RECENT TRENDS IN SMART DRUG DELIVERY

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Abstract: Recent advances in nano medicine in smart drug delivery have fired interest in drug delivery research. The traditional chemotherapy in cancer treatment often results in high toxicity and cause side effects to healthy tissues. Many widely-used chemotherapeutic agents used in cancer treatment contain adverse physicochemical properties like low solubility, lack of chemical or biological stability which slow down or limit their therapeutic applications. More over it can easily spread to healthy tissue and kill it. To overcome these problems. Nano technology has emerged as key research area in targeted drug delivery. This system is multidisciplinary system and requires highly integrated various disciplines, such as chemists, biologists, and engineers, to join forces to optimize this system. It aims to maximize the effectiveness of the drug (bioavailability) and to reduce its adverse side effects. The aim of this technique is to prolong, localize, target and have a protected drug interaction with the diseased tissue. In usual traditional drug delivery system drug is absorbed of across a biological membrane and causes damage to healthy tissue whereas the targeted release system releases the drug in a dosage form. The advantages of this system is the reduction in the frequency of the dosages, having a more uniform effect of the drug, reduction of drug side-effects, and reduced fluctuation in circulating drug levels. This helps maintain the required plasma and tissue drug levels in the body, thereby preventing any damage to the healthy tissue. The disadvantage of the system is high cost, which makes productivity more difficult and the reduced ability to adjust the dosages. It was also found that carrier systems themselves may impose risks to the patient which are much more dangerous than the risks caused by conventional chemotherapy.
This research paper describes the process of mechanisms and how various types of nano materials can be used in smart drug delivery to localize and target the diseased tissue. The goal of this review is to provide an overview of the recent achievements during the past few years in developing nano carriers and highlighting the challenges and drawbacks of this approach.

Keywords: Nano particles, targeted drug delivery, chemotherapy.

Introduction: According to National Cancer Institute (NCI) , the Centers for Disease Control and Prevention(CDCP) and the North American Association of Central Cancer Registries (NACCR) and mortality data from the National Center for Health Statistics a total of 1,660,290 new cancer cases and 580,350 cancer deaths are projected to occur in the United States in 2013[1]. The costs related to these diseases projected to exceed $150 billion per year. Therefore, there is an urgent need to come up with a best possible revival system. It is also found that more than $65 billion are wasted each year due to poor bioavailability. The key to solving this problem lies in the effective use of drugs that can be targeted directly to the diseased tissue which reduces the quantity of drug enhances bioavailability and efficacy. This technique also can help to develop many more regenerative techniques to cure various other diseases. The Smart drug delivery system focuses on maximizing bioavailability both at specific places in the body and over a period of time. Another benefit of using these nanomaterials in medical technologies is that smaller devices are less persistent and can perhaps be implanted inside the body. Besides as these devises are faster and more sensitive than typical drug delivery the biochemical reaction times are much shorter [2].

In general, patients would prefer to take a drug orally instead of getting an injection. Unfortunately, many drugs, especially those made from large proteins, can't be given as a pill because they get broken down in the stomach before they can be absorbed and may cause many side effects and that too requires large quantity of the drug. But the nano devises of size 1-100 nm, with unique functions at the cellular, atomic and molecular levels may solve these problems. Today nanomedicine is spreading its branchs to address the key problems in the field of medicine. By using different Nanoparticles targeted smart drug delivery can be employed to treat many diseases like cancer, cardiovascular diseases and diabetes In traditional drug delivery systems (oral ingestion or intravascular injection) the medication is distributed throughout the body through the systemic blood circulation and only a small portion of the medication reaches the affected organ. But in smart drug delivery system only required amount of medication reaches in the tissues of interest and reduce the relative concentration of the medication in the remaining tissues. Thus targeted drug delivery is believed to improve effectiveness by reducing side-effects. For the effective implementation of this

system, it requires to study the drug properties, side effects, type of the disease and route taken for the delivery of the drug. An ideal drug delivery carrier must be bio degradable, on-toxic, biocompatible, non-immunogenic [3], [4],and must avoid recognition by the host's defense mechanisms [5].

Recently, nanomedicine advances have been found in various medical applications for nano-scale structures in smart drug delivery. The smart drug delivery systems should own some important qualities such as pre-scheduled rate, self controlled, targeted, predetermined time and monitor the delivery. These drug carriers are made up natural, semi-synthetic, and synthetic polymeric nature at the nano-scale to micro-scale range. The polymeric particles are collectively named as spheres and capsules [6], [7].

Scientists set out to create a framework that can effectively transport the drug through the body and deliver it to target cells. But some drugs fail to fully penetrate cell membrane while some other drugs wear away before they find their targets. Thus it requires increased dosages, which are expensive and can produce unwanted side effects in patients. Nanotechnology has provided the possibility of delivering drugs to specific cells using nanoparticles. The overall drug consumption and side-effects may be lowered significantly by depositing the active agent in the affected region without any higher dose. Smart drug delivery is also proposed to reduce treatment expenses, side effects of drugs with associated decreases in consumption and maximizing bioavailability [8], [9]. The ideal size of nanoparticle should be between 50 and 100 nanometers so that it can easily penetrate the cancer cell. The pH level also plays an important role in this system. As the body's pH level is around 7.4, the extracellular microenvironments of cancer cells generally have lower pH. Upon entering the cancer cell, the lower pH level triggers a chemical reaction that releases the drug [10]. It is the body's own mechanisms that trigger the release of the drug, which is a huge advantage. When the nanosphere enters the cancer cell, the lower pH level destabilizes the structure, which begins to break apart and releases the drug so it can begin to do its job of attacking and killing cancer cells. As they are small in size (diameter 1–100 nm) nanocarriers can deliver drugs to otherwise inaccessible sites around the body. Various types of nonmaterial being used in nanocarriers allows for hydrophobic and hydrophilic drugs to be delivered throughout the body [11]. As the human body contains 70-80% of water, nanocarriers can easily and effectively deliver the ability to deliver hydrophobic drugs into specific sites [12]. But one possible problem with nanocarriers is unwanted toxicity from the inorganic nonmaterial as it accumulates in certain cell organelles [13]. Recently protein based nanocarriers are being used as they occur naturally, and show less cyto toxicity than synthetic molecules [14].

Methodology: This research review paper is based on information from the fact sheets from NCBI [15] and CDC [16].Information was also obtained from Ministry of health and nutrition web sites and articles addressing nanomedicine in drug delivery. Selected references to the articles reviewed can be found in the Appendices of the working document. In addition, many press releases have been reviewed on a regular basis. Meetings with local doctors and experts from RD Gardi medical college, Ujjain have also been a useful source of information that provided opportunities for exchanging views. . Information was also obtained from blogs, research centers and other private sources. In addition, many press releases have been reviewed on a regular basis. Data and information was also gathered by personal meetings with experts and researchers.

Results And Discussion: Data obtained by the above methodology clearly shown that different nanocarriers are being applied to their potential use in drug delivery, especially in chemotherapy. Since nanocarriers can be used to exclusively target the small pores, lower pH's, and higher temperatures of tumors, they have the ability to lower the toxicity of many chemotherapy drugs [17], [18], [19]. Besides, it is known that many anticancer drugs are hydrophobic, and therefore show difficulty in delivery inside human cells. But it can be solved by using of micelles which stabilize and effectively mask the hydrophobic nature of drugs [12]. In the drug delivery process nanocarriers can deliver drugs to site-specific targets, allowing drugs to be delivered in certain organs or cells without affecting the neighboring cells. Site-specificity is a major therapeutic benefit since it prevents drugs from being distributed to the wrong places [4]. Thus the overall drug consumption and side-effects may be lowered drastically by depositing the active agent in the affected region only with appropriate dose and also lowers the treatment expenses.

In smart drug delivery systems mainly lipid- or polymer-based nanoparticles can be designed to improve the pharmacokinetics and biodistribution of the drug. But the properties of drug and other pharmacodynamics of nanomedicine is highly unpredictable among different patients [20]. When designed to avoid the body's defense mechanisms, nanoparticles have beneficial properties that can be used to improve drug delivery. Recently few other complex drug delivery mechanisms are being developed which have the ability to get drugs through cell membranes and into cell cytoplasm. In

this type, drugs are placed in the body and they can only activate on encountering a particular signal. For example, a drug with poor solubility will be replaced by a drug delivery system where both hydrophilic and hydrophobic environments exist, improving the solubility. Smart drug delivery systems may also be able to prevent tissue damage through regulated drug release, reduce drug clearance rates; or lower the volume of distribution and reduce the effect on non-target tissue.

Delivery Vehicles: Different types of drug delivery vehicles, like polymeric micelles, liposomes, lipoprotein-based drug carriers, nano-particle drug carriers, dendrimers, etc. have been designed for targeted drug delivery for various diseases. But overall an ideal drug delivery carrier must be non-toxic, biocompatible, non-immunogenic, biodegradable [4], and must avoid recognition by the host's defense mechanisms [5].

Liposomes: This is most common vehicle currently used for targeted drug delivery [22]. They are are non-toxic, non-hemolytic, biocompatible and biodegradable and non-immunogenic .They are specially designed to avoid clearance mechanisms like reticuloendothelial system (RES), renal clearance, chemical or enzymatic inactivation, etc.) [23] Lipid-based, ligand-coated nanocarriers can store their goods in the hydrophobic shell or the hydrophilic interior depending on the nature of the drug/contrast agent being carried [24]. But difficulty with liposomes in vivo is their immediate uptake and clearance by the RES system and their relatively low stability in vitro. Polyethylene glycol (PEG) can be added to the surface of the liposome to overcome this problem [4].

Micelles and dendrimers: These are prepared from certain amphiphilic co-polymers consisting of both hydrophilic and hydrophobic monomer units [20]. They are mainly used to transport the drugs which have poor solubility. Hence this method offers modest in the terms of size control or function flexibility [5].

Dendrimers are also polymer-based repetitively branched molecules and used as drug delivery vehicles. They have a core that branches out in regular intervals to form small, spherical, and very dense nanocarriers [24]. Dendrimers have been explored for the encapsulation of hydrophobic compounds and for the delivery of anticancer drugs. It can be also used as detecting agents (such as a dye molecule), targeting components, radioligands, imaging agents, or pharmaceutically active compounds.

Biodegradable particles: Due to better bioavailability, better encapsulation and less toxic properties biodegradable nanoparticles have been used frequently as drug delivery vehicles especially for cardio vascular diseases [25]. Biodegradable particles have the ability to target diseased tissue as well as deliver their payload as a controlled-release therapy [3]. These drug vehicles bearing ligands to P-selectin, endothelial selectin (E-selectin) and ICAM-1 have been found to adhere to inflamed endothelium [26]. Therefore, the use of biodegradable particles can be also be used for cardiac tissue.

Artificial magnetic DNAs: The success of DNA nanotechnology has led to thought that artificial nucleic acid nanodevices can be used to target drug delivery. These methods make use of DNA exclusively as a structural material and a chemical, and do not make use of its biological role as the carrier of genetic information. Nucleic acid logic circuits that could potentially be used as the core of a system that releases a drug only in response to a stimulus such as a specific mRNA have been demonstrated [27]. In addition, a DNA "box" with a controllable lid has been synthesized using the DNA origami method. This structure could encapsulate a drug in its closed state, and open to release it only in response to a desired stimulus [28]. Though this method is still under trail but with further development it may provide another tool for the effective treatment of a variety of diseases.

Advantages:

- Patients would not feel any pain from the drug injection.
- No side effects of the drug
- Healthy tissue damage can be prevented.
- It is a safe and effective drug delivery
- The kinetics are much better, faster-onset, than those seen with traditional therapy
- For molecules that are particularly difficult to absorb, this method would be a way of actually administering them at much higher efficiency.
- This approach could also be used to administer vaccines that normally have to be injected.

Drawbacks:

- The most significant one is the potential cytotoxicity of smart polymers involved in the delivery of bimolecular drugs, such as peptides, proteins and nucleic acid drugs.
- In majority of cases, it occurs on a reasonably slow time.
- Expensive and requires new versions to be engineered for each drug.
- Slow rate of biodegradability
- Acrylamide or acrylic acid polymers are not hydrolytically degradable and often are associated with neurotoxicity. So these adverse effects limit the field of smart polymeric drug delivery.

- Due to higher molecular weight smart polymers are more effective in reaching their cellular targets, but they are not biodegradable and not excreted and tend to accumulate in the body. This may be why they have not been tested in clinical trials.
- The misdistribution of these Nanoparticles is still imperfect due to the complex host's reactions to nano- and micro sized materials and the difficulty in targeting specific organs in the body.
- The dangers of nanotoxicity become an important next step in further understanding of their medical uses.
- Nanoparticles may cause the same effects as 'traditional' particles like inflammation and lung cancer but they may be more potent because of their greater surface area. Nanoparticles could also cause new types of effects not previously seen with larger particles or bulk chemicals.
- Upon inhalation of nano particles during manufacture may cause certain epidemiological diseases.

Conclusions: With the progression of new drug delivery systems, smart polymeric drug delivery systems provide a link between therapeutic need and drug delivery. This review highlights the current literature and describes the principles and mechanisms of smart materials. Though there are many exciting challenges smart polymeric drug delivery systems have a very wide range of applications and are likely to have an exciting future. The newly developed smart polymeric drug delivery systems have not yet made the clinical progress. Besides few drawbacks, a lot of work is still ongoing to optimize and better understand the potential and limitations of nanoparticulate systems. While advancement of research proves that targeting and distribution can be amplified by nanoparticles, nanoparticles can be also used in combination therapy for decreasing antibiotic resistance or for their antimicrobial properties [28]. Nanoparticles might also used to avoid multidrug resistance (MDR) mechanisms [29]. [30].

The applications of Nanotechnology in medicine and more specifically drug delivery are set to spread rapidly to reduce toxicity and side effects of traditional drugs. Till today it was not realized that these carrier systems themselves may impose risks to the patient but the type of risks that are introduced by using Nanoparticles for drug delivery are more that posed by conventional hazards imposed by chemotherapy. However, so far, the scientific example for the possible (adverse) reactivity of Nanoparticles is lacking and we have little understanding of the basics of the interaction of Nanoparticles with living cells, organs and organisms. A theoretical understanding of biological responses to nonmaterials is needed to develop and apply safe nonmaterials in drug delivery in the future. Moreover a close collaboration is required pharmaceutical companies and particle toxicology is necessary for the exchange of ideas, concepts, methods and other issues concerned.

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