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Review Article

Novel Functionalized Polymers in Drug Delivery: A Brief Review

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Abstract

During the last few years, the science and technology of functionalized biodegradable polymers have received considerable interest in the field of polymer chemistry as well as pharmaceuticals. The novel concept behind the approaches is to produce improved polymers with enhanced desirable properties. In the recent years the functionalized polymers are synthesized and used in the form of Polymeric micelle, Polymer vesicles / Polymersomes, Films, Nanocomposite particles, "Smart" polymer conjugates, Hydrogels, Nanogels / Hydrogel nanoparticles, Mesoporous silica nanoparticles, Magnetic nanoparticles (MNPs) and Nanoparticles for improving pharmaceutical properties and therapeutic efficacy of the drugs. The functionalized polymers not only used as carriers but also improves the complications associated with the novel drug delivery formulations like: reduce P-glycoprotein drug efflux function and prevent drug resistance, improves drug loading, improved gene delivery in mesenchymal stem cells etc. In future these functionalized polymers are going to play a vital role in pharmaceutical and biological sciences in order to improve the therapeutic efficacy of a desired drug in field of cancer therapy, tuberculosis therapy, antimicrobial therapy and gene delivery.

Keywords: Biodegradable, films, nanoparticles, nanogels, smart polymer conjugates.

1. Introduction

The recent trend in polymer science that is the novel functionalization of polymer has created a scope to develop new innovative polymers with novel and tailor-made properties out of existing polymers. This aspect has created vast scopes for follow a line of investigation in areas like such as biochemistry, microfluidics, nanotechnology, pharmaceutical technology and colloidal based drug delivery systems[1].Literature study signifies that mostly the existing biodegradable polymers which are extensively used in the field of pharmacy like polyesters, polyamides, polyurethanes, polyphosphazenes, polyorthoesters, polyanhydrides, and poly (alkyl cyanoacrylates) etc. have lend themselves to develop novel functionalized polymers[2-4]. All these polymers contain specific active functional groups on them which provide a basis to develop functionalized biodegradable polymers by reacting with certain additives[5]. According to IUPAC, polymers bearing "specified chemical groups" and polymers having "specified physical, chemical, biological, pharmacological, or other uses which depend on specific chemical groups" are known as functional polymer[6].The said approach has been successful to fabricated polymers with various shapes and sizes, with tailored pore morphologies, mechanical properties, and degradation kinetics to suit a variety of applications compared to other materials for use in drug delivery systems such as nanoparticles. In recent years, significant effort has been devoted to develop colloidal drug delivery systems which focuses on formulating nanoparticles, nanocapsules, micellar systems, and conjugates for drug delivery since it offers a suitable means of delivering low molecular weight drugs, as well as macromolecules by either localized or targeted delivery to the tissue of interest. As nanotechnology formulations are polymeric

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and submicron in size, so they have multifaceted advantages in drug delivery such as provide targeted (cellular / tissue) delivery of drugs, improve oral bioavailability, sustain drug/gene effect in target tissue, solubilize drugs for intravascular delivery, and improve the stability of therapeutic agents against enzymatic degradation[7]. The aim of this review is to provide an updated, comprehensive review on recent developments and applications of functionalized polymers in pharmaceutical sciences with main emphasis on design of drug delivery systems.

Benefits of Using Functionalized Polymers over Conventional Polymers in Drug Delivery Systems

1. These improve the physical and mechanical properties of the existing biodegradable polymers such as ductility and toughness.
2. Effective for cell specific targeting of antitumor agents.
3. They significantly improve the potency of antibacterial agents.
4. They enhance the internalization of the polymeric micelles in tumor endothelial cells that over express $\alpha_v\beta_3$ integrins, apparently through receptor-mediated endocytosis[8].
5. They possess higher transfection efficiency and gene expression in MSCs and hence, used for improved gene delivery in mesenchymal stem cells (MSCs)[9].
6. They promote osteogenic differentiation of MSCs and control cell physiology and cell aging phenomena[10].
7. They can be fabricated into several formulations; those can be used in multi route of administration.
8. They are highly resistant to non-specific adsorption in contact with human serum but the fabricated microarrays using these functionalized polymers can capture multiple molecules[11].
9. They increase drug loading efficiency and stability (due to low critical micellar concentration) of nanoparticles.
10. They make interesting drug delivery systems because the functionalized polymeric nanoparticles existed in different morphologies, including spherical, star-like, and cuboid shapes.
11. They reduce systemic toxicity and enhanced drug efficiency at the target sites.
12. They increase the permeability as well as relative bioavailability of drugs[12].
13. They are used for protein detection.
14. They reduce P-glycoprotein drug efflux function and prevent drug resistance[13].
15. They improve the aqueous solubility properties of the poorly aqueous soluble drugs.

Different Types of Functionalized Polymeric Delivery Systems

In the last few decades (1990 to 2012) the functionalized polymers are synthesized and used in pharmaceutical and biological science in the form of Polymeric micelle, Polymer vesicles / Polymersomes, Films, Nanocomposite particles, “Smart” polymer conjugates, Hydrogels, Nanogels/Hydrogel nanoparticles, Mesoporous silica nanoparticles, Magnetic nanoparticles (MNPs) and Nanoparticles. The different types of polymers which have been functionalized in order to improve the efficacy of drug delivery system are enlisted in table 1. Fig. 1 depicts the various drugs that have been delivered by using functionalized polymers.

Table 1: List of polymers which has been functionalized in order to improve the therapeutic efficacy of drug delivery systems.

Sl. No	Polymer	Functionalization by	Delivery system
1	Poly(N-isopropylacrylamide) (poly(NIPAM))	Tetrathiafulvalene (TTF)	Polymeric micelles
2	Methoxy-poly(ethylene glycol)/poly(epsilon-caprolactone)	Folate	Polymeric micelles

3	Poly(ethylene oxide)-b-poly(4-vinyl benzaldehyde) (PEO_{45}-b-$PVBA_{26}$)	Benzaldehyde	Polymersomes
4	Pectin	Vinyl	Hydrogel
5	Chitosan	Acrylic Acid	Hydrogel
6	Poly(amino PEG-cyanoacrylate-co-hexadecyl cyanoacrylate)	Folic acid	Nanogels
7	Chitosan	Boronic acid	Nanospheres
8	Poly (ethylene glycol) - poly (lactic acid) (PEG-PLA) or PEG -poly (lactic-co-glycolic acid) (PEG-PLGA)	Wheat germ agglutinin	Nanoparticles
9	Poly(ethylene glycol)–poly(lactic acid) PEG-PLA	Penetratin	Nanoparticles
10	PEG-PLA	F3 peptide	Nanoparticles

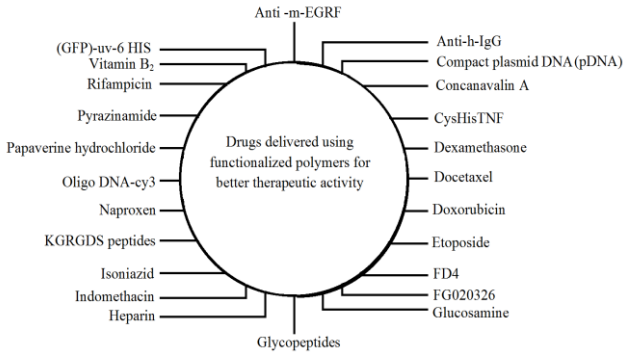

Fig. 1: Different types of drugs delivered by using functionalized polymers.

Polymeric micelle

A polymeric micelle is a macromolecular assembly having spherical inner core and an outer shell and are made up of synthetic block copolymers or graft copolymers[14].The merits of the polymeric micelles as drug carriers are: they are very small size (diameter 10-100 nm) as a result they escape from the reticulo endothelial system and hence prolonged drug circulation time, have low toxicity and have high structural stability, drug loading efficiency[14].Polymeric micelle prepared from novel functionalized polymers have gained popularity for effective drug delivery to cancerous cells. The resistance of cancer cells to multiple structurally unrelated chemo therapeutic drugs termed as ‘‘multi drug resistance (MDR)’’.This is a major cause of failure of cancer chemotherapy. The major mechanism involved in drug resistance is the classical efflux mechanism associated with the function of P-glycoprotein (P-gp).This protein acts as a drug efflux pump that extrudes a wide range of structurally and mechanistically different chemotherapeutic drugs out of cancer cells and hence results in failure of action in drugs, including vinca alkaloids, anthracyclines, epipodophyllotoxins, taxanes and other natural products. Biodegradable diblock copolymers of foliate -poly(ethylene glycol) and poly(epsilon-caprolactone) prepared by multistep reaction was found to self assemble into tumor targeted core-shell micelle structures smaller than 100 nm in diameter with a hydrophobic PCL core capable of encapsulating FG020326, a potent MDR modulator. The *in vitro* release of FG020326 was found to be dependent on pH (faster at pH 5.0 compared to pH 7.4).The most encouraging object that was established from the study is conjugated polymeric micelle inhibits the P-glycoprotein drug efflux function significantly which reduces the chances of multi drug resistance[13]. Liver targeted delivery Polymeric micelles containing doxorubicin (DOX · HCl) prepared from modified poly(ethylene glycol)–b-poly(γ-benzyl l-glutamate) block copolymer along with glycyrrhetinic acid (GA, a liver targeting ligand) was able to deliver the drug successfully at the desired site (4.9-fold higher DOX concentration than that for free DOX · HCl). The DOX-loaded micelles exhibited almost two

fold more potent cytotoxicity compared with DOX HCl, and the cytotoxicity was time and dosage-dependent[15]. Polymeric micelles containing a hydrophobic substance Nile Red was prepared from a amphiphilic polymer i.e. Tetrathiafulvalene (TTF) functionalized Poly(N-isopropylacrylamide) which self-assembled and form a thermo-responsive micelles, that releases Nile Red at lower critical solution temperature of the N-isopropylacrylamide backbone. At the lower critical solution temperature oxidation of TTF unit occurs and hence releases the Nile red[16].

Polymer vesicles /Polymersomes

Polymer vesicles are composed of closed bilayer membranes with hollow cavities and are supramolecular assemblies of amphiphilic block copolymers or complementary random copolymers with sizes ranging from tens of nanometers to several hundreds of microns[17]. These controlled drug delivery systems have high potential for encapsulation of both hydrophobic and hydrophilic drug moieties. Their structures can be manipulated on both polymeric and supramolecular levels to afford tunability of their properties through reactions with the functionalities installed at the chain ends of the hydrophilic segments. Modifications of wall domains of polymersomes by radical polymerization, photo induced [2+2] cycloaddition, base-catalyzed self-condensation of siloxanes and ring opening of epoxides[17]. Polymersomes in the range 100-600 nm formulated using block copolymer Poly (ethylene oxide)-*b*-poly(4-vinyl benzaldehyde) PEO_{45}-*b*-$PVBA_{26}$ with modifications of wall domains by introduction of highly reactive functionalities like benzaldehyde (a diverse electrophile that undergoes reaction under mild conditions) has been done. These nanostructures showed their ability to associate with the cell membrane, which wide its application as a nanoscopic device for repair or modification of cellular membrane functions[17]. Polymersome surface functionalizations have been reported through reactions with the functionalities installed at the chain ends of the hydrophilic segments for the development of leuko-polymersomes. In the above approach terminal end of the water soluble polyethylene oxide has been functionalized with 4-fluoro-3-nitrobenzoic acid terminated polymer, followed by addition of biotin formed polymersomes having the adhesive properties like leukocytes and which can be used for the detection and treatment of inflammatory disease[18].

Films

Thin polymer films with thicknesses of tens of nanometers are used extensively in technological applications such as optical coatings, protective coatings, adhesives, barrier layers and packaging materials because they provide ideal sample geometry for studying the effects of one dimensional confinement on the structure, morphology and dynamics of the polymer molecules[19]. Grondahl *et al.* prepared a film of acrylic acid functionalized Poly (3-hydroxybutyrate-co-3-hydroxyvalerate) using Poly (3-hydroxybutyrate-co-3-hydroxyvalerate) melt processed disks and solvent cast films by graft co-polymerization with acrylic acid in methanol solution at ambient temperature using gamma irradiation. They claimed the above polymeric film can be used for tissue engineering applications[20].

Nanocomposite particles

Nanocomposite particles are typically consisting of an inorganic solid containing an organic component or vice versa but at least one of the phases i.e. organic/inorganic is in the nano size[21]. Azioune *et al.* prepared novel polypyrrole-silica nanocomposite particles bearing reactive surface *N*-hydroxysuccinimide functional groups in aqueous solution by copolymerization of pyrrole and *N*-esterified pyrrole (pyrrole-NHS) using $FeCl_3$ in the presence of an ultrafine silica sol. The resulting nanocomposite provided a high specific surface area for adsorption of high milligrams of (HSA) protein per gram of colloid and formation of covalent attachment via amide bond formation. The functionalized nanocomposites exhibited good long-term dispersion stability. Incubation of the HSA-grafted nanocomposite with anti-HSA resulted in immediate flocculation, an indication that they are alternative candidates for visual diagnostic assays[22].

"Smart" polymer conjugates

Smart polymers respond to relatively small changes in conditions (i.e. temperature, pH, concentration of specific ions, specific

wavelengths of UV light, visible light, or in rare cases, the application of an electric field) with large and sharp changes in the polymer solubility and can be conjugated to many different types of proteins and hence can be effectively used as a carrier for site specific drug delivery[23]. Vazquez-Dorbatt *et al.* prepared Boc-protected aminooxy end-functionalized poly (N-isopropylacrylamide) (pNIPAAm) by reversible addition-fragmentation chain transfer (RAFT) polymerization by using N-Isopropylacrylamide (NIPAAm) in the presence of a Boc-protected aminooxy trithiocarbonate chain transfer agent (CTA) utilizing 2, 2′-azobis (2-isobutyronitrile) (AIBN) as the initiator in dimethylformamide (DMF) at 70^0C. The Boc group was then removed, and the polymer was incubated with N-levulinyllysine-modified bovine serum albumin (BSA). Subsequently the aminooxy end-functionalized pNIPAAm was also immobilized on a gold surface after reduction of the trithiocarbonate end group. The aldehyde-modified heparin was finally immobilized on pNIPAAm surface through oxime bond to yield the polysaccharide-functionalized surface. The prepared bioconjugates could be applied for the stabilization and storage of growth factors on surfaces or used to coat medical devices such as renal dialysis instruments[24].

Hydrogels

Hydrogels are permanent or chemical gel stabilized by covalently cross-linked networks which have the capacity to hold water within its porous structure and is used extensively in various biomedical applications[25]. Guilherme *et al.* formulated pectin-vinyl-co-PDMAc hydrogels using vinyl functionalized pectin and N,N-dimethylacrylamide (DMAc) whose water absorption profile dependent on the polymer relaxation mechanism and its apparent swelling rate constant decreases significantly pH less than 6[26]. Barbu *et al.* synthesized nanoparticulate hybrid polymeric hydrogels (10-70 nm) to develop controlled release ophthalmic drug delivery system[27]. Hybrid polymeric networks were prepared and formulated as nanoparticles in a one-step procedure that involved the water-in-oil emulsion copolymerization of either *N*-isopropylacrylamide or 2-hydroxyethyl methacrylate with a chitosan derivative in which 67.2% of the free amino groups had been functionalized with acrylic acid. The vinyl group of the grafted acrylic acid provided the functionality that allowed radical copolymerization with NIPAM or 2-hydroxyethyl methacrylate and facilitated the formation of three-dimensional network structures. The zeta potential of these nanoparticles was found to be dependent on the relative proportion of chitosan in the formulation and to be affected by temperature. The water retention capacity of nanoparticles was found to be sensitive to pH. Lower pH favors high water accommodation. NIPAM-based materials containing a low percentage of chitosan were the most adhesive towards model mucosal surfaces. Lysozyme-induced degradation of nanoparticles was found to be dependent on chitosan content. *In vitro* drug release studies demonstrated the potential suitability of the nanoparticles for the delivery of ophthalmic drugs.

Nanogels/Hydrogel nanoparticles

Nanogels are swollen nanosized networks composed of hydrophilic or amphiphilic polymer chains but, they spontaneously absorb biologically active molecules through formation of salt bonds, hydrogen bonds, or hydrophobic interactions[28]. Siegwart *et al.* prepared well-controlled water-soluble HO-POEOMA by AGET ATRP of OEOMA in the presence of HO-EBiB in water and inverse miniemulsion of water/ cyclohexane at ambient temperature (30°C). Biotin-conjugated POEOMA was synthesized by the reaction of HOPOEOMA with carboxylic acid group of biotin using a carbodiimide coupling reaction. The avidin–HABA assay determines the amount of biotin in polymers to be 11.4 $nmol.mg^{-1}$ polymer and showed that the biotin conjugated POEOMA was still able to bind to avidin. GRGDS-functionalized POEOMA nanogels were synthesized by the reaction of GRGDS-NH_2 with HOOCPOEOMA nanogels. These GRGDS-conjugated nanogels have the ability to be used in directed drug delivery applications[29].

Mesoporous silica nanoparticles

In the recent days although many targeted drug delivery systems claims to deliver the entrapped drug at the particular site but in fact

except some more of them fails to fulfill this criteria due to zero" premature release factor. So this factor presents a major dispute for the site-selective delivery of protein, nucleotide-based drugs and cytotoxic drugs via oral route. Current research has paying attention on developing structurally stable drug delivery carrier systems that are clever to deliver a relatively large amount of drug molecules lacking any early leakage problem to targeted tissues and intracellular organelles. So out of many structurally stable materials the Mesoporous silica nanoparticles have been found to be fit for designing drug delivery system for achieving the above goal. The mesoporous silica, (MCM-41 and SBA-15 silica) have two functional surfaces that is an internal surface which is having porous structure similar to that of a honeycomb with hundreds of empty channels without any interconnectivity between individual porous channel and an exterior particle surface. They also have good chemical and thermal stability, high surface area (>900 m^2/g), large pore volume (> 0.9 cm^3/g), tunable pore size with a narrow distribution (2– 10 nm) and has the capability to encapsulate a relatively large amounts of bioactive substances. These unique properties make them potentially appropriate carrier system for various controlled release applications. The major disadvantages of these drug carriers is the interactions of surface silanols with cellular membranes and this can be reduced by functionalization of the nanoparticles by forming polymer shells. The polymer shells can provide colloidal stability, handle for chemoligation (targeting moieties) and improve the blood circulation life times, which are vital for capable of *in vivo* drug delivery[30]. Xi *et al.* prepared Doxorubicin hydrochloride (DOX) loaded spherical shaped nanoparticles for cancer therapy from chondroitin sulfate functionalized mesostructured silica nanoparticles. They were able to develop a simplistic and effective method to coat chondroitin sulfate-based macromer on to amine mesoporous silica nanoparticles to generate pH responsive nanocarriers. In this approach they first synthesized aminated MSNs by reacting MSNs with APTES, (3-aminopropyl) triethoxysilane. Then they prepared NMChS functionalized MSNs by adding NMChS solution (*O*-maleyl chondroitin sulfate) under some specific condition and procedure and finally was able to load a higher % of doxorubicin in to it by utilizing strong electrostatic interaction between NMChS and DOX. The prepared carrier system was able to prevent release of doxorubicin under undesirable conditions due to anchored chondroitin sulfate on the surface of the silica. The DOX release from the carrier system was faster in low pH condition to that of higher pH condition (Fig. 2).

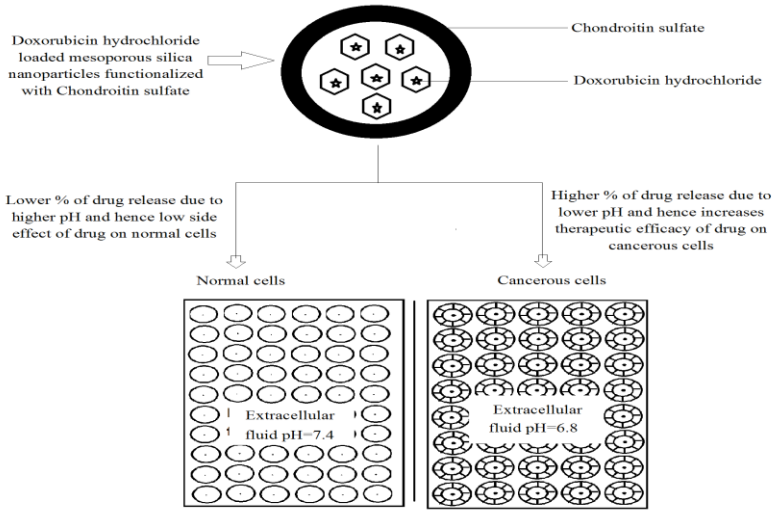

Fig. 2: pH responsive Chondroitin sulfate functionalized mesoporous silica nanoparticle loaded with doxorubicin hydrochloride releasing higher % of drug within the environment of cancerous cell due to lower pH condition.

This is because the drug release from the NMChS-MSNs is mainly determined by the effect of electrostatic interaction between DOX and polymer nanoshell. According to them the higher pH of the medium forms more negative charges on the surface of the NMChS-MSNs, the stronger attraction exists between the positively charged DOX and the negatively charged carriers, so the more difficult for the loaded DOX to be released out of the NMChS functionalized MSNs. The in vitro cellular cytotoxicity test demonstrates that the NMChS-MSNs are highly biocompatible and suitable to utilize as drug carriers Furthermore, DOX-NMChS-MSNs show a more efficient cytotoxicity than free DOX to HeLa cells[31]. Hartono *et al.* develop a novel and facile method to attach PLL (poly- L-lysine) onto LP-MSNs (large pore mesoporous silica nanoparticles) to produce LP-MSN-P (poly-L-lysine functionalized large pore mesoporous silica nanoparticles) and use it as a carrier to deliver a gene that is oligo DNA-Cy3 (a model for siRNA) into cancer cells. Large pore mesoporous silica nanoparticles with 100-200 nm in diameter with cavities is about 28 nm and an entrance size of 13.4 nm were used in order to increase the loading efficiency of the aforementioned gene. In this approach LP-MSNs was used as hosts, which was subsequently functionalized by grafting of epoxysilane (3-glycidoxypropyl trimethoxysilane (3-GPS)) to yield LP-MSN-E followed by surface functionalization with PLL through covalent immobilization method under the influence specific condition. The coating with PLL developed positive charges on the silica surface (both outer and inner), which in turn permits electrostatic interactions with negatively charged DNA/siRNA and hence increase in adsorption of gene in to carrier system. More over the prepared LP-MSNs had a strong binding capacity to negatively charged surface membrane which enhances cellular uptake. The system effectively delivered functional siRNA against mini brain-related kinase and polo-like kinase 1 in osteosarcoma cancer cells. The functionalized particles confirmed potential for efficient gene transfer into cancer cells as a decrease of the cellular viability of the osteosarcoma cancer cells was induced. The PLL-modified silica nanoparticles also exhibited a high biocompatibility, with low cytotoxicity *in vivo*[32].

Magnetic nanoparticles (MNPs)

Magnetic nanoparticles (MNPs) have achieved considerable attention in modern ages for various biomedical purposes. Nanoparticles which exhibit magnetic properties and consisting of iron, nickel and/or cobalt are called magnetic nanoparticles[33]. Nowadays due to the development of nanobiotechnology, magnetic nanoparticles are used in magnetic resonance imaging, virus detection, magnetic cell separation, enzyme catalysis, gene therapy, targeting chemotherapy and radiotherapy[34]. Yallapu *et al.* in 2010 developed PEG-functionalized magnetic nanoparticles for targeted drug delivery and magnetic resonance imaging applications successfully. They prepared an iron oxide core bare nanoparticle using Iron (III) chloride hexahydrate ($FeCl_3 \bullet 6H_2O$) 99 % pure granulated (Fe (III)), Iron (II) chloride tetrahydrate ($FeCl_2 \bullet 4H_2O$) 99 + % (Fe (II)) in presence of Ammonium hydroxide and coated it with oleic acid (OA) and then with OA-PEG which forms a water-dispersible MNP formulation. They loaded the doxorubicin into the nanoparticles by partitioning into the OA layer. For the purpose of active targeting to breast cancer they conjugated amine functional group of transferrin on to the N-hydroxysuccinimide group (NHS) on the OA-PEG-80. The optimized formulation had a mean hydrodynamic diameter of 184 nm with ~8 nm iron-oxide core. Loaded MNPs showed sustained drug release characteristics with a long circulation time *in vivo* and dose-dependent antiproliferative effects in vitro condition. The OE-80MNPs were found to enhance the T2 MRI contrast with a long circulation time *in vivo* with 30% relative concentration 52 min post-injection in the mouse carotid artery following tail vein injection[35].The popularity of using pristine nanoparticles of iron oxides for targeted drug delivery purpose is under question due to some serious drawbacks like short blood half-life of the nanocrystals for *in vivo* applications and non-specific targeting and anisotropic dipolar attraction tend to aggregate into large

clusters and thus lose the specific properties associated with single-domain magnetic nanostructures. The latter problem can be modified by surface modification of MNP to form superparamagnetic nanocrystals which do not retain magnetism after the removal of the external magnetic field. Superparamagnetic involves re-dispersion of the magnetic nanoparticles in solution without the occurrence of severe aggregation that ferromagnetic nanoparticles usually suffer from. Cao *et al.* in 2009 construct a particle targeted drug delivery system via layer-by-layer method in which β-CD's hydrophobic cavity is combined with (3-aminopropyl) triethoxysilane)-coated superparamagnetic Fe_3O_4 (APTES-MNP) nanoparticles. The prepared superparamagnetic nanosystem inner core respond to an externally applied magnetic field and outermost linked β-CD behaves as inclusion sites and specific containers for drugs and biomolecules. They found the saturation magnetization of CD-MNP to be 69 emu/ g by carrying out vibration sample magnetometer study. The value is relatively lower than that for MNP because of the two coating layers of APTES and CD[36].

Nanoparticles

Nanoparticles (NPs) which includes both nanospheres and nanocapsules, for the purpose of drug delivery are defined as submicron (<1μm) colloidal particles and are made from biocompatible and biodegradable materials such as polymers or solid lipids. As drug carriers, nanoparticles possess high stability, high carrier capacity, can be tuned for site specific drug delivery, feasibility of incorporation of both hydrophilic and hydrophobic substances; and feasibility of variable routes of administration[4].

Levere *et al.* in 2011 prepared azlactone-functionalized nanoparticles from a series of well-defined copolymers of PNIPAM-b-P(VDM-co- DMA) and PDMA-b-P(VDM-co-NIPAM) that are synthesized by RAFT polymerization. The resulting copolymers are thermoresponsive and the molar composition within the copolymer affects the LCST. Both have a LCST that occurs at the physiological temperature above which the structures self-assemble to form nanoparticles. The resulting nanoparticles were covalently stabilized by reacting an azlactone rings with diamine solution at 40 °C. The DLS analysis particle at 25 °C reveals an average hydrodynamic diameter of 29 nm. The FTIR study confirm the intactness of azlactone ring in the core of particles after copolymerization and used for binding amine containing drug like dansylhydrazine[37].Corneal targeted drug delivery of nanoparticles have been focused as a great challenge in the recent years because intact epithelial layer of cornea have low permeability to drug that causes reduction in efficiency of gene delivery and drug absorption. Functionalized polymeric nanoparticles to target injured eye corneal epithelial cells through RGD-cell surface receptors has been successfully developed by Lu *et al*. 2008 for the treatment of corneal epithelial defects such as corneal neovascularization, dystrophies, neurotrophic keratopathy, recurrent erosion, and dry eye syndrome etc. Modifications of surfaces with targeting ligands of self-assembled polymeric nanoparticles are suitable for localized cell delivery. Coumarin-modified lysine (K) of the KGRGDS peptide conjugated to the poly(TMCC-co-LA)-g-PEG azide-functionalized nanoparticles using the azide-alkyne Huisgen 1,3 cycloaddition reaction resulted in 400 conjugated peptides per nanoparticle, allowing for interactions with rabbit corneal epithelial cells that having $\alpha_v\beta_1$-integrin receptors up-regulated system. The prepared bioconjugated NPs are small enough for sterile filtration[38]. TNF is a transmembrane protein (membrane or memTNF) which is originally expressed at the cell surface. By action of the metalloproteinase TACE (tumor necrosis factor alpha converting enzyme) the membrane bound form is converted to soluble TNF (sTNF). Both memTNF and sTNF bind to two different cell membrane receptors, termed TNF receptor (TNFR) 1 and 2. Membrane TNF strongly activates both receptors, whereas sTNF is capable to only stimulate TNFR1 but not TNFR2. Only role of sTNF has been studied mostly which keeps the role of TNFR2 largely in dark. Inorder to investigate the role of TNFR2 Bryde *et al.* in 2005 constructed a synthetic-biological hybrid system consisting of chemically nanostructured core-shell particles with a diameter of 100 nm, 1 μm, or 10 μm

and the cytokine TNF to obtain a tool that mimics the bioactivity of naturally occurring membrane-bound TNF. The prepared artificial core-shell nanoparticles consist of an inorganic silica core with an ultrathin organic shell containing a maleimide group at the shell surface. The maleimide group allowed for a covalent and site-directed coupling of CysHisTNF mutants. The TNF mutants were modified at the N-terminus by PCR cloning by introducing a His-Tag for purification and a free cysteine group for reaction with the particle-attached maleimide group. The resulting nanostructured hybrid particles initiated strong TNF receptor type 2 specific responses which is the mimicking action of memTNF[39].

Conclusion

From the above review we concluded that most of the functionalized polymers synthesized till date are used in pharmaceutical and biological sciences in different dosage forms like Polymeric micelle, Polymer vesicles /Polymersomes, Films, Nanocomposite particles, “Smart” polymer conjugates, Hydrogels, Nanogels/Hydrogel nanoparticles, Mesoporous silica nanoparticles, Magnetic nanoparticles (MNPs) and Nanoparticles but out these most are developed in the form nanoparticles with improved pharmaceutical and pharmacological properties.

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