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Review

In situ forming implants — an attractive formulation principle for parenteral depot formulations

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ABSTRACT

In the area of parenteral controlled release formulations, in situ forming implants (ISFI) are attractive alternatives to preformed implants and microparticles. ISFI avoid the use of large needles or microsurgery and they can be manufactured in simple steps with a low requirement of equipment and processes. They are injected as low viscous solutions and transform in the body to a gel or solid depot. Different triggers can be used to stimulate this transformation: (1) in situ cross-linking, (2) in situ solidifying organogels, and (3) in situ phase separation. The review discusses the principles and the pros and cons of each strategy. It also gives examples of clinically used products or systems which are currently in clinical trials.

Although the principle of ISFI is so attractive, key issues remain to be solved. They include (i) variability of the implant shape and structure, (ii) avoidance of burst release during implant formation, and (iii) toxicity issues. Unfortunately, until now our knowledge concerning the detailed processes of the implant formation is still very limited. This is due to the fact that the processes of implant formation and degradation, drug release and tissue response are complex, heterogeneous, interconnected and not easy to follow, especially in vivo. Despite this statement, many efforts are made in industry and academia to improve current approaches. New materials and approaches enter the preclinical and clinical phases and one can be sure, that ISFI will gain further clinical importance within the next years.

Contents

1. Introduction

Due to the steadily increasing number of biotechnology-based drugs and compounds which cannot be administered via the oral route, parenteral drug delivery systems received significant research interest in the last two decades. Although intensive efforts have been devoted to alternative application routes (e.g. pulmonal, transdermal, oral, nasal), poor and highly variable absorption remains as the key issue of the alternative administration routes. In addition, further problems may arise (e.g. increased antibody formation, impact of smoking, cough or food…). Significant progress has also been made to tackle the main concerns of parenteral administration:

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the safety and the pain. Parenteral delivery systems can be designed to provide flexible delivery characteristics. Many drugs combine a high activity with a short half-life. Parenteral depot formulations are therefore a formulation option to avoid a constant infusion or a very high frequency of injections. Depot formulations with release kinetics from days, over weeks, months to even years have been developed [1]. Thereby parenteral depot systems enhance patient compliance by diminishing the frequency of applications. Furthermore, these depot formulations can minimize undesirable side effects caused by fluctuating drug blood levels which are typical of immediate release products [1]. In the case of localized parenteral delivery systems that allow for the drug to deposit directly at the site of action, the drug dosage and therefore the system toxicity can be reduced. Typical applications of parenteral depot systems include the treatment of hormone sensitive breast or prostate cancers (with GnrH agonists or antagonists), local chemotherapy, the local treatment of infections or the local delivery to the eye.

Various types of parenteral dosage forms are available, such as solutions, emulsions [2], liposomes [3], micelles [4], implants [5], microparticles [6], nanoparticles and nanocapsules [7]. However, only implants and microparticles gained importance as controlled release systems [8]. Preformed implants are made by melt extrusion administered subcutaneously by a special application device or through a larger needle. In the case of non-biodegradable systems (e.g. Vantas®, Viadur®), the implants have to be removed after the release periods. In the case of biodegradable materials, the polymers degrade during and after the release processes to monomers which are metabolized and excreted. Typical preformed subcutaneous implants are 10 mm long and of cylindrical shape with a diameter of 1 mm (e.g. Zoladex® and generic formulations for the treatment of hormone sensitive breast and prostate cancer). They are injected through a 16 gauge needle (outer diameter 1.65 mm). Smaller implants are used for the treatment of eye diseases [9]. For subcutaneous implants, also larger sizes have been commercialized. The non-biodegradable one year implant Vantas® has a length of 35 mm and a thickness of 3 mm. Preformed implants permit a rapid administration, however, the large diameters of the injection needles cause fear and discomfort for the patient. Microparticulate systems can be given to patients with smaller needles, which is more comfortable to the patient. Most widely, emulsion–solvent evaporation, spray drying and phase separation technologies are used for their manufacturing. Supercritical techniques will certainly become more important within the next years [10]. Microparticles are often filled in two chamber syringes which separate the dispersion medium from the particles to prevent premature degradation. The disadvantages of microparticulate systems include complex and more expensive production processes and – compared to preformed implants – a more time consuming and difficult administration procedure with the danger of incomplete dispersion of the microparticles, syringe clogging and the administration of an incomplete dose. Due to the drawbacks of preformed implants and microparticles, large efforts have been made to develop alternative depot systems with the following characteristics: (i) rapid, painless and easy administration through small needle sizes, and (ii) easy manufacturing at low costs. As a result, an increasing number of injectable and biodegradable in situ forming systems have been developed as alternatives [11–13]. Prior to injection the in situ forming systems represent a low viscous and injectable system. Once administered these low viscous polymeric formulation solidify into a semi-solid or solid depot. Thus it turns into a 'solid' dosage form as it is illustrated in Fig. 1 for a thermally-induced gelling system.

Biodegradable implants formed from injectable fluids have one general advantage compared to pre-shaped parenteral depot systems. From the patient's point of view, the application of in situ forming implants (ISFI) is less invasive and so less painful. An improved patient compliance and comfort can be achieved by the avoidance of invasive techniques in the implantation and removal of the implants. These characteristics encouraged many researchers to investigate their use

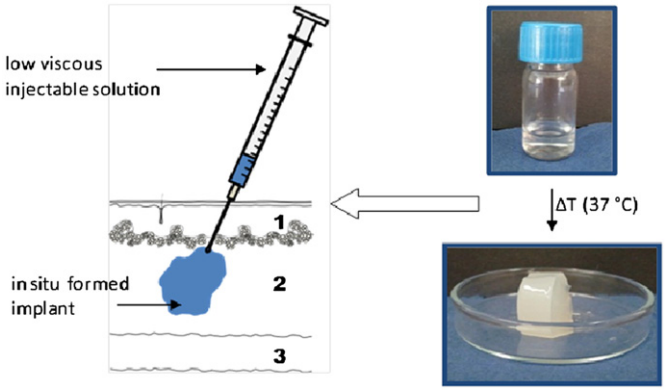

Fig. 1. Example of an in situ forming thermally-induced gelling system (1 epidermis and dermis, 2 subcutis, 3 muscle).

for various purposes. ISFI have been investigated for controlled drug delivery in systemic treatments as well as localized therapies. In addition ISFI have found applications in tissue engineering, three dimensional cell culturing, cell transplantation, or for orthopedic and dental administrations [12–15].

In situ forming systems can be classified according to their mechanisms of implant formation into (Fig. 2):

- in situ cross-linked polymer systems
- in situ solidifying organogels and
- in situ phase separation systems.

2. In situ cross-linked systems

In situ forming cross-linked polymer networks can be achieved by photo-initiated polymerization [16,17], chemical cross-linking with cross-linking agents [18] or physical cross-linking [19] of specific monomers. There are several issues that must be considered. In particular the demands for in vivo reaction conditions are quite restricted, such as the need of non-toxic monomers, cross-linking agents and solvents, oxygen rich environments, narrow range of physiologically acceptable temperatures and suitable rates of rapid polymerization [12].

2.1. Photo-initiated polymerized systems

Photo-initiated polymerization fulfills many of the requirements for in vivo polymerization. The initial materials are liquid solutions, which can be easily placed. Afterward the rapid polymerization at

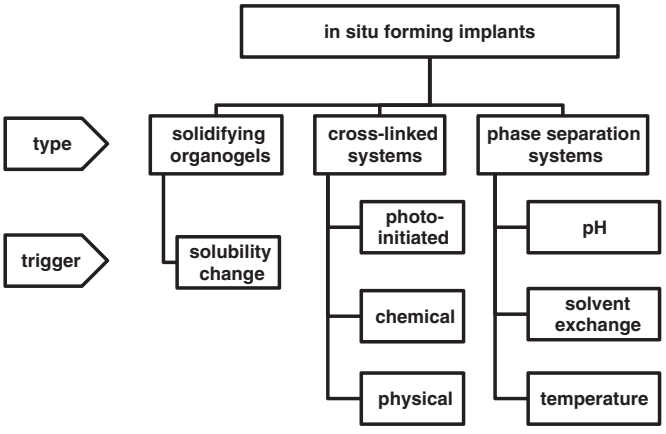

Fig. 2. Overview of in situ forming implant technologies. Modified from Refs. [12,13].