Volume 9, Issue 2, February 2024 International Journal of Innovative Science and Research Technology
ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24FEB1356

An Overview on Stimuli Sensitive Drug Delivery System

Kreena Patel[1]; Naiya Patel[1]
Student Department of Pharmaceutics

M. A. Gupta[2]; Dr. C.N. Patel[3]
Principal; Professor[3]
Faculty Department of Pharmaceutics[2]
Shri Sarvajanik Pharmacy College,Mehsana,Gujarat

Abstract:- Stimuli-sensitive systems are a state of reactivity to sensory stimulation or excitability. These systems respond to changes in the body's physiology due to environmental factors such as temperature, enzymes, glucose, magnetic fields, redox reactions, ions, and more. They are particularly useful for the controlled and sustained delivery of drugs in the body. Controlled drug delivery has become a standard criterion in modern pharmaceutical product design, with ongoing intensive research aimed at achieving a superior drug product characterized by effectiveness, reliability, and safety. These stimuli-sensitive systems are employed in various forms for different purposes, including parenteral, ocular, peroral, rectal, vaginal, nasal, dermal, and transdermal drug delivery. This study focuses on the latest advancements in stimuli-sensitive drug delivery systems, aiming to address the limitations of traditional therapeutic methods. The goal is to achieve targeted drug release in specific areas using various endogenous and exogenous stimuli. This allows for personalized and patient-centric treatment strategies. The development of stimuli-sensitive drug delivery systems remains a significant human endeavor for successful drug delivery, given the various shortcomings of existing conventional systems. To overcome these limitations, various stimuli-sensitive drug delivery systems (DDSs) have been developed in recent years.

Keywords:- *Endogenous Stimuli, Exogenous Stimuli, Stimuli Sensitive Drug Delivery Systems, Stimuli Responsive Drug Delivery Systems.*

I. INTRODUCTION

Systems for delivering drugs that are sensitive to stimuli, such as light, temperature, pH, ions, glucose, and redox processes, are made to react to these changes and release the drug in different ways. These systems are used for a variety of purposes, such as drug delivery via the parenteral, ophthalmic, peroral, rectal, vaginal, nasal, dermal, and transdermal routes.

The use of thermosensitive liposomes for localized drug release by hyperthermia first presented the idea of stimuli-responsive drug delivery in the late 1970s. These devices, also known as intelligent or smart drug delivery systems (DDS), have the ability to sense changes in the body and modify medication release by adjusting drug release rates in response to physiological demands.

A sophisticated platform designed to react intelligently to certain environmental stimuli and internal body signs is known as a stimuli-sensitive DDS (endogenous stimuli). Light, temperature, magnetic fields, ultrasound, pH levels, enzyme activity, and more are all examples of these triggers. Through the utilization of these stimuli, stimuli-sensitive drug delivery systems can accomplish targeted drug release at certain sites, optimizing therapeutic effects and reducing the risk of negative reactions.

The medicine is immediately supplied to the target spot or released as needed in a stimuli-sensitive DDS, which lessens the drug's negative effects on adjacent tissues. The medication is very carefully and selectively accumulated at the target site over time, increasing the system's therapeutic activity.

A stimuli-sensitive DDS should fulfill a number of essential requirements. First, the substance that is employed to build the matrix of the system needs to be biocompatible or, at the absolute least, not harmful to the body. Secondly, the medication must to be able to enter the system and be effective even after that. Third, there should be no need for any external devices; the drug release should be triggered in a non-invasive way. Lastly, the system needs to make sure that no medication is released before it has been turned on or activated.

- *Endogenous Stimuli:*

These include redox-responsive, enzyme-responsive, pH-responsive, and ionic microenvironment-responsive drug delivery systems. They come from biological and chemical sources. By controlling tissue microenvironments, overexpressing particular enzymes, recognizing host-guest moieties in a particular condition, and interacting with antigens, these systems initiate the release of medication.

- *Exogenous Stimuli:*

It is possible to overcome inter-patient variability with exogenous stimuli. Drug release in these systems is governed by precisely controllable external parameters. It has been reported that a variety of external stimuli, including temperature, magnetic fields, light, electrical fields, and ultrasound, can be utilized to regulate medication releases.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24FEB1356

➢ *Various Stimuli-Sensitive DDSs [1].*

- pH- sensitive DDS.
- Thermo -Sensitive DDS.
- Hydrolysis- Sensitive DDS.
- Glucose- sensitive DDS.
- Ion-Sensitive DDS.
- Mechanical- Activated DDS.
- Enzyme-Activated DDS
- Magnetically- Activated DDS

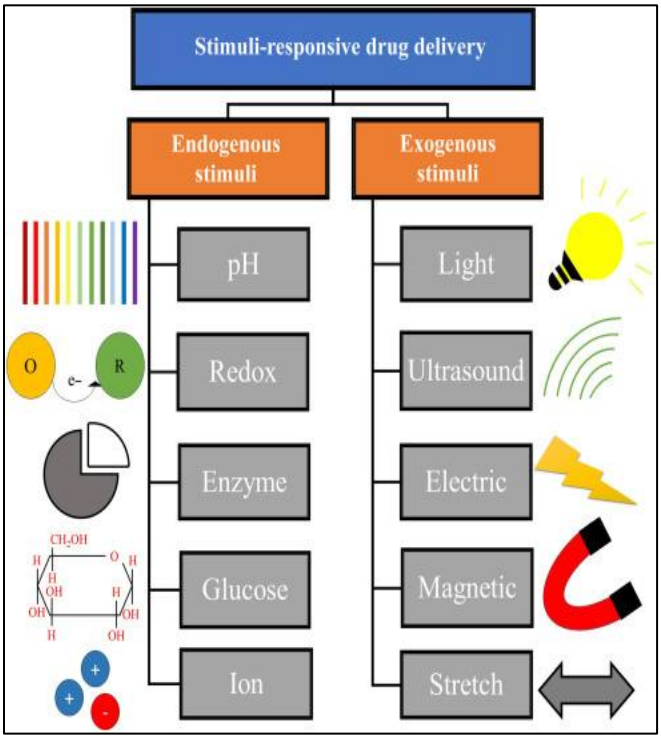

Fig 1 Classification of Stimuli-Responsive Drug Delivery

➢ *pH- Sensitive DDS[6].*

With this type of activation-controlled drug delivery system, a drug can be delivered specifically to a location with a particular pH range. It is made by covering the drug-filled core with a blend of polymers that react differently to pH.

One way to protect a medicine that is sensitive to gastric fluid is to encase it in a polymer membrane that is resistant to the deteriorating effects of the pH of the stomach. Ethyl cellulose and hydroxy methyl cellulose phthalate can be combined to accomplish this.

Stomach acid cannot break down the medication molecules because the coated membrane in the stomach is resistant to the action of gastric fluid (pH less than 3).

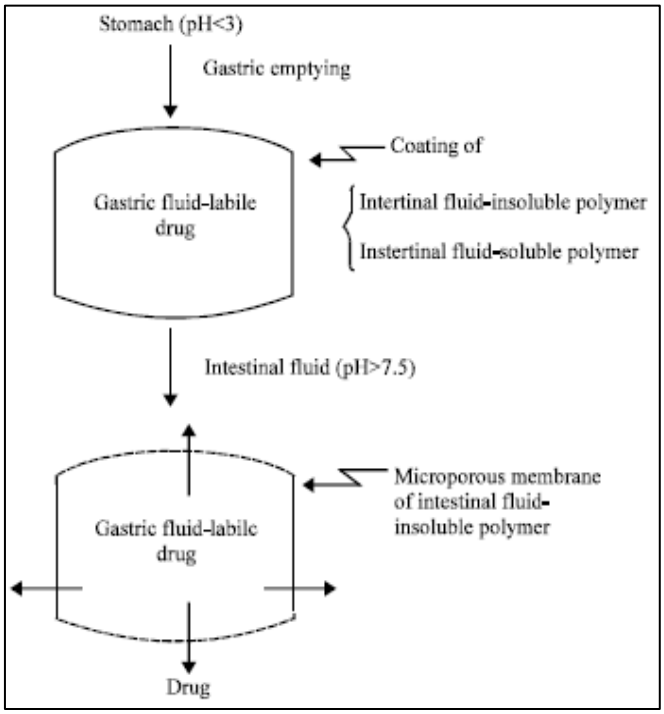

Fig 2 Schematic Diagram of pH Sensitive Drug Delivery System[7].

Table 1 Various Cellular/Tissue Component Showing Different pH[26].

Cellular/Tissue Component	pH
Blood	7.35-7.45
Duodenum	7.0-8.5
Colon	7.0-7.5
Stomach	2.0-3.0
Lysosome	4.5-5.0
Golgi	6.4

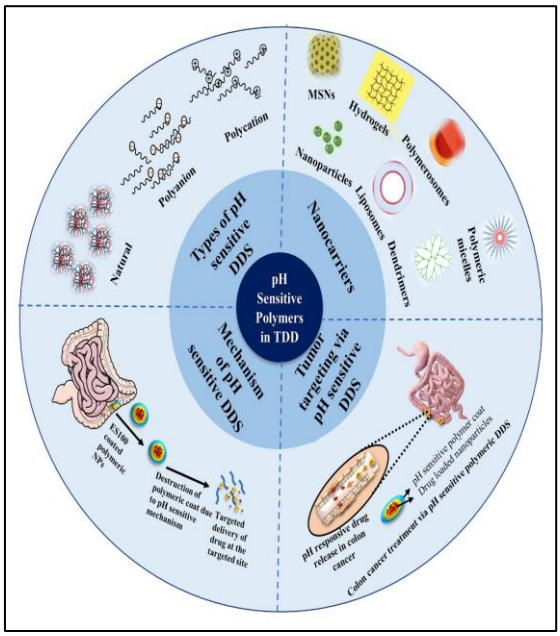

Fig 3 pH Sensitive Polymers[9].

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24FEB1356

➢ *Advantages*[1]

- **Stability in Drug Blood Levels:** There is less fluctuation in drug blood levels, ensuring a consistent therapeutic effect.
- **Reduced Dosing Frequency:** The need for frequent dosing is reduced, making the treatment regimen less burdensome.
- **Enhanced Patient Convenience & Adherence:** The treatment regimen is easier to follow, leading to improved patient compliance.
- **Increased Safety Margin:** High potency drugs have an increased safety margin, reducing the risk of adverse effects.
- **Lower Health Care Costs:** The overall cost of health care is reduced due to the efficient use of medications.
- Reduced Side Effects: There is a decrease in side effects, enhancing patient comfort and safety.
- **Dower Dose Requirements:** The dose of medication to be administered is decreased, reducing the risk of toxicity.
- **Direct Drug Availability at Target Site:** The drug is directly available at the target site, increasing its effectiveness.
- **Mucosal Protection**: The mucosa is protected from irritating drugs, preventing damage to these delicate tissues.
- **Targeted Drug Delivery:** The drug can be targeted to specific sites, like the colon, improving the effectiveness of the treatment.
- **Improved Patient Compliance:** The overall patient compliance is improved due to the convenience and reduced side effects of the treatment regimen.

➢ *Disadvantages*[1]

- **Reduced Systemic Availability**: Compared to immediate-release conventional dosage forms, these systems have decreased systemic availability.
- **Poor In Vivo-In Vitro Correlation**: There is a poor correlation between the in vitro (laboratory) and in vivo (body) responses.
- **Risk of Dose Dumping**: There is a possibility of dose dumping, where the entire dose is released at once, leading to potential toxicity.
- **Difficult Drug Retrieval**: Once administered, it is challenging to retrieve the drug from the system.
- **Increased Formulation Cost**: The cost of formulating these systems is higher compared to conventional dosage forms.

➢ *Ion- Activated Drug Delivery Systems*[7].

This type of system is initially prepared by forming a complex between an ionic drug and an ion-exchange resin that contains an appropriate counterion. For instance, a complex can be formed between a cationic drug and a resin that has an SO3 group, or between an anionic drug and a resin with an N(CH3) group.

The granules of the drug-resin complex are first treated with an impregnating agent, such as polyethylene glycol 4000. This treatment reduces the rate of swelling in an aqueous environment. Following this, the granules are coated with a water-insoluble yet water-permeable polymeric membrane, such as ethyl cellulose, using an air suspension coating technique.

This membrane acts as a rate-controlling barrier that regulates the influx of ions and the release of the drug from the system. When the system is in an electrolyte medium, like gastric fluid, ions diffuse into the system, react with the drug-resin complex, and trigger the release of the ionic drug.

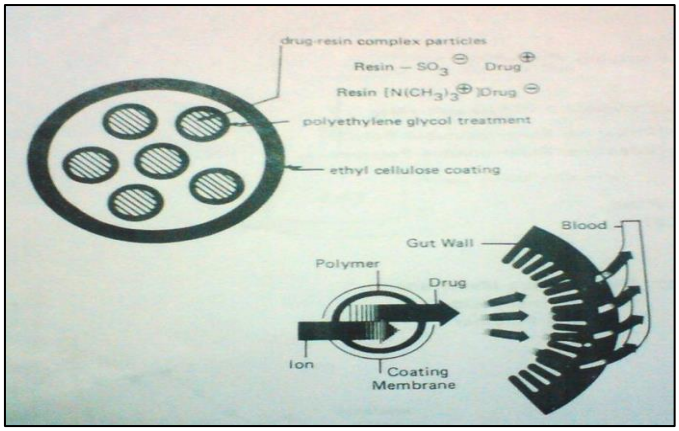

Fig 4 Schematic Representation of Ion- Activated DDS

➢ *Advantages*[7].

- **Dose Reduction**: Ion-exchange resinates of the drug can assist in reducing the dosage required.
- **Stable Concentration Levels**: These systems can achieve reduced fluctuations in blood and tissue concentration levels.
- **Protection and Controlled Release**: The drug is protected from gastric enzymes, and its release is controlled for optimal effectiveness.
- *Disadvantages*[7].
- **Reduced Systemic Availability**: The systemic availability of the drug is decreased, which may affect its effectiveness.
- **Poor In Vitro-In Vivo Correlation**: There is a poor correlation between the laboratory (in vitro) and body (in vivo) responses, which can complicate predictions of the drug's behavior.
- **Risk of Dose Dumping**: There is a possibility of dose dumping, where the entire dose is released at once, potentially leading to toxicity.
- **Difficult Drug Retrieval**: In cases of toxicity, poisoning, or hypersensitivity reactions, retrieving the drug from the system is challenging.
- **Limited Dosage Adjustments**: The potential for dosage adjustments is reduced, limiting the flexibility of the treatment.
- **Increased Formulation Cost**: The cost of formulating these systems is higher compared to conventional dosage forms.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24FEB1356

➢ *Hydrolysis Activated Drug Delivery System[8].*

The release of drug molecules in this kind of activation-controlled drug delivery system is dependent on the hydrolysis process. The drug reservoir in this method is either uniformly distributed in microspheres or nanoparticles for injection, or it is enclosed within microcapsules.

Another option for the system's design is an implanted one. Biodegradable or bioerodible materials, such as co(lactic-glycolic) polymer, poly (Orthoester), or poly(anhydride), are used to create all of these systems.

Drug release from the polymer matrix is regulated by the rate of polymer breakdown, which is triggered by hydrolysis-induced polymer chain degradation.

A typical example of a hydrolysis-activated drug delivery system is the development of a biodegradable subdermal implant that releases LHRH. This implant is designed to deliver Gosselin, a synthetic LHRH analog, for the monthly treatment of prostate carcinoma.

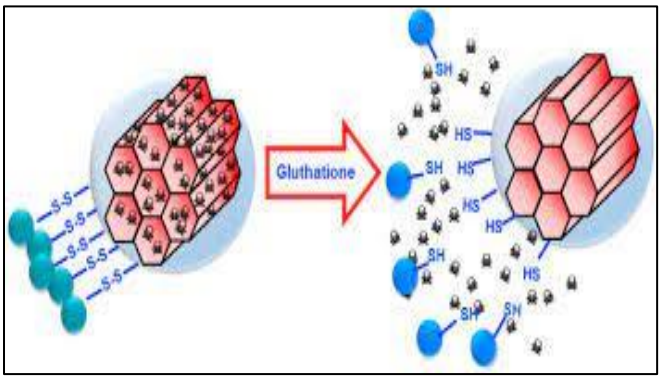

Fig 5 Schematic Representation of Hydrolysis Activated DDS[10].

➢ *Advantages*[11]

- **Controlled Drug Release**: These systems provide a controlled release of the drug.
- **Swelling-Controlled Drug Release**: They demonstrate drug release controlled by swelling.
- **Wound Healing Applications**: These systems are applicable in the field of wound healing.
- **Tissue Engineering Applications**: They have uses in tissue engineering.
- **Ocular Drug Delivery**: These systems are highly beneficial for delivering drugs to the eye.

II. ENZYME – ACTIVATED DRUG DELIVERY SYSTEM[12].

This kind of activation-controlled drug delivery system relies on enzymatic processes to trigger the release of the drug. In this system, the drug reservoir is either physically trapped within microspheres or chemically attached to polymer chains derived from biopolymers, such as albumins or polypeptides.

The drug release is activated by the enzymatic hydrolysis of the biopolymers by a specific enzyme present in the target tissue. For instance, albumin microspheres can release the drug 5-fluorouracil in a controlled way through protease-activated biodegradation.

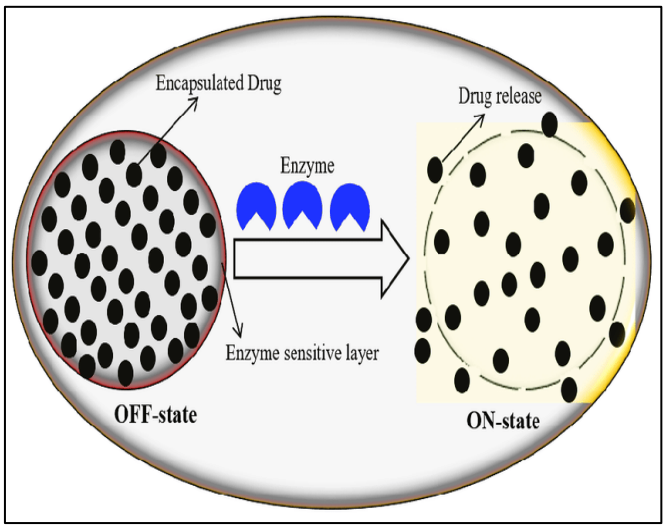

Fig 6 Schematic Representation of Enzyme- Activated DDS[11].

Table 2 Different Enzymes Sensitive Polymers

Enzyme Sensitive Polymers	Enzymes	Enzyme Sensitive Funtionality
PolyEthyleneGlycol (PEG)	Trypsin	D-AFK
PEG	Papain	GGG
Gelatin	Alpha-chymotrypsin	Gelatin
Dextran cross-linked with diisocynate	Dextranase	Dextran

III. MECHANICALLY-ACTIVATED DRUG DELIVERY SYSTEM[13].

The drug reservoir in this kind of activation-controlled drug delivery system is a solution formulation kept in a container with a mechanically triggered pump. When the medication delivery pump is manually engaged, a measured dose of the drug formulation is reliably supplied through the spray head into a bodily cavity, like the nose.

It is possible to regulate the amount of solution released, ranging from 10 to 100 µl, and it remains unaffected by the strength and length of activation used, in addition to the volume of solution within the container.

Developing a metered-dose nebulizer to provide a precise amount of buserelin, a synthetic counterpart of luteinizing hormone-releasing hormone (LHRH), and insulin intranasally is a typical example of this kind of rate-

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24FEB1356

controlled drug delivery device. These peptide-based medications escape the hepatic first-pass elimination process by means of nasal absorption.

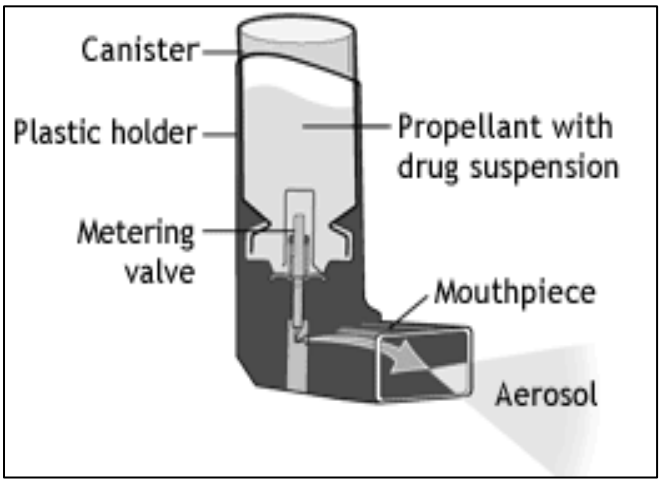

Fig 7 An Example of Mechanically Activated DDS (Metered Dose Inhaler)

➢ *Types of Devices*

- *Metered Dose Inhalers*
- *Dry Powder Inhalers*
- *Nebulizers*

V. GLUCOSE-TRIGGERED INSULIN DRUG DELIVERY SYSTEM[14]

In this system, the insulin reservoir is contained within a hydrogel membrane that has a -NR2 group. When in an alkaline solution, the -NR2 groups are neutral, and the membrane remains unswollen and impermeable to insulin.

Glucose can penetrate this membrane and is enzymatically oxidized by the glucose oxidase that is trapped within the membrane, resulting in the formation of gluconic acid. This process causes the -NR2 group to be protonated, forming -NR2H+. As a result, the hydrogel membrane swells and becomes permeable to insulin molecules.

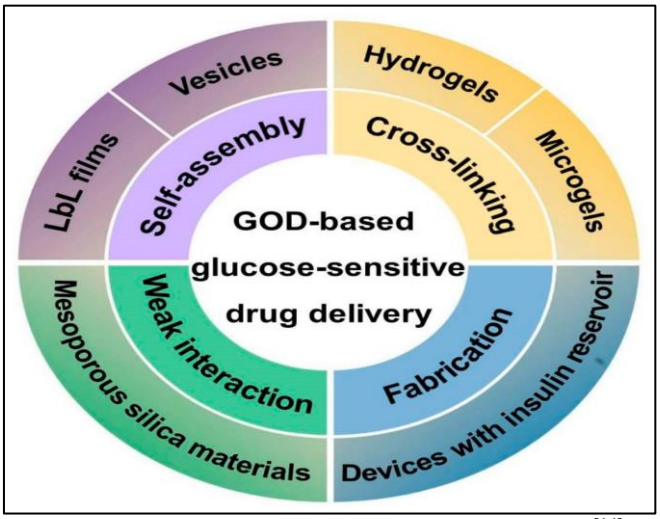

Fig 8 GOD-based Glucose -Sensitive Drug Delivery[14]

V. THERMO-SENSITIVE DDS[15]

The use of temperature as a trigger is justified by the fact that body temperature often varies from the normal physiological temperature (37°C) in the presence of pathogens or pyrogens. This variation serves as a useful stimulus that activates the release of therapeutic agents from temperature-responsive drug delivery systems, particularly for diseases that cause fever.

These temperature-responsive drug delivery systems leverage various properties of polymers, including the thermally reversible transition of polymer molecules, changes in network swelling, glass transition, and crystalline melting.

Examples of thermos-responsive polymers include Poly (N,N- diethyl acrylamide), Poly (methyl vinyl ether), Poly (n-vinyl caprolactam), Pluronic's, and Tectonics.

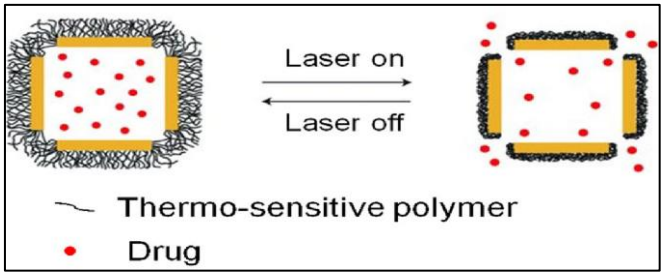

Fig 9 Schematic Representation of Thermosensitive DDS

Table 3 Thermosensitive Polymer Classes with Examples

Polymer Classes	Examples
Polysaccharides	Cellulose derivatives (methyl cellulose, HPMC), Xyloglucan, Chitosan & glycerophosphate
N-isopropylacrylamide copolymers	Poly (N-isopropylacrylamide-co-acrylic acid) Poly (N-isopropylacrylamide)/poly(ethylene oxide)
Poloxamers systems	Poloxamer 188, Poloxamer 407
Carbomer	Poly (acrylic acid)
Poly(ethylene oxide)/poly(D,L-lactic acid – co – glycolic acid)	Poly (lactic-co-glycolic acid) – poly (ethylene oxide)- poly (lactic – co- glycolic acid)
Miscellanous	Poly (organophosphazene) derivatives

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24FEB1356

VI. MAGENTICALLY ACTIVATED DDS[16].

Peptide or protein powders are dispersed into a polymer matrix to form the drug reservoir in this kind of activation-controlled drug delivery system. The gradual delivery of macromolecular medications is made possible by this arrangement.

By adding an electromagnetically triggered vibration mechanism to the polymeric delivery device, the rate of distribution can be increased. This results in a constant (zero-order) medication delivery profile when paired with a hemispherical architecture.

To develop a magnetically activated subdermally implantable drug delivery device, a hemispherical drug-dispersing polymer matrix is first filled with a tiny magnet ring at its center. After that, a drug-impermeable polymer, such as silicone elastomers or ethylene-vinyl acetate copolymer, is applied to the exterior of this matrix, leaving one cavity in the middle of the flat surface unprotected.

The peptide medication can be released through this uncoated chamber, which is situated right above the magnet ring.
By using a straightforward diffusion mechanism in non-triggering environments, the resultant hemispherical magnetic delivery device has been used to distribute protein medications, such as bovine serum albumin, at a low basal rate.

The medication molecules are given at a substantially higher rate when an external electromagnetic field causes the magnet to vibrate.

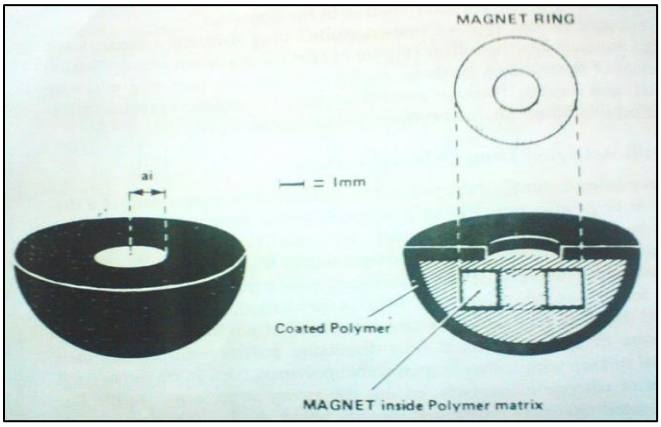

Fig 10 Schematic Represntation of Magnetically- Activated DDS

VII. CONCLUSION

In conclusion, stimuli-sensitive Drug Delivery Systems (DDS) play a crucial role in delivering drugs to different parts of the body. The intriguing properties of these systems hold promise for numerous future applications. The development of various types of stimuli-sensitive DDS has led to the availability of new and innovative controlled and sustained delivery systems.

REFERENCES

[1]. Bhardwaj A, Kumar L, Mehta S, Mehta A. Stimuli – sensitive systems –an emerging delivery system for drugs. ArtifCells Nanomed Biotechnol. 2015; 43(5);299-310.
[2]. Liu D, Yang F, Xiong F, Gu N. The smart drug delivery system and its clinical potential. Theranostics. 2016;6(9):1306-23. doi: 10.7150/thno.14858, PMID 27375781.
[3]. Gupta M, Sharma V. Targeted drug delivery system a review. Res J Chem Sci. 2011;1:135-8.
[4]. Muller RH, Keck CM. Challenges and solutions for the delivery of biotech drugs-a review of drug nanocrystal technology and lipid nanoparticles. J Biotechnology. 2004;113(1-3):151-70. doi: 10.1016/j.jbiotec.2004.06.007, PMID 15380654.
[5]. Elema Buzu. Stimuli-sensitive drug delivery systems: a review, scenic Publisher; 2020. https://www.researchgateresearchgate.net/publication/363095261.
[6]. Novel Drug Delivery System- Y.W. Chien. Published by Marcel Dekker, inc., New York Pg. no. 17-36 & 57-11
[7]. https://scialert.net/fulltext/citedby.php?doi=ajdd.2011.24.48&linkid=cite
[8]. Ballard, B.E. and Robinson, J.R., Eds., In; A overview of prolonged action drug dosage form, In sustained and controlled release drug delivery systems, Marcel Dekker, New York, 795, 1978. Biopharmaceutics & pharmacokinetics- Brahmankar. Pg. no. 335-370
[9]. Ankur Bhardwaj, Lalit kumar, Shuchi Mehta & Abhinav Mehta (2015) Stimuli-sensitive Systems- an emerging delivery system for drugs, Artificial cells, Nanomedicine, and Biotechnology, 43:5, 299-310.
[10]. Shyam Sudhakar Gombe, Tejas Girish Agnihotri, Shivani Khopade & Aakanchha Jain (2024) Exploring the potential of pH-sensitive polymers in targeted drug delivery, Journal of Biomaterials Science, Polymer Edition, 35:2, 228-268, DOI: 10.1080/09205063.2023.2279792
[11]. https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/drug-hydrolysis.
[12]. Fundamentals of controlled release drug delivery-Robinson. Pg. no. 482-508
[13]. Controlled and Novel Drug Delivery - N.K. Jain CBS Publishers & Distributors, New Delhi.
[14]. Zhao, L.; Wang, L.; Zhang, Y.; Xiao, S.; Bi, F.; Zhao, J.; Gai, G.; Ding, J. Glucose Oxidase-Based Glucose-Sensitive Drug Delivery for Diabetes Treatment. *Polymers* **2017**, *9*, 255. https://doi.org/10.3390/polym9070255
[15]. Raza, A.; Rasheed, T.; Nabeel, F.; Hayat, U.; Bilal, M.; Iqbal, H.M.N. Endogenous and Exogenous Stimuli-Responsive Drug Delivery Systems for Programmed Site-Specific Release. *Molecules* **2019**, *24*, 1117. https://doi.org/10.3390/molecules24061117
[16]. Siegel R A and Rathbone M J; Overview of Controlled Release Mechanisms; Advances in Delivery Science and Technology, 2012.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24FEB1356

[17]. Vyas, S. P. and Roop, K. Khar., Controlled Drug Delivery: Concepts and Advances, 1st Ed., 258, 2004
[18]. Park, K. (1997). Controlled drug delivery: Challenges and strategies (p. 629). Washington, DC: American Chemical Society.
[19]. Nagashree Kotturi, Novel Drug Delivery System; Research and Reviews: Journal of Pharmaceutics and Nanotechnol
[20]. Shah Nihar, Patel Nishith, (2013), A Sequential Review on Intelligent Drug Delivery System. International Journal of Advance in Pharmaceutical Research.3(5). pp.158-162.
[21]. Patel DM, Patel DK, Patel BK, (2011). An overview on Intelligent Drug Delivery System, International Journal of Advance in Pharmaceutical Research.2(2), pp.57-63
[22]. Preksha Vinchhi, ... Mayur M. Patel, in DRUG DELIVERY DEVICE AND THERAPEUTIC SYSTEMS
[23]. Bhardwaj A, Kumar L, Mehta S, Mehta A. Stimuli-sensitive systems--an emerging delivery system for drugs. Artif Cells Nanomed Biotechnol. 2015;43(5):299-310. PMID: 26561681.
[24]. Ali raza 1, Tahir Rasheed 2, faran nabeel 2, uzma hayat 1, Muhammad bilal 3, and hafiz M.N. Iqbal 4, endogenous and exogenous stimuli responsive drug delivery systems for programmed site-specific release : school of biomedical engineering, sanghai jiao tong university, sanghai 200240, china:21 march 2019.
[25]. Rasheed t.; Bilal, m.; Abu -Thabit. N.Y.; Iqbal, h.m. The smart chemistry of stimuli-responsiove polymeric carriers for target drug delivery applications. In stimuli responsiove polymeris nanocarriers for drug delivery applicationas: Elsevier:Amsterdam , The Netherlands; wood head publishing ; Cambridge, UK. 2018; Volume1 , pp. 61-99.
[26]. Crosstalk of physiological pH and chemical pKa under the umbrella of physiologically based pharmacokinetic modeling of drug absorption, distribution, metabolism, excretion, and toxicity - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/pH-values-of-human-body-fluids_tbl1_353214781 [accessed 23 Feb, 2024]