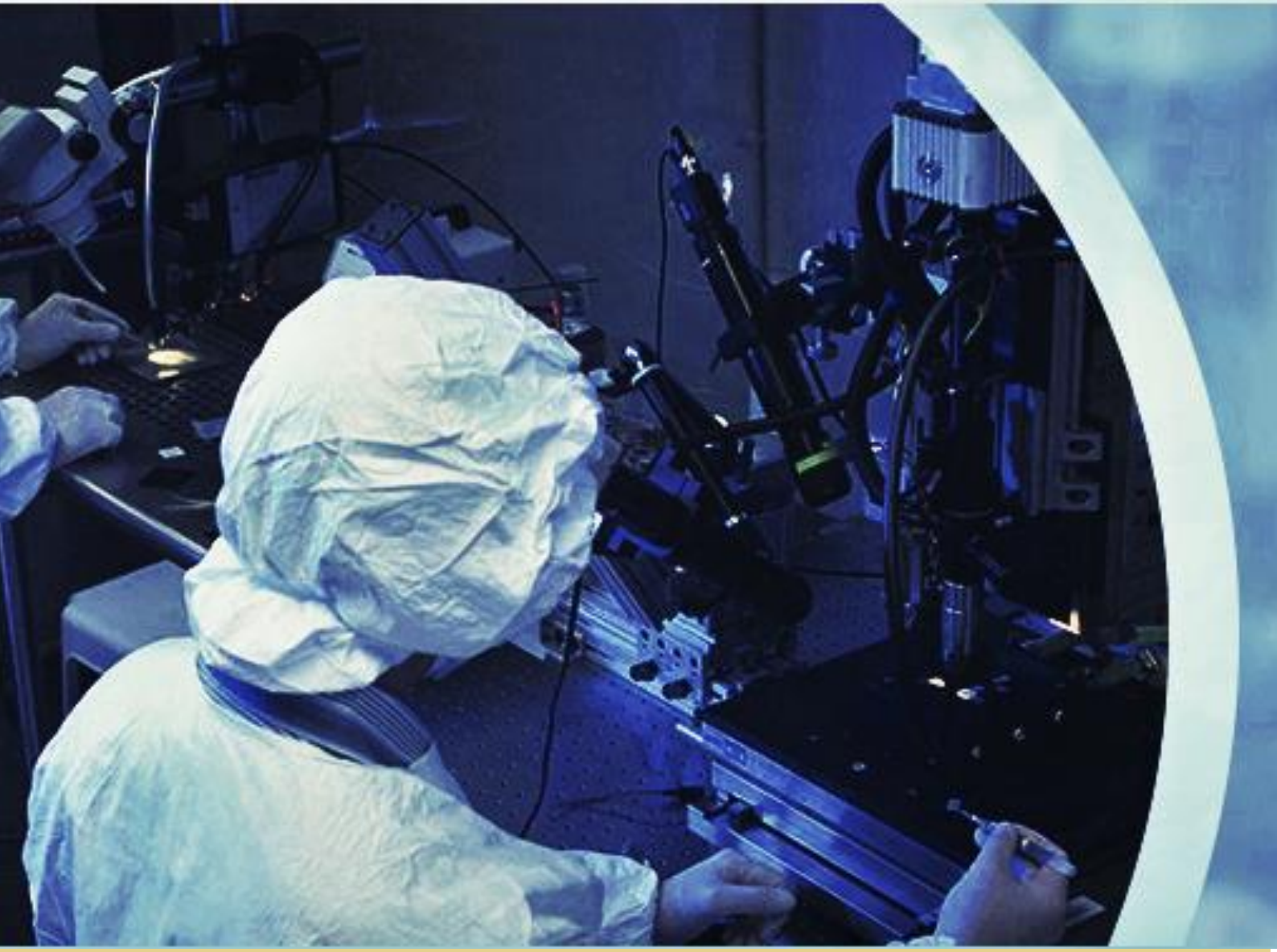

Ana Margarida Rocha Borges

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Monografia realizada no âmbito da unidade Estágio Curricular do Mestrado Integrado em Ciências Farmacêuticas, orientada pelo Professor Doutor António José Ribeiro e apresentada à Faculdade de Farmácia da Universidade de Coimbra

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UNIVERSIDADE DE COIMBRA

O Orientador da Monografia

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(Professor Doutor António José Ribeiro)

A Aluna

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(Ana Margarida Rocha Borges)

Eu, **Ana Margarida Rocha Borges**, estudante do Mestrado Integrado em Ciências Farmacêuticas, com o nº 2011169455, declaro assumir toda a responsabilidade pelo conteúdo da Monografia apresentada à Faculdade de Farmácia da Universidade de Coimbra, no âmbito da unidade curricular de Estágio Curricular.

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Coimbra, _____de_____de 2016.

A Aluna

(Ana Margarida Rocha Borges)

Index

Abstract

In the recent years, protein and peptide macromolecules have emerged as promising therapeutic agents. However, their susceptibility to denaturation and degradation, short half-life and, consequently, poor bioavailability, can interfere with their delivery to the target site.

Parenteral administration is the primary route of delivery for these drug compounds. However, namely in chronic diseases, there is a need of multiple injections that lead to poor compliance.

This way, implants present an attractive parenteral delivery option for these kind of drugs due to their ease of application, sustained-release properties, tissue biocompatibility and simple manufacture.

There are already several sustained-release injectable pharmaceutical products on the market and this number keeps growing. Injectable depot systems are becoming one of the most effective systems for long-term drug delivery.

Furthermore, there are numerous products that are still being developed. Biopharmaceutical companies are developing implant delivery technology and submitting the products into clinical trials, in order to improve patients' compliance.

These companies, committed to improve patients' quality of life, can represent the future of drug delivery.

Keywords: Biopharmaceutics; Compliance Drug delivery; Implants; Parenteral delivery; Protein; Sustained-release;

Resumo

Nos últimos anos, macromoléculas como proteínas e péptidos, têm tido especial atenção como possíveis moléculas terapêuticas. Contudo, a sua suscetibilidade à desnaturação e degradação, tempo de meia-vida curto e, consequentemente, baixa biodisponibilidade, são fatores que podem interferir com a sua entrega no local alvo.

A administração parenteral representa a primeira opção como via de administração destes fármacos. Todavia, nomeadamente nas doenças crónicas, a necessidade de injeções frequentes leva a uma baixa adesão à terapêutica.

Deste modo, os implantes representam uma opção atrativa para a administração destas moléculas terapêuticas, devido à sua facilidade de aplicação, propriedades de libertação controlada dos fármacos, biocompatibilidade dos tecidos e produção fácil.

Atualmente já existem no mercado diversos produtos farmacêuticos de injetáveis de libertação controlada, e este número continua a crescer. Estes sistemas injetáveis estão-se a tornar num dos sistemas mais eficientes de libertação prolongada do fármaco.

Além disso, inúmeros produtos estão neste momento em desenvolvimento. Empresas biofarmacêuticas encontram-se a desenvolver implantes e a submeter os seus produtos a ensaios clínicos, com o objetivo de aumentar a adesão à terapêutica.

Estas empresas de biotecnologia, com foco na melhoria da qualidade de vida dos doentes, podem representar o futuro da administração de fármacos.

Palavras-chave: Adesão à terapêutica; Administração de fármacos; Administração parenteral; Empresas biofarmacêuticas; Implantes; Libertação-controlada; Proteínas;

Introduction

Parenteral administration is the most common and the most efficient route for the delivery of active drug substances that have either a poor bioavailability or a narrow therapeutic index.

Drug delivery with subcutaneous injection allows easy access to systemic circulation and, consequently, rapid drug absorption. Nevertheless, this rapid drug absorption is also accompanied by a quick decline in the drug levels in the systemic circulation. When it comes to chronic conditions, there is a need of daily or multiple weekly injections for years or even lifetime that lead to a poor patient compliance.

A few decades ago, sustained parenteral drug delivery started to be seen as a sub-area of pharmaceutics. This development has been significantly influenced by advances in areas like pharmacokinetics and pharmacodynamics, which served to bring out the need for controlled, extended drug delivery and sustained drug plasma/tissue levels in order to reach desired therapeutic responses. There have been significant benefits to the patient and to the practitioner in terms of efficacy, convenience, duration of therapy, side effects and patient compliance, by using this treatment procedure. (WRIGHT, J.C. and HOFFMAN, A.S., 2012)

When it comes to proteins and peptides, rapid advances in their pharmacology, and the use of DNA recombinant technology for large-scale manufacture, has given these molecules the status of being safe, effective and extremely potent therapeutic agents. Nonetheless, the therapeutic delivery options for patients are generally limited to injections and infusions that lead to pain and compliance issues. Furthermore, the delivery profile is frequently non-optimal, what affects negatively the treatment outcomes. Spikes in concentration immediately following injections often cause side effects, while the reduced concentrations after molecules are eliminated can reduce efficacy. (CLELAND, J.L. [et al.], 2001)

Hence, there is a need to develop new solutions in drug delivery. Extended release, constant-rate implants address all of these issues, and may even improve patient outcomes. In addition to producing constant-rate delivery, an optimal device would be small, easy to implant, and most importantly, safe over the duration of the implantation.

Protein drugs and parenteral delivery

Protein and peptide molecules have recently arisen as promising therapeutic agents. However, they have some characteristics that can make the delivery to the target site a challenging situation. These molecules are susceptible to denaturation and degradation, have a short half-life and, as a consequence, poor bioavailability. Moreover, their chemical and enzymatic instability, large molecule size, low lipophilicity, among others, can cause poor permeation through biological barriers. (AGARWAL, P. and RUPENTHAL, I.D., 2013)

Therefore, parenteral administration is the primary route of delivery for this group of drug compounds. Controlled release parenteral formulations of peptide and proteins can provide prolonged drug release, rise the apparent *in vivo* half-life, prevent degradation of the peptide or protein, and increase the comfort and compliance of the patient, mainly by reducing the frequency of injections. (PISAL, D.S. [et al.], 2010)

Release studies that have been made, showed that it is possible to obtain sustained drug release for not only a couple of days, but also for several months.

To achieve controlled release of peptide and protein drugs, several formulations have been studied, including hydrogels, micro- and nanoparticles, liposomes and implants. *In situ* forming implants present an attractive parenteral delivery platform for proteins and peptides owing to their sustained-release properties, ease of application, tissue biocompatibility and simple manufacture. (JENSEN, S.S. [et al.], 2016)

The success of protein and peptide parenteral delivery depends on the development of novel delivery approaches. Several strategies have been evaluated in an effort to overcome challenges associated with therapeutic protein and peptide delivery. The widely studied approaches can be generally categorized as chemical modifications and colloidal delivery systems. Among chemical modifications, pegylation and glycosylation are the most extensively studied subjects, as it can be seen in table 1.

Chemical modifications	Definition	Improvements	Advantages of the strategy	Products on the market
PEGylation	Covalent conjugation of activated PEG to the therapeu-tic proteins	Stability, pharmacokinetics, and therapeutic activity of protein, by altering physicochemical properties such as molecular weight, size, solubility and steric hindrance	- Non-immunogenicity - Low protein/cellular adsorption among polymers used for drug delivery - Non toxicity - Solubility in water - FDA and EMA approval for injection with biotechnological drugs	- Oncaspar® - PEG-Intron® - Pegasys® - Neulasta® - Somavert® - Mircera® - Cimzia®
Glycosylation	Co- or post-translational enzymatic process that conjugates proteins, lipids or other organic molecules with polysaccharides to form a glycoconjugate	Reduce interactions with the clearance process and antigen presenting cells, leading to prolonged systemic circulation and reduced immunogenicity	Biodegradable nature of carbohydrates (whereas the intact PEG is eliminated from the body without biodegradation)	Darbepoetin α, (Amgen, USA) – a hyperglycosy-lated form of recombinant human erythropoietin (rhu-EPO)

Table I – Chemical modifications on therapeutic proteins or peptides of interest (PATEL, A. [et al.], 2014)

Colloidal delivery systems such as liposomes and nanoparticles are extensively investigated for the parenteral delivery of protein due to several advantages, such as protection of sensitive proteins, prolonged release, reduction of administration frequency all contributing either to improve patient compliance or to better control drug plasma levels (Table 2).

Extensive research efforts made several parenteral products clinically available applying these strategies. These technologies have not only improved therapy, but also reduced cost of therapy and enhanced patient compliance.

Colloidal Delivery Systems	Definition	Characteristics	Biodegradable Polymers	Marketed Formulations	Advantages
Microparticles (composed of biodegradable polymers)	Submicron carriers with size below 1000 μm	- High protein loading capacity - High encapsulation efficiency - Provide sustained release of biologically active proteins	- Starch - Alginate - Collagen - Poly (lactide-*co*-glycolide) (PLGA) - Polycaprolactones (PCL)	- Lupron Depot® - Decapeptyl® - Sandostatin LAR® Depot - Somatuline® LA	Depot formulation - provide controlled release over several days to months
Nanoparticles (polymeric nanoparticles)	Colloidal carriers with size ranging from 10 to 1000 nm	- Can be fabricated from natural or synthetic polymers - Can be generated as nanospheres or nanocapsules using different fabrication methods	- Chitosan - Alginate - PCL - Polylactic acid (PLA) - Poly (glycolide) - PLGA		- Protect biologics from degradation - Prolong *in vivo* half-life - Provide long term drug release
Liposomes	Bilayered vesicles with an aqueous core enclosed by phospholipid membrane	- Cationic - PEGylated liposomes	N/A	- DepoFoam®	- Highly biocompatible - Less toxic in nature - Protect therapeutic proteins from *in vivo* degradation - Prolonged half-life - Longer systemic circulation time - Higher bioavailability

Table 2 – Colloidal drug delivery systems (PATEL, A. [et al.], 2014)

1.1. Sustained delivery of a drug

In general, there are two routes by which long-acting parenteral injections are most frequently administered: intramuscular and subcutaneous. Subcutaneous route is often the preferred route for administering a drug by injection due to the greater area for target injection sites, ease of self-administration, use of shorter needles, less discomfort and

inconvenience for patients, and better safety profile. This continues to represent the primary route of delivery for protein-based drugs. (MANSOUR, H.M. [et al.], 2010)

Reproducible sustained delivery of a drug at a target site is one of the main subjects in controlled drug-delivery systems. The most frequently used drug-delivery systems, which can release drugs longer than one week, are parenteral injections and implants. Some implant systems can deliver drugs for more than one year. For instance, Microchips Biotech has already developed a microchip-based implant that can store 100's of therapeutic doses over months and years. This implant, that has been clinically-validated in human studies, is activated by a wireless signal which triggers the micro-reservoirs to release the drug on a pre-programmed dosing schedule. It was tested in women with osteoporosis to deliver teriparatide, a synthetic parathyroid hormone (PTH) typically administered via daily injections to increase bone mass. (FARRA, R. [et al.], 2012)

1.1.1. Controlling drug release

Release pattern can be modified by changing the size of the drug particle, drug load and/or chemical modifications that affect the solubility or clearance. Changing the drug particle size, the diffusion and erosion phases can also be changed. Actually, changes in a single manufacturing parameter can cause many consequences on the drug release profile. (DEYOUNG, M.B. [et al.], 2011)

Treatment efficiency can be assured if systemic drug levels are kept within the therapeutically effective concentration range for as long as the treatment last. Several attempts have been made in order to achieve a constant drug level in the systemic circulation. (Figure 1)

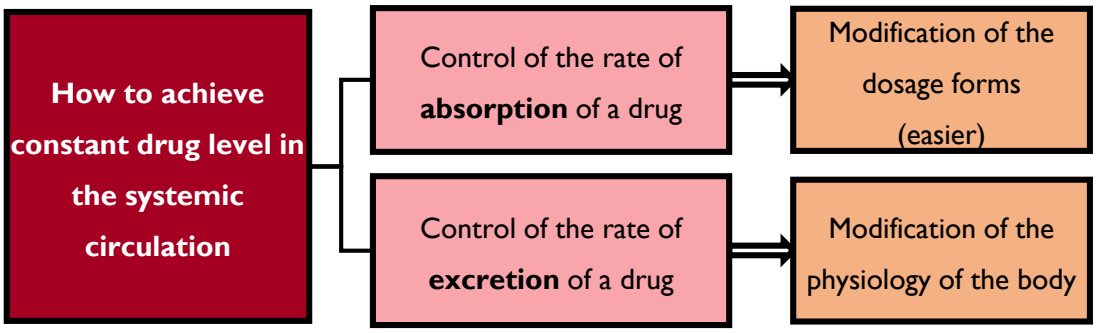

Figure 1: Strategies to achieve constant drug level in the systemic circulation (BARI, H., 2010)

Continuous intravenous infusion has been recognized to maintain a constant and sustained drug level within a therapeutic concentration range for as long as an effective treatment requires. However, it involves certain health hazards and, consequently, requires continuous hospitalization and close medical supervision. (BARI, H., 2010)

The development of new injectable drug delivery system (parenteral depot formulation) has received considerable attention over the past few years. There are already some applications where this type of modified release parenteral delivery has been studied (Figure 2).

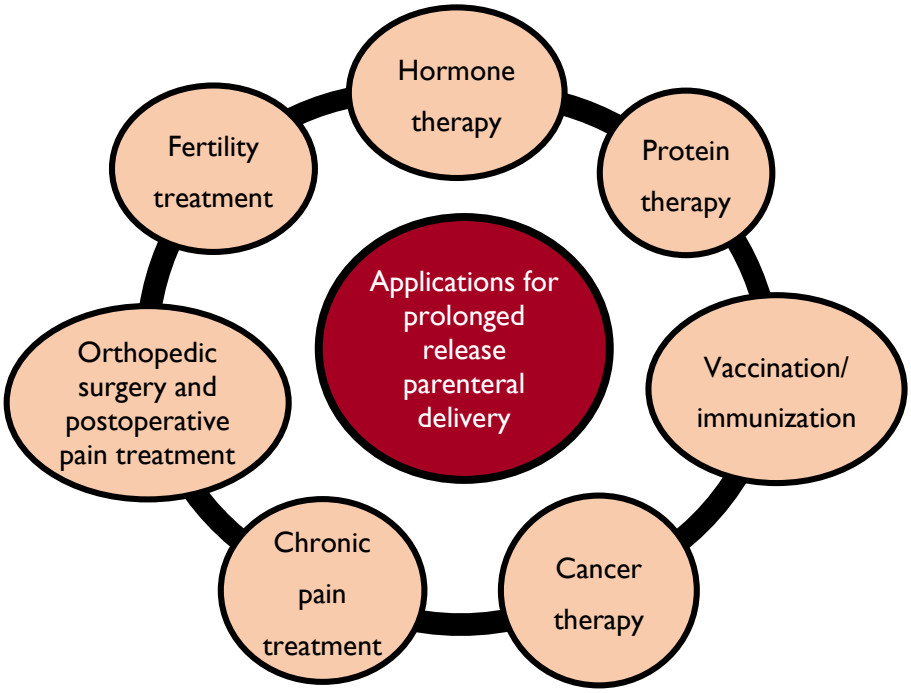

Figure 2: Examples of applications for modified parenteral release (BARI, H., 2010)

1.1.2. Advantages of long-acting injectable formulations

Advantages of parenteral injections are immediate systemic drug availability and rapid onset of action. When compared with conventional formulations, long-acting injectable formulations advantages include: a predictable drug-release profile during a certain period of time following each injection; ease of application; better patient compliance; improved systemic availability by preventing first-pass metabolism; reduced dosing frequency (i.e., fewer

injections) without compromising the effectiveness of the treatment; decreased incidence of side effects; and overall cost reduction of medical care. (MANSOUR, H.M. [et al.], 2010)

1.1.3. Problems with current treatments

In chronic diseases a frequent administration is often required, meaning daily or multiple weekly injections that can be painful and lead to poor patient compliance (Figure 3). Consequently, this leads to reduced patient outcomes.

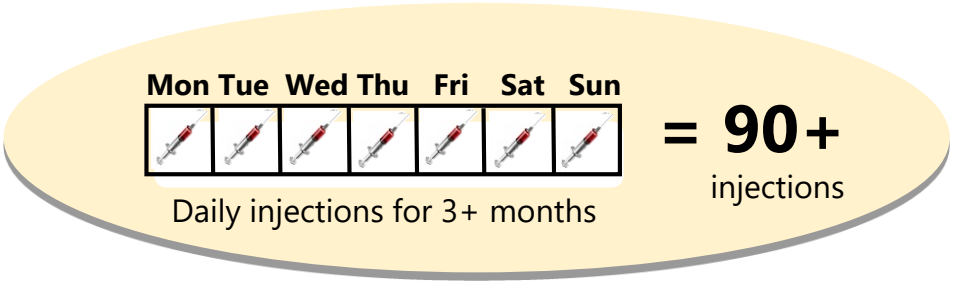

Figure 3: Current treatment of chronic diseases - Adapted from (NANO PRECISION MEDICAL, I., 2016) (© 2016 Nano Precision Medical, Inc.)

The development of an implant that lasts for weeks or months and ensures continuous dosing for the duration of the treatment can be a valid alternative (Figure 4). Implantation can be performed in a quick, outpatient procedure.

Comparing to conventional formulations, controlled-release formulations can be more challenging to formulate, but they offer several advantages, as it was mentioned before.

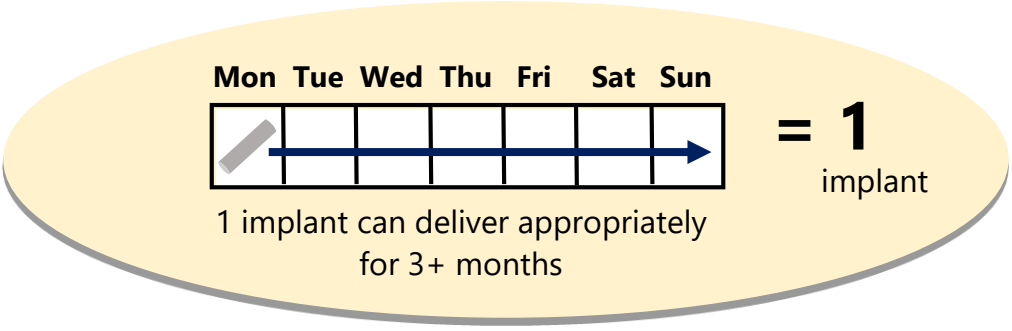

Figure 4: Implant delivery - Adapted from (NANO PRECISION MEDICAL, I., 2016) (© 2016 Nano Precision Medical, Inc.)

Implants

Implants are an attractive parenteral delivery platform for proteins and peptides because of their ease of application, sustained-release properties, tissue biocompatibility and simple manufacture. They present therefore a formulation option to avoid a constant infusion or a very high frequency of injections. (KEMPE, S. and MÄDER, K., 2012)

Injectable implants can deliver proteins and peptides at a controlled rate over a prolonged period of time, thereby reducing the dose and frequency of administration. Consistent delivery rates are expected to eliminate either concentration peaks or lower concentrations, overcoming the pharmacokinetic inadequacies of standard injection therapy. (NANO PRECISION MEDICAL, I., 2016).

On the other hand, the sensitivity of implant behavior to a number of factors including the polymer type, solvent, and drug properties can partially explain the current lack of clinical applications (SOLORIO, L. and EXNER, A.A., 2015)

1.2. *In situ* forming implants

These implant systems are a liquid solution outside of the body that change into solid drug eluting depots when in contact with an aqueous environment through a process known as phase inversion (Figure 5). They are made of biodegradable products which can be injected via a syringe into the body. (SOLORIO, L. and EXNER, A.A., 2015)

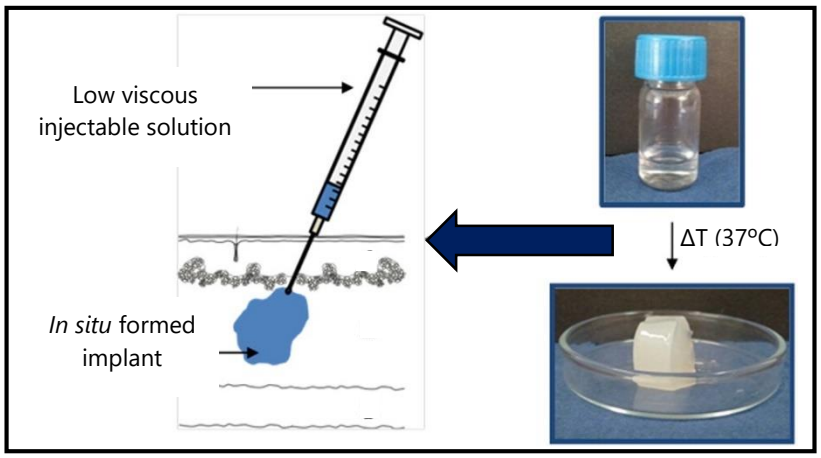

Figure 5: Example of an *in situ* forming thermally-induced gelling system – Adapted from (KEMPE, S. and MÄDER, K., 2012)

The ability to inject a drug incorporated into a polymer to a localized site and have the polymer form a semi-solid drug depot has a number of advantages. It is less invasive and painful compared to pre-shaped parenteral depot systems, which require local anesthesia and a small surgical intervention. (HATEFI, A. and AMSDEN, B., 2002)

In order to be not only efficient but also safe, there are some important characteristics that an *in situ* forming implant should have (Figure 6).

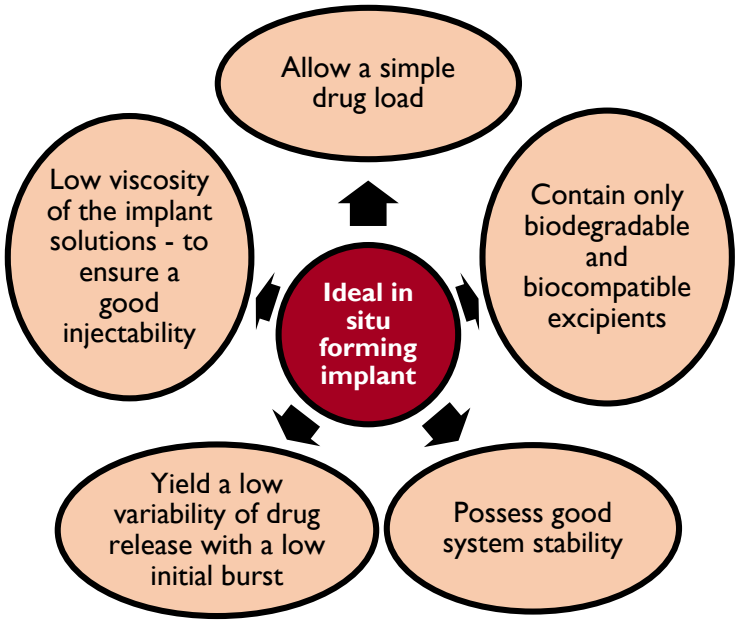

Figure 6: Ideal *in situ* forming implant (KEMPE, S. and MÄDER, K., 2012)

One of the major challenge of these implant systems is the reliable formation of the implant regarding to size, shape and structure. It is a result of several parameters that result from different causes, as illustrated in Figure 7.

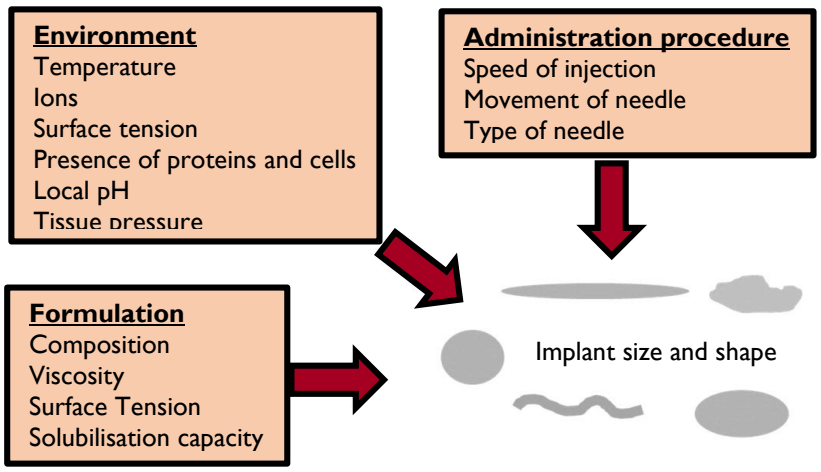

Figure 7: Sources of the variability of the implant shape and size – Adapted from (KEMPE, S. and MÄDER, K., 2012)

As mentioned before, the in vivo environment has been shown to change the implant behavior. However, little has been carried out to determine the mechanisms that drive in vitro/in vivo discrepancies. The in vitro–in vivo correlation (IVIVC), that corresponds to the ability to correlate drug release data between in vitro and in vivo systems, can be used to reduce time and cost involved in drug development, as it decreases the number of human studies required during formulation and development. Nonetheless, the establishment of accurate IVIVC for biodegradable systems has not been easy due to the complexity of these release systems. (PATEL, R.B. [et al.], 2010)

By determining the causes that lead to poor IVIVC, release systems can be designed to more accurately predict how drug eluting systems will behave *in situ*. Changes in the implant microstructure that happen *in situ* can significantly modify the drug release and the degradation rate of the implants. This way, by designing implants that are able to reduce these changes in microstructure, the correlation between in vitro/in vivo drug release profiles can be achieved. (SOLORIO, L. and EXNER, A.A., 2015).

1.3. Limitations of implants

One major limitation is the high initial burst release. Due do this burst effect, the amount of drug released can sometimes be higher than the recommended safety margin. Consequently, it can cause tissue irritation, pain and even toxicity. There have been made several attempts to decrease unwanted burst release. (Figure 8)

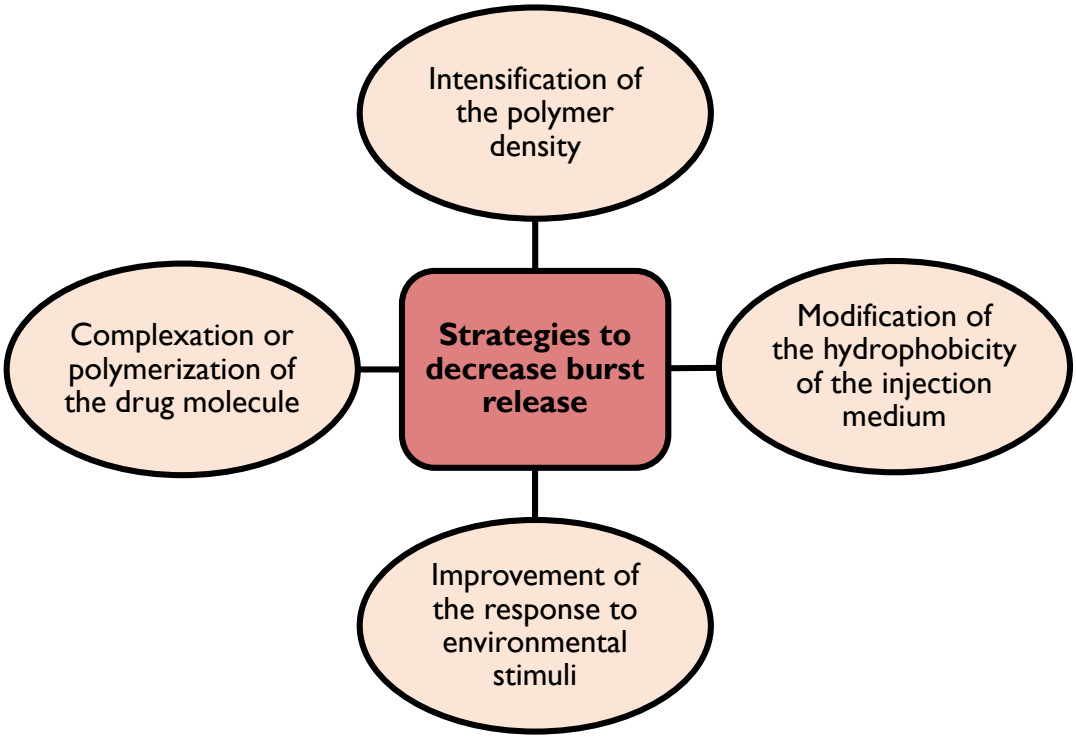

Figure 8 – Strategies to decrease high initial burst release of injectable implants (AGARWAL, P. and RUPENTHAL, I.D., 2013)

Despite the fact that incorporation into polymer matrices frequently inhibits enzymatic denaturation of proteins, drug instability can also arise due to polymer–protein interactions. Hydrophobic interactions between hydrophilic proteins and hydrophobic polymers can lead to irreversible aggregation, causing a decreased activity of the protein (AGARWAL, P. and RUPENTHAL, I.D., 2013)

Furthermore, as far as the host is concerned, implantation of devices or biomaterials may activate host reactions at the injury site. (Figure 9)

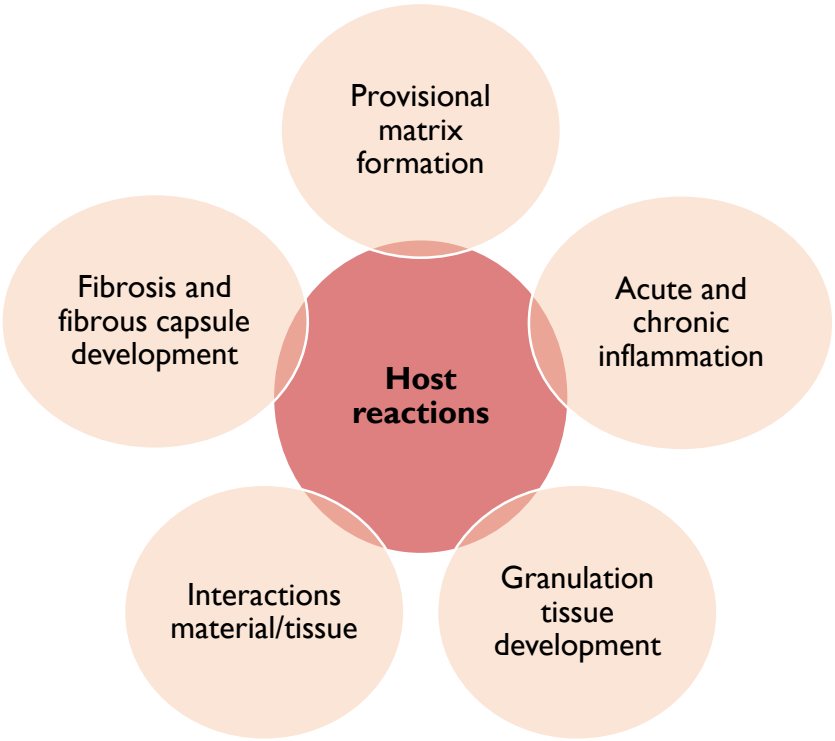

Figure 9 – Possible host reactions at the injury site (SOCARRÁS, T.O. [et al.], 2014)

The foreign body response refers to the non-specific immune response to implanted foreign materials. It results from persistent inflammatory stimuli, for example the presence of implant devices in which a series of cellular alterations such as continuous inflammation are mediated by the various cell lineages. In this inflamed environment, macrophages, lymphocytes, mast cells, and their granular products contribute to the formation of foreign body giant cells and the development of a dense of layer of fibrotic connective tissue which is detrimental to the implants' function, safety, and biocompatibility. (MORAIS, J.M. [et al.], 2010)

1.4. Marketed Products

Several injectable implant systems are already on the market.

Diabetes, a condition that affects more than 371 million people globally, is a chronic disease where implantable systems offer unique patient solutions. Continuous glucose monitoring (CGM) involves implanting sensors subcutaneously to measure blood sugar. Commercial examples include Dexcom G4 Platinum™ (Figure 10), Medtronic's Enlite® (Figure 11), and GlySens ICGM® (Figure 12).

Figure 10: Dexcom G4 Platinum™
(©2016 Dexcom, Inc)

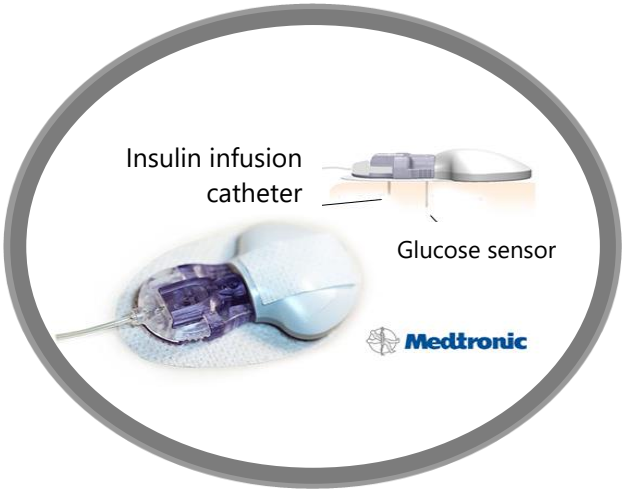

Figure 11: Medtronic's Enlite®
(© 2010 Medtronic MiniMed, Inc.)

Figure 12: GlySens ICGM®
(©2016 GlySens Incorporated)

Currently, there are several biopharmaceutical companies committed to develop innovative therapies that merge medicine with technology, and are dedicated to improve quality of life of patients by revolutionizing drug delivery.

Table 3 discriminates some of these companies that are developing implant delivery technology as well as the ones that are currently in clinical trials phase.

Company	Product	Active Ingredient	Application	Clinical trials
Intarcia Therapeutics, Inc.	ITCA 680	Exenatide	Type II diabetes	Phase 3
Delpor™ Delivering the Future of Medicine	DLP-414	Exenatide	Type II diabetes	Preclinical
Nano Precision Medical	NanoPortal™	Exenatide	Type II diabetes	-
VIACYTE Regenerating Health™	VC-01™	ViaCyte's Encaptra® drug delivery system and human embryonic stem cells (pancreatic PEC-01™ cells)	Type I diabetes	Phase 1/2a

Table 3: Biopharmaceutical companies and their products in development

US-based Intarcia Therapeutics is developing a non-biodegradable drug-eluting device to treat type 2 diabetes (T2D), ITCA 650 which is a small, matchstick-sized osmotic pump consisting of a cylindrical titanium alloy reservoir that is implanted subcutaneously and delivers a steady flow of exenatide, a glucagon-like peptide-1 receptor agonist, for 12 months. It's currently in Phase III of the clinical trials. (HENRY, R.R. [et al.], 2014)

Delpor's titanium drug-eluting is another device that delivers exenatide for treatment of T2D. DLP-414 is a system capable of delivering therapeutic levels of exenatide for 3-6 months. Delpor's system also is designed to deliver drugs for treating bipolar disorder, growth hormone deficiencies, and hepatitis C. (DELPOR, 2016)

NanoPrecision Medical is developing NanoPortal™, a rice-size titanium implant that delivers exenatide for T2D. (FISCHER, K. [et al.], 2014)

ViaCyte is developing VC-01™ to treat type I diabetes (T1D). VC-01 is a subcutaneous implant composed of ViaCyte's Encaptra® drug delivery system and human embryonic stem cells (pancreatic PEC-01™ cells). (AGULNICK, A.D. [et al.], 2015)

Future perspective

Great efforts have been made in the last decade with chemical modifications, colloidal and thermosensitive hydrogel based delivery systems to improve *in vivo* half-life, stability and efficacy of protein and peptide therapeutics. In order to get these products to the market, a lot of research and development is needed.

Chemical modifications may be an alternative to improve stability, *in vivo* circulation time, reduce toxicity of peptide drugs to normal cells/tissues and improve drug efficacy in diseased cells. Thus, conjugation of a targeting to the PEGylated protein/peptide may be safer, specific in drug delivery, more efficacious and may also improve patient compliance. Carrier systems like micro- and nanoparticles and thermosensitive hydrogels sustain drug release, provide stability and prevent from enzymatic degradation. (PATEL, A. [et al.], 2014)

Some of these products are already on the market. However, delivery of drugs in therapeutic concentrations to its site of action, especially when the target is out of systemic circulation, is still a challenge. Dual strategy such as protein/peptide chemical modification followed by encapsulation into a carrier system may further improve their release kinetics, *in vivo* half-life, circulation time and stability. Moreover, protein/ peptide-loaded targeted-carrier systems may be dispersed in the hydrogel system, which forms depot and further sustain protein/peptide drug release. (PATEL, A. [et al.], 2014)

Advanced techniques and methods are required to access the protein/peptide stability in the carrier system and to study in vitro/in vivo correlation.

Hence, biopharmaceutical companies need to continue their research to develop innovative therapeutic drug delivery systems in order to provide improved therapeutic outcomes while enhancing patients' quality of life.

Conclusion

The incessant advancement in biotechnology and DNA recombinant mechanisms have resulted in the appearance of numerous protein and peptide therapeutics. Nonetheless, one of the major challenges to their clinical success is the lack of an effective delivery method. As a result, there is a demand for efficient drug delivery methods. Currently, there are several therapeutic proteins approved and under clinical trials and this number keeps increasing.

Abundant efforts have been made towards a protein and peptide delivery via noninvasive routes, still parenteral delivery remains upfront.

In the past few years, significant progress has been made to improve parenteral delivery of proteins and peptides using various delivery technologies such as microparticles, liposomes, nanoparticles, *in situ* thermosensitive gels as well as by chemical modification via PEGylation and hyperglycosylation.

With continuing efforts, injectable implants can further be optimized to respond to internal and/or external stimuli and, thus, modify their protein release properties.

Extensive research efforts made several parenteral products clinically available utilizing these strategies. These technologies have shown positive outcomes as reduction of costs and improved patience compliance. However, the numbers of clinically available products are fewer compared with the extensive efforts put towards the development of proteins and peptides delivery systems. The complexity of scale-up, difficulty in preserving bioactivity of proteins and peptides and high cost of manufacturing are hampering successful development of such formulations.

Despite this fact, the number of sustained-release injectable pharmaceutical products on the market keeps growing. Injectable depot systems are becoming one of the most effective systems for long-term drug delivery.

Owing to the improved quality of life and cost of therapy supported by the advances in drug formulation and polymer science, more sophisticated injectable depot systems will be developed and commercialized in the near future. Moreover, the introduction of more potent drugs and protein/peptide drugs particularly good candidates for formulation as long-acting parenteral depot systems will drive development of more and better injectable delivery systems.

Polymer-based injectable depot systems for protein/peptide drugs have many advantages such as protection of sensitive proteins from degradation, prolonged or modified release, pulsatile release patterns, and improvement of patient compliance.

In addition, controlled-release formulations have an important role as part of a lifecycle management strategy that allows pharmaceutical companies to differentiate their products from generic drug competition and thereby extend market exclusivity.

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