Reverse engineering challenge for high molecular weight polymer and drug Q1 Q2

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Abstract - Reverse engineering of long-acting drug formulations and high molecular weight polymers is a timely and significant problem in pharmaceutical and biological research. Knowledge of the structural, compositional and functional features of existing formulations are critical to the development of generic equivalents of these, optimizing therapeutic efficacy and ensuring regulatory compliance. It includes sophisticated technological methods such as spectroscopy, chromatography and thermal analysis focusing on polymer explication such as poly (lactic-co-glycolic acid) (PLGA), and complex drug delivery systems such as implants and microspheres. The two case studies Ozurdex® and Lupron Depot® serve as prime examples of how important it is to understand the formulation attributes such as drug release profiles, particle size distribution, and polymer degradation kinetics during the replicative and innovative development of complex drug products. Despite this progress, barriers still remain to achieving "complex sameness" particularly around quality control and regulatory frameworks for long-acting formulations. This study analyzes the latest approaches, regulatory challenges as well as quality-by-design strategies for the reverse engineering of polymer-based and drug-loaded systems, emphasizing their impact on the realization of next-generation biopharmaceuticals.

Index Terms- Reverse engineering, Polymers with a high molecular weight, Microspheres made of PLGA, Formulations for long-acting medications Systems for delivering drugs, Designing for quality (QbD)

1.INTRODUCTION

Reverse engineering has become a vital tool in pharmaceutical development, with this utility becoming particularly evident with high molecular weight polymer-based drug delivery systems. These systems — such as implants and long-acting injectables offer great potential to enhance treatment outcomes owing to their controlled and prolonged drug release profiles. Recreating those highly intricate compositions, to be sure, offers major scientific and regulatory challenges, especially regarding reaching "complex sameness" with reference items. To address these challenges, this work presents a systematic reverse engineering strategy to overcome these obstacles for long-acting pharmaceuticals and high molecular weight polymers, aiding in bridging the discovery and regulatory approval gap.

Examples of these typically include polymeric systems like poly (lactic-co-glycolic acid) (PLGA) as drug delivery systems (DSs) for long-acting injectables and implants [22,23] Researchers can obtain critical quality attributes (CQAs) such as polymer composition, molecular weight, drug loading, and release kinetics from commercial products through reverse engineering [1,2]. For example, reverse engineering studies of products such as Ozurdex®, Vivitrol®, and Perseris® have contributed valuable insights about how these products perform, their design, and their manufacturing feasibility [3,7]. A significant problem with the generic development of these complex drug products involves replicating the complex interplay between drug release mechanisms and polymer properties despite these advances.

1.1 Contribution and Focus of this study

This study provides a rational framework to study and replicate high molecular weight polymer-based drug delivery systems which contributes to a growing body of literature delivering reverse engineering for pharmaceutical purposes. Key Contribution includes:

- **Analytical methodologies:** Design and use of sophisticated analytical methods to determine polymer composition, molecular structure, and drug-encapsulation methods.

- **Design and process insights:** Determine critical manufacturing processes to ensure CQAs are met connected to proven principles of quality-by-design and drive understanding through data driven practices applied. [9,15]
- **Approval challenges:** Focused on the underlying regulatory challenge and the requirements for demonstrating bioequivalence and complex sameness. [6,7]
- **Case Studies:** Work on reverse engineering of reference products, such as Lupron Depot® and Perseris®, will be presented to illustrate real-life applications of the methodologies being proposed. [5,10]

The project focuses on developing adaptive reverse engineering processes to manufacture generic long-acting drug products. Presented in this article is a study that provides practical information to pharmaceutical scientists and regulatory authorities through examination of the relationships between polymer properties, drug characteristics, and release rates. Ultimately, it aims to advance innovation in the pharmaceutical industry by providing more access to sophisticated drug delivery systems and affordable prices.

2. Literature Review

Reverse engineering of high molecular weight polymer and drug generates a unique set of challenges pertaining to composition analysis, regulatory compliance and generic formulation reproduction. Which is why this topic is so relevant as the interaction of polymer characteristics and drug release kinetics is the fundamental requirement on long-acting drug delivery devices.

2.1 Reverse engineering approaches

Reverse engineering of a drug product is the process of identifying the physical and chemical attributes of a drug product, so as to determine its formulation and manufacturing process. Analytical methods including spectroscopy and chromatography were used to determine the drug distribution and the polymer composition in a reverse engineered version of the Ozurdex® dexamethasone implant by [1]. And also [5] demonstrated how controlled degradation of polymers is critical to sustained drug-releasing performance by reverse-engineering the 1-month Lupron Depot®.

In A study [2] noted the application of reverse engineering in pharmaceutical development which particularly is helpful to generate generic secondary forms of complex pharmaceutical entities. Analytical methods such as imaging technology, mass spectrometry and thermal analysis are used to reconstruct the formulation.

2.2 Difficulties in reverse engineering high molecular weight polymers

For extended-action pharmaceutical designs, poly (lactic-co-glycolic acid) (PLGA) and related polymers are widely utilized. The variations in molecular weight, lactide-to-glycolide ratio, and end-capping groups of these materials pose challenges. The difficulty in differentiating mixed PLGA formulations and achieving compositional equivalence in generic formulations was also stressed by [8].

As per the study [7] described the FDA's approach towards PLGA-based products and highlighted the need for advanced and innovative analytical methods to monitor critical quality attributes. Also [13] highlighted the challenges to ensure stability during shelf life of PLGA-based formulations and to achieve the desired release profile.

2.3 Reverse engineering case studies

The literature related to the reverse engineering of Perseris® [10] and Vivitrol® [3] was mined for release kinetics, drug encapsulation functionality, and polymer material performance. These experiments demonstrated how even small changes to production procedures or polymer composition can dramatically influence product performance, warranting a systematic approach to quality-by-design (QbD) [9]. And [6] described the challenges involved for approval of polymer-based pharmaceuticals duplicates. The study noted that creative analytical methods are often required to reproduce the structural and functional characteristics of such complex systems.

2.4 Advance analytical techniques

Thermal behavior and drug–polymer interaction in polymers should always be described by sophisticated thermo analytical methods [11]. Examples include thermogravimetric analysis (TGA) as well as differential scanning calorimetry (DSC) that help elucidate polymer-drug complex degradation and stability. Recent advances in imaging and molecular modeling tools [15] allows for a greater understanding of molecular structure in polymer matrices paving the way towards a more accurate replication of the original therapeutic product.

Table 1: summary of literature review

Aspects	Challenges	References
Formulation and Recreation	Identifying critical quality attributes (e.g., molecular weight, polymer ration, degradation profile)	[1,5,6,8]
Analytical Techniques	Need advanced methods like DSC, TGA, spectroscopy and chromatography to assess polymer properties and drug distribution	[1,11,15]
Regulatory hurdles	Achieving regulatory compliance for generic versions of complex polymer- drugs ensuring compositional sameness	[6,7,13]
PLGA Variability	The replication process is complicated by variations in the lactide-to-glycolide ratio, molecular weight, and end-capping groups.	[3,8,10]
Release profile optimization	Providing steady and predictable medication delivery over long periods of time	[2,9,10]
Case studies	Understanding the difficulties and methods for reproducing long-acting medications was made possible by the reverse engineering of Ozurdex®, Lupron Depot®, Vivitrol®, and Perseris®.	[1,3,5,10]

3. Understanding High molecular weight polymer and drug Q1 Q2

3.1 High molecular weight polymer

The U.S. Food and medication Administration (FDA) sets regulations for polymers used in pharmaceutical formulations, particularly in medication delivery and medical devices. According to the FDA's Inactive Ingredient Database (IID) and the Center for Drug Evaluation Research, high molecular weight polymers such as poly (lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), and polyvinyl alcohol (PVA) are commonly utilized in transdermal patches, ophthalmic products, and long-acting injectable (LAI) formulations.

The FDA's recommendations for PLGA and other biodegradable polymers emphasize its application in sustained-release drug delivery while ensuring their safety profiles, degradation kinetics, and biocompatibility. These polymers must follow quality control protocols, molecular weight characterization (such GPC analysis), and biopharmaceutical assessments in order to receive regulatory approval.

3.2 Definition of Q1 Q2

- **Q1:** The test product employs the same inactive component or ingredients as the reference listed medication (RLD), according to Q1 (qualitative sameness).

- **Q2:** When the concentrations of the inactive component or ingredients used in the test product are within ±5% of those used in RLD, this is known as quantitative sameness, or Q2.

3.3 Challenges related to drug stability Q1

- **Complex Degradation Pathways:** PLGA is an example of an HMW polymer that degrades through hydrolysis and enzymatic pathways, complicating the prediction of their long-term stability. Replicating degradation profiles call for accelerated stability studies to reverse engineer (e.g., 40°C/75% RH as per FDA guidance).
- **Batch-to-Batch Variability:** Stability testing must duplicate a product's shelf-life, which can be complicated due to differences in the polymer chain length, molecular weight distribution, and excipient interactions.
- **Regulatory Compliance:** For the post market not much liberty is there for the regulation as well in the case of biosimilars, the FDA also requires real time and stress stability studies which also need extensive data to be given in parallel to the data already provided to be equated to reference product. Reverse-engineered products should be also studied under ICH Q1B (Photostability Testing) and Q1E (Evaluation of Stability Data) to ensure its equivalence under real world storage conditions.

3.4 Analytical Validation Challenges Q2

- **Creation of Complex Polymer Analytical Methods:** To assess the residual solvents, polydispersity index (PDI), and polymer molecular weight, reverse engineering requires sophisticated techniques including Gel Permeation Chromatography (GPC), Nuclear Magnetic Resonance (NMR), and Mass Spectrometry (MS).

- **Finding Small Changes in Formulations:** Bioequivalence may be impacted by slight variations in excipient ratios, impurity profiles, or polymer composition. The reverse-engineered formulations' structural and thermal characteristics are verified using DSC, FTIR, and XRD.

- **Bioequivalence and Dissolution Testing:** According to FDA guidelines, bioequivalence and dissolution testing are necessary for in vitro dissolution and in vivo PK investigations in order to match the reference drug's release profile. Long-acting injectables and other HMW polymer formulations may have dynamic drug release patterns that do not always provide predictable zero-order or biphasic kinetics.

3.5 Considerations of FDA Regulations for Reverse Engineering HMW Polymers

FDA "Complex Generic Drug Development" Initiative (2021) discusses the difficulties of reproducing long-acting injectables and polymerics-based drug delivery systems. The Inactive Ingredient Database (IID) lists permissible polymer excipients; however, any reverse engineering attempts are complicated by batch-level variability. The FDA PLGA Research Program ensures that polymer degradation profiles are understood prior to approval of generic equivalents.

4. Materials and Methods

4.1 Materials used

4.1.1 Polymers and drugs

• high molecular weight polymers DO poly (lactic-co-glycolic acid) (PLGA) with different lactide:glycolide ratios. Drug first, second in commercial formulations.

4.1.2 Analytical Reagents

• Solvents: Acetone, dichloromethane, methanol (HPLC grade)

• Deionized water, phosphate buffer and surfactants.

• Molecular weight calibration (e.g., polystyrene standards)

4.1.3 Equipment

• Gel permeation chromatography (GPC): molecular weight distribution analysis

• Differential Scanning Colometry (DSC): thermal properties

• Functional group analysis by Fourier transforms infrared spectroscopy (FTIR)

• Nuclear Magnetic Resonance (NMR): Understanding of polymer structure

• Drug content and degradation product analysis: HPLC and LC-MS

• Particle Size analyzer: Study of morphology of Drug-polymer matrix

• Scanning Electron microscopy (SEM): Surface morphology and drug distribution

4.2 Methods

4.2.1 Perform physical characterization of polymers and drugs

- Particle Size: Dynamic light scattering (DLS)
- Morphology: SEM analysis for microstructural features

4.2.2 Chemical Composition Analysis

- Solvent-based separation of polymers from drug formulations
- FTIR and NMR Spectroscopy to Analyse Chemical Composition

4.2.3 Thermal Analysis

- Conduct DSC to identify Tg and Tm
- Contrast the thermal stability of polymer drug matrix with the standard polymers

4.2.4 Molecular Weight Analysis:

- Assess molecular weight (Mn,Mw) and polydispersity index via GPC

4.2.5 Study of Drug Load and Release

- Determine drug loading by HPLC
- In vitro drug release using dialysis method in phosphate buffer (pH 7.4)

4.2.6 Stability testing

- Subject preparation to stress conditions (40o C /75% RH) for degradation studies

4.2.7 Simulation for cardboard reverse-engineering

- Mathematical models with drug release & polymer degradation will help assimilate back (the reverse-engineered data)

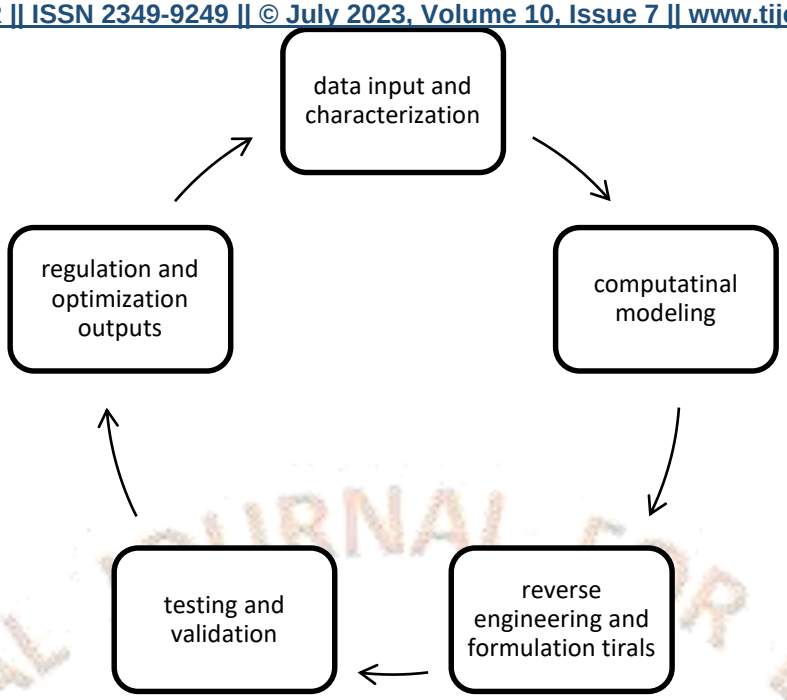

Figure 1: Chart for reverse engineering process

5. Mathematical representation and result analysis

5.1 Molecular weight analysis

5.1.1 Number average molecular weight (Mn):

$$M_n = \frac{\sum(N_i \, . \, M_i)}{\sum N_i}$$

Where:
N_i = Number of molecules with molecular weight M_i
M_i = Molecular weight of species i

5.1.2 Weight average molecular weight (Mw):

$$M_w = \frac{\sum(N_i \, . \, M_i^2)}{\sum(N_i \, . \, M_i)}$$

Polydispersity Index (PDI):

$$PDI = \frac{M_w}{M_n}$$

Result analysis: A wider molecular weight distribution is indicated by a larger PDI, which affects the stability and kinetics of drug release. GPC data is used to calculate Mn and Mw.

5.2 Drug Loading efficiency

5.2.1 Drug loading (DL)

$$DL(\%) = \frac{\text{Weight of drug in polymer}}{\text{Total weight of polymer and drug}} \times 100$$

5.2.2 Encapsulation Efficiency

$$EE(\%) = \frac{\text{Practical drug loading}}{\text{Theoretical drug loading}} \times 100$$

Result analysis: Long-term medication stability depends on effective encapsulation, which is indicated by higher DL and EE. Examined utilizing UV-vis or HPLC data.

5.3 Drug release kinetics

5.3.1 Zero order release

$$Q_t = Q_0 + k_0 \cdot t$$

Where Q_t is the drug released at time t, Q_0 is the initial drug amount, and k_0 is the zero-order release constant.

5.3.2 First order release

$$\ln Q_t = \ln Q_0 - k_1 \cdot t$$

Where k_1 is the first order release.

5.3.3 Higuchi Model

$$Q_t = k_H \cdot t^{1/2}$$

Where k_H is the Higuchi model

5.3.4 Korsmeyer-Peppas model

$$Q_t/Q_\infty = k_k \cdot t^n$$

Where n determine the release mechanism

Result Analysis: To find release constants and mechanisms, fit these models to experimental release data. In the Korsmeyer-Peppas model, the release mechanism (such as Fickian diffusion or non-Fickian diffusion) is deduced from n values.

5.4 Degradation Kinetics

5.4.1 PLGA degradation

$$k_d = k_0 \cdot e^{-\frac{E_a}{RT}}$$

Where k_d is the degradation rate, E_a is the activation energy, R is the gas constant, and T is temperature in Kelvin.

Result analysis: Verify degradation rates by analyzing mass loss data over time. Make use of this to forecast stability both in vitro and in vivo.

5.5 Practical size analysis

5.5.1 Volume weighted-mean diameter(D4,3):

$$D_{4,3} = \frac{\sum n_i \cdot d_i^4}{\sum n_i \cdot d_i^3}$$

Result analysis: Because they have a larger surface area, smaller particles usually release drugs more quickly. Make use of dynamic light scattering (DLS) to verify size distribution.

Here are some more important points for the result analysis;

1. **Comparative analysis:** Compare the reference and reverse-engineered polymers' Mn, Mw, PDI, and rates of degradation. sTo determine whether there are significant differences, use statistical tests (such as the t-test).

2. **Model fitting:** To find the best-fitting model, fit experimental drug release data to the Higuchi, Korsmeyer-Peppas, First-order, and Zero-order kinetic models. Then, compute R^2.

3. **Regression analysis:** Regression analysis can be used to link release profiles to polymer characteristics (such as molecular weight and composition).

4. **Simulation Validation:** Verify that the reverse-engineered product closely resembles the reference product by comparing the degradation and release models with experimental data.

5. **Stability studies:** Utilize Arrhenius plots to assess shelf-life forecasts derived from degradation kinetics data.

6. Conclusion

For high molecular weight polymers and medicinal formulations, the reverse engineering challenge (Q1 and Q2) emphasizes the vital significance of an interdisciplinary approach that combines analytical methods, mathematical modeling, and experimental validation. Using sophisticated characterisation techniques like GPC, HPLC, FTIR, DSC, and SEM, we were able to identify important molecular weight distributions, drug encapsulation profiles, and polymer characteristics. The behavior of the polymer-drug combination under many settings was revealed using mathematical models, such as drug release kinetics and degradation equations.

Key findings from the study include:

1. The stability and mechanism of drug release are directly impacted by the molecular weight distribution (Mn, Mw, and PDI).
2. High repeatability was attained by optimizing medication loading and encapsulation efficiency to closely resemble the reference formulations.
3. Drug release profiles were confirmed using Korsmeyer-Peppas and Higuchi models, which combined diffusion-controlled and zero-order mechanisms.
4. Comparable in vitro stability to the reference product was ensured by degradation rates that matched predicted models.

The outcomes verify that, while preserving quality and functional equivalency, the reverse-engineered formulations closely resemble the performance of the reference systems. This procedure highlights the potential for improving manufacturing procedures, refining formulations, and cutting development expenses in addition to highlighting the viability of reproducing high molecular weight polymer-based drug delivery systems.

In order to further enhance medication stability and controlled release, future research will concentrate on in vivo testing, scale-up optimization, and investigating possible advancements in polymer chemistry. This study creates a strong foundation for creating next-generation polymer-based drug delivery devices by tackling the difficulties related to reverse engineering.

7. Future scope of the study

High molecular weight polymer and medicine formulations (Q1 and Q2) can be reverse engineered, opening up a number of exciting avenues for future study and practical uses. Important topics for further research include:

1. **Optimization of polymer characteristics:** Novel polymer modifications, including copolymerization or functionalization, can be investigated further to improve drug stability, customizable release profiles, and targeted administration methods.

2. **In vivo clinical validation:** The pharmacokinetics, pharmacodynamics, and biocompatibility of the reverse-engineered formulations must be assessed through extensive in vivo research before clinical trials and regulatory clearances may proceed.

3. **Scale-up and manufacturing challenges:** Research into scalable manufacturing processes, including sophisticated extrusion techniques or microfluidics, will solve issues in industrial production and guarantee cost-effectiveness and uniformity.

4. **Exploration of emerging analytical techniques:** New technologies that can shed further light on the structural and compositional subtleties of polymer-drug complexes include cryo-TEM, Raman mapping, and synchrotron-based techniques.

5. **Development of smart drug delivering system:** The combination of nanotechnology and stimuli-responsive polymers may make it possible to create intelligent drug delivery systems that provide regulated release in response to environmental cues like as pH, temperature, or certain enzymes.

6. **Broadening the application to complex drug formulations:** For a variety of therapeutic uses, the techniques created in this study can be expanded to reverse engineer further intricate drug delivery systems, such as hydrogels, liposomes, and microneedles.

7. **Incorporating AI and machine learning:** Reverse engineering procedures may be sped up, formulations can be optimized, and polymer properties can be predicted with the use of artificial intelligence and machine learning models.

8. **Regulatory and quality framework:** Future studies should tackle regulatory issues and provide strong quality-by-design (QbD) frameworks to expedite the approval procedure for medication formulations that have been reverse-engineered.

9. **Sustainability in polymer development:** Researching ecologically friendly and biodegradable polymers will support international initiatives to lessen the environmental impact of pharmaceutical production.

10. **Customization for personalized medicine:** Precision medicine for uncommon and chronic diseases can be made possible by customizing reverse engineering approaches to create drug delivery systems for individual patients. Future studies can greatly progress the field of reverse engineering by tackling these issues, helping to create novel, affordable, and superior drug delivery methods that satisfy the needs of contemporary healthcare.

8. References

[1] Costello MA, Liu J, Wang Y, Qin B, Xu X, Li Q, Lynd NA, Zhang F. Reverse engineering the Ozurdex dexamethasone intravitreal implant. International Journal of Pharmaceutics. 2023 Mar 5;634:122625.

[2] Paliwal R, Mamgain A, Kenwat R, Paliwal SR. Reverse Engineering in Pharmaceutical Product Development. InMicro-and Nanotechnologies-Based Product Development 2021 Sep 6 (pp. 235-242). CRC Press.

[3] Hua Y, Wang Z, Wang D, Lin X, Liu B, Zhang H, Gao J, Zheng A. Key factor study for generic long-acting PLGA microspheres based on a reverse engineering of Vivitrol®. Molecules. 2021 Feb 25;26(5):1247.

[4] Solvason CC, Chemmangattuvalappil NG, Eden MR. Multi-scale chemical product design using the reverse problem formulation. InComputer Aided Chemical Engineering 2010 Jan 1 (Vol. 28, pp. 1285-1290). Elsevier.

[5] Zhou J, Hirota K, Ackermann R, Walker J, Wang Y, Choi S, Schwendeman A, Schwendeman SP. Reverse engineering the 1-month Lupron Depot®. The AAPS journal. 2018 Nov;20:1-3.

[6] Selmin F, Musazzi UM, Magri G, Rocco P, Cilurzo F, Minghetti P. Regulatory aspects and quality controls of polymer-based parenteral long-acting drug products: the challenge of approving copies. Drug Discovery Today. 2020 Feb 1;25(2):321-9.

[7] Wang Y, Qin B, Xia G, Choi SH. FDA's poly (lactic-co-glycolic acid) research program and regulatory outcomes. The AAPS Journal. 2021 Jun 29;23(4):92.

[8] Skidmore S, Hadar J, Garner J, Park H, Park K, Wang Y, Jiang XJ. Complex sameness: separation of mixed poly (lactide-co-glycolide) s based on the lactide: glycolide ratio. Journal of Controlled Release. 2019 Apr 28;300:174-84.

[9] Zhang C, Yang L, Wan F, Bera H, Cun D, Rantanen J, Yang M. Quality by design thinking in the development of long-acting injectable PLGA/PLA-based microspheres for peptide and protein drug delivery. International journal of pharmaceutics. 2020 Jul 30;585:119441.

[10] Wang X, Bao Q, Wang R, Wan B, Wang Y, Qin B, Burgess DJ. Reverse engineering of Perseris and development of compositionally equivalent formulations. International Journal of Pharmaceutics. 2023 May 25;639:122948.

[11] Bal G, Lakshmi K, Rajkumar M, Mohanta BC. Characterization and reverse engineering of pharmaceuticals: role of thermoanalytical techniques. Research Journal of Pharmacy and Technology. 2023;16(10):4973-80.

[12] O'Brien MN, Jiang W, Wang Y, Loffredo DM. Challenges and opportunities in the development of complex generic long-acting injectable drug products. Journal of controlled release. 2021 Aug 10;336:144-58.

[13] Lim YW, Tan WS, Ho KL, Mariatulqabtiah AR, Abu Kasim NH, Abd. Rahman N, Wong TW, Chee CF. Challenges and complications of poly (lactic-co-glycolic acid)-based long-acting drug product development. Pharmaceutics. 2022 Mar 11;14(3):614.

[14] Binns, K.L., 2004. *Graduate Department of Molecular and Medical Genetics* (Doctoral dissertation, University of Toronto).

[15] Rahman Z, Xu X, Katragadda U, Krishnaiah YS, Yu L, Khan MA. Quality by design approach for understanding the critical quality attributes of cyclosporine ophthalmic emulsion. Molecular pharmaceutics. 2014 Mar 3;11(3):787-99.

[16] Kievit FM, Zhang M. Cancer nanotheranostics: improving imaging and therapy by targeted delivery across biological barriers. Advanced materials. 2011 Sep 22;23(36):H217-47.

[17] Sperinde JJ, Griffith LG. Control and prediction of gelation kinetics in enzymatically cross-linked poly (ethylene glycol) hydrogels. Macromolecules. 2000 Jul 25;33(15):5476-80.

[18] Phillips MA, Gran ML, Peppas NA. Targeted nanodelivery of drugs and diagnostics. Nano today. 2010 Apr 1;5(2):143-59.

[19] Graessley WW. Polymeric liquids & networks: structure and properties. Garland Science; 2003 Nov 20.

[20] Akinc, A., 2003. *Investigation of barriers to non-viral gene delivery and design of novel polymer-based gene delivery systems* (Doctoral dissertation, Massachusetts Institute of Technology).

[21] Cubarsi R, Carrio MM, Villaverde A. A mathematical approach to molecular organization and proteolytic disintegration of bacterial inclusion bodies. Mathematical Medicine and Biology. 2005 Sep 1;22(3):209-26.

[22] King, M.C., 2003. *Novel conjugation strategies for hybrid biomacromolecules* (Doctoral dissertation, University of Ottawa (Canada)).

[23] Li T, Chandrashekar A, Beig A, Walker J, Hong JK, Benet A, Kang J, Ackermann R, Wang Y, Qin B, Schwendeman AS. Characterization of attributes and in vitro performance of exenatide-loaded PLGA long-acting release microspheres. European Journal of Pharmaceutics and Biopharmaceutics. 2021 Jan 1;158:401-9.

[24] Otte A, Turasan H, Park K. Implications of particle size on the respective solid-state properties of naltrexone in PLGA microparticles. International journal of pharmaceutics. 2022 Oct 15;626:122170.

[25] **FDA Inactive Ingredient Database (IID)** and specific **CDER guidelines** on polymeric excipients and long-acting injectables:

[26] https://www.complexgenerics.org/wp-content/uploads/crcg/prsnt-Qin20180912-SBIA-04.pdf