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REVIEW ON IN-SITU DEPOT-BASED CONTROLLED DRUG DELIVERY FOR TREATMENT OF RHEUMATOID ARTHRITIS TREATMENT

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic, progressive autoimmune disorder characterized by persistent inflammation of synovial joints, leading to pain, swelling, and eventual joint deformity. Conventional systemic administration of anti-rheumatic drugs often results in suboptimal therapeutic efficacy due to rapid clearance, poor site-specificity, and systemic side effects. In-situ depot-based controlled drug delivery systems have emerged as a promising approach to overcome these limitations by providing localized, sustained, and controlled release of therapeutic agents directly at the site of inflammation. These systems, typically formulated as thermosensitive gels, injectable microspheres, or polymeric depots, undergo sol–gel transitions or form depots upon administration, allowing for prolonged drug residence time and reduced dosing frequency. Such delivery platforms can encapsulate disease-modifying antirheumatic drugs (DMARDs), corticosteroids, or biologics, enhancing their pharmacokinetic and pharmacodynamic profiles. This strategy minimizes systemic toxicity, improves patient compliance, and ensures sustained therapeutic concentrations within the joint microenvironment. The present review highlights the design principles, formulation strategies, and recent advancements in in-situ depot-based controlled drug delivery systems for the effective management of rheumatoid arthritis, emphasizing their potential to revolutionize RA therapy through localized and sustained drug action.

KEYWORDS: Rheumatoid arthritis; In-situ depot; Controlled drug delivery; Biodegradable polymers; Sustained release; Localized therapy.

INTRODUCTION

For drugs that cannot be taken by oral route, parenteral drug delivery systems have gained significant research interest over the past two decades. Due to the gradually increasing number of biotechnology-based drugs and compounds that cannot be executed via the oral route, parenteral formulations are the best choice.[1] Even though intensive efforts have been devoted to alternative routes (pulmonary, oral, nasal, transdermal), poor and highly variable absorption persists as the key issue of those routes.[2]

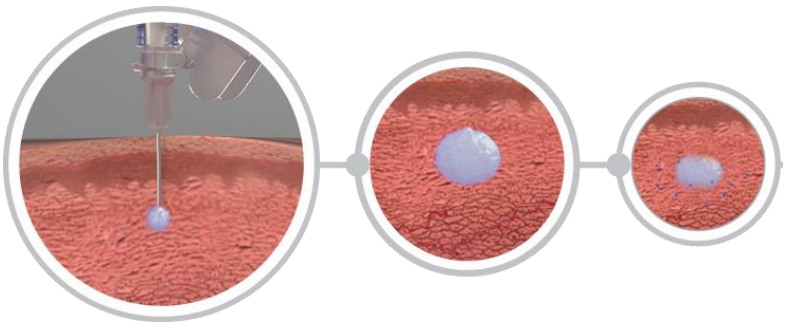

Figure: In-situ depot.

The depot delivery systems can be created to contribute flexible delivery characteristics. Many drugs have high activity with a short half-life.[3] *In-situ* implant forming formulations are therefore a formulation opportunity to evade a constant infusion or a very huge frequency of injections, Depot formulations show that release kinetics have been established from days, weeks, over months, to even years. Thereby parenteral depot formulations build up patient compliance by lessening the frequency of applications.[4]

Moreover, depot formulations can deprecate unwanted effects caused by fluctuating drug blood levels which are commonplace in immediate-release products. In the case of localized delivery, it allows the drug to be deposited directly at the site of action. Therefore, the system toxicity and drug dosage fluctuations can be minimized. Regular application of parenteral depot systems involves the treatment of hormone-sensitive breast or prostate cancers, local treatment of infections, local therapy, or local delivery to the eyes.[5]

For effective treatment, it is often desirable to maintain systemic drug levels within the therapeutic effective concentration range for a long time. To achieve this objective new injectable drug delivery systems have been developed which are termed *in-situ* forming implants (ISFI).[6]

In-situ comes from a Latin word that means in position. *In-situ* forming implants can be characterized as a liquid formulation generating solid or semi-solid depot after administration. This concept of generating in-situ gel was suggested for the first time in the early 1980s. They prolonged drug release kinetics even for more than weeks to month's duration. Different types of parenteral dosage forms are available, such as solutions, emulsions, liposomes, micelles, implants, microparticles, nanoparticles, and nanocapsules.[7]

Depot formulations made by melt-extrusion can be administered subcutaneously by a special application device or through a large needle. In the case of non-biodegradable systems, implants should be removed after release periods. In the case of bio-degradable materials, the polymers degrade during and after the drug release process in the form of metabolism and excretion. Commonly performed subcutaneous implants are 10 mm long and 1 mm diameter with cylindrical shape.[8]

They are injected through a 16-gauge needle. The non-biodegradable one-year implant has a length of about 35 mm and 3 mm of thickness. Small implants can be used for eye treatment. The release of the drug is due to the degradation of the biodegradable polymer. Gelation occurs by cross-linking of polymer chains that can be formed by covalent bond formation (chemical cross-linking), or non-covalent bond formation (Physical cross-linking).[9]

In-situ forming implants have been developed for controlled drug delivery in systemic treatment as well as localized therapies. In delay, *in-situ* forming implants have found applications in tissue engineering, three-dimensional cell culturing, orthopedic, dental administration, and cell transplantation. *In-situ* forming implant systems can be classified according to their mechanism of implant formation.[10]

1. *In-situ* cross-linked polymer systems
2. *In-situ* solidifying organic gels
3. *In-situ* polymer precipitation
4. Thermoplastic paste
5. Thermally induced gelling systems

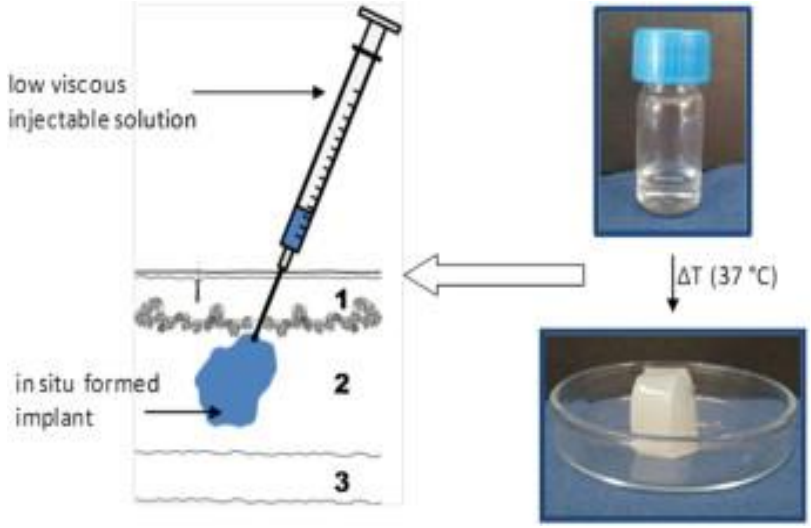

Figure 1: Mechanism of in-situ depot formation (schematic illustration showing sol-to-gel transition at the injection site).

OBJECTIVE[11]

- ✓ To perform pre-formulation study of Tofacitinib.
- ✓ To perform UV estimation assay for Tofacitinib.
- ✓ Formulation and Optimization of Tofacitinib *in-situ* depot system.
- ✓ Optimization of depot system to get drug release up to one-week using Design of Experiment.
- ✓ Evaluation of *in-situ* depot formulations.
- ✓ *Invitro* release studies

MATERIALS AND METHODS[12]

In-situ depot systems are liquid formulations that convert to a gel or solid matrix upon administration. This transition can be triggered by temperature, pH, or solvent exchange. The resulting depot allows sustained release of drugs at the target site, improving therapeutic outcomes.

Table 1: Common polymers used in in-situ depot systems and their triggering mechanisms.[13]

Polymer	Trigger Mechanism	Examples/Applications
PLGA	Solvent exchange	Methotrexate, Triamcinolone
Poloxamer 407	Thermo-sensitive gelation	Celecoxib, Diclofenac
Chitosan	pH-sensitive precipitation	Leflunomide, Dexamethasone
Alginate	Ionic crosslinking	NSAID depot formulations
PEG-PLGA-PEG	Temperature-sensitive	Protein-based RA therapies

The choice of polymer significantly affects the release kinetics. Synthetic polymers like PLGA and PEG offer controlled degradation, while natural polymers such as chitosan and alginate provide biocompatibility and bioadhesion. Hybrid systems combining both classes are being explored for improved performance.[14]

Drug release from depot systems follows diffusion, polymer degradation, or erosion mechanisms. In the case of PLGA-based depots, solvent exchange leads to polymer precipitation, forming a matrix that gradually releases the drug. Thermosensitive systems like poloxamers gel upon exposure to body temperature, offering minimally invasive application.[15]

Table 2: Comparative summary of in-situ depot formulations for RA therapy.

Drug	Polymer System	Release Duration	Outcome
Methotrexate	PLGA/NMP system	14–28 days	Sustained anti-inflammatory activity
Celecoxib	Poloxamer 407	7–10 days	Reduced systemic toxicity
Leflunomide	Chitosan-gelatin blend	21 days	Prolonged joint retention
Triamcinolone acetonide	PLGA microsphere depot	30 days	Decreased relapse frequency
Adalimumab	PEG-PLGA hydrogel	21–35 days	Sustained therapeutic levels

Preclinical studies have confirmed that depot-based delivery of methotrexate and corticosteroids significantly reduces joint swelling and inflammatory cytokine levels compared to conventional therapy. Clinical translation is underway, particularly for corticosteroid depots.[16]

RESULTS AND DISCUSSION

1. Overview of In-Situ Depot Systems

In-situ depot systems are injectable formulations that undergo sol-to-gel or liquid-to-solid transitions upon administration. The depot acts as a drug reservoir, enabling continuous release through diffusion, degradation, or erosion mechanisms. These systems are minimally invasive and improve patient adherence by reducing dosing frequency.[17]

2. Mechanism of In-Situ Depot Formation[18]

The formation mechanism is dictated by external physiological conditions such as temperature, pH, or ionic strength. Major mechanisms include.

- **Thermosensitive systems:** Utilize polymers like PLGA-PEG-PLGA or poloxamers that gel upon exposure to body temperature.
- **pH-triggered systems:** Employ polymers like chitosan or Eudragit that precipitate under physiological pH.
- **Solvent exchange systems:** Based on biodegradable polymers such as poly(lactide-co-glycolide) dissolved in organic solvents (e.g., N-methyl-2-pyrrolidone), which precipitate upon solvent exchange with aqueous body fluids.

3. Polymeric Materials Used

Polymeric carriers play a crucial role in controlling drug release kinetics and biocompatibility. Common materials include.

- **Synthetic Polymers:** PLGA, PEG, PCL, and poloxamers are widely used due to predictable degradation profiles.
- **Natural Polymers:** Chitosan, alginate, gelatin, and hyaluronic acid offer biocompatibility and bioadhesive properties but may exhibit batch variability.

4. Advantages Over Conventional Formulations

- Sustained drug release minimizes dosing frequency.
- Reduced systemic toxicity due to localized action.

- Improved patient compliance and therapeutic efficacy.
- Enhanced stability of biologics and peptides.

5. In-Situ Depot Systems in Rheumatoid Arthritis
Several formulations have been designed to deliver anti-inflammatory and immunomodulatory agents directly into inflamed joints.

a) Corticosteroid: Triamcinolone acetonide and dexamethasone have been formulated in thermosensitive PLGA-based systems, showing prolonged anti-inflammatory effects up to four weeks post-injection.

b) NSAID
Celecoxib-loaded poloxamer gels provided sustained release for over seven days, demonstrating reduced local irritation compared to conventional formulations.

c) DMARD
Methotrexate and leflunomide incorporated into chitosan or PLGA depots have exhibited enhanced residence time in synovial fluid and improved disease suppression in animal models.

d)BiologicAgents
Emerging studies report depot-based delivery of monoclonal antibodies (e.g., adalimumab) via injectable hydrogels for maintaining therapeutic levels over extended durations.

6. Release Kinetics and Drug Stability
Drug release from in-situ depots occurs through a combination of diffusion, degradation, and swelling mechanisms. The rate can be modulated by altering polymer composition, molecular weight, and crosslinking density. Mathematical models such as Higuchi, Korsmeyer–Peppas, and zero-order kinetics are applied to describe release profiles.

7. Safety and Biocompatibility
Biocompatibility is a key requirement. Biodegradable polymers such as PLGA degrade into lactic and glycolic acids, which are metabolized via the Krebs cycle. However, acidic degradation products can sometimes induce local inflammation, necessitating polymer modification or incorporation of buffering agents.

8. Preclinical and Clinical Evidence
Preclinical studies in arthritic rat models have shown that methotrexate-loaded PLGA depots significantly reduce paw swelling and inflammatory markers compared to free drug formulations. Few clinical trials have reported promising results, especially with corticosteroid depots, leading to extended therapeutic action and decreased relapse frequency.[19]

9. Challenges and Future Prospects[20]
Despite notable progress, several challenges remain.

- Limited predictability of in-vivo gelation and degradation.
- Scale-up difficulties and sterilization issues.

CONCLUSION
In-situ depot-based controlled drug delivery represents a transformative approach in the management of rheumatoid arthritis. By enabling sustained, localized, and controlled drug release, these systems offer significant therapeutic advantages over conventional formulations. Advanced polymeric systems and engineering innovations have paved the way for achieving prolonged anti-inflammatory activity with minimized systemic toxicity. Continued interdisciplinary research combining materials science, pharmacology, and rheumatology is crucial to translating these systems from laboratory to clinical applications.

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