UTILIZATION OF ULTRABRIGHT NANOCARRIERS IN BIOIMAGING TECHNIQUE

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ABSTRACT

The review article focuses on development and pharmaceutical applications of ultrabright nanocarriers in advanced drug delivery due to their biocompatibility, size, target-specificity and increased efficacy properties. These include dendrimers, polymeric micelles, solid-lipid nanoparticles, C dots, integrins etc. Their objective is safe and effective delivery of highly hydrophobic drugs, improving their pharmacokinetics as well as bio-distribution potential, thus minimizing their potential toxicity. Various researchers have emphasized on the assembling organic molecules into biodegradable nanoparticles featuring much higher brightness than single dye molecules. Modifications in nanoparticles have been implemented to change the color in response to single biomolecule such as proteins and nucleic acids. Nanoparticle technology has been as an analytical tool in both cancer cell research and medical diagnostics.

Keywords: Ultrabright Nanocarriers, Cancer therapy, Nanoparticles, Polymer dots, Silica Nanoparticles

INTRODUCTION

The common diseases of neurodegeneration, cancer, cardiovascular disease, and musculoskeletal disorders are particularly dangerous for the elderly. Advanced theragnostics, or instruments that blend diagnostic tests and therapeutic treatments, can be used to quickly identify these problems and cure them, allowing patients to live long and active lives [1]. The possibility for the development of target-oriented carriers that precisely identify even the tiniest patches of tissue defective in the very early stages of the disease is offered by the fast-expanding class of ultrabright carriers known as photoluminescent (PL) carbon dots (C-dots). These ultrabright nanocarriers penetrate the diseased cells and release the medicine in a controlled manner as soon as they identify the malignant or unhealthy lesions, acting continually as surveillance nanoprobes to track the efficacy of the treatment in real time [2].

SIGNIFICANCE OF NANOCARRIERS AS DRUG DELIVERY SYSTEMS [3]

1. Improvement in water solubility, stability of a number of therapeutic agents like peptides.

2. Enables the drugs to remain in circulation for longer period of times bypassing the Endosome Lysosome processing.

3. Good compatibility with cells and tissues.

4. These are GRAS (Generally Recognized as Safe) excipients.

Formulation Approaches of Nanocarriers [4]

A number of techniques have been utilized for the synthesis of nanocarriers (table 1 and figure 1).

Table 1: Various approaches for nanocarriers

S. No.	Nanocarriers Approaches	Description
1.	Top down Approach	Involves the breaking down of larger particles into smaller nanosized particles through milling, grinding or by use of laser.
2.	Bottom up Approach	Create huge aggregates with precipitation, antisolvent techniques etc.
3.	Co-precipitation	Involves a complex Coacervation method thus aiding the preparation of nanoscale core-shell particles, which provides good dispersion stability to highly insoluble drugs.
4.	Solid Lipid Nanoparticles	Spherical with an average diameter between 10 and 1000 nanometers. They possess a solid lipid core matrix, can incorporate both hydrophilic and hydrophobic drugs, avoid organic solvents, uses physiologically biocompatible lipids leads to improved bioavailability and enhanced controlled release characteristics.
5.	Lipid-Drug Conjugates	Promising nanoparticles which can overcome low capacities to load hydrophilic drugs due to partitioning effects. An insoluble drug-lipid conjugate is synthesized either by salt formation (with fatty acid) or by covalent linking (to ester). Conjugate is then subjected to processing by any surfactant solution, which then yields a nano-formulation using high pressure homogenization. These particles may have wide-spread applications in brain targeting of these drugs in protozoal infections.
6.	Polymeric Micelles	Core-shell structures created by spontaneous self-assembly of the Amphiphilic di/tri-block copolymers at concentration above a known specific concentration, which is also called as the Critical Micellar Concentration (CMC).
7.	Dendrimers	Highly monodispersed, branched with prolific drug entrapment properties. They possess multi-dimensional properties such as the presence of a hydrophobic core and hydrophilic surface thus providing a better loading platform for both hydrophobic as well as hydrophilic drugs. They can be easily conjugated with imaging and also targeting the agents owing to their multi-branched structures. Because of these favorable binding characteristics, they serve as excellent carriers for chemotherapeutic agents.

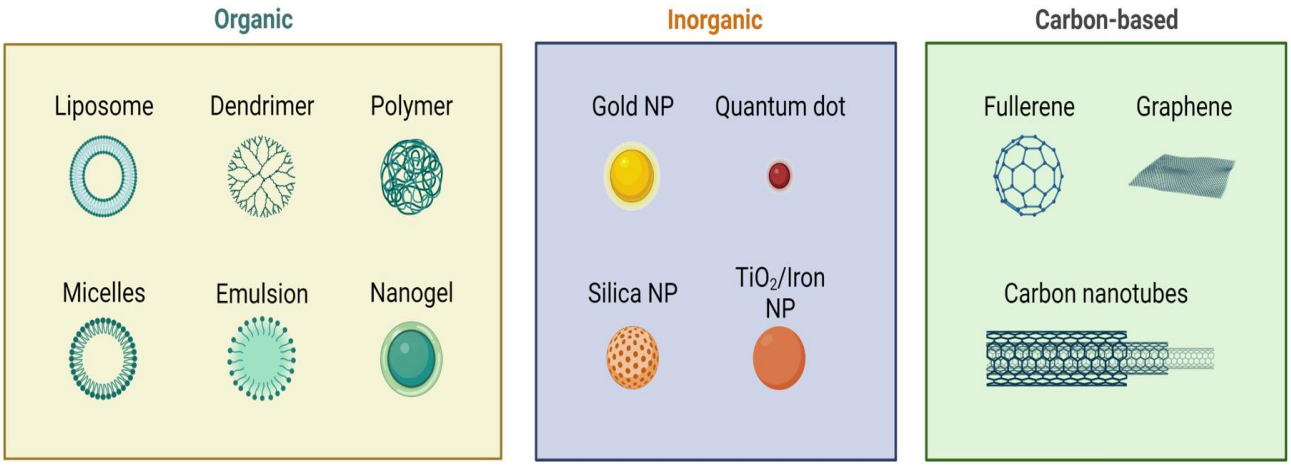

Figure 1: Different Types of Nanocarriers (Diagram created with the Biorenders software Licence number - Student Plan - OV24XQ9HD4)

FLUORESCENCE IN NANOTECHNOLOGY

A substance that has absorbed light or other electromagnetic radiation will emit light when it undergoes fluorescence. It has a luminescent quality. Most of the time, the released light has a longer wavelength and less energy than the radiation that was absorbed. It is a potent tool for real-time, high-resolution mapping of biological phenomena. Fluorescent probes are molecules that examine biological material by absorbing light of a particular wavelength and emitting light of another, usually longer, wavelength. High sensitivity requires ultra-bright probes, which are often produced by combining a large number of fluorophores onto a single nanoparticle (NP). Colloidal particles' fluorescence is commonly produced by adding fluorescent inorganic or organic dyes to the particle's makeup [5].

Nanoparticles have primarily been used as basic labels rather than as biomolecules probes up until now. The creation of novel methods for the detection of proteins and nucleic acids has always been necessary. We aim to directly identify biomolecules in living cells, whereas the current approaches typically need for fixing or even destroying the cells at the cellular level [6]. New possibilities for cell analysis in biomedicine are provided by nanoparticles. These are frequently tiny enough to enter live systems, including individual cells and disease targets. Because fluorescent particles are more visible than organic dyes, they seem to be suitable replacements for fluorescent molecular probes already in use. Bright nanoparticles, on the other hand, are typically non-biodegradable and incapable of responding to single molecule stimuli.

The following criteria apply when selecting nanoparticles for use in fluorescence imaging [22]:

(a) Plain imaging

(b) Targeted (cellular) imaging

(c) NPs for use in chemical sensing

(d) NPs for use in imaging of temperature (T)

(e) NPs for use in multimodal imaging

(f) NPs for use in optical imaging

(g) Bioimaging

(h) Optical bio-imaging

(i) Fluorescence bio-imaging

Successfully created ultrabright fluorescent organic nanoparticles (FONs) are able to combine the responses of numerous dyes into a single, easily observable particle in response to a single biomolecular stimulus. Organic dyes and inorganic quantum dots, which are semiconductor particles with a diameter of between five and fifty nanometers (nm), are used in fluorescence bio-imaging. They are often not degraded in the body once injected and are orders of

magnitude brighter than the dyes. The use of Ultra-Bright Nanoparticles generated from polymer drug-delivery vehicles, which may go to intracellular places since they are organic and are therefore biodegradable and of low toxicity, is correcting this imbalance, though. These also respect the environment [6]. Solvatochromic dyes have the ability to alter colour in response to polarity. While they can emit red in extremely polar water, they can also emit green or blue in apolar oil. This is as a result of their ability to communicate with molecules in their environment. As a result, the energy of these dyes' excited states is reduced due to strong dipole-dipole interactions with polar water molecules, which causes the red emission. These interactions are weak in apolar media, which explains why they are emitted in the high-energy blue area. Because biomolecules exhibit substantially lower environmental polarity than water, this colour change is crucial for biosensing.

MULTI-MODAL IMAGING USING NANOPARTICLES IN BIOLOGICAL SYSTEM

In comparison to imaging agents based on molecules, nanoparticles can significantly extend the duration that the imaging agent circulates in the blood and localise considerably more precisely in the target tumour tissues. For multi-modal imaging, they can carry several imaging agents (such as fluorescence and MRI), or they can carry both imaging and therapeutic compounds for theranostics. However, the use of nanoparticles raises some questions about the difficult to assess long-term toxicity in vivo. The development of the smallest fluorescent organic particles with such high brightness, measuring 7 nm, possibly expands the scope of biomedical applications. It has become possible to create ultrabright nanoparticles with regulated diameters between seven and 80 nm that are far brighter than commercial quantum dots and stable in living things, including cells. The ultrabright fluorescent nanoparticle probes in development will work with low-powered devices like specially designed smartphones, making it simple and affordable for medical practitioners to identify disease-related biomolecular markers. This will make it possible to monitor and track illnesses like cancer from their very earliest stages and aid in determining the precise type of carcinoma found. Polymer-based multifunctional nanoparticles have recently been developed for combination imaging and medication delivery. The hydrophobic polylactide was coupled with the weak fluorescent polyethyleneimine (PEI) to create the amphiphilic PEI, which was used to create nanoparticles with vivid, multicolor fluorescence and a high drug loading capacity [7].

USE OF LANTHANIDES, ORGANOSILICATES, FLUOROPHORES IN MULTI-MODAL IMAGING

Photon-harvesting antenna ligands surface functionalize terbium-doped LaF3 nanoparticles. Ultrabright nanoparticles with the typical green luminescence signature of the Tb atoms and much extended excited states are produced by surface capping with antenna ligands. For luminescence microscopy imaging, these lanthanide dots can be inserted at nanomolar quantities into living cells [8]. Crossed out For the purpose of creating dye-centered, individually caged nanoparticle building blocks, supranano particle assemblies were created. Plasma treatment hydrophilized the particle surface, making it water-dispersible and open to further functionalization. Unique core-shell organosilicate structures and supranano particle assemblies were used to tackle the current challenges of dye leaching and quenching due to dimerization, respectively. The supranano particles display photostable, ultrabright emission, making them desirable fluorescent tags for bioimaging and chemosensory applications [9]. The well-known chemical fluorophore N-(7-nitrobenz-2-oxa-1, 3-diazol-4-yl) (NBD) was rationally structurally modified to make fluorophores that self-assemble in nanoparticles in a biocompatible environment without significantly lowering the fluorescence quantum yield. The resultant NP displayed brightness that was more than six orders of magnitude more in an aqueous environment than the molecular component in the organic solvent. Nanoparticles were created by the process of nanoprecipitation, and since non-covalent interactions are the only means by which they can be stabilized, they are stable and can be seen as distinct bright spots that are freely diffusing in solution at concentrations as low as 1 nM [10].

Fluorescent Silica NP (FSNP) has been investigated as protective nanocarriers, resolving the issue with standard organic dyes' high photo-bleaching rates. These enable cellular identification and internalization, tracking, bio-distribution, and specificity in addition to colloidal stability in water. These systems are suitable for bio-imaging applications due to the adaptability of the surface chemistry on silica platforms and the inherent hydrophilicity and biocompatibility of these materials [11].

RECENT DEVELOPMENT IN FORMULATION TECHNIQUE FOR NANOCARRIERS

Using the reverse microemulsion process, ultrabright fluorescent silica nanoparticles were created and engineered to include (2, 20-bipyridine), 2-(5-aminophenanthroline), and Ru bis (hexafluorophosphate) (Rubpy-phen). The morphology and characteristics of the nanoparticles were investigated using transmission electron microscopy (TEM), scanning electron microscopy (SEM), dynamic light scattering (DLS), inductively coupled plasma (ICP),

and fluorescence spectra [12]. The development of a method for dispersing bulk silicon into discretely scaled ultrasmall, ultrabright nanoparticles. A series of discrete sizes of hydrogen-capped Si11H clusters with n more than 20 are produced electrochemically etched. These diameters were 1.67 (Si. 23), 2.15, 2.9, and 3.7 nm in diameter (Si. 29), respectively. Direct electron imaging, excitation and emission optical spectroscopy, chromatography, and colloidal crystallisation were used to analyse the particles. The emission bands and band gaps are measured. Ultrabright blue, green, yellow, and red luminescent particles make up the bottom four. For biological tagging, RGB displays, and flash storage, discrete sizes and distinct emission in the red, green, and blue range are advantageous [13]. New equipment and chemical combinations have greatly improved the methods for creating silicon nanoparticles. There are several different ways to make silicon nanocrystals with unique properties. Physical techniques can remove impurities coming from byproducts but only generate small quantities of pure goods [14].

Hollow Drug Delivery Nano-platform has been created and tested for both in vitro and in vivo cancer treatment. This composite nanosystem was created by adding transferrin (Tf) targeting moieties to hollow mesoporous silicon nanoparticles (HMSNs) via redox-liable linkage. It was able to transport therapeutic cargos (doxorubicin) selectively to the tumour location and then release them on demand [14]. To create extremely effective and reliable fluorescent nanomaterials, conjugated oligomers have been added to silica nanoparticles. When a conjugated oligomer precursor was added to the resultant hybrid NPs at a molar content of 0.025 percent to 0.05 percent, the fluorescence quantum yields reached as high as 97 percent [15].

The extraordinary color-tunability that results from the addition of a small number of carbogenic nanoparticles to powder compositions are achieved without impairing the flowability. Hybrid nanopowders are used to improve the appearance of latent fingerprints, and they successfully address problems with low contrast against patterned or multicoloured backgrounds. There are numerous uses for fluorescent micro- and nanosized particles in biology, medicine, and engineering. The materials should be highly emission efficient and have good photostability for these applications. But many organic fluorophores experience photobleaching and quenching effects brought on by aggregation [16-20].

Chemical and medicinal researchers have recently become more and more interested in semiconducting organic nanoparticles [21, 22], which are primarily made of -conjugated molecules. Compared to current inorganic nanoparticles, they have properties including quick production, simple tuning, decreased toxicity, and higher biocompatibility [23-27].

Biocompatible hollow mesoporous silica nanocarriers with tumor-targeting and glutathione-responsive release dual characteristics were designed to specifically carry medications into cancer cells with targeted recognition and controlled release [28-30]. The construction of these multipurpose nanocarriers involved coupling transferrin to the surface of hollow mesoporous silica nanoparticles to form a disulfide bond that could be broken in the presence of glutathione. Over the past few decades, researchers have looked into polymer-based drug delivery depots as a way to address intravenous chemotherapy therapies' significant systemic morbidities and lack of tumour targeting [31-34].

Materials based on carbon have been crucial to the progress of the material sciences. Fundamental research and applications of carbon-based materials are always popular in the fields of chemistry, materials, and other interdisciplines due to their environmental friendliness. This is true for both traditional industrial carbon and new industrial carbon, as well as for new carbon nanomaterials like graphene and carbon nanotubes. Macroscopic carbon material, however, lacks the requisite band gap, making it impossible to function as an efficient luminous material. Due to their excellent and tunable photoluminescence, high quantum yield, low toxicity, small size, appreciable biocompatibility, and abundant low-cost sources, carbon dots have attracted considerable attention and found important applications in many fields, such as biomedicine, catalysis, optoelectronic devices, and anti-counterfeiting [35-37].

The integrin family is a large set of ubiquitous heterodimeric receptors that may adopt a number of different conformations and bind to a wide variety of ligands. These molecules play a crucial role in signalling and homeostasis by mediating interactions between cells and of these cells with the extracellular matrix. Integrins transduce both extracellular mechanochemical stimuli and intracellularly generated signals in a bidirectional fashion across the plasma membrane by establishing dynamic links between the actin cytoskeleton and the extracellular matrix [38-40].

CONCLUSION

Due to their biocompatibility, size, target-specificity, and enhanced efficacy, ultrabright nanocarriers are the subject of this review article and their pharmaceutical applications. The list goes on and on: dendrimers, polymeric micelles, solid-lipid nanoparticles, C dots, integrins, etc. The goal is to improve the pharmacokinetics and bio-distribution of highly hydrophobic medicines while reducing their potential for toxicity through safe and efficient administration.

The assembly of organic molecules into biodegradable nanoparticles with significantly greater brightness than single dye molecules has been a focus of numerous studies. Nanoparticles have been modified in order for their color to shift in reaction to single biomolecules like proteins and nucleic acids. Cancer cell studies and medical diagnostics have both benefited from the use of nanoparticle technology as an analytical tool.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

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CONFLICTS OF INTEREST

None

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