Chapter 1

Introduction:
Chapter 1A: Introduction to eutectic mixture

1A Introduction to eutectic mixture

A eutectic mixture is a homogenous blend of two or more solid compounds at a composition that has the lowest melting point. Usually, the equilibrium phase diagram (Fig. 1A.a) is used to identify eutectic point of components A and B. \(^1\)

![Equilibrium phase diagram for a binary system](image)

**Figure 1A.a** Equilibrium phase diagram for a binary system

As shown in Fig.1A.a, the eutectic point is the point at which the liquid phase \(L\) borders directly on the solid phase \(\alpha + \beta\) (a homogeneous mixture composed of both A and B), representing the minimum melting temperature of any possible alloy of A and B. Many substances such as chloral hydrate and beta naphthol, lidocaine and prilocaine, ibuprofen and menthol form eutectic mixtures.
Chapter 1A: Introduction to eutectic mixture

Dinsmore et al. studied the efficacy and safety of a metered-dose aerosol spray containing a eutectic mixture of lidocaine and prilocaine for treatment of premature ejaculation.\(^2\) Koh et al. reported parental application of eutectic mixture of local anaesthetics for reducing children’s pain and distress during intravenous insertion.\(^3\)

Camphor and menthol forms a hydrophobic eutectic mixture.\(^4\) The use of camphor and menthol is well documented in the literature. Camphor is readily absorbed through the skin and produces a feeling of cooling similar to that of menthol and acts as mild local anesthetic and antimicrobial substance.\(^5\) Camphor water was official in I.P. 1955.\(^6\) Menthol is widely used in pharmaceuticals, confectionery, and toiletry products as a flavoring agent or odor enhancer.\(^5\) Both camphor and menthol are well known dermal penetration enhancers.\(^7\)\(^-\)\(^13\) They cause leaching of the lipids present in the skin resulting into subsequent pore formation.\(^14\) A PCT Int. Appl. WO 0397027 narrated the use of O/W emulsion of L-menthol for controlling the peristalsis.\(^15\) JP 2003335662 demonstrated the use of L-menthol and dl-camphor for the preparation of granules of caffiene.\(^16\) PCT Int. Appl. WO 2003082247 demonstrated use of sublimable materials.\(^17\) JP 2002154952 shows that presence of camphor can prevent crystallization of menthol in anti-itching paste.\(^18\) A patent number WO/2005/018530 describes novel pharmaceutical foam prepared using eutectic mixture of drug.\(^19\)
Eutectic mixture of ibuprofen and menthol is also well explored. Yong et al. prepared and evaluated ibuprofen loaded liquid suppositories using eutectic mixture of ibuprofen and menthol. Improvement of in vitro dissolution of ibuprofen from poloxamer gel prepared using eutectic mixture with menthol is also reported. Yong et al. studied the influence of poloxamer and menthol in improvement of bioavailability of ibuprofen in the rectum.

Negative effect of eutectic mixture in formulation design is also demonstrated. Ibuprofen forms eutectic mixture with stearic acid, magnesium stearate and polyethylene glycol (PEG 6000). Therefore, while preparing tablets such combinations should be avoided.

**1A.1 References:**


Chapter 1A: Introduction to eutectic mixture


Chapter 1A: Introduction to eutectic mixture


Fungi exist in yeasts and moulds. Fungi can cause superficial as well as systemic infection. Generally systemic infection occurs because of direct inhalation into the lung or by invasion of a wound site. Fungal infection is normally seen in persons with suppressed immune system.

1B.1 Superficial fungal Infections:

Superficial fungal infections occur in the outermost layers of the skin, nails, hair and mucous membranes. Dermatophytes such as Trichophyton spp., Microsporum spp. and Epidermophyton spp. are responsible for most superficial fungal infections, although yeasts and some non-dermatophyte moulds can also be causative agents. Specific dermatophyte infections are named according to their location on the body (Table 1B.a).
## Table 1B.a Clinical classification of some frequently observed fungal infections

<table>
<thead>
<tr>
<th>Infection type</th>
<th>Disease</th>
<th>Clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial (outermost layers of skin, nails, hair and mucous membranes)</td>
<td>Tinea pedis (feet)</td>
<td>Scaling and itching between the toes which may spread to the sole</td>
</tr>
<tr>
<td></td>
<td>Tinea capitis (scalp)</td>
<td>Scalp hair loss and scaling</td>
</tr>
<tr>
<td></td>
<td>Tinea unguium or onychomycosis (nails)</td>
<td>Thickened, discoloured and broken nail with separation of the nail plate from its bed</td>
</tr>
<tr>
<td></td>
<td>Tinea versicolor (chest, back, neck and arms)</td>
<td>Slightly scaly lesions on white skin, hypo- or hyper-pigmentation on black or white skin</td>
</tr>
<tr>
<td></td>
<td>Oral and genital candidiasis</td>
<td>White plaques, itching, redness, thick white discharge and irritation when urinating</td>
</tr>
<tr>
<td>Subcutaneous (skin and subcutaneous tissues)</td>
<td>Sporotrichosis</td>
<td>Localised cutaneous or subcutaneous lesion which may spread via the lymphatic system and form further lesions</td>
</tr>
<tr>
<td></td>
<td>Chromoblastomycosis</td>
<td>Raised, crusted lesions of the skin</td>
</tr>
<tr>
<td></td>
<td>Chronic mucocutaneous candidiasis</td>
<td>White fissured lesions, hyperkeratotic, lesions, autosomal recessive trait associated with endocrine disorders</td>
</tr>
<tr>
<td>Systemic (deep tissue invasion of one or more internal organs)</td>
<td>Opportunistic: Invasive candidiasis/candidaemia</td>
<td>Prolonged antibiotic-resistant fever often associated with weight loss, abdominal pain and hepatic and/or spleen enlargement</td>
</tr>
<tr>
<td></td>
<td>Invasive aspergillosis</td>
<td>Prolonged antibiotic-resistant fever</td>
</tr>
<tr>
<td></td>
<td>Cryptococcosis</td>
<td>Meningitis</td>
</tr>
</tbody>
</table>
1B.2 Subcutaneous fungal infections:

Although subcutaneous mycoses can disseminate, they are usually limited to the dermis and subcutaneous tissues. Disease is caused by a variety of pathogens, which are often restricted to tropical and subtropical regions of the world. Sporotrichosis, for example, is caused by the dimorphic fungus (Sporothrix schenckii) and is the most prevalent subcutaneous infection in parts of Latin America. Infection manifests as a lesion, which may spread to other subcutaneous sites via the lymphatic channels. Lymphocutaneous sporotrichosis is a non-life-threatening disease and normally responds well to treatment with itraconazole. Chromoblastomycosis is a chronic cutaneous or subcutaneous fungal infection caused by Fonsecaea pedrosoi, Cladosporium carrionii, F. compacta, Phialophora verrucosa and Rhinocladiella aquaspersa (Figure 1B.a). Diagnosis is made by the histological examination of scrapings or biopsy material, where the presence of sclerotic bodies confirms the disease. There is no standard treatment for this disease, but combinations of therapies have proved to be effective. Chronic mucocutaneous candidiasis is a rare syndrome consisting of chronic infection of mucous membranes (usually by C. albicans), which may extend to the skin and nails. The condition is associated with impaired cell-mediated responses to Candida, although the underlying defect remains poorly understood.
Figure 1B.a Clinical presentations of some frequently observed fungal infections:
(a) Tinea capitis, (b) onychomycosis, (c) chronic oral candidiasis, (d) chromoblatomycosis, (e) cutaneous lesions in patient with disseminated candidiasis, (f) histopathological appearance of an aspergilloma

1B.3 Systemic fungal infections:

Opportunistic systemic fungal infections occur primarily when some aspect of the normal host defence is compromised. Such infections are life threatening and are associated with high rates of death. Because of the growing population of immuno-compromised individuals, the frequency of systemic fungal infections is increasing significantly. Diagnosis of systemic fungal infections is problematic and many infections are confirmed only at autopsy. Direct microscopic examination of clinical samples may provide a tentative diagnosis, but this is often difficult to confirm by culture because of the presence of atypical fungal elements or sparse fungal populations. Other diagnostic tests widely used are
Chapter 1B: Introduction to fungal infection

high-resolution computed tomography (CT) scanning, polymerase chain reaction (PCR) and enzyme-linked immunosorbent assay (ELISA).

1B.4 Treatment:

Various drugs are used to treat fungal infection (Table 1B.b).

Table 1B.b Various drugs used for treatment of fungal infection

<table>
<thead>
<tr>
<th>Drug</th>
<th>Common use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>Wide variety of fungal infections</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>Aspergillus, candidal and possibly other infections</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Candidal and other fungal infections including cryptococcal</td>
</tr>
<tr>
<td>Flucytosine</td>
<td>Candidal and cryptococcal infections</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Candidal and other fungal infections</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Aspergillus, candidal and many other fungal infections</td>
</tr>
<tr>
<td>Vorniconazole</td>
<td>Aspergillus and candidal infections</td>
</tr>
</tbody>
</table>

1B.5 Reference:

1C. Introduction to hypertension

1C.1 Definition and classification:

Hypertension is a medical condition in which the blood pressure is chronically elevated. It is classified as essential and secondary hypertension. Individual is said to be suffering from hypertension if his/her systolic blood pressure is consistently 140 mm Hg or greater.

1C.2 Essential hypertension:

Essential hypertension is defined as hypertension with no identifiable cause. However, several risk factors have been identified associated with it such as obesity, salt sensitivity, renin homeostasis, genetics and age.

1C.2.1 Obesity:

The risk of hypertension in the obese individual as compared to those of normal weight is higher. The probable reason for it could be activation of the sympathetic nervous system and renin-angiotensin-aldosterone system.

1C.2.2 Sodium sensitivity:

Approximately one third of the essential hypertensive population is responsive to sodium intake. Increasing the salt intake causes cells to release water, thereby increasing the pressure within the blood vessel walls.
1C.2.3 Renin homeostasis:
As renin level increases, there is increase in angiotensin II leading to vasoconstriction and subsequent hypertension.8

1C.2.4 Genetics:
At present the genetic influence upon hypertension is not fully understood; however, it is believed that hypertension can be caused by mutations in single genes, inherited on a mendelian basis.9

1C.2.5 Age:
Hypertension can also be age related. The possible reason for it could be reduction in vascular compliance due to the stiffening of the arteries with increase in age.10

1C.2.6 Vitamin D:
Vitamin D inhibits renin secretion and hence a deficiency of vitamin D leads to an increase in blood pressure.11

1C.3 Secondary hypertension:
Secondary hypertension is defined as hypertension with identifiable cause such as sleep apnea, use of liquorice, renal disorder, cushing syndrome, use of drugs, rebound hypertension and pregnancy.

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Chapter 1C: Introduction to hypertension

1C.3.1 Sleep apnea:

Sleep apnea is a common under recognized cause of hypertension.\textsuperscript{12} Sleep apnea is generally associated with nocturnal nasal continuous positive airway pressure, mandibular advancement splint, tonsilectomy, adenoidectomy, septoplasty and weight loss.

1C.3.2 Liquorice:

Consumption of liquorice may lead to a surge in blood pressure.\textsuperscript{13} People with hypertension or history of cardio-vascular disease should avoid consumption of liquorice products.

1C.3.3 Renal disorder:

Hypertension can be because of various renal disorders such as chronic glomerulonephritis.\textsuperscript{14} Treatment of such disorders can eliminate hypertension

1C.3.4 Cushing's syndrome:

Cushing's syndrome is a condition where both adrenal glands can overproduce the hormone cortisol. Increase in amount of cortisol leads to hypertension and hence it is important to treat cushing syndrome in such patients to eliminate hypertension.\textsuperscript{15}
1C.3.5 Drugs:

Certain medications, especially non steroidal anti-inflammatory drugs and steroids can cause hypertension.\(^ \text{16} \)

1C.3.6 Rebound hypertension:

Rebound hypertension is defined as high blood pressure that is associated with the sudden withdrawal of various antihypertensive medications. Rebound hypertension can be avoided by gradually reducing the dose. Drugs commonly associated with rebound hypertension include centrally-acting antihypertensive agents, such as clonidine and beta-blockers.

1C.3.7 Pregnancy:

Few pregnant women have high blood pressure higher than normal women. Follow up and control with medication of hypertension is necessary for such individuals.\(^ \text{17} \)

1C.4 Pathophysiology:

Secondary hypertension generally is because of inability of the kidneys to excrete sodium, an overactive renin-angiotension system leading to vasoconstriction and retention of sodium and water and finally overactive sympathetic nervous system leading to increased stress responses.\(^ \text{8} \)
1C.5 Diagnosis:

Hypertension is diagnosed by measuring blood pressure level at regular intervals. Along with measurement of blood pressure, some additional tests such as electrocardiogram, creatinine, blood glucose and cholesterol level may be carried out to find exact cause of the disease.

1C.6 Treatment:

Hypertension can be treated by eliminating the causes which may lead to the disease and taking medicaments on prescribed time. The commonly used drug includes:

i. ACE inhibitors such as creatine captopril, enalapril, fosinopril, lisinopril, quinapril and ramipril

ii. Angiotensin II receptor antagonists: e.g., telmisartan, irbesartan, losartan, valsartan and candesartan

iii. Alpha blockers such as prazosin and terazosin.

iv. Beta blockers such as atenolol, labetalol, metoprolol and propranolol.

v. Calcium channel blockers such as nifedipine, amlodipine, diltiazem and verapamil

vi. Direct renin inhibitors such as aliskiren
1C.7 References:


Chapter 1C: Introduction to hypertension


1D. Introduction to Inflammation

Inflammation is the complex biological response of vascular tissues, pathogens, damaged cells, chemical irritants, toxins, ionizing radiation and foreign bodies including splinters and dirt. It is a protective attempt by the organism to remove the injurious stimuli as well as initiate the healing process for the tissue. In the absence of inflammation, wounds and infections would never heal and progressive destruction of the tissue would compromise the survival of the organism. However, inflammation which runs unchecked can also lead to a host of diseases, such as hay fever, atherosclerosis and rheumatoid arthritis.

Inflammation can be classified as either acute or chronic. Acute inflammation is the initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leukocytes from the blood into the injured tissues. Prolonged inflammation, known as chronic inflammation, leads to a progressive shift of plasma and leukocytes in the injured tissues. Table 1D.a shows comparison of acute and chronic inflammation.
### Comparison between acute and chronic inflammation

<table>
<thead>
<tr>
<th></th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Causative agent</strong></td>
<td>Pathogens and injured tissues</td>
<td>Persistent acute inflammation due to non-degradable pathogens, persistent foreign bodies or autoimmune reactions</td>
</tr>
<tr>
<td><strong>Major cells involved</strong></td>
<td>Neutrophils and mononuclear cells (monocytes, macrophages)</td>
<td>Mononuclear cells (monocytes, macrophages, lymphocytes, plasma cells) and fibroblasts</td>
</tr>
<tr>
<td><strong>Primary mediators</strong></td>
<td>Vasoactive amines and eicosanoids</td>
<td>IFN-γ and other cytokines, growth factors, reactive oxygen species and hydrolytic enzymes</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Immediate</td>
<td>Delayed</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Few days</td>
<td>Up to many months or years</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Abscess formation</td>
<td>Tissue destruction and fibrosis</td>
</tr>
</tbody>
</table>
Inflammation is characterized by redness, increased heat, swelling, pain and loss of function (Figure 1D.a). Redness and heat are due to increased blood flow at body core temperature to the inflamed site whereas swelling is caused by accumulation of fluid. Pain is due to release of chemicals that stimulate nerve endings. Loss of function has multiple causes. These signs appear when inflammation occurs on the body's surface, whereas acute inflammation of internal organs may not result in the full set. Pain only happens where the appropriate sensory nerve endings exist in the inflamed area e.g., acute inflammation of the lung (pneumonia) does not cause pain unless the inflammation involves the parietal pleura, which does have pain-sensitive nerve endings.
1D.1 The drugs used in inflammation:

Non steroidal anti-inflammatory drugs like aspirin, ibuprofen, diclofenac sodium, diclofenac potassium, paracetamol, naproxen, ketoprofen, phenylbutazone, piroxicam, acetaminophen, fenclofenac, indomethacin, sulindac, diflunisal, etc are widely prescribed for treatment of inflammation. When pain is severe narcotic analgesic such as morphine, codeine, dihydrocodeine, naloxone, etc. are given to patient under strict medical supervision.

1D.2 References:


1E. Introduction to colon cancer

Colorectal cancer, also called colon cancer or large bowel cancer includes cancerous growths in the colon, rectum and appendix. Many colorectal cancers are thought to arise from adenomatous polyps in the colon.¹ These mushroom-like growths are usually benign, but some may develop into cancer over time (Figure 1E.a). The majority of the time, the diagnosis of localized colon cancer is through colonoscopy. Therapy is usually through surgery, which in many cases is followed by chemotherapy.

Figure 1E.a Gross appearance of a colectomy specimen containing one invasive colorectal carcinoma

1E.1 Symptoms:

The first symptoms of colon cancer are usually vague, like bleeding, weight loss, and fatigue (tiredness).² Local (bowel) symptoms are rare until the
Chapter 1E: Introduction to colon cancer

Tumor has grown to a large size. Symptoms and signs are divided into local, constitutional and metastatic.

1E.1.1 Local symptoms:

Local symptoms include change in bowel habits like frequency of stool, appearance of stool from bloody red to black with/without mucus and bowel obstruction.

1E.1.2 Constitutional (systemic) symptoms:

Constitutional symptoms include unexplained weight loss, anemia, dizziness, fatigue and palpitations.

1E.1.3 Metastatic symptoms:

Metastatic symptoms include jaundice, pain in abdomen, liver enlargement and blood clot.

1E.2 Causative factor:

Causative factor leading to colon cancer includes: polyps, heredity, smoking, diet, physical inactivity, inflammatory bowel disease, environmental factors and exogenous hormones.
Chapter 1E: Introduction to colon cancer

1E.3 Diagnosis:

There are several different tests available for diagnosis of colon cancer which chiefly includes digital rectal examination, fecal occult blood test, colonoscopy, sigmoidscopy and double contrast barium enema. Figure 1E.b shows endoscopic image of colon cancer identified using colonoscopy in sigmoidal region.

Figure 1E.b Endoscopic image of colon cancer identified in sigmoid colon on screening colonoscopy in the setting of Crohn's disease.

1E.4 Treatment:

The treatment depends on the staging of the cancer. When colorectal cancer is caught at early stages (with little spread) it can be curable. However when it is detected at later stages it is less likely to be curable. Surgery remains the primary treatment while chemotherapy and/or radiotherapy may be recommended depending on the individual patient's staging and other medical
Chapter 1E: Introduction to colon cancer

factors. The first line choice of drugs includes 5-fluorouracil, leucovorin, oxaliplatin, bevacizumab and irinotecan.\(^5\)

1E.5 References:


1F. Introduction to fluconazole

1F.1 Synonyms:

Synonyms of fluconazole are fluconazol, fluconazolum, flukonatsoli and flukonazol

1F.2 Chemical name:

The chemical name of fluconazole is 2-{2,4-Difluorophenyl}-1,3-bis{1H-1,2,4-triazol-1-yl}propan-2-ol. The chemical structure of fluconazole is represented in Figure 1F.a.

![Chemical structure of fluconazole](image)

Figure 1F.a Chemical structure of fluconazole

1F.3 Molecular formula:

The molecular formula of fluconazole is 306.3.

1F.4 Description:

Fluconazole is a white or almost white, crystalline powder. It is slightly soluble in water, soluble in alcohol, sparingly soluble in isopropyl alcohol, freely soluble in methyl alcohol and very slightly soluble in toluene.
Chapter 1F: Introduction to fluconazole

1F.5 Pharmacokinetics:

Fluconazole is well absorbed after oral doses with bioavailability more than 90% followed by oral administration. Mean peak plasma concentrations of 6.72 μg/ml have been reported in healthy subjects after a 400 mg oral dose. Peak concentrations are reached within 1 to 2 h of oral administration. Plasma concentrations are proportional to the dose over a range of 50 to 400 mg. Fluconazole is widely distributed and the apparent volume of distribution is close to that of total body water. Concentrations in breast milk, joint fluid, saliva, sputum, vaginal fluids, and peritoneal fluid are similar to those achieved in plasma. Concentrations of fluconazole in the cerebrospinal fluid range from 50 to 90% of plasma concentration. Protein binding is only about 12%. About 80% of a dose is excreted in the unchanged form in the urine and about 11% as metabolites. The elimination half life of fluconazole is about 30 h and is increased in patients with renal impairment.

1F.6 Uses and Administration:

Fluconazole is a triazole antifungal used for superficial mucosal (oropharyngeal, oesophageal, or vaginal) candidiasis and for fungal skin infections. It is also given for systemic infections including systemic candidiasis, coccidioidomycosis, and cryptococcosis, and has been tried in blastomycosis, histoplasmosis and sporotrichosis. Fluconazole is given by mouth or intravenous infusion in similar doses. For intravenous infusion it is given as a solution containing 2 mg/ml at a rate of 5 to 10 ml/min. For superficial mucosal
Chapter 1F: Introduction to fluconazole

candidiasis the usual dose of fluconazole is 50 mg daily by mouth, although 100 mg daily may be given if necessary. Treatment usually continues for 7 to 14 days in oropharyngeal candidiasis (except in severely immuno-compromised patients), for 14 days in atrophic oral candidiasis associated with dentures, and for 14 to 30 days in other mucosal candidal infections including oesophagitis. Fluconazole 150 mg by mouth as a single dose may be used for vaginal candidiasis or candidal balanitis. Systemic candidiasis, cryptococcal meningitis, and other cryptococcal infections may be treated with fluconazole by mouth or by intravenous infusion; the initial dose is 400 mg followed by 200 to 400 mg daily. Duration of therapy is based on clinical and mycological response, but is usually at least 6 to 8 weeks in cryptococcal meningitis.

1F.7 Contraindication and adverse effects:

Fluconazole is contraindicated in patients with known hypersensitivity to fluconazole or other azole antifungals. Fluconazole therapy has been associated with QT interval prolongation, which may lead to serious cardiac arrhythmias. Long term fluconazole therapy may be burden to liver and may cause lethal hepatotoxicity. The other adverse drug reactions associated with fluconazole therapy include rash, headache, dizziness, nausea, vomiting, abdominal pain, diarrhea, anorexia, fatigue, constipation oliguria, hypokalaemia, paraesthesia, seizures, alopecia, Stevens-Johnson syndrome and thrombocytopenia.
1F.8 Preparations:

The common fluconazole preparations available in Indian market includes flumyc, fluzon, forcan, logican, nipcan and syscan.

1F.9 Reference:

1G. Introduction to captopril

1G.1 Synonyms:

The synonyms of captopril are captoprilum, kaptopriili, kaptopril, kaptoprilis and SQ-14225.

1G.2 Chemical name:

The chemical name of captopril is 1-[(2S)-3-Mercapto-2-methylpropionyl]-L-proline. The chemical structure of captopril is shown in Figure 1G.a.

![Chemical structure of captopril](image)

Figure 1G.a Chemical structure of captopril

1G.3 Molecular formula:

The molecular formula of captopril is 217.3.

1G.4 Description:

Captopril is a white or off-white crystalline powder with characteristic sulfide-like odour. Captopril is freely soluble in water, alcohol, chloroform and methyl alcohol.
Chapter 1G: Introduction to captopril

1G.5 Pharmacokinetics:

About 60 to 75% of a dose of captopril is absorbed from the gastrointestinal tract and peak plasma concentrations are achieved within 1 h. Absorption has been reported to be reduced in the presence of food, but this may not be clinically relevant. Captopril is about 30% bound to plasma proteins. It crosses the placenta and is found in breast milk at about 1% of maternal blood concentrations. It is largely excreted in the urine, 40 to 50% as unchanged drug, the rest as disulfide and other metabolites. The elimination half life of captopril is 2 to 3 h.

1G.6 Uses and Administration:

Captopril is a sulfhydryl-containing ACE inhibitor. It is used in the management of hypertension, in heart failure, after myocardial infarction and in diabetic nephropathy. In the treatment of hypertension the initial dose of captopril is 12.5 mg twice daily by mouth, increased gradually at intervals of 2 to 4 weeks according to the response. In the treatment of heart failure initial dose of 6.25 to 12.5 mg is given by mouth under close medical supervision. The usual maintenance dose is 25 mg two or three times daily and doses should not normally exceed 50 mg three times daily.
1G.7 Contraindication and adverse effects:

Captopril is contraindicated with non-steroidal anti-inflammatory drugs, oral antidiabetics and lithium. The adverse drug reaction (ADR) profile of captopril is similar to other ACE inhibitors, with cough being the most common ADR. However, captopril is also commonly associated with rash and taste disturbances (metallic or loss of taste), which are attributed to the unique sulfhydryl moiety. Hypotension is also a possible adverse effect, if the dose is too high. Hyperkalemia is possible, due to ACE inhibition reducing aldosterone production. Captopril can also be the cause of glomerulonephritis.

1G.8 Preparations:

The common preparations of captopril marketed in India include aceten, capace and capoten.

1G.8 Reference:

1H. Introduction to ibuprofen

1H.1 Synonyms:

The synonyms of ibuprofen are Ibuprofeeni, Ibuprofenas, ibuprofeno and ibuprofenum.

1H.2 Chemical name:

The chemical name of ibuprofen is 2-{4-Isobutylphenyl}propionic acid. The chemical structure of ibuprofen is shown in Figure 1H.a.

Figure 1H.a Chemical structure of ibuprofen

1H.3 Molecular formula:

The molecular formula of ibuprofen is 206.3.

1H.4 Description:

Ibuprofen is a white to off-white crystalline powder with characteristic odour. Ibuprofen is practically insoluble in water; very soluble in alcohol acetone, in chloroform, and in methyl alcohol; slightly soluble in ethyl acetate.
Chapter 1H: Introduction to ibuprofen

1H.5 Pharmacokinetics:

Ibuprofen is well absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1 to 2 hours after ingestion. Some proportion of ibuprofen is absorbed from skin after topical application. Ibuprofen is 90 to 99% bound to plasma proteins and has a plasma half-life of about 2 hours. It is rapidly excreted in the urine mainly as metabolites and their conjugates. About 1% is excreted in urine as unchanged form.

1H.6 Uses and Administration:

Ibuprofen is used in the management of mild to moderate pain and inflammation in conditions such as dysmenorrhoea, headache including migraine, postoperative pain, dental pain, musculoskeletal and joint disorders. Ibuprofen is also used to reduce fever. The usual dose by mouth for painful conditions in adults is 1.2 to 1.8 g daily in divided doses although maintenance doses of 600 mg to 1.2 g daily may be effective in some patients. Modified release preparations of ibuprofen are available for once- or twice daily dosing, although actual dosages vary with different preparations. Patients with rheumatoid arthritis generally require higher doses of ibuprofen than those with osteoarthritis. The recommended dose for fever reduction in adults is 200 to 400 mg every 4 to 6 hours to a maximum of 1.2 g daily. Ibuprofen is also applied topically as a cream, foam, gel, or spray solution.
Chapter 1H: Introduction to ibuprofen

1H.7 Contraindication and adverse effects:

Ibuprofen is contraindicated in individuals with Inflammatory Bowel Disease (IBD-Crohn's Disease and Ulcerative Colitis) due to its ability to cause gastric bleeding and form ulceration in the gastric lining. The common ibuprofen drug interactions are found with ACE inhibitors, diuretics, warfarin and H₂ antagonists. The common adverse effects of ibuprofen includes nausea, dyspepsia, gastrointestinal ulceration/bleeding, raised liver enzymes, diarrhea, epistaxis, headache, dizziness, unexplained rash, salt and fluid retention, hypertension, oesophageal ulceration, heart failure, hyperkalaemia, renal impairment, confusion, bronchospasm, and rash.

1H.8 Preparations:

The common preparation of ibuprofen marketed in India includes brufen, butafen, cipgesic, emflam and ibugesic.

1H.9 Reference:

11. Introduction to diclofenac

11.1 Synonyms:

The synonyms of diclofenac are diclofenaco, diclofenacum, diklofenaakki and diklofenak.

11.2 Chemical name:

The chemical name of diclofenac is [2-{2,6-Dichloroanilino}phenyl]acetic acid. The chemical structure of diclofenac is shown in Figure 11.a.

![Chemical Structure of diclofenac](image1)

Figure 11.a Chemical Structure of diclofenac

11.3 Molecular formula:

The molecular formula of diclofenac is 296.1.

11.4 Pharmacokinetics:

Diclofenac is rapidly absorbed when given as an oral solution, sugar-coated tablets, rectal suppository, or by intramuscular injection. It is absorbed more slowly when given as enteric-coated tablets, especially when this dosage form is given with food. Although diclofenac given orally is almost completely absorbed, it is subject to first-pass metabolism. Diclofenac is also absorbed percutaneously. At therapeutic concentrations it is more than 99% bound to plasma proteins. Diclofenac penetrates synovial fluid where concentrations may
Chapter II: Introduction to diclofenac

Persist even when plasma concentrations fail. The terminal plasma half-life is about 1 to 2 hours. Diclofenac is metabolised to 4'-hydroxydiclofenac, 5-hydroxydiclofenac, 3'-hydroxydiclofenac and 4',5-dihydroxydiclofenac. It is then excreted in the form of glucuronide and sulfate conjugates, mainly in the urine.

11.5 Uses and Administration:

Diclofenac is used mainly as the sodium salt for the relief of pain during rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, tendinitis, sprains, renal colic, acute gout, dysmenorrhea and migraine. The usual dose of diclofenac sodium by mouth or rectally is 75 to 150 mg daily in divided doses. Modified release preparations of diclofenac sodium are available for oral use. Doses of the potassium salt are similar to those for diclofenac sodium. Diclofenac potassium is also used in the treatment of migraine in an initial dose of 50 mg taken at the first signs of an attack; if necessary further doses of 50 mg may be taken every 4 to 6 hours to a maximum daily dose of 200 mg. Diclofenac sodium may also be given by deep intramuscular in a dose of 75 mg once daily or, if required in severe conditions, 75 mg twice daily. To prevent postoperative pain, 25 to 50 mg diclofenac sodium may be given after surgery over 15 to 60 minutes followed by 5 mg/hour to a maximum of 150 mg daily. The maximum period recommended for parenteral use is 2 days. Diclofenac diethylamine is used topically as a gel containing the equivalent of 1% of diclofenac sodium for the local symptomatic relief of pain and inflammation. A topical solution of diclofenac sodium 1.6% is also available for the treatment of osteoarthritis.
11.6 Contraindication and adverse effects:

Diclofenac is contraindicated in patients with hypersensitivity against diclofenac, history of allergic reactions (bronchospasm, shock, rhinitis, urticaria) following the use of Aspirin or another NSAID, third-trimester pregnancy, active stomach and/or duodenal ulceration or gastrointestinal bleeding, inflammatory intestinal disorders such as Crohn's disease or ulcerative colitis, severe insufficiency of the heart (NYHA III/IV), severe liver insufficiency and severe renal insufficiency. The side effects of diclofenac includes nausea, dyspepsia, gastrointestinal ulceration/bleeding, raised liver enzymes, diarrhea, epistaxis, headache, dizziness, unexplained rash, salt and fluid retention, hypertension, oesophageal ulceration, heart failure, hyperkalaemia, renal impairment, confusion, bronchospasm, and rashes.

11.7 Preparations:

The common preparations of diclofenac marketed in India includes diclomol, diclomol, diclonac, dicloran, doflex, dolocide plus, solunac, tromagesic, tromax and voveran.

11.8 Reference:

1J. Introduction to ethyl cellulose

1J.1 Nonproprietary name:

The nonproprietary names of ethyl cellulose is ethylcellulosum.

1J.2 Synonyms:

The synonyms of ethyl cellulose are ethocel and surelease.

1J.3 Empirical formula:

The empirical formula of ethyl cellulose is $C_{12}H_{23}O_5(C_{12}H_{22}O_5)_nC_{12}H_{23}O_5$.

1J.4 Structural formula:

The structural formula of ethyl cellulose is shown in Figure 1J.a.

![Structural formula of ethyl cellulose](image)

Figure 1J.a Structural formula of ethyl cellulose

1J.5 Functional category:

The ethyl cellulose finds its place as coating agent, tablet binder, tablet filler and viscosity increasing agent.

1J.6 Applications in pharmaceutical formulation:

Ethycellulose is widely used in pharmaceutical formulation (Table 1J.a).
Table 1J.a Uses of ethyl cellulose

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microencapsulation</td>
<td>10-20</td>
</tr>
<tr>
<td>Sustained release tablet coating</td>
<td>3-20</td>
</tr>
<tr>
<td>Tablet coating</td>
<td>1-3</td>
</tr>
<tr>
<td>Tablet granulation</td>
<td>1-3</td>
</tr>
</tbody>
</table>

1J.7 Description:

Ethyl cellulose is a tasteless, free-flowing, white to light tan colored powder.

1J.8 Typical properties:

The bulk density of ethyl cellulose is 0.4 g/cm³. Ethyl cellulose absorbs very little water from humid air or during immersion, and that small amount evaporates readily. The particle size and viscosity of various grades of ethyl cellulose is displayed in Table 1J.b. Ethyl cellulose is practically insoluble in glycerin, propylene glycol and water. The specific gravity of ethyl cellulose is 1.12–1.15 g/cm³.
Table 1J.b Particle size and viscosity of various grades of ethyl cellulose

<table>
<thead>
<tr>
<th>Grade</th>
<th>Solution viscosity (mPas)</th>
<th>Mean particle size (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethocel Std 7FP Premium</td>
<td>6-8</td>
<td>5-15</td>
</tr>
<tr>
<td>Ethocel Std 10FP Premium</td>
<td>9-11</td>
<td>3-15</td>
</tr>
<tr>
<td>Ethocel Std 10P Premium</td>
<td>9-11</td>
<td>375</td>
</tr>
<tr>
<td>Ethocel Std 100FP Premium</td>
<td>90-110</td>
<td>30-60</td>
</tr>
<tr>
<td>Ethocel Std 100P Premium</td>
<td>90-110</td>
<td>465</td>
</tr>
</tbody>
</table>

1J.9 Stability and storage conditions:

Ethyl cellulose is a stable material. It is chemically resistant to alkalis, both dilute and concentrated, and to salt solutions. Ethyl cellulose is subject to oxidative degradation in the presence of sunlight or UV light at elevated temperatures. Ethyl cellulose should be stored at a temperature not exceeding 328°C in a dry area away from all sources of heat.

1J.10 Incompatibilities:

Incompatible with paraffin wax and microcrystalline wax.
1J.11 Regulatory Status:

Ethyl cellulose is GRAS listed and included in the FDA inactive ingredients guide (oral capsules, suspensions and tablets, topical emulsions and vaginal preparations), and in the Canadian list of acceptable nonmedicinal ingredients.

1J.12 Reference:

1K. Introduction to polyethylene oxide

1K.1 Synonyms:

The synonyms of polyethylene oxide are polyox, polyoxirane and polyoxyethylene.

1K.2 Structural formula:

The structural formula of polyethylene oxide is (CH₂CH₂O)n, where n represents the average number of oxyethylene groups.

1K.3 Molecular weight:

The molecular weight of polyethylene oxide of different grade of polyethylene oxide is represented in Table 1K.a.
Chapter 1K: Introduction to polyethylene oxide

Table 1K.a Molecular weight of polyethylene oxide

<table>
<thead>
<tr>
<th>Polyox grade</th>
<th>Molecular weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>WSR N10</td>
<td>100000</td>
</tr>
<tr>
<td>WSR N80</td>
<td>200000</td>
</tr>
<tr>
<td>WSR N750</td>
<td>300000</td>
</tr>
<tr>
<td>WSR N3000</td>
<td>400000</td>
</tr>
<tr>
<td>WSR 205</td>
<td>600000</td>
</tr>
<tr>
<td>WSR 1105</td>
<td>900000</td>
</tr>
<tr>
<td>WSR N12K</td>
<td>1000000</td>
</tr>
<tr>
<td>WSR N60K</td>
<td>2000000</td>
</tr>
<tr>
<td>WSR 301</td>
<td>4000000</td>
</tr>
<tr>
<td>WSR 303</td>
<td>7000000</td>
</tr>
</tbody>
</table>

1K.4 Functional category:

Polyethylene oxide finds its place as mucoadhesive, tablet binder and thickening agent.

1K.5 Applications in pharmaceutical formulation:

Polyethylene oxide is used as a tablet binder at concentrations of 5-85%. The higher molecular weight grades of polyethylene oxide provide delayed drug release. Polyethylene oxide is a mucoadhesive polymer. Polyethylene oxides at lower concentration are effective thickeners. Polyethylene oxides are radiation crosslinked in solution to produce a hydrogel for treatment of wound.
1K.6 Description:

Polyethylene oxide is white to off-white free-flowing powder with slight ammoniacal odor.

1K.7 Typical properties:

The true density of polyethylene oxide is 1.3 g/cm³. The melting point is 65-70°C. The moisture content is less than 1%. Polyethylene oxide is soluble in water, acetonitrile, chloroform and methylene chloride. It is insoluble in aliphatic hydrocarbons, ethylene glycol, and most alcohols. The viscosity of polyethylene oxide is represented in Table 1K.b.
Table 1K.b Polyethylene oxide viscosity at 25° C (mPas)

<table>
<thead>
<tr>
<th>Polyox grade</th>
<th>5% solution</th>
<th>2% solution</th>
<th>1% solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>WSR N10</td>
<td>30-50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WSR N80</td>
<td>55-90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WSR N750</td>
<td>600-1200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WSR N3000</td>
<td>2250-4500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WSR 205</td>
<td>4500-8800</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WSR 1105</td>
<td>8800-17600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WSR N12K</td>
<td></td>
<td>400-800</td>
<td></td>
</tr>
<tr>
<td>WSR N60K</td>
<td></td>
<td>2000-4000</td>
<td></td>
</tr>
<tr>
<td>WSR 301</td>
<td></td>
<td></td>
<td>1650-5500</td>
</tr>
<tr>
<td>WSR 303</td>
<td></td>
<td></td>
<td>7500-10000</td>
</tr>
</tbody>
</table>

1K.8 Storage condition:
Polyethylene oxide is stored in tightly sealed containers in a cool dry place.

1K.9 Incompatibilities:
Polyethylene oxide is incompatible with strong oxidizing agents.
1K.10 Regulatory Status:

Polyethylene oxide is included in the FDA inactive ingredients guide (sustained release tablets) and in the Canadian list of acceptable nonmedicinal ingredients.

1K.11 Reference:

1L. Introduction to polymethacrylates

1L.1 Synonyms:

The synonyms of polymethacrylates are Eudragit®, Eastacryl 30D, Kollicoat MAE 30 D and Kollicoat MAE 30 DP.

1L.2 Structural formula:

The structural formula of polymethacrylates is represented in Figure 1L.a.

\[
\begin{align*}
\text{R}_1 &= \text{CH}_3, \text{H} \\
\text{R}_2 &= \text{CH}_3, \text{CH}_3\text{CH}_2 \\
\text{R}_3 &= \text{COOH} \quad (\text{Eudragit® L and S}) \\
\text{R}_3 &= \text{COOCH}_2\text{CH}_2\text{N} \quad (\text{CH}_3)\text{Cl}^- \quad (\text{Eudragit® RL and RS})
\end{align*}
\]

Figure 1L.a Structural formula of various grades of Eudragit®

1L.3 General description:

Polymethacrylates are synthetic cationic and anionic polymers of dimethylaminoethyl methacrylates, methacrylic acid and methacrylic acid esters in varying ratios. Several different types of Eudragit® are commercially available as the dry powder, as an aqueous dispersion or as an organic solution. Table 1L.a describes summary of properties and uses of commercially available Eudragit®. Figure 1L.b represents behavior of Eudragit® films in digestive track.
### Chapter 1L: Introduction to polymethacrylates

#### Table 1L.a Summary of properties and uses of commercially available Eudragit®

<table>
<thead>
<tr>
<th>Type of Eudragit®</th>
<th>Chemical name</th>
<th>Supply form</th>
<th>Polymer dry weight content (%)</th>
<th>Recommended solvents</th>
<th>Solubility</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>E 12.5</td>
<td>Poly(butyl methacrylate, 2-dimethyl aminoethyl methacrylate, methyl methacrylate) 1:2.1</td>
<td>Organic solution</td>
<td>12.5</td>
<td>Acetone, alcohol</td>
<td>pH &lt; 5</td>
<td>Film coating</td>
</tr>
<tr>
<td>E 100</td>
<td>Granules</td>
<td>98</td>
<td>Acetone, alcohol</td>
<td>pH &lt; 5</td>
<td>Enteric coating</td>
<td></td>
</tr>
<tr>
<td>L 12.5P</td>
<td>Poly(methacrylic acid, methyl methacrylate) 1:1</td>
<td>Organic solution with plasticizer</td>
<td>12.5</td>
<td>Acetone, alcohol</td>
<td>pH &gt; 6</td>
<td></td>
</tr>
<tr>
<td>L 12.5</td>
<td>Organic solution</td>
<td>12.5</td>
<td>Acetone, alcohol</td>
<td>pH &gt; 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L 100</td>
<td>Powder</td>
<td>95</td>
<td>Acetone, alcohol</td>
<td>pH &gt; 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L100-55</td>
<td>Poly(methacrylic acid, ethyl acrylate) 1:1</td>
<td>Powder</td>
<td>95</td>
<td>Acetone, alcohol</td>
<td>pH &gt; 5.5</td>
<td></td>
</tr>
<tr>
<td>L30 D-55</td>
<td>Aqueous dispersion</td>
<td>30</td>
<td>water</td>
<td>pH &gt; 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S 12.5 P</td>
<td>Poly(methacrylic acid, methyl methacrylate) 1:2</td>
<td>Organic solution with plasticizer</td>
<td>12.5</td>
<td>Acetone, alcohol</td>
<td>pH &gt; 7</td>
<td></td>
</tr>
<tr>
<td>S 12.5</td>
<td>Organic solution</td>
<td>12.5</td>
<td>Acetone, alcohol</td>
<td>pH &gt; 7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Chapter 1L: Introduction to polymethacrylates

<table>
<thead>
<tr>
<th>Material</th>
<th>Formulation</th>
<th>Solvent(s)</th>
<th>pH</th>
<th>Permeability</th>
</tr>
</thead>
<tbody>
<tr>
<td>S100</td>
<td>Powder</td>
<td>Acetone, alcohol</td>
<td>pH &gt; 7</td>
<td>High permeability</td>
</tr>
<tr>
<td>RL 12.5</td>
<td>Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride)</td>
<td>Organic solution</td>
<td>12.5</td>
<td>Acetone, alcohol</td>
</tr>
<tr>
<td>RL 100</td>
<td>Granules</td>
<td>Acetone, alcohol</td>
<td>High permeability</td>
<td></td>
</tr>
<tr>
<td>RL PO</td>
<td>Powder</td>
<td>Acetone, alcohol</td>
<td>High permeability</td>
<td></td>
</tr>
<tr>
<td>RL 30D</td>
<td>Aqueous dispersion</td>
<td>Water</td>
<td>High permeability</td>
<td></td>
</tr>
<tr>
<td>RS 12.5</td>
<td>Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride)</td>
<td>Organic solution</td>
<td>12.5</td>
<td>Acetone, alcohol</td>
</tr>
<tr>
<td>RS 100</td>
<td>Granules</td>
<td>Acetone, alcohol</td>
<td>Low permeability</td>
<td></td>
</tr>
<tr>
<td>RS PO</td>
<td>Powder</td>
<td>Acetone, alcohol</td>
<td>Low permeability</td>
<td></td>
</tr>
<tr>
<td>RS 30D</td>
<td>Aqueous dispersion</td>
<td>Water</td>
<td>Low permeability</td>
<td></td>
</tr>
<tr>
<td>NE 30D</td>
<td>Poly(ethyl acrylate, methyl methacrylate) 2:1</td>
<td>Aqueous dispersion</td>
<td>30</td>
<td>Water</td>
</tr>
</tbody>
</table>
1.4 Stability and storage conditions:

Dry powder polymer forms are stable at temperatures less than 30° C. Above this temperature powders tend to form clumps. Dry powders are stable for at least 3 years if stored in a tightly closed container at less than 30° C. Dispersions are sensitive to extreme temperatures and phase separation occurs below 0° C. Dispersions should therefore be stored at temperatures between 5 and 25° C.
Chapter 1L: Introduction to polymethacrylates

1L.5 Incompatibilities:

Dispersions of Eudragit® L 30 D, Eudragit® RL 30 D, Eudragit® L 100-55 and Eudragit® RS 30 D are incompatible with magnesium stearate. Eastacryl 30D, Kollicoat MAE 30 D, and Kollicoat MAE 30 DP are also incompatible with magnesium stearate.

1L.6 Regulatory status:

Eudragit® is included in the FDA inactive ingredients guide (oral capsules and tablets) and in the Canadian list of acceptable nonmedicinal ingredients.

1L.7 Reference:

1M. Introduction to Glyceryl behenate

1M.1 Synonyms:
The synonyms of glyceryl behenate are Compritol® 888 ATO, 2,3-dihydroxypropyl docosanoate, docosanoic acid, 2,3-dihydroxypropyl ester and glyceryl monobehenate.

1M.2 Empirical formula and molecular weight:
The USPNF 23 describes glyceryl behenate as a mixture of glycerides of fatty acids, mainly behenic acid.

1M.3 Functional category:
Glyceryl behenate finds its place as coating agent, tablet binder and tablet and capsule lubricant.

Table 1M.a Uses of glyceryl behenate

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipophilic matrix or coating for sustained released tablets and capsules</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Tablet and capsule lubricant</td>
<td>1-3</td>
</tr>
<tr>
<td>Viscosity increasing agent in silicon gels (cosmetics)</td>
<td>1-15</td>
</tr>
<tr>
<td>Viscosity increasing agent in w/o or o/w emulsions (cosmetics)</td>
<td>1-5</td>
</tr>
</tbody>
</table>
Chapter 1M: Introduction to glyceryl behenate

1M.4 Applications in pharmaceutical formulation:

Glyceryl behenate is widely used in oral pharmaceutical formulations (Table 1M.a).

1M.5 Description

Glyceryl behenate occurs as a fine white powder or hard waxy mass with a faint odor.

1M.6 Typical properties:

The melting point of glyceryl behenate is 65-77°C. Glyceryl behenate is soluble when heated in chloroform and dichloromethane. It is practically insoluble in ethanol (95%), hexane, mineral oil and water.

1M.7 Stability and storage conditions:

Glyceryl behenate should be stored in a tight container, at a temperature less than 35°C.

1M.8 Regulatory status:

Glyceryl behenate is GRAS listed and included in FDA inactive ingredients guide (capsules and tablets) and Canadian list of acceptable nonmedicinal ingredients.

1M.9 Reference:

1N. Introduction to carbomer

1N.1 Nonproprietary name:

The nonproprietary name of carbomer is carbomera.

1N.2 Synonyms:

The synonyms of carbomer are acritamer, acrylic acid polymer, Carbopol, carboxy polymethylene, polyacrylic acid, carboxyvinyl polymer, pemulen and ultrez.

1N.3 Empirical formula and molecular weight:

Carbomers are synthetic high molecular weight polymers of acrylic acid that are cross-linked with either allyl sucrose or allyl ethers of pentaerythritol. They 56-68% of carboxylic acid (COOH) groups calculated on the dry basis. The molecular weight of carbomer resins is theoretically estimated at $7 \times 10^5$ to $4 \times 10^9$.

1N.4 Structural formula:

The structural formula of carbomer is shown in Figure 1N.a.

![Structural formula of carbomer](image)

Figure 1N.a Structural formula of carbomer
1N.5 Functional category:

Carbomer finds its place as bioadhesive, emulsifying agent, release modifying agent, suspending agent, tablet binder and viscosity increasing agent.

1N.6 Applications in pharmaceutical formulation:

Carbomers are mainly used in liquid or semisolid pharmaceutical formulations as suspending or viscosity increasing agents. Formulations include creams, gels and ointments for use in ophthalmic, rectal, and topical preparations. Carbomer having low residuals of ethyl acetate such as carbomer 971P or 974P are used in oral preparations, in suspensions, tablets, or sustained release tablet formulations. In tablet formulations, carbomers are used as dry or wet binders and as a rate controlling excipient. Carbomers are also used as emulsifying agents in the preparation of oil-in-water emulsions for external use. Table 1N.a represents concentration of carbomer used in pharmaceutical dosage form.

Table 1N.a Uses of carbomers

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emulsifying agent</td>
<td>0.1-0.5</td>
</tr>
<tr>
<td>Gelling agent</td>
<td>0.5-2</td>
</tr>
<tr>
<td>Suspending agent</td>
<td>0.5-1</td>
</tr>
<tr>
<td>Tablet binder</td>
<td>5-10</td>
</tr>
</tbody>
</table>
1N.7 Description:

Carbomers are white-colored, fluffy, acidic, hygroscopic powder with a slight characteristic odor.

1N.8 Typical properties:

The bulk and tapped density of carbomer are 1.76–2.08 g/cm³ and 1.4 g/cm³ respectively. The melting point of carbomer is 260° C. The moisture present in carbomer is upto 2% w/w. The average particle size is about 0.2 mm in diameter. Carbomer is soluble in water, glycerin and alcohol. The specific gravity of carbomer is 1.41. Carbomer after solubilization into the solvent and after subsequent neutralization with sodium hydroxide or triethanolamine yields highly viscous gel. The viscosity increases with increase in pH.

1N.9 Stability and storage conditions:

Carbomers are stable and hygroscopic materials that may be heated at temperatures below 104° C for up to 2 hours without affecting their thickening efficiency. Dry powder forms of carbomer do not support the growth of molds and fungi. Aqueous carbomer gels may be sterilized by autoclaving with minimal changes in viscosity or pH. At room temperature, carbomer dispersions maintain their viscosity during storage for prolonged periods. Exposure to light causes oxidation that is reflected in a decrease in dispersion viscosity. Stability to light may be improved by the addition of 0.05–0.1% w/v of a water-soluble UV absorber. Carbomer powder should be stored in an airtight, corrosion-resistant container in a cool, dry place.
1N.10 Incompatibilities:

Carbomers are discolored by resorcinol and are incompatible with phenol, cationic polymers, strong acids and high levels of electrolytes.

1N.11 Regulatory acceptance:

Carbomers are included in the FDA inactive ingredients guide (oral suspensions, tablets; ophthalmic, topical preparations, transdermal preparations, vaginal suppositories) and in Canadian list of acceptable non-medicinal ingredients.

1N.12 Reference: