International Journal of Scientific Research and Modern Technology (IJSRMT) ijsrmt.com
Volume 4, Issue 10, 2025
DOI: https://doi.org/10.38124/ijsrmt.v4i10.912

Smart Drug Delivery Systems: Current Technologies, Clinical Applications, and Future Perspectives in Precision Therapeutics

Hafsa Ayaz[1]; Abbas Khan[2]; Numan Khan[3]; Muhammad Hasnain[4]; Suhaib Mesbah[5]; Akhlaq Ahmad[6]; Muhammad Rehan Ahmed[7]; Hajra Ayaz[8]; Ramiz Ahmed[9]; Azka Sana[10]

[1,9,10]Department of Chemistry, COMSATS University Islamabad, Abbottabad Campus, Abbottabad-22060 KPK Pakistan.
[2,3,4,5,6,7]Bachelor of Medicine and Bachelor of Surgery, Northwest School of Medicine, Peshawar-25000, KPK, Pakistan.
[8]Department of Biotechnology, COMSATS University Islamabad, Abbottabad Campus, Abbottabad-22060, KPK Pakistan.

Publishing Date: 2025/10/24

Abstract

The pharmaceutical industry has come a long way with the introduction of smart drug delivery systems in terms of increasing control level over the therapeutic agents release and measurement of their effects. The recent achievements have demonstrated that these networks are useful in very specific pharmacotherapeutic treatment using high-technological equipment. Various types of diverse classes of delivery systems have been invented including nanoparticulate-based carriers, hydrogel-based matrices and implantable therapeutic systems that are associated with their own advantages in the clinical practice. In current investigations, several technologies has been developed in the controlled theraputic delivery and concomitant work in real time monitoring technology to measure delivery of therapeutic agents. Even though scientific evidence is uniform with regard to the potential of such systems to have a positive effect on therapy, challenges that hinder clinical translation which encompass system stability, biocompatibility determination, and complex regulatory compliance still exist. According to the literature, these limitations can be overcome by implementing artificial intelligence and new technologies in personalized medicine to offer more treatment choices to be administered by intelligent medication systems. It is possible that the evolving character of inventions they can have a significant positive effect on system efficacy and applicability in clinical settings. The available data is indicative of the existence of quantifiable possibilities to improve patient treatment and treatment outcome in various clinical applications. The paper has an extensive literature review on the existing information on smart drug delivery devices and their mechanisms, types of systems, and use in clinical practice. It evaluates the current findings and describes the colorful prospects of the way of further development of the therapeutic regimes and enhancement of the patient-centered healthcare services.

Keywords: *Drug Monitoring, Controlled Drug Delivery, Artificial Intelligence, Biocompatible Materials, Pharmaceutical Preparations, Precision Medicine.*

I. INTRODUCTION

The pharmaceutical science has undergone a paradigm shift which entails the complex, smart delivery vehicles that can be applied to the modern elements of medicine which embrace precision, personalization as well as patient-centricity [1]. The effective tools of the modern technologies are used to design the modern delivery system that allows providing the specific transport of the drugs to the specific anatomical site to reach the greatest therapeutic outcomes and minimize the systemic exposure [2]. The revolutionary technology is exemplified by the

Ayaz, H., Khan, A., Khan, N., Hasnain, M., Mesbah, S., Ahmad, A., … Sana, A. (2025). Smart Drug Delivery Systems: Current Technologies, Clinical Applications, and Future Perspectives in Precision Therapeutics. *International Journal of Scientific Research and Modern Technology*, *4*(10), 18–38. https://doi.org/10.38124/ijsrmt.v4i10.912

analogy of the conventional systemic therapies and the new precise-targeted nanocarrier systems that have demonstrated tremendous selectivity on diseased cellular targets [3]. Improved performance indicators that define the contemporary delivery systems include; a surge of automation, enhanced sharp precision targeting as well as an augmented therapeutic effect [4]. These innovations eliminate the translation barriers that have been experienced in the past in as

Pharmaceutical delivery has also been developed with consideration of patient comfort in a system such as transdermal therapeutics that has the least rejection rates, most convenient and highly acceptable by the patients [7]. In spite of the fact the oral route of administration remains the most desirable, the severe gastrointestinal environment presents a huge bioavailability risk, and prompts innovation into complex formulations that can protect therapeutic agents during transit to their targets and liberate them on-target. The most noticeable feature of the contemporary pharmaceutical delivery is the increasing degree of intelligence. Nanoparticulate platforms were also given a great deal of attention since they have greater bioavailability and target delivery [5]. Such systems are eco-receptive and are designed to differ in response to the physiological condition, sickness conditions or specific biological factors [8]. It is presumed that the further development will be even more developed, and the intel

The pharmacotherapy of the modern medicine is the control of the drugs that are released to achieve the optimal therapeutic effect. The most recent pharmaceutical interventions have evolved into complicated mechanisms that control the therapeutic levels within a predetermined range to a significant duration of time [1]. The classical immediate-release formulations are intrinsically weak in achieving the long-term goal and decrease of side effects [10]. Modern controlled release systems define predetermined patterns of plasma concentration with release rates that are inherently the basis of determining absorption profiles, and thus decreasing the need to dose a person as frequently [11].

The conventional formulations often cause variable plasma concentrations which lead to intervals of inadequate therapeutic effect and possibly dangerous peak concentrations [9]. Newer controlled release technologies are able to offer consistent profiles to maintain therapeutic concentrations with minimal concentration-dependent side effects [12]. New technologies show never before seen levels of control, and the possibility of initiation, modulation, or discontinuation of drug release on demand is possible [13].

Initial approaches of combining therapeutic drug monitoring and controlled release systems have proven to be imperative in personalized medicine. Therapeutic drug monitoring assists healthcare providers in measuring the drug concentrations accurately to achieve maximum results with minimal risks of toxicity [14]. This is a crucial method when dealing with narrow therapeutic index drugs [15]. The recent technological innovations in sensor and wearable technologies have transformed the monitoring capabilities by making them revolutionary [16] and biosensor integration is a promising area of development that can provide real-time optimization of therapeutic processes [17]. The new technologies overcome the current inefficiencies like the requirement to have professional operators, pain to patients as a result of the frequent blood taking, and inability to detect dynamic instantaneous changes [18].

The convergence of the controlled release technology and the sophisticated monitoring devices is a new dimension of truly personalized pharmacotherapy. Real-time monitoring of modern systems can allow clinicians to maximize outcomes by adjusting dosages based on actual plasma concentrations and not on population-based algorithms [19]. It is expected that in the future, the advances will include artificial intelligence and machine learning algorithms that forecast optimal dosing regimens based on patient-specific factors and real-time monitoring [20].

The goal of this comprehensive review is to evaluate and synthesize existing information on targeted drug delivery systems, the mechanisms of sustained-release and therapeutic monitoring of drugs. The review analyses the evolution of smart delivery platforms, investigates different types of controlled release mechanisms and their clinical implications and determines the integration of therapeutic drug monitoring technology in personalized medicine practices. Furthermore, it studies upcoming technologies such as nanotechnology and the integration of artificial intelligence, it analyzes clinical applications in numerous medical fields, and considers regulatory issues and developmental challenges.

By applying the systematic analysis of comparative effectiveness, monitoring technology potential, and optimization opportunities of the system, this review addresses knowledge gaps, defines research priorities, evaluates the emergent technology clinical readiness, and examines the economic implication of healthcare systems. The purpose is to create evidence on various approaches to research and come up with evidence-based suggestions on clinical practice, research priority, and how to strategically advance the smart therapeutic delivery system that increase the effectiveness of the therapeutic approach but also ensures patient safety and the personalization of the treatment. We find an opportunity standing on the verge of a more effective future of curing, which is indeed a more precise, individualized, and patient-focused approach with an ever-expanding scientific boundary.

II. FUNDAMENTALS OF SMART DRUG DELIVERY SYSTEMS

One of the recent technological advancements in pharmaceutical technology is that of smart drug delivery systems which offers smarter, responsive platforms with autonomous decision-making of therapeutic distribution which utilizes on critical constraints of traditional drug

delivery technologies that consist of nonspecific distribution, uncontrolled release, and lacklustre bioavailability using advanced nanocarrier-based technology as a targeted therapeutic delivery technique at lower dosage frequency as well as spatially controlled mechanisms[2, 21]. These advanced systems are dynamically responsive to endogenous pH changes the use of tumor acidity at pH 6.5-7.0 with healthy tissue at pH 7.4, temperature changes, redox conditions, enzyme activity and hypoxic conditions) and exogenous (light, magnetic, electric fields, and mechanical pressure) stimuli [8] [22]. The working mechanisms include pH-responsive systems that act by ionization-dependent protonation and deprotonation of functional groups (carboxylic acid, amine, imidazole moieties) in polymer networks, which induce dramatic conformational changes and swelling/deswelling behavior and effectively use biological pH gradients to deliver drugs orally and target cancer-related therapies [23] [24-26]. and temperature-responsive polymers which experience thermally-driven phase transitions with Lower Critical Solution Temperatphotoswitchable nanoparticles, and photodegradation and photothermal effects of photo switchable molecular groups are the basis of light-responsive materials used in targeted drug delivery [27, 28]. whilst responses to magnetic fields as magnetothermal heating and mechanical deformation are used in magnetic field-responsive systems [29] [30] [31]. Multi-stimuli systems multi-stimuli platforms are systems that have multiple responsive modalities, with some systems having dual-and three-responsive modalities (both pH and temperature sensitive) and cascading responses that recapitulate natural biological responses [32] [33, 34] [35]. Multi-stimuli systems can also be cell-mediated delivery systems where erythrocytes, immune cells, stem cells, and exosomes are used to deliver therapeutics with increased precision [36]. These smart systems can provide superior treatment efficacy with specifically targeted mechanisms, less systemic toxicity with targeted pharmacokinetics of drug, greater patient compliance with more optimized dosing, and overcome poor bioavailability and drug resistance because of enhanced drug efficacy and decreased adverse reactions [27-37. Such advances include artificial intelligence and machine learning algorithms to predictive responses, computational modeling of optimally structured molecules to better therapeutic response, and new advancements in which smart delivery can respond to enzyme activity, the use of ultrasound, and electrochemical switching, making smart delivery system development at the merging point of pharmaceutical science, nanotechnology, and computational biology the way to transform therapeutic interventions through adaptive delivery mechanisms into proactive, personalized medicine strategies.

III. SMART THERAPEUTICS DELIVERY SYSTEMS

Smart medication transport systems have revolutionized the pharmaceutical world by solving some of the most severe shortcomings of conventional formulations like low rapid clearance, solubility, non-specific localization and side effects. These systems allow to optimize release profile, specific mechanisms and bioavailability of complex therapeutic challenges.

➢ *Nanoparticulate Drug Delivery Systems*

- *Liposomes:*

The liposomes are the first clinically successful nanocarrier which is a phospholipid bilayer that is similar to a natural membrane, which surrounds hydrophilic drugs in aqueous cores and lipophilic drugs in lipid layers as demonstrated in figure 1. These systems can be classified into three major categories: classical liposomes with various charge states and size ranges (SUVs <100 nm to MLVs >1 μm), stealth liposomes modified with PEG or polysaccharides to evade immune clearance and prolong half-life of circulation days, and targeting liposomes functionalized with ligands for receptor-mediated delivery. PEGylation develops long-circulating preparations that are not removed by the immune system and have a plasma half-life of minutes to days. Doxil has been shown to be clinically successful in cancer therapy, minimizing cardiotoxicity and allowing the accumulation of tumors in the body via its increase in permeability and retention effects. Modern innovations are stimuli-responsive formulations that deliver cargo to respond to variations in pH, enzymatic activity, or redox gradient, and theranostic hybrids are formulations with a combination of therapeutic and diagnostic properties [38-41].

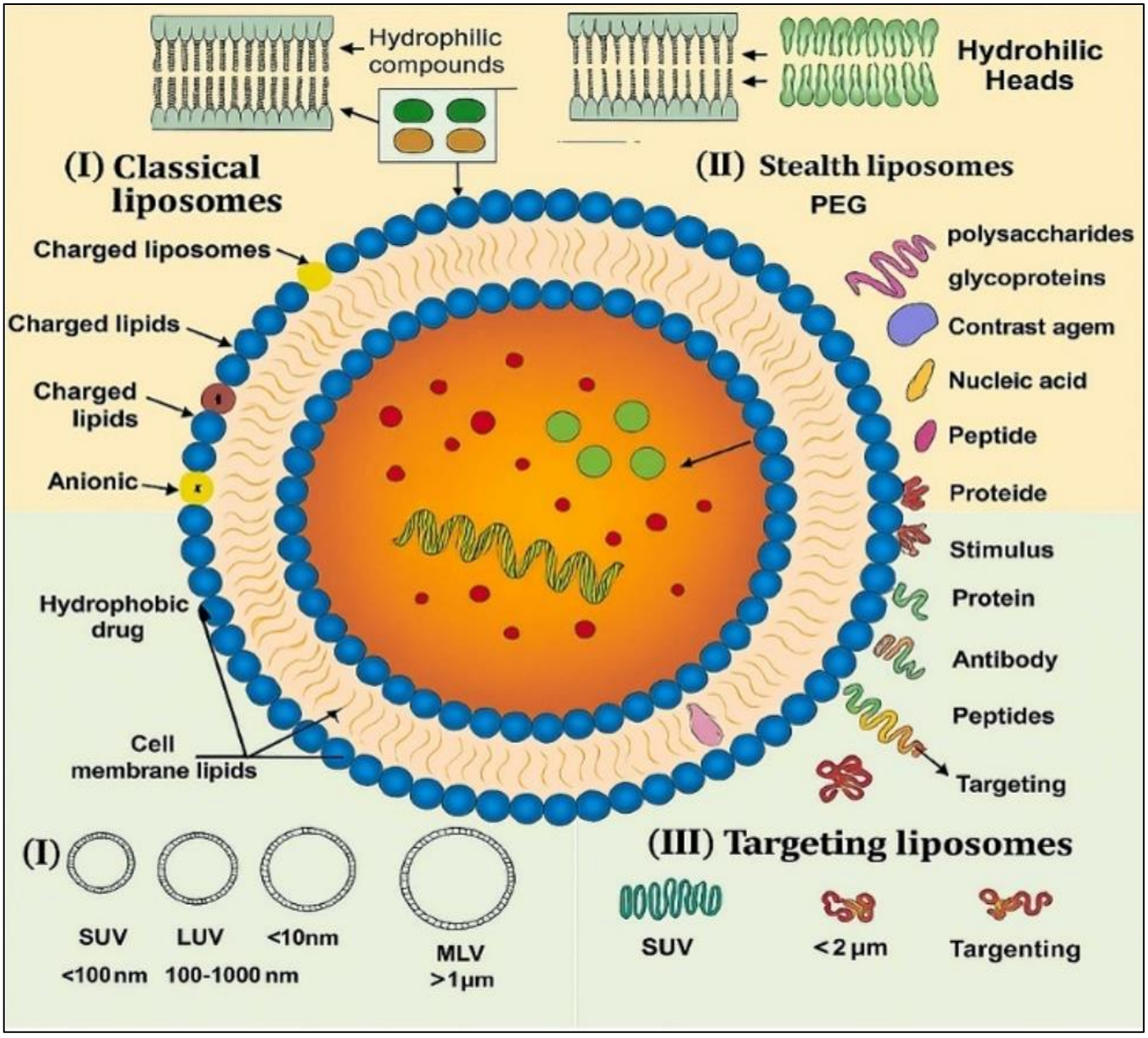

Fig 1 Extensive Diagram of Liposome Classification and Structural-Functional Characteristics in Drug Delivery [41].

- *Polymeric Nanoparticles:*

The polymeric nanoparticles are more manageable due to biodegradable polymers, which are poly (lactic-co-glycolic acid), poly (lactic acid) and poly(caprolactone) that break down to non-toxic metabolites. Physical encapsulation, chemical conjugation and adsorption are all drug loading mechanisms. Surface functionalization allows targeting ligand, stealth properties and stimulus responsive features to react to acidic tumor microenvironments, elevated enzymes, or redox. Nanoprecipitation, emulsification-solvent evaporation, microfluidics and electrospraying are used in manufacturing with optimization of the diameter of particles, the zeta potential and release kinetics. Recent developments are on multifunctional systems that combine both therapeutic agents and imaging contrast agents on theranostic applications [42-49].

- *Dendrimers:*

Figure 2 showcasing the highly-branched three-dimensional macromolecular carriers dendrimers are with a highly engineered structure and highly controlled architecture. Dendrimer research has been growing since 1978 with synthesis to biomedical use [50]. They possess distinct characteristics of nanoscopic dimensions, multi-functionalized surfaces, high multi-branched and cavernous internal spaces with unparalleled drug loading capability [51]. The structure is made up of a central core, branching in the interior and terminal surface groups and the synthesis is repeated to enable a strict control of molecular weight [52]. The drug loading is performed by means of physical entrapment, electrostatic forces, hydrogen bond formation and covalent conjugation. Their design forms micro environments which dissolve drugs that are insoluble in water [53]. It can be used in cancer, neurological disorders, infectious diseases, and inflammatory conditions, and the future is associated with multifunctional platforms focuse.

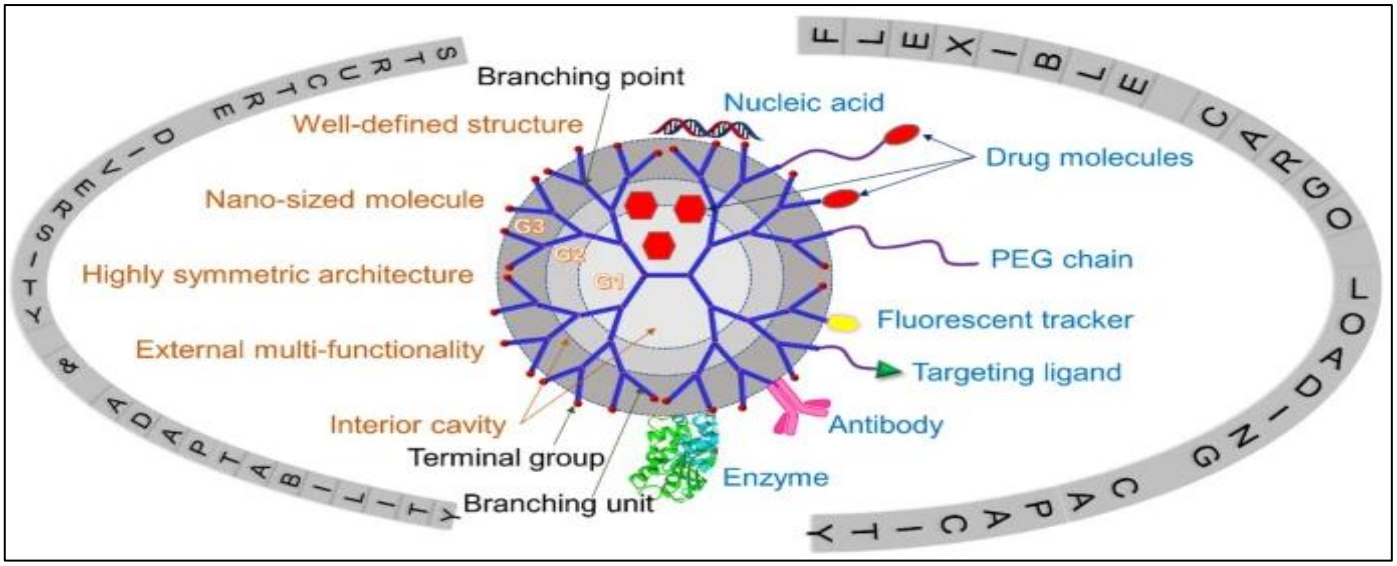

Fig 2 Schematic Representation of Dendrimer Structure and Functional Modifications for Drug Delivery Applications [57].

- *Hydrogel-Based Systems:*

Hydrogels are versatile biomaterials that are crosslinked polymer networks that create three-dimensional structures that can absorb a great amount of fluid but do not collapse depicted in figure 5. They are highly water-soluble, soft, porous structures of tissue which make them invaluable in drug delivery, tissue engineering, wound healing, and regenerative medicine [58-60].

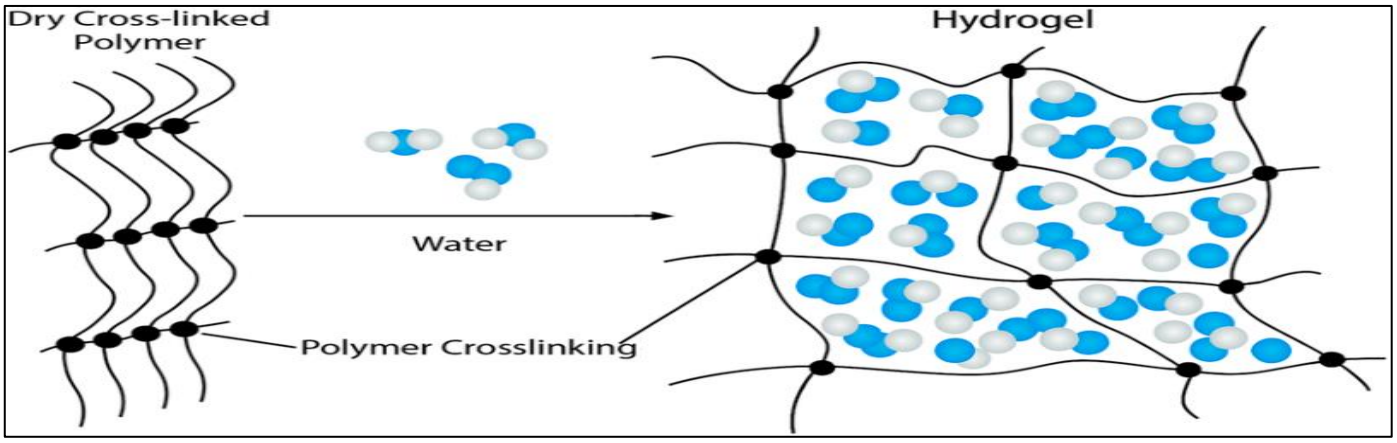

Fig 3 Transformation of Dry Cross-Linked Polymer into Hydrogel Structure Upon Water Absorption [61].

- *Structural Foundation and Preparation:*

The physical crosslinks to form the structural basis are through hydrogen bonding, ionic interactions and hydrophobic forces as found in thermoreversible networks, and the use of covalent bond as the chemical crosslink to form permanently crosslinked networks of greater stability. Collagen, gelatin, alginate and hyaluronic acid can be used as natural hydrogels to provide biocompatibility and biological activity, whereas polyethylene glycol, polyvinyl alcohol and polyacrylamide can be used as synthetic hydrogel types to control mechanical properties and degradation rates. pH responsive, temperature responsive, light responsive and multi-stimuli responsive systems exist [62-64].

- *Functional Properties:*

Molecular architecture, crosslinking density and environmental conditions control functional behavior. Behavior of swelling which is dependent on osmotic pressure and elastic restoring force can be controlled by network design. Mechanical properties range between soft brain tissue imitators and high cartilage substitutes with elastic modulus adjustable between pascals and megapascals. Viscoelastic properties can be manipulated by means of dynamic crosslinks, and diffusion and transport properties can be manipulated by mesh size [65-67].

- *Stimuli-Responsive Hydrogels:*

Stimuli-responsive hydrogel is a type of hydrogel that uses molecular switches to alter dynamic properties of hydrogel in response to external stimuli mimicking tissue properties [68]. Temperature responsive systems: These systems undergo a fast reversible change of phase, pH responsive systems [69]. These systems take advantage of ionizable groups to swell or deswell, light responsive systems: These systems can be controlled at a distance remotely. Traditional systems with single networks are characterized by low mechanical strength and low biocompatibility which are solved by interpenetrating polymer networks with both responsive properties and

high performance. Multi-stimuli responsive hydrogels are a great progress in biomimetic materials [67, 70].

- *Applications:*

Drug delivery systems control the release of drugs of small molecules up to large proteins and nucleic acids through diffusion, degradation and stimuli release control, and envelop them. Minimally invasive injection of hydrogel that can be injected into sites can be used to deliver hydrogels. The applications of tissue engineering offer three-dimensional scaffolds that assist cellular attachment, growth, and differentiation, and cell-adhesive peptides, growth factors, and bioactive molecules allow instructive scaffolds. The use of wound healing offers moist conditions that enhance quick healing and prevent infection by bacteria. Neural tissue engineering has soft mechanical properties that are equal to the neural tissues and this minimizes inflammation and enhances integration [71].

- *Advanced Developments:*

Minimally invasive Injectable hydrogels as an alternative material, in situ gelling systems have shifted to liquid to gel with the aim of becoming injectable [59]. Some of the innovations are thermoresponsive systems, photocrosslinkable systems, and dual-component systems [72]. The incorporation of nanoparticles into nanocomposites by nanotechnology resulted in the production of hydrogels that had superior properties [73]. The area is developing to more advanced materials that replicate the complexity of the biological systems where multi-functional hydrogel is a multi-purpose material that is able to deliver therapeutic care, diagnostic performance and regenerative processes as well. Machine learning and artificial intelligence promote the creation of optimized materials [74].

➢ *Microsphere Technology*

Microsphere technology is a new emerging technology which has been applied to counter the inherent shortcomings of the traditional drug delivery systems through an enhanced level of control of the drug delivery rate, increased target localization and an amazing capacity to synergize with other therapeutic agents. These versatile carriers are described as free-flowing spherical particles of between one to one thousand micrometers that are biocompatible and biodegradable and have excellent versatility in encapsulating small molecules, proteins, peptides, nucleic acids as well as viable cells. Recent innovations have drifted to intelligent, stimuli-responsive platforms which dynamically change with physiological microentities, which allows unprecedented spatiotemporal control [66, 75, 76].

- *Architectural Design:*

The development of drug-loaded microspheres represents a sophisticated approach to controlled drug delivery, combining various biocompatible polymers with therapeutic agents including chemicals, peptides, antibodies, and nucleic acids. Microsphere architectures of the future are in the form of matrix microspheres with therapeutic agents uniformly dispersed all through the polymer matrix, reservoir microspheres, which have drug-carrying cores within polymer membranes that allow complex release profiles, and advanced multiparticulate architectures combining multiple populations of microsphere with distinct release properties. As illustrated in Figure 4, they exhibit biphasic release kinetics in which a burst release event is followed by a sustained release with time, which is a key benefit over traditional methods of drug administration. The ability to precisely adjust polymer contents, particle dimension build, and inside organizational framework provides powerful tools to create bespoke delivery frameworks that maintain long-term therapeutic effects even with a single dose, thereby improving patient compliance through targeted delivery to specific tissues and cells [77, 78].

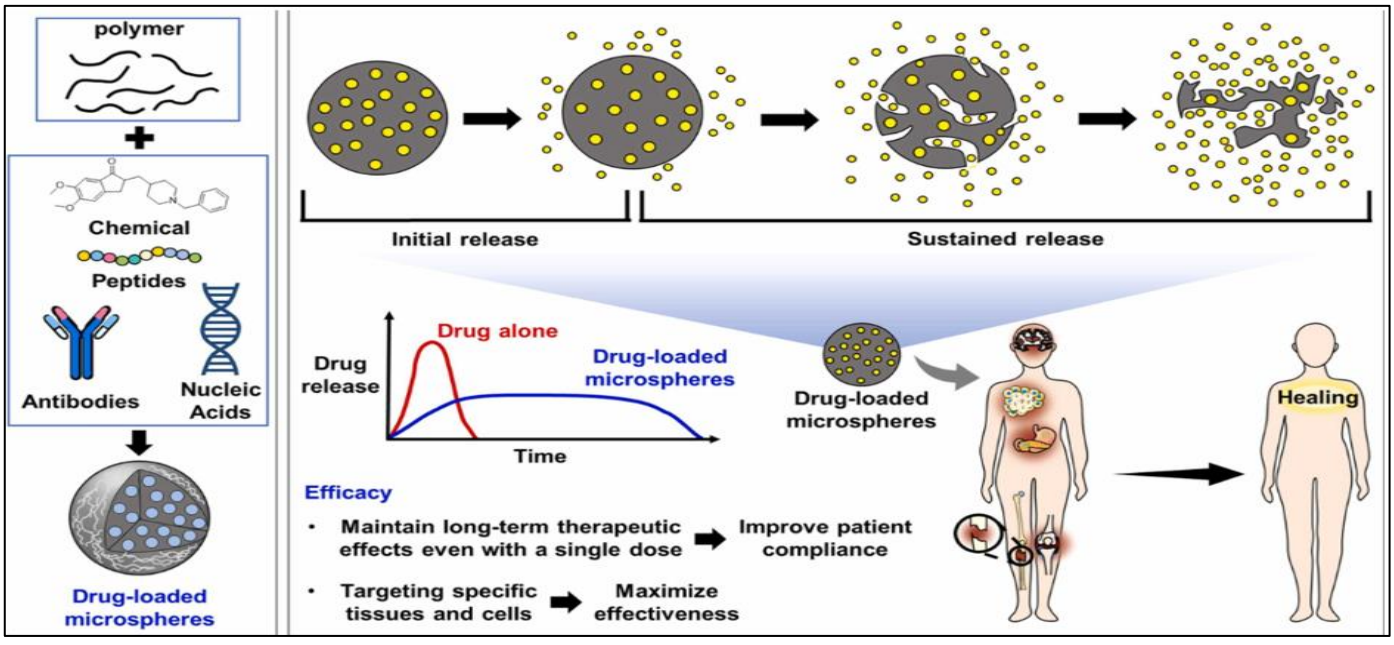

Fig 4 Topographical Representation of Fabrication and Controlled Release Mechanism of Drug-Loaded Microspheres.

The illustration indicates the entrapment mechanism of diverse therapeutic agents into polymer matrices and subsequent dual release profile of the bioactive molecule with an initial burst release then a sustained and extended drug release, promoting targeted delivery and enhanced therapeutic outcome [79].

- *Selection of Material and Drug Incorporation:*

The most primary option, which has been found to be of the best choice has been Poly (lactic-co-glycolic acid) which is characterized by the fact that it is well defined biodegradable and that it is favorable by FDA. The lactide to glycolide ratio provides an ability to control the degradation rates. The biocompatibility of natural polymers like chitosan, gelatin, alginate and albumin is outstanding but synthetic polymers have a better mastery over the material property The most common one is the physical encapsulation during the stage of microsphere formation. This is because hydrophilic drug encapsulation is often faced with the problem of drug partitioning, which requires particular approaches such as ion-pairing agents. The use of protein and peptide therapeutics poses difficult challenges because it is more prone to denaturation, necessitating stabilizing agents, including trehalose, mannitol, or bovine serum albumin detail is illustrated in table 1 [80-82].

Table 1 Comparative Study of Polymeric Materials in Microsphere Base Drug Delivery Systems

S. No	Aspect	Poly (lactic-co-glycolic acid	Natural polymer	Synthetic polymer
1	Biodegrability	Well-defined and bio-degradable	Outstanding biocompatibility	Controlled properties
2	FDA Approval	Favorable by FDA	Varies	Varies
3	Degradation control	controlled by lactide to glycolide ratio	Not applicable	Not applicable
4	Drug encapsulation	Commonly uses physical encapsulation	Challenges with drug partitioning	Challenges with drug partitioning
5	Challenges with proteins	Requires stabilizing agents for protein/peptide therapeutics	Generally more stable	Require stabilizing agent
6	Stabilizing agents	Trehalose, mannitol, BDA	Not typically needed	Trehalose, mannitol,BSA

- *Release Mechanisms and Fabrication:*

Drug release from polymeric microspheres happens via a number of concomitant processes, such as Fickian diffusion, relaxation and swelling of a polymer, osmotic pressure-mediated release, and progressive degradation of a polymer (Figure 5). As illustrated in Figure 5A, diffusion-controlled systems can be designed as either reservoir systems, where drugs are encapsulated within a polymeric membrane and diffuse through the barrier, or matrix systems, where therapeutic agents are uniformly dispersed throughout the polymer and release via matrix diffusion. These systems exhibit distinct release profiles: reservoir systems below drug saturation show decreasing release profiles, while systems loaded above saturation levels demonstrate zero-order constant release kinetics. PLGA microspheres characteristically display complex release patterns consisting of initial burst release, a lag period, and accelerated release as polymer degradation increases. Figure 5B demonstrates dissolution-controlled release systems where drug liberation is governed by polymer dissolution rates. In reservoir configurations, membrane thickness determines the release rate, where in a matrix system, drugs are released at the rate of boundary layer dissolution. Different methods have been established to manage burst release through optimization of processing conditions and use of release-modifying excipients.

Advanced solvent-activated and stimuli-responsive systems offer sophisticated control over drug release (Figure 5C). Swelling-controlled systems utilize expandable hydrogels that allow drug diffusion upon hydration, osmotic gradients Mechanisms of osmotic pumps use semipermeable membranes with controlled orifices to regulate the release rate using osmotic pressure gradients, and stimuli-activated systems use external physical stimuli e.g. heat, light, pH, ultrasound or magnetism to control drug liberation in a programmable way.

Systems of controlled release through chemicals rely on polymer degradation mechanisms to achieve sustained drug delivery (Figure 5D). These include pendant chain systems where drug molecules detach from polymeric side chains through hydrolytic or enzymatic cleavage, bulk erosion mechanisms characterized by gradual degradation throughout the entire polymer matrix with pore formation, and surface erosion systems where degradation occurs predominantly at the polymer surface, maintaining structural integrity during the release process. The most extensively utilized fabrication method is emulsification-solvent evaporation because of its high versatility and scalability. Spray drying offers benefits for heat-sensitive drugs with excellent control of particle size distribution and narrow size ranges. Supercritical fluid technology has proved to be an appealing alternative for thermolabile drugs, operating at relatively low temperatures without utilizing potentially toxic organic solvents [83-84].

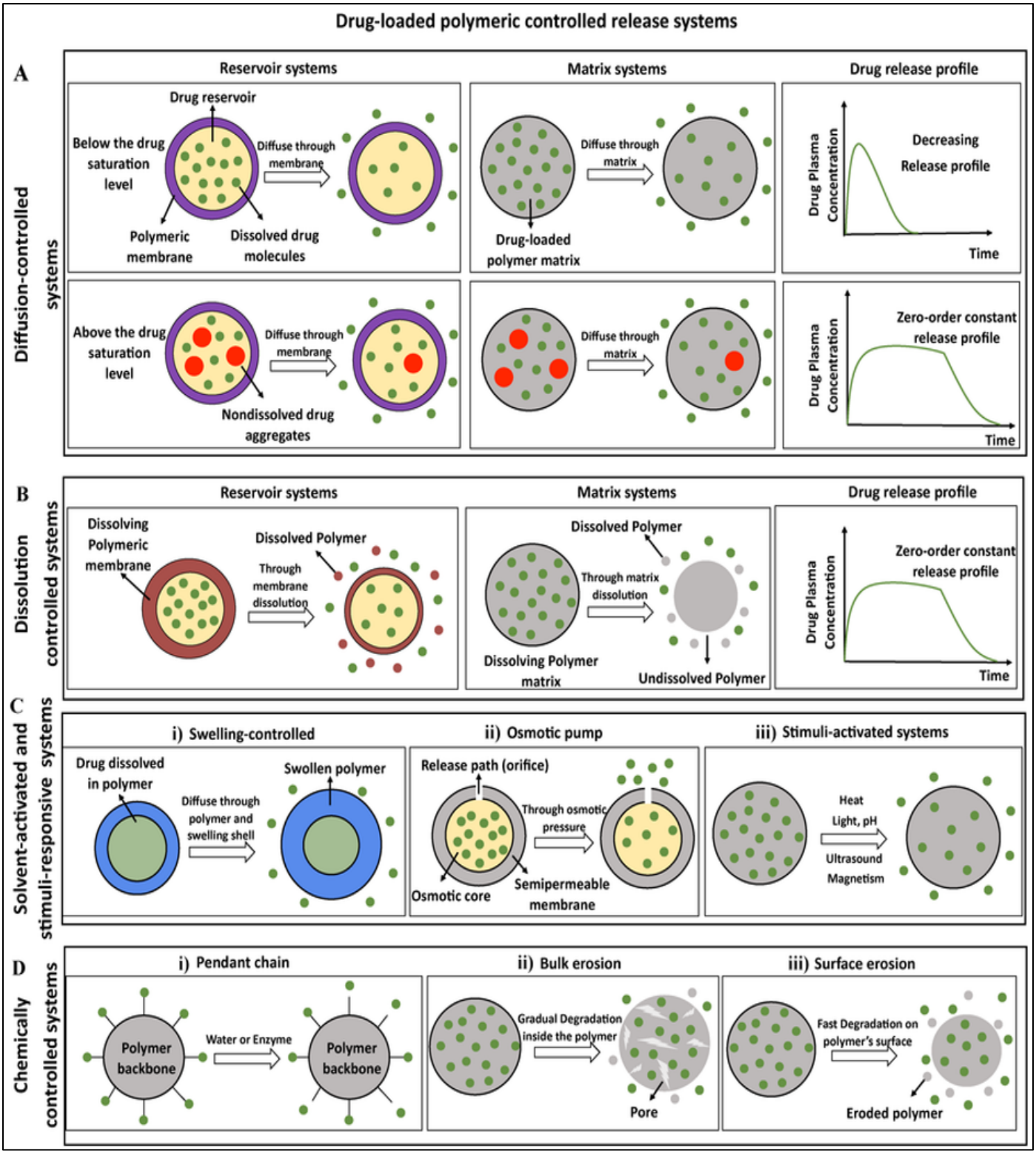

Fig 5 Polymeric Controlled Releases. Comprehensive Overview of Drug Release Mechanisms Including (A) Diffusion-Based, (B) Dissolution-Controlled, (C) Solvent-Activated and Stimuli-Responsive, and (D) Chemically-Mediated Controlled Release Systems [83].

- *Advanced Developments and Characterization:*

Microspheres that are stimuli-responsive use molecular switches that allow them to respond dynamically to pH changes, temperature changes, enzymatic activity, or redox conditions, pH-responsive microspheres exploit pH gradient in tumors and the gastrointestinal tract, and temperature-responsive microspheres can be based on the critical solution temperature behavior of polymers. Enzyme-responsible microspheres take advantage of the high concentrations of proteolytic enzymes in the diseased tissues. Surface modification strategies adopt a targeted delivery approach that uses passive targeting based on increased retention and permeability efficiency and active targeting through conjugation of the ligands. (antibodies, peptides, aptamers and others) [8, 85]. Extensive characterization involves physical characterization such as the size distribution related to the size of particle, morphology and surface features through the application of laser diffraction and

dynamics light scattering. Chemical characterizationbehaviour [86].

- *Clinical Translation and Future Directions:*

Long-acting injectable products have revolutionized the therapy of chronic conditions, with successful examples of such products being Lupron Depot, Risperdal Consta, and Sandostatin LAR being successful examples of monthly or quarterly injectable formulations based on PLGA [87]. Transarterial chemoembolization of hepatocellular carcinoma has been advantageous to cancer treatment. Vaccine delivery has benefits of antigen protection and augmentation of immune responses The way forward would be to create advanced systems that will be able to offer individualized therapy and face-to-face monitoring [88]. Recent innovations have involved the use of porous polymeric microspheres in bioinks to be used in three-dimensional bioprinting. Next-generation delivery systems are possible due to the combination with artificial intelligence and nanotechnology, in which machine learning is able to optimise the formulation parameters. Therapeutic/diagnostic microspheres Theranostic microspheres (a combination of therapeutic and diagnostic) is a brighter future. A convergence in regenerative medicine is given the opportunity to develop conversion systems with preference towards tissue repair [89].

➢ *Implantable Devices*

Implantable drug delivery systems are an example of such an area of development of biomedical engineering that offers unprecedented opportunities of continuous therapeutic intervention and real-time physiological monitoring that transforms the manner in which chronic diseases are treated [90]. These high-tech equipments are autonomous self-managing, prolonged drug delivery across extended periods, as well as site-specific delivery, and its level of systemic exposures and optimum therapeutic effect is quite high. Modern era implantable devices aid in filling in such gaps between passive drug delivery and active therapeutic management and accomplish these by integrating the sensing, processing and delivery functions of biocompatible systems [91].

- *Design:*

It has to be properly multidisciplinarily evaluated in terms of bio compatibility profiles, optimization of mechanical property, power management, implementation of communication protocols and improvement of therapeutic performance. Basic device design is biocompatible housing, minimized sensors continuously measuring physiological conditions, embedded microprocessors that do real-time data processing, intensively engineered drug delivery systems, renewed energy sources, and wireless communication integrated circuits. The most significant design factor is biocompatibility, which demands the choice of materials to provide a balance between mechanical stability, chemical stability, and positive biological reactions. The use of power management is an engineering challenge and the emerging energy harvesting technologies are taking advantage of piezoelectric, thermoelectric, and electromagnetic developed using the principle of sustainability to harness power out of physiological processes [92-94].

- *Controlled Release Mechanisms:*

Diffusion-controlled systems Use rate-limiting polymer membrane, with drugs diffusing through by molecular diffusion, and their release rates adjusted by the thickness of the membrane, porosity, and polymer composition. Osmotic pumping systems use osmotic pressure differentials to force desired drug expulsion using laser-drilled microorifices, with very consistent delivery that is not dependent on physiological variables. Advanced mechanical pumping systems introduce miniaturised actuators which are controlled by sophisticated microprocessors and allow programmable multi-drug delivery control with programmable kinetic profiles and programmable dosing responses [95].

- *Advanced Sensing and Closed-Loop Systems:*

The current implantable sensors track the overall parameters such as glucose levels, blood pressure, tissue temperature, local pH, oxygen saturation, drugs concentrations, and biomarkers [96]. Continuous biochemical monitoring is mainly overtaken by electrochemical sensing because of outstanding sensitivity and selectivity of the molecules. Optical sensing technologies make use of light-tissue interactions to monitor on a non-invasive basis. The intracranial pressure and the cardiac chamber pressures can be measured accurately with mechanical sensing using the use of micro-electromechanical systems [97].

Closed-loop therapeutic systems can be seen as a progressive step forward because of autonomous response to instant physiological feedback changing treatment regimens. An example of this method is artificial pancreas systems, which are capable of automatically regulating blood glucose levels, and combine continuous glucose level monitors with insulin delivery pumps, controlled by complex control algorithms. The closed-loop pain management system involves the use of multimodal sensors that are fused with intrathecal drug delivery pumps. The high cardiac rhythm management devices have detailed monitoring and treatment functions summarize in figure 6 [98].

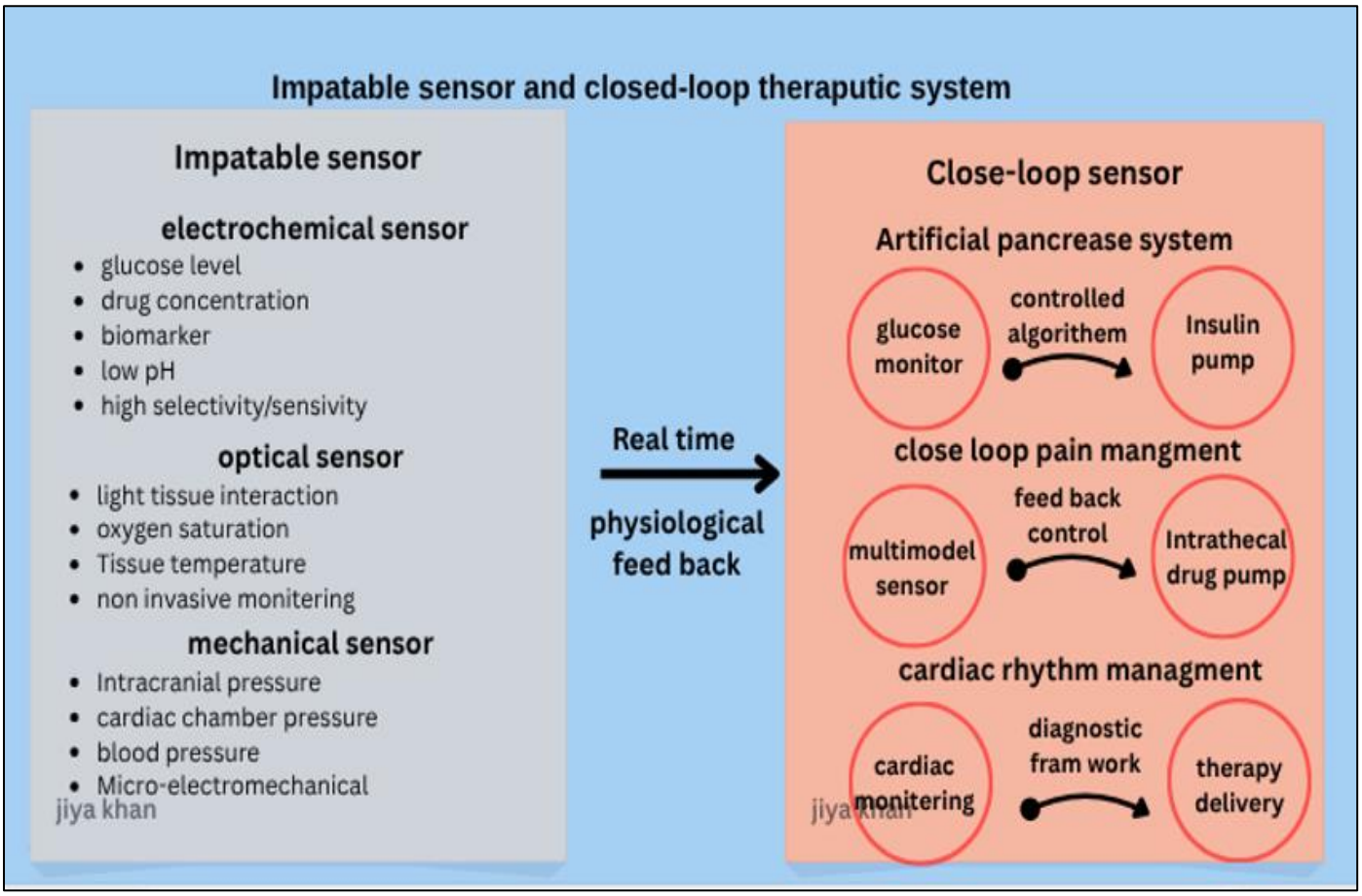

Fig 6 Impatabe Sensor and Close Loop Therapeutic System

- *Wireless Communications and Advanced Materials:*

The integration of wireless communication has transformed the way patients are treated by enabling the capacity to track the patients as they go on, and dynamically optimize the treatment. Modern devices embrace some communication standards that have been developed, including radiofrequency transmission, Near-field communication and Bluetooth Low Energy. Remote monitoring will allow medical personnel to identify the state of the patient at all times and optimize, treatment programs. Some of the advanced cybersecurity tools include multi-factor authentication and encryption algorithms, which protect sensitive physiological data [99-100].

It can be used to develop next-generation devices with high performance and biocompatibility through advanced materials development. More recent advances are biodegradable electronics that resorb safely after an accomplishment of therapeutic missions, self-healing materials, and biomimetic surface structures. Electronic materials that are more flexible and stretchable allow close provision to adherent biological tissues. Functional integration is facilitated by advanced manufacturing platforms such as additive manufacturing, micro-electromechanical systems fabrication and nanoscale assembly techniques [100-101].

- *Theranostic Applications and Clinical Translation:*

Theranostic implantable devices are diagnostic and therapeutic devices that are able to monitor disease-specific biomarkers, administer targeted therapy and quantify treatment responses [102]. The applications of cancer treatment monitor the parameters of the tumor microenvironment and provide a high level of accuracy when delivering the chemotherapeutic agents. The applications in neurology take advantage of integrated monitoring to treat brain disorders by monitoring patterns of pathological neural activity and providing electrical stimulation or drugs [103].

Clinical translation has attained exceptional success with many of the devices becoming regular care standard. Cardiac pacemakers are examples of pioneers that have more than one million implantation of cardiac pacemakers each year across the world. The MiniMed 670G artificial pancreas is the first FDA-approved closed-loop system of insulin delivery. Spinal cord stimulation devices are used to treat refractory chronic pain with high degree of success, whereas deep brain stimulation is useful in treating movement disorders, and psychiatric disease [104-105].

- *Challenges and Future Directions:*

Thus, although there has been impressive progress, there are still some major challenges that limit adoption. The presence of biocompatibility issues and foreign body reactions may result in the fibrotic encapsulation of the functioning of the device. Power management limitations also limit the capabilities and lifespan of the device, which must be replaced periodically by surgery. Reliability and failure prevention of devices is still of vital concern, especially to life-sustaining applications. Complex

regulatory pathways that demand a lot of preclinical characterization pose significant development challenges [93-106].

IV. TECHNOLOGIES FOR CONTROLLED RELEASE

The pharmaceutical drug delivery has fundamentally changed due to nanotechnology as it overcomes the fundamental limitations of traditional formulations especially in reaching optimal drug loading capabilities and controlled release kinetics as well as the ability to control pharmacokinetics, bioavailability and targeted therapeutic delivery at unprecedented levels. The poor loading efficacy of conventional delivery systems is also common with most hydrophobic drugs loading with less than twenty percent in conventional nanocarriers [107-108].

➢ *Drug Loading Strategies*

Biodegradable polymer polymeric nanoparticles such as PLGA and chitosan have superior drug loading, physical entrapment, and chemical conjugation drug loading mechanism. Maximizing the interaction of polymers with drugs and the utilization of complex strategies, including nanoprecipitation and emulsification-solvent evaporation, greatly improves the encapsulation efficiency. Solid lipid nanoparticles and nanostructured lipid carriers obtain high drug loading of lipophilic drugs by capitalizing on the drug solubility in lipid matrices with loading efficiencies sometimes approaching ninety percent of selected hydrophobic drugs using controlled crystallization. Carrier-free nanosystems such as drug nanocrystals, in which the drug itself is the core of the nanocarrier, demonstrate very high loading efficacies to the extent of being almost one hundred percent, an overcoming burden limitation on a carrier material and retaining the benefits of nanoscale such as enhanced dissolution and cellular uptake [109-111].

➢ *Controls Release Mechanisms.*

Controlled release systems allow accurate time regulation that is directed to the particular treating needs. Diffusion-controlled release is when drug molecules diffuse via polymer matrices or nanocarrier membranes under the laws of the Fickian diffusion, release rates are regulated by altering the molecular weight, crosslinking density, and porosity of matrices. Controlled release Erosion-controlled release systems offer a zero-order kinetics by means of controlled degradation of biodegradable carriers, as is the case with PLGA nanoparticles, where drug release is regulated by polymer hydrolysis and matrix erosion, which is useful in sustained-release preparations with constant plasma levels. The most advanced system is the stimuli-responsive nanosystems, which react to certain physiological/pathological needs such as pH-reactive systems taking advantage of acidic tumor microenvironment or lysosomal compartments, and temperature-sensitive liposomes that release drugs during mild hyperthermia [8, 84, 112].

- *State-of-the-Art Release Modulation.*

The more sophisticated methods are multi-reservoir systems that permit the use of complicated profiles including biphasic and pulsatile profiles and delayed release profiles using multilayered nanoparticles in various polymer blends that will permit controlled release of drugs sequentially. The core-shell architectures offer initial burst release of shells and then continuous core release, and model ideal pharmacokinetic releases. Smart delivery systems that include feedback systems react to drug concentration signals, disease biomarkers, or external trigger to adjust release rates on a real-time basis. Magnetic nanoparticles can be externally manipulated by the application of magnetic fields that give on-demand delivery of therapy [113-115].

➢ *Issues that Affect Performance.*

The compatibility of the carrier with drugs plays a great role in loading efficiency and release kinetics. Hydrophobic drugs are generally loaded more in lipid-based carriers whereas hydrophilic drugs are more suitable in the hydrogel nanoparticles. Maximum achievable loading capacity is dependent on molecular weight and size compatibility between drugs and carrier pores. Surface modification strategies have a significant effect on both properties, as PEGylation increases circulation half-life and has an effect on the release rates due to change in surface properties. Targeting ligands that are conjugated to surfaces induce a particular release process when bound to target cells or tissues. The physiological systems have environmental factors that can play an important role in the kinetics of release because protection on nanoparticle surfaces through protein adsorption in biological fluids may change nanoparticle surface properties, and later release rate, whereas enzymatic degradation is another controlled release mechanism that should be highly considered in the application of nanoparticle drugs [38-59].

➢ *Clinical Translation Considerations*

Clinical translation necessitates that consideration be made of highly important aspects such as scalability to manufacturing with a lot of laboratory scale preparation methods not being able to be translated to an industrial level and that optimization of the processes to ensure the same drug loading and release properties in large batches as in small batches must be undertaken. Regulatory considerations of nanomedicines focus on supporting the full characterization of drug loading, release kinetics, and stability profiles, and in vitro-in vivo correlations are important to predetermine the clinical performance of nanomedicines. Parameters of quality control peculiar to nanosystems such as distribution of particle size, uniformity of drug loading, and reproducibility of release profile are required to gain regulatory approval. Disease state, age and specific genetic variations are all patient factors that have a significant impact on nanosystem performance. Another way forward of precision medicine in nanotechnology-driven drug delivery is personalised nanomedicine where individual patient properties are taken into account in order to optimize drug loading and release processes [38, 107, 116].

V. MONITORING DRUG RELEASE

Accurate measuring of drug delivery system release is core to the knowledge of therapeutic performance, formulation optimization and clinical efficacy. The superior methods of monitoring allow real-time evaluation of release kinetics of drugs in real life systems and in the laboratory, which offers the necessary data in drug development and clinical translation.

➢ *In Vitro Monitoring Methodologies.*

The traditional in vitro drug release research employs well-known and recognized methodology with the United States Pharmacopeia (USP) dissolution apparatus becoming the gold standard of conventional dosage form. However, such systems have dire deficiencies to be applied to the nanotechnology-based delivery systems due to the challenges of isolating the released drug to the encapsulated drug in colloidal systems, special techniques are necessary [86].

- *Techniques of Membrane Diffusion.*

The most common method of studying the release of drugs through nanocarriers relies on membrane diffusion methods especially dialysis-based techniques. The systems utilize semi-permeable membranes that permit free drugs to pass through and retain the delivery system such that the cumulative drug release can be monitored continuously and hence determine the kinetics and drug release mechanisms. Nevertheless, the membrane selection is a very important factor of the outcome, because pore size and material structure might introduce artificial membrane resistance that might not occur in nature [117-118].

- *Sample and Separate Methods*

Sample and separate techniques, such as ultrafiltration and ultracentrifugation, allow direct separation of released drug and carrier-bound drug by not using any membrane barriers, which is particularly useful in lipophilic drugs that can be bound to dialysis membranes. Ultrafiltration involves the use of molecular weight cut-off filters to distinguish between free drug and drug-loaded nanoparticles to give accurate and rapid determination of release rates. The combination of coupling reverse-phase high-performance liquid chromatography with sample separation methods is the most precise strategy of analyzing drugs to identify the drug degradation products and the metabolites to provide a complete evaluation of the release profiles and drug stability. The DLS approach allows real time observation of changes in nanocarrier size during drug release, which is a mechanistic method as it can determine if release happens by matrix erosion, swelling, or other sources [119-121].

- *Advanced Technologies*

Continuous flow systems are closer to the physiological conditions due to the presence of sink conditions and the ability to offer controlled hydrodynamic environments that are tightly controlled in terms of flow rates, temperature, and pH [122]. Through these systems, it is possible to simulate different sites of the anatomy and avoid the buildup of released drug, which could influence release kinetics in stationary systems artificially. The latest trend in in vitro drug release monitoring is microfluidic devices, which allow the microenvironment to be controlled and certain physiological conditions such as pH gradients, enzyme concentrations, and fluid flow patterns can be modeled. Their use in small sample volumes allows them to be optimally used with costly drug formulations and high-throughput screening. The automated sampling and analysis systems allow non-manual continuity in monitoring and minimize variability and enhance reproducibility. It can be fully automated with the integration with analytical tools, including UV-Vis spectrophotometers or HPLC systems [123-124].

➢ *In Vivo Monitoring Technologies*

The creation of drug-fluorophore conjugates, where fluorescence changes when drug is released, and fluorescence resonance energy transfer (FRET) or quenching of fluorescence to reportedly report drug release events, combined with fluorescence fluorophore technology in the near-infrared has proven to be a powerful tool in real-time monitoring of drug release in living subjects [125]. The second near-infrared window (NIR-II) fluorescence imaging has a reduced background interference and better tissue penetration than the traditional fluorescence techniques, which means that the gastrointestinal drug release can be monitored with a better clarity and depth through longer wavelengths, which offer a better signal-noise ratio and a lesser light scattering in biological tissues [126].

Categorized as drug release monitoring MRI based drug release monitoring systems make use of contrast agents in which relaxation properties change upon release of a drug and gadolinium-based systems have been developed in which the contrast agent is released concomitantly with the therapeutic drug, allowing to indirectly monitor drug distribution and release through the measurement of relaxation times (T1, T2) which provide quantitative measures of relaxation properties with very high spatial resolution igliantz [126, 127]. Temperature responding contrast agents permit tracking of hyperthermic drug release of thermosensitive liposomes, through the temperature sensitivity of contrast agent characteristics, of drug release in response to focused heating, with real-time MRI thermometry and contrast enhancement giving comprehensive information on both triggering application and drug release [128]. Radiolabeled drugs or carriers are used to perform positron emission tomography imaging, which gives the most sensitive information regarding the distribution and release of drugs in vivo, which gives quantitative evaluation of drug pharmacokinetics, whole-body imaging of radiotracers with picomolar sensitivity [129]. The introduction of dual-label systems which combine a PET tracer with a therapeutic drug enables this simultaneous tracking of carrier distribution and drug release to give a direct correlation between the carrier localization and

therapeutic drug availability at target sites with a time resolution that can giv

Multi-modal monitoring systems that combine several techniques offer extensive evaluation of the drug release mechanisms where combination of fluorescence imaging and MRI offers the possibilities of correlating drug release kinetics with anatomical localization [39]. The multi- modal strategies eliminate the weaknesses of single methods and offer cross validation of findings. The future of the drug release characterization is in the real-time monitoring systems that integrate in vitro mechanistic knowledge with in vivo performances evaluation, allowing the optimization of the delivery systems in light of both principles of mechanics and clinical needs [133].

VI. ADVANCES IN IMAGING TECHNOLOGIES FOR REAL-TIME MONITORING OF DRUG DELIVERY SYSTEMS

Nevertheless, the latest advancement of imaging technologies has altered the concept of real-time monitoring of drug delivery systems and provided unprecedented opportunities of non-invasive visualization of therapeutic procedures in live organisms. The technological advances enable the dynamism in the evaluation of drug release, distribution and therapeutic efficacy at a higher level of time and space resolution.

- *Innovations in Near-Infrared Fluorescence Imaging.*

The emergence of second near-infrared window (NIR-II, 1000-1700 nm) fluorescence imaging is the paradigm shift in real-time drug monitoring properties as it has much less tissue scattering and autofluorescence in comparison with the traditional visible and NIR-I imaging. Longer wavelengths offer greater penetration depth of tissues in biological tissue over 10 mm, which makes them visible to deep-seated therapeutic targets [126]. The advances in the small-molecule fluorophores used in NIR-II imaging in recent years have made extraordinary progress in improving quantum yields and photostability, showing improved signal-to-noise ratios and allowing imaging to be used continuously over long periods without considerable photobleaching. These fluorophores systems fitted in drug delivery systems give real-time visualization of carrier distributions and drug release kinetics [134].

Systems of high-speed NIR imaging have been developed, allowing faster frame rates of greater than 100 fps can be used to follow the rapid physiological events, with sensitive InGaAs detectors and optimized optical systems that provide sub-millimeter spatial resolution and microsecond time resolution. Its high sensitivity and quick acquisition allows to monitor changes of single nanocarriers and drug release rates at the cellular scale. Multiplexed NIR imaging technologies can combine multiple fluorescent channels to visualize carrier distribution, drug release, and biological responses to allow the correlation of therapeutic delivery to physiological parameters and give a global evaluation of the treatment efficacy. The applications of spectral unmixing algorithms in the recent years have enhanced the precision of multi-channel quantification in complicated biological settings [135-136].

- *Photoacoustic Imaging Discovery.*

It has been developed as an effective technique of real-time monitoring of drugs, which is a combination of the specificity of optical imaging and penetration of ultrasonic signaling [130]. Recent innovations in the technology of photoacoustic have reached imaging depths of more than 7 cm in human subjects and maintained respiratory rates under 200 micrometers in spatial resolutions, providing the capacity to monitor drug delivery to deep tissue organs such as liver, kidneys and brain tissue non-invasively [137]. Photoacoustic monitoring has especially boosted the development of NIR-triggered drug release systems that allow real-time visualization of drug release events driven by near-infrared light, and which provides a high spatiotemporal control over drug delivery. The photoacoustic signal that is emitted during drug release gives quantitative information on how the treatment parameters can be optimized [138].

Recent advances in the nanophotonic enhancement have significantly enhanced the sensitivity and contrast of photoacoustic imaging with plasmonic nanoparticles and quantum dots incorporated in drug delivery vehicles, which generates enhanced photoacoustic signals and provides the ability to detect drug concentrations at the nanomolar range [139]. These nanophotonic probes are also biocompatible and offer high imaging contrast during a long period, when the nanophotonic probe is being monitored. Multi-wavelength photoacoustic systems can be used to measure multiple therapeutic agents with different absorption spectra simultaneously, which has been especially useful in combination therapy where multiple drugs are administered by a different release mechanism. The spectroscopic data acquired as a result of the use of multi-wavelength imaging offers the information on drug-tissue interactions and metabolism [140, 141].

- *State of the Art Magnetic Resonance Imaging.*

The capacity to image magnetic resonance imaging has attained unprecedented progressions by developing responsive contrast markers in real-time drug release and the concept of temperature-dependent and pH-dependent MRI contrast markers, which has allowed indirect monitoring of drug release by reporting the local environmental variations. Such intelligent contrast systems can offer quantitative evaluation of release kinetics at a high level of spatial resolution over the body. Recent advancements in chemical exchange saturation transfer (CEST) MRI have allowed the detection of drug molecules to be done via the natural magnetic properties of therapeutic agents without exogenous contrasts being used to generate image contrast which has direct visualization of drug distribution and concentration. CEST-MRI is sensitive enough to act like nuclear medicine methods and has a good spatial resolution [127-128].

Recent technology of ultra-high field MRI systems (7 Tesla and higher) has transformed the real-time drug monitoring systems with a spatial and temporal resolution as never before, allowing the visualization of drug delivery on a cellular scale in living subjects and also a detailed insights into the mechanism of the therapy. High field strengths increase the signal to noise ratio, allowing acquisition sequences to be completed within a short length of time; this can be used in real-time monitoring. Functional MRI systems combined with drug delivery imaging allow measurement of both therapeutic effects and physiological activity and are thus able to give an overall analysis of the treatment results by comparing the distribution pattern of drugs with the dynamic changes of the target tissues. Live-time tracking of drug delivery and real therapeutic response allows optimization of treatment regimens in the process of administration [142-143].

- *Ultrasonic Imaging Innovations*

With high frame-rate ultrasound technology, real-time monitoring of drugs in clinical environments has been altered to achieve a frame rate of more than 10000 frames per second and allow the visualization of high-rate events like the destruction of microbubbles or drug release. High temporal resolution and a good spatial resolution allow the detailed evaluation of drug delivery dynamics. Functional ultrasound imaging can also be used to monitor blood flow alterations with the delivery of drugs providing indirect measures of effectiveness of treatment by visualizing hemodynamic responses to therapy. Ultrasound is non-invasive and real-time, which renders it to be suitable in clinical monitoring applications [144-145].

Recent development of ultrasound contrast agents have permitted the real-time imaging of drug-conjugated microbubbles and drug-bubble dismantling kinetics and has made a quantitative evaluation of drug release by sounding of the bubble rupture process. The localized destruction of drug-containing microbubbles allows the control of the delivery of therapeutic agents in space and time. Targeted ultrasound contrast agents are developed that contain special binding ligands to allow a selective accumulation of the contrast at disease locations that provide a greater contrast to track drug delivery to a particular type of cell or pathological tissue. With the possibility of targeting and acoustic monitoring, it is possible to use precision medicine when approaching individual patients [146].

- *Artificial Intelligence Implementation.*

Utilization of AI and machine learning algorithms has enhanced significantly the analysis of real time imaging data in drug monitoring applications with deep learning approaches making it possible to automatically identify and quantify drug release events on complex imaging data. These artificial intelligence (AI) systems have the ability to process large volumes of imaging data in real-time and give instant feedback to optimize the treatment. Predictive software based on machine learning and trained on high volumes of imaging and pharmacokinetic data has the potential to foresee drug delivery performance, forecast therapeutic success using early imaging results and coordinate proactive changes in the treatmen. The ability of AI systems to learn continuously enhances their accuracy of prediction as time progresses with the availability of additional clinical data. New high-end imaging systems have introduced AI-based decision support features that can deliver real-time treatment advice based on the analysis of imaging data and the comparison of the findings with the conventional treatment regimens to give appropriate treatment parameters. It is proposed that the combination of patient-specific information and imaging data allow individual treatment solutions [147-148].

- *Multi-Modal Imaging Approaches*

The advanced imaging multi-modal systems allow the simultaneous installation of multi-modal information concerning drug delivery mechanisms by the combination of multiple imaging techniques, including fluorescence, photoacoustic and MRI to offer a complete analysis of therapeutic delivery. There are several modalities that are related to the possibility of enhancing accuracy and reliability of drug monitoring results. The existing trends in hybrid imaging systems have managed to record multi-modal data in time and space and this enables the outcome of different imaging procedures to be compared directly. This is observed to be particularly handy in the requirement of checking drug release measurements and making monitoring results precise. Multi-modality integration also possesses the merit of offering redundancy that improves reliability of systems that are implemented in clinical practices ammers [133-149].

VII. CHALLENGES AND LIMITATIONS

Despite the glittering technological advances in the sphere of smart drug delivery, the idea is still confronted with monumental difficulties in terms of long-term stability and commercial viability of the matter of clinical translation and mass use.

- *Stability Challenges:*

Smart drug delivery systems are prone to instability issues since they are multi-component systems with delicate response processes. Stimuli-responsive carriers and polymers are commonly degraded by physiological factors, resulting in untimely drug delivery, or responsiveness, and multiple functional elements result in a large number of possible points of failure [8]. Protein and peptide pharmaceuticals have specific issues because of their vulnerability to denaturation, aggregation, and in vivo catabolism. Temperature-dependent systems can also experience a storage phase change and temperature variation that will irreversibly damage stimuli-responsive parts [8, 150].

The same properties that allow responsiveness to biological stimuli also result in systems that are susceptible to uncontrolled variations in the environment and enzyme-responsive systems are subjected to inter-patient variance in enzyme expression [151]. Components may be degraded by oxidative stress and reactive oxygen species and light-sensitive systems must be packaged in a special

way or risk being triggered inadvertently. Conventional accelerated stability testing is not necessarily a good one to determine the sensitive-to-stimulus performance of a system. Architecture of a delicate constituent may be disturbed by Lyophilization and preservation procedures. To formulate in a suitable manner, there has to be a great depth of knowledge of the degradation processes, and the selection of cryoprotectants and stabilizing excipients must be attentively done to ensure the proper functioning of both the drug and the responsive system [152, 153].

- *Scalability Challenges:*

The scaling of laboratory-scale to commercial manufacturing is a major challenge since the preparation techniques that entail the meticulousness of various elements present a technological challenge when scaling up. Small-scale microfluidic methods of synthesizing specific nanoparticle types at small scale frequently cannot be simply scaled up to commercial needs. The variability problem of batch-to-batch is more of a problem at larger scales, as small processing differences greatly affect responsiveness, and that multi step synthesis processes add more variability to manufacturing and quality control problems. To achieve real-time monitoring, more sophisticated process analytical technology (PAT), than the conventional quality control system might be insufficient to determine the integrity of the stimuli-responsive mechanisms. Scale-up should include comprehensive knowledge about the critical parameters of the processes, and design of experiments must take into consideration complex interactions among drug stability and system performance. Further production technologies result in significantly higher costs of production, special equipment, controlled conditions and intensive testing make it more costly. Stimuli-reactive materials and high-tech polymers are also too expensive in raw materials. Cost benefit analysis is economic feasibility and it will be suitable to invest with improved clinical outcomes [154-156].

- *Regulatory and Quality Control Challenges:*

The intelligent delivery systems require the comprehensive characterization to the traditional pharmaceutical criteria and the testing of stimuli-responsiveness, targeting efficiency, and controlled release systems require the specifically crafted analyzing instruments. The standard dissolution tests may not reflect in vivo performance and this needs biorelevant test conditions with quality control specification that will involve functional performance properties The process of approval is far more complex than the conventional pharmaceutical and multiple paths can be used depending on the nature of components. This can result in excessive reviews and increased data requirements in the absence of formal guidelines. The harmonization process remains incomplete to create global commercialization impediments, and specialized skills requirements are those aspects that predispose the process of approval to be lengthy [86-157].

- *Technical Limitations:*

Despite the fact that the targeting strategies have improved, the effectiveness of the targeting is not optimum. The EPR effect is characterized by a high inter-patient variability, and active targeting with the help of ligand-receptor interactions frequently results in only moderate improvement in comparison to passive targeting. Targeting functions can be kept under complex biological barriers such as formation of protein corona, immune recognition, and clearance procedures and disease heterogeneity poses challenges in the development of universally effective strategies. In order to determine predictable and reproducible reactions to biological stimuli, it is still a challenge where inter-patient unpredictability with regard to physiological states leads to inconsistent performance. Target sites cannot be reliably attained at threshold stimulus concentrations. Mechanisms of robust response need to be heavily clinically validated, feedback control mechanisms are still technical and non-clinically feasible [158].

- *Future Perspectives:*

Future systems involve self-healing materials and adaptive systems that are used to reduce the effects of degradation, and more complex multi-layer encapsulation methods are used to protect sensitive parts. Computational modeling finds more stable forms of the molecules contrary to the machine learning methods which estimate the stability issues and optimization of formulation parameters. The quality control in a form of AI will provide real-time evaluation, and constant manufacturing technologies will be able to provide scalability and a decrease in costs. There is a possibility of modular production enabling ability to have flexible production through usage of common platforms. The standardized protocols and the collaboration with the industry will allow obtaining regulatory approval and cost-effective solutions [159].

VIII. BIOCOMPATIBILITY, REGULATORY HURDLES, AND PATIENT COMPLIANCE IN SMART DRUG DELIVERY SYSTEMS

There is a high risk in the Biocompatibility analysis, regulatory approval processes and patient compliance of the translation of smart drug delivery systems out of the laboratory research to clinical practice that is paramount challenges requiring an organized effort to ensure patient safety and therapy efficacy.

- *Biocompatibility Challenges:*

Smart drug delivery systems bring new material into the market that in most scenarios lack full data about its biocompatibility which is very much of safety concern. The stimuli responding systems of novel and advanced polymers can possess uncertain biological behaviors and be under hard testing in various physiological circumstances. Metallic nanoparticles (e.g. gold, silver) could be stored in the tissues and lead to its subsequent toxicity, but carbon-based nanomaterials is dangerous due to its persistent form and its ability to cause inflammatory states. Other challenges are in immunogenicity, where

complex structures can induce the negative immune responses especially when administered repeatedly. The need of long-term safety research is because there is the risk of accumulation of non-biodegradable materials in the long run and the complications associated with reproductive toxicity testing is because of the possibility of passing through the placental barrier [59, 160-162].

- *Regulatory Hurdles:*

Smart delivery systems have a tendency to be in the grey areas of regulation, and as such, their approval is complicated. Although nanomedicines have regulations by the FDA and the EMA, new technologies regularly surpass regulations. These systems can be classified differently which influences the regulatory pathways and data requirements. It is necessary to do extensive characterization outside of conventional parameters such as the ability of the stimuli-responsiveness, and the consistency of the batch. These complex systems require new designs of clinical trials to determine safety and efficacy and there are problems with dose selection and patient enrollment strategies that are caused by the heterogeneous nature of patient populations. There is a variation between regulatory methods across countries which makes it hard to develop products globally [163-165].

- *Patient Compliance and Usability Issues:*

Smart drug delivery system may be complex and may overwhelm the patient, especially elderly ones or ones with limited technical skills. Some of the barriers that complicate the effective use of the devices include cognitive deterioration, visual issues, inabilities to manipulate devices, etc. Health literacy can be low and result in the absence of awareness about the connection between device use and therapeutic outcome and there is a high difference in technology acceptance. User interfaces put more emphasis on technical functionality than on usability, which presents potential medication errors. The necessity to support on a regular basis only exacerbates the problem of patient compliance and makes it an ongoing responsibility and something that may not be within the capacity of the patients [166-168].

- *Strategies for Improvement:*

Application of the human-centered design concepts through user research and trial and error will be important in the development of useful interfaces [169]. Automation can help to simplify the interaction of users and offer detailed education programs to promote the understanding and engagement of patients. Combination with the existing healthcare technology and AI use can facilitate experiences and anticipate patient needs. Standardization of interface design of systems can help to reduce the learning loads, and the expenses can be overcome through the training of healthcare providers to deliver services and make use of smart delivery systems by the patients.

IX. CONCLUSION

Finally, smart drug delivery systems represent the leading inventions of personalized medicine that has both controlled release and tracking, which greatly increase the level of therapeutic response. This review shows the different categories of the smart systems, their action mechanisms and the technologies involved in developing smart systems. Although obstacles still exist especially in terms of stability and regulatory licensure, continued innovations promise a lot in terms of solving the problems. With the field developing, the opportunities of smart drug delivery systems to transform the paradigm of treatment and enhance the outcomes of patients cannot be overestimated. Further studies and interdisciplinary cooperation will be necessary to reach the maximum potential of such systems in clinical practice.

REFERENCES

[1]. Mitchell, M.J., et al., Engineering precision nanoparticles for drug delivery. Nature reviews drug discovery, 2021. 20(2): p. 101-124.

[2]. Banik, B.L., P. Fattahi, and J.L. Brown, Polymeric nanoparticles: the future of nanomedicine. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology, 2016. 8(2): p. 271-299.

[3]. Bae, Y.H. and K. Park, Targeted drug delivery to tumors: myths, reality and possibility. 2011, Elsevier. p. 198-205.

[4]. Lou, J., et al., Advances in oral drug delivery systems: challenges and opportunities. Pharmaceutics, 2023. 15(2): p. 484.

[5]. Patra, J.K., et al., Nano based drug delivery systems: recent developments and future prospects. Journal of nanobiotechnology, 2018. 16(1): p. 71.

[6]. Fenton, O.S., et al., Advances in biomaterials for drug delivery. Advanced Materials, 2018. 30(29): p. 1705328.

[7]. Jeong, W.Y., et al., Recent advances in transdermal drug delivery systems: A review. Biomaterials research, 2021. 25(1): p. 24.

[8]. Mura, S., J. Nicolas, and P. Couvreur, Stimuli-responsive nanocarriers for drug delivery. Nature materials, 2013. 12(11): p. 991-1003.

[9]. Adepu, S. and S. Ramakrishna, Controlled drug delivery systems: current status and future directions. Molecules, 2021. 26(19): p. 5905.

[10]. Kompella, U.B. and H.F. Edelhauser, Drug product development for the back of the eye. Vol. 2. 2011: Springer.

[11]. Jantzen, G.M. and J.R. Robinson, Sustained-and controlled-release drug delivery systems. Drugs and The Pharmaceutical Sciences, 2002. 121: p. 501-528.

[12]. Park, K., Controlled drug delivery systems: past forward and future back. Journal of Controlled Release, 2014. 190: p. 3-8.

[13]. Langer, R., Drugs on target. Science, 2001. 293(5527): p. 58-59.

[14]. Kang, J.-S. and M.-H. Lee, Overview of therapeutic drug monitoring. The Korean journal of internal medicine, 2009. 24(1): p. 1.

[15]. Habet, S., Narrow therapeutic index drugs: clinical pharmacology perspective. Journal of Pharmacy and Pharmacology, 2021. 73(10): p. 1285-1291.

[16]. Sempionatto, J.R., et al., Wearable chemical sensors for biomarker discovery in the omics era. Nature Reviews Chemistry, 2022. 6(12): p. 899-915.
[17]. Bian, S., et al., Towards wearable and implantable continuous drug monitoring: A review. Journal of pharmaceutical analysis, 2021. 11(1): p. 1-14.
[18]. Liu, Y., et al., Revolutionizing precision medicine: Exploring wearable sensors for therapeutic drug monitoring and personalized therapy. Biosensors, 2023. 13(7): p. 726.
[19]. Darwich, A.S., et al., Model-informed precision dosing: background, requirements, validation, implementation, and forward trajectory of individualizing drug therapy. Annual review of pharmacology and toxicology, 2021. 61(1): p. 225-245.
[20]. Aliper, A., et al., Deep learning applications for predicting pharmacological properties of drugs and drug repurposing using transcriptomic data. Molecular pharmaceutics, 2016. 13(7): p. 2524-2530.
[21]. Chenthamara, D., et al., Therapeutic efficacy of nanoparticles and routes of administration. Biomaterials research, 2019. 23(1): p. 20.
[22]. Karimi, M., et al., Smart micro/nanoparticles in stimulus-responsive drug/gene delivery systems. Chemical society reviews, 2016. 45(5): p. 1457-1501.
[23]. Kumar, R., S.V. Dalvi, and P.F. Siril, Nanoparticle-based drugs and formulations: current status and emerging applications. ACS Applied Nano Materials, 2020. 3(6): p. 4944-4961.
[24]. Chu, S., et al., pH-responsive polymer nanomaterials for tumor therapy. Frontiers in oncology, 2022. 12: p. 855019.
[25]. Kocak, G., C. Tuncer, and V. Bütün, pH-Responsive polymers. Polymer Chemistry, 2017. 8(1): p. 144-176.
[26]. Guo, X., et al., Multifunctional nanoplatforms for subcellular delivery of drugs in cancer therapy. Progress in Materials Science, 2020. 107: p. 100599.
[27]. Yao, C., et al., Near-Infrared-Triggered Azobenzene-Liposome/Upconversion Nanoparticle Hybrid Vesicles for Remotely Controlled Drug Delivery to Overcome Cancer Multidrug Resistance. Advanced Materials (Deerfield Beach, Fla.), 2016. 28(42): p. 9341-9348.
[28]. Mahdi, K., et al., Smart Nanostructures for Cargo Delivery: Uncaging and Activating by Light. 2017.
[29]. Estelrich, J., et al., Iron oxide nanoparticles for magnetically-guided and magnetically-responsive drug delivery. International journal of molecular sciences, 2015. 16(4): p. 8070-8101.
[30]. Perigo, E.A., et al., Fundamentals and advances in magnetic hyperthermia. Applied Physics Reviews, 2015. 2(4).
[31]. Rajan, A. and N.K. Sahu, Review on magnetic nanoparticle-mediated hyperthermia for cancer therapy. Journal of Nanoparticle Research, 2020. 22(11): p. 319.
[32]. Meng, F., Z. Zhong, and J. Feijen, Stimuli-responsive polymersomes for programmed drug delivery. Biomacromolecules, 2009. 10(2): p. 197-209.
[33]. Jia, R., et al., Advances in multiple stimuli-responsive drug-delivery systems for cancer therapy. International journal of nanomedicine, 2021: p. 1525-1551.
[34]. Cheng, R., et al., Dual and multi-stimuli responsive polymeric nanoparticles for programmed site-specific drug delivery. Biomaterials, 2013. 34(14): p. 3647-3657.
[35]. Xiao, W., et al., Dual stimuli-responsive multi-drug delivery system for the individually controlled release of anti-cancer drugs. Chemical Communications, 2015. 51(8): p. 1475-1478.
[36]. Aseyev, V., H. Tenhu, and F.M. Winnik, Non-ionic thermoresponsive polymers in water. Self organized nanostructures of amphiphilic block copolymers II, 2010: p. 29-89.
[37]. Luong, D., et al., PEGylated PAMAM dendrimers: Enhancing efficacy and mitigating toxicity for effective anticancer drug and gene delivery. Acta biomaterialia, 2016. 43: p. 14-29.
[38]. Suk, J.S., et al., PEGylation as a strategy for improving nanoparticle-based drug and gene delivery. Advanced drug delivery reviews, 2016. 99: p. 28-51.
[39]. Sercombe, L., et al., Advances and challenges of liposome assisted drug delivery. Frontiers in pharmacology, 2015. 6: p. 286.
[40]. Lammers, T., et al., Cancer nanomedicine: is targeting our target? Nature Reviews Materials, 2016. 1(9): p. 1-2.
[41]. Chelliah, R., et al., Liposomes for drug delivery: Classification, therapeutic applications, and limitations. Next Nanotechnology, 2025. 8: p. 100209.
[42]. Karami, L., et al., A new insight into the mechanism of loading of Granisetron, Naltrexone and Risperidone in poly(ortho ester) and poly (lactic-co-glycolic acid) as the controlled release drug delivery systems using a computational molecular approach. Journal of Drug Delivery Science and Technology, 2024. 102: p. 106377.
[43]. Nair, L.S. and C.T. Laurencin, Biodegradable polymers as biomaterials. Progress in polymer science, 2007. 32(8-9): p. 762-798.
[44]. Kumari, A., S.K. Yadav, and S.C. Yadav, Biodegradable polymeric nanoparticles based drug delivery systems. Colloids and surfaces B: biointerfaces, 2010. 75(1): p. 1-18.
[45]. Avgoustakis, K., Pegylated poly (lactide) and poly (lactide-co-glycolide) nanoparticles: preparation, properties and possible applications in drug delivery. Current drug delivery, 2004. 1(4): p. 321-333.
[46]. Valencia, P.M., et al., Single-step assembly of homogenous lipid− polymeric and lipid− quantum dot nanoparticles enabled by microfluidic rapid mixing. ACS nano, 2010. 4(3): p. 1671-1679.

[47]. Prabhu, R.H., V.B. Patravale, and M.D. Joshi, Polymeric nanoparticles for targeted treatment in oncology: current insights. International journal of nanomedicine, 2015: p. 1001-1018.
[48]. Colilla, M. and M. Vallet-Regí, Targeted stimuli-responsive mesoporous silica nanoparticles for bacterial infection treatment. International Journal of Molecular Sciences, 2020. 21(22): p. 8605.
[49]. Xie, J., S. Lee, and X. Chen, Nanoparticle-based theranostic agents. Advanced drug delivery reviews, 2010. 62(11): p. 1064-1079.
[50]. Buhleier, E., W. Wehner, and F. Vögtle, " Cascade"-and" nonskid-chain-like" syntheses of molecular cavity topologies. Synthesis, 1978. 1978(02): p. 155-158.
[51]. Tomalia, D.A., J.B. Christensen, and U. Boas, Dendrimers, dendrons, and dendritic polymers: discovery, applications, and the future. 2012: Cambridge University Press.
[52]. Grayson, S.M. and J.M. Fréchet, Convergent dendrons and dendrimers: from synthesis to applications. Chemical reviews, 2001. 101(12): p. 3819-3868.
[53]. Svenson, S. and D.A. Tomalia, Dendrimers in biomedical applications—reflections on the field. Advanced drug delivery reviews, 2012. 64: p. 102-115.
[54]. Campagna, S., P. Ceroni, and F. Puntoriero, Designing dendrimers. 2011: John Wiley & Sons.
[55]. Kesharwani, P., K. Jain, and N.K. Jain, Dendrimer as nanocarrier for drug delivery. Progress in Polymer Science, 2014. 39(2): p. 268-307.
[56]. Medina, S.H. and M.E. El-Sayed, Dendrimers as carriers for delivery of chemotherapeutic agents. Chemical reviews, 2009. 109(7): p. 3141-3157.
[57]. Wang, J., et al., Dendrimer-based drug delivery systems: History, challenges, and latest developments. Journal of biological engineering, 2022. 16(1): p. 18.
[58]. Ahmed, E.M., Hydrogel: Preparation, characterization, and applications: A review. Journal of advanced research, 2015. 6(2): p. 105-121.
[59]. Peppas, N.A., et al., Hydrogels in pharmaceutical formulations. European journal of pharmaceutics and biopharmaceutics, 2000. 50(1): p. 27-46.
[60]. Zhu, J. and R.E. Marchant, Design properties of hydrogel tissue-engineering scaffolds. Expert review of medical devices, 2011. 8(5): p. 607-626.
[61]. Deshpande, P., et al., Tissue engineering approaches for lymphedema: biomaterial innovations and clinical potential. Frontiers in Cell and Developmental Biology, 2025. 13: p. 1537050.
[62]. Okay, O., General properties of hydrogels, in Hydrogel sensors and actuators: engineering and technology. 2009, Springer. p. 1-14.
[63]. Xu, Q., et al., Collagen-and hyaluronic acid-based hydrogels and their biomedical applications. Materials Science and Engineering: R: Reports, 2021. 146: p. 100641.
[64]. Hoffman, A.S., Hydrogels for biomedical applications. Advanced drug delivery reviews, 2012. 64: p. 18-23.
[65]. Peppas, N.A. and R. Langer, New challenges in biomaterials. Science, 1994. 263(5154): p. 1715-1720.
[66]. Roy, D., J.N. Cambre, and B.S. Sumerlin, Future perspectives and recent advances in stimuli-responsive materials. Progress in Polymer Science, 2010. 35(1-2): p. 278-301.
[67]. Ullah, F., et al., Classification, processing and application of hydrogels: A review. Materials Science and Engineering: C, 2015. 57: p. 414-433.
[68]. Koçak, G., C. Tuncer, and V. Bütün, Stimuli-responsive polymers providing new opportunities for various applications. Hacettepe Journal of Biology and Chemistry, 2020. 48(5): p. 527-574.
[69]. Schmaljohann, D., Thermo-and pH-responsive polymers in drug delivery. Advanced drug delivery reviews, 2006. 58(15): p. 1655-1670.
[70]. Wichterle, O. and D. Lim, Hydrophilic gels for biological use. Nature, 1960. 185(4706): p. 117-118.
[71]. Drury, J.L. and D.J. Mooney, Hydrogels for tissue engineering: scaffold design variables and applications. Biomaterials, 2003. 24(24): p. 4337-4351.
[72]. Tai, H., et al., Thermoresponsive and photocrosslinkable PEGMEMA-PPGMA-EGDMA copolymers from a one-step ATRP synthesis. Biomacromolecules, 2009. 10(4): p. 822-828.
[73]. Gaharwar, A.K., N.A. Peppas, and A. Khademhosseini, Nanocomposite hydrogels for biomedical applications. Biotechnology and bioengineering, 2014. 111(3): p. 441-453.
[74]. Finster, R., P. Sankaran, and E. Bihar, Computational and AI-driven design of hydrogels for bioelectronic applications. Advanced Electronic Materials, 2025: p. 2400763.
[75]. Jain, A. and S.K. Jain, In vitro and cell uptake studies for targeting of ligand anchored nanoparticles for colon tumors. European Journal of Pharmaceutical Sciences, 2008. 35(5): p. 404-416.
[76]. Vert, M., et al., Terminology for biorelated polymers and applications (IUPAC Recommendations 2012). Pure and Applied Chemistry, 2012. 84(2): p. 377-410.
[77]. Roca-Arroyo, A.F., et al., Hydrogel network architecture design space: impact on mechanical and viscoelastic properties. Gels, 2025. 11(8): p. 588.
[78]. Annabi, N., et al., 25th anniversary article: Rational design and applications of hydrogels in regenerative medicine. Advanced materials, 2014. 26(1): p. 85-124.
[79]. Lee, Y.J. and M.S. Kim, Advances in drug-loaded microspheres for targeted, controlled, and sustained drug delivery: Potential, applications, and future directions. Biomedicine & Pharmacotherapy, 2025. 189: p. 118244.
[80]. van de Weert, M., W.E. Hennink, and W. Jiskoot, Protein instability in poly (lactic-co-glycolic acid)

microparticles. Pharmaceutical research, 2000. 17(10): p. 1159-1167.
[81]. Dalvadi, H. and J.K. Patel, Chronpharmaceutics, pulsatile drug delivery system as current trend. Asian journal of pharmaceutical sciences, 2010. 5(5): p. 204-230.
[82]. Dash, M., et al., Chitosan—A versatile semi-synthetic polymer in biomedical applications. Progress in polymer science, 2011. 36(8): p. 981-1014.
[83]. Geraili, A., M. Xing, and K. Mequanint, Design and fabrication of drug-delivery systems toward adjustable release profiles for personalized treatment. View, 2021. 2(5): p. 20200126.
[84]. Fredenberg, S., et al., The mechanisms of drug release in poly (lactic-co-glycolic acid)-based drug delivery systems—A review. International journal of pharmaceutics, 2011. 415(1-2): p. 34-52.
[85]. Danhier, F., O. Feron, and V. Préat, To exploit the tumor microenvironment: Passive and active tumor targeting of nanocarriers for anti-cancer drug delivery. Journal of controlled release, 2010. 148(2): p. 135-146.
[86]. D'Souza, S.S. and P.P. DeLuca, Methods to assess in vitro drug release from injectable polymeric particulate systems. Pharmaceutical research, 2006. 23(3): p. 460-474.
[87]. Kapoor, D.N., et al., PLGA: a unique polymer for drug delivery. Therapeutic delivery, 2015. 6(1): p. 41-58.
[88]. Di Giuseppe, G., et al., Surveying willingness toward SARS-CoV-2 vaccination of healthcare workers in Italy. Expert Review of Vaccines, 2021. 20(7): p. 881-889.
[89]. Chen, F.-M., et al., Homing of endogenous stem/progenitor cells for in situ tissue regeneration: promises, strategies, and translational perspectives. Biomaterials, 2011. 32(12): p. 3189-3209.
[90]. Farra, R., et al., First-in-human testing of a wirelessly controlled drug delivery microchip. Science translational medicine, 2012. 4(122): p. 122ra21-122ra21.
[91]. Elman, N., H.L. Ho Duc, and M.J. Cima, An implantable MEMS drug delivery device for rapid delivery in ambulatory emergency care. Biomedical microdevices, 2009. 11(3): p. 625-631.
[92]. Staples, M., et al., Application of micro-and nano-electromechanical devices to drug delivery. Pharmaceutical research, 2006. 23(5): p. 847-863.
[93]. Ambrożewicz, E., et al., Cross talk between redox signalling and metabolic activity of osteoblasts and fibroblasts in the presence of hydroxyapatite-based biomaterials influences bone regeneration. Journal of Applied Biomedicine, 2019. 17(2).
[94]. Zurbuchen, A., et al., Energy harvesting from the beating heart by a mass imbalance oscillation generator. Annals of biomedical engineering, 2013. 41(1): p. 131-141.
[95]. Heng, P.W., Controlled release drug delivery systems. Pharmaceutical development and technology, 2018. 23(9): p. 833-833.
[96]. Windmiller, J.R. and J. Wang, Wearable electrochemical sensors and biosensors: a review. Electroanalysis, 2013. 25(1): p. 29-46.
[97]. Polikov, V.S., P.A. Tresco, and W.M. Reichert, Response of brain tissue to chronically implanted neural electrodes. Journal of neuroscience methods, 2005. 148(1): p. 1-18.
[98]. Thabit, H. and R. Hovorka, Coming of age: the artificial pancreas for type 1 diabetes. Diabetologia, 2016. 59(9): p. 1795-1805.
[99]. Poon, A.S., S. O'Driscoll, and T.H. Meng, Optimal frequency for wireless power transmission into dispersive tissue. IEEE Transactions on Antennas and Propagation, 2010. 58(5): p. 1739-1750.
[100]. Halperin, D., et al. Pacemakers and implantable cardiac defibrillators: Software radio attacks and zero-power defenses. in 2008 IEEE Symposium on Security and Privacy (sp 2008). 2008. IEEE.
[101]. Kang, S.-K., et al., Bioresorbable silicon electronic sensors for the brain. Nature, 2016. 530(7588): p. 71-76.
[102]. Cai, W. and X. Chen, Nanoplatforms for targeted molecular imaging in living subjects. Small, 2007. 3(11): p. 1840-1854.
[103]. Famm, K., et al., A jump-start for electroceuticals. Nature, 2013. 496(7444): p. 159-161.
[104]. Benabid, A.L., et al., Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. The Lancet Neurology, 2009. 8(1): p. 67-81.
[105]. Bergenstal, R.M., et al., Safety of a hybrid closed-loop insulin delivery system in patients with type 1 diabetes. Jama, 2016. 316(13): p. 1407-1408.
[106]. Kramer, D.B., S. Xu, and A.S. Kesselheim, Regulation of medical devices in the United States and European Union, in The ethical challenges of emerging medical technologies. 2020, Routledge. p. 41-48.
[107]. Shi, J., et al., Cancer nanomedicine: progress, challenges and opportunities. Nature reviews cancer, 2017. 17(1): p. 20-37.
[108]. Xu, X., et al., Cancer nanomedicine: from targeted delivery to combination therapy. Trends in molecular medicine, 2015. 21(4): p. 223-232.
[109]. Danhier, F., et al., PLGA-based nanoparticles: an overview of biomedical applications. Journal of controlled release, 2012. 161(2): p. 505-522.
[110]. Müller, R.H., M. Radtke, and S.A. Wissing, Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. Advanced drug delivery reviews, 2002. 54: p. S131-S155.
[111]. Junghanns, J.-U.A. and R.H. Müller, Nanocrystal technology, drug delivery and clinical applications. International journal of nanomedicine, 2008. 3(3): p. 295-310.
[112]. Siepmann, J. and N.A. Peppas, Higuchi equation: Derivation, applications, use and misuse. International journal of pharmaceutics, 2011. 418(1): p. 6-12.

[113]. Freiberg, S. and X. Zhu, Polymer microspheres for controlled drug release. International journal of pharmaceutics, 2004. 282(1-2): p. 1-18.
[114]. Timko, B.P., T. Dvir, and D.S. Kohane, Remotely triggerable drug delivery systems. Advanced materials, 2010. 22(44): p. 4925-4943.
[115]. Wahajuddin, n. and S. Arora, Superparamagnetic iron oxide nanoparticles: magnetic nanoplatforms as drug carriers. International journal of nanomedicine, 2012: p. 3445-3471.
[116]. Sainz, V., et al., Regulatory aspects on nanomedicines. Biochemical and biophysical research communications, 2015. 468(3): p. 504-510.
[117]. Zambito, Y. and G. Di Colo, Thiolated quaternary ammonium–chitosan conjugates for enhanced precorneal retention, transcorneal permeation and intraocular absorption of dexamethasone. European Journal of Pharmaceutics and Biopharmaceutics, 2010. 75(2): p. 194-199.
[118]. Washington, C., Drug release from microdisperse systems: a critical review. International Journal of Pharmaceutics, 1990. 58(1): p. 1-12.
[119]. Lin, C.-F., et al., Maximizing dermal targeting and minimizing transdermal penetration by magnolol/honokiol methoxylation. International Journal of Pharmaceutics, 2013. 445(1-2): p. 153-162.
[120]. Seo, P.R., et al., Lipid composition effect on permeability across PAMPA. European journal of pharmaceutical sciences, 2006. 29(3-4): p. 259-268.
[121]. Bhattacharjee, S., DLS and zeta potential–what they are and what they are not? Journal of controlled release, 2016. 235: p. 337-351.
[122]. Shen, J. and D.J. Burgess, In vitro–in vivo correlation for complex non-oral drug products: where do we stand? Journal of controlled release, 2015. 219: p. 644-651.
[123]. Rothbauer, M., H. Zirath, and P. Ertl, Recent advances in microfluidic technologies for cell-to-cell interaction studies. Lab on a Chip, 2018. 18(2): p. 249-270.
[124]. Andersen, J.M., C. Klykken, and J. Mørland, Long-term methadone treatment reduces phosphorylation of CaMKII in rat brain. Journal of Pharmacy and Pharmacology, 2012. 64(6): p. 843-847.
[125]. Weissleder, R. and V. Ntziachristos, Shedding light onto live molecular targets. Nature medicine, 2003. 9(1): p. 123-128.
[126]. Hong, G., A.L. Antaris, and H. Dai, Near-infrared fluorophores for biomedical imaging. Nature biomedical engineering, 2017. 1(1): p. 0010.
[127]. Viglianti, B.L., et al., In vivo monitoring of tissue pharmacokinetics of liposome/drug using MRI: illustration of targeted delivery. Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine, 2004. 51(6): p. 1153-1162.
[128]. de Smet, M., et al., Magnetic resonance imaging of high intensity focused ultrasound mediated drug delivery from temperature-sensitive liposomes: an in vivo proof-of-concept study. Journal of Controlled Release, 2011. 150(1): p. 102-110.
[129]. Pérez-Medina, C., et al., A modular labeling strategy for in vivo PET and near-infrared fluorescence imaging of nanoparticle tumor targeting. Journal of Nuclear Medicine, 2014. 55(10): p. 1706-1711.
[130]. Weber, J., P.C. Beard, and S.E. Bohndiek, Contrast agents for molecular photoacoustic imaging. Nature methods, 2016. 13(8): p. 639-650.
[131]. Emami, J., In vitro-in vivo correlation: from theory to applications. J Pharm Pharm Sci, 2006. 9(2): p. 169-189.
[132]. Kostewicz, E.S., et al., In vitro models for the prediction of in vivo performance of oral dosage forms. European Journal of Pharmaceutical Sciences, 2014. 57: p. 342-366.
[133]. Lammers, T., et al., Theranostic nanomedicine. Accounts of chemical research, 2011. 44(10): p. 1029-1038.
[134]. Li, C., et al., Advanced fluorescence imaging technology in the near-infrared-II window for biomedical applications. Journal of the American Chemical Society, 2020. 142(35): p. 14789-14804.
[135]. Zhu, S., et al., Near-infrared-II molecular dyes for cancer imaging and surgery. Advanced Materials, 2019. 31(24): p. 1900321.
[136]. Fonseca, G., et al., Antimicrobial Photodynamic Therapy (aPDT) for decontamination of high-speed handpieces: A comparative study. Photodiagnosis and Photodynamic Therapy, 2020. 30: p. 101686.
[137]. Lin, L., et al., Single-breath-hold photoacoustic computed tomography of the breast. Nature communications, 2018. 9(1): p. 2352.
[138]. Hannah, A., et al., Indocyanine green-loaded photoacoustic nanodroplets: dual contrast nanoconstructs for enhanced photoacoustic and ultrasound imaging. ACS nano, 2014. 8(1): p. 250-259.
[139]. De La Zerda, A., et al., Carbon nanotubes as photoacoustic molecular imaging agents in living mice. Nature nanotechnology, 2008. 3(9): p. 557-562.
[140]. Jokerst, J.V., et al., Gold nanorods for ovarian cancer detection with photoacoustic imaging and resection guidance via Raman imaging in living mice. ACS nano, 2012. 6(11): p. 10366-10377.
[141]. Luke, G.P., D. Yeager, and S.Y. Emelianov, Biomedical applications of photoacoustic imaging with exogenous contrast agents. Annals of biomedical engineering, 2012. 40(2): p. 422-437.
[142]. Yarnykh, V.L., Fast macromolecular proton fraction mapping from a single off-resonance magnetization transfer measurement. Magnetic resonance in medicine, 2012. 68(1): p. 166-178.
[143]. Liu, G., et al., Nuts and bolts of CEST MR imaging. NMR in Biomedicine, 2013. 26(7): p. 810.
[144]. Tanter, M. and M. Fink, Ultrafast imaging in biomedical ultrasound. IEEE transactions on ultrasonics, ferroelectrics, and frequency control, 2014. 61(1): p. 102-119.
[145]. Provost, J., et al., 3D ultrafast ultrasound imaging in vivo. Physics in Medicine & Biology, 2014. 59(19): p. L1.

[146]. Willmann, J.K., et al., Dual-targeted contrast agent for US assessment of tumor angiogenesis in vivo. Radiology, 2008. 248(3): p. 936-944.
[147]. Topol, E.J., High-performance medicine: the convergence of human and artificial intelligence. Nature medicine, 2019. 25(1): p. 44-56.
[148]. Hosny, A., et al., Artificial intelligence in radiology. Nature Reviews Cancer, 2018. 18(8): p. 500-510.
[149]. Cherry, S.R. Multimodality imaging: Beyond pet/ct and spect/ct. in Seminars in nuclear medicine. 2009. Elsevier.
[150]. Ta, T. and T.M. Porter, Thermosensitive liposomes for localized delivery and triggered release of chemotherapy. Journal of controlled release, 2013. 169(1-2): p. 112-125.
[151]. Hu, Q., P.S. Katti, and Z. Gu, Enzyme-responsive nanomaterials for controlled drug delivery. Nanoscale, 2014. 6(21): p. 12273-12286.
[152]. Rwei, A.Y., W. Wang, and D.S. Kohane, Photoresponsive nanoparticles for drug delivery. Nano today, 2015. 10(4): p. 451-467.
[153]. Fonte, P., et al., Effect of cryoprotectants on the porosity and stability of insulin-loaded PLGA nanoparticles after freeze-drying. Biomatter, 2012. 2(4): p. 329-339.
[154]. Barenholz, Y.C., Doxil®—The first FDA-approved nano-drug: Lessons learned. Journal of controlled release, 2012. 160(2): p. 117-134.
[155]. Liversidge, G.G. and K.C. Cundy, Particle size reduction for improvement of oral bioavailability of hydrophobic drugs: I. Absolute oral bioavailability of nanocrystalline danazol in beagle dogs. International journal of pharmaceutics, 1995. 125(1): p. 91-97.
[156]. Allen, T.M. and P.R. Cullis, Liposomal drug delivery systems: from concept to clinical applications. Advanced drug delivery reviews, 2013. 65(1): p. 36-48.
[157]. Brito, L. and M. Amiji, Nanoparticulate carriers for the treatment of coronary restenosis. International journal of nanomedicine, 2007. 2(2): p. 143-161.
[158]. Wilhelm, S., et al., Analysis of nanoparticle delivery to tumours. Nature reviews materials, 2016. 1(5): p. 1-12.
[159]. Vargason, A.M., A.C. Anselmo, and S. Mitragotri, The evolution of commercial drug delivery technologies. Nature biomedical engineering, 2021. 5(9): p. 951-967.
[160]. Nel, A., et al., Toxic potential of materials at the nanolevel. science, 2006. 311(5761): p. 622-627.
[161]. Guo, Z., et al., Cell-penetrating peptides: Possible transduction mechanisms and therapeutic applications. Biomedical reports, 2016. 4(5): p. 528-534.
[162]. Li, X., et al., Biocompatibility and toxicity of nanoparticles and nanotubes. Journal of Nanomaterials, 2012. 2012(1): p. 548389.
[163]. Lu, Y., et al., Bioresponsive materials. Nature Reviews Materials, 2016. 2(1): p. 1-17.
[164]. Etheridge, M.L., et al., The big picture on nanomedicine: the state of investigational and approved nanomedicine products. Nanomedicine: nanotechnology, biology and medicine, 2013. 9(1): p. 1-14.
[165]. Rodríguez-Gómez, F.D., et al., Classification system for nanotechnology-enabled health products with both scientific and regulatory application. Frontiers in Medicine, 2023. 10: p. 1212949.
[166]. Baryakova, T.H., et al., Overcoming barriers to patient adherence: the case for developing innovative drug delivery systems. Nature Reviews Drug Discovery, 2023. 22(5): p. 387-409.
[167]. Sabaté, E., Adherence to long-term therapies: evidence for action. 2003: World health organization.
[168]. Nieuwlaat, R., et al., Interventions for enhancing medication adherence. Cochrane database of systematic reviews, 2014(11).
[169]. Norman, D.A. and S.W. Draper, User centered system design; new perspectives on human-computer interaction. 1986: L. Erlbaum Associates Inc.