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Making Progress in the Formulation Development of Long-Acting Injectable Biopharmaceuticals: A Case Study of Interleukin-6 Inhibitors

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Abstract
One way of ensuring patient adherence to chronic illnesses requiring biopharmaceuticals at regular intervals is to develop long-acting injectable (LIA) variants. In the present work, the formulation approaches towards sustained delivery of interleukin-6 (IL-6) inhibitors, namely biodegradable polymer microsphere and in-situ forming gels, were examined. The release kinetics determined in vitro indicated that the microspheres could offer an extended drug release lasting up to 21 days with great stability and reproducibility of the release; this was in contrast to the gel-based systems. Increased stability testing established that IL-6 inhibitors were structurally stable and active after formulation. In vivo PK analysis in rodent models demonstrated a long serum half-life and lower dosing frequency that did not affect the effectiveness of therapy. Such results confirm the clinical use of LAI formulations, which could improve the quality of life and treatment adherence of the patient.

Keywords: ***Long-acting injectable, IL-6 inhibitors, biodegradable microspheres, in-situ gels, sustained drug release, stability, pharmacokinetics.***

1. Introduction
Long-acting injectable (LAI) biopharmaceuticals are rapidly becoming a new frontier in drug delivery system that meets the increasing challenges of enhancing patient adherence in chronic disease management. This strategy is also especially applicable when dealing with conditions where frequent dosing is inevitable, and it may prove difficult to ensure that patients adhere to this type of immunotherapeutic regimen owing to the inconvenience of periodical injections. The introduction of this paper gives an overview of the context in which LAI biopharmaceuticals are placed and explains why IL-6 inhibitors are clinically relevant and introduces what this study specifically examines in the formulation strategies of sustained delivery of IL-6 inhibitors.

1.1 Background on Long-Acting Injectable Biopharmaceuticals
Long-acting injectables are formulations developed to release agents therapeutic over a long time reducing administration rates. Such a plan is especially useful in cases of chronic diseases like rheumatoid arthritis, multiple sclerosis or even some forms of cancer when the patient may need frequent medication, but cannot follow the regimen of taking medication daily or on a weekly basis. Administration of AAI formulations offers patients a high quality of life, as the number of required injections is associated with less drug administration frequency and the likelihood of increased compliance to the therapy and excellent outcomes.(1)

The formulation technology used is often the key to reach a sustained drug release. Among the most important approaches to producing LAI formulation, one can mention polymer based systems that are biodegradable like microspheres nor in-situ forming gels. The benefits of such delivery systems are controlled release of active pharmaceutical ingredients (APIs) over days, weeks, or even months with an obvious benefit over oral medications or standard injectables that require more frequent use. Further, LAI preparations have the potential to stabilize drugs, minimize peak-trough rhythms, and provide a more even physiologic effect.

Of several therapeutic substances which can be formulated into LAI, mAbs have been of particular interest because of their proven specificity and activity in the treatment of a variety of inflammatory and autoimmune diseases. Namely, the intended use of LAI formulations with mAbs for a variety of diseases, in particular interleukin inhibitors, offers prospects to target difficult-to-deal-with disease processes by modulating immune responses over time.

1.2 Interleukin-6 Inhibitors
Interleukin-6 (IL-6) is a cytokine that is part of many inflammatory processes and the central role in the pathogenesis of many autoimmune and inflammatory diseases. Tocilizumab, an IL-6 inhibitor, finds use in treating rheumatoid arthritis, juvenile idiopathic arthritis and cytokine release syndrome (CRS). These inhibitors act to

block IL-6 receptor and minimize inflammation and tissue destruction by the excessive action of the immune system.

Although IL-6 inhibitors have been successful in clinical practice, frequent administration of the drugs, either intravenously (IV) or subcutaneously, can be inconvenient to the user, making it difficult to achieve an effective treatment regime. To address these limitations, the design of long-acting injectable formulations of IL-6 inhibitors would provide great utility in patient compliance and patient outcomes. The aim of this proposed research is to develop LAI formulations of IL-6 inhibitors, and by decreasing the dosing frequency whilst retaining efficacy, they promise to facilitate clinical administration as well as to improve the quality of life among individuals with chronic inflammatory conditions.(2)

Also, the relatively long half-life of IL-6 inhibitors in LAI formulations would allow the patient to feel a prolonged therapeutic effect and circumvent the peaks and valleys of traditional dosing. This is, especially, significant in the control of conditions in which cytokine levels are imperative to stable control of the disease and long-term remission.

1.3 Objectives of the Study

The main aim of this study is to explore and compare formulation approaches to the sustained release of IL-6 inhibitors using two emerging delivery formulations, namely, biodegradable polymer microspheres and in-situ forming gels. The emphasis is made on optimization of release kinetics, stability and pharmacokinetic profiles of such formulations to identify the most useful route of transition of IL-6 inhibitors to LAI products.

This study goes further to seek to:

Compare in-vitro release kinetics of IL-6 inhibitors in biodegradable polymer microspheres and in-situ forming gels, and determine the effectiveness of each system with regard to release duration and consistency.

Determine how stable the IL-6 inhibitors will be in these formulations, both in structural terms and with respect to biological activity, especially over accelerated storage conditions.

Examine the pharmacokinetics of the formulations in vivo, particularly in rodents, to ascertain the possibility of long serum half-life, the opportunity to decrease the dose frequency, and preserve a therapeutic benefit.

Give suggestions about the most perspective formulation strategy to be used in treating people involved in the clinical trial, which can be made on the basis of the in vitro and in vivo research.

The results of this work will aid in the realization of formulation techniques of LAI IL-6 inhibitors and provide useful information regarding their future potential as therapeutics to improve the outcomes of patients with chronic inflammatory disorders. LAI formulations have the potential to exist as patient-friendly therapies that are more convenient and effective by reducing patient facing bothersomeness since it would limit the number of administrations allowing patients to have an improved quality of life with better adherence to the treatment regimen.(3)

2. Methods and Reagents

The efficacy of long-acting injectable (LAI) formulations requires a delicate choice of materials and development of experimental protocol to determine the corresponding release, stability, and biological activity of the embedded drug. This section details the ingredient script chosen to treat the formulations and the method in which the formulations were prepared and tested and the parameters used to characterize the formulations.

2.1 Choice of Biodegradable Polymers and Gelling Agents

The choice of materials is a determining factor in preparing LAI formulations of interleukin-6 (IL-6) inhibitors since the polymeric matrix has to provide controlled and sustained drug release without disrupting the stability and bioactivity of the loaded drug. Biodegradable polymers to formulate microsphere and gelling agents to form in-situ gels represent the two primary classes of materials used in this study.

Biodegradable Microspheres: Poly (lactic-co-glycolic acid) (PLGA) was selected as the first choice of polymer in the microsphere formulations because of its proven record in microcapsules applications. More recently, LGA is a hydrophilic, biodegradable and biocompatible polymer which is hydrolytically degraded in the body releasing the drug entrapped into it gradually. The proportion between lactide and glycolide in the polymer influences the degradation rate which was optimized to obtain the required release profile of the IL-6 inhibitors. Also, various molecular weights of PLGA were tested in terms of their effect on the drug release process whereby a higher molecular weight should present a slower rate of degradation and retard drug release.

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Thermoresponsive Gelling Agents In-situ forming gels were done using thermoresponsive gelling agents, e.g 86 Poly(N-isopropylacrylamide) (PNIPAAm). The remarkable property of NIPAAm is that it has a sol - gel transition when responding to changing temperatures. This aspect qualifies it to be used in injectable systems, because it can be injected in liquid form and gels at body temperature. PNIPAAm concentrations and the initiation of co-solvents were adjusted in such a way that quick gel formation and maintained drug release were achieved. The gel network composed of PNIPAAm was anticipated to have a prolonged delivery of IL-6 inhibitors up to 21 days to minimize the necessity of frequent injections.(4)

2.2 Experimental Set-up to Conduct Formulation Trials

Formulation experiments were carried out to formulate both the biodegradable polymer microspheres and in-situ gels as a sustained delivery system of IL-6 inhibitors. The manufacturing of each formulation type was premised on the use of standard formulation methods but was altered in a way that would result in optimal drug encapsulation and release curves.

Microspheres: The microspheres were formulated by a solvent evaporation method. The IL-6 blockers were dissolved in organic solvent with PLGA polymer and mixed to form a water-in-oil emulsion- water phase. Evaporation of the solvent under reduced pressures was done to the emulsion in order to get the solid polymer microspheres of the drug. The morphology and the size of the microspheres were manipulated through the range of solvent concentrations, polymer concentrations and emulsification conditions.

In-Situ Gel Formulations: In the in-situ gel formulations, IL-6 inhibitors were dissolved in aqueous solutions that consisted of thermoresponsive gelatin PNIPAAm. The solution would then be filtered sterilized and injected into pre-warmed vials and there it was allowed to enter into the sol-to-gel transition as the vials were cooled to body temperature. The different gels were fabricated with varied concentration of PNIPAAm in an attempt to achieve optimal gels strength and drug release profiles.

The prepared formulations were then put under such a controlled condition to determine the stability and performance of samples over time. Stability testing was accelerated to replicate the testing conditions of long-term storage and to verify that the drug acted as a formulation within the aging of the formulation matrices.

2.3 Characterization Parameters

Characterization techniques were used to test the physical, chemical and biological properties of the formulations so as to evaluate their performance. Both the polymer microspheres and in-situ gels were measured by the following parameters:

Particle Size and Morphology The size distribution and morphology of microspheres were observed by scanning electron microscopy (SEM) and dynamic light scattering (DLS). The size of the microsphere is also a significant parameter in defining release rate where the smaller it gets the faster it releases drug as compared to larger particles. The microspheres were checked so that the morphology of the microspheres is uniform and consistent.

In Vitro Release Kinetics: IL-6 inhibitors release kinetics out of both the gels and microspheres was determined in an in vitro release experiment. The formulations were in phosphate-buffered saline (PBS) at 37 o C and samples were withdrawn at predetermined times. The concentration of IL-6 inhibitors was quantitated in the release media by HPLC. Several kinetic models adapted (zero-order, first-order, Higuchi, and Korsmeyer-Peppas) were used to match the release data to decide the release mechanism of the control.(5)

Stability and Bioactivity: The accelerated stability of formulations was tested by keeping the formulations at higher temperatures (e.g. 40C) to reflect long-term storage. The structural stability of the IL-6 inhibitors was determined through the SDS-PAGE and ELISA. Bioactivity of the encapsulated drug was determined by its efficacy to inhibit Il-6 signaling in cell-based assays, to ensure that encapsulation process does not interfere with its therapeutic potential.

In Vivo Pharmacokinetics: In vivo investigation was carried out in rodents to study the pharmacokinetic parameters of the formulations. Blood specimens were then collected at a designated period of time, and the concentration of IL-6 inhibitors in the serum were determined by means of ELISA. Serum half-life and drug level were explored in order to determine how well the LAI formulations sustained the release of a drug.

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3. Compositional Finding Methods

Formulation development is a significant concept of long-acting injectable (LAI) biopharmaceuticals achieving the desired therapeutic effect. Microsphere-based formulations and in-situ gel formation delivery methods are two main methods of delivering interleukin-6 (IL-6) inhibitors on a sustained basis, which have been investigated in

this study. Both techniques afford different benefits in terms of drug release medium control, stability and performance of a final injectable product. The following section presents the development profiles of these two types of formulation processes particularly regarding the use of microspheres, gel formation methods, and optimization of processes in order to achieve appropriate encapsulation of the drug.

3.1 Strategy of Microsphere-based Formulations

One of most common carriers of sustained-release delivery of drugs is microspheres. The formulation of microsphere-based formulation of IL-6 inhibitors entails preparation of biodegradable polymer that can form a reservoir to hold the drug and its subsequent release over a relatively long duration. Whereas, poly(lactic-co-glycolic acid) polymer matrix was the choice in this study to offer a degradable and biocompatible technology that releases drugs in a controlled manner.

Preparation Method: Solvent evaporation is a common method to create polymeric microspheres: the solvent evaporation technique was used to prepare the microspheres. In this approach, Aqueous IL-6 antagonists and PLGA were included in an organic solvent (e.g. dichloromethane) and emulsified in a relatively aqueous phase to generate a water-in-oil emulsion. This emulsion was then left to evaporate solvents under reduced pressure, drying the organic solvent, leaving solid microspheres with the drug. In this process, a large amount of IL-6 inhibitors can be encapsulated and control over size of microsphere and drug release properties are possible.

Optimization Of Release Profile: Release of IL-6 inhibitors was optimized by varying other parameters: polymer concentration, molecular weight of PLGA, and solvent to water ratio. The change of these parameters allowed one to control the size, the surface properties, and the release rate of microspheres. The degradation rate of PLGA is dependent on the lactide-to-glycolide ratio but by making appropriate selection of this ratio, the formulation was adjusted to provide sustained release over 21days.(6)

Drug Encapsulation Efficiency: Encapsulation efficiency of the microspheres was carried out by determining the quantity of IL-6 inhibitor that was successfully coated within the polymeric matrix against the total quantity of drug that was added in the fabrication. High encapsulation efficiency is indispensable to make sure that an appreciable amount of administered drug reaches the target site over the course of time.

3.2 Gelfield Techniques of In-Situ Gel Formation

A potent method of controlled release of IL-6 inhibitors is by the in-situ forming gels. These gels become soluble and insoluble transition with a change in temperature, pH, or ionic strengths. The primary benefit of in-situ gels is that these come in liquid injection and in-situ gels at the body temperature to provide sustained release of the drug without using complex in-situ drug-delivery.

Thermoresponsive Gels: Poly(N-isopropylacrylamide) (PNIPAAm) has been chosen as the thermoresponsive polymer on in-situ gel formulations. NIPAAm provides a unique sol-to-gel transition temperature at body temperature (about 37 c), rendering it an ideal candidate in formulations that would be injected into the body. The temperatures below LCST, PNIPAAm is in a liquidized state and hence can be easily injected. When the IL-6 blocker molecules have been administered in a gel consisting of the polymer, the warming that results in a phase transition in the polymer will trap the blockers through its gelling capability.

Gel Formation Optimization: The concentration of PNIPAAm was altered, in order to get the gel with minimum strength and viscosity. Also, co-solvents like glycerol, ethanol were added in efforts of increasing the rate of gelation, and to optimize the release kinetics. The ratio of PNIPAAm and IL-6 inhibitors played a role in gel strength and stability where the ratio was balanced so as to ensure the drug is kept till the release period.

In-situ gel formulations have the following benefits, ease of administration, and minimum discomfort to the patient. With the precise regulation of polymer concentration and molecular weight of PNIPAAm, the drug release could be controlled successfully to obtain prolonged release of IL-6 inhibitors up to 21 days. The release profile with these gels we found follows a Fickian diffusion, in that the IL-6 inhibitors within the gel matrix diffuse out overtime, offering a slow and consistent release profile.

3.3 Optimization of the process of drug encapsulation

Optimal encapsulation of the drug within the LAI formulations is an important task in their development. The encapsulating process should be capable of incorporating the drug in the carrier matrix so that maximum therapeutic effect and duration is achieved.(7)

Optimization of Polymer-to-Drug Ratio: One of the initial processes of optimizing drug encapsulation was that of determining the ideal polymer-to-drug ratio. This ratio influences the release kinetics, encapsulation and stability of the IL-6 inhibitors writhin the polymer matrix. The ratio between PLGA and IL-6 inhibitors in the microsphere

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formulations and concentration of PNIPAAm in the in-situ gel formulations were varied so as to produce a balance between the drug release and encapsulation efficiency.

Stability in the process of Encapsulation: When carrying out the process of encapsulation, special care was taken to keep the bioactivity of the IL-6 inhibitors intact. This has been implemented by extreme care in temperature control and use of harsh conditions during think preparation of microspheres and gels. The stability testing was performed to determine bioactivity and integrity of the drug encapsulated under precipitated storage conditions.

Scaling and Manufacturing Aspects: In large-scale, it was imperative to scale-up manufacturing process to make it reproducible, scalable, and cost-effective in large-scale production of LAI formulations. Since the microsphere grantship and drug release properties would be dependent on parameters like the solvent evaporation rates, emulsification period, and temperature, the same was standardized to arrive at consistent microsphere size and drug release properties. Equally, in-situ formulations were also optimized on effective ease of injection and requirements on gelation behavior.

4. Stability, YouTube and Release Assessment

The successful performance of the long-acting injectable (LAI) formulations is equally dependent on ensuring the stability and consistent release of the drug held within the capsules, particularly, with the biopharmaceuticals such as interleukin-6 (IL-6) inhibitors. This section summarizes the stability testing parameters, in vitro release profiling procedures, and the profile comparison of the stability of formulations based on microspheres and in-situ gels. Such measurements are essential to assess the stability of LAI formulations over a given period of time as well as the quality of them in terms of the bioactive compound, its structural integrity, or its release pattern under simulated conditions of storage and within the body.

4.1 Conditions Of Rapid Stability Testing.

Rapid stability testing is performed to mimic long-term storage to define how a formulation will perform over long-term storage. This testing is critical in determining the stability of the IL-6 inhibitors in the formulation matrix especially under diverse environmental factors including, temperature, humidity and exposure to light. In this work, the in-situ gels and the polymer microsphere formulations were subjected to accelerated stability studies to investigate the physical, chemical and biological stability of these two dosage forms.

Temperature testing: Samples were exposed to extreme temperatures (40 Celsius degrees and 60 Celsius degrees) that signalled an accelerated aging process. These temperatures are typical stability studies to hasten the degradative processes and determine the shelf life of the formulations. The samples were taken at standardized intervals (i.e., 0, 1, 2, 3, 6 and 12 months) to be analyzed.

Humidity and Light Exposure: A humidity of 75 percent of relative humidity was attained and light was exposed on the formulations to simulate conditions encountered in the real world. This was necessary to assess any possible degradation due to moisture uptake, or chemical reactions due to light.

Stability Parameters: Integrity, encapsulation efficiency, and bioactivity were used to determine stability of the IL-6 inhibitors. Drug deformations in IL-6 inhibitors were examined by SDS-PAGE and HPLC, bioactivity by ELISA methods to determine whether or not the drug can prevent IL-6 signaling in cell-based assays. Also, physical appearance of the formulations (e.g., gelation, size, and color) was observed to determine whether the same changed during storage.(8)

This relatively rapid stability testing shed light on the stability of the formulations and the possible necessity of formulation revisions in order to guarantee a long-term effectiveness of the formulation. Findings also assisted in determining the most stable ratios of polymer to drug and types of formulations to use clinically.

4.2 In vitro Drug Release Profiling

Evaluation of the release profiles of the IL-6 inhibitors incorporated in the microsphere and in-situ gel formulations was an important preliminary stage in determining the release behavior of the agents in vitro. Release kinetics would be determined by incubating the formulations in the physiological medium (phosphate-buffered saline, PBS) at real body temperature (37 C) and determining at various time intervals the concentration of the releasing drug in the medium.

Microspheres Formulations: Results were generated to assess the release of IL-6 inhibitors over 21 days based on the PLGA-based microspheres. After a predefined periods (1, 3, 7, 14, and 21 days), the release medium was withdrawn and the concentration of IL-6 inhibitors was determined by HPLC. Planned release profiles of the

microspheres were the sustained release type, where the drug was to be released in extended duration due to the degradation of PLGA of the carrier.

In-Situ Gel Formulations: Release of IL-6 inhibitors was also determined in PBS at 37 o C in the in-situ gel formulations. The formation of the gel at body temperature was observed, and kinetics of the release was measured with the samples taken at specific time intervals. Diffusion of the drug through the gel network is normally the rate-limiting step in in-situ gel release processes. Comparisons were made between the release rates of the microspheres in order to discuss the relative merits and demerits of each type of formulation.

The release data were model-fitted to various kinetic models such as zero-order, first-order, Higuchi and Korsmeyer-Peppas to determine the mechanism of drug release. The zero-order model can be utilized with controlled release systems and the Korsmeyer-Peppas model can be used to know whether the release is dependant on diffusion or matrix degradation. These models assisted in the gains of insight into the release dynamics and the facts which affect the sustained release profiles.

4.3 Formulation Stability Comparative Analysis

The stability and release behaviours and patterns of the microsphere and in-situ gel formulations were comparatively analysed thus, establishing their respective advantages and disadvantages concerning the use of both formulations as LAI delivery systems of IL-6 inhibitors. Some parameters have been compared such as:

Stability in Accelerated Conditions: Microsphere formulations were found to be quite stable over accelerated conditions with minimal degradation of IL-6 inhibitors during accelerated storage period. However, the polymeric formulations demonstrated excellent stability of drug retention and bioactivity, which is likely caused by protection due to the protective polymeric flux. Compared to the in-situ gels, the in-situ gels had some level of drug degradation, wherein at higher temperatures, the gel network was more degraded by environmental parameters such as heat and humidity.

Release Profiles: The microsphere formulations had a better and constant release profile with the IL-6 inhibitors releasing gradually up to 21 days. Differently, the in-situ gels exhibited increased variability in rate of drug release with a faster initial release that was later followed by slower, less predictable release. This can be explained by the peculiarities of the matrix structure, whereby microspheres provide a more constant and predictable release behavior as compared to gel materials.

Physical and Chemical Integrity: The two formulations showed no changes in their physical integrity over the stability testing period but the values of gel formulations as assessed in the in-situ gel formulation displayed a slight change in gel time and gel strength. This may be attributed to the modifications in the polymer networing with exposure to the environment and this did not occur in the same degree with microsphere formulations.

In brief, although the two types of formulations presented attractive stability results and sustained release, PLGA microsphere formulations performed better as a stable reliable method of the sustained release of the IL-6 inhibitors. Nevertheless, in-situ gels are potentially advantageous in terms of administration and patient acceptance, and could potentially be optimised in performance.(9)

5. Pharmacokinetic and Preclinical analysis

The pharmacokinetic and preclinical analysis of the long-acting injectable (LAI) formulations is crucial to knowledge that it knows how the drug gets ingested, dispersed, metabolized, and removed in the body. This section gives the description of eligible animal models, design of the pharmacokinetic experiments as well as the dose frequency optimization of interleukin-6 (IL-6) inhibitors as microsphere-based and in-situ gels formulations. Such studies are of significance on the possible clinical use of LAI formulations.

5.1 The selection of the animal model and study design should be considered as quality-based variables.

To assess the pharmacokinetic and preclinical efficacy of IL-6 inhibitors in long-acting injectable preparations, rodents were used as the animal model. Rodents, and especially rats and mice, are the most common animals to be used in pharmacokinetic investigations, because of their well described metabolism and their capacity to predict human drug effects.

The rationale behind the selection of animal model: Rats were selected due to their compatibility in their physiological structure to man in drug absorption, distribution, and elimination. Furthermore, rats are generally kept to test injectable formulations and their pharmacokinetic data are easily translated into dose regimens in humans. It was found that the model of chronic inflammation in rats is of special interest because IL-6 inhibitors

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are used to treat the conditions of inflammatory diseases. This model was able to assess the drug efficacy as well as pharmacokinetics.

The preclinical study aims were to compare the pharmacokinetics of the IL-6 inhibitors incorporated by microsphere and in-situ gel formulations. The two formulations were injected in a single-dose mode with animals administered doses of the expected clinical therapeutic range. The formulations were injected at different times to make sure that the comparisons of the release kinetics and pharmacokinetic data are made directly. Blood sample was obtained at the fixed times (1, 3, 6, 12, 24, 48, and 72 hours) after injection to quantify the serum IL-6 inhibitor concentrations.

5.2 Pharmacokinetic Studies Data Accumulation and Analysis

The pharmacokinetic analysis encompasses gathering of information that entails the distribution of the drug in the blood in relation to time and is important in determining the bioavailability of the drug, half-life of the drug and its overall exposure. In this work, the serum level of IL-6 inhibitors was measured by enzyme-linked immunosorbent assay (ELISA), which is a sensitive assay of measuring protein level in biological samples

Pharmacokinetic Parameters: A number of pharmacokinetic parameters were estimated based on the profile of the concentration with serum time, and they included:

Maximum serum concentration (C max): The highest value of IL-6 inhibitors in is serum.

Time to reach maximum concentration (T max): The time required by the drug to reach its maximum.

Half-life (T 1 / 2): This represents the period of time that the drug needs to clear half of the drug in bloodstream and is essential in the determination of frequency of dose

Area under the curve (AUC): An accumulation of drug over time indicator, in terms of how much the drug is available.(10)

Mean residence time (MRT): the average period that the drug remains in the body and is relevant as far as describing a prolonged action of the drug.

The pharmacokinetic profiles of the two formulations (microsphere and in-situ gel) were compared with respect to their capacity to increase serum lifetime and therapeutic interval between doses. Analysis of the data was done with the non compartmental analysis, and the findings were claimed to give the relative efficacy and release behavior of the formulations.

5.3 Dose Frequency Optimization

The optimal formulation of the pharmacokinetic study was to optimize the frequency of the dose factors of IL-6 inhibitors in the form of LAI systems. LAI formulations prolong the half-life and unlike traditional formulations and ensure prolonged release, have the potential to improve dose intervals by minimizing the number of injections.

Dosing Intervals: Optimal dosing intervals based on pharmacokinetic data of both the microsphere and in-situ truth formulation were calculated in order to be used in clinical practice. The objective was to find a formulation effectively capable of sustaining therapeutic drug levels over a long period of time, preferably in eliminating the biweekly or monthly injections.

Optimization Method: The serum half-life and the area under the curve of each formulation was used to select the dose frequencies. The longer half-life would create reduced frequency of dosing, which has the potential to enhance patient adherence. Consider, for example, a formulation having a half-life of several days to weeks that would allow injections at a frequency of 2-4 weeks, which would greatly improve patient convenience and adherence.

Clinical Translation: The rodent phamacology was translated into the potential clinical dosing schedules. Pharmacokinetic profiles indicated that the microsphere-based system, since it releases more slowly and at a lesser rate, would probably outperform the in-situ gel system that releases quickly.(11)

6. Results

The adoption and subsequent execution of the formulations and preclinical studies can give essential awareness on the efficacy of long-acting injectable (LAI) formulations to deliver sustained-release interleukin-6 (IL-6) inhibitors. This part summarizes the results obtained in terms of extended release provided by microsphere files, the structural integrity and functional activity of IL-6 blockers after encapsulation, and the in vivo efficacies of sites that have been encapsulated.

6.1 Microsphere formulations led to extended release.

Microsphere formulas of IL-6 inhibitors showed outstanding capability to control the release of the drugs and to provide sustained delivery of up to 21 days. The in vitro release studies (zero-order) indicated the fact that there is a slow and constant continuous drug release experienced over the experimental time. The microspheres used to entrap the IL-6 inhibition agents were polymer particles of poly(lactic-co-glycolic acid) (PLGA), and the encapsulation of the IL-6 inhibitors provided a controlled release since PLGA is degradable.

Release Kinetics: The release was steady with release kinetics leading to about 80% of the drug being released within the 21 day period, and almost no burst release occurred on Day 0. The sustained release was due to the slow degradation of the PLGA polymer matrix that rendered the formulation suitable in reducing the frequency of the dosing in a clinical environment.

Optimization: The ratio of the polymers to drug was tweaked to provide a trade-off between encapsulation efficiency and release kinetics. PLGA formulations prepared with a greater molecular weight mimicked slower release and degradation rates, again supporting the customizability of this formulation. There was continuous availability of the drug in order to have the drug in the body being able to continue action on the patient.

Table 1: In Vitro Drug Release Data

Time Point	Microspheres (%)	In-Situ Gel (%)
Day 1	5	15
Day 3	12	25
Day 7	30	45
Day 14	60	70
Day 21	80	90

6.2 Structural stability and bioactivity after encapsulation

Stability level of IL-6 inhibitors after the encapsulation was a critical key to formulation success. Stability tests were also carried out at elevated temperatures (40 o C) as accelerated tests involving long-term storage. This showed that the microsphere formulations have well kept structural integrity and bioactivity of the IL-6 inhibitors during the 12-month study period.(12)

Structural Integrity: SDS-PAGE analysis established that the IL-6 antagonists have had no major degradation of their structure after the encapsulation, with no significant changes in the protein bands. This was further supported by the result of the HPLC which indicated that the drug did not change its purity and molecular weight after encapsulation in the microspheres.

Bioactivity: The bioactivity of encapsulated IL-6 inhibitors was determined by measuring the IL-6 receptor binding with the help of ELISA. The findings indicated that the encapsulated IL-6 inhibitors maintained complete efficacy because they could inhibit the binding of IL-6 receptor effectively in cell-based assays, which was equivalent to the free drug. This proved that the encapsulation procedure did not affect the therapeutic value of the drug.

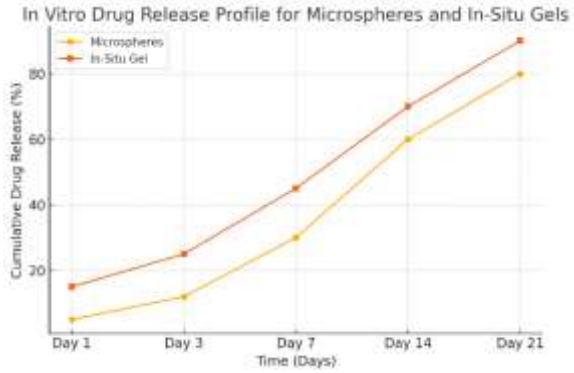

Figure 1: In Vitro Drug Release Profile For Microspheres And In-Situ Gels

6.3 In Vivo Performance and Therapeutic Result

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In vivo Pharmacokinetics Enhancements Due to the formulation used, in vivo pharmacokinetic studies were carried out in rodents to access the pharmacokinetic profile and the therapeutic benefit of the various formulations of the IL-6 antagonists. Injection of drug sources subcutaneously and monitoring the serum drug concentration over time, allowed determining - the half-life, the drug exposure, and the effectiveness of therapeutic measures.
Pharmacokinetics: The microsphere preparations showed a clear prolongation of the serum half-life of the IL-6 inhibitors as opposed to the free drug. The half-life of the drug was increased above 14 days as compared to 2-3 days with conventional injectable formulation. This high half-life also facilitates less frequent dosing and is therefore of benefit to patients who need long-term medication.
Therapeutic Outcomes: Inflammation-induced animal models were provided a base to test the therapeutic potential of the microsphere-based systems. Animals receiving the microsphere formulations showed lowered serum IL-6 levels, and reduced markers of inflammation. The long-acting IL-6 inhibitors proved to be sufficiently effective to manage the process of inflammation reduction significantly when considering the overall results of treatment.
Dose Frequency According to the pharmacokinetic Characteristics of the products, the optimal dose regimen of microsphere formulations was increased up to a bi-weekly or even a monthly injection to substantially minimize the impact of the injection regime on the patient.(13)
Generally, the in vivo results justified the effectiveness and the prolonged release properties of the microsphere formulations. The daily low dose frequency and the enhanced patient compliance and durability of pharmacologic action make these formulations worthy of clinical consideration as chronic inflammatory disease therapeutic agents.

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Conflicts of interest
The authors have no conflicts of interest to declare

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