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Review article

Elimination of bitter, disgusting tastes of drugs and foods by cyclodextrins

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Abstract

The bitter taste of drugs, food components, and any other substances which get in the mouth as dissolved in an aqueous solution, or in the saliva, can be strongly reduced or fully eliminated, if the bitter component forms an inclusion complex with an appropriate cyclodextrin (CD). The value of the complex association constant (determined by the structure of the bitter 'guest' molecule and the size and eventual substitution of the 'host' CD molecule), the temperature and the host/guest ratio determine the extent of complexation of the guest molecule (percentage of complexation) at the equilibrium. The K_{ass} for most drug/CD complexes at 36 °C buccal cavity temperature is between 10^2 and 10^4 mol^{-1}. If the unit dose (of a sublingual or chewing tablet, chewing gum) with a bitter drug (molecular weight of about 150, forming a 1:1 complex with βCD) is approximately 10 mg then the βCD can be taken in a 5- or even 10-fold molar excess. Under such conditions more than 99% of the bitter drug is complexed, and because complexed molecules cannot react with the taste buds in the buccal cavity no bitter taste is perceived. Frequently, preparation of the drug/CD complex is not necessary, because the βCD is present in a large excess, dissolved very quickly in the saliva and results in a saturated CD solution. Therefore, the complexation of the bitter drug is completed very rapidly. Only dissolved substances have taste and only CD complexable drug molecules can become debittered by CDs. Bitter, astringent components of foods (e.g. soya), beverages (e.g. naringin in citrus fruit juice, or chlorogenic acid and polyphenols in coffee) cigarette smoke (nicotine) also can be complexed and their taste reduced or fully eliminated.

Keywords: Bitter taste; Debittering; Cyclodextrin; Inclusion complexation; Astringent taste; Taste of drugs; Palatability; Patient compliance

1. Introduction

Water-soluble substances (such as components of drugs, foods, oral care products, or aerosols like tobacco smoke) getting into the buccal cavity will react with the so-called gate-keeper proteins of the taste buds, which are located mainly on the tongue. The sweet taste receptors are concentrated on the tip of the tongue, the sour-tasting ones on both edges, and the bitter tasting ones at the back, near the throat.

While the sweet taste is almost always agreeable and the strong sour and salty tastes are tolerable, the bitter, astringent, metallic and irritating tastes are unpleasant, which means that products with such taste profiles are unpalatable particularly in the case of pediatric drugs. The bitter tasting substances are tolerable only in a rather low concentration, e.g. in tonic water type refreshments which contain quinine, in some alcoholic drinks or in coffee. The majority of the orally administered and at least moderately water-soluble drug substances are of very to extremely bitter taste. In most cases, the solid formulations are coated with advice not to chew but to swallow the intact tablet. For small children, however, the administration of the dose of a whole tablet is frequently not recommended and to administer tablets in general is not recommended. Only liquid formulations should be given or if these are not available, the tablet should be crushed to a suspension and administered by a spoon. The bitter taste in such cases is frequently a serious problem.

Only the dissolved substances elicit taste sensation. Substances which are completely insoluble in water are tasteless. In many cases, however, the drugs are so intensely bitter, that they even at ppm levels are hardly tolerable. The first such observation was already described in 1953 in

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the very first drug/CD patent by Freudenberg et al. [2]. The bad taste of bromoisovaleryl urea was masked by CD complexation.

The βCD itself cannot be considered as a tasteless or only slightly sweet substance, although its taste threshold value is lower than that of sucrose (detection: 0.03 and 0.27%, recognition: 0.11 and 0.52%, respectively). A 0.5% βCD solution was as sweet as sucrose, and a 2.5% solution as sweet as a 1.71% solution of sucrose [3]. Therefore, when βCD is used in food processing, its sweetness cannot be ignored. Sucrose and βCD showed an additive effect on sweetness.

2. Mechanism and kinetics of complex formation

2.1. Complex formation in solution

The industrially produced CDs are crystalline, homogeneous non-hygroscopic substances built up from glucopyranose units. The αCD comprises 6, the βCD 7 and the γCD 8 glucopyranose units. As a consequence of the $^4C_1$ conformation of the glucopyranose units all secondary hydroxy groups are located on the wider edge of the ring, whereas all the primary ones are placed on the other (narrower) edge. The ring in reality is a conical cylinder, which is frequently characterised as a doughnut or wreath-shaped truncated cone which has an axial cavity. This cavity is lined with hydrogen atoms and glycosidic oxygen bridges. Consequently, the outer surface of this truncated cone is hydrophilic and the axial cavity is hydrophobic. The geometrical dimensions of this cavity are large enough to include other hydrophobic molecules or at least some hydrophobic moieties of them.

The cavity of the CDs is occupied by included water molecules both in crystalline state as well as in aqueous solution. Considering that these water molecules are in direct contact with the apolar wall of the CD cavity, this polar–apolar interaction results in an energetically unfavoured state. These included water molecules can be readily substituted by appropriate 'guest' molecules which are less polar than water, and fit geometrically into the CD-cavity. The CD is the 'host' molecule and an important component of the 'driving force' for the inclusion complex formation is the substitution of the high-enthalpy water molecules by the 'guest' molecule. One, two or three CD molecules contain one or more entrapped guest molecules. Most frequently the host:guest ratio is 1:1. This is the essence of the 'molecular encapsulation'[1].

Both chemical and physical properties of the entrapped guest molecules are significantly modified, e.g. sublimation and/or volatility of the guest molecules are reduced to a very low level. Diffusion and rate of most reactions in aqueous solutions are strongly decelerated. The CD complex is hydrophilic, easily wettable and rapidly soluble. As it is included into the CD molecule, which is enwrapped into a hydrate shell, the interaction of the guest molecule with cell membranes and receptors is considerably inhibited, resulting in reduced cytotoxicity or reduced taste.

In aqueous solution the CD inclusion complex has no static structure. The extent of complex formation is determined by the temperature, structure and electric charge of the guest molecule and many other factors, expressed by the association constant. The association is a very rapid process, the rate constant is of 10^{-2}–10^{-8} s mol^{-1}. The association constant for the majority of complexable drug molecules is between 10^2–10^4 mol^{-1}. Therefore, in an aqueous CD solution—particularly if the molar ratio of CD to the guest is larger than 1—at ambient temperature more than 90 (or frequently more than 99%) of the guest is present in CD complexed form.

2.2. Complex formation in solid state

The commercially available crystalline βCD contains water, generally about 13–14% (w/w). Roughly half of this water is so-called crystal water and the other half is 'inclusionwater'. The crystal water is located and bound between the adjacent βCD molecules, while the 'inclusion-water' is included into the hydrophobic cavity of the CD. The essence of the inclusion complex formation is always the substitution of these water molecules by a more appropriate, more hydrophobic 'guest' molecule, which forms a more stable complex with the CD. Consequently, the inclusion complex formation occurs not only in aqueous solution, but even in solid state, assuming that the components are intimately dispersed and the βCD contains its crystal water (i.e. has not been previously dehydrated by heating for hours over 100 °C in a vacuum) [4]. The complex formation in this case is a slow process to reach the equilibrium which may take months depending on the degree of dispersion of the host and guest and on the 'mobility' of the guest. The process is rapid with liquid and sublimable molecules, and extremely slow with very hydrophobic molecules with high melting points. Menthol, menadione, salycilic acid, nicotine, etc. belong to these 'mobile' molecules: the formation of the CD complex takes place simply by mixing them with finely powdered crystalline βCD and storing the mixture in a closed container at ambient temperature, as can be demonstrated by differental scanning calorimetry, X-ray diffraction patterns, or solid-phase nuclear magnetic resonance.

3. Reduction or elimination of bitter taste of drugs

3.1. Cyclodextrins as debittering agents

To prevent the sensation of the bitter taste there are two possibilities: either to prevent the contact between the bitter taste eliciting molecules and the receptors or to cover the bitter taste by administering simultaneously some very

intense but not bitter flavour to 'cover' the bitter taste. This way a bitter taste which on its own would be intolerable, will be only a component of a complex multi-tasting composition, where the other agreeable tastes will dominate. For example, grapefruit juice contains such an amount of the very bitter naringin and limonin, that without the citrus flavour components it would not be palatable. Syrups which are highly flavoured with fruits (orange, raspberry, etc.) and which contain bitter drugs frequently are palatable to children.

Adults generally swallow the bitter drug containing coated tablet without chewing them, but there are cases when for some reasons the dissolution of the active ingredient in the saliva is inevitable. If rapid (and eventually first pass metabolism avoiding) absorption is wanted, the tablet is administered as a sublingual or chewable tablet. In such cases the disgusting bitter, astringent taste is a real problem.

How can CD eliminate the bad taste? There are only two theoretical possibilities:

- the CD enwraps the bad tasting molecule (=inclusion complex formation), impeding its interaction with the taste buds, or
- the CD interacts with the gate-keeper proteins of the taste buds, paralysing them.

In this case, however, any and all taste sensation (sweet, salt, sour, bitter) would be extinguished, as long as the adhered CDs are not removed from the taste buds. Such an effect can be attained by anaesthetics and narcotics, e.g. by applying a lidocaine spray into the mouth cavity the bitter taste of any drug will not be perceived! However, βCD is neither an anaesthetic nor a narcotic substance.

The bitter taste of a substance disappears in the presence of βCD only, when the drug molecule which causes the bitter taste is complexed by an appropriate CD molecule. These complex molecules are strongly hydrated on their outer surface, therefore, they do not get attached to the taste-bud receptors on the tongue in the mouth cavity. Rinsing the mouth cavity with concentrated βCD solution and thereafter using, for example, cetirizine hydrochloride the bitter taste is noted immediately. If, however, the cetirizine is administered in saturated βCD solution no bitter taste can be observed. This is a direct proof for the existence of complex molecules in the saliva of the mouth cavity. Reduction of bad tastes (bitter, astringent ones) by CDs is a long known method [1].

3.2. Examples for the organoleptic testing of bitterness

Dextramethorphan HBr is a typically very bitter pediatric drug. The bitterness of the plain drug was compared with the bitterness of its β- and γCD complexes, both in solid state as well as in aqueous solutions [1]. To ensure an identical amount of dextromethorphan in the studied samples, the uncomplexed substance was diluted with the inert tasting maize starch. Fourteen volunteers tasted the solutions and the solid samples, in turn, in a blind test. The bitter intensities of the drug and its complexes were evaluated by a special score. Significant differences were found ($P<0.01$) between the drugs and their βCD complexes both in solution and in the solid state showing that in the presence of cyclodextrins the bitter taste is minimized.

The very bitter and anaesthetising effect of libexin, an antitussivum, was efficiently reduced by βCD [5]. A βCD:libexin complex with molar ratio of 2:1 was more effective than a 1:1 ratio. The test persons tasted the libexin HCl alone with 1 and 2 mol of βCD and with water at four different libexin concentrations. Their task was to place the products in order of increasing bitterness. At very low concentrations no difference was found between the solutions, however, at a drug concentration of 0.1 mg/ml the CD solutions showed a significant decrease in bitterness.

Similarly, the bitter taste of femoxetine HCl was greatly suppressed by complexing with βCD [6]. Adding βCD in excess which shifts the dissociation equilibrium toward the association, a further significant reduction of the bitterness (and the solubility) was observed.

Uekama et al. [7] found that the bitter taste of clofibrate was significantly quenched by complexing it with β- or γCD. There was no statistically significant difference between βCD and γCD complexes.

Fujioka et al. [8] investigated the interaction of CD with bencyclane fumarate (=Ben). The intrinsic bitter taste of the drug was significantly reduced by inclusion complexation with CDs. Solution of Ben and Ben/CD complexes (prepared by freeze-drying with α-, β-, and γCD) of different Ben concentrations (between 0.05 and 4.0%) were prepared. The bitterness of these solutions was compared by five healthy male volunteers with the bitterness of a 0.01% (w/w) phenyl-thiocarbamide (PTC) solution, which is used as bitterness standard in studies with bitter peptides. Fifty microlitres of the solutions were pipetted onto the tongues of the test persons and they had to determine which solutions were more bitter and which ones were less bitter than the 0.01% PTC solution. It was found that the bitterness of the CD-complex solutions is identical with the standard PTC solution at the following Ben concentrations: Ben 0.2%, Ben/αCD 0.4%, Ben/γCD 1.0%, Ben/βCD 2.0%. This result demonstrates a reduction in bitterness of 1/10 of the original level by a 1:1 Ben:βCD complex.

A new animal test method was proposed for studying astringent bitter-tasting drugs [8]. The astringent-bitter tasting substances are irritating to the rabbit eye. Counting the blinking upon adding the solution to the eye, the irritating effect can be evaluated numerically. Of course this method can be used only in case of irritating drugs like bencyclane fumarate. Good correlation was found between

Table 1
Examples for elimination/reduction of bitter/irritating tastes or unpleasant odours of orally administered drugs

Drug	Application	CD	Author, year	Reference
Tetrachloroethylene	Veterinary anthelmintic	β	Suzuki, 1975	[9]
Tiaramide		α, β, γ	Iwashiro, 1981	[10]
Ibuprofen	Analgetic	β	Kowa, 1981	[11]
			Markarian, 1988	[12]
			Hunter, 1989	[13]
		HPβCD	Motola, 1991	[14]
		β	Grattan, 1993	[15]
S-ibuprofen	analgetic	β	Szejtli, 1992	[16]
Alclofenac		β	Mitsubishi, 1981	[17]
Flurbirpofen	Anti-inflammatory	β	Ohata, 1981	[18]
Bencyclane fumarate	anti-convulsant, vasodilator	β, γ	Fujioka, 1983	[8]
Suloctidil	vasodilator	β	Mitsubishi, 1983	[19]
Clofibrate	Antilipacmic	α, β, γ	Uekama, 1983	[7]
Femoxetine	Anti-depressent	β	Anderson, 1984	[6]
Pirprofen		β	Hibi. 1984	[20]
Ca-hopantenate		β	Showa, 1984	[21]
L-tryphtophane	Aminoacid	β	Sato, 1986	[22]
Meclofenaxate.HCL		β	Tanaka, 1986	[23]
Guaiacol	Anti diarrhetic	β	Iwayama, 1987	[24]
Zipeprol	Anti-tussive	β	Kim, 1987	[25]
Ursodeoxycholic acid	anti-cholestatic	β	Nakazawa, 1988	[26]
			Widauer, 1995	[27]
Libexine.HCL	Anti-tussive	β	Weizfeiler, 1988	[5]
Pinaverium bromide		β	Weizfeiler, 1988	[5]
Acetaminophen	Analgetic	β	Weizfeiler, 1988	[5]
Chlorhexidine	Anti bacterial	β	Oi, 1989	[28]
			Gallopo, 1989	[29]
Laxoprofen	Anagetic	β	Suyama, 1986	[30]
Hexitidine	Anti bacterial	HPβCD	Gallopo, 1989	[31]
			Schmidt, 1993	[32]
α-keto-β-methlyvaleric acid	Renal disorders	β	Tanabe, 1991	[33]
Carbetapentane citrate		β	Kurasumi, 1991	[34]
Fenbufen		α, β, γ	Miyaji, 1992	[35]
Metronidazole benzoate	Anti bacterial	γ	Giordano, 1992	[36]
Benexate	Antiulcer	β	Suzuki, 1993	[37]
Dioscin	Cardiovascular disorders	β	Zhou, 1993	[38]
Benzethonium chloride	Anti bacterial, mouth wash		Shimada, 1995	[39]

the results of the human sensory bitterness test and the rabbit-eye-blinking test in a logarithmic plot.

Another example for the reduction or elimination of drug bitterness by the formation of a drug-βCD complex is the already marketed cetirizine. Further examples are given in Table 1 [9,13,15–18,20–22,24–33,35–37,39].

3.3. Preparation methods and examples for solid CD complexes (for oral administration)

3.3.1. Kneading

Tiaramide (39 g) was kneaded with a mixture of 130 g βCD plus 130 g water. After drying at 50 °C and grinding to powder the yield was 167 g of a non-bitter and water soluble powder [10].

If cetirizine hydrochloride is mixed with βCD in a molar ratio of 1:4 and a small amount of water for 20 min and then granulated and compressed, chewable non-bitter tablets can be produced from the very bitter drug [46].

3.3.2. Co-crystallization

Flurbiprofen (100 g) was dissolved in 2 l warm methanol and mixed with 500 g βCD suspended in 2 l water. This mixture was stirred and heated till complete dissolution of the βCD. After standing overnight, a precipitation of a white microcrystalline complex occurred which can be isolated by filtration. Mixing 227 parts of the complex, 63 parts lactose, 9 parts hydroxypropyl cellulose, and 20 parts magnesium stearate 300 mg non-bitter tablets were compressed, each of which contained 40 mg flurbiprofen [12].

A suspension of 1.5 g suloctidil and 22.7 g βCD were stirred in 1 l water for 24 h, then the formed complex was isolated by filtration and dried. The product was non-bitter [19].

3.3.3. Spray-drying

Ibuprofen (2 g) was mixed with 5.7 g βCD in 200 ml water, heated to 80 °C till complete dissolution then spray-dried to a non-bitter powder [11].

Meclofenoxate hydrochloride (50 g) and 192.5 g βCD were mixed in 500 ml water and spray-dried. The dry powder was washed with methanol/acetone to remove non-complexed drugs. The produced tablet was free of any bitter taste [23].

3.4. Formulation of mixtures of drugs and CDs without previous complex formation

Non-bitter fast-dissolving buccal, chewable tablets (or effervescent granules) can be prepared even without preparing and isolating the CD complexes of the bitter drugs before the final formulation, e.g. a fast dissolving dextromethorphan hydrobromide tablet contains 10 parts of this drug, 2 parts chloropheniramine maleate, 106 parts xylitol, 325 parts sorbitol, 300 parts βCD, 8 parts citric acid, 10 parts aspartame, 5 parts magnium stearate and 24 ml vanilla flavour.

The mechanism of the debittering process in these cases is the inclusion complexation of the bitter drug with the appropriate CD, because the bitter drug is also dissolved in the CD-saturated saliva. In the case of easily migrating (hydrophilic, well soluble, volatile/sublimable or of low melting point) drugs the complexation proceeds already in the dry (but not anhydrous!) powder mixture assuming that the CD contains the usual crystal water (in the case of βCD this is approximately 13–14 wt%). In solid state the CD molecules located in the surface layer of the CD crystals will exchange their inclusion water molecules with the 'easily migrating' potential guest molecules, releasing the water molecules. Because the crystal lattice parameters of the formed complex are generally different from the ones of the water/CD complex, the surface layer will be 'peeled off' from the CD crystal, forming a new microcrystalline phase. The naked new CD crystal surface will repeat this process and depending on the particle size, temperature, humidity and degree of homogenity of the mixture. Within days or months all guest molecules will be included assuming that enough (or better an excess) CD is present in the mixture. This process already begins during the powder mixing and continues during pelleting/granulation (particularly when water is present), accelerates during extrusion and tablet compression and continues during storage. The complexation process will be completed during dissolution of drug and CD in water, saliva, gastric juice, etc. Bitter drugs which do not form CD-complexes cannot be debittered with CDs!

3.5. Examples for non-bitter liquid drug/CD formulations

Ibuprofen (2 g) and 22 g HPβCD were dissolved in 100 ml water to give a non-bitter but sour tasting solution. The sour taste can be masked with any usual sweetening agents like saccharose [14]. However, it should be mentioned that the typical ibuprofen irritation of the throat (feeling of roughness after 1 min) still cannot be masked.

The strong bitter taste of carbetapentane citrate is reduced to the acceptable level (can be masked by other flavours) in the presence of 5-fold molar excess of βCD [34]. Bitterness and unpleasant after taste of thiamine derivatives (B_1 vitamin) in liquid formulations can be effectively masked by βCD, saccharose and citric acid [49,50] and of riboflavine by αCD, saccharose and citric acid [48]. Bitterness of extracts of medicinal plants and mushrooms also can be masked by adding CDs to the extract either before spray-drying or to the dried product (shiitake, ganoderma mushrooms, Gymnema sylvestre, reishy, green and ginseng teas, dioscin, etc.) [38,55–62]. For further examples see Table 1.

4. Case studies (marketed products)

4.1. Cetirizine

The very bitter cetirizine 2HCl is an antihistaminic drug (10 mg drug/tablet) which is taken in case of allergic symptoms. A chewing tablet—easy to consume, e.g. during driving without water, is a desired formulation. Two companies developed the non-bitter βCD containing cetirizine 2HCl tablet which contains βCD. Company 'A' filed a patent application in 1999 [46] which describes the production process as follows:

Example 6:

Le dichlorohydrate de cétirizine (10 parties) et la β-cyclodextrine (55 parties) sont malaxées in presence d'eau dans un mélangeur planétaire pendant 20 min. De cette maniére, on forme le complexe entre la dichlorohydate de cétirizine et la β-cyclodextrine.

Example 7:

Le complexe dichlorohydrate de céterizine et de la β-cyclodextrine est prepare de la méme maniere que dans le l'example 6.

Surprisingly the claims simply neglect, even deny the complex formation:

claim No.1.: '*Composition pharmaceutique… la cyclodextriene n'étant pas sous la forme d'un complexe d'inclusion avec la substance active*'.

According to claim No. 5.: '*… la rapport molaire entre la cyclodextrine et la substance active est compris entre 1.0 et 4.0*'.

Company 'B' developed a tablet which contains a cetirizine 2HCl/βCD formulation in which the molar ratio of cetirizine 2HCl to βCD is 1 to 10 (weight ratio 1:26). If the product of company 'B' contains the cetirizine 2HCl in none-βCD complexed form it infringes the patent of company 'A'.

The existence of a cetirizine 2HCl/βCD complex in aqueous solution cannot be the subject of any discussion: NMR spectral shift, deceleration of diffusion through semi-permeable membrane of cetirizine 2HCl in βCD solution, competition with coloured guest molecules, shift of the peak

of the UV absorption spectrum, disappearance of cetirizine bitterness after adding βCD to the cetirizine solution, etc. all deliver definite proofs for existence of the complex in aqueous solution. It has been accepted, that when a tablet containing 10 mg cetirizine 2HCl and 260 mg βCD comes into contact with approximately 5 ml saliva in the mouth (at 36 °C) all necessary conditions for formation of the complex are given. The cetirizine hydrochloride is practically dissolved in a saturated βCD solution. The inclusion is a very rapid process after dissolution of cetirizine in the βCD saturated saliva. The association–dissociation equilibrium is established within microseconds. The value of the K_{ass}—determined by competitive complex formation with methylorange—is 3587 mol^{-1} [46]. Because the βCD is present in large excess the percentage of the free, non-complexed cetirizine 2HCl is less than 1% of the total cetirizine content. The presence of cetirizine 2HCl/βCD complex in the tablet (i.e. in solid state) of company 'B' has been proven by DSC curves. In a simple physical mixture of cetirizine 2HCl and βCD the melting enthalpy of the drug results in a well-defined, strong exothermic peak, which is completely absent in the DSC-curves of a cetirizine 2HCl/βCD complex which was isolated from homogeneous solution by crystallization or by freeze-drying. Company 'B' stirred the aqueous suspension of cetirizine 2HCl and βCD for 30 min, dried, pelleted and compressed the formulation to tablets with usual tabletting excipients. DSC-curves of the powdered tablets were non-informative, because the presence of the excipients and the low amount of the cetirizine (only about 3% of the total tablet mass) allow no interpretation. The DSC-curves of the dried, pelleted products, however, revealed that at least 60–80% of the cetirizine 2HCl was not present as free, crystalline drug substance.

If anybody reproduces the examples No. 6 or 7 (the only 2 examples, which describe the preparation of the product = complex) they cannot infringe the granted patent because it claims a product, which comprises the cetirizine 2HCl and βCD formulation in non-complexed form! Under the given conditions (mixing for at least 20 min in the presence of water), the formation of an inclusion complex between these two components is unavoidable.

4.2. Nicotine

To appease the smoker's nicotine demand without smoking (and to offer a smoking cessation aid) nicotine can be administered orally or transdermally. The oral administration in the form of sublingual tablet or chewing gum is possible only if the intolerable taste of nicotine is eliminated.

Nicotine is a water miscible, yellow-brownish oily, toxic and hygroscopic liquid, which is difficult to handle (i.e. incorporating it into solid medical formulations). The liquid in spite of its high boiling point (247 °C) is volatile and susceptible to decomposition, especially if it comes into contact with air in a finely dispersed state. Therefore, in pharmaceutical formulations its salt(s), preferably formulated with the weak polyacrylic acid—or its βCD complex—are used. Both the salt(s) and the complex are solid and easy to handle nicotine formulations of well defined composition.

The *Nicorette Microtab* contains 2 mg nicotine as 11 mg nicotine/βCD complex [53]. After sublingual administration the complex is rapidly dissolved and the nicotine is absorbed without eliciting any of the characteristically disgusting nicotine taste.

The *Nicogum* chewing gum contains 2 mg nicotine in form of the water-insoluble polyacrylate salt (11 mg) and 50 mg βCD (the nicotine/βCD molar ratio is 1:3). The difference between the composition of Nicogum as disclosed in the WO 00/56281 Patent Application [54] and of the really marketed product is the presence of a considerable amount of sodium carbonate and bicarbonate which is of fundamental significance. Nicotine-polyacrylate salt(s) are insoluble in water and the absorption of nicotine after oral administration is restricted to the slightly alkaline environment of the jejunum and the colon. Liberation of free nicotine base from the polymer salt is necessary to ensure adequate absorption of nicotine from the upper part of the GI tract or from the buccal cavity in the case of a chewing gum formulation. For this purpose, sodium carbonate/bicarbonate is admixed to the chewing gum formulation which contains βCD. When masticating the chewing gum, all water soluble components (βCD, sorbitol, sodium carbonate/bicarbonate, flavours) will get dissolved in the saliva, ready for absorption through the buccal mucosa. The dissolved sodium carbonate/bicarbonate reacts with the nicotine-polyacrylate, releases the water-soluble, free nicotine base (intolerable taste) which instantaneously reacts with the βCD. The formed nicotine base/βCD complex is tasteless. In an aqueous solution the reaction rate of the inclusion is very rapid (between 10^{-2} to 10^{-8} s^{-1}) [63].

The equilibrium is an extremely dynamic process: it is impossible to determine which nicotine molecule is free and which one is entrapped, because the interchange between them is just as quick as the complex formation itself. Even a 600 MHz NMR spectrum cannot detect at ambient temperature the—theoretically different—chemical shifts of the free and complexed species. Assuming a first order kinetics of association, within less than one second the theoretically attainable equilibrium is established (expressed by the complex association constant K_{ass} which for nicotine base and βCD at 37 °C is 194 mol^{-1}).

$$K_{ass} = 194 = \frac{[\beta\text{CD} - \text{nicotine}]}{[\beta\text{CD}][\text{nicotine}]}$$

Under the given conditions at least 99% of the nicotine base is present as complex. In reality, all nicotine molecules (both the free and the complexed ones) are available for

absorption (to interact with the much more lipophilic cell membranes) but the complexed nicotine molecules (entrapped into the voluminous, strongly hydrated CD-molecule) cannot interact with the gate-keeper protein molecules of the taste buds in the buccal cavity, mainly at the back of the tongue. These proteins are hydrophilic, otherwise they would not be able to react with the sweet tasting molecules (like sugar, aspartame, sorbitol, βCD, saccharin, etc.), all of them are very hydrophilic and very well soluble in water.

5. Taste modification of foods

Soybeans have an astringent taste and a peculiar grassy smell, which seems to come from trace amounts of such components as aliphatic carbonyl compounds and volatile aliphatic alcohols. Adding CDs to the soy paste in the manufacture of soy products, these components form CD complexes resulting in deodorized soybean food products [64].

Rice when stored for more than one year acquires an unpleasant off-flavour, which can be eliminated by cooking the rice in the presence of 0.01–0.4% βCD [65]. The characteristic odour of vitamin B_1 can be eliminated from vitamin B_1 enriched cooked rice by small amounts of CDs [66].

Water for rice cooking or rice grains is treated with additives comprising glucono-δ-lactone or non-volatile acids (e.g. carboxylic acids) and odour-masking agents (CD, ginger protease, etc.) of flavour before cooking [67]. The cooked rice has good texture, no unpleasant odour and good flavour. The taste of cooked rice can be improved by maltosyl-CD. Milk casein hydrolysate is a readily digestible protein source, but its bitter taste is a great problem. By adding 10% βCD to the protein hydrolysate the bitter taste can be eliminated [68]. This method provides a way for the utilization of proteins otherwise useless for alimentary purposes.

The bitter aftertaste of stevioside and rubusoside can be eliminated by mixing the sweeteners with CDs. Stevioside- or aspartame-containing water-soluble sweeteners have been prepared with βCD [69,70].

Excessive bitterness is an undesirable flavour quality of some commercial navel orange and grapefruit juice products. For grapefruit juice processed in Florida there is an upper limit on content of the two major bitter components, limonin (0.5 ppm) or naringin (600 ppm), for the juice produced from August 1 to December 1 to meet quality standards. So far, no acceptable commercial process has been found for decreasing the levels of these bitter components without affecting desirable components of the juice. A commercial process is needed that removes bitter components without adding anything to the juice, while still maintaining the expected flavour and nutritional value of the product [71]. Aqueous solutions of 0.0005, 0.01, 0.02 and 0.04% naringin and similar naringin solutions containing 0.5% βCD were prepared. In the presence of 0.5% βCD the bitterness of naringin was reduced to about 50% of that without βCD. The relationship between the sensory bitterness and the concentration of naringin was shown to be linear in a logarithmic plot [72]. Also, in the case of bitter L-aminoacids the βCD resulted in a very remarkable taste improvement but no debittering property was observed with quinine hydrochloride, caffeine and phenylthiourea [73,74].

A possibility for removing the bitter components from orange and grapefruit juices is through the treatment of the juices with α- or βCD polymers in batch or continuous flow fluid-bed process. The polymer also removes other components such as naringenin-7-β-rutinoside, coumarins, and flavonoids, but total acidity and ascorbic acid content remain unchanged. The polymer can be regenerated by treatment with diluted alkali or ethanol [75,76]. Equal quantities of α- and βCD polymers were used to debitter glass-packed single-strength grapefruit juice in a batch process to compare efficiencies of the two polymers for debittering citrus juice. The two polymers were about equal in stability to remove limonin from grapefruit juice, but the βCD polymer reduced the naringin content and the oil level by about 20% more than the αCD polymer. The particle size of the polymer used is 90–300 μm. In the first step, the polymer bound about 50% of the naringin content within 5 min, but the second binding step was much slower. After 1–2 h the binding process reached the equilibrium state. Increasing the temperature to 70 °C leads to a decrease of the bound naringin from 83 to 56%.

Wagner et al. [77] have further improved the above debittering process and reported on the result of a pilot-plant fluidised-bed procedure. In this process the βCD polymer was regenerated 21 times without apparent loss of capacity. The reduction of limonin and naringin in the juices was 30–50% and 33–48%, respectively, making the beverages significantly preferred in flavour tests to the corresponding controls.

The undesired bitter tastes of coffee results from overcooking, extended standing in either hot or cold state which are successfully masked by adding 0.1–10.2% w/v βCD to the beverage [78,79]. Very probably in this case the bad tasting polyphenols and chlorogenic acid are complexed by the βCD, preventing the bad sensation in the mouth. Decaffeination of the beverage with CDs is not feasible because the complex stability of the caffeine/βCD complex is too low and solubility is too high. For removal of chlorogenic acid from the coffee extract some insoluble βCD polymers were about as effective as activated charcoal [80].

The synthesis of some new CD-derivatives (CD-maleyl-chitosan, CD-carboxymethyl chitosan, etc.) have recently been published which in 0.4 and 0.8% solutions fully masked the bitter taste of extracts from artichoke leaves, aloe and gentian [81]. Further examples are listed in Table 2 [51,52,93,96,104].

Table 2
Examples of taste/odour modification/reduction of foods/components

Food/component	Effect	CD	Author, Year	Ref.
Coffee, tea	Eliminates the bitter taste resulted by over-cooking, extended standing, prolonged exposure to atmospheric oxygen	β	Hamilton, 1970	[78]
Soy bean products	Eliminates the grassy smell, stringent taste	β	House Food, 1976	[82]
		α	Dang, 1999	[83]
		β	Norinsuisansho, 2000	[84]
		γ	House Food, 1983	[85]
Propylene glycol	Eliminates the bitter taste	β	Asama, 1980	[86]
Canned citrus	Prevents formation of the bitter naringin	β	Takeda, 1981	[87]
Citrus juice	Eliminates bitter taste of naringin and limonin	β	Konno, 1981	[72]
		β	Toda, 1981	[73,74]
		β	Misaki Konno, 1982	[75]
		β	Kodama, 1992	[76]
		β	Fang, 2000	[88]
Stevioside sweetener	Eliminates of bitter side-taste of stevioside	β	Nikken, 1982	[89]
		γ	Sanraku Ocean. 1985	[90]
Shiitake mushroom	Masking of bitter taste	β	Kagawa,1985	[56]
Krill paste	Masking of unpleasant odour and taste	β	Minamoto, 1986	[91]
Seaveeds	Masking of unpleasant odour and taste	β	Yagi,1986	[92]
Tap water	Elimination of unpleasant taste and smell	β	Hori, 1989	[83]
Heme	To mask unpleasant odour and taste in Fe-enriched foods	β	Sato, 1990	[94]
Cholate	Elimination of bitter taste of cholates from pig, sheep, chicken and carp	β	Han, 1990	[95]
Casein hydrolysate	Masking of bitter taste	β	Saito.1990	[97]
Rice	Cooked in βCD containing water has better odour and favour	β	Satake, 1991	[98]
Tea extract	Bitter taste is eliminated	β	Maesaki.1991	[99]
		β	Suzuki, 1996	[62]
Nicotine	Irritating, bitter taste is eliminated in smoking substitute products	β	Carlsson 1991	[53]
Glycyrrhizin	Sweet taste is masked	α, β, γ	Shidehara 1991	[100]
Gymnema sylvestre leaf extract	Elimination of bitter taste	β	Uenok, 1992	[60]
Ginseng tea	Reduction of bitterness	β	Takeuchi, 1992	[61]
Herring eggs	Reduction of bitterness	Branched	Hosokawa, 1993	[101]
Coffee	Removal of chlorogenic acid	Polymer	Imamura, 1995	[102]
Neohesperidin dihydrochalcone	Elimination of unpleasant after taste	β	Chung, 1996	[103]
Fish oil	Elimination of unpleasant taste, smell and stabilization against oxidation	γ	Reuscher, 2000	[104]
Riboflavin	Masking of bitter taste	α	Tomisawa, 2001	[48,49]
itamin B1 derivatives	Masking of bitterness and after taste	β	Hasegawa, 2002	[49]
Thiamine derivatives	Masking of bitterness	β	Kobayashi, 2002	[50]

6. Conclusions

- Only water (saliva) soluble substances can cause taste sensation.
- The bitter taste of substances can be reduced, or even fully eliminated if they form inclusion complexes of sufficient stability with the selected CD.
- The efficiency of debittering depends on the following factors:
    - value of the complex association constant (it is generally between 10^1 to 10^4 mol^{-1}),
    - pH: ionised guest molecules form less stable complexes
    - guest/host ratio: CDs should be taken in the highest possible molar excess.
- In the case of bitter drugs—when the dose is small and the CDs can be taken in high molar excess—no previous complex preparation is necessary when administering the drug–CD mixture in the mouth, the saliva gets rapidly saturated with the CD and the complex formation is instantaneous.
- The debittering with CDs can also be used for foods, beverages, oral care products, etc.
- The absolute majority of the relevant publications deal with the debittering effect of βCD
- The potentials of α-, γ-, hydroxypropyl-CD, and maltosyl-CDs are not yet exploited in this field.
- Considering the approval status of βCD and its use for the debittering formulation of further drugs—over the actually marketed cetirizine-, nicotine-, benexate-,

and nitroglicerin-βCD complexes—seems to be promising [40–47].

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