e-ISSN: 2349-2678, p-ISSN:2961-6050

available online on www.ijpba.in

International Journal of Pharmaceutical and Biological Science Archive

NLM (National Library of Medicine ID: 101732687)

Index Copernicus Value 2019: 71.05

Volume 11 Issue 5; 2023; Page No. 13-22

Review Article

Advancement and New Technology in Drug Delivery: An Updated Review

Arushi Sharma*, Ajeet Pal Singh, Rajesh Kumar & Amar Pal Singh

Department of Pharmaceutics, St. Soldier Institute of Pharmacy, Lidhran Campus, Behind Nit (R.E.C.), Jalandhar –Amritsar By Pass, Nh-1, Jalandhar -144011, Punjab, India

Article Info: Received: 05-07-2023 / Revised: 07-08-2023 / Accepted: 30-08-2023

Address for Correspondence: Arushi Sharma

Conflict of interest statement: No conflict of interest

Abstract

The need to selectively target the cells involved in the onset and progression of illnesses has arisen as a result of developments in molecular pharmacology and a better knowledge of the mechanism of most diseases. Most illnesses that endanger human life need treatment medicines with significant adverse effects, making precise tissue targeting essential to reduce unnecessary systemic exposure. In order to maximize therapeutic effectiveness and minimize off-target accumulation, modern drug delivery systems (DDS) are developed using cutting-edge technology to speed up systemic drug delivery to the precise target location. Therefore, they are crucial in the prevention, diagnosis, and treatment of illness. Improved performance, automation, accuracy, and effectiveness are just some of the ways in which modern DDS outshine its less sophisticated predecessors. Nanomaterials or tiny devices having several functions, such as those with high viscoelasticity and a long half-life in circulation, are used to create these materials. Therefore, this article serves as a thorough introduction to the development and evolution of drug delivery methods over time. New drug delivery methods are discussed together with their therapeutic uses, difficulties in implementation, and potential solutions.

Keywords: Theraputic, Treatment, Implementation, Potential, Development, Illness, Automation, Nanomaterial

Introduction

Technology in the form of medication delivery systems may convert drug molecules into tablets or liquids that are easier to administer. They expedite the delivery of medications to their intended sites inside the body, increasing therapeutic effectiveness while decreasing off-target accumulation. There are several ways to provide medication to a patient, including but not limited to the following: orally, buccally, sublingually, nasally, ophthalmically, transdermally, subcutaneously, anally, transvaginally, and intravenously. The physiochemical qualities of a drug and the physiological responses to its administration are determined by the drug's constituents. DDS have been used successfully in the treatment of illnesses and the enhancement of health over the last several decades because to improved systemic circulation and management of the drug's pharmacological action. Controlled release was first conceived after advances in pharmacology and pharmacokinetics revealed the significance of medication release in influencing therapeutic efficacy. Since its initial approval in the 1950s, the controlled-release formulation of a medicine has gained a lot of interest thanks to its many benefits over regular pharmaceuticals. The drug release is controlled and sustained throughout time. In addition,

regulated medication delivery systems may be used for extended periods of time (weeks to years) without deteriorating due to the body's natural processes. It allows for both temporal and geographical regulation of medication delivery. It also enhances medication toxicity mitigation, patient acceptability and compliance, drug solubility, target site accumulation, effectiveness, pharmacological activity, pharmacokinetic features, and drug efficacy. Several novel drug delivery systems (NDDS) with improved accessibility, precision, and control have been created recently. The pace and method of medication release are both unique to each drug delivery system. The reason for this lies in the fact that different drug compounds will have different effects on people with different physical, chemical, and morphological qualities. According to the research done on these, the primary release mechanisms are as follows: diffusion, chemical reaction, solvent reaction, and stimulus control. For instance, the medicine may readily infiltrate through this hole to reach the target tissues since most cancer cells can multiply the porous blood arteries and lymphatic system. This improvement in both permeability and retention is called EPR. Many chemotherapeutic drugs are delivered by EPR, a passive diffusion process that has seen much study and use. Despite the fact that EPR is a contentious notion, several researchers have seen this effect across a wide range of human tumor types, providing a foundation for the application of nanomedicine to the treatment of cancer. The lack of selectivity and the increased toxicity are drawbacks. When compared to active targeting, passive targeting lacks the ability to be selective and precise. To do this, molecules that can actively connect to the surface of target tissues must first adhere to the carriers, ligands, and other components of the carriers. By doing so, absorption by non-target cells is blocked, which lessens the drug's toxicity and adverse effects. There are still significant obstacles to the complete development of actively targeted Drugs, including as the selectivity of ligands to target cells, the risk of immunogenicity, and the possibility of lysosomal breakdown after macrophage endocytosis. In the process of responsive stimuli targeting, these delivery systems may also reach the target cells by manipulating one or more of their physical or chemical characteristics. The pH, temperature, ultrasonic, magnetic, and electric fields are all examples of such physical qualities.

1.1.1 Ancillary medication delivery systems in their infancy

People back then relied heavily on plants with healing properties. They helped, but the medication distribution wasn't reliable, uniform, or targeted. All medications were manufactured and kept in pill or capsule forms prior to the advent of controlled drug administration. It is taken into the circulation via the tiny blood vessels of the digestive tract after dissolving in stomach acid and intestinal fluids. The kinetics of drug release could not be controlled. Coated technology was developed by Rhazes and Avicenna to mask the unpleasant taste of medications. The drug's release time was modified thanks to the coating procedure. It wasn't until the 10th century that gold, silver, and pearl-covered tablets became the standard form of documentation. However, keratin and shellac proved ineffectual because of storage instability and high pH for appropriate dissolving in the small intestine, whereas sugar, enteric coating, and pearl coating all performed well. The polymeric cellulose acetate phthalate used by Malm et al. as an enteric-coating material dissolves at a mild alkaline pH, like that of the small intestine, making it well suited for use in enteric controlled release. The first generation was quite fruitful, as it established controlled drug-release mechanisms and developed various oral and transdermal controlled-release formulations for clinical application. After Lipowski layered the medicine and the coat alternately, resulting in gradual, regular, and periodic release of the drug, he patented the first oral sustained-release formulation in 1951. In 1952, Smith, Klein Beecham, and French (SKF) improved upon this concept with the invention of Spansule technology, an oral predetermined-release formulation that maintains and regulates the kinetic release of a drug over time. Micro-pelleted drug-loaded beads of varying thicknesses of natural water-soluble wax are the building blocks of this formulation. The drug-loaded beads are released from the outer capsule upon ingestion, and the waxy coating

surrounding the beads progressively dissolves as the capsule travels through the gastrointestinal system. By streamlining the dose regimen, this increased patient compliance and gained widespread acceptance. To improve upon this technique even further, wax was swapped out for synthetic polymers that could be replicated more easily. In 1955, Jatzkewitz reported creating the first nanoparticle therapy by making the first polymer-drug conjugate. Liposomes, also known as lipid vesicles, were the first nanotechnology to be found, in the 1960s. The first nanocarriers were polymer-drug conjugates and liposomes. The ALZA Corporation did not develop new pharmaceuticals this decade, but instead focused on strategically delivering existing medications to patients. Scheffel and his coworker made the first microspheres from of protein in 1972. The research group led by Peter Paul Speiser began manufacturing drug-loaded nanoparticles and microcapsules in 1976 using "micelle" and "emulsion" polymerization processes.

In 1977, Couvreur et al. created the first quickly biodegradable acrylic nanoparticles and described their lysosomotropic effects. Although the 2G drug delivery formulations were outstanding, they failed to meet their therapeutic potential. Nanotechnology-based formulations, in particular nanoparticle formulations, were of special interest to the researchers, as were self-regulating, long-term depot formulations, and consistent drug release rates. Peptide and protein medicines with depot-sustained release formulations were created during this time period. Drug delivery methods that are sensitive to environmental variables including pH, temperature, electric field, and glucose have also inspired the creation of "smart polymers" and "smart hydrogels." In addition, biodegradable polymers in nanoparticle shapes such polymeric micelles, chitosan, lipids, and dendrimers were used in an attempt to construct targeted nanotechnology DDS for cancers and gene delivery. The goal was to improve medication accumulation at the site of action by modifying the nanoparticles so that they could be injected directly into the body. Animal experiments showed promising results for this nanotechnology-based DDS in inhibiting tumor development, however the FDA has only authorized a small number of medications using this approach. Modern controlled release technology emerged with the third generation of medication delivery devices. To be useful and effective, it must get through the physicochemical and biological obstacles of traditional drug delivery methods. Problems with targeted and controlled drug release, as well as low water solubility and the large molecular weight of therapeutic proteins and peptides, go under the physiochemical category, whereas problems with systemic drug distribution fall under the biological barrier category. In order to increase performance and sustainability, several new drug delivery systems will need to be created within this time period to tackle the problems associated with previous types of drug administration. Targeting a medicine to a particular place and ensuring continuous release over a set length of time provide significant problems in the design of an appropriate carrier system.

1. Drug Delivery Systems in Regenerative Medicine

When healthy tissues or organs are lost due to illness, injury, or birth abnormalities, regenerative medicine may repair or replace them. This opens up the possibility of treating a broad variety of illnesses and disorders that were formerly thought to be hopeless. This allows us to get beyond transplantation therapy's limitations, such as a lack of donor tissue and the risk of inducing detrimental host immunological responses. Regenerative medicine employs a wide range of techniques towards this goal, including cell therapy, tissue engineering, and the localized administration of therapeutic agents like medicines, proteins, and even genes, all of which promote the regeneration of damaged tissues.

Regenerative medicine employs either isolated or combined approaches to the extracellular matrix (ECM), cells, and a broad variety of signaling molecules that are essential to the process of tissue regeneration. Direct injection of the restorative factor is advised when the regeneration capacity has diminished as a result of age or systemic health conditions. However, this strategy seldom works since it is either

quickly neutralized or easily diffused away from the target area. Because of their low solubility and short half-life, the macromolecules that have resulted from recent advances in drug discovery and biotechnology need frequent dosing. In cases when regulated distribution is possible, protecting the therapeutic substance against deterioration requires a suitable delivery mechanism.

The chemical structure of a drug (such as its functional groups and amino acid sequences) and its binding ability to the targeted ligands may be altered throughout the medication's modification process. As a result, the intended function of the molecules will be altered via altered interactions with their target location. This procedure resulted in the identification of novel classes of remedial medicines with improved therapeutic activities for the treatment of systemic disorders (such as cancer and invasive fungal infections). Low solubility, adequate and sustained delivery, and the provision of effective routes of administration are only some of the additional difficulties in administering these agents that need advances in delivery technology.

In order to achieve the intended therapeutic effects of the given medications and bioactive substances in a safe manner, drug delivery scaffolds are promising techniques. In addition to facilitating targeted delivery to certain tissues or organs, these vehicles also play a role in controlling the timing and distribution of the drug's action throughout the body. The pharmacokinetics (distribution, metabolism, and pharmacodynamics) of the medication are often the focus of the administration technique. The wide variety of physicochemical properties of pharmacological substances necessitates a deeper familiarity with material sciences and production technology to guarantee accurate dosing. Understanding the drug kinetics and the biological barriers that prevent systemic drug access has been facilitated by the focus on noninvasive routes of administration (i.e., oral, transdermal, inhalation, and mucosal delivery). Significant progress in delivery technologies has resulted in novel techniques, such as nanofibers, nanogels, and micelles, for this purpose. (See Image 1).

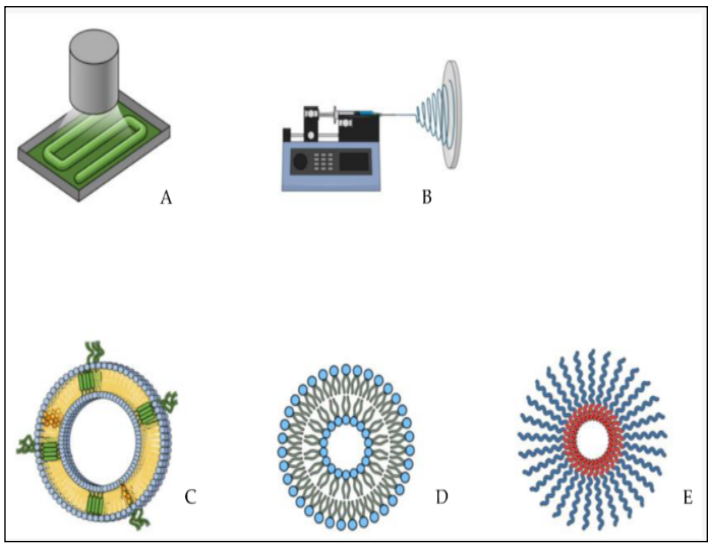

Figure 1: Examples of techniques and drug delivery systems tested in regenerative medicine: (A) 3D Bioprinting, (B) Electrospinning, (C) Extracellular vesicles, (D) Liposome, (E) Polymeric micelles.

In addition, several kinds of endogenous cells have been employed as delivery vehicles for treating illnesses including cancer, autoimmune disorders, and infectious diseases, all of which need a thorough knowledge of cell biofunctions (i.e., cell-cell and cell-tissue interactions). As a result, cell-based delivery systems were established as a game-changing therapeutic modality, ushering in a sea shift for the industry of medication delivery. This study aimed to

provide an overview of the delivery methods used in regenerative medicine.

1. Drug Delivery: Advancements And Challenges

The introduction of a whole new class of noble designed nanocarriers and system made possible by nanotechnology has had a profound impact on the current methods of medication delivery. These days, scientists are working to develop smaller carriers without sacrificing drug loading, all in an effort to deliver medicines to previously unreachable biological regions, such as the central nervous system (CNS), more rapidly and effectively. Researchers have produced a wide range of organic and inorganic materials with specific physicochemical features that make them ideal for biodistribution of drugs (Farokhzad and Langer, 2009). The molecular scale manufacturing and engineering of materials allows us to access biological regions like the brain blood barrier (BBB) where even blood is not circulating (Buse and El-Aneed, Bidros and Vogelbaum, 2009). Targeted drug delivery with extreme precision and control over release of drug; combination therapy by co-delivery of more than one drug; improved imaging techniques by nano-markers that would also help in visualizing the site of drug delivery by modulating the nanocarriers; and improved delivery of hydrophobic drugs are all made possible thanks to advancements in nanotechnology. Biocompatibility, bioacceptability, cell uptake support, and low-cost mass manufacturing are the foundations of a perfect nanocarrier for drug delivery. Attaching targeted ligands or altering the shape, size, and surface features of nanocarriers might improve cellular absorption of medicines (Dobson and Kell, 2008; Zhang et al.). Nanocarriers and systems have the potential to increase the efficacy of modern drug delivery by introducing a new class of therapeutics with ultra-precise targeting, while also overcoming the drawbacks of traditional methods, such as increased toxicity, through reduced side effects. Targeted medication administration has received considerable attention over the last decade because of its potential to improve accuracy and decrease the risks of drug overuse. Many different nanomaterials have been created for use in contemporary medicine. This chapter provides an in-depth look at some notable nanomaterials. The danger of exposure to nanoparticles has increased as their manufacturing has expanded rapidly for several uses ranging from electronics and coatings to food packaging and biological applications. The potential danger that nanoparticles like carbon nanotubes pose to human health and the environment has been the subject of recent investigations. The toxicological impact of nanoparticles requires more study. With a focus on nanocarriers and nanosystems, this chapter attempts to detail the developments and toxicological difficulties in contemporary therapeutics, which span almost all facets of oral to targeted drug delivery systems.

Intracranial administration of drugs: The drug or capillary permeability may be manipulated to boost intravascular drug delivery, or the drug can be administered locally at the location, both of which can be used to transport medications to the brain. medicine packaging, barrier disruption, and the intraarterial route are just a few examples of how scientists throughout the globe are trying to maximize the quantity of intravascular medicine that reaches tumor cells (Gabathuler). However, only a tiny percentage of intravascular medications really make it to the tumor cell, which is a serious problem (GuhaSarkar and Banerjee). On the other hand, neurotoxicity results from the unexpected spatial distribution of the medication and the fluctuating drug concentration that occurs when it is administered directly into the tumor cell or cerebrospinal fluid. Most medications are unable to cross the blood-brain barrier. The explanation for this is because brain capillaries have interendothelial connections, as well as a small number of pinocytotic vesicles but no fenestrations. Diffusion allows the medications to get over the BBB, or blood-brain barrier. Permeability in brain tumors is a very nuanced topic. has proposed that there are at least three microvessel populations present in a typical brain tumor. The first kind of microvessel resembles normal brain capillaries in that it is neither fenestrated nor segmented. In contrast, big molecules are not allowed to pass through the second kind of capillary, which consists of continuous and fenestrated capillaries with

greater permeability to tiny molecules. In the third kind, capillaries with interendothelial gaps of up to 1 m are present. Drug diffusion over the barrier is significantly affected by the capillary network's spatial organization. Numerous medication delivery systems exist, each with its own set of pros and cons.

2. Recent Advances In Novel Drug Delivery Systems

The success of a pharmacological treatment often depends on how it is administered. Some medications have a safe and effective dosing range, and outside of that range, they may be harmful or have no therapeutic effect. The extremely modest improvement in the effectiveness of treating severe illnesses, on the other hand, has revealed an increasing need for a multidisciplinary strategy in the delivery of medicines to targets in tissues. Consequently, this led to the development of novel strategies for manipulating pharmacological properties such as their pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition, and therapeutic effectiveness. Polymer science, pharmaceutics, bio-conjugate chemistry, and molecular biology have all come together to provide the basis for these novel techniques, which are collectively referred to as drug delivery systems (DDS). New innovations in technology and products have brought about profound shifts in the status quo. Osmotic pumps, wearable ambulatory pumps, electrically assisted medication administration, and several additional delivery techniques based on diverse polymer technologies have replaced conventional capsules and ointments in certain circumstances. Because old methods are sometimes useless and inefficient, new pharmaceuticals sometimes need new delivery systems. As more precise drug delivery technologies become available, it's possible that certain treatments may need very high drug concentrations at very particular places inside the body. Increasing the quantity and permanence of a drug near a target cell while decreasing the drug exposure of non target cells is key to the development of new drug delivery systems. Both physical and biological processes may be used in the development of novel medication delivery systems. Osmosis, diffusion, erosion, dissolution, and electro transport are all examples of physical phenomena that may be used as controlled drug delivery methods. Some examples of biochemical processes include monoclonal antibodies, vector systems for gene therapy, polymer drug adducts, and liposomes. Optimizing the medication's duration of action, reducing dosing frequency, regulating the location of release, and keeping drug levels stable are only a few of the therapeutic advantages of several innovative drug delivery systems. Microcapsules, cells, cell ghosts, lipoproteins, liposomes, and micelles are all examples of drug carriers. Soluble polymers and microparticles formed of insoluble or biodegradable natural and synthetic polymers are other examples. The carriers may be designed to break down slowly, respond to stimuli (such as pH or temperature), and be targeted (by, for example, being conjugated with antibodies against certain distinctive components of the target region). The ability to target a specific area allows the medication delivery system to go directly to the intended organ or tissue. There are two main ways to deliver drugs to where they need to go: (i) passive targeting and (ii) active targeting.

4.1 Drug Delivery Carriers

Micelle solutions, vesicle dispersions, liquid crystal dispersions, and nanoparticle dispersions with particles between 10 and 400 nm in diameter are all examples of colloidal drug carrier systems that have significant potential as drug delivery methods. Optimal drug loading and release qualities, as well as a long shelf life and minimal toxicity, are sought for when creating such formulations. The integrated drug is a part of the system's microstructure and, depending on its molecular interactions, may even affect it. This is particularly true if the drug has amphiphilic and/or mesogenic capabilities.

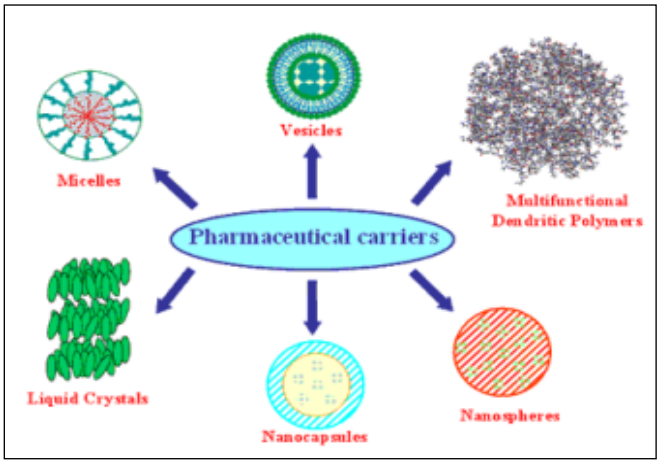

Figure 2: Drug Delivery carriers

4.2 Liposomes

Lipid (or fat) vesicles with a water core are often employed in cancer therapy. Vaccine delivery and the prevention of infectious illnesses both benefit from the use of liposomes. They encase cancer medications, protecting healthy cells from their toxicity and avoiding drug buildup in organs like the kidneys and liver. Nausea and hair loss are two frequent adverse effects of cancer therapy that liposomes may help alleviate or perhaps prevent entirely. They are a kind of vesicle made up of several, a few, or even a single phospholipid bilayer. Liposomal core's polar nature allows for the lation of polar medicinal compounds. Depending on their affinity for phospholipids, amphiphilic and lipophilic compounds are solubilized within the phospholipid bilayer.

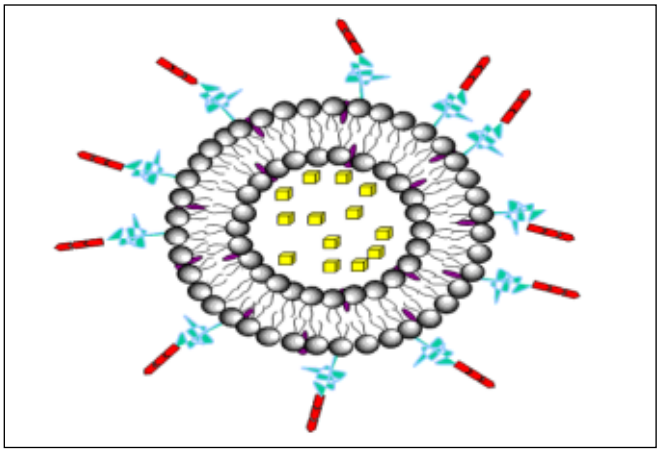

Figure 3: Liposomes

2. Recent Drug Delivery Systems And Applications

Organic, inorganic, and hybrid nanoparticles have all shown promise as drug carriers for active targeting in recent years, with particular success in the field of chemotherapy. Newer drug delivery systems (DDS) have been developed to provide advantages over their predecessors in areas such particle size, permeability, solubility, effectiveness, targeted administration, stability, toxicity, and duration of action. They have the potential to vastly outperform more traditional dose forms of medicinal agents. Recent drug delivery systems are acknowledged as the most up-to-date and creative understanding of pharmacokinetic and pharmacodynamicbehavior of medicines, which is essential in developing an effective drug delivery system. Due to their transporter nature, these DDS can maintain therapeutic concentrations of medications for extended periods of time and transfer materials to the site of action. The innovation's commercial and therapeutic success depends on how widely the delivery system is implemented. Patients should

be consulted early in the design phase to help pinpoint potential issues and optimize the device for their needs. Enhancing the safety and effectiveness of current distribution methods.

5.1 Nanocarrier drug delivery methods based on hyaluronic acid

One method of administering medication is by the use of hyaluronic acid. Hyaluronic acid is an innovative polymer with potential use in drug delivery. Mucopolysaccharide chains of glucuronic acid and N-acetylglucosamine are linked in a linear fashion. It has excellent viscoelasticity, is biocompatible, and biodegrades; it may also be combined with a targeted cell surface receptor. As long as the integrated medicines are delivered regularly, using Hyaluronic acid as a carrier for ocular drug delivery makes sense since it is a natural component of eye tissue and plays a vital role in wound healing. They help with medication targeting, thickening, prolonged release, and transdermal absorption. Using active targeted HA-based drug nanocarriers greatly increased drug distribution to cancer cells. Also, lipid nanoparticles coated appropriately with HA have been produced as biocompatible drug carriers with significant promise for targeted medication delivery to the target tissue while limiting side effects and hurting other tissues. greater drug delivery, enhanced therapeutic effectiveness, greater cytotoxicity, and a significant decrease in tumor formation, as well as a high potential for targeted chemotherapy, are only some of the benefits of using HA-based nanocarriers for malignancies with heightened expression of the CD44 receptor.

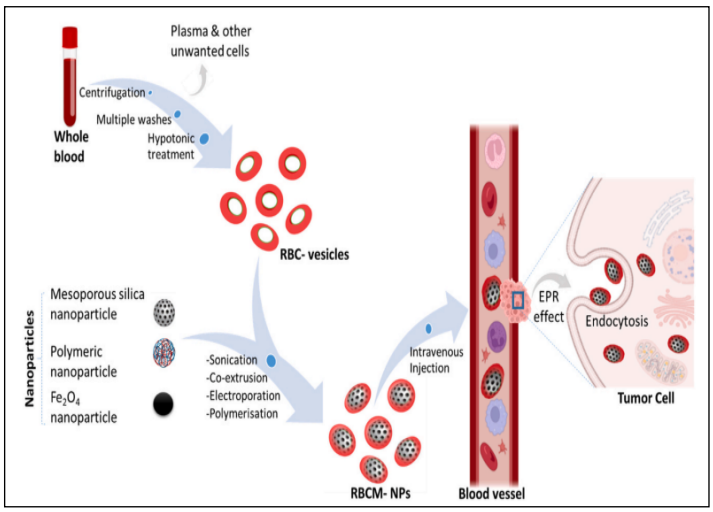

Figure 4: Synthetic methods for creating RBCM-NPs with anticancer activity. The plasma and other undesirable cells are separated out of whole, fresh blood by centrifuging and washing it many times.

5.2 Hexagonal Boron Nitride nanosheet drug delivery system

Materials that may aid in the delivery of drugs are the subject of increasing scientific investigation and technological development. Boron nitride (BN) is one such substance; it is a crystalline compound consisting equally of nitrogen (N) and boron (B) atoms. Different crystal structures of boron nitride are found in nature, including cubic BN (c-BN), hexagonal BN (h-BN), wurtzite BN (wBN), and rhombohedral BN (r-BN). Hexagonal boron nitride has a sp2 hybridized B-N bond structure and exists in a two-dimensional (2D) layered density. White graphene is a kind of graphite that has certain properties with graphite. The B-N atoms stand in for the carbon atoms and create interlocking rings bound together by a strong covalent connection. The interlayer distance is 3.331 angstroms, while the bond length between the layers is 1.466 angstroms in this material held together by van der Waals forces. Because of the compound's partly ionic nature, the B-N bonds in it are electrically charged. H-BN, like graphene and graphene oxide, is an insulator that has found widespread use in industries as diverse as cosmetics, dentistry, cement, ceramics, and, most notably, medicine as a drug carrier.

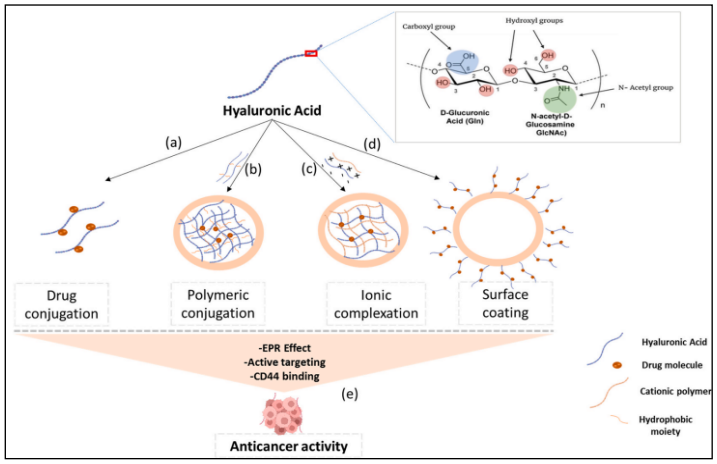

Figure 5: Hyaluronic acid-based nanocarriers for the treatment of cancer. Hyaluronic acid-based drug nanocarriers permeate cancerous tissues via the EPR effect, bind to the CD44 receptor site, and elicit anticancer activity. (a) and (b) Direct conjugation of cytotoxic drug with HA or hydrophobic moiety results in self-assembly of nanoparticles (NPs) that can be administered intravenously for cancer cell targeting.

Conclusion

Over the last several years, researchers, scientists, and medical professionals have paid a great deal of attention to the field of drug delivery and nanomedicine. The recent drug delivery system has great potential, despite the obstacles that have slowed its clinical application; however, realizing that potential will require a team effort spanning theory, experimentation, knowledge of medicine and pharmaceuticals, and extensive research. Cell treatments, according to Vargason et al., will not only generate an effective single dosage that prevents large accumulation of pharmaceuticals in the system, but will also go a long way toward solving the bio-acceptability concerns that drug delivery systems confront. Cell treatments, on the other hand, hold the promise of becoming a seemingly endless supply of sophisticated biologics, dismantling intrinsic biological barriers, and eliciting seemingly natural reactions from the body. Drug distribution presents several difficulties, and Adepu have proposed using inorganic mesoporous nanoparticles, micro fluids, and molecular imprinting polymers to address these issues. Priming agents, which alter the form and function of tissues in a way that is beneficial to the administered drug without causing harm to the patient, are a way to increase the efficiency of drug delivery, as stated by Khalid et al. Since cells are naturally occurring in the human body, it is important to think about cell-based drug systems in the field of biomaterials. This involves using cells in conjunction with nano biomaterials, which is a novel approach that is still theoretical but appears to be the most creative, encourages drug delivery method with hopes of achieving maximum drug delivery pattern. There is still a great deal of work to be done in terms of research and clinical trials to improve the efficacy of these cutting-edge drug delivery systems and to address the difficulties associated with their use.

References

1. B.M. Rayaprolu, J.J. Strawser, G. Anyarambhatla, Excipients in parenteral formulations: selection considerations and effective utilization with small molecules and biologics, Drug Dev. Ind. Pharm. 44 (2018) 1565–1571, https://doi.org/10.1080/03639045.2018.1483392.
2. A.M. Vargason, A.C. Anselmo, S. Mitragotri, The evolution of commercial drug delivery technologies, Nat. Biomed. Eng. 5 (2021) 951–967, https://doi.org/10.1038/s41551-021-00698-w.
3. M.S. Alqahtani, M. Kazi, M.A. Alsenaidy, M.Z. Ahmad, Advances in oral drug delivery, Front. Pharmacol. 12 (2021), 618411, https://doi.org/10.3389/fphar.2021.618411.
4. D. Sahoo, R. Bandaru, S.K. Samal, R. Naik, P. Kumar, P. Kesharwani, R. Dandela, in: P. Kesharwani, S. Taurin,

K.B. T.-T., A. of N.N. GreishGreish (Eds.), Chapter 9 - Oral Drug Delivery of Nanomedicine, Academic Press, 2021, pp. 181–207, https://doi.org/10.1016/B978-0-12-820466-5.00009-0.

5. J.O. Morales, P.R. Vuddanda, S. Velaga, Controlled drug delivery via the buccal and sublingual routes, in: Fundam. Drug Deliv., 2021, pp. 433–448, https://doi.org/10.1002/9781119769644.ch17.
6. N.R. Hussein, H.K. Omer, A.M.A. Elhissi, W. Ahmed, in: W. Ahmed, D.A. Phoenix, M.J. Jackson, C.P.B.T.-A. in M., S.E. Charalambous (Eds.), Chapter 15 - Advances in Nasal Drug Delivery Systems, Academic Press, 2020, pp. 279–311, https://doi.org/10.1016/B978-0-12-819712-7.00015-2.
7. S. Mahant, A.K. Sharma, H. Gandhi, R. Wadhwa, K. Dua, D.N. Kapoor, Emerging trends and potential prospects in vaginal drug delivery, Curr. Drug Deliv. (2022), https://doi.org/10.2174/1567201819666220413131243.
8. M. Cho, M. Joo, K. Kim, Y. Wook, S. Lee, Y. Mi, I. Ho, Biochemical and Biophysical Research Communications the immunotherapeutic effects of recombinant Bacillus rin resistant to antimicrobial peptides on Calmette-Gu e bladder cancer cells, Biochem. Biophys. Res. Commun. (2018), https://doi.org/10.1016/j. bbrc.2018.12.097.
9. L. Palugan, M. Cerea, M. Cirilli, S. Moutaharrik, A. Maroni, L. Zema, A. Melocchi, M. Uboldi, I. Filippin, A. Foppoli, A. Gazzaniga, International Journal of Pharmaceutics : X Intravesical drug delivery approaches for improved therapy of urinary bladder diseases, Int. J. Pharm. X. 3 (2021), 100100, https://doi.org/10.1016/j.ijpx.2021.100100