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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

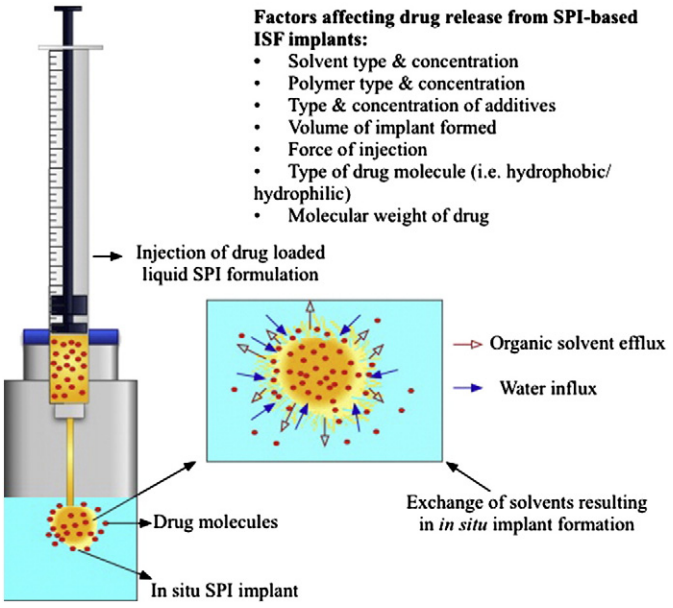

Fig. 1. Schematic representations of SPI implant formation, solvent exchange and drug delivery.

described in the earliest work completed by Dunn et al. [13]. It has been approved for parenteral use [32,33] by the US Food and Drug Administration (USFDA). It is prepared by polymerisation of lactic acid and glycolic acid monomers [34]. The glass transition temperatures (T_g) of PLGA copolymers are above physiological temperatures of 37 °C, which imparts a moderately rigid chain configuration and therefore the mechanical strength at ambient temperatures. Jamshidi et al. observed a decrease in T_g when the ratio of lactic acid monomers also decreased [35]. The availability of PLGA in different commercial grades such as lactide to glycolide ratio and molecular weight has also raised its popularity, as this can allow researchers to obtain different drug release profiles [32,34]. SPI-based implants, containing PLGA, have been used to deliver a wide range of molecules ranging from small hydrophilic and/or hydrophobic to large protein/peptide molecules such as bupivacaine [8], diltiazem [36], leuprolide acetate [37], human growth hormone [9], buserelin acetate [36], aspirin [38], naltrexone [39], fenretinide [40], thymosin alpha-1 [32] and risperidone [41]. Poly (caprolactone) (PCL) is another widely studied polymer but its popularity wane due to the rise in interest of PLGA and related polymers. PCL is a semi-crystalline polymer with a T_g of around −60 °C and a low melting point of 59–64 °C. The rate of PCL degradation is markedly slower than that of PLA, with the homopolymer taking up to 2 to 3 years to degrade [42]. Its use for extremely prolonged release implants is therefore ideal. This polymer is widely accepted as being non-toxic and so biocompatibility is not an issue [43]. Recently, Ueda et al. investigated the use of the linear, polyester polymer poly(propylene-fumarate) (PPF) (an alternative to poly-α-hydroxy acid family) in SPI systems. PPF was used to study *in vitro* release of fluocinolone acetonide (FA) intended for ocular drug delivery applications. A release period of up to 62 weeks was observed for the implants with an overall conclusion being drawn that PPF shows promise as a biocompatible polymer for use in SPI in ocular drug delivery [44].

However, PLGA, PLA, and PLA-PEG cause an accumulation of acidic degradation products generated during the hydrolysis and show a non-linear release profile, which is especially challenging for the delivery of hydrophilic macromolecules (*i.e.* peptides and proteins). To overcome this issues a collaborative research between Philipps-University of Marburg and Novartis Pharma AG led to the use of poly(ethylene carbonate) (PEC) polymer in SPI systems. PEC degrades through surface erosion, providing linear release profile. PEC containing SPI system has shown selective reduction in burst release of bovine serum albumin, which was dependent on the solvent type chosen [45].

Just recently, a research group based in Thailand has investigated a biodegradable copolymer ([poly(ε-caprolactone)-random-poly(D,L-lactide)]-*block*-poly(ethylene glycol)-*block*-[poly(ε-caprolactone)-random-poly(D,L-lactide)]), known as PLEC. It is obviously the copolymer of ε-caprolactone (CL) and D,L-lactide (LA). The basis behind the synthesis of this copolymer was to overcome the issue of low hydrophilicity of previously reported LA and CL copolymers; therefore PEG was introduced into the copolymer to improve this property. Combining this polymer with tetrahydrofurfuryl alcohol (GF), a biocompatible solvent that has been used to deliver drugs such as phenytoin and diazepam as well as proteins by injection [46,47], results in a polymer solution that solidifies upon injection into a tissue, even the brain. This group concluded that this material was a successful candidate for further investigations relating to the development of ISF [48].

2.2. Non-polymeric carriers

Recently biodegradable non-polymeric carrier has also been used for SPI based drug delivery such as sucrose acetate isobutyrate (SAIB). SAIB is produced through the esterification of sucrose with acetic anhydride and isobutyric anhydride, which produces a clear, very viscous liquid with a high molecular weight [49]. SAIB has been previously used as a food stabilizer but mixing it with small amounts (15–30%) of solvents such as NMP (N-Methylpyrrolidone), triacetin or ethanol, produces a low viscosity, injectable gel. Similar to the systems that incorporate polymers, once these SAIB formulations are injected into a tissue, the solvent diffuses out leaving a matrix that is both adhesive and viscous. The advantages associated with this system, are the low cost of materials in comparison to PLGA and the simplicity of manufacturing. There is however an appreciable burst release that occurs due to the lag-period between injection and formation of the implant [50].

3. Solvents used in SPI system

A SPI system uses solvents that are water miscible, biocompatible and organic in nature. Importantly, solvents should efficiently dissolve the polymer, and be miscible with water and bodily fluids. Polarity of the solvent should be such that at least 10% should be soluble in water [51] (Table 1). Solvent viscosity also plays an important role in SPI implant formation. For example, highly viscous solvents, combined with around 30% of polymer as well as drug, could pose difficulty when injecting *via* conventional needles. Therefore overall viscosity should be within the range that is syringeable. Formulations with a rate index of below one are those, which exhibit shear-thinning behaviour. This would therefore be beneficial as the application of force to inject the polymer formulation would exert a shear stress and therefore cause thinning of the material [52]. Solvent strength and its affinity for water direct the nature of phase inversion and implant formation. For example, solvent that has a high water affinity exhibits fast forming phase inversion (fPI) such as NMP [38,53,54] and DMSO [10,36,54]. Hydrophobic solvents exhibit slow forming phase inversion (sPI) such as triacetin [20,36,53] and ethylbenzoate [55,20]; this is further discussed in Section 4. Solvents that posses a water solubility of below 7% w/w have been shown to result in slower drug release due to a reduction in water uptake [16].

A number of other solvents have also been detailed in the literature such as glycofurol [33,57] and tetrahydrofuran [2] but studies on these solvents are limited. The mixture of BA and BB can also be used to obtain desired release profile [41,58]. However, SPI systems most commonly use DMSO and NMP solvents preferentially due to their pharmaceutical precedence over other solvents [59]. Schoenhammer et al. have described the use of poly(ethylene glycol) 500 dimethylether (PEG500DME) and also poly(ethylene glycol) dialkylether (PEG-DAE) as novel solvents for

Table 1
Properties of commonly used solvents in the preparation of SPI formulations. Information obtained from Sigma-Aldrich [56].

Solvent	Type	Physical characteristics	Water solubility	Melting point (°C)	Boiling point (°C)
NMP	HP	Colourless liquid	Completely miscible	−24	202
DMSO (Dimethyl sulfoxide)	HP	Colourless liquid	Completely miscible	16–19	189
Triacetin	HO	Colourless liquid	61.2 g/L at 20 °C	3	258–260
Ethyl benzoate	HO	Colourless liquid	Limited solubility	−34	212
Benzyl benzoate (BB)	HO	Colourless liquid	15.4 mg/L at 20 °C	17–20	323–324
Benzyl alcohol (BA)	HP	Colourless liquid	33 g/L at 20 °C	−16–13	203–205
PEG500DME	HP	Light brown liquid	Completely miscible	−23	>250

HP—hydrophilic; HO—hydrophobic

use in SPI systems [60,61]. PEG500DME shown to stabilize the PLGA containing SPI systems and resulted in rapid phase inversion as the solvent has a high affinity for water [60]. The use of PEG-DAE also showed stability of injectable SPI systems for up to two months [61]. Limited number of studies also showed use of glycerol formal and triacetin in SPI systems, these solvents has earlier history of using in veterinary formulations [62].

The search for novel solvents for use in SPI systems is an on-going process with a number of factors such as polymer solubility, toxicity, system stability, biocompatibility and the potential for a single unit formulation posing barriers to this development. Although the regulatory authorities approve the 'gold-standard' solvents such as NMP and DMSO, evidence relating to toxicity and suitability is conflicting and sometimes contradictory therefore there is a need for further research and improvement. Movement towards the use of solvent mixtures can be observed through literature in order to obtain the most suitable 'solvent strength' to enable predictable and modifiable controlled release. For example, Zingermann and Chern patented a combination of glycerol formal (hydrophilic) and triacetin (hydrophobic) solvent that showed the blood levels of fipronil (flea adulticide) for 12 months after subcutaneous injection [63].

4. Mechanism of SPI implant formation

Two different forms of phase inversion have been identified and recorded in previous literature, according to their rate of phase inversion as detailed below. For example, rapid injection of the SPI gel formulations results in *rod-like implants* whereas slower injection yields more *spherical implants* [60].

4.1. Fast forming phase inversion (fPI) implants

These systems undergo phase inversion at a rapid rate (from seconds to minutes) resulting in formation of a thin membrane with a porous implant structure [6,12] (Fig. 2a). This change is a result of solvents that are 'strong' and 'hydrophilic' in nature [55]. As the affinity of the solvent for the non-solvent increases, the rate of sol-to-gel phase inversion also increases. fPI systems are of a lower viscosity and, therefore, require lower force of injection. fPI has improved biocompatibility due to the hydrophilic nature of the solvent [64]. Mashak et al. investigated the addition of aliphatic esters, namely ethyl heptanoate, methyl heptanoate and ethyl nonanoate, to a PLGA in NMP solution. Here rapid NMP removal resulted in implant formation, which is due to increased interaction between PLGA and the esters and also by a reduction of the affinity between PLGA/ester and NMP. Additives resulted in highly porous matrix compared control PLGA/NMP system. Most rapid phase inversion was seen in the systems containing ethyl heptanoate [65].

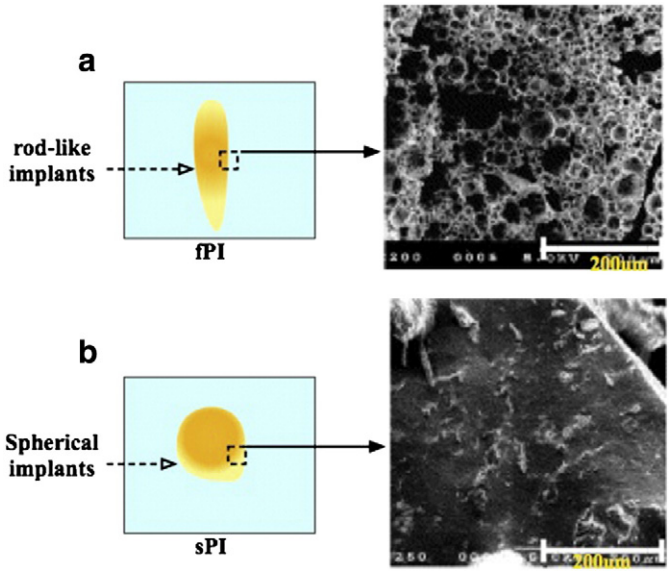

Fig. 2. Schematic illustration and SEMs of (a) fPI and (b) sPI implants. Modified from [55].

4.2. Slow forming phase inversion (sPI) implants

These systems undergo phase inversion at a slow rate (from hours to days) [55]. Solvents used in sPI are weaker and are hydrophobic in nature, therefore gelation/implant formation occurs at a slow rate. In contrast to the fPI, the implant conformation can be described as being uniformly dense with a limited number of pores [3,55,64] (Fig. 2b). Limited pores result in slower drug release from these implants than that from fPI implants but burst release is highly reduced. The extended period of time for solidification of implant formation is not ideal. The viscosities of sPI solutions are usually of an order that makes injection difficult unless the system is pre-emulsified or preheated to 37 °C [64]. These systems have an inherent disadvantage in relation to drug delivery as the hydrophobicity of the solvent can result in foreign protein adhesion to the implant surface and therefore inhibition of drug release [55].

5. Characterisation of SPI implants

Although ISF implants due to SPI emerged in the 1980s, it wasn't until 1999 that a method was detailed and published by McHugh and colleagues (1999) to allow visualization of the implant formation process. The dark ground video imaging technique enables visualization of diffusion, phase separation, gel formation and also quantification of the dynamics of phase inversion [6,20]. This technique involves the polymer and organic solvent solution being held in a quartz cell, which is then exposed to water. The video analysis allows visualization of the concentration gradient that occurs as the water diffuses into the polymer solution. Interference fringes are observed as striations in the dark ground image, which correspond to the water penetration distance. In areas where phase inversion has taken place and a two-phase structure is observed, reflected light is used to illuminate this area (Fig. 3). With this being the first method detailed allowing in depth analysis of this process, limitations were inevitable. This method is only suitable for *in vitro* analysis for up to a couple of hours along with thin polymer films.

Kempe et al., sought to develop a non-invasive method for *in vitro* analysis of implants as microscopy and chromatographic techniques involve intrusive removal of implants by surgery and the possibility of continuous analysis of the implant is unlikely. The method developed by this group focused on the use of electron paramagnetic resonance spectroscopy (EPR) also referred to as electron spin resonance (ESR), which utilises the unpaired electrons in paramagnetic compounds to detect the interaction between these compounds in a non-invasive manner [66]. This method has been previously investigated to characterize drug delivery systems in terms of homo- or heterogeneity and also to determine whether the release mechanism determined through an *in vitro* method corresponds to the *in vivo* release seen in a small mammal [67]. This method does however have limitations, as samples must be prepared before evaluation as small molecular spin probes are required and images of the final implant are not created.

Relatively simple techniques have also been utilised to investigate and state the changes observed during implant formation. Thermal analysis using differential scanning calorimetry (DSC) and flow investigations carried out through rheological investigations were conducted by Wang and colleagues, in 2003, in order to evaluate the behaviour of the polymer solutions once administered *in vitro*. When considering the DSC results, an endothermal peak observed at 47 °C for the PLGA/BB after 92.1 h of ageing, indicated the aggregation of polymer particles and therefore structure formation. Growth of the gel structure was demonstrated by an increase in endothermal peak area at the subsequent

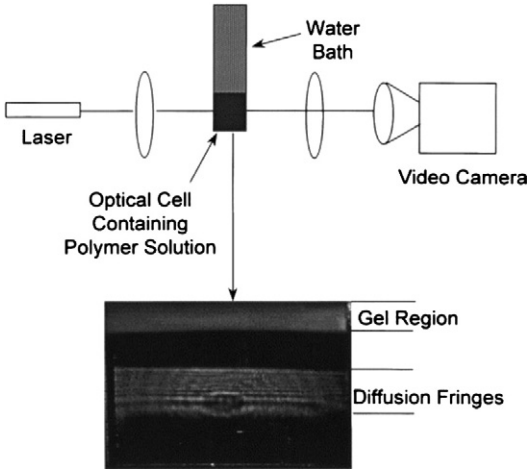

Fig. 3. Schematic diagram of the dark ground optical system. Adapted from [6].

time point. The rheological investigations yielded similar information about gel formation after ageing was allowed to take place. Ageing for 6 h resulted in a 20% increase in dynamic viscosity, which is credited to gel formation over time [68]. Rafienia and Mirzadeh utilised thermogravimetric analysis (TGA) in order to determine the final quantity of solvent within the implant formed. The initial polymer solution consisted of PLGA and NMP, which was subjected to a temperature ramp of between 50 and 400 °C at a heating rate of 10 °C/min. The amount of solvent in the system was determined through the percentage of mass loss at around 202 °C, which is the boiling point of NMP [69].

Most recently a noninvasive diagnostic ultrasound based technique was developed for implant characterization. This method relies on a difference in impedance with the surrounding environment, which occurs during the phase inverting process. As phase inversion occurs, ultrasound is used to visualize the change as the impedance of the implant is altered. The image produced can be described as an 'acoustic map' of the mechanical interactions within an object (Fig. 4). A wide range of implant properties can be determined *via* this method such as implant formation, drug and solvent release, and implant swelling. The non-destructive and non-invasive properties of this method have a distinct advantage over the EPR method as continuous analysis can be carried out over a prolonged period of time, with both *in vitro* and *in vivo* analysis possible [70].

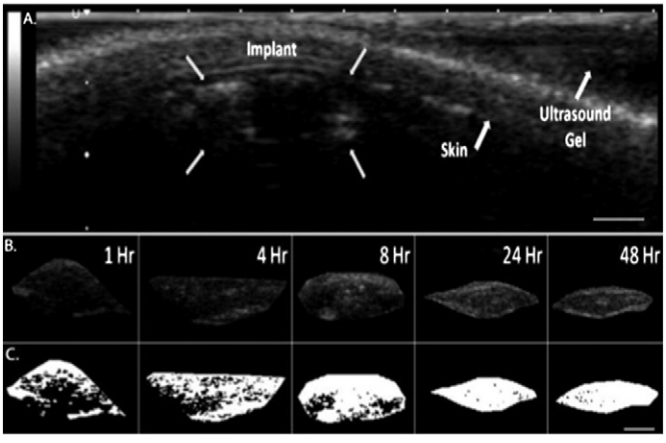

Fig. 4. Ultrasound images of *in situ* formed implants taken after 1 h, following subcutaneous injection of SPI system. The arrows indicate the localization of the implant, skin and ultrasound gel. The first row shows isolated grey-scale images of the *in vivo* subcutaneous implant over time, whilst the second row rows the threshold image of each implant. The scale bar represents 0.25 cm. Adapted from [70].

In terms of determining the final morphologies of the implants formed, SEM has been widely used. As mentioned above, for *in vivo* investigations implant removal is required and continuous analysis of the same implant is not possible. Nevertheless, this technique has elucidated important information about the structure that forms within the implant and also on the surface. Information relating to the internal structure has allowed the effect of solvent quality, polymer properties and formulation additives to be determined. In the study conducted by Graham et al., SEM images showed that increasing the water content of the phase inverting system made up of PLGA and NMP did not significantly change the internal morphology of the implant, as shown in Fig. 5 [6]. Astaneh et al. used SEM technique to examine external and internal morphologies of SPI implants formed from polymers of different MWs (Fig. 6) [18]. Of all the techniques, SEM is an easy tool to exam implant morphologies, as it is commonly available in research laboratories. However, sample processing can have an effect on the final implant structure.

6. *In vitro* drug release from SPI implants

SPI's ability to allow sustained release of drugs has been the focus of many research groups. Once injected into an aqueous environment SPI system forms a polymeric implant that controls drug release over a defined time period (Fig. 1) [71]. A number of publications and patents over the last few decades have indicated that release can be modified so that SPI implants can deliver drugs over a 2-week to 6-month period. Fredenberg et al. identified three basic ways in which drugs could be released from PLGA-based matrices as (i) transport through water-filled channels, (ii) transport through the polymer, and (iii) due to dissolution of the encapsulating polymer. Biopharmaceuticals, proteins and peptides are released through water-filled pores, as these molecules are large and hydrophilic in nature [32]. Hydrophobic molecules transport through the polymer phase.

An ideal prolonged drug release profile would conform to zero-order release kinetics. Typically the drug release profile from SPI implants can be described as triphasic; (i) a sudden burst release of drug that is attributed to a lag period before the implant forms after injection, where drug is released from the surface of the system through pores, (ii) a slow diffusion facilitated release of non-entailment drug molecules in the matrix, and (iii) degradation of polymer matrix in which once the molecular weight of the polymer reaches a lower threshold, erosion results in a second rapid phase of release in the profile [37,72,73]. The rate of drug release can be attributed to a number of parameters such as molecular weight of polymer, concentration of polymer solution, solvent/solution hydrophilicity and system additives. Modification of theses parameters can allow the tailoring of the drug delivery. The

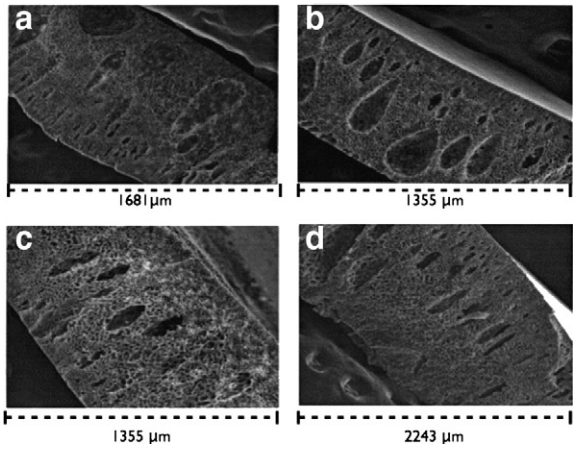

Fig. 5. SEM morphologies of implants made by water quenching 50 wt.% PLGA/NMP solutions with (a) 0% wt.%, (b) 1.25 wt.%, (c) 2.5 wt.% and (d) 4.5 wt.% water added to the formulation. Adapted from [6].

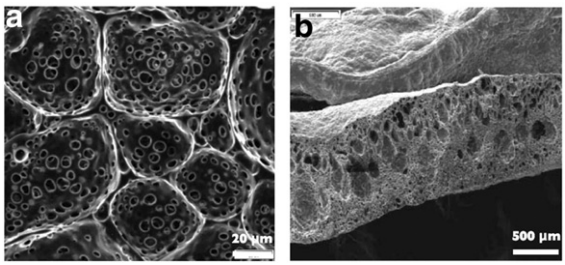

Fig. 6. SEM images of *in situ* formed SPI implant after 3 days of solidification (a) surface morphology and (b) cross section morphology. Adapted from [18].

following sections detail the effect of each parameter on drug release from SPI implants.

6.1. Burst release from SPI implants

Upon injection into the body, SPI systems take certain period of time before an implant is formed [2], and during this process the surface layer of the implant quickly inverts [6] resulting in a relatively large bolus amount of drug released before the release rate reaches a stable profile. This initial phase of the drug release is termed as 'burst release' that normally occurs within first 24 h of implant formation [7]. A number of studies have explained the process of burst release both experimentally and theoretically. Commonly it is observed with drugs of low molecular weight due to the small molecular size and osmotic pressures that heighten the gradient of concentration [74]. It stands to sense that small molecular weight drugs have the ability to pass easily through porous structures of implants and those drugs that are hydrophilic are therefore soluble in aqueous environments that promote drug release.

Depending on the intended use, burst release can either have positive or negative effects. It is however seen as being detrimental due to large amounts of drugs being released in a short period that potentially result in concentrations outside of therapeutic levels, leading to adverse effects [75]. Potent drugs with narrow therapeutic windows, such as chemotherapeutics and human growth hormones may therefore be problematic [7]. High burst release also reduce the effective lifetime of the implant [74,76], as potential for local or systemic toxicity, a shortened half-life of drugs *in vivo*, the drug is wasted in both economic and therapeutic manners and also the total drug release profile is shortened therefore more frequent dosing is required [74]. Burst release has however been utilised to deliver drugs at high release rates to achieve an initial loading dose, such as antibiotics [77]. Huang et al. recorded the instances where burst release may be advantageous such as in wound treatment, for encapsulating flavours, to target delivery *via* triggered burst release and the ability of pulsatile release. Even in instances that burst release is desired, the drug release profile is unpredictable, and variable amounts of drug are released and it is difficult to control the amount of drug released during the period [78].

A large volume of work has been carried out in relation to the modification of burst release. The majority of studies have investigated methods to alter this initial, extensive drug release and prevent it from occurring to produce a better control release system, typical zero-order release kinetics. The following studies show that a number of formulation parameters have been investigated to eliminate burst release.

6.1.1. Addition of a rate-modifying agent

It is important to understand the extent of implant formation and percentage of burst release, as this information can often be utilised to reduce initial drug release. For example, sPI systems may have limited burst release but they take a lengthier period of time to form an implant, compared to that of fPI systems. As a way of compromising, the hydrophilicity of fPI solvents such as NMP and DMSO is reduced by the addition of more hydrophobic solvents (*e.g.* ethyl benzoate, triacetin, and BB) to act as a co-solvent. As solvent quality and water miscibility is reduced, the drug release progresses from a profile that involves high burst release to one that follows zero-order release kinetics. This can be attributed to a change in the implant morphology from a porous structure to a more uniformly formed dense structure [55]. Similarly, by selecting appropriate ratio of hydrophilic BA and hydrophobic BB modification of the release rate is possible. Table 2 gives an overview of the additives that have been used in the modification of burst release of SPI implants.

Astaneh et al. investigated the effect of ethyl benzoate on peptide release from PLGA implants. Ethyl benzoate has extremely limited water miscibility (~0.4%) and it was found that the addition of this co-solvent to NMP resulted in a reduction in burst release by a factor of 2.8 [72]. Triacetin is relatively hydrophobic as it is a short chain triglyceride with limited water miscibility (~7%) [20]. The addition of this solvent reduces the solvent quality and affinity between water and polymer causing a slower rate of phase inversion, which consequently means that the overall release rate is reduced, not just the burst release [6]. However, Tang and Singh did not observe this phenomenon when investigating the effect that aspirin had on matrix degradation and drug release. They found that initial burst release was increased to 65% from 36% by the addition of triacetin to a PLGA/NMP system. This

Table 2
Effect of different additives on burst release from SPI implants.

Additive	Polymer/Solvent system	Drug	Amount of additive	Mean burst release (no additive)	Mean burst release (with additive)	Ref
Triacetin	PLGA/NMP	Aspirin	ND	36.9%	65%	[38]
PVP	PLGA/NMP	Chicken egg lysozyme	3%	ND	8 fold increase	[6]
Ethyl benzoate	PLGA/NMP	Leuprolide acetate	12.8%	14.50%	5.53%	[72]
PEG 400	PLGA/NMP	Aspirin	20%	36.9%	30%	[38]
Glycerol	PLGA/NMP	Naltrexone HCl	1%	67%	62%	[39]
			3%		61%	
			5%		60%	
Ethyl heptanoate	PLGA/NMP	Naltrexone HCl	1%	67%	62%	[39]
			3%		50%	
			5%		44%	
PEG 4000	PLLA/NMP	Heparin	5%	40%	5%	[79]
	PLLGA/NMP			20%	ND	
Glyceryl monosterate	PLGA/BB and BA	Risperidone	2%	32.2%	4.7%	[41]
Steric acid	PLGA/BB and BA	Risperidone	2%	32.2%	23.4%	[41]
Zinc complexation	PLGA/NMP, triacetin, ethyl benzoate, BB	Human growth hormone	30 mM	ND	Reduction in all cases	[9]
Pluronic L101	PDLA/NMP	Lysozyme	5.4%	25%	18%	[80]
Pluronic L121	PDLA/NMP	Lysozyme	5.4%	25%	10%	[80]

ND—no details.

was attributed to the limited solubility of hydrophilic aspirin in hydrophobic triacetin resulting in the aspirin only being in suspension that caused high burst release [38].

Bakhshi et al. showed that the addition of glycerol or ethyl heptanoate to a PLGA/NMP system prolonged the release of naltrexone hydrochloride from few days to 4 weeks. Here increasing additive contents caused the greater retardation of NMP removal that led to a more sustained drug release [39]. Tan et al. investigated the effect of hydrophilic PEG 4000 addition on heparin release from PLLA and PLLGA matrices. Outcomes showed that PEG 4000 had the ability to significantly suppress the burst release from the PLLA matrix but not from the PLLGA matrix. This suppression was attributed to the heparin and PEG both being hydrophilic and so the heparin solubility in the polymer matrix was increased as the matrix was rendered more hydrophilic by the PEG [79].

Dong et al. investigated the widely used solid lipids namely steric acid and glyceryl monosterate, as potential release modifying additives. The study was successful in showing that the addition of steric acid or glyceryl monostearate to a PLGA and BB/BA (in a ratio of 9:1) system in low concentrations (2%) was sufficient to reduce burst release of risperidone as phase inversion was slowed due to a more hydrophobic environment. Glyceryl monosterate, due to greater hydrophobicity, showed most favourable effect of slowing risperidone release [41].

Brodbeck and co-workers uniquely modified the release of human growth hormone (hGH) from PLGA implants. Unlike additives, here hGH particle properties were altered by complexation and densification processes. Complexation of the protein with zinc was shown to lengthen the dissolution time in water from seconds to hours. The burst effect was practically eliminated by the addition of 30 mM of zinc into the system. Densification of the protein particle however had a limited effect on protein dissolution rate as it was only slowed by a number of minutes [9].

Poloxamers are triblock copolymers of poly(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide) (PEO–PPO–PEO) that have gained increased interest in drug delivery investigations due to their wide-ranging properties and biocompatibility. Variation of chemical and physical properties can be achieved by modifying the molecular weight and block size of the poloxamer. Vast amount of literature attests to the thermoreversible nature of poloxamers in aqueous solutions and this advantageous property has been exploited in a wide range of areas such as rectal [81], ophthalmic [82], topical [83] and parenteral drug delivery [84]. DesNoyer and McHugh realized the potential of poloxamers for use in SPI systems. The use of strong, hydrophilic solvents results in the problematic issue of burst release. In this study, it was determined that preferential segregation plays an important role during the course of phase inversion, where hydrophilic materials will separate into the implant surface and polymer lean phase (hydrophilic regions). This then beneficially affects the overall drug release as an increased barrier to diffusion within the interconnected polymer lean phase is created. Being hydrophilic in nature poloxamer was investigated to determine their preferential segregation behaviour within the PDLA/NMP system. The results showed that the addition of poloxamer had a favourable effect in reducing the burst release from the implant, with the higher molecular weight poloxamer causing the most profound reduction and also that a critical concentration of poloxamer resulted in a more extended release profile of lysozyme [80].

6.2. Effect of polymer molecular weight

Polymer molecular weight (MW) is an extremely important property that can affect a number of physico-chemical and mechanical properties such as solubility, viscosity, diffusivity, glass transition temperature and modulus [85]. It is well known that the greater the MW of the polymer, the greater will be the reduction in drug release. The availability of polymers in a vast range of MWs also makes it easier to modify drug release rate from SPI implants, as addition of external additives can be avoided. Accordingly a number of studies have documented the effect of polymer MW on drug release rate.

Astaneh et al. studied the effect of varying PLGA MW on the leuprolide acetate release profile of from SPI implants. The results showed that the SPI system prepared with the highest MW PLGA (*i.e.* 48 kDa) had a significantly lower initial release within the first 24 h compared to the lower polymer MW implant (*i.e.* 12 and/or 34 kDa) [18]. Although burst release is reduced in this case, the higher MW means an increase in viscosity and therefore an increase in the work of syringeability, which will be problematic for obvious reasons. A lower bioavailability may also be observed with increasing MW, as the incorporated drug my not show 100% release from the implants.

Lui et al. also investigated the effect that modification of MW would have on thymosin alpha 1 (Tα1) release. It was concluded that a lower polymer MW resulted in reduced viscosity of the formulation causing more rapid release of organic solvent and Tα1, indicating an fPI type implant formation. fPI implants have greater porosity therefore a higher burst release was observed. In contrast, high MW PLGA showed a much lower initial drug release and also a more prolonged release period, compared to the lower MW polymers [86].

6.3. Effect of polymer concentration

The increase in polymer concentration results in a slowing of the phase inversion rate of SPI implants, which in turn results in a reduction in drug release rate. Graham et al. accredited this slowing of phase inversion to a slowing of water influx into the system and therefore a change in morphology of the implant from finger-like, porous structure to a more spongy, dense structure due to an increase in polymer concentration [6]. Lambert and Peck also examined the effect that PLGA polymer concentration had on FITC-bovine serum albumin release. They also concluded that an increase in concentration resulted in a reduction in burst release as diffusion of water into the system is hindered and so phase inversion is slowed [87]. Liu et al. also observed a 52.3% of the Tα1 being released initially by lowering PLGA polymer concentration but a slow rate of phase inversion, with low initial release of Tα1, was seen when polymer concentration was increased [86]. Ueda et al. investigated the effect of PPF concentration on PPF/NMP implant formation and FA release. A significant burst release (≈68.2%) was seen with the lowest concentration of PPF (*i.e.* 25%w/w), severely reducing the lifespan of the implant. However, the same formulation with twice the concentration of polymer experienced a burst release reduced by around a third [44]. Similar to increasing polymer MW, increasing the concentration of polymer has a number of effects such as changing viscosity and therefore syringeability, lower diffusivity and increased system hydrophobicity, some of which can be detrimental [6,86].

6.4. Effect of polymer end-capping

When considering the polymers employed in SPI systems, the functional groups present at the end of the polymer chains can have a profound effect on the drug release profile, especially of proteinaceous drugs. Studies conducted by Wang et al. showed that the modification of the acidic end group of the polymer to a lauryl ester group reduced the release of sirolimus from a multi-layered PLGA stent [88]. This trend was also seen when Luan and Bodmeier investigated the release of leuprolide from a PLGA microparticulate system. They found that a higher release rate was observed when the carboxylic end groups were esterified [19].

In a study conducted by Chhabra et al. the aim was to determine the influence of carboxylic acid and ester groups at the end of PLA/PLGA polymers on the release of lysozyme. It was seen that the end groups of the polymer chains had a significant effect on the type of solvent that would be required for optimal solubility of the polymer. The polymers consisting of acid end groups were more hydrophilic than ester

end group polymers therefore a solvent of a hydrophilic nature was required for a solution to be formed successfully. Consequently, the more hydrophobic polymers were not soluble in hydrophilic solvents and required more hydrophobic solvents. Upon investigating the release of lysozyme from systems produced using the polymer variations, they found that those systems that contained polymer with carboxylic acid groups resulted in a greatly reduced burst release of approximately 4% compared to 20–30% for the other formulations containing polymers with ester end groups. This reduction in burst release was attributed to the theory that the carboxylic acid end groups of the polymer have the ability to form chemical linkages with amino acid residues of the lysozyme that contain hydroxyl groups [89].

6.5. Effect of monomer ratios

Co-polymers such as PLGA have been widely used to produce SPI implants, as modification of release is possible by varying the ratio of monomers within the polymer. PLGA is a copolymer of lactic acid and glycolic acid monomers and is available for purchase in a variety of monomer ratios. It is reported that water uptake into the system is promoted by a reduction in the number of lactic acid monomers and therefore a simultaneous increase in glycolic acid monomers. This is due to the ester bonds being more accessible to hydrolysis as the methyl groups on the lactic acid moieties are less bulky. The increase in water uptake therefore speeds up the rate of degradation and therefore the rate of drug release [90]. A PLGA polymer comprising of 85% lactic acid and 15% glycolic acid has an approximate degradation time of 5 months whereas a polymer consisting of 50% of each monomer has an approximate degradation time of only 2 months in a hydrophilic environment.

6.6. Effect of polymer crystallinity

The majority of studies involving release from injectable SPI implants have been based on amorphous polymers such as PLGA. There is however a growing body of work that is investigating the role that polymer crystallinity has on drug release profiles. An ideal injectable implant system that employs a crystallisable polymer should initially be amorphous to allow easy injection but should then crystallise rapidly once injected [23].

Miyajima et al. over a decade ago, examined how the crystallinity of Poly(L-lactic acid) (PL(L)A) influenced the release of papaverine from rods. The results showed that an increase in crystallinity would result in a faster release rate due to the microporous structure associated with a crystalline polymer. Initially the PL(L)A was amorphous but once immersed into the aqueous medium, the polymer became semi-crystalline and therefore microporous. The emergence of micropores resulted in drug release occurring *via* water filled channels and therefore a faster release profile [91]. DesNoyer and McHugh continued this path of study and employed semi-crystalline PCL and amorphous PDLA to examine the effect that crystallinity would have on drug release. Whilst investigating this property of polymers, they came across a 'delayed burst phenomena' that they had previously not witnessed when working with amorphous polymers. This delayed burst release was observed after a lag period of extremely slow release and was attributed to the onset of crystallisation. Systems with limited crystallinity result in more uniformly, dense morphologies, lacking in micropores and this is due to mild liquid–liquid demixing and therefore slower release rates of proteins. In contrast, the more crystalline a system is, phase separation will result in porous morphologies and therefore a more rapid release rate after the lag period during which crystallisation occurs. Two distinct regions are therefore observable in the drug release profile of systems based on crystallisable polymers 1) lag phase and 2) burst release. Knowledge about this important polymer parameter therefore allows tailoring of drug release profiles by altering the semi-crystalline: amorphous polymer ratios [23].

7. Stability of SPI systems

As with all pharmaceutical products aiming to be released onto the markets worldwide, stability is a major issue with rigorous testing and data evaluation required. Non-solvent induced SPI systems are no exception. SPI formulation is potentially made up of a number of components, all of which could play an important part in the overall product stability and performance. The main issues are the stability of the polymer, biocompatible solvent and the drug in the system. Also the formulation additives may all affect the stability of the formulation. Within literature, there are a number of different methods of polymer solution preparation *e.g.* using heat to aid polymer dissolution. This may inherently pose problems in relation to the system stability.

Dong et al. investigated the effect of a number of parameters on a polymer solution comprising of PLGA, biocompatible solvent and leuprolide acetate. They determined that PLGA was soluble in all of the tested organic solvents, apart from 2-pyrrolidone and PEG 400 at 4 °C, with more rapid degradation rates being witnessed with increasing temperatures. They also determined that the stability of leuprolide acetate was reduced when dissolved in PLGA solutions, but by suspending it in solvent maintained its stability [92].

Ahmed et al. determined the most suitable storage conditions for PLGA-based SPI systems containing haloperidol. Three temperatures namely 4, 25 and 40 °C were investigated with the drug content of the systems being determined after 90 days with a small decrease in drug content observed for those stored at 4 and 25 °C (99.51% and 98.09%). As expected, a greater decrease in original drug content to 95.65% was observed when the temperature was elevated to 40 °C. An alteration in the pH of the systems was also detected with the rise in temperature. At the commencement of the study, the pH of the systems was 9.65, with the pH values decreasing to 9.60, 8.61 and 7.13 for the temperatures 4, 25 and 40 °C respectively, indicating an increased rate of polymer degradation as the temperature is increased. Further studies were conducted that focused on storage at 4 °C. After 12 months, it was determined that over 95% of the drug content remained intact with the drug degradation following zero-order kinetics and the final shelf life for these systems containing haloperidol was calculated to be 2.84 year [73].

Those phase inverting systems that are currently available on the market utilise a two-syringe system to ensure that stability is maintained for the shelf life. The two syringe contents are mixed just prior to injection and this is the case for both Atridox® and Eligard®, that are based on Atrigel® technology [93]. One syringe contains the dry drug powder, whilst the other contains the required amount of polymer solution. Before injection, the syringes are coupled and both components are mixed thoroughly in a cyclical fashion between the two syringes for nearly 100 times to form a homogeneous mixture prior to injection [94]. This process of mixing has disadvantage as patients may find this difficult to do at home and may also make a conscious decision not to follow the mixing guidelines and therefore not completely mix the formulation. Even though a single ready to use delivery system will be helpful to overcome this issue, long-term storage stability of drug molecules and polymer in the desired solvent is of major concern. Importantly, protein and peptide based molecules will tend to degrade faster and therefore improvements are necessary to overcome these hurdles.

8. Biodegradation of SPI implants

Injectable implants are advantageous as this mode of delivery avoids any surgical intervention. Equally important is the biodegradation of the formed implant, as this will result in natural loss of the implant material without the need for any surgery. Most of polymeric implants are biodegraded either through hydrolysis or oxidation degradation mechanisms. Degradation by hydrolysis is rather a fast process that can be influenced by a number of factors such as pH, type of chemical bond,

copolymer composition, drug type, and water uptake [95]. Degradation by oxidation is an intrinsically very slow process [96]. In addition to mode of biodegradation, properties such as hydrophilicity, stability, reactivity and swelling behaviour are important parameters that govern the biodegradability of implants. It is also important to take into consideration polymers' physical and physico-mechanical properties (*e.g.*, molecular weight, polydispersity, melting point), as well as morphology of the formed implant. Table 3 gives degradation and physico-chemical characteristics of polymers that have been commonly used in SPI systems.

Polyesters have a half-life of approximately 3.3 years [98] and undergo hydrolytic degradation. Nucleophilic attack of the ester carbon by water occurs once the polymer is exposed to an aqueous environment. During the chain cleavage step of the hydrolysis mechanism, the resultant alcohol has the ability to abstract a proton from the carboxylic acid to become protonated whilst the carboxylic acid becomes deprotonated [95]. Fig. 7 shows the hydrolysis mechanism that occurs within PLGA. The hydrolysis of the chains results in exposed carboxylic acid end groups and these acids have the ability to catalyse the hydrolysis reaction. Thus, esterified end groups show lower PLGA hydrolysis than the carboxylic acid end groups. Li and McCarthy observed that the catalysis results in an irregular rate of degradation, with quicker degradation being observed in the core of the matrix than on the surface, which has a reduced acidity [99,100]. Degradation results in a reduction in polymer molecular weight. Due to the rapid hydration of PLGA, bulk erosion is observed rather than surface erosion [101]. The consequence of surface erosion is that material is lost from the surface only, which gives the advantage that the erosion process is predictable [95]. PLGA degradation can be tailored by changing the LA/GA ratio *e.g.* increase in GA content will result in an increased water uptake of PLGA and therefore more rapid degradation will be observed [79,90]. The degradation of PLGA with LA-50%/GA-50% has been reported as between 1 and 6 months [7,79]. PLGA hydrolysis is also dependent upon the average molecular weight and polydispersity. Higher molecular weight PLGA experiences more rapid hydrolysis after an initial lag phase due to autocatalysis [102].

PPF also shows hydrolytic degradation that results in fumaric acid and propylene glycol. Degradation of PCL yields caprolactic acid [43,44]. PLEC copolymers, alteration of the CL and LA ratio can have a profound effect on degradation. PLEC, a copolymer of CL and LA, shows slower rates of degradation with low LA content and *vice versa*. With low LA content, fewer ester bonds are available for cleavage and therefore the rate of degradation is reduced. Results from the degradation studies within the research conducted by Nasongkla and colleagues concluded that the incorporation of LA facilitated the degradation of the PLEC implants [48].

Although Liu et al. recently demonstrated the use of PEC in SPI systems; it has been widely used previously in stent [103], elastomer [46], and nanoparticle [47] preparations. PEC is a carbonic acid derivative and is known not to degrade *in vitro* by hydrolysis at physiological pH, but known to degrade by oxidation *in vivo*. *In vivo* it degrades through surface erosion, where the molecular weight of the polymer mass remained unchanged. Subcutaneous implants of PEC disappear within weeks to months from the body, with ethylene carbonate as the product of degradation [96,104]. Acemoglu proposed a chain reaction mechanism for the biodegradation of PEC *in vivo* (Fig. 8). Superoxide anion radicals, according to an anionic- or radical-based mechanism can initiate the proposed chain reaction [96].

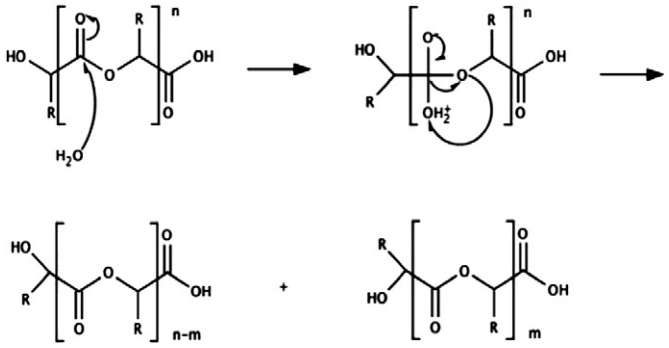

Fig. 7. Hydrolysis of PLGA ester linkages. The R groups represent methyl groups in lactide monomers and hydrogen groups in glycolide monomers. Adapted from [102].

A number of studies have shown that drug type can have a profound effect on the degradation rates of polymer matrices, which in turn affects drug release rate. For example, a study comparing the base and salt forms of lidocaine showed increased rate of water uptake and implant degradation. The salt form of lidocaine resulted in an accelerated degradation profile along with a biphasic release pattern, with the base form showing a triphasic release profile [90]. Similarly, Siegel and co-workers studied the effect of a range of commonly used drugs on the degradation of 50:50 PLGA; bulk erosion was observed in samples without drug whereas surface erosion was seen in samples with haloperidol [105]. Tang and Singh in 2008 investigated the effect that aspirin would have on PLGA/NMP implant degradation. A steady drug release was observed for 7 days after an initial burst of 36% of the drug. The presence of hydrophilic aspirin enhanced water uptake into the implant, resulting in more rapid degradation and drug release. The acidic property of aspirin also contributed to the faster rates of degradation and release due to the core of the PLGA matrix becoming more acidic, leading to more rapid bulk erosion [38]. These studies clearly indicate that the drug type can significantly affect the degradation of the implant and also the drug release rate from SPI systems. Overall, biodegradation of SPI implants is dependent upon the polymer type, molecular weight, co-polymer ratio, polydispersity and drug type and concentration. It is also dependent upon the site of administration, as the locally available micronutrients and enzymes further effect the overall biodegradation.

9. Biocompatibility of SPI implants

As with any system that is introduced into the body, safety is of paramount importance. Dorland's Medical Dictionary defines biocompatibility as 'the quality of not having toxic or injurious effects on biological systems'. As the SPI systems are composed of a number of different components, the biocompatibility should be considered both

Table 3
Characteristics of polymers commonly used in SPI formulations. Adapted from [43].

Polymer	Melting point (in °C)	Glass transition (in °C)	Approximate degradation time (in months)	Mode of degradation & degraded products
PGA	225–230	35–40	6–12	Hydrolysis & GA
PLA	173–178	60–65	>24	Hydrolysis & L-LA
Poly(D,L-lactic acid)	Amorphous	55–60	12–16	Hydrolysis & D,L-LA
PLGA (85/15)	Amorphous	45–55	1–6	Hydrolysis & D,L-LA & GA
PCL	58–63	−65–60	>24	Hydrolysis & caproic acid
PPF	Amorphous	31.9 for infinite Mw (Mw dependant [97])	Several months	Hydrolysis & fumaric acid, propylene glycol
PLEC	ND	ND	Weeks to months	Hydrolysis & CL & D,L-LA
PEC	ND	ND	Weeks to months	Oxidation & ethylene carbonate

ND—no details.

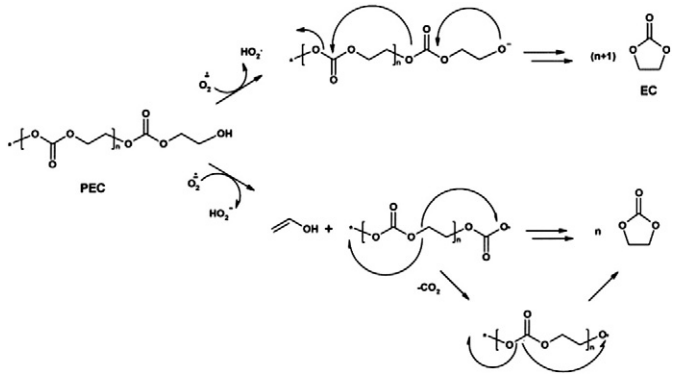

Fig. 8. Proposed biodegradation pathways of PEC *in vivo*. Adapted from [96].

individually and collectively. Typical solvents that are preferred for injection include isotonic sodium chloride, glucose solution (5%) and also distilled water. It is however recognized that the use of organic solvents is required when drug compounds or polymers are insoluble in aqueous media [72]. The intended site of injection and implant formation must also be taken into account as immune responses vary depending on the biological tissue. For example, it has been reported that the eye exhibit immune privilege due to the blood-ocular barrier and lymphatic drainage among other features [106]. It would therefore stand to sense that injection of a system into these ocular tissues would result in a limited immune response.

As stated, the polymers used in ISF SPI systems are biocompatible and have been used widely for numerous pharmaceutical and biological purposes. For over 30 years, PLGA polymers have been utilised to produce the biodegradable sutures Dexon® and Vicryl® which demonstrates their stellar safety and biocompatibility profiles [22]. The extensive study of biodegradable polymers in different bodily tissues such as brain tissue, Schwann cells, peripheral nerve cells and eye tissues, has revealed that they are well tolerated with a limited host response witness that fades with time and is not associated with toxicity or allergy [107,108]. As mentioned previously, PLGA degrades into normal bodily components (CO_2 and H_2O) and can be removed by the metabolic system. Dhawan et al. conducted a study to evaluate the biocompatibility of PLGA polymer solutions and they determined through SEMs and histopathological studies that the treated tissue contained no macrophage accumulation and no tissue damage was observed [109]. PPF is another biocompatible polyester polymer that has shown promise in the area of SPI drug delivery system. The biodegradation products are non-toxic and can be removed *via* the tricarboxylic acid cycle, therefore no accumulation of toxic components occurs [44]. Rat implant studies conducted in the last decade indicated that mild inflammation responses occurred but not long-term damage was observed when PPF was implanted [110,111]. PCL tissue responses have also been investigated but this polymer is widely accepted as non-toxic polymer. A biocompatibility assessment of PCL films using L929 mouse fibroblasts further enforced the conclusion that this polymer is suitable for use in the body and therefore is biocompatible [112]. PCL, as a tissue scaffold, showed no adverse host tissue reactions even after 6 months after implantation [113]. The PLEC copolymers were evaluated in terms of toxicity and tissue damage when injected into the cerebral cortex for the potential use as controlled release systems for the delivery of chemotherapeutics. A weight loss study along with haematological data indicated that the injection of 10 to 40 μL of polymer solution did not cause significant systemic toxicity. However, a study to assess dose-dependant neurological reactions and damage identified that the incidence of hydrocephalus and enlargement of the cerebral ventricles increased with an increase in the volume of polymer solution. The injection of up to 10 μL was determined to be safe with no neurological or systemic effects [48].

Organic solvents required to produce SPI implants are widely considered to be the main drawback when evaluating for biocompatibility. There are conflicting opinions on the use of organic solvents for pharmaceutical applications as they have been widely used for parenteral delivery systems but published data does present myotoxic tendencies. Pain and local irritation are associated with the use of organic solvents therefore their inclusion in pharmaceutical formulations is often debated and seen as controversial. The majority of data published in the past relating to the myotoxicity of organic solvents focused on delivery *via* the oral, intraperitoneal and intravenous routes whereas ISF implants have been developed mainly for intramuscular and subcutaneous administration [99].

NMP and DMSO are the most commonly employed organic solvents and they both have low systemic toxicities upon consideration of the LD_{50} (lethal dose, 50%) values in rats. The LD_{50} for DMSO in rats is over 12 g kg^{-1} [114], with the LD_{50} for NMP being over 4 g kg^{-1} [115]. The European Agency for the Evaluation of Medical Products in 2002 produced guidance on the permissible daily exposure for NMP as there had been suggestions that NMP should be moved from class 2 to class 3, with an increase in PDE to 207 mg day^{-1} from 48.4 mg day^{-1}. Investigations however led to the final conclusion that NMP should remain in class 2 with a modified PDE of 5.3 mg day^{-1}, FDA also approved this and indicated its use as a constituent in medical devices [114,116]. A review carried out by the European Commission Scientific Committee on Consumer Safety concluded that NMP has low acute toxicity by oral, dermal, and inhalation routes [117]. In order to determine the intramuscular and subcutaneous effects that NMP and DMSO would have, Royals et al. investigated the consequences of injecting these solvents in rhesus monkeys. Through their studies, they concluded that polymer solutions containing either NMP or DMSO resulted in no systemic toxicity as the monkeys experienced behavioural or weight changes and they remained healthy and active throughout the study. They also determined that the tissue irritation levels reported were similar to those previously published data regarding preformed biodegradable implants through histological studies [71]. For veterinary use, although NMP is widely used for human applications, it was found during an in-house study conducted by Matschke et al. that NMP resulted in unacceptable pain reactions during administration coupled with local inflammatory effects after application. These findings therefore place a question mark over the suitability of this popular organic solvent for veterinary applications [17].

Other solvents that are relatively widely used such as triacetin and propylene glycol have also been investigated to determine their safety profile. Triacetin inherently possesses similar problems to NMP and DMSO whereas the haemolytic potential of propylene glycol is sufficiently substantial to result in it not being recommended for use [118]. In the biocompatibility study conducted by Kang and Singh, a PLGA and BA/BB system was evaluated in terms of tissue irritation, inflammation and macrophage infiltration. Results indicated that 1 week after administration a large number of macrophage infiltration was observed in the surrounding tissue, indicating an inflammatory reaction [119]. Upon continuing with the study, evaluation after 8 weeks showed only a small number of macrophages and inflammatory cells. After 12 weeks there were no indicators of cell damage such as swollen mitochondria and normal tissue was observed. It therefore indicates that any irritation initially witnessed with the PLGA and BA/BB system faded over time and tissue returned to normal, with no adverse effects [58]. Another study carried out by Singh and Singh investigated a PLA and BA/BB system for the release of leuprolide acetate. Here significantly high cell viability was observed in the growth media that was diluted with polymer solution, suggesting that the lactic acid produced through polymer degradation was acting as a metabolic substrate within the mitochondria of the cells [120].

As there are still conflicting opinions regarding the use of established organic solvents, work to develop new solvents to be used in SPI systems has been carried out. Schoenhammer et al. investigated PEG500 DME as a suitable solvent to be used in these parenteral systems.

Previous work detailed that this solvent had been shown to stabilize PLA and PLGA in solution and also possess a low haemolytic potential in comparison to NMP and PEG 600 [60,61]. The results of this study indicated that the biocompatibility and the resultant immune response of tissue to SPI systems that employed PEG500 DME as the solvent was similar to those systems that contained NMP and DMSO [27]. Although conflicts exist in relation to the type of solvent usage in SPI preparation and important factor to be considered is the volume of injection to be administered. A higher volume of SPI injection could drastically compromise the biocompatibility, therefore volumes of injection should be kept minimum to avoid biocompatibility related issues but at the same time desired release rates are achievable.

10. Sterilisation of SPI system

As these drug delivery devices are for parenteral administration, it is paramount that effective sterilisation is achievable without affecting the formulation itself. Methods detailed in literature to ensure these preparations are sterile including filtration, aseptic preparation techniques and gamma irradiation [94]. The use of gamma irradiation therefore raises concerns about the final preparation stability relating to drug loading and release profiles. PLA stability following exposure of microsphere formulations to varying doses of gamma irradiation exposure has been previously studied with an increase in carboxylic acid content and an overall decrease in polymer molecular weight observed. It was also concluded that the overall release profile of progesterone was not affected by irradiation of up to 25 kGy but irradiation at a dose of 100 kGy resulted in an abrupt release of drug due to polymer degradations [121]. Similar results were obtained during a study conducted by Montanari et al. This group determined that exposure of up to 25 kGy of irradiation had no effect on polymer stability [122]. This study therefore indicates the need for maximal threshold values of sterilisation irradiation exposure to be determined for formulations, as use of irradiation above the threshold could have detrimental effects on the preparation and therefore the patient.

With numerous studies having been conducted concentrating on the effect of irradiation on polymer stability, Rafienia et al. identified a gap in knowledge relating the effect gamma irradiation had on drug stability and release profiles of corticosteriods. Using fourier transform infrared spectroscopy (FTIR) and DSC, the group determined that sterilising gamma irradiation had no effect on betamethasone (BTM) and betamethasone acetate stability within PLGA/NMP polymeric systems and no change was seen regarding the chemical and physical properties of the drugs. Release studies of both drugs were also carried out to compare the potential affect of the irradiation on release profiles. Formulations containing varying concentrations of each drug were produced and exposed to 25 kGy of irradiation. No effect on release was seen in the 5% formulation of BTM but a significant decrease ($p < 0.05$) in release from the formulations containing 7 and 10% was observed, which was unexpected. The group however also concluded that a dose of 25 kGy of irradiation had no significant effects on the BTMA formulations [69]. Montanari's group continued their work to investigate the stability of clonazepam and bupivacaine after exposure to irradiation. The clonazepam rate of release increased by 10% after irradiation and did not increase further during storage. A decrease in bupivacaine content of 4% was observed after irradiation and this was attributed to radiolytic decomposition. The drug release however increased and continued to do so for the first 90 days of storage but this stabilized. In both studies, it was concluded that the microspheres stabilized after irradiation as the release did not increase for the whole storage period [123,124]. Therefore, careful evaluation of the effect of irradiation on the SPI formulations is necessary, knowing that in certain scenarios the process of sterilisation techniques may have a detrimental effect on product performance and marketability.

11. Currently marketed SPI products and their clinical studies

In situ implant forming SPI technology showed great promise in the field of drug delivery, which led to commercial products approved by the FDA, whilst some are currently undergoing clinical trials, as shown in Table 4. Most attracting feature of SPI systems has been its applicability to a wide range of clinical indications. Dunn and co-workers, in the 1990s, developed Atridox®, the first SPI-based system that was released onto the market after FDA approval in the late 1998, marketed by

Table 4
List of SPI based ISF drug delivery products that are either commercially available or under clinical development phase.

Product	Company	Drug	Composition	Clinical application	Product status	Ref
Atridox®	Zila Inc.	Doxycycline, 21 days release	Poly DL-lactide & NMP	Chronic periodontal disease	FDA approval in late 1998	[125,127]
	Atrix Laboratories Ltd.				MHRA approval in 2003 (in UK)	[126]
Atrisorb® FreeFlow™	Zila Inc.	Used as barrier structure that remain for 6 months	PLA & NMP	Guided Tissue Regeneration (GTR) barrier for use after periodontal surgery	FDA approval in 2006	[129,130]
Atrisorb-D® FreeFlow™	Zila Inc.	4% Doxycycline, control release for a period of 7 days	PLA & NMP	To inhibit local bacterial growth as healing takes place	FDA approval in 2000	[125]
Eligard®	Sanofi-Aventis	Leuprolide acetate, Control release up to 6 months	PLGA & NMP	Management of advanced prostate cancer	FDA approved in 2002	[131,132]
Lupron Depot™	AbbVie Inc.	Leuprolide acetate, Control release up to 6 months	PLGA & NMP	Palliative treatment of advanced prostate cancer, endometriosis and fibroids.	FDA approval in 1995	[134]
Lupron Depot-Ped™	AbbVie Inc.	Leuprolide acetate	PLGA & NMP	Treatment of children with central precocious puberty	-	[135]
Sandostatin® LAR	Novartis Pharmaceuticals Corp.	Octreotide. Given monthly once instead of 3 times a day Sandostain injection	PLGA & NMP	Treatment of acromegaly & gastroenteropancreatic neuroendocrine tumours	FDA approval 1998	[136,137]
	Novartis Pharmaceuticals UK Limited (Trading as Sandoz Pharmaceuticals)				MHRA approval in 2007 (in the UK)	[140]
POSIDUR™	DURECT Corp.	Bupivacaine. Release for 3 days	Sucrose acetate isobutyrate	Treatment of post-surgical pain	Submitted NDA in April 2013	[141,142]
Relday™	DURECT and Zogenix, Inc.	Risperidone,	Sucrose acetate isobutyrate	Treatment of schizophrenia and bipolar disorder	Phase I conducted in 2012/2013	[141,143]
SucroMate™ Equine (a veterinary product)	DURECT Corp. in collaboration with CreoSalus, Inc.	Deslorelin acetate	Sucrose acetate isobutyrate	For inducing ovulation	Launched in 2011	[141]

Tolmar Inc. in the United States. The Atridox® system consists of poly DL-lactide, NMP and doxycycline. In September 2009, Zila and TOLMAR joined to form a new company called Zila, Inc. that is currently marketing the Atridox® [125]. MHRA (Medicines and Healthcare products Regulatory Agency), in the UK, granted a marketing authorisation for Atridox® to Atrix Laboratories Ltd. in 2003 [126]. Atridox® is licensed for the treatment of chronic periodontal disease and it utilises the initially liquid state of the polymer solution to allow injection of the antibiotic into the periodontal pocket. This system has been reported to allow the release of doxycycline over 21 days [127]. Advantages of this product as detailed by the company in relation to marketing draw on the advantages of ISF systems. Atridox® allows local treatment of the periodontal disease *via* direct application of the antibiotic and also that removal is not required as the system of bioabsorbable. A number of clinical studies were conducted to determine the benefits of this treatment compared to previously licensed treatment modalities. Garrett et al. conducted two multi-centre studies comparing locally delivered doxycycline to oral hygiene measures, scaling and root planning and also a placebo measure. It was determined that the local delivery of doxycycline resulted in a gain in clinical attachment and also a reduction in probing depths. A similar study indicated that the local delivery resulted in a reduction in bleeding on probing [128]. Zila Inc. also market Atrisorb® FreeFlow™ which was granted FDA approval on 21st March 2006 [129]. This product utilises the *in situ* gelation of a polymer and solvent formulation (PLA and NMP) to produce a Guided Tissue Regeneration (GTR) barrier for use after periodontal surgery. The formation of the gel at the site of surgery encourages the growth of tissue *via* custom-fitted barrier. A study of this formulation by Coonts et al. determined that the integrity of the barrier structure remained intact for approximately 6 months, with complete bioabsorption within 9 to 12 months [130]. An advancement of this product involves the introduction of 4% doxycycline into the formulation to inhibit local bacterial growth as healing takes place. This system is marketed as Atrisorb-D® FreeFlow™ and it was granted FDA approval in September 2000. Currently the Atrisorb®FreeFlow™ products are not licensed for use in the United Kingdom.

Eligard® is a sustained release delivery system marketed by Sanofi-Aventis, that employs a similar polymeric delivery system (PLGA and NMP) utilised by Atridox® to deliver leuprolide acetate, a gonadotropin releasing hormone (GnRH) agonist [131]. It is licensed for the management of advanced prostate cancer and allows flexible dosing regimes of every 1, 3, 4 or 6 months due to variation of polymer MW and solvent concentrations. This system requires the mixing of the leuprolide acetate with polymer/solvent combination immediately prior to injection *via* a 20-gauge needle into subcutaneous tissue. Clinical trials conducted by Chu et al., indicated that both the 1-month and 3-month formulations were effective in reducing the levels of testosterone in patients below castration levels previously stated by the FDA of 50 ng dL^{-1} but also those levels advocated by the NCCN for LHRH agonist monotherapy ($\leq$20 ng dL^{-1}) [131,132]. GnRH agonist administration may increase the risk of diabetes and certain cardiovascular diseases and therefore medical professionals are advised to exercise diligence when its administration to treat advanced prostate cancer [133].

Lupron Depot™ is a prolonged release formulation of leuprolide acetate, composed of PLGA and NMP, like Eligard®, and was initially approved in the US in 1995 for the palliative treatment of advanced prostate cancer. Three different formulations are available which allow a variety of dosing intervals for prostate cancer. The 22.5 mg formulation releases drug over a 3-month period therefore a single intramuscular injection is required every 12 weeks. The 30 mg formulation releases over 4 months and so dosing is needed every 16 weeks and the 45 mg formulation requires dosing every 24 weeks as it has the ability to release controlled amounts of leuprolide over 6 months [134]. Further developments include 3.75 mg and 11.25 mg depot formulations for the treatment of endometriosis and fibroids. As with Eligard®, the Safety Alert issued in relation to GnRH agonists applies to Lupron Depot™ therefore prescribers are advised to exercise caution. A further formulation development has resulted in the production of Lupron Depot-Ped™ 7.5 mg, 11.25 mg and 15 mg for 1-month and 11.25 mg and 30 mg for 3-month administration for the treatment of children with central precocious puberty [135].

Sandostatin® LAR is a prolonged-release Octreotide formulation consisting of PLGA and NMP. Octreotide is a synthetic analogue of somatostatin that is used to treat acromegaly by controlling the levels of growth hormone (GH) and IGF-1, which reduces the size of tumours and regulates symptoms. It is also used in the treatment of gastroenteropancreatic neuroendocrine tumours (GEP NETs) by controlling gastrointestinal hormone secretion. FDA approval of the LAR formulations was granted to Novartis Pharmaceuticals Corporation on the 25th of November 1998 [136,137], with Novartis Pharmaceuticals UK Limited trading as Sandoz Pharmaceuticals granted marketing authorizations by the MHRA for 10, 20 and 30 mg formulations in June 2007 [138]. This product is injected intramuscularly and the prolonged release nature of the formulation allows for monthly dosing, regardless of dose. Modlin et al. reviewed a number of articles that focused on the use of Sandostatin® LAR in the treatment of GEP NETs, as well as other SST analogues. The review consisted of examining 15 previously published studies, which included 481 patients. They determined that the use of Sandostatin® LAR accomplished symptomatic relief in 74.2%, biochemical response in 51.4% and tumour response in 69.8% [139]. A multicenter study compared patient outcomes in relation to GH levels, IGF-1 levels and tumour size after treatment of acromegaly with the subcutaneous or long acting octreotide formulations. Upon completion of the study, 79% of patients showed a mean serum GH level of less than 5 mU L^{-1}, 53% had normalized IGF-1 levels and a 23% reduction in tumour volume was reported in 73% of patients [140].

Southern Biosystems patented sucrose acetate isobutyrate-based, a non-polymeric carrier, SPI technology with the license granted to DURECT™ under the trade name of SABER®. This technology is the basis of POSIDUR™ that delivers bupivacaine for the treatment of post-surgical pain. The release of bupivacaine has been shown to be successful for 3 days after injection during surgery [141]. A New Drug Application (NDA) for POSIDUR™ has been recently filed with the FDA [142]. The SABER® technology is also the basis for Relday™, which recently completed Phase I studies in the US [141,143]. DURECT™ and its collaborator Zogenix Inc., expect that the Relday™ can be delivered subcutaneously on a once-monthly basis, which will have advantages such as simplified dosing regimen, improved pharmacokinetic profile and significant reduction in injection volume [141]. In Phase I clinical studies (in 30 patients) with Relday™, it was reported that the adverse events in patients diagnosed with schizophrenia were generally mild to moderate and consistent with other risperidone products. Zogenix Inc. is expected to secure a development and commercialization partner for Relday™. Finally, SABER® technology has also produced SucroMate™ Equine, a veterinary product that was recently launched into the market [141].

12. Current issues and future developments of SPI implant technology

Although SPI implants are an attractive alternative to other currently used ISF methods of drug delivery, they do however face a number of problematic issues. The first to consider is the susceptibility to burst release. As shown, this can be extensive within the first 24 h after injection. A large initial release may result in drug levels that are above the therapeutic window and could be toxic. This is obviously is more problematic for those drugs that have narrow therapeutic window. As this review has shown, many groups have investigated a range of methods to modify this burst release, but to date no product with an altered release profile has made it to market. Secondly, due to the issue of the stability of PLGA in NMP, the Atridox® system is only available as a two component syringe system that must be mixed back and forth for $\approx$100 times prior to injection. This can be a lengthy process and is

Table 5
SPI based drug delivery patents field by leading pharmaceutical companies for different clinical applications.

Company	Drug molecule	Composition	Intended clinical application	Ref
Bausch & Lomb Inc.	Flucinolone acetonide	Polymer: PPF Solvents: NMP & DMSO	Ocular drug delivery	[111,145]
Novartis AG	Somatostatin	Polymer: PLGA Solvents: PEG500DME, PEGDEE	Acromegaly & cancer (*e.g.* carcinoid tumour & Cushing's disease)	[146]
pSivida Corp.	Morphine/Diclofenac	Polymer: PLGA Solvent: PEG	No details	[147]
Pfizer Inc.	Bone growth hormone	Polymer: PLGA, PLG-PEG Solvent: NMP	Implant to delivery bone growth promoting compound to bone tissues	[148]
ALZA Corp.	Resperidone	Polymer: PLGA Solvents: Triacetin, BA, BB, Ethanol	Psycho therapeutic application	[149]
Merck & Co.	Ivermectin, eprinomectin	Polymer: PLGA Solvent: Triacetin, Glycerol formal	Veterinary application	[150]

obviously not ideal. A two-component system could therefore be detrimental in terms of progress towards a patient self-administered formulation. Due to conflicting data relating to the toxicity of these SPI drug delivery system, this area is still of concern to research groups and may be limiting their use in practice. The main concern relates to the use of organic solvents. However, some work has been completed to combat the issue of PLGA instability in the form of alternative solvents. It has been shown that PLGA stability is increased when formulated in end-capped PEGs (PEG500DME and PEG-DAE) and the resultant solvents have shown favourable release and toxicity profiles [60,61]. The consideration of other solvents has also resulted in ethyl benzoate and low molecular weight PEGs being shown to be compatible [144].

Regardless of the current issues associated with the SPI systems many commercial products have been developed or under development, as shown in Table 4. Interest in this is due to the unique advantage of SPI implants that allows the delivery of small hydrophilic/hydrophobic as well as protein/peptide molecules and is applicable for a wide range of clinical conditions. For the same reason this technology has attracted wide interest among major pharmaceutical companies such as Bausch & Lomb Inc., Novartis AG, pSivida Corp., Pfizer, Alza Corp., and Merck & Co. This is clearly evident from their patents, as shown in Table 5, which promises future developments of this drug delivery technology. For example, Bausch & Lomb Inc. patented the use of SPI technology developed Mikos's research group from Rice University, Houston, USA [111,145]. This patent indicated the use of PPF based *in situ* implants for sustained ocular drug delivery. Here PPF was dissolved in NMP and DMSO solvents, which showed control release of FA for long-term (*e.g.* 16 weeks). Novartis AG filed a patent that showed the use of PEG500DME and PEG-DAE as solvents to deliver somatostatin for acromegaly and cancer application, which was initially developed by Schoenhammer's research group from the University of Regensburg, Germany [60,61,146]. pSivida, a leading provider of sustained ocular drug delivery systems, has shown interest in using PEG as a solvent, which is considered more safe than organic solvents [147]. Pfizer Inc. patented SPI technology that uses PLGA/NMP system for delivery of bone growth promoting compounds to bone tissues [148]. ALZA Corp. that later merged with Johnson & Johnson in 2001 has patented delivery of resperidone from PLGA and triacetin/BB/BA and/or ethanol system for psychotherapeutic applications [149]. Merck & Co. patented SPI system containing PLGA and triacetin and/or glycerol formal for delivery of different molecules (*e.g.* Ivermectin) for veterinary application [150]. Looking at the growing interest among major pharma companies and the ongoing developments clearly indicates the importance of this technology, which promises to deliver wide range of drugs in treating a rage of clinical conditions.

13. Conclusion

The need for novel and alternative forms of drug delivery is ever growing. There has been a powerful drive towards controlled release preparations due to the advantages in terms of drug release, administrations and also patient compliance. ISF systems are now gaining more interest from the pharmaceutical industry as feasible methods of delivering drugs over a prolonged period of time. ISF implants have a distinct advantage over their close relations involving microspheres, as the production method for microspheres is extremely complex. Within the realm of ISF implants, those that are formed by non-solvent induced polymer precipitation inherently have a number of benefits that have been discussed, mainly the ease of production, biocompatibility, favourable release profiles and also the accommodation of both hydrophilic and hydrophobic drugs including protein/peptide molecules. A number of research groups and companies are now focusing on the development of more polymer precipitation systems that can be used to effectively deliver and extend the range of drugs for various clinical applications. One of the most recent publications focused on the utilisation of ISF implants to deliver enfuvirtide, a new entry inhibitor anti-HIV drug [67]. Extensive work is also being carried out to develop new polymers that can be used to form the implants *in situ*. As described earlier, non-polymeric carriers are emerging, with an increasing number of copolymers such as PLEC being shown to effectively deliver drugs in this manner to more areas of the body including the brain [63]. As of yet, there are a limited number of products on the market utilising this promising technology and efforts are ongoing to produce more commercial products that will benefit patients worldwide.

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