light, or chemical initiators. This method is advantageous for the preparation of uniform particles but may require the removal of residual monomers and initiators, which can be challenging [22].

4.4. Ionic Gelation

Ionic gelation is a method where polyelectrolytes are crosslinked by multivalent ions to form nanospheres. This technique is particularly useful for the encapsulation of proteins and peptides, as it operates under mild conditions that do not denature the drug [23].

5. Characterization of nanospheres

Characterization of nanospheres is a crucial step in determining their suitability for drug delivery applications, as it directly impacts their stability, release profile, and biological interactions. Various techniques are employed to assess the physicochemical properties of nanospheres. Particle size and size distribution, typically measured using dynamic light scattering (DLS) or nanoparticle tracking analysis (NTA), are critical parameters that influence

the circulation time, cellular uptake, and biodistribution of nanospheres. Surface charge or zeta potential, determined by electrophoretic mobility measurements, is important for understanding colloidal stability and interactions with biological membranes. Nanoparticles with a high absolute zeta potential tend to exhibit better stability in suspension by preventing aggregation. The morphology and surface topology of nanospheres can be examined using scanning electron microscopy (SEM) and transmission electron microscopy (TEM), providing detailed insights into particle shape, surface texture, and any aggregation tendencies. Drug loading capacity and encapsulation efficiency are also critical characterization parameters which can be quantified through high-performance liquid chromatography (HPLC) or UV spectrophotometry. *In vitro* drug release studies, often conducted in simulated biological fluids, provide information on the release kinetics of the drug from the nanospheres, revealing whether the system offers a controlled or sustained release. Additionally, Fourier-transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) are used to confirm chemical interactions between the drug and polymer matrix, ensuring drug stability and compatibility within the formulation. These characterization techniques are vital for optimizing nanosphere formulations and ensuring their performance in clinical settings [20-23].

6. Drug Loading and Release Mechanisms

The effectiveness of nanospheres in drug delivery is largely determined by the drug loading capacity and release profile. Drug loading can be achieved through adsorption, encapsulation, or chemical bonding to the polymer matrix. The choice of method depends on the drug's physicochemical properties, the desired release profile, and the intended therapeutic application.

6.1. Drug Loading

In adsorption, the drug is adsorbed onto the surface of the nanospheres, which is suitable for hydrophilic drugs but may result in rapid release due to the surface-bound nature of the drug. Encapsulation involves the incorporation of the drug within the polymer matrix, offering a more controlled release. Chemical bonding, where the drug is covalently attached to the polymer, can provide the most controlled release but may require complex synthesis and modification processes.

6.2. Drug Release

Drug release from nanospheres can occur through diffusion, erosion of the polymer matrix, or a combination of both. Diffusion is typically observed with hydrophilic drugs, where the drug diffuses through the polymer matrix or along water channels formed within the nanosphere. Erosion-based release occurs when the polymer matrix degrades over time, releasing the encapsulated drug in a sustained manner. Controlled release profiles can be achieved by modifying the polymer composition, molecular weight, and method of preparation. For example, increasing the molecular weight of the polymer or using a more hydrophobic polymer can slow down the degradation rate, thereby prolonging the drug release [20-23].

7. Applications of Nanospheres in Disease Treatment and Drug Delivery Systems

Nanospheres, as versatile drug carriers, have significantly enhanced the therapeutic potential of drugs across various treatment modalities and delivery systems. By leveraging their small size, high surface area, and customizable surface chemistry, nanospheres can improve drug solubility, protect drugs from degradation, enable controlled release, and provide targeted delivery to specific tissues. This has opened new avenues for treating complex diseases like cancer, cardiovascular diseases, and neurological disorders, among others.

7.1. Cancer Treatment

One of the most prominent applications of nanospheres is in oncology. Traditional chemotherapy is often limited by systemic toxicity and non-specific drug distribution, leading to harmful side effects and suboptimal therapeutic outcomes. Nanospheres can be engineered to preferentially accumulate in tumor tissues through the enhanced permeability and retention (EPR) effect, a phenomenon observed in tumors due to their leaky vasculature. For instance, PLGA-based nanospheres loaded with paclitaxel have shown a significant reduction in tumor growth in preclinical models by delivering the drug specifically to the tumor site and minimizing its accumulation in healthy tissues [24]. This targeted approach not only enhances the efficacy of the drug but also reduces its systemic toxicity.

7.2. Neurological Disorders

Delivering drugs to the brain is challenging due to the presence of the blood-brain barrier (BBB), which restricts the passage of most therapeutic agents. Nanospheres offer a promising solution by enabling the transport of drugs across the BBB. PEGylated nanospheres, for example, have been developed to deliver anti-Alzheimer's and anti-Parkinson's drugs, effectively bypassing the BBB and achieving sustained drug release at the target site [25, 26]. This approach has improved the therapeutic efficacy of these drugs, potentially reducing the frequency of administration and improving patient compliance.

7.3. Cardiovascular Diseases

In cardiovascular therapies, nanospheres have been used for the targeted delivery of drugs like statins and anti-thrombotic agents. Nanospheres encapsulating atorvastatin have demonstrated enhanced drug bioavailability and prolonged circulation time, leading to improved management of hyperlipidemia and atherosclerosis. Additionally, nanospheres coated with targeting ligands have been explored for the delivery of clot-dissolving agents, ensuring that the drug is released only at the site of the thrombus, thereby minimizing the risk of systemic bleeding [27].

7.4. Pulmonary Drug Delivery

Nanospheres are also being explored for the treatment of respiratory diseases, such as asthma and chronic obstructive pulmonary disease (COPD). Inhaled corticosteroids delivered via nanospheres have shown improved drug retention in the lungs, leading to prolonged therapeutic effects and reduced systemic side effects. Moreover, nanospheres can be engineered to deposit in specific regions of the lungs, offering targeted treatment for localized respiratory conditions.

7.5. Ocular Drug Delivery

The eye presents unique challenges for drug delivery due to its protective barriers, such as the tear film and the corneal epithelium. Nanospheres have been shown to enhance drug retention and absorption in the eye, making them suitable for the treatment of ocular diseases like glaucoma, age-related macular degeneration (AMD), and diabetic retinopathy. Chitosan-based nanospheres, for instance, have been used to deliver anti-glaucoma drugs, increasing their bioavailability and prolonging their therapeutic effect [29].

7.6. Alginate-based Nanospheres: Alginate, a natural polysaccharide extracted from brown algae, has been widely used in nanosphere formulations due to its biocompatibility and ability to form hydrogels. Alginate-based nanospheres have been successfully utilized for the oral delivery of insulin, protecting the drug from degradation in the acidic environment of the stomach and enabling its controlled release in the intestines. This approach has shown improved bioavailability of insulin in diabetic patients, demonstrating the potential of alginate-based nanospheres for peptide drug delivery [16].

7.7. Gum Arabic-based Nanospheres: Gum Arabic, a natural exudate from the Acacia tree, has been explored for the development of nanospheres for the targeted delivery of anti-cancer drugs. Gum Arabic-based nanospheres loaded with doxorubicin, a commonly used chemotherapeutic agent, have shown enhanced drug stability and sustained release, leading to better therapeutic outcomes in cancer treatment. These nanospheres exhibit preferential accumulation in tumor tissues due to their biocompatible surface, reducing the frequency of administration and minimizing the side effects associated with systemic chemotherapy [30].

7.8. Guar Gum-based Nanospheres

Guar gum, derived from the seeds of the guar plant, has been used in the formulation of nanospheres for the treatment of gastrointestinal disorders. Guar gum-based nanospheres encapsulating anti-inflammatory drugs, improved bioavailability and targeted drug release in the colon, offering a more effective treatment for conditions like ulcerative colitis and Crohn’s disease. This natural polymer's ability to protect drugs from premature degradation and provide sustained release has made it a valuable material in designing nanospheres for oral drug delivery [31].

In summary, the application of nanospheres in drug delivery has revolutionized the treatment of various diseases by enhancing drug efficacy, reducing side effects, and enabling targeted delivery. This demonstrate the versatility of nanospheres and their ability to address the challenges of modern drug delivery systems.

8. Challenges and Future Directions

Despite the promising potential of nanospheres in drug delivery, several challenges remain, including scale-up production, regulatory hurdles, and long-term stability. The reproducibility of nanosphere synthesis and the scalability of production processes are critical factors that need to be addressed to facilitate the translation of nanosphere-based drug delivery systems from the lab to the clinic. Regulatory challenges also arise due to the complexity of nanosphere formulations and the need for rigorous testing to ensure safety and efficacy.

The long-term stability of nanospheres, particularly in terms of drug release and polymer degradation, is another area that requires further investigation. Future research should focus on developing novel polymers and surface modifications to improve the targeting and controlled release capabilities of nanospheres. The integration of nanospheres with other drug delivery platforms, such as hydrogels and implantable devices, may also offer new opportunities for combination therapies and personalized medicine.

9. Conclusion

Nanospheres offer remarkable benefits in modern drug delivery systems, enhancing the therapeutic potential of various drugs through controlled release, improved bioavailability, and targeted delivery. Their application in treating chronic and life-threatening diseases has significantly improved therapeutic efficacy while reducing systemic side effects. As research continues, the versatility of nanospheres—whether synthetic or biodegradable—promises further innovations in drug delivery technologies, potentially leading to more effective treatments and better patient outcomes across a wide range of diseases. Nanospheres represent a vital and growing area in pharmaceutical development, transforming the future of therapeutic interventions.

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References

[1] Farokhzad, Omid C., and Robert Langer. "Impact of nanotechnology on drug delivery." *ACS nano* 3, no. 1 (2009): 16-20.

[2] Haleem, Abid, Mohd Javaid, Ravi Pratap Singh, Shanay Rab, and Rajiv Suman. "Applications of nanotechnology in medical field: a brief review." Global Health Journal 7, no. 2 (2023): 70-77.

[3] Kumar, Parveen, Nishant Yadav, Benu Chaudhary, Vivek Jain, Vishal M. Balaramnavar, Khalid Saad Alharbi, Sattam Khulaif Alenezi et al. "Promises of phytochemical based nano drug delivery systems in the management of cancer." Chemico-Biological Interactions 351 (2022): 109745.

[4] Lee, Jinhyun Hannah, and Yoon Yeo. "Controlled drug release from pharmaceutical nanocarriers." Chemical engineering science 125 (2015): 75-84.

[5] Kilic AC, Capan YI, Vural I, Gursoy RN, Dalkara TU, Cuine A, Hincal AA. Preparation and characterization of PLGA nanospheres for the targeted delivery of NR2B-specific antisense oligonucleotides to the NMDA receptors in the brain. Journal of microencapsulation. 2005 Sep 1;22(6):633-41.

[6] Leong, K. W., H-Q. Mao, V. L. Truong-Le, K. Roy, S. M. Walsh, and J. T. August. "DNA-polycation nanospheres as non-viral gene delivery vehicles." Journal of controlled release 53, no. 1-3 (1998): 183-193.

[7] Gamisans, F., F. Lacoulonche, A. Chauvet, M. Espina, M. L. García, and M. A. Egea. "Flurbiprofen-loaded nanospheres: analysis of the matrix structure by thermal methods." International journal of pharmaceutics 179, no. 1 (1999): 37-48.

[8] Guterres, Sílvia S., Marta P. Alves, and Adriana R. Pohlmann. "Polymeric nanoparticles, nanospheres and nanocapsules, for cutaneous applications." Drug target insights 2 (2007): 117739280700200002.

[9] Jung, Jua, In-Hyun Lee, Eunhye Lee, Jinho Park, and Sangyong Jon. "pH-sensitive polymer nanospheres for use as a potential drug delivery vehicle." Biomacromolecules 8, no. 11 (2007): 3401-3407.

[10] Gref, Ruxandra, Yoshiharu Minamitake, Maria Teresa Peracchia, Vladimir Trubetskoy, Vladimir Torchilin, and Robert Langer. "Biodegradable long-circulating polymeric nanospheres." Science 263, no. 5153 (1994): 1600-1603.

[11] Srivastava, Apurva, Tejaswita Yadav, Soumya Sharma, Anjali Nayak, Akanksha Akanksha Kumari, and Nidhi Mishra. "Polymers in drug delivery." Journal of Biosciences and Medicines 4, no. 1 (2015): 69-84.

[12] Masotti, Andrea, and Giancarlo Ortaggi. "Chitosan micro-and nanospheres: fabrication and applications for drug and DNA delivery." Mini reviews in medicinal chemistry 9, no. 4 (2009): 463-469.

[13] Kadare, P., P. Maposa, A. Dube, and C. C. Maponga. "Encapsulation of isoniazid in chitosan-gum Arabic and poly (lactic-co-glycolic acid) PVA particles to provide a sustained release formulation." J. Pharm. Pharmacol 1 (2014): 01-06.

[14] Ye, Ziyang, Yuxuan Wang, Penghui Shen, Leonard MC Sagis, and Jasper Landman. "Effect of gum Arabic coating on release behavior of curcumin-loaded kafirin and zein composite nanoparticles." Food Hydrocolloids (2024): 110254.

[15] Chandel, Deepika, Shivani Uppal, Surinder Kumar Mehta, and Geeta Shukla. "Preparation and characterization of celecoxib entrapped guar gum nanoparticles targeted for oral drug delivery against colon cancer: an in-vitro study." Journal of Drug Delivery and Therapeutics 10, no. 2-s (2020): 14-21.

[16] Sarmento, B., A. Ribeiro, F. Veiga, P. Sampaio, R. Neufeld, and D. Ferreira. "Alginate/chitosan nanoparticles are effective for oral insulin delivery." Pharmaceutical research 24 (2007): 2198-2206.

[17] Rohilla, S., G. Chawla, D. P. Bhagwat, and A. Rohilla. "Natural gum: an option to prepare nanocarriers." Med Theor Hypothesis 6, no. 3 (2023): 15.

[18] Sánchez-López, Elena, M. A. Egea, Amanda Cano, M. Espina, A. C. Calpena, Miren Ettcheto, A. Camins, Eliana B. Souto, Amélia M. Silva, and Maria Luisa García. "PEGylated PLGA nanospheres optimized by design of experiments for ocular administration of dexibuprofen—In vitro, ex vivo and in vivo characterization." Colloids and surfaces B: biointerfaces 145 (2016): 241-250.

[19] Sinha, Vivek Ranjan, Ashu Aggarwal, and Aman Trehan. "Biodegradable PEGylated microspheres and nanospheres." American Journal of Drug Delivery 2 (2004): 157-171.

[20] Desgouilles, Stéphanie, Christine Vauthier, Didier Bazile, Joël Vacus, Jean-Louis Grossiord, Michel Veillard, and Patrick Couvreur. "The design of nanoparticles obtained by solvent evaporation: a comprehensive study." Langmuir 19, no. 22 (2003): 9504-9510.

[21] Chorny, Michael, Ilia Fishbein, Haim D. Danenberg, and Gershon Golomb. "Lipophilic drug loaded nanospheres prepared by nanoprecipitation: effect of formulation variables on size, drug recovery and release kinetics." Journal of controlled release 83, no. 3 (2002): 389-400.

[22] Xu, Hong, Longlan Cui, Naihu Tong, and Hongchen Gu. "Development of high magnetization Fe3O4/polystyrene/silica nanospheres via combined miniemulsion/emulsion polymerization." Journal of the American Chemical Society 128, no. 49 (2006): 15582-15583.

[23] Hritcu, Doina, Marcel I. Popa, NUCULINA POPA, Vasile Badescu, and Vera Balan. "Preparation and characterization of magnetic chitosan nanospheres." Turkish Journal of Chemistry 33, no. 6 (2009): 785-796.

[24] Danhier, Fabienne, Nathalie Lecouturier, Benoît Vroman, Christine Jérôme, Jacqueline Marchand-Brynaert, Olivier Feron, and Véronique Préat. "Paclitaxel-loaded PEGylated PLGA-based nanoparticles: in vitro and in vivo evaluation." Journal of controlled release 133, no. 1 (2009): 11-17.

[25] Jain, Dhara, Md A. Rashid, and Farhan J. Ahmad. "Recent Advances in Targeted Drug Delivery Approaches Using Lipidic and Polymeric Nanocarriers for the Management of Alzheimer's Disease." Current Pharmaceutical Design 27, no. 43 (2021): 4388-4403.

[26] Hu, Kaili, Yanbin Shi, Wenming Jiang, Jiaying Han, Shixian Huang, and Xinguo Jiang. "Lactoferrin conjugated PEG-PLGA nanoparticles for brain delivery: preparation, characterization and efficacy in Parkinson's disease." International journal of pharmaceutics 415, no. 1-2 (2011): 273-283.

[27] Hashem, Fahima M., Majid M. Al-Sawahli, Mohamed Nasr, and Osama AA Ahmed. "Optimized zein nanospheres for improved oral bioavailability of atorvastatin." International journal of nanomedicine (2015): 4059-4069.

[28] Ige, Pradum P., Sagar R. Pardeshi, and Raju O. Sonawane. "Development of pH-dependent nanospheres for nebulisation-in vitro diffusion, aerodynamic and cytotoxicity studies." Drug Research 68, no. 12 (2018): 680-686.

[29] Jain, Kunal, R. Suresh Kumar, Sumeet Sood, and G. Dhyanandhan. "Betaxolol hydrochloride loaded chitosan nanoparticles for ocular delivery and their anti-glaucoma efficacy." Current drug delivery 10, no. 5 (2013): 493-499.

[30] Hasanin, Mohamed, Nesrin Fouad Taha, Aya Rashad Abdou, and Laila Hasanin Emara. "Green decoration of graphene oxide Nano sheets with gelatin and gum Arabic for targeted delivery of doxorubicin." Biotechnology Reports 34 (2022): e00722.

[31] Garg, Sourbh Suren, and Jeena Gupta. "Guar gum-based nanoformulations: Implications for improving drug delivery." International Journal of Biological Macromolecules 229 (2023): 476-485.