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Review

PNIPAM Poly (N-isopropylacrylamide): A Thermoresponsive "Smart" Polymer in Novel Drug Delivery Systems

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ABSTRACT: Over the past years, extensive research has been carried out in designing and optimizing various drug delivery systems in order to maximize therapeutic effect and minimize unwanted effects of drugs. Many drug carrier systems have been developed on the basis of nanotechnology including systems based on polymeric nanoparticles. Polymeric drug delivery research has been extended to targeting of the drug at the specific site by utilizing various stimuli responsive systems which depend upon physiological conditions of the body such as pH of biological fluids and temperature of the human body. Thermoresponsive polymers with Lower Critical Solution Temperature (LCST) have been investigated for various biomedical and pharmaceutical formulations. One such polymer of considerable focus is PNIPAM Poly (N-isopropylacrylamide). PNIPAM is a thermosensitive polymer which has been utilized in many drug delivery systems including for cancer therapeutics. The present article deals with the properties of PNIPAM and their applications in different drug delivery systems.

KEY WORDS: ***PNIPAM; LCST; Properties; Synthesis; Applications***

INTRODUCTION

One of the main drawbacks of conventional therapy as compared to newer drug delivery systems is the non specific action of the administered drugs which leads to an increase in side effects. As a result, in recent times, extensive research has been carried out in designing and optimizing various drug delivery systems in order to maximize therapeutic effect and minimize unwanted effects of drugs. Nanoscale based drug carriers have received enormous attention in developing an ideal drug delivery system.[1,2] Nanocarriers, as implied by their name, are those having dimensions within 200nm. Many drug carrier systems have been developed on the basis of nanotechnology which may include liposomes, systems based on polymeric nanoparticles, dendrimers to name a few.

Over the past few years, considerable attention has been conferred to nanoparticles and their potential in drug delivery. Being submicron in size, such drug delivery systems can be administered intravenously thereby avoiding many barriers in the human body and first pass metabolism. In addition, these nanoparticles aid in controlling the release of the drug, the administration of lipophilic drugs and an improvement in the stability of fragile drugs. Nanoparticulate based drug delivery systems would help in better targeting and penetration. The particle size, surface charge, composition and the presence of ligands on the surface of the nanocarriers are the parameters which will direct their pharmacokinetics within the human body. Also, a preferential accumulation of the entrapped

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drug at desired sites can be achieved either by passive or active targeting.

Polymeric drug delivery research has been extended to targeting of the drug at the specific site by utilizing various stimuli responsive systems which depend upon physiological conditions of the body such as pH of biological fluids and temperature of the human body.[3,4] Such stimuli sensitive systems may be termed as thermoresponsive drug delivery systems & pH responsive drug delivery systems which are dependent upon changes in temperature and pH respectively. For example, pH responsive drug delivery systems are extensively researched for use in cancer therapy. Cancer cells possess slightly different pH from normal cells. This difference between the two can be utilized for triggering the release and targeting the anticancer agents specifically towards the cancer cells thereby reducing the toxicity due to non specific activity. Similarly, thermoresponsive polymers with Lower Critical Solution Temperature (LCST) have been investigated for various biomedical and pharmaceutical formulations.

THERMORESPONSIVE POLYMERS: THE CONCEPT

The temperature of the human body is 37°C under normal conditions. Under certain pathological conditions or in the presence of pyrogens, the body temperature deviates from normal. This change in temperature can be utilized as a stimulus for the delivery of drugs from thermoresponsive delivery systems. Thermoresponsive drug delivery systems have also been of focus in cancer therapeutics.

In thermoresponsive systems, many polymers have been utilized which are thermosensitive. Such polymers when introduced in the formulation in solution form, enable it to undergo a reversible, temperature induced gel-sol transition upon heating or cooling of the solution. This reversible gel-sol transition is associated with the LCST (Lower Critical Solution Temperature) of the thermosensitive polymers. Below this temperature, the solution is homogeneous, the polymer chains are swollen and the polymer exists in water soluble form. At this stage, water and hydrophilic moieties of the polymer are bound to each other. This prevents interactions of the polymer chains and intrapolymer association. Above this temperature, a phase transition takes place. At this stage, the hydrogen bonds between the water molecules and the hydrophilic moieties are disrupted, water is expelled from the polymer chains which lead to their contraction and subsequently they shrink. Hydrophobic interactions among the polymer chains persist and lead to the aggregation or precipitation of the polymer. The temperature at which phase transition occurs is termed cloud point. With the help of this, an on-off drug delivery system could be achieved and hence such thermosensitive polymers are also termed smart polymers or intelligent polymers.[5-7] Apart from the fact that such polymers should be biocompatible, biodegradable and nontoxic, another prerequisite for the utilization of such polymers in drug delivery systems is that their LCST should be around 37°C i.e. close to normal body temperature. Such thermoresponsive polymers would include PNIPAM Poly (N-isopropylacrylamide).

Currently, extensive research is going on with regard to the modification of the LCST of the thermosensitive polymers in drug delivery systems for specific targeting of the drugs. One such polymer of considerable focus is PNIPAM. PNIPAM is a thermosensitive polymer which has been utilized in many drug delivery systems including for cancer therapeutics.

The present article deals with the properties of PNIPAM and their applications in different drug delivery systems.

PROPERTIES OF PNIPAM

PNIPAM i.e. Poly (N-isopropylacrylamide) is a thermoresponsive polymer having Lower Critical Solution Temperature at 32°C. It undergoes a coil-to-globule transition at this temperature which is close to normal physiological body temperature. As a result, extensive research has been carried out on utilizing this property of PNIPAM for the delivery of drugs in stimuli responsive drug delivery systems.[5-7]

PNIPAM contains a hydrophobic as well as a hydrophilic moiety. The isopropylic moiety is hydrophobic whereas the amide moiety is hydrophilic. In response to changes in temperature, solutions of PNIPAM exhibit rapid, reversible phase transition / phase separation phenomena. At temperatures below LCST, the polymeric chains are expanded, hydrated and in a hydrophilic water-swollen state while above this, they are dehydrated, collapsed and in a hydrophilic globular state.[8-9]

The cloud point of PNIPAM can be adjusted with the help of addition of salts, surfactants or co-polymerization with various hydrophilic or hydrophobic comonomers.[10-14] Hydrophobic monomers decrease the LCST while hydrophilic monomers aid in elevating its LCST. For example, studies have been reported of increase in the LCST of PNIPAM after carrying out its copolymerization with hydrophilic methacrylic acid and PEG (polyethylene glycol). This resulted in the polymer being pH sensitive for drug delivery applications.[10,11] In one of the studies, copolymerization of PNIPAM with hydrophilic maleic acid increased the LCST from 32°C to 38°C.[14] Besides modifying the LCST of the polymer, incorporation of a biodegradable

polymeric segment within the polymeric chain also enhances the therapeutic activity of the drugs incorporated into such nanoparticles.[12,13]

SYNTHESIS OF PNIPAM:

Free radical precipitation polymerization

This is one of the most widely used methods for the synthesis of PNIPAM based gels. In this method, NIPAM monomers are made to react with a cross linking agent like N-N'-methylene-bis-acrylamide (BIS) along with an initiator like potassium persulphate (KPS) in nitrogen environment.[14] Sodium dodecyl sulphate (SDS) may also be added as a stabilizer and a surfactant which aids in reducing the size of the nanogels.[15] The concentration of SDS is the most important factor that affects the size of the nanogels. This polymerization is carried out at high temperatures around 70°C under constant stirring at a controlled pressure. After the polymerization is complete, purification can be carried out through centrifugation and removing the unreacted components of the mixture.

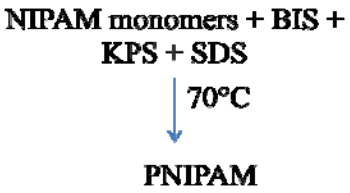

Figure 1: Schematic representation of synthesis of PNIPAM based nanogels through free radical polymerization method

After the addition of the initiator, the polymerization of NIPAM monomer takes place and the chain starts to grow. The chain length continues to grow and then reaches a certain critical length. At this point, it collapses on itself giving rise to precursor particles. The chain collapses as the polymerization temperature is maintained higher than the LCST of the polymer. The precursor particles then grow by two mechanisms: they either aggregate with the other precursor particles or are captured by existing colloid stable particles.

Metallic nanoparticle templating method

Hollow polymeric nanoparticles can be synthesized with the help of metal templating method. It has been reported that Poly (N-isopropylacrylamide) (PNIPAM) shells can be synthesized onto a metal nanoparticle seed.[16] The adsorption of NH2-terminated PNIPAM can be carried out on Au nanoparticles. When heated above the LCST, the adsorbed PNIPAM layer collapses onto the Au nanoparticle surface which serves as a hydrophobic nucleus for growing PNIPAM oligoradicals during polymer synthesis. Au core can be etched from the polymer-coated particles with KCN resulting in the hollow hydrogel nanoparticles. With the help of this method, nanogels can be synthesized with size range within 50nm. The size of the inner cavity of the hollow polymeric nanoparticles is same as the diameter of the metal template used.
In addition to gold, silica nanoparticle templates have also been utilized for the synthesis of polymeric hollow nanoparticles. However, with the help of such methods, larger sized nanoparticles resulted which made it unsuitable for its application in drug delivery.

APPLICATIONS

PNIPAM based nanogels have found applications in drug delivery, biosensors and separation media.[17] PNIPAM based gels can be conjugated with specific molecules for site specific drug delivery thereby reducing the side effects and increasing the therapeutic activity of the drugs.[14] The drugs to be delivered are incorporated within the nanogels and delivered to the target site. At the target site, they are exposed to a temperature above LCST as a result of which the polymer collapses and releases the drug.
The peculiar characteristic of PNIPAM has been utilized for the regulation of cell attachment and detachment on/from matrices which are grafted with PNIPAM-based polymers by the change in temperature.[18,19] Above the LCST, the PNIPAM nanogels are hydrophobic and interact with the components of the cells while below that they are hydrophilic and do not interact with them.

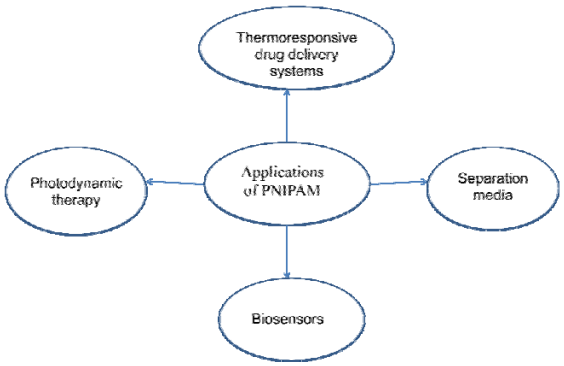

Figure 2: Schematic representation of the various applications of PNIPAM based systems

In addition, PNIPAM based hydrogels can be utilized for photodynamic therapy and drug delivery driven photo-thermally. In such cases, photosensitive moieties are attached to PNIPAM hydrogels and volume transitions are achieved by irradiating the entire system at the resonance wavelength of the photosensitive moieties. Upon

irradiation, the light energy is absorbed and gets converted into heat energy. As a result, the hydrogels get heated up and the temperature rises beyond the LCST of the polymer which results in its deswelling. If the drug is loaded within the polymer, shrinking of the same leads to the release of the drug at the target site. Such systems have been reported wherein gold nanorods were utilized as the photosensitive material.

Thus, PNIPAM promises to be a smart polymer for is applications especially in drug delivery systems. However, being nonbiodegradable, questions of its toxicity still arise and hence considerable research should be carried out on its safety aspects.

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