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Review Article

Natural and synthetic smart polymers in drug targeting: A smart approach

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Among various polymers, smart polymers have taken much importance in drug delivery systems due to their targeting ability. This review mainly describes the expansion of biodegradable polymers in pharmaceuticals drug delivery that provides mechanism of targeting from both physiological and pathological point of view. Thus, smart polymers due to various actions and responsive drug delivery get more importance in era of novel techniques especially in nanotechnology by formulation of nanoparticles. This progress descends into two categories: i) open loop system that is also known as externally regulated or pulsatile systems, ii) closed loop system that is actually self-regulated systems. External triggers like ultrasonic, magnetic, electric, light and chemical or biochemical agents involved in release of open loop or pulstile drug delivery system whereas self-regulated systems are the systems where controlled variable is detected due to which the system output is adjusted consequently. Several approaches like thermal response, pH-sensitive drug or polymers action, enzyme-substrate reactions are applied for achieving targeted drug delivery systems. The release rate can also be controlled by selection of natural and synthetic nature of smart polymers on the basis of their feedback mechanism.

Keywords: Biodegradable, Closed Loop, Open Loop, Novel, Natural, Synthetic and Smart Polymers.

1. INTRODUCTION

These days a lot of work is being done on stimulus-responsive polymeric hydrogels. A rapid change in the physical nature of these hydrogels show that they responsed quickly to external or internal stimuli (Cao *et al,* 2006) (Spohr & Reber, 1988). This property could be useful in several drug delivery applications. The external stimuli could be a pH, ionic strength, pH, ionic strength, ultrasonic sound, electric current, etc (Okana *et al,* 1990) (Chen & Hoffmann, 1995). Most of the literature concerned to the the development of stimulus-responsive drug delivery systems deal with temperature-sensitive poly(N-isopropyl acrylamide)(pNIPAAm) and its assorted derivatives. However, acrylic-based pH-sensitive systems with weakly acidic/basic functional groups have also been extensively studied. This article gives a concise introduction and latest development in the field of stimulus-responsive hydrogels, especially those which show a response to temperature, pH, and have applications in drug delivery system the (Gil & Hudson, 2004) (Lou *et al,* 2000) decades have witnessed an immense development in this area. SP which are also known as stimuli-responsive soluble–insoluble polymers or environmentally sensitive polymers are being used in the fields of biotechnology, medicine and engineering (Lou *et al,* 2000;Jeong & Gutowska, 2002). This review is meant to emphasize on the applications of SP when these polymers are presented in three common physical forms (i) linear free chains in solution where polymer undergoes a reversible collapse after an external stimulus is applied, (ii) covalently cross-linked reversible gels where swelling or shrinking of the gels can be triggered by environmental change and (iii) chain adsorbed or surface-grafted form, where the polymer reversibly swells or collapses on surface, once an external parameter is changed (Haung & Wu, 1999).

2. ADVANTAGES OF SMART POLYMERS

Smart polymers are non-thrombogenic strong, flexible, tough, biocompatible, easy to color & mould, maintain stability of the drug, and maintain drug level in therapeutic window increase patient compliance, easy to produce, used for blood contacting

application, they are good transporter of nutrients to cells and products from cell, can be easily tailored with cell adhesion ligands, they can be injected in vivo as a liquid that gels at body temperature. However there are few problems with these polymers like they are usually mechanically weak, difficult to handle, drug and cell loading is hard and crosslink in vitro as a prefabricated matrix, not easy to sterilize (Kokufuta *et al,* 1993).

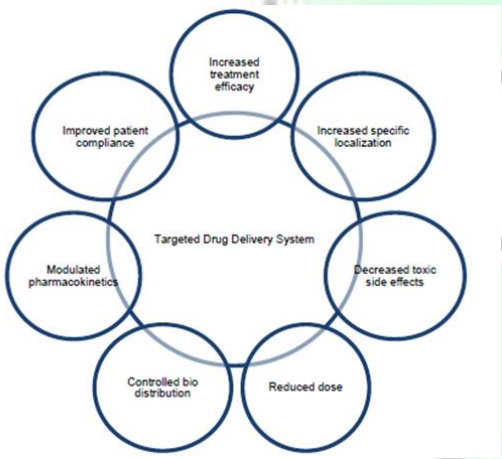


Figure 1: Advantages of smart polymers

3. CLASSIFICATION OF SMART POLYMERS

A. Based on action at targeted site: (Higuchi, 2004)

1. pH sensitive smart polymers
2. Temperature sensitive smart polymers
3. Polymers with dual stimuli-responsiveness
4. Phase sensitive smart polymers
5. Light sensitive smart polymers

B. Based on composition: (Singh, 2004)

1. Natural
2. Synthetic

A. Classification based on action at targeted site:

1. *pH sensitive smart polymers*

weak acidic or basic groups present in polyelectrolytes (which are pH sensitive smart polymers) can accept or release protons when pH of the environment changes (Gan *et al,* 2000) weakly acidic (anionic) groups also known as polyacids show increase in swelling in response to increased external pH , however a decreases if polymer have a weak basic (cationic) groups known as polybases. The majority of the anionic pH sensitive smart polymers are based on polyacrylic acid (PAA) (Carbopol) or its derivatives, polymethacrylic acid (PMAA), poly (ethylene imine), poly (L-lysine), and poly (N,N-dimethylaminoethyl methacrylamide). Another type of polyacidic polymer is the polysulfonamides (derivatives of p-amino benzene sulfonamide). These weak polyacids shows a pKa which narrowly vary from 3 to 11, depending on the electro-withdrawing nature of the substituent on the nitrogen (Sheppard *et al,* 1995). Examples of cationic polyelectrolytes are poly (N,N-dialkyl aminoethyl methacrylates), poly (lysine) (PL), poly (ethylene-imine) (PEI), and chitosan. Other examples of pH sensitive smart materials are sulfonamide and L-histidine.which because of the ionizable group characteristic shows a pH responsive solubility or property. Various actions on smart polymers based on targeted site are shown in figure 2.

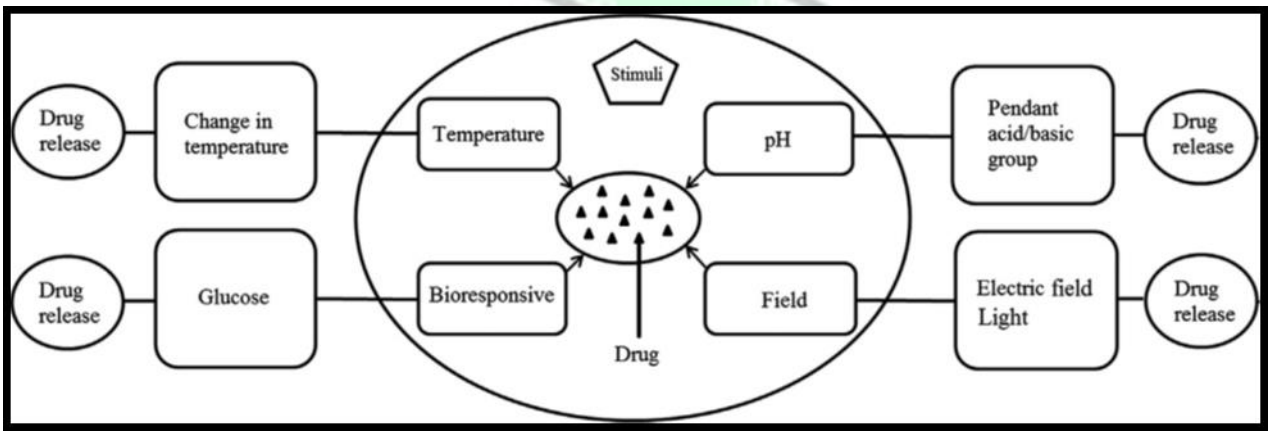


Figure 2: Smart polymers actions on targeted site

2. *Environmental activation/stimuli responsive smart delivery system*

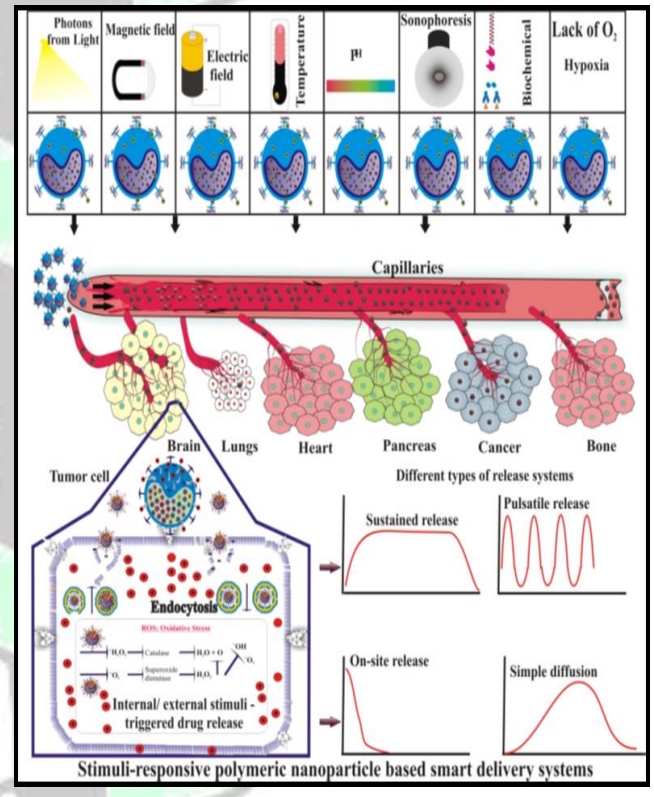
The smart drug delivery with activation-modulated system has been achieved by external or environmental stimuli; these environmental responsive smart delivery systems achieved a lot more with double and multiple-responsive delivery system (Raun *et al,* 2003)(Kikuchi & Okano, 2005). The numerous activation/stimuli responsive drug delivery vehicles have been developed and tested, in different particle sizes, ranges from nanometers to a few micro-meters sized carriers for various routes of administration. The most efficient model developed in this regard is transdermal electro-activated or electro-modulated drug delivery. In this group of activation-modulated controlled drug delivery system, physical, chemical, electrical, environmental condition or biochemical processes or an energy supplied externally activate the system to release the active drug from the system. The input energy actually controls the release profile. The release profile has been controlled by the input energy(Shimizu *et al,* 2003). Depending on the activation/stimulation process applied or energy form used, this activation-modulated controlled drug delivery system can be classified into the different classes which are given in the Table 1.

Table 1 Various stimuli and responsive materials.

Environmental stimulus	Responsive material
Temperature	Poloxamers Poly(*N*-alkylacrylamide)s Poly(*N*-vinylcaprolactam)s Cellulose, xyloglucan Chitosan
pH	Poly(methacrylicacid)s Poly(vinylpyridine)s Poly(vinylimidazole)s
Light	Modified poly(acrylamide)s
Electric field	Sulfonated polystyrenes Poly(thiophene)s Poly(ethyloxazoline)
Ultrasound	Ethylenevinylacetate

The physicochemical characteristic of these stimuli-responsive materials changes as the environmental condition changes. These changing properties can be completely utilized in smart delivery system, which are definitely analogous to the biological response behavior (Diamond & Hsu, 1992) (Scopes, 1994). Various types of body organs, tissues and different types of cellular compartments may have large differences in each stimulus with great response. All the important cases considered in this chapter, deal with various environmental responsive smart delivery systems. Any specific behavioral change in the system leads to a phase transition, these transitions will be key factors for the stimuli-responsive drug delivery system and some selected examples of applications are described in the Figure 3.

Figure 3: Environment and stimuli based response of smart polymers



3. Temperature sensitive smart polymers

These are those polymeric systems which are sensitive to temperature changes. These polymers show gel-to-gel transition as a function of environmental temperature that can be used to deliver therapeutic agents in vivo. These type of systems show a critical solution temperature (typically in water) at which the phase of polymer and solution is changed in accordance with their composition (Mattiason & Kaul, 2003). Many polymers exhibit abrupt changes in their solubility as a function of environmental temperature as shown in table 2. This property is used to develop aqueous solutions of these polymers which undergo

sol-gel transition in response to temperature changes (Kukoi *et al.,* 2000).

An upper critical solution temperature (USCT) is shown by those Temperature sensitive smart polymers which exibit one phase above certain temperature and phase separation below it. While those polymer solutions which are monophasic below a specific temperature and biphasic above it, generally show a lower critical solution temperature (chen wt al., 2003). The LCST can be defined as the critical temperature at which polymer solution undergo phase separation from one phase (isotropic state) to two phases (anisotropic state) rich and poor in polymer. Such solution also appears as monophasic below a specific temperature and biphasic above it. Below the LSCT, the dissolution of polymer occurs because of the enthalpy term associated to hydrogen bonding present between water molecules and the polymer. Poly (ethylene oxide) (PEO) is one of the most biocompatible polymer which exhibits LCST behavior (Lee, 2002).

When temperature goes above the LCST the precipitation of the polymer occur because of the dominating entropy term.PEO aqueous solutions show a transition in LCST Depending upon the molecular weight at temperature ranging from 1000 C to1500 (Cleland *et al.,* 2001) (Kim & Peppas, 2002) the polymer which contains hydrophobic parts (e.g. ethylene, EE) and ethylene oxide (EO) parts should show a phase transition at lower temperatures than the PEO LCST. The linear polymers made up of short EO and EE segments (for prevention of micelle formation) can show a precipitation from aqueous solution which can be envisioned to be a sharp LCST transition. Furthermore the PEO and PE phase behavior in water, a linear alternating EO-EE copolymer sequence across the polymer should lead to an LCST determined by the hydrophobic/hydrophilic balance, in absence of intra- and intermolecular hydrogen bonding (Kim & Peppas, 2002).

The polymers which show temperature poly ethylene (glycol)- sensitivity are following; poly (propylene oxide)- poly (ethylene oxide) triblock copolymers (PEO-PPO-PEO) poly (N-isopropylacrylamide) (PNIPAAM),), poly (ethylene oxide) triblocks (PEG-PLA PEG) -, poly (lactic acid)- poly (ethylene glycol) The most frequently used temperature sensitive polymers include poly (N-alkyl substituted acrylamides) and poly (N-isopropyl acrylamide) with transition temperature of 320 C and poly (Nvinylalkylamides) like poly (N-vinyliso-butyramide) with transition temperature of 390 C. Beyond lower critical solution temperature (LCST) polymer becomes insoluble in water because the Temperature-sensitive smart polymeric solubility actually originates from it. For those polymers which show hydrogen bonds to water this behavior is very usual and can be employed for use in other like DNA sequencing smart drug release and patterning (Kim & Flamme, 2003) (Masteikova *et al.,* 2003).

4. Phase sensitive smart polymers

Biocompatible formulations for controlled delivery of proteins in a biologically active and conformationally stable form can be developed by the use of Phase sensitive smart polymers. These polymeric systems have gained advantage over other due to less stressful manufacturing conditions for sensitive drug molecules, ease of manufacture and high loading capacity (Gonclves *et al.,* 2005) (Albin *et al.,* 1985). In this method those polymers are used which do not dissolve in water but dissolve in pharmaceutically acceptable solvent and biodegradeable at same time like poly (D, L-lactide), poly (D,L-lactideco-e-caprolactone) and poly (D,L-lactide-co-glycolide) are used. The drug to be loaded is disoolved in the solvent to form a suspension or solution. When injected to body and water penetrates into the organic phase and the water-miscible organic solvent dissipates. As a result depot formation occurs at the site of injection due to precipitation of the polymer and phase separation. The organic solvents used are; hydrophilic solvents,

Table 2 Various smart polymeric drug delivery systems.

Stimulus	Advantage	Limitation
Temperature	Ease of incorporation of active moieties Simple manufacturing and formulation	Injectability issues under application conditions. Low mechanical strength, biocompatibility issues and instability of thermolablile drugs
pH	Suitable for thermolabile drugs	Lack of toxicity data Low mechanical strength
Light	Ease of controlling the trigger mechanism Accurate control over the stimulus	Low mechanical strength of gel, chance of leaching out of noncovalently attached chromophores Inconsistent responses to light
Electric field	Pulsative release with changes in electric current	Surgical implantation required Need of an additional equipment for external application of stimulus Difficulty in optimising the magnitude of electric current
Ultrasound	Controllable protein release	Specialized equipment for controlling the release Surgical implantation required for nonbiodegradable delivery system
Mechanical stress	Possibility to achieve the drug release	Difficulty in controlling the release profile

such as N-methyl-2-pyrrolidone (NMP), tetraglycol, and glycofurol and include hydrophobic solvents, such as triacetin, ethyl acetate, and benzyl benzoate. (Ishihara *et al,* 1984). Major applications of phase sensitive smart polymer are

a. lysozyme release which are prepared by adding lysozyme to poly (D,L-lactic acid) (PLA)-triacetin solutions.

b. Controlled release of proteins Phase sensitive smart polymeric formulations have broad application for the controlled release of a number of other proteins.

But the major problem in the use of these polymers as injectible is the burst release within the few hours .the reason can be a lag time between gel depot formation and the injection of the delivery system. A modulation was made in the burst release of lysozyme and insulin by using benzyl benzoate/benzyl alcohol solvent systems and polymer concentration. Burst release increase as the proportion of the hydrophilic solvent increases. The affinity between water influx rates increase by the addition of hydrophilic solvent (Ito *et al,* 1989) (Hassan *et al,* 19997). These polymeric systems are also known to exhibit a high initial release Higuchi square root of time relationship of the drug followed by a more sustained release profile. Initial high burst release occurs when following. In phase sensitive smart polymeric systems severe tissue irritation or necrosis can be avoided at the site of administration by using the nontoxic and biocompatible solvents (Hassan *et al,* 19997).

5. Light sensitive smart polymers

In industrial bioseparation techniques visible light sensitive smart polymer that forms aqueous two phase systems are potentially used because they are capable of avoiding many problems of two phase system like; they cannot be recycled , environmental pollution ,result in increasingly expensive bioproducts, and purification at least one region which is biodegradable processes. In macromers at least two free radical polymerizable regions, at least one region which is biodegradable and one water soluble region are present. Polymerization occurs in macromers by free radical initiator through visible light, ultraviolet light or thermal energy, and excitation (Heller *et al,* 1999). The biodegradable regions may be polymers composed of polylactic acid, polyglycolic acid, poly (anhydrides), poly (amino acids) and polylactones. The core water soluble region can consist of PEG, polysaccharides such as hyaluronic acid, or proteins such as albumin. Preferred polymerizable regions include, methacrylates, diacrylates, acrylates, or other biologically accepted polymerizable groups.free radicals are grenrated from initators which includes; ethyl eosin acetophenone derivatives, or camphorquinone. Example of light sensitive smart polymers with its applications is ; a. Light sensitive smart polymer prepared by using N-isopropylacrylamide, n-btutyl acrylate and chlorophyllin sodium copper salt as monomers.

B. Classification based on polymer composition:

1. Natural Smart Polymers

These smart polymers are also bio-polymers metabolized or excreted through normal physiological ways. They are of three type's i.e. natural, semi synthetic, and synthetic, depending upon their nature and sources. For application of drug delivery systems, a variety of biodegradable polymers are used which show desirable sustained, controlled and targeted effect by maintaining drug concentration within the therapeutic range. Release profiles can be improved by the changing nature and physical properties of polymers like polymer molecular weight, monomer composition, and by choosing synthetic or natural origin (Irvin *et al,* 2001).

Chitosan

It is a hetero-polymer of N-acetyl-d-glucosamine and D-glucosamine linked by beta-(1–4)glycosidic bonds as shown in Figure 4. It is obtained by the partial de-acetylation of naturally derived chitin. Chitosan is hydrophilic and soluble in acidic solution by protonation of the amine groups, and is degraded by enzymes such as lysozymes, some lipases and proteases. It behaves as cation with anionic polymers and as an anion with cationic polymers. Chitosan increases cell membrane permeability; therefore, it also acts as absorption enhancer across intestinal epithelia by extending the residence time of drug delivery systems at absorption sites. It also has ability to open the tight junctions of cell membranes (Ecsobar *et al,* 2006).

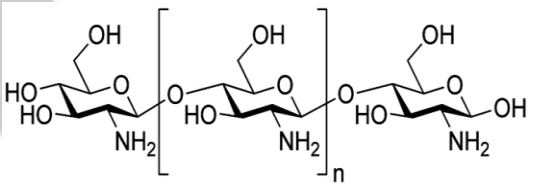


Figure 4: Structure of Chitosan

Sodium tripolyphosphate (TPP)

TPP is a non-toxic anionic molecule as shown in Figure 5, which has been commonly used for the preparation of crosslinked chitosan nano and microparticles; various drugs have been encapsulated within these particles. TPP and chitosan crosslinked particles have been used for delivery of protein, oligonucleotides and plasmid due to their extraordinary physical stability and encapsulation productivities (Dumortier *et al.,* 2006).

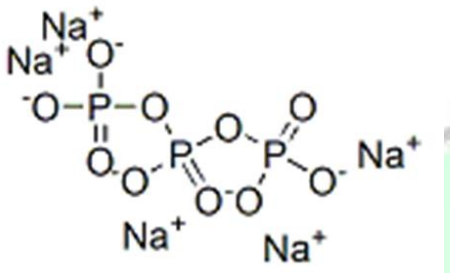


Figure 5: Sodium tri-polyphosphate

Carrageenan

Carrageenanis a hydrocolloid found from Rhodophyceae (red sea weed). It contains mainly potassium, sodium, magnesium, calcium, and ammonium sulfate esters of galactose and 3, 6-anhydro-galactose copolymers. These hexoses are consecutively linked at the a[α]-1, 3 and b[β]-1, 4 sites in the polymer as shown in Figure 6. It is a water soluble polymer and has been biocompatible, biodegradable, anionic, and non-toxic in nature. Nano/micro-particles can be formed with carrageenan by adding a polycationic solution like chitosan. Chitosan/carrageenan/TPP crosslinked particles were prepared by corporation of polyelectrolyte complexation and ionic gelation (Irvin *et al.,* 2001) (Dumortier *et al.,* 2006).

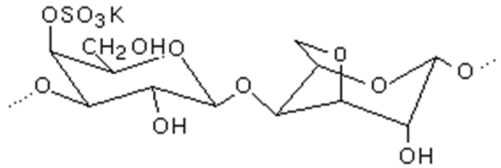


Figure 6: Structure of Carrrageenan

Casein

Casein is the major milk protein component and is easily self-assemble into micellar structure by intermolecular hydrophobic interactions due to its amphiphilic nature, which is a suitable feature for the application as delivery carriers. Sodium caseinate is formed by acidification of skimmed milk at pH of 4.6 due to which colloidal calcium phosphate dissolves in and the various casein proteins precipitate out. By washing; soluble salts, whey proteins and lactose are removed and ultimately the precipitated caseins are again dissolved through re-neutralization of the system after enhancing pH to 7 by NaOH. In a sodium caseinate solution; the different caseins have ability to self-associate into small masses of about 10-12 nm. Functional properties of sodium caseinate include emulsification, thickening, gelling, water-binding and fat-binding. Sodium caseinate is also used as a stabilizer for emulsions, due to its strong amphiphilic nature. Casein is an edible material; it is often used as a drug carrier for an oral-delivery system. Several types of hydrophobic chemotherapeutics such as mitoxantrone, vinblastine, irinotecan, docetaxel and paclitaxel have been encapsulsted in β-casein micelles for target-activated release of drugs by oral drug delivery (Ecsobar *et al,* 2006) (Jeong & Gutowska, 2002).

Sodium alginate

From past, alginate is widely used due to biodegradable, biocompatible and muco-adhesive nature of alginate polymers. Sodium alginate is a sodium salt of alginic acid that is attained from marine brown algae. It contains 2 uronic acids, α-L-guluronic and β-D-mannuronic acids as shown in Figure 7. Sodium alginate is widely used in microparticle preparation due to its ionotropic gelation property on reaction with cations. The multiple guluronate units in the sodium alginate molecules form a crosslinked structure with metal ions by polyelectrolyte complexation in which the cations can be packed and are coordinated. The crosslinked structure formed by this approach is kinetically stable from dissociation (Dumortier *et al,* 2006) (Jeong & Gutowska, 2002).

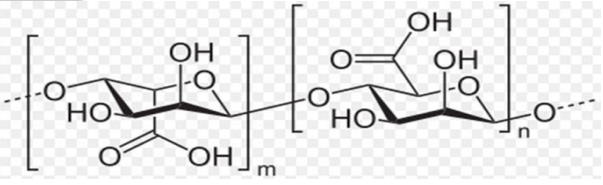


Figure 7: Structure of Sodium alginate

Anionic and cationic reaction results in spherical

bead formation by swelling properties of alginate during ionic gelation with cations. Swelling property of alginate depends upon various factors such as valency and size of ions; e.g. monovalent cations do not induce gelation while divalents do and Magnesium as a divalents not have gelling property but some divalents also have priority upon one another e.g. Ba2+ produce more stable beads/ particles than Ca2+.

2. Synthetic smart polymers

Eudragit S100/ Poly(methyl methacrylate)

EUDRAGIT S100 is an anionic copolymers based on methacrylic acid and methyl methacrylate. The free carboxyl groups ratio to that of the ester groups is approx. 1:1 in EUDRAGIT L100 and approx. 1:2 in EUDRAGIT S100. Eudragit S100 Soluble in intestinal-fluid at pH > 7. It is white free- flowing powders also used in enteric coatings Sustained delivery of drugs can be established that can bypass the stomach and release the loaded drug for extended period of time into the intestine by coating the eudragit S100 polymer. Eudragit L &Eudragit S is commercially available enteric acrylic resins. Both are responsible to produce films resistant to gastric fluid (Morishita *et al.,* 2002) (Peppas, 2004).

Latest trends in drug formulation by using smart polymers

In this era polymers are extensively used as biomaterials because of their favorable characteristic like good biocompatibility, easy design and preparation, a variety of structures and interesting bio-mimetic character. Polymers have played a significant role in the field of smart drug delivery which can deliver therapeutic agents directly into the intended site of action, with superior efficacy (Morishita *et al,* 2002) (Peppas, 2004). For designing nano-particulate delivery system the ideal requirements are; effectively controlled particle size, surface character, flexibility, enhance permeation, and release of therapeutically active agents to get the specific activity and to reach the target at a predetermined rate and time The advances in polymer science in the bio-nanotechnology field have actually made possible the development of smart drug delivery system recently smart drug delivery have found application in medical field for nano-scale structures. The smart drug delivery systems must possess some important feature like pre-scheduled rate, predetermined time, self controlled, targeted, and monitor the delivery as shown in figure 8.

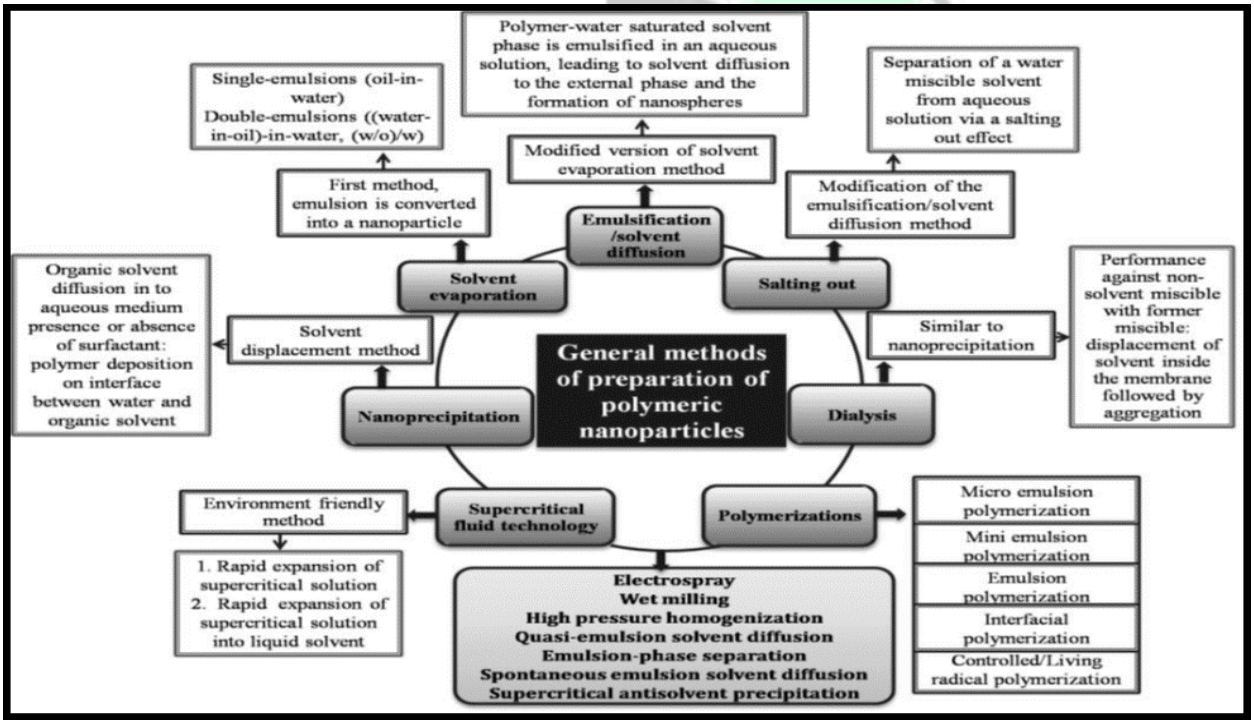


Figure 8: Latest trends in drug formulation by using smart polymer

The smart drug delivery system increases the polymer nanoparticle improved stage to their therapy regimen. They are drug carriers of natural, semi-synthetic, and synthetic polymeric nature at the nano-scale to micro-scale range (Palasis, 2003) (Bae & Park, 2000). The polymeric particles are collectively called as spheres and capsules. Those polymeric naoparticle which contain surfactant offer stability to various type of the active drugs and are also helpful for smart release properties. Various biological applications have been reported for nao to micro scale size particles like enhanced bioavailability, sit- targeting, controlled for hydrophobic drugs (Risbud, 2000).

4. CONCLUSION

The targeted drug delivery applications of the drugs have been broadened due to naoparticle size property and this feature is especially useful in cancer targeting. Furthermore, polymeric particles have proven their effectiveness in stabilizing and protecting the drug molecules like proteins, peptides and the DNA molecules from various environmental hazards and degradation. So these polymers have made possible the effective use for various proteins and gene delivery .a number of methods can be used to prepare the naoparticles depending upon the physical and chemical nature of the active drug and the polymer. By considering the advances of the science in the field of control drug delivery that has been achieved or still under process , this controlled drug delivery system can be classified in four main classes as; (i) rate-programmed drug delivery, in which drug diffusion from the system follow a specific release rate profile, (ii) activation-modulated drug delivery, where the drug release is induced by various factors like physical, chemical electrical or biochemical modules, (iii) feedback-regulated drug delivery, In which the rate of release is determined by biochemical substance (triggering agent) concentrations, it is dependent on the concentration exhibit in the target and (iv) site-targeting drug delivery systems, it is a complex process which consists of multiple steps of diffusion rate and partitioning. The rate of drug release is regulated by the specific targeting moiety, solubilizer and drug moiety.

Conflict of Interests

Authors declared no competitive interests for the presented work.

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