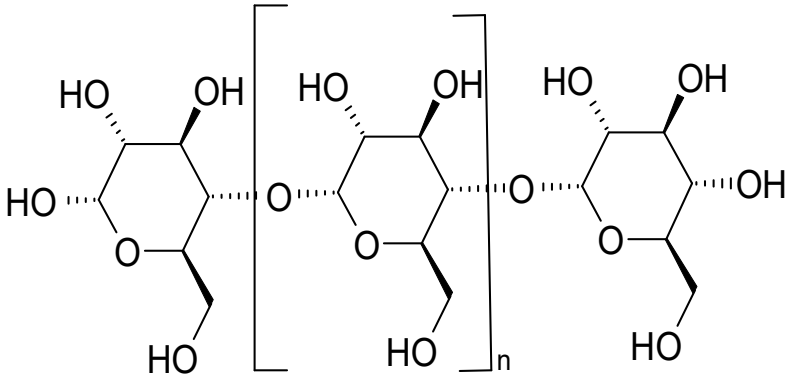
Polysaccharides

Compounds supporting disintegration of tablets

starch

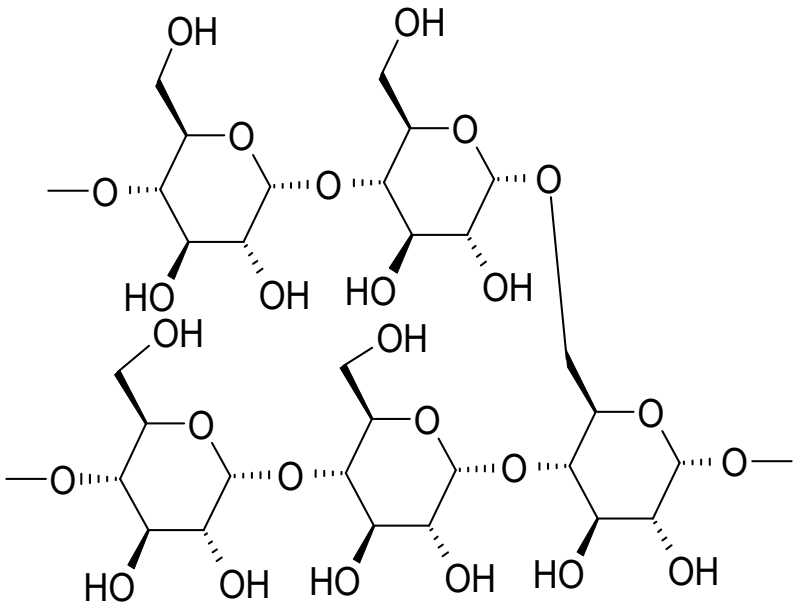
- mixture of amylose and amylopectine [9005-25-8]
- PhEur: *Maydis amylum, Oryzae amylum, Solani amylum, Tritici amylum*
- USPNF: Corn starch, Potato starch, Tapioca starch, Wheat starch



amylose

300 < n < 1000

(1→4)-α-D-glucopyranan



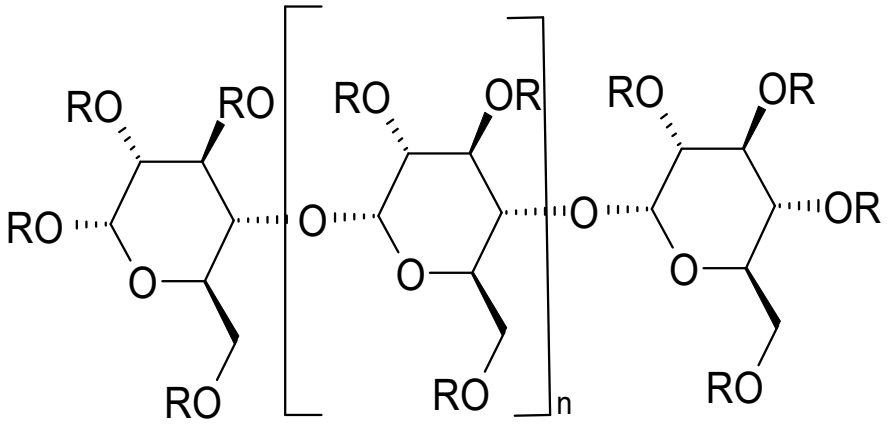
amylopectin fragment

- trituration diluent, tablet granulate binder, tablet disintegrant

Polysaccharides

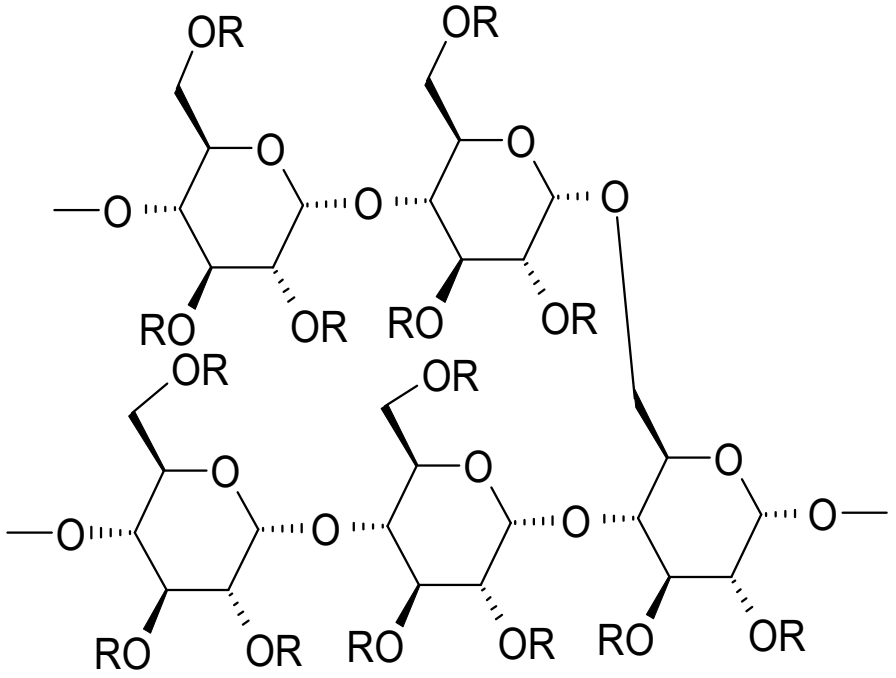
Compounds supporting tablet disintegration and stabilizers of aggregate properties of coarsely dispersed systems

hydroxypropylstarch [113894-92-1, 9049-76-7], E1440

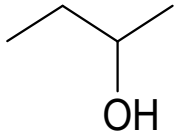


hydroxypropylamylose

300 < n < 1000

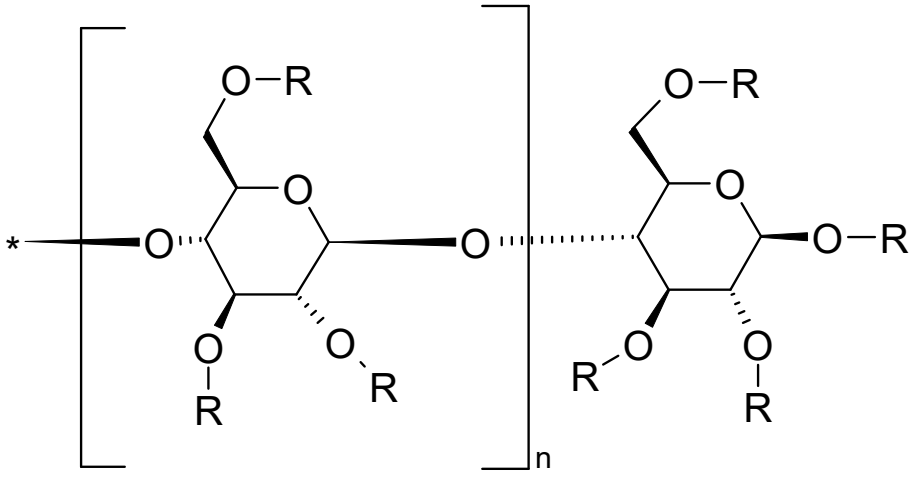


hydroxypropylamylopectine fragment

R =  or -H

•a compound stabilizing suspensions and emulsions by increasing viscosity; capsule binder; disintegrant

Constitutive excipients and stabilizers of aggregate properties of coarsely dispersed systems
Celullulose and its ethers



R = H **cellulose** = (1→4)-β-D-glucopyranan; microcrystalline - n ≈ 220 – binder and tbl. disintegrant (Avicel ®); amorphous n ≈ 500

R = CH_3 (27 – 32 %) or **H** **methylcellulose** 50 ≤ n ≤ 1000, viscosity enhancer – emulsion and suspension stabilizer, tbl. binder and disintegrant (Methocel®, E461)

R = CH_2CH_3 ethylcellulose compound for hydrophobic coating of tbl., binder and filler of tbl., viscosity enhancer (Aquacoat ®, E462)

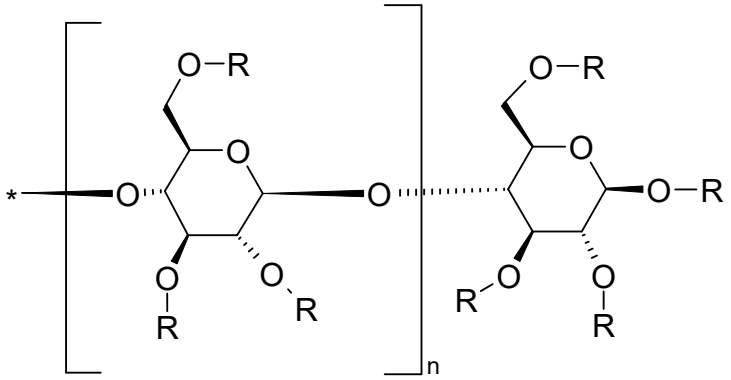
R = $(CH_2CH_2O)_mH$ or **H** **hydroxyethylcellulose** compound for coating of tbl., binder and filler of tbl., viscosity enhancer (Cellosize HEC ®, Tylose PHA®)

R = $(CH_2CH_2O)_mH$ or **CH_3** or **H** **hydroxyethylmethylcellulose** compound for coating of tbl., binder and filler of tbl., viscosity enhancer, suspension stabilizer (Tylopur MH ®, Tylose MB®)

R = $(CH_2CH(CH_3)O)_mH$ or **H** **hydroxypropylcellulose**, hyprolose: compound for coating of tbl., binder and filler of tbl., viscosity enhancer, suspension stabilizer (Klucel ®, Nisso HPC®)

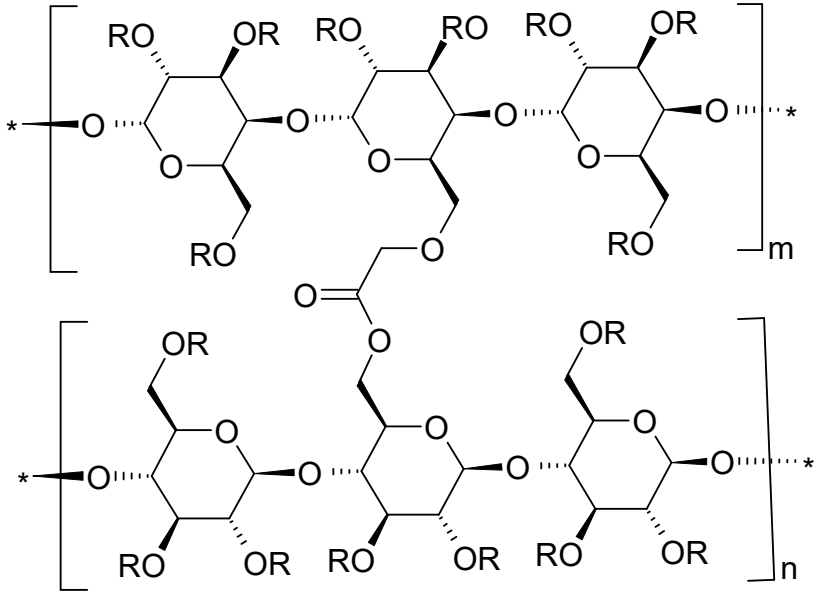
R = $(CH_2CH(CH_3)O)_mH$ or **CH_3** or **H hypromellose** = hydroxypropylmethylcellulose – coating and film-forming substance, release rate controlling polymer, viscosity enhancer, suspension stabilizer (Benecel MHPC®, E464)

Cellulose ethers continued



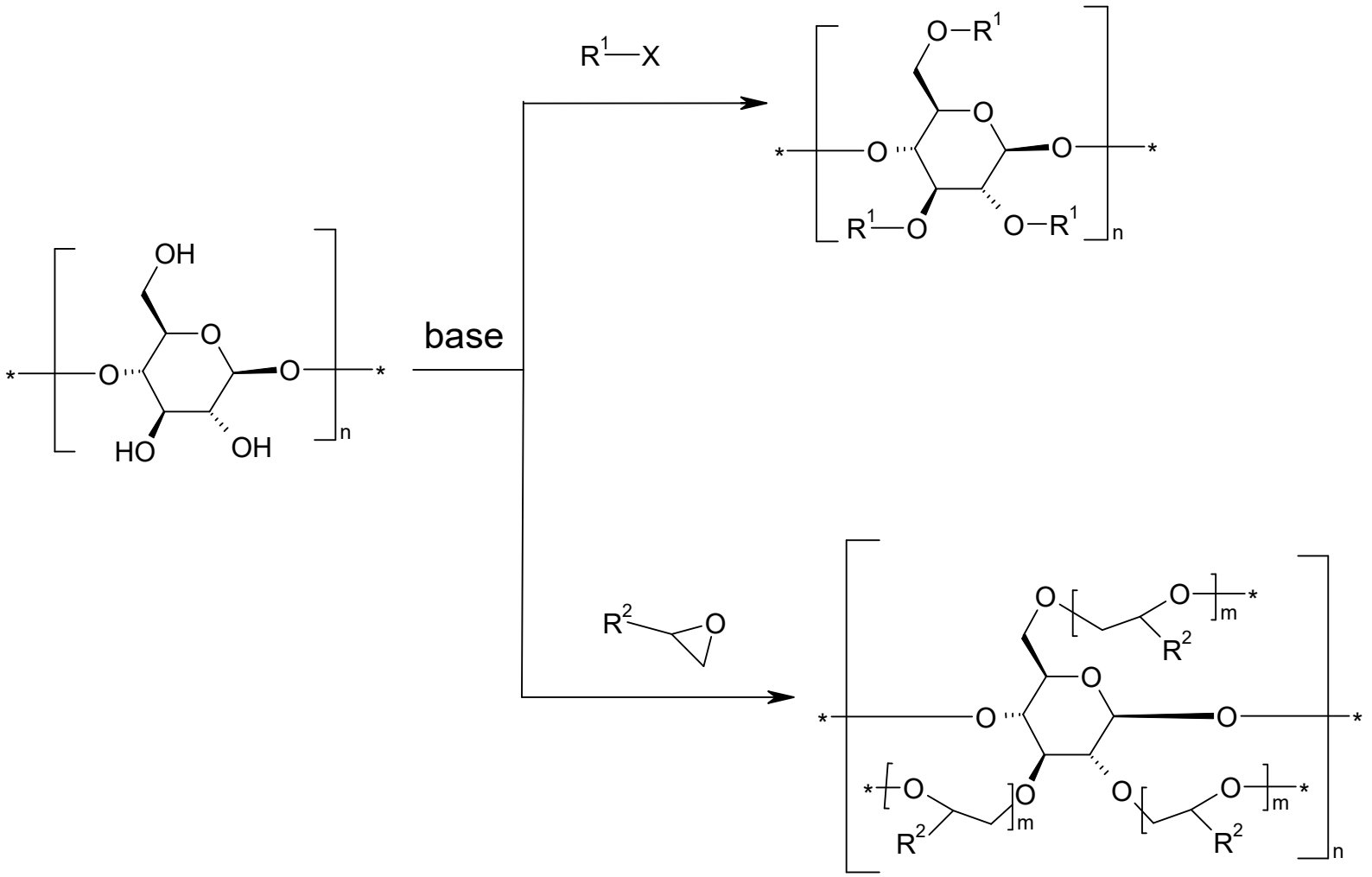
carboxymethylcellulose R = -CH_2COOH or **-H**, carmelose, most often Na^+ or Ca^{2+} salt:

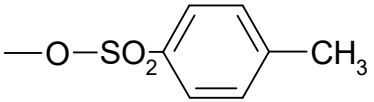
Carmellosum natricum and *calcicum PhEur* **-** binder and disintegrant of tbl. and cps., viscosity enhancer, suspension stabilizer, coating substance (E466, Tylose CB® - Na^+ salt, Nymcel ZSC® – Ca^{2+} salt)



croscarmellose – crosslinking with carboxymethyl fragments linked by ester and ether bonds

Synthesis of saccharide ethers

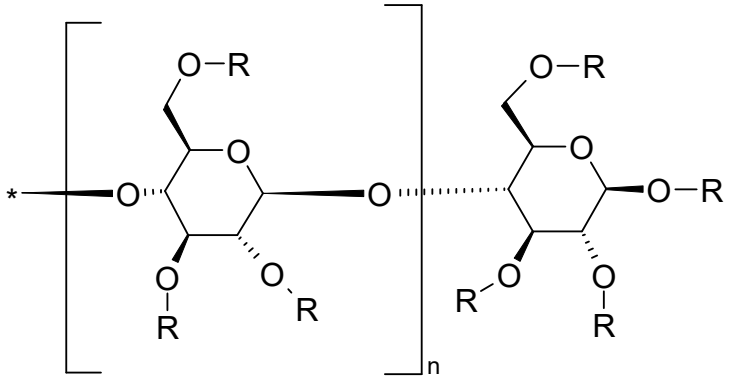


X = -Cl, -Br, -I, $-OSO_2OR^1$, 

R^1 = $-CH_3$, $-CH_2CH_3$, $-CH_2COO^-Na^+$

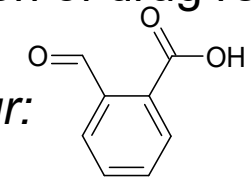
R^2 = -H, $-CH_3$, $0 \leq m < \infty$

Cellulose esters



R = -NO_2 or **-H** **cellulose nitrate** 4% solution in Et_2O = *Collodium* = *Collodion* = *Pyroxylin;* film-forming a gel-forming substance, wound sealant (*Sol. Novikov*)

R = -$OCCH_3$ or **-H** **celullose acetate** = *Cellulosi acetas PhEur* compound for coating of tbl. and prolongation of drug release from them, diluent for tbl. and cps.

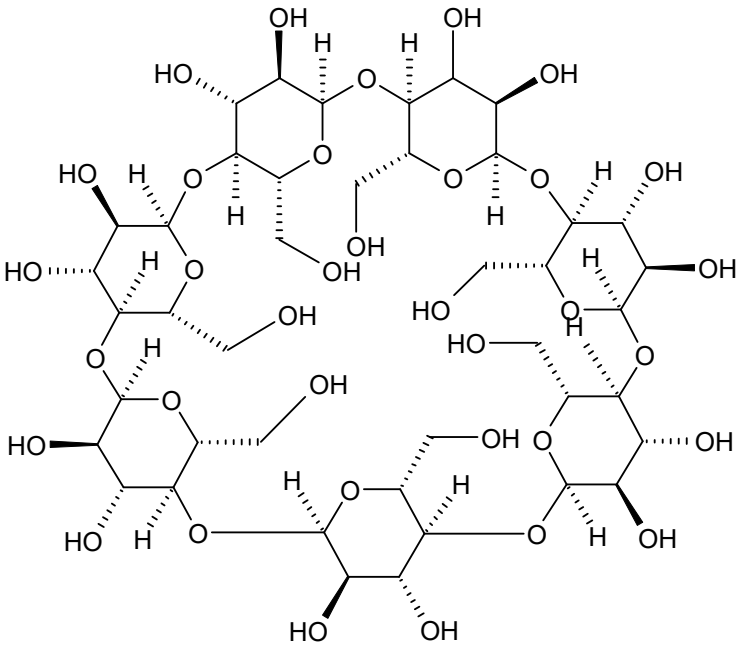
R = -$OCCH_3$ or  or **H** **celacefate** = cellulose acetate phthalate, *Cellacefatum PhEur:* 30.0 – 36.0 % hydrogenphthalate groups, 21.5 – 26 % acetate groups film-forming compound for coating of tbl., matrix binder

R = -$OCCH_3$ or **-$OC(CH_2)_2CH_3$** or **-H** **celaburate** = cellulose acetate butyrate, *Cellaburatum PhEur:* 2.0 – 30.0 % acetyls, 16.0 – 53.0 % butyryls; hydrophobic contact lens material (Cabufocon A, [9004-36-8])

Cyclic oligosaccharides

Cyclodextrins and their derivatives

•cyclic glucose oligomers with 5 – 8 units: cyclo-α-(1→4)-D-oligoglucopyranosides



betadex

alfadex = α–cyclodextrin = cycklo-α-(1→4)-D-hexaglukopyranoside

•parenteral DP, complexes only molecules of low M_r

betadex = β-cyclodextrin = cyclo-α-(1→4)-D-heptaglukopyranoside

•*Betadexum* PhEur (the only one listed in the pharmacopoeia); solubilizer – complexing agent, masking of unpleasant taste, reducing of local irritation (mucosa, eye), enhancer of permeation of a drug through mucosa etc.

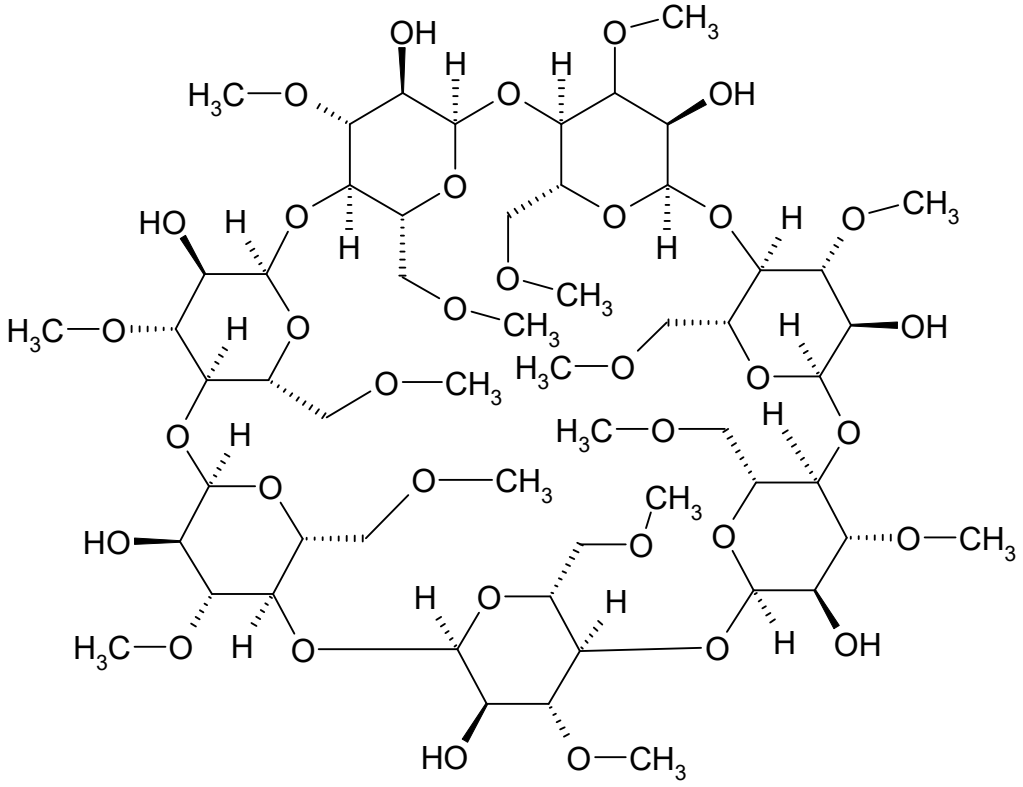
•nephrotoxic - not applicable for parenteral products

gamadex = γ-cyclodextrin = cycklo-α-(1→4)-D-octaglucopyranoside

β-cyclodextrin ethers

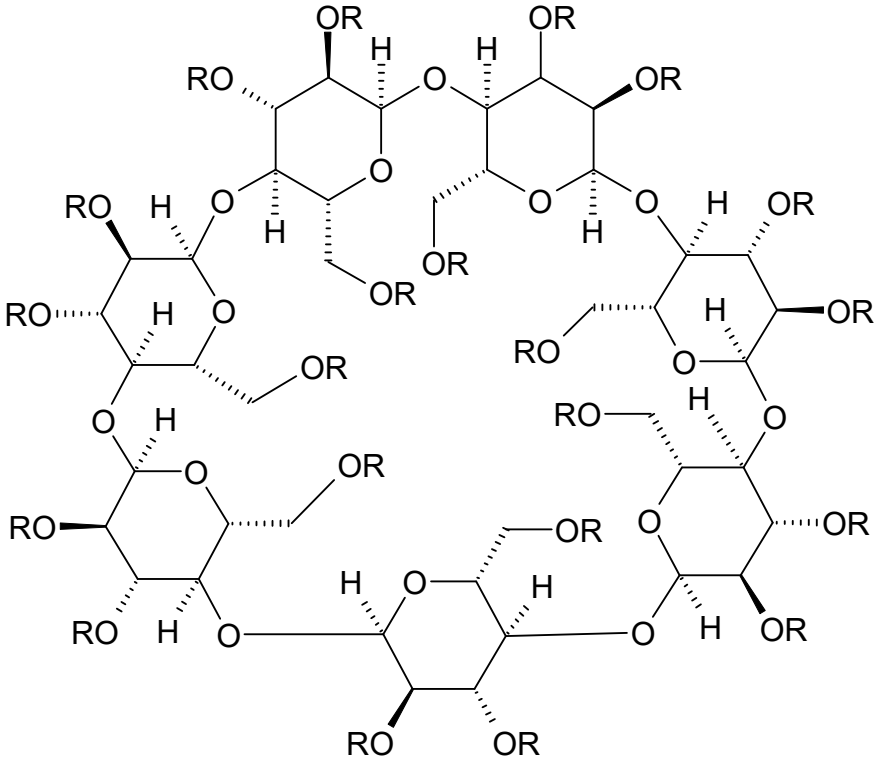
Dimethyl-β-cyclodextrin

•selectively methylated in positions 2 and 6 of each anhydroglucose unit



•similar usage as betadex

β-cyclodextrin ethers continued



R = -$(CH_2CH_2O)_nH$ **2-hydroxyethyl-β–cyclodextrin**

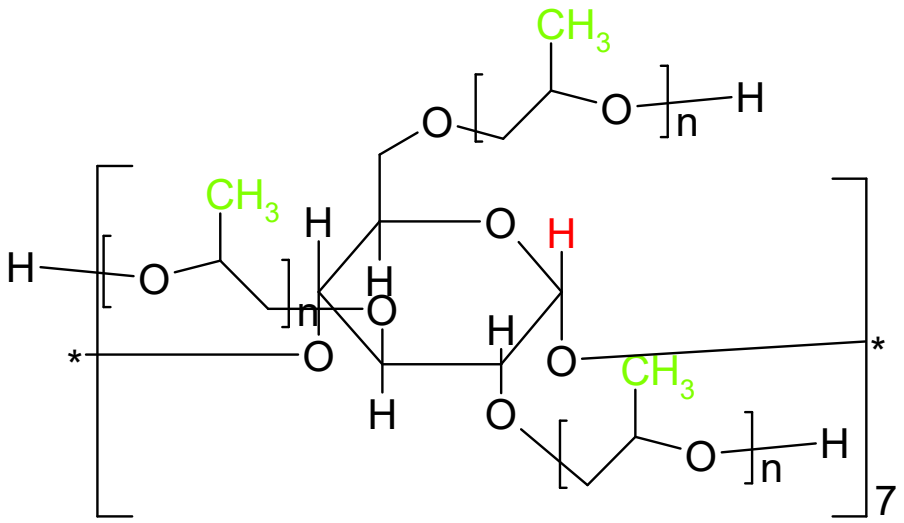
•R = -$(CH_2CH(CH_3)O)_nH$ **2-hydroxypropyl-β–cyclodextrin**

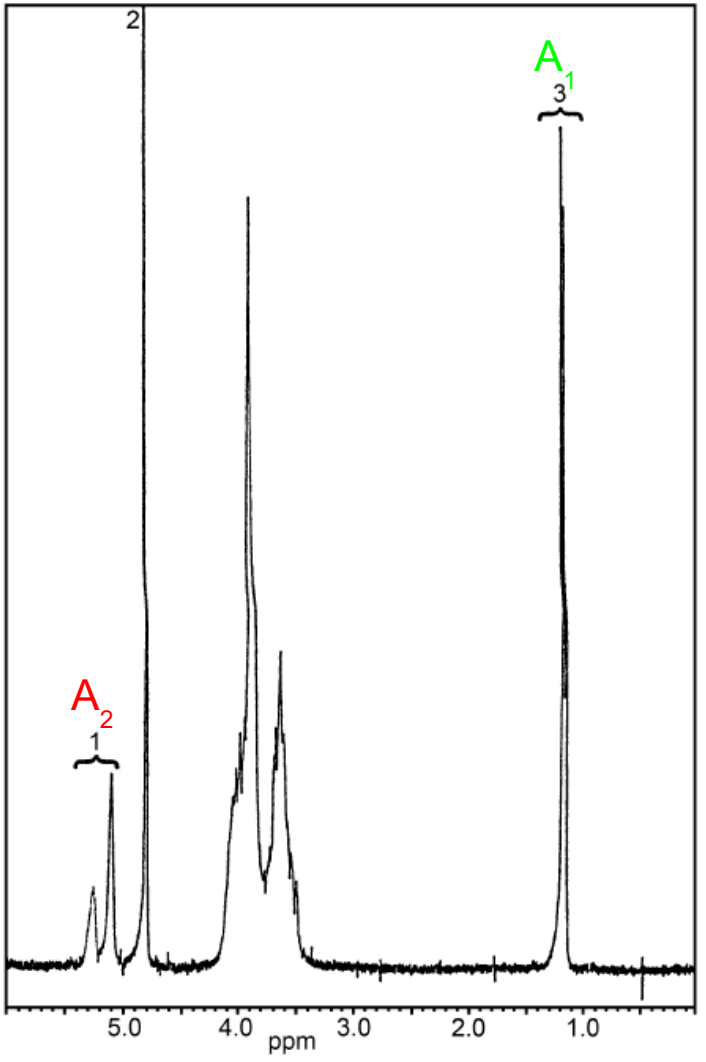
•more suitable for parent. applications than betadex: not nephrotoxic

•*Hydroxypropylbetadexum PhEur:* molar substitution MS; 0.40 ≤ MS ≤ 1.50 is a number of 2-hydroxypropyl units per 1 (anhydro)glucose unit, determined by ^{1}H-NMR

Molar substitution of hydroxypropylbetadex in accordance with PhEur (article No. 1804)

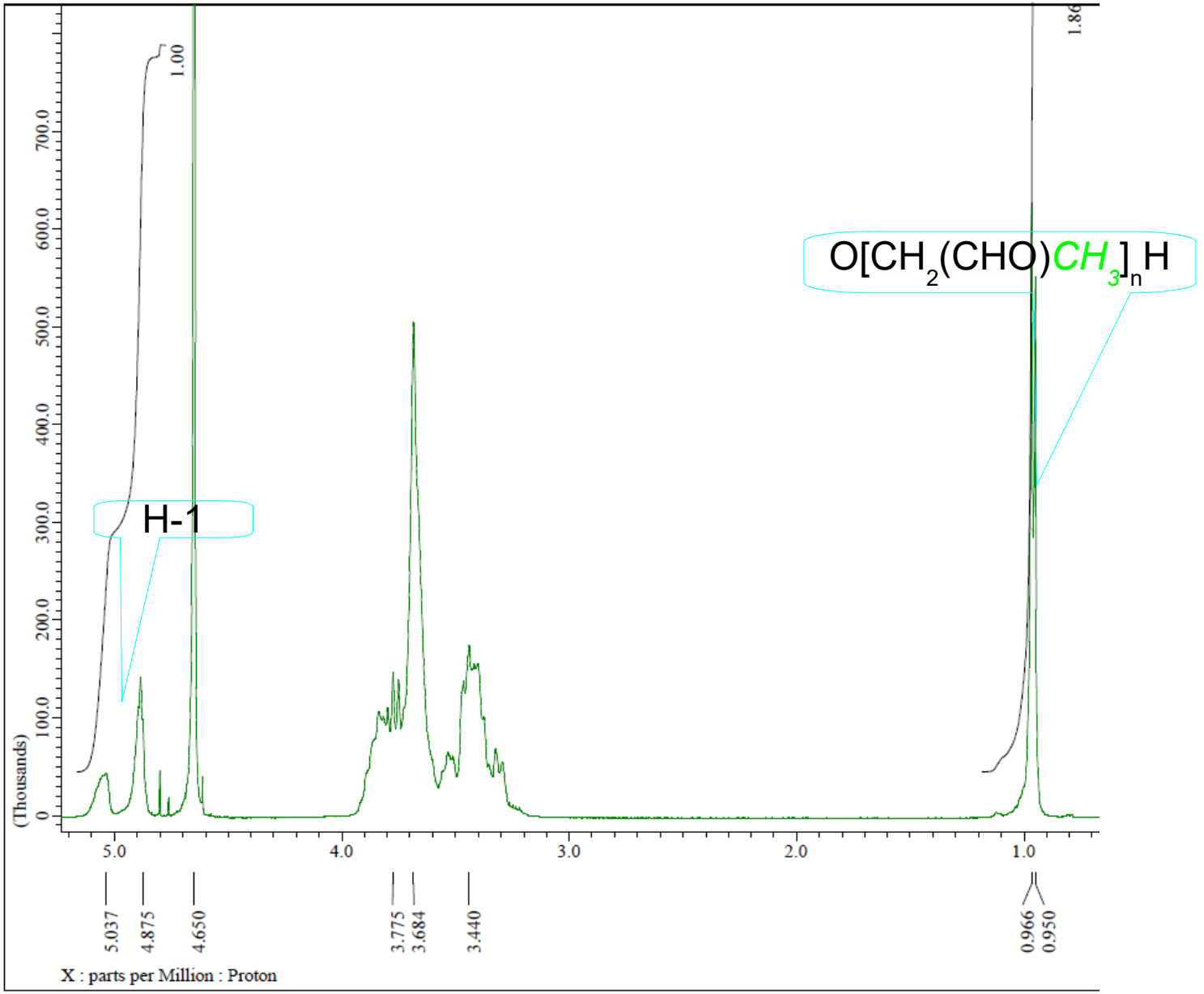
$$MS = \frac{A_1}{3A_2}$$





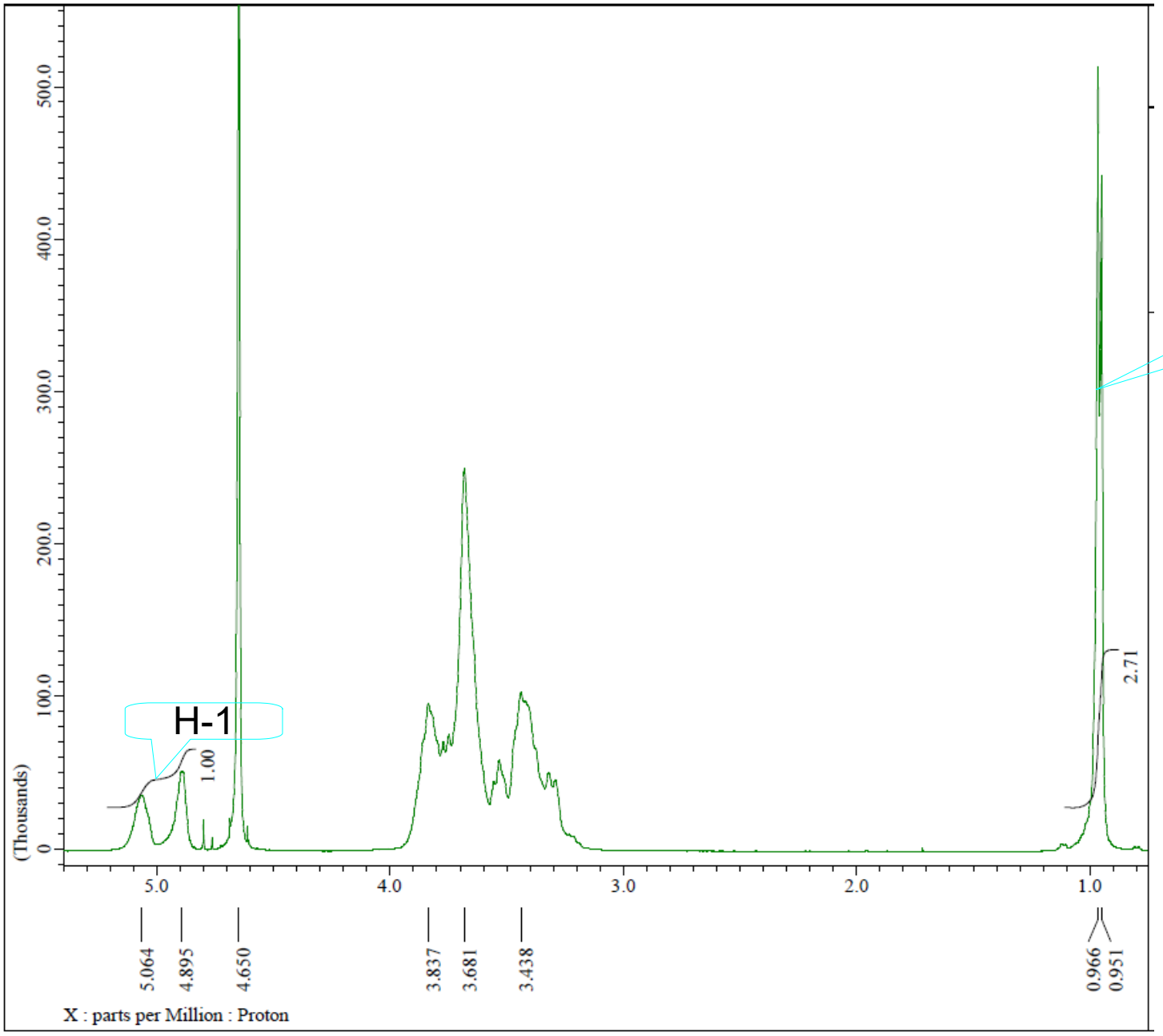
- in D_2O
- MS is calculated from the ratio between the signal from the 3 protons of the methyl group that is part of the hydroxypropyl group and the signal from the proton attached to the C_1 carbon (glycosidic proton) of the anhydroglucose units.

A practical example of molar substitution of hydroxypropylbetadex
Kleptose HPB, batch No. E0266, EZC400R 400 MHz, D_2O



MS = 1.83/3 = **0.62** **corresponds with the pharmacopoeia**

A practical example of molar substitution of hydroxypropylbetadex
Kleptose HP, batch No. E0010, EZC400R 400 MHz, D_2O



$O[CH_2(CHO)\mathit{CH}_3]_nH$

MS = 2.71/3 = **0.90**
corresponds with the pharmacopoeia

Substituted oligo- and polymers of glucose of ether type in PhEur and characterization of their molar substitution

Compound	Expression of molar substitution
Hydroxypropylbetadex	from ratio of areas in ^{1}H-NMR spectrum
Carmelose (carboxymethylcellulose)	-
Carmelose sodium salt	by means of content of Na: 6.5 – 10.8 %
Carmelose calcium salt	-
Low substituted carmelose sodium salt	by means of content of Na: 2,0 – 4,0 %
Methylcellulose	content of methoxy groups 26.0 – 33.0 % - determination as CH_3I by means of GC
Ethylcellulose	content of ethoxy groups 44.0 – 51.0 % - determination as CH_3CH_2I by means of GC
Hyprolose (hydroxypropylcellulose)	-
Hypromelose (hydroxypropylmethylcellulose)	content of both methoxy- and 2-hydroxypropoxy groups defined for each type of substitution, determination as CH_3I and $ICH_2CH(I)CH_3$ by means of GC
Carboxymethylstarch A, B, C	by means of content of Na: A 2.8 – 4.2 %; B 2.0 – 3.4 %; C 2.8 – 5.0 %
Hydroxypropylstarch	0.7 – 5.0 % hydroxypropyl groups; partial hydrolysis by DCl / D_2O directly in NMR tube, measurement of ^{1}H-NMR, comparison of areas of dublet of methyl of 2-hydroxypropyl group and internal standard 3-trimethylsilylpropan-1-sulfonic acid

Substituted oligo- and polymers of glucose of ester type in PhEur and characterization of their molar substitution

Compound	Expression of molar substitution
Cellulose acetate	Content of acetyl groups 29.0 – 44.8%: splitting off CH_3CO groups with NaOH, titration of unreacted NaOH with H_2SO_4
Celaburate (cellulose acetate butyrate)	2.0 – 30.0 % acetyl groups and 16.0 – 53.0 % butyryl groups; determination of acetic and butanoic acids by HPLC after hydrolysis
Celacefate (cellulose acetate phthalate)	30.0 – 36.0 % phthaloyl groups and 21.5 – 26.0 % acetate groups; determination of hydrogenphthalate groups by a direct titration with NaOH; acetate groups: splitting off CH_3CO groups with NaOH, titration of unreacted NaOH with H_2SO_4