A New Approach for the Functionalisation of Polysulfone with β-cyclodextrin

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Abstract

Functionalisation of polysulfone (PSU) with β-cyclodextrin (β.CD) is a potential vehicle for the design of drug delivery devices via complexation. In this approach, PSU film was first pre-activated by air plasma to facilitate a post-grafting reaction with methacrylic acid (MAA) and then amination by diamino-dipropylamine (DADPA). Finally, β.CD was anchored on to PSU-PMAA-DADPA surfaces via covalent bonding with amino groups. Creation of functional groups was confirmed by ATR-FTIR and functionalisation of PSU-PMAA-DADPA film with β.CD was verified by UV absorbance following immersion in phenolphthalein (PHP), which formed inclusion complexes with the attached β.CD. A reduction in absorbance of the PHP solution was observed, together with an increase in PHP exhaustion on to the PSU-PMAA-DADPA films as a result of functionalisation with β.CD. Increasing the amount of β.CD attached to the PSU-PMAA-DADPA films progressively increased PHP exhaustion until saturation was achieved.

Keywords: Polysulfone film; Air Plasma; Post-grafting; β-cyclodextrin; Phenolphthalein

1. Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides generally composed of six, seven or eight α-D-glucose units (α, β and γ, respectively).[1] CDs are cage-shaped molecules consisting of a hydrophobic cavity which can host a variety of long chain of aliphatic or aromatic molecules like drugs, pesticides, hormones, detergents, fragrances and vitamins.[2] Commercially, the most common compound in use is β-cyclodextrin (β.CD) due to its simple production method, availability, favourable cavity diameter, and relatively low cost. It represents at least 95% of all CD production.[3] Otherwise; polysulfone (PSU)is an aromatic thermoplastic polymer that possesses superior mechanical properties, thermostability, chemical stability, and processability.[4] due to its superior thermal, chemical and mechanical properties, PSU has found uses in several applications like in filtration membranes [5-9], coatings[10, 11], composites[12, 13], and thin-film technology.[14, 15] It has also been in combinationwith biomolecules.[16]

Without degrading basic polymer properties, chemical modifications of the end-groups or backbone of PSU polymer can yield good results compared with blended systems in which two or more different polymers are combined to introduce hybrid polymeric systems for specific purposes.[17] Recently, two ways have been widely applied for the modification of PSU: (i) introduction of functional monomers and (ii) post-polymerisation approaches.[17] both of them serve to introduce functional groups onto the PSU backbone to enhance properties and act as access points to further modification. There have been many studies reporting the uses of these two approaches for the modification of PSU.[18-31]

Phase inversion techniques have been described for the functionalisation of PSU with β.CD for filtration applications like the removal of endocrine disrupting chemicals (EDCs). These were found to intrduce high flux [32], be effective in removal natural organic matter (NOM) with enhanced antifouling properties [33], be effective in enantiomer separation from a racemic mixture of α-amino acids [34], and to remove humic acid from water.[35] The study herein focuses on the functionalisation of PSU with β.CD using a plasma pre-treatment approach. Following air plasma treatment of a PSU film to create hydroxyl groups on the surface, graft polymerisation of MAA monomer was initiated by Ce(IV) to introduce carboxyl groups.[36] The carboxyl groups were then reacted with (DADPA) to introduce amino groups.[36] Finally, β.CD was attached covalently on to the PSU film surface by oxidised primary OHs of β- CD [37] by wet air oxidation[38] to obtain aldehyde and carboxyl groups.[37] This was followed by the Schiff base reaction between aldehyde groups of the oxidised β-CD and amino groups [37] of the PSU-PMAA-DADPA film. Creation of functional groups on the modified PSU film was verified by Attenuated total reflectance Fourier-transform Infra-Red (ATR-FTIR) Spectroscopy and a phenolphthalein (PHP) test method was used to characterise the presence of β.CD on the functionalised film.

2 Materials and Methods

2.1. Materials

Polysulphone (PSU; Mw ~16,000), dimethylformamide (DMF), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDAC), N-hydroxysuccinimide (NHS), 2-(N-morpholino) ethanesulphonic acid (MES), methacrylic acid (MAA), sulphuric acid, sodium hydroxide, diamino-dipropylamine (DADPA), ammonium cerium(IV) nitrate, β- cyclodextrin (β.CD), phenolphthalein (PHP), ethanol, sodium carbonate were all purchased from Sigma–Aldrich, UK and used without further purification.

2.2. Preparation of PSU film

0.25 g ml^{-1} PSU solution was prepared by stirring the PSU in 50ml DMF with a magnetic stirrer at room temperature for 24 h until a clear homogenous solution was obtained. PSU films (thickness 0.34 mm) were then cast from this solution by swirling the solution on a petri dish and were solidified by drying at room temperature for 24 h.

2.3. Modification of PSU film with Plasma induced graft polymerization

Air plasma treatment of the PSU film was done in a low temperature low pressure plasma machine (Model: Diener Electronic GmbH, PICO; 40 kHz). The plasma treatment was carried out for 30 min each side with a plasma power of 60W, a flow rate of 15 sccm and an initial pressure of 0.51 mbar. An aqueous solution of MAA was prepared by dissolving 10 ml of MAA in 40 ml of distilled water (DI). 1.07 ml of $0.4MH_2SO_4$ and 2g ammonium cerium (IV) nitrate was added to the MAA solution, mixed, and refluxed at 80ºC for 30 min in an inert nitrogen atmosphere. 0.2g of plasma treated film was added to the reaction mixture and the reaction was continued at 80°C for 40 min in the inert nitrogen atmosphere. The resulting material is notated as PSU-PMAA film. The PSU-PMAA was thoroughly rinsed with 50 ml 0.01 mol dm^{-3} NaOH for 6h to remove the unreacted monomer and then the film was rinsed in 50 ml DI water for 24 h. The neutralised PSU-PMAA film was immersed into a glass bottle containing 50 ml of MES buffer (1g MES, 0.5g NHS and 0.5g EDAC; pH 5.5) at room temperature for 1 h with stirring by magnetic stirrer. This reaction was carried out to catalyse the formation of amide bonds between carboxyl groups and primary amino groups.[39] The film was then immersed in an aqueous solution of 15 ml DADPA in 35 ml DI water and reacted at 4°C using an ice bath for 2 h. The PSU–PMAA–DADPA film was rinsed with DI water thoroughly to remove residual DADPA.

2.4. Functionalisation of PSU-PMAA-DADPA film with β.CD

Fig. 1 shows a schematic of the process in which β.CD is covalently bonded to PSU-PMAA-DADPA film. Varying amounts of β.CD (Table 1) was added in 30 ml DI water in an Erlenmeyer flask with a rubber stopper and was shaken in a water bath (Grant OLS200) at 140 cycles min^{-1} at 60°C for 10 min (heat/wet air oxidation of β.CD). 0.03g of PSU-PMAA-DADPA film was then added and the reaction was maintained at 60°C for 1 h. The temperature of the reaction was then increased to 85°C at 2.5°C min^{-1} and maintained at 85°C for 1 h. At the end of the reaction, the film was removed and was washed with DI water. The resulting material is referred to as PSU–PMAA–DADPA–β.CD film. The treatment profile with β.CD is shown in Fig.2.

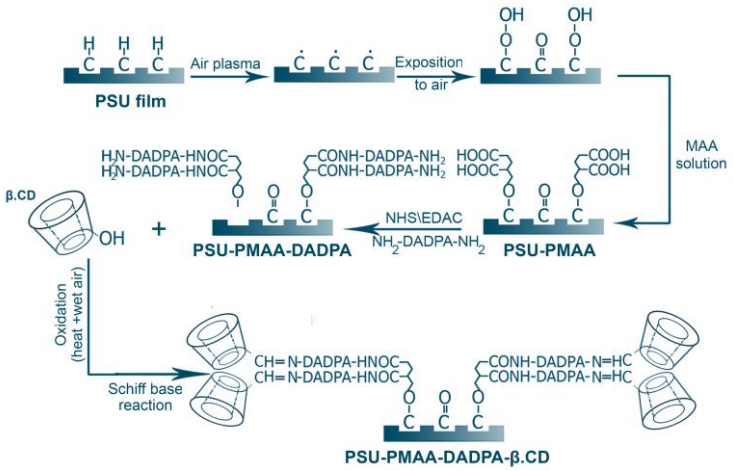

Figure 1. Schematic representation of the PSU surface modification procedures and the functionalisation with β.CD, where NH_2-DADPA-NH_2 is $NH_2CH_2CH_2CH_2NHCH_2CH_2CH_2$- NH_2

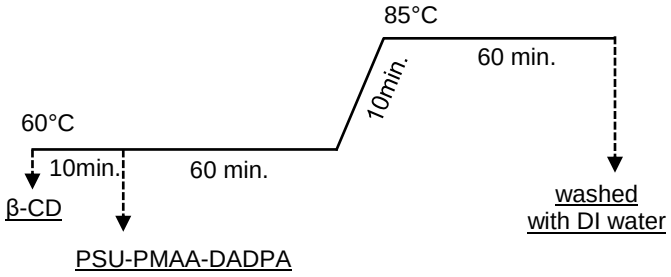

Figure 2. Schematic of the functionalisation of PSU-PMAA-DADPA film with β.CD

2.5. Characterisation

The structural changes to the PSU film were analysed using a Perkin-Elmer Spectrum BX spectrophotometer with diamond ATR attachment (Attenuated Total Reflectance-Fourier Transform Infrared (ATR-FTIR)). Scanning was conducted from 4,000 to 600 cm^{-1} with 32 repetitious scans averaged for each spectrum. Resolution was 4 cm^{-1} and interval scanning was 1 cm^{-1}. The cavity of β.CD form inclusion complex with phenolphthalein (PHP)[40] and this method was used to characterise the PSU film functionalised with β.CD; the resulting change in colour was measured with a UV-VIS spectrophotometer (JASCO V-630) at 554 nm (λ_{max}). A solution was prepared by adding 1 ml of 4mM PHP solution and 4 ml of ethanol to 100ml of 125mM sodium carbonate solution. The solution was mixed and 5 ml of the prepared solution was added to sample vials with 0.03 g of PMAA–DADPA–β.CD film. After mixing for 18 h, a portion of the solution was placed in a cuvette and the absorbance of the solution was measured. The exhaustion (E%) of PHP by the PSU-PMAA-DADPA-β.CD film was calculated using Eq. 1,

where PHP Abs_b is the PHP absorbance of blank solution without β.CD and PHP Abs_a is the PHP absorbance of solution containing β.CD. Fig.3, shows the calibration curve of PHP exhaustion by known concentrations of β.CD and Eq. 2 was derived from this calibration curve.

$$\text{PHP exhaution} = \frac{\text{PHP Abs}_b - \text{PHP Abs}_a}{\text{PHP Abs}_b} * 100 \qquad \text{Eq.1}$$

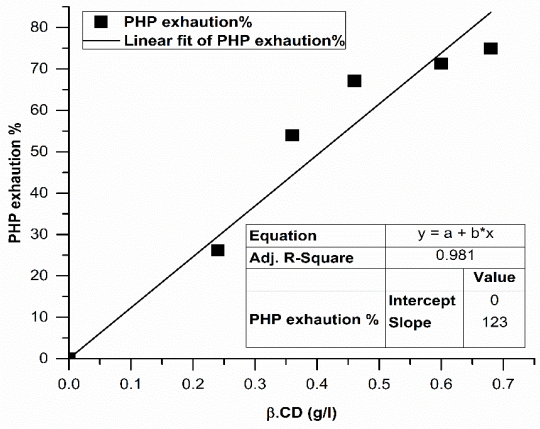

Figure 3. Calibration curve for β.CD at known concentrations and corresponding PHP exhaustion [β.CD (0-0.7) g/l, PHP solution:(5ml), time (18h) at room temperature]

$$\text{PHP exhaution}_{\beta.CD} = 123 * C_{\beta.CD} \quad (R2 = 0.98) \quad \text{Eq.2}$$

3. Results and Discussion

3.1. Attenuated total reflectance Fourier-Transform Infra-Red (ATR-FTIR) Spectroscopy

Fig. 4 shows a comparison between the original and surface functionalised PSU film (PSU-PMAA-DADPA-β.CD). Fig. 4a exhibits the spectra of β.CD. The β.CD produces a broad peak between 3200 and 3550 cm^{-1} attributable to the stretching vibrations of hydroxyl groups. The peak at 1021 cm^{-1} is due to C-O bending vibration and the absorption band at 1152 cm^{-1} is due to C-O-C (alkyl substituted ether). Fig. 4b reveals the absorption spectra of PSU film. For the PSU–PMAA–DADPA film (Fig. 4c), the spectrum shows a broad adsorption between 3100 and 3500 cm^{-1} which is due to the $–NH_2$ groups of DADPA and the peak at 1644 cm^{-1} is due to amide bonds formed between the –COOH groups of MAA and the $–NH_2$ groups in DADPA. The PSU-PMAA-DADPA film functionalised with β.CD shows a broad peak between 3200 and 3550 cm^{-1}; this indicates the vibrational stretching of the OH bond. The absorption at 1032 cm^{-1} was due to the stretching of C–O ether bonds. These findings indicate the formation of PSU-PMAA-DADPA-β.CD film [Sample 4; Table 1] (Fig. 4d).

3.2. Phenolphthalein (PHP) method

PHP forms an inclusion complex with β.CD. When PHP is included in the β.CD cavity, accordingly; the colour of the solution changes and the absorbance of the resulting solution decreases also. This makes PHP a convenient colorimetric indicator of the availability of β.CD cavities for inclusion complex formation. In this regard, PHP has therefore been used for the qualitative detection of β.CD and evaluation of inclusion sites. The PHP method proved to be a convenient and reliable method of quantifying the presence of β.CD on the functionalised film (PSU-PMAA-DADPA-β.CD).[41] The functionalised film was immersed in a solution containing PHP and the sorption of PHP in an alkaline solution was determined at 554 nm (λ_{max}). It is evident from Fig.5 that the PHP exhaustion after immersion of the PSU–PMAA–DADPA–β.CD film [Sample 4, Table 1] is higher than the untreated PSU film, which is indicative of successful functionalisation of PSU–PMAA–DADPA film with β.CD.

The amount of β.CD attached to the PSU-PMAA-DADPA film was calculated using Eq.1 and Eq.2. From Fig.6 and Table 1, the relationship between the amount of β.CD functionalised PSU-

Table 1. Different concentrations of β.CD and its PHP absorbance, PHP exhaustion and the exact amount of attached β.CD

Sample number	β.CD in treatment solution	PHP	PHP	Attached β.CD
	(g/l)	(Abs)	(E %)	(w/w)
1	0	0.9	0	0
2	33	0.8	11	1.48
3	67	0.6	33	4.47
4	100	0.5	44	5.97
5	133	0.5	44	5.97

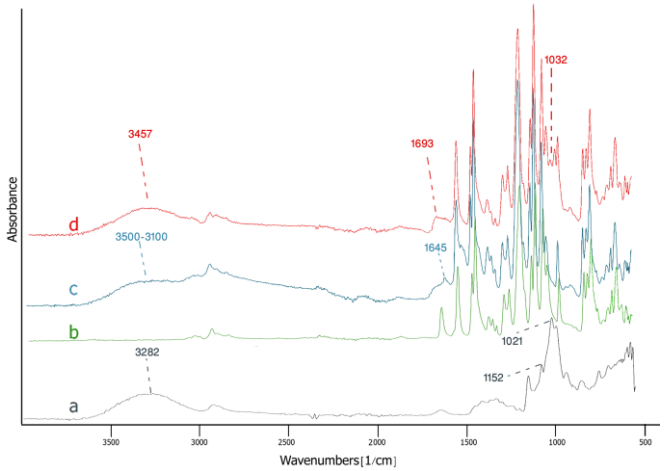

Figure 4. ATR-FTIR spectra of (a) β.CD, (b) untreated PSU film, (C) PSU-PMAA-DADPA film and (d) PSU-PMAA-DADPA- β.CD film [Sample 4, Table 1]

PMAA-DADPA film and the exhaustion (E%) of PHP by the PSU-PMAA-DADPA-β.CD film is revealed. The increase in PHP exhaustion (E%) is due to the increase in β.CD that is attached to the PSU-PMAA-DADPA film. At higher β.CD concentrations, the PHP exhaustion (E%) reaches a maximum, which is likely to be due to the saturation of $-NH_2$ groups on the PSU-PMAA-DADPA film with β.CD, as well as the restricted penetration of β.CD solution in to the depth of the film as a result of the high viscosity of the β.CD solution at higher concentrations.[42]

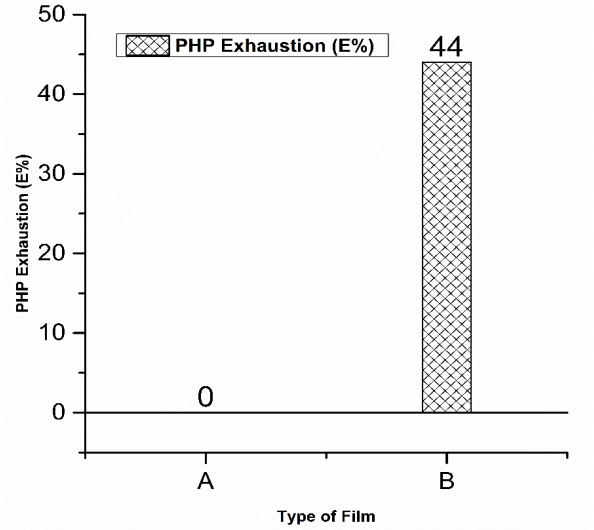

Figure 5. PHP exhaustion of (A) untreated PSU film and (B) PSU-PMAA-DADPA-β.CD film [Sample 4, Table 1]

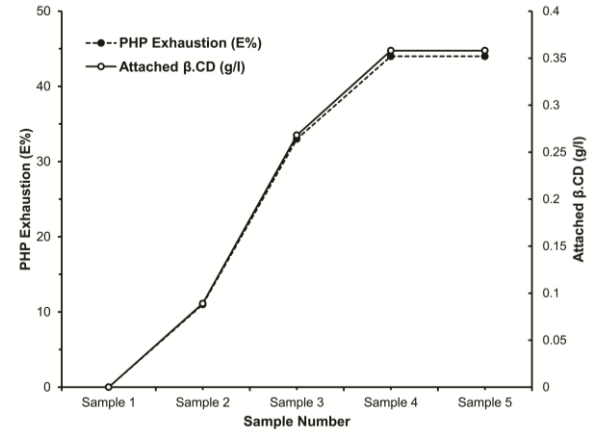

Figure 6. Relationship between the amount of β.CD attached to PSU-PMAA-DADPA film and the PHP exhaustion (E%) with different β.CD concentrations

4. Conclusions

PSU was functionalised using a procedure involving pre-activation via air plasma exposure, followed by a post grafting reaction with methacrylic acid (MAA), and then amination and functionalisation with β.CD. Successful covalent attachment of β.CD was confirmed by assessing the sorption of PHP in alkaline solution at 554 nm (λmax). A decrease in absorbance was confirmed due to inclusion complexation with the β.CD attached to the PSU-PMAA-DADPA film. The feasibility of using PSU-PMAA-DADPA as a means to covalently attach β.CD was demonstrated. Given that the complexation with β.CD is only possible if the compound fulfils certain chemical and dimensional characteristics and the inherent biological inertness of PSU and stability under sterilisation, the resulting materials are promising candidates for use as drug delivery substrates.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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