KLEPTOSE® HPB

A safe solubilizing excipient for nasal and pulmonary drug delivery
KLEPTOSE® HPB
at a glance

➢ Enhances drug solubility
➢ Low toxicity
➢ High aqueous water solubility: ideal for small volume for nasal or pulmonary drug delivery
➢ Low viscosity: 20 mPa.s at 20°C and 40% HPBCD
➢ Chemically stable
➢ Can be sourced worldwide reliably.
A safe solubilizing excipient for nasal and pulmonary drug delivery

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The nasal route is ideal for local diseases such as allergic rhinitis and nose congestion. But it is also the entry point for the systemic delivery of numerous drugs and therapies (e.g., hormone replacement therapy, osteoporosis, pain management, smoking cessation, motion sickness, central nervous system disorders, and vaccines)\(^1\).

**Advantages of nasal and pulmonary drug delivery system\(^2\):**

- No drug degradation in the gastrointestinal tract.
- Hepatic first-pass metabolism is absent.
- Rapid drug absorption and quick onset of action achievable.
- Nasal bio-availability for small drug molecules is good.
- Bio-availability of large drug molecules can be improved by absorption enhancement.
- Alternative to parenteral route, especially for protein and peptide drugs.
- Alternative to oral route, for low oral bio-availability drugs.

**Limitations\(^2, 3, 4\):**

- Rapid mucociliary clearance
- Enzymatic degradation in the mucus layer and nasal epithelium
- Low permeability of the nasal epithelium
- Large interspecies differences in the nasal administration of drugs
- Drugs of lipophilic nature are difficult to deliver through the nasal route due to their poor water solubility
KLEPTOSE® HPB hydroxypropyl betacyclodextrin is an attractive excipient for nasal and pulmonary drug delivery because it:

- Solubilizes drugs
- Strengthens absorption enhancer activity
- Has a low toxicity profile.

Figure 1: Barriers to macromolecule absorption in the respiratory tract (from Koushik⁵)

In order to enter the systemic circulation, the drug has to dissolve in the aqueous nasal fluids. Nasal formulations are limited by the fact that only 25-150µl of liquid can be sprayed into each nostril⁴. Unlike the limited surface area (approximately 180cm²) available for drug absorption in the nasal cavity, the lung offers a large surface area (approx 75m²). In addition, the alveolar epithelium is very thin (0.1 – 0.5µm), thereby permitting rapid drug absorption⁶.
**HPBCD solubilizes drugs**

**The aqueous solubility of a drug is always a limitation for nasal drug delivery in solution.**

HPBCD serve as a biocompatible solubilizer and stabilizer in combination with lipophilic absorption enhancers.

Cyclodextrins are normally used to increase the aqueous solubility of lipophilic drugs. However, lipophilic cyclodextrins can also interact with biological membranes, to serve as penetration enhancers, especially in nasal delivery of peptides. Methylated cyclodextrins are efficient absorption enhancers and this is one reason why they are the most commonly studied cyclodextrins in nasal drug delivery.

Many studies show that nasal delivery of drugs is substantially enhanced by a number of cyclodextrins, especially those that seem to have a membrane-disturbing effect.

HPBCD is a hydrophilic cyclodextrin that combines the solubilizing effect with safety because it does not disturb the membranes.

The use of a non-membrane-disturbing cyclodextrin such as HPBCD to enhance the drug solubility raises fewer safety concerns.

Solubilization of drugs by cyclodextrins can dramatically improve the drugs’ systemic delivery via nasal administration by presenting overall higher concentrations to the nasal epithelium.

Intranasal spray of the antiviral lipophilic drug pirodavir with 10% HPBCD as a solubilizer was effective in preventing rhinovirus infection.

HPBCD has shown an enhanced and sustained level of morphine in plasma and cerebrospinal fluid.

Dihydroergotamine mesylate solubility was significantly enhanced by HPBCD in a nasal spray dosage form.

In nasal spray preparation of peptides such as insulin and buserelin acetate, HPBCD was found useful as a solubilizer for lipophilic absorption enhancers.
Nasal mucosa are almost impermeable to a molecular size greater than 1000 Daltons. To overcome the problem of poor membrane permeability the most common approach is to use absorption enhancers\(^2\).

Many absorption enhancers act by altering the structure of epithelial cells in some way. Although they should accomplish this while causing no damage or permanent change to nasal mucosa\(^2\), many permeation enhancers reported in the literature have been shown to cause significant mucosal damage at concentrations required to enhance nasal absorption\(^3\).

Shao reported the effectiveness of cyclodextrins as pulmonary absorption enhancers. Among all the cyclodextrins tested, HPBCD exhibited the least effect as absorption enhancer. This illustrates the fact that HPBCD itself is not an absorption enhancer. HPBCD can be used to reduce the nasal toxicity of other enhancers without affecting their absorption enhancing property\(^10\).
Many cyclodextrin derivatives have been studied for nasal or pulmonary drug delivery; none of them have the same properties nor exhibit the same effects.

DMBCD (dimethyl beta cyclodextrin) was shown to act as an absorption enhancer, whereas HPBCD had no effect on the permeability of the tested compounds. Moreover, in some cases, damages to the nasal mucosa were noted: DMBCD appeared to affect the mucosa more than did HPBCD.

A summary of published toxicological studies on HPBCD is available upon request at: kleptose-hpb@roquette.com

Safety in the use of absorption enhancers or enzyme inhibitors is a major concern, both in the short-term and the long-term.

With no absorption enhancement effect, HPBCD should be considered as an attractive solubilizing excipient offering the safest approach to nasal formulations.
The large molecular size together with the hydrophilicity and lability (both chemical and enzymatic) of proteins and peptide drugs virtually exclude their formulation in traditional oral dosage forms such as tablets and capsules.

The respiratory tract delivery is being studied intensively as it is a more convenient route for administration. Hydrophilic drugs like proteins and peptides have low nasal absorption in humans that decreases with increasing molecular size. Cyclodextrins have been shown to increase nasal absorption of oligopeptide drugs.

Like other tissues, the nasal mucosa are readily permeable to lipophilic drugs and poorly permeable to polar substances of larger molecular weight, such as proteins and peptides. Absorption enhancers are necessary to deliver them effectively. The rapid metabolism of proteins and peptides by enzymes must also be inhibited. Nasal mucosa possess enzymatic activity as a protective mechanism against exogenous materials.

Lysozyme is especially present in nasal secretion and very active at acidic pHs. It is therefore advisable to keep the formulation at a pH between 4.5 and 6.5.

HPBCD was found to inhibit the metabolic inactivation of methionine enkephalin by rabbit nasal mucosa extract.

Buserelin nasal delivery is not enhanced by HPBCD, but a combination of HPBCD and the absorption enhancer HPE 101 has a dramatic effect, through solubilisation of the absorption enhancer by HPBCD.

HPBCD does not solubilise insulin, nor has it absorption-enhancing effects. However, in insulin preparation HPBCD displayed unusual properties: at neutral pH the HPBCD significantly inhibited the adsorption to containers and self association of insulin. HPBCD may interact with hydrophobic amino acid residues to prevent direct contact with insulin molecules, i.e. aggregation.


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kleptose-hpb@roquette.com

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ROQUETTE WORLDWIDE

EUROPE

FRANCE
Roquette Frères
Corporate Headquarters
62080 Lestrem cedex - France
Telephone: +33 3 21 63 36 00
Fax: +33 3 21 63 38 50

DENMARK
Roquette ApS
Gydevang 39-41
DK - 3450 Aalborg
Telephone: +45 69 663 200
Fax: +45 69 663 209

FINLAND
Roquette Nordica Oy
Arvenlie 4A, 20
FI-02170 Espoo - Finland
Telephone: +358 9 315 85 700
Fax: +358 9 8632 113

GERMANY
Roquette GmbH
Darmštädtier Landstrasse 182
60598 Frankfurt - Deutschland
Telephone: +49 69 60 91 050
Fax: +49 69 60 91 05 59

ITALY
Roquette Italia S.p.A
Via Serravalle 26
15063 Cassano Spinola
Alessandria - Italy
Telephone: +39 0 143 7741
Fax: +39 0 143 477 295

ROMANIA
Roquette Romania S.A.
Platforma Industrială
Sud-Vest Nr 5
205200 Caleafat - Dolj - Romania
Telephone: +40 251 333 067
Fax: +40 251 306 262

SPAIN
Roquette Laaisa España, S.A
Avenida Jaime I, S/N
46450 Benifaió - Valencia - España
Telephone: +34 96 178 98 00
Fax: +34 96 178 98 10

UNITED KINGDOM
Roquette UK Ltd
Sallow Road
Weldon Industrial Estate
Corby Northants NN17 5JX
United Kingdom
Telephone: +44 15 36 273000
Fax: +44 15 36 263873

RUSSIA
OOO Roquette Rus
17, Vorontsovskaya street
Business Center
"Mosenka Capital Plaza"
109147, Moscow - Russia
Telephone: +7 (495) 775-75-87
Fax: +7 (495) 775-75-88

TURKEY
Roquette Tarım ve Gıda
San. ve Tic. Ltd. Sti.
Büyükdere Cad. Harman Sok.
Duran İş merkezi No:4 K:3
34394 Levent İstanbul - Turkey
Telephone: +90 212 234 83 73
Fax: +90 212 234 83 74

AMERICA

USA
Roquette America Inc.
Geneva Innovation Center
2211 Innovation Drive
Geneva, IL 60134 - USA
Telephone: +1 630 463 9430
Fax: +1 630 232 2157

MEXICO
Roquette México S.A. de C.V
Blvd. Bernardo Quintana 9750 of 321
Fracc. Centro sur Queretaro Gro.
CP 76090 - México
Telephone: +52 44 2229 1270
Fax: +52 44 2229 1270

ASIA

CHINA
Roquette Shanghai
Room 505 - K. Wah Centre,
1010 Huai Hai Zhong Road,
Shanghai 200031 - P.R. China
Telephone: +86 21 54 03 99 22
Fax: +86 21 54 03 66 06

INDIA
Roquette India Private Limited
Office no. 702, 7th Floor Powai Plaza
Hiranandani Gardens - Powai
Mumbai 400 076 - India
Telephone: +91 22 2570 6775
Fax: +91 22 2570 6770

JAPAN
Roquette Japan K.K.
Tokyo Head Office
2F. Kasuga Business Center Building
1-15-15 Nishikata - Bunkyo-Ku
Tokyo 113-0024 - Japan
Telephone: +81 3 3830 1510
Fax: +81 3 3830 1525

KOREA
Roquette Korea Ltd.
12th FL., Samheung Yeoksam bldg.,
Teheran-ro 14-gil 5, Gangnam-qu 735-10
Yeoksam dong, Kangnam Ku,
Seoul 135-923 - Korea
Telephone: +82 2 2141 3400
Fax: +82 2 2141 3482

SINGAPORE
Roquette Singapore Pte. Ltd.
298 Tuang Bahru Road,
#14-02/03 Central Plaza,
Singapore 168730 - Singapore
Telephone: +65 6416 3377