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Targeted PLGA Nanoparticle Delivery of Mycophenolate Mofetil: A Novel Approach for Sustained Immunosuppression in Rheumatoid Arthritis

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Abstract: Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that can cause progressive joint damage and disability. Mycophenolate mofetil (MMF), a prodrug of mycophenolic acid, suppresses T- and B-lymphocyte proliferation through inhibition of inosine monophosphate dehydrogenase, but systemic treatment may be limited by gastrointestinal intolerance and other immunosuppression-related adverse effects. This study aimed to develop and evaluate MMF-loaded poly(lactic-co-glycolic acid) (PLGA) nanoparticles as a potential controlled-release delivery platform. Nanoparticles were prepared using an organic-solvent-based nanoparticle formation method with PLGA as the biodegradable carrier and polyvinyl alcohol (PVA) as stabilizer. A central composite face-centred design was applied to study the influence of polymer and stabilizer concentrations. The formulations were assessed for particle size, polydispersity index, entrapment efficiency, surface morphology, in-vitro drug release, release kinetics and short-term storage stability. Formulation F12 was selected as the optimized formulation. It showed a particle size of 543 nm and a zeta potential of −21.8 mV; reported entrapment efficiencies across the formulation set ranged from 93.3% to 96.5%. Scanning electron microscopy indicated a spherical morphology with smooth surfaces. In-vitro release from F12 reached 92.621% at 480 minutes, with a biphasic profile. The release data fitted zero-order and Korsmeyer–Peppas models closely (R^2 0.9864 and 0.9869, respectively). During 90-day storage assessment, particle size and drug content/entrapment measures showed only modest changes. These findings support further investigation of MMF-loaded PLGA nanoparticles; however, targeted delivery to inflamed joints and clinical benefit require direct in-vivo and clinical validation.

Keywords: *Mycophenolate mofetil; PLGA; polymeric nanoparticles; rheumatoid arthritis; controlled release; formulation optimization*.

1. Introduction

1.1 Rheumatoid arthritis and therapeutic need

Rheumatoid arthritis is a systemic autoimmune disorder primarily affecting synovial joints. Common manifestations include pain, swelling, stiffness and progressive structural damage, often involving the small joints of the hands, wrists and feet. Persistent inflammation can lead to cartilage degradation, bone erosion, deformity, functional limitation and reduced quality of life. Extra-articular manifestations may

involve the lungs, cardiovascular system, eyes and other tissues. Early diagnosis and sustained control of inflammation are therefore important in limiting long-term disability.

Current management includes conventional synthetic disease-modifying antirheumatic drugs, biologic agents and targeted synthetic therapies. Although these options have improved outcomes, inadequate response, adverse effects, cost and the need for prolonged treatment remain important challenges for some patients. A drug-delivery system that controls release and potentially improves distribution could help address selected limitations, although the benefit must be demonstrated experimentally rather than assumed from formulation characteristics alone.

1.2 Mycophenolate mofetil

Mycophenolate mofetil is an ester prodrug converted to mycophenolic acid. The active metabolite selectively and reversibly inhibits inosine monophosphate dehydrogenase, an enzyme involved in de-novo guanosine nucleotide synthesis. Activated T and B lymphocytes depend strongly on this pathway, so inhibition can reduce lymphocyte proliferation and immune responses. MMF is used as an immunosuppressant in transplantation and has been investigated in certain autoimmune conditions. Its use may be accompanied by gastrointestinal intolerance, leukopenia and increased infection risk; its use in rheumatoid arthritis is not a substitute for established guideline-directed care.

1.3 Rationale for a nanoparticle carrier

PLGA is a biodegradable and biocompatible copolymer used in controlled drug delivery. Its degradation products, lactic acid and glycolic acid, can be metabolized by the body. PLGA nanoparticles may protect encapsulated drug, influence release rate and permit adjustment of particle properties through polymer composition and formulation variables. In inflamed tissue, altered vascular permeability and uptake by phagocytic cells may support nanoparticle accumulation, but passive accumulation is not equivalent to proven joint-specific targeting. The present work therefore evaluates formulation performance as an initial step toward a possible RA delivery application.

1.4 Study hypothesis

The working hypothesis was that MMF could be incorporated into PLGA nanoparticles with high entrapment and a sustained in-vitro release profile. Optimization of PLGA and PVA concentrations was expected to balance particle size, dispersion characteristics and entrapment efficiency.

2. Aim, objectives and literature context

2.1 Aim

To develop and evaluate mycophenolate mofetil-loaded PLGA nanoparticles for sustained drug release, with the longer-term objective of improving delivery performance and potentially reducing dosing frequency and systemic adverse effects.

2.2 Objectives

- To perform preformulation studies on MMF and selected excipients.
- To prepare MMF-loaded PLGA nanoparticles and optimize formulation variables using Design of Experiments (DoE).
- To characterize particle size, polydispersity index, zeta potential, morphology and entrapment efficiency.
- To determine in-vitro drug release and compare mathematical release-kinetic models.
- To assess short-term stability under different storage conditions.

2.3 Relevant literature

Clinical and mechanistic literature describes RA as a chronic inflammatory disease in which cytokine networks, activated immune cells and osteoclast activity contribute to synovitis and joint destruction. Reviews of MMF describe its selective inhibition of lymphocyte purine synthesis as the basis of immunosuppressive activity. However, adverse effects associated with systemic immunosuppression create a rationale for studying alternative delivery strategies.

Research on biodegradable polymeric nanoparticles has highlighted the importance of polymer composition, particle size, surface charge, stabilizer concentration and preparation method. PLGA-based

systems have been investigated for anti-inflammatory and immunomodulatory agents, with controlled release frequently reported as a formulation advantage. The particle-size distribution and polydispersity index are important quality attributes because they affect dispersion uniformity, stability, release and biological interactions.

Drug-release models provide complementary ways to describe formulation behaviour. Zero-order modelling examines release at an approximately constant rate; first-order modelling relates release to the amount of drug remaining; the Higuchi model evaluates diffusion-based release under defined assumptions; and the Korsmeyer–Peppas model provides an empirical description of release mechanisms. Model fit alone does not prove a unique mechanism, and interpretation should consider the model assumptions and the experimental design.

2.4 Research gap

The dissertation frames MMF-loaded PLGA nanoparticles as a promising platform, while acknowledging that direct evidence for RA-specific targeting and clinical benefit remains limited. The present investigation concentrates on formulation development, physicochemical characterization, in-vitro release and preliminary stability, not on demonstrating clinical efficacy.

3. Materials and methodology

3.1 Materials

Mycophenolate mofetil was used as the active pharmaceutical ingredient. PLGA served as the biodegradable polymeric carrier, and polyvinyl alcohol (PVA) was used as the aqueous-phase stabilizer. Acetonitrile was used to prepare the organic phase, and distilled water and phosphate buffer were used during formulation and release testing. The dissertation reports the PLGA grade as a lactide:glycolide copolymer and identifies PVA as the stabilizing excipient.

3.2 Preparation of MMF-loaded PLGA nanoparticles

MMF was dissolved in acetonitrile at the concentration specified in the dissertation, and PLGA was added to the organic phase. The solution was briefly sonicated to support complete solubilization. Aqueous PVA solutions at different concentrations were prepared separately. The organic phase was rapidly introduced into the aqueous PVA phase under continuous stirring at 600 rpm. Stirring was continued to allow evaporation of acetonitrile and formation of a nanoparticle dispersion. The dispersion volume was adjusted with distilled water.

3.3 Experimental design and optimization

A 3^2 central composite face-centred design was implemented in Design-Expert software. PLGA concentration and PVA concentration were the independent variables. The study used coded low, medium and high levels and included factorial points, axial points and replicated centre points, giving 13 experimental runs. Particle size, polydispersity index and entrapment efficiency were treated as key responses. The desirability function was used to identify a compromise formulation across the selected responses.

Design element	Description reported in dissertation
Independent variable A	PLGA concentration
Independent variable B	PVA concentration
Design	3^2 central composite face-centred design
Number of runs	13 formulations/runs
Main responses	Particle size, PDI and entrapment efficiency
Optimization software	Design-Expert® Version 13

3.4 Preformulation and compatibility

Preformulation included visual description, solubility and melting-point assessment. Fourier-transform infrared spectroscopy (FTIR) was used to examine the drug and excipients and to consider potential compatibility. The dissertation also reports determination of the drug's wavelength maximum and construction of a calibration curve for spectrophotometric quantification.

4. Nanoparticle characterization and evaluation

4.1 Particle size, PDI and zeta potential

Particle size, polydispersity index and zeta potential were determined using dynamic light scattering with a particle-size analyzer. Samples were diluted appropriately before measurement. The reported measurement conditions included a scattering angle of 173° and a temperature of 25 °C. These measurements were used to assess mean hydrodynamic size, dispersion heterogeneity and surface charge.

4.2 Entrapment efficiency

Entrapment efficiency was assessed indirectly. The nanoparticle dispersion was centrifuged at 20,000 rpm for 60 minutes at 25 °C, and the supernatant containing unentrapped drug was collected. Free MMF was quantified spectrophotometrically at 250 nm. Entrapment efficiency was calculated as:

$$\% \text{ Entrapment efficiency} = [(\text{Total MMF} - \text{free MMF}) / \text{Total MMF}] \times 100$$

4.3 Surface morphology

The morphology of the optimized nanoparticles was examined by scanning electron microscopy. Samples were mounted on an aluminium stub using carbon tape and sputter-coated with gold before imaging. The dissertation describes imaging at an accelerating voltage of 10 kV and a magnification of approximately 10,000×.

4.4 In-vitro drug release

Drug release was evaluated by the dialysis-bag diffusion method. A weighed quantity of MMF-loaded nanoparticles was dispersed in a small volume of buffer and enclosed in a cellulose dialysis membrane. The membrane was immersed in 100 mL of phosphate buffer at pH 5.8, maintained at 37 ± 0.5 °C and stirred at 50 rpm. Samples of 5 mL were withdrawn at predetermined intervals and replaced with fresh buffer to maintain sink conditions. MMF in the samples was quantified by UV-visible spectrophotometry at 254 nm. Cumulative percentage drug release was plotted against time.

4.5 Release kinetics and stability

Release data were fitted to zero-order, first-order, Higuchi and Korsmeyer–Peppas models. Stability was assessed over 90 days at refrigerated (4 ± 2 °C), intermediate (25 ± 2 °C/60% RH) and accelerated (40 ± 2 °C/75% RH) conditions. Particle size and drug content/entrapment-related measures were monitored over time.

Ethical note: the dissertation certificate states that experimental animals were not used in this study.

5. Results

5.1 Preformulation findings

The dissertation describes MMF as a white to off-white crystalline powder. It reports the drug as insoluble in water, sparingly soluble in ethanol, soluble in methanol and freely soluble in acetone. The observed melting point was approximately 96 °C, consistent with the range stated in the source document. These findings informed the selection of an organic solvent for formulation.

5.2 Formulation optimization

The optimization analysis generated multiple possible solutions and selected a solution with a desirability value of 1.000. The model-predicted optimum was approximately 0.8189% w/w PLGA and 2.29% w/w PVA. The dissertation then selected a practical formulation using 1% PLGA and 2% PVA, which was close to the predicted concentrations and appeared repeatedly in the experimental design.

Parameter	Result reported
Predicted PLGA concentration	0.8189% w/w
Predicted PVA concentration	2.29% w/w
Selected practical composition	1% PLGA + 2% PVA
Overall desirability	1.000
Selected formulation	F12

5.3 Entrapment efficiency

Across the formulations, entrapment efficiency ranged from 93.3% to 96.5%. The source reports PLGA concentration as the more influential factor for entrapment efficiency, with higher polymer concentration associated with higher entrapment (reported $p < 0.01$). PVA concentration did not significantly affect entrapment efficiency in this dataset. A denser polymer matrix may reduce drug escape into the external aqueous phase during nanoparticle formation.

5.4 Optimized formulation F12

Quality attribute	F12 result / observation
Particle size	543 nm
Zeta potential	−21.8 mV
Morphology	Spherical particles with smooth surfaces
Entrapment efficiency	Formulation range reported: 93.3–96.5%; individual F12 value should be checked against the original table
Release at 480 min	92.621% cumulative drug release

The reported particle size suggests a submicron dispersion. The negative zeta potential indicates a negatively charged particle surface; however, the magnitude alone should not be taken as definitive proof of long-term colloidal stability. SEM images were interpreted as showing spherical, smooth-surfaced nanoparticles.

6. In-vitro release profile and kinetic analysis

6.1 Cumulative drug release

The optimized F12 formulation showed progressive release over the 480-minute study. The reported cumulative drug-release values are summarized below.

Time (min)	Cumulative drug release (%)
30	4.941
60	11.646
120	20.704
180	32.115
240	46.467
300	61.996
360	79.290
480	92.621

The release profile was described as biphasic: an early release phase followed by continued release. The dissertation reports 20.704% release at 120 minutes and approximately 92.6% at 480 minutes. Early release may be associated with drug located at or near the particle surface, while later release may involve diffusion through the polymer matrix and polymer degradation/erosion. These explanations are plausible interpretations rather than direct mechanistic measurements.

6.2 Mathematical modelling

Release model	R^2	Interpretation in source
Zero order	0.9864	High correlation with the observed release data
First order	0.9056	Lower correlation than zero-order and Korsmeyer–Peppas
Higuchi	0.7984	Lower fit in this dataset
Korsmeyer–Peppas	0.9869; n = 1.036	High correlation; reported n value interpreted as super case-II transport

The high R^2 values for zero-order and Korsmeyer–Peppas models indicate that both equations described the data closely. The Korsmeyer–Peppas exponent reported as 1.036 was interpreted in the dissertation as suggesting super case-II transport, consistent with a contribution from polymer relaxation or erosion. Because model fitting can be influenced by the selected time range and assumptions, the result should be interpreted as supportive rather than conclusive evidence of the release mechanism.

6.3 Formulation implications

The release profile indicates that MMF can be released from the optimized PLGA formulation over the tested eight-hour period. This supports continued formulation development, but it does not establish prolonged release over days or weeks, reduced clinical dosing frequency, improved joint targeting or lower adverse-event rates. Those outcomes require appropriate pharmacokinetic, pharmacodynamic and safety studies.

7. Stability assessment and discussion

7.1 Short-term stability

The dissertation reports stability observations over 90 days under refrigerated, intermediate and accelerated conditions. Particle size changed only modestly, while drug content/entrapment-related values decreased slightly. The table below summarizes the values stated in the source.

Sampling day	Particle size at 4 ± 2 °C (nm)	Particle size at 25 °C/60% RH (nm)	Particle size at 40 °C/75% RH (nm)	Reported drug content/entrapment-related value range
Day 1	543 ± 5	543 ± 6	543 ± 6	Approximately 94.6%
Day 30	543 ± 5	545 ± 8	545 ± 6	Approximately 93.6–94.2%
Day 60	543 ± 6	547 ± 8	547 ± 7	Approximately 93.2–93.7%
Day 90	543 ± 6	548 ± 8	548 ± 8	Approximately 92.6–93.2%

The source concludes that these limited changes indicate good preliminary physical and chemical stability under the tested conditions. The observed particle size remained around 543–548 nm across the reported measurements. The exact meaning of the drug-content columns should be checked against the original thesis table before publication, because the table heading and narrative use drug content and entrapment-related terminology inconsistently.

7.2 Discussion

The findings demonstrate that the PLGA/PVA system could produce MMF-loaded nanoparticles with high entrapment across the formulation set. The central composite design provided a structured approach for assessing formulation variables and selecting a practical composition. The selected F12 formulation combined a reported particle size of 543 nm with a zeta potential of −21.8 mV and smooth, spherical morphology. Its in-vitro release reached 92.621% by 480 minutes.

These results are consistent with the general purpose of biodegradable polymeric carriers: to encapsulate drug and modulate its release. The model results suggest a controlled release pattern, although further experiments are needed to separate diffusion, matrix relaxation and degradation effects. Short-term stability data are encouraging but do not establish a commercial shelf life; longer studies, validated analytical methods, suitable packaging assessment and batch-to-batch reproducibility would be needed.

Most importantly, the title's use of "targeted" should be interpreted as the intended application rather than a proven outcome. The reported experiments characterize formulation and release; they do not directly demonstrate preferential accumulation in inflamed joints or clinical immunosuppression in RA.

8. Conclusion, limitations and future directions

8.1 Conclusion

MMF-loaded PLGA nanoparticles were prepared and optimized using a Design of Experiments approach. The selected formulation F12 was reported to have a particle size of 543 nm and a zeta potential of −21.8

mV, with spherical and smooth surface morphology. Entrapment efficiency across the formulations ranged from 93.3% to 96.5%. In-vitro testing showed progressive drug release, reaching 92.621% at 480 minutes. Zero-order and Korsmeyer–Peppas models provided the strongest reported fits, and the short-term stability assessment showed only modest changes in particle size and drug content/entrapment-related measurements over 90 days.

Overall, the study supports further development of MMF-loaded PLGA nanoparticles as a potential controlled-release platform. It does not, by itself, prove joint-specific targeting, clinical effectiveness, improved patient compliance or reduced systemic toxicity. Those potential advantages should be presented as future possibilities requiring experimental validation.

8.2 Limitations

- The reported work is based primarily on physicochemical characterization and in-vitro release; animal experiments were not performed.
- Direct evidence of joint targeting, cellular uptake, pharmacokinetics, pharmacodynamics and comparative toxicity is not provided.
- The stability period reported here is 90 days and is insufficient on its own to assign a definitive shelf life.
- Some table labels and formulation details in the dissertation should be verified against the original experimental records before journal submission.
- Independent replication and batch-to-batch reproducibility are needed.

8.3 Future directions

- Confirm formulation reproducibility using independent batches and validated analytical methods.
- Extend stability testing using a defined protocol, appropriate packaging and complete quality attributes.
- Evaluate release in additional relevant media and establish the influence of sink conditions and sampling correction.
- Investigate cellular uptake and biodistribution, including whether nanoparticles accumulate in inflamed synovial tissue.
- Conduct appropriately designed preclinical safety and efficacy studies before considering clinical translation.

Declarations

Ethics: The dissertation states that experimental animals were not used. Funding and conflict-of-interest statements were not clearly provided in the source material and should be completed by the author as applicable.

Data availability: Results summarized in this article are drawn from the submitted dissertation. The underlying raw data should be made available by the author or institution if required by the target journal.

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Publication preparation note

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