Emprove® Program – Two Decades of Easing Risk Management

Twenty Years of Speeding up Your Journey. And Still Accelerating.

Maintaining compliance with current Good Manufacturing Practices (cGMPs) at any given time in your drug manufacturing process can be complex and challenging – especially in a global, dynamic environment. As a drug manufacturer, you need to compile a vast amount of information from your suppliers to ensure that the raw materials and components you purchase meet the technical, regulatory and supply needs for their designated application, use and function. This can be resource- and time-intensive, as well as expensive.

20 years ago, we launched the Emprove® Program to accelerate your risk assessments and help you maintain compliance. As your processes evolved, so did the Emprove® Program, anticipating challenges and keeping you ahead of the curve. With a comprehensive digital platform, the Emprove® Program speeds your drug development journey by offering convenient access to reliable information for a broad portfolio of high-quality products. This way, the Emprove® Program enables you to:

- make more agile, risk-based decisions
- maintain compliance and
- demonstrate control – saving you time and money

Ordering Information

Cyclodextrin HPB EMPROVE® EXPERT Ph. Eur., NF

Cat. No.	Pack Size	Packaging
1.42020.0050	50 g	Plastic bottle in corrugated box
1.42020.2500	2.5 kg	Plastic bottle in corrugated box

Sulfobutylether-β-Cyclodextrin sodium salt EMPROVE® EXPERT Ph. Eur., NF

Cat. No.	Pack Size	Packaging
1.42022.0050	50 g	Plastic bottle in corrugated box
1.42022.2500	2.5 kg	Plastic bottle in corrugated box

The typical technical data above serve to generally characterize the product. These values are not meant as specifications and they do not have binding character. The product specification is available separately at: **SigmaAldrich.com**

We provide information and advice to our customers on application technologies and regulatory matters to the best of our knowledge and ability, but without obligation or liability. Existing laws and regulations are to be observed in all cases by our customers. This also applies in respect to any rights of third parties. Our information and advice does not relieve our customers of their own responsibility for checking the suitability of our products for the envisaged purpose.

For additional information, please visit **SigmaAldrich.com**
To place an order or receive technical assistance, please visit **SigmaAldrich.com/contactAF**

MilliporeSigma

unlock the possibilities

Enhancing Solubility and Stability with Cyclodextrins

Formulation Product Finder App

Find the right product for your application with our Formulation Product Finder App at:

Formulation-app.SigmaAldrich.com

MilliporeSigma is the U.S. and Canada Life Science business of Merck KGaA, Darmstadt, Germany

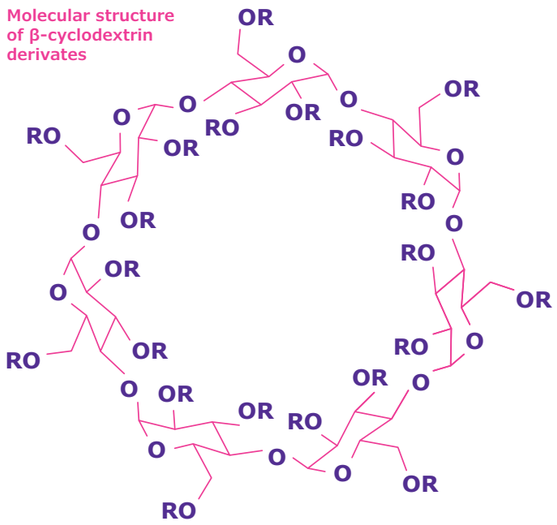
SAFC®
Pharma & Biopharma Raw Material Solutions

cyclodextrin for enhanced possibilities.

Insufficient stability and low solubility are frequent hurdles during pharmaceutical development as they directly impair drug bioavailability and, in consequence, the efficacy and success of the final drug product. Aqueous formulations, e.g. for oral or parenteral application, bear the risk of chemical degradation for compounds prone to hydrolysis or oxidation. In addition, as newly developed compounds are becoming more and more complex and hydrophobic, the need for approaches to overcome both stability and solubility issues is continuously increasing.

Cyclodextrins can help to overcome these hurdles. First discovered as early as in the 19th century, these natural molecules have become a frequently used type of excipients in both pharmaceutical and biopharmaceutical formulations.

Molecular structure of β-cyclodextrin derivates



HP-β-CD
R=CH_3-CH(OH)-CH_2 or R=H

SBE-β-CD
R=$(CH_2)_4SO_3Na$ or R=H

Due to their unique characteristics, cyclodextrins can exert a broad range of functions such as protection of compounds against chemical degradation, reduction of protein aggregation, increase of drug solubility as well as masking of odors and tastes.

Our cyclodextrin derivates 2-Hydroxypropyl-β-Cyclodextrin (HP-β-CD) and Sulfobutylether-β-Cyclodextrin Sodium Salt (SBE-β-CD) will help you ease your mind, regardless of your desired application or dosage form. As part of our Emprove® Expert portfolio, our cyclodextrins meet very low microbial and endotoxin limits, specifically optimized to address the demands of high-risk applications.

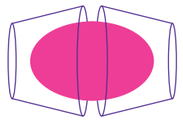
Benefits

- Increase solubility and stability
- Enhance bioavailability
- Mask odors and tastes
- Reduce aggregation behavior of biologic APIs
- Emprove® Expert products with very low microbial and endotoxin limits for high-risk applications

Mode of Action

Cyclodextrins are cyclic oligosaccharides derived from natural starch. The α-1,4-D-glucopyranoside units are arranged in the form of a hollow cone with a hydrophilic exterior and a hydrophobic cavity. Within this cavity, cyclodextrins can “complex” hydrophobic, poorly water-soluble active pharmaceutical ingredients (APIs), forming an API-cyclodextrin inclusion complex. This “host-guest” interaction is reversible, and the API is easily released once administered to the body.

API-cyclodextrin complex with the API in the cyclodextrin cavity (schematic)

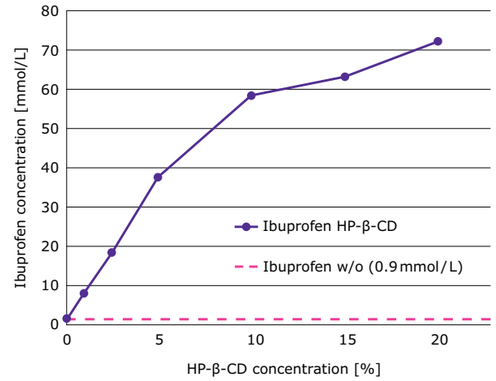


Increased API Solubility

API-cyclodextrin complexes usually show strongly improved solubility, thus rendering our products HP-β-CD and SBE-β-CD an excellent choice for bioavailability enhancement of poorly water-soluble APIs.

In the figure on the right, it is shown that solubility of the model API Ibuprofen was significantly increased when complexed with HP-β-CD. At an API:cyclodextrin ratio of 1:10, Ibuprofen solubility was approx. 80 times higher in comparison to pure API.

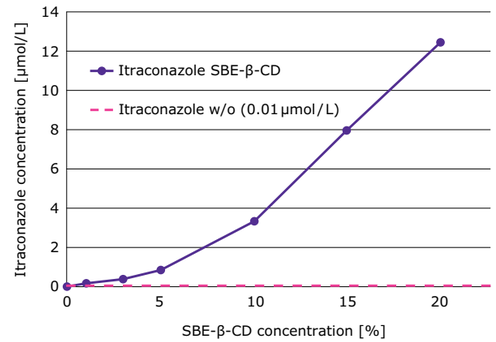
Solubility of Ibuprofen as a function of HP-β-CD concentration. Experimental conditions: Incubation of Ibuprofen with different concentrations of HP-β-CD (0 – 20 %) at pH 5.0 (50 mmol/L acetate buffer) for 24 h at 25 °C; centrifugation at 16,000 rpm; determination of Ibuprofen concentration in supernatant by HPLC.



As reported in literature, SBE-β-CD has been shown to even further enhance solubility of certain APIs compared to complexation with HP-β-CD. One basis for this fact is the longer hydrophobic chain of sulfobutyl ether present in SBE-β-CD, thus enlarging the cavity’s hydrophobic region in which the API is complexed. The decision which cyclodextrin derivate to use needs to be evaluated and decided based on the specific API’s characteristics.

Complexation of the model API Itraconazole with SBE-β-CD strongly enhanced solubility up to 1200-fold (even in a non-optimized formulation) in comparison to pure API. For this experiment an API:cyclodextrin ratio of up to 1:10 was used. Results are shown in the figure on the right.

Solubility of Itraconazole as a function of SBE-β-CD concentration. Experimental conditions: Incubation of Itraconazole with different concentrations of SBE-β-CD (0 – 20 %) at pH 5.0 (50 mmol/L acetate buffer) for 24 h at 25 °C; centrifugation at 16,000 rpm; determination of Itraconazole concentration in supernatant by HPLC.



Improved API Stability

Cyclodextrins are also an excellent option for increasing the stability of your API. As complexation with cyclodextrins can prevent API-excipient as well as API-API interactions, the encapsulated parts are better protected against hydrolysis or oxidation, thus reducing chemical degradation of small molecule APIs. In case of biologic APIs, the shielding effects of cyclodextrins increase resistance against mechanical and temperature stress, thus reducing aggregation behaviour and helping maintaining high monomer content.

Safety and Purity

Cyclodextrins have been used in pharmaceutical products for decades. HP-β-CD and SBE-β-CD are cited in the FDA’s list of Inactive Ingredient Database. Numerous safety reports as well as dosing thresholds for different application routes exist. Parenterally administered cyclodextrins are usually renally excreted intact without metabolization. In case of HP-β-CD, oral bioavailability has been reported as very low. In fact, HP-β-CD and SBE-β-CD can be applied to reduce adverse effects of APIs and, thus, improve safety of the final dosage form.

Broad Application Range

Due to their shielding effects, cyclodextrins can help minimizing or even preventing gastrointestinal and ocular irritation. They can be applied to reduce undesired characteristics of the API, such as unpleasant taste or odor, or toxicity. In addition, cyclodextrins can also be used to convert liquid or oily APIs into a free-flowing, solid powder which can then be processed into tablets.

The application of HP-β-CD is not limited to a specific formulation type or administration route. In fact, the application range of this product is very wide: it can be used in liquid, semi-solid and solid formulations, and marketed products exist intended for oral, dermal, rectal, ocular and parenteral application.

SBE-β-CD is today primarily used for dosage forms intended for parenteral application. It is especially suitable for respective pH ranges and has higher solubilization characteristics for certain APIs compared to many other cyclodextrins and derivates.