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NANOCARRIERS: A REVIEW

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ABSTRACT

Nanocarriers have the possibility of providing endless opportunities in the areas of drug delivery as Cell-specific targeting can be accomplished by attaching drugs to specially designed carriers with small particle size range. Various nanostructures, including liposomes, Micelles, dendrimers, silicon or carbon nanomaterials, and magnetic nanoparticles, have been tested as drug carrier nanoplatforms. This review embodies an in-depth discussion of nanocarriers with respect to types, formulation aspects, adavanced fabrication techniques, characterized methods to detect, and retrospectively summarizes the recent advancements in their clinical applications by using the nanomaterials are included in this review to emphasize the importance of nanotechnology in the current research scenario.

INTRODUCTION

Nanocarriers are colloidal drug carrier systems having particle size typically, <500 nm[1]. In recent advances nanocarriers have been extensively investigated as they showed great promise in the area of drug delivery and provides a variety of nanoplatforms. Nanocarriers, owing to their high surface area to volume ratio, have the ability to alter thier basic properties and bioactivity of drugs. Improved pharmacokinetics and biodistribution, decreased toxicity levels, improved solubility and stability, controlled release and site-specific delivery of therapeutic agents are some of the features of that nanocarriers can incorporate as drug delivery systems [2,3]. Furthermore, the physiochemical features of nanocarriers can be regulated by altering their compositions (organic, inorganic or hybrid), sizes (large or small), shapes (sphere, cube or rod) and surface properties (functional groups, surface charge, PEGylation or other coating, attachment of Targeting moieties) [4]. The overall goal of utilizing nanocarriers in drug delivery is to treat a disease effectively with minimum side effects [2].Tumors by exploiting the pathophysiology of tumor microenvironment, thereby significantly improving the therapeutic outcomes with targeting ligands [5]. They usually consists of macromolecular materials with the therapeutic agent either dissolved within a polymeric matrix, encapsulated, or adsorbed onto surfaces of particles, entrapped inside lipid and they can be classified as two types: nanocapsules and nanospheres. The former are vesicular systems in which drug molecules are surrounded by a membrane, whereas the nanospheres are matrix system with the drug molecules uniformly dispersed throughout [6].

TYPES OF NANOCARRIERS

Nanocarriers form three types such as organic nanocarriers, inorganic nanocarriers and

hybrid nanocarriers with high surface-to-volume ratio majorly. The structure and characteristics of different forms of nanocarrier are presented in Fig. 1.

LIPOSOMES: Liposomes have been first to be investigated as nanocarriers. They are nano/micro-particular or colloidal carriers, usually with 80–300 nm size range [7]. Liposomes are spherical vesicles with a hydrophilic cavity surrounded by one or several lipid bilayers that allows the encapsulation of drugs with different solubility. Hydrophobic drugs can be entrapped by the lipid bilayer and hydrophilic drugs can be encapsulated in the central aqueous core. Those containing one bilayer membrane are termed as small unilamellar vesicles or large unilamellar vesicles based on their sizes. If more than one bilayer (made of natural and synthetic lipids) is present, then they are called as multilamellar vesicles. Liposomes vary with respect to composition, size, surface charge and method of preparation [8].

SOLID LIPID NANOPARTICLES

Solid lipid nanoparticles (SLNs) are stable colloidal carriers prepared by high-pressure homogenization or microemulsification and generally made up of a solid hydrophobic core containing in which the drug is dissolved or dispersed. The main characteristics of SLNs have comparatively more entrapment efficiency, controlled drug release, stability of drug, prevents degradation and their production with good reproducibility. Smaller size (around 10 to 200 nm) and narrow size range (100 to 200 nm) allows them to cross tight endothelial cells of the blood-brain barrier (BBB), escape from the reticuloendothelial system (RES) and bypass liver [9]. SLNs have been extensively used as a carrier for several antitumor chemotherapeutic moieties. Due to their versatile properties they became as promising nanocarrier to minimize the drawbacks of conventional chemotherapy. Types of SLNs are the lipids in which they solid at body temperature includes SLN (solid lipid nanoparticles), NLC (nanostructured lipid carriers) and LDC (lipid drug conjugates) are types of carrier systems based on solid lipid matrix [10].

POLYMERIC NANOPARTICLES

Polymeric nanoparticles (PNPs) are structures with a diameter ranging from 10 to 100 nm. They are made up of natural polymers and synthetic polymers which are biodegradable and non biodegradable based on invivo behaviour[11]. Moreover, drug release by desorption, diffusion, or nanoparticle erosion in target tissue. In addition to being used directly as drug delivery carriers, polymers are commonly used for nanocarriers modification to improve their stability, biocompatibility and specificity. Reports show that higher entrapment efficiency in PNPs can be achieved by incorporation of drug during their preparation rather than adsorption on preformed nanoparticles [12]. Polymers approved by the U.S. Food and Drug Administration (FDA) for administration in human beings are polylactic acid (PLA), poly(glycolic acid) (PGA), PLGA, poly-ecaprolactone, and poly(methyl methacrylate). A variety of therapeutic agents like anticancer drugs, protein and peptides, vaccine, and so forth, can be effectively delivered and targeted through PNPs Bioavailability of the other protein and peptide drugs can be improved using suitable mucoadhesive polymers.

DENDRIMERS:

Dendrimers are highly tree like branched, monodisperse, and uniformly distributed polymeric macromolecules with unique host-guest entrapment properties possessing both hydrophobic core and hydrophilic surface; therefore, drug molecules. Theyare unimolecular, monodisperse, micellar nanostructures, around 20 nm in size, with a well-defined, regularly robust, covalently fixed, three dimensional structures consists of three distinct architectural regoins solvent filled initiator core, layers of branching units and surface active high density of functional end groups at their periphery[13]. Drugs can be loaded to the cavities in the dendrimers cores through hydrogen bonds, chemical linkages or hydrophobic interactions. Each level of added branches to the core throughout the synthesis process is called as a generation. Dendrimer–drug conjugate is formed when the drug is covalently bonded to a dendrimer at the core or on the terminal groups prominently effective concentration of drug reached at the target site Being monodispersed, structurally controlled macromolecules with a definite size and molecular weight, dendrimers–drug conjugate is a carrier of choice over conventional polymeric drug delivery carriers. Recently, they have been

extensively used as targeting, imaging and also in fields of biomedicine, including gene delivery, immunology, magnetic resonance imaging, vaccines and antibacterial, antiviral and anticancer drug delivery[14].

MICELLES:

PMs are nanosized (10–100 nm) colloidal particles formed by the self-assembly of synthetic amphiphilic molecules with nonpolar tail (hydrophobic) facing the centre and polar head (hydrophilic) having contact with the aquous media forms micelles at abobe certain temperature called critical micellar concentration(CMC)determines the proper micelle formation[15]. Below the critical micellar concentration, proper micelle formation will not occur. Along with amphiphilic molecules, polymeric micelles are formed in certain solvents by means of two copolymers, insoluble copolymer forms the core and soluble copolymer forms the shell in which the copolymer form the chain or micellar aggregate. Hydrophobic core of PMs allows the entrapment of hydrophobic drugs and controls the drug release of PMs. However, the hydrophilic shell of serves to stabilize the core, ensures the PMs' solubility in the aqueous media and controls in vivo pharmacokinetics. Compared with liposomes, micelles are considered to be more suitable for poorly water soluble drugs [16]

METALIC AND INORGANIC NANOCARRIERS

GOLD NANOPARTICLES

Gold nanoparticles are most promptly used due to their excellent optical and photoelectric properties.Moreover, gold exhibits some specific advantages, like inertness and nontoxicity, higher stability, ease of preparation, and possibility of bioconjugation and biomodification with thiol, disulfide, and amine functional groups. They are extensively used in cancer therapy and in gene delivery. There are different anisotropes of gold nanoparticles like nanostar, nanorod, nanocage, nanoshell, nanoprism etc.[17].

QUANTUM DOTS (QDS)

Quantum dots (QDs) are colloidal semiconductor nanocrystals and coreshell nanocrystals containing interface between different semiconductor materials size up to 2 to 10 nm composed of atoms from groups II–VI or III–V of the periodic table are having unique optical and fluorescent properties. Those most commonly used are cadmium selenide (CdSe), cadmium telluride (CdTe), and indium arsenide (InAs).

Their core can serve as the structural scaffold, the imaging contrast agent and small molecular hydrophobic drugs can be immersed between the inorganic core and the amphiphilic polymer coating layer. Hydrophilic therapeutic agents including small interfering RNA (siRNA) and antisense oligodeoxynucleotide (ODN)) and targeting biomolecules such as antibodies, peptides and aptamers can be immobilized onto the hydrophilic side of the amphiphilic polymer via either covalent or non-covalent bonds due to their small size. Upon their interaction with photon, they get excited and emit energy in UV, visible, or near-infrared (IR) regions, which can be detected. Among different elements, dihydrolipoic acid (DHLA)-coated cadmium selenide-zinc sulfide (CdSe- ZnS) QDs have shown a more stable fluorescent intensity and higher photosatbility[18]. Continuous use of QDs under certain conditions, like high radiation exposure or ultraviolet oxidation, may lead to the leakage of cytotoxic cadmium ions from CdSe QDs, thus generating oxidative free radicals, which could be lethal to liver and kidney cells.

CARBON NANOTUBES

They are tube like hollow structures single walled or multi-walled carbon nanotubes containing sheets of graphene rolled together at discrete and specific angles. The cross section of these tubes can be 0.4–100 nm in diameter while the length of the tube elongates thousand times the diameter. In drug delivery process, this carbon nanotubes has a wide applications through its distinct characteristics such as high aspect ratio, ultralight with high surface area, nanosized needle structure, distinguished chemical, thermal, mechanical and electrical properties[19]. Carbon nanomaterials like carbon nanotubes (CNTs), fullerenes, carbon NPs, graphenes, carbon nanocaps, and carbon nanohorns, nanodiamonds exhibit electronic, mechanical, optical, and magnetic characteristics that appear from the p-electron cloud combined with their particular architectural structures.

The functionalized nanotubes are water soluble with long circulation period in the serum and non-functionalized carbon nanotubes are toxic and water insoluble in nature. The structural

stability, flexibility and surface modification enable it as a suitable agent to target the cancer cells. In that concept, functionalized carbon nanotubes are widely used to encapsulate or link with anticancer drugs like Paclitaxel Graphene is another important carbon based nanocarrier which is efficient in drug delivery[20].

MESOPOROUS SILICA NANOCARRIERS

Mesoporous silica has been used as a targeted nanocarrier due to its large pore volume with high surface area, high encapsulation efficiency, controlled structural properties, and biocompatibility, and thermochemical stability. In cancer treatment, both active and passive targeting can be successfully carried out through this mesoporous silica[21,22]. Due to its simplicity and availability, it has a tremendous application in the biomedical field. It can encapsulate both the hydrophobic and hydrophilic drugs which can be attached to a ligand molecule for targeted drug delivery.

NEED FOR NANOCARRIERS FOR DRUG DELIVERY: AN OUTLINE

Different kinds of nanocarriers responsiveness to various stimuli, have been developed with well designed chemical composition or physical structure, these nanoscale drug delivery systems can be triggered by either intrinsic (e.g. pH, redox, and enzyme) and external or physical (e.g. light, magnetic field, magnetic force, electricity, temperature, mechanical agitation, or ultrasound),) stimuli, thus providing spatiotemporally controllable drug release to potentiate the anti-cancer efficacy [23].

Thermoresponsive nanoparticles

Heat and temperature are the most prevalent parameters adopted to trigger the release of medicines in a stimulus-responsive drug-delivery strategy that is spatiotemporally regulated. The hyperthermic character of most infected pathological areas and also tumors may possibly represent an interior stimulus. Appropriate exterior temperature adjustments can likewise be used to switch on thermoresponsive NPs, offering an appealing choice for a stimulus-responsive drug-delivery system, and NPs can swiftly respond to temperature alterations. Another significant potential of these kinds of drug delivery is implantation in the infected tissue and cells. The effective drug-delivery system must retain its load in improper situations and locations and discharge the medicine, with regulated kinetics, inside the target cells and tissues, for example, tumors.

Magnetic-responsive nanoparticles

The power of magnetism is seen as undoubtedly one of the best alternatives for an exterior stimulus because it hardly carries any kind of physical interaction with the entire body, compared with some other stimuli, for example, light irradiation and other types of electrical fields. Individual domain NPs with inherent superparamagnetic abilities above their controlling temperature (blocking temperature) are dubious applicants for biomedical requirements in comparison with ferromagnetic NPs, in as far as they exhibit absolutely no dipolar attraction within magnetic fields but possess good-quality colloidal stability, with uniform distribution and dispersion within an appropriate polymeric matrix [24].

Electrical-responsive nanoparticles

Electrically governed drug-delivery based on nanomaterials can be applied for continuous, 00pulsed, or as-required medicine release by making use of stimulated external electric fields. Electroresponsive medicine release is usually carried out with a variety of media such as electroresponsive nanostructures, electroresponsive compound-loaded materials, or the combination of electroresponsive materials with vehicles responsive to various stimuli, including temperature as well as magnetic field influences. The inclusion of polyelectrolytes containing a wide variety of ionisable species confers response to an electrical stimulus by means of tapering or even expansion of the polymers. To illustrate, Ying et al. designed electroresponsive hydrogel NPs for specifically targeted delivery of an antiepileptic medicine. A heightened level of ionization in the structure was accomplished under the effect of an electric field because of the presence of the polyelectrolyte poly(sodium 4-vinylbenzene sulfonate). The swelling ratio and particle size can be adjusted using the exterior electricfield. Researchers at Nagoya University (National University of Japan) found another way to generate stimulus-responsive materials in a foreseeable manner. These researchers employed the following procedure to design a unique material: an assortment of carbon nanorings together with iodine was assembled, which was

electrically conducting and also irradiated white light once it was subjected to electricity. The modern strategy could assist in producing a group of reliable stimulus-responsive materials that can be used in storage devices, in synthetic muscles,and as pharmaceutical delivery systems [25,26].

Light-responsive nanocarriers

Light with a specific wavelength has been extensively used as an external stimulus for triggering on-demand drug delivery due to its non-invasiveness and spatiotemporal precision. Recently, a visible light-responsive drug delivery MSN was designed, and drug release and antitumor activity of this smart nanocarrier were evaluated in osteosarcoma cells. The pore outlets of drug-loaded MSN were restricted with porphyrin nanocaps through ROS-cleavable linkages. Upon visible light irradiation, porphyrin nanocaps could produce ROS species that are able to break the sensitive bonds and therefore triggering pore uncapping and allowing drug release. However, limited tissue penetrating capability of this short-wavelength light is the main drawback for In vitro and In vivo experiments. Near infrared (NIR) light has acquired substantial interest in photoactivated drug delivery due to its unique advantages such as deep tissue penetration and low risk of photo damage [27]. Among the number of stimuli used in worthwhile drug-delivery systems, light irradiation sparks considerable interest because of the simplicity of tuning its intensity, the capability to regulate the exposure time as well as the specific location of the tissue, the choice of desirable beam criteria, and the indisputable fact that photoregulated stimulation is considered noninvasive. UV (10e300 nm), visible, or even near-infrared radiation zones (650-900 nm) of the light spectrum are often used to prompt pharmaceutical or gene release from properly developed nanocarriers [28].

pH-responsive nanoparticles

It is actually well established that considerable pH gradients can be found throughout the entire body (particularly the gastrointestinal system tract); significant pH variations really exist and these pH rates fluctuate among the lysosomes (4.5-5), endosomes (5.5-6), Golgi apparatus (6.4), and cytosol (7.4). pH differences may be caused by the presence of microbes; there is certainly an acidic milieu in healing wounds and also an alkaline milieu in nonhealing injuries [29]. These pH-sensitive nanocarriers could store and stabilize antitumor drugs at physiological pH, but rapid release of the drugs at an acidic environment by the introduction of acid-sensitive linkers such as acetal, hydrazone, and glycerol ester groups.

Redox-responsive nanoparticles

Redox-responsive drug-delivery systems are one of the more beneficial techniques for stimulus-responsive tumors as well as gene treatment. Redox-sensitive degradable nanosystems render certain positive aspects over many other stimuli including pH. An excellent response to excessive intracellular amounts of blood glutathione, the release of medicine directly into the nucleus and cytosol, and consistency in extracellular surroundings in which blood glutathione ranges are at minimum are examples of these benefits. The redox surroundings are influenced by a connected group of redox partners, for example, NADPþ/NADPH. The cytoplasm possesses consistent metabolic oxidases, which make an environment for redox signaling that is affected by nitric oxide synthases and NADPH oxidases. Mitochondria in each cell almost all have reducing contents because they are tremendously sensitive to oxidation. The amount of electron transport in mitochondria is greater than in various other cellular spaces. Nuclei are very resilient against oxidation; however, they possess lower redox potentials. The secretory path provides disulphide bonds in proteins that can be exported, through the effects of oxidizing systems and enzymes. The redox possibilities of a cell are typically influenced by the functional state of the cell, most notably the induction of apoptosis, differentiation, adhesion, and proliferation [30].

Hybrid nanocarriers

Hybrid nanocarriers are nanocarriers combining two or more organic and inorganic nanocarriers together or individually. It includes organic–inorganic, inorganic–inorganic, multi components. Some of the examples are a lipid-polymer hybrid, ceramic-polymer hybrid etc. incorporating two nanoparticles together will possess the dual nature of both the nanoparticles enhancing its properties [31]. In the case of organic nanocarriers like liposomes, having internal solution leakage as well as less stability. This makes it to be removed easily from the circulating blood. Therefore, additional

stabilization is required. Hence hybrid nanocarrier systems are useful in those cases. There is different research works carried out. The mesoporous silica nanoparticle lipid bilayer hybrid nanocarrier system has showed a distinguished intracellular delivery of zoledronic acid in the breast cancer with high retension rate. This system enables a stimuli-response release of drug preventing the premature release of drug into the body and having benefit of long stability with high cellular uptake and is efficient in the theranostic application for gene silencing [32].

POLYMERS USED IN NANOCARRIERS

Natural polymers: Chitosan,Alginate,Cellulose.

Synthetic polymers:

Synthetic polymers like polyvinyl alcohol, polyurethanes, poly acrylates, synthetic biodegradable polymers (Polylactide (pLA), polyglycolide (pGA), polyesters). For example, polyethylene glycol makes the nanoparticles target-specific, enhanced permeability, enhances sustain release of drug and retention effect (Matsumura and Maeda 1986; Petros and DeSimone 2010).

PREPARATION OF NANOCARRIERS.

High-pressure homogenization

High-pressure homogenization is widely used reliable and powerful technique for the large-scale production of nanostructured lipid carriers (NLCs), lipid drug conjugate (LDC), solid lipid nanoparticles (SLNs), and parenteral emulsions. Homogenization process is performed either at elevated temperature (hot homogenization for lipophilic drugs) or below room temperature (cold homogenization for hydrophilic drugs). The lipid is homogenized at high pressure (100 to 2000 bar) under high shear stress, which results in disruption of particles down to the submicrometer or nanometer range[33]. In this method, lipids and poorly water soluble drug are melted at 5–10°C above its melting point and aqueous solution of emulsifier is also heated at the same temperature. Both liquids are mixed with constant stirring and homogenized under high pressure. According to desired particle size range, Number of cycles and pressure can be varied and 500bar for three homogenization cycles is proved efficient with monodispersed particles and narrow size distribution.

Solvent evaporation

This method is also known as precipitation method in which lipid is allowed to precipitate from the o/w microemulsion. In brief, the lipid is dissolved in water immiscible organic solvent that is emulsified in an aqueous phase containing emulsifier to obtain o/w microemulsion. Once the microemulsion is formed, subsequent solvent evaporation is performed to achieve the nanoparticle dispersion by precipitation of the lipid in the aqueous medium. It does not utilize heat and therefore applicable to thermal sensitive drugs. There are chances of organic solvent residues in the final dispersion.

Solvent diffusion

Depending upon the physicochemical properties of the drug and lipid in organic solution, the temperature, mixing speed, lipid-to-organic ratio, and organic-phase-to-aqueous-phase ratio can be adjusted and optimized to achieve the lipid nanocarriers with desired characteristics.

The resulting organic solution can immediately be poured into an aqueous emulsifier solution under stirring. Similar to solvent evaporation technique, microemulsion is obtained, and then instead of evaporating solvent, water dilution is performed, which leads to the formation of nanoparticles. This method is a modification of solvent evaporation technique[34].

Phase inversion technique: In this method, a two-step process in which by heating the aqueous phase and the lipid phase separately above their melting point and then the aqueous phase is added dropwise while mixing at a particular temperature higher than the phase inversion temperature to the lipid phase then primary w/o emulsion is formed. The emulsifier leads to an emulsion inversion from w/o emulsion to an o/w emulsion when temperature is above its phase inversion temperature. In general, total of three temperature cycles (85–60–85°C) are performed to reach inversion process insplace of shock cooling. This method has also been widely used for the preparation of lipid nanocarriers including SLNs, NLCs, and LDCs [35].

Complex coacervation methods: Complex coacervation is a spontaneous phase separation process of two liquid phases in colloidal systems, which forms by the interaction of two oppositely charged polyelectrolytes upon mixing in an aqueous medium. The process leads to the formation of micrometric or nanometric colloidal particles depending on the process

variables such as pH, temperature, molecular weight, ionic strength, polyelectrolyte concentration and so forth. However, this method exhibits poor drug stability and less drug loading efficiency, which can be improved by cross-linking of the complex by chemical reagents, such as glutaraldehyde [36].

Solvent emulsification–diffusion method: Solvent emulsification–diffusion (SED) is the most commonly used method for preparation of SLNs and PNPs. An o/w emulsion is prepared with oil phase containing polymer along with oil in organic solvent and emulsified with the aqueous phase, containing stabilizer, in high shear mixer then followed by addition of water to urge the diffusion of organic solvent thus resulting in formation of nanoparticles. The selected organic solvent must be partially soluble in water (for diffusion step) and have the capacity to dissolve both the oil and polymer.

Supercritical fluid technique: Super critical carbon dioxide solution is usually used as a solvent for coating drug molecules with phospholids which must have good solubility with liquid carbon dioxide. These solid lipid compounds mixed with liquid carbon dioxide in high pressure chamber until they dissolves. After they dissolved, the chamber should be depressurized to convert the fluid to gaseous state. As the liquid carbon dioxide gets converted to the gas, subsequent precipitation of the lipid takes place on the crystal surfaces leading to the formation of drug-loaded lipid nanoparticles [37]. Recent advances in SCF process are to create nanoparticulate suspension of particle size of 5 to 2000nm in diameter.

CHARACTERISATION OF NANOCARRIERS

Particle size distribution and morphology

Smaller particle size offers larger surface area hence faster drug release takes place at target site. Various techniques to determine the particle size are dynamic light scattering (DLS), scanning electron microscopy (SEM), transmission electron microscopy (TEM), Atomic force microscopy, differential mobility analysis, electroacoustic spectroscopy, Turbidity method, Nuclear magnetic resonance, Filtration etc.

Dynamic light scattering (DLS): This method is also known as photon correlation spectroscopy which is popularly and widely used to determine the size of Brownian nanoparticles to submicron or nano ranges causing the dopler shift, determines the diffusion coefficient using autocorrelation function. This method is frequently used to estimate the particle size and size distribution accurately [38]. The intensity-average hydrodynamic diameter and polydispersity index of nanocarriers was estimated by preparing their aqueous dispersion in double distilled water, analyzing it before and after filtration using DLS or malvern zetasizer instrument.

Surface charge: The surface charge of nanocarriers determines their interaction with the biological environment and electrostatic interaction with bioactive compounds. It depends on certain factors like strength and valency of the ions, pH, and hydrogen ion concentration in the medium. Zeta potential (positive or negative) values have a significant role in stabilizing particle suspension and avoids aggregation of particles.Zeta potential of ±30mV indicates particle stability, where >30mV infers the stable condition and <30mV infers instability, aggregation, flocculation, etc.[39]. However, it has the drawback of electro osmotic effect that will reduce the precision and reproducibility of the measurement.

Entrapment/incorporation efficiency: Nanocarriers were solubilized in solvent and analyzed after filtration and suitable dilution for estimation of entrapment efficiency by a suitable technique estimated to optimize the drug entrapment in nanocarriers. The incorporation efficiency was calculated as % drug content by using Eq. (1),[40].

Incorporation efficiency = Amount of drug in nanocarriers/Initial amount of drug×100… (1)

Chemical composition: Knowing the chemical composition of nanomaterials has become a fundamental descriptor and it is also a regulatory requirement in all jurisdictions. It determines the purity and performance of the nanocarrier. Generally, the composition can be measured by X-ray photoelectron spectroscopy (XPS). Other methods involve chemical digestion of nanoparticles followed by wet chemical analysis using mass spectrometry (MS), atomic emission spectroscopy, or ion exchange chromatograph.

Fig. 1 Examples of nanocarriers. Different types of nanocarriers such as inorganic nanocarriers: single walled carbon nanotube, gold nanocarrier, magnetic nanocarrier, quantum dot, mesoporous silica nanocarrier; organic nanocarriers: solid lipid nanocarrier, liposome, dendrimer, polymeric nanocarrier; and hybrid nanocarrier: polymeric-lipid nanocarrier.

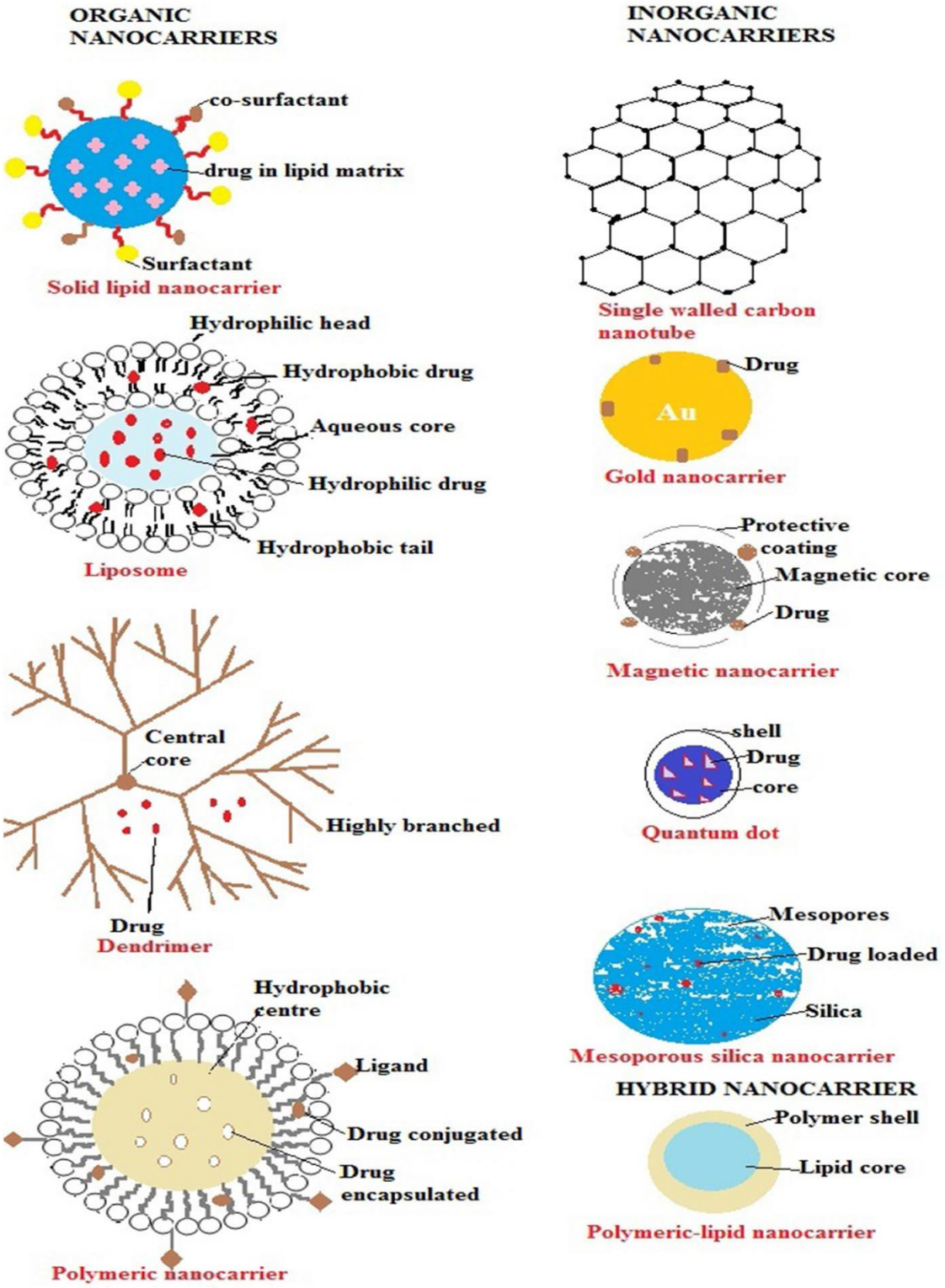

TABLE 1: List of drugs

Nanocarrier System	Polymers	Drug	Preparation Method	Therapeutic Benefit
SLNs (Solid lipid nanoparticles)	Stearic acid in 0.1% Poloxamer 188	Insulin	Hot homogenization	80% entrapment efficiency
PNPs (Polymeric nanoparticles)	PLGA	Dexamethasone	Solvent evaporation	Sustained release for 10 days
PLMs (phospholipid micelles)	DSPE-PEG2000 plusegg phosphatidylcholine	Indisulam	Coprecipitation	40-fold indisulam more solubility
NCLs (nanosized colloidal liposomes)	DOPE-glycol chitosan liposome	Nasal DNA vaccine	Dehydration-rehydration method	53% entrapment efficiency
QDs (Quantum dots)	Fluorescent QDs withHER2 cellular marker	Diagnosis of breast cancer	QDs conjugated with cellular markers	Multiple molecular targets in cancer therapy
SLNs	Compritol 888-Tween80	Tretinoin	Hot homogenization	Prolonged anti-inflammatory effect
MNPs (magnetic nanoparticles)	Dextran-coatediron oxide	Cancer treatment	Co-precipitation followed by separation	74% to 95% drug entrapment
Metal and inorganic nanoparticles	Au nanoparticles conjugated with anti-EGFR antibody	Chemotherapy	Surface coatingwith immunogold NPs	Photodiagnosis and photothermal cancer therapy
Dendrimer	PAMAM (polyamidoamine)	Propranolol	Cascade reaction, either convergent or divergent approach, self-assembly	Hypertension
PNPs	PBLG-PEG diblock co- polymer	Paclitaxel	Solvent evaporation	90% drug encapsulation efficiency
PMs (polymeric micelles)	Pluronic-PAA micelles	Solid tumor treatment	Copolymerizatio n	Increase solubility of hydrophobic drugs

Surface chemistry

Surface chemistry refers to the chemical nature of the nanomaterial surface in terms of functional groups and elements. As they have large surface area, the interaction between their surface and surroundings will be more than the bulk materials. Techniques such as ultraviolet-visible (UV-VIS) or Fourier-transform infrared (FTIR) spectroscopy are available to analyze the composition of the entire particles [41].

***In vitro* permeability or penetration study**

In vitro permeability of drug-loaded nanocarriers was estimated through drug is diffused through a synthetic or biological membrane(donor compartment) into the receiver medium (filled with a suitable solvent) maintained at desired pH and temperature (370 C) against time using a Franz diffusion cell kept under suitable stirring. At predetermined time

intervals, aliquots from receiver compartment were withdrawn and analyzed by the suitable spectroscopic method for determination of drug content. On the other hand withdrawn volume of aliquots was subsequently replaced with a fresh solution. Further, the flux through the predefined area of the skin surface was estimated from the plot of the cumulative drug amount diffusing or permeating the human stratum corneum epidermis against the time. Effect of different factors that affect the drug permeability through the membrane such as the type of vehicle, exposed skin surface area, volume of the receiver compartment, physicochemical properties of drug (e.g., solubility, pKa, log P), etc.

Stability studies

Stability of a nanocontainer depends on various factors such as solvents, light, temperature, moisture, enzymes, impurities, radiation exposure, etc. Stability of a dosage form refers to the retention of the same properties over a time period without degradation after the product is manufactured [42]. Ideally, a nanocontainer should be stable in the bloodstream until it reaches the target and so its stability evaluation becomes an important aspect for a successful drug delivery system. Moreover, instability of nanoparticles leads to premature drug release and altered biodistribution, ultimately affecting the product's efficacy. The procedures for stability study of new drug products, new dosage forms and on biotechnological-based drug products are practicable in the ICH guidelines Q1A (R2), Q1C, and Q5C, respectively.

***In vivo* parameters**

These include longevity, targetability, biodistribution, cellular uptake, dose response, oral and relative bioavailability, pharmacokinetics, drug delivery and diagnostics, safety, efficacy, toxicity, and specific pathological activity testing, etc.

***In vivo* biodistribution and pharmacokinetics**

Pulmonary delivery of nanocarriers was studied earlier for the study of effective drug transport at the desired site of action. Cell uptake, as well as distribution studies, also include the study of cell binding, nanocarrier internalization, and receptor targeting.

Toxicity studies

In vitro and *in vivo* tests for nanocarriers were used to match their physicochemical parameters with biological function. In vitro testing for clinical or biomedical use (in vivo diagnostics, therapeutics, etc.) needs to be tested in animals due to similar physiology in humans. In vivo tests in animals gave faithful therapeutic outcomes of the nanocarriers inside the body. Some of these in vivo tests for nanocarriers include dose response relationship; acute and multidose safety and efficacy; biodistribution; determination of route of administration; and Distribution, Metabolism, and Excretion (ADME) [43].

APPLICATIONS OF NANOCARRIERS

Nanocarriers in drug delivery

Many drugs have poor solubility and low bioavailability to release at their target level then cleared by reticuloendothelial system in the body and use of pharmaceutical active agents frequently limited by drug resistance owing to physiological barriers cellular mechanism is encountered as shown in Table 1. Furthermore efficacy of different drugs have dose dependent side effects.

Brain: brain is the probably least accessible to most of the drugs like exogenous and endogenous compounds and control their transport due to the presence of blood-brain barrier (BBB). Drugs unable to cross the barrier and could be delivered after binding to surface modified poly (butyl cyanoacrylate) PBCA nanoparticles. PEGylated nanolipsomes and SLNs loaded with galantamine and memantine showed enhanced brain targeted delivery with neuroprotective properties for Alzheimer's disease.

Gastro intestinal tract: The smaller the particles, the faster they can diffuse through gastrointestinal mucus and their uptake to reach blood stream to facilitate all over the target sites. Targetting strategies to interact the nanocarriers with absorptive sites like enterocytes, M-cells of payers patch utilizes specific binding to ligands or receptor or nonadsorptive mechansims. Enterocytes and M cells surface have certain cell specific carbohydrates which can serve as ligands to many nanoparticulate drug carriers [44].

Respiratory tract: lung is the most effective and convenient delivery of various therapeutic drugs

as it is more advantageous due to non-invasive administration via aerosols, avoidance of first pass metabolism and delivery to the site of action to treat various pulmonary disorders like asthma, tuberculosis, Chronic obstructive pulmonary disease (COPD) etc., nanocarrier systems provide more surface area for local action and systemic circulation, provides sustained release to reduce dosing frequency, improves patient compliance.

1. Based on several investigations, metallic NPs such as Au and TiO2 have been suggested as potential nanocarriers for COPD treatment[45].
2. Noninvasive nanoparticle-mediated high-contrast imaging methods may be promising for the diagnosis of pulmonary inflammation[46].
3. A particle size below 1 μm is suitable to deliver the drugs to the pulmonary alveoli.The use of neutral NPs as drug delivery vehicles is the most common approach in anti-TB therapy.

Nanomedicines in cardiovascular diseases

Importantly, nanomaterials avoid rapid renal excretion and remain in circulation for extended durations. This characteristic feature facilitates extravasation through the vascular system and allows nanomaterials to accumulate and distribute well in the desired tissue or organs, thereby achieving maximum therapeutic efficacy at minimum drug dosage for cardiovascular diseases (CVDs). For treating Myocardial ischemia-reperfusion injury, ONO-1301 NPs helped down regulate troponin I along with the inflammatory cytokines IL-1β, IL-6 and tumor necrosis factor-α, which eventually led to enhanced myocardial blood flow and reduced infarct size. Myocardial blood flow was significantly improved, and upregulated pro-angiogenic cytokines (e.g., vascular endothelial growth factor and angiopoietin-1) were reported in the ischemic myocardium, which preserves the dense vascular network and facilitates myocardial blood flow [47].

Targeted Cancer therapy

Cancer is a very complicated biological phenomenon, and can be considered a disease of many diseases. Cancerous cells are that they divide and multiply rapidly and out of control. Common features of tumors include leaky vasculature and poor lymphatic drainage. Several methods (nanocarrier) have been proposed for targeting tumors, e.g., the enhanced permeation and retention effect where the leaky vasculature promotes the permeation of small molecules. While there are several other forms of nanoparticles that have shown promise in cancer treatment, like liposomes, polymer based nanoparticles, micelles, dendrimers etc., one of the most recent system is the carbon nanotubes. Buckminsterfullerene C60 (spherical molecule) and its derivatives are determined for the treatment of cancer [48].

Diagnosis and bioimaging

Eventhough there are number of molecular imaging techniques available, like optical imaging (OI), magnetic resonance imaging (MRI), Ultrasound imaging (USI) and CT scan etc., nanocarrier system is promising, bioimaging technology for diagnosing various diseases as well as organs. Current developments in luminescent nanoprobes for OI, magnetic nanoparticles for MRI, Gold nanoparticles to detect cancer biomarkers.

Nutraceutical Delivery

Nutraceuticals are lipophilic molecules such as fat-soluble vitamins (A, D, E and K), polyunsaturated lipids and other phytochemicals. Nanotechnology again offers comprehensive assistance and most of the investigations have been focused at improving the dissolution mechanism of nutraceuticals via nanoparticle formulations.

Nanoparticles in retinal therapy

Nanoparticles can deliver genes effectively to stem cells and have been explored as a means of gene delivery in the diagnosis and treatment of ocular disease. A description of nanocarriers used in the field of retina, aiming on cyclodextrin nanoparticle suspension, liposomes, nanospheres and nanoemulsions have been provided. The use of nanoparticles for gene therapy has also been highlighted [49].

CONCLUSION

Nanotechnology enabled as promising technology in health care and medical related applications however drug delivery is emerging prospective future in pharmaceutics as in delivering therapeutic agents like oral delivery of proteins and peptides, targeted cancer therapy, and biosensing, bioimaging like invivo tumor imaging. This effective nanoformulations can made effective impact on all routes of administration from oral to rectal, this is being made possible through the use of advanced material, improved control of particle size, and better understanding of interface between the biological and material surfaces, and their

effects in vivo. Some nanoparticle based products are already approved by the US FDA; some others are currently under development and clinical assessment.

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