The pH Role in Nanotechnology, Electrochemistry, and Nano-Drug Delivery

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ABSTRACT: *Most chemical and biological processes are affected by pH. Also, different physiology organs and subcellular partitions could be characterized by their pH levels, as well as their pathophysiological characterization. Sometimes the pH has an extremely critical role in some procedures that the entire research or article focused on pH effect for example the pH was found to play a crucial role, pH has a high effect on different parts of nanotechnology such as shape, size, stability, activity, and morphology of nanostructure materials. Also, several nanochannels and smart doors are developed based on pH changes. In electrochemistry, pH has brilliant roles in oxidation/reduction potential land sensitivity of peak. In the biosensing process, the pH could affect the interaction of the analyte and biorecognition layer by different force and strategies, in some chemical and biochemical reaction and H^+ has a catalytic effect, therefore, pH act as a catalyst in several chemical and biological processes. Therefore, finding the best pH for the optimum speed of these processes is critical, especially in biological processes. Electron and proton transfer are rather strongly coupled in many biological processes, also in the separation process for cleaning or measuring process. It is best to check the role of pH in the adsorption and release steps. Usually, it is necessary to find the optimum pH in the first step of the study before optimizing the other parameters.*

KEYWORDS: *pH; Nanotechnology; Electrochemistry; Extraction; Nano-drug delivery.*

INTRODUCTION

pH, hydrogen ion potential, is very critical in all fields of life, it is used for all processes from food preparation to the maintenance of the body, and also for industrial purposes, for example, determining the value of drinking water. All water-based biological or chemical systems depend on aqueous acid-base equilibrium; could be affected by pH changes. The body cans only lever confident pH ranks and everything below or above that, elevation could be toxic [1,2]. pH has an important effect on body organisms especially the metabolism of the test organism. Hydrogen (H+) ions (or protons) are the smallest yet debatably the most responsive ions in living organisms. All biological solutions take a certain concentration of H+ ions ascending between deprotonation and protonation reactions of weak acids and weak bases in water. Changes in the pH of the medium affect the activity of enzymes in organisms. Unusual pH associations are to be predictable if the chemical structure of the reacting molecule changes with pH.[1,3].

The effect of pH on chemical and biological activity is related to the pK of chemical compounds. At pH levels below pK change in pH has no influence on activity; but,

as the pH is raised above pK, activity decreases rapidly; i.e. higher concentrations are needed to produce a standard response. The concentration of undissociated molecules remains constant below pK, shows a slight rise around pK, and decreases at higher pH levels. Different types of proton transfer occur in biological systems and electron and proton transfer are rather strongly coupled in many biological processes. The sensitivity of proteins to pH has an exceptional bearing on cells because proteins act as pH buffers, and their function can change substantially if the ionization state is altered by the binding or release of H+ ions (a form of post-translational modification) [4].

When blood pH escapes microbes in the blood become pathogenic, oxygen delivery will damage, protein structure will destruct, some organs such brain and heart befall accord this condition, a mineral merger can be inconsecutive, and all biochemical reactions in the body will be affected. pH will affect the electrical properties of the material. The electrical resistance of solution and substances will increase in higher pH value. Almost in biological, chemical, and nanotechnology research, the effect of pH on the procedure should be checked. For example, pH could affect the size, shape, stability, and activity of materials, especially nanomaterials. Occasionally the pH has an extremely critical role in some procedures that the entire research or article focused on pH effect, for example, pH was found to play a crucial role in the monodispersity of the nanorods. ,2 Similarly pH plays an important role in nanotechnology especially nanoparticle size, behavior, and half-lives Especially in drug delivery application of nanomaterial, pH, and temperature should be quantified in human body fluids condition [5,6]

For these reasons, it is concluded that although the pH of molecules and solutions is an important factor in determining the activity of chemical and biological processes and mediums, therefore in this review, we briefly have described the effect of pH in nanotechnology, electrochemistry, and nano drug delivery.

THE WORD OF pH

Almost pH has a significant role in all branches of science. Several processes of biology, chemistry, physic, geology, agriculture, and nanotechnology are affected by pH value. Here, we are trying to mention the effect of pH in a small part of science such as nanotechnology, chemistry, and drug delivery.

pH in nanotechnology

pH plays an important role in ambient conditions and nanoparticle size. The pH acting an important role in the biosynthesis of nanoparticles, especially metal nanoparticles. As pH and temperature of the medium are key parameters influencing the dissolution of metals assessed using in vitro assays The pH will possibly change the production output of nanoparticles by affecting the availability of functional groups related to reducing agents [6]

In the nanoparticle synthesis process, usually at high pH, the reduction rate is high. At low pH (below 5) as an alternative to reduction-oxidation will occur. At a very high pH (above 9, 10) reduction rate will be too high resulting in the aggregation of nanoparticles [6]. All nanomaterial and bulk analogs displayed significantly higher solubility at low pH than at neutral pH. In the context of classification and read-across approaches, the pH of the dissolution medium was the key parameter. The main insinuation is that pH and temperature should be specified in solubility testing when evaluating anomaterial dissolution in human body fluids.

The size of the nanoparticles

pH in the synthesis process has a key role to obtain the certain particle size of nanomaterials. Several studies were performed about the effect of pH in the preparation of nanomaterials. Hou's research group synthesized PEG-lipid-PLA hybrid nanoparticles for drug delivery purposes they used phosphate buffers with different pH. They found the size of nanoparticles increased as pH decreased from 7.4 to 5.5 [5,7].

Rochman's group studied the effect of pH on the purity and particle size of ZnO nanoparticles. They used the Sol-Gel method for the synthesized process. By decreasing pH value from 12 to 7 the size decreased from 74 to 1.3 nm. Similarly, by increasing the pH from 7 to 12, the purity will be increased from 43% to 100%. [8]. Also, the changing of pH could alter the surface charge of nanomaterials and affect their stability and aggregation of them thus pH could affect the size of nanoparticles such as TiO_2.

pH and stability and aggregation of nanoparticles

Newly many efforts have been made to progress techniques for the preparation of mono-dispersed colloidal uniform nanoparticles in shape and size. Different methods
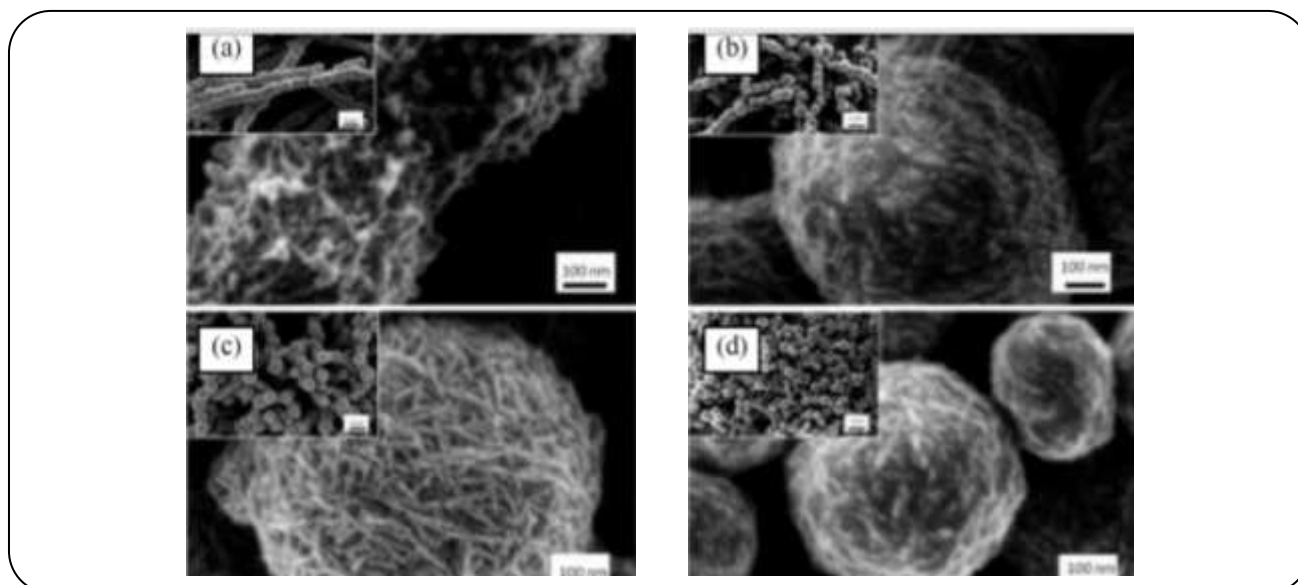
Fig. 1: Synthesis Ni chain-like nanostructure particles (a, b) and ball wool-like nanostructure composed (c, d) by changing the pH from 6 to 12 by changing OH⁻/Ni⁺ ratio 4 (a) b (8), 10 (d), and 20 (d).(Open access, Permitted by author) [11].

are used for this purpose chemical synthesis, and laser ablation, but in all methods, some parameters such as temperature, pH, assistant organic material, and solution composition must be optimized. Many characterizations of the nanomaterial including shape, size, phase composition, morphology, and aggregation ability will be under influence of pH value. [9]

pH was affected by the size of nano-TiO_2 nanoparticles in presence of surfactants such as CMC, Triton X-100. *Darnault* and *Godinez* found that aggregation is dependent on the point of zero charge and the presence of surfactant. [9] Faiyas's research group studied the dependence on pH on the synthesis of Fe_3O_4 nanoparticles. Results show that pH has a major role in the phase formation of Fe_3O_4 nanoparticles. In higher pH, the smaller size of the nanoparticle and c-Fe_3O_4 phase will be synthesized and in pH 6 and 9, the chemical phase of nanoparticles will be ε-Fe_2O_3 [10].

In 2013, *Roselina* and *coworkers* investigated the synthesis of nickel nanostructures by the reduction method in different pHs. They found by changing the pH from 6 to 12 resulted in the formation of Ni wool-like nanostructure composed of chain-like nanostructure particles [11]

The effect of OH⁻/Ni^{2+} molar ratio on as-synthesized nanoparticles was investigated to study the effect of OH⁻/Ni^{2+} molar ratio on the particle size distribution and morphology were investigated. SEM results of as-synthesized nanoparticles at ratios of 4 (P4), 8(P8), 10(P10) and 20(P20) are shown in Fig. 1(a-d). It was found that nanoparticles will be possessing ball wool-like

by piling together for P8, P10, and P20, not for P4.

pH could affect the shape of nanoparticles. Roselina's research group investigated the effect of pH on the formation of Nickel Nanostructures, in this study changing the pH from 6 to 12 following pattern changing was resulted in Ni wool-like nanostructure composed of chain-like nanostructure particles [11]

Manhabosco and *coworkers* studied pH effect on Electro-polymerized polyaniline films with TiO_2 nanoparticles. Several pHs (1.5, 3.9, and 5.9) were studied in this study. The nanoparticles have no significant effect on film properties, at pH 1.5, However, at low pH (pH1.5) H atoms have a tendency to bind TiO_2 nanoparticle surface that gives a positive charge to surface nanoparticles and a layer of SO_4^{-2}anion will be absorbed on the nanoparticle surface. This layer prevents physical contact between nanoparticles and polyaniline monomers.

The pH has a very important effect on the nanoparticles on optical and electrical properties of the prepared films. In acid environments (pH 1.5), H⁺ ions tend to bind TiO_2 surface and make a positively charged surface that could electrostatically absorb the SO_4^{-2} anions that are present in the solution. In this case, highly acidic conditions, there is no effect on the film, are observed. At fewer acid environments (pH 3.9 and 5.9) the TiO_2 surface is partially covered by anions, which allow electrons to transfer. The interaction between the film and TiO_2 nanoparticles was observed [12].
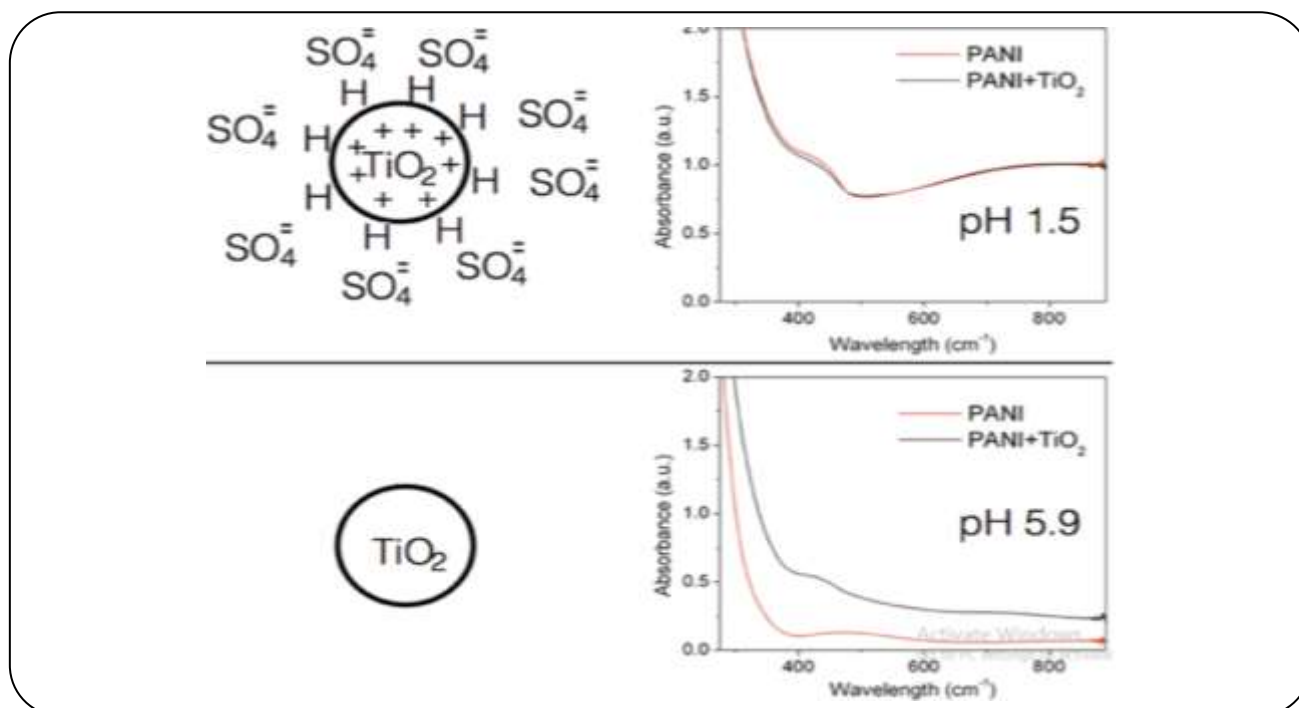
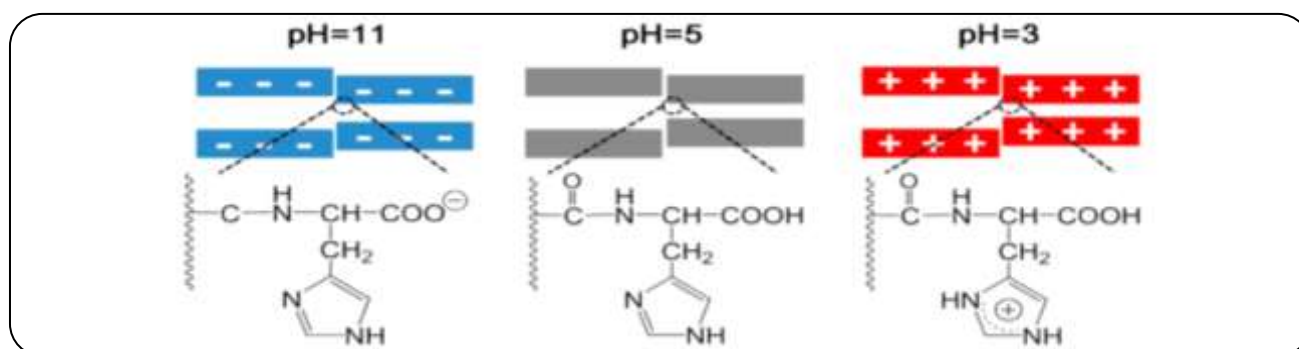*Fig. 2: The surface charge of TiO₂ nanoparticles in ph 1.5 and 5.9(permitted by ACS publication)[12].*

Fig. 3: Surface Charge on the bichannel modified histidine from pH 11 to 3, where the charge of histidine changes
from negative to electroneutral and after that to positive [16] (permitted by ACS publication).

Smart nano-doors

Effect of pH on nanochannels

Various types of nanochannel based on pH were developed [13,14]. pH value could perform as a mobility force for drug or biological markers throwing bichannels or nanochannels. *Arki*'s group prepared an electrokinetic sensor based on Nano/microfluidic channels [15].

Zhai's group has studied the effect of pH-dependent transport within two symmetric-structured nanochannels. They used two poly(ethylene terephthalate) (PET) films with nanochannel arrays varying in surface charge and size that it has pH-dependent tunability. This group reported pH effect on ion transport within two nanochannels. pH-dependent degree of rectification and tunability could be superior by histidine modification. The ion current rectification and the pH-dependent tunability are credited to the effect of the mobile ions and the half-channels [16].

Vancso's group designed a pH-responsive behavior from the nanoporous platforms. They prepared nanoporous silicon nitride films using particle lithography. Then they functionalized pH-responsive poly (methacrylic acid) (PMAA). The polymer will be an as smart door for nanoporous platforms. At pH 4, nanoporous is open and will be closed at pH 8 [17].

Witoon's group studied pH effect on CuO-ZnO nanocomposite. The crystallite size will decrease with

increasing the pH [18]. In 2015 a study was done on the effect of pH on CeO_2 nanoparticle dissolution. In this research, Arai's group found the dissolution of CeO_2 nanoparticles will decrease by increasing the pH, and also phosphate ligands lessen the release of Ce using chemisorption [19]. Scheme 2. The charge changing on the surface bichannel that is modified by histidine changing pH from 11 to 3, where the immobilized histidine changes from negative to positive form.

The ratio between the forward current and the reverse current (under 1 V) of the entire bichannel decreased from 1.89 to 0.88, from pH 11 to 3. These showed that the bichannels with ion current rectification could be reached, by organizing two columnar nanochannel arrays with different pore sizes in the device. It is worth noting that the unmodified biochannels with different pore: a nanofluid diode under basic conditions and a normal nanochannel under neutral and acidic conditions had two pH-dependent states that have no current rectification reversal.

An hourglass-shaped Al_2O_3 nanochannel was introduced by *Fan* and *coworkers*. This nanochannel has pH and light-responsive properties and could be used as an intelligent biological membrane. The behavior of nanochannels was investigated in pH 4-9. At pH 6 the channels have the highest ionic conductivity [20]. *Hsu's* group developed a Nanofluidic channel for separation based on a concentration gradient [21].

pH in chemistry

Key requirements for process chemistry are process control, analysis, and data Variations in parameters such as temperature, pressure, rate of addition, pH, etc. can have a dramatic effect on the quality of a chemical process. Being able to control and data log variables such as these and analyze other parameters such as turbidity, reaction power, enthalpy change, etc. is extremely valuable to understanding a chemical process. Syrris products are designed and built specifically for process chemists and process engineers, with these requirements in mind. For an excellent control procedure, the mixing of parameters such as temperature, and pressure reaction time should be optimized [19].

The major advantages of the selection of the best pH are faster reactions, cleaner products, safer reactions, quick reaction optimization, easy scale-up, and the integration of typically separate processes (such as synthesis, work-up, and analysis)

Some parameters such as driving force, electrolyte type, the distance of donor and acceptor, and pH have a very important role in the rate of hole and electron transfer across the electrode surface.

pH & electrochemistry

The pH was found to bring important changes in the potentiodynamic behavior of some analytes on the electrode surface. Electron transfer via a film to an electron surface is dependent on the energy difference between the donor-acceptor orbitals. The redox mechanism is likely occurring via a hole superexchange mechanism [21]. Forster's group used high-speed chronoamperometry to investigate the pH dependence of heterogeneous electron transfer rate across the electrode fluorine-doped tin oxide/monolayer interface.

In 1998, Lazarescua and Clavilier studied pH effects on the potentiodynamic behavior of the Pt(111) electrode in $NaClO_4$ acidic solutions. They found that the surface H^+ discharge step will have disappeared in some pH in the high potential region. The pH dependence of the peak A-2 is a more faradaic process. The pH in the electrode surface will decrease by the H^+ diffusion from the bulk at lower scans and this diffusion is very important in the potentiodynamic behavior observed. Results showed the cyclic voltammograms (v=40 mV/s) of Pt(111) electrode in 0.1 M $NaClO_4$ solutions are different for pH values. Lower pH values were more sensitive to analytical reasons, a potential range [22].

pH effect on the electrochemical redox reaction of disulfide was investigated by Chung and coworkers. The effect of pH on the electrochemistry behavior of poly(neutral films)was done by Bento and coworkers. Benito found that pH has an important role in the behavior of film [23].

Dodelet's research group reported on pH effect on the oxygen reduction activity of Fe/N/C-catalysts, and electro-catalysts. The oxygen reduction reaction activities of both are Pt/C activity is four times lower at pH 13 than at pH 1. The activity Fe/N/C- catalyst is 7- 10 times higher at pH 13 than at pH 1 while an activity of 46%. Each electrode was tested at different pH by cyclic voltammetry of O_2-saturated solution at 10 mV/s [1].

Prakash in 2001 studied pH effect on the electrochemistry of polyaniline. Pt, Ni, Ti, and SnO_2-coated glass electrodes were used as working electrodes for deposition and
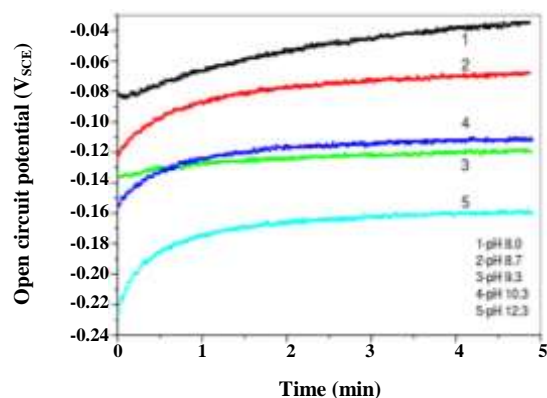
Fig. 4: The open circular potential for Cu electrode in different pHs in borax buffer [25]. (open access, permitted by author).

for recording the behavior of polyaniline. At various pHs, cyclic voltammetry studies were performed of polyaniline film derived electrochemically over a Pt electrode. The various experimental parameters, such as pH, temperature, and aniline concentration were studied. The pH was one of the most effective parameters on the electrochemical properties of polyaniline. Redox peaks are due to benzoquinone/hydroquinone pair in the acid electrolyte. The three oxidation/reduction peaks of polyaniline film were merged with all the acidic media, not including H_2SO_4, it is because of the higher pH of the electrolyte. In a lower potential redox peak, a reversible reaction of aniline radical cations can achieve [24].

In another research, Antonijevic's group studied the influence of pH on the electrochemical behavior of copper. The open circuit potential of more negative [25].

Rusling and coworkers investigate pH effect on the electrochemistry of myoglobin. The reduction potential of Heme protein myoglobin (MbFe(III)-H_2O) shifts to a negative amount by increasing the pH from 5 to 8 increases. At high pH (MbFe(III)-H_2O) changes to (MbFe(III)-OH) that could reduce at the electrode surface faster than the first form [25].

The influence of pH on the corrosion and electrochemical behavior of AZ91D magnesium alloy was studied by Ambat and coworkers. The rate of corrosion is very high in a highly acidic condition relative to neutral and alkaline pH. AZ91 microstructure consisting of b phase, eutectic a, and primary a, and change in morphology of these phases resulting from the processing route could behave differently under varying pH conditions and chloride concentration [26].

In 2015, *Liang* group studied pH effect of the electrochemical reduction reaction of oxygen on nitrogen-doped carbon catalyst by using a rotating ring-disk electrode and cathodic stripping voltammetry. The electrochemical behavior was investigated in different pHs electrolyte solutions. The CV result has shown that there are a variety of reversible redox couples on the surface, and the pH has a significant outcome. Fig. 6 shows the corresponding polarization curves of the ORR at the three pHs. It is seen that increasing the KOH concentration has some effects on the electrochemical signal: first, increasing the KOH concentration. Second, the generation of hydrogen peroxide at a lower potential. Finally, both the KOH concentration and the electrode potential have an influence on the hydrogen peroxide yield, and when the KOH concentration increases from 0.010 to 1.0 M the electron transfer number decreases from 4 to 3.3 [27].

pH & DNA biosensor

Ulianas and *co-workers* checked pH influence on hybridization DNA biosensors, The pH effect on the micro biosensor response as specified by the hybridization current with complementary DNA in Na-phosphate buffer solution. *Heng* and *coworkers* studied the pH effect on DNA hybridization response of the biosensor. The response of DNA micro biosensor was studied in varying pH from pH 6.0–8.5. At last pH 7.5 was selected [28].

pH has a critical role in the chemical bonding of amino-modified single strands on carboxylic acid–the modified surface of the electrode for electrochemical measurements. pH 5.5 is best for this goal [29]

pH roles in extraction and analytical process

pH has a critical role in the extraction and microextraction process, especially for the extraction of acidic or basic and ionic compounds. The ionic compounds are hydrophilic species that prefer aqueous media to organic solvent, but by removing the charge from the chemical compound, it could transfer to organic media. Especially in three-phrase liquid micro-extraction, pH plays a very important role to extract a compound from an aqueous phase to another aqueous media by using an intermediate organic layer. The running force in this procedure is pH.

pH, greatly affected arsenic speciation and solubility in polluted soil. Outcomes generated identified soil redox-pH conditions, this can be clarified by the pH-dependent

adsorption characteristics of As(V) onto the oxide surfaces. pH 6-8 were suitable for absorption of As(V) onto iron oxide/activated carbon magnetic composite [30].

Removal of Cr (VI) from wastewater was done by Padmavathy and co-workers. There are two oxidation states for ChromiumIII and VI. Cr (III) is not hazardous in low concentrations, but Cr(VI) is hazardous in low and high concentrations. The Optimum pH was 3.0 for the adsorption of Hexavalent chromium (Cr (VI)) on Magnetite nanoparticles from synthetically prepared wastewater [31].

Li's group studied the absorption of tetracycline on magnetic resin, and they found pH 5-6 was best for tetracycline absorption and pH 12 was good for the release of it and regeneration of magnetic microspheres [32].

Absorption of phosphate ions on mesoporous spheres was done by Braga's research group. These particles contained ion/aluminum oxide. They checked the effect of pH on the kinetic and equilibrium of the absorption process. The optimum pH was 7.0 at 30∘C [33].

Shi and *coworkers* investigated pH effect of Uranium (VI) adsorption onto graphene oxide nanosheets [34].

Silica modified with 2,6-diacetylpyridine-monosalicyloylhydrazoneas a sorbent for extraction of molybdenum ions. In this study, pH had the most important role in the absorption of ions because there are different forms of oxo-anionic in different pH. The maximum adsorption of molybdenum was in pH 5-6 [35]. Chen's group studied the effect of Zn^{2+} ions on the kinetic and equilibrium of removal of arsenic by adsorption to magnetic nanoparticles in pH 4.5-8.0. pH 8.0 was the best for their purpose. Chen's group studied pH effect on zinc and arsenic adsorption on magnetic particles for extraction purposes [36].

pH in biology

All living parts are water-based systems that depend heavily on aqueous equilibrium, especially acid-base equilibrium. The physiology process of humans and animal needs special pH. changing the body in large amounts can cause a dangerous situation or maybe death. Therefore, the role of pH in living creations is more critical than the above-mentioned branch of science [37,39]

pH and drug delivery

Nano drug and nano-based therapeutics and diagnostics strategies, and the potential use of nanomedicines in therapy and drug delivery are discussed in a good deal of research in recent years. Nano-drug systems have been used to improve the ability, safety, and physicochemical properties. Cell entry is a critical step for taking effect of the targeted nano-drug and pH can help the nano-drug enter the cell. Nano-drug systems provide maximized pharmacological belongings and minimized side effects, perhaps leading to better clinical outcomes. Biological fluids and tissues can regulate and adapt to a particular pH distribution through different ways of interaction between pH and proteins. Therefore nano drugs must be matched with the Biological fluid and tissues pH and conditions[40]. pH of biosmart nano drugs that could vary the size, charge, and other characteristics at the correct time and can help the accurate drug release. Also, Carrier-free nano drugs refer to those nano-sized self-delivery drugs that are made up of some active agents without or with the lowest use of inert compounds[41].

Targeting drug delivery is essential to raise the drug's effectiveness and reduce the side effect. To achieve this usually purpose physicochemical changes are using for drug release at the target tissue. These external varying are included (i) *physical* signals such as temperature, magnetic field, electric field, and ultrasound; and (ii) *chemical* signals such as pH, redox potential, ionic strength, and enzymatic actions. Nanoparticle (NP) systems that contain liposomes, polyplexes, lipoplexes, and polymeric micelles have been industrialized to use these physical and chemical cues to modify drug release properties. [42]

Nanocarriers such as self-assembled nanoarchitecture, liposomes, micelles [42,43], polymeric [44], lipoplexes, polyplexes, and inorganic nano-frames are usually used for drug delivery purposes [45]. The nanocarriers could be applied in different ways such as gastrointestinal systems (oral and rectal), injection (intravenous, intramuscular, and Intra-arterial injection), transmucosal, transnasal, pulmonary (inhalation), transdermal, intra-osseous.

Classification of carriers for drug delivery could be as: *polymeric* drug delivery, *nanocluster* drug delivery, *nanoparticle* drug delivery, *micelles* drug delivery

Polymeric-based drug delivery

Several types of polymer were used for drug delivery purposes [46-48]. Polymeric-based carriers currently available could be classified into four different categories: chemically controlled solvent-activated, diffusion-controlled, and magnetically controlled methods.
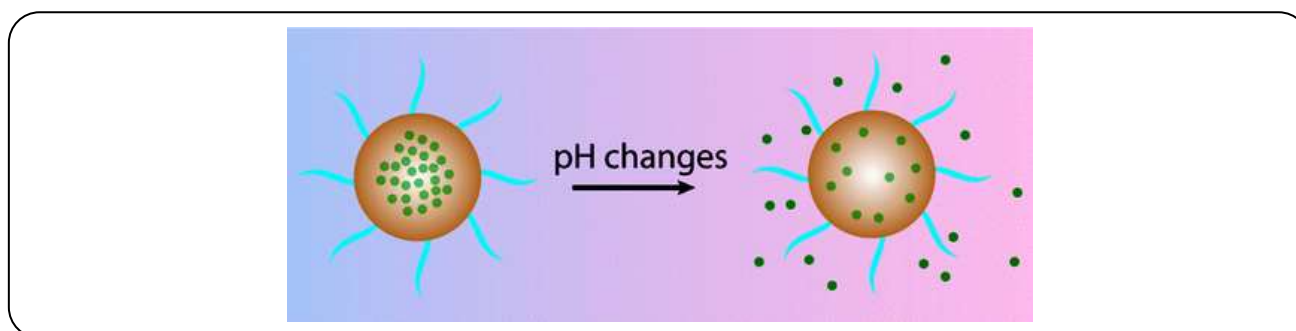
Fig. 5: Nanoparticle-based material for drug delivery that responds to pH gradients within the microenvironments of cell organelles and tissues [51] (permitted by ACS publication).

The PDMAEMA is particularly motivating because it shows both temperature and pH-responsive behavior. The pH-responsive copolymers containing polybasic blocks, with pK_a of 7.0–7.5, such as the tertiary amine-based methacrylate polymers, PDMAEMA [49].

Drug Modification/Protection

Pumps (drug delivery strategy): One can envision that if the drug is in solution it would be very suitable to pump it into the body through a thin tube. This is in fact the technique of choice in hospitals, and presently there are sophisticated syringe pumps, which are accessible to be automatic to pump a drug solution through an intravenous line. This, however, requires that the recipient is under constant supervision by trained personnel, and also that the protective barrier of the skin is broken to allow the addition of a spine.

1- Bottom-up strategy provides a simple and feasible way.

2- The precipitation approach as another route is developed to adapt hydrophobic pure drugs into nano-objects. During the precipitation procedure, the free drug is primarily dissolved with a spot of a suitable solvent, which is then injected into an aqueous solution to determine pre-liquefied drug molecules to self-collective into nano drugs, leaving part of the hydrophilic part unprotected to the aqueous environment. The negligible organic solvent can be removed through dialysis or reserved in the bulk solution.

Drug delivery has been studied from a human condition perspective to expand the efficient delivery of drugs to target sites in the body [50]. pH-responsive drug delivery systems are very useful for cancer drug delivery. Human tumors have an acidic pH situation. The acidity of tumor environments is caused by a lactic acid increase in rapidly growing tumor cells. Cancer cell increases rates of glucose uptake and high lactate production. Therefore, researchers tried to formulate modified nanoparticles and nanopolymers that have pH-dependent changes in their physical and chemical properties, based on local pH levels. Some nanoparticle-based materials that respond to pH gradients within the microenvironments of cell organelles and tissues, maybe useful as vehicles available for diagnostic and therapeutic drug delivery purposes [51].

Every part of the gastrointestinal (GI) tract has pH level, from the acidic stomach lumen (pH 1-3) for absorption,12 to the alkaline duodenum and ileum (pH 6.6-7.5).

Vast research has been done on synthesized nanomedicines that incorporated pH-responsive mechanisms for systemic exposure by means of cellular targeting, transepithelial transport, greater gastric retention, and with a functionalized surface [51].

pH of the gastrointestinal region has a very critical role in the absorption of oral drugs and their bioavailability. *Abuhelwa et al*. reviewed the food and gastrointestinal pH on modeled oral drug absorption. pH has a brilliant influence on drug solubility, stability, release rate, absorption, bioavailability, and intestinal permeability in oral rectal. Completed knowledge about this topic will help scientists with better formulation for better absorption performance and oral bioavailability of drugs. Weakly basic drugs solubility and absorption will increase the acidic pH of the stomach. For weakly acidic drugs (pH 2.95_6.5), dissolution in the stomach will not be very good. But in the presence of drugs that evaluate the stomach pH the solubility of the weakly acidic drug could increase [51].

The hydrophobic-to-hydrophilic interaction also may be used to control polymer dissolution. Sometimes

the polymer matrix collapses, used for drug release purposes. *Wu et al.* used PEG-poly(-amino ester) for drug delivery purpose. Polymer solubility increased at pH 6.4-6.8 and induced a high-pitched micellization-demicellization change for drug release. *Criscione et al.* used dendrimers as dug delivery based on pH strategy. They showed that self-assembly of poly (amidoamine) dendrimers will occur at physiological pH, and drug release from NP will take place at pH <6.44. In addition, acrylic-based polymers such as poly(methacrylic acid) (PMAA copolymers that contain other components such as polyethylacrylate (PMAA-PEA) and polymethacrylate (PMAA-PMA) show pH-dependent dissolution that may be tailored to reply to the pH of different intestinal regions. 24 For example assay and confocal laser scanning microscopy showed that the HAP@Alg were effectively uptake by liver cancer cells (HepG2) without apparent cytotoxicity

Collagen microparticles have been tested as a carrier arrangement for glucocorticoids, namely hydrocortisone. It was found that the relief performance of this drug was not influenced by the pH of the surrounding medium [49].

He's group developed intracellular pH-Sensitive Metallo-supramolecular nano gels for Anticancer drug delivery. They used the metallo-supramolecular coordinated interaction between histidine and iron-meso-tetraphenylporphin., for capacity and release doxorubicin (DOX). DOX is an anticancer drug with excellent biocompatibility and special supramolecular pH sensitivity. DOX was loaded at pH 7.4 and will be quickly at pH 5.3 [52].

Wang and *coworkers* reported PEG-coated polymeric lipid vesicles. They used amphiphilic dextran derivatives for the construction of this devise and doxorubicin (DOX) antitumor drug was loaded in it at pH 7.4.and released in pH 5.0 solution had higher antitumor activity than DOX-loaded PPLVs treated with pH 7.4 solution. [53].

Nanoparticle-based drug delivery:

The multifunctional nano drugs containing influential drugs, photosensitizers, and targeting agents for inclusive cancer diagnosis and therapy, display preferable antitumor effects. It can also notably help with early cancer detection and better therapeutic plans [41].

Cui and coworkers used mesoporous silica nanoparticles encapsulated in a copolymer−lipid bilayer as drug carriers based on pH and thermo response

These carriers could carry doxorubicin into the cells and as most tumor sites usually exhibit, a more acidic environment or a higher temperature drug can be released at the tumor region [54].

Poly(lactic-co-glycolic acid) hydroxypropyl methylcellulose phthalate nanoparticles were used by *Guo*'s group for drug delivery purposes. Poly(lactic-co-glycolic acid is a hydrophobic polymer and hydroxypropyl methylcellulose phthalate group is a pH-sensitive part of the nanoparticle. For stabilizing the nanoparticle, a hydrophilic polymer such as polyvinyl alcohol was adsorbed on the other surface of the nanoparticles. In studies conducted by Hou's group, a dual-controlled drug delivery release was performed by using PEG-lipid-PLA hybrid nanoparticles for delivery of Mitomycin C- soybean phosphates to choline complex as an anticancer drug. With this nanoparticle, there are two phases for drug delivery. The drug-phospholipid conjugate is responsible to early-phase drug release and the polymer-lipid hybrids nanoparticle, as a pH-sensitive group, is responsible for late-phase controlled drug release. In this method, the drug release at pH 5.5 is about 85% after 120 h, but at pH 7.4, it is about 60%.

Sathiyaseelan and *coworkers* used pH-controlled nucleolin targeted release of dual drug from chitosan-gold founded aptamer functionalized nano drug delivery system for glioblastoma handling.[55] *Rostami* and coworkers developed the $ZnFe_2O_4$@mZnO–N/RGO nano-composite as a carrier for nano drugs and as an intelligent pH-sensitive drug releaser. [56].

Micelles-based drug delivery

Dextrans was used by *Chen*'s group as an efficient platform for drug delivery based on Ph Strategy, DOX was loaded at PBS pH 7.4 and was released at pH 5.5, and the efficiency of drug loading was measured by the fluorescence method at (λ_{ex} = 480 nm). About 90% of DOX was released from carrier micelles in PBS at pH 5.5 during 24 h, [57]

Micelles also have been used for drug delivery purposes by several groups. Acidic pH-sensitive have been used for cancer drug delivery. CU's group to enhance the delivery capacity of lipophilic prodrugs, stearoyl gemcitabine used micelle. This group reported PEG and lipids with an acidic pH cleavable linker [58].

Govender et.al. Reviewed hydrazine linkages. In pH-sensitive drug delivery. Hydrazine linkages are pH-sensitive due to different hydrolysis rates in different
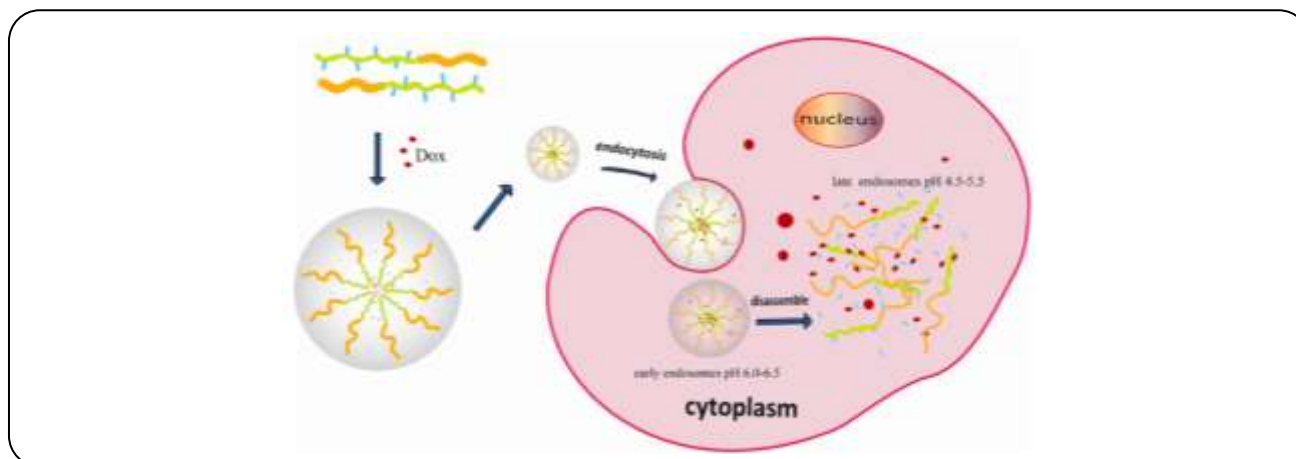
Fig. 6: Design of DOX Loading and Intracellular Microenvironment Triggered Release from DOX-Loaded PEG-b-AC-Dex Micelles [57] (permitted by ACS publication)

pH. The hydrolysis rate acidic pH is faster than neutral pH [59]. It has both electrophilic and nucleophilic characteristics. pH degradation of hydrazone by Hydrolytic breakdown in an acidic environment makes it is a suitable linker for cancer drug delivery purposes in various types such as polymer-drug conjugates, micelle, nanoparticles, and inorganic-based, liposomes [59].

pH- and the ion-sensitive polymer was developed for drug delivery purposes by Yoshita's group. They illustrated that cationic polymers, having pH sensitivity, could cover the drug taste and will release drugs in the stomach at low pH. Also, anionic polymers could be used for preventing gastric degradation of drugs and will be released in high pH intestinal [60].

In 2005, *Fischer* and *coworkers* used pH-degradable copolymer micelles for the delivery of Doxorubicin, as a hydrophilic drug, and Paclitaxel, as a hydrophobic drug. Poly (ethylene glycol) / polylactic acid copolymer was used to overcome two problems of the previous delivery problem: release from the carrier or release from in internalizing endolysosome. The copolymer changes into micelles at low pH. This micelle can disrupt lipid membranes and enhance drug delivery performance. Doxorubicin was almost complete at pH=5.5 and was about 60% at pH=7.4.[51] [61]

Hu and coworkers studied A pH-responsive multifunctional Nano-carrier in the chemo-Photodynamic therapy process. Camptothecin (CPT) phthalocyanine (PcZn) was encapsulated into the nanoparticle as an anticancer drug and as a photosensitizer respectively during the fabrication processing. The pH value influenced the PcZn fluorescence behavior and CPT release behavior of the nanoparticle [62]. *Ruan* and *coworkers*, 2021 developed micelles-based multifunctional glioma-targeted drug delivery[63]

In Table 1 some important pHs, in nanotechnology, electrochemistry, biosensors, extraction, and drug delivery, are mentioned.

CONCLUSIONS

pH has a magic role in all parts of science, chemistry, biology, nanotechnology, physics, electrochemistry, and environment, pH has an important role in kinetic or thermodynamics of several processes, some processes could be faster in some special value of pH. The effect of pH on chemical and biological activity is related to pK of chemical compounds. Some procedures would be stopped in other values of pH, Shape, charge, and size of material in particular nanomaterials, especially pH play important role in the size of nanoparticles. pH of the medium is a key parameter influencing the dissolution of metals. pH has the main effect on the extraction process and the potential of electrochemical process. The most important role of pH is in the biological process of continuing life. In all research in every branch of science, checking pH is an important step of research. Therefore, finding the optimum pH should be one of initialing steps of research. pH/biology interaction in the management of disease especially in cancer drug delivery and therapy is very important.

Table 1: List of some important pH in nanotechnology, electrochemistry, biosensors, extraction and drug delivery.

Field	Effect	Detail	Optimum pH	Ref.
Nanotechnology	Size of nanoparticle	PEG-lipid-PLA hybrid nanoparticles	7.4	[7]
		ZnO nanoparticles	7	[8]
		c-Fe$_3$O$_4$ nanoparticles	9	[9]
	Shape of nanoparticles	Ni wool-like nanostructure	6	[10]
		Ni chain-like nanostructure	12	
	Smart door (pH-responsive anoporous platforms)	nanopores is open	4	[14]
		nanopores is closed	8	
	Nanofluidic Channels	Silica-based channel	6	[20]
Electrochemistry	electrochemistry of myoglobin	myoglobin. Reduction potential	4	[26]
	Electrochemistry of polyaniline	The behavior of polyaniline.	Acidic	[24]
	oxygen reduction activity	Fe/N/C-catalysts	1	[1]
DNA Biosensor	DNA microbiosensor	DNA hybridization	7.5	[28]
	Immobilization of single strand on an electrode	By using carboimide bond	5. 5	[29]
Extraction process	arsenic speciation	Adsorption of As(V) onto the oxide surfaces.	6-8	[30]
	removal of (Cr (VI)) from wastewater	Absorption of (Cr (VI)) from wastewater by magnetite nanoparticles	3.0	[31]
	Removal of tetracycline	Absorption of tetracycline by magnetic resin	5-6	[33]
Drug delivery	Metallo-Supramolecular Nanogels	Release condition of drug	5.3	[52]
	PEG-lipid-PLA hybrid nanoparticles	Mitomycin C- soybean phosphates to choline complex as an anticancer drug.	5.5	[46]
	Dextrans	Doxorubicin anticancer drug	5.5	[53]
	Poly(ethylene glycol) / polylactic acid copolymer	Doxorubicin anticancer drug	5.5	[43]

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