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Nano formulation

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ABSTRACT

Nano formulation is able to provide, superior drug delivery system for better management and treatment of disease. In the future, the pharmaceutical market, nano medicine and healthcare system will largely depend on drug non particle formulation technology. Strategies depend on the controlled particle size, narrow size distribution stability reproducibility. nano particles are stable , solid, organic or inorganic particles with size range of 10-1000 nm. In this review, including liposomes ,dendrimers , Cellulose and inorganic nanoparticles.

Keyword :nano drugs formulation, drug nanoparticles, nanomedicine, drug delivery.

INTROUCTION

The nano structures employed as drug delivery system have multiple advantages which make them superior to conventional delivery system. Nanoparticles and other colloidal drugs delivery system modify the body distribution and drug delivery release of unwanted side effects by a controlled release.

Liposomes are forms of vehicle that consist either of many few or just one phosphorlipidbilayers .dendrimers consist of a central core, branching unit and terminal functional groups. In this study, implemention and preparation methods of each drug delivery system used in diagnosis and treatment of cancer disease have been evaluated.

Fundamentals of nanotechnology based techniques in designing of drug

Nanomedicine is the branch of medicine that utilizes the science ofnantechnology in the preclusion and cure of various disease using the nanoscale materials. Drugs with very low solubility possess various biopharmaceutical delivery issues including limited bio accessibility after intake through mouth ,less diffusion capacity into the outer membrane , require more quantity for intravenous intake and unwanted after effects preceding traditional formulated vaccination process.however all these limitions could be overcome by the application of nanotechnology approaches in the drug delivery mechanism .

Drug designing at the nanoscale has been studied extensively and is by far the most adavanced technology in the area of nanoparticle applications because of its potential advantages such as the profiles ,diffusivity, bioavailability and development routes , lower toxicity, fewer side effect , improved biodistribution and extended drugs life cycle . the engineered drug delivery system are either targeted to particular ;location or are intended to particular location or are intended for the controlled release of therapeutic agents at a particular site .their formation involves self-assembly where in well defined structures or patterns spontaneously are formed from building blocks .

There are two ways through which nanostructure delivery drugs :

1. Passive
2. Self - delivery

In the former, drugs are incorporated in the inner cavity of the structure mainly via the hydrophobic effect. When the nanostructure materials are targeted to a particular sites the intended amount of the drug is realeased because of the low content of the drugs which is encapsulated in a hydrophobic enviroments. Conversely, in the latter , the drugs intended for release are directly conjugated to the carrier nanostructure material for easy delivery. In this approach, the timing of realease is crucial as the drug will not reach the target site and it dissociates from the carrier very quickly, and conversely , its bioactivity and efficacy will be decreased if it is realeased from its nanocarrier system at the right time. Targeting of drugs is another significant aspect that uses nano uses nanoformualtions as the drugs delivery system and is classified into active and passive. In active targeting, moieties, such as antibodies and peptides are coupled with drug delivery system to anchor them to the receptor structure expressed at the

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target site. In a passive targeting, the prepared drug carrier complex circulates through the target site by properties like Ph , temperature, molecular site and shape

Drug designing and drug delivery process and mechanism

With the progression of nanomedicine and, due to the advancement of drug discovery/design and drug delivery systems, numerous therapeutic procedures have been proposed and traditional clinical diagnostic methods have been studied, to increase the drug specificity and diagnostic accuracy. For instance, new routes of drug administration are being explored, and there is focus on ensuring their targeted action in specific regions, thus reducing their toxicity and increasing their bioavailability in the organism

In this context, drug designing has been a promising feature that characterizes the discovery of novel lead drugs based on the knowledge of a biological target. The advancements in computer sciences, and the progression of experimental procedures for the categorization and purification of proteins, peptides, and biological targets are essential for the growth and development of this sector . In addition, several studies and reviews have been found in this area; they focus on the rational design of different molecules and show the importance of studying different mechanisms of drug release . Moreover, natural products can provide feasible and interesting solutions to address the drug design challenges, and can serve as an inspiration for drug discovery with desired physicochemical properties

Also, the drug delivery systems have been gaining importance in the last few years. Such systems can be easily developed and are capable of promoting the modified release of the active ingredients in the body. For example, described an interesting review using nanocarriers for imaging and sensory applications and discussed the, therapy effect of these systems. In addition, an up-to-date overview of several applications of nanocarriers to nanomedicine and discussed new opportunities and challenges for this sector.

Interestingly, each of these drug delivery systems has its own chemical, physical and morphological characteristics, and may have affinity for different drugs polarities through chemical interactions (e.g., covalent bonds and hydrogen bonds) or physical interactions (e.g., electrostatic and van der Waals interactions). As an example, the release profile of neem bark extract-grafted biogenic silica nanoparticles (chemical interactions) was lower than neem bark extract-loaded biogenic silica nanoparticles. Hence, all these factors influence the interaction of nanocarriers with biological systems , as well as the release kinetics of the active ingredient in the organism [68]. In addition, designed a crosslinkable lipid shell (CLS) containing docetaxel and wortmannin as the prototypical drugs used for controlling the drug discharge kinetics; then, they studied, its discharge profile, which was found to be affected in both in vivo and in vitro conditions. Apart from this, other parameters, such as the composition of the nanocarriers (e.g., organic, inorganic, and hybrid materials) and the form in which drugs are associated with them (such as core–shell system or matrix system) are also fundamental for understanding their drug delivery profile . Taken together, several studies regarding release mechanisms of drugs in nanocarriers have been conducted. Diffusion, solvent, chemical reaction, and stimuli-controlled release are a few mechanisms that can represent the release of drugs in nanocarriers .a widespread review of controlled-release systems with a focus on studies related to controlling drug release from polymeric nanocarriers.

Although there are several nanocarriers with different drug release profiles, strategies are currently being formulated to improve the specificity of the nanostructures to target regions of the organism , and to reduce the immunogenicity through their coating or chemical functionalization with several substances, such as polymers , natural polysaccharides , antibodies , cell-membrane , and tunable surfactants , peptides , etc. In some cases where drugs do not display binding and affinity with a specific target or do not cross certain barriers (e.g. blood–brain barrier or the blood–cerebrospinal fluid barrier) , these ligand-modified nanocarriers have been used to pass through the cell membrane and allow a programmed drug delivery in a particular environment. For example, hyaluronic acid (a polysaccharide found in the extracellular matrix) has been used as a ligand-appended in several nanocarriers, showing promising results to boost antitumor action against the melanoma stem-like cells , breast cancer cells , pulmonary adenocarcinoma cells , as well as to

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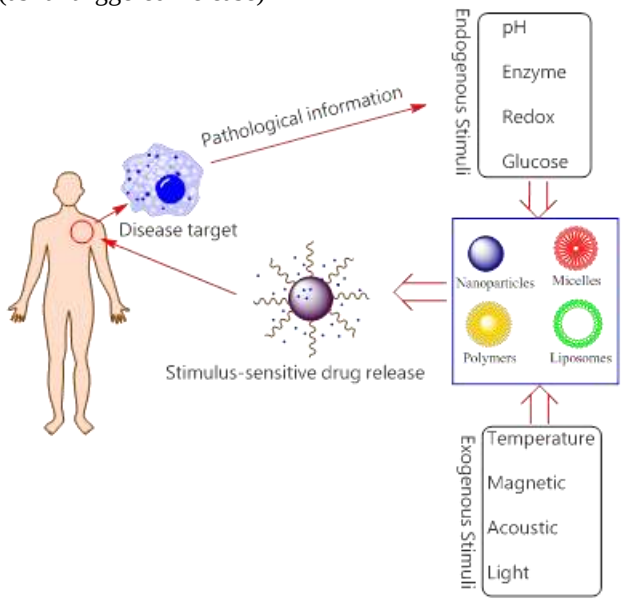
facilitate intravitreal drug delivery for retinal gene therapy and to reduce the immunogenicity of the formed protein corona . However, the construction of the ligand-appended drug delivery systems is labor-intensive, and several targeting designs must be performed previously, taking into account the physiological variables of blood flow, disease status, and tissue architecture . Moreover, few studies have been performed to evaluate the interaction of the ligand-appended in nanocarriers with cell membranes, and also their uptake mechanism is still unclear. Furthermore, has been known that the uptake of the nanoparticles by the cells occurs via phagocytic or non-phagocytic pathways (e.x. clathrin-mediated endocytosis, caveolae-mediated endocytosis, and others) , meanwhile due some particular physicochemical characteristics of each delivery systems have been difficult to standardize the mechanism of action/interaction of these systems in the cells. For example, Salatin and Khosroushahi, in a review highlighted the main endocytosis mechanisms responsible for the cellular uptake of polysaccharide nanoparticles containing active compounds.

On the other hand, stimuli-responsive nanocarriers have shown the ability to control the release profile of drugs (as a triggered release) using external factors such as ultrasound , heat , magnetism , light , pH], and ionic strength , which can improve the targeting and allow greater dosage control . For example, superparamagnetic iron oxide nanoparticles are associated with polymeric nanocarriers or lipids to initially stimulate a controlled release system by the application of external magnetic field. In addition, Ulbrich et al. recent achievements of drug delivery systems, in particular, on the basis of polymeric and magnetic nanoparticles, and also addressed the effect of covalently or noncovalently attached drugs for cancer cure . Moreover, Au/Fe3O4@polymer nanoparticles have also been synthesized for the use in NIR-triggered chemo-photothermaltherapy . Therefore, hybrid nanocarriers are currently among the most promising tools for nanomedicine as they present a mixture of properties of different systems in a single system, thus ensuring materials with enhanced performance for both therapeutic and diagnostic applications (i.e., theranostic systems). Despite this, little is known about the real mechanisms of action and toxicity of drug delivery systems, which open opportunity for new studies. In addition, studies focusing on the synthesis of nanocarriers based on environmentally safe chemical reactions by implementing plant extracts and microorganisms have increased



Nanoparticles used in drug delivery system

Biopolymer nanoparticles

There are numerous biopolymeric materials that are utilized in the drug delivery systems. These materials and their properties are discussed below.

Cellulose

Cellulose and its derivatives are extensively utilized in the drug delivery systems basically for modification of the solubility and

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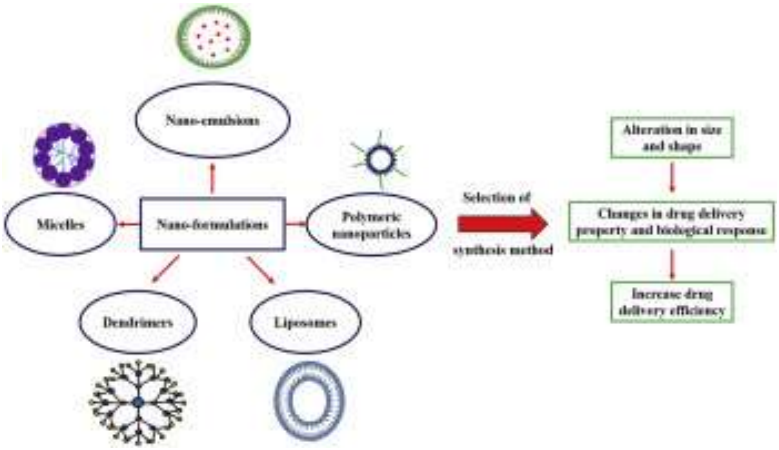
gelation of the drugs that resulted in the control of the release profile of the same .investigated the utilization of cellulose nanocrystals and chitosan nanoparticles for the oral releasing of repaglinide (an anti-hyperglycemic—RPG). The chitosan nanoparticles showed a mean size distribution of 197 nm while the hybrid nanoparticles of chitosan and cellulose nanocrystals containing RPG. Chitosan hybrid



nanoparticl mixed with es and oxidized cellulose nanocrystals containing RPG had a mean diameter of 251–310 nm. The presence of the hydrogen bonds between the cellulose nanocrystals and the drug, resulted in sustained release of the same, and subsequently the nanoparticles made with oxidized cellulose nanocrystals presented lower release when compared to the nanoparticles produced with native cellulose nanocrystals.

developed a drug targeting mechanism which is based on the conjugation of calcium alginate beads with carboxymethylcellulose (CMC) loaded 5-fluoroacyl (5-FU) and is targeted to the colon. The beads with lower CMC proportions presented greater swelling and muco-adhesiveness in the simulated colonic environment. With existence of colonic enzymes there was a 90% release of 5-FU encapsulated in the beads. Hansen et al. investigated four cellulose derivatives, including, meteylcellulose, hydroxypropyl methylcellulose, sodium carboxymethylcellulose and cationic hydroxyethyl cellulose for application in drug release into the nasal mucosa. The association of these cellulose derivatives with an additional excipient, was also evaluated. The drug model employed in this process was acyclovir. The viability of the polymers as excipients for nasal release applications was also scrutinized for its ciliary beat frequency (CBF) and its infusion through the tissue system of the nostril cavity. An increase in thermally induced viscosity was observed when the cellulose derivatives were mixed with polymer graft copolymer. Further an increased permeation of acyclovir into the nasal mucosa was detected when it was combined with cationic hydroxyethylcellulose. None of the cellulose derivatives caused negative effects on tissues and cells of the nasal mucosa, as assessed by CBF.

Liposomes

They were discovered by Alec Bangham in 1960. Liposomes are used in the pharmaceutical and cosmetics industry for the transportation of diverse molecules and are among the most studied carrier system for drug delivery. Liposomes are an engrained formulation strategy to improve the drug delivery. They are vesicles of spherical form composed of phospholipids and steroids usually in the 50–450 nm size range . These are considered as a better drug delivery vehicles since their membrane structure is analogous to the cell membranes and because they facilitate incorporation of drugs in them . It has also been proved that they make therapeutic compounds stable, improve their biodistribution, can be used with hydrophilic and hydrophobic drugs and are also biocompatible and biodegradable. Liposomes are divided into four types: (1) conventional type liposomes: these consists of a lipid bilayer which can make either anionic, cationic, or neutral cholesterol and phospholipids, which surrounds an aqueous core material. In this case, both the lipid bilayer and the aqueous space can be filled with hydrophobic or hydrophilic materials, respectively.

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(2) PEGylated types: polyethylene glycol (PEG) is incorporated to the surface of liposome to achieve steric equilibrium, (3) ligand-targeted type: ligands like antibodies, carbohydrates and peptides, are linked to the surface of the liposome or to the end of previously attached PEG chains and (4) theranostic liposome type: it is an amalgamation kind of the previous three types of liposomes and generally consists of a nanoparticle along with a targeting, imaging and a therapeutic element

The typical synthesis procedure for liposomes are as follows, thin layer hydration, mechanical agitation, solvent evaporation, solvent injection and the surfactant solubilization. One aspect to point out on liposomes is that the drugs that are trapped within them are not bioavailable until they are released. Therefore, their accumulation in particular sites is very important to increase drug bioavailability within the therapeutic window at the right rates and times. Drug loading in liposomes is attained by active (drug encapsulated after liposome formation) and passive (drug encapsulated during liposome formation) approaches . Hydrophilic drugs such as ampicillin and, 5-fluoro-deoxyuridine are typically confined in the aqueous core of the liposome and thus, their encapsulation does not depend on any modification in the drug/lipid ratio. However, the hydrophobic ones such as Amphotericin B, Indomethacin were found in the acyl hydrocarbon chain of the liposome and thus their engulfing are subjected to the characteristics of the acyl chain Among the passive loading approaches the mechanical and the solvent dispersion method as well as the detergent removal method can be mentioned .

There are obstacles with the use of liposomes for drug delivery purposes in the form of the RES (reticuloendothelial system), opsonization and immunogenicity although there are factors like enhanced permeability and EPR (retention effect) that can be utilized in order to boost the drug delivery efficiency of the liposomes . Once liposomes get into the body, they run into opsonins and high density lipoproteins (HDLs) and low density lipoproteins (LDLs) while circulating in the bloodstream by themselves. Opsonins (immunoglobulins and fibronectin, for example) assist RES on recognizing and eliminating liposomes. HDLs and LDLs have interactions with liposomes and decrease their stability. Liposomes tends to gather more in the sites like the liver and the spleen, this is an advantage because then a high concentration of liposomes can help treat pathogenic diseases, although in the case of cancers this can lead to a delay in the removal of lipophilic anticancer drugs. This is the reason why as mentioned at the beginning, different types of liposomes have been developed, in this case PEGylated ones. Dimov et al. reported an incessant procedure of flow system for the synthesis, functionalization and cleansing of liposomes. This research consists of vesicles under 300 nm in a lab-on-chip that are useful and potential candidates for cost-intensive drugs or protein encapsulation development . This is very important because costs of production also determine whether or not a specific drug can be commercialized. Liposome-based systems have now been permitted by the FDA

Dendrimers

Dendrimers are highly bifurcated, monodisperse, well-defined and three-dimensional structures. They are globular-shaped and their surface is functionalized easily in a controlled way, which makes these structures excellent candidates as drug delivery agents.Dendrimers can be synthesized by means of two approaches: The first one is the different route in which the dendrimer starts formation from its core and then it is extended outwards and the second is the convergent one, starts from the outside of the dendrimer. Dendrimers are grouped into several kinds according to their functionalization moieties: PAMAM, PPI, liquid crystalline, core–shell, chiral, peptide, glycodendrimers and PAMAMOS, being PAMAM, the most studied for oral drug delivery because it is water soluble and it can pass through the epithelial tissue boosting their transfer via the paracellularpathway .Dendrimers are limited in their clinical applications because of the presence of amine groups. These groups are positively charged or cationic which makes them toxic, hence dendrimers are usually modified in order to reduce this toxicity issue or to eliminate it. Drug loading in dendrimers is performed via the following mechanisms: Simple encapsulation, electrostatic interaction and covalent conjugation

Drug is basically delivered by the dendrimers following two different paths, a) by the in vivo degradation of drug dendrimer’s covalent bonding on the basis of availability of suitable enzymes or favorable environment that could cleave the bonds and b) by discharge of the drug due to changes in the physical environment like pH, temperature etc., . Dendrimers have been

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developed for transdermal, oral, ocular, pulmonary and in targeted drug delivery .

described the folate attached poly-L-lysine dendrimers (doxorubicin hydrochloride) as a capable cancer prevention drug carrier model for pH dependent drug discharge, target specificity, antiangiogenic and anticancer prospective, it was shown that doxorubicin-folate conjugated poly-L-lysine dendrimers increased the concentration of doxorubicin in the tumor by 121.5-fold after 24 h compared with free doxorubicin. Similarly, (Kaur et al. developed folate-conjugated polypropylene imine dendrimers (FA-PPI) as a methotrexate (MTX) nanocarrier, for pH-sensitive drug release, selective targeting to cancer cells, and anticancer treatment. The in vitro studies on them showed sustained release, increased cell uptake and low cytotoxicity on MCF-7 cell lines . Further, it has to be pointed out that the developed formulations, methotrexate (MTX)-loaded and folic acid-conjugated 5.0G PPI (MTX-FA-PPI), were selectively taken up by the tumor cells in comparison with the free drug, methotrexate (MTX).

Inorganic nanoparticles

Inorganic nanoparticles include silver, gold, iron oxide and silica nanoparticles are included. Studies focused on them are not as many as there are on other nanoparticle types discussed in this section although they show some potential applications. However, only few of the nanoparticles have been accepted for its clinical use, whereas the majority of them are still in the clinical trial stage. Metal nanoparticles, silver and gold, have particular properties like SPR (surface plasmon resonance), that liposomes, dendrimers, micelles do not possess. They showed several advantages such as good biocompatibility and versatility when it comes to surface functionalization.

Studies on their drug delivery-related activity have not been able to clear out whether the particulate or ionized form is actually related to their toxicity, and even though two mechanisms have been proposed, namely paracellular transport and transcytosis, there is not enough information about their in vivo transport and uptake mechanism . Drugs can be conjugated to gold nanoparticles (AuNPs) surfaces via ionic or covalent bonding and physical absorption and they can deliver them and control their release through biological stimuli or light activation . Silver nanoparticles exhibited antimicrobial activity, but as for drug delivery, very few studies have been carried out, for example, Prusty and Swain synthesized an inter-linked and spongy polyacrylamide/dextran nano-hydrogels hybrid system with covalently attached silver nanoparticles for the release of ornidazole which turned out to have an in vitro release of 98.5% . Similarly in another study, the iron oxide nanoparticles were synthesized using laser pyrolysis method and were covered with Violamycine B1, and antracyclinic antibiotics and tested against the MCF-7 cells for its cytotoxicity and the anti-proliferation properties along with its comparison with the commercially available iron oxide nanoparticles

Application:

Advancements in nanotechnology have resulted in the technology being widely used in various industries and fields from medicine to energy where it is used to help improve our day to day lives.

While research studies are still being conducted to improve and perfect nanotechnology for medical use several advancements have allowed the technology to be used in healthcare,one of the most recent example of this is the use of gold nanoparticles as probes .

Todays, gold nanoparticles are being use for the purpose of detecting nucleic sequences .in addition the technology has detecting nucleic sequence . addition the technology has also been shown to have the potential of helping in cancer treatment.

The technology has also been shows to have the potential to not only diagnose but also treat atherosclerosis. Here scientists have already managed to create a nanoparticles that is similar to HDL [high-density lipoprotein] used to reduce the size of plaque in arteries this can greatly help. Patients with high blood pressure.

Currently more studies are being directed towords the use of nanotechnology for regenerative medicine these studies aim to improve nanotechnology for regerative medicine for bone and tissue engineering this will allow scientists to grow complex tissues for oragan transplant as well as use the technology to repaire spinal cord injuries in doing to the technology will help treat numerous condition that continue to affect many patients today.

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Routes of administration	Limitation to drug delivery efficacy	Characteristics to give nanoparticles
Oral safer route for the admistration of drugs well accepted to patients	Enzymatic degradation absorption across the digestive mucosa	Biocompatible and eventually biodegradable Protection of drugs against degradation by enzymes Adhesion on the mucosa to slow down the transit through the GIT and to delivery the drugs near the absorption sites included in the gut epithelium
Intravenous major route of administration for drugs which are poorly or non absorbed by the oral route	Enzymatic degradation non specific delivery	Biocompatible and biodegradable protection of drug against degradation by enzymes Stealth to defence system of the organism and targeted to specific cells .stealth properly is required to escape massive uptake by macrophages of the mononuclear phagocyte system which hampered specific delivery to targeted property is required to achieve drug delivery to define cells with a high specificity .

Marking formulation

Even though has been huge number of reports and studies related to nanoformulation of drugs, only a handful of such nanosystems have progressed to market-related assessment and and again an even smaller handful have received final approval.

The multifunctional structure and activity of some nanoformulations could be another challenge on the road to nanoformulationapproval .many investigative

Nanoparticle formulations currently available on the market.

Product	Company	Drug	Formulation/ROA	Application	Status
Abraxane	Abrasix Bioscience, AstraZeneca	Paclitaxel	Albumin-bound nanoparticles/iv	Metastatic breast cancer	Marketed
Caelyx	Schering-Plough	Doxorubicin	Pegylated liposome/im	Metastatic breast and ovarian cancer; Kaposi sarcoma	Marketed
Myocet	Zeneus Pharma Ltd	Doxorubicin	Liposome/iv	Metastatic breast cancer	Marketed
Doxil	Sequus Pharmaceutical	Doxorubicin	Liposome/iv	Kaposi sarcoma	Marketed
L-Annamycin	Callisto Pharmaceuticals	Annamycin	Liposome/iv	Children and young adults with refractory or relapsed ALL or AML	Phase I/II
Genexol-PM	Samyang Pharmaceuticals	Paclitaxel	Methoxy PEG-PLA/iv	Breast and lung cancer	Phase II
CALAA-01	Calando	Anti-R2	Cyclodextrin-containing	Solid tumors that are	Phase I

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