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NARRATIVE REVIEW
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Principles and Advantages of New Drug Delivery Technologies

Hussein K. Alkufi[1*], Ahmed H. Salman[2], Salam Shanta Taher[3]

[1]Department of Pharmacognosy , College of Pharmacy, Thi-Qar University, Iraq
[2]Department of pharmaceutics, college of pharmacy, Al-bayan university, Baghdad, Iraq
[3]Department of pharmaceutics, college of pharmacy, University of Baghdad, Baghdad, Iraq

ABSTRACT

Advanced drug delivery systems offer undeniable benefits for drug delivery. In the past three decades, new methods have been proposed to develop a novel carriers for drug delivery. Nowadays, the major goal is to maximize therapeutic benefit while minimizing side effects. Drug delivery technique is clearly shifting from the micro to nanoscale. Nano-drug delivery systems (NDDSs) are the most promising approach utilized to improve the accuracy of drug delivery and the efficacy of drugs. In this narrative review article, we evaluate how delivery challenges associated with commercial marketed products and discuss newer DDS is being carried out to overcome these challenges .Different colloidal carrier systems such as carbon nanotube ,liposome , were being studied and extensively investigated.

Corresponding Author e-mail: husseinalkufi21@utq.edu.iq

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INTRODUCTION

Rapid advancements in genomics sciences, combined with rational drug design and rapid screening techniques, have revolutionized the cycle of drug discovery process and lead to the introduction of a significant number of novel therapeutics in the market .However, the ineffectiveness of these novel therapeutic agents in reaching the target tissues frequently hinders the application of these new therapeutics in the field of medicine. Therefore, in the last decade, much a lot of attention has been received by researchers on developing a new drug delivery systems for disease management with high efficiency. In a simple definition, drug delivery is method of releasing a delivered bioactive moiety to a particular site. Active drug candidates frequently present a variety of delivery obstacles, such as poor aqueous solubility, chemical or physical stability issues, a poor pharmacokinetics profile, and undesirable toxicity, all of which must be addressed concurrently in order for the new drug to be a successful and effective agent. Researchers and Formulations developers have always encountered difficulties to overcome these issues, but with introduction of the nanotechnology approach, the traditional challenges could be viewed as new opportunities. In fact, a variety of therapeutic Nano carriers have been extensively studied to address this emerging need. Nano medicine has major applications in disease diagnosis and the design of efficient and safe drug delivery systems, delivering specific drugs to target sites and supporting disease treatment . For their applications in human medicine and biology, a broad categories of nanomaterials such as carbon nanotube, liposomes, niosome can be designed such that they can easily interact with the targeted human cells and tissues of with a high specificity.[1] The surfaces of these agents is modified to carry a variety of ligands materials such that they can be utilized as imaging agents(quantum dots), drug carrier, special fluorescent tags, and many other biological and research tools. Nanoparticles aid in site-specific tissue targeting, which may enhance the effectiveness of the incorporating medication being administered while reducing side effects. Because of their small size, they are not easily identified by the human immune system and can easily cross the blood-brain barrier (BBB). Liposomes, Niosomes, and Carbon nanotubes are examples of nanoparticles that can be used in drug delivery systems. These nano-carrier agents can also be used for tumor detection, magnetic resonance imaging, tumor targeting, and tumor destruction.[2]

ADVANCED DRUG DELIVERY SYSTEM

2.1 Carbon nanotube

In recent years, nanomaterials have been extensively investigated as new drug delivery applications to address issues associated with traditional drug treatment, such as low intrinsic drug solubility, lack

of selectivity, in appropriate bio distribution and undesirable pharmacokinetic properties. Carbon nanotubes (CNTs) have gotten a great interest because of their unique physicochemical architecture style. Carbon nanotubes (CNTs) have been applied in the nanotechnology approach due to their nanosize range and unique structure properties. Carbon nanotubes are hollow cylinders made of structured carbon atoms with nanoscale (10^{-9} m) which is much smaller than the width of a human hair. Several nanocarriers, including carbon nanotube (CNT), liposomes, Niosomes are being used for drug delivery and enhanced cancer therapy. With proper functionalization of the surface, CNTs have been widely used as nanocarriers agents to transport antitumor medications, genes, and even proteins for treatment of various tumors .It also has been utilized experimentally as mediators for photodynamic treatment (PDT) and photo thermal therapy (PTT) and to directly and completely eradicate of tumor cells.[3]

Biomedical Application

A- Breast cancer therapy

Breast cancer(BC) is an abnormal growth of the cells that line the lobules or ducts of the breast tissue. These type of cells proliferate uncontrollably and have the ability to spread to other regions of the human body. Both male and female patients can develop breast cancer disease, although it is rare in male. Triple-negative breast cancer (TNBC) is rare disease and considered the most aggressive form of breast cancer. TNBC lacks estrogen, progesterone, and human epidermal growth factor-2 (HER-2) receptors, such that it is difficult to diagnose and treat. TNBC treatment includes chemotherapy and radiation therapy, which have serious limitations such as multidrug resistance(MDR), cytotoxicity, and non targeted tissue damage. Hormone therapy is not usually recommended for the treatment of TNBC disease because of losing of target receptors. To date, surgical procedures and conventional chemotherapy, alone or in combination, are considered the only standard treatments for TNBC. Nanotechnology approaches for delivering various therapeutics could be applied as an efficient strategy for overcoming the majority of the adverse effects associated with conventional chemotherapeutic regimen. Carbon nanotubes (CNTs) have attracted great attention as a novel drug delivery system for engaging therapeutic agents in the management of various cancers diseases such as breast, lung, and liver cancer. N.J. Singhai, et al. developed carbon-nanotubes of multi wall type (MWCNTs) that were chemically functionalized using hyaluronic acid (HA) and α-tocopheryl succinate (α-TOS) and incorporated with doxorubicin (Dox) drug to obtain a new synergistic anticancer formulation. HA a naturally carbohydrate has been extensively utilized as a targeting tool due to its high specificity to CD44 receptors overexpressed on cancer cells. α- Tocopheryl succinate (α-TOS) which is a succinyl derivative of vitamin E, recognized for its anticancer effect primarily through the apoptotic pathway and has also been reported to be non-toxic to healthy cells. Doxorubicin (Dox) was used in this formulation as the major chemotherapeutic agent that reduces the progression of TNBC. An apoptotic assay test showed the ablation of more than of 85% of cancer cells after treatment with the optimized formulation. In term of stability studies, the Storage of the developed formulation in light resistant glass vial at cool temperature (refrigerator temperature) was found appropriate to keep the developed CNTs stable for ninty days. These results demonstrate the application of carbon nanotubes as effective carriers to deliver multiple drugs and the possibility of preparing viable formulations for managing cancer diseases.[4]

Hyperthermia (HT) has been introduced as an alternative therapies for breast cancer disease but has the major disadvantage of damaging normal healthy cells. Carbon nanotubes provide an exceptional combination of attributes for the development of the next generation of photo thermal agents .Carbon Nano tubes can effectively absorb near infrared radiation (NIR) and the absorbed NIR light transmits heat to the nanotubes surface. This unique thermo conductive characteristics of carbon nanotubes has been introduced as a technique for killing tumor cells via thermal effects. A group of researchers successfully developed multi-walled carbon-nanotubes (MWCNTs) as mediator for induction local hyperthermia in mice with breast cancer disease. Results from this study demonstrated that MWCNT formulations in combination with a local hyperthermia therapy showed complete tumor destruction in tested mice, accompanied by increase in the median survival time of the tested animal. The findings of this research study proposed the possibility of MWCNTs-mediated hyperthermia as a novel an anticancer therapeutic agent, which could be useful in the treatment of breast cancer disease in the future.[5]

B- Human immunodeficiency virus vaccination

The successful development of a human immunodeficiency virus (HIV-1) vaccine is a major worldwide challenge. The majority of HIV-1 transmission occurs through the mucosal barrier. The majority of available vaccines are currently administered either intramuscularly(IM) or subcutaneously (SC). Most of the developed vaccine do not induce an adequate local immune response such as immunoglobulin A (IgA), which is important for the effective prevention of HIV-1 infection. Yang Xu developed carbon nanotube for nasal delivery and known as "CNTVac." The diameter of the designed carbon nanotubes (CNTS) is experimentally processed to incorporate HIV-1 particle and efficiently delivering of such particles through the nasal passages. Intranasal administration of developed CNTVac in animal(mice) successfully induce mucosal immunity responses, with significant induction of both immunoglobulin IgG and IgA. CNTVac accelerated the systemic IgG immune response from the second dose, two weeks earlier than from the administration of antigen alone. These findings showed the clinical potential of the CNTVac delivery approach for delivering multiple antigens through mucosal route and as a new vaccine platform to prevent transmission of HIV-1 infections disease. Because of the new design of this type of delivery approach, it could be applied to other infectious disease vaccine developments in the near future.[6]

Liposomes

Liposomes are bilayer vesicles consist of either natural or synthetic phospholipids. Due to hydrophobicity, hydrophilicity and small size range; liposomes are considered as a promising drug delivery approach. A lot of experimental results of various researches have been revealed that changes in

liposome diameter can affect plasma circulation time. A vesicle diameter of 80–200 nm is considered to provide sufficient reservoir capacity without decreasing drug bioavailability. In addition to biocompatibility, biodegradability, low toxicity and immunogenicity, liposomal formulations are capable of incorporating a wide variety of molecules at high concentrations. Therefore liposomal formulations are considered as promising approach for drug delivery. Liposome-based drug formulations to date have not been commercialized in large quantities. For a drug to be on the market, it must be stable for at least 1.5 to 2 years.Several techniques could be used to increase the shelf life of the developed liposomal formulation. Recently liposomes have gained considerable attention as carriers for systemic drugs after the approval of several vesicle formulations. There are very limited products available on the market that contain liposomal nanocarriers. In general there are two categories of drugs directed against infections and tumor diseases which incorporated in liposome were extensively investigated for the treatment in human being. There is increasing number of newly designed liposomal loaded drugs are under clinical assessment or already in the market such as Doxil, Dauno-Xome and Ambiosome

Capecitabine drug is a fluoropyrimidine carbamate with antitumor activity, used for management breast cancer and colorectal cancer . Capecitabine drug is rapidly absorbed from the gastrointestinal tract tract after oral administration. The significant pharmacokinetics problems associated with Capecitabine drug are its short half-life and extensive hepatic metabolism. Therefore high doses of Capecitabine drug is administered in the clinical therapy cause some unwanted adverse effects. Therefore, an extended-release formulation of capecitabine was needed. Honmane, *et al*. was developed liposomal formulation containing Capecitabine for prolonged release of drug in cancer disease. Stability studies data show that the liposomal formulation is stable under cold storage conditions (4°C). Thus, the nanoliposomal formulation of capecitabine drug could decrease dosing frequency requirement and target the specific site of action, which would ultimately reduce the adverse effects associated with high-dose of capecitabine drug. Additional *in-vivo* bioavailability studies could be determined for these type of nanocarrier to develop efficient drug delivery system (DDS).[7]

Taxanes are a class of microtubule inhibitors that are widely utilized as chemotherapeutic medications for management of several kinds of cancers . These inhibitors include Larotaxel) Paclitaxel (PTX), Docetaxel (DTX) and Cabazitaxel (CBZ) drug. Cabazitaxel (Jevtana®) was approved by the U.S. Food and Drug Administration in 2010 for the treatment of hormone-resistant prostate cancer disease .It is a micellar based formulation that include co-solvent (ethanol) to increase the solubility of CBZ drug and administered as an intravenous (IV) infusion . The main drawback of the available dosage form is neutropenia which appear in more than 90% of treated patients. Febrile fever was also clinically observed in 8% of cancer diagnosed patients. The commercially available CBZ formulation lacks the ability to target tumors and its unequal distribution in the body compartments causes toxicity to non targeted organs. Strong binding to plasma protein and rapid clearance of CBZ drug so it require multiple dosing of the drug, which could be fatal to the patient. A group of researchers were developed liposomal formulations of CBZ drug to address toxicity concerns associated with marketed CBZ solution. Apoptosis assay test indicate both CBZ solution and developed CBZ loaded liposomes caused apoptosis and necrosis but CBZ loaded liposomes caused more apoptosis than marketed formulation which would be more beneficial for the management of breast cancer disease. Furthermore, CBZ liposomes formulation showed high reduction in red blood cell hemolysis (1.6-fold) in comparison to CBZ solution at 20 µg/mL concentration. Pharmacokinetic data proved that there was an increase in half -life (~7.6 h) of the developed liposomal formulations, which provided the extending release profile of CBZ and in turn decreased the dosing frequency. In conclusion, designed CBZ liposomes could act as a promising new delivery system for breast cancer management with minimum toxicity.[8]

Niosomes

Noisome was developed in the middle of the 1980s considered a Novel drug delivery technology that encapsulates the medication in a vesicle. Because they are stable and affordable, noisome are generally preferred to liposomes. Niosomes are vesicular Nano carriers that have received a lot of attention due to their unique properties. Many pharmacological agents may benefit from use of niosomal drug delivery for their action against various diseases. Noisome are novel nanocarriers consisting of a cholesterol and biodegradable nonionic surfactant and show high potential to cross the stratum corneum barrier. Niosome are able to alter the stratum corneum layer by loosening the intercellular lipid matrix along with the existence of surfactant molecules (non-ionic type), which enhances the skin permeability when administered by transdermal route. Niosomal formulations exhibit better stability compared to other nancarrier (liposomes) and are more economical/easier to scale.

Propofol drug is a highly lipophilic molecule that is administered to patients via either continuous IV infusion or intermittent bolus injection . Although the induction of anesthesia is quick, effective, and clinically safe, there are significant drawbacks to intravenous administration, such as hypersensitivity reaction and pain at the injection site.Oral administration of propofol drug is not preferred as it exhibits extensive first-pass hepatic metabolism. It is known that transdermal delivery of the propofol drug can achieve the same steady-state drug delivery as IV infusion while avoiding the first-pass effect. Wenjia Zhang and his colleagues were prepared niosomal formulation for transdermal delivery of propafol drug. The improved relative bioavailability with successfully designed niosomal propafol gel formulation when compared to propofol gel and was supported by the in vivo pharmacokinetic studies in the animal model. Ex vivo release studies revealed that optimized niosomal formulation (92.2% release) had significantly better release profiles than propofol gels (25.3% release).These developed niosomal gel formulation provided a potential alternative painless and efficient route of administration of propofol medication for procedural sedation effect especially in the pediatric patients.[9]

Celecoxib is a nonsteroidal anti-inflammatory drug (NSAID) that has excellent anti-inflammatory and antipyretic properties. Celecoxib (CXB) drug showed poor oral bioavailability after oral administration due to its poor solubility in

water and high volume of distribution (VD) and that could be due to the hydrophobic characteristics of CXB . For a better therapeutic effect, it is administered to patients orally in large doses regimen, leading to an increased risk of adverse cardiovascular events .A study was done by Sayed H. Auda to prepare niosomal hydrogels for transdermal celecoxib delivery. The finding of the study showed that significant release of the drug from optimized niosomal gel formulation (72 % release after twelve hours) over the marketed dosage forms and it is also revealed high anti-inflammatory activity (75.45 %) of the niosomal gel formulation on animal paw edema compared to marketed formulation. The optimized formulation could be utilized in future to reduce oral adverse effects associated with marketed formulation and decrease drug dosing and enhance patient compliance [10].

CONCLUSION

As an advanced system, nanotechnology has great chance to revolutionize drug delivery. Rapid development in this field has enabled several Nano-drug formulation products on the market to provide better pharmacokinetic and pharmaco-dynamics characteristics, reduce systemic toxicity, improve patient compliance and in turn clinical health outcomes. The incorporation of new Nano-particulate drug delivery approaches (carbon nanotube ,noisome ,liposome,) into pre-formulation research not only speeds up the designing of a novel therapeutics, but also helps in the reduction of attrition of new molecular drugs due to unwanted biopharmaceutical and pharmacodynamics properties .

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