The potential of cucurbit[*n*]urils in drug delivery

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Abstract

In this paper we review cucurbit[*n*]urils (CB[*n*]), a relatively new family of macrocycles that has shown potential in improving drug delivery. Encapsulation of drugs within the homologues CB[6], CB[7] or CB[8] can impart enhanced chemical and physical stability, improve drug solubility and control drug release. The formulation of CB[*n*] into a dosage form suitable for clinical use is a non-trivial task as the free macrocycle and its host-drug complex generally exhibit pseudo-polymorphism in the solid state. Despite this, cucurbiturils have been included in tablets for oral delivery and inserts for nasal delivery. Here we examine the potential use of cucurbiturils in drug delivery in the context of getting a new drug into clinical trials and discuss what further research is needed in this area.

Introduction

Macrocycles (or cavitands)[1] represent an important class of drug delivery vehicle as, unlike other classes of delivery vehicle such as dendrimers, nanoparticles or carbon nanotubes, they are able to sequester drugs within their structure, providing a steric barrier to drug degradation and/or deactivation. Whilst liposomes and micelles can sequester drugs within their cores, the size of a macrocycle can be tuned to control the rate of drug release and binding strength of the host-guest complex. Although there are a large number of macrocycles that are potentially useful in drug delivery only three types have been studied extensively: cucurbit[*n*]urils (CB[*n*]), cyclodextrins and calixarenes. Of particular interest are cucurbiturils, a family of barrel-shaped macrocycles that take their name from the pumpkin family (*cucurbitaceae*) whose shape they are thought to resemble (Figure 1).[2]

Cucurbiturils can be synthesised in a number of different sizes, with either 5, 6, 7, 8 or 10 glycoluril subunits.[3] All homologues are the same height (9.1 Å), however, they all differ in the diameter of their portals and cavities. The most commonly used homologues in drug delivery are CB[6], CB[7] and CB[8], as CB[5] is too small to incorporate drugs and CB[10] is, at times, too large to bind a guest molecule strongly. Cucurbiturils have been shown to form host-guest complexes with a wide range of organic and inorganic small molecule drugs where encapsulation is facilitated through hydrophobic effects within the cucurbituril cavity and further stabilised by hydrogen bonding or ion-dipole interactions with the cucurbituril portal.[4] Examples of drugs which have been studied with cucurbiturils include: paracetamol (analgesic),[5] memantine (NMDA glutamate antagonist),[5] cisplatin (antineoplastic),[6] prilocaine (local anaesthetic),[7] coumarin (anticoagulant)[8] and sanguinarine (alkaloid)[9] (Figure 2).

The formation of drug-CB[*n*] host-guest complexes may provide many benefits, including: increased drug chemical and physical stability, improved drug solubility and controlled drug release. In this review paper we examine the potential use of cucurbiturils in drug delivery, focusing on their possible applications and discuss in the context of the wider pharmaceutical sector, in particular, the further research that needs to be undertaken before a cucurbituril-based drug can be brought into human clinical trials.

Cucurbituril pharmaceutical scale production

The first step in the development of cucurbiturils as potential drug delivery vehicles is their synthesis and purification on the industrial scale and at an economical cost. Fortunately, recent advances in both the synthesis and separation of different sized cucurbiturils mean that this is now possible. Cucurbiturils are made from the condensation reaction of glycoluril and formaldehyde (or paraformaldehyde) in strong acids by heating at 70-100 ^{o}C overnight.[3a, b, 10] This yields a mixture of cucurbiturils where CB[6] is the most abundant homologue, along with varying amounts (<20%) of CB[5], CB[7], CB[8]. Cucurbit[10]uril and cucurbituril derivatives, such as inverted cucurbituril,[11] usually account for less than 1% of the products obtained. The homologue CB[9] has yet to be definitively synthesised.

Recently, microwave synthesis has been shown to be an energy efficient method for the production of cucurbituril mixtures. When the synthesis is conducted at a power of 400 W, at a temperature of 160 ^{o}C and in either sulfuric or hydrochloric acid, the reaction is complete within 3-10 minutes.[12] Whilst the reaction is very fast it also yields the same ratio of cucurbituril homologues as the standard bench top method. In addition, a green method for the separation and purification of potentially the most important homologue for cucurbituril-based drug delivery, CB[7], has been developed.[13] Using alkyl-imidazolium, CB[7] is

separated from the other water soluble homologue CB[5]. Usefully, the alkyl-imidazolium ion, once removed from CB[7], can be recycled and used again on subsequent CB[7] batches. Together, these developments make production of cucurbituril at the scale needed for commercial pharmaceutical application possible.

Cucurbituril toxicity and safety

For cucurbiturils to find clinical use in drug delivery they must be superior to other macrocycles, not just in terms of the chemical/physical benefit they provide, but they must be just as toxicologically safe, or safer. Ideally, cucurbiturils should also decrease the severity of the toxic side-effects of the drugs with which they are being used. As such, the inherent cytotoxicity (the extent to which a compound kills cells or inhibits cell growth) and toxicity (the type and severity of a compound's side-effects) of cucurbiturils have begun to be examined.

For comparison, cyclodextrins have previously been shown to be non-toxic with lethal doses (LD_{50}) in rats and mice of between 0.3 to 18.8 g/kg depending on the cyclodextrin size/type and the route of administration.[14] Cyclodextrins are not completely safe however, as *β*-cyclodextrin has been shown to be nephrotoxic when administered parenterally.[15] Sulfonated calixarenes are also relatively non-toxic, although at much lower doses. *Para*-sulfonato-calix[4]arene shows no toxicity at concentrations up to 100 mg/kg, but with a lethal dose (LD_{50}) less than 400 mg/kg.[16]

Complete toxicity, phamacokinetic and pharmacodynamic profiles for cucurbiturils have yet to be comprehensively determined, but several studies have demonstrated the relative safety of these macrocycles. *In vitro* cell growth assays using free cucurbiturils, and some linear

cucurbituril derivatives, have shown practically no cytotoxicity at up to millimolar concentrations.[17] This includes experiments using both animal and human derived cell lines, which are either healthy or cancerous: Chinese hamster ovary cells, human kidney and liver cells, human blood tissue, mouse embryo cells and the human cancer cells: A549, SKOV-3, SKMEL-2, XF-498 and HCT-15.[18] Cucurbiturils have also been shown to be non-cytotoxic to some bacteria.[17a] Fluorescent marking of CB[7] and CB[8] has shown that cucurbiturils are able to cross the cell membrane of mouse embryo cells,[17c] and macrophages have been identified as one possible mechanism for their uptake.[17a] Using live cell imaging it was shown that they do not appear to cause internal damage to the cell (as assessed by mitochondrial activity).[17b] Therefore, the lack of cucurbituril cytotoxicity in mammalian cells, and in bacteria, is not due to a lack of cellular uptake.

Cucurbiturils have also been shown to be relatively non-toxic *in vivo*, although all studies to date have only been in mice. Free CB[7] intravenously administered has demonstrated no toxicity at doses up to 200 mg/kg.[17b] At doses between 200-250 mg/kg, and when administered as a fast injection, mice were found to go into a shock-like state. When administered at a slow rate the maximum tolerated dose of CB[7] was found to be 250 mg/kg. In contrast, a 1:1 mixture of CB[6]:CB[8] administered orally demonstrated no toxic side-effects to a doses up to 600 mg/kg.

Cucurbituril and their drug host-guest complex solubility

It was originally thought that one of the biggest hurdles to the successful use of cucurbiturils in drug delivery may have been their perceived poor aqueous solubility. Many drugs are only therapeutically active at millimolar concentrations, and in some cases those that are active at lower concentrations still need to be prepared in solution (IV bags) or dissolved in the

relatively low volume of the stomach at high concentrations before they are diluted to their therapeutic concentrations in the rest of the body. Compared to cyclodextrins and sulfonated-calixarenes, the solubility of all cucurbiturils in pure water is relatively low. Only the odd numbered cucurbiturils, CB[5] and CB[7], are moderately soluble (~ 3-4 mM). The even numbered cucurbiturils have pure water solubility of less than 50 μM, with CB[8] considerably less soluble than CB[6]. We have recently found, however, that the solubility of cucurbiturils in biologically relevant media is much higher than expected.

There are five main fluids within the human body in which cucurbiturils and their drug host-guest complexes may be dissolved and transported following administration: blood plasma, gastric, intestinal and nasal fluids. The high salt and acid concentrations of these biological media mean that cucurbiturils and their drug host-guest complexes can be solubilised to therapeutically relevant concentrations (Table 1). We have recently shown that CB[6] is soluble in simulated gastric fluid at concentrations up to 4 mM,[19] but in other fluids it can dissolve to concentrations as high as 45 mM. It is important to note however, that the cations found in these bodily fluids are likely to bind at the cucurbituril portals,[20] which may affect the release of some drugs or affect how strongly the drug is encapsulated.[21] This effect may be greatest when a molecule is small enough to be almost totally encapsulated by the macrocycle, in which case the cations may act as lids,[22] significantly slowing or even preventing the guest's release. Research is therefore needed into the effect that salt binding to cucurbiturils has on drug release and binding strength.

As well as their inherent solubility, in many cases of cucurbituril host-guest formation, the drug can greatly increase the aqueous solubility of the cucurbituril, or alternatively, the cucurbituril may increase the solubility of the drug.[23] Host-guest complexes of CB[8] with

cationic di- and trinuclear platinum anticancer complexes have been shown to increase the solubility of CB[8] to millimolar concentrations,[6] whereas the addition of CB[6], CB[7] and CB[8] to albendazole increase the drug's solubility from 3 μM to 2-7 mM, depending on which cucurbituril is used.[24] Likewise, a benzimidazole derivative forms drug host-guest complexes with CB[6], CB[7] and CB[8], increasing the drug's solubility from 8 μM to 2-9 mM. In this latter case, CB[8] was better at solubilising the drug compared to both CB[6] and CB[7].[25] The solubility of camptothecin has also been shown to increase (3 to 8-fold) when encapsulated by either CB[7] or CB[8].[26]

Unfortunately, whilst cucurbiturils can sometimes be used to increase drug solubility, in other instances the formation of drug host-guest complexes can also significantly decrease a drug's solubility. This has been observed with some phenanthroline containing platinum complexes, particularly when bound to CB[6] and CB[8].[27]

Cucurbiturils improve drug chemical stability

By far the most widely examined potential use of cucurbiturils in drug delivery has been as agents which provide chemical stability to many small molecule drugs. This is best exemplified by their application as vehicles for platinum-based anticancer drugs. All platinum drugs contain carrier am(m)ine ligands and labile ligands, such as chlorides or carboxylate ligands.[28] The toxicity of these drugs is related to how fast the labile ligands are removed when the drug is aquated in the blood stream and/or the cell. More importantly, the effectiveness of the drug is related to how much of the drug reaches its target (nuclear DNA) intact. In the human body there are a number of nucleophiles which rapidly bind to platinum. These nucleophiles, such as thiol-containing proteins and peptides (e.g. glutathione), cysteine and methionine are able to replace the am(m)ine and labile ligands, rendering the drugs

inactive.[28] Full or partial encapsulation of a platinum drug within the cavity of a cucurbituril can provide steric protection to the drug from such nucleophilic attack. This is because the cucurbituril macrocycle binds platinum drugs over the hydrophobic components of their amine carrier ligands, for example the cyclohexane component of oxaliplatin. Binding is further stabilised by hydrogen bonds from the drugs' amines to the cucurbituril carbonyls.[6, 18, 20b, 27, 29] Such binding places the platinum atom at the junction of the macrocycle cavity and portal (Figure 3); here the cucurbituril carbonyl groups prevent access by nucleophiles. Such binding has been shown to slow the reaction of platinum drugs with guanosine and cysteine by as much as 9-fold,[29i] without significantly affecting the drugs' cytotoxicity.[29a, 30]

These reduced reaction rates result in a significant reduction in the severity of the drug's side effects. An example of this is the encapsulation of the dinuclear platinum drug BBR3571[31] by CB[7] which increased the drug's maximum tolerated dose from 0.1 mg/kg to 0.45 mg/kg, an effective increase of 70% in the deliverable dose. When administered at 0.27 mg/kg, the drug-CB[7] complex was just as active as the free drug at the equivalent dose.[30] More recently we have been able to show that encapsulation of the mononuclear drug cisplatin by CB[7] not only decreases the severity of the drug's side-effects, through what is thought be a pharmacokinetic effect of reduced blood plasma protein binding, but the cisplatin-CB[7] complex (Figure 3) is also able to overcome acquired-cisplatin resistance *in vivo* in an ovarian tumour xenograft.[32] More surprisingly, the cisplatin-CB[7] is active when delivered orally, a route of administration not previously thought possible for cisplatin.[32]

Protection of drugs from chemical degradation or change is not limited to platinum agents. Cucurbit[6]uril and CB[7] have been shown to prevent the acylation of the drug isoniazid, a reaction that is readily catalysed by acetyl coenzyme A in the human body.[33] Similarly,

encapsulation of sanguiraine alkaloid by CB[7] protects the drug from nucleophilic attack by hydroxide and hinders photooxidation.[9] Finally, encapsulation of vitamin B12 and coenzyme B12 by CB[7], which is effected through binding to the 5,6-dimethylbenzimidazole α-nucleotide base, stabilises the base-off form of the compounds.[34]

Cucurbituil encapsulation may also stabilise the ionic or neutral form of a drug, as for some guests binding has been shown to significantly increase the pKa of their functional groups. For instance, CB[7] binding of the benzimidazole-based drugs albendazole, carbendazim, thiabendazole, fuberidazole increases their pKa values by between 2 to 4 units.[23] Similar pKa shifts for the drugs omeprazole and lansoprazole have also been observed.[35] These pKa shifts may have several effects on the drugs, from increasing their water solubility (as they are now protonated and cationic at higher pH) to their cell uptake or penetration, and altering these need to be examined using appropriate *in vitro* models.

Cucurbiturils for controlled or targeted drug delivery

In addition to acting as a drug delivery vehicle, cucurbiturils may potentially also be used in the production of multi-component nanoparticluate delivery vehicles designed for controlled or sustained drug release. Of particular interest are nanoparticles where cucurbiturils are used as reversible rotaxane-based stoppers that regulate the release of drugs. In the first such example, mesoporous silica nanoparticles are loaded with drug and short chain aliphatics are attached to the surface in a monolayer. Cucurbiturils form rotaxanes with these aliphatic chains through hydrophobic effects and hydrogen bonding to amine groups, acting as a physical barrier to the drugs' release from the silica nanoparticles. The cucurbiturils can then be made to move up the chain, or completely off the chain, using a variety of techniques, thus releasing the drug. For instance, this process can be activated through changes in solution

pH,[36] through enzymatic decarboxylation,[37] reductive cleavage of disulfide bonds,[38] or oscillating magnetic fields.[39]

Alternatively, cucurbiturils can be used to mask the inherent cytotoxicity of a nanoparticle. Gold nanoparticles containing a monolayer of diaminohexane-terminated polyethylene glycol polymer are cytotoxic against human breast MCF-7 cancer cells. When the nanoparticles are capped with CB[7] the particles become non-toxic and non-cytotoxic, and thus safer to administer in high doses. Once taken up into cancer cells the addition of adamantine, which binds competitively to the CB[7], removes the macrocycle from the nanoparticle thus rendering it cytotoxic to the cell.[40]

Cucurbiturils may be used to create nanoparticles within which a drug can be stored and released. Functionalised cucurbiturils have been shown to form polymer nanoparticles where multiple cucurbituril molecules are linked to each other via disulfide bridges.[41] Cleavage of the disulfide bonds that hold the cucurbituril nanoparticle together degrades the polymer, thus releasing the drug. Additionally, cucurbit[6]uril has also been used in the formation of alginate hydrogel beads,[42] and in vesicle formation.[43]

Finally, functionalised cucurbiturils have been synthesised which are capable of actively targeting cancerous cells. Some cell types express or overexpress proteins and peptides on their surfaces which can be used for drug targeting. For example, some cancer cell lines overexpress carbohydrate receptors, and cucurbituril derivatives have been developed that are functionalised with carbohydrate clusters[44] or have been galactosylated.[45] Both of these types of functionalised cucurbiturils demonstrated significantly higher uptake of drug/gene transfer compared with their free forms.

Cucurbituril and its drug host-guest complexes: polymorphism and preformulation

All small molecule drugs have the potential to display some degree of polymorphism, or pseudo-polymorphism in the solid state as there are usually various ways in which a drug can assemble in the crystal form.[46] This is in addition to possible amorphous states that a drug may adopt. Polymorphism is a problem in drug development as different polymorphs may display different physiochemical properties, such as: solubility, dissolution rates, bioavailability, processability and stability.[46] More importantly, different polymorphs of a drug may display varying levels of efficacy and toxicity as a result of these physiochemical differences. The interconversion from one polymorph to another during drug manufacture, formulation or storage is therefore of much concern and methods to produce the preferred crystal form during manufacture, or stabilisation of a preferred crystal form, are of vital interest to pharmaceutical companies.[47]

Usefully, the formulation of drug-cucurbituril host-guest complexes can impart significant thermal/physical stability on many drugs. Encapsulation of paracetamol, glibenclamide, memantine, atenolol, camptothecin, isoniazid, pyrazinamide and the dinuclear platinum complex *trans*-$[\{PtCl(NH_3)_2\}_2\mu\text{-dpzm}]^{2+}$ resulted in a large increase in the melting point of the drug-cucurbituril host-guest complexes when compared to the free drugs.[5, 26, 48] In fact, in most cases, heating of the host guest complex 100-200 ^{o}C beyond the melting point of the free drug saw no melting of the samples until the cucurbituril itself began to decompose at temperatures higher than >370 ^{o}C.

As potential excipients in pharmaceutical formulations, cucurbiturils themselves must be of a suitable solid form during production, with the particles being a uniform size and shape to

allow for consistent powder characteristics. Whilst CB[6] crystals of high purity can be obtained by recrystallisation of the crude product from concentrated HCl, these crystals are of inconsistent morphology (generally a mixture of hexagonal and square/rectangular shapes), and are generally too large (up to the order of centimetres in width) to be included in a homologous bulk powder mix.[49] We have recently reported a reproducible method of producing microcrystalline CB[6], whereby large crystals are redissolved in concentrated HCl and rapid precipitation is forced by the addition of an antisolvent.[49a] This method has produced particle sizes in the range 30-165 μm which are soluble in simulated gastric fluid to a concentration of 4.5-4.7 g/mL, with more consistent and rapid dissolution characteristics than their large crystal counterparts.[49a]

In general, each different sized cucurbituril, and their drug host-guest complexes, are generally associated with anywhere between 3-30 water molecules in the solid form.[27] We have recently found that preparation of microcrystalline CB[6] by antisolvent precipitation methods using different solvents, antisolvents, precipitation rates and precipitation methods generates a number of CB[6] hydrates (or pseudo-polymorphs)[50] where water is incorporated into the crystal lattice, and observed using powder X-ray diffraction (Figure 4).[49a] Most of the co-crystallised water in solid cucurbiturils can be removed by heating at 110 ºC for several hours, but all homologues of the macrocycle have been shown to be hygroscopic, and will absorb water when not stored under moisture-free conditions.[49a]

Cucurbituril and its drug host –guest complexes in pharmaceutical formulations

The oral route is currently the most common route for systemic drug delivery and is associated with a high degree of patient acceptability.[19] It is the simplest, safest and most convenient way to administer a drug which can withstand the challenging environment of the

gastrointestinal (GI) tract and partition across GI membranes.[47] We have recently reported the formulation of CB[6] into an oral tablet preparation.[49a] A viable tablet cannot be produced from CB[6] alone, and so a formulation was developed that contains a number of pharmaceutical excipients. In our formulation the tablets contain up to 50% microcrystalline CB[6] (w/w) with the rest of the tablet containing lactose (diluent/bulking agent), Avicel (aids tablet compaction), talc (lubricant), magnesium stearate (lubricant/glidant) and Ac-Di-Sol (disintegrant).[14, 49a] This formulation displays suitable tablet hardness, disintegration time in simulated gastric or intestinal fluid, less than 2% weight loss on friability testing, and produces tablets with smooth surfaces with no pitting or chipping upon compaction and which could be easily ejected from the die.[49a]

As a new tablet excipient, the potential interactions between CB[6] and other tablet constituents have been examined by differential scanning calorimetry (DSC).[51] No significant interaction was observed between microcrystalline CB[6] and talc, Avicel or Ac-Di-Sol up to 500 ºC. Significant interactions were, however, observed between microcrystalline CB[6] and both lactose and magnesium stearate. A change in melting temperature and enthalpy were observed for magnesium stearate and lactose when they were hand mixed with microcrystalline CB[6]. Even more significant changes to their DSC profiles were observed when the microcrystalline CB[6] was ground with these excipients in a mortar and pestle. ^{1}H NMR analysis of microcrystalline CB[6] solutions with lactose and magnesium stearate showed no change in chemical shift which would be indicative of encapsulation of either excipient within the CB[6] cavity. As such it has been hypothesised that these solid state interactions result from hydrogen bonding of the lactose hydroxyl groups to the CB[6] portals and hydrophobic effects between magnesium stearate chains and the methane/methylene regions of CB[6].

The enhanced solubility of CB[6] in nasal fluid, as discussed in an earlier section, makes cucurbiturils excellent candidates as drug delivery vehicles in nasal drug formulations. Currently we have been able to produce dosage forms based on the polymers: hydroxypropyl methylcellulose (HPMC) and sodium carboxymethylcellulose (NaCMC). Dissolution of CB[6] in a NaCMC hydrated matrix before lyophilisation is easily achieved due to complexation of the macrocycle by the sodium cations. In contrast, hydrated HPMC gel does not dissolve CB[6] easily, but can be made to do so by the addition of NaCl.

Summary and outlook

Since the different sized cucurbiturils were reported in 2000, and their first use as a drug delivery vehicle in 2004, the application of cucurbiturils in this field has grown rapidly. As we have discussed, cucurbiturils have demonstrated considerable potential as drug delivery vehicles in a variety of ways. Although the physical formation of drug-cucurbituril host-guest complexes is now well studied and well understood, there is still a considerable amount that is not known such as their target organs and metabolism in the body. In addition, all toxicity data is for short term exposure in one animal type, and it is not known what the long-term/chronic effects of cucurbiturils exposure are likely to be. Furthermore, comprehensive studies are needed to better determine their safety profile. In addition to these health and human use issues, the problem of cucurbituril polymorphism remains and methods to produce single crystalline forms of all cucurbituril homologues are needed. Additionally, the long-term stability of free cucurbiturils and their drug host-guest complexes, and their interactions with potential packaging materials, needs to be examined. Finally, the development of cucurbiturils into appropriate human dosage forms has only just begun. Many more formulations and dosage forms types need to be explored in order to fully exploit this new

family of macrocycles. Such additional dosage forms could include: implants, such as hydrogels;[42] effervescent tablets for oral delivery; enteric coated tablets for controlled release; suppositories, and inhaled dosage forms by delivery through nebulisers and/or metered dose inhalers. Our group is already attempting to answer many of these issues regarding safety, metabolism, stability and dosage formulation and hope to continue to publish further papers in this area.

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Table 1. Solubility of cucurbit[6]uril in various simulated human biological fluids.

Fluid	**Major cation/anion contents**	**Salt concentration (mM)/pH**	**CB[6] solubility (mM)**
Pure water	Nil	0/7	<0.05
Gastric	H^+, Na^+, Cl^-	34/1-3	1-4[19]
Intestinal	K^+, Na^+, OH^-, PO_4^{3-}	72/6.8	5-7
Blood plasma	Na^+, K^+, Cl^-, CO_3^-	100/7	33-37
Nasal	K^+, Na^+, Ca^{2+}, Cl^-	195/7	34-45

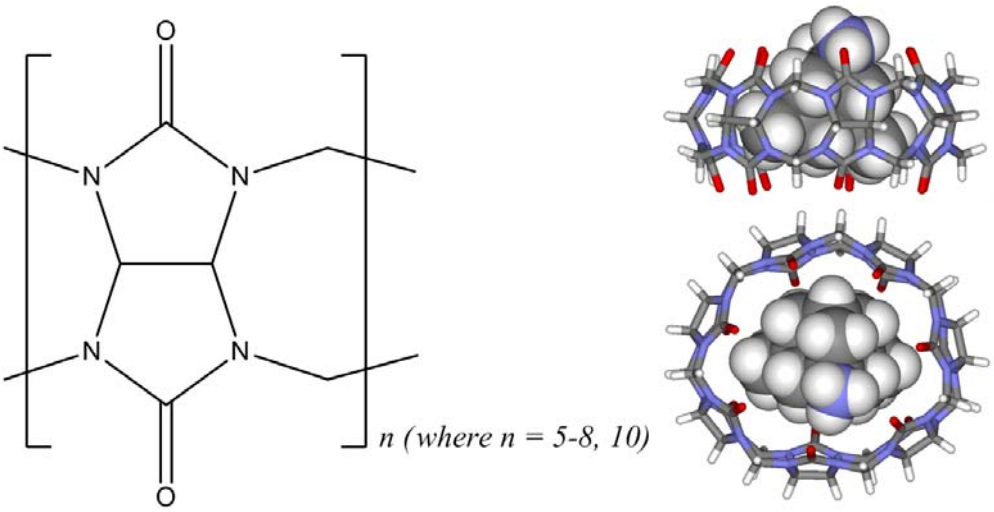

Figure 1. The chemical structure of cucurbit[*n*]urils and an X-ray crystal structure of CB[7] forming a host-guest complex with the anti-Alzheimer's drug memantine; an example of small molecule drug binding by the macrocycle.[5] Generally, binding occurs in the cucurbituril cavity where the host-guest complex is stabilised by hydrophobic effects. This may also be further stabilised by ion-dipole or dipole-dipole interactions at the cucurbituril portals.

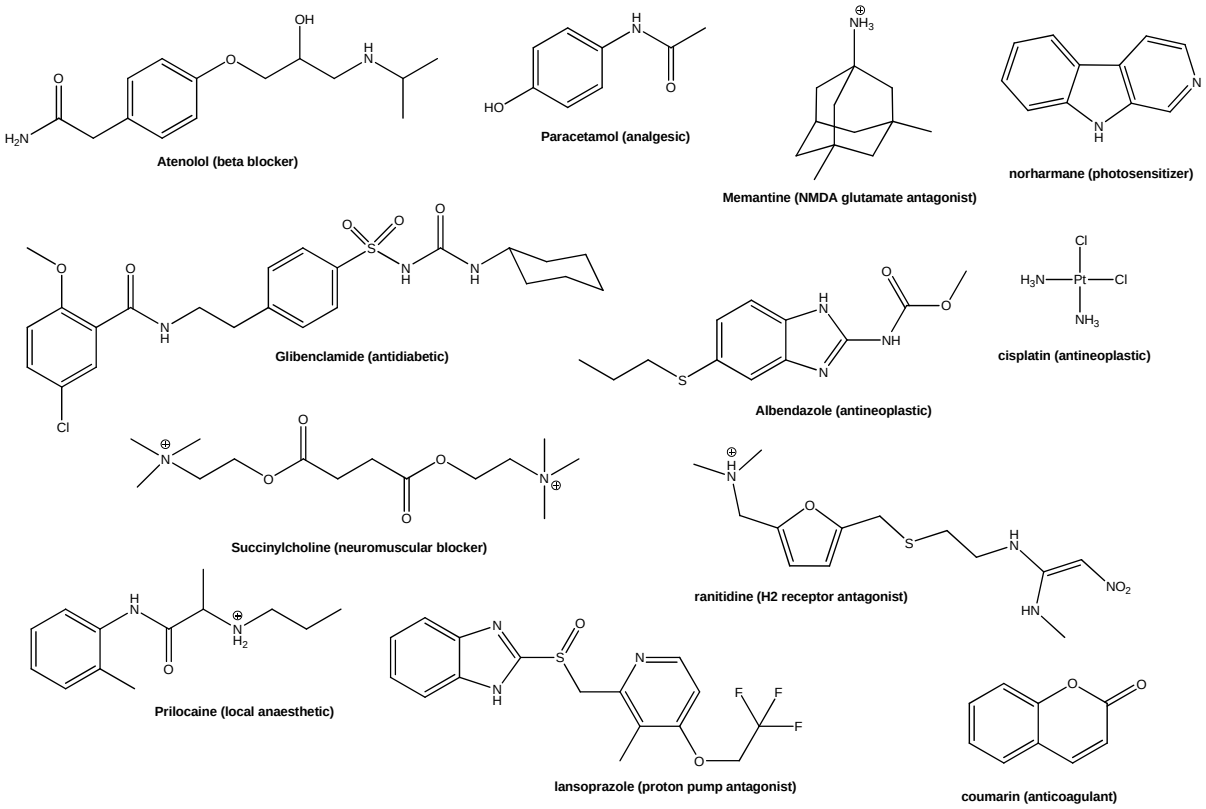

Figure 2. Examples of drugs, and their uses, which have been found to form host-guest complexes with cucurbiturils.

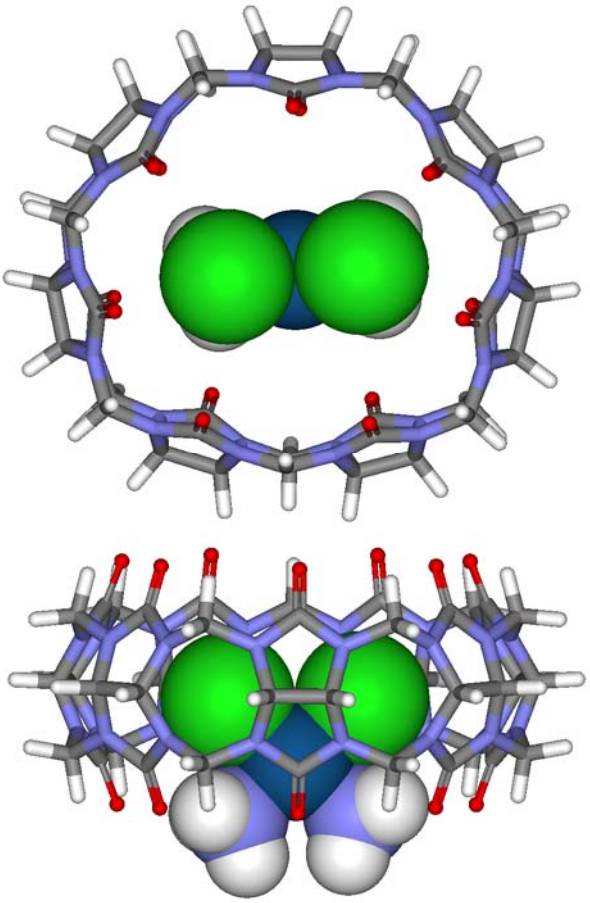

Figure 3. A molecular model of the binding of the anticancer drug cisplatin to CB[7], showing sequestration of the platinum atom (at its van der Waal size) inside the macrocycle's cavity, where it is protected from attack by biological nucleophiles.[52]

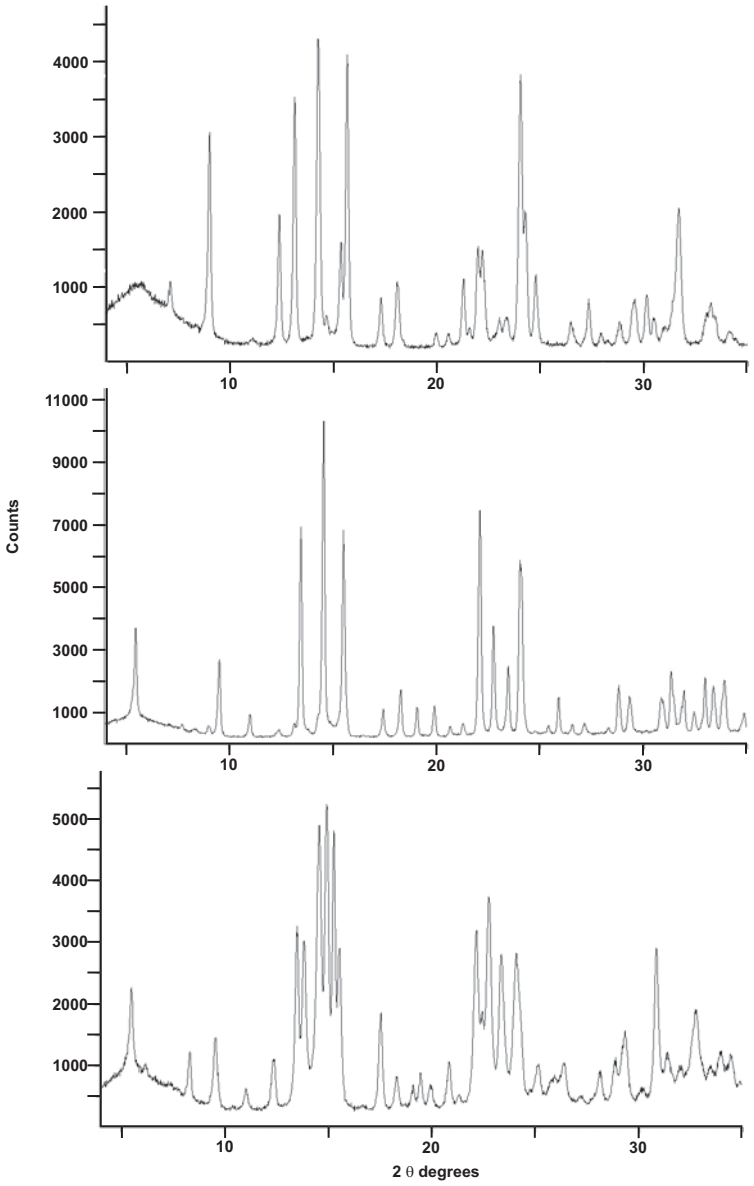

Figure 4. Powder X-ray diffraction spectra demonstrating examples of the different pseudo-polymorphs of CB[6] microcrystals made by a variety of methods including: (top) precipitation from HCl by H_2O with stirring, (middle) precipitation from HCl by H_2O without stirring, and (bottom) precipitation from a mixture of HCl and H_2O by rotary evaporation.

Biographical sketches

Shonagh Walker

Shonagh has a Master in Science (Chemistry with Drug Discovery) from the University of Strathclyde (2009). During her degree she completed an industrial placement year with Pfizer Veterinary Medicine where she worked on a number of projects dealing with quality control, pharmaceutical formulation and materials science. She is currently completing a PhD in the group with a focus on the design and production of pharmaceutical dosage forms of cucurbiturils and their host-guest complexes. She has published work on the production of cucurbituril containing tablets for oral drug delivery and is developing cucurbituril based nasal inserts.

Rabbab (Ruby) Oun

Ruby completed her undergraduate course at the University of Glasgow where she obtained a Bachelor of Science in Medical Biochemistry (2008). She then attended Napier University and graduated with a Master of Science in Drug Design and Biomedical Science (2009). She is currently completing a PhD in the group where she splits her time between the University of Strathclyde and the Beatson Institute of Cancer Research. The focus of her work is on the

controlled delivery of platinum-based drugs. She is currently developing cucurbituril-based hydrogel implants for cancer treatment.

Fiona J. McInnes

Fiona graduated from the University of Strathclyde with a Master of Pharmacy degree (1998) and PhD (2003), which she completed under the supervision of Prof Howard Stevens. After completing an industry funded postdoctoral position into the use of gamma pharmacoscintigraphy she was appointed a Lecturer in Pharmacy at the University of Strathclyde. Her current research interests include: bioadhesive nasal drug delivery, IVIVC evaluation of drug delivery devices and formulations, gastrointestinal transit and the effect of food on oral formulations, and oral modified release formulations design and performance.

Nial J. Wheate

Nial is a graduate of the Australian Defence Force Academy (1997) and University of New South Wales with a Bachelor of Science (Honours, 1998) and PhD (2002). After undertaking various roles in the Royal Australian Navy, he was appointed as a Senior Fellow at the University of Western Sydney (2005) and a Lecturer in Medicinal Chemistry at the University of Strathclyde (2007). His research interest is primarily in the field of controlled and targeted drug delivery, particularly for platinum agents, using a range of novel delivery vehicles, including cucurbit[*n*]urils.