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Review

Evolution of implantable and insertable drug delivery systems

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ABSTRACT

The paper describes the development of implantable and insertable drug delivery systems (IDDS) from their early stage in the 1960s until the current stage in the 2010s. It gives a detailed summary of non-degradable and biodegradable systems and their applications in different areas such as vascular disease treatment, birth control, cancer treatment, and eye disease treatment. It also describes the development of various implantable pump systems and some other atypical IDDS, the challenges and the future of IDDS.

Contents

Abbreviations: BVS, bioabsorbable vascular solutions; CoCr, cobalt/chromium alloy; DES, drug eluting stent; PAE, poly(anhydride ester); IDDS, implantable drug delivery systems; PBMA, poly(n-butyl methacrylate); PC, a copolymer composed of 2-methacryloyloxyethyl phosphorylcholine, lauryl methacrylate, hydroxypropyl methacrylate, and trimethoxysilylpropyl meth-acrylate; PEVA, poly(ethylene-co-vinyl acetate); PLA, poly(D,L-lactic acid); PLGA, poly(lactic-co-glycolic acid); PLLA, poly(L-lactic acid); PTFE, polytetrafluoroethylene; PVDF, poly(vinylidene fluoride); PVDF·HFP, poly(vinylidene fluoride-*co*-hexafluoropropylene); SIS, poly(b-styrene-b-isobutylene-b-styrene); SS, stainless steel.

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1. Introduction

Implantable drug delivery systems (IDDS) originated in the 1960s when silicones were used to prolong the effectiveness of a therapy. From this beginning, the potential was recognized that this mode of delivery could overcome the problems associated with oral administration of specific therapies. Despite considerable effort since the beginning, initial progress has been slow to commercialize safe and effective implants. Some of the major hurdles that needed to be overcome were stability, reproducibility, toxicity, lack of biocompatibility, carcinogenicity, lack of compatibility between drug and carrier leading to burst release or shutdown, and physician and patient acceptability. However, the appeal, activity and approval of IDDS accelerated when the silicone-based device Norplant® was approved by the FDA in 1990. Good evidence is the proliferation of academic and industrial research, the increase in the number of published articles and the increased number of commercialized products.

Classification of IDDS is difficult because there will be exceptions and hybrids that may fall under more than one category. When the term IDDS is used in this article, as much as possible, it will use the classifications that are historically used: drug implants and implantable pumps that contain and deliver drug. Drug implants can be further subdivided into non-degradable and degradable systems.

Additionally, it was recognized that therapeutic opportunities existed for insertable drug delivery systems that could be inserted into a specific body location and later easily removed when the systems were exhausted. Examples of such systems include intraocular, vaginal and intrauterine inserts. Therefore, the term IDDS used in this article would also refer to insertable drug delivery system. The IDDS topic is vast in scope, so for conciseness some modalities, such as hydrogels and depot injections are not covered in this review.

2. History

The concept and research of implantable drug delivery systems started with Deansby and Parkes who described in 1938 the effect of subcutaneous implantation of compressed pellets of crystalline estrone upon castrated male chickens. Implantable formulations with drug release rates controlled by a polymeric membrane were pioneered by Folkman and Long in the 1960s [1] who investigated the use of silicone rubber (Silastic®) as a method for prolonged systemic drug administration. Silicone rubber capsules containing a variety of different drugs were prepared and implanted into the cardiac muscle of dogs. These rudimentary IDDS succeeded in the controlled release of many different classes of drugs and were shown to be biocompatible.

Since these early days, the research using IDDS has proliferated with the use of many different carriers, biostable and bioerodible, a wide variety of different classes of drugs, many different implantation techniques and implantation sites. A vast number of specific reviews, more comprehensive reviews and specific articles on very specific implant types can be found in the literature originating with veterinary applications and quickly followed by human therapies [2–9]. These references will provide the reader with an appreciation of both the richness of the history as well as the diversity of biomaterials and class of drugs examined.

3. Rationale

To mitigate or avoid the problems associated with oral (liquid, powder, gel or tablet) dosage form administration, other modes of delivery evolved. Among alternative modes are implants and inserts which have progressed into controlled release IDDS. Numerous design approaches have been pursued depending upon the specific drug therapy under development [10]. The primary end-goal of any design approach is to improve safety and efficacy by carefully controlling dose and dose rate at the desired site.

Some of the issues with oral dosage forms that can be overcome with IDDS are described in Table 1. Benefits of IDDS are described in Table 2 and potential drawbacks are summarized in Table 3.

Despite all the hurdles that need to be overcome, the examples of IDDS provided in the next sections indicate that they can be manufactured cost-effectively and administered to a desired site to achieve the goal of reliability, safety, efficacy and patient acceptance. The examples that are provided are a small representation and not comprehensive since it is impossible to cover all the approved applications and the ever-increasing amount of research within universities and industry. More expansive reviews can be found within this area, both past and more current [2–4,11–13].

4. Implantable drug delivery systems

Implantable drug delivery systems include non-degradable and degradable systems. For non-degradable and degradable IDDS, most key components are normally produced from polymeric materials. In addition to drug delivery, the components may have additional functions, such as structural support and improvement of biocompatibility or stability. Some of the key polymers that have been approved for IDDS are listed in Table 4 [14]. Biomedical applications other than drug delivery are also included.

4.1. Non-degradable system and its applications

Several types of non-degradable implants are presently commercially available, but by far the most common are membrane enclosed reservoir and matrix controlled systems. Matrix systems are also called monolithic systems. The material used in all these systems is typically a polymer with a long history of being evaluated both pre-clinically and clinically. Some of the most common polymers used are silicones, acrylates and their copolymers, ethylene vinyl acetate copolymers (PEVA), vinylidene fluoride copolymers, and urethanes.

In this section, three applications will be highlighted. They include Norplant®, Implanon®, and drug eluting stents with a non-degradable coating. Space limitations preclude including additional applications, therefore the reader is referred to the review by Dash [11] as a good starting point to obtain additional information.

4.1.1. Application of non-degradable system for birth control

The most common reservoir non-degradable system is Norplant®. This IDDS was developed and trademarked by the Population Council in 1980, introduced in certain countries worldwide in 1983, approved by the USFDA in December 1990, and was marketed in the US starting February 1991. Norplant® is a 5-year contraceptive system consisting of the hormone levonorgestrel (LNG) encapsulated into six thin, flexible silicone capsules (Silastic tubing) that are implanted subcutaneously on the inside of a woman's upper arm as seen in Fig. 1A and B (Population Council, 1990). So far, this device has been approved in over 60 countries.

Later in the US, the 6-rod Norplant® proved to be cumbersome and became associated with removal problems due to operator inexperience