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SMART POLYMERS FOR DRUG DELIVERY SYSTEM: AN OVERVIEW

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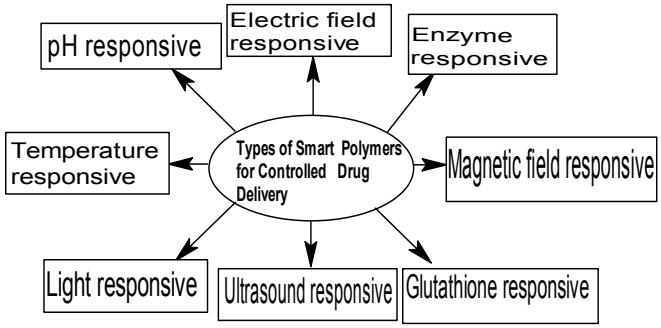
The interest in modifying the traditional drug release system has persisted over many decades. A large number of studies have been dedicated to find smarter ways to deliver drugs at target site. The researchers are concentrating on smart polymers for synthesizing different types of novel drug delivery systems for the past thirty five years. A review on drug delivery systems based on smart polymers is presented in this paper. In this paper smart polymers are discussed in a group wise manner with respect to the changes induced by different stimuli such as pH, electric field, enzyme, temperature, light, ultrasound, magnetic field, and other changes in the environment. Different types of newly synthesized stimuli responsive polymers have been discussed and the benefits of such polymers have been indicated.



INTRODUCTION

Smart Polymers for Intelligent Drug Delivery System (DDS) have a large number of applications in the area of drug and active agent delivery for commercial interest. Various beneficial features of smart polymers make this area an important applicable interface between biology and chemistry. Smart Polymers are able to deliver drug at the appropriate time and site of function and provide a link between therapeutic need and drug delivery. Smart polymers are also applicable for targeted and triggered controlled delivery of drugs viz. treatment of cancerous tumor. Smart polymeric materials change their properties after a noticeable change in their environment. Some stimuli are temperature, ultraviolet radiation, light, chemical, magnetic, electric field, pH, ionic factor, etc. Smart polymers change their microstructures in a changed environment and when stimuli are removed they reversibly return to their initial state. Some responses produced in smart polymers are swelling or collapsing, change in shape, degradation, hydrophilic/hydrophobic surface, etc. Some polymers are single while others are dual or multi stimuli responsive. From the last twenty five years scientists have been making polymers that mimic these smart behaviors. A large number of studies have been conducted for making and developing smart polymers for controlled drug delivery because smart polymers are flexible, tough, strong, maintain drug stability, versatile, tunable sensitive, phase changeable, available at low cost, easy to transport, biocompatible and biodegradable. Smart polymers are biodegradable so easily eliminated from organism after completing their task. Smart polymers may be degraded into nontoxic polymeric fragments which are eliminable by renal route. A large number of mechanisms are known for assembling polymer

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system *in situ* for sustained release of therapeutic macromolecules. For predictable rate of drug delivery, special devices were used to give a therapeutic agent at a known rate *in vivo* when given by a noninjected or an injected route. Controlled drug delivery occurs when a polymer is judiciously attached with a drug in such a manner that the drug is released from the material in a proper preplanned manner.[1-8]

CLASSIFICATION OF STIMULI RESPONSIVE SMART POLYMERS

1. pH responsive smart polymers
2. Electric field responsive smart polymers
3. Enzyme responsive smart polymers
4. Temperature responsive smart polymers
5. Glutathione responsive smart polymers
6. Light responsive smart polymers
7. Ultrasound responsive smart polymers
8. Magnetic field responsive smart polymers

1. pH responsive smart polymers

pH as stimuli is the most important variable to trigger drug release in the body system. The oral route of delivery is most convenient for it. Such polymers act as polyelectrolytes which can take or release protons to influence the pH change. They are with a large number of ionizable groups. Ions are formed when polymer is dissolved in water or other polar solvent. These polymers are of two types (a) Weak polyacids and (b) Weak polybasic. Weak polyacids at low pH accept protons and at neutral and high pH release protons due to solubility changes by changing their electrical charge on polymer molecule.[9] Commonly applicable pH-responsive polyacid are poly (methacrylic acid) and poly (acrylic acid). Polymers with basic functional group like ammonium salt are called polybases or polycations. They can be protonated at higher pH and positively ionized at neutral or lower pH viz. poly (N, N-dialkylaminoethylmethacrylate), poly (lysine), chitosan etc. Chitosan is a natural pH responsive polymer. It is a cationic polysaccharide. Chitosan is resorbable, nontoxic, biodegradable and biocompatible. It is applicable in oral or mucosal delivery of drug and it also delivers the DNA to the action site. Site specific delivery in gastrointestinal tract, where pH value changes to acid-base-acid medium through gastric, intestinal and colonic part of the tract can be done by pH responsive polymers. The difference in pH between healthy and cancer tissues gives an idea to make a pH responsive drug delivery system. The pk_a value is also an important parameter for biomedical application. Its value should be between 4 and 8. The pk_a value of polymers can be regulated by controlling the molecular weight.[10-12] For controlled drug delivery Raenata Negrini *et al.* reported pH-responsive lyotropic liquid crystals. These crystals are able to respond pH variations reversibly in the structure and physical properties, so it is an ideal mode for oral delivery of drugs in the intestine or colon tracts.[13] Andreas Riedinger *et al.* studied "Nanohybrids" (prepared on pH responsive hydrogel and inorganic nanoparticals) for the same function.[14] Delivery of Doxorubicin for cancer treatment is effectively done by pH responsive polymers. A composite microsphere as a hopeful drug delivery system for this work was reported recently. It is coated with shell poly (methacrylic acid)/chitosan (PMAA-CS) after which it becomes stable in pH range of 5-8. At low pH, the release rate is high for DOX-loaded composite microspheres.[15] The poly (acrylic acid) polymer retains the drug in the presence of acidic pH (stomach) and when it reaches the small intestine, ionization of acid groups of polymer occur in alkaline pH, so polymer swells and delivers the drug in small intestine, this process is used for oral drug delivery system. Jin-zhi Du worked on tailor made dual pH responsive polymeric nano particles of Doxorubicin for active anti cancer drug delivery to improve improper cellular uptake and for removing drug resistance by tumor cells.[16] Dual and multi stimuli responsive polymeric nanoparticles are also a good medium to give programmed, accurate and site specific drug delivery. Examples of such multi responsive polymers are such as temperature/pH, pH/redox, pH/magnetic field, double pH, pH/diols, temperature/pH/redox, temperature/pH/magnetic, pH/redox/magnetic, temperature/pH/guest molecules. Such polymers have been used for drug delivery with unprecedented control resulting in superior *in vitro* and/or *in vivo* efficacy of anticancer drugs.[17] Catechol polymers have been studied for introducing anticancer drug Bortezomib (BTZ) to cancer cells. Exploitation of the Catechol moiety was done for its quality to take and release therapeutics (borate-containing) such as BTZ in a pH responsive manner for chemo selective type approach, for controlling the delivery of BTZ in

targeted cancer cells, exhibiting a good concept that can be applied in the coming future toward other boronic acid containing therapeutics for the treatment of a broad range of diseases.[18] Yunlu Dai *et al.* recently prepared luminescent microspheres of NaYF4:Yb^{3+}/Er^{3+} coated with the smart hydrogel Poly (N-isopropyl acryl amide)-*co*-(methacrylic acid) (NIPAM-*co*-MAA) Shell based new controlled release system. This is both thermal and pH sensitive. It is very much useful for delivery of Doxorubicin by changing value of pH and temperature.[19] For this purpose pH responsive mesoporous silica nanoparticles are also very much applicable in controlled drug delivery. It contains mesoporous silica nanoparticles (isopoly (acrylic acid) grafted) and due to pH sensitive nature loading content and the entrapment efficiency could reach up to 95% of DOX. The rate of drug release of DOX at polyacrylic acid mesoporous silica nanoparticles (PAA MSN) is pH dependent and increases with the decrease of pH level. It is highly suitable and biocompatible to use as drug carrier especially for cancer therapy.[20] J. Jiang *et al.* used mussel-inspired surface functionalization (protein mediated) of electro spun nanofibres for pH responsive drug delivery. They studied on a mussel-inspired protein polyamide coating that can tune the loading and releasing rate of charged molecules from electrospun poly (ε-caprolactum) (PCL) nanofibres in solution with different pH values.[21] Some smart Hydrogels made up of pH responsive poly (acrylic acid) (PAA) and temperature sensitive biodegradable hydroxyl-propyl cellulose-*g*-acrylic acid (HPC-*g*-AA) are made for application in controlled drug delivery. Variation in release rate according to provided conditions indicates that HPC-*g*-AA plays a very important role in the drug release behavior.[22] For thermal and pH (dual) response with good reversibility, a facile one step strategy, for graphene oxide interpenetrating poly(N-isopropylacrylamide) PNIPAM hydrogel network is made by bonding (covalently) Graphene oxide sheets and Poly(N-isopropylacrylamide) co acrylic acid (PNIPAM-*co*-AA) microgels in water.[23] Smart pH responsive carriers for intracellular delivery of hydrophobic drugs is the applicable feature of ABC block copolymer.[24] For the treatment of human glioma cell, Rupei Tang *et al.* studied enhanced drug delivery, based on block copolymer micelles with *ortho* ester side chains (acid labile by nature). This system is helpful for the pH started delivery of poor water soluble anti-cancer drugs.[25] Some micelles which are acid and reduction cleavable comb like amphiphilic copolymer type are used for a helpful encapsulation and release of Doxorubicin.[26] Protonation and deprotonation of the polymer in micellar structure can help in breaking and drug release trigger in tumor tissue (in solid form). A hybrid system developed by mesoporous nanosilica MCM-41(as a nanocarrier) and a pH responsive polymer as gatekeepers which is smart and reversible is good to use as nanocarrier for drug delivery.[27] Self immolative polymers as novel pH responsive gate keepers for drug delivery have been reported by M.Gisbert Garzaran *et al*.[28] One basic disadvantage to use pH responsive smart polymer is that in many cases they are required to react to small changes in pH which in some cases is a very difficult task to achieve.[29]

2. Electric field responsive smart polymers

Electric field stimuli responsive polymers are very effective and site specific mode of drug delivery because it has advantage of availability of equipment that gives precise control for the magnitude of current, electric pulse duration, etc. These types of polymers contain a large number of ionizable groups and are also pH responsive. Electric field sensitive polymers convert electrical energy to mechanical energy.[30-32] Breaking of H-bonding in influence of electric current leads to drug release. They have ability to change in shape and size with the influence of electric current. Some examples of natural electroactive polymer are chitosan, hyalouronic acid and synthetic polymers like methacrylic acid, polypyrrol, polyaniline, polyethylene, polythiophene, sulphonated polystyrene. Electro responsive nanomaterials are usually made up of polyelectrolytes that undergo deformation by swelling and deswelling process during function. Polarizable group is a must for electro responsivity in the case of neutral polymers. In the presence of electric field, they undergo swelling/deswelling. Cirillo, Giuseppe *et al*. extensively reviewed the applicability of carbon hybrid materials for improving the release of drugs in the presence of external current voltage. Carbon nanohybrids also function as electro responsive drug delivery system.[33-37] An important application of an electro sensitive polymer is the edrophonium hydrochloride and hydrocortisone delivery in a pulsatile manner by the polymer poly(2-acrylamido-2-methyl propane sulphonic acid-*co*-n

butyl methacrylate).[38] Qiang Yan *et al.* synthesized vesicles (voltage responsive) based on orthogonal assembly of poly(styrene)-β-cyclodextrin (PS-β-CD) and poly(ethylene oxide)-ferrocene (PEO-Fe) orthogonally self assemble with supramolecular diblock type copolymer (PS-β-CD/PEO-Fe). These assemblies in the next step act as supramolecular vesicles. These vesicles function as nanocapsules carrier in hollow cavities of it and the external voltage strength measures accurately the time regulation of drug release.[39] A new electric field and temperature responsive nanoparticle system is made for drug delivery in a programmed manner. Therapeutic pharmaceuticals with nano particles of a conducting polymer (polypyrrole) are subcutaneously localized *in vivo* along with the assistance of a hydrogel (temperature sensitive) (PLGA-PEG-PLGA).[40] Ania Servant *et al*. reported an electro responsive multiwalled carbon nanotube/poly (methacrylic acid)(MWNT/PMAA) hybrid material. It is for controlled drug release by the electric field ON/OFF application, giving rise to *in vivo* and *in vitro* profiles of pulsatile release.[41] By electro spinning method transdermal drug delivery electro-sensitive system has been reported. A polymer network with semi-interpenetrating matrix, made with polyethylene oxide and polymers of pentaerythritol triacrylate has been found to increase the electrical sensitivity, when used multiwalled carbon nanotubes as an additive.[42] Electrodynamic techniques permit revisiting manufacturing of old scaffold approach by using electrostatic forces as the driving force [43] to arrange particles from an electrically charged solution. Selecting materials carefully and stringent processing conditions allowed good control of characteristics sizes and shapes from micro to sub micrometric scale level and incorporate biopolymers for space and time controlled release for use in drug delivery. Vincenzo *et al.* focus on recent advances to design and construct micro or nanostructured polymer platforms by electrodynamic techniques, to be used as 3-dimensional models for preclinical *in vitro* studies of *in vivo* tumor growth as innovative scaffolds. Electro-conductive hydrogels are applicable on electro stimulated drug release devices for programmed delivery. These hydrogels are stimuli responsive, biomimetic polymeric materials.[44] Polyelectrolytes and electrostatic assembly of nanoparticles are versatile by nature and are very much applicable for controlled drug delivery. Engineered nanoparticles are made from noble metals, rare earth oxides or semiconductors.[45] Polymeric implants of graphene based electro responsive scaffolds are recently applied for on demand drug delivery. Ania Servant *et al.* worked on fabrication of previously unreported graphene hydrogel hybrid scaffolds which are electro active and capable of controlled small molecule release. Drug release in pulsatile fashion upon the ON/OFF application of low electrical voltages, at low graphene concentration and by maintaining their structural integrity, has been studied.[46] For drug delivery Magnetic and Electric responsive hydrogel-magnetic nanocomposites have also been used. N Narayana Reddy *et al.* synthesized such composites through acrylamide monomer polymerization in the presence of carboxy-methylcellulose or methyl cellulose with N,N-methylene bisacrylamide, (a cross linker) with the redox initiating system ammonium persulphate/tetra-methylethylenediamide.[47] The supramolecule vesi-cles function as nanocapsules carrying molecules within their hollow cavities and that the drug release time is regulated by external voltage strength.[48] Magneto-Electric nanocarriers have high potential for drug delivery. They have capacity of high drug loading, site specificity and precise on-demand drug delivery.[49] For this purpose Chaobo Huang *et al.* reported stimuli responsive electro spun nanofibres which are gaining considerable attention.[50] PVA/PAA/MWCNT nanofibres have been used as electro-responsive transdermal drug delivery material. These nanofibres are prepared by electro spinning of poly (vinyl alcohol)/poly (acrylic acid)/multiwalled carbon nanotubes nanocomposites. Uniform distribution of the oxyflurinated MWCNTs in the nanofibres was crucial to the swelling of electro responsive type and drug delivery behavior of nano fibers.[51]

3. Enzyme responsive smart polymers

Enzymes are macromolecular biological catalysts and they are necessary for almost all metabolic processes in living cells. Bacteria present in the colon produce special enzymes which can degrade various types of polysaccharides, such as chitosan, cyclodextrin, amylase, etc. The most important advantage of such polymers (enzymes) is that any external trigger is not required for their function. The quality of enzyme sensitive polymers is that they are highly specific and selective toward their substrates and milder reaction conditions are required for their performance. Protease, Glycoside responsive polymers are some very effective

enzyme responsive polymers for drug delivery. They can be exploited as immaculate, ancient biological triggers ready for material responses and for proper drug release at target site. Protease, Glycosidase based reactions are studied to succeed controlled release of drugs.[52-58] Laura Mondragon *et al.* recently reported an intracellular controlled release which is enzyme responsive using silica mesoporous nanoparticles (capped with ε-poly-L-Lysine). This method offers a new potential platform for cancer treatment.[59] Enzyme-responsive controlled drug release with surface erosion of poly (ethylene carbonate) is an interesting way of drug delivery. Poly (ethylene carbonate) under mild physiological environment for drug delivery and Cholesterol Esterase (CE) induced surface erosion of Poly (ethylene carbonate) (PEC) have been investigated.[60] Deregulations such as hypo/hyper expression of the enzymes can lead to the development of a range of disease states and thus such deregulations could be exploited to trigger release in the affected tissues or sites of the body.[61] Enzymes are sensitive drug carriers and they can alter the drug release rate. Enzyme responsive DDSs are useful for specific release in inflammation sites and tumor, for microorganism-triggered release of antimicrobial agents.[62-64] Zhen Gu *et al.* studied the combination of enzyme nano capsules and glucose responsive micro gels for closed loop insulin delivery and for reduction of blood glucose levels.[65] Recently some hydrogels have been prepared by the use of an enzyme system like transferases, tyrosinases and lysyl oxidases for controlled release of drugs. Enzymes help in the formation of more complex structures. Use of enzymes in the formation of hydrogel in the form of cross linking has been discussed to overcome some limitations like cytotoxicity, low mechanical strength, stability, etc.[66] Some Nanomaterials have been prepared to improve drug release by decreasing the side effects and increasing the treatment efficiency. Nanomaterial prepared by using single stranded DNA encapsulated mesoporous silica (functional) nanoparticles has been used in an efficient controlled release carrier system which is enzyme responsive by nature.[67] Smart micellar nanocarriers assembled with enzyme responsive amphihilic PEG-Dendron have been reported by Assaf J Harnoy *et al.* for a smart drug delivery system. This system has been found to be highly selective for activating enzymes. They also reported an improved smart design for the simple and efficient synthesis of amphiphilic block copolymers based on a linear hydrophilic polyethylene glycol (PEG) and an enzyme responsive hydrophilic dendron for adjusting the release rate for drug delivery application.[68] Yuetong Kang *et al.* made enzyme responsive polymeric supra amphiphiles by the complexation of chitosan and Adenosine-5′-triphosphate (ATP). This enzyme responsive system is better and cheaper than chitosan based enzymes responsive assemblies and also more biocompatible.[69] Nowadays enzymes are also used in triggered release for hollow mesoporous silica/poly (L-lysine) material for delivery of drugs. This system has very good application in the field of cancer therapy and biomedicine.[70] Recently, enzyme responsive nanoparticles have been reported, which are much helpful for the drug release with outstanding catalytic properties and exceptional biorecognition capabilities. Several nanomaterials (enzymes responsive) such as liposome, polymer based nanoparticles, gold quantum dots and nanoparticles, have been studied which exhibit improvement of enzymatic activity and improved physiochemical properties. Hydrolases such as lipases, proteases, glycosidases, and oxidoreductases are also studied.[71] Jinming Hu *et al.* studied some polymeric assemblies, nanoparticles and hydrogels which are sensitive for enzymes. Self assembly and aggregation of polymers triggered through the action of enzyme; enzyme triggered sol to gel and gel to sol transitions and enzyme driven disintegration and structural reorganization of polymeric assemblies and nanoparticles have been described.[72] Several diseases have been associated with the presence of specific enzymes in higher levels for example plasmin (which is involved in wound healing), which comes from fibrinolysis. Enzyme sensitive intracellular controlled release using "Saccharides" capped nanometric silica mesoporous supports has been studied by Andra Bernardos *et al.*[73] Difficulty in establishment of a precise starting response time is the main disadvantage of enzyme responsive polymers.[74]

4. Temperature responsive smart polymers

Thermosensitive polymers undergo fast change in their phase, structure or solubility due to a small change in temperature. In the presence of a temperature change their solubility gets altered and also their aqueous solution undergoes sol to gel

transition such that polymers have the advantage of not requiring solvent (organic) for the delivery of drugs.[75-78] Thermosensitive polymers contain a hydrophobic group such as methyl, ethyl and propyl groups. Thermosensitive polymeric systems are generally applicable for injectable depots, injectable thermogelling tissue-engineering scaffolds as good filler in cast cavity, construction blocks for thermo-responsive micelles.[79-81] By changing the temperature range two phase changes occur in such polymers. The avoidance of toxic organic solvents, site specific drug delivery, reduced systemic side effects and sustained release properties are their basic advantages.[82] A new drug delivery platform for Doxorubicin viz. biodegradable thermo responsive polymeric magnetic nanoparticles have been reported by Nidhi Andhariya *et al*. They also demonstrated that temperature can be exploited successfully as an external parameter.[83] Synthesis of Temperature sensitive Dextran methacrylated poly(N-isopropylacrylamide) Dextran-MA/PNIPAAm particles for controlled drug delivery using super hydrophobic surfaces was reported by Ana Catarina Lima *et al*.[84] Super magnetic iron oxide nanoparticles (SIONPs) core and pluronic shell made temperature responsive magnetic drug delivery system has been developed. Polymer shell formed by pluronic F127 poly (ethylene oxide)-poly (propylene oxide)-poly(ethylene oxide) PEO-PPO-PEO (stimuli responsive) block copolymer work as the carrier for both types: hydrophilic and hydrophobic drugs.[85] Hybrid alginate beads are an interesting way of drug delivery with thermal responsive gates. It has been prepared with grafting PNIPAAm onto hybrid aligate beads and to enhance mechanical strength and ensure higher graft efficiency and is biomineralized. It is constructed with polyelectrolyte layer.[86] Xiao Zhang *et al.* studied on smart polymer brushes gated Multifunctional up converting nanocomposites mesoporous silica for a controlled release of drug with Thermo/pH dual responsive nature. On the up-conversion luminescent nano particles of NaYFu:$Yb^{3+/}Er^{3+}$ core (UCNPs) (Multifunctional nanocarriers based) and mesoporous silica shell with thermo/pH coupling sensitive polymer poly((N-isopropyl-acrylamide)-*co*-(methacrylic acid)) (P(NIPAm-*co*-MAA)) gated have been reported for cancer treatment, including controlled drug delivery and fluorescence imaging for therapy.[87] The Doxorubicin hydrochloride (DOX) can be absorbed into nano-spheres of UCNPs@mSiO_2-P(NIPAm-co-MAA) and a low level of leakage at low temperature/ high pH values by the composite drug delivery system (DDS) shows only an improved release at higher temperature/lower pH values, and an "ON-OFF" pattern for drug release by thermo/pH controlled nature.[88] Temperature sensitive Poly (N-isopropylacrylamide-acrylamide-allylamide) coated iron oxide magnetic nanoparticles (TPMNPs) have been used as possible targeted drug carriers for treatment of Advanced Thyroid Cancer (ATC).[89] Jun Akimoto *et al.* prepared temperature sensitive polymeric micelles for optimized solid tumor targeting by drug. It has special properties such as intracellular uptake system and temperature-triggered drug release. Temperature responsive (TR) micelles with integration of other targeting systems to pursue the ideal pharmacodynamics in conjugation with thermal therapy (future prospective of the TR system) have been reported.[90] Some newly developed thermo responsive drugs such as leuprolide and Docetaxel have been reported. Leuprolide drug is made by polymer polybenzofulvene for the application of treatment of tumors and its study goal is to cover the oligopeptide drug and regulated release rate by temperature change in the surrounding.[91] Docetaxel is made for gastric cancer peritoneal dissemination with excellent antitumor activity and hydrogel produced controlled release. It is made up by pluronic F-127 polymer coupled conjugated linoleic acid.[92] For controlled drug delivery of vitamin D_3 (Vitamin) *in vitro* evaluation of thermosensitive and magnetic nanoparticals has been carried out. Vitamin D_3 is an anti proliferative and anti cancer agent. PNIPAM SiO_2/Fe_3O_4 nanoparticles have been effectively used as a potential drug delivery system for controlled release of D_3.[93] The Chitosan hydrogels led to new advanced drug delivery systems that, under varying environmental stimuli, can release their payloads at the desired site.

Hydrogel (thermosensitive) variants have been developed to make a hydrogel (chitosan) *in situ*, with surgical implantation. Recent developments have been made, i.e. the preparation of chitosan hydrogel and finding the design parameters for the improvement of chemically and physically cross-linked Hydrogels.[94] Younging Shen *et al.* recently prepared photoluminescent dendrimers which are degradable. Dual pH and temperature responsive polymer Poly (α-amino ester) dendrimer is one example of this type of polymer which is an ideal

drug carrier. The thermal sensitivity allows the loading of drug without using organic solvents.[95] Some examples of thermo responsive polymers are poly (N-isopropylacrylamide/acrylic acid, poly (N-vinylcaprolactam), poly (N-ethyl oxazoline), elastin-like oligopolypeptides and poly (acrylic acid-*co*-acrylamide).[96-100]

5. Glutathione responsive smart polymers

To obtain intra cellular specific release in the biological system glutathione (GSH) triggered release is a helpful mode.[101] The therapeutic potential of the glutathione sensitive system is in knowledge for animals, using micelles and polymersomes loaded with anticancer drugs.[102-104] Thiol-responsive micelles (degradable) on a new ABP based on a pendant disulfide-labelled methacrylate polymer block and a poly (ethylene oxide) (PEO) block (hydrophilic) were studied as effective nanocarriers (intracellular) for drugs used in anticancer treatment. This system is glutathione trigger based. This GSH-responsive (degradable) PEO-b-PHM_{ss}Et micelle gives versatility in multi functional application of drug delivery.[105] For intracellular drug delivery glutathione responsive nanocarriers which are Raman scattering (surface enhanced) traceable, have been presented by Shenfel Zong *et al*. Nanocarrier of this type would be very effective in improving the working ability of cancer chemotherapy by removing premature drug leakage.[106] Camptothecin prodrug with disulfide linker (glutathione-responsive) is also effective in cancer therapy. It is based on polyethylene glycol monomethyl ether-block-poly (2-methacrylester hydroxyethyl disulfide-graft CPT). Two anticancer drugs at the same time delivered by the DOX-HCl-loaded CPT prodrug could be used to produce a cytotoxicity of collaborative nature toward cancer cells.[107] Nanoprecipitation of hydrophilic polymers made isothermally responsive polymer glutathione-triggered disassemble able nanoparticles. Daniel J. Philips said that it is effective for selective and encapsulated delivery of therapeutic compounds to polymeric nanoparticles for treating a variety of diseases.[108] A new type of poly(methacrylic acid) (PMAA), (redox/pH dual stimuli responsive) based nanohydrogels was prepared from N,N-bis(acryloyl)cyst amine and methacrylic acid cross-linker (*via* distillation-precipitation polymerization). It has excellent adequate, biocompatible, biodegradable properties and good capacity of drug loading, under an extracellular condition (nonreductive), with minimal drug release and fast drug release in response to the reducing potential and intracellular level of pH, so this system is very effective for cancer treatment.[109]

6. Light responsive smart polymers

Light, either visible or ultraviolet, is very good for biomedical applications as a source of energy. Light sensitive smart polymers contain photosensitizers such as stilbene or azobenzene. These polymers are biodegradable and biocompatible by nature. They can be used for delivering drugs to distinct locations using optical fibers.[110-112] They are especially used for treatment of skin cancer, laser triggered drug release, and laser irradiation of tumors. Near IR part of the spectrum is more useful than visible light due to less harmful nature and deeper penetration ability in tissue.[113-114] By the use of filters and photo masks or lasers, its intensity and wavelength can easily be controlled that allow for fabrication of complex features and exposure areas with approx. 1μm resolution.[115] Huaizhi Kang *et al* worked on a drug delivery (near-infrared light responsive) platform based on DNA cross-linked polymeric shell coated Au-Ag nanorods (Au-Ag NRs). DNA complementarily used to develop a polyacrylamide based transition system (in sol-gel form) to encapsulate drugs for anticancer treatment into the gel scaffold. This is very useful for specific examination of tumor cells, and for quick release of the encapsulated payload with good controllability.[116-118] Some photo responsive hydrogels are also reported for the same function. Near Infrared light responsive polymer-nanorod composites which release small molecules in enhanced form is an effective drug delivery system. Kolin C. Hribar *et al.* studied on this and found it suitable for controlling the release of a small drug molecule (<800 Da). Its Glass transition temperature (T_g) is in the range of body temperature. The effective heating system of this polymeric structure is used to chemotherapeutic drug Doxorubicin by triggered release.[119] Light responsive micelles are site specific and a time controlled system. Spiropyran hyper branched poly glycerols (SP-hp-PG) micelles are superior and biocompatible DDs using WI-38 cells, HeLa cells.[120] A versatile system which is sensitive to a number of wavelengths is made by polymer (light-sensitive) with a multiple light sensitive triggering group containing a Quinone-methide moiety which

is self-immolative by nature. It has been formulated into nano particles encapsulating by a model pharmaceutical Nile Red.[121] An aggregate made by Qiang Yan *et al.* reversibly assemble and disassemble using UV/Visible light for drug delivery. This aggregation orthogonally self assemble two homopolymers into a terminal host guest interaction based pseudo-copolymer. Further fabrication of these supramolecular copolymers produces one dimensional nanotube in water.[122] Light responsive block copolymer micelles in solution (aqueous) can be altered often reversibly by light; this has potential application in controlled drug delivery. Such type of stimuli responsive polymer micelles have received increasing attention.[123] The main disadvantage of using this type of polymers is the fact that tissues are generally permeable for long wavelength light only.[124-128]

7. Ultrasound responsive smart polymers

Ultrasound is an interesting tool that can be used to improve drug deposition, trigger drug release and track drug carriers, with high precision (spatial).[129-130] For therapeutic needs ultrasound responsive drug delivery systems (URDDs) include many different types, such as liposomes, micelles, nanodroplets, microbubbles and emulsions.[131] For ultrasonic drug delivery, ultrasound wave characteristics, i.e. peak negative pressure, number of cycles per ultrasound pulse, and frequency play a very important role. At higher acoustic pressure inertial cavitation is shown by an ultrasound contrast agent. 1 MHz frequency allows microbubbles in the 1-3 μm size range to respond to ultrasound so that generally the frequency of ultrasound waves is set at 1 MHz.[132] Microbubble agents have been investigated as good carriers for systematic drug administration. For improved targeted drug delivery other therapeutic materials and plasmid DNA may pack to the micro bubbles. Sonoporation is the mechanism for application. The pressure gradient and shear stress produced by high speed micro streams or microjets improve the cell membrane permeability enabling plasmid DNA transport and therapeutics inside the cell.[133] The Polymeric micelle with chemical conjugation of Doxorubicin is used to increase the antitumor type activity of doxorubicin and in A_{549} cells circumvent multidrug resistance. Polymeric micelles have so many properties such as diameter in the nano range, low critical concentration, controlled release behavior, good penetration ability and high loading efficiency which are suitable for developing URDDs for cancer therapy.[134] The body using conventional physiotherapeutic equipment can use ultrasound techniques for treatment. Ultrasound waves cause local increase in temperature and bubble cavitation, facilitating the penetration of nanostructures into specific regions and the triggering of drug release.[135] A combination of polymeric micelles and liposome is reported by Tinghui Yin *et al*. This is for tumor penetrating codelivery of siRNA and paclitaxial with ultrasound responsive nanobubbles heteroassembled with polymeric micelles and liposomes. It will be helpful for minimizing drug resistance in systematic chemotherapy of hepatocellular carcinoma and for nanomedicines loaded with both chemotherapeutic agents and siRNA'S targeting antiapoptosis genes.[136] Application of ultrasound enables a pulsated drug delivery.[137] N. Huebsch *et al* presented ultrasound self healing and triggered disruption of reversibly cross-linked hydrogels for drug delivery with enhanced rate. They work *in vivo* with the hydrogel system to treat xenograft type tumors along with mitoxantrone, and found that ultrasound stimulated drug release at daily basis substantially slows down tumor growth compared with sustained drug release.[138]

8. Magnetic responsive smart polymers

Magnetic sensitive polymer systems are important in various biomedical applications including implementation of iron oxide nanoparticles based (superparamagnetic by nature) drug delivery. With decreasing size of the nanoparticles magnetic properties of ferrites also decrease nonlinearly.[139-142] Chih-Yu-Wang *et al.* prepared electrostatic droplet assisted synthesis of supramagnetic chitosan micro particles (*in situ*) for controlled drug release (magnetic-responsive).[143] Opportunity to use magnetic induction for thermo responsive polymer materials actuation can also give promising result for the above aim.[144] Magnetic nanoparticles (MNPs) have been used for the next generation of targeted drug delivery systems. Application of MNPs depends largely on the process of preparation, selection of agents and on conditions used to modify their surface.[145] Moom S. Aw *et al.* worked for magnetic responsive delivery of drug carriers using nanotubes of titania arrays loaded with polymer micelle as drug carriers.[146] For Antitumor delivery of drug magnetic and pH

sensitive nanoparticles are reported by Shufang Yu *et al*. The MPEG segments and Fe_3O_4@SiO_2, Poly (L-Asparagine) serve as a Super-paramagnetic core, a pH responsive shell, and a corona (hydrophilic), respectively. Through combined actions of hydrophobic interaction and hydrogen bonding, Doxorubicin (an antitumor agent) was successfully loaded into the nanocarrier.[147] By application of an oscillating magnetic field, the reversible, On-Off drug release can be provided by use of nanocomposite membrane based drug delivery devices containing thermo responsive nanogels and super paramagnetic nanoparticles.[148] Smart drug delivery through DNA/Magnetic nanoparticles gates can also be performed. Mesoporous silica network (loaded with iron oxide) of super paramagnetic nanocrystals gives the potential to working targeting and magnetic resonance imaging. Here the work shows that DNA/Magnetic nanoparticle conjugates can cap the magnetic silica particles pores upon both DNA strands hybridization. It is important for the development of drug delivery systems at an advanced level for thermo chemotherapy against cancer by its capacity to increase the temperature level of surrounding media.[149]

The quality of a magnetic nanoparticles based delivery system for 1, 3-bis(2-choloethyl)-1-nitrosourea (BCNU) in the Gliomas treatment has been studied recently. The study explains the preparation and characterization of carriers for drug made by the Poly [aniline-*co*-N-(1-one butyric acid) aniline] (SPAnH) coated on Fe_3O_4 core based polymer to prepare three types of nanoparticles which are magnetic by nature. These nanoparticles are good for improving the therapeutic capacity and enhancing the thermal stability of 1, 3-bis (2-chloroethyl)-1-nitrosourea (BCNU), a compound used to treat brain tumors. It is helpful to provide improved tumor treatment by lower therapeutic doses and potentially reducing the side effects of chemotherapy.[150] By using silane coated magnetic nanoparticles as a template for radical polymerization of N-isopropyl acryl amide and methacrylic acid, Poly (N-isopropyl acryl amide-methyl methacrylic acid) PNIPAAM-MAA)-grafted magnetic nanoparticles have been synthesized. The properties of these nanoparticles viz. size, drug release kinetics and drug loading efficiency have been studied *in vitro* for controlled and targeted drug delivery.[151] Magnetite loaded fluorine-containing polymeric micelles for drug delivery are an interesting topic. Magnetite loaded polymer micelles (Magneto micelles) have been made by fluorine containing amphiphilic poly (HFMA-*g*-PEGMA) copolymers by a self assembly process with Fe_3O_4 nanoparticles (oleic acid modified) in aqueous medium.[152-155]

Some improved nanoparticles, dendrimers, micelles and copolymers for a controlled drug delivery system

Polymeric nanoparticles are promising for controlled drug delivery application and give a valuable basis for advancement for pulmonary delivery applications in the future. Some substantial barriers exist in the respiratory tract that need to be removed for success of pulmonary applications. In this regard, micro and nano particles offer novel concepts for the developments of therapeutic tools (optimized) in research of pulmonary application. Due to prolonged retention in the lung polymeric nano-carriers are generally good and preferred as controlled pulmonary drug delivery systems.[156-158]

Dendrimers are considered as "Polymers of 21st century". Dendrimers perform with the complex efficiency in the cell. For example, ibuprofen a pure drug reaches the cell in 3 hrs but the ibuprofen with dendrimer complexes entered into the cell wall in 1 hr. The dendrimers facilitate the passive performance of drug to tumors. The reason is due to enhanced plasma circulation time and solubility of the complex viz. Doxorubicin. Due to unimolecular micellar nature, dendrimers are able to enhance the solubility of poorly soluble drug.[159] For *in vivo* transport of biologically active molecules aliphatic polyester type dendrimers were found to act as good carriers, as studied by Xinpeng Ma *et al.* and these are biocompatible and biodegradable. Such dendrimer can be synthesized by two monomers of AB_2 type via including a click reaction of Michael addition of thiol/acrylate and its esterification. It is then pegylated to prepare a biocompatible dendrimer (water soluble) capable of encapsulation and controlled release of an anticancer drug (Dox) (hydrophobic) delivery.[160] Biodegradable polymeric micelles offer a very good pathway for targeted and controlled anticancer drug delivery. Chao *et al.* reported that they exhibit excellent biocompatibility, prolonged circulation time, enhanced accumulation in tumor and *in vivo* degradable, low side effects and improved drug tolerance.[161] Wei Cao *et al.* recently worked on a selenium containing (coordination responsive) polymer. The platinum coordinating micelles by the competitive coordination of the

platinum cations with glutathione are helpful for the proper release of Doxorubicin. They concluded that for drug delivery coordination micelles are more biocompatible and exhibit a new dimension in a multidrug system for chemotherapy which is cooperative by nature.[162] The physico-chemical properties of micelles are good for applications in the delivery of drug due to the possibility to carry hydrophobic drugs in the core place leading to lower drug cytotoxicity, extended half life time and tumor accumulation.[163, 164]

CONCLUSIONS

The purpose of this review is to show the versatility, unexplored potential, basic knowledge, possibilities and recent work on stimuli responsive polymers for drug delivery. A large number of researchers have been carrying out their work in this field towards developing polymers that respond to different stimuli in order to increase the effectiveness in the delivery of therapeutic agents. Responsive polymers provide a programmable and accurate system of delivery of drugs. Different stimuli cover different areas of treatment, viz. pH responsive polymers for oral drug delivery and cancer treatment, thermo responsive systems for tissue engineering and radiotherapy and magnetic sensitive polymers for magnetic resonance imaging. Responsive polymers have been used in all important areas related to human health such as: medical sciences, diagnostics, life science, drug delivery system and patient treatment which shows the efficiency of such polymers.

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