Targeted Drug Delivery Systems for Cancer Therapy

Antonio Clementi  
*Dublin Institute of Technology, antonio.clementi@dit.ie*

Christine O’Connor  
*Dublin Institute of Technology, christine.oconnor@dit.ie*

Mary McNamara  
*Dublin Institute of Technology, Mary.McNamara@dit.ie*

A. Mazzaglia  
*Institute of nanostructured materials, Agata (ME), Italy*

M. C. Aversa  
*University of Messina*

See next page for additional authors

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The role of cyclodextrin’s (CD) in drug delivery has advanced in recent years and this may be attributed to its biocompatibility and well established synthesis. Chemical modification of CDs has shown to extend the physicochemical properties and the host capacity for a variety of drugs. β-CD has been widely used in the early stages of pharmaceutical applications because of its ready availability and its cavity size suitability for a wide range of drugs. Chemical modification of β-CD has proven to enhance aqueous solubilisation, microbiological stability and reduced toxicity in previous studies. Folate Receptors are over-expressed in several human cancers including ovarian, breast and renal carcinomas. This property has been utilised to develop tumour-selective anti-neoplastic drugs. Folate has been bound to chemotherapeutic drugs and since tumour cells have a huge appetite for folate, their folate receptors ‘pull’ the drug-folate conjugate towards the tumour site. However the direct conjugation of folate to the bioactive drug can lead to loss of targeting or alter the function of the conjugate. Folate-cyclodextrin bioconjugates have been prepared with polyethylene glycol (PEG) linkers; however this conjugate partially prevents drug degradation. This study describes the synthesis and characterisation (UV-Vis, Emission, IR, Raman, NMR, MALDI-MS and ESI-MS) of a novel folate-cyclodextrin bioconjugate (CDEn-FA). As mentioned previously it was found that direct conjugation of folate to the bioactive molecules led to loss of targeting or an alteration of the function of the conjugate and most of the conjugates to date cannot be further modified to improve targeting or anti-tumour activity. Preliminary biological evaluation of the tumour targeting device will be discussed.

SYNTHETIC STRATEGY


The role of cyclodextrin’s (CD) in drug delivery has advanced in recent years and this may be attributed to its biocompatibility and well established synthesis. Chemical modification of CDs has shown to extend the physicochemical properties and the host capacity for a variety of drugs. β-CD has been widely used in the early stages of pharmaceutical applications because of its ready availability and its cavity size suitability for a wide range of drugs. Chemical modification of β-CD has proven to enhance aqueous solubilisation, microbiological stability and reduced toxicity in previous studies. Folate Receptors are over-expressed in several human cancers including ovarian, breast and renal carcinomas. This property has been utilised to develop tumour-selective anti-neoplastic drugs. Folate has been bound to chemotherapeutic drugs and since tumour cells have a huge appetite for folate, their folate receptors ‘pull’ the drug-folate conjugate towards the tumour site. However the direct conjugation of folate to the bioactive drug can lead to loss of targeting or alter the function of the conjugate. Folate-cyclodextrin bioconjugates have been prepared with polyethylene glycol (PEG) linkers; however this conjugate partially prevents drug degradation. This study describes the synthesis and characterisation (UV-Vis, Emission, IR, Raman, NMR, MALDI-MS and ESI-MS) of a novel folate-cyclodextrin bioconjugate (CDEn-FA). As mentioned previously it was found that direct conjugation of folate to the bioactive molecules led to loss of targeting or an alteration of the function of the conjugate and most of the conjugates to date cannot be further modified to improve targeting or anti-tumour activity. Preliminary biological evaluation of the tumour targeting device will be discussed.

SYNTHETIC STRATEGY

The conjugate is fully studied by HPLC-PDA, NMR, MS, UV-VIS, IR and Raman spectroscopy.

DISCUSSION OF RESULTS

1H-NMR was assigned by COSY NMR. The 1H-NMR shows three groups of signals (three for each aromatic proton) which are representative of the folate acid portion in three different configurations as shown in Figure 5. By ROESEY NMR it was possible to assess the phenyl group of the folate moieties which can interact with the cavity of the CD. ESI-MS confirms the formation of the CD conjugated product as shown in Figure 7. UV-VIS absorption analysis of CDEn, FA and product, CDEn-FA show different absorption spectra as shown in Figure 6. The HPLC-PDA has evaluated the stability and purity of the product. The material presents traces of CDEn and FA not reacted. Preparative HPLC experiments are in progress to optimize the purification. During preliminary biological testing, HeLa cells were not affected when they were treated with CDEn-FA. These initial biological evaluations allows for further experimentation on cell systems to develop a drug target vehicle.

CONCLUSION

In summary CDEn-FA was synthesized with an attempt to eliminate the polydispersity of the modified CD. This fact is vital in the design and characterisation (thermodynamic properties, photophysics, etc.) of new multifunctional host-guest systems having different sites of complexation. By designing a molecular system with a controlled number of binding sites (i.e. targeting moiety, CD cavity, metal coordination environment) it will be possible to modulate the properties of recognition towards receptor proteins. Such versatility of the CDEn-FA can be exploited in the field of photodynamic therapy (PDT) – organic and inorganic drugs in conventional anticancer therapy, metal nanoparticles (Photothermic Therapy of Tumours, PTT).

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