Chapter 8

Polymer Nanoparticles for Smart Drug Delivery

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Additional information is available at the end of the chapter

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1. Introduction

In the recent decades, polymers are widely used as biomaterials due to their favorable properties such as good biocompatibility, easy design and preparation, a variety of structures and interesting bio-mimetic character. Especially in the field of smart drug delivery, polymer played a significant role because it can deliver therapeutic agents directly into the intended site of action, with superior efficacy. The ideal requirements for designing nano-particulate delivery system are to effectively be controlled particle size, surface character; enhance permeation, flexibility, solubility and release of therapeutically active agents in order to attain the target and specific activity at a predetermined rate and time. The smart drug delivery systems have been successfully made by the advances in polymer science in the bio-nano-technology field. Recently, these advances have been found in various medical applications for nano-scale structures in smart drug delivery. The smart drug delivery systems should possess some important feature such as pre-scheduled rate, self controlled, targeted, pre-determined time and monitor the delivery. The smart drug delivery system enhances the polymer nanoparticle better 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. The polymeric particles are collectively named as spheres and capsules. The most of the polymeric nanoparticles with surfactants offer stability of various forms of active drugs and have useful to smart release properties. There are numerous biological applications have been reported for the nano-scale to micro-scale sized particles, such as site-targeted, controlled, and enhanced bioavailability of hydrophobic drugs [1-4]. Due to the nanoparticles size the drugs have been targeting into various applications, such as, various cancers targeting has been shown to be promising [5]. Moreover, polymeric particles proved their effectiveness in stabilizing and protecting the drug molecules such as proteins, peptides, or DNA molecules from various environmental hazards degradation [2-4, 6, 7]. So these polymers are affording the potential for various protein and gene delivery. Numerous methods had been available to fabricate

nanoparticles; it depends on the physical and chemical properties of polymer and active ingredients. Most of the formulation techniques involve different mechanisms such as using organic solvents, temperature, ultra-sonication and mechanical agitation which can degrade the pharmaceutical active ingredients. So the nano-particulate system can be developed to consider the formulation methodology should not damage the active pharmaceutical ingredients. There are numerous biodegradable and biocompatible polymers with different physicochemical characters are offered to prepare smart nanoparticles, those polymeric nanocarriers can be natural or semi-synthetic or synthetic. Those nanoparticles can enhance the systemic circulation half-life and minimize unwanted internalization and prevents the denaturation of the therapeutically active moiety and could use to deliver the target agents. Several polymer systems are approved by the U.S. Food and Drug Administration (FDA) for human use. It is the belief that when inventions in fabrication can catch up with those in materials, design and development of drug delivery system can enter a new generation of enhancing clinical healthcare.

The most recent advances in the uses of carriers for sustained and targeted delivery, micro and nano fabricated self-regulated devices [8], bio-recognizable systems; micro-needles for transdermal drug delivery have shown the flexibility and enhanced permeability of these polymeric materials. Ultimately the goal in smart drug delivery is the emergence of a micro and nano-fabricated therapeutic drug release device with the capacity to enough hold and release of various active agents on demand. In modern system the micro-electro-mechanical systems give a distinctive possibility to produce micro-fabricated biomedical devices for different intentions, from implantable systems to lab-on-a-chip systems. The constant and prolonged drug release micro-fabricated systems have the several benefits, such as many active ingredients could be stored in an nano form within the system and sustainably released, the drug release is initiated by the dissolution and disintegration of outer membrane barrier by an mechanical/electric stimuli, the most potential drugs could be released more specifically with this technique, the complex drug release system such as simultaneous stable and periodically could be attained for local therapy by the micro-fabricated system; it can be achieved in high or low dose of drugs at the targeted site and increase the stability of drugs by the membrane barrier for preventing water diffusion into the reservoirs [9]. Owing to the advanced scientific sophistication of the controlled drug release system that has been achieved till now, or that are in dynamic progress, this delivery model can be categorized into various classes. The controlled drug delivery systems can be categorize four main mode of drug delivery, such as (1) rate-programmed drug delivery, where drug diffusion from the system has follow a specific release rate profile, (ii) activation-modulated drug delivery, where the drug release is induced by various factors such as physical, chemical electrical or biochemical modules, (iii) feedback-regulated drug delivery, where 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, this is a complex process that consists of multiple steps of diffusion rate and partitioning for the rate of drug release is regulated by the specific targeting moiety, solubilizer and drug moiety. This chapter will brief discussion on recent innovative nano-fabrication methods for novel drug delivery system. Also, highlights some of these new technologies and consider their possibility ongoing clinical

transformation of nanoparticles, which the particles are well-controlled formulated. This chapter will be followed by a more detailed novel drug delivery system development from a polymeric material viewpoint and their various bio-applications will be covered without attempting to all the work that has been done in this field.

Over a decade, investigators have appreciated the enrichment of potential uses of bio-nanotechnology in offering huge advancements in novel drug delivery and targeting. The novel drug delivery platform that provides diminishes toxicity and enhances therapeutic efficacy gives most possible benefits to clinical levels. In approaches to drug delivery systems the route of administration is one of the crucial roles of drug targeting. These nanoparticles can be used for various routes, including oral, nasal, transdermal, parenterals, pulmonary, ocular, etc. Nonetheless, the oral route is most convenient, preferred, and in several cases, also its cost-effective, but it does not cross easily some biological barrier; also easily degraded by various body fluids, then rapid hepatic clearance and other organs. So the drug delivery systems focus on overcoming the various membrane barriers, such as the blood brain barrier, tight junction barrier, to achieve the effective drug target and enhance the efficacy. To find an alternative and satisfiable route of administration for the effective drug delivery system should overcome the digestive tract problems, where the degradation could take place via acid-hydrolysis, enzymatic degradation and bacterial fermentation in the alimentary canal. This chapter will cover the more detailed novel route of administration and development from a polymeric material viewpoint and their brief discussion will be covered without attempting to all the work that has been done in this field.

2. General methods for polymeric nanoparticles preparation

Recently, various kinds of polymers are used to prepare the polymeric nanoparticles, among this all polymer biodegradable polymers and their co-polymers such as di-block, tri-block, multi-block or radial block copolymer structures have been generally used to prepare polymeric nanoparticles and to encapsulate the active ingredients. These multi-functionalized polymeric nano-carriers include micelles, capsules, platelets, fibers, spheroids colloids, dendrimers, core-shells, nanoparticle incorporated polymer matrixes, etc. The first polymeric nanoparticles were developed between the year of 1960 to 1970 for the therapeutic application, and this were Micelles[10-12].The micelles are formed by polymerisation methods, commonly the formation of polymer nano-carriers during the polymerization of monomers [13-16]. Then the various advanced polymerization techniques have been developed for the preparation polymeric based nanoparticles, and the nanoparticles were stabilised using various surfactants [1, 9]. The stabilised drug loaded nanoparticles consist of drug and non-toxic biocompatible polymer with stabilizing agents, the biocompatible polymer is either biodegradable or non-biodegradable. Numerous techniques are available for the preparation of the polymeric nanoparticles and mainly top-down and bottom up processes. The polymer nanoparticle drug carriers can be further categorized into nano/micro-capsules and nano/micro-spheres depends on the size and structure [1, 9, 17-19]. The fine particles are 100 - 2,500 nm and ultrafine particles are 1 to100 nm in size, and are collectively known as nanoparticles. 50 to 300 nm sized

nanoparticle have been prepared by emulsion polymerization method [20]. Drawbacks in polymerization techniques are evolving noxious factors such as toxic, reactive residues, unreacted monomers, the risk of a chemical reaction and the formation of unwanted oligomers [1], and these drawbacks are overcome by using preformed polymers for the polymerization process [1]. Generally the drug loaded nanoparticles were prepared by dissolving the drug and polymer into the water-immiscible organic solvents and producing a nano-emulsion, as an example by probe-sonication method. The organic solvent is removed by using elevated temperature or reduced pressure [21-23], as an example of rotary evaporation method, and the nanoparticle is washed and collected by certification. Followed by various changes and improvements of the emulsification techniques have been reported [24-29]. For example, the sonication process is a crucial step in the preparation of the sensitive drug loaded nanoemulsion, and the sonication process can increase the temperature, that leads to inactivate the active ingredients. In order to avoid the problems researchers utilized an on/off cycle to maintain a low temperature. Other examples of general methods to prepare the drug polymer nanoparticle are described in the Figure 1. The biodegradable polymeric nanoparticles are commonly prepared by five different techniques such as emulsification-solvent evaporation, solvent displacement, salting-out, emulsification-solvent diffusion and double emulsion solvent evaporation. The synthesizing methods include salting-out method [1, 30, 31]; it is based on the separation of a water miscible solvent from aqueous solution through the salting out effect, solvent displacement method [1, 32-34], phase separation method [35], evaporation precipitation [36, 37], antisolvent precipitation and electrospray methods [38].

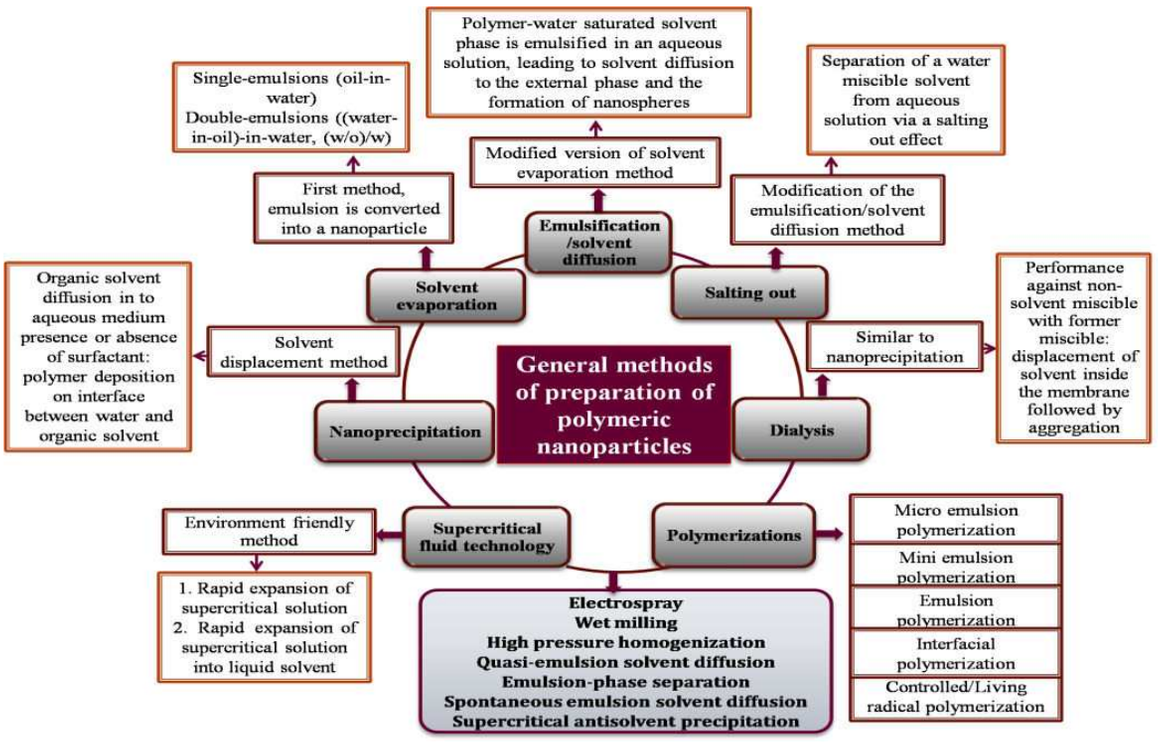

Figure 1. General methods of preparation of polymeric nanoparticles and their principle involved in the mechanisms

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Also, many approaches have been developed for the drug particle size reduction (increase in the surface) to the nanometer size range. For size-reduction, high pressure homogenization or wet bead milling is frequently used technique to produce reduced size nanoparticle [39-43]. Among these the high-pressure homogenization has been shown to be effective methods to produce size reduction particle. Moreover, its need sophisticated equipment to resist increasing pressures and temperature. Then, in order to obtain dried polymeric nanoparticle formulations researchers used various drying techniques such as atmospheric freeze drying, spray freeze drying, vacuum freeze drying, and lyophilisation. The uniformity of spray-dried nanoparticle is better than a freeze-dried nanoparticle. Moreover the lyophilisation and spray-drying are used to prepare the nanoparticle [44, 45], these nanoparticles easily tends to aggregates. Also the polymeric nanoparticles have also been synthesized by supercritical fluid techniques [46-52]. This method can get a dry product without any solution, also no need additional drying stages, but the supercritical fluid can swell some of the polymers and act as a softener, extender, and lubricant, which lead to aggregation. Moreover, this method is not easy to get the mono-dispersed multi-component particles because of different kinetics [52]. Nanoparticles prepared by spray-drying technique are one-step based on the conversion of a droplet to a dry particle by evaporation [53-55]. These one-step techniques have been revealed that the nanoparticle could be prepared without any problems [56-58], and the drug content in the particles is almost high [59], but produce an amorphous residual structure. In all above technique induce some unwanted noxious factors, as well as the organic solvents used in the preparations are increasing the risk of pharmaceutical application, also the increased processing time leads to microbial contamination [60, 61, 62]. Understanding the all risk factors, recently the modern instrument provides a promising and viable platform for the preparation polymeric nanoparticles.

3. Modern methods for preparation of polymeric nanoparticles

Recently, the polymeric nanoparticles have emerged as a most promising and viable technology platform for recognizing the targeted, environment-responsive and, multi-functional with navigated controlled drug delivery system. Polymer in smart drug delivery is a rapid-emerging new technological discipline in which various therapeutic applications of nano products are expected to overcome the patient complaints in healthcare. Smart delivery will give new solutions for therapeutic interventions. There is great interest from the beginning in smart medicine of advanced and well-characterized bionanotechnological products that will be especially effective in fighting diseases like cardiovascular diseases [63], diabetes [64], cancer [65, 66], aging [67, 68], some chronic metabolic syndrome and various degenerative diseases and disorders [69, 70]. For example, the innovative smart polymers with nanoparticulate drug-delivery systems can obviously advances in therapeutics by guiding the drugs to target cells and reducing the adverse-effect/side-effect on well being. At present, some of the smart polymer with multi-functioned nanoparticle system approaches in clinical trials, and it shows promising outcome. Certainly the morbidity and mortality rate of disease affected

patients could improve their lifestyle by the early course of smart therapeutic intervention. This smart intervention can be attained by developing high sensitivity and reliable smart drug delivery.

The rapid advancement in the above direction has been made with the initiation and development of more advanced alternative nanofabrication techniques to produce structures in various nano-scales level of controlled manners. Drug loaded polymeric nanosystems can provide controlled release of both hydrophilic and hydrophobic drugs over a long period of time while minimizing unwanted side effects in the body. This involves the synthesis of various novel biocompatible polymers with well-defined nanometers to a few micro-meters structures using several modern techniques such as microelectromechanical systems [71] microfluidic systems [72-76], electrodropping system [77], microneedle based system [78-81], advanced high pressure homogenization, interfacial emulsion polymerization and combined systems. Figure 2 described the few modern techniques for polymeric nanoparticles preparation with various concepts. The physiochemical characters of polymeric nanoparticles have to be optimized based on the specific application. Various methods can be used to produce various nano-particulate systems with various polymers. The multifunctional polymeric nanoparticles developments such as environment-responsive micelles, colloids, nano hydrogel, core-shell nanoparticles, nano-spheres and core-shell nano-spheres with layer-by-layer assembly for single/dual or multi drug release have been achieved so far. In order to get the desired properties, the mechanism of formulation method plays a vital role. Thus, it is extremely beneficial to have synthesis mechanism at hand to approach multi-functional polymeric nanoparticles with exact physiochemical properties for a specific application.

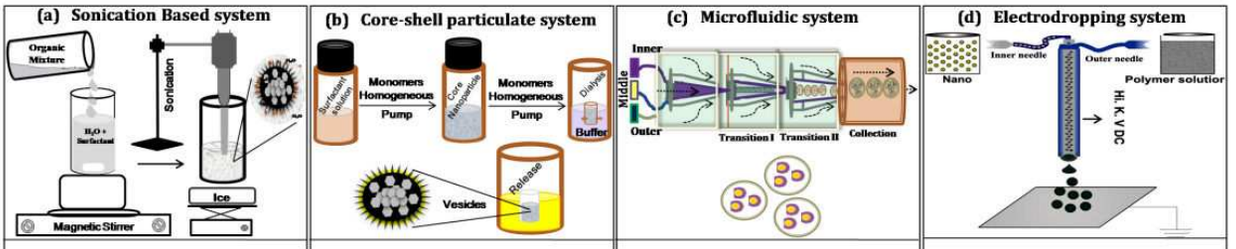

Figure 2. Schematic diagrams represent the advanced techniques of preparation of polymeric nanoparticles

The smart delivery systems of target bio-molecules have been concentrated of recent researches for various interventions. Particularly, various proteins, peptide, growth factors and cytokine therapy for various diseases play a vital role in regulating cellular responses, and thus the design of multi-functional polymeric particles delivery vehicles are closely associated with the regulation of multiple cellular events, likewise a wide variety of target bio-molecules have been investigated in numerous literature reports [82, 83]. Also numer-

ous of delivery vehicles have been studied and reported recently, this chapter will cover same viewpoint and their brief discussion will be covered without attempting to all the work that has been done in this field. Various concepts are utilized in the design of delivery vehicles that are capable of ferrying multiple active ingredients in a self-controlled manner, with different release profile kinetics. The distinctive self-assembly of multifaceted nanostructures from an easy colloidal system has been of interest to design a material with distinctive characters for the use of drug delivery vehicles. The inter-and intra-molecular linkage via van der Waals interaction leads to dense-packed self-assembly periodic nanostructures. These structures could be colloidal particle or clusters, based on the assembly [84, 85]. The natural or semi-synthetic polymer-based self-assembled nanostructures have inherent capacity of the nano-carrier for delivering many kinds of active ingredients, because of good biocompatibility and degradation/resorption properties [86]. In the sonication methods (Figure 2a), the self-assembled nanoparticle was achieved by probe sonication, the process has been done by cavitation, nucleation and reversible locking concept, the formed nanostructure have more flexibility in the nature [87]. In this self-assembled and core-shell particulate delivery systems, including water-soluble polymeric drug compounds conjugates [88], block polymeric micelles [89-93], long-circulating polymeric micelles [94, 95], nano encapsulations [96, 97], and core-shell nano-spheres [98, 99] have been synthesized by in situ two-step semi-batch emulsion polymerization technique (Figure 2b), as vehicle to target suitable dose of drugs in an accurate and controlled manner. Also the core-shell nano-spheres have been achieved for pH-responsive controlled release, and delivery of hydrophobic anticancer agents for acidic tumor tissues [100]. Recently Choi DH, et al have optimized electrodropping system to produce a homogeneous biocompatible core shell capsules for angiogenesis in dual delivery system [77], and they particularly focused on regenerative medicine. This electro-dropping system can overcome from the particle aggregation and drug encapsulation efficiency (Figure 2d). Coming to the micro-fluidics, the recent science and advanced technology of manipulating micro/nano-scale volumes in micro-fluidic channels have significant impact on the various applications. Advances and inventions in micro-fluidics are awaited to enhance the preparation of polymer nanoparticles and shifting to clinical evaluation [101] most of the micro-fluidic systems for synthesis, polymer nanoparticles are still under development and they have the widest possible to develop because they are highly reproducible, easily modifiable and can be incorporated with other techniques [102]. Recently, various micro-fluidic systems provide rapid mixing without any stimulator, such as stirring or electric force; have been originated [103]. Among these various systems the flow-focusing [104], droplet mixers [105] are widely utilized and it enables micro-mixing within the micro channel [106]. The flow focusing squeezes the solvent stream between two anti-solvent streams, resulting in a rapid solvent exchange via diffusion take place (Figure 2c). The effectuation of these rapid mixing methods for the development of nanoparticles in continuous flow; the micro-fluidic system has been achieved the continuous flow, narrow sized, mono dispersed with high drug entrapment and better batch-to-batch uniformity in compared with conventional methods [107].

4. Controlled drug delivery systems

4.1. Rate-programmed drug delivery systems

The recent advances in smart drug delivery systems with rate-programmed drug delivery systems have been achieved by functionalization of rate-controlling surface. The transdermal drug delivery have been achieved a new rate pre-programmed drug delivery system, transdermal patch which delivers a particular concentration of drugs to the blood circulation via the skin, it provides the therapeutic advantage to clinical levels. The rate-programmed drug delivery systems, the release of drug molecules from the rate controlling membrane system has been pre-programmed at particular rate kinetics. The rate controlling membranes made from natural and semi-synthetic polymeric material and proves their ability to use as a rate controlling membranes in any dosage form even nano to microscale level particle embedded matrixes or implantable or transdermal patches. It must be simple, cost-effective, and flexible enough not to split or crack on bending or stretching. Recently, some of novel rate-controlling composite membranes have been developed as rate controlling barriers for transdermal application, with flexible and smooth surface nanoparticles embedded scaffold which could reduce the risk of wounding or being rubbed off during dressing, and thereby improves upon traditional dressings and its can provides better patient compliance [108, 109]. This is achieved by optimized system design, which determines the diffusivity of active agents across the membrane. This rate-programmed drug delivery system can be categorized by various controlling dependencies, such as (1): membrane permeation-controlled, (2): diffusion-controlled, (3): membrane/matrix hybrid-type and (4): reservoir partition-controlled systems. The recent advance in the smart rate-programmed drug delivery systems the polymer and their scaffolds play vital roles, such as greater drug-loaded nano/micro-particle encapsulation ability, overcome pre-systemic metabolism, enhanced bioavailability and environmental responsive properties for various applications. For selecting the polymers, need to consider some important key factors for pharmaceutical application such as reduced tensile strength [110], water vapor permeability rate, biocompatibility, non-toxic [111], anti-infective, controlled release [112, 113], flexibility, emollient, adhesion, spreadability and retention properties of the drug-loaded nano/micro-particle encapsulation scaffold or film preparation [114-116]. So it can prevent the immunogenesis, secondary damage to cells, disease recurrence and finally enhance patient compliance [117]. In this type of rate-programmed controlled drug delivery systems, a drug-loaded nano formulation or rate-controlled nano formulation can be either totally or partially loaded in the reservoir space whose surface is covered by the rate pre-programmed polymeric membrane. The pre-programmed polymeric membrane can be optimized and achieved by multi-functionalization with block copolymers. The scaffold or membrane can be produced by the homogeneous or heterogeneous non-porous polymeric compounds or a micro/nano-porous or semi-permeable material. The drug release profile should be at a constant pre-fixed rate. The release profile is controlled by a pre-programmed rate-controlling membrane; it's based on the molecules, diffusivity, partition coefficient, and dimension of the outer membrane. Also the rate of release is determined by

the cross-linking ratio of the polymer network. The rate controlled release profile exists in many kind therapeutic formulations such as intrauterine devices [118], ocular insert [119, 120], some transdermal therapeutic system [109], polymer matrix, sub-dermal [121] and subcutaneous implantation [122-125].

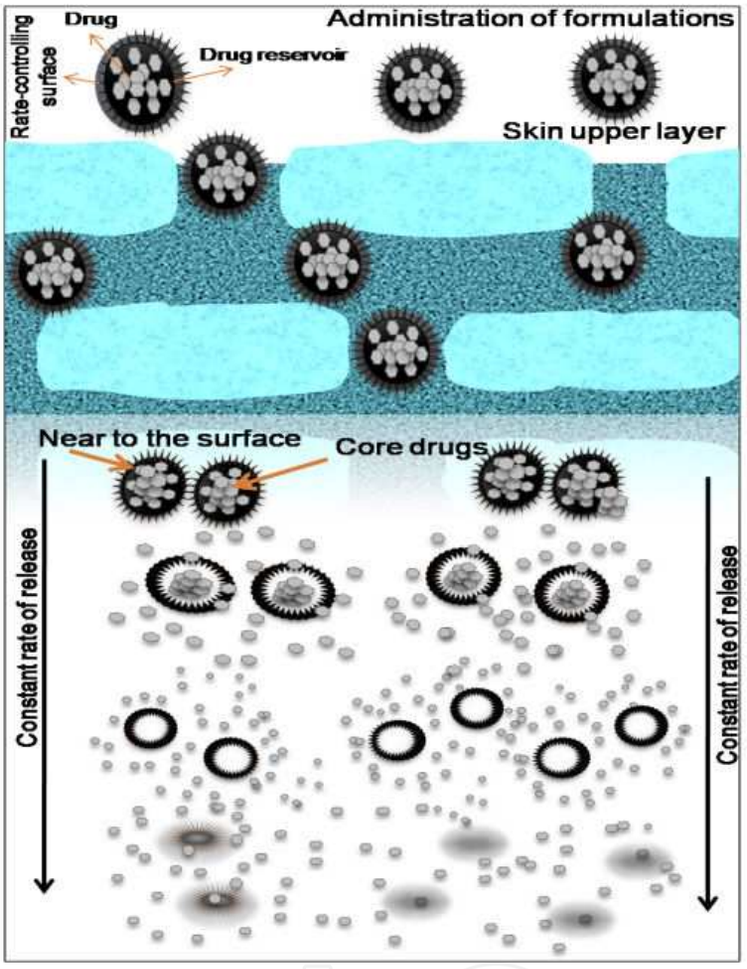

Figure 3. Schematic diagrams represent the rate controlled drug delivery systems of topical applications

4.2. Activation-modulated drug delivery

4.2.1. 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. The various activation/stimuli responsive drug delivery vehicles have been synthesized and tested, in various particle sizes, ranges from nanometers to a few micro-meters sized carriers for different routes of administration. The transdermal electro-activated or electro-modulated drug delivery has been established as an efficient model. In this group of activation-modulated controlled drug

delivery system, the release of active agents from the systems is activated by some physical, chemical, electrical, environmental condition or biochemical processes and/or facilitated by an energy supplied externally. The release profile has been controlled by the input energy. Based on the activation/stimulation process applied or energy type used, this activation-modulated controlled drug delivery system can be categorized into the various classes which are given in the Table 1. These stimuli-responsive materials show changes in the physicochemical character during the environmental condition changes. These changing properties can be fully utilized in smart delivery system, which certainly similar to the biological response behavior. Different types of body organs, different tissues and various types of cellular compartments might have great differences in every stimulus with great response. So that all the important cases considered in this chapter, deal with various environmental responsive smart delivery systems. Any specific behavioral changes in the system lead 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 4. The preclinical and clinical studies have demonstrated that drug-loaded polymeric nanoparticles has been well tolerated, extended systemic circulation, higher accumulation in the tumor sites through enhanced permeability and retention effect, minimized side effects and adverse effect, and/or higher bioavailability [153-155]. And most of the drug delivery systems are based on biodegradable polymer [156, 157]. Most of the environment-sensitive polymeric nano-particulate systems are leading to degradation and or disintegration by the internal or external local environmental stimulus such as pH, glucose, low oxygen content, ions, redox potential, and lysosomal enzymes; and then temperature, magnetic field, electric, ultrasound, and light respectively (Table 1).

These activations grew to achieve smart, targeted drug release in a particular time (spatial and temporal control release) [158-160]. At this place we describe a few examples. Particularly, the acidic pH levels in the body vary according to the different body environments (site and the organ) such as tumor cells and tissues (pH 6.5-7.2), endosomes (pH 5.0-6.5), lysosomes (pH 4.5-5.0) and entire GI tract with different pH value as comparatively varied with normal physiological (pH of 7.4) conditions in blood and tissues. So, the pH-responsive nano system have been considered and formulated to release the active agents in pH sensitive targets such as cancer site or endo/lysosomal regions [161,162]. The cytosol and cell nuclei have surrounded with elevated redox potential (in reducing glutathione) it higher than normal body fluids and it have been developed for intracellular release of various active bio-molecules [163-165]. Additionally, the cancerous tissues are extremely low in oxygen content (hypoxia) with higher glutathione levels compared to normal tissues [166]. This has been targeted with hypoxia-responsive polymeric nanoparticles. These internal stimuli-responsive nanoparticles have their own benefit of self-regulated drug delivery and effective target in clinical therapeutics. Also the external activated nanoparticles provide their own advantages such as high reproducible nature, also remote controlled delivery possible, then the release profile can be pulsatile delivered (means that switched on and off) possible [167]. On the other hand, the various light-responsive polymeric nanoparticles system has been developed for activating antitumor drug release [168]. Also numerous of temperature-sensitive multi-functionalized polymeric and copolymers nanoparticles have been formulated based on thermally-respon-

sive release [169, 170]. Magnetically guided nano-carriers have been developed for the remote controlled cancer therapy and diagnosis [171, 172]; also the core-shell nanoparticles have demonstrated for improved tumor accumulation and antitumor therapeutic efficacy in various models.

Based on	Stimulus	Mode	Ref.
Physical stimuli	Osmotic pressure	Controlled through the permeability of water Controlled through a gradient of osmotic pressure	[126]
	Hydrodynamic pressure	Generate hydrodynamic pressure gradient Forces the drug to release through the orifice	[127]
	Vapor pressure	Pumping system contains vaporizable fluid Creates vapor pressure, vaporizes at body temperature	[128] [129]
	A mechanical force	Equipped with a mechanically activated pump First-pass elimination and pressure-sensitive delivery	[130]
	Magnetics	Electromagnetism-triggering vibration mechanism Magnetically activated, vibrate by an electromagnetic field	[131]
	Sonophoresis	Utilizes ultrasonic energy to activate the delivery	[132]
	Iontophoresis	Electrical current to activate and diffuse the charged drug	[133]
	Hydration	Utilized swellable polymer matrix Activated by hydration-induced swelling delivery	[128] [126]
	Electricity	Electric-sensitive capsule Electrically erodible matrix for delivery	[134] [135]
Chemical stimuli	pH	Deliver the drug in the intestinal tract not in the stomach Deliver the drug in the ulcer stomach by floating delivery	[136] [137]
	Salt concentration	Prepared by ionizable drug with ion-exchange resin Controlling the delivery of an ionic or an ionisable drug	[128] [138]
	Hydrolysis	Hydrolysis-induced degradation of polymer chains Hydrolysis activate the release of drug molecules	[139]
Biochemical stimuli	Enzyme	Polymer chains fabricated with biopolymers Deliver the drug by enzymatic hydrolysis of polymers	[140] [141]
	Biochemical	Enzymatic-activated, biodegradation Feedback-regulated delivery concept has been applied	[142] [143]
Environmental stimuli	Temperature	Depends on the transition temperature Shifting the hydrophilic/hydrophobic balance	[144] [145]
	Light	Polymers undergo isothermal phase transitions by photon Reversible phase separations through photo-irradiation	[146] [147]

Based on	Stimulus	Mode	Ref.
	Hypoxia	Hydrophobically modified imidazole derivative was conjugated to the carboxymethyl dextran, it can release the hydrophobic agents under hypoxic conditions	[148]
Dual-stimuli	Two different responses	Based on the polymer architecture	[149]
		Micelles are reported pH and thermo-responsive	[150]
Multi-stimuli	More than two responses	Functionalization of pyrene-quaternized segments form a light-responsive shell and the unquaternized segments form a temperature/pH-responsive core	[151] [152]

Table 1. Overview of various stimuli responsive nano-carriers for smart drug delivery systems with mode of drug release applications

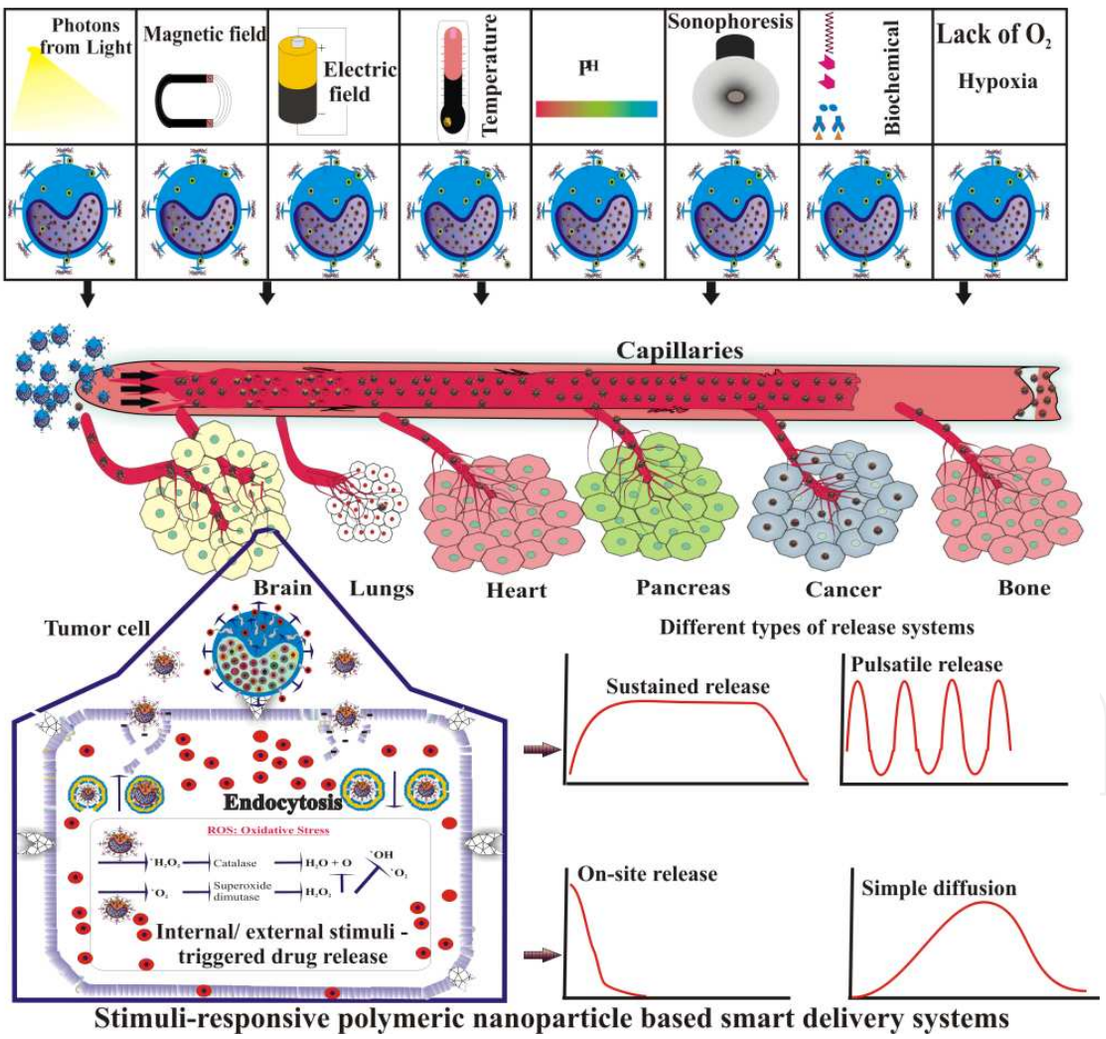

Figure 4. Schematic diagrams represent the activation-modulated drug delivery systems, which the polymeric nanoparticle activated by various stimuli such as physical, chemical, biochemical, environment, and/or a combination of two or more.

4.2.2. Dual and multi-stimuli responsive smart delivery system

In this chapter, provide the recent proposes and formulations of dual and multiple-stimuli responsive multi-functionalized polymeric nanoparticles and their promising targets in smart drug delivery in specific to the cancer therapy. With the booster development of the smart drug release and increase therapeutic efficiency of intelligent drug loaded nano-particulate system, polymeric nanoparticles that respond to dual and multi-stimuli, which have been aggressively reported. The double-response and multiple-responsive nano-particulate systems were described in the Table 2. It must be mentioned that the stimuli and responses happened at the same time at the same site or different mode. These dual and multi-stimuli responsive polymeric nanoparticles can provide control over the drug release profile, which leads to greater anti-tumor efficiency in vitro and in vivo models, and on the other side the nanoparticle formulation and drug loading under moderate conditions. In this section we describe a few examples. Especially, redox-responsive drug release multi-functionalized nano-particulate system have been formulated based on temperature and reduction, dual responsive tri-block copolymers functionalized by increasing temperature above the lower critical solution temperature after that cross-linking [173, 174]. These multi-functionalized nano-particulate systems were targeted to cancer cells and triggered by reduction oxidation mechanism, which leads to dissociate to release the active agents by de-crosslinking followed by disruption and degradation of nano-particulate system. pH/redox dual-stimuli multi-functionalized disulfide cross-linked micelles have been developed for increased drug release and accumulation in the cancer target, due to endo/lysosomal pH and intracellular redox environment the drug release was taken place [175].

4.2.3. Considerations for stimuli responsive targeted molecular systems

These multi-functional polymeric nanoparticles are capable to face the current problems of nanoparticle drug formulations including formulation and drug encapsulation, prolong stability, cellular internalization, site-targetability, enhanced cellular uptake, and inside cell target and drug release. These dual and multiple-activation responsive characteristics have provided novel and enthusiastic power over drug release kinetics and greater efficiency. All the described studies in dual and multiple-stimuli responsive drug delivery systems are mostly trial and error models, because most them non-biodegradable carriers, low encapsulation, and nonviable to clinical therapeutics. To overcome all the unfavorable conditions, immediate efforts could be focussed to improvement of dual and multiple-stimuli responsive biocompatible, biodegradable, non-toxic, and non-immunogenic smart polymeric nanoparticles that could effectively entrap and sustain the drug release in the systemic circulation, enhanced accumulation in the cancer target, and efficient release kinetics in response to more efficient external or internal stimuli. Moreover the smart polymeric nanoparticle system does not produce any secondary damage and any harmful to the healthy cells. In the case of clinical studies on dual and multiple stimuli responsive system shall be performed to obtain a real mechanism of action in anti-cancer target. In addition, the multi-functionalized smart polymeric nanoparticles system construct with targeting ligands and shall be incorporated into dual/multiple stimuli responsive nanoparticles to be achieved multidrug resistant cancers by

site targeting, site-specific, and rapid/sustained release, and we sure that dual and multiple stimuli responsive smart nano-particulate system going to be a good future in cancer therapy.

Responses	Stimulus	Nanoparticles	Ref.
Dual-stimuli	pH & Thermo	P(NIPAAm-co-DMAAm-co-UA) nanoparticles	[176]
		P(NIPAAm-co-AA)-b-PCL nanoparticles	[177]
		PLA-g-P(NIPAAm-co-MAA) nanoparticles	[178]
		P(NIPAAm-co-DMAAm)-b-PCL/PLA micelles	[179]
		PNIPAAm and PAA hollow nanogels	[180]
	pH & redox	PEG-SS-PDEA polymersomes	[181]
		DS-g-PEG/cRGD nanoparticles	[182]
		Poly(b-amino ester)s-PEG micelles	[183]
		PMAA-based nanogels	[184]
		mPEG-PAsp(MEA)-PAsp(DIP) micelles	[185]
	pH & magnetic	Fe_3O_4 nanocarrier with peptide mimic polymers	[186]
		DOX-tethered Fe3O4 conjugates nanoparticles	[187]
		mPEG-b-PMAA-b-PGMA-Fe_3O_4 nanoparticles	[188]
		Fe_3O_4-capped MSNs	[189]
		MCM-TAA-Fe_3O_4-capped MSNs	
	T & redox	EO-PAA-PNIPAAm polymersomes	[190] [191]
	Double pH	PPC-Hyd-DOX-DA nanoparticles	[192]
		Poly-b-amino ester ketal nanoparticles	[193]
	pH & diols	PEG-b-dendritic cholic acid telodendrimers nano-carriers containing boronic acid	[194]
	T & magnetic	Pluronic with Fe_3O_4 nanoparticles	[195]
	T & enzyme	DNA-capped MSNs	[196]
Multi- stimuli	T/pH/redox	PNIPAAm-SS-P(THP-protected HEMA) micelles	[197]
	T/pH/magnetic	P(NIPAAm-co-MAA) coated magnetic MSNs	[198]
	pH/redox/ magnetic	Fe(II) loaded PMAA crosslinked by N,N-methylene-bisacrylamide and N,N-bis(acryloyl)- cystamine	[199]
	T/redox/guest molecule	Vesicles based on hosteguest complex formation between C4AS and MVC12	[200]
	T/pH/guest molecule	Cucurbit(8)uril micelles, methylviologene-functionalize PNIPAAm and naphthalene-terminated PDMAEMA	[201]
	Light/pH/T	Pyrene-functionalized poly (dimethylaminoethyl methacrylate)	

Table 2. Overview of dual and multi-stimuli responsive materials for nano-carriers of various smart drug delivery systems

4.3. Feedback-regulated drug delivery

The recent advances in smart delivery systems with feedback-regulation of drug release. This self-regulated or feedback-controlled drug delivery comes under closed-loop systems. The self-regulated system drug release rate is controlled by feedback information, without any external stimulation, and utilized several approaches to control the release rate [202-205]. The feedback-regulated drug delivery concepts were schematically depicted in Figure 5. The feedback-regulated drug delivery concept has been applied to the development of various controlled delivery systems such as bio-erosion regulated, bio-responsive regulated and self-regulating drug delivery systems. Among this one of the concepts has been involved in the smart controlled delivery systems. For that various research efforts are also in progress to develop such nanoparticles that contain drugs capable of a feedback-modulated drug release. The drug release is activated by a triggering agent, such as a biochemical substance, in the body via some feedback mechanisms. The release rate has been determined by triggering agent concentration. When the triggering agent is above a certain level, the release is activated. This can induce and stop the drug release. It would be a high potential benefits if they were delivered by a system that recognized the particular warning signal caused by disease affected part, then they estimated the magnitude ratio of the signal, and then acted to release the exact quantity of active drugs in response. This kind of drug delivery system required to fulfil the physiological need by means of some feedback mechanism. The self-regulated drug delivery systems utilize several approaches for the rate-control release: pH-responsive polymers, temperature-responsive polymers, enzyme-substrate reactions, antibody interactions, enzyme-mediated, pH-dependent drug solubility nature, competitive binding mechanism and metal concentration-dependent hydrolysis. A hydrogel can swell in aqueous medium and retain their structure. The multi-functionalized polymer nanoparticle can be incorporated into hydrogel, such hydrogel used for the feedback-regulated drug delivery system. This hydrogels can protect the drug from dangerous environments such as enzymes and low pH in the stomach. This can control drug release through changing the network structure in response to particular stimuli, which can enable the sensor leads to reversible volume phase transitions upon small changes in the environment condition. For example, the polymers characterized by lower critical solution temperatures generally shrink, as the temperature is increased via lower critical solution temperature. Decreasing the temperature below lower critical solution temperature, the polymer can swell. Biomolecules can be encapsulated on or within the heat responsive polymers.

The sensor grafted in the delivery system can enable to mimic the recognition function of various bio-chemicals such as enzymes, cell mediated receptors and various proteins in human beings for maintaining the regulation and equilibrium. This approach is utilized for drug incorporated polymeric feedback controlled delivery systems, and this system approach is based on the observation that changes in control mechanisms, e.g.: pH or ionic strength or temperatures can affect large changes in drug solubility; this can be the main factor for control release rate. The external trigger molecule and polymer-bound enzyme can alter the pH inside the polymeric system. If the pH alteration happened inside the polymer system that can lead to changes in drug solubility, which is induces the diffusion or dissolution or disintegration,

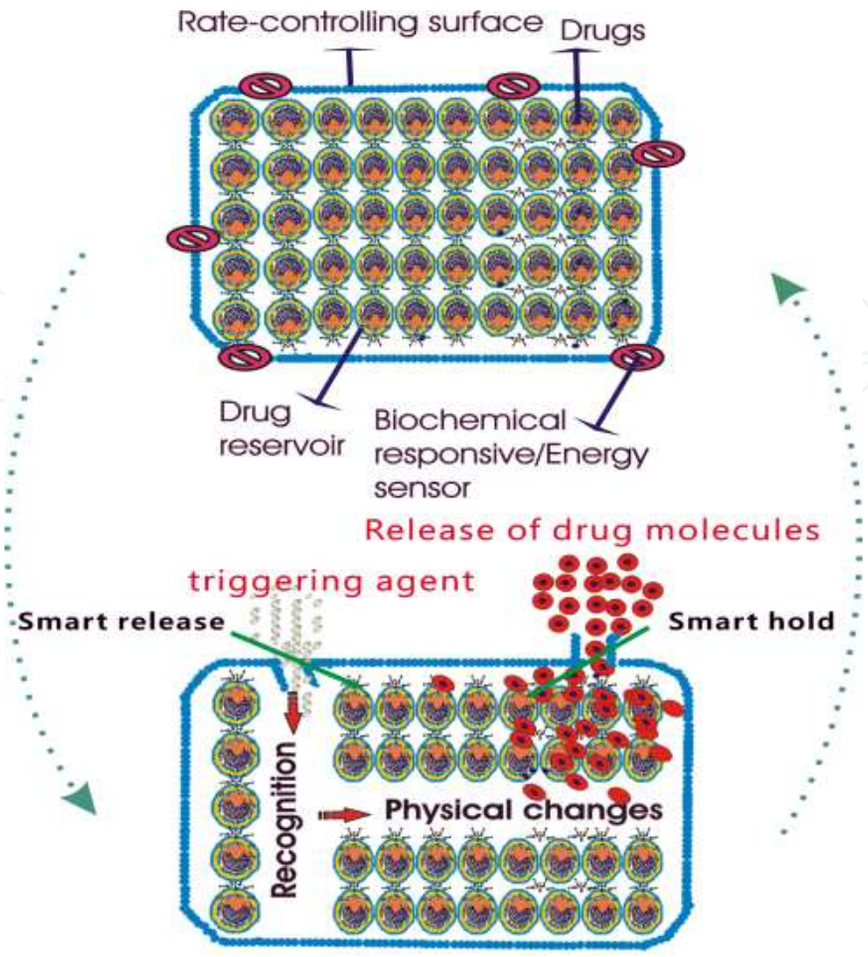

Figure 5. Schematic diagrams represent the feedback-regulated drug delivery systems

and rate of release has been changed accordingly. Many researchers have been developed a membrane to bypass the rumen but it allows the polymeric system to release the drug in the stomach via gastric retention mechanism [206]. Because of the polymer membrane it is impermeable to the rumen pH 7, but the swells and release at pH 4, which is the fourth stomach. Several studies have been performed on various polymers holding weakly acidic or basic functional groups in the polymeric backbone [207-112]. This polymeric system can swell or de-swell by changing the pH of the environments. By this way the drug will release from a matrix or device, which is developed by pH dependent polymers and this system can provides controlled release rates.

The bio-erosion controlled drug delivery system comprises of a drug-encapsulated bio-erodible scaffolds developed from biocompatible polymers (poly (vinyl methyl ether)), and were layered using immobilized urease. In a neutral pH the polymer erodes gradually, but in existing with urea, urea is metabolized by the system containing urea to form ammonia, it leads to increase the pH in the surrounding area, this increased pH degrade the polymer scaffolds then the drugs has been released [213], and some polymers require high pH to degrade.

The bio-responsive controlled drug delivery system, glucose-triggered insulin delivery has developed [214], the insulin is encapsulated within biocompatible polymer hydrogel scaffold comprising abundant NR2 functional groups present in the normal state. So in this state scaffolds are un-swollen and thus impermeable to insulin molecules. Enzymatically oxidized glucose is to form gluconic acid, this triggers the NR2 groups to form NR2 H+, it leads to swollen and insulin molecules deliver through the polymer membrane, and the amount of delivery has been controlled by glucose penetrating concentration.

The reversible and competitive binding mechanism also has been reported to insulin delivery. This mechanism role is to activate and to regulate the release of drug in the target; also it depends upon the glucose level present in the systemic circulation. Insulin-sugar-lectin complex has been prepared and entrapped into the semi-permeable polymeric membrane to achieve controlled release. The diffused blood glucose has competitively bound to particular binding sites, then activates the complex to release insulin derivatives, and the release acted based on the concentration of glucose presented in the systemic circulation. By this way the self-controlled drug delivery has been achieved. A further improvement on insulin delivery, they used glycosylated insulin-concanavalin A complex and entrapped inside polymeric membrane and the release has been achieved by self-regulated mechanism, depends on the glucose concentration permeate into the system [215]. Again in the development of self-regulating insulin delivery has achieved by enzymatically controlled implantable glucose-dependent insulin delivery systems [216]. Followed by various researches developed the different kinds of glucose-responsive insulin delivery [217-223]. Also the molecular imprinting technology developed system able to identify the specific compounds on the cell surface, and this can be appropriate for further developing and targeting the delivery system to specific tissues or cells. Recently, the pH-Sensitive polymer multi-functionalized with block co-polymeric nanoparticles have been developed for the triggered release of paclitaxel within a tumor microenvironment which the polymer acted as a feedback-regulated drug delivery carrier [224], and this carrier have a reversed swelling behavior. Most recently, the feedback controlled drug delivery system has been developed for cerebral cortical disorders with a feedback controlled mechanism. Drugs have been delivered via subdural/subarachnoid space, then diffuse into neocortical tissue and this diffusion can be controlled by electrophysiological feedback, the cerebral cortical area is exposed to the drug, and they were optimized for the drug concentration, delivery, frequency of delivery [225]. Moreover, the molecular imprinting technology has a huge possibility for producing acceptable dosage forms in the feedback-regulated drug delivery systems. The application of molecular imprinting enables the design of new systems and also in polymer based device fabrications. The advances in the preparation of molecular imprinting as spherical uniform particles [226] and scaffolds [227] can increase the field application potentiality of several polymers in drug delivery system. Moreover, these imprinted delivery systems have not yet touched in clinical therapeutics.

4.4. Site-targeting drug delivery systems

The recent advances in the smart delivery systems with site-targeting drug release. A site targeted drug delivery systems are complex of multiple steps of diffusion and partitioning.

Nowadays the site targeted drug delivery systems involve deep investigation as they are very eager to overcome the modern medical application [228]. A well-designed multi-functionalized polymeric carrier for site-targeted drug delivery in the interventions of various diseases such as colon disease, kidney/renal disease, nasal disease and genitourinary disease has been reported recently [229-234]. A variety of both natural and synthetic water-soluble polymers have been used for biomedical applications. These polymers have been used routinely in biopharmaceutics because of the effectiveness in controlled drug release. The traditional formulations are not significantly efficient at targeting molecules, thus the new and smart drug delivery systems are being studied to overcome the problem. The goal of the smart drug delivery systems is to allow a localized drug delivery, at the same time; it does not affect the healthy tissues and no unwanted effects. The drugs composed of micro-or nano-sized particulate system, which is able to spread through the systemic circulation, and transport through various body organs and body areas such as arteries, veins, and capillaries and even cross membrane barriers. The nanoparticle transport and targeting tissue are the complex process, so the transportation and communication have been viewed by the molecular communication paradigm. This transport of drug-loaded particles in the human body has been viewed, where the nanoparticle has transported this information is conveyed by signaling molecule. This communication system provides a clear reading of particle diffusion, distribution, disintegration over time throughout the biological system, which provides the importance to the invention of a smart particulate delivery system. Initially, the kinetic Monte Carlo method [235, 236], have been used computer simulation to solve the communication system. Lately, researchers developed an analytical approach based on the abstraction of targeted particulate delivery systems as a communication mechanism. This information is passed between sender and receiver by intracellular and intercellular signalling [237]. Different kinds of molecular communication have been analyzed so far, which involve passive or active transport of molecules [238, 239]). The smart site targeted delivery system takes an advantage of the systemic circulation for the distribution of active drug particle from where it's ingested to the systemic circulation to a targeted site. Basically, the delivery systems have been made with purpose and intention to control the rate of release from the systems, but the transport of nanoparticle to the target site still needs more control. Preferably, the route of administration and nanoparticle transport should also be strong enough controlled.

In this section also provides a few examples of site-targeted drug delivery systems, The ideal example is that the kidney site-targeted drug delivery systems, it acted as a smart delivery to enhance drug efficacy and safety in the therapeutics of kidney diseases. By this smart drug delivery treatment provides that reduces inflammation and reduce the formation of excess fibrous to proximal tubular cells, it can protect systemic infection and renal tubular inflammations. So targeting the renal proximal tubular cells is the novel and efficient routes to cure kidney disease [240-244]. Kidney-targeted drug delivery system can overcome from the various obstacles such as kidney transplantation, ureteral obstruction, diabetes, and other some important kidney disease. Figure 6 shows the kidney drug delivery of nano-particulate systems. Among all drug carriers the macromolecular carriers are extremely powerful targeting the kidney, because of the selective accumulation in the kidneys. Macromolecular carriers with prodrugs play crucial roles in targeting drugs to particular target cells in the

kidney. The molecular weight and electric charge of polymers is one of the crucial role for effective renal clearance [245, 246], thus the active polymeric system can uptake and exists in the renal cells [247]. Especially the multi-functionalized polymeric nanoparticles showed higher uptake in glomerular mesangial cells [248, 249]. For nasal site-targeting specificity, the multi-functional particulate system design is the main role for site-targeting. So, design and preparation method has to be controlled according to the needs, the materials should be with quality of properties such as biocompatible, biodegradable, modifiable, mucoadhesive, antimicrobial, tumor or particular cell recognition, and maintain the drug release. In the example, N,N,N-Trimethyl chitosan nanoparticles achieved controlled intra nasal delivery to treat various diseases including hepatitis B and allergic rhinitis [250]. Also the amine functionalized chitosan has been shown their eminent characters such as biocompatible, enhanced solubility, strength, porosity, absorption efficacy, chemical tolerance, non-immunogenic and non-antigenic properties, and it has been used for various nasal delivery.

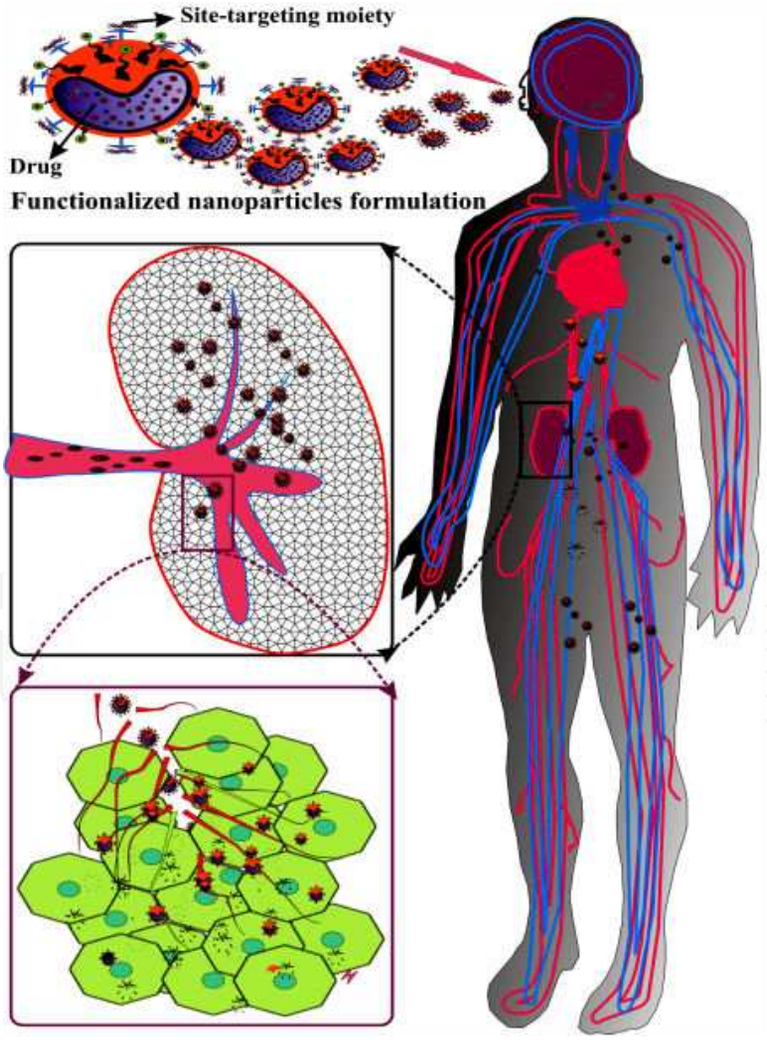

Figure 6. Schematic diagrams represent the site-targeting specificity particulate drug delivery systems

4.5. Targeting strategies for kidney diseases

Macromolecule is a very large molecule, which can accumulate in the kidneys. Generally, the molecular weight of the macromolecular vehicle is bigger than that of the prodrugs, so this kind of system can achieve the goal. Pro-drugs have the ability to select the target in the kidney because it can release the active drug by the action of renal enzymes. The various strategies of kidney-targeted drug delivery systems has to be considered such as biodynamical strategy of renal artery perfusion, macromolecular carriers which includes enzymes, immune proteins and peptide hormones, pro-drugs which includes folate, sugars, and amino acids, and other strategies including various nano-particulate systems. The molecular weight and charge [245, 246] of polymers is the main factor, it can influence their distribution in various organs including kidney. In general, increasing the molecular weight of polymers leads to decreases urinary clearance. Some of the polymers have been eliminated rapidly from the systemic circulation but it does not excrete from the kidney, and its accumulated in the renal systems. So it clearly proposed that the selection of effective and active multi-functionalized polymeric nanoparticles can uptake by the particular kidney cell types. So the selection of polymers is one of the prime strategies for consideration to achieve the efficient kidney targeting. These new possibilities to develop kidney targeting conjugates and other nano-particulate drug delivery systems. Including various polymers based nanoparticles give excellence strategies to achieve the goal of targeting drugs to the various renal diseases.

4.6. Common strategies for smart polymeric particulate targeted delivery

The ideal proposed model for site-targeting delivery is fabricated from a biocompatible, non-immunogenic and biodegradable polymer and acts as the central of support to three main characteristics of attachments such as site-specific targeting moiety, solubilizer and drug moiety, which should have drug delivery capacity, capable of transport and active molecule should bonded to the polymer via spacer, and the linkage is cleaved by particular enzyme(s) at the final targeted site respectively. In order to develop a new polymeric vehicle for a particular drug, the polymer distribution in the systemic circulation has to be analyzed since it's right away affects on activity of drugs. For controlling the systemic distribution of drugs, we need to consider minimum two strategies which are active or passive targeting. Previously, the drug is delivered to target site using some specific antibodies, which are specific to target cell-surface [251-254]. This method gives efficient targeting to tumor site; however, the antibodies can produce immunogenic activity. But, the passive targeting with bio-polymers vehicles cannot produce immunogenicity or toxicity, this might enhance the active molecule efficacy, such as increased half-life by increased size of the nano-particulate complex, increased permeability at the targeted area and polymer vehicle interacts to the body organs. Those elements must be increase the absorption of the drug molecule; which minimize the dosage and low unwanted effects [255, 256]. Moreover, in the advanced fabrication of molecular imprinting technology can provide efficient smart polymeric systems with the ability to recognize specific bio active molecules. This advanced fabrication technology has tremendous possibility to meet the requirements for satisfactory dosage forms developments. Depends upon the particular application the fabricated systems can decide the delivery, efficiency,

safety of the drugs, and when it should be reached. Described all above application strategies have a significant interest in targeting drugs into specific regions [257, 258].

5. Bioengineered materials: Ideal and recent advances for drug delivery systems

5.1. Nano-engines of drug delivery systems

Engineered materials have been utilized for developing smart drug delivery systems. Design and multi-functionalities fabricate of efficient smart drug delivery systems are vitally necessary for medicine and healthcare development. In the material science field provides biodegradable, biocompatible, environment-responsive, and highly effective novel polymeric system for targeted delivery. Nanotechnology provides bottom-up and top-down nanofabrication with size controlled and multi-functionality of particulate for targeted delivery. New materials invention and advanced technology have been synergistically achieved in drug delivery so far. The essential goals of medical pharmacology provide the right medicine, right dosage, and right route at the right time to the right patient, so more research need to optimize the therapeutic efficacy of the drug. This is the essential principles is behind the smart drug delivery. A smart, controlled delivery system needs synergistic consideration of several factors; these have been summarized in Figure. 7. It is difficult to get all consideration factors in a smart controlled delivery system due to other influencing factors. Also high quality, reliability, efficiency and reproducibility are the most significant issue while designing such a smart system. Also the smart systems have to induce the drug release and stop the release by their own manner. It would be highly benefited, if the system recognizes the disease affected part, estimated the disease affected ratio, and then acted to release the exact quantity of active drugs. This kind of drug delivery system can fulfil the medicine and healthcare requirements.

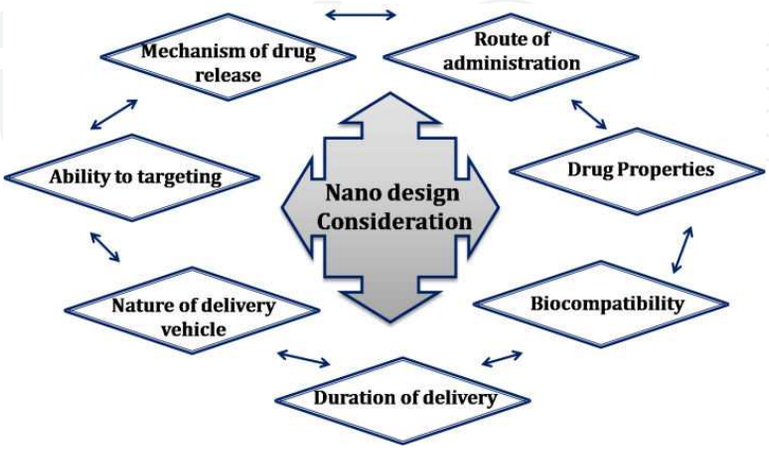

Figure 7. Requirements of several factors for simultaneous consideration to design a polymeric nanoparticle for the smart drug delivery system

6. Polymeric nanoparticles functionalization and considerations for smart application

In this section provides the recent research on the preparation and functionalization of various polymeric hybrid nano-materials including nanoparticles and microparticles by various techniques. Several techniques have been developed for the functionalization of polymeric nanoparticles with different therapeutic applications. The polymeric nanoparticles have been studied for their enriched properties in biological systems, with the nature of the materials and whether it has the specific properties for chemical modification and functionalization of the nanoparticle developed from various materials including bio-macromolecules. There are several researchers have been studied for functionalization and surface modification of nanoparticles and it would not cover all this in this section; so, this section covers some examples of nanoparticles functionalization and some important criteria to consider the fabrication process. In addition, the richness of surface chemistry and potential biomedical applications are described. The polymeric nanoparticles surface functionalization are mainly two types, one is functionalization with biological (macro)molecules such as peptides, carbohydrates, lipids, fatty acids, proteins, and nucleic acids (genes, oligomers, aptamers, and ribozymes/DNAzymes); another one is functionalization with specific ligands such as mono- or oligosaccharides (carbohydrates), folate receptor, antibodies and biotin are commonly used. This surface functionalization have been made by various modifications on preformed nanoparticles through adsorption, functional surfactants, emulsification, polymerization, covalently bounded functional molecules and various forms of bio-conjugation. There are few considerations for functionalization of polymeric nanoparticles properties such as: 1) the bio-molecule ratio should controlled by calculating the number of conjugate sites presents in the nanoparticles with different applications, 2) due to the environment and electrostatic interactions the alignment of functionalization has been varying, so the non specific attachment should be avoided in the performed nanoparticles, 3) depends on the applications requirements the nanoparticles bio-molecule distance should be maintained, 4) control the conjugation moiety attachment/linking affinity to the performed nanoparticles, 5) should maintain the optimal efficiency of physiochemical characters and 6) it should be high reproducible for all batches. The above all criteria can fulfil the requirement of design and functionalization of nanoparticles for a controllable release profile that satisfies the desired application. And better protection against environmental factors and maximum optimal control is achieved if drug loading is carried out by encapsulation instead of adsorption on to the particle surface. With the combinations of these above criteria in the fabrication of nanoparticles are potential to increase the clinical therapeutics by reducing unwanted effects.

With the field of bio-nanotechnology, enormous new research on the synthesis of polymeric nanoparticle based top-down or bottom-up approaches have been recently developed. Recent developed polymeric systems engrafted nanoparticles provide the optimal characteristic of the functionalized nanoparticles for various therapeutic approaches in harsh environments such as in the acidic and alkali environment [259]. Also polymer nanoparticles are broadly used in several therapeutic applications, mostly cancer targeting and therapeutics. And we

provide some examples of various nanoparticles with different functionalization and different therapeutic uses based on the target, shown in Table 3. Therefore, the multi-functionalized nanoparticle over comes from the drawbacks of conventional therapy. In the latest study provided that more than 26 nanoparticle based therapeutic system have been approved for clinical treatment and several nanoparticles are under consideration [281]. In order to achieve the efficient nano-particulate system based therapeutics the nanoparticle synthesis and functionalization methods have to consider very carefully. Although several surface modified methods for various bio-applications have been reported previously, in this section highlight particular examples where this type of functionalization has been used.

Nanoparticles	Functionalization	Drug	Use	Refs.
Human serum albumin	Amino/acid group	Doxorubicin	Antineoplastic	[260]
Trimyristin	Sterically stabilized	Paclitaxel	Ovarian, lung, breast cancer	[261]
PLLA-b-PEG	Folate targeted	Doxorubicin	Solid tumors	[262]
PEG-PE	Lipid conjugated	Paclitaxel	Various cancers	[263]
PEG	Lipid conjugated	Tamoxifen	Lung carcinoma	[264]
Polymer-lipid hybrid	Lipid conjugated	Doxorubicin	Solid cancer	[265]
PCL-b-trimethylene carbonate-PEG	Serum protein	Ellipticin	Anticancer	[266]
PAMAM dendrimers	Folic acid	ethotrexate	Epithelial cancer	[267]
PEG	Albumin bound	Doxorubicin	Various cancers	[268]
Micelles	Biotin-antibody-conjugated	Daunomycin	Brain tumor	[269]
PLGA	Alendronate	Estrogen	Bone-osteoporosis	[270]
Poly(DEAP-Lys)-b-PEG -b-PLLA	Poly(lysine)	Doxorubicin	pH sensitive tumor	[271]
PLGA-b-PEG-COOH	PSMA	Anti cancer	Prostate- cancer	[272]
PEG or PE particles	Transferrin	Oligonucleotide	Brain- gene	[273]
PLLA-PEG	Biotin	Anti cancer	Cancer therapy	[274]
Polystyrol	Sc-TNF	Anti cancer	Cancer therapy	[275]
PLA	Aptamer	Anti cancer	Prostate cancer	[276]
PE	RGD peptides	siRNA	Vasculature cancer	[277]
mPEG/PLGA	Peptidomimetics	Anti cancer	Brain cells cancer	[278]
PLA	Galactose	Retinoic acid	Hepatocytes	[279]
PLGA	MP lipid A	Anti cancer	Dentritic cells	[280]

Table 3. Examples of various nanoparticles with different functionalization and therapeutic uses based on the target

Functionalization is defined as the improving performance of nanoparticle by a chemical functional group on their surface. Some basic components of functionalized nanoparticle are enabling to increasing the multifunctional applications in the field of biomedicine; the basic components are diagnostic agent, targeting ligand, spacer group, therapeutic agents, and polymer nano-carrier with proper functionalization. Here we introducing two strategies for surface functionalization, first one is direct functionalization, where the functional ligand is a bi-functional compound. In this method, one of the reactive groups is used to bind to the nanoparticle surface and the second group contains the required active functionality. Another one is post-functionalization, here the strategy is not changeable and the nature of the functionalizing group cannot be compatible with good control over the size and dispersion of the nanoparticles in the solvent used for the fabrication. Commonly, the nano-carriers have been functionalized with various chemical functional groups such as thiols, disulfides, amines, nitriles, carboxylic acids, phosphines and bio-macromolecules [282-287], based on their application. The functionalization of nanoparticle is to modify their outer surface with other specific chemical agents based on the desired application. After functionalization the particle physiochemical character has been changed. Also, it is a very important step for control because it can change their size and self-organization during the formation and should not promote aggregation. The prepared polymeric nanoparticles have emerged promising technology platform for recognizing the target with navigated controlled drug delivery system. Figure 8 shows the various functionalizations of the nano-engines for the development of smart drug delivery systems (Left side) and pre-regulated nanoparticle recognizes the tumor cells not the healthy (right side). This therapeutic drug concentration reaches the tumor site not in the normal cells or tissues. Polymer base smart drug delivery can overcome the patient complaints in healthcare.

In polymeric based nano-composites fabrication, the nanoparticles is used as backbone to enhance the physiochemical characters [288-290] such as flexibility, smoothness, enough strength and stiffness, which are much essential in the field of tissue engineering and bio-medical applications. The mechanical strength of polymer based nanocomposites is low due to the poor linkage between nanoparticles and the polymer, which leads to artificial defects in the composites [291-293]. It could be engineered with the appropriate interface to enhance the flexibility, smoothness, strength, stiffness and compatibility of the composite character [294]. The advanced functionalization of the nanocomposite have been prepared with suitable surface active agents, including anionic and non-ionic surfactants, it can lead to strong linkage between the nanoparticle and the polymer. The multi-functionalized nanocomposite enhances the physicochemical properties and no untoward effect on the biological system had been reported [295]. For the hydrophobic drug the phage display technique has been used for the functionalization [296], and the bioavailability have enhanced by post-polymerization. Additionally, the post-polymerization with copolymer produces efficient targeting in the extracellular compartment of the biological system [297-300]. With the nanoparticles the polymers like PEG establishes for prolonged systemic circulation [301, 302]. For the stimuli responsive targeted drug delivery has been achieved by the functionalization of suitable materials (light or magnetic or thermal or ionic responsive material). Particularly, the magnetic induction systems have been used with functionalized magnetic nanoparticles for cell or tissue

specific targeted delivery. For targeting brain delivery system the nanoparticles has been functionalized for specific or nonspecific binding mechanisms [303]. The fabrication and functionalization science has merged with software oriented technology for the development of controlled and targeted nanoparticle loaded micro-device system [304]. The recent trends in novel polymer and block co-polymer synthesis methods like radical polymerization and click chemistry has been provide well-desired multi functionality polymeric structures [305-312]. This is the potential method to fabricate the desired molecular weight polymer with well-defined characteristic features. This unique method of polymer synthesis gives the successful nano formulation for potential bio-application. The functionalized nanoparticles have been synthesized with potential biochemical moieties. Then these multi-functionalized nanoparticles have been examined for desired physicochemical property and biocompatibility.

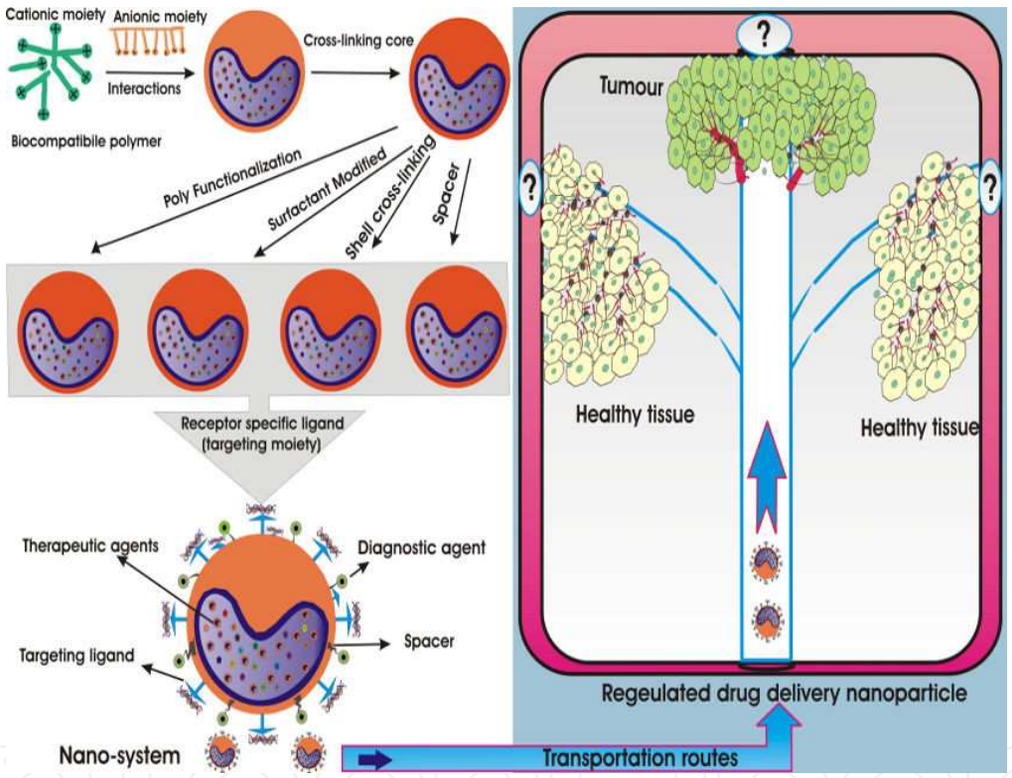

Figure 8. Schematic diagrams represent the various functionalizations of the nano-engines for smart drug delivery systems, which the pre-regulated nanoparticle recognizes the tumor cells not the healthy.

7. Recent developments, significant route of administration and targeting strategies

The route of administration of therapeutics is crucially important to cure the disease. Despite the invention of potential therapeutic moieties, the inefficient drug targeting by pills or injection on the appropriate site of the body limits therapeutics values to a larger extend. There

are multiple barriers involve in the anatomical and physiological system to lack the drug efficiency, including enzymatic degradation in the stomach, absorption across the intestinal epithelium, hepatic clearance, and accumulation in non-targeted tissues. These barriers also involve a range of complexities from the tissue to the organelle level along with the time that mismatch the drug potency in vivo. Collectively, these conditions challenge the active utilization of potent therapeutic molecules for disease treatment or prevention. Extensive research has been carried out in the field of drug delivery to overcome these challenges and thus to contribute a significant role in the overall drug-development process. After the evolution of nanotechnology and vast increment in knowledge about the human body, advances have been achieved in the drug delivery field as targeted delivery and sustained/controlled delivery system. By tuning the kinetic properties of therapeutics, the potentiality could be secured until it reaching the targeted organ and this factor is considered to be the most important in the field of pharmacology. Progresses in the nanomaterials development have been fruitful to fulfil the goals of drug delivery. Pharmacologically, the drug delivery is better explained based on the routes of drug administrations. Development of alternative drug delivery methods is crucially important to overcome the challenges experienced throughout the history of medicine. Scientists have been working on the creation of the smart drug delivery system and such approaches could provide an easy route of administration, ensuring patient compliance, decreasing toxicity, improving bioavailability and achieving precise therapeutic targeting. Creation of smart drug carrier as delivery systems and the discovery of new pharmacological compounds will potentially advance disease diagnosis and treatment beyond expectation. A variety of novel drug delivery systems have been developed using various nanomaterials during the last decade and several of them are already marketed. Nanotechnology manipulates the multiple properties including the size and other physical characteristics and thus achieves both controlled and targeted delivery of drugs. The bio-adaptability and multi-functional properties of smart delivery system minimize the undesirable properties of drugs in various routes of administration, including oral, rectal, nasal, ocular, topical route such as transdermal, and dermal, parenteral route such as intravenous/intravascular, intramuscular, subcutaneous, intradermal/intracutaneous, intraperitoneal and intrathecal. Figure 9 depicts the tremendous applications of new nanomaterials for the development of various routes of administration and targeting for therapeutics such as transdermal vaccine delivery, intranasal vaccine delivery and lung targeted delivery. Nasal mucosa offers numerous benefits as a target tissue for drug delivery, particularly for brain targeting because drug penetration through the BBB is favored by lipophilicity.

In particular, the non-invasive intranasal delivery offers large interests in the targeted route of administration. Nasal delivery helps drugs to bypass the blood-brain barrier and hence acts as an excellent platform for brain targeting. The intranasal drug delivery several approaches should be considered, attending, specifically, to the nature of pathological condition (acute or chronic) and intended effects of drug treatment (local, systemic or at CNS). Local delivery, nasal vaccines, systemic delivery and CNS delivery through nasal route is the prime route for drug administration to treat the various diseases. So the nasal vaccination is a promising alternative to the classic parenteral route because the nasal mucosa possesses abundant nasal associated lymphoid tissue (NALT), dentritic cells, large surface area, and low proteolytic

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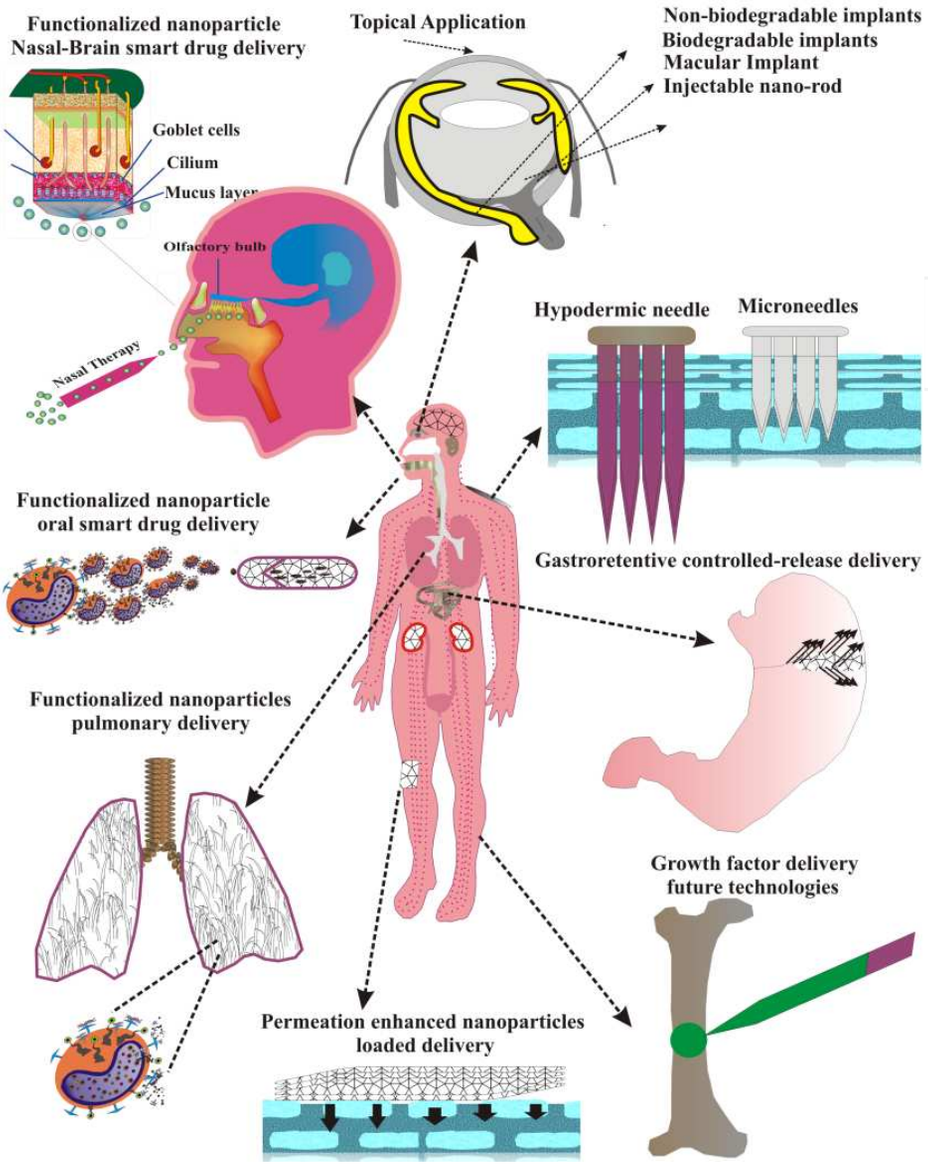

Figure 9. Schematic diagrams represent the recent developments of various significance routes of administration and targeting strategies

enzymes that serve as a primary defense system against pathogens. It can exhibit high drug concentration, permeation, no first-pass effect and compliance administration without enzymatic destruction. Moreover, antigens encapsulated nanoparticles ensure enhanced uptake and controlled release of antigens from the nasal vasculature membrane with strong immunogenicity and improved systemic therapeutic responses. Also, the bio-nanotechnology applied to the parenteral administrations techniques such as microneedles, jet-injections, ultrasound, iontophoresis, and electrophoresis. Theses systems extend painless, patient-friendly alternatives to injections for the delivery of molecule [313-317]. Drug administration using microneedles for the transdermal delivery routes have been reported elsewhere [318-320]. Microneedles are arrays of micrometer-sized shallow needles that penetrate only into the superficial layers of skin, thereby eliminating the pain associated with standard

hypodermic needles [321]. Microneedles have been made from a variety of materials and in particular the polymers have been shown to be effective. They have also been produced in solid and as well as in hollow forms. Solid microneedles are used to render skin permeable, whereas hollow microneedles actively deliver drugs into the skin at a controlled rate. In contrast, jet injectors deliver a high-velocity liquid jet stream into the skin, delivering drugs into various skin layers, depending on the jet parameters [322]. Jet injectors have a long history, particularly in the delivery of vaccines, insulin, and growth hormone. Ultrasound enhances skin permeability by cavitation, which temporarily disrupts skin structure [323]. Iontophoresis and electroporation use electric fields to alter the skin structure and/or provide additional driving force for drug penetration through the skin [324]. These new routes of administration of therapeutics with improved responses have been achieved by high drug concentration in target, permeation, no first-pass effect, high bioavailability and compliance administration without enzymatic destruction [325, 326].

8. Conclusion

The uses of bio-nanotechnology in therapeutics a number of unexpected inventions have been done recently on polymer based nanometers, which have great attention in the field of smart drug delivery applications. The biomaterials including protein based polymers, polysaccharide based polymers, natural or synthetic or semi-synthetic polymers, various biomaterials and combination of polymer have utilized to prepare various kinds of nano-formulations towards the smart drug delivery applications. Several polymeric nanoparticle-based therapeutic systems have been established for the treatment of various diseases. Several nanoparticle based drug delivery systems have been approved in clinical trials, some of them in under pre-clinical trial levels, this nanoparticle based system can provide the increased half-life, high biocompatibility, and minimum immunogenicity, site targeting and overcome the membrane barriers. Also the last era, major and new identifications have been drastically established in the smart material that alter its own structure and function in response to the environment. This performance has been used for the fabrication smart drug delivery systems, Smart polymer matrices release drugs by environment responses this system have been successfully achieved. In parallel the new method of bottom-up and top-down nanofabrication technologies provided precisely controlled size and shaped nano-particulate delivery system. Simultaneously, various advanced significant routes of targeting have developed and successfully achieved to the site of action. At present, the field of microfluidics for synthesis, micro-needle for transdermal and site targeted delivery is still in its infancy. So the pharmaceutical industry has to bring these products into industry-led investigation and the improvement in this would possibly to quicken their progress.

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9. Future perspectives

Although there are considerable amount researches have been done in the field of drug delivery so far. In the polymeric nanoparticle based drug therapy has to be enhanced by incorporating by the combination therapies, Smart delivery has been achieved successfully in the case of cancer, but need to be concentrating more on other pathologies, also numerous challenges remain. From the material viewpoint, most of the smart delivery systems mechanism do well in vitro studies but flops the in vivo studies. So the research has to be re-considering to come up with simple, straightforward, efficient and reasonably accurate preparations with broadly applicable strategies, the pharmacologically active agent targeting to pathological sites, for the development of smart drug delivery systems. In technology vice the research has to focus into the fusion technologies. Although several specific specialized technologies have been shown to in polymer synthesis, functionalization, analysis, in vitro and in vivo study in the field of polymer science, the combinations of two or more techniques are often more effective than single technologies like a combination of controlled radical polymerization with click chemistry. The fusion technologies can fulfil the various existing drawbacks of some individual technologies, and this has the high potentiality, synergistic enhancement in safest nanoparticle based drug delivery. Consider merging and adopting two or more right technologies for getting a high-throughput technology by selecting the right combinations is a fruitful area for research that is still largely unexplored. This new understanding must be incorporated into the future of newer polymeric based nanoparticle synthesis development and evaluation of smart drug delivery. Also the next generation of polymeric nanoparticle based delivery systems with drugs like growth factors, hormones, antibodies, genes, peptides, etc.; should also enhance the efficiency and minimize the unwanted effects.

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