Review Article

An Update on Biodegradable Microspheres Loaded with Naltrexone

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ARTICLE INFO

Received: 04 Mar 2020
Accepted: 18 Apr 2020

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. Injectable 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
Acetylhomotaurinate (Acamprosate®), Naltrexone (Revia®), and calcium phosphate have not been very effective. Disulfiram pharmacological (psychosocial) treatment methods, and As regards alcohol abuse, detoxification, non-pharmacological treatment methods, and detoxification followed by longterm 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].

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 dispersility 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).

\[ \text{Fig 1: The diagrammatic representation of triggered drug delivery system of naltrexone embedded with biodegradable microsphere} \]

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].

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

| Drug               | Brand name       | Admins  | Dosing frequency | Indications       | Company            | Region     |
|--------------------|------------------|---------|------------------|-------------------|--------------------|------------|
| Haloperidol        | Haloperidol      | M       | once a month     | Schizophrenia     | Ortho-McNeil Pharm | US         |
| Flupenthixol       | Flupenthixol     | M       | Every 2-4 weeks  | Schizophrenia     | Lundbeck           | Europe     |
| Fluphenazine       | Fluphenazine     | M       | Every 2-4 weeks  | Schizophrenia     | APP Pharm          | US         |
| Fluphenazine       | Fluphenazine     | M       | Every 2-5 weeks  | Schizophrenia     | Sanofi              | Europe     |
| Zuclopentol        | Lipoxol          | M       | Every 2-4 weeks  | Schizophrenia     | Sanofi              | Europe     |
| Pipothiazine       | Sportil depot    | M       | Every 4 weeks    | Schizophrenia     | Endo                | US         |
| Testosteron        | Delatestryl      | M       | Every 2-4 weeks  | Androgen therapy  | pfizer              | US         |
| Estradiol          | Depo-Estradiol   | M       | Every 3-4 weeks  | Androgen therapy  | pfizer              | US         |

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.   | Conformation 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

| Polymers        | Description                                                                                                                                                                                                 |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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. |
| Lupon Depot®    | The first FDA-cleared PLGA product was the drug-delivery system (TAP Pharmaceutical Inc.). Lupon Depot® is a microsphere formulation based on the biodegradable polymers of poly(lactic 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.

5. ACKNOWLEDGEMENTS

The authors are thankful to the Head Department of Pharmaceutics and the authors are also thankful to the Principal of College for support and encouragement.

6. REFERENCES

1. Vyas S P, Khar R K, 1990. Targeted and Controlled Drug Delivery. 7th Edn., Vallabh Prakashan, New Delhi, India, pp: 418.
2. Brahmankar, D.M. and S.B. Jaiswal, 2009. Biopharmaceutics and Pharmacokinetics. 2nd Edn., Vallabh Prakashan, New Delhi, India, Pages: 488.
3. Prasanth V V, Mou A C, Mathew S T, Mathapan R, Microspheres-An overview. Int J Res Pharm Biomed Sci 2011; 2: 332-338.
4. Mathiowitz E. Encyclopedia of controlled drug delivery. New York; 1999. p. 570.
5. Heller J. Controlled drug release from poly (orthoesters)-A surface eroding polymer. J Control Release 1985; 2: 167-77.
6. Tamada J, Langer R, The development of polyanhydrides for drug delivery applications. J Biomater Sci Polym Ed 1992;3:315-53.
7. Leong KW, Brott BC, Langer R. Bioerodible polyhydrides as drug-carrier matrixes. J Biomed Mater Res 1985;19:941-55.
8. Muthushamy K, Shibi KP, Ravi TK. Preparation and evaluation of albumin-chitosan microsphere containing theophylline. Indian J Pharm Sci 2004;66:245-8.
9. Heller J. Chemically self-regulated drug delivery systems. J Control Release 1988;8:111-10.
10. Sahil, K., M. Akanksha, S. Premjeet, A. Bilandi and B. Kapoor, 2011. Microsphere: A review. Int J Res Pharm Chem 2011; 1: 1184-98.
11. Roy H, Chakraborty AK, Nayak BS, Bhanja S, Mishra SR, Ellaiah P. Design and in vitro evaluation of sustained release matrix tablets of complexed Nicardipine Hydrochloride. Int J Pharm Pharm Sci 2010; 2:128-32.
12. Vainionpaa S, Rokkanen P, Tormala P. Surgical application of biodegradable polymers in human tissue. Prog Polym Sci 1989; 14:679-716.
13. Leong KW. Biodegradable polymers as drug delivery systems. *In: Tarcha PJ, editors. Polymers for Controlled Drug Delivery. CRC Press: Boca Raton; 1991. p. 142.*

14. Sah H, Chien YW, *In: Hillery AM, Lloyd AW, Swarbrick J, editors. Drug delivery and targeting for pharmacist and pharmaceutical scientist. Taylor and Francis: London; 2001. p. 101.*

15. Brem H, Gabikian P. Biodegradable polymer implants to treat brain tumors. *J Control Release 2001;74:63-67.*

16. Dang WB, Daviau T, Ying P, Zhao Y, Nowotnik D, Clow CS, *et al.* Effects of Gliadel wafer initial molecular weight on the erosion of wafer and release of BCNU. *J Control Release 1996;42:83-92.*

17. Pitt CG, Poly (*ε*-caprolactone) and its copolymers. *In: Chasin M, Langer R, editors. Biodegradable polymers as drug delivery systems. Marcel Dekker: New York; 1990. p. 71.*

18. Spiegel AJ, Noseworthy MM. Use of non-aqueous solvents in parenteral products. *J Pharm Sci 1963;52:917-27.*

19. Polson AM, Dunn RL, Fulfs JC, Godowski KC, Polson AP, Southard GL, *et al.* Periodontal pocket treatment with subgingival doxycycline from a biodegradable system. *J Dental Res 1993;72:360-4.*

20. Polson A, Garrett S, Stoller N, Bandt C, Haner P, Killoy W, *et al.* Multicenter comparative evaluation of subgingivally delivered sanguinarine and doxycycline in the treatment of periodontitis, II: Clinical results. *J Periodontol 1997;68:119-26.*

21. Ravivarapu HB, Moyer KL, Dunn RL. Parameters affecting the efficacy of a sustained release polymeric implant of leuprolide. *Int J Pharm 2000;194:181-91.*

22. Dunn RL, Moyer KL, Ravivarapu HB. Sustained activity and release of leuprolide acetate from an in situ forming polymeric implant of leuprolide acetate. *J Pharm Sci 2000;89:732-41.*

23. Roy H, Brahma CK, Kumar R, Nandi S. Formulation of saquinavir mesylate loaded microparticle by counterion induced aggregation method: Approach by hyperosmotic technique. *Drug Invent Today 2013;5:259-66.*

24. Bhanja S, Sudhakar M, Neelima V, Roy H. Development and evaluation of mucoadhesive microspheres of Irbesartan. *Int J Pharm Res Health Sci. 2013;1:17-26.*

**Conflict of Interest:** None

**Source of Funding:** Nil