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Review Article of Nanotechnology

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Abstract: *Nanotechnology can be described as the manipulation of matter at an atomic, molecular or supramolecularscale in the range of 1-100 nanometers. Nanotechnology is a modern science that is gaining immense popularity and applications in multiple scientific fields such as surface science, micro fabrication, semiconductor, molecular biology, electronics, medicine, consumer products and many other industrial and military applications. Nanotechnology also raises various issues like the impact of nanoparticles on the environment, toxicity, regulation of nanotechnology and nanoparticles and the overall impact of nanotechnology on global economics. The present article focuses on the past, present and future of nanotechnology with a special focus on the application of nanotechnology in various fields of medicine. Nanotechnology is the exploitation of the unique properties of materials at the nanoscale. Nanotechnology has gained popularity in several industries, as it offers better built and smarter products. The application of nanotechnology in medicine and healthcare is referred to as nanomedicine, and it has been used to combat some of the most common diseases, including cardiovascular diseases and cancer. The present review provides an overview of the recent advances of nanotechnology in the aspects of imaging and drug delivery.*

Keywords*:* Nanotechnology, Nanomedicine, Devices based on Nanotechnology, Disease diagnosis, drug delivery

I. INTRODUCTION

Nanotechnology is the engineering and manufacturing of materials at the atomic and molecular scale. In its strictest definition from the National Nanotechnology Initiative, nanotechnology refers to structures roughly in the 1−100 nm size regime in at least one dimension. Despite this size restriction, nanotechnology commonly refers to structures that are up to several hundred nanometers in size and that are developed by top-down or bottom-up engineering of individual components. Herein, we focus on the application of nanotechnology to drug delivery and highlight several areas of opportunity where current and emerging nanotechnologies could enable entirely novel classes of therapeutics. [1]

Nanoscience is the study of the unique properties of materials between 1-100 nm, and nanotechnology is the application of such research to create or modify novel objects. The ability to manipulate structures at the atomic scale allows for the creation of nanomaterials . Nanomaterials have unique optical, electrical and/or magnetic properties at the nanoscale, and these can be used in the fields of electronics and medicine, amongst other scenarios. Nanomaterials are unique as they provide a large surface area to volume ratio. Unlike other large-scaled engineered objects and systems, nanomaterials are governed by the laws of quantum mechanics instead of the classical laws of physics and chemistry. In short, nanotechnology is the engineering of useful objects and functional systems at the molecular or atomic scale. [2], Nanotechnologies have had a significant impact in almost all industries and areas of society as it offers.

i) Better built,
ii) Safer and cleaner,
iii) longer-lasting
iv) Smarter products for medicine, communications, everyday life, agriculture and other industries. [3]

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The use of nanomaterials in everyday products can be generally divided into two types. First, nanomaterials can be merged or added to a pre-existing product and improve the composite objects' overall performance by lending some of its unique properties. Otherwise, nanomaterials such as nanocrystals and nanoparticles can be used directly to create advanced and powerful devices attributed to their distinctive properties. The benefits of nanomaterials could potentially affect the future of nearly all industrial sectors. [4]

The beneficial use of nanomaterials can be found in sunscreens, cosmetics, sporting goods, tyres, electronics and several other everyday items. Additionally, nanotechnologies have revolutionized advances in medicine, specifically in diagnostic methods, imaging and drug delivery.

Nanomaterials allow mass-creation of products with enhanced functionaly significantly lower costs, and greener and cleaner manufacturing processes, to improve healthcare and reduce the impact of manufacturing on the environment. [5]

II. LITERATURE REVIEW

1. TusharMadan.et.al:

Comprehensively explores nanotechnology's pivotal role as a smart drug delivery tool in modern healthcare. With a focus on improving therapeutic outcomes and mitigating adverse effects, Madaan likely examines the intricate properties of nanoscale materials and their applications in targeted drug delivery systems. By harnessing the unique characteristics of nanoparticles, such as their high surface area-to-volume ratio and tunable surface properties, researchers can design sophisticated drug carriers capable of precise targeting and controlled release. Madaan's review is expected to highlight recent advancements in nanotechnology-enabled drug delivery, discussing innovative strategies for enhancing drug solubility, stability, and bioavailability. Moreover, the review may shed light on the potential of nanotechnology to enable personalized medicine approaches, catering to individual patient needs and optimizing treatment efficacy. Overall, Madaan's work provides a comprehensive overview of the transformative impact of nanotechnology on modern healthcare delivery.

2. SnehLata, et.al:

Nanotechnology has revolutionized drug delivery by enhancing drug solubility, stability, and targeting, thus improving therapeutic efficacy and reducing side effects. Nanoparticles, liposomes, and dendrimers are widely explored nanocarriers due to their ability to encapsulate drugs, protect them from degradation, and deliver them to specific sites in the body. Surface modification of nanoparticles allows for controlled release and targeted delivery to diseased tissues, minimizing systemic toxicity. Additionally, nanotechnology enables the co-delivery of multiple drugs or therapeutic agents, enhancing synergistic effects. However, challenges such as scalability, regulatory hurdles, and potential toxicity require further research. Overall, nanotechnology holds immense promise in advancing drug delivery.

III. DRUG DELIVERY SYSTEM

For centuries, drugs have been used to treat ailments, improve health and extend the lives of both humans and animals. The substances used as drugs have evolved greatly from the mixtures of medicinal plants and other ingredients found in ancient times. As the science of drugs and medicine developed into the heavily researched and tested chemical compounds that pharmaceutical companies produce today, the ways in which these drugs can be delivered to patients has evolved as well. [6]

The idea of how patients would receive these medications, however, was not a widely discussed topic until the past few decades. Advancements in drug delivery have vastly changed the landscape of the effectiveness of medications, and even greater changes are anticipated for the near future.[7]

What is Drug Delivery?

Drug delivery is the process of administering medication or other pharmaceutical compounds to achieve a therapeutic effect. Drug delivery has become an important topic in the pharmaceutical industry over the last several decades because it has been discovered that a drug's efficacy can be impacted by the way in which it is delivered. Therefore, by

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finding the delivery system that is best suited for a specific medication, it's possible to optimize the drug within the body.

What is a Drug Delivery System?

A drug delivery system is defined as a formulation or device which presents a drug to the body for administration and absorption. The goal of using drug delivery systems is to provide a therapeutic amount of medication while improving safety and efficacy by controlling the location, rate, and time of release of a particular drug in the body.Drug delivery systems have greatly evolved over the last six decades. In the last 12 years specifically, there have been huge advancements in drug delivery technology. For instance, advanced medication delivery systems, such as transdermal patches, are able to deliver a drug more selectively to a specific site, which frequently leads to easier, more accurate, and less dosing overall. Drug delivery devices such as these can also lead to a drug absorption that is more consistent with the site and mechanism of action. There are other drug delivery systems used in both medical and home care settings that were developed because of various patient needs, and researchers continue to develop new methods.[8]

What Are Drug Delivery Devices?

Drug delivery devices are the physical agents that are included in the drug delivery system. There are a multitude of devices that people interact with every day which fall under this category. In modern pharmaceuticals, novel drug delivery devices and combination products are being designed for a number of reasons, including giving patients the ability to self-administer some medications at home, which can help them adhere to recommended regimens. With modern technology and medicine, the combination product market is evolving. Any combination device, especially drug device combination devices, must follow strict guidelines. [9]

These types of devices are very commonly used both inside and outside of clinical settings. A few examples include:

- Prefilled syringes
- Autoinjectors
- Infusion pumps
- Metered dose inhalers (MDIs)
- Nebulizers
- Nasal sprays
- Eyedroppers
- Intrauterine devices (IUDs)
- Transdermal patche

Types of Nanoparticles

Their are several nanoparticles and nanomaterials have been investigated and approved for clinical use. Some common types of nanoparticles are discussed below.

I. Micelles

Micelles are amphiphilic surfactant molecules that consist of lipids and amphiphilic molecules. Micelles spontaneously aggregate and self-assemble into spherical vesicles under aqueous conditions with a hydrophilic outer monolayer and a hydrophobic core, and thus can be used to incorporate hydrophobic therapeutic agents. The unique properties of micelles allow for the enhancement of the solubility of hydrophobic drugs, thus improving bioavailability. The diameter of micelles ranges from 10-100 nm. Micelles have various applications, such as drug delivery agents, imaging agents, contrast agents and therapeutic agents.[13]

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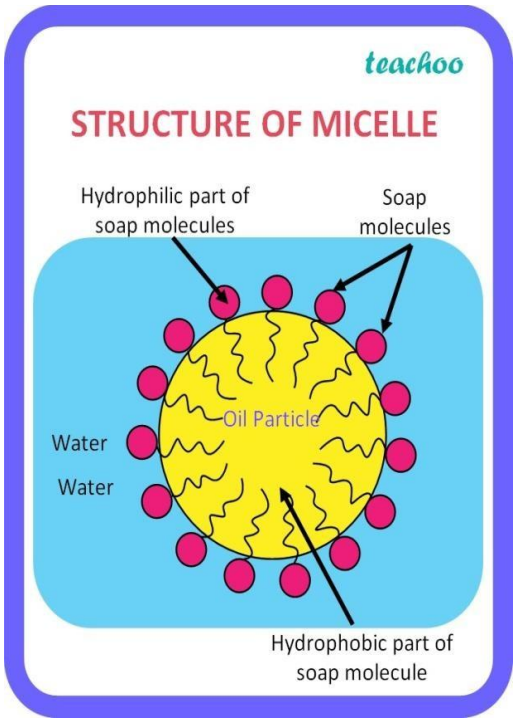

Fig.1

II. Liposomes

Liposomes are spherical vesicles with particle sizes ranging from 30 nm to several microns, that consist of lipid bilayers. Liposomes can be used to incorporate hydrophilic therapeutic agents inside the aqueous phase and hydrophobic agents in the liposomal membrane layer. Liposomes are versatile; their surface characteristics can be modified with polymers, antibodies and/or proteins, enabling macromolecular drugs, including nucleic acids and crystalline metals, to be integrated into liposomes . Poly(ethylene glycol) (PEG)ylated liposomal doxorubicin (Doxil) is the first FDA-approved nanomedicine, which has been used for treatment of breast cancer, and it enhances the effective drug concentration in malignant effusions without the need to increase the overall dose.[14]

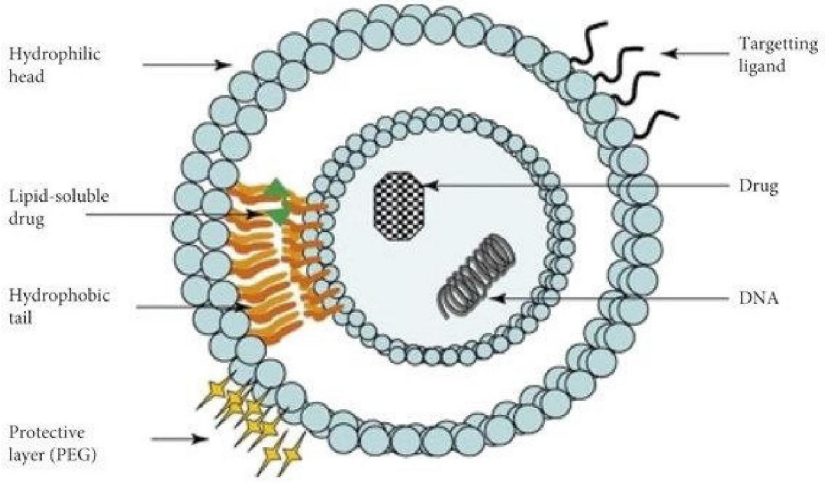

Fig.no.2

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III. Dendrimers

Dendrimers are macromolecules with branched repeating units expanding from a central core and consists of exterior functional groups . These functional groups can be anionic, neutral or cationic terminals, and they can be used to modify the entire structure, and/or the chemical and physical properties. Therapeutic agents can be encapsulated within the interior space of dendrimers, or attached to the surface groups, making dendrimers highly bioavailable and biodegradable. Conjugates of dendrimers with saccharides or peptides have been shown to exhibit enhanced antimicrobial, antiprion and antiviral properties with improved solubility and stability upon absorption of therapeutic drugs . Polyamidoaminedendrimer-DNA complexes (called dendriplexes) have been investigated as gene delivery vectors and hold promise in facilitating successive gene expression, targeted drug delivery and improve drug efficacy dendrimers are promising particulate systems for biomedical applications, such as in imaging and drug delivery, due to their transformable properties.[15]

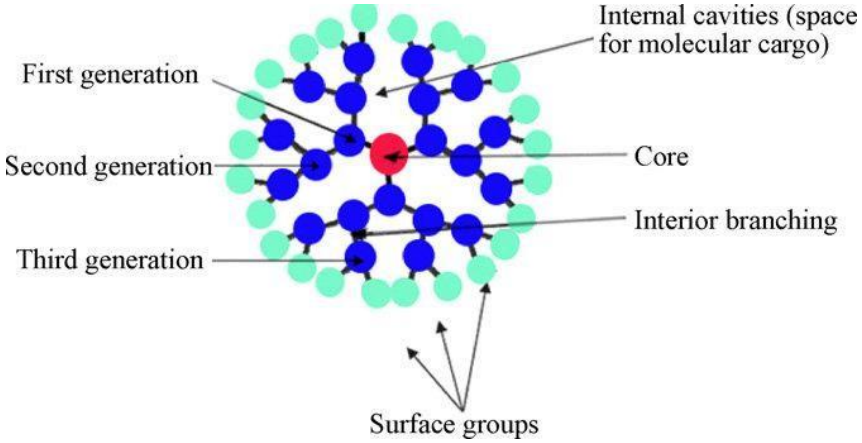

Fig.no.3

IV. Carbon nanotubes

Carbon nanotubes are cylindrical molecules that consist of rolled-up sheets of a single-layer of carbon atoms (graphene). They can be single-walled or multi-walled, or composed of several concentrically interlinked nanotubes . Due to their high external surface area, carbon nanotubes can achieve considerably high loading capacities as drug carriers. Additionally, their unique optical, mechanical and electronic properties have made carbon tubes appealing as imaging contrast agents and biological sensors.

A carbon nanotube is a carbon allotrope that resembles a tube of carbon atoms. Carbon nanotubes are extremely robust and difficult to break, but they are still light. Because of their exceptional mechanical, electrical, and thermal properties, carbon nanotubes are one of the most investigated nanomaterials.CNTs can act as antennas for radios and other electromagnetic devices. Conductive CNTs are used in brushes for commercial electric motors. They replace traditional carbon black. The nanotubes improve electrical and thermal conductivity because they stretch through the plastic matrix of the brush.[16]

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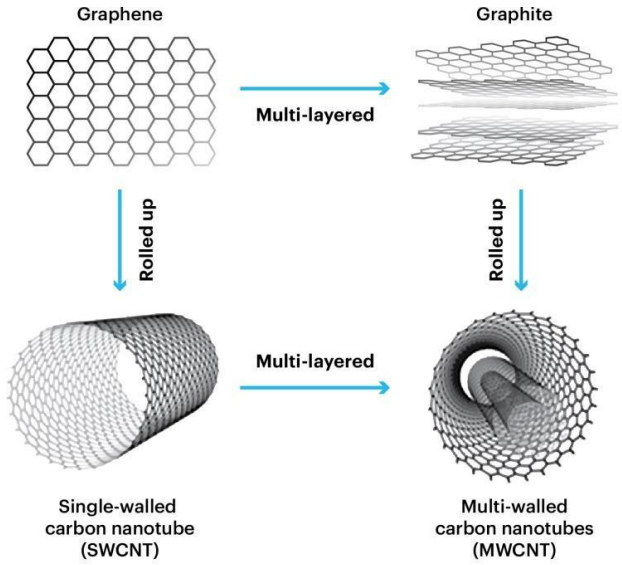
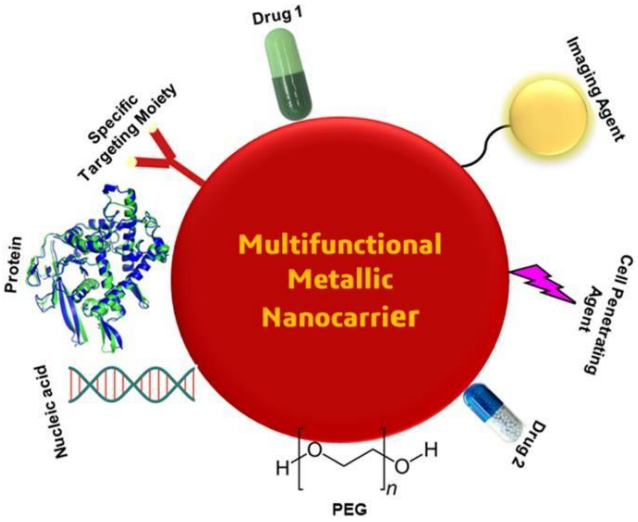


Fig,no.4

V. Metallic nanoparticles

Metallic nanoparticles include iron oxide and gold nanoparticles. Iron oxide nanoparticles consist of a magnetic core (4-5 nm) and hydrophilic polymers, such as dextran or PEG. Conversely, gold nanoparticles are composed of a gold atom core surrounded by negative reactive groups on the surface that can be functionalized by adding a monolayer of surface moieties as ligands for active targeting. Metallic nanoparticles have been used as imaging contrast agents , in laser-based treatment , as optical biosensors and drug delivery vehicles.

CNTs can act as antennas for radios and other electromagnetic devices. Conductive CNTs are used in brushes for commercial electric motors. They replace traditional carbon black. The nanotubes improve electrical and thermal conductivity because they stretch through the plastic matrix of the brush.The metallic nanoparticles include silver, copper, gold, zinc, platinum, and palladium nanoparticles, whereas the nonmetallic nanoparticles are titanium dioxide, zinc oxide, and cadmium oxide. Carbon-based nanomaterials include multiwalled carbon nanotubes and carbon–silicon nanomaterials.[17]



Fig,no.5

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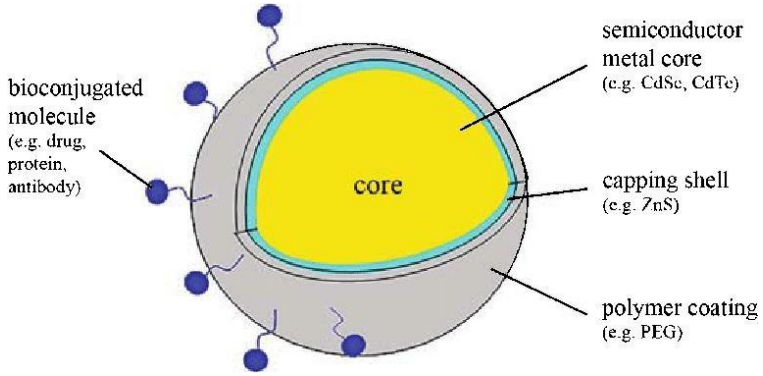
VI. Quantum dot

Quantum dots (QDs) are fluorescent semiconductor nanocrystals (1-100 nm) and have shown potential use for several biomedical applications, such as drug delivery and cellular imaging. Quantum dots possess a shell-core structure, in which the core structure is typically composed of II-VI or III-V group elements of the periodic table. Due to their distinctive optical properties and size, with high brightness and stability, quantum dots have been employed in the field of medical imaging.[18]



Fig,no.6

IV. NANOTECHNOLOGY IN DRUG DELIVERY

Therapy typically involves delivering drugs to a specific target site. If an internal route for drug delivery is not available, external therapeutic methods, such as radiotherapy and surgical procedures are employed. These methods are often used interchangeably or in combination to combat diseases. The goal of therapy is to always selectively remove the tumours or the source of illness in a long-lasting manner. Nanotechnologies are making a compelling contribution in this area through the development of novel modes for drug delivery, and some of these methods have proven effective in a clinical setting and are clinically used. For example, doxorubicin a drug which exhibits high toxicity, can be delivered directly to tumour cells using liposomes (Doxil) without affecting the heart or kidneys. Additionally, paclitaxel incorporated with polymeric mPEG-PLA micelles (Genexol-PM) are used in chemotherapeutic treatment of metastatic breast cancers. The success of nanotechnologies in drug delivery can be attributed to the improved in vivo distribution, evasion of the reticuloendothelial system and the favorable pharmacokinetics.[19]

A perfect drug delivery system encompasses two elements: Control over drug release and the targeting ability. Side effects can be reduced significantly, and drug efficiency can be ensured by specifically targeting and killing harmful or cancerous cells. Additionally, controlled drug release can also reduce the side effects of drugs . Benefits of nanoparticle drug delivery systems include minimized irritant reactions and improved penetration within the body due to their small size, allowing for intravenous and other delivery routes. The specificity of nanoparticle drug delivery systems is made possible by attaching nano-scaled radioactive antibodies that are complementary to antigens on the cancer cells with drugs, and these approaches have produced desirable results , exhibiting improved

i) drug bioavailability

ii) delivery of drugs specifically to the target site

iii) uptake of low solubility drugs summarizes the advantages of nanoparticles over conventional fine particles.[20]

Nanotechnology is getting developed at various levels such as materials, systems and devices. At present in commercial applications and scientific information, the most innovative level is nanomaterials. In nanotechnology, a minor object that acts as a complete unit in terms ofits properties and transport is known as a particle. It can be categorized according to sizes as fine particle and ultrafine particle. In terms of diameter, fine particles are sized between 100 and 2500 nanometers, while ultrafine particles cover a range between 1 and 100 nanometers. Nanoparticles are also sized between 1 and 100 nanometers similar to the ultrafine particles. Nanoparticles may or may not demonstrate sizerelated properties that vary knowingly from those observed in bulk materials and fine particles.

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Thus nanoparticles are sized less than a few 100 nm. This reduction in size brings about significant changes in their physical properties with respect to those observed in bulk materials. They can be mineral, metallic, polymer-based or a combination of materials. Due to a wide variety of potential applications in optical, electronic fields and biomedical, Nanoparticle research is currently an area of intense scientific interest. The reason behind nanoparticles are attractive is based on their unique and important features, such as their surface to mass ratio, which is much larger than that of other particles and materials, their ability to adsorb and carry other compounds such as drugs, probes and proteins as well as permitting the catalytic promotion of reactions[21]

Advantages

• After parenteral administration to achieve both passive and active drug targeting particle size and surface characteristics of nanoparticles can be easily manipulated.
• To achieve high drug therapeutic efficacy and less side effects, during the transportation they control and sustain release of the drug and at the site of localization, altering distribution of the drug and subsequent clearance of the drug.
• By attaching targeting ligands to surface of particles or use of magnetic guidance site- specific targeting can be achieved.
• Including oral, intra-ocular, parenteral and nasal, the system can be used for various routes of administration.
• Within the body, drug delivery to tiny areas can be achieved better bynanoparticles.
• Engineering enables researchers to exercise precisely on this scale and previously control over the biomaterials and physical features of polymers
• Nanoparticles provide efficient delivery of drug to various parts of the body by overcoming the resistance offered by the physiological barriers in the body.[22]

4.1 Preparation of nanoparticles

For the preparation of nanoparticles, the selection of the appropriate method is based on the drug to be loaded and physicochemical properties of the polymer. The primary preparation methods of nanoparticles include:

a. Emulsion-Solvent Evaporation Method;

The nanoparticles are mostly prepared by using this method. Two steps are mainly involved in this method. In an aqueous phase, emulsification of the polymer solution required in the first step. While in the second step, evaporation of polymer solution occurs and nanospheres are formed by inducing the polymer precipitation. Collection of nanoparticles is done by ultracentrifugation and to remove free drug or residue, washed with distilled water and for storage these are lyophilized. 18This method is also known as solvent evaporation method andhigh pressure emulsification. 19 This technique involves homogenization under high pressure and overall stirring to remove organic solvent.20 By adjusting the stirring rate, viscosity of organic and aqueous phases, temperature, type and amount of dispersing agent the size can be controlled. 21 However to lipid soluble drugs, this technique can be applied and by the scale up issues limitation are imposed. Polymers used are PLA, Poly (β- hydroxybutyrate) (PHB)22 Poly (caprolactone) (PCL)23, PLGA24, cellulose acetate phthalate25, and EC26 in this method.[23]

b. Double Emulsion and Evaporation Method:

Poor entrapment of hydrophilic drugs is the main drawback of this method. Therefore to encapsulate hydrophilic drug the double emulsion technique is engaged, inwhich aqueous drug solutions is added to organic polymer solution with vigorous stirringto form w/o emulsions. With continuous stirring to form mixed emulsion (w/o/w), this w/o emulsion is added into another aqueous phase. Then by the evaporation solvent is removed and by centrifugation at high speed nano particles can be isolated. Before lyophilisation the prepared nanoparticles must be washed. The variables used in this method are; incorporated quantity of hydrophilic drug, the amount of polymer, the volume of aqueous phase andthe stabilizer concentration. The characterization of nano particles also affected by these variables[24]

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c. Salting Out Method:

By using salting-out from aqueous solution the water-miscible solvent is separated using this method. Initially in a solvent, polymer and drug are dissolved which is consequently containing the saltingout agent (electrolytes, such as calcium chloride and magnesium chloride or sucrose as non- electrolytes) and polyvinylpyrrolidone(PVP) or hydroxyethylcellulose as a colloidal stabilizer into an aqueous gel areemulsifiedThis oil in water emulsion is diluted with water or with an aqueous phase to increase the diffusion of solvent,which indicates the formation of nanospheres. Several parameters such as electrolyte concentration, concentration of polymers in the organic phase, type of stabilizer, stirring rate, internal/external phase ratio can be varied. This technique leads to high efficiency and easily scaled up in the preparation of Ethyl cellulose, PLA and Poly(methacrylic) acids nanospheres Salting out may be useful for heat sensitive substances because an increase of temperature does not require in this technique. An exclusive application to lipophilic drug and the extensive nanoparticles washing steps are the drawbacks of this method.[25]

d. Emulsions Diffusion Method

To prepare nanoparticles, emulsions diffusion method is another method which iscommonly used. The encapsulating polymer is dissolvedin a solvent which is partially miscible with water such as propylene carbonate, benzyl alcohol and the initial thermodynamic equilibrium of both liquids saturated with water should be ensured. Subsequently, The polymer-water saturated solvent phase is emulsified in an aqueous solution containing stabilizer, leading to solvent diffusion to the external phase and according to the oil-topolymer ratio nanospheres or nanocapsules are formed. Finally, according to boiling point the solvent is removed by evaporation or filtration. This technique has several advantages, such as high reproducibility (batch-to-batch), no requirement of homogenization, high encapsulation efficiencies (generally 70%),simplicity, narrow size distribution and ease of scale-up. But some drawbacks of this method are: the high volumes of water to be eliminated from the suspension and reduced encapsulation efficiency during emulsification becausein the saturated-aqueous external phase leakage of water solubledrug. Examples of some drug- loaded nano particles which were produced by this technique; cyclosporine (cy-A-); loaded sodium glycolate nanoparticles, mesotetra (hydroxyphenyl) porphyrin-loaded PLGA (p-THPP) nano particles and nano particles of doxorubicin-loaded PLGA.[26]

e. Solvent Displacement/Precipitation method

Solvent displacement includes from an organic solution, the precipitation of a preformed polymer and in the aqueous medium the diffusion of the organic solvent in the presence or absence of surfactant. In a semi-polar water miscible solvent such as acetone or ethanol, polymers, drug and lipophilic surfactant are dissolved. Then solution is poured or injected using the magnetic stirring, into stabilizer containing aqueous solution. By the rapid solvent diffusion nano particles are formed. Then under reduced pressure solvent is removed from the suspension. The particles size is also affected by rate of addition of the organic phase into the aqueous phase. It was observed that by increasing the rate of mixing, both particles size and drug entrapment decreases. For most of the poorly soluble drugs nano precipitation method is well suited. By adjusting preparation parameters; nanosphere size, and drug release can be controlled effectively. While adjusting concentration of polymer results in good production of smaller sized nanospheres.[27]

f. Polymerization method

In this method, polymerization of monomers is done in an aqueous solution and after polymerization completed, drug is incorporated either by adsorption onto the nanoparticles or by being dissolved in the polymerization medium. To remove various stabilizers and surfactants, employed for polymerization by ultra centrifugation the nanoparticle suspension is then purified and in an isotonic surfactant-free medium re-suspending the particles. For making polybutyl cyanoacrylate or poly(alkylcyano acrylate) nanoparticles, this technique has been reported. Formation of nanocapsule and their particle size affected by the surfactants and stabilizers concentration used.[28]

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g. Coacervation or ionic gelation method

On the preparation of nanoparticles much research has been focused using biodegradable hydrophilic polymers such as chitosan, sodium alginate and gelatin. A method for preparing hydrophilic chitosan nanoparticles by ionic gelation developed by Calvo and co-workers.39,40 The method contains two aqueous phases, in which one is the polymer chitosan and the other phase is a polyanioni.e. sodium tripolyphosphate In this method, interaction of positively charged amino group of chitosan with negative charged tri polyphosphate occurs which form coacervates with an anometer size range. Electrostatic interaction between two aqueous phases results in the formation of coacervates, while ionic interaction conditions at room temperature results in transition from liquid to gel due to ionic gelation.[29]

4.2 Different Routes of Drug Delivery System:

Drug delivery is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals. For the treatment of human diseases, nasal and pulmonary routes of drug delivery are gaining increasing importance. These routes provide promising alternatives to parenteral drug delivery particularly for peptide and protein therapeutics. For this purpose, several drug delivery systems have been formulated and are being investigated for nasal and pulmonary delivery. These include liposomes, proliposomes, microspheres, gels, prodrugs, cyclodextrins, among others. Nanoparticles composed of biodegradable polymers show assurance in fulfilling the stringent requirements placed on these delivery systems, such as ability to be transferred into an aerosol, stability against forces generated during aerosolization, biocompatibility, targeting of specific sites or cell populations in the lung, release of the drug in a predetermined manner, and degradation within an acceptable period of time.[30]

A. BEADED DELIVERY SYSTEMS:

Although not used with oxybutylin, beaded delivery formulations are another method used to achieve long-acting drug levels associated with the convenience of once-a-day dosing. This system has been successfully linked to tolterodine tartrate and is available as Detrol LA (Pharmacia, Peapack, NJ). Essentially, the beaded system consists of multiple, small beads that are composed of inert substances (such as polystyrene). The active drug is overlaid on the beads and encased in a delivery capsule. The drug delivery from this system is acid sensitive, in that drug levels are dependent on gastric acidity for release. This process produces a pharmacokinetic pattern roughly similar to a zero-order pattern, with C max obtained approximately 4 to 6 hours after ingestion and sustained levels observed for 24 hours after initial dosing. Comparative advantages are seen for both efficacy (improved incontinence rates) and tolerability with Detrol LA over immediate-release tolterodine. In a double-blind, placebo-controlled, randomized study of 1529 patients the LA formulation resulted in 18% less incontinence episodes than the immediate-release tolterodine, whereas both formulations were statistically superior to placebo in reducing urinary frequency and increasing voided urinary volume..[31]

B. Liposomal and Targeted Drug Delivery System

Drug delivery systems can in principle provide enhanced efficacy and/or reduced toxicity for anticancer agents. Long circulating macromolecular carriers such as liposomes can exploit the ‘enhanced permeability and retention’ effect for preferential extravasation from tumor vessels. Liposomal anthracyclines have achieved highly efficient drug encapsulation, resulting in significant anticancer activity with reduced cardio toxicity, and include versions with greatly prolonged circulation such as liposomal daunorubicin and pegylated liposomal doxorubicin. Pegylated liposomal doxorubucin has shown substantial efficacy in breast cancer treatment both as monotherapy and in combination with other chemotherapeutics. Additional liposome constructs are being developed for the delivery of other drugs. The next generation of delivery systems will include true molecular targeting; immunoliposomes and other ligand-directed constructs represent an integration of biological components capable of tumor recognition with delivery technologies.[32]

As discussed, currently approved liposomal drug delivery systems provide stable formulation, provide improved pharmacokinetics, and a degree of ‘passive’ or ‘physiological’ targeting to tumor tissue. However, these carriers do not directly target tumor cells. The design modifications that protect liposomes from undesirable interactions with plasma

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proteins and cell membranes, and which contrast them with reactive carriers such as cationic liposomes, also prevent interactions with tumor cells. Instead, after extravasation into tumor tissue, liposomes remain within tumor stroma as a drug-loaded depot. Liposomes eventually become subject to enzymatic degradation and/or phagocytic attack, leading to release of drug for subsequent diffusion to tumor cells. The next generations of drug carriers under development features direct molecular targeting of cancer cells via antibody-mediated or other ligand-mediated interactions.[33]

Immunoliposomes, in which mAb fragments are conjugated to liposomes, represent a strategy for molecularly targeted drug delivery. Anti-HER2 immunoliposomes have been developed with either Fab' or scFv fragments linked to long-circulating liposomes. In preclinical studies, anti- HER2 immunoliposomes bound efficiently to and internalized in HER2-overexpressing cells, resulting in efficient intracellular delivery of encapsulated agents. Anti-HER2 immunoliposomes loaded with doxorubicin displayed potent and selective anticancer activity against HER2-overexpressing tumors, including significantly superior efficacy versus all other treatments tested (free doxorubicin, liposomal doxorubicin, free mAb [trastuzumab], and combinations of trastuzumab plus doxorubicin or liposomal doxorubicin). Anti-HER2 immunoliposomes are currently undergoing scale up for clinical studies.[34]

C. Lung-specific drug delivery

Pulmonary drug delivery offers several advantages in the treatment of respiratory diseases over other routes of administration. Inhalation therapy enables the direct application of a drug within the lungs. The local pulmonary deposition and delivery of the administered drug facilitates a targeted treatment of respiratory diseases, such as pulmonary arterial hypertension (PAH), without the need for high dose exposures by other routes of administration. The intravenous application of short acting vasodilators has been the therapy of choice for patients with PAH over the past decade. The relative severity of side effects led to the development of newprostacyclin analogues and alternative routes of administration. One such analogue, iloprost (Ventavis), is a worldwide approved therapeutic agent for treatment of PAH. Inhalation of this compound is an attractive concept minimizing the side effects by its pulmonary selectivity. Unfortunately, the short half-life of iloprost requires frequent inhalation manoeuvres, ranging up to 9 times a day. Therefore, an aerosolizable controlled release formulation would improve a patient's convenience and compliance. Controlled drug delivery systems have become increasingly attractive options for inhalation therapies. A large number of carrier systems have been developed and investigated as potential controlled drug delivery formulations to the lung, including drug loaded lipid and polymer based particles. The use of colloidal carrier systems for pulmonary drug delivery is an emerging field of interest in nanomedicine.[35]

V. TARGET DRUG DELIVERY SYSTEM

Targeted drug delivery is a method of delivering medication to a patient in a manner that increases the concentration of the medication in some parts of the body relative to others.

Targeted drug delivery seeks to concentrate the medication in the tissues of interest while reducing the relative concentration of the medication in the remaining tissues. This improves efficacy of the while reducing side effects.[42]

The biological effects of a drug in a patient depend on the pharmacological properties of the drug.These effects arise due to the interactions between the drug and the receptors at the site of action of the drug. The efficacy of this drug-target interaction has been undermined unless the drug is transported to its site of action at such a concentration and rate that causes the minimum side-effects and maximum therapeutic effects. Targeted drug delivery, is the method of treatment that involves the transportation of the therapeutic agent to specific tissue without reaching the remaining part of the body. Therefore, it delivers the medication only to areas of interest within the body.

The technology of the drug delivery system has become advanced and controls the drug bioavailability, drug absorption and pharmacokinetic parameters. The process of drug targeting requires four principles, first, the ability to load the drug to the target site, second, avoid the degradation by body fluid, third, reaching the target site and fourth, release the drug at the specific site at the predetermined time. Different sites of interest within the body necessitate the use of different drug delivery systems, depending upon the route to be followed. [43]

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The advantages of drug targeting
1. The protocol of drug administration becomes simpler
2. The toxicity of the drug is decreased by targeting a specific site.
3. The desired drug response can be reached by a small dose.
4. Avoid the first-pass effect.
5. Improvement in the drug absorption from the target site.
6. Drug targeting resulted in no peak and valley plasma concentration.

The disadvantages of drug targeting
1. Rapid drug elimination from the body results in high dose frequency.
2. The carrier of the targeted drug delivery system may result in the immune response.
3. The drug delivery system is not localized at the tumor tissue for sufficient time.
4. The diffusion and redistribution of released drugs.

Carries applied for drug targetinga. Drug targeting can be attained by using carrier systems.
b. The carriers are systems which required for transportation of entrapped drug to target sites.
c. The carriers entrap the drug moiety and deliver it into the target site without releasing it in the nontarget site.[44]

Different types of carriers for drug targeting

• Quantum dots:

A quantum dot is a semiconductor nanostructure that confines the motion of conduction band electrons, valence band holes, or excitons (bound pairs of conduction band electrons and valence band holes) in all three spatial directions. The confinement can be due to electrostatic potentials (generated by external electrodes, doping, strain, impurities), the presence of an interface between different semiconductor materials (e.g. in core-shell nanocrystal systems), the presence of the semiconductor surface (e.g. semiconductor nanocrystal), or a combination of these. Quantum dots are particularly significant for optical applications due to their theoretically high quantum yield. The ability to tune the size of quantum dots is advantageous for many applications and it is one of the most promising candidates for use in solid-state quantum computation and diagnosis , drug delivery, Tissue engineering, catalysis, filtration and also textiles technologies.[45]

• Transdermal Approach:

Transdermal drug delivery system is topically administered medicaments in the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate. A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative route for administering medication. These devices allow for pharmaceuticals to be delivered across the skin barrier. In theory, transdermal patches work very simply. A drug is applied in a relatively high dosage to the inside of a patch, which is worn on the skin for an extended period of time. Through a diffusion process, the drug enters the bloodstream directly through the skin. Since there is high concentration on the patch. and low concentration in the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow.[46]

• Folate Targeting:

Folate targeting is a method utilized in biotechnology for drug delivery purposes. It involves the attachment of the vitamin, folate (folic acid), to a molecule/drug to form a "folate conjugate". Based on the natural high affinity of folate for the folate receptor protein (FR), which is commonly expressed on the surface of many human cancers, folate-drug conjugates also bind tightly to the FR and trigger cellular uptake via endocytosis. Molecules as diverse as small radio diagnostic imaging agents to large DNA plasmid formulations have successfully been delivered inside FR-positive cells and tissues. FA also displays high affinity for the folate receptor (FR), a glycosylphosphatidyinositol-linked protein that

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captures its ligands from the extracellular milieu and transports them inside the cell via a non-destructive, recycling endosomal pathway. The FR is also a recognized tumor antigen/biomarker. Because of this, diagnostic and therapeutic methods which exploit the FR's function are being developed for cancer.[47]

• Brain targeted drug delivery system:

The brain is a delicate organ, and evolution built very efficient ways to protect it. The delivery of drugs to central nervous system (CNS) is a challenge in the treatment of neurological disorders. Drugs may be administered directly into the CNS or administered systematically (e.g., by intravenous injection) for targeted action in the CNS. The major challenge to CNS drug delivery is the blood-brain barrier (BBB), which limits the access of drugs to the brain substance. Advances in understanding of the cell biology of the BBB have opened new avenues and possibilities for improved drug delivery to the CNS. Various strategies that have been used for manipulating the blood-brain barrier for drug delivery to the brain include osmotic and chemical opening of the blood-brain barrier as well as the use of transport/carrier systems. Other strategies for drug delivery to the brain involve bypassing the BBB. Various pharmacological agents have been used to open the BBB and direct invasive methods can introduce therapeutic agents into the brain substance. It is important to consider not only the net delivery of the agent to the CNS, but also the ability of the agent to access the relevant target site within the CNS. Various routes of administration as well as conjugations of drugs, e.g., with liposomes and nanoparticles. [48]

• Liposomes:

These are vesicular concentric structures, range in size from a nanometer to several micrometers, containing a phospholipids bilayer and are biocompatible, biodegradable and non immunogenic. Liposomes have generated a great interest because of their versatility and have played a significant role in formulation of potent drugs to improve therapeutics. Enhanced safety and efficacy have been achieved for a wide range of drug classes, including antitumor agents, antiviral, antimicrobials, vaccines, gene therapeutics etc. Recently pharmaceutical science is using liposomes to reduce toxicity and side effect of drugs. The various problems like poor solubility, short half life and poor bioavailability & strong side effect of various drugs can be overcome by employing the concept of liposomes especially in various diseases like cancer etc. Liposomes offer ample opportunities for the investigators to explore the unidentified breakthrough in the field of pharmaceutical technology.[49]

• Ufasomes

Ufasomes are a dispersion of unsaturated fatty acid vesicles prepared from fatty acid and ionic surfactant (soap) in presence of cholesterol. Ufasomes are a good carrier for drugs intended for topical application. The outermost layer of the skin, which is the stratum corneum, is considered the main barrier for drug penetration. This problem can be overcome by using ufasomes as DDS because the ufasomes consist of lipid membrane which has the ability to attach to the skin. Kaur et al. studied and enhanced the antifungal activity of oxiconazole loaded ufasome against Candida albicans.

• Nanobots

Nanorobotics is a new technology of drug delivery systems. They are a nanoscale machine with a diameter of 10-9 m.Andhari et al. prepared self-propelling targeted magneto-nanobots for deep tumor penetration.

• Transferosomes

Transferosomes are such a novel vesicular drug delivery system. Transformers are specially self- optimizing, selfregulating, ultra deformable "ultra-flexible". possessing an inner aqueous core surrounded by a complex lipid bilayer with unique properties, due to the presence of "edge activators" into a vesicular membrane, the surfactant has been used as edge activators. So it can penetrate the skin efficiently by squeezing themselves through pores from 5 to 10 times less than their diameter. This will avoid complete rupture of the vesicle and remaining the drug intact after

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penetrating the skin.Qushawy et al. prepared miconazole nitrate transferosomal gel for effective treatment of skin candida infection.[50]

Strategies for drug targeting Passive targeting

Passive targeting usually refers to the drug delivery systems which target the drug to the systemic circulation The passive targeting is done as a response from the body to the physicochemical properties of the drug or the drug delivery system which entrap the drug till reaching the target site, see. Zhang et al. used salinomycin passive targeting micelles for suppression of breast cancer and stem cell cancer.

Double targeting

The double targeting strategy is a combination of both temporal and spatial, so it is called double targeting.The spatial delivery involves the targeting of the drug to the target site, while the temporal delivery involves the controlling of drug release at the target site.4 Pitto-Barry et al. applied a double targeting mechanism for targeting a dendrimer-loaded anticancer drug to the tumor site dose and thus the side effect of the drugs. There are several delivery systems used in drug targeting such as liposome, transferosome, gold nanoparticles, niosomes, cubosome, virosome, nanotube. The targeted drug delivery system is very important in the treatment of several types of cancer such as brain cancer, breast cancer, prostate cancer and colon cancer. Now, there is progress in the field of drug targeting to overcome the problems associated with conventional drug delivery systems. [51]

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