NANOTECHNOLOGY IN DRUG DELIVERY

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ABSTRACT

With the emerging field of polymer sciences synthesis of smart nanogel drug delivery systems have become inevitable which can prove effective for treatment as well as clinical progress . Nanogels are innovative drug delivery agents which play a vital role in pointing out issues related to old and modern courses of treatment. They possess high water content , desired properties and are biocompatible in nature . They ranges in the nanoscale 1- 100nm and contains a bulk which can be tuned to procure desirable effects. Nanotechnology leaves us with a ray of hope for treating neuro degenerative disorders like Alzheimer's, Parkinson's with less cost and risk among various other practices. As target specific release of payload is executed by these nanogel ,these are used as potential drug delivery vehicles in treating bacterial infections and CANCER .The pursuit of this review article is to concisely describe what nanoparticles are , what are their characteristics. Nanogels based drug delivery and their types of synthesis (wet chemical , green synthesis) .advanced nanoparticulate drug delivery mechanics including carbon nanotubes, nanoflowers ,their types, characteristics , preperatory approaches and applications in current research trends. Manifesting responses based on various external stimuli like temperature, pH, magnetic field and bacteria responsive nanogels and their mechanism of drug delivery

Key words ; nanogels, drug delivery, encapsulation, nanoparticles, carbon nanotubes, nanoflowers.

INTRODUCTION

Eventhough chemotherapy is used in ministering cancer in humans , numerous side effects like early menopause , fatigue , chemobrain , raised the need of discovering another effective treatment practice , which was fulfilled by nanogels . Nanogels are hydrogel nanoparticles or nanohydrogels which are made up of cross linking hydrophilic polymers . They comprise huge water quantity . Nanogels acts as vehicles which encapsulate the biological micromolecules like drugs , proteins and deliver them in a controlled approach at the specific site . A nanogel should have the following properties which make them suitable for human use . 1) A nanogel should be biocompatible biologically available 2) they should posses high drug loading capacity 3) they should be highly stable to promote prolonged circulation in the blood stream . 4) a nanogel should release the drug encapsulated in its hydrophilic core in a controlled manner in response to the stress or external stimuli . 5) the poly ethylene glycol coated nanogels must be efficient enough to camouflage the immune system . Nanogels have attained appreciable attention as nanoscopic drug carriers particularly for time directed and site specific

bioactive component release . The size of nanoparticles ranges from 1 - 1000nm in diameter. Advancements in the field of nanotechnology have reached a point where both hydrophobilic and hydrophobic drugs are being carried in the same core of the gel . Nanogels are grouped into various categories depending on their response to the type of external stimuli such as temperature responsive nanogels, nanogels which respond to pH , light , magnetic field , biological recognition molecules, bacteria responsive nanogels etc . Due to thier reduced toxicity levels and side effects in comparison to other treatment procedures , nanogels are being used in cancer treatment . Applications of nanotechnology not only includes cancer treatment but also in energy storage production agriculture productivity enhancement, waste water treatment and remediation etc.

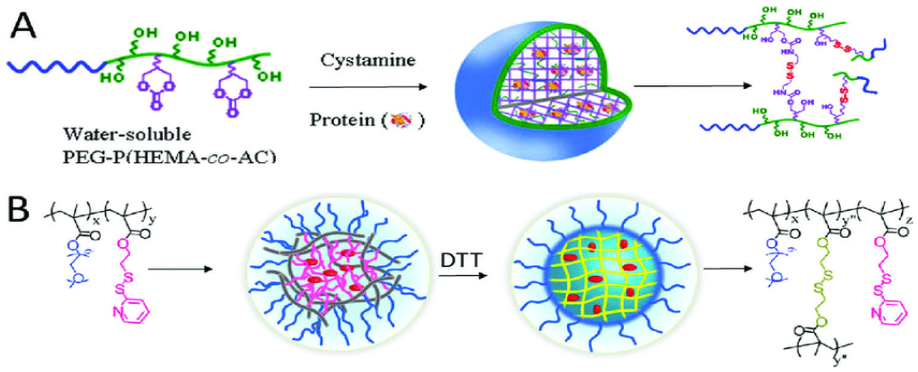
Preparation of Nanogel

Nanogels are unique assembly of hydrophilic or amphiphilc polymer that gained a lot of attention from world-wide researcher for multi-purpose drug delivery system. Nanogels are synthesized from copolymerization of hydrophilic or water soluble monomer in the presence of di-functional or tri-functional cross-linkers. There are diverse methods for the preparation of nanogel like inverse mini-emulsion polymerization, inverse micro-emulsion polymerization, and controlled/living radical polymerization etc. Here we have focused primarily on chemical methodologies which are majorly responsible for synthesis of large quantities of nanogel. With this restriction under consideration, we have divided methods of preparation of nanogel into two categories:-

- Synthesis of nanogel from pre-formed polymer
- Synthesis of nanogel through direct polymerization of monomers

Synthesis of nanogel from pre-formed polymer

Disulfide cross-linking:- Protein and peptides generally have disulfide bonds. They are generally responsible for stability and rigidity of protein. They are stable in certain condition and reversible in other conditions. Due to their reversible characteristics, they are used as cross-linking agents. Disulfide bonds can reversibly reduced to thiol group depending upon the concentration of thiol group in environment and under different pathological conditions. For example, in blood plasma the concentration of thiol group is different from the concentration of thiol in cytoplasm. Disulfide bonds can also reduced to thiol group by various other methods like application of U.V radiation, zinc dust etc. The thiol group can also react with highly reactive group such as disulfide group, iodoacetyl group and thiol containing biomolecules. Thayumanavan and coworkers prepared a nanogel by using RAFT-copolymerization technique in which oligo-ethylene glycol methacrylate polymerize with pyridyl disulfide derived methacrylate in which dithiothreitol was added in deficient amount. The dithiothreitol reduces the pyridyl disulfide group to thiol group which further react with equivalent amount of pyridyl disulfide to form disulfide cross-linked nanogel. Nanogel of different sizes is formed due to varying amount of polymer concentration and utilizing lower critical solution temperature of polymer.



Source-: DOI: 10.1039/c7tb02239e

This is a disulfide cross- linked core-shell nanoparticles made up of self assembled amphiphilic block copolymer that is hydrophobic cyclic carbonate and pyridyl disulfide moieties. The core of this gel is hydrophobic in nature initially but converted to hydrophilic nanogel matrix due to cross-linkage of cystamine and dithiothreitol . This hydrophilic matrix core is used as a carrier for protein and drug delivery.

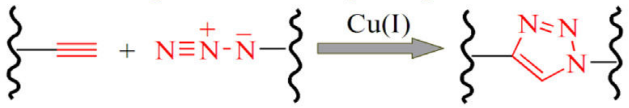
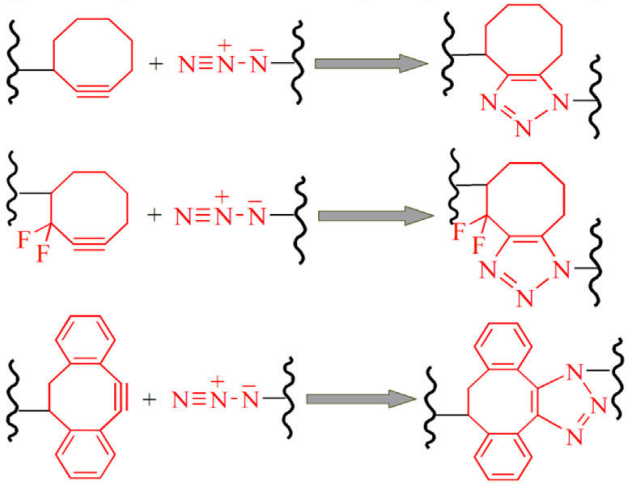
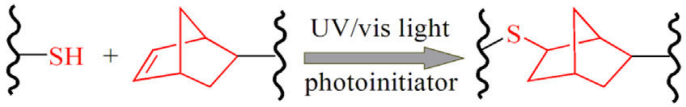
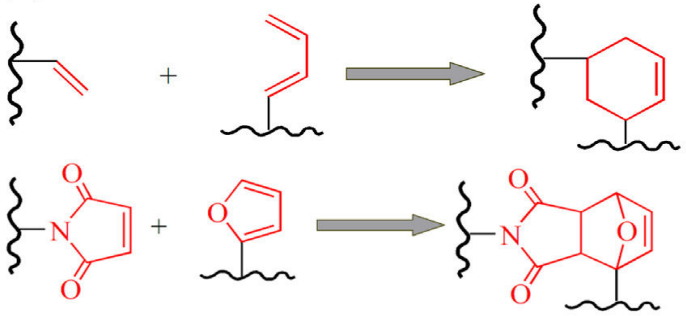
An ideal polymer associate's must be stable for the target delivery of DNA into the cell. The polymers associates must maintain their stability in prolong blood circulation and release DNA in controlled manner in response to chemical stimulus. The formation of core-shell nanogel (PIC) poly ion complex which contain disulfide cross-link inside the core, will dissociate in response to chemical stimulus for target drug delivery into the target cell. The poly ion complex such as polyethylene glycol block poly L lysine modified with thiol group using succinimidyl 3-(2 pyridyl dithio) propionate are used to form PIC micelle having disulfide cross-linkage core used to deliver plasmid DNA or non coding DNA into the target cell.

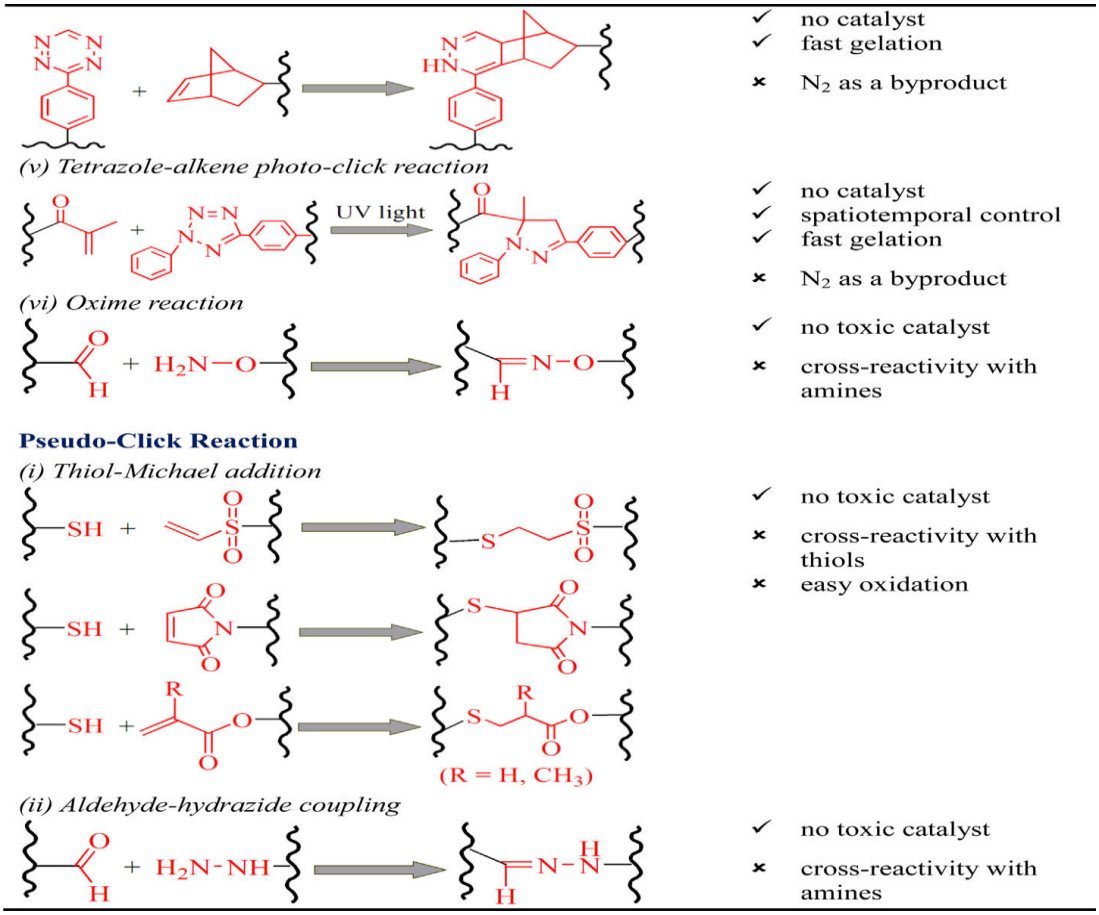
Other PIC complex like poly (ethylene glycol) –b-poly (L lysine) having iminothiolane cross linking agent is used to deliver siRNA to target cell. These PIC complex (PEG-b-PLL) have cationic amidine group that form interaction with anionic siRNA. They have also free sulfhydryl group for micelle inner core disulfide cross link formation. These disulfide cross link dissociated in subcellular site of activity where disulfide reducing agent is present in higher concentration than in blood plasma.

Click chemistry- Click chemistry is a quick reaction which is used for the preparation of nanogel. This reaction is highly specific; it gives us a quantitative yield, and has a high tolerability to different functional group. This reaction is carried out in water at room temperature. This reaction is also known as 1, 3 dipolar cycloaddition reaction or Huisgen cycloaddition. In this type of reactions, organic azide reacts with terminal alkynes to form 1, 2, 3 triazole. Later on, this triazole is used for various other applications like in the form of drug delivery vehicle.

Physically cross-linked nanogel like thermosensitive nanogel, ion cross-linked nanogel is synthesized under mild conditions and shows less stability near the target tissue. Whereas chemically cross-linked nanogel which are synthesized from photo- polymerization or enzymatic cross-linking shows more stability, durability and mechanical characteristics. But this chemical cross-linked nanogel requires initiator or enzymes which may shows some potential toxicity. Moreover, they also show some poor specificity, and unwanted cross linking with drugs and protein. Click chemistry overcome all these problems, they are highly reactive, highly selective and prepare nanogel under mild conditions. The nanogel synthesized from click chemistry is compatible with bioactive compounds like drug, and other bioactive like living cell and proteins. Recent development shows that we can also develop nanogel, microgel using click chemistry without the use of toxic catalyst.

Wooley and Hawker introduced nanogel preparation method by using click chemistry. Alkynes shell consist of functionalized dib lock copolymer micelle composed of poly (acrylic acid)-b-poly (styrene) which can be used as nanoscaffolds for the synthesis of nanogel. They had found that the first generation of azido termninated dendrimers form stable cross link with hydrophilic shell of micelle because of hydrophobicity of the azido terminated dendrimer of this generation is more than the others which are proved to be incompatible with hydrophilic corona of the micelle within aqueous solution. By observing this, they had changed the cross linking site from hydrophilic shell to hydrophobic core of the micelle and finally formed core cross-linked nanogel.:

Click Reactions	Features
Cu(I) Catalyzed Azide-Alkyne Cycloaddition (CuAAC) 	✓ bioorthogonality × toxic copper catalyst
Copper-Free Click Reaction *(i) Strain-promoted azide-alkyne cycloaddition (SPAAC)* 	✓ no catalyst ✓ bioorthogonality × difficult synthesis of cyclooctynes
(ii) Thiol-ene photocoupling 	✓ spatiotemporal control ✓ fast gelation × potential toxicity from photoinitiators and radicals × cross-reactivity with thiols
(iii) Diels-Alder reaction 	✓ no catalyst ✓ accelerated by H_2O ✓ thermoreversible × slow gelation
(iv) Inverse electron demand Diels-Alder reaction	



✓ no catalyst
✓ fast gelation
× N_2 as a byproduct

✓ no catalyst
✓ spatiotemporal control
✓ fast gelation
× N_2 as a byproduct

✓ no toxic catalyst
× cross-reactivity with amines

✓ no toxic catalyst
× cross-reactivity with thiols
× easy oxidation

✓ no toxic catalyst
× cross-reactivity with amines

Source-10.1016/j.biomaterials.2014.03.001

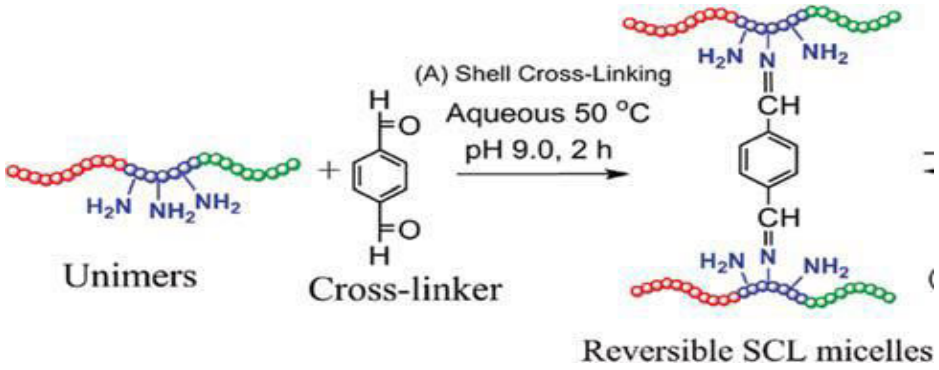
Different strategies of click chemistry to form nanogel

By using click chemistry, core cross-linked PIC (Polyion complex) micelle can by synthesized with thermoresponsive coronas. Azide containing monomers are incorporated into two oppositely charged backbone of graft ionomers P(MAA-co-AzPMMA)-g-PNIPAM and P(QDMA-co-AzPMA)-g-PNIPAM containing thermoresponsive PNIPAM graft chain. The self assembled PIC micelle are core stabilized by click reaction in aqueous solution by the addition of difunctional reagent propargyl ether.

Amine based cross-linking-: Nanogels are also formed through amino based cross-linking. This amino based cross-linking is possible because amine group is highly reactive towards carboxylic acid, esters, isocyanate etc. Researchers has made SCK (shell cross-linked knedel) like structure which is actually a unimolecular micelle like structure or a spherical micelle which gets stabilized by amino based cross-linking. They have also made a amphiphilic block copolymer which contain polyacrylic acid as a hydrophilic group and undergoes into cross-linking through amino group. Following the self assembly of amphiphilic block copolymer, carboxylic group undergoes into amidation reaction with diamine group which form a cross-linking into polymeric

micelle and leads to formation of nanogel. The remaining carboxylic group on the shell undergoes into other functionalities for orthogonal surface modification. Researchers also developed a pH responsive nanogel in which diamine cross-link contain acetal group. Following the self assembly of amphiphilic block copolymer into micelle structure, block copolymer containing poly(acrylic acid) and poly(styrene) were undergone into cross-link through amidation reaction containing acetal group.

Imine bond-induced cross-linking-: Imine bond-induced cross linking is also used to form nanogel. Polymeric micelles get stablished in response to external stimuli because of dynamic covalent interaction. Dynamic covalent imine bond is used to cross link between linear polymer chain to form core cross-linked polymer or nanogel nanoparticle. RAFT-polymerization is used to form cross link between novel aldehyde and amine functional styrenic and methyl methaacrylic based copolymer to form core cross-linked polymer micelle and spherical nanogel or nanoparticle. Researchers had developed a reversible SCL micelle. They had developed a temperature responsive triblock copolymer that is alpha-methoxypoly(ethylene oxide)-b-poly N-(3-aminopropyl) methacrylamide)-b-poly(N-isopropyl acrylamide) (mPEO-PAPMA-PNIPAM) by aqueous RAFT-polymerization. When the temperature get increased above LCST of PNIPAM, the polymer get self assemble into micelle form and the shell PAPMA get cross-linked with terephthaldicarboxyaldehyde to form SCL micelle with cleavage imine linkages.

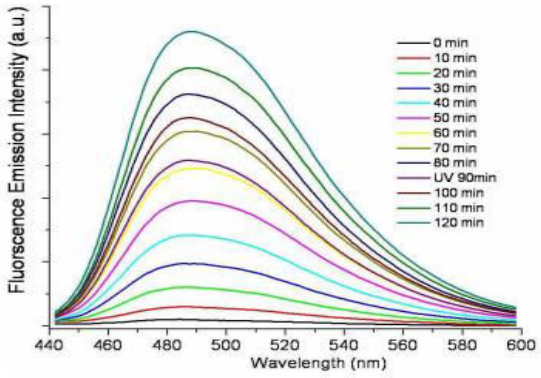


Source- **10.1081/E-EBPP-120050693**

PNIPAM SHELL CROSS-LINKED WITH TEREPHTHACARBOXALDEHYDE TO FORM SHELL CROSS-LINKED MICELL HAVING CLEVABLE DIAMINE LINKAGE

Photo induced cross-linking-: All the cross-linking method that we have discussed so far till now requires cross-linking agent or catalyst. The polymeric micelle that gets stabilized from such kind of conventional cross-linking method requires purification and must be separated from poor reactive cross-linking groups or its byproduct. Due to all these disadvantages, photo induced cross-linking method have been introduced. In this method, photo induced cross-linkers are used for stabilization of polymeric micelle, without using any chemical cross-linking agent or catalyst. Researchers have developed a photo responsive nanogel which is based on photo-controllable cross-linkers. In this method, they have used double hydrophilic block copolymer which consist of coumarin which can be dimerize when exposed to UV light of more than 310 nm wavelength.

Examples of recorded UV-vis and fluorescence emission spectra in the photocontrolled release experiments and determination of LCST are given below.



Source-: Photoresponsive nanogel based on photo controllable cross-link
Département de chimie, Université de Sherbrooke, Sherbrooke, Québec, Canada J1K 2R.1

Fluorescence emission spectra of dipyridamole λext = 415nm loaded in an un cross-linked micelle PEO-b-P(MEOMA-co-CMA). This micelle solution is placed in a dialysis membarne which is present in water/dioxane (2:1, v/v) solution filled in a UV cell. The increase in fluorescence only occur when dipyridamole is diffused through the dialysis membrane to the solution. After 80 min, the nanogel is exposed to UV light of wavelength less than 260nm for 3 min, and the rate of release of dipyridamole from the nanogel is increased due to cleavage of photo-induced cross-linkage.

They have combined the self assemble diblock copolymer micelle with photo-cross linking reaction. In this diblock copolymer, one block shows LCST (lower critical solution temperature) and have photo chromic side group, so when this self-assembled diblock copolymer gets heated up above LCST (T > LCST) then it forms diblock copolymer micelle and the reversible cross-link is carried out when photo chromic side group is illuminated with specific wavelength λ1 . By cooling the solution, T < LCST, the reversible cross-linked nanogel is formed. Because of the reversibility of photo controllable cross-linking reaction, the cross-link of nanogel get reduced when it gets illuminated by λ2 that causes swelling of nanogel

Preparation of nanogel from monomer polymerization

Synthesis of nanogel from monomer polymerization is a rapid process and it involves the polymerization-induced self assemble of the in situ formed polymer.

Precipitation polymerization- In precipitation polymerization, homogeneous mixture is formed. Polymerization process initiate from homogeneous solution and the polymer thus formed from such type of

polymerization is not swellable but soluble. To isolate the particle from homogeneous solution, cross-linker is used to cross-link the polymer chain. For example the synthesis of nanogel based on PNIPAM based polymer and its derivative. PNIPAM is a thermo-responsive polymer which shows thermo-sensitive properties. PNIPAM based nanogel undergoes into volume transition around LCST in water at 32degree Celsius. When PNIPAM based nanogel is heated above 32 degree then it becomes hydrophobic in nature and when they are heated below 32 degee Celsius, it becomes hydrophilic in nature and swelling of nanogel takes place. PNIPAM based nanogel has also some limitations due to narrow physical and chemical property.

Inverse mini-emulsion polymerization- Inverse mini-emulsion polymerization is water in oil heterogeneous polymerization process which forms kinetically stable inverse mini-emulsion around CMC (Critical micelle concentration). The aqueous solution contains water soluble monomers which dispersed in continuous organic medium with the help of oil soluble surfactant.
The inverse micro-emulsion is formed under high shear either by homogenizer or high speed mechanical stirrer. Oil soluble non-ionic surfactant is used to stabilize the colloidal particle of the inverse-mini emulsion. Radical initiators are used to initiate polymerization in aqueous solution to form colloidal particles. This method is used to develop water soluble nanoparticles. Water soluble nanoparticles are formed from PNIPAM, PAA, and PAAm. This method is also used to form PNIPAM based temperature sensitive hollow microsphere, core-shell nanocapsules which consist of hydrophobic shell and hydrophilic core. This method has been used to develop difunctinal cross-link nanogel. . By using this method we can introduce water soluble drug that can disperse into organic solvent. Temperature and pH sensitive nanogel P(NIPAM-co-AA) minigel and PAAm/PAA interpenetrating nanogel are synthesized in the presence of N,N-methylene bisacrylamide Swelling properties of such nanogel are studied by measuring the diameter of particle.

Stable inverse micro-emulsion polymerization- Stable inverse micro-emulsion polymerization is a process which forms thermodynamically stable inverse micro-emulsion in or around critical micelle concentration (CMC) by the addition of emulsifier agent more than the critical threshold.. This process involves aqueous droplets that get dispersed in continuous organic medium with the help of oil soluble surfactant. Polymerization involves the formation of water soluble colloidal nanoparticles having a diameter of around 50nm-100nm. Magnetic polymer nanoparticles and nanogel having difunctional cross-linkers are synthesized by using this method. Moreover, this method is also used to form Poly (vinylpyrrolidone) based nanogel incorporate with Dex as water soluble macromolecular carbohydrate drug. (HEA-co-AETMAC) nanogel are prepared in the presence of oligo(ethylene glycol dimethacrylate) (OEGDMA) as a cross-linker. The size or diameter of nanogel gel decreased as more cross-linking takes place. This small size nanogel can be used for gene delivery. The presence of quaternary ammonium ion side group helps the incorporation of DNA into the nanogel with the help of electrostatic interaction with phosphate group.

Atomic-transfer radical polymerization – Atomic transfer radical polymerization is a process by which we can prepare polymer with predetermined molecular weight and have a narrow molecular weight distribution. Atomic transfer radical polymerization is used to prepare bioconjugates like polymer with protein/peptides, polymer modified polysaccharide, hydrogels, nanogels, ligand stabilizing metal nanocrystal for cellular imaging.
The mechanism of ATRP is that lower oxidation state of transition metal CuI(I)/Lm act as an activator and react reversible with dormant species RX. X---CuI(II)\Lm is formed and radical R proceed to react with monomers for propagation which is rapidly get deactivated by reacting with X---CuI(II)\Lm to regenerate CuI(I)/Lm and a halogen terminated polymeric chain. Versatile method has been developed to prepare nanogel which consist of various characteristics, this method include ATRP, inverse miniemulsion and

disulfide-thiol exchange. The nanogel prepared from this method has various characteristics like high loading capacity, uniform network, bromine end group and degrade through hydrolysis or disulfide-thiol exchange.PANIPAM based nanogel are synthesisd by precipitation polymerization through ATRP in water . The cross-link biodegradable nanogel are synthesized by ATRP in inverse miniemulsion by disulfide functionalized dimethacrylate nanogel (DMA). The nanogel consist of halide end which functions as to extend the chain to fomr block copolymer. The nanogel prepared from such method are non-toxic and degrade to individual polymer chain in the presence of reducing environment having a narrow molecular weight distributiom to form uniform cross-linked nanogel. The swelling ratio, degradation capacity and colloidal stability of nanogel synthesized from ATRP is far more better than nanogel synthesized from conventional method.

Reverse addition-fragmentation chain transfer- Control or living radical polymerization is a very advance method for preparation of macromolecules. This method helps to synthesize macromolecule with predetermined molecular weight, having narrow molecular weight distribution. Among the many living or controlled radical polymerization, the RAFT is the most recommended technique for the polymerization of monomers.

There are various advantages of RAFT- polymerization:-

- Polymerization of monomers can take place in many different solvent like water, chain transfer agent and radical initiators.
- This method is highly tolerable to different functional groups. It can perform polymerization with pendant, omega and alpha end functional group for several biological applications.
- The RAFT method is compatible to various other polymerization method like bulk, suspension, emulsion and dispersion polymerization.
- RAFT polymerization has the ability to perform polymerization with different kinds of substrate, helps in surface modification and in situ formation of biopolymer bioconjugates

Two types of poly (N, N-dimethylacrylamide) with trithiocarbonate is produced by RAFT solution polymerization method are used as RAFT agent or act as a stabilizer in nanogel synthesis by RAFT precipitation/dispersion polymerization method. Two different types of PDMA which are produced by RAFT solution polymerization may be hydrophilic or amphiphilic depends on the type of R group RAFT agent have. When N, N- methylenebisacryamide is used as a cross-lining agent then thermosensitive nanogel is formed. In the absence of cross-linking the nanogel get dissociated to form individual block copolymer which can be studied for characterization of polymer.

Components of RAFT polymerization

(1) Initiators- It generates radical for polymerization process. Radicals can be thermo initiators or photo initiators. Low concentration of initiators is required for polymerization process and reduces the chances of termination.
(2) RAFT agent- RAFT agent is chosen depending on the type of monomer. If the monomer is methacrylate, then RAFT agent must be reactive.
(3) Solvent- It helps to slow down the process of polymerization

Mechanism-

- Initiators generate a radical species that polymerize monomers to form growing polymer chain.

- RAFT pre-equilibrium- The growing polymer chain with active radicals react with electrons of double bond of sulfur group of thio carbonyl thio compound and form RAFT agent with growing polymer species and radical R group. This R group radical goes on and initiate new polymer chain.
- Re-initiation- In re-initiation process, radical from new polymer chain
- RAFT main equilibrium step:- In this main equilibrium step, the polymer chain react with RAFT agent and form intermediate radical species that consist of dormant polymer chain on either side of RAFT agent. One of the two polymer chain from both side get dissociated and initiate polymerization of new polymer chain.
- Termination- Termination takes place when two radical groups combine to form dormant species. This can occur in the presence of initiators, radicals and two growing polymer chain. When two growing polymer chain interact with each other then it forms disproportion or coupling reaction. This can happen when large amount of monomer undergo polymerization to form new polymer chain. The main product formed from RAFT polymerization consist of polymer group having R group on one end and thio carbonyl thio compound on other end.

Types of stimulus responsive nanogel for drug delivery

pH responsive nanogels

PH is one of the factors which varies from one loacalized area of our body to another such as tissues, organoids , organs ,extra cellular environment etc.. Due to this differences , pH can be used as a criteria to deliver drugs at a specified regions using nanogels . PH responsive nanogels can be used as potential drug delivery vehicles which are characterized by the presence of benzoic imide bonds. Hydrogels possess a wide range of tunable bulk structure which can be tailored to produce desirable structures for therapeutic approaches. The cross linkings can protect the loaded drug from fluctuations in pH or by enzymatic activity . The crosslinking mesh work can be varied by altering the density of the crosslinking polymer . The pH responsive nanogels releases the encapsulated drug by two ways namely 1) pH triggered swelling and deswelling . The process completely depends on the ionic groups existing on the nanogel surface. PH responsive nanogel can be instigated into the body by three means namely , sub cutaneous injections , intravenous and oral methods depending on the target of action and number of barriers. The basic strategies for imparting pH behavior is by the ionic molecules undergoing confirmational changes in response to external environment or by cleavage of acid sensitive bonds and liberating the drug molecule attached to the polymer backbone. PH responsive nanogels are of three types ,polyanionic , polycationic and polyplex which is a combination of both . The key parameter for imparting pH dependent response is the pHc of the tissues which is the critical pH where the micro environment serves to release the drug encapsulated . Poly Acrylic Acid (PAA) which is a weakly acidic electrolyte that consists of poly polyanionc & polycationic nature can accept protons in acidic environments and can contribute protons in basic environment, whereas the trend is entirely different for weakly basic electrolytes they contribute protons in acidic environment and accept protons in the basic environment for eg : poly vinyl pyridine (PVP) , which paved way for pH dependent self charge converting nanogel which can be used as a anti cancer drug delivery agent

which enhances the drug absorption and aids in killing cancer cells (**Liusheng Zha et al.,DOI: 10.1039/c0sm01307b**) .

General rule for swelling ratio decreases as the number of crosslinks increases. Polymers such as poly ethylene glycol- poly methyl acrylate (PEG- PMA) incresses in size with increase in the pH whereas , poly ethylene oxide (PEO) , poly ethylene imide (PEI) decreases in size with increase in pH.

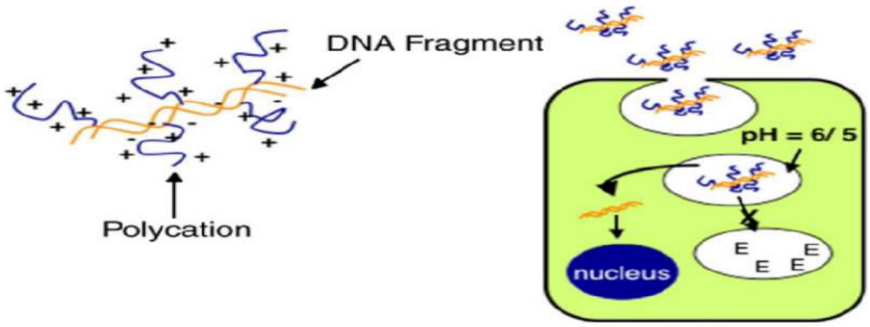
One step method for preparing pH responsive nanogels :

PH responsive nanogels can be prepared by two ways . One of them is copolymerization of monomers using bifunctional cross linkers . Wang and his colleagues have copolymerized acrylic acid and N,N bis acryloyl cistamine in the presence of azo bis(butyronitrile) as an initiator . The obtained nanogel can be conjugated with poly ethylene glycol (PEG) .(note : PEG can act as a camouflage against immune system). But the copolymerized nanogel was non- biodegradable which makes them inappropriate for human use as it becomes difficult to remove the remnants after delivering the drug . Another disavdvantage is that the process is time consuming and non cost effective.

The other method of synthesizing pH responsive nanogels is by crosslinking predormed pH responsive self assembled micelles . Chen et al., formed methoxyl poly ethylene glycol, - poly b (N , diaminomethyl methacrylate) and prepared a micellar solution to this diblock polymer . The cores of the micelles was linked by a bifunctional cross linker. This nanogel showed rapid release of the payload with decrease in the pH from 7.4 to 6.8 .(**Yi Li et al., DOI: 10.1021/acs.biomac.8b00195)**

Cellular uptake of polyplexs (polyanions + polycations)

A molecule which initiates cure can not essentially be a chemical source or substance, it can be a protein, a peptide, a nucleotide or a fragment of DNA. Non viral gene delivery has to satisfy numerous requirements. Primarily condensation of polycations and polyanions is to be met. The charge of the polyplex is slightly more positive so as to stabilize the DNA molecule . The polyplex after reaching the target cell enters the cell by pinocytosis or by receptor mediated endocytosis. Endosomes receives these polyplex . The environment is favoured as pH gets dropped ,hydrolyzing enzymes starts getting accumulated , this is when the polycationic nature of the polyplex comes into picture as soon as the cell starts acidifying the environment the polycations tries to maintain pH higher than expected range , this results in increased Osmotic pressure which leads to burst of the endosomes and releases the contents outside but yet the aim is not reached, the conjugated molecule has to reach the nucleus and express the protein ,but this is favourable only during cell division where the nuclear envelop is temporarily dissapeared. (**Dirk Schmalijohann .doi:10.1016/j.addr.2006.09.020)**



Cellular uptake of polyplex .

Source : doi:10.1016/j.addr.2006.09.020

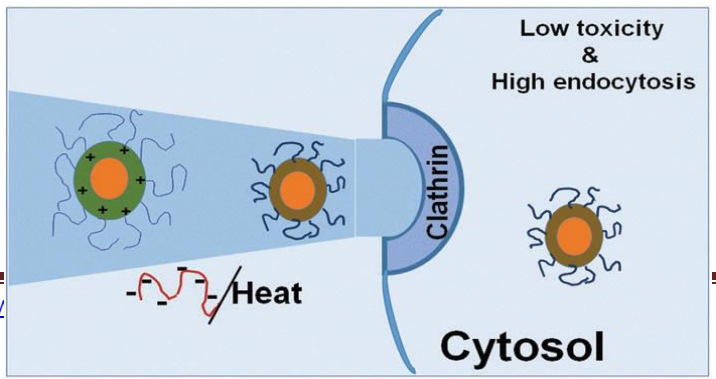
The concept of pH response can also be coupled with other responsive featured nanogels like , temperature or magnetic field or biological recognition molecules to enhnace the effect of drug delivery by creating a combined effect .these are termed as multi responsive drug delivery agents.

Temperature responsive nanogel for drug delivery: - Temperature responsive nanogel is a type of nanogel which undergoes volume transition around certain temperature called volume phase transition temperature (VPTT). There are two types of temperature responsive nanogel:-

- Negative temperature responsive nanogel
- Positive temperature responsive nanogel

Negative temperature responsive nanogel is a type of nanogel which has LCST (Lower critical solution temperature). The most studied negative temperature responsive nanogel was PNIPAM based nanogel (poly-N-isopropyl acryl amide nanogel).It has LCST 33 degree Celsius which is slightly lower than physiological temperature. Due to this disadvantage, it can prematurely release the encapsulated drug from nanogel before it reach to target tissue. This can be avoided by adding more hydrophilic monomers to the PNIPAM based nanogel that will weaken the volume transition and thus require higher temperature to release the encapsulated drug from nanogel. But this is not exactly the appropriates solution for temperature controlled drug release. Researchers have developed the non-PNIPAM based nanogel that has narrow volume phase transition temperature. That mean they are highly sensitive to a narrow range of temperature changes which cause volume transition which is very advantageous for temperature controlled drug release.

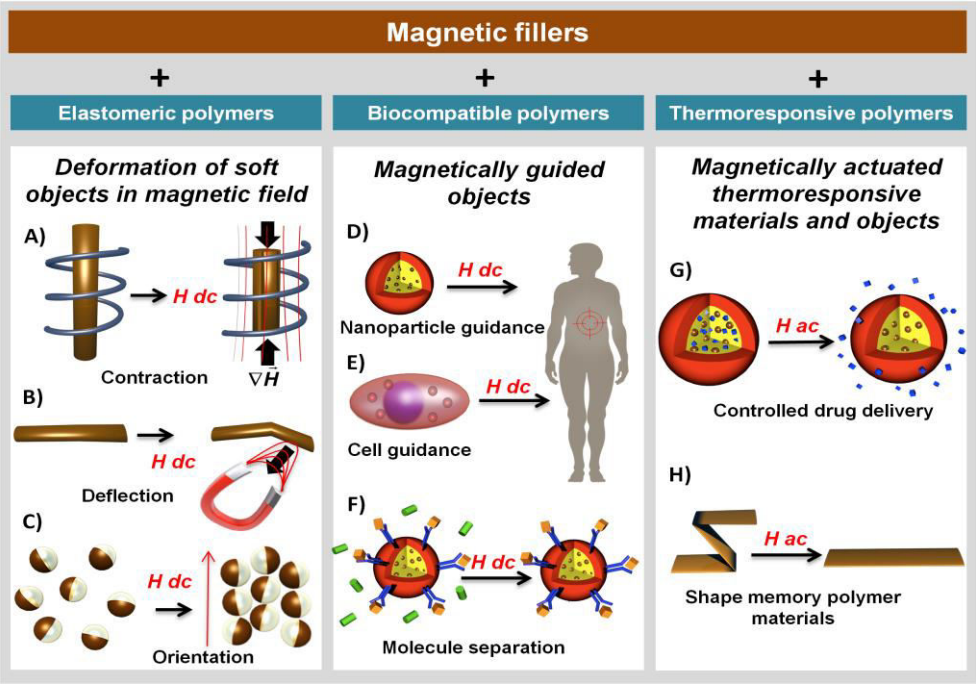
Positive temperature responsive nanogel- Positive temperature responsive nanogel is a type of nanogel which undergoes volume transition above UCST (Upper critical solution temperature). It requires higher temperature to undergo volume transition. Positive temperature responsive nanogel is more advantageous in case of drug delivery process. In this method, the drug incorporated into the



collapsed nanogel undergo into competitive interaction with polymer between species in biological fluid and drug incorporated into the nanogel which prevents the premature release of drug under physiological condition.. The drug release from nanogel in response to temperature is more advantageous than the squeezing release from de-swelling of nanogel.

Source- DOI: 10.1039/C5TB00366K

This is a representation of temperature sensitive nanocarrier, ionically complex nanogel PEG-PK-PA/HA compact by 37 degree Celsius get internalized through clathrin mediated endocytosis. Blue curve of first nanogel indicate PEG, Green domain indicate positive charge PK shell and Orange core indicates PA core of nanogel. Thick blue curve, brown domain of second nanogel indicate heat-induced partially shunken PEGs, Complex formation between Hyaluronic acid negative charge (red curve) and positive charge(PK) shell.



Source- 10.1039/c3cs60058k

This is a representation of Magnetic field responsive polymer obtained from doping of polymer with magnetic particles and their response when exposed to static H dc or alternating magnetic field H ac. Elastomeric polymer are deformed when exposed to homogeneous field or gradient in controlled fashion. MRPC (magnetic responsive polymer composite) are used for controlled drug delivery using magnetic field. MRPC are activated by induced magnetic field using alternating field.

Magnetic field responsive nanogel- Magnetic field responsive nanogel is a type of hybrid nanogel that consists of magnetic nanoparticles like Fe2O3, Fe3O4. Super paramagnetic nanoparticles are preferred for nanogel formation because it does not consist of any residual magnetism once applied magnetic field get stop. Magnetic nanoparticles are incorporated into the nanogel through various emulsion polymerization method. But this polymerization method does not actually confirm the uniform distribution of magnetic nanoparticles in nanogel. The toxicity of various magnetic nanoparticles varies depending on their size, composition, shape and surface functionalities. The contents of magnetic nanoparticles in nanogel and heat produced by magnetic field are important in determining the degree of responsiveness of magnetic field responsive nanogel. Researchers had developed a magnetic nanoparticles which were confirmed by transmission electron microscopy. The surface of magnetic nanoparticles are modified through silanization reaction which introduce amino group on surface that cause coupling reaction between hydroxypropyl cellulose and magnetic nanoparticles occur on the surface of particle.

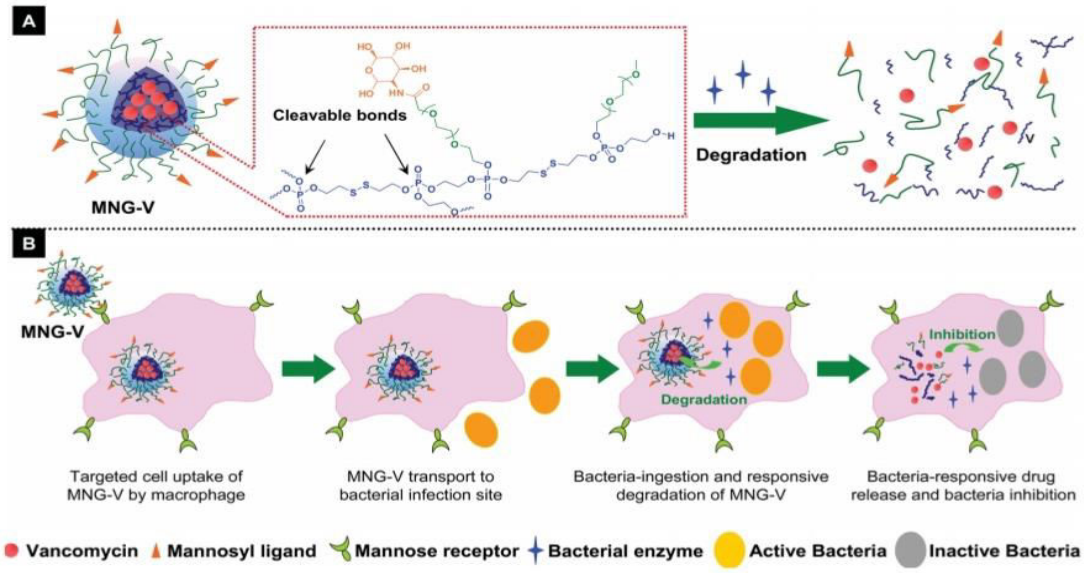
Magnetic field responsive nanoparticles are also used for remote control drug delivery process. The magnetic field responsive nanogel is transferred to the therapeutic site by the action of permanent magnetic field and finally the encapsulated drug gets released. For example – Researchers had developed a magnetic field responsive nanogel which was loaded with Bleomycin A5 hydrochloride.

This loaded nanogel was injected into rabbit which had auricular VX2 tumor. A permanent magnet was placed on to the tumor for 24 hours and after two weeks its size was getting reduced. It is due to accumulation of large amount of magnetic field responsive nanogel loaded with BLM on to the tumor. In another research, a permanent magnetic field was applied on to back right leg of rabbit and it was observed that magnetic polyacrylamide nanogel was accumulated in higher concentration on back right leg as compared to back left leg of rabbit

BACTERIA RESPONSIVE NANOGEL

Tactics that use distinct microenvironments as a molecular nod to release the drug encapsulated and cellular uptake has grabbed attention in the modern research sector. One such practice is the preparation of bacteria responsive nanogels ,one of the major advantage of bacteria responsive nanogels over other drug delivery approaches is that these nanoparticles uses the specific microenvironment as a construct to release the drug . The microenvironment might be a toxin, change in temperature or pH at the infected site ,or bacterial enzymes or lipase . The contents released by the cancer cellsare usually acidic in nature . Bacteria responsive nanogels are made up of two layers the first layer is usually of a poly ethylene glycol (PEG) which furnish hydrophilic properties to the gel and also escapes the gel from immune system providing camouflage effects. The second layer is made up of

polyphosphoester which can only be cleaved by polyphosphatase or lipase activity . Bacteria can survive even after phagocytic ingestion ,macrophages have capacity to release drugs at infected region by chemitactic method . So macrophages are made as used as a platform to reduce microbial growth or completely wipe out infection. Prof.wang et al., developed a mannosylated nanogel which is coated with poly ethylene glycol (PEG) . Mannose ligands arms are conjugated to the PEG layer and polyphosphoester core encapsulates the drug (bacteria suppressor or duxorubicin or vanomycin for cancer cell treatement). Bacteria have evolved to such a level where macrophages directly are not capable for manifesting phagocytosis . The mannose receptors present on the macrophages conjugates with the mannosylated nanogel's mannose ligands and uptakes the gel .The infection causing bacterial cells releases bacterial enzymes which cleaves the polyphosphoester layer and results in the release of drug which supresses the bacterial growth and the remnants are cleaned by the macrophages as a routine cell process. These nanogels are efficiently used in cancer treatements due to the pin pointed effect on its target cells ,unless there is no release of toxic conents from the infected area the drug buried in the hydrophobic core is not released outside ,which reduces the toxic effect and these nanogels are biodegradable in nature which makes it easy for the body to remove leftovers with ease.(**prof. J wang et al., DOI: 10.1002/adma.201202847**)



Representation of vanomycin loaded mannosylated nanogel system and bacteria responsive drug release (A). Representation of mannosylated nanogel transport ,degradation, release of payload and bacterial inhibition (B)

Source: DOI: 10.1002/adma.201202847

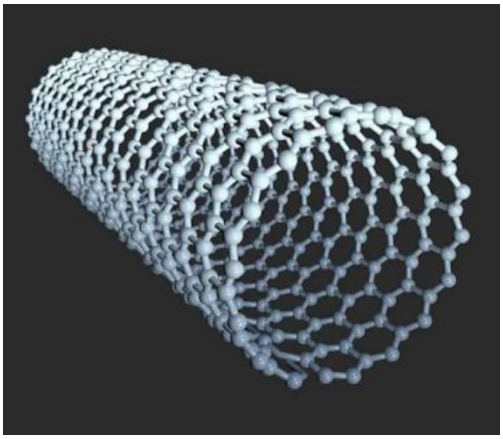
CARBON NANOTUBES

Carbon nanotubes are nano structures which can be conjugated with drugs , proteins , nucleic acids to afford biofunctionalities . Carbon nanotubes are allotropes of carbon which are produced as a result of

rolled graphene sheets . Each unit of the rolled graphene sheet is a hexagon . They are efficient drug delivery systems due to their larger surface area which helps in loading appreciable amount of drugs which are absorbed at the target site with enhanced permeability and retention effect . Carbon nanotubes were first studied by Sumio Ijima in 1991. Based on number of layers carbon nanotubes are classified into two Categories 1) Single walled carbon nanotubes (SWCNTS) , 2) multi walled carbon nanotubes (MWCNTS).

SINGLE WALLED CARBON NANOTUBES :

The name itself is self explanatory carbon nanotubes that consist of only one layer of rolled graphene sheet are called single walled carbon nanotubes with the diameter ranging from 0.4 to 2 nm depending on the temperature at which they are synthesized . Higher growth temperature results in increased diameter. They have a larger surface area of approximately 1300m²/g which makes them suitable for drug delivery approaches. Due to ultra high surface area and high drug loading capacity single walled carbon nanotubes are considered effective drug delivery agents . Studies confirmed that SWCNTS complexed with drugs have longer duration in the blood circulation making them suitable for controlled and prolonged drug release at the site specified .



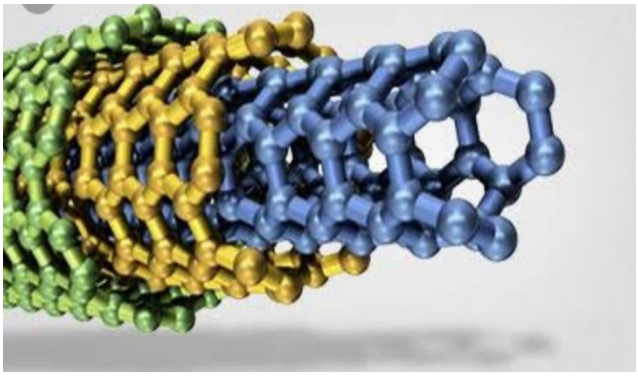
Single walled carbon nanotubes.

(Each unit in the graphene sheet is a hexagon.)

MULTI WALLED CARBON NANOTUBES ;

Carbon nanotubes which consists of more than one layer of rolled graphene sheets are called multi walled carbon nanotubes. MWCNTS . The diameter of the outermost graphene sheet ranging from 2-100 nm and inner graphene sheet from 1-3 nm . Based on the arrangement of the graphene layers MWCNTS are classified into two types further namely . a) RUSSIAN DOLL , b) PARCHMENT .

If , the graphene sheets are arranged layer by layer over one another then the resulting structure is called a russia doll. If , only one graphene sheet is rolled numerous times to give a structure which looks like a multi walled carbon nanotube then it is referred to as parchment. The young's modulus of MWCNTS is 1.8 terra Pascal which is much stronger than steel



Parchment (MWCNTS) **RUSSIAN DOLL (MWCNTS).**

Carbon nanotubes are further classified into two types based on the chirality namely 1) Achiral carbon nanotubes 2) chiral carbon nanotubes. Achiral carbon nanotubes are further classified intlo two types based on the arrangement of atoms into arm chair carbon nanotubes and zig zag carbon nanotubes. (**parijit pandey , mandeep dahiya ISSN: 2455-4685, Volume 1; Issue 4; May 2016; Page No. 15-21)**

Characteristic properties

1) As these nanostructures are made up of carbon due to the high tensile strength of the 2D matrices they exhibit structural stability

2) every carbon atom in the nanotubes are attached to one another by covalent linkages . The presence of numerous covalent bonds ensures high melting point of the structure which is approximately closer to 3400 kelvin.

3) YOUNG'S MODULUS of these carbon nanotubes is ~ 1 terra Pascal (note : young modulus is a measure of stiffness of a material)

4) they exhibit high thermal conductivity due to the presence of sp^2 hybridized atoms.

5) every unit in the nanotube is a hexagon which suggests that one carbon atom is bonded to 3 carbon atoms leaving one electron free. Which contributes to ballistic transport of electrons in a medium and therefore the sea of delocalized electrons makes them good conductors of electricity.

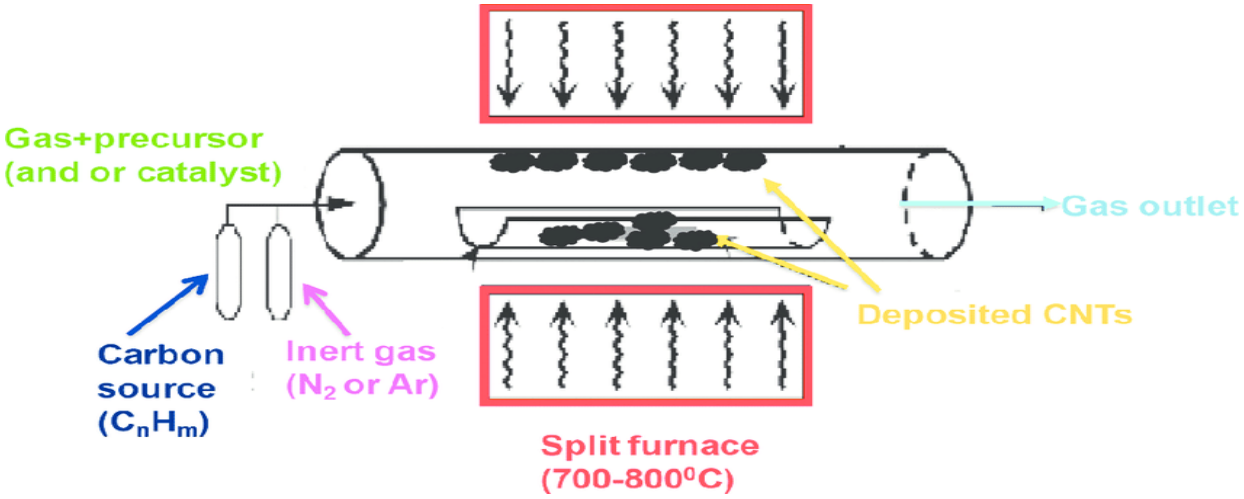
6) carbon nanotubes are hydrophobic in nature .

PREPERATION OF CARBON NANOTUBES BY LASER ABLATION METHOD ;

Light amplification by stimulated emission of radiation ablation is a method of preperation of carbon nanotubes by using high energetic pulsed beam laser with ŕan intensity of 10^7 W / cm^3 . The laser is projected or incident on a target material and the emmitted desirable particles in vapour form is carried by a gaseous medium on to a coolant where the vapourized desirable particles are condensed and are seperated . The target material must be a rich source of carbon , so, garaphite composite is recommened to use as it is readily available . The graphite composite is placed in a Quartz furnace which consists of Argon gas . Argon gas acts as a carrier for the vapourized carbon particles . Graphite composite is mixed with 1% of either copper or nickel which acts as a catalyst prior to laser treatment. The laser which is used in the process is ND-YAG laser (neodymium doped Yttrium Aluminum Garnet). (garnet is a silicate material). ND-YAG laser is a four level laser sysytem which is capable of cleaving carbon - carbon covalent linkages in the graphite composite. Once the laser is incident on to the graphite composite due to its high intensity the carbon particles in the graphite composite gets vapourized which are carried onto the coolant by argon gas medium . The cooled carbon particles forms carbon nanotubes . Laser ablation method can be used to synthesize both single walled carbon nanotubes and multi walled carbon nanotubes . Single walled carbon nanotubes produced feom this technique ranges from 1.0 - 1.6 nm in diameter which are 90% pure. The only disadvantage of this process is it is not cost effective.

PREPERATION OF CARBON NANOTUBES BY CHEMICAL VAPOUR DEPOSITION ;

In this process chemical reaction occurs on the surface of the substrate . The major requirements for the preperation of carbon nanotubes by chemical vapour deposition are reaction substrates which is powder activated carbon commonly called as (PAC). A catalyst such as nickel or , copperor , iron or , or molybdenum . A precursor gas which serves as the actual source of carbon like acetylene , or ethylene or ethanol or methanol. and a carrier gas / forced gas such as ammonia , hydrogen . The reaction chamber consists of the substrate which is impregnated with catalyst molecules prior to precursor gas treatment. Precursor gas / carbon containing gas is passed on to the substrate which is placed in between a split furnace maintained at 700 -800°C . But the movement and adsorption of precursor gas is facilitated by the forced gas which makes sure that the precursor gas is getting reacted with the substrate . Reaction is carried out on the surface of the substrate and the undesirable byproducts are removed out of the reaction chamber by the forced gas. A newly evolved method called plasma enhanced chemical vapour deposition is also used in the preparation of carbon nanotubes.

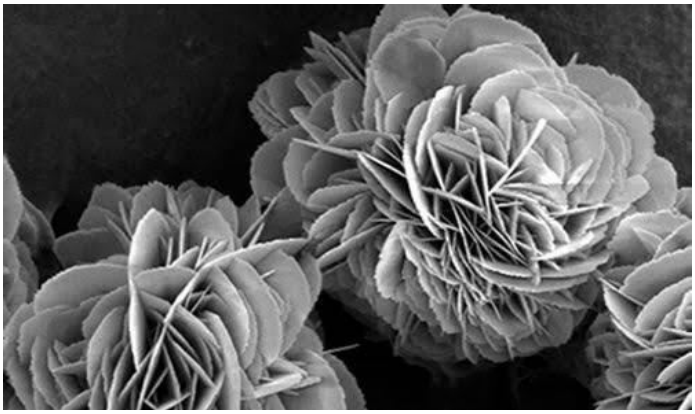


Chemical vapour deposition approach of carbon nanotubes preperation.

NANOFLOWERS

Nanoflowers are advanced nanoparticulate systems which has the potential to deliver drugs at the site specified with maximum intensity . Due to their efficiency , simple methods of preperation and enzyme stabilizing capacity they have grabbed attention in the modern pharmaceuticals sectors . They are used in drug delivery , waste water treatments , biosensors , energy storing cells , removal of toxins and impurities from the body , diabetes management , optoelectronics , reorography , nanoliners , single negatron transistors , anti cancer therapies etc.. the applications of nanoflowers are determined by their size , shape, protein ratio. Nanoflowers are typically in the shape of a flower with petals ranging in the nanoscale from 100-500 nm. Nanoflowers can be synthesized by organic and inorganic means or a combination of both . Petals of nanoflowers circumscribe increased surface ratio and increased stability . The efficiency of nanoflowers are increased by coupling with external stimuli like pH, flouroscenes, surface charges etc.

Nanoflowers are of various types namely 1) gold nanoflowers, 2) siver nanoflowers, 3) monooxide nanoflowers , 4) elemental nanoflowers, 5) sulphide , sellenide, telluride nanoflowers, 6) nanoflower hydroxides and oxosalts (**review on nanoflowers, Dangara ekta et al.,)**



Nanoflowers

PREPERATION OF NANOFLOWERS

Most common type of nanoflowers used are Au nanoflowers / gold nanoflowers which are produced as a result of reduction of metal .It requires a source of gold and reaction directing agents . HAuCl4 acts as a souce of gold . The aqueous solution of HAuCl4 cobined with poly vinyl pyrolidine (PVP) and ethanol in the presence of silver ions (Ag ions) irradiated with Ultraviolet light results in a sheet of gold plated nanoflowers ,here ethanol and Ag ions acts as reaction directing agents . The other method of preperation of nanoflowers is by using N -2 hydroxy ethylene pipersine and N-2 ethane sulphonic acid as reducing or stabilizing agents and HAuCl4 as the souce of gold . Citrate can also be used as a precursor molecule for the synthesis of nanoflowers. Recently a novel Au / pt nanoflowers has been developed by electronic deposition of H2PtCl6 and HAuCl4 on a polyamido amine dendrimer which acts as source of pt and Au respectively. The hexagonal flowers cobalt crystalline covered multi walled carbon nanotubes are also used as drug delivery agents .

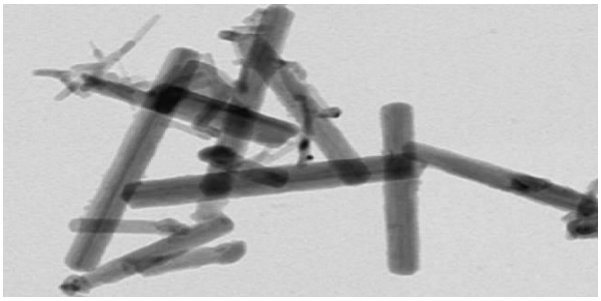
GREEN SYNTHESIS OF NANOPARTICLES:

(Using leaf extract :)

TUNGSTEN OXIDE NANORODS SYNTHESIS BY HYDROTHERMAL APPROACH

Nanoflowers are nanoparticle drug delivery vehicles which ranges in the nanoscale of 1 - 100 nm . The size of the nanoparticles we end up obtaing after the experiment are affected by numerous factors like temperature at which the set up is maintained , its PH , amount or quantity of precursor used and its nature of reactivity , quantity of capping agent or stabilizing agent involved , amount of reducing agent added in grams ,etc.. In tungsten oxide nanorods synthesis the requirements are silver tungstate , oxalic acid , hydrochloric acid, potassium sulphate, and deionised water . Initially silver tungstate and oxalic acid is dissolved in deionized water (quantities are optimized to obtain the required size of nanoparticles and depends on the type of use as well) . Hydrochloric acid is added drop wise into the solution till pH of the solution becomes 8.0. Then add potassium sulphate into this solution till the solution turns light yellow . The solution is then shifted into a hydrothermal setup which is maintained

at 100°C for 24 hours , the yellow coloured precipitate is colleceted which consists of our tungsten oxide nanorods .



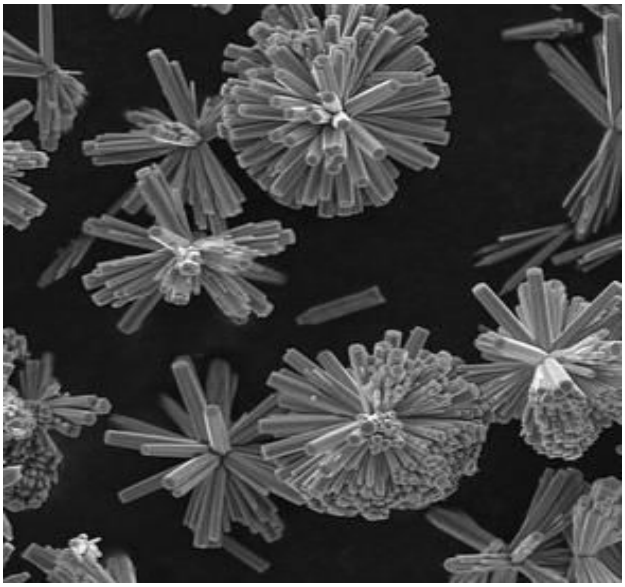
Tungsten oxide nanorods (50nm)

COPPER NANOPARTICLES SYNTHESIS ;

Requirements include deionised water, copper nitrate as precursor or source of the metal , capping / stabilizing agent is polyvinyl pyrolidine , and reducing agent is hydrazine hydrates . 200ml pf deionized water is taken into which polyvinyl pyridine -30 is taken for about 4g and strillered thoroughly by maintaining the temperature at 60°C and to this solution add CuNO3 2gm is added and stirred for 10 min till the colour reaches light green which indicates formation of nanoparticles which are seperated out via centrifugation and further analyzed .with the above mentioned quantities the nanoparticles obtained ranges less than 10nm in diameter and UV absorption spectroscopy peak would be attained at 600 nm

ZINC OXIDE NANOFLOWERS PREPERATION ;

Silver coated zinc oxide nanoflowers are characterized by numerous adsorption surfaces which is prepared by reacting potassium hydroxide with zinc nitrate . The temperature should not exceed more than 60°C , initially add KOH into Zn (NO3)2 .6H2O maintaining at 60°C . The suspension thus formed is centrifuged at 5000-7000 rpm till a white colured poweder is formed , the poweder is subjected to calcination at 500°C for 3 hours (calcination is a process of heating materials in the presence of oxygen at high temperature in simple terms). The above mentioned process results in the production of zinc oxide nanoflowers which are spherical and 30nm in diameter with a UV visible spectroscopy range of 380 nm .



Zinc oxide nanoflowers (spherical)

SILVER NANOPARTICLES GREEN SYNTHESIS FROM DESIRED LEAF EXTRACT Requirements includes a deionized water , Silver nitrate , desired leaves . The leaf parts are washed with deionized water and are made into pieces . The pieces are transferred into a beaker containing deionized water and stirred properly till the water becomes light green which indicates the transfer of leaf extracts into the beaker containing deionized water . The solution is filtered to remove the solid waste and the filtered solution is taken into a burette . This solution is added drop wise into the container of silver nitrate drop wise till the white coloured solution turns light yellow which indicates formation of silver nanoparticles . It can also be performed with copper nitrate to produce copper nanoparticles by replacing silver nitrate in the above mentioned process where the colour turns light green instead of yellow.

Note : precursor type and nature , capping agent , reducing agent determines the size of the nanoparticles ultimately formed . Polyvinyl pyrolidine ,polyvinyl chloride are recommended to use as capping agents or stabilizing agents the lesser is the concentration of the capping agents the greater or bigger is the size of the nanoparticles. Similarly the more is the concentration of precursor the bigger is the size of nanoparticles. Reducing agents like hydrazine hydrates are highly recommended for better results ,the higher is the concentration of reducing agents the grater is the size of the resultant particles. Temperature is one the deciding factor higher temperature results in better nanoparticle size but it should not exceed more than 60°C as increase in temperature leads to inappropriate structures.

MAGNESIUM - OXIDE NANOFLOWERS PREPERATION AND USAGE IN WASTE WATER TREATMENT ;

Activated carbon is used in the treatment of wastewater. Removal of heavy metals from polluted water by adsorption using activated carbon has its own disadvantages like poor adsorption capacity, resabsorption etc. Inorder to overcome this hurdle magnesium oxide nanoflowers were synthesized which is cost effective, bioavailable and with high adsorption capacity. 0.2M Mg^{2+} solution is to be prepared by mixing MgCl2. 6H2O in distilled water to which 0.5M NaOH is added dropwise and continuously stirred at 600 rpm using magnetic stirrer till precipitate is formed .The precipitate thus formed is subjected to centrifugation at 500 rpm for 15 min . The centrifuged precipitate is then washed with distilled water and is dried in hot air oven at 60°C for 48 hours , the dried Mg (OH)2 is grounded in a tube mill and calcinated in a muffle furnace to remove the moisture content forming the water free MgO paricles (MgO particles can also be synthesized by GREEN SYNTHESIS method using spinach leaves but the later process is time consuming which involves seperation of nanoparticles from the solution). The MgO particles are treated with acacia gum to introduce surface modifications(due to this surface modifications flower shaped appearance is obtained), both 10% acacia solution is prepared and 20% acacia solution is prepared and efficiency is compared among bare MgO nanoflowers, 10% acacia mixed MgO and 20% acacia treated MgO nanoflowers.

It is observed that these nanoflowers removed divalent ions like Ni, Pb, Cu,Cd , Zn, Co,Mn from the water as an experiment was conducted by preparing synthetic waste water which is mixed with divalent ions and agitated using temperature controlled agitator. Bare MgO nanoflowers are positively charged wheras acacia is negatively charged .Both the acacia treated nanoflowers are efficient in removing ions from the waste water to a greater extent with minimum differences in order of adsorption in ions ,this difference might be due to the surface charge distribution. **Varsha srivasthava et al., DOI: http://dx.doi.org/10.1016/j.ceramint.2015.01.112)**

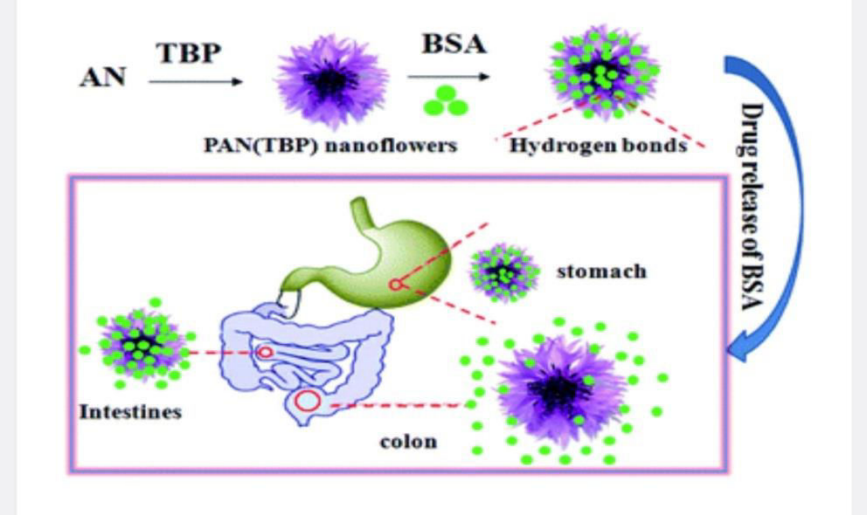
ADVANTAGES ANDDISADVANTAGES OF NANOFLOWERS AS A WHOLE ;

Due to the presence of petals which increases the surface area of absorption these nanoflowers are advantageous over regular oral drug delivery vehicles as they have increased surface to volume ratio . The increased surface to volume ratio enhances drug loading capacity and targeted release of payload. For example the Ag coated ZnO nanoflowers shows numerous surface areas for adsorption by enhanced Raman spectroscopy. They can be used for protein instability and immobilization which ensures pin pointed activity . The disadvantages are the petals and the dimensions of these nanomaterials cannot be controlled while or after the reaction .Apart from green synthesis method Nanoflowers can be prepared by ionotropic gelation method , and also by precipitation but in synthetic reactions the temperature might exceed 550°c which results in formation of toxins and other waste byproducts.

MECHANISM OF PAN NANOFLOWERS ON ULCERATIVE COLITIS;

Ulcerative colitis is a recurrent chronic condition where lesions in colon are observed with characterized ulcers . Traditional oral drug delivery of sustainable drugs treats the condition to certain extent but the major disadvantage includes absorption of drug by the blood before reaching target site is observed which decreases the overall drug concentration and intensity of action at the target site .

So there was a need to develop nano drug delivery vehicles which can overcome the disadvantage, also the increase in nanoparticle size can affect the drug loading rate , decrease in size would lead to aggregation and impacts the normal movement in the gastrointestinal tract . Considering all the requirements , poly acrylonitrile (PAN) nanoflowers which ranges from 300 -500 nm coupledwith pH are introduced using Bovine serium Albumin as potential drug to treat colitis has been developed , which has high drug loading rate and due to its smaller size compared to regular drug delivery vehicles they donot affect the normal transport in GIT as well . At the site of disease due to the presence of excess hydrogen ions , the nanoflower and its petals which are pH sensitive gets triggered and expands which releases the payload (BSA) at the site of action .



(**Source : https://doi.org/10.1039/D0RA01427C**)

Representation of pH sensitive PAN nanoflowers in Ulcerative colitis treatement .

Applications:-

Nanotechnology has revolutionized the drug delivery system. It has given promising results in delivery of drug to target tissues because of their biocompatibility, water solubility and their capacity to encapsulate drug. Researchers had developed a pH- responsive charge conversional nanogel for tumor cell uptake and Dox drug delivery. These types of nanogels are synthesized from poly (2-aminoethyl methacrylate hydrochloride) which reacts with 2, 3- dimethyl maleic anhydride to produce a negative charge nanogel. In another application of nanotechnology, treatment of inflammatory disorder like rheumatoid arthritis is done by delivery of therapeutic molecules. Macrophages cells are targeted by using photodynamic therapy. Researchers had developed a chitosan based nanogel decorated with hyalronate loaded with photosensitizer to treat macrophages. Nanotechnology has also been used to deliver local anesthetic drug. Researchers had developed

a poly (ε-caprolactone)-poly (ethylene glycol)-poly (ε-caprolactone) (PCL-PEG-PCL or PCEC) nanoparticlesfor target delivery of lidocain drug. This nanoparticle is coated with hydrophilic thermo sensitive pluronic acid F-127 hydrogel to form composite carrier nanoparticles. In studies it shows that this type of nanogel can successfully infiltrate the wound to deliver anesthetic drug in post operation periods.

The functionalization of carbon nanotubes makes them flexible for using in various fields. The structure of these nanoparticles which consists of an external core and internal core can be modified using various functional groups and can be used as drug delivery agents , bio sensors , water resistant material manufacturing, the high young's modulus factor makes these carbon nanotubes makes them suitable for bullet proof jacket making etc. In blood cancer treatment especially in the case of acute lymphoblastic leukemia which starts in the bone marrow and slowly effects the other tissues and organs . Taghdisi et al., designed a complex of effective acute lymphoblastic leukemia drug daunorubicin and single walled carbon nanotubes and named it as DAU OPTAMER -SWCNT which was effective in drug release at the infected sites. They can also be used in the treatment of breast cancer , cervical cancer , liver cancer , brain cancer , immunotherapy, biosensing , tissue engineering etc.

Nanoflowers are used in enzyme purification, adsorption is one of the predominant characteristic element of these nanoparticle which can be used as replacement for activated carbon in removing heavy metals from the water which helps in waste water treatment as they cannot undergo desorption and regeration which is an added advantage . In removal of dyes , ultrasensitive detection of photo sensitive biomarkers of a disease , anti cancer therapeutic practices etc. Recent advancements suggest that they can be capable of angiogenesis in the furture (angiogenesis: formation of new capillaries feom the pre existing ones).

Conclusion- Here in this review paper, we have discussed about all the recent development of nanogel as drug delivery carriers for biological and biomedical applications. Among various synthetic strategies available so far, we have discussed about chemical approaches for synthesis of nanogel, that is synthesis of nanogel from preformed polymer and synthesis of nanogel from monomer polymerization. The synthesis of nanogel from preformed polymer involves locking of self assembled amphiphilic block copolymer. This method involves cross-linking of polymer which we have discussed in great detail. The other chemical method for synthesis of nanogel involves direct polymerization of monomer like heterogeneous free radical polymerization and free/controlled radical polymerization. Heterogeneous polymerization method involves polymerization of hydrophilic monomers in the presence of difunctional or multifunctional cross-linkers for synthesis of nanogel. Controlled radical polymerization method like ATRP and RAFT are also discussed to form stable nanogel of well controlled polymer. Among various ATRP methods, combination of ATRP, inverse mini-emulsion polymerization and thiol-disulfide exchange are used to form water-soluble biodegradable polymer. We have also discussed about the classification, properties, application and limitations of carbon nanotubes. We have discussed not only unique properties but also its toxic effect during the use of metal. Chemical vapour deposition method is the best method for preparation of carbon nanotubes. Among the various other nanoparticle system, we have also discussed about the recently developed nanoflowers which shows similarity to plant flower. The method of preparation of nanoflowers is quite easy. Nanoflowers are synthesized from

both organic and inorganic molecules and sometime it requires the combination of both. It has various advantages like it shows high surface to volume ratio to enhance surface adsorption for accelerating the kinetics of reaction. It shows high charge and carrier immobility due to large surface area, the efficiency of surface reaction is increased in the 3D structure of nanoflowers. In this review paper, we have also discussed about different types of stimulus responsive nanogel. Many researches is going on to find out the mechanism which will deliver the therapeutic agent to target tissues through various physiological barrier. These physiological barriers prevent the internalization of large size drug with undesirable property. The development of stimulus responsive nanogel helps us to treat cancer with less toxicity and with less side effect method. In future the nanogel is designed in such a way that it will specifically bind to any particular residue and able to uptake by any particular cell especially cancerous cell. Chemist and biologist are learning from each other and try to understand the specific interaction between bimolecular and cellular integrin receptor which will be added in in future advanced drug delivery system.

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