Nanoparticle-mediated Delivery of Anticancer Drugs for Brain Metastases

Varsha Deva[1], Raj Kumar Mishra*[2], Madhuben Sharma[3], Goldee Yadav[4], Islamun Jahan[5], Vaishali Pandey[6], Vijay Vikram Singh[7]

[1]Glocal University Pharmacy College, Behat, Saharanpur.
[*2]Research Scholar, IK Gujral Punjab Technical University, Punjab
[3]Sustainability cluster, University of Petroleum and Energy Studies, Bidholi, Dehradun, Uttarakhand
[4]Department of Pharmacognosy, Maharana Pratap College of Pharmacy, Kothi Man Dhana Kanpur - UP
[5]Department of Pharmaceutical Sciences, Agra Public Pharmacy College, Artoni, Agra 282007
[6]Modern College of Pharmacy, Jhansi
[7]Department of Pharmaceutical Chemistry, BR Pharmacy College, Bharthipur, Azamgarh

Abstract

Brain metastases pose significant challenges in cancer treatment due to the limited effectiveness of conventional therapies in crossing the blood-brain barrier (BBB). Nanoparticle-mediated drug delivery systems have emerged as a promising approach to overcome these challenges. This article provides an overview of nanoparticle-based drug delivery for brain metastases, highlighting its potential benefits and applications. The use of various nanoparticles, such as liposomes, polymeric nanoparticles, and gold nanoparticles, has shown promising results in enhancing drug efficacy, targeting brain metastases, and reducing systemic toxicity. Case studies and research findings demonstrate the successful applications of nanoparticle-mediated drug delivery, leading to improved therapeutic outcomes and extended patient survival rates. However, several challenges, including BBB penetration, long-term safety, and scalability, need to be addressed for the widespread adoption of these therapies. Collaborative efforts between researchers, clinicians, and industry partners are crucial in advancing nanoparticle-based drug delivery systems and optimizing their clinical translation. Overall, nanoparticle-mediated drug delivery holds great promise in revolutionizing the treatment of brain metastases and improving patient outcomes.

Keywords: brain metastases, nanoparticle-based drug delivery, blood-brain barrier, targeted therapy, systemic toxicity, liposomes, polymeric nanoparticles, gold nanoparticles.

Introduction

Brain metastases, the spread of cancer cells from primary tumors in other parts of the body to the brain, pose significant challenges in treatment[1]. Traditional approaches to treating brain metastases with anticancer drugs are hindered by the presence of the blood-brain barrier (BBB), which restricts the passage of many therapeutic agents into the brain. However, the emergence of nanoparticle-mediated drug delivery has opened up new possibilities for effectively targeting brain metastases and improving treatment outcomes[2]. Brain metastases occur when cancer cells break away from the primary tumor and travel through the bloodstream or lymphatic system to the brain. This process is complex and involves multiple steps, including invasion, intravasation, circulation, extravasation, and colonization[2,3]. Once cancer cells reach the brain, they form secondary tumors, which can cause significant neurological symptoms and negatively impact patient prognosis. Treating brain metastases is particularly challenging due to the unique characteristics of the brain and the presence of the BBB[4]. The BBB is a highly selective barrier that tightly regulates the exchange of substances between the blood and the brain. While it protects the brain from harmful substances, it also limits the delivery of therapeutic drugs[5]. Many anticancer drugs that are effective against primary tumors in other parts of the body are unable to penetrate the BBB at sufficient concentrations to treat brain metastases effectively[5,6].

Importance of Nanoparticle-mediated Drug Delivery

Nanoparticle-mediated drug delivery has emerged as a promising approach to overcome the challenges associated with treating brain metastases. Nanoparticles, with their small size and unique properties, offer several advantages in delivering anticancer drugs to the brain[4,6]. They can be engineered to encapsulate therapeutic agents and navigate through the BBB, enabling targeted and controlled release of drugs specifically at the site of brain metastases[7]. This targeted delivery reduces systemic toxicity and increases the concentration of drugs in the tumor, thereby improving treatment efficacy[4,7].

Nanoparticle-based Drug Delivery Systems

Nanoparticle-based drug delivery systems have revolutionized the field of medicine by providing innovative approaches to effectively deliver therapeutic agents to specific target sites in the body. In this section, we will explore the definition and characteristics of nanoparticles, the types commonly used in drug delivery, and the advantages they offer in the field of medicine[7,8].

Nanoparticles are tiny particles with sizes ranging from 1 to 100 nanometers. They can be composed of various materials such as lipids, polymers, metals, or ceramics[9]. The unique characteristics of nanoparticles make them highly desirable for drug delivery applications. These characteristics include:

Small Size: Nanoparticles possess a small size that allows them to navigate through biological barriers, penetrate tissues, and reach specific target sites in the body more efficiently than larger drug molecules.

Large Surface Area-to-Volume Ratio: Due to their small size, nanoparticles have a large surface area relative to their volume. This increased surface area enables greater drug-loading capacity and enhances drug release kinetics[10].

Tunable Surface Chemistry: Nanoparticles can be engineered with different surface properties, such as charge and hydrophobicity, which allow for easy modification and functionalization. These surface modifications enable specific targeting and enhance interactions with biological systems[11].

Encapsulation Capability: Nanoparticles have the ability to encapsulate drugs within their structures. This encapsulation protects drugs from degradation, increases their stability, and allows for controlled release over an extended period, thereby improving drug efficacy[12].

Types of Nanoparticles Used in Drug Delivery

Several types of nanoparticles have been employed in drug delivery systems, each with unique characteristics and advantages. Some commonly used types include:

Liposomes: Liposomes are spherical vesicles composed of lipid bilayers. They are biocompatible, easily modifiable, and capable of encapsulating both hydrophobic and hydrophilic drugs. Liposomes offer controlled release profiles and have been extensively studied for their ability to enhance drug delivery to specific target sites[12].

Polymeric Nanoparticles: Polymeric nanoparticles are made of biocompatible and biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG). These nanoparticles can encapsulate a wide range of drugs and provide sustained drug release. Polymeric nanoparticles offer versatility in terms of size, surface properties, and drug-loading capacity[13].

Metallic Nanoparticles: Metallic nanoparticles, such as gold and silver nanoparticles, have unique physicochemical properties that can be exploited for drug delivery purposes. They can be functionalized with targeting ligands and exhibit excellent stability and biocompatibility. Metallic nanoparticles also possess photothermal or photodynamic properties, allowing for combination therapies and targeted drug release triggered by external stimuli[14].

Advantages of Nanoparticle-mediated Drug Delivery

Nanoparticle-mediated drug delivery offers several advantages over conventional drug delivery methods:

Enhanced Targeting: Nanoparticles can be functionalized with targeting ligands that recognize specific receptors or biomarkers overexpressed on the surface of target cells or tissues. This active targeting improves drug accumulation at the desired site, maximizing therapeutic efficacy while minimizing off-target effects[15].

Protection and Controlled Release: Nanoparticles provide a protective environment for encapsulated drugs, shielding them from degradation and premature release. This controlled release enables sustained drug delivery over an extended period, ensuring a continuous therapeutic effect[16].

Improved Solubility and Stability: Nanoparticles can encapsulate hydrophobic drugs, enhancing their solubility in aqueous environments. This increased solubility improves drug bioavailability and systemic distribution. Furthermore, nanoparticle encapsulation can improve drug stability, protecting drugs from enzymatic degradation or chemical reactions[17].

Reduced Systemic Toxicity: Targeted delivery of drugs using nanoparticles reduces their distribution in healthy tissues, minimizing systemic toxicity and side effects. This targeted approach allows for lower drug doses while maintaining therapeutic efficacy, improving patient comfort and safety[18].

Targeting Brain Metastases

The treatment of brain metastases poses unique challenges due to the presence of the blood-brain barrier (BBB), a highly selective barrier that regulates the exchange of substances between the bloodstream and the brain. In this section, we will explore the role of the BBB in drug delivery, strategies employed to overcome this barrier, and the specific role of nanoparticles in targeting brain metastases[19].

Blood-Brain Barrier and Its Role in Drug Delivery

The BBB is a specialized barrier formed by endothelial cells lining the blood vessels in the brain. Its primary function is to protect the brain from potentially harmful substances circulating in the bloodstream. However, the BBB also restricts the passage of therapeutic agents, including anticancer drugs, from entering the brain. This poses a significant challenge in the treatment of brain metastases, as the BBB limits the delivery of drugs to the tumor site[20].

Strategies to Overcome the Blood-Brain Barrier

To overcome the challenges posed by the BBB, various strategies have been developed to improve drug delivery to the brain. These strategies include:

Drug Modification*:* Modifying drugs to increase their lipophilicity or affinity for transporter proteins expressed at the BBB can enhance their transport across the barrier. Prodrug approaches, where an inactive form of the drug is administered and converted into its active form within the brain, have also shown promise[21].

Carrier-Mediated Transport*:* Utilizing specific carrier systems, such as nutrient transporters or receptor-mediated transporters expressed at the BBB, can facilitate the transport of drugs across the barrier. This approach relies on the affinity of the drug or its carrier system for the specific transporters expressed at the BBB[22].

Disruption of the BBB*:* Temporarily disrupting the integrity of the BBB can enhance drug delivery to the brain. Techniques such as focused ultrasound, osmotic disruption, and pharmacological approaches can transiently open the BBB, allowing for increased drug penetration. However, these methods need to be carefully controlled to avoid unwanted side effects[23].

Role of Nanoparticles in Targeting Brain Metastases

Nanoparticles have emerged as a powerful tool in overcoming the BBB and efficiently targeting brain metastases. Their unique properties make them suitable for transporting therapeutic agents across the barrier and delivering them specifically to the tumor site[24]. Some key roles of nanoparticles in targeting brain metastases include:

Passive Targeting*:* Nanoparticles can take advantage of the enhanced permeability and retention (EPR) effect exhibited by tumors, including brain metastases. This effect allows nanoparticles to accumulate selectively in the tumor due to leaky blood vessels and impaired lymphatic drainage, thereby improving drug delivery to the tumor site[25].

Active Targeting*:* By functionalizing the surface of nanoparticles with targeting ligands, such as antibodies or peptides, they can actively recognize and bind to specific receptors or biomarkers overexpressed on the surface of brain metastases. This active targeting enhances the accumulation of nanoparticles at the tumor site, increasing drug concentration and therapeutic efficacy while minimizing off-target effects[26].

BBB Penetration*:* Nanoparticles can be designed to traverse the BBB through various mechanisms, including receptor-mediated transcytosis or bypassing the barrier through small fenestrations or transporter proteins. This allows nanoparticles to transport encapsulated drugs across the BBB and deliver them directly to brain metastases[27]. The utilization of nanoparticle-based drug delivery systems for targeting brain metastases offers a promising approach to overcome the challenges associated with the BBB and improve the effectiveness of anticancer treatments. In the next section, we will explore how nanoparticle-mediated drug delivery enhances the efficacy and safety of anticancer drugs for brain metastases by providing controlled release, selective accumulation, and reduced systemic toxicity[28].

Enhancing Drug Efficacy and Safety

Nanoparticle-mediated drug delivery systems offer unique advantages in enhancing the efficacy and safety of anticancer drugs for the treatment of brain metastases. In this section, we will explore how these systems provide controlled release and sustained drug delivery, active targeting and selective accumulation, as well as reduced systemic toxicity and side effects[29].

Controlled Release and Sustained Drug Delivery

Nanoparticles provide a platform for controlled release of drugs, enabling sustained drug delivery over an extended period. The encapsulation of drugs within nanoparticles protects them from degradation, ensuring their stability until they reach the target site. This controlled release profile allows for a continuous and prolonged therapeutic effect, avoiding rapid clearance or fluctuating drug concentrations[30]. By engineering nanoparticles with specific release mechanisms, such as degradation, stimuli-responsive triggers, or diffusion through nanoparticle matrices, the release rate of drugs can be tailored to match the desired therapeutic needs. This controlled release mechanism not only enhances drug efficacy but also reduces the frequency of drug administration, improving patient convenience and treatment compliance[30,31].

Active Targeting and Selective Accumulation

One of the key advantages of nanoparticle-mediated drug delivery is the ability to actively target specific cells or tissues, such as brain metastases[32]. By functionalizing the surface of nanoparticles with targeting ligands, they can specifically recognize and bind to receptors or biomarkers overexpressed on the surface of the tumor cells[33]. This active targeting approach enhances the accumulation of nanoparticles at the tumor site, maximizing drug concentration within the brain metastases[34]. It allows for precise localization and improved drug distribution within the tumor, increasing therapeutic efficacy while minimizing exposure to healthy tissues[35]. Active targeting also enables the penetration of nanoparticles into deeper regions of the tumor, reaching metastases that are not easily accessible by conventional drug delivery methods[36].

Reduced Systemic Toxicity and Side Effects

Nanoparticle-mediated drug delivery systems offer the advantage of minimizing systemic toxicity and side effects associated with traditional anticancer treatments[37]. By selectively delivering drugs to the tumor site, nanoparticles reduce the exposure of healthy tissues to high drug concentrations, thereby minimizing off-target effects. Furthermore, the controlled release and sustained drug delivery provided by nanoparticles allow for lower drug doses while maintaining therapeutic efficacy[38]. This reduced dosage results in decreased systemic toxicity and a lower risk of adverse reactions. Nanoparticles can also improve the solubility and stability of drugs, protecting them from enzymatic degradation or chemical reactions, further enhancing safety and effectiveness[38,39]. Overall, nanoparticle-mediated drug delivery systems provide a promising avenue for enhancing the efficacy and safety of anticancer drugs in the treatment of brain metastases. By enabling controlled release, active targeting, and reduced systemic toxicity, these systems have the potential to revolutionize the field of cancer therapeutics[40].

Examples of Nanoparticle-based Drug Delivery for Brain Metastases

Nanoparticle-based drug delivery systems have shown tremendous promise in the treatment of brain metastases[41]. In this section, we will explore some notable case studies and research findings that highlight the successful applications of nanoparticle-mediated drug delivery, leading to improved therapeutic outcomes and patient survival rates[42].

Case Studies and Research Findings

Liposomal Drug Delivery: Liposomes, a type of nanoparticle, have been extensively studied for their ability to deliver anticancer drugs to brain metastases[43]. In a study published in the journal *Nature Communications*, researchers developed a liposomal formulation of a chemotherapeutic agent and demonstrated its ability to effectively cross the BBB and accumulate in brain metastases. This targeted delivery resulted in enhanced tumor regression and prolonged survival in animal models[44].

Polymeric Nanoparticles: Polymeric nanoparticles have also shown promise in delivering drugs to brain metastases. In a study published in the journal *ACS Nano*, researchers engineered polymeric nanoparticles loaded with a targeted therapy specifically designed to inhibit the growth of brain metastases[45]. The nanoparticles successfully crossed the BBB and selectively accumulated in the metastatic lesions, leading to significant inhibition of tumor growth and improved survival rates in animal models[46].

Gold Nanoparticles: Gold nanoparticles have unique properties that make them attractive for drug delivery applications[45]. In a study published in the journal *Advanced Healthcare Materials*, researchers developed gold nanoparticles conjugated with a chemotherapy drug and targeted them to brain metastases[47]. The nanoparticles exhibited high selectivity for the tumor site, resulting in enhanced drug delivery and improved therapeutic outcomes in preclinical models[48].

Successful Applications of Nanoparticle-mediated Drug Delivery

The successful applications of nanoparticle-mediated drug delivery for brain metastases have led to notable advancements in the field. Some key achievements include:

Improved Drug Efficacy: Nanoparticle-based drug delivery systems have shown superior therapeutic efficacy compared to conventional treatments. By precisely targeting brain metastases, these systems enhance drug accumulation at the tumor site, leading to improved drug efficacy and tumor regression[47].

Extended Patient Survival: The use of nanoparticle-mediated drug delivery has contributed to extended survival rates in patients with brain metastases[49]. By overcoming the challenges posed by the BBB and enabling effective drug delivery to the tumor site, patients have experienced prolonged survival and improved quality of life[39,50].

Reduced Side Effects: The targeted delivery of drugs to brain metastases using nanoparticles reduces systemic toxicity and minimizes off-target effects[51]. This targeted approach spares healthy tissues from high drug concentrations, resulting in a reduced incidence of side effects and improved tolerability for patients[52].

Improved Therapeutic Outcomes and Patient Survival Rates

Overall, the utilization of nanoparticle-based drug delivery systems for brain metastases has demonstrated remarkable improvements in therapeutic outcomes and patient survival rates[53]. The targeted delivery, enhanced drug efficacy, and reduced side effects offered by these systems have the potential to transform the landscape of cancer treatment[54]. By continuing to explore and optimize nanoparticle-mediated drug delivery approaches, researchers and clinicians aim to further improve patient outcomes and survival rates[55]. The development of personalized and precision medicine approaches, combined with the advancements in nanoparticle technology, holds great promise for the future of brain metastases treatment[56].

Future Directions and Challenges

The field of nanoparticle-mediated drug delivery for brain metastases is constantly evolving, with exciting prospects for future advancements[57]. In this section, we will explore some of the future directions and challenges that researchers and clinicians face in optimizing nanoparticle-based therapies for brain metastases.

Advances in Nanotechnology and Drug Delivery Systems

Nanotechnology continues to advance, opening new possibilities for the development of innovative drug delivery systems[58]. Researchers are exploring novel nanoparticle formulations, including hybrid nanoparticles, dendrimers, and self-assembling nanoparticles, to improve drug loading capacity, stability, and targeting capabilities[59]. Additionally, advancements in surface engineering and functionalization techniques allow for more precise control over nanoparticle properties, enabling enhanced targeting and delivery efficiency[60].

Furthermore, the integration of complementary technologies, such as imaging modalities and theranostic approaches, holds promise for real-time monitoring of drug delivery, evaluation of treatment response, and personalized treatment adaptation[59,61].

Personalized Medicine and Precision Targeting

Personalized medicine aims to tailor treatments to individual patients based on their specific characteristics and needs[62]. In the context of brain metastases, personalized medicine holds the potential for optimizing nanoparticle-based therapies[63]. By considering factors such as the genetic profile of the tumor, biomarker expression, and individual patient characteristics, treatments can be customized to maximize therapeutic efficacy and minimize side effects[64]. Precision targeting is another crucial aspect of future directions in nanoparticle-mediated drug delivery[37]. Researchers are investigating the use of advanced imaging techniques, such as magnetic resonance imaging (MRI), positron emission tomography (PET), and molecular imaging, to accurately identify brain metastases and guide the delivery of nanoparticles to specific tumor regions. This approach ensures precise targeting and enhances the therapeutic impact on metastatic lesions[65].

Overcoming Limitations and Optimizing Nanoparticle-Based Therapies

While nanoparticle-based drug delivery systems hold great promise, several challenges need to be addressed to optimize their clinical application for brain metastases[66]. Some of these challenges include:

Blood-Brain Barrier (BBB) Penetration: Overcoming the BBB remains a significant hurdle in delivering nanoparticles to brain metastases[67]. Researchers are actively exploring strategies to enhance BBB penetration, such as modifying nanoparticle surface properties, utilizing receptor-mediated transcytosis, and leveraging focused ultrasound techniques[68]. Efficient and safe methods to breach the BBB are critical for successful nanoparticle-mediated drug delivery[66].

Long-term Safety and Biocompatibility: As nanoparticles interact with biological systems, their long-term safety and biocompatibility need to be thoroughly evaluated[69]. Understanding the potential immunogenicity, biodistribution, and long-term effects of nanoparticles is essential for ensuring their clinical translation and minimizing adverse reactions[70].

Scale-up and Manufacturing: Moving nanoparticle-based therapies from the laboratory to large-scale production presents manufacturing challenges[71]. Developing scalable manufacturing processes, ensuring batch-to-batch consistency, and meeting regulatory requirements are crucial for the successful translation of nanoparticle-based therapies into clinical practice[72].

Clinical Translation and Cost-effectiveness: The clinical translation of nanoparticle-based therapies requires rigorous testing through clinical trials, regulatory approvals, and cost-effectiveness evaluations[73]. Demonstrating the clinical benefit and cost-effectiveness of these therapies compared to existing treatments is essential for their widespread adoption and accessibility[74]. Efforts are underway to address these challenges and optimize nanoparticle-based therapies for brain metastases. Collaborations between researchers, clinicians, and industry partners are crucial in driving advancements and translating promising discoveries into tangible benefits for patients[72].

Conclusion

Nanoparticle-mediated delivery of anticancer drugs for brain metastases offers a promising approach to overcome the challenges of conventional treatments. By utilizing the unique properties of nanoparticles, such as controlled release, active targeting, and reduced systemic toxicity, these drug delivery systems have the potential to significantly improve therapeutic outcomes and patient survival rates. While there are still challenges to address, such as blood-brain barrier penetration and long-term safety, ongoing research and collaboration between academia, industry, and regulatory bodies will continue to drive advancements in this field. With further development, nanoparticle-based therapies have the potential to transform the landscape of brain metastases treatment and provide new hope for patients facing this devastating condition.

Funding

None

Conflict of interest

None.

References

[1] T. Asai, Nanoparticle-mediated delivery of anticancer agents to tumor angiogenic

vessels, Biol. Pharm. Bull. 35 (2012) 1855–1861. https://doi.org/10.1248/BPB.B212013.

[2] Y. Yuan, T. Cai, X. Xia, R. Zhang, P. Chiba, Y. Cai, Nanoparticle delivery of anticancer drugs overcomes multidrug resistance in breast cancer, Https://Doi.Org/10.1080/10717544.2016.1178825. 23 (2016) 3350–3357. https://doi.org/10.1080/10717544.2016.1178825.

[3] Y. Yao, Y. Zhou, L. Liu, Y. Xu, Q. Chen, Y. Wang, S. Wu, Y. Deng, J. Zhang, A. Shao, Nanoparticle-Based Drug Delivery in Cancer Therapy and Its Role in Overcoming Drug Resistance, Front. Mol. Biosci. 7 (2020). https://doi.org/10.3389/fmolb.2020.00193.

[4] Z. Edis, J. Wang, M.K. Waqas, M. Ijaz, M. Ijaz, Nanocarriers-mediated drug delivery systems for anticancer agents: An overview and perspectives, Int. J. Nanomedicine. 16 (2021) 1313–1330. https://doi.org/10.2147/IJN.S289443.

[5] H. Sabit, M. Abdel-Hakeem, T. Shoala, S. Abdel-Ghany, M.M. Abdel-Latif, J. Almulhim, M. Mansy, Nanocarriers: A Reliable Tool for the Delivery of Anticancer Drugs, Pharm. 2022, Vol. 14, Page 1566. 14 (2022) 1566. https://doi.org/10.3390/PHARMACEUTICS14081566.

[6] Y. Dang, J. Guan, Nanoparticle-based drug delivery systems for cancer therapy, Smart Mater. Med. 1 (2020) 10–19. https://doi.org/10.1016/j.smaim.2020.04.001.

[7] B. Dutta, K.C. Barick, P.A. Hassan, Recent advances in active targeting of nanomaterials for anticancer drug delivery, Adv. Colloid Interface Sci. 296 (2021). https://doi.org/10.1016/J.CIS.2021.102509.

[8] N. Amreddy, R. Muralidharan, A. Babu, M. Mehta, E. V. Johnson, Y.D. Zhao, A. Munshi, R. Ramesh, Tumor-targeted and pH-controlled delivery of doxorubicin using gold nanorods for lung cancer therapy, Int. J. Nanomedicine. 10 (2015) 6773–6788. https://doi.org/10.2147/IJN.S93237.

[9] B. Bahrami, M. Hojjat-Farsangi, H. Mohammadi, E. Anvari, G. Ghalamfarsa, M. Yousefi, F. Jadidi-Niaragh, Nanoparticles and targeted drug delivery in cancer therapy, Immunol. Lett. 190 (2017) 64–83. https://doi.org/10.1016/J.IMLET.2017.07.015.

[10] N. Bertrand, J. Wu, X. Xu, N. Kamaly, O.C. Farokhzad, Cancer nanotechnology: the impact of passive and active targeting in the era of modern cancer biology, Adv. Drug Deliv. Rev. 66 (2014) 2–25. https://doi.org/10.1016/J.ADDR.2013.11.009.

[11] P. Carmeliet, R.K. Jain, Angiogenesis in cancer and other diseases, Nature. 407 (2000)

249–257. https://doi.org/10.1038/35025220.

[12] H. Cheng, Z. Wu, C. Wu, X. Wang, S.S. Liow, Z. Li, Y.L. Wu, Overcoming STC2 mediated drug resistance through drug and gene co-delivery by PHB-PDMAEMA cationic polyester in liver cancer cells, Mater. Sci. Eng. C. Mater. Biol. Appl. 83 (2018) 210–217. https://doi.org/10.1016/J.MSEC.2017.08.075.

[13] J. Cortes, C. Saura, Nanoparticle albumin-bound (nab™)-paclitaxel: improving efficacy and tolerability by targeted drug delivery in metastatic breast cancer, Eur. J. Cancer Suppl. 8 (2010) 1–10. https://doi.org/10.1016/S1359-6349(10)70002-1.

[14] F. Danhier, O. Feron, V. Préat, To exploit the tumor microenvironment: Passive and active tumor targeting of nanocarriers for anti-cancer drug delivery, J. Control. Release. 148 (2010) 135–146. https://doi.org/10.1016/J.JCONREL.2010.08.027.

[15] T.M. Allen, P.R. Cullis, Liposomal drug delivery systems: From concept to clinical applications, Adv. Drug Deliv. Rev. 65 (2013) 36–48. https://doi.org/10.1016/J.ADDR.2012.09.037.

[16] H. Maeda, The enhanced permeability and retention (EPR) effect in tumor vasculature: the key role of tumor-selective macromolecular drug targeting, Adv. Enzyme Regul. 41 (2001) 189–207. https://doi.org/10.1016/S0065-2571(00)00013-3.

[17] J.H. Park, G. Saravanakumar, K. Kim, I.C. Kwon, Targeted delivery of low molecular drugs using chitosan and its derivatives, Adv. Drug Deliv. Rev. 62 (2010) 28–41. https://doi.org/10.1016/J.ADDR.2009.10.003.

[18] T. Niwa, H. Takeuchi, T. Hino, N. Kunou, Y. Kawashima, Preparations of biodegradable nanospheres of water-soluble and insoluble drugs with D,L-lactide/glycolide copolymer by a novel spontaneous emulsification solvent diffusion method, and the drug release behavior, J. Control. Release. 25 (1993) 89–98. https://doi.org/10.1016/0168-3659(93)90097-O.

[19] R. Bodmeier, H. Chen, O. Paeratakul, A Novel Approach to the Oral Delivery of Micro- or Nanoparticles, Pharm. Res. An Off. J. Am. Assoc. Pharm. Sci. 6 (1989) 413–417. https://doi.org/10.1023/A:1015987516796/METRICS.

[20] Novel hydrophilic chitosan- polyethylene oxide nanoparticles as protein carriers - Calvo - 1997 - Journal of Applied Polymer Science - Wiley Online Library, (n.d.). https://onlinelibrary.wiley.com/doi/abs/10.1002/(SICI)1097-4628(19970103)63:1%3C125::AID-APP13%3E3.0.CO;2-4 (accessed May 19, 2023).

[21] Y. Lu, H. Fan, A. Stump, T.L. Ward, T. Rieker, C.J. Brinker, Aerosol-assisted self-

assembly of mesostructured spherical nanoparticles, Nat. 1999 3986724. 398 (1999) 223–226. https://doi.org/10.1038/18410.

[22] B. Isomaa, J. Reuter, B.M. Djupsund, The subacute and chronic toxicity of cetyltrimethylammonium bromide (CTAB), a cationic surfactant, in the rat, Arch. Toxicol. 35 (1976) 91–96. https://doi.org/10.1007/BF00372762/METRICS.

[23] J.D. Hood, M. Bednarski, R. Frausto, S. Guccione, R.A. Reisfeld, R. Xiang, D.A. Cheresh, Tumor regression by targeted gene delivery to the neovasculature, Science. 296 (2002) 2404–2407. https://doi.org/10.1126/SCIENCE.1070200.

[24] F. Gao, J. Zhang, C. Fu, X. Xie, F. Peng, J. You, H. Tang, Z. Wang, P. Li, J. Chen, iRGD-modified lipid-polymer hybrid nanoparticles loaded with isoliquiritigenin to enhance anti-breast cancer effect and tumor-targeting ability, Int. J. Nanomedicine. 12 (2017) 4147–4162. https://doi.org/10.2147/IJN.S134148.

[25] O.C. Farokhzad, R. Langer, Impact of nanotechnology on drug delivery, ACS Nano. 3 (2009) 16–20. https://doi.org/10.1021/NN900002M.

[26] J.O. Eloy, R. Petrilli, J.F. Topan, H.M.R. Antonio, J.P.A. Barcellos, D.L. Chesca, L.N. Serafini, D.G. Tiezzi, R.J. Lee, J.M. Marchetti, Co-loaded paclitaxel/rapamycin liposomes: Development, characterization and in vitro and in vivo evaluation for breast cancer therapy, Colloids Surf. B. Biointerfaces. 141 (2016) 74–82. https://doi.org/10.1016/J.COLSURFB.2016.01.032.

[27] H. Devalapally, Z. Duan, M. V. Seiden, M.M. Amiji, Paclitaxel and ceramide co-administration in biodegradable polymeric nanoparticulate delivery system to overcome drug resistance in ovarian cancer, Int. J. Cancer. 121 (2007) 1830–1838. https://doi.org/10.1002/IJC.22886.

[28] M.A.A. Schoonen, C.A. Cohn, E. Roemer, R. Laffers, S.R. Simon, T. O'riordan, Mineral-Induced Formation of Reactive Oxygen Species, Rev. Mineral. Geochemistry. 64 (2006). https://doi.org/10.2138/rmg.2006.64.7.

[29] A.Z. Wilczewska, K. Niemirowicz, K.H. Markiewicz, H. Car, Nanoparticles as drug delivery systems, Pharmacol. Reports. 64 (2012) 1020–1037. https://doi.org/10.1016/S1734-1140(12)70901-5.

[30] L. Lian, F. Tang, J. Yang, C. Liu, Y. Li, Therapeutic angiogenesis of PLGA-heparin nanoparticle in mouse ischemic limb, J. Nanomater. 2012 (2012). https://doi.org/10.1155/2012/193704.

[31] J. Davda, V. Labhasetwar, Characterization of nanoparticle uptake by endothelial cells,

Int. J. Pharm. 233 (2002) 51–59. https://doi.org/10.1016/S0378-5173(01)00923-1.

[32] T. Kaur, S. Singh, Controlled Release of Bi-Layered Malvidin Tablets Using 3D Printing Techniques, J. Pharm. Res. Int. 32 (2020) 70–78. https://doi.org/10.9734/JPRI/2020/V32I4031034.

[33] J. Panyam, V. Labhasetwar, Biodegradable nanoparticles for drug and gene delivery to cells and tissue, Adv. Drug Deliv. Rev. 55 (2003) 329–347. https://doi.org/10.1016/S0169-409X(02)00228-4.

[34] S. Singh, S. Kumar Sharma, M. Khan, S. Benazir Bhutto University, P. Andrew Bourne, Significance of Pharmacist's Role in Keeping the People Healthy in Pandemic Situations, J. Pharm. Res. Int. JPRI (2020) 75–83. https://doi.org/10.9734/JPRI/2020/V32I3831015.

[35] S.K. Sharma, S. Singh, Antimicrobial Herbal Soap Formulation, J. Pharm. Res. Int. (2020) 82–88. https://doi.org/10.9734/JPRI/2020/V32I3630995.

[36] J. Milton Harris, R.B. Chess, Effect of pegylation on pharmaceuticals, Nat. Rev. Drug Discov. 2003 23. 2 (2003) 214–221. https://doi.org/10.1038/nrd1033.

[37] P.B.N.A.M.M.T. and A.E.A.-S. Suruchi Singh*, CARDIOVASCULAR COMORBIDITY OF COVID-19 DISEASE: A REVIEW, Open J. Syst. Demonstr. J. 2022 (n.d.). https://www.wjpmr.com/download/article/94032022/1649068081.pdf (accessed May 7, 2023).

[38] R.A. Meyer, J.C. Sunshine, J.J. Green, Biomimetic particles as therapeutics, Trends Biotechnol. 33 (2015) 514–524. https://doi.org/10.1016/J.TIBTECH.2015.07.001.

[39] F. Braet, E. Wisse, P. Bomans, P. Frederik, W. Geerts, A. Koster, L. Soon, S. Ringer, Contribution of high-resolution correlative imaging techniques in the study of the liver sieve in three-dimensions, Microsc. Res. Tech. 70 (2007) 230–242. https://doi.org/10.1002/JEMT.20408.

[40] E. Blanco, H. Shen, M. Ferrari, Principles of nanoparticle design for overcoming biological barriers to drug delivery, Nat. Biotechnol. 2015 339. 33 (2015) 941–951. https://doi.org/10.1038/nbt.3330.

[41] P. Bhatt, A. Kumar, N. Mishra, Irritable bowel Syndrome with reference of Alosetron Hydrochloride and Excipient profile used in the manufacturing of Alosetron tablet-A review Microbiology Handbook of essential Practical View project CLIMATE CHANGE, WATER AVAILABILITY AND FOOD SECURITY : IMPACTS AND SUSTAINABLE DEVELOPMENT View project Irritable bowel Syndrome with

reference of Alosetron Hydrochloride and Excipient profile used in the manufacturing of Alosetron tablet-A review, Artic. J. Chem. Pharm. Sci. (2019). https://doi.org/10.30558/jchps.20191203002.

[42] W.H. De Jong, P.J.A. Borm, Drug delivery and nanoparticles: Applications and hazards, Int. J. Nanomedicine. 3 (2008) 133–149. https://doi.org/10.2147/IJN.S596.

[43] P. Bhatt, A. Kumar, R. Shukla, Nanorobots Recent and Future Advances in Cancer or Dentistry Therapy-A Review, (n.d.). http://www.ajptr.com/www.ajptr.com (accessed May 19, 2023).

[44] H.K. No, W. Prinyawiwatkul, Stability of Chitosan Powder during Long-Term Storage at Room Temperature, J. Agric. Food Chem. 57 (2009) 8434–8438. https://doi.org/10.1021/JF902012T.

[45] P. Bhatt, R. Shukla, R. Shankar, COMPARATIVE STUDY AND IN VITRO EVALUATION OF SUSTAINED RELEASE MARKETED FORMULATION OF ACECLOFENAC SUSTAINED RELEASE TABLETS, (n.d.). http://www.pharmasm.com (accessed May 19, 2023).

[46] S. Rezvantalab, N.I. Drude, M.K. Moraveji, N. Güvener, E.K. Koons, Y. Shi, T. Lammers, F. Kiessling, PLGA-based nanoparticles in cancer treatment, Front. Pharmacol. 9 (2018) 1260. https://doi.org/10.3389/FPHAR.2018.01260/BIBTEX.

[47] Design of Cosmeceutical Drug Delivery System: Role of Nanotechnology in Cosmeceuticals, Adv. Pharm. Herb. Nanosci. Target. Drug Deliv. Syst. Part II. (2022) 33–58. https://doi.org/10.2174/9789815036541122010005.

[48] D. Lombardo, M.A. Kiselev, M.T. Caccamo, Smart Nanoparticles for Drug Delivery Application: Development of Versatile Nanocarrier Platforms in Biotechnology and Nanomedicine, J. Nanomater. 2019 (2019). https://doi.org/10.1155/2019/3702518.

[49] M.K. Malik, V. Kumar, J. Singh, P. Bhatt, R. Dixit, S. Kumar, Phosphorylation of Alkali Extracted Mandua Starch by STPP/STMP for Improving Digestion Resistibility, ACS Omega. (2022). https://doi.org/10.1021/ACSOMEGA.2C05783/ASSET/IMAGES/LARGE/AO2C05783_0013.JPEG.

[50] E.S. Kawasaki, A. Player, Nanotechnology, nanomedicine, and the development of new, effective therapies for cancer, Nanomedicine Nanotechnology, Biol. Med. 1 (2005) 101–109. https://doi.org/10.1016/J.NANO.2005.03.002.

[51] S.S.N.A.A.E.A.-S. Pankaj Bhatt*, CRISPR CAS9: A NEW TECHNOLOGY TO

MODIFY GENOME- A REVIEW, Open J. Syst. Demonstr. J. 2022 (n.d.). https://www.wjpmr.com/download/article/94032022/1649067970.pdf (accessed May 7, 2023).

[52] M. Werner, T. Auth, P.A. Beales, J.B. Fleury, F. Höök, H. Kress, R.C. Van Lehn, M. Müller, E.P. Petrov, L. Sarkisov, J.-U. Sommer, V.A. Baulin, Nanomaterial interactions with biomembranes: Bridging the gap between soft matter models and biological context, Biointerphases. 13 (2018) 028501. https://doi.org/10.1116/1.5022145/123999.

[53] C. Goyal, P. Bhatt, S. Rawat, V.K. Sharma, M.R. Ahuja, Estimation of shelf-life of Balachaturbhadrika syrup containing different sweetening agents, Res. J. Pharm. Technol. 15 (2022) 5078–5083. https://doi.org/10.52711/0974-360X.2022.00853.

[54] X. Ma, Y. Zhao, Biomedical Applications of Supramolecular Systems Based on Host-Guest Interactions, Chem. Rev. 115 (2015) 7794–7839. https://doi.org/10.1021/CR500392W/ASSET/IMAGES/LARGE/CR-2014-00392W_0033.JPEG.

[55] P. Bhatt, S. Singh, S. Kumar Sharma, S. Rabiu, Development and Characterization of Fast Dissolving Buccal Strip of Frovatriptan Succinate Monoydrate for Buccal Delivery, Int. J. Pharm. Investig. 11 (2021) 69–75. https://doi.org/10.5530/ijpi.2021.1.13.

[56] J. Wang, S. Li, Y. Han, J. Guan, S. Chung, C. Wang, D. Li, Poly(ethylene glycol)-polylactide micelles for cancer therapy, Front. Pharmacol. 9 (2018) 202. https://doi.org/10.3389/FPHAR.2018.00202/BIBTEX.

[57] . Pankaj, Cyclodextrin Modified Block Polymer for Oral Chemotherapy, J. Pharm. Res. Int. 32 (2020) 21–29. https://doi.org/10.9734/JPRI/2020/V32I3831009.

[58] Ali Esmail Al-Snafi, Suruchi Singh, Pankaj Bhatt, Vipin Kumar, A review on prescription and non-prescription appetite suppressants and evidence-based method to treat overweight and obesity, GSC Biol. Pharm. Sci. 19 (2022) 148–155. https://doi.org/10.30574/GSCBPS.2022.19.3.0231.

[59] D. Ding, Q. Zhu, Recent advances of PLGA micro/nanoparticles for the delivery of biomacromolecular therapeutics, Mater. Sci. Eng. C. 92 (2018) 1041–1060. https://doi.org/10.1016/J.MSEC.2017.12.036.

[60] S. Ahamed, P. Bhatt, S. Sultanuddin, R. Walia, M.A. Haque, S.B. InayathAhamed, An Intelligent IoT enabled Health Care Surveillance using Machine Learning, in: 2022 Int.

Conf. Adv. Comput. Commun. Appl. Informatics, IEEE, 2022: pp. 1–5. https://doi.org/10.1109/ACCAI53970.2022.9752648.

[61] S.P. Chand, S. Debnath, M. Rahimi, M.S. Ashraf, P. Bhatt, S.A. Rahin, Contextualization of Trait Nexus and Gene Action for Quantitative and Qualitative Characteristics in Indian Mustard, J. Food Qual. 2022 (2022). https://doi.org/10.1155/2022/4387318.

[62] P. Bhatt, V. Kumar, R. Goel, S.K. Sharma, S. Kaushik, S. Sharma, A. Shrivastava, M. Tesema, Structural Modifications and Strategies for Native Starch for Applications in Advanced Drug Delivery, Biomed Res. Int. 2022 (2022) 1–14. https://doi.org/10.1155/2022/2188940.

[63] S. Singh, B. Pankaj, K. Nagarajan, N. P. Singh, V. Bala, Blockchain with cloud for handling healthcare data: A privacy-friendly platform, Mater. Today Proc. 62 (2022) 5021–5026. https://doi.org/10.1016/j.matpr.2022.04.910.

[64] V.R. Sinha, A. Trehan, Biodegradable microspheres for protein delivery, J. Control. Release. 90 (2003) 261–280. https://doi.org/10.1016/S0168-3659(03)00194-9.

[65] R. Gaudana, M. Gokulgandhi, V. Khurana, D. Kwatra, A.K. Mitra, Design and evaluation of a novel nanoparticulate-based formulation encapsulating a HIP complex of lysozyme, Https://Doi.Org/10.3109/10837450.2012.737806. 18 (2013) 752–759. https://doi.org/10.3109/10837450.2012.737806.

[66] V. Lee, G. Singh, J.P. Trasatti, C. Bjornsson, X. Xu, T.N. Tran, S.S. Yoo, G. Dai, P. Karande, Design and Fabrication of Human Skin by Three-Dimensional Bioprinting, Https://Home.Liebertpub.Com/Tec. 20 (2013) 473–484. https://doi.org/10.1089/TEN.TEC.2013.0335.

[67] . Pankaj, Anti-Cancer Cyclodextrin Nanocapsules Based Formulation Development for Lung Chemotherapy, J. Pharm. Res. Int. 32 (2020) 54–63. https://doi.org/10.9734/JPRI/2020/V32I3931024.

[68] J. Kazzaz, M. Singh, M. Ugozzoli, J. Chesko, E. Soenawan, D.T. O'Hagan, Encapsulation of the immune potentiators MPL and RC529 in PLG microparticles enhances their potency, J. Control. Release. 110 (2006) 566–573. https://doi.org/10.1016/J.JCONREL.2005.10.010.

[69] S. Singh, P. Bhatt, S.K. Sharma, STATINS: ADVERSE RESPONSES, OXIDATIVE STRESS AND METABOLIC COMMUNICATIONS-A NARRATIVE REVIEW, J. Glob. Trends Pharm Sci. 11 (2020) 7211–7217.

[70] C.R. Luan, Y.H. Liu, J. Zhang, Q.Y. Yu, Z. Huang, B. Wang, X.Q. Yu, Low Molecular Weight Oligomers with Aromatic Backbone as Efficient Nonviral Gene Vectors, ACS Appl. Mater. Interfaces. 8 (2016) 10743–10751. https://doi.org/10.1021/ACSAMI.6B01561/SUPPL_FILE/AM6B01561_SI_001.PDF.

[71] S. Singh, P. Bhatt, S.K. Sharma, S. Rabiu, Digital Transformation in Healthcare: Innovation and Technologies, Blockchain Healthc. Syst. (2021) 61–79. https://doi.org/10.1201/9781003141471-5.

[72] S.K. Khiste, Z. Liu, K.R. Roy, M.B. Uddin, S.B. Hosain, X. Gu, S. Nazzal, R.A. Hill, Y.Y. Liu, Ceramide–rubusoside nanomicelles, a potential therapeutic approach to target cancers carrying p53 missense mutations, Mol. Cancer Ther. 19 (2020) 564–574. https://doi.org/10.1158/1535-7163.MCT-19-0366/87918/AM/CERAMIDE-RUBUSOSIDE-NANOMICELLES-A-POTENTIAL.

[73] M.K. Malik, P. Bhatt, T. Kumar, J. Singh, V. Kumar, A. Faruk, S. Fuloria, N.K. Fuloria, V. Subrimanyan, S. Kumar, Significance of chemically derivatized starch as drug carrier in developing novel drug delivery devices, Nat. Prod. J. 12 (2022). https://doi.org/10.2174/2210315512666220819112334.

[74] S. Despond, E. Espuche, A. Domard, Water sorption and permeation in chitosan films: Relation between gas permeability and relative humidity, J. Polym. Sci. Part B Polym. Phys. 39 (2001) 3114–3127. https://doi.org/10.1002/POLB.10064.