### Appendix

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<th>Page no.</th>
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Renuka Mishra  
Nirma University
Appendix 1

1. Drug-excipient compatibility study

Figure 1
FTIR of Cetirizine hydrochloride

The FTIR spectra of the pure drug (Cetirizine hydrochloride) showed significant band at 3427, 2839, 2587, 1741 and 1600 cm$^{-1}$ which indicates the presence of hydroxyl, ether stretching, tertiary amine salt, carbonyl groups and phenyl nucleus skeletal stretching respectively which confirms the purity of the drug. The FTIR of the sample was compared with the reference as shown in Indian Pharmacopoeia, 2007.
Figure 2
FTIR of Cetirizine hydrochloride and HPMC E3 LV powder

Figure 3
FTIR of Cetirizine hydrochloride and sucralose powder
Figure 2, 3 and 4 indicate FTIR of cetirizine hydrochloride in presence of HPMC E3 LV, aspartame and sucralose respectively. It was observed that prominent peaks of cetirizine hydrochloride were present in the respective FTIR spectra. Thus, it can be concluded that there was no interaction between the drug and the excipients selected in the study.

Figure 5
FTIR of batch T3
FTIR of batch T3 indicates absence of peak at 2587, 1741 and 1600 cm\(^{-1}\) for tertiary amine salt, carbonyl groups and phenyl nucleus skeletal stretching respectively. It indicates some inherent change in the characteristic of drug which might be responsible for taste masking.

Figure 6
FTIR of Pullulan
The FTIR spectra of the pure drug (Cetirizine hydrochloride) showed significant band at 3427, 2839, 2587, 1741 and 1600 cm\(^{-1}\) which indicates the presence of hydroxyl, ether stretching, tertiary amine salt, carbonyl groups and phenyl nucleus skeletal stretching respectively which confirms the purity of the drug (Figure 1). FTIR of pullulan and cetirizine powder (Figure 7) indicates presence of tertiary amine salt, carbonyl groups and phenyl nucleus skeletal stretching. It can be concluded that there is no interaction between pullulan and cetirizine hydrochloride.
Figure 8
FTIR of Hydroxypropyl β cyclodextrin

Figure 9
FTIR of Hydroxypropyl β cyclodextrin and cetirizine powder
FTIR of Hydroxypropyl β cyclodextrin and cetirizine powder (Figure 9) indicates presence of tertiary amine salt and carbonyl groups. It can be concluded that there is some change in the characteristic peak of cetirizine hydrochloride.
FTIR of Tulsion 335 and cetirizine powder (Figure 11) indicates presence of tertiary amine salt, carbonyl groups and phenyl nucleus skeletal stretching. It can be concluded that there is no interaction between Tulsion 335 and cetirizine hydrochloride powder.

Figure 12
FTIR of Cetirizine-tulsion 335 complex

FTIR of Cetirizine-tulsion 335 complex (Figure 12) indicates absence of prominent peaks of cetirizine hydrochloride. It can be concluded that there is formation of complex between Tulsion 335 and cetirizine hydrochloride.
Appendix 2

2. Profile of excipients

2.1 Hydroxypropyl methylcellulose(1)

2.1.1 Non proprietary Names
BP: Hypromellose
PhEur : Hypromellosum
USP: Hypermellose

2.1.2 Synonyms
Benecel MHPC, Cellulose, hydroxypropylmethyl ether, Methocel, methylcellulose propylene glycol ether, methyl hydroxypropylcellulose, Metolose, Pharmacoat, HPMC.

2.1.3 Chemical name and CAS Registry number
Cellulose, 2-hydroxypropyl methyl ether [9004-65-3]

2.1.4 Structural Formula

\[
\begin{align*}
\text{CH}_2\text{OR} & \quad \text{OR} \\
\text{O} & \quad \text{O} \\
\text{CH}_2\text{OR} & \quad \text{OR}
\end{align*}
\]

2.1.5 Description
HPMC is an odorless and tasteless, white or creamy white colored fibrous or granular powder.

2.1.6 Typical properties:
1. Acidity/alkalinity: pH = 5.5-8.0 for a 1% w/w aqueous solution.
2. Ash: 1.5-3.0% depending upon the grade.
3. Auto ignition temperature: 360 °C
4. Density (tapped): 0.557g/cm³
Melting point: Browns at 190-200 °C, glass transition temperature is 170-180 °C.
5. Moisture content: HPMC absorbs moisture from the atmosphere, the amount of water depending upon the initial moisture content and the temperature & relative humidity of the surrounding air.

6. Solubility: Soluble in cold water, forming a viscous colloidal solution. It is practically insoluble in chloroform, ethanol (95%), and ether, but soluble in ethanol and dichloromethane.

7. Specific gravity: 1.26

8. Viscosity: wide ranges of viscosities are available.

2.1.7 Stability and storage conditions:
HPMC powder is a stable material although it is hygroscopic after drying.
Solutions are stable between pH 3-11. Increasing temperature reduces the viscosity of the solutions. HPMC undergoes a reversible sol to gel transformation upon heating and cooling respectively. The gel point is 50-90 °C depending upon the grade of the material. Aqueous solutions are comparatively enzyme resistant, providing good viscosity stability during long-term storage. However they are prone to microbial spoilage and should be preserved with an antimicrobial preservative. HPMC powder should be stored in a well-stored container, in a cool, dry place.

2.1.8 Safety: HPMC is a widely used as an excipient in oral and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products.
LD 50(mouse, IP): 5g/kg
LD 50(rat, IP): 5.2 g/kg

2.1.9 Functional category:
Coating agent, film former, rate-controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent.
2.1.10 Pharmacopoeial Specifications:

<table>
<thead>
<tr>
<th>Test</th>
<th>PhEur 1992</th>
<th>USP 25</th>
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<td>+</td>
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<tr>
<td>Characters</td>
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<td>-</td>
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<tr>
<td>Appearance of the solution</td>
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<td>-</td>
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<tr>
<td>pH(1% w/w solution)</td>
<td>5.5-8.0</td>
<td>-</td>
</tr>
<tr>
<td>Apparent viscosity</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Loss on drying</td>
<td>≤10%</td>
<td>≤5%</td>
</tr>
<tr>
<td>Residue on ignition</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>For viscosity grade &gt; 50 mPa s</td>
<td>-</td>
<td>≤1.5%</td>
</tr>
<tr>
<td>For viscosity = 50 mPas</td>
<td>-</td>
<td>≤3%</td>
</tr>
<tr>
<td>For type 1828 of all viscosities</td>
<td>-</td>
<td>≤5%</td>
</tr>
<tr>
<td>Sulfated ash</td>
<td>≤1%</td>
<td>-</td>
</tr>
<tr>
<td>Arsenic</td>
<td>-</td>
<td>3 ppm</td>
</tr>
<tr>
<td>Chloride</td>
<td>≤0.5%</td>
<td>-</td>
</tr>
</tbody>
</table>

2.1.11 Regulatory status:
GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients guide (ophthalmic preparations, oral capsules, suspensions, syrup and tablets, topical and vaginal preparations) Included in non parenteral medicines licensed in the UK.

2.1.12 Application in the pharmaceutical formulation and technology:

HPMC is widely used in oral and topical pharmaceutical formulations.

In oral products, HPMC is primarily used as tablet binder, in film coating and as an extended release tablet matrix.

Concentration between 2-5% w/w may be used as a binder in either wet or dry granulation processes. High viscosity grades may be used to retard the release of water-soluble drugs from the matrix. Concentration between 2-20% is used as film forming solutions to film
coat tablets. Lower viscosity grades are used in aqueous film coating, while higher viscosity grades are used with organic solvents. HPMC is also used as suspending and thickening agent in topical formulation, particularly ophthalmic preparations. Concentrations between 0.45 to 1% w/w may be added as a thickening agent to vehicles for eye-drops and artificial tear solutions. HPMC is used as an emulsifier, suspending agent and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating thus inhibiting the formation of sediments. In addition, HPMC is used as an adhesive in plastic bandages and as a wetting agent for hard contact lenses. It is also used in cosmetics and food products.

References:

2.2 Pullulan(1,2)

Pullulan is a linear homopolysaccharide of glucose that often is described as an \( \alpha-(1-6) \) linked polymer of maltotriose subunits. This unique linkage pattern endows pullulan with distinctive physical traits. Pullulan has adhesive properties and can be used to form fibers, compression moldings, and strong, oxygen-impermeable films. Pullulan is derivatized easily to control its solubility or provide reactive groups. Consequently, pullulan and its derivatives have numerous potential food, pharmaceutical, and industrial applications. Pullulan is produced as a water-soluble, extracellular polysaccharide by certain strains of the polymorphic fungus Aureobasidium pullulans(formerly known as Pullularia pullulans). *Aureobasidium pullulans* is also known as “black yeast” because it produces melanin.

2.2.1 Historical Outline

*Aureobasidium pullulans* was first described (as Dematium pullulans) by De Bary in 1866959). Bauer (1938) made early observations on polysaccharide formation by *A. pullulans*, and Bernier (1958) isolated and began to characterize the polymer. Bender et al. (1959) studied the novel polysaccharide and named it. Bender and Wallenfels (1961) discovered the enzyme pullulanase, which specifically hydrolyzes the \( \alpha-(1-6) \) linkages in pullulan and converts the polysaccharide almost quantitatively to maltotriose. Thus, pullulan is commonly viewed as an \( \alpha-(1-6) \) linked polymer of maltotriose subunits.

Pullulan has been used as a food ingredient for over 20 years in Japan. It has Generally Regarded As Safe (GRAS) status in the US for a much wider range of applications and thus higher intakes than the current application.

The proposed use is in the production of capsule shells and of coated tablets for the preparation of dietary supplements and as a matrix for edible flavoured films (breath fresheners). The toxicological database for pullulan is limited but indicates that pullulan is of low toxicity. Human volunteer studies have only reported abdominal fullness at doses of 10g pullulan per day with other mild gastrointestinal symptoms at higher doses. Exposure in adults at the specified worst case assumptions (12 tablets and a packet of breath freshening films) would be around 23% of this amount.
On the basis that pullulan is similar to other poorly digested carbohydrates and that the current proposed usage levels are below the level likely to cause abdominal fullness, the Panel considers that the expected intakes of pullulan would not present any concern when used as a food additive in the proposed uses and at the usage levels requested. If higher levels of use or other uses were to be requested then more data might be required.

Pullulan is a naturally occurring, fungal exopolysaccharide first described by Bender has film-forming properties and can be used as a substitute for gelatin or other film-polymers in certain foods. Pullulan is used in production of gelatin-free capsules and coated tablets for dietary supplements and flavoured films for consumption as breath fresheners.

According to the petitioner pullulan has been extensively used for more than twenty years in Japan where it is classified as a food ingredient. Its main use has been as a glazing agent having oxygen-barrier properties. Pullulan is accepted for use as an excipient in pharmaceutical tablets and is listed in the Japanese Standards for Ingredients for Drugs.

2.2.2 Terms of reference
The molecular weight of pullulan can vary considerably. Molecular weight standards are available ~1000 daltons.

The commercial product for which authorization is requested is Pullulan PI-20 (P for pullulan, I to indicate that the product is deionised and 20 the average molecular weight of 200,000 daltons). The product as commercialized (PI-20) “has a number average molecular weight (Mn) of about 100,000 to 200,000 daltons and a weight average molecular weight (Mw) of about 362,000 to 480,000 daltons (Okada et al., 1990).

Pullulan can be made into very thin films (down to 0.01 mm, Yuan, 1974). These have a high tensile strength and are stable over a range of temperatures. Pullulan films have low oxygen permeability, are oil and grease resistant and dissolve rapidly in water. Pullulan films are usually prepared by rapid evaporation of a 5-10% aqueous pullulan solution applied to a smooth surface and dried; it may also involve the use of high temperature and pressure.

Pullulan can also be made into shaped bodies. Optimally such bodies are made from pullulan of a molecular weight of around 250,000 daltons. This process usually involves rapid evaporation of water, compression moulding or extrusion at high temperature. A wide range of food, industrial and pharmaceutical applications has been cited for pullulan.
films. Pullulan can be mixed with a range of other food or non-food materials to alter the physical characteristics of pullulan films. Commonly pullulan may be mixed with gelatin, amylose and polyvinyl alcohol. Pullulan films or shaped bodies may also contain polyhydric alcohols as plasticisers; e.g. maltitol, sorbitol, glycerol and water soluble polyvinyl alcohol.

2.2.3 Description
A white to off-white tasteless, odourless powder that forms a viscous non-hygroscopic solution when dissolved in water at 5-10%. It can be made into films of high tensile strength and low oxygen permeability. Pullulan starts to decompose at 250°C and chars at 280°C.

2.2.4 Solubility
Highly soluble in water, dilute alkali, insoluble in alcohol and other organic solvents except dimethylsulphoxide and formamide. According to the petitioner a 10% w/w solution of PI-20 has a pH between 5 and 7.

2.2.5 Viscosity
Pullulan solutions are viscous but do not gel. There is a linear relationship between the viscosity and molecular weight. Viscosity is relatively independent of pH (<2 to >11) and temperature. Heating at 90°C for an hour reduces the viscosity of large polymers (around 300,000 daltons) by about 10% whereas there was little change in the molecular weight of smaller molecules (60,000–100,000 daltons). Viscosity is also unaffected by heating to 100°C for 6 hours in 30% NaCl.

References:
2. Opinion of the scientific panel on food additives, flavourings, processing aids and materials in contact with food on a request from commission related to Pullulan PI-20 for use as food additive, The EFSA Journal (2004), 85,1-32.
2.3 Hydroxypropyl cellulose(1)

2.3.1 Non proprietary names:
BP: Hydroxypropyl cellulose
JP: Hydroxypropyl cellulose
PhEur: Hydroxypropylcellulosum
USPNF: Hydroxypropyl cellulose

2.3.2 Synonyms
Cellulose, hydroxypropyl ether, E463, hyprolese, klucel, Methocel, Nisso HPC, oxypropylated cellulose

2.3.3 Chemical name and CAS registry name
Cellulose, 2-hydroxypropylether (9004-64-2)

2.3.4 Molecular weight
50 000-1 250 000

2.3.5 Structural formula

\[
\text{R is H or } [\text{CH}_2\text{CH}(\text{CH}_3)\text{O}]_n\text{H}
\]

2.3.6 Functional category
Coating agent, emulsifying agent, stabilibilising agent, tablet binder, thickening agent, viscosity-increasing agent
2.3.7 Applications in Pharmaceutical Formulation or Technology

Hydroxypropyl cellulose is widely used in oral and topical pharmaceutical formulations.

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extended release matrix former</td>
<td>1.5-3.5</td>
</tr>
<tr>
<td>Tablet binder</td>
<td>2-6</td>
</tr>
<tr>
<td>Tablet film coating</td>
<td>5</td>
</tr>
</tbody>
</table>

2.3.8 Description

Hydroxypropyl cellulose is a white to slightly yellow-coloured, odourless and tasteless powder.

2.3.9 Typical properties

Acidity/alkalinity: pH = 5-8.5 for a 1% w/v aqueous solution

Density (bulk) = 0.5 g/cm³

Melting point: softens at 130°C, chars at 260-275°C

Solubility: soluble 1 in 10 parts dichloromethane, 1 in 2.5 parts ethanol (95%), 1 in 2 parts methanol, 1 in 5 parts propylene glycol and 1 in 2 parts water.

Specific gravity: 1.2224 for particles, 1.0064 for 2% w/v aqueous solution at 20°C.

Viscosity (dynamic): a wide range of viscosity types are commercially available.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Viscosity (mPa s) of various aqueous solutions of stated concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1%</td>
</tr>
<tr>
<td>Klucel HF</td>
<td>1500-3000</td>
</tr>
<tr>
<td>Klucel MF</td>
<td>-</td>
</tr>
<tr>
<td>Klucel GF</td>
<td>-</td>
</tr>
<tr>
<td>Klucel JF</td>
<td>-</td>
</tr>
<tr>
<td>Klucel LF</td>
<td>-</td>
</tr>
<tr>
<td>Klucel EF</td>
<td>-</td>
</tr>
</tbody>
</table>

2.3.10 Stability

Hydroxypropyl cellulose powder is a stable powder, although it is hygroscopic after drying. Aqueous solutions of hydroxypropyl cellulose are stable at pH 6-8 with the
viscosity of solutions being relatively unaffected. Hydroxypropyl cellulose powder should be stored in a well-closed container in a cool dry place.

2.3.11 Incompatibilities
Hydroxypropyl cellulose in solution demonstrates some incompatibility with substituted phenol derivatives, such as methyl and propyl paraben. The presence of anionic polymers may increase the viscosity of Hydroxypropyl cellulose solutions.

2.3.12 Safety
Hydroxypropyl cellulose is widely used as an excipient in oral and topical pharmaceutical formulations. It is used extensively in cosmetics and food products.

2.3.13 Regulatory status
GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA inactive ingredients guide.

References:
2.4 Cyclodextrins(1)

2.4.1 Non proprietary name
BP: Betadex
USPNF: Betadex

2.4.2 Synonyms
Cyclodextrin: Cavitron, cyclic oligosaccharide, cycloamylose, cycloglucan, Encapsin
α-cyclodextrin: alfadex, alpha cycloamylose, alpha cyclodextrin, Cavamax W6 pharma, cyclohexaamylose, cyclomaltohexose
β-cyclodextrin: beta cycloamylose, beta-dextrin, Cavamox W7 Pharma, cycloheptamyllose, kleptose
γ-cyclodextrin: Cavamax W8 Pharma, cyclooctaamylose, gamma cyclodextrin

2.4.3 Chemical name and CAS Registry number
α-cyclodextrin [10016-20-3]
β-cyclodextrin [7585-39-9]
γ-cyclodextrin [17465-86-0]

2.4.4 Empirical formula and molecular weight
α-cyclodextrin $\text{C}_{36}\text{H}_{60}\text{O}_{30}$ 972
β-cyclodextrin $\text{C}_{42}\text{H}_{70}\text{O}_{35}$ 1135
γ-cyclodextrin $\text{C}_{48}\text{H}_{80}\text{O}_{40}$ 1297

2.4.5 Structural formula
2.4.6 Functional category
Solubilizing agent, stabilizing agent

2.4.7 Applications in pharmaceutical formulation or technology
Cyclodextrins are crystalline, non hygroscopic, cyclic oligosaccharides derived from starch. Among the most commonly used forms are cyclodextrin, which have 6, 7 and 8 glucose units respectively.

Cyclodextrins are bucket like or cone like toroid molecules, with rigid structure and a central cavity, the size of which vary according to the cyclodextrin type. The internal surface of the cavity is hydrophobic and the outside of the torus is hydrophilic, this is due to arrangement of hydroxyl groups with in the molecules. This arrangement permits the cyclodextrin to accommodate the guest molecules within the cavity, forming a inclusion complex. Cyclodextrins may be used to form inclusion complex with variety of the molecules, resulting primarily in improvement to dissolution and bioavailability owing to enhanced solubility and improved chemical and physical stability. Cyclodextrin inclusion complexes are also used to mask the unpleasant taste of active materials and to convert a liquid substance to a solid substance.

2.4.8 Description
Cyclodextrins are cyclic oligosaccharides containing at least six D-(+)-glucopyranose units attached by α(1-4) glucoside bonds. The three natural cyclodextrins α, β and γ differ in their ring size and solubility. They contain 6, 7, or 8 glucose units respectively. Cyclodextrins occur as white, practically odorless fine crystalline powders having a slightly sweet taste.
### 2.4.9 Specification

<table>
<thead>
<tr>
<th>Test</th>
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<th>USPNF 23</th>
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</tr>
<tr>
<td>Characters</td>
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<td>-</td>
</tr>
<tr>
<td>Color and clarity of the solution</td>
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<td>+</td>
</tr>
<tr>
<td>pH</td>
<td>5-8</td>
<td>-</td>
</tr>
<tr>
<td>Specific rotation</td>
<td>+160 to +164°</td>
<td>+160 to +164°</td>
</tr>
<tr>
<td>Microbial limits</td>
<td>≤0.1%</td>
<td>&lt;1000/g</td>
</tr>
<tr>
<td>Sulfated ash</td>
<td>≤10 ppm</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>+</td>
<td>≤5 ppm</td>
</tr>
<tr>
<td>Light absorbing impurities</td>
<td>≤16.0%</td>
<td>-</td>
</tr>
<tr>
<td>Loss on drying</td>
<td>≤14.0%</td>
<td></td>
</tr>
<tr>
<td>Related substances</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Residual solvents</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Reducing sugars</td>
<td>≤0.2%</td>
<td>≤1.0%</td>
</tr>
<tr>
<td>Assay (anhydrous basis)</td>
<td>98-101%</td>
<td>98-101%</td>
</tr>
</tbody>
</table>

### 2.4.10 Typical properties

Compressibility: 21-44% for β-cyclodextrin

β-cyclodextrin:
- Density (bulk): 0.523g/cm³
- Density (tapped): 0.754
- Melting point: 255-265
- Moisture content: 13-15%w/w
- Particle size distribution: 7-45μm
- Solubility: Soluble 1 in 50 of water at 20°C, 1 in 20 at 50°C, practically insoluble in acetone, ethanol(95%) and methylene chloride.
Specific rotation: +162°
Surface tension (at 25°C): 71 mN/m (71 dynes/cm)

2.4.11 Stability and storage conditions
β-cyclodextrin and other cyclodextrins are stable in solid state if protected from high humidity.
Cyclodextrins should be stored in a tightly sealed container in a cool, dry place.

2.4.12 Method of manufacture
Cyclodextrins are manufactured by the enzymatic degradation of starch using specialized bacteria. β-cyclodextrin is produced by the action of the enzyme cyclodextrin glucosyltransferase upon starch or a starch hydrolysate. An organic solvent is used to direct the reaction that produces β-cyclodextrin and to prevent the growth of microorganisms during enzymatic reaction.
Hydroxyethyl-β-cyclodextrin is made by reacting β-cyclodextrin with ethylene oxide, hydroxypropyl-β-cyclodextrin is made by reacting β-cyclodextrin with propylene oxide.

2.4.13 Safety
Cyclodextrins are starch derivatives and are mainly used in oral and parenteral pharmaceutical formulations. They are also used in topical and ophthalmic formulations. Cyclodextrins are also used in cosmetics and food products and are generally regarded as non toxic and non-irritant materials. However, when administered parenterally, β-cyclodextrin is not metabolized but accumulates in the kidneys as insoluble cholesterol complexes resulting in severe nephrotoxicity. Other cyclodextrins, such as hydroxypropyl-β-cyclodextrin are not associated with nephrotoxicity and are reported to be safe for use in parenteral formulations.
Cyclodextrin administered orally is metabolized by microflora in the colon, forming the metabolites maltodextrin, maltose and glucose which are themselves further metabolized before being finally excreted as carbon dioxide and water. Cyclodextrins are non-irritant to the skin and eyes or upon inhalation.
Hyroxypropyl β cyclodextrin(2)

Hyroxypropyl β cyclodextrins are purified polydisperse products resulting from controlled reaction of propylene oxide and native betacyclodextrin under base catalysis.

CAS number : [128446-35-5]

Synonyms : 2HP- β-CD, Kleptose HPB

Appearance : white crystalline powder

Solubility : >1 in 2 parts of water

Decomposition temperature: above 300°C

Moisture content: Max 5%

Inner diameter: 0.62 nm

Surface tension: 52.0-69.0 mN/m(dyne/cm) at 25°C

Average molecular weight = 1135 + 7 x MS x 58.1

Where MS refers to molar degree of substitution

Stability

Hyroxypropyl β cyclodextrin solution stability in acidic medium. Only slight hydrolysis was observed under harsher conditions at pH 2, 60°C. Hyroxypropyl β cyclodextrin solution was found to be stable to hydrolysis. The batches were found to be stable for 3 years.

Application

It is used in applications similar to those of β cyclodextrin. However, as it is not nephrotoxic it has been suggested for use in parenteral formulations. It is included in oral and parenteral formulations licensed in Europe and USA. The degree of substitution of hydroxyl propyl groups can vary.

References:


2.5 Ion exchange resin

Ion exchange resins are solid and suitably insoluble high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with the surrounding medium. Synthetic ion exchange resins have been used in pharmacy and medicine for taste masking or controlled release of drug as early as 1950s. Being high molecular weight water insoluble polymers, the resins are not absorbed by the body and therefore inert. These groups have an affinity for oppositely charged counter ions, thus absorbing the ions into the polymer matrix. Since most drugs possess ionic sites into their molecule, the resin’s charge provides drug release in the saliva, this complex prevents the means to loosely bind such drugs and this complex prevents the drug release in the saliva, thus resulting in taste masking.

Application

1. Taste masking: Drug resin complexes “Resinates” are insoluble. Hence, the bitter taste of the drug is not sensed as the drug is not released during quick passage through the mouth, but is rapidly released in the gastro-intestinal tract.
2. Tablet disintegration: Amberlite IRP88 swells easily in an aqueous medium and thus disintegrates rapidly the tablet by creating internal pressure.
3. Controlled and modified release: With amberlite IRP69 or Duolite AP 143, a controlled rate of drug allows sustained release. Further control can be obtained by applying a coating to the resinate.
4. Reduced abuse: Controlling the release rate of drugs is in the specific case of drug abuse where a high and rapid release from high dose formulations of certain drugs is sought by abusers.

References:

2.6 Sucralose (1,2)
Sucralose is a sweetener that is produced from sugar to act as a low-calorie substitute. It has a similar taste to sugar but is around 600 times sweeter. Sucralose’s low-calorie characteristic originates from the inability of the body to metabolize most of the substance. Although this molecule is made from sugar, the human body does not recognize Sucralose as a carbohydrate, therefore the molecule is not broken down for energy and the Sucralose molecule(s) is passed through the body unchanged and is eliminated shortly after consumption. Sucralose is not used as an energy source in the body as it does not break down like other sugar (i.e., sucrose). The majority of ingested sucralose is excreted unchanged in the feces and most of what is absorbed appears unchanged in the urine, with only minor amounts appearing as metabolites. Sucralose does not interfere with the utilization of sucrose in man. Sucralose is a free flowing white crystalline solid that is soluble in water and stable both in crystalline form and in most aqueous solutions. Sucralose has been approved for use in 27 plus countries in addition to the US. It has been used commercially since 1991 in more than 400 different food products.

2.6.1 Nonproprietary Name
USPNF: Sucralose

2.6.2 Synonyms
Splenda; TGS; 1’,4’,6-trichlorogalactosucrose; 4,1’,6’—tri-chloro-4,1’,6’-trideoxy-galactosucrose.

2.6.3 Chemical Name and CAS Registry Number
1,6-Dichloro-1,6-dideoxy-β-Dfructofurosyny1-4-chloro-4-deoxy-α-D-galactopyranoside

2.6.4 Empirical Formula and Molecular Weight
C₁₂H₁₉Cl₃O₈     397.64
2.6.5 Structural Formula

![Structural Formula Image]

2.6.6 Functional Category

Sweetening agent

2.6.7 Applications in Pharmaceutical Formulation or Technology

Sucralose is used as a sweetening agent in beverages, foods and pharmaceutical applications. It has sweetening power 300-1000 times that of sucrose and has no aftertaste. It has no nutritional value, is non carcinogenic, and produces no glycemic response.

Use | concentration (%)
---|---
Food products | 0.03-0.24

2.6.8 Description

Sucralose is a white to off-white free flowing crystalline powder.
2.6.9  Pharmocopeial specifications

<table>
<thead>
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<th>USPNF 23</th>
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<tbody>
<tr>
<td>Identification</td>
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<tr>
<td>Specific rotation</td>
<td>+84.0° to +87.5°</td>
</tr>
<tr>
<td>Water</td>
<td>≤2.0%</td>
</tr>
<tr>
<td>Residue on ignition</td>
<td>≤0.7%</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>≤0.001%</td>
</tr>
<tr>
<td>Limit of hydrolysis products</td>
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</tr>
<tr>
<td>Limit of methanol</td>
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</tr>
<tr>
<td>Related compounds</td>
<td>≤0.5%</td>
</tr>
<tr>
<td>Assay (dried basis)</td>
<td>98-102%</td>
</tr>
</tbody>
</table>

2.6.10 Typical Properties

Acidity/alkalinity: 1) = 5-6 (10%w/v aqueous solution at 20 °C)
Density (bulk): 0.35 g/cm³
Density (tapped): 0.62
Density (true): 1.63
Melting point: 130°C
Particle size distribution: 90% < 12um in size.
Partition coefficient = -0.5 I (octanol: water)
Refractive index 1.33-1.37
Solubility: freely soluble in ethanol (95%), methanol and water; slightly soluble in ethyl acetate.
Specific rotation +84.0° to 87.5° (1% w/v aqueous solution), +68.2°(1.1%w/v aqueous solution in ethanol).
Viscosity: 0.6-3.8 mPa s
2.6.11 Stability and Storage Conditions
Sucralose is a relatively stable material. In aqueous solution, at highly acidic conditions (pH<3) and at high temperatures, it is hydrolyzed to limited extent, producing 4-chloro-4-deoxygalactose and 1,6 dichloro-1,6 dideoxyfructose.

2.6.12 Safety
Sucralose is generally regarded as a non-toxic and non-irritant material and is approved, in a number of countries for use in food products. Following oral consumption, sucralose is mainly unabsorbed and is excreted in the feces.
LD50 (mouse, oral): > 16 g/kg
LD50, (rat, oral): 10 g/kg

2.6.13 Regulatory Status
The FDA, in April 1998, approved sucralose for use as a tabletop sweetener and as an additive in a variety of food products. In the UK, sucralose was authorized for use in food products on a 2 year temporary basis in March 2002. It is also for use in many other countries worldwide, included in the Canadian list of Acceptable Non-medicinal Ingredients.

2.6.14 Related Substances
Sucrose.

References:
2.7 Aspartame(1)

2.7.1 Nonproprietary Name:
BP: Aspartame
PhEur: Aspartanum
USPNF: Aspartame

2.7.2 Synonyms
3-amino-N-(α-carboxyphenylthyl) succinamic acid N-methyl ester; 3-amino N-(α-methoxycarbonyl) succinamic acid; APM; aspartyl phenylalanine methyl ester; Canderal F951; Equal; methyl N-α-1 aspartyl phenylalanine; Nutrasweet; Pal Sweet, Tri sweet.

2.7.3 Chemical Name and CAS Registry Number
N 1 Aspartyl phenylalanine 1 methyl ester

2.7.4 Empirical Formula and Molecular Weight
C_{14}H_{18}N_{2}O_{5}  294.31

2.7.6 Functional Category
Sweetening agent

2.7.7 Applications in Pharmaceutical Formulation or Technology
Aspartame is used as an intense sweetening agent in beverage products, food products, and table top sweeteners, and in pharmaceutical preparations including tablets, powder mixes, and vitamin preparations. It enhances flavor systems and can be used to mask
some unpleasant taste characteristics; the approximate sweetening power is 180-200 times that of sucrose. Unlike some other intense sweeteners, aspartame is metabolized in the body and consequently has some nutritive value: 1g provides approximately 17 K (4Kcal). However, in practice, the small quantity of aspartame consumed provides a minimal nutritive effect. Theoretically, aspartame has also been used in the treatment of sickle cell anemia.

2.7.8 Description
Aspartame occurs as an off-white almost odorless crystalline powder with an intensely sweet taste.

2.7.9 Pharmacopeial specifications:

<table>
<thead>
<tr>
<th>Test</th>
<th>PhEur 2005</th>
<th>USPNF 23</th>
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<tbody>
<tr>
<td>Characters</td>
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<tr>
<td>Identification</td>
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<tr>
<td>Appearance of solution</td>
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<td>-</td>
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<tr>
<td>Specific optical rotation</td>
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<td>+14.5 to +16.5°</td>
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<tr>
<td>Related substances</td>
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<tr>
<td>Loss on drying</td>
<td>≤4.5 %</td>
<td>≤4.5%</td>
</tr>
<tr>
<td>Impurities</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Assay</td>
<td>98-102%</td>
<td>98-102%</td>
</tr>
</tbody>
</table>

2.7.10 Typical properties:
Acidity/alkalinity: pH 4.5-6.0 (0.8%w/v aqueous solution)
Brittle fracture index: 1.05
Flowability 44 % (compressibility index)
Density (bulk)
0.5-0.7g/cm³
0.2-0.4g/cm³
0.17g/cm³ (spectrum quality products)
Density (tapped): 0.29g/cm³
Density (true): 1.347g/cm³
Melting point: 246-247°C
Solubility: slightly soluble in ethanol (95%); sparingly soluble in water. At 20°C, the solubility is 1% w/v at isoelectric point (pH 5.2). Solubility increases at higher temperature and more at acidic pH

2.7.11 Stability and storage conditions
Aspartame is stable in dry conditions. In the presence of moisture, hydrolysis occurs to form degradation products L-aspartyl-L-phenylalanine and 3-benzyl-6-carboxymethyl-2,5-dipeptopiperazine. Stability in aqueous solutions is enhanced by the addition of cyclodextrins, and by the addition of polyethylene glycol 400 at pH 2. However, at pH 3.5-4.5 stability is not enhanced by the replacement of water with organic solvents. Aspartame degradation also occurs during prolonged heat treatment; losses of aspartame may be minimized by using processes that employ high temperatures for a short time followed by rapid cooling.

The bulk material should be stored in a well-closed container, in a cool dry place.

2.7.12 Method of manufacture
Aspartame is produced by coupling together L-phenylalanine and L-aspartic acid, either chemically or enzymatically. The former process yields both the sweet α-aspartame and non-sweet β-aspartame from which α-aspartame has to be separated and purified. The enzymatic process yields only α-aspartame.

2.7.13 Regulatory status
GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide. Included in non-parenteral medicines licensed in the UK. Included in the Canadian list of acceptable non-medicinal ingredients.

2.7.14 Related substances
Alitame

References: