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Review Article

An Update on Biodegradable Microspheres Loaded with Naltrexone

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ABSTRACT

The use of biodegradable polymers for microencapsulation of naltrexone using techniques like solvent evaporation is the need of the hour. The naltrexone microspheres for the preparation of matrix devices will help to understand the microencapsulation. Nowadays, the emphasis is being laid on the development of controlled release dosage forms. Interest in this technology has been increasing steadily over the past few years. Although the oral administration of drugs is a widely accepted route of drug delivery, the bioavailability of drugs often varies as a result of gastrointestinal absorption, biodegradation by the first-pass effect. There are many ways of achieving long-term drug delivery of parental origin; biodegradable microspheres are one of the better means of controlling the release of the drug over a long time. Likewise, emulsions, stability on a long-term basis, and in suspensions, rheological changes during filling, injecting, and storage possess a limiting factor. The extent of release rate in these systems cannot be tailor-made to the needs of the patient. Injectables formulations based on biodegradable microspheres can overcome these problems and can control the release of the drug over a predetermined period. In the order of days to weeks and even to the months. The effect of different process parameters, such as drug/polymer ratio and stirring rate during the preparation of microspheres, on the morphology, size distribution, and in vitro drug release of microspheres. The review mainly covers various molecules encapsulated in biodegradable microspheres for parenteral delivery.

Keywords: Biodegradable Microspheres, Naltrexone, polymers.

1. INTRODUCTION

Microspheres are characteristically free-flowing powders consisting of proteins or synthetic polymers, which are biodegradable and ideally having a particle size less than 200 µm [1] and which can be injected by 18 or 20 number needle [2]. The drug absorption and side effects due to irritating drugs against the gastrointestinal mucosa are improved because the biodegradable microsphere is made up

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of small particle size < 200 µm which are widely distributed throughout the gastrointestinal tract [3].

Presently more drug therapies are available based on the types of drugs used with different formulations, fabrications conditions, and release kinetics. There is no single polymer that can satisfy all the requirements. Over the past few decades, there have been tremendous advances in the area of biodegradable copolymers. Polymers first developed in the search for biodegradable suture materials have been proven to be useful and successful for long-term drug delivery applications. As per the literature majority of biodegradable polymers studied are belonging to the polyester family, which includes polyglycolide and polylactides. The other degradable polymers such as polyorthoesters, polyanhydrides and polyphosphazenes are also used.

The drug namely naltrexone is an opiate antagonist used mainly as an adjunct to prevent relapse in detoxified opioid-dependent patients. It is currently given as oral tablets or capsules in a daily dose of 50 mg [4]. Naltrexone is orally active with a relatively short half-life and subject to extensive hepatic first-pass metabolism Naltrexone provides no euphoric effects, and there are no observable pharmacological consequences when a patient discontinues the drug [5]. The naltrexone treatment to be effective a sufficient level of the drug concentration must be maintained. As per the literature, the minimum effective concentration of naltrexone for the treatment of opiate addiction is estimated may be in the range of 0.5 to 1.0 ng/mL [6]. Treatment options for heroin addiction have long been dependent on three main alternatives namely detoxification, opioid agonists (i.e. methadone), and partial agonists (i.e. buprenorphine) maintenance treatment, and oral naltrexone. Detoxification followed by longterm residential treatment was found to cause some reduction in drug use but suffered from problems such as lack of retention in treatment and risk of overdose upon discharge [7].

As regards alcohol abuse, detoxification, non-pharmacological (psychosocial) treatment methods, and pharmacotherapy have not been very effective. Disulfiram (Antabuse®), Naltrexone (Revia®), and calcium acetylhomotaurinate (Acamprosate®) are the three major oral pharmacotherapies used in the treatment of alcoholism. The development of long-acting depot formulations of naltrexone has led to improved results such as increased bioavailability and efficacy of treatment and is considered as a solution to the problem of noncompliance and extensive first-pass metabolism associated with oral naltrexone. Newer formulations of sustained-release naltrexone have been providing more promising results ex. Injectable formulations of naltrexone, [8]. According to the study conducted by Depotrex® was safe, effective, and well-tolerated in opioid abusers who were not seeking treatment for their drug use [9].

An ideal sustained-release parenteral drug delivery system or device of naltrexone must possess the following characteristics such as:

- ✓ Be Easy To Inject or Implant
- ✓ Be Pharmaceutically Acceptable
- ✓ Not Cause Adverse Tissue Reaction
- ✓ Give Relatively Constant Drug Release
- ✓ Biodegrade

According to Sahil [10] an Ideal microsphere must possess specific properties and also described that the preparation of microspheres should satisfy certain criteria:

1. The ability to incorporate reasonably high concentrations of the drug
2. Stability of the preparation after synthesis with a clinically acceptable shelf life
3. Controlled particle size and dispersibility in aqueous vehicles for injectables.
4. Biocompatibility with a controlled biodegradability
5. Susceptibility to chemical modification
6. Control of content release
7. Increase therapeutic efficiency
8. Reduction of toxicity
9. Sterilizability
10. Bioreabsorbability

Among the various approaches to deliver macromolecules parenterally, biodegradable microsphere systems are the most commercially successful. The most crucial factor in the design of injectable microspheres is the choice of an appropriate biodegradable polymer. The release of the drug molecule from biodegradable microspheres is controlled by diffusion through the polymer matrix and polymer degradation (Figure 1).

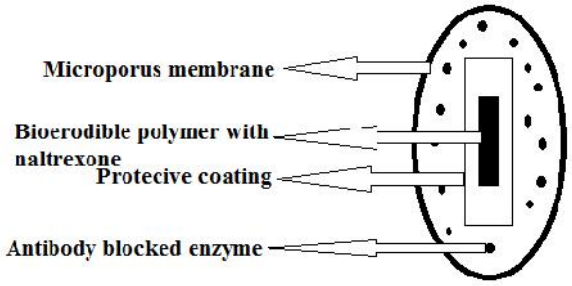

Fig 1: The diagrammatic representation of triggered drug delivery system of naltrexone embedded with biodegradable microsphere

The nature of the polymer, such as the composition of copolymer ratios, polymer crystallinities, glass-transition temperature, and hydrophilicity plays a critical role in the release process. Eventually, the microspheres structure, intrinsic polymer properties, core solubility, polymer hydrophilicity, and polymer molecular weight influence the drug-release kinetics, the possible mechanisms of drug release from microsphere are as follows: initial release from the surface, release through the pores, and diffusion through

the intact polymer barrier, diffusion through a water-swollen barrier, polymer erosion, and bulk degradation.

All these mechanisms together play a part in the release process [11]. Another intensively studied polymeric injectables depot system is an *in-situ*-forming implant system. *In situ*-forming implant systems are made of biodegradable products, which can be injected *via* a syringe into the body, and once injected, congeal to form a solid biodegradable implant. This method has been designed as Atrigel technology (QLT, Vancouver, Canada), which used as a drug-carrier system for Eligard [Table-1].

Table 1: The lists of commercially available drugs injectables of sustain release delivery system with indications and origin.

Drug	Brand name	Administration	Dosing frequency	Indications	Company	Country/ Region
Oil-based injections						
Haloperidol decanoate	Haloperidol decanoate	IM	once a month	Schizophrenia	Ortho-McNeil Pharm	UIS
Flupenthoxol decanoate	Flupenthoxol depot	IM	Every 2-4 weeks	Schizophrenia	Lundbeck	Europe
Fluphenazine decanoate	Fluphenazine decanoate	IM	Every 2-4 weeks	Schizophrenia	APP Pharm	US
Fluphenazine decanoate	Modecate	IM	Every 2-5 weeks	Schizophrenia	sanofi-aventis	Europe
Zuclopenthixol decanoate	Clopixol Depot	IM	Every 2-4 weeks	Schizophrenia	Lundbeck	Europe
Pipothiazine palmitate	Piportil depot	IM	Every 4 weeks	Schizophrenia	sanofi-aventis	Europe
Testosterone enanthate	Delatestryl	IM	Every 2-4 weeks	Hormone therapy	Endo pharma	US
Estradiol cypionate	Depo-Estradiol	IM	Every 3-4 weeks	Hormone therapy	pfizer	US
Injectable Drug suspensions						
Pallperidone palmitate	Invega Sustenna	IM	once a month	Schizophrenia	Janssen	US
Olanzapine	Zyprexa Relprevv	IM	Every 2-4 weeks	Schizophrenia	Eli Lilly	US
Medroxyprogesterone acetate	Depo-Provera	IM	Every 3 month	Hormone therapy	pfizer	US
Medroxyprogesterone acetate	Depo-Subq Provera 104	SC	Every 3 month	Hormone therapy	pfizer	US
Supersaturated drug solution						
Lanreotide acetate	Somatuline Depot	deep SC	once a month	Acromegaly	Tercica	US
Microspheres						
Risperidone	Risperdal Consta	IM	every 2 weeks	Schizophrenia	Janssen	US
Naltrexone	Vivitrol	IM	once a month	Alcohol dependence	Alkermes	US
Octreotide acetate	Sandostatin LAR Depot	IM	Every 4 weeks	Acromegaly	ipsen	Europe

2. BIODEGRADABLE POLYMERS AS DRUG CARRIERS

A polymer is a large molecule composed of many smaller units called monomers that are bonded together. In addition to eliminating the necessity of removal, the five key advantages [12] that polymeric drug delivery products can offer are;

1. Localized delivery of the drug,
2. Sustained delivery of the drug,
3. Stabilization of the drug,
4. Release rate which is less dependent on the drug properties and
5. Steadier release rate with time.

In diffusion-controlled systems, the release rate typically declines with time. On the other hand, a biodegradable system may yield a constant release even with a simple monolithic device if matrix degradation can compensate for this decline, perhaps with an increase of drug permeability. Various limiting factors will affect the biodegradation of polymers (Table 2).

Table: 2 List of factors affecting biodegradation of polymers

S.No	Factor
1.	Chemical structure and composition.
2.	Distribution of repeat units in multimers.
3.	Presents of ionic groups.
4.	Presence of unexpected units or chain defects.
5.	Conꝼguration structure.
6.	Molecular weight and Molecular weight distribution.
7.	Morphology-amorphous/semicrystalline, microstructures, residual stresses.
8.	Presence of low-molecular-weight compounds.
9.	Processing conditions.
10.	Annealing.
11.	Sterilization process.
12.	Storage history.
13.	Shape.
14.	Site of implantation. Adsorbed and absorbed compounds like water, lipids, and ions. Physicochemical factors like ion exchange, ionic strength, and pH.
15.	Physical factors like shape and size changes, variations of diffusion coefficients, mechanical stresses, stress- and solvent-induced cracking.
16.	Mechanism of hydrolysis

3. DISCUSSION

The naltrexone preparations with long-acting microspheres are a major challenge in the current scenario. There are mainly two possible processes i) Solvent Extraction and ii) Solvent Evaporation Process. The challenges were,

i) Acceptable level of yield in the solvent extraction process,
ii) Lower % Entrapment of Drug,
iii) Acceptable morphology of the microspheres,
iv) Acceptable level of Residual Solvents (i.e. Methylene Chloride)

It is evident from the literature that pore-forming agents can contribute to lessening the level of methylene chloride in microsphere by creating the channels. It is also clear that using ethanol as the last wash to extract out the methylene chloride from the microsphere. Several studies have shown that drug release from matrix devices prepared by compression of naltrexone microspheres is much slower than that of microspheres. By applying a higher compression rate

for tablets will result in lower drug release from matrix devices. This will not only suggest the use of biodegradable microspheres thereby regulating different variables with desired release profiles of naltrexone that can be achieved using a matrix device.

The list of Biodegradable Polymers based on different technologies employed and products [13-17] are tabulated Table 3.

Table 3: Showing the list of biodegradable polymers of different commercially available drugs

Zoladex® (AstraZeneca)	The encapsulated drug is released by a combination of diffusion and erosion-controlled mechanisms. However, because the delivery device is monolithic, heterogeneous hydrolysis is thought to be the predominant erosion process.
Lupron Depot®	The first FDA-cleared PLGA product was the drug-delivery system (TAP Pharmaceutical Inc.). Lupron Depot® is a microsphere formulation based on the biodegradable polymers of polylactic acid (PLA) and poly(lactic/glycolic acid)
Gliadel® Wafer	Gliadel wafer was the first new treatment of this kind of brain cancer introduced in over 20 years. Gliadel wafer provides localized delivery of chemotherapy directly to the site of the tumor (as an adjunct therapy) and is the only FDA approved brain cancer treatment.
Alzamer®	The Atrigel® system is protected by more than 140 patents in the United States and the rest of the world. Seven products have already been approved by the FDA using the Atrigel technology like Eligard® and the Atridox® [18-21].

Current drug delivery systems, using non-biodegradable inserts or implants, can provide long-term delivery of beneficial molecules, but there is an advantage, the researchers suggested, to the use of biodegradable microspheres for the delivery to provide "long-term sustained drug release," and "safe dosing of drugs with pharmacokinetics issues such as a rapid systemic clearance or a narrow therapeutic window," as per Bravo-Osuna [22]. By incorporating drugs in biodegradable polymers, dosage forms that release the drug over a prolonged length of time can be prepared in a variety of shapes and sizes [23, 24]. No surgical procedures are needed after completion of the dosage regime since the remaining polymer will degrade and get cleared by the body. As a result, biodegradable polymers offer a novel approach for developing sustained release drug delivery systems that are simple and convenient to the patient. Biodegradable microspheres allow, for multi-loaded delivery systems which help reduce injections while delivering multiple drugs "in a controlled fashion" as part of a combined-therapy approach to various disease.

4. CONCLUSION

A novel tailor-made drug delivery system with biodegradable copolymers with desirable functional groups is needed for researchers whose envision is to use not only for innovative drug delivery systems but also as potential linings for artificial organs, substrates for cell growth, chemical reactors, agents in drug targeting and immunological testing. The most exciting opportunities in controlled drug delivery lie in the arena of responsive drug delivery systems. Shortly, we can expect that device designers and physicians will have a wealth of products using biodegradable polymers that will help speedy patient recovery and eliminate follow-up surgeries. All things considered, total or near-total use of biodegradable polymers is within reach shortly.

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