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Review

Solvent induced phase inversion-based *in situ* forming controlled release drug delivery implants

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ABSTRACT

In situ forming (ISF) drug delivery implants have gained tremendous levels of interest over the last few decades. This is due to their wide range of biomedical applications such as in tissue engineering, cell encapsulation, microfluidics, bioengineering and drug delivery. Drug delivery implants forming upon injection has shown a range of advantages which include localized drug delivery, easy and less invasive application, sustained drug action, ability to tailor drug delivery, reduction in side effects associated with systemic delivery and also improved patient compliance and comfort. Different factors such as temperature, pH, ions, and exchange of solvents are involved in *in situ* implant formation. This review especially focuses on ISF implants that are formed through solvent induced phase inversion (SPI) technique. The article critically reviews and compares a wide range of polymers, solvents, and co-solvents that have been used in SPI implant preparation for control release of a range of drug molecules. Major drawback of SPI systems has been their high burst release. In this regard, the article exhaustively discusses factors that affect the burst release and different modification strategies that has been utilised to reduce the burst effect from these implants. Performance and controversial issues associated with the use of different biocompatible solvents in SPI systems is also discussed. Biodegradation, formulation stability, methods of characterisation and sterilisation techniques of SPI systems is comprehensively reviewed. Furthermore, the review also examines current SPI-based marketed products, their therapeutic application and associated clinical data. It also exemplifies the interest of multi-billion dollar pharma companies worldwide for further developments of SPI systems to a range of therapeutic applications. The authors believe that this will be the first review article that extensively investigate and discusses studies done to date on SPI systems. In so doing, this article will undoubtedly serve as an enlightening tool for the scientists working in the concerned area.

Contents

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1. Introduction

Controlled drug delivery systems are capable of regulating rate of drug delivery, maintaining drug concentration within the therapeutic range for prolong duration, and/or targeting the delivery of drug to a specific tissue. Of the many controlled drug release technologies, *in situ* forming (ISF) implant systems have risen in their popularity for a range of biomedical applications such as tissue repair, cell encapsulation, microfluidics, bioengineering and drug delivery [1]. The widespread interest in ISF systems can be attributed to a range of advantages which include site-specific action due to localized delivery, easy and less invasive application, extended delivery times, reduction in side effects associated with systemic delivery and also improved patient compliance and comfort [2,3]. Importantly, administration by this method allows the injection of a relatively low viscosity material into the body which then solidifies to form a semi-solid depot that controls the drug delivery to provide long-term therapeutic action [2]. Depending upon their mechanism of implant formation the ISF can be categorised into different types such as phase separation systems (*e.g.* thermoresponsive, solvent exchange and pH), crosslinked systems (*e.g.* photo-initiated, chemical and physical) and solidifying organogels (*e.g.* solubility change) [4,5]. Of the most commonly used ISF systems are the thermoresponsive, pH, ions, photocrosslinked and solvent induced phase inversion (SPI) implants. However, SPI based ISF implant technology has attracted worldwide interest among pharmaceutical/drug delivery companies, which led to the development of commercial therapeutic products for a wide range of clinical applications. Importantly, SPI mode of ISF implants has a number of advantages over its counterparts *e.g.* need for critical temperature (for thermoresponsive ISF implants), presence of ions (for charge sensitive ISF implants), and change in pH (for pH sensitive ISF implants) is not required to trigger SPI implant formation. Therefore, considering the growing interest in SPI type ISF drug delivery systems, this review article critically assessed the literature available in relation to SPI implant technology.

SPI system comprises of a water insoluble polymer that is dissolved in an organic, water-miscible, biocompatible solvent, into which a drug is incorporated. Once this system is introduced into an aqueous environment, the organic solvent dissipates out of the system and the water ingresses *via* diffusion [6]. This exchange of solvents results in sol-to-gel transformation causing polymer precipitation that leads to implant formation, which in turn controls the rate of drug release (Fig. 1). SPI is known by a number of different terms throughout literature, namely, non-solvent induced phase separation (NIPS) [7], solvent removal [2,3], solvent exchange [8], liquid–liquid phase separation [9], solvent/non-solvent exchange [10], solvent-removal precipitation [11] and polymer precipitation [11,12]. SPI systems first came into existence through the work of Richard Dunn and colleagues at the Southern Research Institute in the 1990s [13]. In fact the Southern Research Institute carried some of the earliest work out in the 1980s, which focused on the development of injectable SPI depot systems for the treatment of periodontal disease with chemotherapeutics [14,15].

2. Polymers used in SPI systems

A wide number of polymers for their potential to form SPI-based drug delivery systems have been investigated [16]. Polymer selection should consider stability, both in terms of chemical and physical stability, that is required for the production of polymer-based drug delivery systems on industrial scale [17]. To a large extent, synthetic biodegradable and biocompatible polymers were considered for use in SPI systems [2,4,18,19]. The characteristic feature of these polymers is their water insolubility (*i.e.* hydrophobic nature) that allows for polymer precipitation and formation of a solid implant [2,20,3,21].

2.1. Polymeric carriers

Synthetic, water insoluble, biodegradable and/or non-biodegradable polymers are commonly used in SPI drug delivery system. Non-biodegradable system requires invasive surgical interventions to remove the implant from the site of injection [22,23]. For example, the use of a non-biodegradable system in the treatment of vitreo-retinal diseases and subsequent invasive surgery (to remove the implant) has been linked with a number of serious side effects (*e.g.* cataract formation) [24–26]. On the contrary, biodegradable polymers have risen in popularity as the implant degrades to form non-toxic by-product's *e.g.* carbon dioxide and water [27]. Biodegradable polymers that are commonly used in SPI systems are from polyhydroxy acid, polyanhydride and polyorthoester families. Aliphatic esters from the poly-α-hydroxy acid family such as poly(glycolic acid) (PGA), poly(lactic acid) (PLA) and PLGA which is a co-polymer of PGA and PLA, are extremely popular [22,28]. Poly-ε-caprolactone (PCL) [29], poly(lactide-co-caprolactone) copolymer, poly(acrylic acid) (PAA) and its derivatives [30] such as poly(methacrylic acid)(PMA)–poly(ethylene glycol) (PEG) are also being investigated as potential SPI polymers [31].

PLA and PLGA have been the most popular polymers in SPI formulation. PLGA has a long history of use in biomedical applications and was

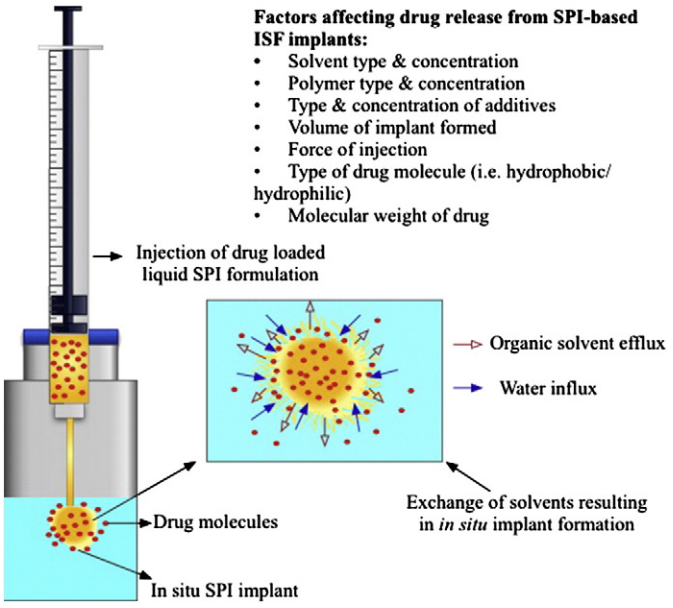

Fig. 1. Schematic representations of SPI implant formation, solvent exchange and drug delivery.