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OVERVIEW OF QUANTUM DOTS

V.Viswanath*, S. Sayeeda Malaika.
Associate professor, Department of Pharmaceutics, PRRM College of Pharmacy, Kadapa 516 003.
Email: viswanath.prrm@gmail.com

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Abstract

Quantum dots are nanoscale semiconductor crystals ranging Usually between 1-10 nano meters and with capability of fluorescence when excited by a light source such as a laser. Quantum dots are tiny bits of microscopic metal, which are thousand times smaller than diameter of a hair. Quantum dots are emerged as a new class of fluorescent probes for biomolecular and cellular imaging. With a focus on the use of quantum dots this review includes a detailed, examination of quantum dot, Characterisation Techniques, properties, their synthesis applications, drugs that can conjugated with Quantum dots & use in imaging and analysis.

Keywords: - conjugation, Quantum yield, Template, fluorescence.

1.0 Introduction

Nanoparticle is defined as a particle with either one or more dimensions of the order of 1000 nm size or less. Nanoparticles (NPs) characteristics are differ from bulk materials of size 100 mm. Nanotechnology has great applications in cancer therapy. Thus, reduces the current limitations of traditional therapy. Passive and ligand-based targeting mechanism, nanoparticles directly target to the tumour site for treatment. Nanomedicines include polymeric nanoparticles, dendrimers, polymer molecules, polymerases, polyplexes, and polymer–drug/protein conjugates. This will result in the improvement of cancer therapeutics. The broad scope for chemically modifying polymer has versatility in delivering system. Nanomedicine has a wide application provides fundamental benefits in nanotechnology. These are generally applicable where devices such as nanomachines, nanofibers, nanoparticles, mechanical and optical Nano sensors.

Nanocarriers selectively use the exclusive pathophysiology of cancerous cell by enhancing their retention effect, permeability and the tumour microenvironment. Active targeting strategies utilize legends or antibodies against selected tumour targets amplifying the specificity. Toxicity and Drug resistance are the

main problem that impedes the efficacy of both conventional chemotherapeutic and molecularly targeted agents. So, nanoparticles might overcome and reduces the obstacles in treatment of cancer. The ability of Nanoparticles being accumulates in cells without recognizing by P-glycoprotein. It results in increased intracellular concentration of drugs. Multiplex and multifunctional nanoparticles are now being dynamically investigated. It is also preferred as the next generation of nanoparticles, modifying cancer treatment techniques.

Types of Nano Particles

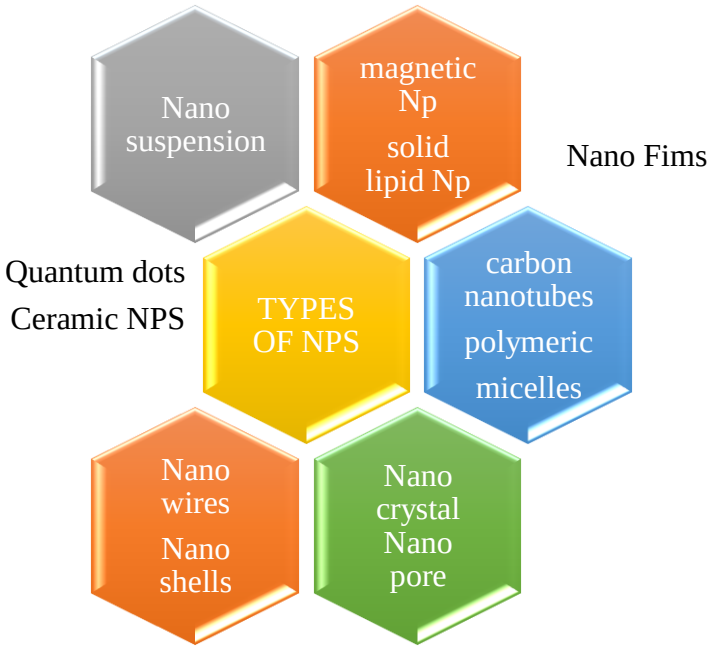

FIG-A: Types of nanoparticles.

2.0-Properties of Quantum Dots (QDs)

2.1 Structural properties

In general, QDs consists of core, shell, and surface-coating parts, which has marked luminescence QY, surface activation, and stability to chemicals and photons. The core composed of single layers of semiconductor material, like CdSe, CdTe, fluorescence emission, as well as excitation of wavelengths, this relies on core's composition. The core is surrounded by Shell, stabilizes the core. Shell also have fluorescence QY, decay kinetics, and photostability of QDs. Organic capping shows biological functionality, stability and solubility. Coating part of QDs initially is hydrophobic nature, whilst in this scenario hydrophilic polymers or molecules are in use. Due to these amphiphilic polymers water solubility of QDs are enhanced which allows incorporation of ionizable functional groups. [13]

2.2 **Optical properties**

Though QDs have semiconductor materials, but due to their small size it shows spectroscopic properties which radially differs from bulk forms. Electrons of the valency band shifts to conductance band when photons are absorbed by QDs. Absorption occurs when energy of photon will be higher than the bandgap energy of QDs; Therefore, excitons are created with in the core with vast range of energies. Excitons with higher energy relaxes to the lowest bandgap energy prior to the emission of photons. Thus, excitation spectrum is broad, whilst the emissive spectrum is narrow. QDs are the artificially synthesized atoms with dimensions from 2 to 10 nm. QD's size can be adjusted which results to have different emissive wavelengths. This adjustment can be done by adjusting the particle's diameter in the visible area and by adjusting the particle's composition in the longer wavelength. By increasing the diameter of QDs, red shift can be observed in the emitted light. [13,14]

2.3 Fluorescence property

When quantum dots are illuminated, their outer shell electrons receive sufficient energy to break, which allows them to move around the atom this creates the conduction band. Electrons of this conduction band gets excited, due to which it conducts electricity. When these excited electrons return to the valence band, they emit a specific colour of light. The light specific is produced due to difference in energy between the conduction band and the valence band. It has been proved from studies, that the higher the energy difference between the conduction band and the valence band, the emissive light turns to the deep blue colour, anyhow, this will shift to red band of the colour spectrum, if the difference is less.[1]

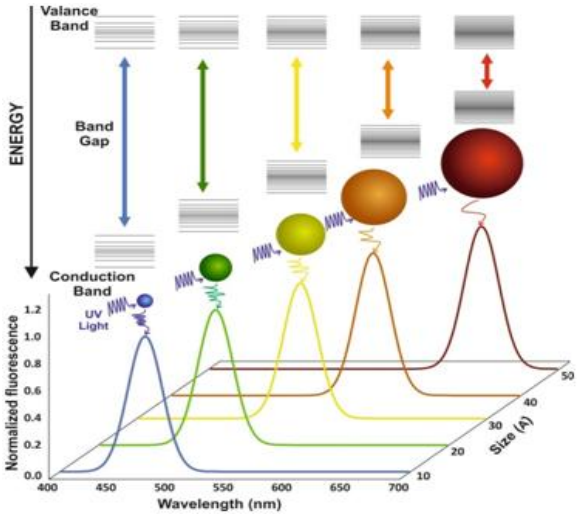

Fig-B: Fluorescence of Quantum dots.

2.4 Other properties

1.QDs are prepared from tiny bits of metal which will be thousand times smaller than the diameter of the hair.

2.QDs can be designed in different shapes and can be coated with various biomaterials.

3.QD's luminescence in UV light, with the size of the dots determines its colour for example- 2nm Quantum dot's luminescence is bright green, whilst the 5 nm Quantum dot's luminescence is red.

4. Fluorescent quantum dots are typical compounds from group II to VI and III to V For example [Ag, Cd, Hg, Ln, P, Pb, Se, and Zn etc.]

5.As the quantum dots size decreases, then the emitted wavelength turns shorter.

6.Quantum dots have a broad excitation range.[11]

7.Quantum dots has specific emissive wavelength, so the spectra won't get overlapped in multiple fluorescent emission.[11]

Table-1: properties of Quantum dots.

Properties	**Quantum dots**
Size	2-10nm
Thermal stability	High, depends on shell
Photostability	High, stable fluorophores due to their inorganic composition
Chemical stability	More resistant to degradation
Brightness	10-20 times more than organic dyes
Absorption spectra	Broader absorption spectra enable selection of excitation wavelength
Molar absorption coefficient	10^5-10^6 cm-1
Emission spectra	A narrow (30-90), symmetric, sharply defined emission peak
Strokes shift	0.1-0.8
Lifetime	Large stokes shift
Excitation by single or multiple sources	Longer lifetime helps to eliminates background signal
Solubility	Ideal for the same source and multicolour experiments

3.0 Synthesis

Synthetic techniques of QDs are classified into two classes, top down and bottom up approaches. This can be achieved via electrochemical or physical, chemical methods.

Top-down approach includes the fragmentation of carbon matter into CNPs, and this comprises of arc discharge, laser ablation, and electrochemical methods.

Bottom-up approach includes thermal method, microwave-assisted method, hydrothermal aqueous method, template method. The quantum yield can be increased in arrangement or posttreatment. The favourable surface properties can be attained by alterations in QDs which plays a key role in solvency and applications. Furthermore, worn tea leaves, grass, light sediment and ground coffee have been used as carbon precursors, for the development of Q-dots. [2,4,5]

3.1 Top-down approach

3.1.1 Arc discharge method

This approach can be used for the developments of Q-dots from crude carbon soot. This sediment i.e. crude was oxidized with 3.3 M Nitric acid to incorporate carboxyl groups, the resultant material then extracted with basic solution if PH-8.4 i.e. NaOH results in dark coloured suspension. The extracted matter is purified by Gel electrophoresis. Separation of highly fluorescent QDs was determined to be 18nm.

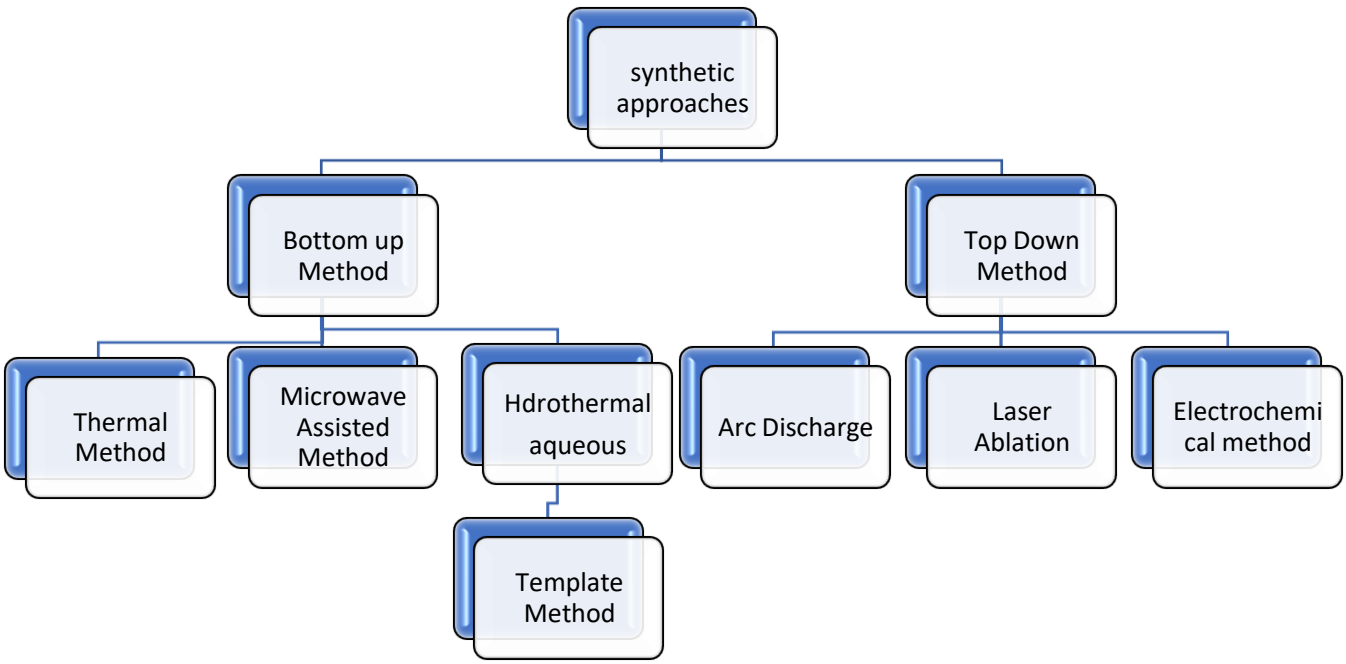

Fig-C: Methods of Quantum dots.

pristine and nitric acid oxidized carbon nanotubes were used to contour the photoluminescent NPs, pristine carbon nanotube which were derived from fluorescent NPs are hydrophobic and composed of limited distribution. Meanwhile, the fluorescent NPs which were derived by the oxidized carbon nanotube have the capability of accumulation when they get scattered in water because they were externally combined with oxygen by a thin layer of carbon. NPs so obtained by the arc discharge approach generates less yield, moreover, the arc discharge soot method composed of number of composite segments. Anyhow, the purification process of these segments is hard.[11]

3.1.2 Laser ablation

In this approach, synthesis of fluorescent Q-dots is achieved by laser irradiation of Carbon target. Sun initially heated a mixture of graphite powder and cement for the preparation of carbon target, later fabricated by using laser ablation or removal of target in a stream of argon gas by fetching water vapor at 900 °C at 75 kPa. Aqueous solution of Nitric acid was reacted with the sample later by refluxed for 12 hours, followed by polyethylene glycol (PEG1500N) or poly propionyl ethyleneimine-co ethyleneimine was treated with the sample, and the Q-dots so obtained will have high photoluminescent, with the size of about 5 nm. By activating these dots at 400 nm, the PL QY was found to be 4% to more than 10%. Furthermore, the use inorganic salts such as zinc acetate and Na2S or NaOH for doping the QDs. This leads to increase in QY, in this the dopants (e.g. ZnOs and ZnS) possibly which acts as a passivating mediator for the C-dots. When these QDs gets activated at 450 nm, the doped Q-dots indicates strong Fluorescent QY up to 45%. This approach has various advantages one of which is effortlessness. Using this ablation method different types of nanostructures can be produced via this approach, and it requires high amount of carbon matter for the synthesis of carbon targets. Irradiation can develop different sizes of nanoparticles.[10]

3.1.3 Electrochemical method

Lu employs high-purity of graphite rods and immensely placed pyrolytic graphite as anode, with a distance of 2 cm, platinum wire as a counter electrode, later installing them into ionic fluid/water solution. Exfoliation of carbon matter was conducted by the application of static potentials. This process occurs due to the complex exchange of anionic intercalation from the ionic fluid and anodic oxidative cleavage of water. They are washed with ethanol and water until the pH of exfoliation products gets neutral. Later separated by filtration and ultracentrifugation at 15,000 rpm at 20 °C, the so obtained Q-dots are with the

size of 6-8 nm and the Quantum yield of about 2.8-5.2%. Yao employs graphite ring as anode and titanium tube as cathode settled these in the centre of the electrolyser. Insulated O-ring is used to partition the cathode and anode and Sterilized water as electrolyte medium. Ultrasonic power and electrolytic voltage were applied at once, due to this pure blue fluorescent Q-dots of 2-3 nm size is produced without the need of purification and they have Quantum yield of about 8.9%. The produced Q-dots composed of splendid fluorescence effect and thermodynamic stability in aqueous solution.[9]

3.2 Bottom approaches

3.2.1 Thermal routes

To synthesise QDs with burning sediment of candles as precursor, this method is very opt. It involves the treatment of sediment with oxidants such as Nitric acid and H2O2/AcOH, which leads to the formation of Q-dots. QDs are isolated using Polyacrylamide gel electrophoresis and determined with highly versatile PL at shorter emission wavelengths and the Quantum yield ranges from 0.8% up to 1.9%. Sediments of natural gas was reacted with HNO3, later neutralises with NaHCO3. later, purified by dialysis, this instigate the development of photoluminescent Q-dots. Nanostructures were formed on the surface of C-dots by the addition of metal salts which includes AgNO3, Cu (NO3)2, and PdCl2, to the Q-dots solution in the presence of a reducing agent i.e. Ascorbic acid. Though this method is easy and clear. but the Quantum yield is considerably less than 0.1%. This increased soot-based method enhances the production of QY around 3% with 2-6nm size. [8,9]

3.2.2 Microwave assisted method

Guan used this approach to develop luminescent Q-dots with folic acid molecules as both nitrogen and carbon source. Firstly, the mixture is prepared which contains 3 ml of diethylene glycol in which 15 mg of folic acid is dissolved and this mixture was placed in a conventional microwave oven of 750 W and heated for 40 seconds. It will lead to the formation of red-brown-coloured suspension and its dialysis process engrossed for 3 days against pure water. Fluorescent NPs of carbon nitride produced after post treatment, with a size range around 4.51 nm and activated at 360 nm, the Quantum yield of about 18.9%. Even when the emission peak was excited at various wavelengths (from 320 nm to 420 nm), but its position remains stable at 460 nm. Wang develops an easy single stage microwave-assisted for the formation of QDs composed of water soluble phosphorous In this approach, blend of 2 mL of 70% phytic acid and 1 mL

ethylenediamine is formulated with 25 mL ultrapure water, and the resulting turbid mixture is heated for 8 min in a microwave oven of 700 W. later, crude is purified which results in the formation of phosphorus dots, and the aromatic structures of these dots are attached covalently to the phosphorous groups .Then the phosphorus dots shows two peaks when activated at shorter wavelengths, whilst the single peak shows fluorescence at 525nm as they get activated at high wavelengths 360-460 nm and Quantum yield of which is 21.65%. In contrast with other strategies, this microwave assisted approach is more convenient and rapidly heats the carbon precursors.[7]

3.2.3 Hydrothermal and aqueous method

Hydrothermal is one of the approaches for the synthesis of QDs. In this method coffee beans are hydrothermally treated. Prior to grinding as powder, the worn coffee beans are kept in an oven for drying process. Followed by autoclaving and calcined in air at 300 °C for 2 hours. QDs are formulated via four consecutive steps i.e. Dehydration, - Polymerization, - Carbonization, and - Passivation. Moreover, a green method was performed to get Qdots from worn green tea leaves for 2 hrs at 300 C. The succeeding dark carbonized powder is re-subjected in sterile water and later, purified by dialysis process. In the passivation process, the enriched catechins molecules in green tea plays a key role. Four eccentric molecules i.e. cadaverine, glycine, ethylene diamine-tetra acetic acid (EDTA) 2-amino2-hydroxymethyl-propane-1,3-diol (TRIS)] comprising either a carboxyl group or an ether group the results that agents with both carboxyl and amino groups are advantageous for the synthesis of highly water diffusible and PL Qdots. Moreover, nitrogenous atmosphere, EDTA is used to generate Q-dots at 400 °C for 2 hours. Despite of EDTA precursors having the disadvantage of degrading, they are still utilised in the production of enhanced hydrophilic QDs.

EDTA comprises of carboxylic group and amino group in an aqueous solution and calcined hydrothermally for 2 hours at 300 °C. The results indicate that starting material contain both groups i.e. carboxyl and amino group, and are advantageous for PL and highly water-dispersible Q-dots. For the production of organ silane-functionalized Q-dots, (3-aminopropyl) trimethoxy silane is used as starting material at 300 °C for 2 hours, with absenteeism of an additional passivating agent. Similarly, 4-aminoantipyrine and ammonium citrate is selected as another precursor of carbon in order to produce Q-dots in air at 300 °C for 2 hours. Many

organic ammonium species are covalently attached to the surface, which acts as a surface modifier, and adjusted the hydrophilic character.[15]

3.2.4 Template method

This Template method is used for the synthesis of QDs. This method consists of two stages – 1. preparing Q-dots via calcination in suitable mesoporous silicon spheres or template. 2.Etching to remove supports and produce nano-sized Q-dots. Zong used this approach for mesoporous spheres of silica as hard templates. The mixture of citric acid and complex salts are used to saturate the silica spheres. Later, mesoporous supports are calcined and expelled, the so obtained dots have magnificent luminescent and photostable properties. Yang concluded this approach for preparing uniform morphologic Photoluminescent Q-dots using a soft-hard template approach. Copolymer P123 Pluronic is used in this approach as a soft template, whilst the hard template is mesoporous silica, many organic molecules such as diamine benzene, 1,3,5-trimethylbenzene as carbon sources. Followed by removal of template, passivation, and carbonization, this results in such dots which composed of tuneable sizes, and crystalline degrees. moreover, it is highly stable with photoluminescent of about 3.3-4.7%. The inconvenience in assemblage formation is avoided via this soft-hard template strategy, and the so produced dots are with narrow distribution of size because of size confinement. Lai reported this approach for generating Nanoparticles of mesoporous silica, which acts as a nanoreactor in order to control size distribution. [15]

Table-2 Properties of different synthetic method.

Serial No.	**Synthetic methods**	**Size range**	**Quantum yield**	**Advantages**	**Disadvantages**
1.	Arc discharge method	-	-	Chiefly used approach	Harsh method with low Quantum yield
2.	Laser ablation method	5 nm	4-10%	Effortless, different sizes of nanoparticles can be prepared	Poor control on sizes, low QY
3.	Electrochemical method	6-8 nm	2.8-9.8%	Stable method, water soluble QDs can be prepared	Complex method

4.	Thermal routes	2-6 nm	0.1-3%	Easy and straight forward method with fluorescence	Low QY
5.	Microwave assisted method	4.51 nm	2.1-6.3%	Simple, inexpensive, eco-friendly method	Poor control on size
6.	Hydrothermal and aqueous method	-	-	Non-toxic, inexpensive Highly water soluble QDs can be prepared	Poor control on size
7.	Template method	-	-	Biocompatible with colloidal stability	Time consuming, expensive, low QY

4.0 Characterization of QDs

The possible characterization techniques available are Nuclear magnetic resonance (NMR), X-ray diffraction (XRD), transmission electron microscope (TEM), Fourier-transform infrared spectroscopy (FTIR), ultraviolet (UV) spectroscopy. [15,3,4]

4.1 Transmission electron microscopy

TEM is used to determine the ultrastructure of samples due to its high resolution of 0.1-0.2 nm. TEM has vast demand in departments like material science, pharmaceuticals, science, and other research and progressing departments. TEM is widely used for the characterization of QDs. Morphological properties of NPs can be explored using this technique, i.e. Shape, size, and dispersion. In order to identify the fine structure of Qdots, high-resolution TEM can also be used. The crystallinity of Q-dots can be categorised into two types of lattice fringes, namely interlayer spacing and in-plane lattice spacing, respectively. Interlayer spacing basically is focuses around 0.34 nm, whilst in-plane lattice spacing focuses around 0.24 nm. [4,16]

4.2 X-ray diffraction

XRD is well used for the characterization of Q-dots in order to acquire the particulars like phase purity, crystal structure and phase purity. XRD also used for crystalline phases recognition of Q-dots. Liu prepared the Q-dots by using hexaperihexabenzocoronene as the starting material. The so obtained Q-dots are with a

size of ~60 nm in breadth and 2-3 nm thickness, this produced after the process of pyrolysis at high temperature, surface functionalization, reduction treatment, and oxidative peeling. It possessed a fluorescence QY of 3.8%. Bourlinos develops the Q-dots by calcination of ammonium citrate salt at 300 °C; the allied XRD design indicates two reflections which were superimposed, which affirms the presence of exceptional surface modified carbon alkyl groups. [4,17,18]

4.3 Fourier transform infrared spectroscopy

Functional groups present on the surface of Quantum dots can be detected by Emission Fourier transform infrared spectroscopy. Owing to the development of Q-dots by the partial oxidation of a carbon precursor, groups like carboxyl or carboxylic acid groups, and ether/epoxy and hydroxyl groups are prominent on the surface of Q-dots. Peng develops the Q-dots of size 1-4 nm via the compound oxidation of carbon strands of one micron, 1-4 nm Q-dots, the so obtained particles gets broke up in polar solvents i.e. dimethyl sulfoxide and dimethyl formamide. The IR range is recorded. Absorption Peaks are obtained around 1724 cm-1 and 3307 cm-1 indicates the presence of carboxyl groups, double bond presence was appeared by the peak of absorption at 1579 cm-1 ether linkage existence was depicted by absorption peak at 1097 cm. [4,16]

4.4 Nuclear magnetic resonance

NMR is a technique which frequently used to determine structural particulars of Q-dots. Hybrid types of C-atoms in the crystalline network and binding mode between carbon atoms are demonstrated by NMR. Tian utilises natural gas burning sludge as a carbon source and performs the reflux with nitric acid, which leads to the formation of Q-dots. Aromatic (sp2) carbons shows resonance in the region from 90-180 ppm, whilst aliphatic (sp3) carbons show resonance in the region from 8-80 ppm, structural features of Q-dots are identified with the help of NMR measurements by differentiating sp3 carbons from sp2. The absenteeism of aliphatic carbons gives the indicatio00n at carbon -13 (13C) in NMR range, this implies the absence of a single peak less than 120 ppm, the region which extends from 120-150 ppm. [4]

4.5 UV spectroscopy

Quantum dots shows strong UV absorption, this is prepared by various techniques, but the positions of absorption peaks of UV are entirely different for different techniques which is used for the synthesis of Q-dots. Li mixed the active carbon of about 4.0 gm into 70 mL of H2O2 to prepare a suspension and sonicated the suspension for 2 hours at room temperature. After filtration, water-soluble Q-dots having fluorescent

property are obtained with 5-10nm of diameter, basic absorption of an aromatic pi bonds are determined by the conventional UV-visible absorption at 250-300 nm. Tang performs pyrolysis of glucose solution via microwave to prepare Q-dots with diameter of 1.65 nm and PL Quantum yield of 7-10%. Two identical UV peaks indicates the aqueous solution of these Quantum dots at 228 and 282 nm. [4,2,16]

5.0 Applications of Quantum Dots

5.1 Pharmaceutical field

In pharmaceutical field, liposomes, polymer based micro and nanoparticles are the subjects of interest in R and D [research and development] from the past the past 3 decades. In this diagnosis department, MRI is one of the first and most sophisticated technique which includes metallic particles. Despite of these advantages, very new generation are available which works biosensors based on the optical properties of colloidal gold and fluorescent nanocrystals, i.e. Quantum dots. It Seems to have applications in diagnosis and medical imaging. In concerned with therapeutics, it is based on potentiality of metal nanoparticles able to satisfy the pre-requisite time and space-controlled release of drugs. It also has the property of identification of active ingredients with fluorescence.[11]

5.2 Quantum dots in diagnosis of cancer

Preliminary diagnosis of cancer is advantageous due to most tumours/cancerous cells are detectable only when they attain a certain size and composed of millions of cells which are metastasized. In this scenario the techniques are tissue biopsy, bioanalytical assay of body fluids by enzyme linked immunosorbent assay (ELISA) and medical imaging are not enough to sensitize and specific detection types of early-stage cancers.

Therefore, Quantum dots based multiplexed approach is used for the concurrent detection of biomarkers. QDs has magnificent characters, this enables the detection of tumours which consists of intense and stable fluorescence for a longer time; resistance to photobleaching, large molar extinction coefficients, and highly sensitive screening because of their capacity of absorption and emission. Due to their large surface area-to-volume ratio, a single Quantum dot can label to many molecules, thus making Quantum dots alluring for the designing of more complex multifunctional small structures. Covalently bound Quantum dots can be conjugated to various biomolecules such as antibodies, peptides, nucleic acids and other ligands as fluorescence probe. [11]

5.3 Internalization of quantum dots by live cells

Usually, the binding of non-targeted particles with living cells results in internalization. This method is achieved by different routes, that relies either on the particle properties i.e. Size, shape, surface functionalization, surface charge and the combination of these properties or on the cell type. The first belief is that the main internalization can be achieved through endocytosis this was concluded by Jaiswal, where human cancer cells and Dictyostelium disodium amoeba cells internalized by negatively-charged DHLA-capped Quantum dots.

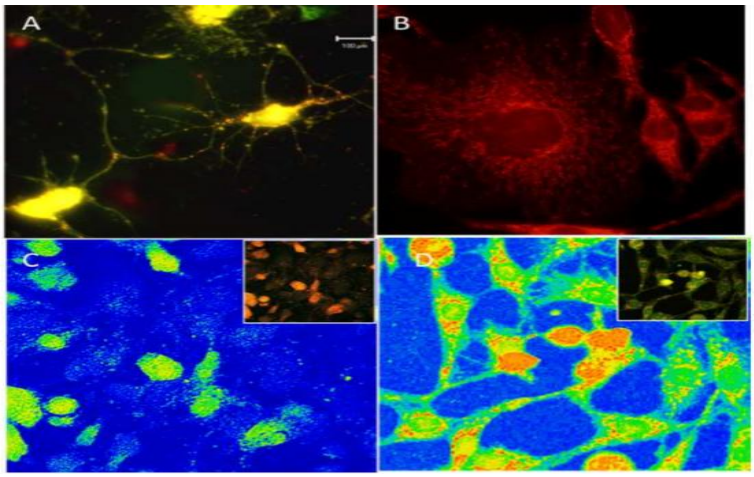

Figure-D: (A)Non targeted glutaraldehyde-capped cds/(OH)2 labelled with live neuron cells.

(B)live glioblastoma cells.

(c)Intensity map images of glial cells

(D)Glioblastomas incubated for 3 minutes with Quantum dots.

5.4 For intracellular delivery

QDs could be employed as probe in order to monitor protein dynamics in live cells, due this desirable character of striking as a fluorescent probe as a long-term imaging for prolonged periods of time this was concluded by Courty. Anyhow, molecular dynamic trafficking specifically in live cells, are engrossed on the surface molecules i.e. membrane proteins, this drawback is because of incapacity of water dispersed QDs to cross the lipid bilayers by simple by Chen & Gerion, 2004. [14,19]

A. Physical Method

This physical method is used to carry out aqueous compounds into desired cells. Though the accurate control on the cell and the amount of materials could deliver. This mainly relies on microinjection and electroporation. The electroporation depends on introduction of one or more strong electrical pulses, which

produced localized pores in the membrane bilayer for increasing permeability – Figure A. Using electroporation, Chen and Gerion delivers the QDs into Human cells (Chen & Gerion, 2004). Quantum dots can detect the cellular machinery and enter the cell nucleus in living cells. Verily, nanoparticle agglomerates have been concluded at 500 nm. Followed by application of electric pulses, even to protein conjugated QDs. By not concerning the agglomeration, as in the case of simple cell labelling, electroporation can be well used.

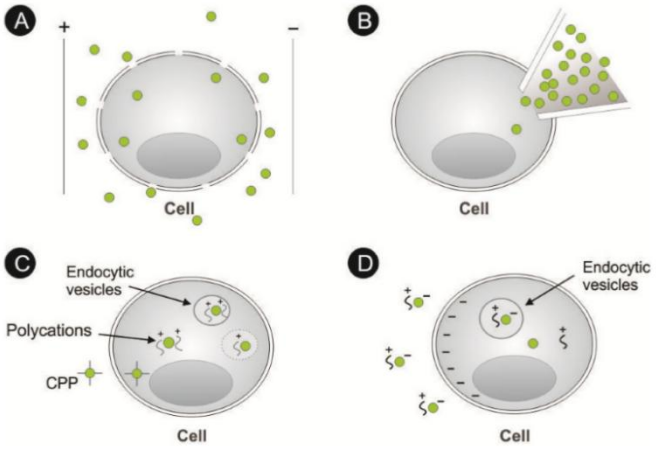

Figure-E: Schematic representations of four types of processes used in the internalization of QDs: electroporation (A); microinjection (B); CPP and polycation-mediated internalization (C) and lipoplex mediated process (D).

B. Chemical Method

Chemical strategy shows a broad range of methods for intracellular delivery of membrane impermeable materials, and comprises of covering cargos surface or coupled with the vehicle, this promotes the labelled material into cytoplasm of large number of cells concurrently in a straightforward way. Furthermore, it can usually be used in living animals. Various approaches permit the Quantum dots to reach the cell cytosol that depends on conjugation of nanoparticles to interact or to be recognized by cells. One of the most magnificent chemical methods for nanoparticle delivery into cells is the conjugation with Cell Penetrating Peptides (CPPs). Numerous publications report the study of this class molecules. For this purpose, in which the mechanism of cell entry is similar to endocytosis reported by Thorén inspite of direct bypass via lipid bilayer, although the harmony of real pathway is still controversial. If trafficked into cells through endocytosis, these bio conjugated Quantum dots required to be delivered from endo/lysosomal compartments to their targets.

5.5. Quantum dots Encapsulation

Quantum Dots can be entrapped in a vehicle for the purpose of delivery instead rather than conjugation as transporter molecules. It is utterly desirable due to its allowance as conjugated targeting moieties i.e. antibodies, ligands on the surface of the nanoparticles, which was otherwise engrossed by the targeting transporter molecules. Furthermore, it can eliminate the rupturing of acidic intracellular vesicles, which has the potential to cause cytotoxic effects. The encapsulating vehicles can be categorised as two groups, namely polymeric and lipid delivering systems. QDs were encapsulated in a suitable polymeric poly (lactic-co-glycolic acid) (PLGA) nanospheres and delivered into the cell cytosol after endocytosis of the complex (Kim 2008). Later, by preferential endocytosis of antibody-coated polymer nanospheres into ErbB2 over expressing cancer cells, the polymer gets degraded in the acidic intracellular compartments causing the release of bio conjugated Quantum dots, this could reach and label intracellular structures such as mitochondria and actin filaments.

The other strategy is by micelles. Profitability of encapsulation of Quantum dots in lipid micelles depends on the small size of the resultant probe of 25 nm. Due to having advantages physically, chemically and photostability of these Quantum dots containing micelles, due to this a group reports this system for the first time for tracking cell lineage developments in live Xenopus embryos. This improved report is one of the first reports on the use of QDs for in vivo imaging.

Liposomes are lipophilic vesicles containing one or more lipid bilayer(s) enclosed in a aqueous compartment and this can entrap the hydrophilic and/or hydrophobic materials this is reported by (Valenzuela, 2007). In case of micelles or other encapsulating systems, their interaction with biological molecules relies on the physical-chemical properties, which can be finely tuned. Yang (Yang 2009) in fact, encapsulated water aqueous CdTe Quantum dots in liposomes conjugated with folates and signifies that these vesicles can be directed to folate-overexpressing cancer cells and can be detected by fluorescent Quantum dots. The consequence is resistant to optical and chemical degradation, with less toxicity. [19]

5.6 Immunoassay

Immunoassay readout approach relies on fluorescent imaging analysis with laser confocal scanner. The ZnS-coated CdSe quantum dots (ZnS/CdSe QDs) are labelled for the detection of antibody. Immunoassay was executed on a glass chip by sandwich assay method, where antibody covalently bound to a glass chip

this permits the capturing of antigen preferentially. Later on, the detection of antibody linked to Quantum dots permits to bind specifically with the captured antigen. The fluorescent signals of the interceded conjugate is detected by a laser confocal scanner. Diode laser is used to excite the fluorescent signals whilst the bovine serum albumin is used to remove nonspecific binding sites. The specificity of the immunoglobulin G (IgG) conjugated Quantum dots is evaluated by conducting experiment using goat IgG and human IgG samples. The result was consistent with the binding specificity in a sandwich-type assay. [11]

5.7 Cell tracking

Quantum dots which are encapsulated in phospholipid micelles can be used to label individual blastomeres in xenopus embryos. These encapsulated QDs are stable in vivo, but doesn't get agglomerated and have the capacity of labelling all types of cells in the embryo. At this fluorescent visualization (2×109/cell) the Quantum dots micelles doesn't produce toxicity to cells, but the concentrations of 5×109/cell did produce abnormalities. The Quantum dots were confined to the injected cell and its progeny, regardless of unintended translocation to the nucleus is at this particular stage in the development of the embryo. Other group labelling Dictyostelium discoideum found that cell labelling for over a week is possible, and labelled Quantum dots had no detectable effects on cell physiology or morphology. variently coloured Quantum dots can be useful for labelling different populations in order to investigate the effect of starvation on developing discoideum. These cells can track for long periods with no perceptible loss of fluorescence.[11]

5.8 Detecting cell death

By merging quantum dots with a novel carrier of MRI agent i.e. Gadolinium, a report is submitted by team of University of Maastricht of Netherlands, that nanoparticle can detect apoptosis/ programmed cell death, using both MRI and fluorescence imaging. Tests in animals indicates that this nanoparticle can supply anatomical particulars using MRI and cellular level information by fluorescence imaging. Imaging apoptosis in the body could furnish the early indication of antitumor therapy, indeed killing cancer cells. Magnetic Resonance imaging experiments shows that the nanoparticle produced an imaging signal that was roughly 40 times stronger than that generated by the gadolinium carrier. Successive imaging could be able to identify the injury-induced apoptosis in mice.[11]

5.9 Plasmid DNA with semiconductor quantum dot

Semiconductor nanocrystal Quantum dots has the empower for long-term imaging in cells with high photo stability. Quantum dots biolabeling approaches have been used for tagging proteins and peptides as well as oligonucleotides. In this benefaction, Quantum dots labelled plasmid DNA is used for long-term intracellular and intranuclear tracking studies for the first time. Conjugation of plasmid DNA with phospholipid-coated QDs is achieved by using peptide nucleic acid (PNA); Nsuccinimidyl-3-(2-pyridylthio) propionate linker. Gel electrophoresis and confocal and atomic force microscopy (AFM) are used to affirm the structure of Quantum dot DNA conjugates. Atomic force microscopy imaging also shows that multiple Quantum dots could linked to cluster at the PNA-reactive site of the plasmid DNA. These PNA Quantum dot; DNA conjugates are able to express protein, increased green fluorescent protein, later, transfection in Chinese hamster ovary (CHO-K1) cells with an efficiency of ca. 62%, which in contrast to unconjugated plasmid DNA14. QDs has various technical advantages over conventional fluorescent dyes and newer DNA chip technologies, which are vivid to detect and track biological molecules. In comparison to organic they are brighter and easy to detect, flexible and yield quick results than present technologies, like DNA chips. Moreover, they are useful in detecting and tracking molecules in basic biomedical studies.[11]

5.10 bio modal molecular imaging

For the synthesis of water-soluble quantum dots with paramagnetic micellular coating as a molecular imaging probe for both fluorescence microscopy and MRI. Targeting ligands can be conjugated to Quantum dots through maleimide or other functional groups. In this investigation, the paramagnetic quantum dots are functionalized by conjugating them with cyclic RGD peptides and are victoriously targeted to human endothelial cells in vitro.[12]

5.11 Quantum dots labelling cells

The optical characterization of QDs, the wavelength of their fluorescence, relies strongly on their size. Due their reduced tendency to photo bleach, colloidal QDs are the desirable fluorescent probes for all types of labelling investigations. Due to Quantum dots unique optical characters, therefore used in cell marking (Derfus2004a, 2004b). QDs can simultaneously labelled multiple inter and intracellular components of living cells ranging from seconds to months. Differently coloured Quantum dots can link with different cell components which can be visualized with fluorescent microscopy or in vivo.

For example, plant bioimaging: CdSe Quantum dots usually binds with cellulose and lignin of the cell wall and thus provide a fluorescent image of plant cells; animal bioimaging, biotinylated Cholera toxin B with QD–avidin conjugates for labelling of ganglion (Cheki 2013); CHPNH2 Quantum dots nanogel has the potential for long-term cell imaging; prokaryotic bioimaging, for the analysis of bacterial cell, core magnetic beads which acts against Escherichia coli coated and streptidine-coated are used.[12]

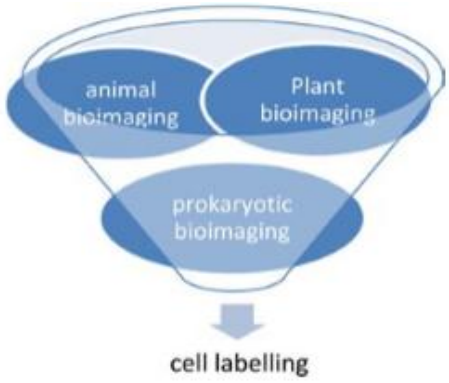

FIG-F: uses of quantum dots in cell imaging.

Table-3: Drugs That Can Conjugate With Quantum Dots.

Serial no.	Drugs	Brand Name	Reference
1	Folic acid	Folvite	24,26,27
2	D-glucosamine	Thera flex	28
3	Folic acid -D-glucosamine	-	28
4	Doxorubicin	Adriamycin	26
5	Folic acid -D- glucosamine -doxorubicin	-	28
6	Immunoglobulin -G	Flub gamma	29
7	Streptavidin	Chemi-Con	33
8	Methotrexate	Trexall, Rhuematrex	32
9	Paclitaxel	Taxol	30
10	Docetaxel	Taxotere	30
11	Gemcitabine	Gemzar	26
12	Hyaluron	Euflexxa	24
13	Ciprofloxacin	Ciplox	31
14	Ampicillin	Amcil, Omni pen	31
15	Vancomycin	Vancocin	31

6.0 Market Research on the Recent Advancement

Quantum dots are in the developing stages. Many applications of quantum dots are reported by industries. Having the particular of Quantum dots conjugating with biological agents to slowly develops, we can expect more commercial products introduced QDs for diagnosis, treatment\, and research purposes. The marketed value of quantum dots was estimated to be USD 1.96 billion in 2017 which will be expected to reach 8.47 billion USD by 2023, at a CAGR of 26.97%. The quantum dots value for cancer imaging / personalized medicine would reach $750 million and quantum dot ID Tags $700 million dollars by 2021. The chief incorporations are attonuclei, chromo zinc, antibodies, Dignan, Helicos biosciences corporation, Luminex corporation and nanocore group are still in the research stage.

Table-5: Commercial products of Quantum dots.

Company	**Product**	**Product Description**	**Reference**
Thermo Fischer Scientific	Qdot ITK Amino (PEG)	*Qdot 655 amino (PEG) quantum dots are the *Ideal starting material for preparing custom *Conjugates of ultralight and photostable fluorescently *Labelled proteins or other biopolymers *It may be used for various labelling and tracking applications that require ultrabright and stable fluorescence.	20
Evident Technologies, Inc	EviFLUORS	*Evifluors are ready to use high quality, activated QDs coupled to secondary antibodies, proteins, Goat anti-mouse, Goat anti-Rabbit, Goat anti-Rat, Streptavidin and Biotin conjugated QDs are available in wide range of wavelengths.	21
Selah Technologies LLC	Selah dots	*Selah Dots are potent-pending photoluminescent carbon-based nanoparticles. *Selah Tubes are enriched for various applications.	22
Helicos biosciences corporation	QDs Biomarkers tSMS	*Helicos developed QDs, used as biomarker for the analysis Of large quantities of genetic material by directly sequencing single molecules of DNA or single DNA copies of ribonucleic acid (RNA CDNA) and its approach of direct sequencing of RNA.	23

Conclusion

*This article portrays the Progress of Quantum dots in Preparative methods, its applications as diagnostic probe, its flexibility in clinical recognition, cancer therapy, targeted delivery, cell tracking, detection of death cell, immunoassay.

*This writing also outlines the drugs that can conjugate with QDs and also about the advancements of Quantum dots in market research

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Corresponding Author

V.Viswanath*,

Associate professor, Department of Pharmaceutics, PRRM College of Pharmacy, Kadapa 516 003.

Email: *Viswanath.prrm@gmail.com*