Cucurbit[n]urils as excipients in pharmaceutical dosage forms

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Abstract

Native, unfunctionalised cucurbit[n]urils (n = 6, 7, or 8) have shown enormous potential as excipients in medical formulations for improving drug delivery. Specific benefits include improved drug stability, solubility, controlled or triggered release, taste masking, inducing drug pKa shifts, and as antidotes. Based on in vitro and in vivo models, cucurbit[n]urils have been found to have little systemic toxicity, although they do show some specific organ toxicity, and appear to not affect developmental biology. Cucurbit[n]urils readily form hydrates in the solid state, which leads to pseudo-crystal polymorphs that can ultimately affect cucurbit[n]uril-drug complex solubility, bioavailability, and through these, drug effectiveness. In creating cucurbit[n]uril-based dosage forms, it has been found that the macrocycles can interact with other excipients in the formulation in both the solid state and in solution. While the nature of the solid state interactions are unclear, several studies of solutions have shown that some excipients are incompatible with cucurbit[n]urils as they can cause precipitates and will compete with the drugs for binding within the cavity. To date, cucurbit[n]urils have been formulated into five different dosage forms: oral solid tablet, topical cream, eye drop, implantable hydrogel, and nasal insert.
Introduction

Cucurbit\(n\)urils (CB\(n\), where \(n = 5, 6, 7, 8, 10\) or \(14\), Figure 1) are a family of synthetic macrocycles that are able to form host-guest complexes with a variety of molecules (1). They have a range of applications, including: waste remediation, chromatography, molecular switches and handcuffs, diagnostics, catalysis, and solid-state chemistry. One of the most studied applications of cucurbit\(n\)urils is their potential in drug delivery (2).

In order to form host-guest complexes with cucurbit\(n\)urils, drugs need to have specific chemical characteristics. A drug must have a hydrophobic region preferably four to six carbon atoms or longer in length, or a substituted aromatic ring, for which a para-conformation is ideal. Examples of compounds with ideal hydrophobic regions are the aliphatic methylene chains of the amino acids lysine and arginine (3), or the aromatic rings of triamterene and histamine (4, 5). In addition to a structural hydrophobic region, a drug should also have one or more am(m)ine groups. These groups facilitate host-guest complex formation via hydrogen bonds to the carbonyl oxygens on the cucurbit\(n\)uril portals. Additionally, if the drug is cationic, then binding can also be stabilised through the formation of ion-dipole bonds between the drug and the cucurbit\(n\)uril portals. An example of this is the encapsulation of memantine, which has a primary amine functional group that is protonated at physiological pH (6).

Cucurbit\(n\)urils can form host-guest complexes with drugs through total encapsulation within their cavity (e.g. memantine), by partial encapsulation of the drug, where it protrudes through either one (e.g. glibenclamide) or both of the cucurbit\(n\)uril portals (e.g. atenolol), see Figure 1 (6).
Figure 1. The chemical structure of cucurbit[n]uril and a molecular model showing the shape and internal cavity of CB[7], and three examples of drugs that form host-guest complexes with cucurbit[n]urils, via total encapsulation (memantine), partial encapsulation with the drug protruding through one portal (glibenclamide) and partial encapsulation with the drug protruding through both portals (atenolol).

However, simply understanding the factors involved in the formation of cucurbit[n]uril-drug host-guest complexes is not sufficient to move the macrocycles from the laboratory to the
To be useful in the treatment of disease all new drug molecules must be formulated into a product that is easy to use by both health staff and patients, gives an accurate dose that is released and absorbed in a predictable way, and keeps the drug stable so it does not chemically degrade and/or change its solid-state properties.

Table 1. Biomedical applications of cucurbit[n]urils as excipients in pharmaceutical dosage forms.

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Drug class</th>
<th>Cucurbit[n]uril size</th>
<th>Application</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>Antihypertensive</td>
<td>7</td>
<td>Thermal stability</td>
<td>(6)</td>
</tr>
<tr>
<td>Albendazole</td>
<td>Antiparasitic</td>
<td>6, 7, 8</td>
<td>Solubility</td>
<td>(7)</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>Antineoplastic</td>
<td>7</td>
<td>Chemical stability</td>
<td>(8)</td>
</tr>
<tr>
<td>Tricaine</td>
<td>Anaesthetic</td>
<td>7</td>
<td>Antidote</td>
<td>(9)</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Antineoplastic</td>
<td>7</td>
<td>Reversal of drug resistance</td>
<td>(10)</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>Analgesic</td>
<td>7</td>
<td>Taste masking</td>
<td>(6)</td>
</tr>
<tr>
<td>Tropicamide</td>
<td>Antimuscarinic</td>
<td>7, 8</td>
<td>Drug pKa shift</td>
<td>(11)</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>Antineoplastic</td>
<td>7, 8</td>
<td>Dissolution rate</td>
<td>(12)</td>
</tr>
<tr>
<td>Temozolomide</td>
<td>Antineoplastic</td>
<td>7</td>
<td>Enhanced activity</td>
<td>(13)</td>
</tr>
<tr>
<td>Hoechst 33258</td>
<td>Diagnostic dye</td>
<td>7</td>
<td>Light-initiated release</td>
<td></td>
</tr>
<tr>
<td>129Xe</td>
<td>Diagnostic noble gas</td>
<td>6</td>
<td>NMR contrast agent</td>
<td>(15)</td>
</tr>
</tbody>
</table>

The formulation of a drug is called a dosage form and comprises two types of ingredients, one or more drug molecules, called active pharmaceutical ingredients (API), and one or more excipients. Excipients are used to give bulk to the dosage form, stabilise the API and ensure the dosage form performs as required. As cucurbit[n]urils have no known physiological effect on the human body their use in any pharmaceutical formulation as drug delivery vehicles classifies...
them as excipients. A list of potential applications of cucurbit[n]urils as excipients in dosage forms is given in Table 1.

In this review, we detail the research that has been completed into the incorporation of cucurbit[n]urils as excipients into dosage forms, including their safety, the effect of their solid state chemistry on the formation of hydrates and pseudo-polymorphs in their crystalline form, their interactions with other excipients, and the different pharmaceutical dosage forms into which cucurbit[n]urils have been formulated.

**Safety and toxicity**

The safety of cucurbit[n]urils has been examined using in vitro, in vivo and ex vivo models. At concentrations up to 1 mM, cucurbit[n]urils have shown no significant effect on the growth of human and mouse cancer cells (8, 16, 17). In vivo studies demonstrate broad short term safety with high maximum tolerated doses when administered via intravenous injection (250 mg kg\(^{-1}\)) for CB[7] and orally (600 mg kg\(^{-1}\)) for a mixture of CB[7] and CB[8] (17).

More recently, ex vivo models have been used to examine organ-specific cardio-, myo-, and neurotoxicity (18). Using a mouse sciatic nerve model, CB[7] was found to have no neurotoxicity. While both CB[6] and CB[7] both displayed some myotoxicity via a presynaptic effect, the toxicity was only observed at concentrations much higher than what would ordinarily be used in the clinic. Both CB[6] and CB[7] also displayed some cardiotoxicity, as measured by changes in the force and rate of heart contraction. Importantly, CB[7] was found
to have a protective effect from the myo- and cardiotoxicity of the anticancer drug cisplatin (18).

Finally, the direct and indirect effect of cucurbit[n]urils on zebra fish larvae has also been examined (19-21). Zebrafish have been used for drug screening since 1980 (22), and are useful *in vivo* models compared with mice and other animals because they need a minimum of care, are cheap, their transparency allows diagnosis of internal organ damage, and mutant strains are readily available to model the effect of gene expression in response to drug administration and pharmacokinetics/dynamics.

Cucurbit[7]uril does not display any developmental toxicity or hepatotoxicity at concentrations up to 750 µM, but was found to induce cardiotoxicity and affect the locomotive movement and behaviour of zebrafish at concentrations of 500 µM and higher. Extended exposure to CB[7] (2 days) at concentrations above 500 µM resulted in the death of the zebrafish, but no mortality was observed over shorter (24 h) time periods (19).

Overall, the various studies have demonstrated the relative safety of cucurbit[n]urils for drug delivery; however, further research is still needed. This includes establishing whether there are any long term side effects from continued administration of cucurbit[n]urils and more studies on specific organ toxicity which should include the reproductive organs, kidneys, liver, and lungs.

**Solubility**
A physical characteristic of cucurbit\[n\]urils that was once thought to limit their medical application is their poor water solubility. Cucurbit\[n\]urils composed of an odd number of subunits are more soluble than the cucurbit\[n\]urils with an even number of subunits. Cucurbit[5]uril and CB[7] have a maximum solubility in pure water of 20-30 mM (23). In contrast, the water solubility of CB[6] and CB[8] are 0.018 and <0.01 mM, respectively (23).

Cucurbit\[n\]uril solubility can be significantly increased by the addition of biocompatible salts that solubilise the macrocycles via the formation of ion-dipole bonds from Na\(^+\), K\(^+\) and Ca\(^+\) cations to the carbonyl oxygens at the cucurbit\[n\]uril portals. Many solution-based pharmaceutical dosage forms contain NaCl as the excipient to achieve isotonicity with blood serum. The highly acidic environment of the stomach (pH 1-3) can also be used to solubilise cucurbit\[n\]urils, again, through bonding of H\(^+\) to the cucurbit\[n\]uril portals.

For an easy comparison of the solubilising effects of different body fluids, the solubility of CB[6] is 1-4 mM in gastric fluid, 5-7 mM in intestinal fluid, 33-37 mM in blood serum, 34-45 mM in nasal fluid (24), and 24 mM when dissolved in 0.9% w/v saline which is used for intravenous injection and eye drop dosage forms (25).

Cucurbiturils can also be used to increase the water solubility of drugs, and the encapsulation of already water soluble drugs can increase the water solubility of cucurbiturils (5, 12, 21, 26, 27).

**Cucurbituril hydrates and pseudo-polymorphism**
When dealing with the solid-state/powdered form of APIs and excipients in pharmaceutics, water is considered an impurity (28). The effect of water can be to hydrolyse or reduce the solubility of some APIs. It is permissible for the powder form of an dosage form ingredient to contain waters of crystallisation if the water quantity is known and it remains constant during manufacture and storage.

Given this, one potential problem to the use of cucurbit[n]urils in pharmaceutical dosage forms is their propensity to form hydrated crystalline solids. Depending on the synthesis method, cucurbit[n]uril powders can contain large quantities of water and they are also known to be hygroscopic. For instance, the method of Day et al to produce CB[8] yields a hydrated form of the macrocycle with 30 waters of crystallisation (29). While different methods of cucurbit[n]uril production can be used to minimise the amount of water, it is almost impossible to produce stable anhydrous cucurbit[n]uril powders.

From our research we have found that the bulk quantity of water in cucurbit[n]uril powders can be controlled through specific selection of solvents and anti-solvents where the cucurbit[n]uril is produced as a fast or slow precipitate (Table 2). For the production of powdered CB[6], the use of sulfuric acid as the solvent, and methanol as the antisolvent, yields a product with the lowest water content after oven drying, which was consistently around 0.5% w/w water.
Table 2. The effect of different solvents and antisolvents on the water content of different cucurbit[n]uril powders produced by fast precipitation or rotary evaporation.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Antisolvent</th>
<th>Oven dried (120 °C)</th>
<th>Water content (% w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfuric acid</td>
<td>Methanol</td>
<td>Yes</td>
<td>0.5</td>
</tr>
<tr>
<td>Hydrochloric acid</td>
<td>Water</td>
<td>No</td>
<td>14</td>
</tr>
<tr>
<td>Hydrochloric acid</td>
<td>Water</td>
<td>Yes</td>
<td>8</td>
</tr>
<tr>
<td>Hydrochloric acid/</td>
<td>Rotary evaporation</td>
<td>Yes</td>
<td>14</td>
</tr>
<tr>
<td>Nitric acid/water</td>
<td>Rotary evaporation</td>
<td>Yes</td>
<td>11</td>
</tr>
<tr>
<td>Hydrochloric acid</td>
<td>Acetone</td>
<td>No</td>
<td>18</td>
</tr>
</tbody>
</table>

Overall, the effect of water in cucurbit[n]uril powders is the formation of pseudo-polymorphs, which can result in an interchange between cucurbit[n]uril crystalline forms as water is gained or lost by the powder. Even when there is no change in the water content of the cucurbit[n]uril powder, its presence can induce crystal changes (30). Different pseudo-polymorphs can be observed and characterised by powder X-ray diffraction (24). Cucurbit[n]uril pseudo-polymorphs are a potential problem as each may display a different density, heat capacity, hygroscopic potential, crystal morphology, crystal growth, and solubility (31). The last is particularly important, given the low inherent solubility of cucurbit[n]urils, and because differences in solubility can lead to changes in bioavailability and drug effectiveness.

What is needed is the development of a reliable production method for each sized cucurbit[n]uril where the quantity of water in the crystal is known and reproducible. More research is also needed in understanding how the hydration of cucurbit[n]uril and
cucurbit\[n\]uril-drug host guest complexes changes during long term storage under a variety of conditions, such as humidity and temperature.

**Interactions with excipients**

In any dosage form, it is unlikely that cucurbit\[n\]urils will be the only excipient. As such, it is possible that they can interact with other excipients in the formulation which may then affect the cucurbit\[n\]urils’ ability to act as drug delivery vehicles. Interactions with excipients can occur in both the solid and solution states.

Traditionally, solid state interactions have been examined using thermogravimetric analysis, thermomicroscopy, isothermal calorimetry, and differential scanning calorimetry (DSC) (32). The solid state interactions of CB[6] with different excipients have been examined using DSC in a number of studies (33, 34). An interaction is generally determined by a change in the melting point of one or both of the excipients. To date, CB[6] has been shown to interact with a range of common pharmaceutical excipients (Table 3). Unfortunately, the tests used to determine solid-state interactions between cucurbit\[n\]urils and other excipients provides no indication about the nature of these interactions and whether they have a positive, negative or negligible effect on the macrocycles’ ability to act as delivery vehicles. Further study is therefore needed to understand these interactions before different cucurbit\[n\]uril-excipient combinations can be defined as safe for use in humans.
Excipients can also interact with cucurbit[n]urils in the solution state. These interactions can involve direct binding of the excipient within the cucurbit[n]uril cavity, where it will compete with drug binding. In some instances, excipient binding by cucurbit[n]uril can also result in the precipitation of the host-guest complex which would make parenteral dosage forms (injections) unsafe, and other dosage forms ineffective. This is particularly the case for some preservative excipients. Chlorocresol and CB[6] precipitate from solution, therefore, dosage forms that usually contain this preservative should instead use phenoxyethanol (33). Similarly, precipitates are observed when the preservatives benzalkonium chloride or chlorhexidine and combined with cucurbit[n]urils with solution. For dosage forms that normally contain these one of these preservatives sodium meta bisulfate is a recommended replacement (25).

Cucurbituril pharmaceutical dosage forms

**Oral tablets.** Tablets and capsules designed to be swallowed by patients have the highest patient compliance rates for medication adherence and the least aseptic constraints. As such, they are ideal dosage forms for any API that can be absorbed in the gastrointestinal track.

There are several key criteria that all solid oral tablets need to meet in relation to their manufacture and performance. Tablets produced via an automated direct compression method require powders that flow freely down the chutes, and do not stick to the punk or die during compression. The resulting tablets must be uniform in shape, size, and mass; have a smooth surface; and need to be stable during manufacture, transport and storage against moisture,
temperature, and shock. The key criteria for the performance of a tablet in the human body are that they must be relatively easy to swallow and that they disintegrate in intestinal fluid within a reasonable and consistent amount of time (generally less than 20 min).
Table 3. List of dosage form excipients known to have solution and/or solid state interactions with cucurbit[n]urils.

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Function in dosage forms&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Phase state examined</th>
<th>CB&lt;sub&gt;n&lt;/sub&gt; size</th>
<th>Compatibility with CB&lt;sub&gt;n&lt;/sub&gt;s</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>Bulking agent, improving tablet compressibility and mouth feel</td>
<td>Solid</td>
<td>6</td>
<td>Unknown</td>
<td>(34)</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>Lubricant</td>
<td>Solid</td>
<td>6</td>
<td>Unknown</td>
<td>(34)</td>
</tr>
<tr>
<td>Chlorocresol</td>
<td>Antimicrobial preservative</td>
<td>Solid</td>
<td>6</td>
<td>Unknown</td>
<td>(33)</td>
</tr>
<tr>
<td>Cetostearyl alcohol</td>
<td>Emollient</td>
<td>Solid</td>
<td>6</td>
<td>Unknown</td>
<td>(33)</td>
</tr>
<tr>
<td>Lanolin</td>
<td>Emollient</td>
<td>Solid</td>
<td>6</td>
<td>Unknown</td>
<td>(33)</td>
</tr>
<tr>
<td>Benzalkonium chloride</td>
<td>Antimicrobial preservative, cationic surfactant, solubilizing agent</td>
<td>Solution</td>
<td>6</td>
<td>Compatible</td>
<td>(25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Solution</td>
<td>7</td>
<td>Incompatible</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Solution</td>
<td>8</td>
<td>Incompatible</td>
<td></td>
</tr>
<tr>
<td>Chlorhexidine</td>
<td>Antimicrobial preservative</td>
<td>Solution</td>
<td>6</td>
<td>Compatible</td>
<td>(25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Solution</td>
<td>7</td>
<td>Incompatible</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Solution</td>
<td>8</td>
<td>Incompatible</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Taken from reference (35).
Solid oral tablets that contain a microcrystalline form of CB[6] have been prepared using direct compression. The tablets contain between 1-50% w/w CB[6] and other excipients including lactose (bulking agent), avicel (a type of microcrystalline cellulose that aids in tablet compression), talc (lubricant), magnesium stearate (lubricant/glidant), and Ac-di-Sol (sodium croscarmellose, disintegrant) (34). The amount of lactose in the tablets can be varied in proportion with the amount of CB[6] included in the formulation. Where the CB[6] accounts for 50% w/w of the tablet, the lactose can be omitted from the formulation.

Potential applications of cucurbituril-based oral tablets include the stabilisation of pH sensitive drugs, slow release formulations (given that cucurbiturils are not absorbed from the gastrointestinal tract), and taste masking. A specific example of the potential taste masking by cucurbit[n]uril is paracetamol. This drug has a bitter taste, but it readily forms host-guest complexes with CB[7]. In solutions of neutral pH the drug remains bound by the macrocycle, thus masking its taste when in tablet or oral solution form. However, paracetamol is ejected from the cucurbit[n]uril cavity when the solution is acidified (6), thus releasing the drug upon entering the stomach.

**Topical creams.** Topical dosage forms include any pharmaceutical product that is designed for external use. Examples include: creams, ointments, lotions, paints, pastes, gels, powders, shampoos, and patches.

Cucurbit[6]uril has been included in two basic topical dosage forms (33) that are described in the Australian Pharmaceutical Formulary; buffered cream aqueous and oily cream,
The macrocycle can be included into the aqueous cream at a concentration up to 32% w/w with no obvious effect on the consistency of the cream. In contrast, the addition of CB[6] to oily cream results in a stiff paste that is too difficult to apply, if too much cucurbit[n]uril is added.

The permeability of CB[6] in the aqueous cream was examined using a fluorescent tag and an ex vivo mouse skin model. The results indicated that CB[6] did not penetrate through the skin at any measurable concentration (33), most likely due to its lack of lipophilicity.

Because CB[6] does not penetrate through the skin, it is potentially not useful for systemic drug delivery, but may have application in the treatment of skin disorders, for example: psoriasis, eczema, acne, superficial infections, and cold sores. Additionally, it may also have a specific application in improving the longevity of sunscreens. Sunscreens only last up to four hours because they are either absorbed through the skin, dissolved out of the skin by sweat or from contact with water, or physically degraded from absorbing UV radiation. Encapsulation of the sunscreen APIs by cucurbiturils, particularly the poorly water soluble macrocycles like CB[6] and CB[8], could theoretically increase the residence time of the sunscreens in the skin and make formulation of a once-a-day sunscreen viable.

Eye drops. Eye drops are a solution-based dosage form used for the localised treatment of ocular diseases and conditions. While they are relatively simple to formulate from a chemical perspective, many drugs can not be used in eye drops due to their poor solubility, poor ocular uptake, and/or rapid eye clearance. The use of delivery vehicles, such as cucurbit[n]urils, may be of assistance in overcoming some of these problems.
Cucurbit[6]uril and CB[7] have been formulated into eye drop dosage forms at concentrations of 2.4 and 3.5% w/v, respectively (25). Due to its poor solubility, CB[8] could not be included in an eye drop formulation. Using ex vivo bovine models, fluorescently tagged CB[7] did not penetrate through the cornea, probably due to its poor lipophilicity. These results indicated that cucurbit[n]urils may not be useful for treating intraocular diseases, like glaucoma, but may still have application in the treatment of superficial eye conditions, such as dry eyes and conjunctivitis.

**Hydrogel implants.** These dosage forms are semi-solid medicines made from a three dimensional network of hydrophilic polymers and water (37) which can be administered in a variety of different ways. When formulated as pre-prepared dosage forms, they can be injected or implanted within the body, after which they slowly degrade as they absorb water (38). Alternatively, some hydrogel dosage forms are solutions that only turn semi-solid when injected into the body (39). Both types of hydrogel have application in the slow or controlled release of drugs.

Cucurbit[7]uril has been formulated into gelatin- and polyvinyl alcohol (PVA)-based hydrogels (40). When used to form a host-guest complex with the anticancer drug cisplatin, the subcutaneous implantation of the hydrogels meant that they were able to act as a slow release delivery system. An in vivo human ovarian cancer model using the hydrogels demonstrated that they were highly effective, with a 2% PVA formulation with cisplatin@CB[7] (10) being just as effective as a 5 x higher dose of free cisplatin delivered via an intraperitoneal injection (40).
**Nasal inserts.** Delivery via the nose is an effective method for bypassing the blood brain barrier and for the treatment of localised conditions, such as hay fever. Unfortunately, the currently available nasal sprays and gel dosage forms are prone to incorrect use by patients. As a result, many patients receive an inaccurate and variable drug dose that limits the effectiveness of the medication. One solution to this problem has been the development of nasal insert dosage forms. These are solid formulations with a styrofoam-like appearance that are easily handled and inserted by patients. They hydrate rapidly in the nasal cavity to produce a gel from which the API can be absorbed by the nasal cavity (41, 42).

Nasal insert dosage forms based on hydroxypropylmethylcellulose (hypermellose, HPMC) have been formulated with both CB[6] and CB[7] (43). The addition of either macrocycle at concentrations between 1 and 3% w/w was found to increase the hardness of the inserts when added at low concentrations, but decrease the inserts’ hardness at higher concentrations. Neither CB[6] or CB[7] had any effect on the springiness or mucosal adhesion of the inserts. While both macrocycles reduced the amount of water the inserts absorbed, both increased the rate of water absorption.

When used in combination with drug models, both CB[6] and CB[7] were found to make the drug distribution throughout the inserts more homogenous compared with nasal inserts without cucurbit[n]uril. Additionally, they were also found to slow the rate of drug release.
The applications of cucurbit[n]urils in nasal inserts relate to their ability to modulate the properties of the insert and the API. The residence time of the insert in the nasal cavity and the rate of drug release can be changed by altering the cucurbit[n]uril concentration.

Conclusions

Cucurbit[n]urils have shown potential as excipients in pharmaceutical dosage forms for a range of applications, including: oncology, anesthesia, infection, pain, cardiovascular disease, and biodiagnostics. To date they have been formulated into a range of dosage forms including oral solid tablets, topical creams, eye drops, implantable gels, and nasal inserts. They have also been shown to be relatively safe for human use. While cucurbit[n]urils are poorly water soluble, the addition of biocompatible salts and/or reliance on the variable pH of the body means that many dosage forms can be formulated so that they contain cucurbit[n]urils in effective concentrations. However, before they are ready to be tested in humans, there are a number of issues that need to be addressed. This includes the variability in water content of crystalline cucurbit[n]urils and their hygroscopic nature, their solid state interactions with other dosage form excipients, and any potential side effects from long term use.

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