PDEAS International Journal of Research in Ayurved and Allied Sciences
Volume 4 Issue 1; 28th February 2022 ISSN (online): 2583-2018

PDEAS International Journal of Research in Ayurved and Allied Sciences

Review Article

ph sensitive drug delivery systems: A critical assessment

Bhavana Sakpal[1], Shubhangi Karkhile[1], Parijat Suryawanshi[1], Vijaya Barge[3*], Amit Kasabe[2], Ashok Bhosale[3]
P. G. Scholar[1], Associate Professor[2], Professor[3]
[1]Dept. of Pharmaceutical Quality Assurance, Dept. of Pharmaceutical Chemistry[2], Dept. of Pharmaceutics[3]
[1,2,3]PDEA's Shankarrao Ursal College of Pharmaceutical Sciences and Research Centre, Kharadi, Pune, Maharashtra, India.

Article Received on: 04/12/2021 Accepted on: 10/02/2022.
***Corresponding Author:** *Dr. Vijaya Barge*, **E-mail:** vijayabarge@pdeasubpharm.edu.in

ABSTRACT:
One of the most well studied stimuli responsive drug delivery systems is pH labile. A controlled release medication delivery system known as a "pH labile" system is one that responds to a certain range of PH (pH values). They are becoming more important because they ensure that the medicine is administered at the precise moment needed to address the disease's underlying aetiology, and since the desired therapeutic result cannot be achieved with constant drug plasma concentrations. This type of drug delivery system allows medications to be distributed just within a certain pH range for administration. In the small intestine, the pH of drugs may vary from 5-7; in the stomach, it can be 1-4; and in the mouth, it can be 7 As a result, the stomach is designed in such a way that the GIT fits comfortably within. The pH variation in the gastrointestinal tract can be compensated for by introducing an adequate buffering agent in the formulation. Hypertension, Peptic ulcer, cardiovascular disease, and cancer are just a few of the illnesses for which the PSDDS system has the potential to help. In order to get the best results from therapy, patients must take their prescription at the right time each day. If a disease's symptoms change on a regular basis, the amount of medicine released should too. pH sensitive drugs' pharmacokinetics mean that when setting a dosage, it's important to account both the patient's illness status and the drug's plasma concentration change. PSDDS is a drug delivery system in which the stimuli-induced delivery system is the primary control mechanism. There are numerous issues with this DDS, but it is advantageous for pharmacological dosage forms delivery.Many aspects relate to pH labile drug delivery systems are discussed in the current review.

KEY WORDS: pH labile, Drug Delivery Systems, pH sensitive.

INTRODUCTION:
The drawbacks of standard drug formulations have been solved by controlled drug delivery systems, which are designed to administer medications at fixed rates for specified periods of time. The controlled drug delivery field has advanced significantly, but there is still a long way to go in the treatment of many clinical illnesses, such as diabetes and cardiac rhythm problems. It is necessary to provide the medication in these situations in reaction to the body's pH level. When it comes to medication delivery, it's ideal if the pharmaceuticals can be given at exact times and/or locations based on what the body requires (temporal modulation) (site-specific targeting). The regulated distribution of peptide and protein therapeutics also need further research and development in this field. A feedback mechanism known as "homeostasis" regulates the appearance in the body of various bioactive peptides that are necessary to maintain a healthy metabolic balance. Having a system that detects illness signals, assesses the degree of the signal, and then releases the correct quantity of medicine in response would be very advantageous. A feedback mechanism would be required to link the medication delivery rate to physiological demand in such a system. Environmental cues

for responsive drug release may be provided by the pH range of fluids in different segments of the gastrointestinal system. Polymers with mildly acidic or basic groups in the polymeric backbone have been studied by numerous research groups. According on the outer solution's pH and ionic composition, the charge density of polymers might vary (the solution into which the polymer is exposed). [1-3] Swelling or shrinkage of the polymer may be caused by adjusting the pH of the solution. Thus, the release rates of drugs from devices composed of these polymers will be pH-dependent. Polyacidic polymers become unswollen at low pH due to protonation and unionisation of the acidic groups. Polyacidic polymers inflate as the pH rises. As pH decreases, the ionisation of the basic groups in polybasic polymers increases. Buffer composition has an effect on the swelling characteristics of polybasic gels. (concentration and pka). Because stomach buffer acids (where swelling and release are supposed to occur) can't be regulated, it's possible that these gels won't consistently mediate pH-sensitive swelling controlled release in oral applications. However, gels may be effective as pH-triggered release mediators when exact rate control is less important. This method makes use of the GIT's pH gradient, which rises from the stomach to the colon from a pH of 5.5-6.8 in the small intestine (6.4-7.0). For pH-sensitive polymers, acrylic acid and cellulose derivatives are the most widely employed options. Polymers and their solubility in various pH settings have been combined to create delivery systems that transport medications to their intended location. Gels composed of copolymers with randomly distributed positively and negatively charged groups were shown to have more than two phases (swollen and collapsed). Electrostatic interactions, hydrogen bonding, and favourable or repulsive electrostatic interactions all play a role in polymer segment interaction in these gels. Because of this, it looks as though there are several stages, each with a different level of swelling and abrupt transitions between them. Macromolecular systems' capacity to adapt to changing external circumstances is likely reflected in the occurrence of these phases. An anionic copolymer gel containing acrylic acid and methacryl-amido propyl-trimethyl ammonium chloride has a maximum of seven phases. Poly (methacrylic acid-g-ethylene glycol) grafted membranes demonstrated pH sensitivity owing to complex formation and dissociation, as postulated by Bell and Peppas (1996). For complexed states, the proportion of uncomplexed equilibrium swelling ratios was between 40 to 90 times greater than that of complexed states. Temporarily regulated drug delivery devices were developed by Giannos et al. (1995) by connecting pH oscillators with membrane-diffusion features. A medication may be made charged or uncharged by altering the pH of a solution in relation to the pka. A pH oscillator in the donor solution may be used to provide a temporally regulated delivery profile since only the uncharged version of a medication can traverse lipophilic membranes.

pH-sensitive bioerodible polymers were initially proposed by Heller and Trescony (1979). Using an enzyme-substrate reaction, they were able to control the erosion of a pH-sensitive polymer containing a dispersed medicinal drug, as detailed in the section on enzyme-based systems. Ghandehari et al. created biodegradable hydrogels with azoaromatic moieties (1997). Rapid degradation was seen for hydrogels with decreased cross-linking density. In a process where the degradation front crept inward to the polymer's core, hydrogels with greater cross-linking densities decomposed more slowly. When pH or temperature adjustments are made, recombinant DNA technologies are employed to make artificial proteins that reversibly gel. Leucine zipper domains at the ends of the proteins are surrounded by a flexible, water-soluble polyelectrolyte segment. Coiled-coil aggregates of the terminal domains develop in near neutral aqueous solutions, causing the polyelectrolyte segment to retain solvent and inhibit chain precipitation, resulting in a three-dimensional polymer network. Increasing the pH or temperature induces dissolution of the gel and a return to the viscous behaviour typical of a polymer solution when the coiled-coil aggregates are dissociated. Bioengineering applications requiring the encapsulation or controlled release of molecules and biological organisms may benefit from the use of these hydrogels.

Advantages-

1. Reduced dosage to be given
2. Due to the reduction in side effects
3. Enhancement of medication efficacy
4. Improved adherence by the patient
5. Due to fewer dose units needed by the patient, the patient's daily expenditure is reduced.
6. Circadian cycles of physiological processes or disorders may be accommodated by a drug.
7. Drugs that target a particular organ, such as the colon, are called "targeted therapies
8. Drugs that irritate the mucosa are protected.

Disadvantages-

Synthetic pH-sensitive polymers have the drawback of being non-biodegradable. As a result, hydrogels containing non-biodegradable polymers must be eliminated from the body after usage. Even though non-biodegradability isn't a problem for oral drug delivery in some cases and a serious limitation in other cases like the development of implantable drugs, researchers have been working to develop biodegradable, pH sensitive hydrogels based on polypeptides, proteins, and polysaccharides. For the crosslinking of 1, 10-diaminodecane with dextran, 4-aminobutyric acid was used to activate it, and dextran was additionally grafted with carboxylic groups. It was found that when the pH of the modified dextran hydrogels was increased from 7.4 to 2.0, they swelled more quickly and to a greater extent. Due to a lack of enzymes in the body to digest dextran molecules, dextran hydrogels may not be completely biodegradable. Polysaccharides that are found in nature are not always biodegradable in the body. Biodegradable hydrogels were also created using synthetic polypeptides because of their more regular structure and less flexible amino acid residues. A few examples of these synthetic polypeptide hydrogels are poly(hydroxyl-L) glutamate, poly (L- or oxinithine), poly(aspartic acid), poly (Lysine), and poly-(L-glutamic acid) (Markland et al., 1999). pH-sensitive synthetic polymer hydrogels may also be affected by secondary structures of their polypeptide backbone, in addition to the usual electrostatic effects. The polypeptide's hydrophobicity and degree of ionisation may be changed to tailor the total magnitude of pH-responsive swelling. [4]

Enteric-coated systems

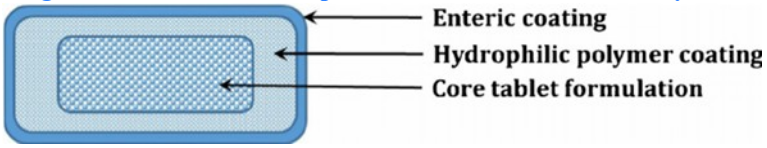
However, the efficiency of this strategy has long been debated. Enteric-coated formulations are excellent vehicles to modulate the release of active compounds such that particular target locations inside the gastrointestinal (GI) tract may be impacted. At least 261 pharmaceutical goods were the subject of a study by Kramer, who examined the usage of enteric coatings. Among the planned uses were masking of taste (9.6%) and odour (1%) as well as stability of drugs (31%), protection from local irritation (38%), and release to specific regions of the digestive system (specified segments) (51 percent). Drugs have typically been coated with enteric coatings to keep them out of the body's digestive system. Most enteric coatings protect medications that are sensitive or unstable at low pH levels. Because enzymes and proteins are quickly hydrolyzed and inactivated in acidic solution, this is especially significant for medications. In addition to being swiftly dissolved by stomach fluids, macrolide antibiotics like erythromycin are also fast degraded. Enteric-coated NSAID's like diclofenac, valproic acid, or acetylsalicylic acid are necessary to protect the stomach mucosa from local irritation. [5-7]

Functions of enteric coatings according to the statements of the pharmaceutical manufacturer.

1. Taste masking;
2. Stability;
3. Protection against local irritation;
4. Drug release in specific parts;
5. Odor masking

In the case of 5-aminosalicylic acid or the prodrugs mesalazine and sulfasalizine, enteric coating may also be used to target drugs. Enteric coating is used in these situations to raise the concentration of the medicine in the lower GI tract. As long as enteric coating has been used to accomplish modified release, it has always been questioned as to its genuine utility in protecting and delivering the coated active agents to the intended target.

Figure No. 1: Schematic representation of enteric coated system.



More than half of German enteric formulations were coated with methacrylate copolymers, roughly 40% with cellulose derivatives, 5% with shellac, and 3% with other materials, according to a market study in Germany. Various papers discuss enteric coating materials. Other polymers (e.g., to get release at a lower pH) are being investigated in addition to those described in. It is not for the protection of the gastrointestinal mucosa that polymers with lower pH dissolution are designed. As a result of the advancements in film-forming polymers, excipient technology and current coating equipment, the creation of enteric-coated formulations that meet the needs for controlled and targeted release has been substantially simplified.

Dosage forms

Generally speaking, film-coated dosage forms may be split into multiple-unit and single-unit dosages. Tablets, film-coated capsules, or other types of monolithic structures make up a single unit. There are many different types of multi-unit dosage forms, such as granule-filled packages, pellet-filled capsules, and compressed film-coated particles. It is in this second case that the whole dose is split into several units, each of which is disseminated throughout the digestive system. Aqueous dispersions or suspensions containing enteric-coated medication have recently been reported to be created. Enteric-coated Time Clock System comprises of a tablet core coated with a combination of hydrophobic and surfactant, applied as an aqueous dispersion, to the tablet surface. The Time Clock system's core releases the medicine after a specified delay. Due to the thickness of the hydrophobic layer, this lag time is not affected by GI pH. The approach for in vitro testing was shown to be a good predictor of in vivo release in investigations that included scintigraphic examinations. When an enteric coat is added to this technology to minimise issues caused by extended stomach resistance times, a higher targeted specificity may be attained. [8-11]

Types of Classification [12]

1) Polyanions/polyacids
2) Polycations/polybasis

Protonation or deprotonation may affect the dimensions of these polymers (dissolution/ precipitation, swelling/collapsing and the creation of hydrophilic and hydrophobic surfaces, as well as changes in the polymer's conformational properties) in response to a macro- or micro-change in pH. At the organ, tissue, and cell (intracellular or extracellular) levels, pH shifts may occur.

Polyanion-based pH-sensitive drug delivery systems [13]

Acid groups, such as carboxylic (COOH), sulfonic (SO3H), phosphonic (PO3H2), and phosphonic (PO3H2), are connected to the polymer backbone. These acid groups undergo protonation, which results in a unionised polymer chain at a lower pH. (less than the pKa of the polymeric network). A polymer's swelling is caused by electrostatic repulsion between negatively charged groups, which is why ionizable groups release protons when the pH is neutral or alkaline (higher than the network's pKa).

pH-sensitive drug delivery systems based on polycations-

Polycations or polybasis pSDDS are PSDDS that have basic groups like amines (NH2) in their backbone or as a pendant group. Electrostatic repulsion of positive charges causes polymers to swell under neutral or acidic pH environments. The swelling or collapsing of pSDDS as a result of pH stimuli may release drugs from polycation-based pSDDS that are suited for stomach or intracellular environments. These pSDDS are synthesised from polyvinyl amine, 2-aminoethylethyl methacrylate, and polyethyleneimine. Anti-protonation of amino groups occurs at high pH, whereas neutralisation occurs at low pH in poly (n,n dimethylamine methyl) methacrylate and poly (n, n dimethylamine methacrylate)

polymers (N,N-dimethylaminoethyl-methacrylate). For DDSs, bio-based polycations based on chitosan have undergone extensive research and development efforts. Chitosan is a naturally occurring polymer that is biocompatible, biodegradable, and less harmful.

Delivery methods for pH-sensitive drugs based on sulphonamides [14]

Because physiological pH levels do not correlate to the pKa of most classic cationic or anionic polyelectrolytes, they cannot be used in biomedicine. Changing the pKa value of current polyelectrolytes such that they can transition quickly in a short pH range is an ambitious aim as an example, the water-soluble polymers polyacrylamide (and its salt polyacrylic acid) and polysulfonamide (and its salt polysulfonamide acid) were modified by Bae et al. to provide pH-sensitive polymeric systems. The strongly electron-withdrawing sulfonyl group at basic pH is responsible for the deprotonation of nitrogen (N1). Electron-withdrawing R2 groups connected to N1 atoms provide a wide range in pKa values for these weak acids, which vary from 3 to 11.

pH-sensitive drug delivery systemsbased on inorganic and hybrid (inorganic/organic) materials

RNA, DNA, and oligonucleotides may now be delivered therapeutically using inorganic nanomaterials. Drugs and biomolecules may be delivered to the target region by infiltrating living cells with these materials. Mesoporous silica (MSN), carbon nanotube, gold (Mn), magnetite (Mn), quartz (Zn), strontium phosphate, calcium phosphate, mangano-calcium phosphate, and anionic clays are only few examples of the complex chemistry that these materials display (double hydroxides). An MSN-based drug carrier that can work at both the endosomal and lysosomal pHs has recently been created by Lee et al. (2010). [15]

General method for formulation [16-18]

pH-Sensitive Nanomaterials

In recent years, a broad variety of delivery methods for medical applications have been created, and merging innovative material engineering technologies with the most appropriate delivery method will allow their better therapeutic efficiency and fewer side effects. The pH-sensitive nanoparticles for the smart medication delivery system have been manufactured. Natural and synthetic polymers, phospholipids, silica nanocomposites, and metal nanocomposites may all be used to create extremely sensitive nanocarriers. oral administration provides a lot of benefits in terms of ease. However, oral administration of medications necessitates that they travel through the digestive system to reach the duodenum, jejunum, and ileum. The stomach is acidic, the pH ranges from 1–3, and the duodenum is alkaline, with a pH value in the middle of the pH scale. By oral delivery, a medicine is exposed to a variety of acidic environments and biological enzymes, which may degrade or inactivate the drug. Acidic properties and other abnormalities in the tumour microenvironment may inhibit the bioactivity of medications administered. In order to preserve the therapeutic payloads from degradation and metabolisms prior reaching their ultimate action sites, innovative drug carriers were needed that might activate the therapeutic payloads in aberrant diseased tissues based on pH gradients or other situations.

pH-sensitive hydrogels Polymer structures

Acidic (e.g. carboxylic and sulfonic) and basic (e.g. ammonium salts) groups are present in all pH-sensitive polymers, which may either take or release protons in response to variations in pH. Polyelectrolytes are polymers having a high number of ionizable groups.

Properties of pH-sensitive hydrogels

As the pH changes, so do the swelling characteristics of these crosslinked polyelectrolyte hydrogels. Just like monoacids and monobases, the acidic or basic groups on polyelectrolytes may be ionised. Electrostatic forces from nearby ionised groups make ionisation on polyelectrolytes more challenging. As a result, the apparent dissociation constant (K a) may vary from that of the monoacid or monobase in question. The inclusion of ionisable groups on polymer chains causes hydrogels to expand far more than nonelectrolyte polymer hydrogels can. Because the electrostatic repulsion between charges on the polymer chain

is the primary cause of polyelectrolyte hydrogel swelling, any circumstance that reduces electrostatic repulsion, such as pH, ionic strength, or the kind of counter ions, will affect the swelling's extent. [19-22]

CONCLUSION:

There are several reasons why oral medication delivery remains the preferred method of administration, including patient compliance and formulation versatility. When it comes to illnesses that follow biological cycles, however, sustained- and controlled-release medications fall short. Patients might benefit from multiparticulate systems because to their great efficiency and resilience. Based on the diverse techniques, there are a variety of technologies available in the market. Using pH-sensitive release methods in the future is expected to be beneficial.

CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

REFERENCES:

[1] Annaka, M. and T. Tanaka, 1992. Multiple phases of polymer gels. Nature, 355: 430-432.
[2] Firestone B.A. and R.A. Siegel, 1988. Dynamic pH-dependent swelling properties of a hydrophobic polyelectrolyte gel. Polym. Commun., 29: 204-208.
[3] Kou, J.H., D. Fleisher and G. Amidon, 1990. Modeling drug release from dynamically swelling poly (hydroxymethyl methacrylate co-methacrylate acid) hydrogels. J. Controlled Release, 12: 241-250.
[4] Pradny, M. and J. Kopecek, 1990. Hydrogels for site -specific oral delivery. Poly[(acrylic acid)-co-(butyl acrylate)] crosslinked with 4,4-di(methacryl amino) azobenzene. Makromol. Chem., 191: 1887-1897.
[5] Kono, K., F. Tabata and T. Takagishi, 1993. pH responsive permeability of poly(acrylic acid)-poly (ethylenimine) complex capsule membranes. J. Membr. Sci., 76: 233-243.
[6] Hariharan, D. and N.A. Peppas, 1993. Modeling of water transport and solute release in physiologically sensitive gels. J. Contr. Rel., 23: 123-135.
[7] Siegel, R.A. and B.A. Firestone, 1988. pH dependent equilibrium swelling properties of hydrophobic poly electrolyte co-polymer gels. Macromolecules, 21: 3254-3261.
[8] Allcock, H.R. and A.M. Ambrosio, 1996. Synthesis and characterization of pH sensitive poly (organophosphazene)hydrogels. Biomaterials, 17: 2295-2302.
[9] Bell, C. and N. Peppas, 1996. Water, solute and protein diffusion in physiologically responsive hydrogels of poly(methacrylic acid-g-ethylene glycol). Biomaterials, 17: 1201-1218.
[10] Jarvinen, K., S. Akerman, B. Svarfvar, T. Tarvainen, P. Vlinikka and P. Paronen, 1998. Drug release from pH and ionic strength responsive poly (acrylic acid) grafted poly(vinylidene fluoride) membrane bags in vitro. Pharm. Res., 15: 802-805.
[11] Siegel, R.A., I. Johannes, A. Hunt and B.A. Firestone, 1992. Buffer effects on swelling kinetics in polybasic gels. Pharm. Res., 9: 76-81.
[12] Giannos, S., S. Dinh and B. Berner, 1995. Temporally controlled drug delivery systems: Coupling of pH ascillators with membrane diffusion. J. Pharm. Sci., 84: 539-543.
[13] Heller, J. and P.V. Trescony, 1979. Controlled drug release by polymer dissolution II. Enzymer-mediated device. J. Pharm. Sci., 68: 919-921.
[14] Ghandehari, H., P. Kopeckova and J. Kopecek, 1997. In vitro degradation of pH sensitive hydrogels containing aromatic azo bonds. Biomaterials, 18: 861-872.
[15] Falamarzian, M. and J. Varshosaz, 1998. The effect of structural changes on swelling kinetics of poly-basic /hydrophobic pH sensitive hydrogels. Drug Dev. Ind. Pharm., 24: 667-669.
[16] Akala, E.O., P. Kopeckova and J. Kopecek, 1998. Novel pH-sensitive hydrogels with adjustable swelling kinetics. Biomaterials, 19: 1037-1047.
[17] Gutowska, A., J.S. Bark, I.C. Kwon, Y.H. Bae and S.W. Kim, 1997. Squeezing hydrogels for controlled oral drug delivery. J. Controlled Release, 48: 141-148.
[18] Bilia, A., V. Carelli, G. Di Colo and E. Nannipieri, 1996. In vitro evaluation of a pH-sensitive hydrogel for control of GI drug delivery from silicone-based matrices. Int. J. Pharm., 130: 83-92.
[19] Carelli, V., S. Coltelli, G. Di Colo, E. Nannipieri and M.F. Serafini, 1999. Silicone microspheres for pH-controlled gastrointestinal drug delivery. Int. J. Pharm., 179: 73-83.
[20] Aikawa, K., K. Matsumoto, H. Uda, S. Tanaka and S. Tsuchiya, 1998. Hydrogel formation of the pH response polymer poly vinylacetaldiethylaminoacetate (AEA). Int. J. Pharm., 167: 97-104.
[21] Aikawa, K., K. Matsumoto, H. Uda, S. Tanaka and S. Tsuchiya, 1998. Drug release from pH-response polyvinylacetaldiethylaminoacetate hydrogel, and application to nasal delivery. Int. J. Pharm., 168: 181-188.
[22] Dong, L.C. and A.S. Hoffman, 1990. Controlled enteric release of macromolecules from pH sensitive macroporousheterogels. Controlled Release Bioact. Mater., 17: 325-326.

Cite this article as:
Bhavana Sakpal, Shubhangi Karkhile, Parijat Suryawanshi, Vijaya Barge, Amit Kasabe, Ashok Bhosale, ph sensitive drug delivery systems: A critical assessment, PDEAS Int. J. R. Ayu. & A. Sc., 4 (1); Feb 2022, p. 12-17.