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Synthesis, Processing and Solid State Excipient Interactions of Cucurbit[6]uril and Its Formulation into Tablets for Oral Drug Delivery

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Abstract: The synthesis, processing, and solid state excipient interactions of cucurbit[6]uril (CB[6]) and its formulation into oral tablets has been examined using a range of physical chemistry techniques. Rapid precipitation from HCl by the addition of water yields microcrystalline CB[6] with smaller and more consistent particle size (30−165 μm) compared with the sieved CB[6] (50−540 μm) produced from large crystals grown by slow evaporation from HCl. The microcrystalline particles also contain fewer water molecules in the crystal compared with the sieved particles: 10 and 16% respectively. Microcrystalline CB[6] can be formulated into tablets suitable for oral delivery with a CB[6] content of 1−50% w/w, with the other excipients including lactose, talc, Avicel, magnesium stearate and Ac-Di-Sol. In the solid state microcrystalline CB[6] does not interact significantly with the talc, Ac-Di-Sol or Avicel, but significant interactions are observed when mixed or ground with either magnesium stearate or lactose, resulting in the lowering of the melting points of both excipients. This work represents the first study of the physical processing and solid state chemistry of CB[*n*]s for pharmaceutical formulation and represents an important development step in the use of CB[*n*]s as drug delivery vehicles.

Keywords: Cucurbituril; processing; formulation; excipient; tablet; solid state interactions

Introduction

Cucurbit[*n*]urils (CB[*n*]) are a family of macrocycles made from the condensation of glycoluril and formaldehyde in strong acid solutions (Figure 1).[1−4] Cucurbit[*n*]urils are able to form host−guest complexes with a range of drugs and drug metabolites through hydrophobic effects within their cavities and/or hydrogen bonding/ion−dipole interactions at the CB[*n*] portals.[5,6] While they can be synthesized in a variety of sizes (n = 5−10),[7−10] it is CB[6], CB[7] and

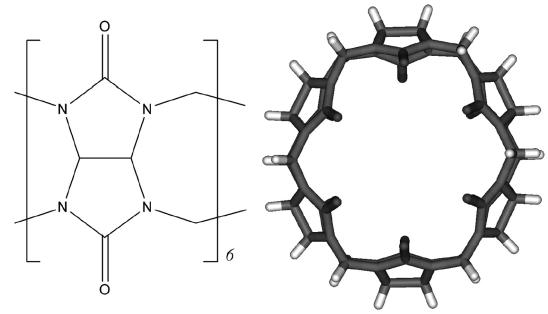

Figure 1. The chemical and X-ray structure of CB[6] showing the macrocyclic nature of the polymer.

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CB[8] which have been most studied. These three macrocycles are roughly the same size as as α-, β-, and γ-cyclodextrins which are now used for pharmaceutical drug delivery.[3]

The high thermal stability,[11] general lack of cytotoxicity or toxicity,[12] ease of synthesis[13] and their high molecular recognition and binding constants[14] make CB[*n*]s ideal for biomedical applications.[15] Previously, CB[*n*]s have been shown to be excellent drug delivery vehicles for platinum-based anticancer drugs,[5,16,17] agricultural fungicides,[18] acetylchloinesterase inhibitors and cholines,[19,20] antituberculosis drugs,[21] and anesthetics,[22] and as physical stabilizers for a range of other drugs, such as memantine, atenolol, glibenclamide and paracetamol.[23] Cucurbit[*n*]urils have also been successfully used as biological inhibitors and enzyme regulators,[24,25] in biocatalysis,[26] in biodiagnostics,[27−29] to determine nicotine concentrations in cigarettes and pseudoephedrine in Sudafed tablets[30,31] and as xenon carriers in NMR biosensing.[32] The further development of CB[*n*]s as drug delivery vehicles is dependent however on reliable methods to synthesize, process and formulate CB[*n*]−drug host−guest complexes into usable forms for human treatment. Oral delivery, particularly in the form of tablets, is the preferred drug administration route because of high patient tolerance compared with other administration routes, the relative ease of manufacture, and because it has the least aseptic constraints.[33] In this study we have examined the

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physical chemistry of the synthesis, processing, solid state interactions and formulation of CB[*n*]s into tablets suitable for oral drug delivery, using CB[6] as a representative macrocycle.

Results and Discussion

Cucurbit[6]uril Synthesis and Processing. Cucurbit[6]uril is the major product formed in CB[*n*] mixtures synthesized using sulfuric or hydrochloric acids and, as such, is the cheapest and easiest to use in tableting studies where large amounts of the macrocycle are needed (>10 g).[13,34] Therefore CB[6] was chosen for practicality reasons in preference to CB[7] or CB[8] which are generally the more useful CB[*n*]s for biomedical applications.

While CB[6] crystals of high purity are easily obtained by slow evaporation from concentrated HCl solutions, the crystals formed can vary greatly in size from a few millimeters to over a centimeter in length and in various morphologies (Figure 2a).[13] These are unsuitable for tableting as the crystals are too large to fit into a reasonably sized tablet and the different pseudopolymorphs will change the CB[*n*] content in each tablet. As such, we first attempted to press the crude CB[6] crystals through a sieve with a 500 μm aperture. While this produced smaller particles (50−550 μm with a mean of 184 μm), their variation in shape and size was quite large (Figure 2b), and subsequent tablets pressed with sieved CB[6] particles were found to be too soft. Instead an antisolvent method was found for producing small, more consistently sized, microcrystalline CB[6] particles (Figure 2c). Cucurbit[6]uril is dissolved in a minimum amount of concentrated HCl yielding a clear orange/brown colored solution to which water is added to precipitate rapidly the macrocycle as a microcrystalline solid (as shown by X-ray powder diffraction; Figure 3) which remains crystalline even after oven drying. Microcrystalline CB[6] produced in this way consists of particles which range in size from 30 to 165 μm with a mean of 80 μm. Both the sieved and microcrystalline CB[6] are equally soluble in simulated gastric fluid (NaCl, 2.0 g; pepsin, 3.2 g; and concentrated HCl, 7.0 mL; per 1 L of water) to a concentration of 4.5−4.7 mg/mL, but at its maximum solubility the microcrystalline form dissolves faster and more consistently.

Both the sieved and microcrystalline CB[6] contain waters of crystallization which can mostly be removed by heating for several hours at 110 °C. From thermogravimetric (TG) analysis microcrystalline CB[6] contains fewer water molecules (10% of total mass) compared with the sieved (16%) particles (Figure 4). Importantly, both forms of CB[6] are hygroscopic and increase in mass when left on the bench (median mass increase 19%) after oven drying and if not stored in an inert atmosphere. This may have substantial implications not only for their pharmaceutical formulation but also for their industrial manufacture for other applications. Different crystalline forms are sometimes known to have different cohesive packing energies and therefore differing physiochemical properties, and hydrated crystals tend to have lower aqueous solubility than their anhydrate forms.[35] This decreased solubility can lead to a reduction in *in vivo* bioavailability. To further complicate the situation, transitions to crystal forms of lower free energies (and consequently lower solubilities) can occur during storage, or during the drying, grinding, milling and/or tableting processes.[35,36]

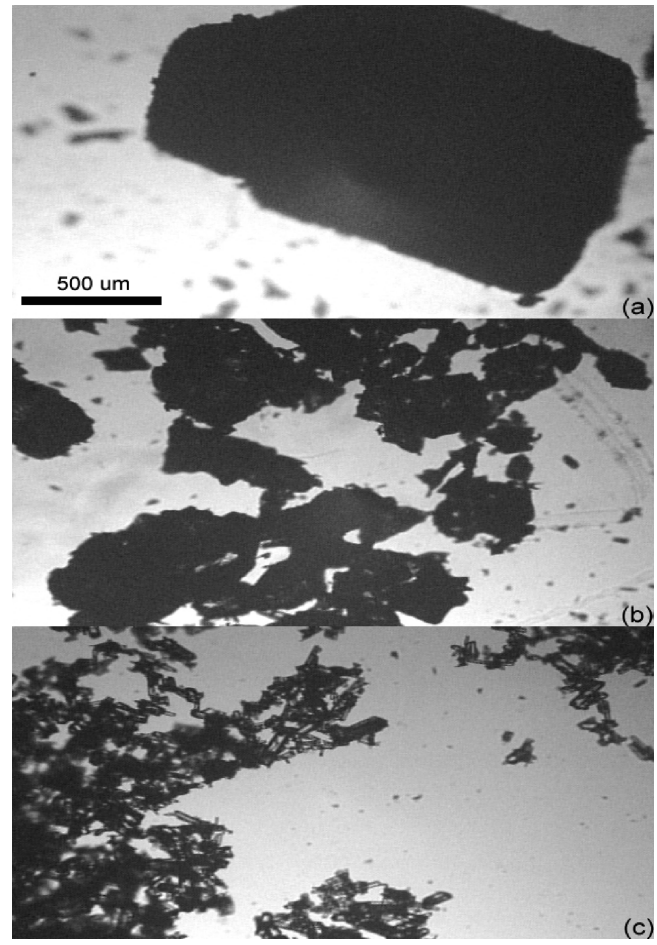

Figure 2. Optical microscope images of (a) crude CB[6] crystals, (b) 500 μm sieved CB[6] crystals and (c) microcrystalline CB[6] produced by its precipitation from concentrated HCl using water.

Tablet Formulation. Attempts to compress microcrystalline CB[6] by itself into tablets was unsuccessful as the resultant compacted material crumbled easy. Different excipients were therefore tried with CB[6] in varying ratios until tablets with suitable properties were obtained: adequate

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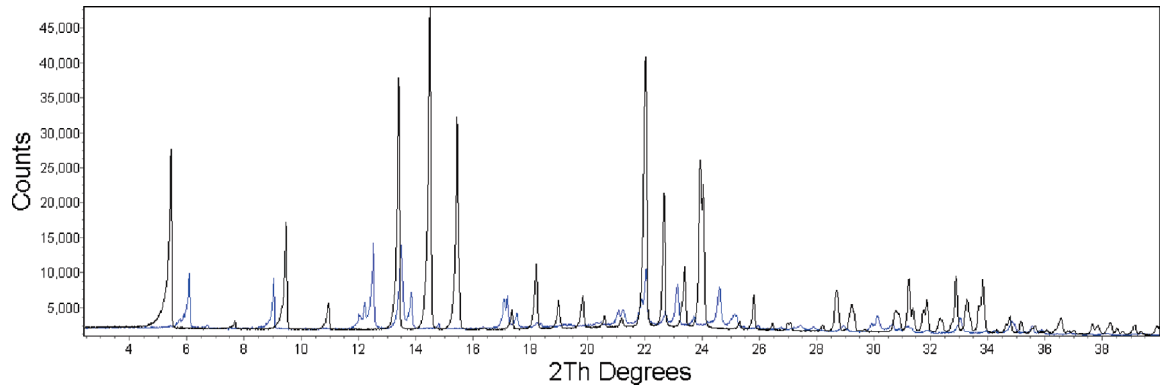

Figure 3. The X-ray powder diffraction spectra of air-dried (black) and oven-dried (blue) microcrystalline CB[6].

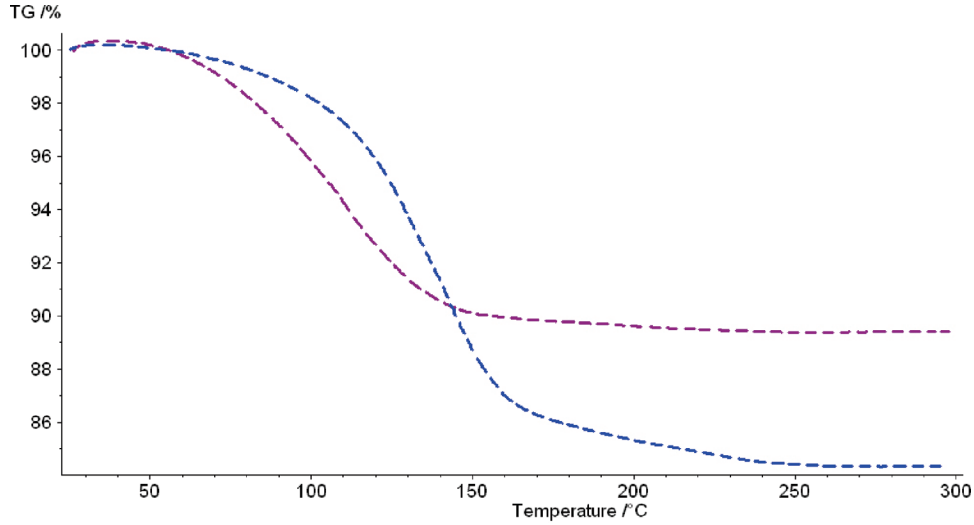

Figure 4. The thermogravimetric analysis curves of microcrystalline CB[6] (violet) and sieved CB[6] (blue).

tablet hardness measured in kiloponds (kp), disintegration in simulated gastric or intestinal fluid in under 15 min, less than 2% weight loss on friability testing, smooth surfaces with no pitting or chipping upon compaction, and tablets that are easily removed from the die and punch. Eight different tablet formulations were examined, which are given in the Supporting Information, before a suitable base formulation for tableting microcrystalline CB[6] was found: microcrystalline CB[6], 25% w/w; lactose, 20%; Avicel, 47.5%; talc, 2.5%; magnesium stearate, 1%; and Ac-Di-Sol, 4%.

We next examined the maximum CB[6] content that could be incorporated into the tablet formulation and still produce suitable tablets. For tablets with greater than 25% w/w microcrystalline CB[6], the lactose content in each tablet was proportionally reduced; the lactose in this formulation is used as a diluent/bulking agent[37] and so its concentration can be varied to an easier extent compared with the other excipients which fulfill other functions; Avicel (helps tablet compaction), talc (lubricant), magnesium stearate (lubricant/glidant) and Ac-Di-Sol (disintegrant).[37] Ultimately tablets with 1−50% microcrystalline CB[6] can be produced. Lowering the CB[6] content below 25% w/w, with a corresponding increase in the lactose content, has no adverse effect on the tablets.

Tablet hardness was found to increase steadily with increasing microcrystalline CB[6] content, and the tablets became more difficult to eject from the die. In an attempt to overcome the issues with excessive tablet hardness, the effect of reducing the compaction pressure was investigated. Lowering the force exerted on the tablets was in turn expected to lower the force the tablets exerted on the die wall, making them easier to eject. Tablets containing 35−45% w/w microcrystalline CB[6] were pressed at 0.5, 1.0, 1.5, and 2.0 tons. As compaction pressure decreased, the tablets became visibly less smooth at the surface, with increasingly roughened edges.

Tablet hardness was consistently lower when produced with low compaction pressure. Hardness at both 1.5 and 1.0 tons was acceptable (between 10 and 20 kp). At 0.5 ton the tablets were too soft, as well as being visibly roughened. It was decided to reduce the compaction pressure used to 1.0 ton as this would provide leeway to increase CB[6] content further. In order to produce tablets containing 50% w/w CB[6], the amount of other excipients had to be altered as

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Table 1. Melting Points of the Excipients Used in the Formulation of Microcrystalline CB[6] Tablets and the Effect of Dry Mixing or Grinding of CB[6] (50:50 w/w) on the Differential Scanning Calorimetry Curves of the Excipients

		effect of addition of CB[6]	
excipient	melting point(s)	by dry mixing	by grinding
Avicel	78 °C	move to 108 °C due to loss of water	no effect
lactose	147 and 217 °C	water peak moves to 150 °C and drop in enthalpy new peak at 166 °C; lactose melting moves to 204 °C and drop in enthalpy	further shifts in peaks to 155, 166, and 204 °C and further drops in enthalpy
talc	no melting <500 °C	no effect, only loss of water observed	no effect, only loss of water observed
magnesium stearate	94 and 117 °C	first peak moves to 90 °C; no change in second peak but increase in enthalpy	first peak moves to 86 °C and broadens; second peak moves to 111 °C
Ac-Di-Sol	70 °C (broad)	move to 100 °C due to loss of water	move to 80 °C due to loss of water

there was already no lactose in the formulation. In such cases, the formulation of a tablet consisting of CB[6] 50% w/w also contained Avicel 43%, talc 2.25%, magnesium stearate 1% and Ac-Di-Sol 3.75%. These tablets were of acceptable hardness and disintegrated very quickly, but were very difficult to remove from the die after pressing.

In an attempt to overcome issues with tablet ejection, the relative concentration of talc was increased in the final formulation to 2.5% w/w at the expense of Ac-Di-Sol (now 3.5%). Tablet hardness was reduced from the previous formulation and the tablets were slightly rough to the touch, but were still acceptable. The tablets disintegrated very quickly in simulated intestinal fluid.

Solid Phase Interactions with Excipients. As a new tablet excipient it is possible that microcrystalline CB[6] may interact unfavorably, or favorably, with the other excipients. Such interactions can be examined in a variety of ways, including differential scanning calorimetry (DSC).[38] Mixtures of microcrystalline CB[6] and each individual excipient were analyzed by DSC to determine if microcrystalline CB[6] interacts physically with any other excipient in the solid state (Table 1). Microcrystalline CB[6] was added to each excipient in a 50:50 w/w ratio and either dry mixed by hand or ground together in a mortar and pestle.

Talc is the most physically stable of all the excipients and only recrystallizes at temperatures above 1,050 °C and melts at 1,500 °C; as such, no exothermic or endothermic peaks are observed in DSC at temperatures below 500 °C.[39] The DSC of talc with the addition of microcrystalline CB[6] shows only a broad peak between 50 and 130 °C due to the loss of water from CB[6], which is consistent with TG curves described earlier and in other work.[11,16,23] Ac-Di-Sol has a single broad melting peak around 70 °C.[40] While this moves to 80 and 100 °C when ground and mixed with microcrystalline CB[6], respectively, this move most likely is dominated by the loss of water from the CB[6] and not from a change in the melting point of the Ac-Di-Sol. Similarly, Avicel has a single broad melting peak at 78 °C.[38] When ground with microcrystalline CB[6], there is no change in the melting point, but when only mixed with CB[6], the peak shifts to 108 °C. Again, this most likely represents water loss, rather than a change in the melting point of Avicel.

In contrast to talc, Ac-Di-Sol and Avicel, very significant solid state interactions are observed between microcrystalline CB[6] with lactose and magnesium stearate. Different grades of lactose melt at different temperatures; anhydrous lactose has a single sharp melting point around 240 °C.[41] Lactose samples that contain waters of crystallization like "Foremost" lactose and "medium regular lactose" (Lactochem) have an additional peak in the DSC around 150−160 °C from the loss of water.[41] In the grade of lactose used in this study two DSC peaks are observed at 147 and 217 °C (Figure 5a), which have enthalpies of fusion of −130 and −95 J/g, representing water loss and melting of α-lactose, respectively. When mixed with microcrystalline CB[6] the lactose water peak shifts slightly to 150 °C, but with a significant drop in enthalpy to −44 J/g. An additional peak is also observed at 166 °C. The lactose melting point, however, shifts to a lower temperature 204 °C and with an 64% drop in enthalpy to −61 J/g. Grinding of microcrystalline CB[6] and lactose induces more significant changes in the both the water peak and the α-lactose melting point. The three peaks observed in the mixed lactose/CB[6] sample are again seen at 155, 166, and 204 °C. The peaks at 155 and 204 °C have decreased in size to −27 and −6 J/g, respectively, and the peak at 166 °C has increased to −27 J/g.

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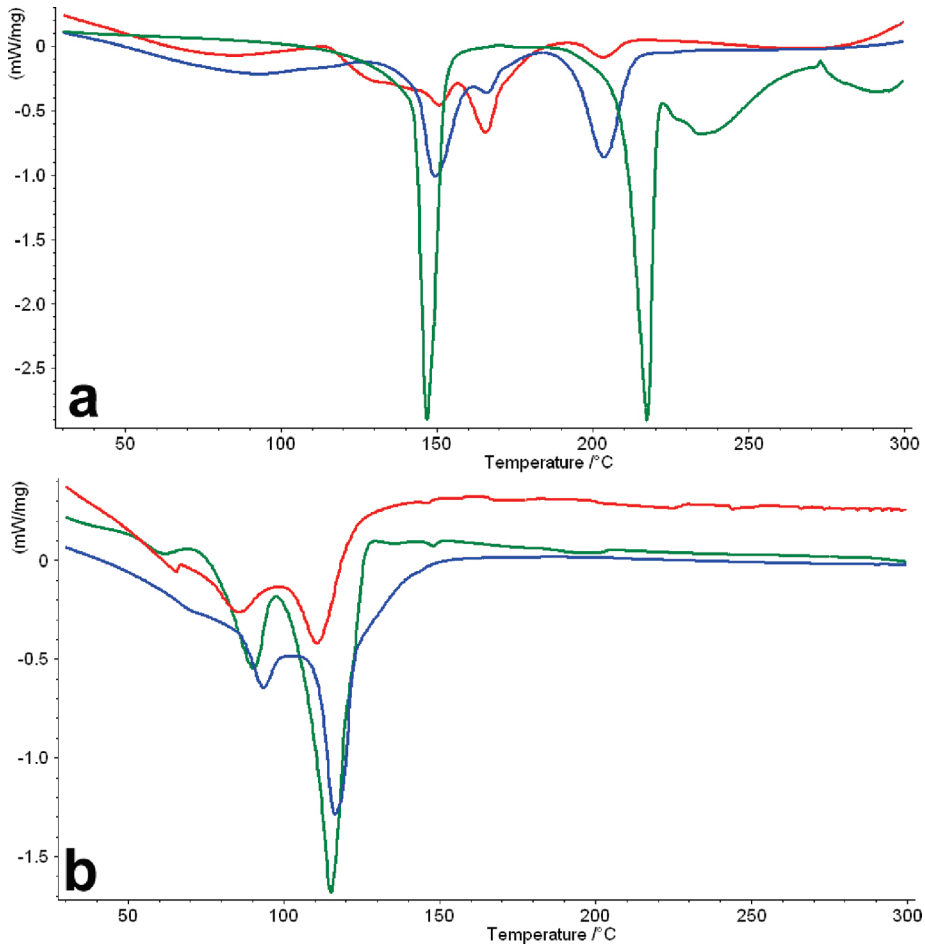

Figure 5. The differential scanning calorimetry curves of (a) lactose (green), hand mixed with microcrystalline CB[6] 50:50 w/w (blue), and ground with microcrystalline CB[6] 50:50 w/w (red); (b) magnesium stearate (green), hand mixed with microcrystalline CB[6] 50:50 w/w (blue) and ground with microcrystalline CB[6] 50:50 w/w (red).

Solid state interactions between microcrystalline CB[6] and magnesium stearate are also observed in the DSC curves (Figure 5b). Magnesium stearate has a melting point of 115 °C.[42] In this work magnesium stearate has two peaks at 94 and 117 °C. Hand mixing of microcrystalline CB[6] shifts the peak to a lower temperature (90 °C) with an enthalpy of fusion of −17 J/g. The second peak does not move significantly (116 °C) and increases in size −116 J/g. Grinding of magnesium stearate and microcrystalline CB[6] moves the first peak to an even lower temperature of 86 °C and broadens significantly into the second peak which is seen at 111 °C.

^{1}H NMR analysis of microcrystalline CB[6] solutions with lactose and magnesium stearate indicate no encapsulation of either excipient inside the cavity (as would be observed by upfield shifts of the stearate methylene or the lactose resonances). As such we hypothesize that the solid state interactions most likely represent hydrogen bonding of the lactose hydroxyl groups to the CB[6] portals and hydrophobic effects between the stearate chains and the methine/methylene regions of CB[6].

Conclusions

In conclusion, we have shown that microcrystalline CB[6] can be synthesized and processed into a form suitable for formulation into tablets for improved drug delivery. Each tablet contains lactose, Avicel, talc, magnesium stearate and Ac-Di-Sol and can contain up to 50% w/w CB[6]. These tablets demonstrate good pharmaceutical properties, such as tablet hardness and fast disintegration times. Both lactose and magnesium stearate interact with microcrystalline CB[6] in the solid state, and while it cannot be determined whether these interactions are favorable or unfavorable in the current study, they do not appear to affect tablet formulation. These results provide a foundation for the further development of CB[*n*]s, particularly CB[7] and CB[8], their host−guest complexes as drug delivery vehicles and their formulation into a variety of solid dosage forms.

Experimental Section

Materials. Glycoluril, paraformaldehyde powder (95%), talc powder, KH_2PO_4, MeOH and concentrated HCl (37%)

(42) Botha, S. A.; Lötter, A. P. Compatibility study between atenolol and tablet excipients using differential scanning calorimetry. *Drug Dev. Ind. Pharm.* **1990**, *16*, 1945.

was purchased from Sigma-Aldrich. NaOH pellets and NaCl were obtained from VWR International Ltd. Avicel (microcrystalline cellulose and sodium carboxymethylcellulose) was supplied by FMC Biopolymer, Europe. Ac-Di-Sol (croscarmellose sodium) and magnesium stearate were supplied by Pfizer. Lactose (Pharmatose DCL 11) was purchased from DMV-Fronterra Excipients. D_2O was acquired from Goss Scientific Instruments Ltd. All water was obtained from a Millipore Direct-Q water purification system. Simulated gastric fluid (SGF) was prepared as per the British Pharmacopeia,[43] and consisted of NaCl (2.0 g), pepsin (3.2 g) and concentrated HCl (7.0 mL) per 1 L of water. Simulated intestinal fluid (SIF_{sp}) was made in accordance with the United States Pharmacopeia using 6.8 g of KH_2PO_4 and 0.89 g of NaOH in 1.0 L of water to obtain a buffer of pH 6.8.

CB[6] Synthesis. 10−100 g of glycoluril was stirred with 4.4−44 g of paraformaldehyde (at a 1:2 mol ratio) in 18 M H_2SO_4 (55 mL per 10 g of glycoluril) at ∼70 °C overnight, producing cream to brown colored solutions with a large amount of precipitate. The reaction mixture was cooled to room temperature before methanol was added (∼300 mL per 55 mL of H_2SO_4). **Warning:** The ensuing reaction is exothermic, accompanied by violent effervescence. The resulting precipitate was then collected by vacuum filtration and washed with copious amounts of warm water. The crude CB[6] was dried under vacuum and redissolved in concentrated HCl. This solution was left uncovered in a fume hood to allow crystallization of pure CB[6] after a period of days to weeks.

CB[6] Processing. Crude CB[6] crystals were collected from the mother liquors and washed with HCl:water (1:1 v/v), then rinsed with water. For the production of microcrystalline CB[6] the crude crystals were redissolved in a minimum volume of concentrated HCl at room temperature, and water was then added to precipitate microcrystalline CB[6]. The precipitate was collected by vacuum filtration on a nylon filter paper (0.22 ìm) and washed with copious amounts of water. Each batch was dried in an oven at 110 °C for several hours and passed through a 500 μm aperture sieve before use. For sieved CB[6], the crude CB[6] crystals were oven-dried at 110 °C for several hours then passed through a 500 μm aperture sieve.

(43) *British Pharmacopeia*; The Stationary Office Limited: London, 2004, Vol. IV.

CB[6] Tablet Formulation. Tablets containing 0−100 mg of CB[6] were produced. Lactose (0−70 mg/tab), Avicel (86−95 mg/tab), talc (4.5−5 mg/tab), magnesium stearate (2 mg/tab) and Ac-Di-Sol (7−8 mg/tab) accounted for the remainder of the formulation. These powders were mixed thoroughly by hand for 15 min, before being pressed in an 8 mm punch/die set using a compression force of 0.5−2 tons in a Research & Industrial Instruments Company 30 ton press to yield tablets with a weight of approximately 200 mg.

Tablet Hardness Testing. The tablet hardness was assessed using a Schleuniger model 2E/205. Tablets were compressed laterally until they fractured, and the force was measured in kiloponds (kp).

Tablet Disintegration and CB[6] Dissolution. For each tablet disintegration experiment, the time taken for six tablets to disintegrate fully in 800 mL of simulated fluid at 37 °C under mechanical agitation was determined using a Copley ERWEKA ZT31 dissolution apparatus. For CB[6] dissolution experiments, sieved or microcrystalline CB[6] (5−50 mg) was added to beakers containing simulated fluid (1−50 mL) and stirred at a constant speed (600 rpm) until all CB[6] had visibly dissolved.

Particle Sizing. Sieved and microcrystalline CB[6] particle sizes were measured with a Malvern Instruments Mastersizer 2000, using water as the dispersant and a particle refraction index of 1.530 for CB[6]. Size was measured in the range 0.02 and 2000 μm and plotted as the percent of total sample as a function of size.

Differential Scanning Calorimetry and Thermogravimetric Analysis. DSC and TG curves were determined on a Netzsch STA 449 C thermocouple, equipped with a Netzsch CC 200 liquid nitrogen supply system and a Netzsch CC 200 C control unit. Each sample was heated at a rate of 10 °C/min from −10 to 300 °C.

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Supporting Information Available: Information on 11 different CB[6] tablet formulations. This material is available free of charge via the Internet at http://pubs.acs.org.

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