PC Technology™ as a platform for drug delivery: from combination to conjugation

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Hydrogel polymers incorporating phosphorylcholine have found widespread use in the manufacture of medical devices with improved haemo- and biocompatibility. Examples include soft contact lenses or coatings for devices, such as coronary stents and extracorporeal circuits. The advent of drug-device combinations has prompted the application of PC Technology™ (Biocompatibles UK Ltd) as a bioinert drug delivery vehicle, particularly in the form of coatings, for targeted delivery from a device surface. The flexible polymer chemistry employed in the synthesis of these materials offers a range of molecular architectures that could find applicability in a wide variety of drug delivery applications, including micellar, vesicular and gel systems, and even drug conjugation.

Keywords: biocompatibility, combination product, gene therapy, hydrogels, medical device, micelles, PCylation, phosphorylcholine, stimulus-responsive materials, targeted drug delivery

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1. Introduction

Polymers have found widespread use in the field of drug delivery. Whether it is an enteric coating around a tablet or conjugation to a protein, the role of the polymer is important in modulating some aspects of the control of the delivery of the therapeutic. Although there is a vast range of polymeric materials available, only a limited number have found commercial use in drug delivery systems. This limitation is a consequence of the need for the system to be nontoxic, compatible and well tolerated within the body. The cost of gaining regulatory approval for a novel polymer is high and, therefore, radical innovation is slow and the focus remains on the use of approved materials, albeit in new ways. One area, however, that is of rapidly growing interest is that of drug-device combinations. This type of product aims to convey a significant clinical advantage by combining the physical function of the medical device with local drug delivery. Perhaps the most successful recent example of a combination device is the drug eluting stent (DES); the stent being placed into a blocked artery and expanded to keep the vessel open, while a drug is delivered from the device into the vessel wall to prevent local cellular overproliferation and, hence, re-narrowing of the artery over time [1,2].

Medical devices are generally made from materials that fulfil the specific physical properties required for the device to function effectively; they are, however, not necessarily designed to be well tolerated by the body. In recent years, various approaches have been adopted in order to improve the biocompatibility of devices. Polymers based on phospholipids that mimic the chemical structure of cell membranes have been used in the fabrication or coating of medical devices with improved haemo- and biocompatibility [3]. More recently, it has been demonstrated that these polymers are suitable for the delivery of a wide range of therapeutic compounds. As a result, a number of DESs that use these polymers have been commercialised, or are in development, in order to both enhance their biocompatibility and modulate the delivery of compounds, such as anti-inflammatory agents (dexamethasone from the Dexamet®

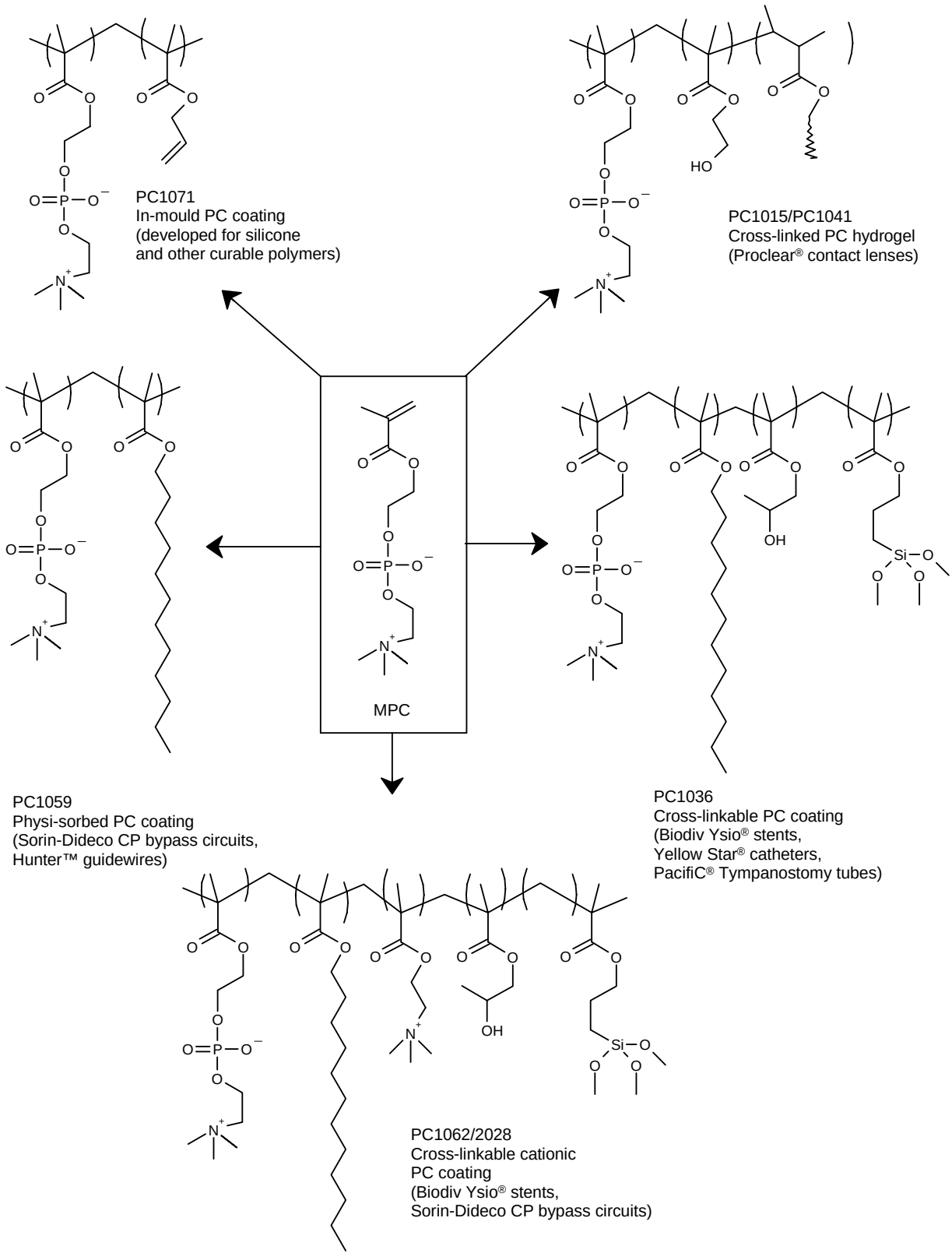

Figure 1. PC Technology: polymers for medical device fabrication and coating.
MPC: 2-Methacryloyloxyethyl phosphorylcholine; PC: Phosphorylcholine.

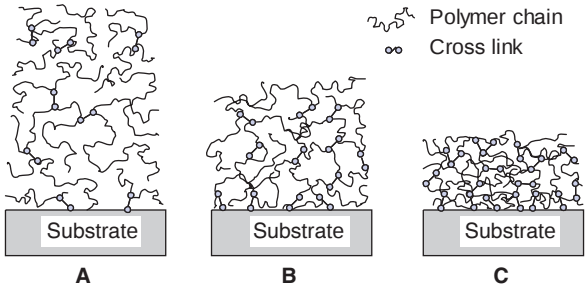

Figure 2. A schematic depiction of the effect of the degree of curing on polymer film structure, resulting in: A) low (30°C); B) medium (75°C); and C) high (150°C) levels of crosslinking.

coronary stent [4], Abbott Vascular Devices, Inc.), and antiproliferatives (ABT-578 on the Zomaxx™, Abbott Vascular Devices, Inc.) and Endeavor™ (Medtronic, Inc.) coronary stents [5]. The significance of this accomplishment was put into perspective by Boston Scientific's CEO, James Tobin, who revealed in May 2005 that they had screened 20 – 30 different polymers before they had identified a suitable polymer-coating candidate, saying 'it's actually easier to find a drug that works than it is to find a polymer that works.' This paper aims to detail more specifically the potential range of drug delivery-application properties of these phosphorylcholine polymers, with a focus on coatings useful for combination devices but also exploring the potential for the use of these materials for drug delivery in a broader sense.

2. PC Technology™

The outer layer of the red blood cell membrane is predominantly composed of phospholipids, which carry the phosphorylcholine (PC) headgroup. This chemical moiety carries both positive and negative charges (i.e., is zwitterionic, yet overall is electrically neutral) [6]. One consequence of the charged nature of the headgroup is its ability to attract a large hydration shell around it, which has been estimated to comprise 12 – 19 water molecules per headgroup [7]. When this group is immobilised at a surface, it forms a layer of bound water that essentially shields the substrate from the nonspecific, irreversible adhesion of proteins [8]. Protein adhesion is the initial stage of a series of events that ultimately results in adverse biological responses to devices that are placed within the body. It has been demonstrated that functionalisation of surfaces with compounds containing PC groups results in a marked increase in their haemo- and biocompatibility [3,9-12]. In the late 1970s, workers in Japan were successful in developing a process for producing a polymerisable phospholipid-like monomer based on methacrylate chemistry. The groups of Nakabayashi and Ishihara have studied materials based on 2-methacryloyloxyethyl phosphorylcholine (MPC; Figure 1) with respect to their interfacial, solution and bulk properties,

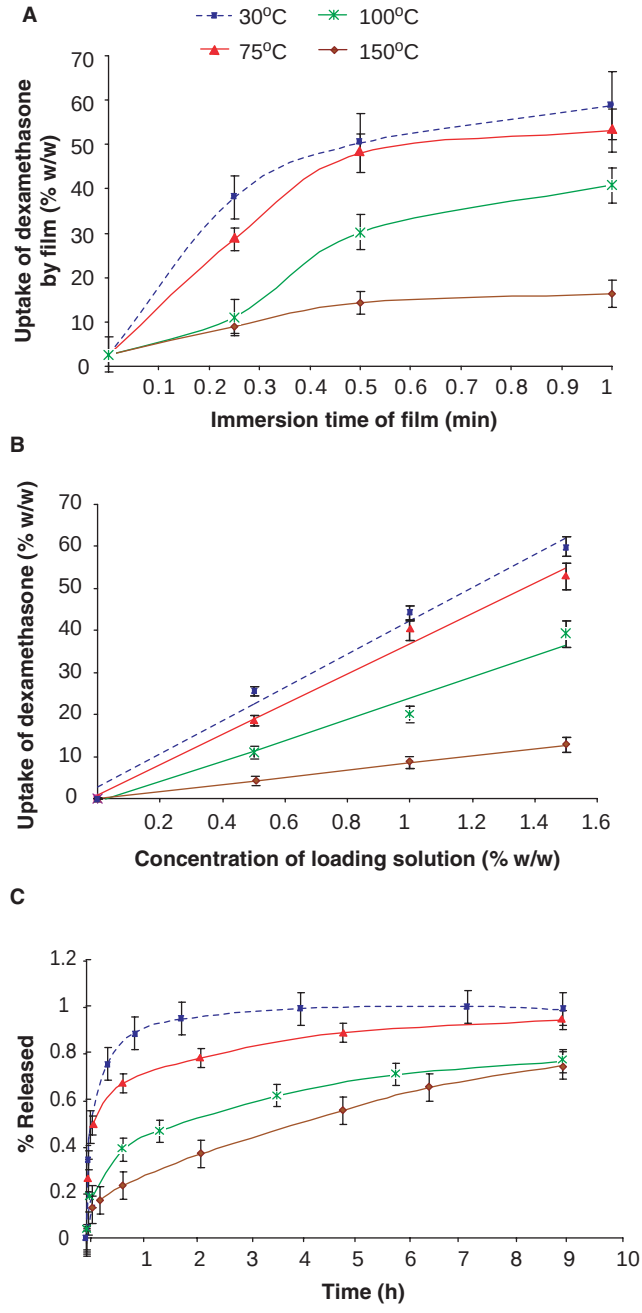

Figure 3. Effect of degree of crosslinking in the coating on dexamethasone A) uptake with immersion time; B) uptake with loading concentration; C) release (mean standard deviation).

and more recently with respect to drug delivery. This work has been well summarised elsewhere in a recent review, but the majority of the work has been presented from an academic perspective [13].

In parallel to the work in Japan, a family of MPC polymers have been developed and commercialised (Figure 1) by Biocompatibles UK Ltd, as a consequence of pioneering

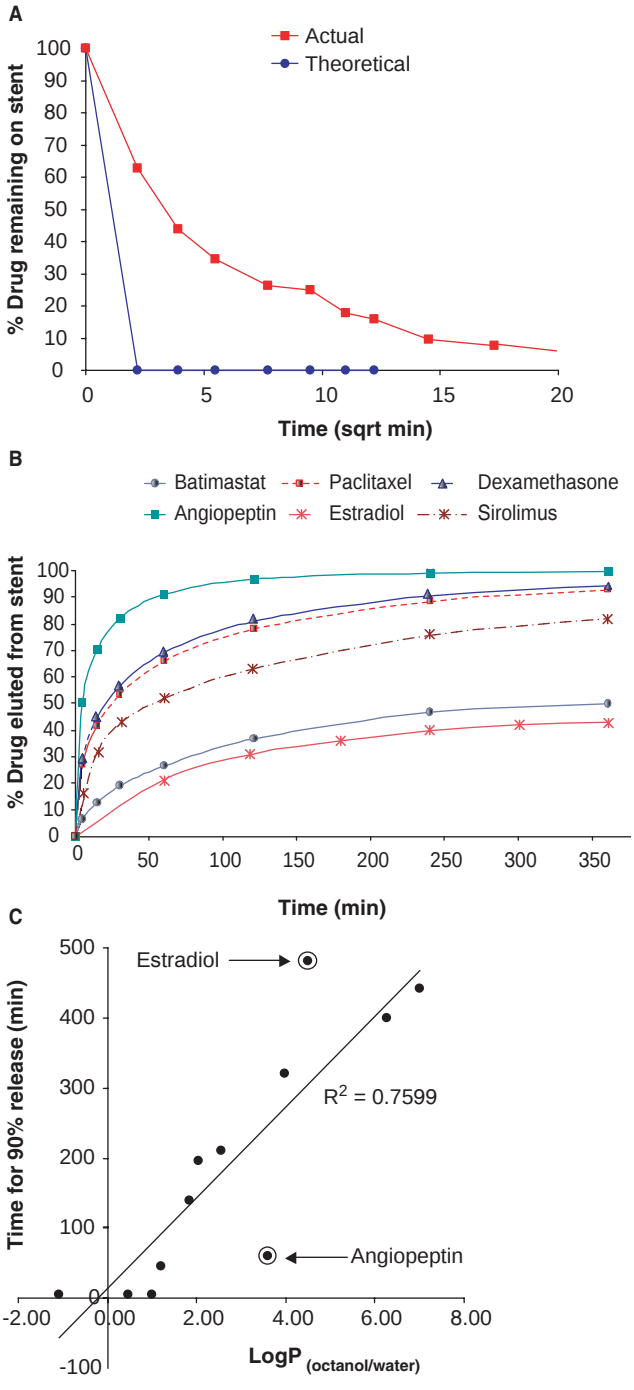

Figure 4. A. Theoretical versus actual dexamethasone release. B. Elution of various drugs from PC-coated stents. **C.** Relationship between time to release 90% of a drug versus the drug $\log P_{(octanol/water)}$ (all experiments carried out at room temperature, error bars omitted for clarity, typical coefficient of variation in the range 5 – 10%, n = 3 for each point).
PC: Phosphorylcholine.

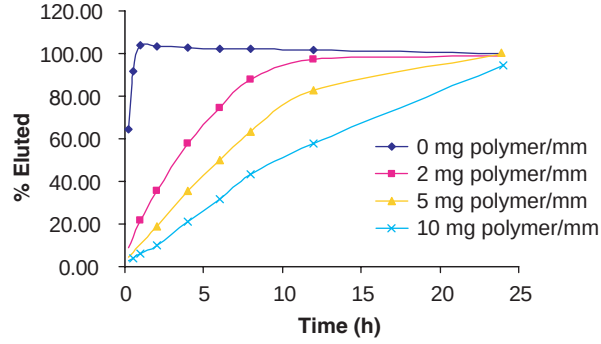

Figure 5. Effect of overcoating weight on model drug-elution kinetics.

work carried out in the early 1980s on PC materials by the company's founder, the late Dennis Chapman. These materials are known collectively as PC Technology™ [14], and have been approved and used in the manufacture of a variety of medical devices including: omafilcon A soft contact lenses (PC1015, PC1041; Proclear® & Proclear® Compatibles, Cooper Vision) [15]; intraocular lens development (PC1059) [16]; coronary stents (PC1036, PC2028) [17]; tympanostomy tubes (PC1036) [18]; ureteric stents and catheters (PC1036) [19]; glaucoma shunts (PC1036); and cardiopulmonary bypass circuits (PC1059) [20].

3. Flexible polymer chemistry

The PC polymers are synthesised by free radical polymerisation techniques of the (meth)acrylic monomers [21]. Entire devices (e.g., contact lenses) can be made by bulk polymerisation methods carried out in moulds. Where the polymer is to be applied as a coating, it is generally made as a linear, random polymer by solution polymerisation, isolation and purification. More specialised techniques, such as atom transfer radical polymerisation, can be employed to obtain living systems for the preparation of more controlled and exotic polymer architectures, such as block, comb and star polymers [22]. This method has been adapted for use in water and protic solvents, such as alcohols, which make it a particularly useful method for the controlled polymerisation of water-soluble monomers such as MPC [23,24].

A vast array of properties can be obtained using this flexible polymer system by appropriate choice of other methacrylate comonomers to combine with MPC. The MPC monomer is essentially responsible for conferring biocompatibility to the systems, and is usually present in excess of 15 mole% of the overall composition (although only ~ 7% in the contact lens); it is exceedingly hydrophilic and, as a result of its incorporation, the polymer systems it forms are generally classed as

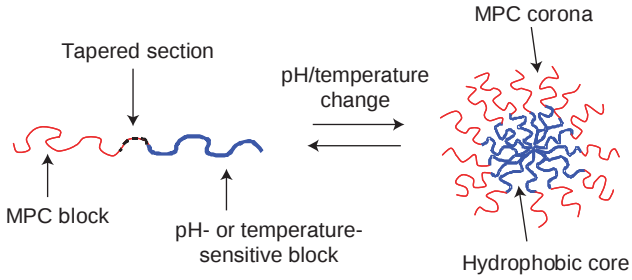

Figure 6. Schematic showing the switch between unimer and micelle form following stimulus.
MPC: 2-Methacryloyloxyethyl phosphorylcholine.

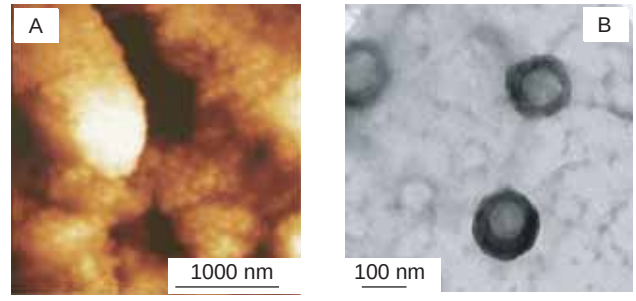

Figure 7. A. Atomic force microscopy image of MPC-micelles; B) transmission electron microscopy image of MPC-vesicles.
MPC: 2-Methacryloyloxyethyl phosphorylcholine.

hydrogels. Depending on the comonomers with which it is combined, the end polymer can, for example, be water soluble or swellable, adherent to surfaces, or prepared with residual functionality for subsequent covalent or ionic attachment to substrates. These polymer systems may be used as coatings and bulk materials, and have a range of water contents. They may optionally contain hydrophobic, ionic and/or crosslinking components that bestow ideal properties for drug delivery matrices on these materials.

By way of illustration, polymers such as PC1036, PC1062 and PC2028 are hydrogels with hydrophobic alkyl co-components that aid in the formation of coherent films, and result in good adhesion to a variety of substrates used in medical device manufacture. These polymers carry a silyloxyalkyl crosslinking group that is capable of thermal crosslinking post application of the coating [25]. Figure 2 gives an indication of how the degree of crosslinking, controlled by the curing temperature and/or the use of γ-irradiation, affects the structure of the matrix. The higher the energy input, the greater the extent of crosslinking within the coating. Additionally, there may also be increased adhesion of the coating to the substrate if the latter possesses functional groups capable of reacting with the silyl moieties. This controllable crosslinking provides a method of varying the interstitial space between polymer chains, and hence the free-water content, through which drugs may diffuse. Furthermore, the crosslinks will restrict the rate and degree of swelling in the film when it is exposed to an aqueous environment. This, coupled with the possibility of including both hydrophobic domains and/or ionic character, results in a capability of modulating the release of a wide range of therapeutic agents with different physicochemical properties.

4. Device drug delivery of small molecule agents

Drug loading into PC polymers can be achieved using a number of different approaches. One particularly facile method was adopted for investigational studies on coronary stents coated with PC Technology (PC1036) [26,27]. Any article possessing a coating of this material can be rendered capable of drug delivery by simply immersing it into a solution of the desired drug; the solvent being selected in order that it will also swell and penetrate into the coating. Techniques such as spectroscopic ellipsometry [28] and surface plasmon resonance [29] have been used to demonstrate that the coating swells rapidly in solvents such as water and lower alcohols, expanding to ~ 80% of its volume within a few minutes of being immersed. Loading assessments have been made with a range of therapeutic agents with different molecular-weights and the molecular weight cut-off of the maximally crosslinked coating was determined to be ~ 1200 Da in size [30]. Figure 3A exemplifies the rapid uptake of dexamethasone into the coating from an ethanolic solution and how this was influenced by coating-curing temperature. Figures 3B and C show that the extent of drug loading and release was related to the drug-loading solution concentration and, again, the crosslink density of the coating.

Simple diffusion of the drug through the coating cannot account for the release rates observed for many of the compounds when eluted from these systems. Pyrene fluorescence spectroscopy [30] and specular neutron diffraction studies [31] have shown the existence of hydrophobic domains within polymers that contain an alkyl chain component, such as PC1036. Naturally, as these copolymers swell in an aqueous environment, there will be an energetic drive for the hydrophobic components to aggregate on the molecular level and, hence, form domains, in addition to the water-filled interstitial spaces within the network structure. It is anticipated that once swollen into the pores of the hydrogel network, drugs that are more hydrophobic in character will interact with the alkyl chain domains, resulting in prolongation of their release rates. This is clearly illustrated in the case of dexamethasone (Figure 4A), where comparison of its theoretical release rate (based on its diffusion and solubility under sink conditions in the elution medium) versus its actual release *in vitro*, shows a significant retardation. Moreover, if one considers the time it takes to achieve 90% release of various compounds from the PC coating (T_{90}; Figure 4B), this can be weakly correlated to the partition coefficient of the compound in an octanol:water mixture ($logP_{[octanol/water]}$), again suggesting

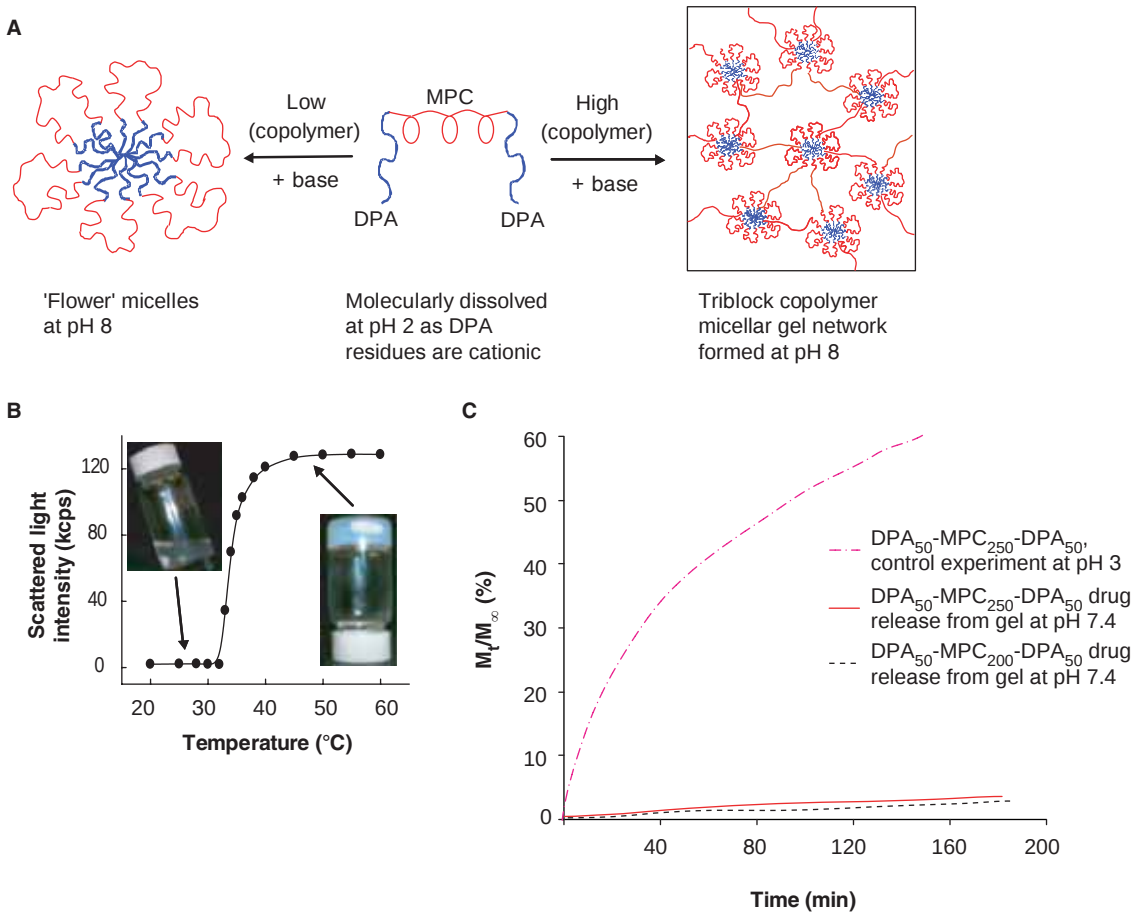

Figure 8. A. Schematic showing the switch from 'flower' micelles to micellar gels following stimulus. B. Drug release from stimulus-responsive phosphorylcholine gels (conditions: 15% copolymer solution with 5% dipyridamole based on copolymer. The total drug concentration in the final gel is 0.6%).
DPA: Diisopropylaminoethyl methacrylate; MPC: 2-Methacryloyloxyethyl phosphorylcholine.

that this involves some hydrophobic interaction between the drug and the polymer (Figure 4C) [30].

Alternative methods of incorporating the drug into the polymer coating include direct application of the drug–polymer combination to the surface of the desired substrate. This can be achieved by various coating techniques including dip, spin and spray, with the latter providing particularly controlled dosing. The drug in this instance, however, must be able to withstand the curing/sterilisation regimes that will be employed post coating. Further control over the rate of delivery of the agent from such coatings can be attained by subsequent application of multiple overcoats of the polymer-only composition, which then performs a barrier function and can modify release kinetics, to produce a zero-order release in some instances (Figure 5).

5. Other drug delivery opportunities

PC Technology also has the potential for use in areas of drug delivery other than coatings. Konno *et al.* recently reported on the use of simple copolymers of MPC and butyl methacrylate for solubilising poorly water-soluble drugs such as paclitaxel [32]. The use of more specialised polymerisation methods such as atom transfer radical polymerisation (see Section 3) can generate a number of useful architectures, the simplest being the diblock copolymer [33,34]. With appropriate selection of the comonomer to be combined with the MPC moiety, amphiphilic blocks can be formed that will self-assemble into structures such as micellar aggregates or vesicles, either spontaneously or under some specific stimulus. For instance, the second block can be selected from a compound that may change its character from hydrophilic to hydrophobic on application of a stimulus, such as pH or temperature (Figure 6) [35].

Thus, 'stealth micelles' in the order of 30 – 100 nm, dependent on block sizes and preparative method, can be created wherein the MPC forms a biocompatible corona around a tunable hydrophobic core into which hydrophobic drugs can be loaded (Figure 7A) [36]. Liccardi *et al.* have shown that drugs such as paclitaxel and tamoxifen can be loaded into these

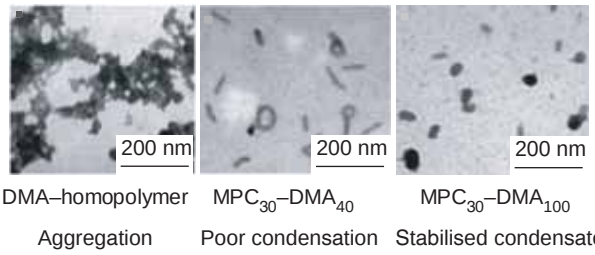

Figure 9. Effect of MPC copolymer block lengths on DNA condensate morphology (2:1 polymer:nucleotide ratio).
DMA: Dimethylaminoethyl methacrylate; MPC: 2-Methacryloyoxyethyl phosphorylcholine.

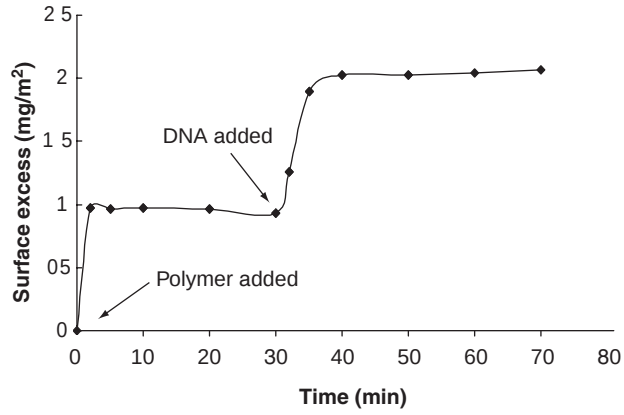

Figure 10. Adsorption of MPC_{30}–DEA_{70} (0 – 30 min) and luciferase-plasmid DNA (30 – 70 min) at the hydrophilic silicon oxide/solution interface at pH 7 and 23° C (all at 100 µg/ml).
MPC: 2-Methacryloyoxyethyl phosphorylcholine.

micellar systems at physiological pH, and that at pH 5 – 6 (similar to that found in the endosome following endocytosis by cells), the micelles deconstruct and release the drug payload as the hydrophobic block becomes hydrophilic following protonation [37]. Moreover, these block copolymers have been functionalised at one end with a conjugated folic acid residue; such that when micellar structures are formed, the outsides are decorated with this ligand to enable targeting of the folic acid receptor, which is overexpressed on the surface of many cancer cells. Under a modified preparation route, the block copolymers can be formed into vesicles in which the central core is hydrophilic in nature, and can be used to carry aqueous-soluble drugs (Figure 7B) [38].

Further variations in the polymerisation process can be used to enable the construction of triblock [39] or even star-block copolymers [40]. Inclusion of similar stimulus-responsive co-components can result in PC-based, reversible gelation systems, that will, for instance, form physical gels following changes of pH or temperature (Figure 8A and B) [39]. These gels can be formed in the presence of drug compounds. When entrapped within the gel matrix, these therapeutics have the potential for interaction with the hydrophobic domains in the gel. This provides a method for modulation of release of the agent from the gel structure (Figure 8C). Versions of these gels have been shown to be nontoxic to cells and used in preliminary cell entrapment studies to assess the materials for potential use in tissue-engineering applications.

6. PC Technology™ for delivery of biomacromolecules

PC Technology has also been developed with the capability to interact with, and deliver, larger biomacromolecules, such as antisense DNA fragments and plasmids. One example of the use of such technology in combination medical devices on the coronary stent; for which the PC2028 coating was designed in order to bind reversibly at the surface of the device with species carrying a net negative charge, such as many nucleic acid derivatives [41]. Preclinical evaluation of such systems have shown proof of concept; in one demonstration, radiolabelled oligonucleotides were delivered to the porcine coronary artery in a sustained fashion over a 14-day period [42]. In another study, plasmid-DNA coding for VEGF production was successfully delivered to the artery in a hypercholesterolemic rabbit model, and resulted in significantly reduced intimal hyperplasia [43].

It has been shown by Lam *et al.* that the PC diblock copolymers made with a complimentary block that is cationic or protonatable in nature can condense DNA into polyplexes; the structure and dimensions of these are dependent on the relative block lengths (Figure 9) [44,45]. Folic acid functionalisation of the diblock, as described in Section 5, enables more efficient targeting of the polyplex to cells bearing the folate receptor, which has been demonstrated by increased transfection efficiency, compared with the non-ligand containing systems [46].

An interesting variant on the use of these diblock copolymers is being investigated by Zhao *et al.*, where they have shown that diblocks will undergo spontaneous interfacial adsorption in a stable fashion to certain surfaces. If the pre-adsorbed substrate is subsequently immersed into a solution containing DNA, the diblock will interact with the material, sequestering it from solution and adsorbing it onto the surface as a complex. The relative charge ratio between the cationic block and anionic macromolecule is ~ 1:1. The amount of bound DNA can be controlled by the amount of diblock copolymer adsorbed onto the surface, the concentration of the DNA in solution, or indeed the contact time between the adsorbed surface and the DNA solution (Figure 10) [47].

7. PCylation of compounds

The vast majority of work performed on the evaluation of PC-containing materials for use in drug delivery applications has focused on the use of the polymer as a vehicle in one

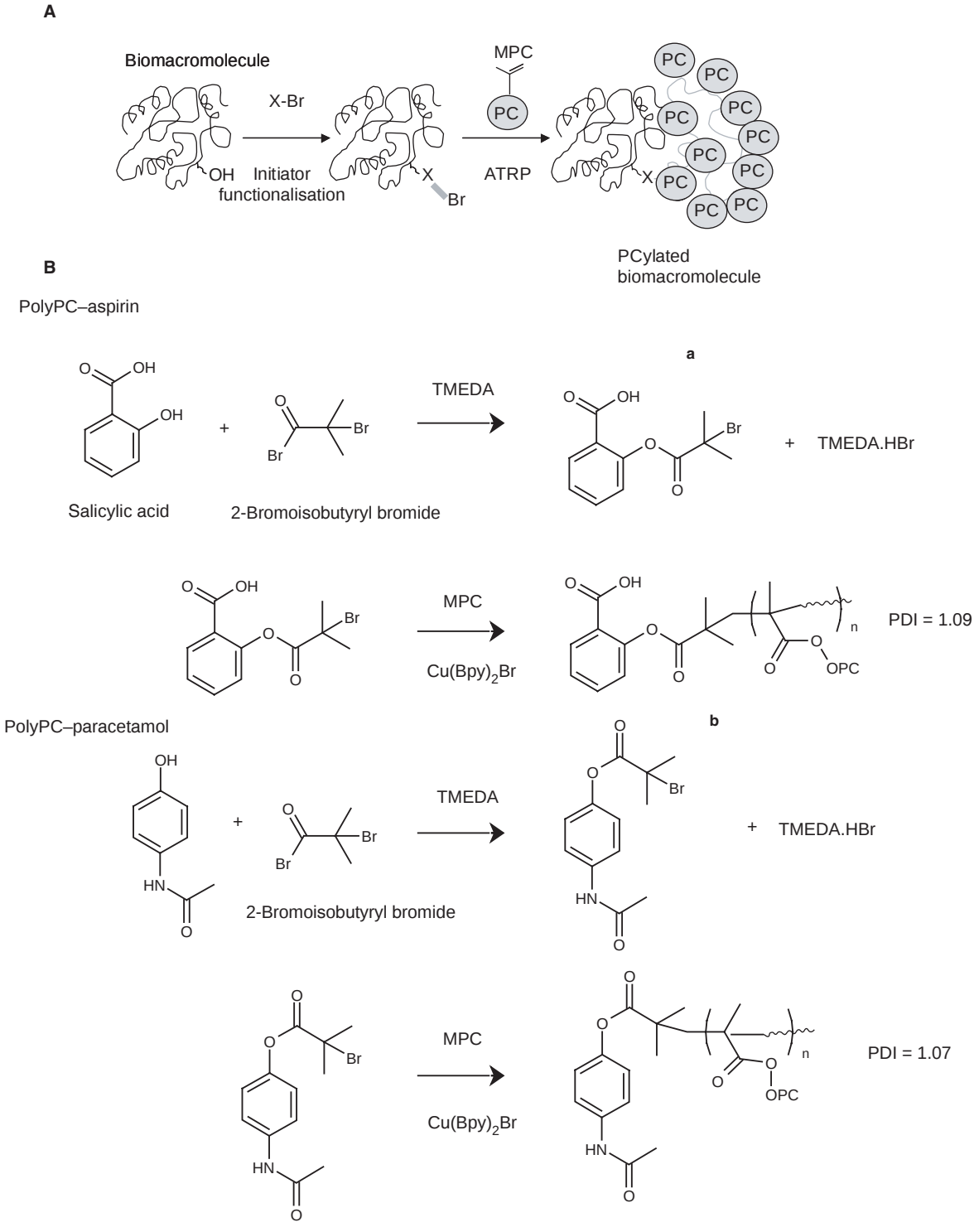

Figure 11. A) Schematic showing the PCylation of biomacromolecules. B) PCylation of small molecule-drug species.
ATRP: Atom transfer radical polymerisation; Br: Bromine; MPC: 2-Methacryloyloxyethyl phosphorylcholine; PC: Phosphorylcholine; PDI: Polydispersity index; TMEDA: Tetramethyl ethylenediamine.

form or another, with which drugs can interact or become entrapped, and their release at their target site is controlled in some fashion. The technology, however, can be extended to the modification of the therapeutic agent itself in order to influence properties key to the performance of the drug, such as plasma half-life, toxicity and immunogenicity. In the

case of small molecule modification, it has been shown that simple compounds, such as aspirin, paracetamol or dexamethasone (which have appropriate functionality in order that they can be converted into a polymerisation initiator), can subsequently be used to grow a drug-functional polymer chain of defined length and polydispersity that will impact greatly on the drugs physicochemical properties (Figure 11A and B) [101]. Perhaps the greatest potential for such technology is the modification of therapeutic proteins. Polymer modification in this field has had a great impact, with the advent of pegylated drugs such as PEG-IFN. Miyamoto *et al.* have synthesised poly(MPC) by a living-radical technique, then conjugated this to the enzyme papain and demonstrated that the conjugated entity is more stable than the native enzyme [48]. Given the vast amount of information available on PC-based materials and their proven performance *in vivo* on a variety of medical devices, PCylation could offer potential benefits in the modification of protein therapeutics of the future, and proof-of-concept work is currently underway to turn this into reality.

8. Expert opinion and conclusions

PC Technology encompasses a wide variety of PC-based polymers that have proven compatibility within the body. Although inherently difficult to deliver small molecules over extended periods of time from very thin films, the inclusion of groups that provide hydrophobic interaction, the variable crosslinking density and the possibility to add multiple layers with different water contents are just a few of the approaches that extol the flexibility of these materials. Although *in vitro* release methods often predict more rapid release, when a device is placed *in vivo*, the release of the therapeutic may be dictated by diffusion into tissue rather than a large volume of liquid; hence, release patterns *in vivo* are often very much longer than predicted otherwise. The technology is, therefore, finding increasing use in the growing area of drug delivery combination devices, and with the array of different polymer architectures that are possible within this technology platform, has great potential for many other areas of drug delivery in general.

The large hydration shell afforded by the phospholipid headgroup may mean that it is a more effective protein-resistant technology than PEG-based systems, although, so far, comparative studies in which the two systems have been truly evaluated side by side have not been carried out. The biomimesis of the polymer systems may provide the key to lessening immunological responses, whereas their polymeric nature offers the advantage of stability over simple lipid analogues. For applications where the materials are blood-borne carriers, or conjugated to therapeutics for intravenous administration, this may translate into reduced opsonisation, extended plasma half-lifes and, hence, sustained efficacy, with a decrease in immunological complications.

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