CYCLODEXTRIN NEWS

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Cyclodextrin-enabled Insulin Delivery

Introduction

Insulin is a peptide hormone produced by beta cells in pancreatic islets. Its main task is the regulation of the metabolism of carbohydrates, fats and protein. In diabetes the insulin production is not enough to keep the blood sugar levels within normal bounds, therefore external insulin should be supplied.

The human insulin is composed of 51 amino acids and 3 disulfide bonds; it has a molecular mass of 5808 Da and low aqueous solubility. Bovine insulin differs from human in only 3 amino acids and porcine insulin in one. Insulin is produced and stored in the body as a hexamer (Fig. 1), while the active form is the monomer. The hexamer is much more stable than the monomer.

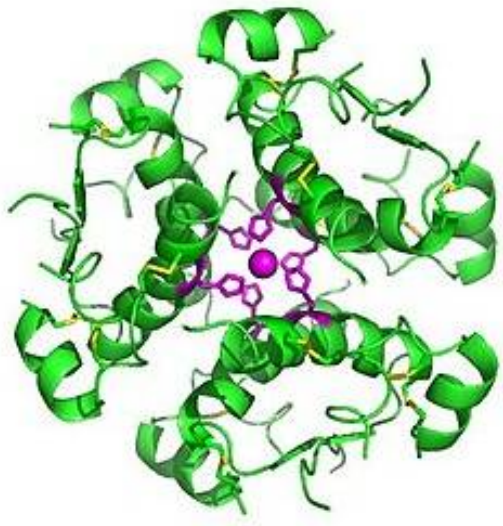

Fig. 1 The structure of insulin hexamer (the magenta sphere is zinc ion, wikipedia)

Human insulin is manufactured by recombinant DNA technology, but some patients observing adverse effects to synthetic insulin use animal-source insulin.

The oral administration of peptides and proteins is of low efficiency because of the enzymatic degradation in the gastrointestinal tract and poor transport characteristics. That is the reason why insulin is administered via parenteral injections.

While developing the devices used for insulin injections (to reduce the pain and local irritation as well as the frequency of application), researchers have been taking continuous efforts on finding novel non-invasive formulations.

- One of the aims is protection of insulin from proteolysis in the digestive tract so that it can be administered orally or sublingually.
- Inhalable insulin is a powdered form of insulin delivered by a nebulizer. Inhaled insulin marketed under the trade name Afrezza absorbs more rapidly than subcutaneous injected insulin.
- The nasal route is an alternative as the nasal cavity is covered by a well vascularized thin mucosa ensuring fast systemic absorption without the first pass hepatic metabolism. The nasal administration, however, is associated with high variability in the amount of drug absorbed (difficulties in dosing, swallowing a part of the liquid, varied permeability for patients with airway infection, etc.).

The nasal administration became extremely interesting after discovering that insulin absorbs directly to the brain and improves memory in addition to helping preserve cognitive function in people with early Alzheimer disease or mild cognitive impairment (Novak et al. 2014). It is a side-effect for patients in diabetes but it is still not clear how this beneficial effect could be utilized for people with normal glucose homeostasis, how to avoid the main effect, the decrease of blood sugar level.

People in diabetes often have chronic or non-healing wounds as a consequence of impaired production or utilization of insulin. It was suggested that applying insulin directly to the skin it helps regeneration of the epidermis. The animal studies revealed that topical insulin facilitates wound contraction and re-epithelization (Oryan & Alemzadeh, 2017). The clinical trials showed statistical difference compared to control in microvessel density, growth of granulation tissue and rate of healing but local insulin application also may have an effect on blood glucose level, so careful dosing is necessary to avoid hypoglycemia.

CD complexation of insulin

The low solubility and stability of insulin calls for cyclodextrin complexation. No wonder that there are 485 publications in the scopus database (20 March, 2018) mentioning both insulin and cyclodextrin in the title and/or abstract.

The first patent described alpha-CD-enabled nasal insulin sprays (Hirai et al., 1983). In another early patent the derivatives of beta- and gamma-CD are claimed to have solubilization and stabilization effect on polypeptides, such as insulin (Hora et al. 1990).

Brewster et al. (1989) in their review on parenteral application of HPBCD mention the solubilization and stabilization of proteins including also insulin. The aggregation of insulin is suppressed by HPBCD, maltosyl BCD and sulfobutyl BCD (SBEBCD) of DS 4 (but not with DS 7) (Brewster et al. 1991; Tokohiro et al. 1997). The efficacy of CDs preventing shaking-induced aggregation follows the order of HPBCD > BCD > ACD, while GCD did not show such an effect (Banga & Mitra 1993). The aggregation of insulin is hindered by HPBCD both in vitro (Stern, 1989) and in vivo by inhibiting the formation of amyloid fibrils at the site of repeated insulin injections in patients with insulin-dependent diabetes (Kitagawa et al. 2015).

The complex formation through the inclusion of aromatic amino acids, such as phenylalanine was confirmed by various spectroscopic techniques (NMR, FT-Raman and FT-IR/ATR) (Valentini et al. 2015).

Studying the energetics of dissociation of bovine insulin in aqueous solution by microcalorimetry revealed that CDs increased dissociation of insulin oligomers (Lovatt et al. 1996). In the presence of CDs (ACD, BCD and derivatives) the dissociation was significantly more endothermic and the apparent dissociation constant decreased in a high extent both at pH 2.5 and 7.4. These studies indicate that complexation favors the monomeric form of insulin.

Dimethyl BCD (DIMEB) enhanced the insulin oligomer dissociation in a higher extent than HPBCD (Shao et al. 1994a).

Kinetic studies confirmed that acidic hydrolysis of insulin is suppressed by methyl BCD (Dotsikas & Loukas 2002).

HPBCD also protected insulin from acidic degradation: 73% versus only 53% of insulin remained undegraded in pH 1 HCl solution with and without HPBCD, resp. (Zhang et al. 2009). The protecting effect was even better in alkaline solution (pH 13 NaOH) 82% versus 51% insulin was measured with and without HPBCD, resp. HPBCD helped insulin to resist heat: at 55 ^{o}C 79% and 61% insulin remained intact with and without HPBCD, resp. HPBCD was also useful for the stability of disulfide bonds in insulin.

Both enzymatic and thermal stability were improved by conjugating glucuronylglucosyl BCD (GUGBCD) to insulin (Sugio et al. 2016).

CD-enabled oral delivery of insulin

The oral route represents the most convenient way of drug administration due to high patient compliance. Oral insulin is subjected to the proteolytic enzymes of the digesting system, such as pepsin, trypsin, chymotrypsin and peptidases. Therefore the orally administered insulin alone, without additives, has little hypoglycemic effect (Yang et al. 2018).

The bioavailability of insulin in the lower jejunal/upper ileal segments of the rat from a solution without CD is very low (~0.06%), when administered enterally at a dose of 20 IU/kg using an in situ closed loop method (Shao et al. 1994a). It can be enhanced by DIMEB to 5.63%, while with HPBCD no significant improvement was observed (0.07%). Histopathological examination of the rat intestine revealed no observable tissue damage, excluding direct membrane fluidization as the primary mechanism for enhanced insulin uptake.

The effect of HPBCD was, however, improved remarkably by introducing carboxymethyl groups to the molecule. Carboxymethyl-hydroxypropyl-BCD (CM-HPBCD) showed higher insulin-binding ability and better transport properties (permeability of the insulin complex across Caco2 cell layer) compared to both HPBCD and CMBCD (Table 1). In the in vivo experiment the insulin/CM-HPBCD complex provided a significant and sustained reduction in the blood glucose levels of diabetic rats (Zhang et al. 2013).

Table 1 Apparent complex (1:1) association constants (K) calculated from UV spectra, transporting efficiency across Caco-2 cells and reduction of blood glucose level after oral administration of insulin/CD complexes to diabetic rats (Zhang et al. 2013)

	K (M^{-1})	Transporting efficiency (transported in 120 min, %)	Reduction in blood glucose level in diabetic rats (%)
no CD	-	1.3	<5
BCD	56.7	2	5
HPBCD	88.9	3.5	10
CMBCD	180.7	6.5	13
CM-HPBCD	311.2	10	21

Another way of improving the efficiency of HPBCD-based insulin formulations is co-administration of cell-penetrating peptides. The transportation efficiency across the Caco-2 cell monolayer was further enhanced and these combinations significantly reduced glycaemia in diabetic rats (Zhang et al. 2012).

A cell-penetrating peptide conjugate of CMBCD (R8-CMBCD) could facilitate the uptake of insulin (Yang et al. 2018). The transportation efficiency of insulin/R8-CMBCD across the Caco-2 cell monolayer was about 3 times higher than that of insulin/CMBCD partly because of the inhibition of Pgp efflux pumps. The formulation showed increased permeability of insulin and biological response (highest and longest lasting effect on blood glucose level) in diabetic rats after oral administration compared to insulin/CMBCD and insulin/R8.

Micro- and nanoparticles of polymeric hydrogels that protect insulin from enzymatic degradation in acidic stomach and deliver it effectively in the intestine is a common approach in the recent research. These nanoparticles show improved properties when combined with CDs as shown by some examples in Table 2.

Table 2 Micro- and nanoparticles formulated with CDs for insulin delivery

Polymer	CD	Result	Reference
Alginate	BCD	Enhanced absorption in rats	Nesamony et al. 2001
Alginate/chitosan	BCD	Reduced aggregation, prolonged release	Moses et al. 2000
Alginate/chitosan	Cationic BCD polymer	Enhanced permeability into cells, sustained release	Huang et al. 2010; Mansourpour et al. 2015
Chitosan	BCD	Enhanced absorption	Izawa et al. 2017 Daimon et al. 2016
Chitosan	CMBCD	Targeted delivery to intestine and colon	Song et al. 2016
Chitosan	Sodium dodecyl sulfate/BCD	pH-selective release (slow in acidic, fast in neutral pH); stabilization	Li et al. 2016
Ethyl cellulose	ACD, BCD, GCD	Decreased initial burst release	Graves et al. 2005
PLGA	BCD (conjugated)	Prolonged delivery	Davaran et al. 2008
Pluronic gel	ACD	Sustained release	Sun et al. 2015
Poly(ethyl cyanoacrylate)	HPBCD	Enhanced absorption in rats	Radwan & Aboul-Enein 2002
Polymethacrylic acid	BCD	Sustained release	Victor & Sharma 2002; Sajeesh & Sharma 2006
Nanoparticles	Enzyme coated BCD*	Sustained release	Anirudhan et al. 2016
Microparticles	BCD	Stabilization	D'Souza et al. 2015

*oleic acid-grafted-aminated beta cyclodextrin coated with a dispersion of glucose oxidase (GOx) and catalase

CD-enabled nasal insulin formulations

The bioavailability of insulin through nasal mucosa of rats is enhanced by ACD and DIMEB, while only a slight effect can be observed for BCD and HPBCD. GCD showed no absorption promoting effect (Fig. 2) (Merkus et al. 1991 and 1999).

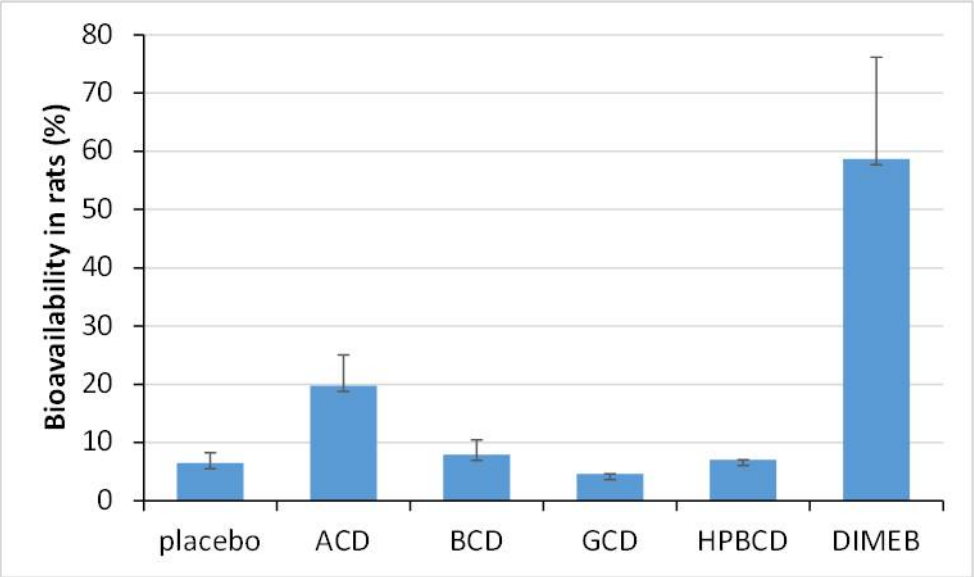

Fig. 2 Bioavailability of insulin after intranasal administration of placebo and of 20 μg insulin together with various CDs applied in 5% w/v concentration except BCD with 1.8% to rats compared to i.v. administration (drawn from the data of Merkus et al. 1991)

In another experiment even the native ACD and BCD (especially BCD compared to its lower concentration) were effective as absorption promoters in nasal insulin delivery to rats (Fig. 3) (Irie et al. 1992). HPCDs having high solubilizing effect on insulin were less efficient in promoting absorption, while DIMEA with lower solubilizing capacity was more efficient. This suggest that the interaction with the membrane lipid components resulting in enhanced permeability of nasal mucosa is more important than complexation of insulin.

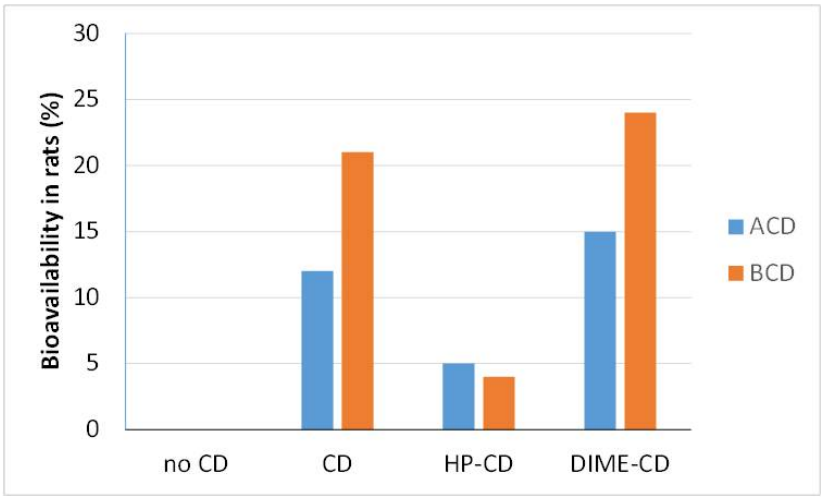

Fig. 3 The practically 0 nasal bioavailability of insulin in rats is enhanced by native ACD and BCD and their hydroxypropyl and dimethyl derivatives in 80 mM concentration except BCD (16 mM) compared to i.v. administration (Irie et al. 1992)

The nasal application of CDs was proved to be safe. No significant morphology change was observed, minor effect of methylated CDs on ciliary beat frequency (playing role in self-cleaning of the nose) lower than that of benzalkonium chloride, an accepted preservative was described (Merkus et al. 1999).

The large interspecies differences between rats, rabbits and humans, the difference between healthy and diabetic patients are a few factors making the development of nasal insulin formulation a difficult task.

Pulmonary administration

Insulin administration by pulmonary route utilize that the lung has relatively low levels of proteases and peptidases and hepatic first-pass metabolism is avoided but the low bioavailability of various formulations need further development. CDs enhance pulmonary insulin absorption in the following rank order: DIMEB > ACD > BCD > GCD > HPBCD. Pharmacokinetic analysis revealed near complete insulin uptake from the pulmonary sacs upon co-administration with 5% DIMEB. A bioavailability of 22% insulin was obtained in the presence of 5% HPBCD. Minimal differences in lactate dehydrogenase activities were found between the control and CD-treated groups, indicating relatively low acute mucotoxicity (Shao et al. 1994).

Table 3 shows some examples of microspheres used for pulmonary administration of insulin.

Table 3 Examples for CD-enabled pulmonary formulations of insulin

Polymer	CD	Result	Reference
Chitosan	CMBCD, SBEBCD	Enhanced decrease of plasma glucose level	Teijeiro-Osorio et al. 2009
Hyperbranched polyglycerol	BCD (conjugated)	Enhanced permeation through mucosal epithelia and decreased blood glucose level	Zhang et al. 2011
Polyethyleneimine	HPBCD (conjugated)	enhanced absorption	Zhang et al. 2015
PLGA microspheres	DIMEB	enhanced reduction of plasma glucose level	Rodrigues Junior et al. 2003

Rectal and vaginal administration

The rectal administration of insulin without CDs did not alter the blood insulin concentrations and glucose levels (Watanabe et al. 1992a and 1992b). The enhancing effect of CD on rectal insulin absorption was higher with chemically modified CDs: DIMEB and HPBCD than that by the non-modified CDs. With DIMEB the absorption was highly enhanced at low dose (~5 IU) of insulin and the absorption was comparable with that after nasal absorption, while at higher dose (26 IU) only slightly higher blood concentrations were measured.

DIMEB as penetration enhancing additive provided longer release of insulin from chitosan gel and enhanced decreasing effect on blood glucose level when administered through the rectal and vaginal membranes (Degim et al. 2005).

CD-enabled insulin formulations for wound healing

The role of CDs in the topical formulations is similar to the other formulations: to keep insulin in monomeric form, to stabilize it, to help its transport to the receptors via controlled release and to enhance its bioavailability.

Treating the wounds in the skin of rats with carbopol gel containing insulin/HPBCD supramolecular complex was not cytotoxically irritating nor cytotoxic (Besson et al. 2017). The slow release of complexed insulin modulated the re-epithelialization process by stimulating cell proliferation and migration of keratinocytes, favoring greater concentration of serum insulin, modulating inflammatory response, matrix remodeling and promoting neovascularization. Angiogenesis extended by the steady release of insulin explains the efficiency of the treatment.

Other clinical studies demonstrated the beneficial effects of insulin/HPBCD complex on healing pressure ulcer. The beneficial effects were manifested in significantly higher rate of tissue revitalization compared to the control gel with uncomplexed insulin (Valentini et al. 2015).

Miscellaneous

A sustained and controllable release subcutaneous formulation was developed by Hirotsu et al. (2017) applying their innovative supramolecular technology combined with polyrotaxane formation: PEGylated BCD and adamantane-appended insulin form supramolecular complex where the PEG chains are further complexed with either ACD or GCD. Both the in vitro and in vivo (subcutaneous injection to rats) tests proved the efficiency of the delivery system.

Conclusion

CDs were found to be useful for improving the pharmacological performance of various insulin formulations aimed for different routes of administration. Still further development is needed till a reliable, non-invasive formulation of CD-enabled insulin formulation can reach the market.

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Cyclodextrin News Retrospective

We wrote 10, 20 and 30 years ago

10 years ago, the use of CDs in capillary electrophoresis (CE) was reviewed. Capillary electrophoresis technique is a reliable, low cost, rapid method wherein increasing family of CD derivatives (both neutral and charged varieties) may be used. In the editorial, the performance of Affinity Capillary Electrophoresis (ACE) method was especially emphasized due to capability of revealing important interaction data even if limited amount of guest substance (few milligrams) is available. By ACE, the following parameters of complex formation with a specific guest may be obtained:

- optimal cavity size of CDs
- effect of neutral or ionic substituent(s) on the CD rims
- effect of monosubstituent function on the CD rims
- effect of persubstitution function on the CD rims
- association constant

Iványi, R.: Cyclodextrin-modified capillary electrophoresis as a versatile tool in analytics and pharmaceutics, CD News, 22(3), 2008.

One of the latest significant advancement in the field is based on the recognition that the robustness of the method may be improved if single isomers are utilized instead of randomly substituted CDs. A recent case study conducted with the contribution of Cyclolab's researchers has dealt with a novel single-isomer sulfobutylated-β-cyclodextrin selector designed for the purpose of chiral recognition. The related publication explains the synthesis of the selector as well as the application in exemplary enantioselective analysis methods performed by CE (Malanga, M., Fejős, I., Varga, E., Benkovics, G., Darcsi, A., Szemán, J., Béni, Sz. Synthesis, analytical characterization and capillary electrophoretic use of the single-isomer heptakis-(6-O-sulfobutyl)-beta-cyclodextrin. Journal of Chromatography A, 1514, 127-133 (2017).

20 years ago, the editorial was an „appetizer" for the next, April issue of CD News, where the topic of Interaction of natural colorants with cvclodextrins was highlighted.

30 years ago, Cyclodextrin News editorial was dedicated to a rather educative explanation on different methods to prepare cyclodextrin inclusion complexes 1.) in solution, 2.) in heterogenous system and 3.) by melting. The efforts of Cyclolab staff to popularize cyclodextrins and related technologies is a major mission of the company even today. Free tutorial presentations are available on our homepage: https://cyclolab.hu/downloads/9.

Bibliography & Keywords of Selected Publications of the Month

Qiu C.; Wang, J.; Fan, H.; Bai, Y.; Tian, Y.; Xu, X.; Jin, Z.

High-efficiency production of γ-cyclodextrin using β-cyclodextrin as the donor raw material by cyclodextrin opening reactions using recombinant cyclodextrin glycosyltransferase

Cyclodextrin opening reactions in the presence of maltose

Carbohydrate Polymers, 2018, 182, 75 - 80;

DOI:https://doi.org/10.1016/j.carbpol.2017.11.014

Fenelon, V. C.; Miyoshi, J. H.; Mangolim, C. S.; Noce, A. S.; Koga, L. N.; Matioli, G.

Different strategies for cyclodextrin production: Ultrafiltration systems, CGTase immobilization and use of a complexing agent

Curdlan and vegetable sponge natural supports, Glycyrrhizin

Carbohydrate Polymers, 2018, - ;

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Graphical method, HPBCD, Multicriterion optimization function

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