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From Depots to Smart Delivery: Evolution of Long-Acting Drug Delivery Systems

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Abstract: ***Long-acting drug delivery systems (LADDS) provide prolonged and controlled drug release, reducing dosing frequency and improving therapeutic consistency. This review discusses the development of long-acting injectable and implantable systems, focusing on crystalline and nanocrystalline depots, oil- and prodrug-based formulations, polymeric microspheres, lipid-based systems, injectable hydrogels, in-situ forming depots, and implantable platforms. The mechanisms governing drug release, including dissolution, diffusion, polymer degradation, swelling, and erosion, are also discussed. Recent advances in smart and programmable systems are highlighted alongside formulation, manufacturing, sterility, stability, and regulatory challenges. Overall, emerging LADDS aim to achieve predictable release, improved patient acceptability, and enhanced clinical translation.***
Keywords: Long-acting drug delivery systems, injectable hydrogels, polymeric microspheres.

I. INTRODUCTION

Long-acting drug delivery systems extend release from hours to weeks, months or years, reducing dosing frequency and exposure fluctuations [1,3]. Long-acting injectables (LAIs),including oil depots, suspensions, microspheres and in-situ forming gels, may improve adherence in chronic diseases [2,3]. Burst release, injection-site reactions and manufacturing complexity remain challenges [2,5].

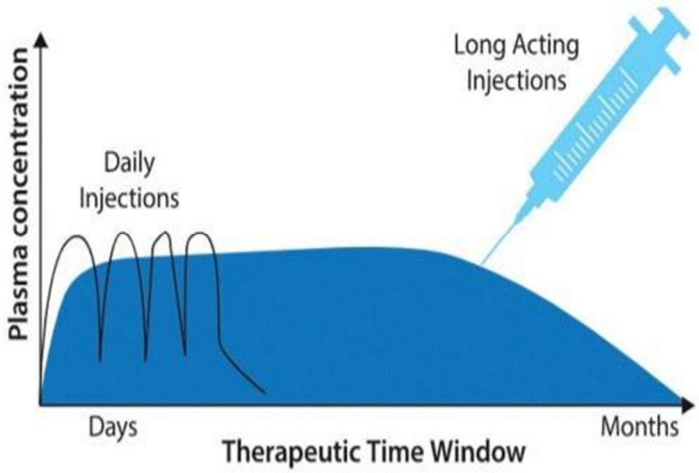

Figure 1 :. PK profiles of long acting versus short acting daily injection formulations [50]

II. PRINCIPLES OF LONG-ACTING DRUG DELIVERY SYSTEMS

A. Depot Formation

The fundamental principle is the formation of a drug reservoir, or depot, at the administration site from which drugs are released gradually. Depending on the drug, formulation and depot structure, release can last from days to weeks, months or longer, reducing dosing frequency and the fluctuations seen with conventional dosage forms [3,4]. Duration and pattern depend on the drug's physicochemical properties, formulation composition, depot structure and interaction with the surrounding biological environment [4,5].

B. Injectable-to-depot transformation

Modern systems convert a formulation into a depot after injection. In-situ forming implants are injected as low-viscosity liquids and become semisolid or solid in the body, combining the prolonged release of an implant with the less invasive administration of an injection. Transformation may occur through in-situ cross-linking, solidification of organogels, or phase separation after solvent exchange [5]. In the last case, solvent leaving the injectate and water entering drive PLGA solidification, and the rate of this phase inversion influences early release [12].

C. Rate-controlling processes in the depot

Once formed, the depot releases drug through one or more rate-controlling processes. In drug-crystal depots, release is mainly governed by gradual dissolution or surface erosion of the poorly soluble drug. In polymeric systems, drug diffuses through the matrix while water penetration, swelling, pore formation and polymer degradation or erosion progressively change the depot. These mechanisms can operate together, and their relative contributions determine the release profile [4,5].

D. Balancing duration and injectability

A practical LAI must release for a long time yet remain injectable. More polymer or depot-forming material improves retention but raises viscosity and may require larger needles; highly dispersed crystals inject easily but, because of their greater exposed surface area, may release for a shorter time. Designs therefore balance drug loading, depot stability, release duration, injectability and local tolerability. Self-aggregating microcrystals address this balance by combining prolonged release, high drug loading and compatibility with small-gauge needles [4].

III. MECHANISMS OF DRUG RELEASE AND RELEASE KINETICS

Release from an LAI depot is rarely governed by a single process. The mechanisms below can act alone or together [5,6].

A. Diffusion-controlled release

Drug molecules move from the depot into surrounding fluid through the polymer matrix,hydrogel network, lipid phase or pores. The rate depends on molecular size, solubility,polymer structure, matrix porosity and drug–matrix interactions [5,6]. Diffusion is particularly important in polymeric microspheres and injectable hydrogels, where water penetration lets dissolved drug migrate through the hydrated or porous matrix. In PLGA systems it contributes mainly to initial release when drug lies near the surface, and in hydrogels it dominates when drug is molecularly dispersed in the hydrated network, so it influences both burst and subsequent duration [6].

B. Dissolution-controlled release

For poorly soluble drugs given as crystalline suspensions or nanocrystals, dissolution is the main rate-limiting step because the drug must dissolve in tissue fluid before it can be absorbed. Smaller particles have a greater surface area and dissolve faster, whereas larger crystals dissolve slowly and sustain the depot. Montelukast illustrates this: 200 and 500 nm particles released over about 5 h, whereas 3 μm crystals extended release to about 48 h [7].Self-aggregating levonorgestrel microcrystals use solvent exchange to compact the crystals,reducing exposed surface area and slowing dissolution [4].

C. Polymer degradation- and erosion-controlled release

PLGA releases drugs through gradual hydration, degradation, erosion and internal pore formation. Water enters the matrix and hydrolyses the polymer chains; as molecular weight falls, the matrix becomes more porous, which facilitates diffusion and eventually erosion [6].In progesterone microspheres, surface drug is released first, the PLGA layer then hydrates and erodes, and deeper crystals are exposed and diffuse out [8]. Degradation rate depends on composition: lactide-rich PLGA degrades more slowly than glycolide-rich PLGA, so PLGA 75:25 released progesterone more slowly than 50:50, with burst release falling from 11.0% to 6.7% [8]. Polymer composition can therefore be used to tune depot duration.

D. Swelling- and relaxation-controlled release

Hydrophilic polymers and hydrogels absorb physiological fluid, swell and undergo structural relaxation, which increases drug mobility and enlarges diffusion pathways. Release therefore combines diffusion through the hydrated network with polymer-chain relaxation, depending on polymer characteristics, cross-linking density, drug loading and drug–polymer interactions [9].Cross-linking limits this effect: the enzymatically cross-linked gelatin hydrogel used for PTH showed restricted swelling and degraded gradually over about 28 days [9].

E. Stimuli-responsive release

Some depots allow physiological conditions such as temperature, pH, enzymes or ionic strength to influence release. Thermoresponsive systems are injected as fluids, undergo a sol–gel transition at body temperature and form a depot; a β-lapachone F127/hyaluronic acid gel, for example, gelled at about 28 °C [10]. pH-responsive systems exploit reversible chemical bonds: in a phenylboronic acid–modified gelatin methacryloyl hydrogel, boronate ester bonds dissociate in the acidic environment of the degenerating intervertebral disc,releasing quercetin [11]. These triggers add a control mechanism beyond passive diffusion and polymer degradation. 3

F. Combined Release Mechanisms

Most LAIs are not governed by a single mechanism. PLGA microspheres typically show early diffusion of accessible drug, followed by a growing contribution from polymer degradation and pore formation [6]. In a PLGA in-situ gel, phase inversion, polymer concentration, PEG and benzyl benzoate together shaped burst and 28-day release [12].

Nested systems provide sequential barriers: drug leaves a liposome and then diffuses through the surrounding hydrogel [9], and TAF-loaded chitosan nanoparticles in an ethyl cellulose oleogel release through two diffusion barriers over about 16 days [13]. The observed profile therefore reflects drug properties, particle size, polymer characteristics, depot architecture, drug loading and the physiological environment.

G. Release Kinetics

Fitting release data to kinetic models helps identify the predominant mechanism, although overlapping mechanisms mean that a good fit suggests, rather than proves, a single process [5]. The models used in the cited studies are summarised in Table 1.

Table 1 : Kinetic models used to interpret release from LAI depots

Sr. No.	Model	Equation	Interpretation	Example
1.	Zero order	$Q = Q_0 + K_0 t$	Constant release rate, independent of drug remaining; hard to achieve in biodegradable depots because depot properties change [5]	
2.	First order	Rate proportional to drug remaining	Release rate falls as the depot is depleted [5]	
3.	Higuchi	$Q=K_H(t)^{1/2}$	Diffusion-controlled release; linear against $\sqrt{t}$ [5]	Meloxicam liposomes, R2 = 0.9677 [14]
4.	Korsmeyer-Peppas	$M_t/M_\infty = Kt^n$	$n \leq 0.45$ Fickian; $0.45 < n < 0.89$ anomalous (non-Fickian); $n \approx 0.89$ Case-II; $n > 0.89$ Super Case-II, for the geometries considered [5]	TAF oleogel $n < 0.45$ [13]; β-lapachone gel $n \approx 0.48–0.53$, diffusion plus relaxation [10]

The overall release sequence involves depot formation, followed by hydration or solvent exchange, dissolution or matrix swelling, and diffusion or polymer degradation, which ultimately leads to tissue release and systemic absorption. The dominant rate-limiting step determines both the duration and the shape of the release profile. Specifically, this is governed by crystal size in dissolution-controlled systems, polymer composition and degradation in polymeric depots, and the cross-linking or network structure in hydrogels.

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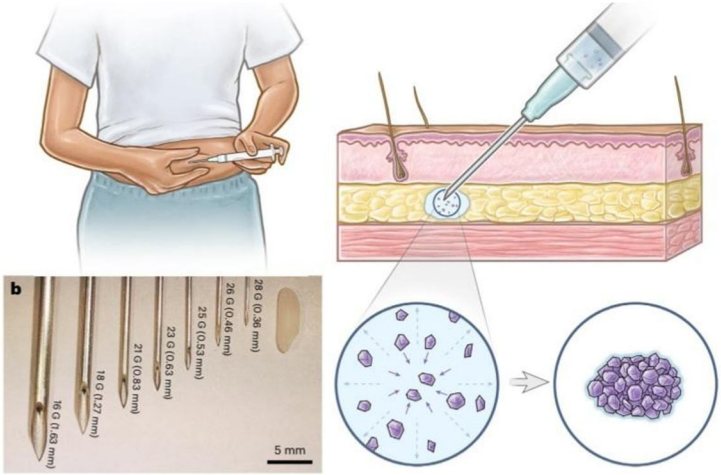
IV. INJECTABLE LONG-ACTING DRUG DELIVERY SYSTEMS

Injectable long-acting drug delivery systems are parenteral formulations designed to maintain therapeutic drug concentrations for an extended period after a single injection, reducing dosing frequency and improving adherence [4]. They do this by placing a depot at the injection site whose physical construction (crystal size, vehicle, polymer matrix, lipid network or hydrogel) rate-limits drug release. This section follows the architecture of the depot, from drug-only crystals to polymeric, lipid and gel-based systems, and uses a small number of representative studies to illustrate each principle.

A. Crystal and Nanocrystal Depots

Crystal depots use the drug itself as the reservoir. Microcrystals are micron-sized crystals of a poorly water-soluble drug dispersed in a liquid vehicle; nanocrystals are the sub-micron equivalent, generally below 1 µm and commonly 200–500 nm, stabilised by small amounts of surfactant or polymer [4,17]. Because the particles are almost entirely drug, loading is high and little excipient is needed.The formulation release mechanism progresses sequentially through injection, crystal deposition or aggregation, gradual dissolution, and systemic exposure. Consequently, the duration of action is primarily governed by the crystal size, solubility, crystallinity, and exposed surface area.[4].

Montelukast nanocrystals. Montelukast provides the clearest quantitative evidence for size-controlled release [7]. Crystalline montelukast was wet-milled with polysorbate 80 as stabiliser into 200 nm, 500 nm and 3 µm suspensions containing about 100 mg/mL drug, with more than 99.8% remaining solid. In vitro, the nanocrystals released over 85% within about 5 h, whereas the 3 µm microcrystals took about 48 h. After a single subcutaneous injection in rats, plasma concentrations stayed above 50 ng/mL for about 14 days and fell below 10 ng/mL by day 28, and the initial elimination half-life rose with crystal size (about 0.2, 0.8 and 3.7 days). The crystals also provoked a transient granulomatous response (macrophage infiltration, fibrosis, necrosis, angiogenesis) that



largely resolved by week 4. This fibrous tissue can act as a secondary diffusion barrier, so release from crystal depots depends on the host response as well as on dissolution, and that response is itself a translational consideration.[7] Salt engineering is another route to poorly soluble crystals: intravitreal benzathine foscarnet crystals persisted for at least 21 days in rabbits, but ocular toxicity attributed to the benzathine counterion shows that counterion safety must be screened [18].

Figure 1 Overview of SLIM. a, Schematic of the self-injection procedure. b, An image of different needle gauges ranging from 18 G to 28 G, compared against a grain of rice. c, Schematic of subcutaneous environment highlighting the solvent-exchange-driven self-aggregation of microcrystals into a compacted implant.[4]

B. Oil- and Prodrug-Based Depots

Oil-based LAIs suspend poorly water-soluble drugs or prodrugs in a persistent oily vehicle. The oil limits contact with interstitial fluid, slowing dissolution and absorption, while prodrug modification can further lower aqueous solubility and increase tissue retention [19,20]. . The entecavir prodrug EV-P (entecavir 3-palmitate) is highly lipophilic and dispersed well in tricaprylin, a medium-chain triglyceride, giving an intramuscular crystalline suspension; low solubility in the oil keeps the drug particulate.

In an aqueous suspension the same particles formed large aggregates and fibrotic depots; in tricaprylin they stayed more dispersed and caused less local inflammation and fibrosis. Exposure was maintained for about 3 weeks. Compared with the aqueous suspension, the oil gave higher initial exposure (Cmax) and a shorter terminal half-life (6.1 vs 9.5 days) with similar 28-day AUC, consistent with a more dispersed particle population that dissolves and is absorbed more readily than a large aggregate. Vehicle choice therefore alters particle aggregation, tissue response and pharmacokinetics even when the drug particles are similar. Because EV-P is itself a lipophilic prodrug, this example also shows the oil and prodrug strategies working together.[19]

Prodrug depots. Prodrug depots work in two steps: a poorly soluble prodrug dissolves slowly and is retained at the injection site, and its subsequent conversion to the active drug maintains therapeutic concentrations. Long-acting nanoformulated antiretroviral prodrugs such as those of rilpivirine illustrate this mechanism [20]. For depot design, the key point is that reduced solubility and altered lipophilicity make the prodrug, rather than the parent drug, rate-limiting for release.

C. Polymeric Microsphere Depots

In polymeric microspheres the drug is embedded or encapsulated in biodegradable polymer particles, typically micrometres in size, that remain at the injection site. The matrix acts as a diffusion and degradation barrier, releasing drugs over weeks to months through diffusion,hydration and erosion, and polymer degradation [6]. Poly(lactic-co-glycolic acid) (PLGA) is the principal polymer, and release is tuned through the lactide:glycolide ratio, molecular weight, particle size, porosity and drug loading. The main liabilities are initial burst release from surface-associated drug or pores, and manufacturing and residual-solvent issues [6].

Progesterone PLGA microspheres. This study shows why a polymer barrier differs from a crystal depot [8]. A progesterone microcrystal suspension released about 90% of its drug within 24 h with a 25.7% burst, which is unsuitable for an LAI. Progesterone-loaded PLGA microspheres (d50 about 8–10 μm) were made by solvent-free hot-melt extrusion and wet milling, giving dense, low-porosity particles with crystalline drug dispersed in the matrix.Release proceeds as surface drug dissolves, the PLGA layer hydrates and erodes, deeper crystals are exposed, and drug diffuses through the polymer. Burst release fell from 25.7%(suspension) to 11.0% with PLGA 50:50 and 6.7% with PLGA 75:25; the higher-lactide 75:25 polymer degrades more slowly and releases more slowly over the 7-day in vitro study. In rats, the microspheres gave lower Cmax, delayed Tmax, more sustained plasma concentrations and higher AUC than the suspension. A limitation was less controllable morphology and size distribution, which required post-production size screening.[8]

Ivermectin microspheres. Two further design points emerge from ivermectin microspheres
[15]. Monthly dosing was considered inconvenient, and ivermectin's low aqueous solubility suits depot delivery, so PLA and PCL microspheres were prepared by emulsification–solvent evaporation and lyophilised, with the aim of 6–12 months of antiparasitic cover. PLA microspheres released ivermectin more slowly than PCL microspheres, and smaller particles released faster, confirming that polymer type and size tune release. Gamma sterilisation (25kGy), however, degraded the drug and reduced polymer molecular weight through chain scission; adding α-tocopherol protected ivermectin and improved 6-month stability. Release behaviour was essentially unchanged after 6 months at 4 °C. Sterilisation must therefore be treated as a formulation-development challenge.

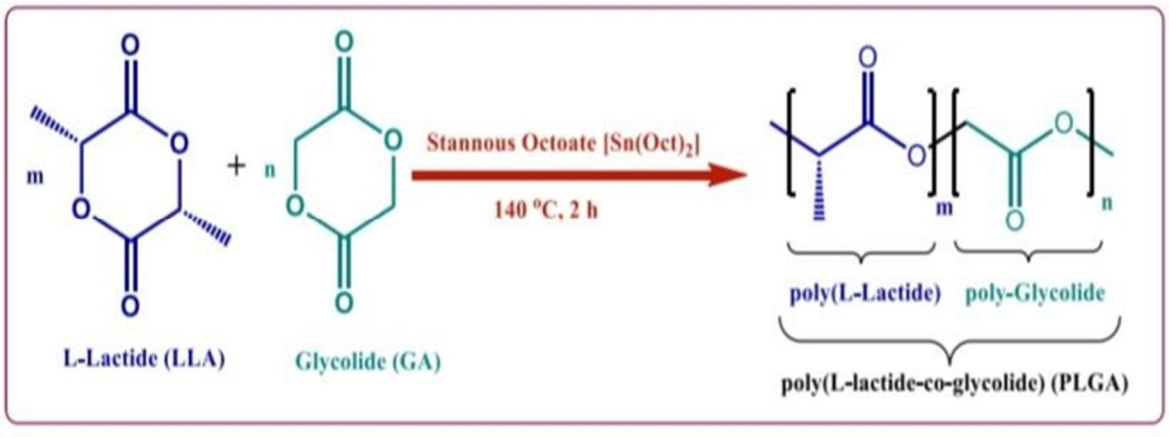


Figure 2: Schematic representation of the synthesis of poly(lactide-co-glycolide) (PLGA: m = number of lactide units, and n = number of glycolide units).

D. Lipid-Based Depots: Oleogels and Liposomes

Lipid-based intramuscular LAIs typically combine an oil carrier, an oleogelator and the drug, sometimes with a cosolvent. An oleogel is a semi-solid three-dimensional network in which the oleogelator immobilises the liquid oil. With a water-miscible cosolvent such as N-methyl-2-pyrrolidone (NMP) the formulation stays injectable at room temperature; after injection NMP diffuses into the tissue, the oleogelator loses solubility and self-assembles, and an oil depot forms in situ. Release then depends on drug diffusion, cosolvent diffusion, solubilisation in the oil and lipase-mediated degradation of the oil. Because the gelled depot has a low specific surface area, surface-driven burst release may be lower than with microspheres [21].

TAF–chitosan nanoparticle oleogel. Tenofovir alafenamide (TAF) shows how an oleogel can add a second release barrier . TAF-loaded chitosan nanoparticles (1:1 drug:chitosan, about 315 nm) released the drug within about 24–26 h, so they were incorporated into an ethyl cellulose–sesame oil oleogel, with NMP lowering viscosity for syringeability. Release from the nanoparticle-loaded oleogels extended to about 55–92% over 16 days, slowing as ethyl cellulose concentration increased, and followed predominantly Fickian diffusion. Ex vivo permeation was about ten-fold lower than that of free TAF, consistent with two sequential barriers (nanoparticle and oleogel). No in vivo pharmacokinetic or efficacy data were reported, so the LAI claim rests on in vitro and ex vivo evidence.[13]

Liposomes. Liposomes are vesicles in which one or more phospholipid bilayers surround an aqueous core. Hydrophilic drugs are carried in the core and hydrophobic drugs in the bilayer;cholesterol stabilises the membrane and limits leakage, and PEG can be added to modify circulation and biodistribution. Release occurs by diffusion across the bilayer, membrane destabilisation or degradation [22]. A liposome is a carrier particle and not automatically a depot; it becomes an LAI only when the formulation prolongs exposure after injection. Phospholipids can also form true depots (suspensions, in situ-forming matrices, multivesicular liposomes and aggregating liposomes) that occupy the intermediate window of days to several weeks between conventional suspensions and polymeric depots [23,24].

Meloxicam liposomes. Intramuscular meloxicam liposomes (Lipoid S 40 with cholesterol;about 108 nm; 81.6% entrapment) demonstrate controlled release with a measurable pharmacokinetic benefit . The conventional meloxicam solution released about 100% within 2 h, whereas the liposomes released about 25% in 30 min and a further 65% over 7 h, best fitted by Higuchi (diffusion-controlled) kinetics. In dogs, the liposomes delayed Tmax(1 vs 0.25 h), gave a non-significantly different Cmax (4.88 vs 6.04 μg/mL), increased AUC0–24 (61.28 vs 33.00 μg·h/mL) and half-life (18.90 vs 16.53 h), and reduced fluctuation, with lower IL-6 and CRP at several time points. This remains a controlled-release product acting over hours to days rather than weeks to months, and scale-up and injection-site histopathology still need evaluation.[14]

E. Injectable Hydrogels and In-Situ Forming Depots

Injectable hydrogels are hydrophilic polymer networks administered as a liquid that gel in situ
under physiological conditions. The delivery principle is: liquid precursor → injection → gel formation → local depot → diffusion- or degradation-controlled release, which suits local delivery of peptides, proteins, nucleic acids and small molecules [25,26]. Networks may be physically, chemically or hybrid crosslinked, and rheology governs performance: shear-thinning allows passage through a needle, and the crossover of the storage (G′) and loss (G″) moduli marks gelation [26]. In-situ crosslinking converts a low-viscosity solution into a covalently or enzymatically crosslinked depot after injection. Release is controlled by crosslink density, polymer concentration, network porosity, drug size and network degradation. Typical concerns are burst release before the network densifies, premature gelation in the syringe, toxicity of residual crosslinkers, and compatibility with proteins and nucleic acids [25,26].

PTH–liposome–gelatin hydrogel. The teriparatide (PTH 1–34) liposome–gelatin hydrogel is the most instructive example . PTH(1–34) is a water-soluble peptide that diffuses rapidly out of the joint. It was encapsulated in liposomes and embedded in a gallic-acid-grafted gelatin hydrogel crosslinked by transglutaminase, which gels at 37 °C within about 5 min after intra-articular injection. Two barriers act in series: the liposome bilayer, considered the main rate-limiting step, and the hydrogel network. PTH release persisted for more than 20 days in vivo compared with about 5 days for the solution, with faster release over the first 3–5 days; increasing the liposome content increased release concentration and duration, although 1 wt% liposome was cytotoxic in preliminary cell work and 0.5 wt% was selected. The hydrogel degraded over about 28 days in PBS. In osteoarthritis models the system raised anabolic markers (SOX9, COLIIA1, ACAN), lowered catabolic and inflammatory markers (ADAMTS5, COX2, IL-6, TNF-α) and protected cartilage in DMM mice. Injection was still required about every three weeks, complete in vivo degradation was not demonstrated, and ATDC5 cells rather than human chondrocytes were used.[9]

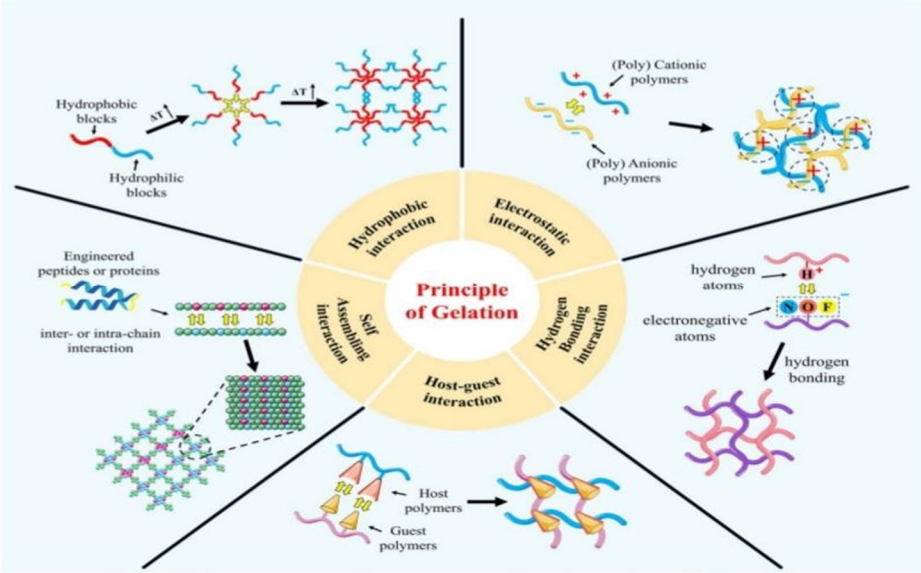


Figure 3 : The typical classification of hydrogel matrix materials and structures of representative polymers.[25]

F. Stimuli-Responsive Injectable Systems

Conventional depots release drug passively by diffusion, dissolution or degradation. Stimuli-responsive depots add a trigger, so that the local microenvironment (temperature, pH
or enzyme activity) modulates release.

Thermosensitive gels. These are based mainly on poloxamer 407 (Pluronic F127), a PEO–PPO–PEO triblock copolymer. As temperature rises the PPO blocks dehydrate, micelles form and pack, and a gel network results, so the system is a liquid for injection and a depot at body temperature [10,27]. A β-lapachone-loaded F127/hyaluronic acid (HA) hydrogel gelled at about 28 °C, was fluid at 25 °C and solid-like at 37 °C ($G' > G''$, storage modulus above 300 Pa), and could be injected with a force of 1.3 ± 0.3 N [10]. Release was biphasic, an initial faster phase followed by sustained release with Korsmeyer–Peppas exponents of 0.48–0.53 (diffusion control), and the gel improved cartilage outcomes in a rabbit osteoarthritis model. Because F127 alone dissociates fairly quickly in aqueous media, HA is included to improve stability, and delayed gelation, which permits early burst, remains the main formulation risk [27].

pH-sensitive gels. These use disease-associated acidity as the trigger. In a phenylboronic acid–modified gelatin methacryloyl (PBA-GelMA) hydrogel, quercetin is bound through a reversible boronate ester; the acidic environment of the degenerating intervertebral disc (hypoxia, glycolysis, lactate) dissociates this bond and releases the drug. A single injection preserved disc height and nucleus pulposus structure at 4–8 weeks in rats, although rat models may repair more readily than human discs.[11]

Enzyme-sensitive gels. These rely on disease-associated enzymes; for example, hyaluronidase degrades a crosslinked HA hydrogel and gradually releases mesenchymal stem cell exosomes over about 14 days in vitro [28].

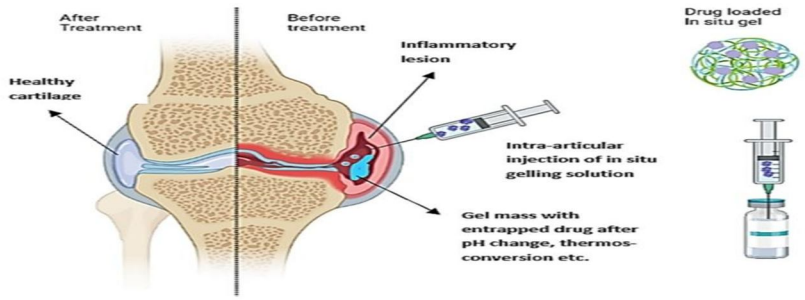


Figure 4 : Schematic representation of the IA administration of an in situ gelling drug formulation into inflamed osteoarthritis (OA) joint and healthy tissue after treatment.[27]

V. IN-SITU FORMING IMPLANTS

In the domain of parenteral controlled release formulations, in situ forming implants (ISFI) form attractive alternatives to preformed implants and microparticles. ISFI bypasses the need for large needles or microsurgery. ISFI can be manufactured in simple steps with a low demand of equipment and processes. They are mostly injected as low viscous solutions which then transform in the body forming a gel or solid depot.

Following are different mechanisms for formation of an in situ implant : (1) in situ cross-linking, (2) in situ solidifying organogels, and (3) in situ phase separation.[29]

A. Biodegradable In-situ implants

Biodegradable in situ implants are liquid or semi-liquid mixtures which are injected into the body via a standard syringe which tends to solidify or gel inside the tissue thus creating a long-lasting, controlled drug delivery depot.They were formulated with the polymer PLGA (Polylactide-co-glycolide) by incorporating the polymer precipitation method.The formulation was evaluated by using FTIR,SEM,DSC studies.Lornoxicam can be successfully formulated as in situ injectable implant which provides immense help in the long term management of various inflammatory disorders this providing improved patient compliance.[30]

B. Polymer based in-situ implants

Polymer-based in-situ forming implants (ISFIs) are liquid drug delivery solutions or suspensions which upon injection into the body solidifies or gels on contact with biological fluids.The main components includes an active pharmaceutical ingredient (API) , a hydrophilic solvent and a biocompatible polymer.The most used phase-sensitive polymer for drug loading is poly(DL-lactide-co-glycolide) (PLGA).[31]

C. Injectable to implant transition systems

Injectable to implant transition systems are advanced drug delivery systems.This consists of
incorporating a formulation in the form of a liquid injection which further changes its phase to a solid or a semi solid type of drug depot.[32]

VI. IMPLANTABLE LONG-ACTING DRUG DELIVERY SYSTEMS

A. Biodegradable implants

Biodegradable implants are types of medical devices which break down and dissolve or resorb in the body after providing the necessary support and drug delivery at the target site, which eliminates the need for another surgery.[33]

B. Non-biodegradable implants

Non-biodegradable implants are type of medical devices which remain intact inside the body without breaking down and dissolving in the body thus often requiring the need of another surgery after the treatment.They provide robust, permanent mechanical support or steady,predictable long-term drug release.[34]

C. Matrix type implants

A matrix (or monolithic) implant is a passive delivery device where the therapeutic drug is homogeneously dispersed or dissolved throughout a solid polymer framework.[35]

D. Reservoir type implants

Reservoir type implants are types of medical devices wherein the active pharmaceutical ingredient (API) is enclosed by a rate controlling polymer thus forming a reservoir.[36]

E. Drug eluting implants and devices

Drug-eluting medical implants are type of advanced medical devices actually which induce healing effects, in addition to their regular task of providing support. This is primarily achieved by controlled release of active pharmaceutical ingredients (API) into the surrounding tissue. [37]

VII. SMART AND PROGRAMMABLE LONG ACTING DRUG DELIVERY SYSTEMS

A. Externally triggered drug delivery

Externally triggered drug delivery makes use of external stimuli to initiate the drug release from the implants which leads to increased patient compliance through the elimination of needles and reminders set for the medications.The initiation of drug release takes place through various external stimuli like the light, ultrasound (US), magnetic fields and Since it aims ultimately towards the target site,this eliminates the potential risk of various side and toxic effects.[38]

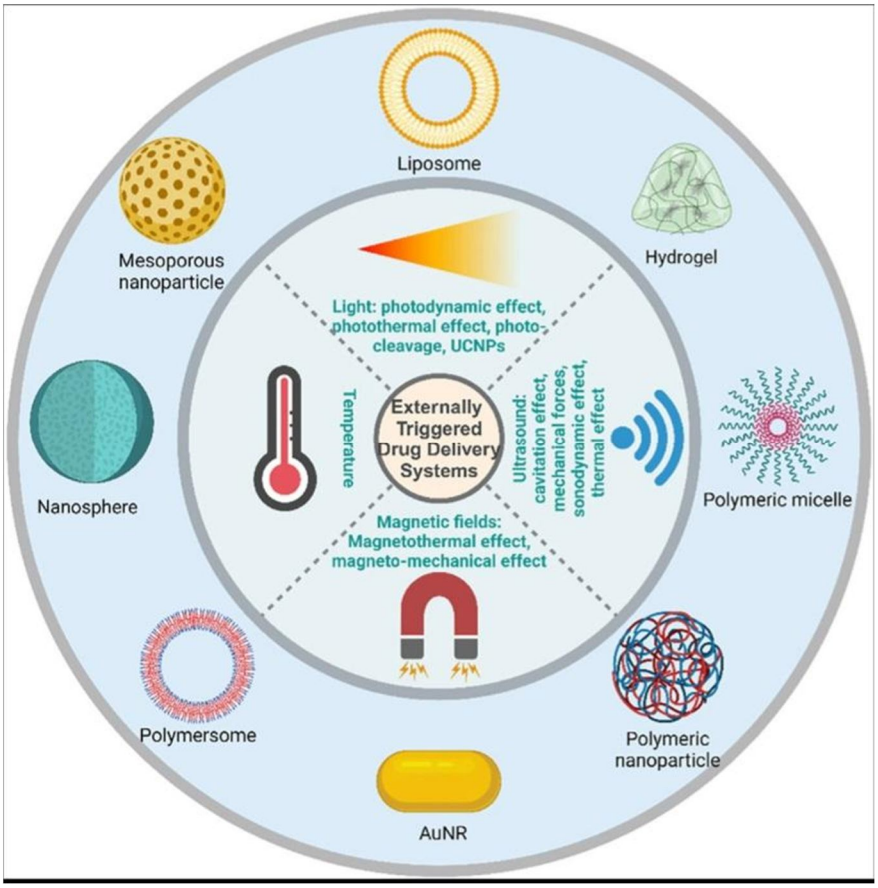


Figure 5:Different types of external stimuli [51]

B. Programmable drug release devices

A programmable, controlled release drug delivery system has been developed.Here the device is in the form of a non-digestible oral capsule which contains the drug in a slowly eroding matrix.The device was designed to utilize an automatically operated geometric obstruction which prevents the device from floating in the stomach and passing through the remainder of the GIT.[39]

C. 3D printed & patient specific implants

3D printing aids in producing the tailor made implants as per the patient's anatomy.Here,medicine shifts toward personalized care: for example, complex bone tumors,craniofacial defects, or unique joint geometries. Nowadays the standard implants are increasingly being treated with bespoke 3D-printed solutions.It makes use of High-resolution imaging like the computed tomography/magnetic resonance imaging [CT/MRI]) to generate digital 3D models of patient anatomy, thus guiding the design of implants or cutting guide.3D-printed patient-specific surgical instruments (such as osteotomy or screw-guidance jigs) also aids in improving the intraoperative precision by fitting the individual bone surface thus reducing the reliance on intraoperative estimation.[40]

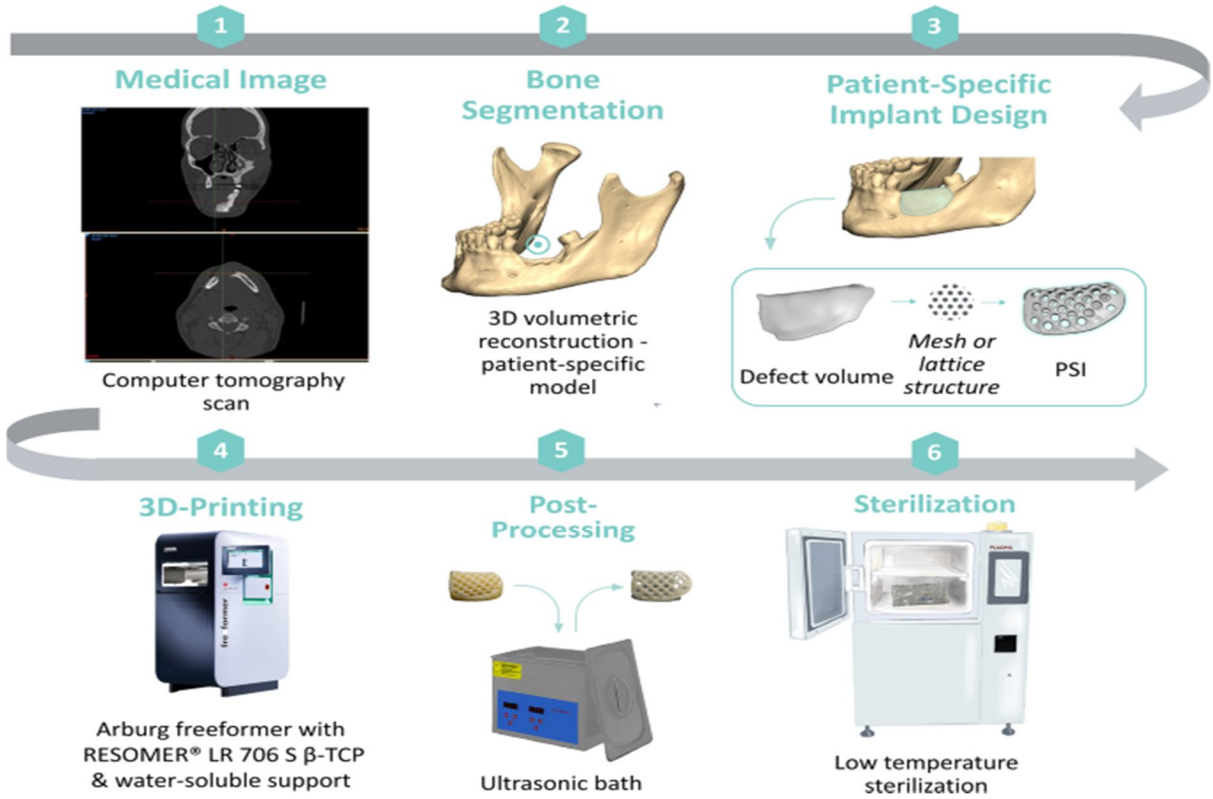


Figure 6: workflow of patient-specific design and fabrication with the mesh for mandibular alveolar bone regeneration. The process begins with the (1) retrieval of patient computed tomography (CT) imaging data and the (2) segmentation of relevant anatomical structures. Based on the segmented data, the (3) patient-specific implant (PSI) is designed. (4) The PSI is then three-dimensional (3D) printed from medical-grade raw material pellets. (5) The water-soluble support structures are removed in an ultrasonic bath. (6) Subsequently, the implant is packaged and then sterilized [52]

VIII. CLINICAL APPLICATIONS OF LONG ACTING DRUG DELIVERY SYSTEMS

1) *Infectious Diseases (HIV/AIDS, TB, Malaria):* Long-acting injectables like Cabotegravir are used for HIV pre-exposure prophylaxis (PrEP) which is dosed every two months thus eliminating the need of daily pill routines and protecting non-adherent patients. Similar sustained-release depots are explored for tuberculosis and malaria.[41][42]
2) *Psychiatry and Neurology*: Long-acting antipsychotic injections (e.g., risperidone or paliperidone palmitate) manage schizophrenia and bipolar disorder thus drastically reducing the relapse rates by avoidance of the missed daily doses.[41]
3) *Endocrinology and Diabetes:* Formulations such as extended-release exenatide microspheres (Bydureon)aims at delivering steady glycemic control for type II diabetes mellitus thus preventing sudden blood glucose spikes and drops while sparing patients daily injections.[43]
4) *Hormonal Regulation and Contraception:* Subcutaneous or intramuscular depot medroxyprogesterone acetate aims to provide multi-month contraception.Also,analogous long-acting implants or injections helps in delivering various hormone replacement therapies.[44]
5) *Ophthalmology*: Biodegradable intravitreal implants (such as Ozurdex for dexamethasone) helps in treating chronic posterior eye segment conditions like macular edema and uveitis promising over extended durations.[45]
6) *Addiction Management:* Extended-release subcutaneous buprenorphine (Sublocade) helps in creating a sustained depot for treatment of moderate-to-severe opioid use disorder.[46]

IX. TRANSLATIONAL, CLINICAL AND REGULATORY CHALLENGES

The primary challenge for these types of formulations still underlines the stability issues faced during manufacturing.Also,the incorporation and maintenance of sterile systems should be taken into account when formulating and designing new LADDS.This is particularly significant for new polymer- or peptide-based strategies.

Additionally, another important aspect,which is often overlooked, is the reaction against the foreign bodies to LADDS after it's administration. The implementation of various kinds of these technologies need to comply with the regulatory clearance and clinical trials as regulatory approval can be particularly challenging for some of these novel strategies, as they often often consist of new chemical entities or unregulated approaches.[47][48]

X. FUTURE PERSPECTIVES

The future of long-acting drug delivery systems (LADDS) will focus on achieving prolonged, predictable and patient-centred drug release while improving clinical translation. Thermoresponsive and other stimuli-responsive systems may form stable depots and provide controlled release in response to temperature, pH, light or magnetic stimuli. Advances in polymers and biomaterials could expand long-acting delivery to poorly soluble drugs, peptides, proteins and other emerging therapeutics. Polymer–drug conjugates and prodrugs may further prolong drug exposure through controlled chemical conversion or degradation. Microfabrication and 3D printing offer opportunities for customised implant geometry, multilayered structures and programmable release profiles. Predictive in-vitro dissolution methods and reliable in-vitro–in-vivo correlations are also needed to improve formulation development and reduce trial-and-error. Ultimately, successful LADDS will require integration of biocompatible materials, reproducible manufacturing, controlled release, injection-site tolerability, patient acceptability and appropriate regulatory strategies.[48][49]

XI. CONCLUSION

Long-acting drug delivery systems have evolved into diverse injectable and implantable platforms capable of providing prolonged and controlled drug release. Injectable depots, polymeric microspheres, lipid-based systems, hydrogels, and implants employ mechanisms including dissolution, diffusion, polymer degradation, swelling, and erosion to extend therapeutic exposure. However, successful LAI development requires more than prolonged release, with burst release, injection-site tolerability, material variability, manufacturing complexity, and prediction of in-vivo performance remaining important challenges. Future development should therefore integrate rational formulation design, appropriate release-kinetic evaluation, predictive in-vitro methods, reproducible manufacturing, and patient-centred considerations. Such integration can support safer, more predictable, scalable, and clinically translatable long-acting therapies.

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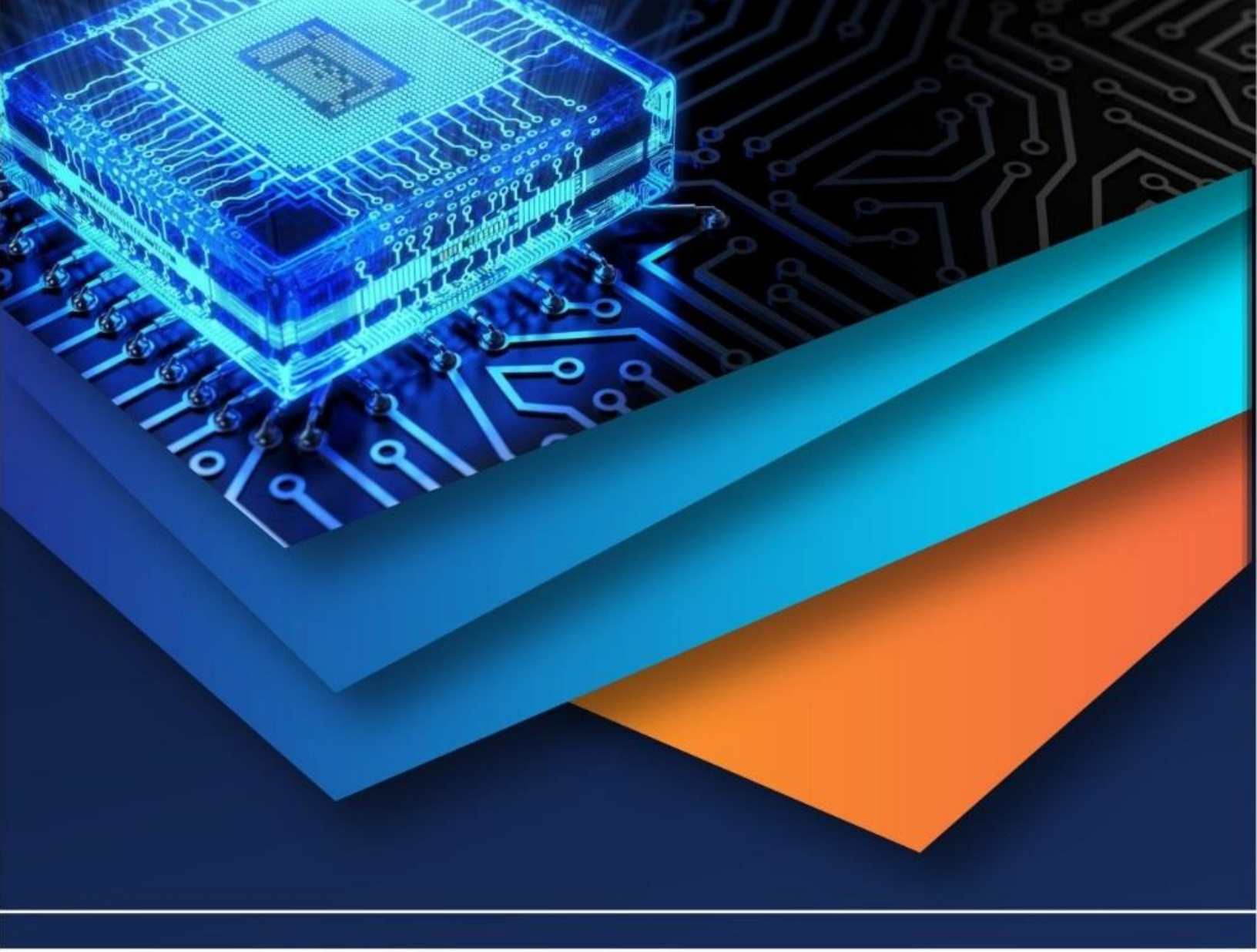

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