

HYDROXYPROPYL BETACYCLODEXTRIN

AN ENABLING TECHNOLOGY FOR CHALLENGING PHARMACEUTICAL FORMULATIONS

Hydroxypropyl betacyclodextrin (HP β CD) encapsulation technology is well known for its solubilizing power. It also has other benefits — as illustrated in this review — making HP β CD the centrepiece in an enabling technology for challenging pharmaceutical formulations. For a long time, this HP β CD technology has been used exclusively by a selected few. During the past few years, the patent environment for HP β CD has become more favourable for new formulations and the use of this technology in pharmaceuticals is now free of any broad-use restrictions in most of the main markets. The main properties of HP β CD are briefly presented and the effects of HP β CD on drugs are reviewed. The full potential formulation power of this technology is becoming apparent; it is applicable in dosage forms for all the main administration routes but is of particular interest for injectable products.

Solubility problems are a genuine challenge for formulators; about 40% of marketed drugs are classified as “practically insoluble,” according to Takagi.¹ This will not improve during the coming decades as most of the drugs in development demonstrate increasingly poor solubility: one third of drugs in development are poorly soluble; and two thirds of synthesized drugs have low solubility.² Many techniques have been developed to overcome these solubility issues and, by association, bioavailability when associated with good permeability. General information about these techniques has been reviewed by Das and Bhupendra, for example.^{3,4} Cyclodextrin complexation is one of these techniques. The ability of cyclodextrins to form inclusion compounds through molecular encapsulation has been known for many years. Several pharmaceutical products on the market use this formulation technology with different cyclodextrin derivatives.

When we look at cyclodextrin complexation, there is a temptation to think that all cyclodextrin derivatives are similar. The principles of the technology are, in effect, the same, but major differences exist between the different derivatives, giving rise to noticeable differences in complex formation, complex properties and formulation opportunities. In particular, the more soluble derivatives, such as hydroxypropyl betacyclodextrin, are in a class of their own and have become available as a powerful solution for today’s challenging formulations. This paper will focus on the hydroxypropyl betacyclodextrin (HP β CD) technology platform, briefly reviewing HP β CD and illustrating the potential formulation power of this technology for dosage forms throughout the main administration routes.

HP β CD at a Glance

Cyclodextrins (CD) are cyclic oligosaccharides derived from starch. The relatively hydrophobic cavity formed by the ring shape of the molecule allows a non-covalent encapsulation of suitably sized drug moieties. Betacyclodextrin (β CD) is a seven glucose unit cyclodextrin; its solubility in water is relatively low (1.8%). Hydroxypropyl betacyclodextrins are modified β CDs having a higher aqueous solubility (above 60%) and a proven safe profile, especially for parenteral uses. The main properties of HP β CD are summarized

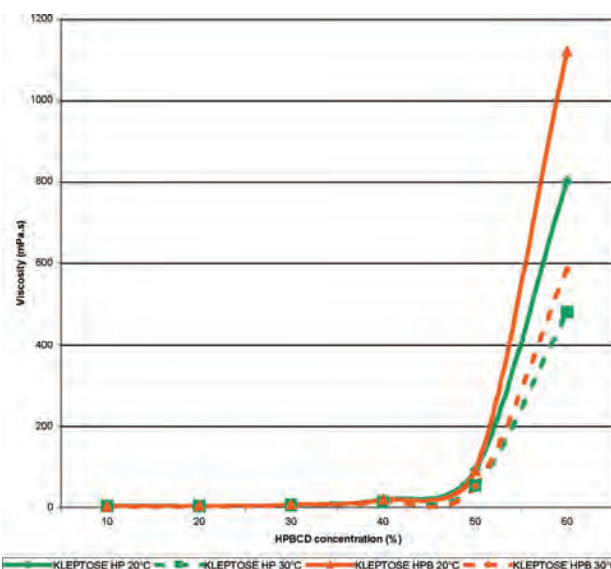


Figure 1: HP β CD viscosity.

in Table I. However, the two characteristic features to keep in mind are that it has a high aqueous solubility and a safe biological profile. These combined characteristics offer huge formulation opportunities because

- the process of complexation is much facilitated compared with native β CD
- the biological safety of this excipient permits wider use and administration routes.

A high aqueous solubility: HP β CD is infinitely soluble in water at room temperature. At very high concentrations, HP β CD forms a gel, the viscosity of which rules out the evaluation of a real limit in solubility. At 25 °C, HP β CD is 65% soluble in water; at 50 °C, it is 80% soluble. At higher temperatures, the viscosity of the solution decreases, which facilitates increased dissolution. Preparing an HP β CD solution is therefore straightforward and instantaneous. The only limit in concentration will be the viscosity or gel forming properties of HP β CD (at more than 50% dry substance), which is not related to its solubility. Figure 1 shows the viscosity of two

| | | |
|------------------------------------|---|------------------------------|
| Definition | HPBCDs are purified polydisperse products derived from the controlled reaction of propylene oxide and native βCD under base catalysis. | |
| CAS | 128446-35-5 | |
| EINECS | 420-920-1 | |
| Regulatory | Compliant with EP and USP monographs. | |
| Patent situation | The use of HPBCDs for pharmaceutical applications was patented by Janssen. In Europe and the rest of the world, the patent expired in 2004. In the USA, the patent expires in 2019. | |
| Production process | Starch is transformed into βCD after enzymatic hydrolysis and cyclization followed by purification. Hydroxypropylation is then performed, followed by purifications and spray-drying. The number of moles of hydroxypropyl group per anhydroglucose unit is called the MS (Molar Substitution) and characterizes the product. | |
| Roquette's range of KLEPTOSE HPBCD | KLEPTOSE HP | High MS |
| | KLEPTOSE HP parenteral grade | High MS |
| | KLEPTOSE HPB oral grade | Medium MS |
| | KLEPTOSE HPB parenteral grade | Medium MS |
| Physical and chemical properties | Appearance | White amorphous powder |
| | Average molecular weight | 1135 + 7 × MS × 58.1 |
| | Aqueous solubility | At 25 °C 65% At 50 °C 80% |
| | Decomposition temperature | >300 °C |
| | Moisture content | Max. 5% |
| Stability | Powder form: no significant variation (formal ICH stability study). Solution: stable to hydrolysis, to sterilization, to freezing. | |
| Safety profile | Reduced haemolytic potential, making it suitable for oral and parenteral applications. | |
| Complex preparation | In aqueous solution | |
| Effects of HPBCD on drugs | Increased solubility Increased speed of dissolution Increased bioavailability Increased stability Reduced side-effects | |

Table I: HPBCD: a summary.

HPBCD TECHNOLOGY CAN OPEN UP NEW PERSPECTIVES FOR BOTH EXISTING AND FUTURE DRUGS — AS NEW DOSAGE FORMS, NEW ADMINISTRATION ROUTES AND NEW FORMULATIONS BECOME AVAILABLE.

commercial grades of HPBCD as a function of dry substance concentration at 20 and 30 °C.

Easy complex formation: With HPBCD, an aqueous drug complex preparation is very simple: all you need is an HPBCD solution, add the drug, stir and wait for the complex to be formed. Ultimately, you can dry the complex, if required, with an appropriate technique (freeze-drying or spray-drying, for example). This exceedingly easy to use method makes HPBCD an ideal routine screening tool to evaluate new drugs and overcome their frequent solubility problems.

A safe profile: Of all the CD derivatives available, HPBCD is the safest, as it does not permeate the membranes. A literature survey shows that the toxicity of HPBCD has been extensively studied. HPBCD has been shown to have a reduced haemolytic potential, making it suitable for parenteral use as well as for oral and/or topical applications. There are several references in the literature concerning the parenteral safety profile of HPBCD, including the parenteral infusion of HPBCD in human volunteers with doses of up to 470 mg/kg/day (30 g in 4 days), and the IV infusion of single doses of up to 3.0 g.⁵ A recent publication from Gould and Scott concludes that HPBCD is well tolerated in most species, particularly if dosed orally, and shows limited toxicity, depending upon dose and route of administration.⁶

| Drug | Free Drug Aqueous Solubility | | Complex HPBCD/Drug Aqueous Solubility | | HPBCD Concentration | Reference |
|-----------------------|------------------------------|------------------------|---------------------------------------|------------------------|---------------------|-----------------------|
| | mg/L | mg/mL | mg/L | mg/mL | | |
| Alendazole | 0.154 × 10 ³ | 0.2 × 10 ³ | 2.16 × 10 ³ | 572 × 10 ³ | 300 mM | Evrad (2002) |
| Carbamazepine | Practically insoluble | 0.01 | 0.01 | 0.01 | 20 mM | Beckovic-Lacan (2002) |
| Carvedilol | Sparsely water soluble | | 0.8 × 10 ³ | | 260 mM | Miro (2006) |
| Diclofenac | | 18 × 10 ³ | | 80 × 10 ³ | 8% | Pose-Vitanovo (1998) |
| Fenofibrate | Practically insoluble | | 0.3 × 10 ³ | | 133 mM | Farrner (1997) |
| Flurbiprofen | Practically insoluble | 0.13 × 10 ³ | | 8 × 10 ³ | 20 mM | Goverdanjan (2005) |
| Glibenclamide | Practically insoluble | 0.01 × 10 ³ | | 0.6 × 10 ³ | 25 mM | Zenouk (2006) |
| Glimepiride | Practically insoluble | 3 × 10 ³ | | 42 × 10 ³ | 20 mM | Armar (2006) |
| Haloperidol | Practically insoluble | 0.05 × 10 ³ | | 0.05 × 10 ³ | 9 mM | Loukas Yannis (1997) |
| Ibuprofen | 18 × 10 ³ | | 140 × 10 ³ | | 120 mM | Lofftson (2002) |
| Indomethacin | 2 × 10 ³ | | 20 × 10 ³ | | 80 mM | Backensfeld (1991) |
| Ketoprofen | 0.8 × 10 ³ | | 12 × 10 ³ | | 20 mM | Hye (1997) |
| Naproxen | Practically insoluble | | | 0.54 | 15% | Lofftson (1993) |
| Rofecoxib | 0.017 | | 0.05 | | 10 mM | Babota (2005) |
| Tenoxicam | Practically insoluble | | | 4.40 | 15% | Lofftson (1999) |
| Ursodesoxycholic Acid | <1 × 10 ³ | | 26 × 10 ³ | | 40 mM | Vandell (2001) |
| Valartan | 0.2 × 10 ³ | 0.085 | 3.5 × 10 ³ | | 55 mM | Cappello (2005) |
| Warfarin | 5.84 × 10 ³ | 18 × 10 ³ | 5.06 × 10 ³ | 1.50 | | Kardag (1994) |
| Acetazolamide | Practically insoluble | | 0.06 | | 180 | Lofftson (1994) |
| Caprofen | | 0.05 | | 2.5 | 16% | Chen (2002) |
| Famotidine | 0.005 | | 0.055 | | 140 | Islam (1991) |
| Nabronin | | 34 × 10 ³ | | 3.5 | 180 | Koontz (2003) |

Table II: HPBCD increases drug solubility.

| Drug | Free Drug Dissolution | | Complex HPBCD/Drug Dissolution | | Reference |
|-----------------------|-----------------------|----------------------|--------------------------------|----------------------|-----------------------|
| | % in 10 min | % in 60 min | % in 10 min | % in 60 min | |
| Alendazole | 20% in 10 min | 25% in 60 min | 75% in 10 min | 55% in 60 min | Castillo (1989) |
| Carbamazepine | 25% in 10 min | 55% in 60 min | 90% in 10 min | 95% in 60 min | Beckovic-Lacan (2002) |
| Carvedilol | 0.4 mg/L in 2 min | 1.8 mg/L in 60 min | 7.4 mg/L in 2 min | 10.4 mg/L in 60 min | Miro (2006) |
| Diclofenac | 7% in 20 min | 10% in 180 min | 17% in 20 min | 30% in 180 min | Pose-Vitanovo (2003) |
| Flurbiprofen | 5% in 30 min | 20% in 180 min | 95% in 30 min | | Nagarsenkar (2000) |
| Glibenclamide | 25% in 5 min | 40% in 45 min | 75% in 5 min | 85% in 45 min | Sanghavi (1994) |
| Glimepiride | 4% in 10 min | 20% in 180 min | 36% in 10 min | 80% in 180 min | Armar (2006) |
| Indomethacin | 50% in 12.5 min | 90% in >300 min | 50% in 1 min | 90% in 1.8 min | Rama (2009) |
| Ketoprofen | 2% in 10 min | 7% in 60 min | 70% in 10 min | 100% in 14 min | Vavia (1989) |
| Nifedipine | 20% in 30 min | 45% in 180 min | 90% in 30 min | 99% in 180 min | Bayorn (2002) |
| Rofecoxib | 8.5% in 5 min | 14.5% in 15 min | 34.8% in 5 min | 54.9% in 15 min | Babota (2005) |
| Ursodesoxycholic Acid | 5% in 10 min | | 100% in 5 min | | Vandell (2001) |
| Valartan | 15 µg/mL in 10 min | 150 µg/mL in 120 min | 260 µg/mL in 10 min | 300 µg/mL in 120 min | Cappello (2005) |
| Warfarin | 2.5% in 10 min | 5.0% in 60 min | 15% in 10 min | 30% in 60 min | Chen (2003) |
| Famotidine | 38% in 2.5 min | 82% in 10 min | 95% in 2.5 min | 100% in 10 min | Islam (1991) |
| Furosemide | 0.5 µg/mL in 8 min | 3.1 µg/mL in 90 min | 4.0 mg/mL in 8 min | 7.5 mg/mL in 15 min | Vlachou (2003) |
| Griseofulvin | 2 mg/L in 10 min | 6.5 mg/L in 180 min | 5.5 mg/L in 10 min | 10.5 mg/L in 180 min | Veiga (1998) |

Table III: HPBCD increases the speed of drug dissolution.

Many different uses: Pharmaceutical and cosmetics products containing HPBCD are already on the market. The Sporanox itraconazol formulation from Janssen has pioneered this technology and is available in injectable and oral dosage forms. An indomethacin eye drop solution has been formulated and marketed by Chauvin Laboratories. Numerous cosmetic products containing HPBCD are available worldwide for topical applications in skincare and haircare.

Effects of HPBCD: A Literature Review

A tremendous body of scientific work on HPBCD is available, illustrating the high level of interest in this technology. The drawback, however, is that no completely exhaustive literature review can be done. Our survey has been limited to drugs of low solubility (Class II and IV in the BCS classification system) and listed in the Top 200 Marketed Drugs Worldwide.¹ From this extensive work, we have extracted some relevant publications to illustrate the benefits of HPBCD on drugs:

- HPBCD increases drug solubility (Table II)
- HPBCD increases drug dissolution speed (Table III)
- HPBCD increases drug bioavailability (Table IV)
- HPBCD reduces drug side-effects (Table V)
- HPBCD stabilizes drugs (Table VI).

| Drug | Model | Route of Administration | Free Drug | | | Complex HP _β CD /drug | | | Reference |
|----------------------|--------|---|----------------------|--------------------------|------------------------------|----------------------------------|--------------------------|------------------------------|-------------------------|
| | | | T _{MAX} (h) | C _{MAX} (mol/L) | AUC (mol/h/L ⁻¹) | T _{MAX} (h) | C _{MAX} (mol/L) | AUC (mol/h/L ⁻¹) | |
| Albendazole | Mice | Oral, 20 mg/kg bwt | 1.25 | 17.0 × 10 ⁻⁶ | 70.5 × 10 ⁻⁶ | 0.33 | 28.6 × 10 ⁻⁶ | 98.6 × 10 ⁻⁶ | Castillo (1999) |
| Albendazole | Sheep | Oral, 5 mg/kg bwt | 9.7 | 4.5 × 10 ⁻⁶ | 100.6 × 10 ⁻⁶ | 2.3 | 10.6 × 10 ⁻⁶ | 138.3 × 10 ⁻⁶ | Evrard (2002) |
| Albendazole | Mice | Buccogastric tube feeding, 15 mg/kg bwt | 0.5 | 12.8 × 10 ⁻⁶ | 9.2 × 10 ⁻³ | 0.5 | 14.5 × 10 ⁻⁶ | 31.6 × 10 ⁻³ | Casulli (2006) |
| Albendazole | Mice | Oral, 50 mg/kg bwt | 3 | 28.4 × 10 ⁻⁶ | 129.3 × 10 ⁻⁶ | 0.5 | 63.9 × 10 ⁻⁶ | 294.7 × 10 ⁻⁶ | Garcia-Rodriguez (2001) |
| Carbamazepine | Rabbit | Oral, 100mg CBZ | 0.50 | 23.2 × 10 ⁻⁶ | 142.5 × 10 ⁻⁶ | 0.875 | 42.0 × 10 ⁻⁶ | 234.9 × 10 ⁻⁶ | El-Zein (1998) |
| Carbamazepine | Dog | Intravenous, 20 mg/kg for the complex Oral (tablet), 20 mg/kg for the drug | 148 | 6.9 × 10 ⁻⁶ | 0.1 × 10 ⁻⁶ | 0 | 137 × 10 ⁻⁶ | 390 × 10 ⁻⁶ | Brewster (1997) |
| Flurbiprofen | Human | Oral (capsules), 50 mg FPN | 1.75 | 34 × 10 ⁻⁶ | NSD | 0.58 | 65.1 × 10 ⁻⁶ | NSD | Govindarajan (2005) |
| Glibenclamide | Dogs | Oral, 3.0 mg | 4.5 | 0.17 × 10 ⁻⁶ | | 2.5 | 1.23 × 10 ⁻⁶ | | Savoleinen (1998) |
| Ibuprofen | Rats | Rectal, 4 mg/kg bwt | 1 | 54.3 × 10 ⁻⁶ | 1595 | 0.5 | 60.1 × 10 ⁻⁶ | 1563 | Injoon (1997) |
| Ketoprofen | Rats | Oral, 5 mg/kg bwt | 0.23 | 29.7 × 10 ⁻⁶ | 88.15 × 10 ⁻⁶ | 0.07 | 178 × 10 ⁻⁶ | 197 × 10 ⁻⁶ | Hye (1997) |
| Ursodeoxycholic Acid | Human | Oral, 450 mg | 1.05 | 7.4 × 10 ⁻⁶ | 9.7 × 10 ⁻⁶ | 1.38 | 15.5 × 10 ⁻⁶ | 20.6 × 10 ⁻⁶ | Panini (1995) |
| Acyclovir | Rabbit | Nasal, 18.66 mg ACV | 1.0 | 2.7 × 10 ⁻³ | 8.2 × 10 ⁻³ | 0.5 | 13.7 × 10 ⁻³ | 38.7 × 10 ⁻³ | Chavanpatil (2004) |

Table IV: HPβCD increases drug bioavailability.

| Drug | Side-Effect | Free Drug Score | HPβCD/Drug Complex Score | Reference |
|--------------|--|-----------------|--------------------------|--------------------|
| Flurbiprofen | Stomach injury (0-4 scale: 0 = no injury; 4 = widespread injury) | 3.3 | 2.0 | Nagarsenker (2000) |
| Indomethacin | Stomach lesions | 45.7 | 18.6 | Lin (1994) |
| Rofecoxib | Stomach injury (0-4 scale) | 1.8 | 0.75 | Baboota (2005) |

Table V: HPβCD reduces drug side-effects.

Advantages of HPβCD Per Route of Administration

The benefits of HPβCD described above can be translated into benefits for both the patient and for the formulating pharmaceutical laboratories (Figure 2). This offers many opportunities to formulators. The HPβCD technology platform enables the use of new routes of administration or the exploration of new dosage forms. HPβCD is much more than just a safe solubilizing excipient and is truly an enabling technology. Some examples of its potential are described for a variety of administration routes.

Injectable: In injectable dosage forms, using HPβCD as a solubilizing excipient is a safe formulation strategy, and has the added benefit of reducing irritation at the injection site. HPβCD is not just an intrinsically safe excipient; it can also circumvent or reduce the use of potentially hazardous substances, such as surfactants and cosolvents. Loftsson, et al. has shown that HPβCD can replace surfactants and cosolvents in some formulations.⁷ Furthermore, HPβCD technology enables formulation at physiological pH. As an example, an aqueous phenytoin parenteral formulation containing HPβCD exhibited reduced drug tissue irritation and tendency to precipitate because its pH levels were closer to physiological values.⁸ This not only opens up new perspectives for some drugs as injectable dosage forms, but also for more atypical routes, such as spinal delivery, for example. HPβCD is recognized as a useful excipient for spinal delivery as it allows relatively high concentrations of lipid drugs to be administered in small volumes, thanks to its solubilizing power and its safety.⁹

Oral: Oral dosage forms are by far the most popular and include

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drug delivery via the gastrointestinal tract. In this case, HPβCD technology can help to alleviate a drug's side-effects. In buccal drug delivery, HPβCD's main application is to effect rapid drug delivery by accelerating dissolution. In liquid dosage forms, HPβCD's obvious advantage is its solubilizing and stabilizing power, leading to the formation of soluble drug complexes and enabling rapid and quantitative drug delivery.

Dermal: HPβCD is a safe formulation aid that enhances drug bioavailability in dermal dosage forms. HPβCD causes neither physical nor chemical changes within the skin barrier.¹⁰ It enhances drug delivery from an aqueous diffusion layer by increasing drug solubility, but not through the lipophilic membrane barrier. In dermal dosage forms, the composition of the vehicle greatly influences overall drug delivery and, as such, the entire formulation has to be evaluated for efficacy. A hydrophilic cyclodextrin such as HPβCD improves the release rate of lipophilic drugs from hydrophilic aqueous vehicles.

Ocular: Low viscosity eye drop solutions are the preferred formulation strategy for ocular drug delivery. HPβCD acts as a carrier by keeping the hydrophobic drug molecules in solution and delivering them through the aqueous mucin layer to the surface of the ocular barrier where they partition into the barrier. HPβCD reduces ophthalmic drug irritation by

- solubilizing drugs
- masking the irritating part of the molecule
- replacing irritating additives
- formulating at physiological pH.



Figure 2: Advantages of HPβCD for laboratories and patients.

| Drug | Effect of HPβCD on Stability to Oxidation | Reference |
|------------------|--|--------------------|
| Sulfamethoxazole | HPβCD increases the half-life: Free drug: $t_{1/2} = 77$ h Complex HPβCD/drug (10% HPβCD): $t_{1/2} = 514.9$ h | Pourmokhtar (2005) |
| Trimethoprim | HPβCD increases the half-life: Free drug: $t_{1/2} = 193.4$ h Complex HPβCD/drug (10% HPβCD): $t_{1/2} = 446.8$ h | Pourmokhtar (2005) |

| Drugs | Effect of HPβCD on Stability to Hydrolysis | Reference |
|----------------------|--|--------------------|
| Carmustine | Increase in stability to hydrolysis | Challa (2005) |
| Doxorubicin | Increase in stability to acid hydrolysis | Challa (2005) |
| Famotidine | Complex formation increases famotidine stability by 22 fold at pH 2.02 | Islam (1991) |
| Ganciclovir prodrugs | Increase in stability to hydrolysis | Challa (2005) |
| Indomethacin | HPβCD decelerates the degradation rate by a factor of 6 | Backensfeld (1990) |
| Melphalan | Increase in stability to hydrolysis | Challa (2005) |
| Paclitaxel | Increase in stability to hydrolysis | Challa (2005) |
| Rutin | Increase in stability to hydrolysis | Challa (2005) |

| Drug | Effect of HPβCD on Stability to Temperature | Reference |
|-----------|---|-----------------|
| Valsartan | After 48 weeks at 80 °C, 75% of the free drug, and 95% of the complex remains | Cappello (2005) |

| Drugs | Effect of HPβCD on Stability to Light | Reference |
|--------------------------------------|---|----------------|
| 2-Ethylhexyl p-dimethylaminobenzoate | Increase in photostability | Challa (2005) |
| Nifedipine | Degradation rate under fluorescent lamp for free drug = 3.97: 0.29 for HPβCD/drug complex Degradation rate under sunlight for free drug = 20.87: 2.68 for HPβCD/drug complex | Bayorni (2002) |
| Promethazine | Increase in photostability | Challa (2005) |

Table VI: HPβCD increases drug stability.

Nasal and pulmonary: The respiratory tract is being studied extensively as a convenient administration route for high potency drugs with low oral bioavailability. HPβCD's strength is its low toxicity and lack of membrane permeation. It acts as a safe carrier.

Conclusion

HPβCD can offer many advantages in pharmaceutical formulations, including the following:

- increased solubility for active ingredients
- increased bioavailability for high permeation, low solubility drugs
- quicker onset of action
- reduced side-effects
- increased shelf-life
- better compliance
- reduced toxicity.

An extensive body of literature backs up the potential contribution that HPβCD technology can make. This opens up new perspectives for both existing and future drugs — as new dosage forms, new administration routes and new formulations become available. Moreover, HPβCD is so soluble in water that it makes complex formation very simple. It is so straightforward that it can be done routinely to evaluate potential drug candidates at a very early stage. HPβCD is not only a safe excipient; it is a multipurpose tool and the centrepiece in an enabling technology for challenging pharmaceutical formulations. **Pharma**

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