Chapter 7. Conclusions and recommendations

7.1 Synopsis

The aim of this thesis was investigated the importance of Na-Alg in water treatment and in drug delivery systems. The removal of Cu^{2+} from aqueous solution was achieved using Ca-Alg_2/GO gel beads. The release profile of RB, Rubpy and CPT was examined using Ca-Alg_2 hydrogel discs. Finally, the modification of Na-Alg by grafting with β-CD was achieved, and the release profile of CPT from CPT/β-CD and CPT/β-CD-g-Alg inclusion complexes was studied.

7.2 Conclusions

From the literature review in Chapter 1 it was found that alginate materials have been used widely for water treatment applications due to their ability to form stable " egg-box " structures, as well as their biocompatibility and relatively low-cost [11-14, 16, 17, 19-21]. Literature has shown that the porous structure of ionotropic metal alginates (e.g., Ca-Alg_2) plays a key role in the adsorption of toxic heavy metals from wastewater [39, 119]. Therefore, recent studies have employed various host materials to enhance the absorption capacity of Ca-Alg_2 [27, 40-43, 133, 142, 146].

It was found that polysaccharide hydrogels have received much attention in drug delivery systems [81]. Literature has shown that many drugs undergo a fast release from Ca-Alg_2 hydrogels and so research has focused on prior blending of Na-Alg with another natural polymers in order to retard the release of the drug from Ca-Alg_2 hydrogels [94, 96, 98-103].

It was observed that β-CD can be used to improve drug delivery systems due to its ability to form an inclusion complex (host-guest complexes) with various guest molecules [108]. Current advances in drug delivery system have already utilised polymers, conjugated with β-CD units, to control the release of poorly soluble drugs [104, 109, 116, 117].

This thesis covers both the use of Ca-Alg_2 hydrogels in water treatment and drug delivery systems as well as the modification of Na-Alg with β-CD to achieved controlled hydrophobic drug release. Chapter 2 described the experimental details for the Ca-Alg_2 and Ca-Alg_2/GO hydrogel bead synthesis and characterisation, and their application in the removal of Cu^{2+} ions from aqueous solution. It also described the application of Ca-Alg_2 hydrogels in drug delivery systems and the modification of Na-Alg and its application in controlled drug delivery.

Chapter 3 concentrated on the fabrication of Ca-Alg_2 and Ca-Alg_2/GO gel bead adsorbents. The synthesis of Ca-Alg_2 and Ca-Alg_2/GO gel bead was characterised by Fourier transform infrared (FT-IR), thermogravimetric analysis (TGA) and focused

ion beam scanning electron (FIB/SEM) spectroscopies and examined the removal of Cu^{2+} ions from aqueous solution. The influence of the use of different adsorbent doses, Cu^{2+} ion concentrations and contact times on the adsorption process was investigated. The adsorption capacity at equilibrium (q_e) of the two adsorbents reduced with increasing adsorbent dose, indicating that the higher adsorbent doses provided more active adsorption sites for the Cu^{2+} ions and remain unsaturated during the adsorption process. The maximum adsorption capacity (q_m) for Cu^{2+} ions increased from 42.7 to 60.2 mg g^{-1} for the Ca-Alg_2 and Ca-Alg_2/GO hydrogel beads, respectively. This difference was attributed to the large surface area of the GO as well as other oxygen containing functional groups on the GO surface and edges participating in the chelation of Cu^{2+} ions. The pseudo-second-order was applied to study the kinetics of the adsorption process. The results showed that the adsorption capacity of the Ca-Alg_2/GO beads (between 17.45 and 33.22 mg g^{-1}) was higher than that of the Ca-Alg_2 beads (between 13.36 and 28.16 mg g^{-1}). Indicating that the larger surface area of GO and oxygen containing functional groups on the GO surface plays a strong role in increasing the adsorption capacity.

Chapter 4 discussed utilising Ca-Alg_2 hydrogels as a delivery vehicle for rose Bengal (RB), Tris(2,2'-bipyridyl) dichlororuthenium (II) hexahydrate (Rubpy) and camptothecin (CPT) at different pH's. The Ca-Alg_2 hydrogel was prepared by sol-gel transformation in the presence of cross-linking cations (Ca^{2+}) by the *in situ* addition method. The effect of the pH of the released media on the release of both the dyes (RB and Rubpy) and the drug (CPT) from Ca-Alg_2 hydrogel was studied. It was found that the release of the three molecules from the Ca-Alg_2 hydrogel at pH ~ 7.4 was higher than the release at pH ~ 2.4, and this was theorised to be caused by the swelling of the Ca-Alg_2 hydrogel in a higher pH solution. The release mechanisms of RB, Rubpy and CPT from the Ca-Alg_2 hydrogels was analysed using Ritger-Peppas and Weibull models and the results revealed that the release at pH ~ 2.4 occurred via Fickian diffusion and Case II transport. However, at pH ~ 7.4, the release mechanisms of the three molecules from the Ca-Alg_2 hydrogel revealed that an anomalous transport mechanism dominated, implying that the release occurred via diffusion and swelling controlled drug release. Ritger-Peppas model was applied to calculate the diffusion coefficients, and it was observed that the diffusion coefficient of RB (3.889 $\times 10^3$ cm^2 s^{-1}) was higher than the diffusion coefficients of Rubpy and CPT (3.077

$\times 10^3$ and 3.065 $\times 10^3$ cm^2 s^{-1}, respectively) at pH ~ 7.4, and this was attributed to the anionic nature and the hydrophilicity of RB compared to that of RB and CPT.

Chapter 5 and 6 focused on the modification of Na-Alg by grafting with β-CD and its subsequent application in controlled drug delivery for the hydrophobic drug (CPT). Chapter 5 investigated the synthesis and characterisation of β-cyclodextrin grafted sodium alginate (β-CD-g-Alg). Attenuated total reflection-Fourier transform infrared (ATR-FTIR) and proton nuclear magnetic resonance (^{1}H NMR) spectroscopies confirmed the synthesis of β-CD-g-Alg. The fabrication of CPT inclusion complexes with β-CD (CPT/ β-CD) and β-CD-g-Alg (CPT/ β-CD-g-Alg) was described and characterised using ATR-FTIR and ^{1}H NMR spectroscopies. It was found that ATR-FTIR and ^{1}H NMR spectroscopies confirmed that the amino quinoline group of the CPT molecule is included into the β-CD cavity away from the wider rim in both inclusion complexes. The thermogravimetric TGA analysis for both inclusion complexes showed that the thermal stability of Na-Alg increased in the presence of β-CD and the ratio of Na-Alg to β-CD was 2:1.

Chapter 6 detailed the release profiles of CPT from the synthesised CPT/ β-CD and CPT/ β-CD-g-Alg inclusion complexes using the dialysis technique, and the results were compared with the release of free CPT through the dialysis membranes. Fick's second law was utilised to analyse the release data. It was found that the initial burst release for free CPT and for non-included CPT from CPT/ β-CD inclusion complexes was in the first 7-8 hours while the release of CPT, which was included in β-CD cavity of the CPT/ β-CD inclusion complex, reached an equilibrium after 9 days. Furthermore, it was found that the release of CPT from the CPT/β-CD-g-Alg inclusion complex did not show the initial burst release, indicating that all CPT molecules were either bound to the Na-Alg matrix or included into the β-CD cavity of the β-CD-g-Alg complex. The release of CPT from the CPT/β-CD-g-Alg inclusion complex showed a constant slow release until an equilibrium was reached after 13 days, indicating the release of CPT molecules from the β-CD cavities and from Na-Alg mucoadhesive matrix. The diffusion coefficients were calculated from Fick's second law. It was found that the diffusion coefficient for the fast release (D_1) values for the release of free CPT and the release of non-included CPT from the CPT/β-CD inclusion complex were the same, at 8.113 $\times$ 10^{-10} mm^2 s^{-1}, while the diffusion

coefficient for the slow release (D_2) for the release of CPT from the CPT/β-CD was 3.651 × 10^{-10} mm^2 s^{-1}, indicating the increased solubility of the CPT. The D_2 value for the release of CPT from the CPT/β-CD-g-Alg inclusion complex showed a slower diffusion rate of 1.217 × 10^{-10} mm s^{-1}, indicating that Na-Alg increased the solubility of CPT/β-CD inclusion complex and enhanced the formation of CPT/β-CD.

The release of CPT from the CPT/β-CD-g-Alg inclusion complex showed a slower diffusion coefficient of 1.217× 10^{-10} mm s^{-1} compared to the release of CPT from Ca-Alg_2 hydrogel (30.65 × 10^3 mm s^{-1}) at pH ~ 7.4. The swelling of Ca-Alg_2 hydrogel at pH ~ 7.4 plays an important role in increasing the release of CPT due to the increasing the pore size of Ca-Alg_2 hydrogel. Whereas the modification of Na-Alg by grafting with β-CD controlled the release of CPT from the CPT/β-CD-g-Alg inclusion complex.

This thesis has shown for the first time the preparation of a CPT/β-CD inclusion complex by including CPT molecules inside β-CD cavities, and how this inclusion complex then affects the release of the CPT. Also, this thesis provide a new drug delivery system for controlled release of an anticancer drug (CPT) by grafting Na-Alg with β-CD.

7.3 Recommendations

This thesis provides a new adsorbent material for water treatment (Ca-Alg_2/GO), by application of GO in polymer matrices (Na-Alg). In Chapter 3, Ca-Alg_2/GO prepared as a hydrogel and it has been observed that the presence of GO increase the adsorption capacity of Ca-Alg_2 gel beads. Therefore, it is worth blending Na-Alg (anionic polymer) with cationic polymer (e.g. chitosan) to combine the good characteristic of both polymers then encapsulated with GO and application in water treatment to remove anionic and cationic dyes. In addition, it would be interesting to functionalize GO with appropriate molecules then encapsulated in Ca-Alg_2 for adsorption of anionic and cationic dyes [218].

Furthermore, This thesis provides an effective drug carrier for hydrophobic drug. In Chapter 5 and 6, CPT/β-CD-g-Alg inclusion complex showed a constant slower release of CPT without burst release while many studies has been focused on decrease the burst release for the drug carrier. It would be interesting to further investigate whether CPT/β-CD-g-Alg inclusion complex would have a protective effect of on CPT's lactone ring against hydrolysis over time under physiological conditions.