CHAPTER 4

DRUG AND EXCIPIENT PROFILE

4.1 DILTIAZEM HYDROCHLORIDE

General information of the drug

Name : Diltiazem hydrochloride
Molecular Formula : $C_{22}H_{26}N_2O_4S \cdot HCl$
Molecular mass : 414.519 g/mol
Structure :

\[
\text{Systematic IUPAC name : } \text{cis}-(+)\text{-}[2-(2\text{-dimethylaminoethyl})\text{-}5-(4\text{-methoxyphenyl}) \text{-}3\text{-oxo}-6\text{-thia}-2\text{-azabicyclo[5.4.0]undeca}-7,9,11\text{-trien}-4\text{-yl}]\text{ethanoate}
\]
CAS number : 42399-41-7

Physical appearance : White to Off-white crystalline powder,

Solubility : Soluble in Water, Methanol and chloroform.

Stability : Thermostable

Pharmacokinetic data

Plasma half life, t\textsubscript{1/2} : 3 – 4.5 h

Bioavailability : 40 % (Well absorbed in proximal portions of GIT than in colon [23])

Metabolised majorly by : Liver

Volume of distribution, Vd : 305L

Elimination rate constant, K_E : 0.1848 hr\textsuperscript{-1}

Clearance, Cl : 56.36 L/h

Metabolism/Transport Effects

Substrate of CYP2C9 (minor), 2D6 (minor), 3A4 (major); Inhibits CYP2C9 (weak), 2D6 (weak), 3A4 (moderate)

Mechanism of Action

DLT inhibits calcium ion from entering the “slow channels” or select voltage-sensitive areas of vascular smooth muscle and myocardium during depolarization, producing a relaxation of coronary vascular smooth muscle and coronary vasodilation; increases myocardial oxygen delivery in patients with vasospastic angina.
Indications Angina:

- Stable angina (exercise-induced). DLT increases coronary blood flow and decreases myocardial oxygen consumption, secondary to decreased peripheral resistance, heart rate, and contractility [76, 77].
- Variant angina. DLT is effective due to its direct effects on coronary dilation.
- Unstable angina (preinfarction, crescendo). DLT may be particularly effective if the underlying mechanism is vasospasm.

Arrhythmia: DLT is effective in treating Atrial fibrillation, atrial flutter, Paroxysmal supraventricular tachycardia, reentrant supraventricular tachycardia [78].

Hypertension: DLT is useful for treating hypertension because of its vasodilatory effects. Calcium channel blockers are well-tolerated and especially effective in treating low-renin hypertension [79].

Pharmacodynamics

Dosage

Angina: Initial: 120-180 mg once daily (maximum dose: 480 mg/day), Tablet, extended release capsules, 180 mg once daily; may increase at 7- to 14-day intervals (maximum recommended dose: 360 mg/day) Tablet, immediate release Usual starting dose: 30 mg 4 times/day; usual range: 180-360 mg/day

Hypertension: Capsule, tablets extended release (Initial: 180-240 mg once daily; dose adjustment may be made after 14 days; usual dose range:
180-420 mg/day; usual dose range: 120-540 mg/day, Children: Initial: 1.5-2 mg/kg/day 3 times daily (maximum dose 6 mg/kg/day up to 360 mg/day) Doses up to 8 mg/kg/day given in 4 divided doses have been used for investigational therapy of Duchenne muscular dystrophy.

**Arrhythmia:** Initial bolus dose: 0.25 mg/kg actual body weight over 2 minutes (average adult dose: 20 mg). Repeat bolus dose (may be administered after 15 minutes if the response is inadequate.): 0.35 mg/kg actual body weight over 2 minutes (average adult dose: 25 mg. Continuous infusion (requires an infusion pump; infusions >24 hours or infusion rates >15 mg/hour are not recommended.): Initial infusion rate of 10 mg/hour; rate may be increased in 5 mg/hour increments up to 15 mg/hour as needed; some patients may respond to an initial rate of 5 mg/hour.

DLT injection is administered by continuous infusion for >24 hours, there is possibility of decreased DLT clearance, prolonged elimination half-life, and increased DLT and/or DLT metabolite plasma concentrations should be considered.

**Dosing comments in renal/hepatic impairment:** Use with caution as extensively metabolized by the liver and excreted in the kidneys and bile.

**Dialysis:** Not removed by hemo- or peritoneal dialysis; supplemental dose is not necessary.

**Contraindications**

**Oral:** Hypersensitivity to DLT, sick sinus syndrome, second- or third-degree AV block (except in patients with a functioning artificial pacemaker), severe hypotension (systolic <90 mm Hg), acute myocardial infarction and pulmonary congestion.
Intravenous (I.V.): Hypersensitivity to DLT or any component of the formulation, sick sinus syndrome, second- or third-degree AV block (except in patients with a functioning artificial pacemaker), severe hypotension (systolic <90 mm Hg), acute MYOCARDIAL INFARCTION and pulmonary congestion, administration concomitantly or within a few hours of the administration of I.V. beta-blockers, atrial fibrillation or flutter associated with accessory bypass tract (eg, Wolff-Parkinson-White syndrome), ventricular tachycardia (with wide-complex tachycardia, must determine whether origin is supraventricular or ventricular).

Pregnancy Considerations

Teratogenic and embryotoxic effects have been demonstrated in small animals. There are no adequate and well-controlled studies in pregnant women.

Breast-Feeding Considerations

Freely diffuses into breast milk; however, the AAP considers DLT to be compatible with breast-feeding. Available evidence suggests safe use during breast-feeding.

Drug-drug interaction

- Beta-blockers: Concomitant use with beta-blockers can result in conduction disturbances, hypotension, and worsened left ventricular function; I.V. administration concomitantly or within a few hours of I.V. beta-blockers is contraindicated.
- Digoxin: Concomitant use with digoxin can result in conduction disturbances.
Adverse drug reactions

- **Cardiovascular**: Edema, AV block (first degree), edema (lower limb), bradycardia, hypotension, vasodilation, extrasystoles, flushing and palpitation.
- **Central nervous system**: Headache, Dizziness and nervousness,
- **Dermatologic**: Rash.
- **Endocrine & metabolic**: Gout.
- **Gastrointestinal**: Dyspepsia, constipation, vomiting and diarrhea.
- **Local**: Injection site reactions: Burning and itching
- **Neuromuscular & skeletal**: Weakness and myalgia.
- **Respiratory**: Rhinitis, pharyngitis, dyspnea, bronchitis, sinus congestion.
- **Others**: Albuminuria, alkaline phosphatase increased, allergic reaction, amblyopia, amnesia, angina, anorexia, arrhythmia, AV block (second or third degree), bruising, bundle branch block, congestive heart failure, crystalluria, depression, dreams abnormal, dry mouth, dysgeusia, electrocardiogram abnormalities, epistaxis, gait abnormality, gynecomastia, hallucination, hyperglycemia, hyperuricemia, impotence, insomnia, muscle cramps, nausea, paresthesia, petechiae, photosensitivity, polyuria, pruritus, tachycardia, tinnitus, tremor, ventricular extrasystoles and weight gain.

**Monitoring Parameters**

Liver function tests, blood pressure and electrocardiogram

**Potential future indications**

Recent research has shown that DLT is able to reduce cocaine cravings in drug-addicted rats. This is believed to be due to the effects of calcium blockers on dopaminergic and glutamatergic signalling in the
brain [80]. DLT also enhances the analgesic effect of morphine in animal tests, without increasing respiratory depression [81], and reduces the development of tolerance [82]. DLT is also being used in the treatment of anal fissures. It can be taken orally or applied topically with equal effectiveness. When applied topically, it is made into a cream form using either vaseline or phlogel. Phlogel absorbs the DLT into the problem area better than the vaseline base. It has good short term success rates [83, 84]. Like all non-surgical treatments of anal fissure it does not address the long term problem of increased basal anal tone and does not decrease the subsequent recurrence rate that can vary between 40 to 60%.

**Table 4.1 Dosage forms available**

<table>
<thead>
<tr>
<th>Dosage form</th>
<th>Brand names</th>
<th>Dose levels available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablets</td>
<td>ANGIZEM, CARDEM, CHANNEL, DICARD, DILTIME, DILCAL, DILCARDIA, DILCONTIN, DILCHEM, DILGARD, DILGINA, DILI, DILTI, DILDISYN, DILZEM, DTM, IONOZEM, ISKI, MASDIL, Q-DIL</td>
<td>30mg, 60 mg, 90mg</td>
</tr>
<tr>
<td>Controlled release or Extended release capsules</td>
<td>CORIEM-XL, DILZEM-CD, KAIZEM-CD, ONZEM-SR</td>
<td>90mg, 120mg, 180mg, 240mg</td>
</tr>
<tr>
<td>Gel</td>
<td>DILTIACT</td>
<td>2%</td>
</tr>
<tr>
<td>I V injection / infusion</td>
<td>DILZEM</td>
<td>5mg</td>
</tr>
</tbody>
</table>
4.2 HYPROMELLOSE (HPMC K4M, K15M) [85]

Nonproprietary Names

- BP : Hypromellose
- JP : Hydroxypropylmethylcellulose
- PhEur : Hypromellosum
- USP : Hypromellose

Synonyms

Benecel MHPC; E464; Hydroxypropyl methylcellulose; HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; Tylopur.

Chemical Name and CAS Registry Number

Cellulose hydroxypropyl methyl ether [9004-65-3]

Empirical Formula and Molecular Weight

The PhEur 2005 describes hypromellose as a partly $O$-methylated and $O$-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPas, of a 2% w/w aqueous solution at 20°C. Hypromellose defined in the USP 28 specifies the substitution type by appending a four-digit number to the nonproprietary name: e.g., hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH3). The second two digits refer to the approximate percentage content of the hydroxypropoxy group (OCH2CH(OH)CH3), calculated on a dried basis.
Structural Formula

where R is H, CH3, or CH3CH(OH)CH2

Functional Category

Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended-release tablet formulations. Concentrations between 2% and 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 drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents.
Hypromellose is also used as a suspending and thickening agent in topical formulations.

Compared with methylcellulose, hypromellose produces aqueous solutions of greater clarity, with fewer undispersed fibers present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions.

Hypromellose is also 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, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

**Description**

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.

**Typical Properties**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acidity/alkalinity</td>
<td>pH = 5.5–8.0 for a 1% w/w aqueous solution.</td>
</tr>
<tr>
<td>Ash</td>
<td>1.5–3.0%, depending upon the grade and viscosity.</td>
</tr>
<tr>
<td>Autoignition temperature</td>
<td>360°C</td>
</tr>
<tr>
<td>Density (bulk)</td>
<td>0.341 g/cm³</td>
</tr>
</tbody>
</table>
Density (tapped) : 0.557 g/cm³
Density (true) : 1.326 g/cm³
Melting point : Browns at 190–200°C; chars at 225–230°C.
Glass transition point : 170–180°C.

Moisture content: Hypromellose absorbs moisture from the atmosphere; the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air.

Solubility: Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents.

Specific gravity: 1.26

Viscosity (dynamic): A wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although hypromellose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w. Dichloromethane and ethanol mixtures may also be used to prepare viscous hypromellose solutions. Solutions prepared using organic solvents tend to be more viscous; increasing concentration also produces more viscous solutions.
Table 4.2 Typical viscosity values for 2% (w/v) aqueous solutions of HPMC. Viscosities measured at 20°C.

<table>
<thead>
<tr>
<th>Methocel product</th>
<th>Nominal viscosity (mPas)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPMC K4M</td>
<td>4,000</td>
</tr>
<tr>
<td>HPMC K15M</td>
<td>15,000</td>
</tr>
</tbody>
</table>

Stability and Storage Conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling, respectively. The gel point is 50–90°C, depending upon the grade and concentration of material. Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

Incompatibilities

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

Safety

Hypromellose is widely used as an excipient in oral and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products.

Hypromellose is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may have a laxative effect.14
The WHO has not specified an acceptable daily intake for hypromellose since the levels consumed were not considered to represent a hazard to health.15

LD50 (mouse, IP) : 5 g/kg

LD50 (rat, IP) : 5.2 g/kg

**Regulatory Status**

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (ophthalmic preparations; oral capsules, suspensions, syrups, and tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

### 4.3 CARBOXYMETHYLCELLULOSE SODIUM [86]

**Nonproprietary Names**

- **BP** : Carmellose sodium
- **JP** : Carmellose sodium
- **PhEur** : Carmellosum natricum
- **USP** : Carboxymethylcellulose sodium

**Synonyms**

Akucell; Aquasorb; Blanose; cellulose gum; CMC sodium; E466; Finnfix; Nymcel; SCMC; sodium carboxymethylcellulose; sodium cellulose glycolate; sodium CMC; Tylose CB.
Chemical Name and CAS Registry Number

Cellulose, carboxymethyl ether, sodium salt [9004-32-4]

Empirical Formula and Molecular Weight

The USP 28 describes carboxymethylcellulose sodium as the sodium salt of a polycarboxymethyl ether of cellulose. Typical molecular weight is 90 000–700 000.

Functional Category

Coating agent; stabilizing agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity-increasing agent; water-absorbing agent.

Structural Formula

Structure shown with a degree of substitution of 1.0.

Applications in Pharmaceutical Formulation or Technology

Carboxymethylcellulose sodium is widely used in oral and topical pharmaceutical formulations, primarily for its viscosity-increasing properties. Viscous aqueous solutions are used to suspend powders intended for either
topical application or oral and parenteral administration. Carboxymethylcellulose sodium may also be used as a tablet binder and disintegrant, and to stabilize emulsions. Higher concentrations, usually 3–6%, of the medium-viscosity grade are used to produce gels that can be used as the base for applications and pastes; glycols are often included in such gels to prevent them drying out. Carboxymethylcellulose sodium is additionally one of the main ingredients of self-adhesive ostomy, wound care, and dermatological patches, where it is used as a muco-adhesive and to absorb wound exudate or transepidermal water and sweat.

This muco-adhesive property is used in products designed to prevent post-surgical tissue adhesions; and to localize and modify the release kinetics of active ingredients applied to mucous membranes; and for bone repair. Encapsulation with carboxymethylcellulose sodium can affect drug protection and delivery. There have also been reports of its use as a cytoprotective agent. Carboxymethylcellulose sodium is also used in cosmetics, toiletries, surgical prosthetics, and incontinence, personal hygiene, and food products.

Table 4.3 Uses of carboxymethylcellulose sodium.

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emulsifying agent</td>
<td>0.25–1.0</td>
</tr>
<tr>
<td>Gel-forming agent</td>
<td>3.0–6.0</td>
</tr>
<tr>
<td>Injections</td>
<td>0.05–0.75</td>
</tr>
<tr>
<td>Oral solutions</td>
<td>0.1–1.0</td>
</tr>
<tr>
<td>Tablet binder</td>
<td>1.0–6.0</td>
</tr>
</tbody>
</table>
Description

Carboxymethylcellulose sodium occurs as a white to almost white, odorless, granular powder.

Physical Properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density (bulk)</td>
<td>0.52 g/cm³</td>
</tr>
<tr>
<td>Density (tapped)</td>
<td>0.78 g/cm³</td>
</tr>
<tr>
<td>Dissociation constant</td>
<td>pKa = 4.30</td>
</tr>
<tr>
<td>Melting point</td>
<td>Browns at approximately 227°C, and chars at approximately 252°C.</td>
</tr>
</tbody>
</table>

Moisture content: Typically contains less than 10% water. However, carboxymethylcellulose sodium is hygroscopic and absorbs significant amounts of water at temperatures up to 37°C at relative humidities of about 80%.

Solubility: Practically insoluble in acetone, ethanol (95%), ether, and toluene. Easily dispersed in water at all temperatures, forming clear, colloidal solutions. The aqueous solubility varies with the degree of substitution.

Viscosity: 1500 – 2500 mPas for SCMC (Medium). The viscosity of sodium carboxymethylcellulose solutions is fairly stable over a pH range of 4–10. The optimum pH range is neutral.

Stability and Storage Conditions

Carboxymethylcellulose sodium is a stable, though hygroscopic material. Under high humidity conditions, carboxymethylcellulose sodium can absorb a large quantity (>50%) of water. In tablets, this has been associated
with a decrease in tablet hardness and an increase in disintegration time. The bulk material should be stored in a well-closed container in a cool, dry place.

**Incompatibilities**

Carboxymethylcellulose sodium is incompatible with strongly acidic solutions and with the soluble salts of iron and some other metals, such as aluminum, mercury, and zinc. Precipitation may occur at pH <2, and also when it is mixed with ethanol (95%).

Carboxymethylcellulose sodium forms complex coacervates with gelatin and pectin. It also forms a complex with collagen and is capable of precipitating certain positively charged proteins.

**Safety**

Carboxymethylcellulose sodium is used in oral, topical, and some parenteral formulations. It is also widely used in cosmetics, toiletries, and food products, and is generally regarded as a nontoxic and nonirritant material. However, oral consumption of large amounts of carboxymethylcellulose sodium can have a laxative effect; therapeutically, 4–10 g in daily divided doses of the medium- and high-viscosity grades of carboxymethylcellulose sodium have been used as bulk laxatives.

Hypersensitivity and anaphylactic reactions have occurred in cattle and horses, which have been attributed to carboxymethylcellulose sodium in parenteral formulations such as vaccines and penicillins.

LD50 (guinea pig, oral) : 16 g/kg

LD50 (rat, oral) : 27 g/kg
Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (dental preparations; inhalations; intra-articular, intrabursal, intradermal, intrallesional, IM, intrasynovial and SC injections; oral capsules, drops, solutions, suspensions, syrups and tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

4.4 CELLULOSE, MICROCRYSTALLINE (Avicel PH-101) [87]

Nonproprietary Names

- BP : Microcrystalline cellulose
- JP : Microcrystalline cellulose
- PhEur : Cellulosum microcristallinum
- USPNF : Microcrystalline cellulose

Synonyms

Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; Pharmacel; Tabulose; Vivapur.

Chemical Name and CAS Registry Number : Cellulose [9004-34-6]

Empirical Formula and Molecular Weight : \((\text{C}_6\text{H}_{10}\text{O}_5)n = 36,000\), where \(n = 220\).

Functional Category : Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.
Applications in Pharmaceutical Formulation or Technology

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct compression processes. In addition to its use as a binder/diluent, Microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting. Microcrystalline cellulose is also used in cosmetics and food products.

Table 4.4 Uses of Microcrystalline cellulose.

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Adsorbent</td>
<td>20–90</td>
</tr>
<tr>
<td>2.</td>
<td>Antiadherent</td>
<td>5–20</td>
</tr>
<tr>
<td>3.</td>
<td>Capsule binder/diluents</td>
<td>20–90</td>
</tr>
<tr>
<td>4.</td>
<td>Tablet disintegrant</td>
<td>5–15</td>
</tr>
<tr>
<td>5.</td>
<td>Tablet binder/diluents</td>
<td>20–90</td>
</tr>
</tbody>
</table>

Description

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder.
composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

**Typical Properties**

- **Density (bulk)**: 0.32 g/cm for Avicel PH-101
- **Density (tapped)**: 0.45 g/cm for Avicel PH-101;
- **Density (true)**: 1.512–1.668 g/cm
- **Melting point**: Chars at 260–270°C.

**Moisture content**: Typically less than 5% w/w. However, different grades may contain varying amounts of water. Microcrystalline cellulose is hygroscopic.

**Particle size distribution**: Typical mean particle size is 20–200 µm. Different grades may have a different nominal mean particle size.

**Solubility**: Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

**Stability and Storage Conditions**

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

**Incompatibilities**

Microcrystalline cellulose is incompatible with strong oxidizing agents.
Safety

Microcrystalline cellulose is widely used in oral pharmaceutical formulations and food products and is generally regarded as a relatively nontoxic and nonirritant material. Microcrystalline cellulose is not absorbed systemically following oral administration and thus has little toxic potential. Consumption of large quantities of cellulose may have a laxative effect, although this is unlikely to be a problem when cellulose is used as an excipient in pharmaceutical formulations. Deliberate abuse of formulations containing cellulose, either by inhalation or by injection, has resulted in the formation of cellulose granulomas.

Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (inhalations; oral capsules, powders, suspensions, syrups, and tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

4.5 CROSPOVIDONE (Kollidon CL) [88]

Nonproprietary Names

- BP : Crospovidone
- PhEur : Crospovidonum
- USPNF : Crospovidone

Synonyms

Crosslinked povidone; E1202; Kollidon CL; Kollidon CL-M; Polyplasdone XL; PolyplasdoneXL-10; polyvinylpolypyrrolidone; PVPP; 1-vinyl-2-pyrrolidinone homopolymer.
Chemical Name and CAS Registry Number: 1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

Empirical Formula and Molecular Weight: \((\text{C}_6\text{H}_9\text{NO})^n \geq 1000\)

The USPNF 23 describes Crospovidone as a water-insoluble synthetic crosslinked homopolymer of \(N\)-vinyl-2-pyrrolidinone. An exact determination of the molecular weight has not been established because of the insolubility of the material.

Structural Formula

![Structural Formula](image)

Functional Category

Tablet disintegrant

Applications in Pharmaceutical Formulation or Technology

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct-compression or wet- and dry- granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of Crospovidone strongly influences disintegration of analgesic tablets. Larger particles provide a faster disintegration than smaller particles. Crospovidone can also be used as a
solubility enhancer. With the technique of co-evaporation, Crospovidone can be used to enhance the solubility of poorly soluble drugs. The drug is adsorbed on to Crospovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

**Description**

Crospovidone is a white to creamy-white, finely divided, free-flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

**Typical Properties**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acidity/alkalinity</td>
<td>pH = 5.0–8.0 (1% w/v aqueous slurry)</td>
</tr>
<tr>
<td>Density</td>
<td>1.22 g/cm³</td>
</tr>
<tr>
<td>Density (bulk)</td>
<td>0.35 g/cm³</td>
</tr>
<tr>
<td>Density (tapped)</td>
<td>0.45 g/cm³</td>
</tr>
<tr>
<td>Moisture content</td>
<td>Maximum moisture sorption is approximately 60%</td>
</tr>
<tr>
<td>Particle size distribution</td>
<td>50% greater than 50 µm and maximum of 3% greater than 250 µm</td>
</tr>
<tr>
<td>Solubility</td>
<td>Practically insoluble in water and most common organic solvents.</td>
</tr>
<tr>
<td>Specific surface area</td>
<td>1.0 m²/g</td>
</tr>
<tr>
<td>Storage Conditions</td>
<td>Crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.</td>
</tr>
</tbody>
</table>
Incompatibilities

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, Crospovidone may form molecular adducts with some materials.

Safety

Crospovidone is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. Short-term animal toxicity studies have shown no adverse effects associated with Crospovidone. However, owing to the lack of available data, an acceptable daily intake in humans has not been specified by the WHO.

LD50 (mouse, IP): 12 g/kg.

Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

Regulatory Status

Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (IM injections, oral capsules and tablets; topical, transdermal, and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.
4.6 SODIUM BICARBONATE [89]

Nonproprietary Names

- BP : Sodium bicarbonate
- JP : Sodium bicarbonate
- PhEur : Natrii hydrogenocarbonas
- USP : Sodium bicarbonate

Synonyms

Baking soda; E500; Effer-Soda; monosodium carbonate; Sal de Vichy; sodium acid carbonate; sodium hydrogen carbonate.

Chemical Name and CAS Registry Number : Carbonic acid monosodium salt [144-55-8]

Empirical Formula and Molecular Weight : NaHCO₃ 84.01

Functional Category : Alkalizing agent; therapeutic agent.

Applications in Pharmaceutical Formulation or Technology

Sodium bicarbonate is generally used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets and granules. It is also widely used to produce or maintain an alkaline pH in a preparation.

Tablets may also be prepared with Sodium bicarbonate alone since the acid of gastric fluid is sufficient to cause effervescence and disintegration. Sodium bicarbonate is also used in tablet formulations to buffer drug molecules that are weak acids, thereby increasing the rate of tablet dissolution and reducing gastric irritation. The effects of tablet binders, such
as polyethylene glycols, Microcrystalline cellulose, silicified Microcrystalline cellulose, pregelatinized starch, and povidone, on the physical and mechanical properties of Sodium bicarbonate tablets have also been investigated. Additionally, Sodium bicarbonate is used in solutions as a buffering agent for Erythromycin, Lidocaine, local anesthetic solutions, and total parenteral nutrition solutions. In some parenteral formulations, e.g., in Niacin parenteral formulation, Sodium bicarbonate is used to produce a sodium salt of the active ingredient that has enhanced solubility. Sodium bicarbonate has also been used as a freeze-drying stabilizer and in toothpastes. Recently, Sodium bicarbonate has been used as a gas-forming agent in alginate raft system and in floating, controlled-release oral dosage forms of Furosemide and Cisapride. Tablet formulations containing Sodium bicarbonate have been shown to increase the absorption of Paracetamol, and improve the stability of Levothyroxine.

Sodium bicarbonate is used in food products as an alkali or as a leavening agent, e.g. baking soda.

Table 4.5 Uses of sodium bicarbonate

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buffer in tablets</td>
<td>10–40</td>
</tr>
<tr>
<td>Effervescent tablets</td>
<td>25–50</td>
</tr>
<tr>
<td>Isotonic injection/infusion</td>
<td>1.39</td>
</tr>
</tbody>
</table>

Description

Sodium bicarbonate occurs as an odorless, white, crystalline powder with a saline, slightly alkaline taste. The crystal structure is monoclinic prisms. Grades with different particle sizes, from a fine powder to free-flowing uniform granules, are commercially available.
Typical Properties

Acidity/alkalinity : pH = 8.3 for a freshly prepared 0.1 M aqueous solution at 25°C; alkalinity increases on standing, agitation, or heating.

Density (bulk) : 0.869 g/cm³

Density (tapped) : 1.369 g/cm³

Density(true) : 2.173 g/cm³

Freezing point depression: 0.381°C (1% w/v solution)

Melting point : 270°C (with decomposition)

Moisture content : below 80% relative humidity, the moisture content is less than 1% w/w. Above 85% relative humidity, sodium bicarbonate rapidly absorbs excessive amounts of water and may start to decompose with loss of carbon dioxide.

Osmolarity : a 1.39% w/v aqueous solution is isoosmotic with serum.

Refractive index : n₂₀ D = 1.3344 (1% w/v aqueous solution)
Solubility:

**Table 4.6** Solubility of sodium bicarbonate.

<table>
<thead>
<tr>
<th>Solvent Solubility</th>
<th>at 20°C unless otherwise stated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol (95%)</td>
<td>Practically insoluble</td>
</tr>
<tr>
<td>Ether</td>
<td>Practically insoluble</td>
</tr>
<tr>
<td>Water</td>
<td>1 in 11</td>
</tr>
<tr>
<td></td>
<td>1 in 4 at 100°Ca</td>
</tr>
<tr>
<td></td>
<td>1 in 10 at 25°C</td>
</tr>
<tr>
<td></td>
<td>1 in 12 at 18°C</td>
</tr>
</tbody>
</table>

**Stability and Storage Conditions**

When heated to about 50°C, Sodium bicarbonate begins to dissociate into carbon dioxide, sodium carbonate, and water; on heating to 250–300°C, for a short time, Sodium bicarbonate is completely converted into anhydrous sodium carbonate. The effects of relative humidity and temperature on the moisture sorption and stability of Sodium bicarbonate powder have been investigated. Sodium bicarbonate powder is stable below 76% relative humidity at 25°C and below 48% relative humidity at 40°C. At 54% relative humidity, the degree of pyrolytic decarboxylation of Sodium bicarbonate should not exceed 4.5% in order to avoid detrimental effects on stability.

At ambient temperatures, aqueous solutions slowly decompose with partial conversion into the carbonate; the decomposition is accelerated by agitation or heat. Aqueous solutions of Sodium bicarbonate may be sterilized by filtration or autoclaving. To minimize decomposition of Sodium bicarbonate by decarboxylation on autoclaving, carbon dioxide is passed through the solution in its final container, which is then hermetically sealed.
and autoclaved. The sealed container should not be opened for at least 2 hours after it has returned to ambient temperature, to allow time for the complete reformation of the bicarbonate from the carbonate produced during the heating process.

Sodium bicarbonate is stable in dry air but slowly decomposes in moist air and should therefore be stored in a well-closed container in a cool, dry place.

**Incompatibilities**

Sodium bicarbonate reacts with acids, acidic salts, and many alkaloidal salts, with the evolution of carbon dioxide. Sodium bicarbonate can also intensify the darkening of salicylates. In powder mixtures, atmospheric moisture or water of crystallization from another ingredient is sufficient for Sodium bicarbonate to react with compounds such as boric acid or alum. In liquid mixtures containing bismuth subnitrate, Sodium bicarbonate reacts with the acid formed by hydrolysis of the bismuth salt. In solution, Sodium bicarbonate has been reported to be incompatible with many drug substances such as Ciprofloxacin, Amiodarone, Nicardipine, and Levofloxacin.

**Safety**

Sodium bicarbonate is used in a number of pharmaceutical formulations including injections and ophthalmic, otic, topical, and oral preparations. Sodium bicarbonate is metabolized to the sodium cation, which is eliminated from the body by renal excretion, and the bicarbonate anion, which becomes part of the body’s bicarbonate store. Any carbon dioxide formed is eliminated via the lungs. Administration of excessive amounts of Sodium bicarbonate may thus disturb the body’s electrolyte balance, leading to metabolic alkalosis.
When used as an excipient, Sodium bicarbonate is generally regarded as an essentially nontoxic and nonirritant material.

LD50 (mouse, oral) : 3.36 g/kg
LD50 (rat, oral) : 4.22 g/kg

**Handling Precautions**

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

**Regulatory Status**

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (injections; ophthalmic preparations; oral capsules, solutions, and tablets). Included in parenteral (intravenous infusions and injections) and nonparenteral medicines (ear drops, eye lotions, oral capsules, chewable tablets, effervescent powders, effervescent tablets, granules, tablets, suppositories and suspensions) licensed in the UK.