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A Review on pH -Sensitive Polymeric Nanoparticles for Cancer Therapy

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Abstract : Nanomedicine is a branch of nanotechnology used worldwide for better treatment of disease.However the basis for the therapy has many hurdles such as MDR(multi-drug resitsnce) in cancer, selecting drug delivery system based on tumor and many other challenges in treatment.The limitations of the therapy has been overcome by this nanotechnology on the basis of targeted delivery of the drug along with nano-medicines based on polymer which shows effective results in the chemotherapy treatment. As thesenano based medicines are expected to stay for longer period in the blood and reach the target easily.pH-sensitive nanoparticles when bound to ligand have significantly effect on the biological efficacy. This review article describes various pH-sensitive nanoparticles and their mechanisms. It also describes the various applications of pH-sensitive nanoparticle in chemotherapy and their emerging opportunities. In the last few decades, there is tremendous increase of research in this area,particularly for effective pharmacological out comes.
Keywords : Polymer, pH-sensitive, nanocarrier, liposome, micelles, cancer.

1. Introduction

For the drugs and genes, stimuli-responsive smart nanomaterials has considered to be attractive vehicles for last couple of decades. These nanoparticles are often called as 'smart or intelligent materials'[1] as they show non-linear response towards various external parameters like temperature, pH, light, ultrasound, mechanical stress, electric and magnetic fields, and biochemical stimuli.[2] Hence, they have been widely used in drug delivery,[3] biosensors,[4] membranes,[5] catalysts,[6] etc. Considering all other stimuli, different materials have different pH sensitivity.[7]The human body have a wide number of pH throughout the body.[8,9]For example, the pH in stomach is 2 where as that of colon is 7. But the cancerous cells shows pH 0.5-1, lower than neighbouring cells due to lactic acid production and glycolysis. The pathogens can be either acidic or basic or can be determined by their site of action in the body. Hence nanocarrers were discovered to act at a particular pH to improve the therapeutic action and lower the unwanted effects.[10-12]

One of the most common used carrier is because of their biocompatibility and biodegradability and biological functionality.[13] Artificial and other polymers act as carrier from macroscale to nanoscale. Properties like solubility, volume, HLB value can alter the pH sensitive polymer.[14]This change in pH can be either reversible or irreversible depending upon the swelling of the polymer.[15]

The main objective of this review is to determine its use in medicine. For example, more acidic environment of the tumorous cells, more specific is the treatment rather than that of normal cellular environment. In contrast, we have discussed about various nanocarriers, their mechanism and their application.

2.Tumor Microenviroment

In chemotherapy, new drugs are designed by studying the microenvironment of the tumor. This microenvironment also allows one to differentiate normal tissue with tumorous environment based on the difference between oxygenation, perfusion, vascular abnormalities, pH and metabolic state. Hence, these differences plays an important role in designing the nanocarriers.

2.1. Angiogenesis in cancer

Angiogenesis can be defined as the formation of new blood vessels (veins, capillaries and arteries) from the existent vessels. In case of solid tumor (1-2mm^3), simple diffusion is the way of carrying oxygen and nutrients. Non-angiogenic tumor mainly depends on their microenvironment for O_2 and nutrient supply as their vasculature are non-functional. As the tumor progress (2mm^3), the supply of oxygen to the tissue gradually decreases (hypoxia) that leads to angiogenesis.[16] Five phases during the process of angiogenesis are: 1. endothelial cell activation, 2.angiogenic remodeling, 3. endothelial cell migration, 4. vessel formation, and 5.basement membrane degradation. Due to hypoxia there is an increase in cellular factor like HIF (hypoxia inducible factor) that lead to activation of proteins such as platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF) or tumor necrosis factor-α (TNF-α).[17] During vessel formation, the activated endothelial cell explicit transmembrane receptor $\alpha_v\beta_3$, that interact with vibronectin and fibronectin (matrix proteins) which controls the movement of endothelial cell via the extracellular matrix.[18] Upon activation, the endothelial cell produces proteolytic enzymes that breakdown the extracellular matrix and basement membrane and then the innermost endothelial layer experience cell forming vessel. The vessel that are not fully formed, may result in dilation, rough shape and may even be tumorous.[19] This progression of tumor from nonangiogenic to angiogenic is the main cause of cancer that leads to metastasis.[16,20]

2.2. Enhanced permeability and retention (EPR) effect

Long-circulating carrier system depends mainly on conformational variations vascular pathophysiology. Abnormalities like proliferating endothelial cells, pericyte deficiency and aberrant basement membrane formation are main characteristics of tumor blood vessels, that changes vascular permeability. Nanocarriers (20-200nm) may accumulate inside or even outside the vessel. The size of endothelial pores ranges from 10-1000nm.[21]In tumor, the lymphatic vessels are dis-functional that may lead to inefficacious flow from tumor tissue. The nanoparticle that accumulate in is difficult to remove effectively and are present in the tumor, hence it is known as EPR effect.[22-24] While selecting macromolecular drug targeting at tissue level, the irregular vascular designing plays an important role for EPR effect in tumor which shown in figure 1.

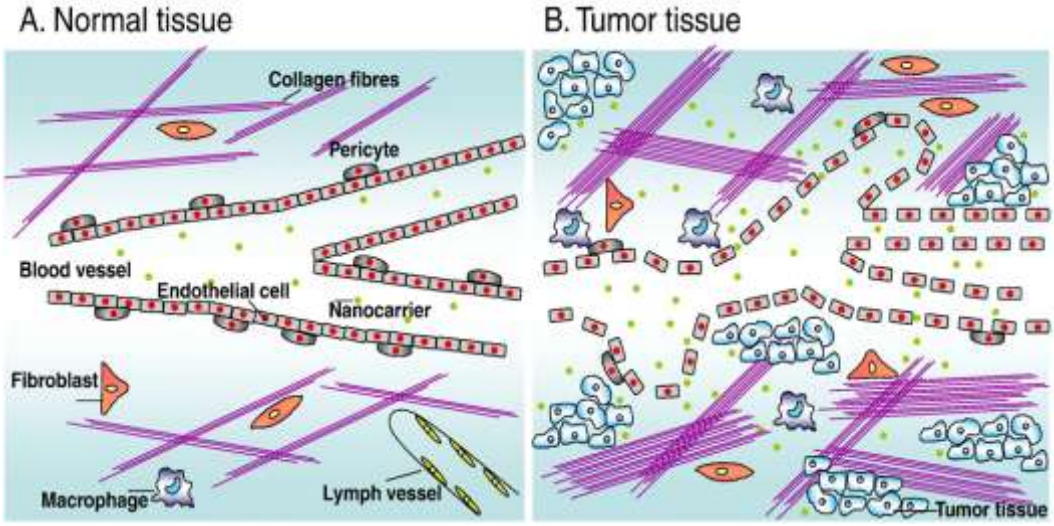


Figure 1: Differences between healthy tissue and tumor tissue.

The Retention effect and enhanced permeability was shown by the nanocarrier that are passively targeted which is elucidated with the difference amid to tumor tissues and normal tissue in figure 1. A. Pericytes maintained blood vessels linear in normal tissue and extracellular matrix contain macrophages, fibroblasts, collagen fibres. Lymph vessels are also present. B. Fenestrations and sac-like formations are seen in the blood vessels, present in defective tissues of tumor. The matrix of extracellular fluid contains more macrophages, collagen fibres and fibroblasts in normal tissue by lacking with lymph vessels.

Jain in the year 1987 assumed a high osmotic pressure in tumors, that can act as an obstacle for drug delivery in cancer.[25] Most of the high molecular weight anticancer drugs are carried from the circulatory system via interstitial space by convection. There is a decreased drug uptake into tumor when interstitial fluid pressure (IFP) coz of flowered transcapillary movement. The density of IFD is more at the centre of the tumor and is less towards the outer surface. The drug molecule show move from entry site to the distant cells in order to assure a proper supply of drug to all the tumor. But this process is hampered by high IFP. Many types of drug molecules effectively overcome such problems and deposited in the tumor.[25-27]

2.3. pH

The intracellular pH of the both the healthy tissues and tumors are same whereas the extracellular pH of tumors are less when compared to healthy tissue. The tumor pH mainly varies depending on their area of invasion. Generally 6.0-7.0 is the average extracellular tumor pH, whereas in healthy tissue the pH is approximately 7.4.[28,29] There is a close line between low pH and pO_2values which plays an important role in the development of tumor.[30] Glycolysis rate in the oxygen deficient cancer cells leads to decreased extracellular tumor pH. The presence of oxygen also blocks ATP-generating pathway.[31] Defects like glycolysis derived biosynthetic intermediates and mitochondrial respiratory chain helps in this metabolism.[31] To generate nicotinamide adenine NAD^+ pyruvate is converted to lactate to maintain high glycolytic rate, by various glycolytic enzymes. For the metabolic flux and the prevent cytotoxicity, lactate should be removed from the cell. The extracellular tumor space is made acidic by monocarboxylate transport that removes one proton molecule with one lactate molecule. Carbonic anhydrase IX also helps in maintaining the pH gradient between intracellular and extracellular space by converting carbondioxide to bicarbonate.[32]

The source of differential drug partitioning and distribution is the result of different pH between intra and extracelluar tumor cell. The neutral element of the weak acid increaes in a low extracellular pH and it can easily diffuse through plasma membrane. This alkaline intracellular spaces promotes molecular ionization that lead to the accumulation of the drugs in the cytosol.[33]Chemotherapy helps to select the favourable tumor clone cells that entrap drugs and lower their activity.

3. pH-Sensitive Nanocarriers

From organic and inorganic substances like lipids, polymers, metals and ceramics, pH sensitive nanocarriers for DDS can be made. There are 3 main classification of pH senitivenano carriers;

1. Polymeric nanocarriers (Nanogels, polymer-drug conjugates, micelles and core-shell polymeric nanoparticles),
2. Liposomes and
3. Inorganic nanoparticles.

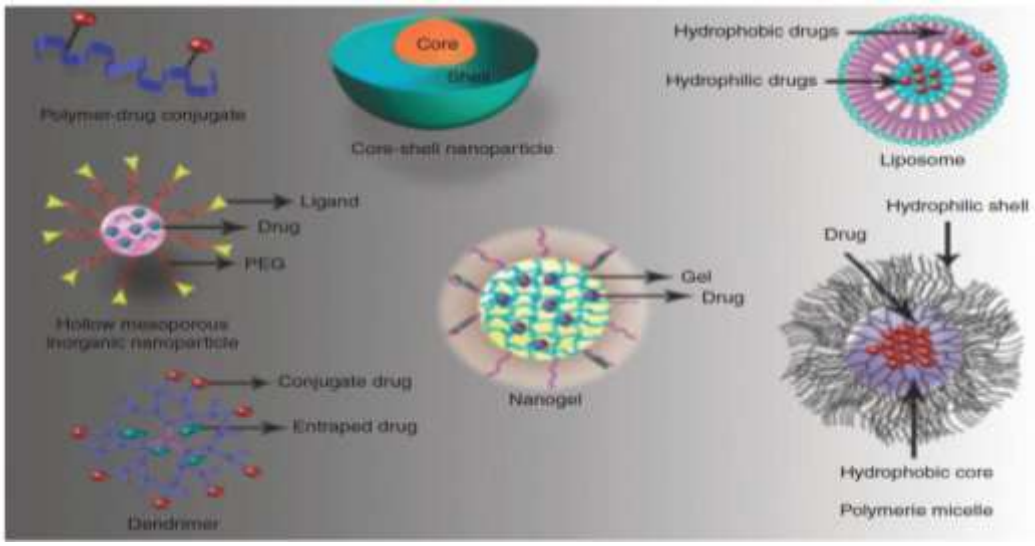


Figure 2: various examples of pH-sensitive nanocarrier.

3.1.Polymeric nanogels

Self assembly or covalent bond formation can help in the formation of cross linked hydrophilic polymer chains which inturn forms highly porous 3D networks. The environmental pH change can lead to the release of encapsulated drug from inner gel structure due to swelling.[34,35] The drug loading capacity of nanogels are higher than micelles and liposomes but they are poor in isolating hydrophobic drugs. So, proper surface modification is required for their acceptance in target delivery.[36] Appropriate combination of amphiphilic block polymers are used in the preparation of nanogels that help in the binding of opposite charged chains of poymer.[37] Chemical cross-linking is one of the method for the preparation of large pore size nanogels. Crosslink in aqueous environment helps in the prevention of rapid dissolution of hydrophilic chains.[38]

3.2 Polymeric Micelles

A colloidal aggregation in a simple geometric form, of a specific number of amphiphatic molecules which form at a well defined concentration called as critical micelle concentration (CMC). Hydrophobic and ionic interaction between the amphiphilic block polymers in aqueous environment help in the formation of nanosized polymeric micelles.[39] Several attractive features like ability to solubilize water insoluble drugs, soubility, low toxicity and the ability to take advantage of EPR effect for passive tumor targetting has proved useful in investigating drug nanocarriers.[40,41] Various functional groups can be attached to the hydrophilic end of the micelle to improve the intracellular uptake. The pH sensitive polymeric micelle usually release its active ingredients at lower pH.[40]

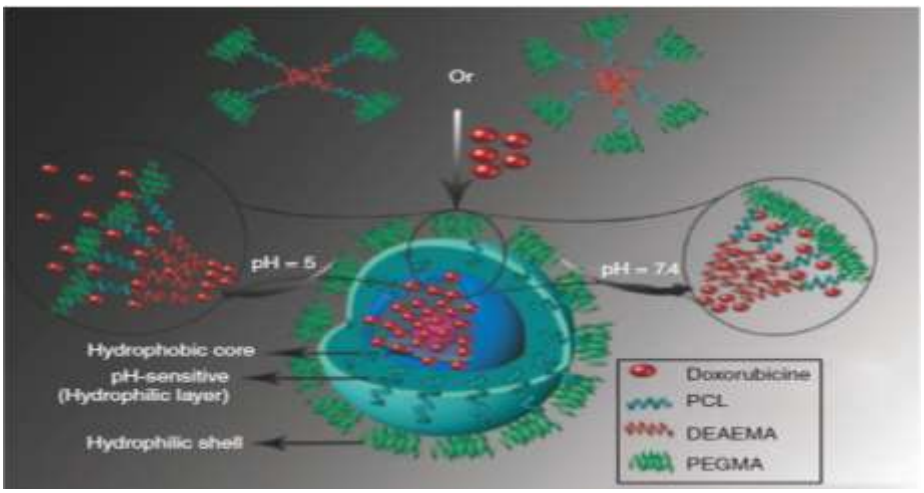


Figure 3:Schematic illustration of drug loading and release of drug in a pH-sensitive micelle.

3.3.Prodrugs(polymer-drug conjugates)

In pH sensitive DDSs, conjugation of drugs can be used as a carrier. Drug molecules can attach covalently to the polymeric chain. The polymeric chain and the drug are bound covalently or the drug can also be encapsulated through electrostatic interactions. Polymer-drug complex have higher circulation time and stability than the normal environmental condition.[42] For example, the stability of poorly water soluble drug can be enhanced by complexing it with water soluble ploymer.[38,43] Hence it is needed to enhance the control the drug release at the site of action.

3.4. Core-shell polymeric NPs

Polymeric nanoparticles having properties such as colloidal, spherical and branching possess core-shell structure. Various methods such as salting out, nanoprecipitation, spontaneous emulsion, supercritical carbondioxide polymerization, emulsion evaporation etc. are used for preparation for polymeric nanoparticles from natural and synthetic biodegradable polymers.[44]

3.5 Liposomes

Liposomes are spherical self-arranged vehicles composed of a single or several concentric lipid bilayers. The size of liposomes varies from 50nm to several micrometers. The surrounding of liposomes is aqueous in nature and their interior is hydrophobic. The liposomes cannot be used for hydrophilic drugs since they cannot easily pass through the hydrophobic membrane. So, liposomes are mostly used for hydrophobic drug molecules as they can easily penetrate the membrane. The properties such as size, surface charge and targeting to diseased cell or tissue can be altered by the addition of agents to the surface membrane.[45,46] When compared to micellar systems, liposomes shows better biocompatibility profile for drug delivery system.[48] But they have a few disadvantages like release rate of drug is too rapid, encapsulation efficiency is low, low storage stability and lack of tunable triggers for drug release.[49] Many research have been carried out to overcome such limitations. For e.g. to improve targeting and drug release, surface modification and arrangement of liposomal layer is carried out. To release the drug into the cytoplasm from endosomes, pH sensitive liposomes have been designed.[47]

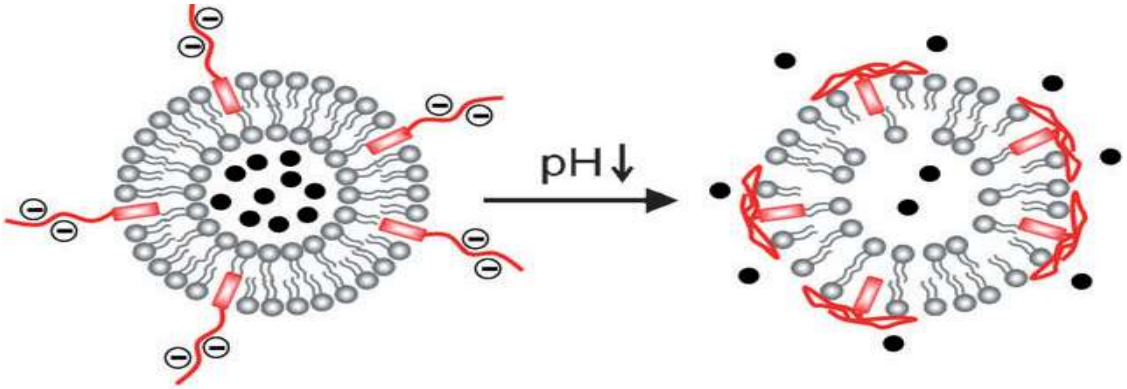


Figure 4: Polyanionic chain collapse due to protonation, converting the liposomal shell porous and hence promotes the oozing of drug from liposome.

3.6. Inorganic NPs

Mesoporous substances such as silica, calcium carbonateor gold have been widely used in preparation of inorganic NPs. Because of its rigid/inflexible surface, it allows proper functionalization and also shows better encapsulation property. Combination of organic compounds like chitosan,[50]polydopamine,[51] with few inorganic NPs are used for pH sensitive materials.

Pore expanding agent 1,3,5-trimethylbenzene is used to obtain a bigger pore size of polydopamine (PDA) coated mesoporous silica NPs (MSNs) where self-polymerisation method is used for coating. They releases DOX in acidic medium but are stable at neutral pH.

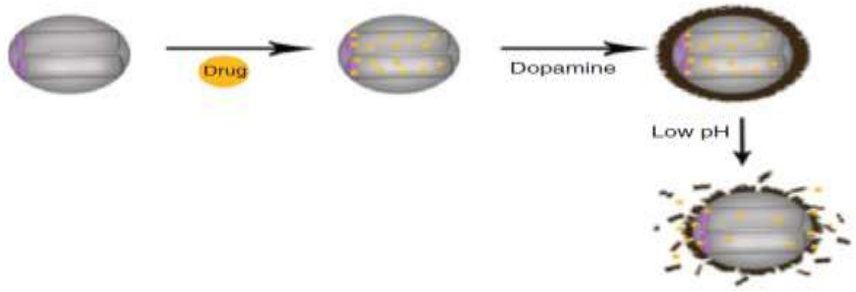


Figure 5: Fabrication of MSNs coated with PDA and pH-dependent drug release.

4. The Mechanisms of Drugrelease From pH-Sensitive NPs

pH responsive delivery system can be formulated for intracellular and extracellular pH by utilizing the acidic microenvironment. Three different mechanisms are ued in designing these nanocarriers:

1. pH triggered protonation to promote intracellular and extracellular release
2. b.Acid labile bond cleavage for extra or intra cellular drug release
3. Acid labile bond cleavage for PEG-detachment.

4.1. pH triggered protonation to promote extracellular or intracellular release

To obtain pH triggered drug delivery, one of the most widely used mechanism is protonation. Biomaterials such as polymers having ionizable chemical groups are used to formulate the nanocarriers. They usually remain deprotonated at biological pH but gets protonated at acidic pH which leads to structural changes of NPs and hence release of encapsulated active component at intra or extracellular sites.[52,53] Protonation caused by acidic pH allows anionic polymers to undergo hydrophilic-hydrophobic phase convertion whereas cationic polymers undergoes hydrophobic-hydrophilic phase convertion. Widely used ionizable groups are amino, sulfonates, carboxyl and imidazolyl groups. At neutral pH, the anionic polymers with carboxylic group gets deprotonated and hydrophilic whereas on acidic pH, they are protonated and hydrophobic which lead to drug release through precipitation. At biological pH, some anionic polymers possess negative charge which gradually turns into positively charged in acidic pH usually called as charge-reversal polymers. Table 1 depicts a brief idea of protonable pH sensitive polymers along with their mechanism of drug release and pKa values.

4.2. Acid labile bond cleavage for extra or intracellular drug release

To achieve highly selective tumor targeting, one of the most important strategy is acid labile bond cleavage that allows extracellular drug release.[54,55] The mechanism to accomplish drug release at acidic pH is hydrolysis of acid labile bonds. This hydrolysis of bonds usually occurs between drug and polymer or within the polymer.

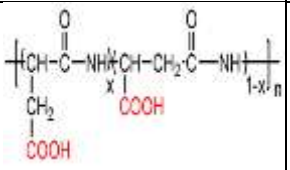
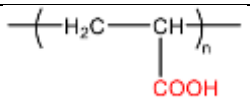
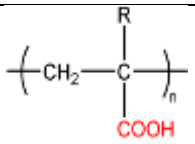
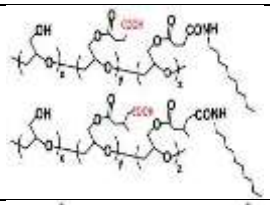
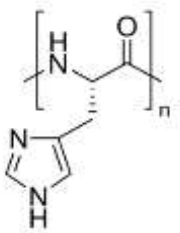
4.3. Acid labile bond cleavage for PEG-detachment

The main limitations of these nanocarriers are slow drug release and poor cellular uptake by endosomes[56,57] that results in poor bioavailability.[58,59]Various efforts have been continuously made for developing strategies for detachment of PEG at target sites. At physiological pH, the PEG shell remains stable which facilitates long circulation till it reaches the targeted tumor cell in PEG detachment mechanism. Due to low extracellular pH at the tumor site, PEG shedding enhances endocytosis along with membrane fusion and endosomal escape. PEG detachment also takes place in the presence of low pH. In combination, these processes shows improved intracellular delivery of active ingredients.[60]

Many other concerns have been identified by the scientists other than the above mentioned limitations about PEGylation. By inducing IgM antibodies, various immune response was reported by repeated injection of PEGylatednanocarriers which ends up showing rapid clearance called as accelerated blood clearance (ABC).[61-64] In some people, the case of acute hypersensitivity was recorded by the use of PEGylated liposomes.

Cellular uptake and intracellular drug delivery can be enhanced by PEG-detachment, but it can't enhance accelerated blood clearance phenomenon. It has also been discovered that hydrophilic polymers like N-(2-hydroxypropyl) methacrylamide and polyvinylpyrrolidone also possess "stealth" property without showing any accelerated blood clearance.[65,66]

Table 1: Examples of pH-sensitive cationic and anionic polymers and their mechanisms for triggered release.

Anionic polymers	pH-sensitive polymer	pKa	Chemical structure	pH-sensitive conformation changes of polymer
	Poly(aspartic acid) (PASP)	4.78		At biological pH 7.4, –COOH groups of PASP are deprotonated but gets protonated at low pH (less than 4.87), which leading to nanocarrier unstable.[67]
	Poly(acrylic acid) (PAA)	4.74		At high pH polymer gets ionized and swell. But in low pH –COOH groups of PAA are protonated and which leading to nanocarrier unstable.[68]
	Poly(ethyl acrylic acid) (PEAA) and Poly(methacrylic acid)(PMAA)	6.31 5.51	 R=CH_2CH_3(PEAA) R=CH_3(PMAA)	Atbiological pH 7.4 polymers are stable. But in low pH they are not stable anymore because –COOH groups of PEAA and PMAA becomes protonated. which breakdown the polymer structure.[69,70]
	3-methylglutarylated poly (glycidol)	6.31		Here –COOH groups of glycidol are protonated at low pH or acidic pH and hence nanoparticles becomes unstable but in normal pH they are stable.[71,72]
Cationic Polymers	Poly(β-amino ester)	6.49		At normal biological pH cationic polymer Poly(β-amino ester) is unionized and stable but when pH is below 6.49 it becomes ionized and unstable because of –RNH_2group of this polymer.[73]
	poly(L-histidine)	~7.0		At normal pH cationic polymer poly(L-histidine) is unionized and stable but when pH is below 7 it becomes ionized and unstable because of –RNH_2group of imidazole ring of this polymers.[74]

5. Current Issues in Cancer chemotherapy

Along with cancer and some other cardiovascular blockage such as syndrome of acquire resistance, deficiency are also been treated with the chemotherapy, but the treatment with the anti-cancer drugs will involve which is involved elevated subject risk as drugs which are used are not precise to cancer treating cells. Because of repeated therapy, subjected person may loss their quality life due to abided severe reactions. The inadequacy and reactions of chemotherapy has first and foremost connected with preparation and distribution of

drug in the biological system, perniciousness to regular cells,theattainment of drug confrontation by the malignant neoplastic diseased cells.Researchers are continuously working out to conquer these issues.

In 1967 US National Institute of Cancer had acknowledged 1st drug to treat,which is "paclitaxel". It is extruded from yew tree (pacific) bark,which produces tubilin that slaughter cells which causes cancer by stabilizing the microtubule agents that stimulate cell division. It is by disrupting the cell wall of the cancer causing cells because of which they have been established as an effective drug frantic in cancer treatment which include lung,breast, head, neck,colon and ovarian cancer. But the limitation for the paclitaxel in application of chemotherapy is that it is prone to less water solubility and evaluated hydrophobicity due to high lipophilicity of group of drugs empathy at the receptor site.[75,76] Because of this, deposition of the drug at the site is seen which lead the blood vessels embolization and even show toxicity at the site due to high drug concentration. Dehydrated ethanol,castor oil polyethoxylate (cremophor EL) are included in the present formulation of paclitaxel.Cardiotoxicity, nephrotoxicity and some hypersensitive reactions are caused due to cremophor EL.[77]Although the solubility of the drug in the formulation may be improved by the addition of critical surfactant,but they undergo precipitation in in-vivo studies due to their concentration of critical micelles in physiologic fluids. For the lesssoluble drugs, they developed thermodynamically constant micellar polymers with hydrophobic origin occupied by a hydrophilic origin which was proposed and checked as a dynamic delivery system.[78-80]

In chemotherapy, drug distribution is an important element for its success. Anticancer drugs when administered via IV, reaches throughout the body by the blood circulation and finally reaches normal and malignant cells. The main objective of chemotherapy is to allow the drugs to reach the site of action where it can remain effective for a longer period of time. Theoretically, properties like sustained, controlled and targeted release are of great significance in anti-cancer drugs for achieving this goal. These parameters can be achieved by preparing drugs which are monitored at nano scale. Enhanced drug targeting property can be achieved by taking into account the properties of the preparation as well as the tumor cells. Acquisition by carcinogenic cells to obtain resistance to drug is the major problematic area in the treatment of cancer. Except many healthy tissues, the interstitial space of cancer cells is high which causes external flow of interstitial fluid and removes the drug along with it. Even though the drug reaches the target site, the drug may not show its desired therapeutic action due to obtained MDR (multidrug resistance).[81,82]Resistance to the multiple drugs is mainly obtained by the P-gp (glycoprotein -P) which is usually present on cell membrane. Administration of P-gp inhibitors along with anticancer drugs encapsulation are used to avoid several strategies.

6. Application and Route of Administration

Hydrogels which are pH sensitive are used in the drug control release mainly in two applications by placing them in the capsule. Gutowska *et al.*[84] prepared hydrogels and examined for drug delivery by squeezing mechanism process. Hydrogels are loaded with drug and are tested in the various media for the release. The gel swells immediately after immersion into the releasing media to a certain extent, till the pores are closed in the capsule. The holes of the capsule open by squeezing, due to shrinkage of gel by changing pH. The proper environmental conditions should be present based on the proper pH for disintegration by cross linking the carriers of the nanosphere.

Sonaje *et al.*[85] said that release of the drug at pH 7 to 7.4 can be seen by γ-PGAi.e.,chitosan-poly(L-glutamic acid) which is stimulated at environment of intestine. Whereas γ-PGA form supporting bonds along with carboxyl group at lower stomach pH that leads to interaction due to electrostatic reduction and thereby forms nanosphere instability. To overcome this problem enteric coated capsules are filled with dry freeze nanospheres.

On the other hand nanocarriers which are pH sensitive can be implanted with matrices of silicone. Carelli*et al.*[86] conducted a study on hydrogels which acts as a network of semiinterpolymer penetrators which contain ethylmethacrylate-polymethacrylic acid, EUD and P8000C i.e., cross linking agent polyethylene glycol 8000 (36%) polymers in varying fractions.88 to 123μm diameter ranged hydrogels are present which are 15wt% filled with PDN(prenisolone) in it, that are positioned in 500-1000μm (size) microsphere made of silicone which have suitable morphology in a vulcanization-method in emulsion i.e., in modified form .

As per Asheley*et al*.[87] liposomes comprises of(DOPE)i.e.,dioleoylphosphatidylethanolamine and shows lesser serum stability. So, as per Wu*et al*,[88] liposome comprises of a copolymer of (SPC)soyphosphatidyl choline in his design to overcome the above mentioned problem . By this, they found that the stability of SPC copolymer-liposome in serum is much better than DOPE-liposomes as it shows release of drug in buffer solution up to 20 hours.

Significantly the excretion of the unwanted drug that is prematurely released is a significant event. For instance the deprivation of the drug from lysosomes will pose a significant problem. The drug is uptaken by the process of endoosmolysis by the endocytosis mechanism.[89]

The drug delivery system that is responsive for various ranges of pH which is responsive for a stimuli are the recent concepts used for the drug targeting. Hence a variety of multiple stimuli sensitive systems like pH/magnetic, pH/temperature, pH/temperature/magnetic systems have been developed which have a controlled release of the drugs and show enhanced efficacy. The pH stimuli and the enzyme esterase is responsible for drug delivery in nanocarrier(Mesoporous Silica Nanoparticles). Similarly the nanocarrierpolyacrylic acid shows drug release only in the acdic environment and in presence of the esterase enzyme.[90]

Thermo responsive and pH responsivedrug delivery system havea therapeutic as well as the imaging capability. The nanoparticulate quantum dots loaded with methotrexate are promising for drug delivery as well as the imaging studies.[91] Another attempt of the pH sensing drug delivery of grapheme oxide gives a targeted drug delivery and a tracing of tumors is done using the fluorescence technique using a dye called rhodamine which triggers reactions in the tumor that is acidic in nature.[92]

The disorders like wilson's disease and the alzheimer's disease are known to alter the pH of the system, hence, the bioresponsive delivery can be employed to this type of diseases.[93]Recent advances have helped in developing a pH sensitive systems having an enhanced stability, less toxicity to the cells and also having anti-oxidant properties, hence these systems can be used in treatment of CVS disease and CNS disorders.[94]

The pH responsive system loaded with docetaxel showed inhibition of the breast cancer tumor showing a good bioavailability orally and targeted delivery to the intestine.[95] These drug delivery systems show enhanced bioavailability as well as the dose and the dosing frequency.[96]Furthermore, in certain conditions of a long term therapy,nanosystems can be utilized for the administration of the drug to the GIT.[97] A pH sensitive system which is sensitive to both intracellular and extracellular pH for the release of the drugs and uptake of the drug by the cells was due to the surface charge of the cells. Delivery of drugs for 2 diseases/disorders simultaneously was also another outcome of the pH responsive DDS. This can also be used in treating a multi drug resistant cancer.[98]

The nanoparticles which are pH-sensitive have very novel applications like metal phenolic network with low fouling faster assembly as well as the pH responsive degradation.[99]Such novel particles could provide new concepts in the design of pH-responsive DDSs.[100]

7. Conclusion

Globally, cancer is one of the major cause of death. With respect to the conventional chemotherapy TDDS has marked new measurement. The extracellular pH of the tumors gives the response to load of drug the EPR effect gets exploited by the carriers of pH sensitive. With comparison to other stimuli the response from pH gets attracted and seek the attention from the nanovehicles. Due to the versatility of the approach it shows predominance as the reason by threefold. Firstly, at pH 4.5-5.6 the endosomes and lysosomes are made to release the drug in acidic pH by controlled release, and for the process of endosomolysis that is destruction of intracellular organelle, the ability is attained. Cytoplasmic milieu is accessed by the ingredients which are active where the optimal effect shown are more attractive. Secondly, the change glycolytic metabolism causes the tumor which is also called as Warburg effect caused in the low pH environment .Thirdly,the important aspect for oral drug delivery is the ability to tailor the drug release in acidic pH having less than 3 otherwise the environment having basic pH having more than pH 7. The trend has increased for the oral drug delivery which was administered previously as injection for example insulin.Recently nanocarriers having multifunctional pH sensitive have grabbed the attention in the development. Forinstance by the tumor cells or peptides which penetrates the cells are recognized by the insertion of ligands. The reduction in side effects, accumulation of

tumors, uptake of cellular by the anticancer drug, selectivity and efficacy is achieved by improving these systems. In the future, these multifunctional nanocarriers will ease the issues in treating the cancer being one of the important components resource of the therapy.

8. Conflict of Interest

The author(s) declare no any conflict of interest for this article content.

9. References

1. Ballauff M, Lu Y. "Smart" nanoparticles: preparation, characterization and applications. Polymer. 2007;48(7):1815-23.
2. Lai F, Li H, Luo R. Chemo-electro-mechanical modeling of ionic-strength-sensitive hydrogel: Influence of Young's modulus. Int J Solids Struct. 2010; 47(22):3141-9.
3. Liu J, Huang Y, Kumar A, Tan A, Jin S, Mozhi A, Liang XJ. pH-sensitivenano-systems for drug delivery in cancer therapy. Biotechnol Adv. 2014;32(4):693-710.
4. Kim JH, Lim SY, Nam DH, Ryu J, Ku SH, Park CB. Self-assembled, photoluminescent peptide hydrogel as a versatile platform for enzyme-based optical biosensors. Biosens Bioelectron. 2011;26(5):1860-5.
5. Kim DY, Kim HJ. pH-sensitive optode membrane covalently incorporated with an ICT dye for low pH values. Sens Actuators B Chem. 2015;206:508-15.
6. Bergbreiter DE, Case BL, Liu YS, Caraway JW. Poly (N-isopropylacrylamide) soluble polymer supports in catalysis and synthesis. Macromolecules. 1998;31(18):6053-62.
7. Engin K, Leeper DB, Cater JR, Thistlethwaite AJ, Tupchong L, McFarlane JD. Extracellular pH distribution in human tumours.Int J Hyperthermia. 1995;11(2):211-6.
8. Iemma F, Spizzirri UG, Puoci F, Muzzalupo R, Trombino S, Cassano R, Leta S, Picci N. pH-Sensitive hydrogels based on bovine serum albumin for oral drug delivery. Int J Pharm. 2006;312(1):151-7.
9. Shaikh RP, Pillay V, Choonara YE, du Toit LC, Ndesendo VM, Bawa P, Cooppan S. A review of multi-responsive membranous systems for rate-modulated drug delivery.Aaps PharmScitech. 2010;11(1):441-59.
10. Alvarez-Lorenzo C, Concheiro A. Smart drug delivery systems: from fundamentals to the clinic. ChemCommun. 2014;50(58):7743-65.
11. Alvarez-Lorenzo C, Concheiro A. From drug dosage forms to intelligent drug-delivery systems: a change of paradigm. InSmart materials for drug delivery 2013(pp. 1-32).
12. Binauld S, Stenzel MH. Acid-degradable polymers for drug delivery: a decade of innovation. ChemCommun. 2013;49(21):2082-102.
13. Prabaharan M, Mano JF. Stimuli-responsive hydrogels based on polysaccharides incorporated with thermo-responsive polymers as novel biomaterials. MacromolBiosci. 2006;6(12):991-1008.
14. De lasHerasAlarcón C, Pennadam S, Alexander C. Stimuli responsive polymers for biomedical applications. ChemSoc Rev. 2005;34(3):276-85.
15. Schmaljohann D. Thermo-and pH-responsive polymers in drug delivery.Adv Drug Deliv Rev. 2006;58(15):1655-70.
16. Bergers G, Benjamin LE. Tumorigenesis and the angiogenic switch. Nat Rev Cancer. 2003;3(6):401-10.
17. Carmeliet P. Mechanisms of angiogenesis and arteriogenesis. Nat Med. 2000;6(4):389.
18. Avraamides CJ, Garmy-Susini B, Varner JA.Integrins in angiogenesis and lymphangiogenesis. Nat Rev Cancer. 2008;8(8):604-17.
19. Stollman TH, Ruers TJ, Oyen WJ, Boerman OC. New targeted probes for radioimaging of angiogenesis.Methods. 2009;48(2):188-92.
20. Naumov GN, Akslen LA, Folkman J. Role of angiogenesis in human tumor dormancy: animal models of the angiogenic switch. Cell cycle. 2006;5(16):1779-87.
21. Torchilin VP. Drug targeting.Eur J Pharm Biopharm. 2000;11:S81-91.
22. Matsumura Y, Maeda H. A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. Cancer res. 1986;46(12 Part 1):6387-92.

23. Maeda H, Sawa T, Konno T. Mechanism of tumor-targeted delivery of macromolecular drugs, including the EPR effect in solid tumor and clinical overview of the prototype polymeric drug SMANCS. J Controlled Release. 2001;74(1):47-61.
24. Maeda H, Bharate GY, Daruwalla J. Polymeric drugs for efficient tumor-targeted drug delivery based on EPR-effect. Eur J Pharm Biopharm. 2009;71(3):409-19.
25. Jain RK. Transport of molecules in the tumor interstitium: a review. Cancer Res. 1987;47(12):3039-51.
26. Heldin CH, Rubin K, Pietras K, Östman A. High interstitial fluid pressure—an obstacle in cancer therapy. Nat Rev Cancer. 2004;4(10):806-13.
27. Bouzin C, Feron O. Targeting tumor stroma and exploiting mature tumor vasculature to improve anti-cancer drug delivery. Drug Resist Updat. 2007;10(3):109-20.
28. Van Sluis R, Bhujwalla ZM, Raghunand N, Ballesteros P, Alvarez J, Cerdán S, Galons JP, Gillies RJ. *In vivo* imaging of extracellular pH using 1 H MRSI.MagnReson Med Sci. 1999;41(4):743-50.
29. Cardone RA, Casavola V, Reshkin SJ. The role of disturbed pH dynamics and the Na+/H+ exchanger in metastasis.Nat Rev Cancer. 2005;5(10):786-95.
30. Fang JS, Gillies RD, Gatenby RA. Adaptation to hypoxia and acidosis in carcinogenesis and tumor progression.Semin Cancer Biol. 2008;18(5):330-337).
31. Feron O. Pyruvate into lactate and back: from the Warburg effect to symbiotic energy fuel exchange in cancer cells. RadiotherOncol. 2009;92(3):329-33.
32. Brahimi-Horn MC, Pouysségur J. Oxygen, a source of life and stress. FEBS letters. 2007;581(19):3582-91.
33. Simon SM. Role of organelle pH in tumor cell biology and drug resistance. Drug Discov Today. 1999;4(1):32-8.
34. Chacko RT, Ventura J, Zhuang J, Thayumanavan S. Polymer nanogels: a versatile nanoscopic drug delivery platform. Adv Drug Deliv Rev. 2012;64(9):836-51.
35. Raemdonck K, Demeester J, De Smedt S. Advanced nanogel engineering for drug delivery. Soft Matter. 2009;5(4):707-15.
36. Soni G, Yadav KS. Nanogels as potential nanomedicine carrier for treatment of cancer: A mini review of the state of the art. Saudi Pharm J. 2016;24(2):133-9.
37. Yallapu MM, Jaggi M, Chauhan SC. Design and engineering of nanogels for cancer treatment. Drug Discov Today. 2011;16(9):457-63.
38. Vinogradov SV. Colloidal microgels in drug delivery applications.Curr Pharm Des. 2006;12(36):4703-12.
39. Lv Y, Huang H, Yang B, Liu H, Li Y, Wang J. A robust pH-sensitive drug carrier: Aqueous micelles mineralized by calcium phosphate based on chitosan. CarbohydrPolym. 2014;111:101-7.
40. Wu H, Zhu L, Torchilin VP. pH-sensitive poly (histidine)-PEG/DSPE-PEG co-polymer micelles for cytosolic drug delivery. Biomaterials. 2013;34(4):1213-22.
41. Kataoka K, Harada A, Nagasaki Y. Block copolymer micelles for drug delivery: design, characterization and biological significance. Adv Drug Deliv Rev. 2001;47(1):113-31.
42. Lv S, Tang Z, Zhang D, Song W, Li M, Lin J, Liu H, Chen X. Well-defined polymer-drug conjugate engineered with redox and pH-sensitive release mechanism for efficient delivery of paclitaxel. J Control Release. 2014;194:220-7.
43. Zou J, Jafr G, Themistou E, Yap Y, Wintrob ZA, Alexandridis P, Ceacareanu AC, Cheng C. pH-Sensitive brush polymer-drug conjugates by ring-opening metathesis copolymerization. ChemCommun. 2011;47(15):4493-5.
44. Soppimath KS, Aminabhavi TM, Kulkarni AR, Rudzinski WE. Biodegradable polymeric nanoparticles as drug delivery devices.J Control Release. 2001;70(1):1-20.
45. Ramasamy T, Haidar ZS, Tran TH, Choi JY, Jeong JH, Shin BS, Choi HG, Yong CS, Kim JO. Layer-by-layer assembly of liposomal nanoparticles with PEGylated polyelectrolytes enhances systemic delivery of multiple anticancer drugs. ActaBiomater. 2014;10(12):5116-27.
46. Blume G, Cevc G. Liposomes for the sustained drug release *in vivo*. BiochimBiophysActa-memb. 1990;1029(1):91-7.
47. Torchilin VP. Recent advances with liposomes as pharmaceutical carriers. Nat Rev Drug Discov. 2005;4(2):145-60.
48. Torchilin VP. Micellarnanocarriers: pharmaceutical perspectives. Pharm Res. 2007;24(1):1.
49. Sihorkar V, Vyas SP. Potential of polysaccharide anchored liposomes in drug delivery, targeting and immunization. J Pharm Pharm Sci. 2001;4(2):138-58.

50. Deng Z, Zhen Z, Hu X, Wu S, Xu Z, Chu PK. Hollow chitosan–silica nanospheres as pH-sensitive targeted delivery carriers in breast cancer therapy. Biomaterials. 2011;32(21):4976-86.
51. Zheng Q, Lin T, Wu H, Guo L, Ye P, Hao Y, Guo Q, Jiang J, Fu F, Chen G. Mussel-inspired polydopamine coated mesoporous silica nanoparticles as pH-sensitive nanocarriers for controlled release. Int J pharm. 2014;463(1):22-6.
52. Fleige E, Quadir MA, Haag R. Stimuli-responsive polymeric nanocarriers for the controlled transport of active compounds: concepts and applications. Adv Drug Deliv Rev. 2012;64(9):866-84.
53. Ganta S, Devalapally H, Shahiwala A, Amiji M. A review of stimuli-responsive nanocarriers for drug and gene delivery.J Control Release. 2008;126(3):187-204.
54. Liu Y, Wang W, Yang J, Zhou C, Sun J. pH-sensitive polymeric micelles triggered drug release for extracellular and intracellular drug targeting delivery. Asian J Pharm Sci. 2013;8(3):159-67.
55. Xu JX, Tang JB, Zhao LH, Shen YQ.Advances in the study of tumor pH-responsive polymeric micelles for cancer drug targeting delivery. Yao xuexuebao= Actapharmaceutica Sinica. 2009 Dec;44(12):1328-35.
56. Hatakeyama H, Ito E, Akita H, Oishi M, Nagasaki Y, Futaki S, Harashima H. A pH-sensitive fusogenic peptide facilitates endosomal escape and greatly enhances the gene silencing of siRNA-containing nanoparticles *in vitro* and *in vivo*. J Control Release. 2009;139(2):127-32.
57. Remaut K, Lucas B, Braeckmans K, Demeester J, DeSmedt SC. Pegylation of liposomes favours the endosomal degradation of the delivered phosphodiester oligonucleotides. J Control Release. 2007;117(2):256-66.
58. Li Y, Liu R, Yang J, Shi Y, Ma G, Zhang Z, Zhang X. Enhanced retention and anti-tumor efficacy of liposomes by changing their cellular uptake and pharmacokinetics behavior. Biomaterials. 2015;41:1-4.
59. Hatakeyama H, Akita H, Harashima H. The polyethyleneglycol dilemma: advantage and disadvantage of PEGylation of liposomes for systemic genes and nucleic acids delivery to tumors. Biol Pharm Bull. 2013;36(6):892-9.
60. Gao Z, Zhang L, Sun Y. Nanotechnology applied to overcome tumor drug resistance. J Control Release. 2012;162(1):45-55.
61. Ichihara M, Shimizu T, Imoto A, Hashiguchi Y, Uehara Y, Ishida T, Kiwada H. Anti-PEG IgM response against PEGylated liposomes in mice and rats. Pharmaceutics. 2010;3(1):1-1.
62. Yang Q, Ma Y, Zhao Y, She Z, Wang L, Li J, Wang C, Deng Y. Accelerated drug release and clearance of PEGylatedepirubicin liposomes following repeated injections: a new challenge for sequential low-dose chemotherapy. Int J Nanomedicine. 2013;8(1):1.
63. Ishida T, Kiwada H. Accelerated blood clearance (ABC) phenomenon upon repeated injection of PEGylated liposomes. Int J Pharm. 2008;354(1):56-62.
64. Ma H, Shiraishi K, Minowa T, Kawano K, Yokoyama M, Hattori Y, Maitani Y. Accelerated blood clearance was not induced for a gadolinium-containing PEG-poly (L-lysine)-based polymeric micelle in mice. Pharmaceutical research. 2010;27(2):296-302.
65. Kierstead PH, Okochi H, Venditto VJ, Chuong TC, Kivimae S, Fréchet JM, Szoka FC. The effect of polymer backbone chemistry on the induction of the accelerated blood clearance in polymer modified liposomes. J Control Release. 2015;213:1-9.
66. Grainger SJ, El-Sayed ME.Stimuli-sensitive particles for drug delivery. Biologically-Responsive Hybrid Biomaterials. 2010:171-90.
67. Kim JH, Oh YT, Lee KS, Yun JM, Park BT, Oh KT. Development of a pH-sensitive polymer using poly (aspartic acid-graft-imidazole)-block-poly (ethylene glycol) for acidic pH targeting systems. Macromol Res. 2011;19(5):453-60.
68. Liu H, Liu M, Ma L, Chen J. Thermo-and pH-sensitive comb-type grafted poly (N, N-diethylacrylamide-co-acrylic acid) hydrogels with rapid response behaviors. EurPolym J. 2009;45(7):2060-7.
69. Lin YL, Jiang G, Birrell LK, El-Sayed ME.Degradable, pH-sensitive, membrane-destabilizing, comb-like polymers for intracellular delivery of nucleic acids.Biomaterials. 2010;31(27):7150-66.
70. Xu Q, Huang W, Jiang L, Lei Z, Li X, Deng H. KGM and PMAA based pH-sensitive interpenetrating polymer network hydrogel for controlled drug release. Carbohydr Polym. 2013;97(2):565-70.
71. Yuba E, Harada A, Sakanishi Y, Watarai S, Kono K. A liposome-based antigen delivery system using pH-sensitive fusogenic polymers for cancer immunotherapy. Biomaterials. 2013;34(12):3042-52.

72. Sakaguchi N, Kojima C, Harada A, Kono K. Preparation of pH-sensitive poly (glycidol) derivatives with varying hydrophobicities: their ability to sensitize stable liposomes to pH.Bioconjug Chem. 2008;19(5):1040-8.
73. Kim MS, Hwang SJ, Han JK, Choi EK, Park HJ, Kim JS, Lee DS. pH-Responsive PEG-Poly (β-amino ester) Block Copolymer Micelles with a Sharp Transition.Macromol Rapid Commun. 2006 Mar 24;27(6):447-51.
74. Li Z, Qiu L, Chen Q, Hao T, Qiao M, Zhao H, Zhang J, Hu H, Zhao X, Chen D, Mei L. pH-sensitive nanoparticles of poly (L-histidine)–poly (lactide-co-glycolide)–tocopheryl polyethylene glycol succinate for anti-tumor drug delivery. Actabiomaterialia. 2015;11:137-50.
75. Lipinski CA. Drug-like properties and the causes of poor solubility and poor permeability.Journal of pharmacological and toxicological methods. 2000;44(1):235-49.
76. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Advanced drug delivery reviews. 1997;23(1-3):3-25.
77. Brannon-Peppas L, Blanchette JO. Nanoparticle and targeted systems for cancer therapy. Advanced drug delivery reviews. 2012;64:206-12.
78. Duncan R. The dawning era of polymer therapeutics. Nature reviews Drug discovery. 2003;2(5):347-60.
79. Kim JH, Kim YS, Kim S, Park JH, Kim K, Choi K, Chung H, Jeong SY, Park RW, Kim IS, Kwon IC. Hydrophobically modified glycol chitosan nanoparticles as carriers for paclitaxel.Journal of controlled release. 2006;111(1):228-34.
80. Brown R, Links M. Clinical relevance of the molecular mechanisms of resistance to anti-cancer drugs. Expert reviews in molecular medicine. 1999;1(15):1-21.
81. Brigger I, Dubernet C, Couvreur P. Nanoparticles in cancer therapy and diagnosis. Advanced drug delivery reviews. 2002;54(5):631-51.
82. Krishna R, Mayer LD. Multidrug resistance (MDR) in cancer: mechanisms, reversal using modulators of MDR and the role of MDR modulators in influencing the pharmacokinetics of anticancer drugs. European Journal of Pharmaceutical Sciences. 2000;11(4):265-83.
83. Gutowska A, Bark JS, Kwon IC, Bae YH, Cha Y, Kim SW. Squeezing hydrogels for controlled oral drug delivery. Journal of Controlled Release. 1997;48(2):141-8.
84. Sonaje K, Chen YJ, Chen HL, Wey SP, Juang JH, Nguyen HN, Hsu CW, Lin KJ, Sung HW. Enteric-coated capsules filled with freeze-dried chitosan/poly (γ-glutamic acid) nanoparticles for oral insulin delivery. Biomaterials. 2010;31(12):3384-94.
85. Carelli V, Coltelli S, Di Colo G, Nannipieri E, Serafini MF. Silicone microspheres for pH-controlled gastrointestinal drug delivery.International journal of pharmaceutics. 1999;179(1):73-83.
86. Ashley CE, Carnes EC, Phillips GK, Padilla D, Durfee PN, Brown PA, Hanna TN, Liu J, Phillips B, Carter MB, Carroll NJ. The targeted delivery of multicomponent cargos to cancer cells by nanoporous particle-supported lipid bilayers. Nature materials. 2011;10(5):389-97.
87. Wu X, Wang Z, Zhu D, Zong S, Yang L, Zhong Y, Cui Y. pH and thermo dual-stimuli-responsive drug carrier based on mesoporous silica nanoparticles encapsulated in a copolymer–lipid bilayer. ACS applied materials & interfaces. 2013;5(21):10895-903.
88. Torchilin VP. Multifunctional, stimuli-sensitive nanoparticulate systems for drug delivery. Nature reviews Drug discovery. 2014;13(11):813-27.
89. Zhou T, Zhao X, Liu L, Liu P. Preparation of biodegradable PEGylated pH/reduction dual-stimuli responsive nanohydrogels for controlled release of an anti-cancer drug. Nanoscale. 2015;7(28):12051-60.
90. Li Z, Xu W, Wang Y, Shah BR, Zhang C, Chen Y, Li Y, Li B. Quantum dots loaded nanogels for low cytotoxicity, pH-sensitive fluorescence, cell imaging and drug delivery. Carbohydrate polymers. 2015;121:477-85.
91. Hsieh CJ, Chen YC, Hsieh PY, Liu SR, Wu SP, Hsieh YZ, Hsu HY. Graphene oxide based nanocarrier combined with a pH-sensitive tracer: a vehicle for concurrent pH sensing and pH-responsive oligonucleotide delivery. ACS applied materials & interfaces. 2015;7(21):11467-75.
92. Treiber C, Quadir MA, Voigt P, Radowski M, Xu S, Munter LM, Bayer TA, Schaefer M, Haag R, Multhaup G. Cellular copper import by nanocarrier systems, intracellular availability, and effects on amyloid β peptide secretion. Biochemistry. 2009;48(20):4273-84.

93. Tang C, Amin D, Messersmith PB, Anthony JE, Prud'homme RK. Polymer directed self-assembly of pH-responsive antioxidant nanoparticles. Langmuir. 2015;31(12):3612-20.
94. Wang Y, Chen L, Tan L, Zhao Q, Luo F, Wei Y, Qian Z. PEG–PCL based micelle hydrogels as oral docetaxel delivery systems for breast cancer therapy. Biomaterials. 2014;35(25):6972-85.
95. Koetting MC, Peppas NA. pH-Responsive poly (itaconic acid-co-N-vinylpyrrolidone) hydrogels with reduced ionic strength loading solutions offer improved oral delivery potential for high isoelectric point-exhibiting therapeutic proteins. International journal of pharmaceutics. 2014;471(1):83-91.
96. Gogoi N, Chowdhury D. Novel carbon dot coated alginate beads with superior stability, swelling and pH responsive drug delivery. Journal of Materials Chemistry B. 2014;2(26):4089-99.
97. Yu H, Xu Z, Chen X, Xu L, Yin Q, Zhang Z, Li Y. Reversal of lung cancer multidrug resistance by pH-responsive micelleplexes mediating co-delivery of siRNA and paclitaxel. Macromolecular bioscience. 2014;14(1):100-9.
98. Ju Y, Cui J, Müllner M, Suma T, Hu M, Caruso F. Engineering low-fouling and pH-degradable capsules through the assembly of metal-phenolic networks. Biomacromolecules. 2015;16(3):807-14.
99. Tu F, Lee D. Shape-changing and amphiphilicity-reversing Janus particles with pH-responsive surfactant properties. J Am Chem Soc. 2014;136(28):9999-10006.

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