4.0 DRUG-POLYMER PROFILE

4.1 DRUG PROFILE

4.1.1 METFORMIN –HCL (MH)

\[
\text{\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{structure_of_metformin_hydrochloride.png}
\caption{Structure of Metformin Hydrochloride}
\end{figure}}
\]

Identification (Drug bank- DB00331, 2013):

- Category: Hypoglycaemic agents; biguanides class
- Molecular Formula: $C_4H_{11}N_5 \cdot HCL$
- Molecular Weight: 165.63
- Chemical Name: 1-carbamimidamido-N, N-dimethylmethanimidamide
- Description: White, crystalline power
- Melting Point: 222°C-226°C
- pKa: 12.2
- Log P: -0.5

Solubility: Freely soluble in water, soluble in methanol is practically insoluble in acetone, ether, and chloroform. BCS class III drug.

Pharmacology (Drug bank- DB00331, 2013):

Pharmacodynamics:

- Metformin increases glucose tolerance in NIDDM patients
- It lowers both basal and postprandial plasma glucose.
- Unlike sulfonylureas, MH doesn’t cause hypoglycemia
- NIDDM or healthy subjects and does not cause hyperinsulinemia.
- Metformin does not affect insulin secretion.
Mechanism of Action (Lorenzati et al., 2010):

Metformin reduces blood-glucose levels by decreasing hepatic glucose output, as well as enhancing sensitivity of the hepatic and peripheral tissues to circulating insulin and thus also referred as insulin sensitizing drug. It also inhibits the intestinal absorption of glucose and exerts anorexic effect.

Absorption: After oral administration, absorbed through the entire GI-mucosa.

Volume of distribution: 654 L /850 mg

Protein binding: Negligibly bound to plasma proteins. It shows less absorption rather than rise in elimination with increasing doses.

Metabolism: Do not metabolize

Absolute bioavailability: 50 to 60% (500 mg tablet, under fasting conditions)

Route of elimination: Approx. 90% of the drug through healthy renal function

Half-Life: 5.0 - 6.2 h

Indications and Contraindications (Drugs.com, 2013)

Indications

It is indicated in the treatment of T2DM in adults, mostly in obese patients, when food management and/or exercise do not result in sufficient glycaemic control. It is used as initial treatment and/or in sulphonylurea failures, either single or in its combination (Drugs.com, 2013) with other oral agents or with insulin dependent diabetes.

Contraindications

- Juvenile DM (well regulated by insulin)
- DM controlled by diet alone
- During or immediately next to surgery (insulin is essential in this time)
- Hypersensitivity to metformin hcl
- Diabetic ketoacidosis, diabetic pre-coma
- Renal failure/ renal dysfunction (creatinine clearance < 60 mL/min)
- Lactation
o Alcoholism

o Acute conditions with the potential to alter renal function like:
  • Shock
  • Dehydration
  • IV administration of iodinated-contrast agents
  • Severe infection

o Acute or chronic disease that may cause tissue hypoxia such as:
  • Cardiac failure
  • Gangrene
  • Sepsis
  • Shock
  • Severe hepatic insufficiency
  • Acute significant blood loss
  • Pulmonary embolism
  • Myocardial infarction
  • Respiratory failure
  • Pancreatitis

o Acute alcohol intoxication

Precautions:

• Avoid use of alcohol if metformin is prescribed
• Should not recommended during pregnancy
• Should be avoided in patients with Liver disease, heart problem, kidney disease

Adverse Effects:

• Feeling dizzy, tired, or weak
• Tongue, lips, face or throat -swelling
• Lactic acidosis
• Freezing arms and legs
• Muscles pain and weakness

Storage: Protected from light and moisture, Store below 25°C.
4.1.2 REPAGLINIDE (RG) (Drug bank- DB00912, 2013)

![Structure of RG](image)

**Figure 4.2: Structure of Structure of RG**

**Identification**

Category: Hypoglycaemic agents; Meglitinides

Molecular Formula: $\text{C}_{27}\text{H}_{36}\text{N}_{2}\text{O}_{4}$

Molecular Weight: 452.586 g/mol

Chemical Name: (S)-2-Ethoxy-4-[2-[[methyl-1-[2-(1-piperidinyl)-phenyl]butyl]amino]-2-oxoethyl]-benzoic acid

Description: RG is a white to off-white powder with needle shaped crystals.

Melting Point: 130-131 °C

PKa: $\text{pK}_{a1}$ (acid) = 3.9; $\text{pK}_{a2}$ (amine) = 6.0.

Log P: - 5.9

**Solubility:**

- Slightly in aqueous acid,
- BCS Class II drug.
- Very slightly in aqueous base and
- Freely in ethanol and methanol.

**Pharmacology:**

**Pharmacodynamics:**

RG will increase insulin unleash by inhibiting ATP-sensitive K+ channels in a very glucose-dependent manner. The ATP-sensitive K+ channels open & shut that
causes repolarize & modify membrane and shut & opens L-type metal channels the other way around. The arrival of calcium ions stimulates calcium-dependent exocytosis of hypoglycaemic agent granules.

**Mechanism of Action:**

RG activity is dependent on the presence of effective β cells and aldohexose. It stimulates unleash of insulin by blockage of ATP-dependent K+ channels within the membrane of these cells. This de-polarizes the β cells, create gap in between the Ca-channels, and thus subsequent Ca+ stream provokes insulin secretion.

**Absorption:**

Quickly and entirely absorbed after oral admin. The absolute bioavailability is about 56%. Maximal outcome is detected within 3-3.5 hours and plasma insulin levels stay high for 4-6 h.

**Volume of distribution:** 31 L/ IV administration

**Protein binding:** >98%

**Metabolism:** rapidly metabolized via oxidation and dealkylation by cytochrome P450 3A4 and 2C9

**Absolute bioavailability:** 56% (approximately)

**Route of elimination:** eliminated 90% in feces and 8% in urine

**Half-Life:** 1 h

**Indication:** Along with food and workout to recover glycemic control in adults with T2DM.

**Precautions:**

- In case of surgery /dental surgery, if you are taking RG, inform the doctor
- Inform the doctor if you are allergic to any drugs or if having liver or kidney disease or T1DM.
- Inform the doctor if you are pregnant or are breast-feeding.
Adverse Effects:

- Jerkiness
- Dizziness
- Perspiring
- Pale skin
- Nervousness or touchiness
- Hunger
- Sudden variations in conduct or temper
- Headache
- Numbness or tingling nearby mouth
- Faintness
- Clumsy or jerky movements

Storage: Store at +4°C (desiccating conditions).

4.1.3 MARKETED FORMULATION- PRANDIMET® (FDA, 2012; Daily med, 2012)

PRANDIMET® is a combination of Repaglinide (RG) and Metformin HCL (MH) in conventional form. Along with a diet and regular work-out, it is used to control high blood sugar in patients with T2DM.

Initial U.S. Approval: June 2008, FDA approved PrandiMet® - the first and only FDC tablet of RG and MET for the T2DM.

Dosage & Administration:

- Initial dose: 1 mg/500 mg FDC - 2 to 3 times a day
- Do not go beyond 10 mg /2500 mg daily or 4 mg /1000 mg per meal.
- Give in separated doses within 15 minutes prior to meals.
- PrandiMet should skip if the meal is skipped.

Dosage form & strength:

- RG/ MH: 1 mg /500 mg , 2 mg /500 mg
Contraindications: Do not use in patients:

- With renal impairment.
- Receiving gemfibrozil.
- With metabolic acidosis, including diabetic ketoacidosis.

Adverse Reactions:

- Hypoglycemia and headache-
  - in case of drinking huge quantities of alcohol,
  - In case of not taking enough calories from food
  - doing unusually heavyweight workout,
  - Common adverse reactions in this case (≥10%).

- GI reactions i.e. nausea, vomiting and diarrhea, (More common at advanced MH doses.

Boxed Warning:

LACTIC ACIDOSIS

- Lactic acidosis occurrence is due to MH accumulation
- The risk enlarges with condition such as sepsis, excess alcohol consumption, dehydration, hepatic - renal impairment, and acute CHF
- In occurrence of acidosis, stop PrandiMet & hospitalized the patient right away

Storage:

- Keep away from freezing & childrens
- In a tightly-closed vessel
- Repel from heat, dampness, and direct sun-light
- At room temperature
4.2 POLYMER PROFILE

4.2.1 HYDROXYPROPYLMETHYLCELLULOSE:

<table>
<thead>
<tr>
<th>PhEur, BP, USP</th>
<th>Hypromellose</th>
</tr>
</thead>
<tbody>
<tr>
<td>JP</td>
<td>Hydroxypropylmethylcellulose</td>
</tr>
</tbody>
</table>

Synonyms: Methocel, Metolose, Tylopur, Benecel MHPC.

Chemical Name: Cellulose hydroxypropylmethyl ether

CAS R. Number: 9004-65-3

Description: White or creamy- fibrous or granular Odorless and tasteless, powder.

Formula:

![Figure 4.3 Structure of HPMC](image)

Where R is H, CH₃, or CH₃CH (OH) CH₂

Functional Category:

* Coating agent
* Stabilizing agent
* Tablet binder
* Rate-controlling polymer for SR
* Film-former
* Suspending agent
* Viscosity-increasing agent.

**Table 4.1- HPMC Matrices and Factors involved in API Release**

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Factor</th>
<th>Effect on Drug Release Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HPMC viscosity</td>
<td>As the HPMC grade for viscosity increases, the drug release rate decreases</td>
</tr>
<tr>
<td>2</td>
<td>HPMC/ API Ratio</td>
<td>As the concentration increases or the concentration of drug decreases, &amp; its release rate decreases from the matrices.</td>
</tr>
<tr>
<td>3</td>
<td>particle size</td>
<td>The greater the particle size of the HPMC powder the greater is the drug release rate from HPMC tablet matrices.</td>
</tr>
</tbody>
</table>
| 4       | Drug particle size | For water- insoluble drugs, a decrease in particle size, enhance the release rate from matrices.  
|         |                  | water- soluble drugs, the effect of drug particle size is generally insignificant.            |
| 5       | Drug solubility | As the solubility of the drug increases, the release rate increases from HPMC tablet matrices. |

**Typical Properties**

* **Acidity/alkalinity:** for a 1% w/w aqueous solution pH = 5.5–8.0.
* **Ash:** 1.5–3.0%, as per grade and viscosity.
* **Auto ignition temperature:** 360°C
* **Truedensity:** 1.326 g/cm$^3$
* **Bulkdensity (BD):** 0.341 g/cm$^3$
* **Tappeddensity (TD):** 0.557 g/cm$^3$
* **Specific gravity:** 1.26
* **Moisture content**: HPMC take up moisture from the damp air; the amount of water taken up depends upon the initial moisture, temperature and relative humidity of the atmosphere.

* **Melting point**: Chars at 226–230°C. Browns at 191–200°C; Glass transition Temperature is 171–180°C.

* **Solubility**: In cold water- Soluble, Forms viscous colloidal solution; In chloroform, ethanol (95%), and ether, practically insoluble but in mixtures of methanol and dichloromethane; ethanol and dichloromethane and water and alcohol, it is soluble.

### Table 4.2: Methocel™ -Premium Products

<table>
<thead>
<tr>
<th>Methocel product</th>
<th>USP 28 designation</th>
<th>Nominal viscosity (mPa s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methocel K100 Premium LVEP</td>
<td>2208</td>
<td>100</td>
</tr>
<tr>
<td>Methocel K4M Premium</td>
<td>2208</td>
<td>4000</td>
</tr>
<tr>
<td>Methocel K15M Premium</td>
<td>2208</td>
<td>15 000</td>
</tr>
<tr>
<td>Methocel K100M Premium</td>
<td>2208</td>
<td>100 000</td>
</tr>
<tr>
<td>Methocel E4M Premium</td>
<td>2910</td>
<td>4000</td>
</tr>
<tr>
<td>Methocel F50 Premium</td>
<td>2906</td>
<td>50</td>
</tr>
<tr>
<td>Methocel E5 Premium LV</td>
<td>2906</td>
<td>5</td>
</tr>
</tbody>
</table>

**Viscosity (dynamic):**

A wide vary of viscosity sorts are available in market for commercial purpose. Generally aqueous solutions are prepared, though HPMC may additionally be dissolved in alcohols like ethanol and propan2ol provided the where alcohol content is < 50% w/w. Methylene chloride and ethanol mixtures may additionally used to prepare viscous Hydroxypropylmethylcellulose solutions. Solution’s victimization in
organic solvents tend to be additional viscous; increasing concentration conjointly produces additional viscous solutions.

**Stability and Storage Conditions:**

HPMC in powder form is usually a stable excipient, but it becomes hygroscopic after drying. Rise in heat decreases the viscosity of prepared solutions. HPMC experiences a vice-versa sol–gel transformation when heated and cooled, respectively. Liquid preparations are stable at pH 3–11. The temperature at which it converts into gel- gel point is 51–90°C, based on the type of grade and concentration. (Banker et al., 1982)

HPMC solutions prepared in aqueous are reasonably enzyme-resistant, giving good stability (of viscosity) while storage for long-term. However, solutions prepared in aqueous are accountable to microbial spoilage and while preserving it, requires antimicrobial preservative: when HPMC is used as a viscosity-enhancing agent in solutions for ophthalmic preparation, the most commonly used preservative is benzalkonium chloride. HPMC solutions prepared in aqueous may also be autoclaving for sterilization; if polymers get coagulated, it must be shake when cooled to redispersed.

HPMC dry powder should be, stored in well-closed bottles, in a dry & cool place.

**Incompatibilities:**

Hydroxypropylmethylcellulose is not compatible with few oxidizing agents. Since HPMC are nonionic, it will not complex with ionic organics or metallic salts to and will not prepare non-soluble precipitates.

**Manufacture Method:**

Pure cellulose, got from wood pulp or cotton-linters, is allow to countered with NaOH solution that will produce alkali cellulose in swollen form and it is chemically more sensitive than raw cellulose. The obtained reactive cellulose is then kept with chloromethane and propylene-oxide to produce methylhydroxypropylethers
of cellulose. Thus obtained product is then filtered and pulverized to a granules or fine, uniform powder.

Safety:

HPMC is widely and extensively used in oral and topical formulations. It is used extensively also in food products and cosmetics.

HPMC is normally viewed as a safe and nonirritant material, even though extreme oral ingesting may produce laxative effect. The WHO has not stated the satisfactory daily consumption for HPMC since the stages consumed were not measured to signify a hazard to health, (FAO/WHO, 1990).

Mouse: LD$_{50}$ (IP): 5 g/kg

Rat: LD$_{50}$ (IP): 5.2 g/kg

Handling Precautions:

Usual precautions suitable to the conditions and amount of material handled. HPMC powder in air may be irritant to the eyes and thus protection for is suggested. Extreme dust formation must be avoided to reduce the risks of explosion. Hydroxypropylmethylcellulose is flammable.

Regulatory Status:

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

Applications in Formulation

As Emulsifier and stabilizing agent in ointments;
HPMC is extensively being used,

In oral products,

* As a tablet binder (2% and 5% w/w, wet or dry)
* In film-coating (2–20% w/w)
* As a matrix (10–80% w/w) for use in XR tablets and capsules
* High-viscosity grades, better retard the release

In topical formulations,

* suspending and thickening agent
* stabilizing agent

In ophthalmics,

* Thickening agent (0.45–1.0% w/w)
4.2.2 ACYRPOL

Acrypol range is a wide derivative of synthetic high molecular weight cross-linked water-soluble polyacrylic acids that conforms to “Carbomer” -USP/NF specification. The general molecular structure can be as follow. Acrypol has an average equivalent weight of 76 (Rowe et al., 2009).

Structure:

![Figure 4.4 Structure of Acrypol](image)

Acrypol is water soluble, macro-molecular substance with high affinity to water, glycol and alcohol. When dissolved in water, glycol and alcohol, sometimes followed by nullification with an alkali it gives extraordinary transparent, gel like, highly viscous, thixotropic fluid with a high yield worth also in a reduced concentration. Acrypol is superior in comparison with other, synthetic and neutral hydrophylllic polymers, in certain hugely useful presentation characteristics. It is having an aptitude to raise viscosity, hindrance to aging, capability to steady dispersions and resistance to microbes and molds to growth. Acrypol is available in number of viscosity grades that can be used for precise applications as per necessities.

Carbomer 1342, Carbomer 941, Carbomer 940, Carbomer 934P and Carbomer 934 are official in USP. The viscosities of neutralized watery dispersion of Acrypol are given in table 3.3 Acrypol is a polymer of acrylicacid and make hydrogel in water or alkaline solution due to carboxyl groups in its structure get hydrated.
Table 4.3 Different Acrypol Grades with Viscosity

<table>
<thead>
<tr>
<th>Carbomer grade</th>
<th>Viscosity in cps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbomer 934</td>
<td>30,500 – 39,400</td>
</tr>
<tr>
<td>Carbomer 934P</td>
<td>29,400 – 39,400</td>
</tr>
<tr>
<td>Carbomer 940</td>
<td>40,000 – 60,000</td>
</tr>
<tr>
<td>Carbomer 941</td>
<td>4000 – 11,000</td>
</tr>
<tr>
<td>Carbomer 1342</td>
<td>9,500 – 26,500</td>
</tr>
<tr>
<td>Carbomer 910</td>
<td>3,000-7,000</td>
</tr>
</tbody>
</table>

Other synonyms of Carbomer are Pemulen, Acritamer, Uitrez, Polyacrylic acid and Carbopol.

**Characteristics and benefits:**

Increase in viscosity can be got by dissolving Acrypol (by swelling) in diluents such as water and glycol or alcohol and at last addition of alkali to neutralization it. Acrypol yields a influential viscosity enhancing effect even if little quantities are added (Rowe et al., 2009).

- Thixotropic fluids with high productivity can be achieve
- Viscous fluid having better emulsion and dispersion stability can be achieved
- It gives outstanding see-through viscous liquid.
- Although of its high viscosity, it is not sticky and that is why pumping / injecting or stirring is also possible.
- Used in a wide variety of pH value.
- It is a synthetic material and has resistance to oxidation and hydrolysis.
- Acrypol are stable even in change in temperature
- It is non-toxic and USP/NF grade product.
- Excellent shelf life.
- Uniform reproducibility and performance

Types of Acrypol in SR formulation

a. Acrypol 934P (Carbomer 934P, USP/NF)

Acrypol 934P is specially tailored for pharmaceutical industries. It can be useful for internal pharma dosage forms. Acrypol 934P is high purity grade and used for thickening, suspending and emulsifying. It is also useful in tablets for binding and sustained release formulations.

b. Acrypol 974P

Acrypol 974P is specially tailored for pharmaceutical industries. It can be used for internal pharma dosage forms. Acrypol 974P is high purity grade and used as thickening, suspending and emulsifying agent. It is also useful in tablets for binding and sustained release formulations.

c. Acrycoat 971 G

It is available as granular form. It has been widely used in sustained release formulation. Due to the granular form it results in efficient mixing at post granulation stage. Manufacturing problems like dustiness, poor mixing can be avoided by using Acrycoat 971 G. As it is benzene free grade, it has a wide acceptance in sustained release formulation.

Physical and Chemical Properties

Acrypols are different in performance but their general properties are same. (Table-4.4)

<table>
<thead>
<tr>
<th>Table 4.4 Specification of Acrypols</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameters</td>
</tr>
<tr>
<td>Appearance</td>
</tr>
</tbody>
</table>
Specific gravity | 1.41  
---|---
Bulk density | 0.2 – 0.22 gm/ml  
Moisture content | 2.0 % max.  
PH of 1% W/V dispersion | 2.5-3.0 %  
PH of 0.5% W/V dispersion | 2.7-3.5 %  
Equilibrium moisture content | 8-10 % at humidity 70% RH & temp.30°C  
Equivalent weight | 76  
Glass transition temperature (Tg) | 100-105°C  
Ash content | 0.01 %  
Heavy metals | < 20 ppm  
Carboxyl content | 56-67 %  
Benzene content | < 0.5 % (for 940, 934, 941, 907, 910)  
< 0.01 % (for 934 P)  
Arsenic content | < 1.0 ppm  
Free monomer content | < 0.01 %  
Viscosity | RVT Brookfield viscosity cp. With 20 rpm spindle, 25°C neutralized solution in distilled water  

Acrypol can be a replacement for Sodium CMC, all gums, Xanthane gum, Sodium Alginate, Poly-acrylic acids etc.

**Functions**

Readily water-swellable; Various grades of Acrypol are used in a varied range of pharmaceutical applications to deliver:

- **Controlled release**: From pH-dependent semi-enteric release to near zero-order drug dissolution kinetics, Acrypol polymers propose steady performance over a wide range of desired parameters in tablets at lower concentrations than other competitive systems.
• Gelling at very little concentrations (< 1%) to produce a wide range of flow properties and viscosities in topical lotions, creams and gels, oral suspensions, and in transdermal gel reservoirs.

• **Bioadhesion in buccal**, intestinal, ophthalmic, vaginal, nasal, and rectal applications.

• In topical and oral suspensions

• Topical Emulsifying oil-in-water systems, with even at raised up temperatures.

**Toxicity**

Acrypol is a weak-acidic, molecular weight high polyacrylic acid. Body tissue does not absorbed when oral consumption and it is harmless for human. Toxicological tests for tolerance display that it does not have any marked physiological exploit and it is nontoxic. Tests of eye irritation, skin irritation and acute toxicity have exposed it to be comparatively safe substance.

**(A) Eye irritation test:**

1.5 % Acrypol gel was made ready by neutralizing with NaOH. Dropped 0.1 ml of the gel to the rabbits’ conjunctiva. The conjunctiva and cornea iris were observed. No irregularities were noticed.

**(B) Skin irritation test in rabbits:**

1. Non-neutralized Acrypol was tested of for initial skin irritation: A mixture of Acrypol (0.5g) and purified water (0.5ml) were applied to skin. No irregularities were noticed.

2. Neutralized Acrypol test for skin irritation: Acrypol 1% gel prepared. Neutralization of prepared aqueous Acrypol dispersion by NaOH was done and applied to rabbits’ skin. No irregularities were observed.

**(C) Acute toxicity test:**

Acrypol 10 % dispersion in oil was formulated by mixing Acrypol & edible oil. Administer the prepared dispersion to mice orally. This test of acute toxicity specified an LD50 value of >5000 g/kg.
4.2.3 GUAR GUM

BP: PhEur: Guar Galactomannan

USP-NF: Guar Gum

**Synonyms:** Guar flour; Galactosol; jaguar gum; guar galactomannanum; Meyprodor; Meyprofin, Meyprogat (Rowe et al., 2009).

**Chemical Name:** Galactomannan polysaccharide

**CAS R. Number:** [9000-30-0]

**Empirical Formula:** (C6H12O6)n,

**Molecular Weight:** 220000

**Structural Formula:**

![Figure 4.5 Structure of Guar gum](image)

**Functional Category:**

* Viscosity increasing agent.
* Tablet binder
* Suspending agent
* Tablet disintegrant
Table 4.5: Uses of guar gum

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablet binder</td>
<td>Up to 10</td>
</tr>
<tr>
<td>Emulsion stabilizer</td>
<td>1</td>
</tr>
<tr>
<td>Thickener for lotions and creams</td>
<td>Up to 2.5</td>
</tr>
</tbody>
</table>

Description

Guar gum is yellowish-white, an odorless, with a bland taste powder. It is obtained from Cyamopsis tetragonolobus (L.) Taub’s seeds (Fam. Leguminosae). The endosperms of seed grounded and partial hydrolysis gives polysaccharides D-mannose and D-galactose (Rowe et al., 2009).

Typical Properties

Acidity/alkalinity pH = 5.0–7.0 (1% w/v aqueous dispersion)

Density 1.492g/cm$^3$

Solubility:

- In hot or cold water, guar gum swells and disperse almost quickly and forms thixotropic, highly viscous sol
- In organic solvents, almost insoluble
- The ideal hydration, at pH 7.5–9.0.
- Takes 2-4 h in water at 37°C to develop viscosity up to maximum.
- Finely grounded powders rapidly swell

Viscosity (dynamic) 4860cP (4.86Pas) for a 1% w/v dispersion.

Stability and Storage Conditions

* Guar gum aqueous dispersions acts as buffer and are stable in pH 4.0–10.5 although heating for long time decrease the viscosity.
* Addition of 0.02% propylparaben and 0.15% methylparaben may increase the bacteriological stability. In food applications, citric acid, benzoic acid, sorbic acid, or sodium benzoate may be used.

* The powder should be stored in a dry place, cool and in well-closed bottle.

**Incompatibilities**

Guar gum gel formation can be prevented by decreasing the pH to below 7, or by heating. It is incompatible with ethanol (95%), acetone, strong acids, tannins, and alkalis.

**Applications**

In topical and oral products, such as a thickening, suspending, stabilizing agent and also as a controlled-release carrier.

It has also investigated well for formulation of SR (sustained-release) matrix tablets and in colonic drug delivery.

Guar gum, in food products can be used as diet part with diabetes mellitus patients. Also used in cosmetics

Used as a binder and disintegrant, in solid-dosage forms
4.2.4 HYDROGENATED CASTOR OIL, HCO-FLAKES

HCO-flakes are extremely used in manufacturing for various formulation and industrial purposes. These HCO-flakes are available in different amounts as per the requisite of our customers (Rowe et al., 2009).

**Structural Formula**

![Structural Formula of Hydrogenated Castor Oil](image)

**Figure 4.6 Structure of Hydrogenated Castor oil**

**Product Specification:**

- Acid Value: 2.0 Max.
- Melting Point: 85-88°C.
- Hydroxyl Value: 156 Min.
- Iodine Value: 3 Max.
- Saponification Value: 175.0 Min.
- Colour Gardner: 1 Max.

**Applications:**

HCO-flakes find no. of expanded uses due to its exclusive mixture of physico-chemical properties.

- In the manufacture of soaps & cosmetics
- In the manufacture of multipurpose high performance aviation grease and Lithium/Calcium grease
- As mold release agent in the processing of plastics and rubbers
- As a specialty wax blends’ component like crayons, lipsticks, pencils and anti-deodorant sticks

- As anti-foaming agent and as a for paper coating agent

- In the production of coatings of hot-melt and sealant requiring water resistance

- In the making of automotive Acrylics for refinish

- Rheological thixotropy agent that provides coatings, paints, adhesives, inks, sealants and many industrial conformation.

- Thick film epoxy, chlorinated rubber, and vinyl coating

- Manufacture of polyamide fiber’s spin finish oil

- Anti static agent and flame retardant for fiber

- As plasticizer for cellulosic

- In preparation of emulsified, ointments, sustained release capsules, virus vaccines, face paint, wetting/bodying agent

- For colour concentrates, as Processing aid

- In the production of hot-melt adhesives used for packaging books, carpet backing binding footwear, and in product assembly

- Surface treatment agents

- In the production of chemicals that is being used for different applications such as metal working, plasticizers, and textile auxiliaries in the form of different derivatives such as esters, sulfates, ethoxylates, etc.

- Anti-slip and tack additives for plastics processing
4.2.5 STEARIC ACID

BP, JP, PhEur, USP-NF: Stearic Acid

Synonyms cetylacetic acid; Cristal G; Crodacid; Acidum stearicum; Cristal S; E570; Dervacid; Extra AS; Edenor; Extra P; Extra ST; Emersol; Hystrene; Extra S; Industrene; 1-heptadecanecarboxylic acid; Pearl Steric; Kortacid 1895; stereophanic acid; Tegostearic, Pristerene (Rowe et al., 2009);

Chemical Name: Octadecanoic acid

CAS Registry Number: 57-11-4

Empirical Formula: C_{18}H_{36}O_{2}

Molecular Weight 284.47

Structural Formula

![Figure 4.7 Structure of stearic acid]

Description

Stearic acid is a white to yellow faintly -colour, hard, crystalline, somewhat glossy solid. It has a taste suggesting tallow and with slight odour

Functional Category

* Capsule and tablet lubricant
* solubilizing agent
* Emulsifying agent

Solubility:

Freely soluble in, CCl_{4}, benzene, ether; and chloroform. Soluble in hexane, (95%) ethanol, and PG-propylene glycol; practically insoluble in water.
Specifications

- **Density (bulk)** 0.537g/cm³
- **Density (tapped)** 0.571g/cm³
- **Acid value** 195–212
- **Density (true)** 0.980g/cm³
- **Boiling point** 383°C
- **Melting point** 69–70°C
- **Flash point** 113°C (closed cup)
- **Specific surface area** 0.51–0.53m²/g
- **Refractive index** 1.43 at 80°C
- **Saponification value** 200–220
- **Partition coefficient** Log (oil:water) = 8.2
- **Moisture content** practically Contains no moisture content

Applications

- Stearic acid is extensively used in topical and oral formulations, mainly used as a binder and lubricant in capsule and tablet
- It is used in combination with shellac for tablet coating.
- Stearic acid is used in topical formulations, as solubilizing and an emulsifying agent
- It has also been proposed as a sustained-release drug carrier and in tablet enteric coatings
- Stearic acid is used in the preparation of creams after partly neutralized with triethanolamine
- Stearic acid is used in glycerin suppositories as hardening agent.
4.2.6 METHACRYLIC ACID COPOLYMERS

These are copolymers, anionic in nature and are usually utilized for enteric coating formulations. This range of copolymers is mainly marketed under the brand name Eudragit. The Eudragit for enteric grades solubilize at high pH due to ionization. The ionization of the groups forms salts (Rowe et al., 2009).

The most frequently working methacrylate polymers are Eudragit-L & Eudragit-S that are copolymers of methacrylic acid and methyl methacrylate. Their solubility in water depends on the ratio of -CO to –RCOOR groups; it is approx. 1:1 in Eudragit-L 100 and 1:2 in Eudragit-S 100.

![Figure 4.8 Eudragit S](image)

Eudragit L 100-55 - copolymer of ethyl acrylate and methacrylic acid, and it get solubilized at pH above 5.5. Eudragit FS30D is the only aqueous polymer, ready to use in 30% dispersion

![Figure 4.9 Eudragit L](image)

A distinction made between is,

- Poly(meth)acrylates: insoluble polymer though permeable in GI track in GI fluids Eudragit®NE polymers with neutral and EUDRAGIT®RS and
RL polymers with alkaline groups allow controlled spell release of the API by swelling that is pH-independent.

Poly(meth)acrylates: soluble in GI track in GI fluids by salt formation Eudragit®S, L, E and FS polymers with alkaline or acidic groups permit release of the API, pH-dependently.

Advantages

- Protection of API to gastric fluid if sensitive to the same, pH reliant medicament release, guard gastric mucosa, from violent API, increase in drug effectiveness, good storage stability and GI and colon targeting.
- Eudragit®S and L polymers are allowing targeting to particular areas of the small and large intestine. Also, mixture of different grades with each other can be making and that can adjust the dissolution pH, and in this way it can attain the prerequisite GI targeting for the medicament.

Figure 4.10: Various Eudragit type in dissolution study
Table 4.6: Dissolution characteristics of different Eudragit

<table>
<thead>
<tr>
<th>EUDRAGIT</th>
<th>Availability</th>
<th>Dissolution properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>L 30D-55</td>
<td>30% Aqueous Dispersion</td>
<td>Dissolve pH &gt;5.5</td>
</tr>
<tr>
<td>L 100-55</td>
<td>Powder</td>
<td></td>
</tr>
<tr>
<td>L 100</td>
<td>Powder</td>
<td>Dissolve pH &gt;6.0</td>
</tr>
<tr>
<td>L 12.5</td>
<td>12.5% Organic Solution</td>
<td></td>
</tr>
<tr>
<td>S 100</td>
<td>12.5% Organic Solution</td>
<td></td>
</tr>
<tr>
<td>S 12.5</td>
<td>Powder</td>
<td>Dissolve pH &gt;7.0</td>
</tr>
<tr>
<td>FS 30D</td>
<td>30% Aqueous Dispersion</td>
<td></td>
</tr>
</tbody>
</table>

Characteristics of Eudragit FS30D

Eudragit® FS30 D, is preferred coating for colon release formulation as it is technically advantageous like,

- Highly flexible coatings.
- Aqueous processing.
- Suitable for multiparticulate formulation

EUDRAGIT® RS 100, RL 100

<table>
<thead>
<tr>
<th>USP/NF, Ph. Eur.</th>
<th>Ammonio Methacrylate Copolymer, Type A / Type B - NF</th>
</tr>
</thead>
<tbody>
<tr>
<td>JPE</td>
<td>Ammonioalkyl Methacrylate Copolymer, Type A / Type B</td>
</tr>
</tbody>
</table>
Chemical structure

![Chemical Structure of Eudragit](image)

**Figure 4.11 Structure of Eudragit**

EUDRAGIT® RS 100 / RS PO and EUDRAGIT® RL 100 / RL PO are copolymers of methyl methacrylate, ethyl acrylate and a methacrylic acid ester with tri methyl ammonio ethyl meth acrylate chloride (quaternary ammonium). The groups-ammonium is existing as salts and makes it permeable. The molar-ratio of methyl methacrylate, ethyl acrylate, and tri methyl ammonio ethyl meth acrylate is 2:1:0.1 in EUDRAGIT® RS and 2:1:0.2 in EUDRAGIT® RL approx.

**Apparent viscosity** 1-15 mPa.s

**Kinematic viscosity** (JPE): 1.0-4.0 mm²/s

**Refractive index**: 1.380-1.385

**Relative density**: 0.816-0.836
4.2.7 ETHYL CELLULOSE (EC)

**Synonyms:**

Surelease, Aqualon; E462, Aquacoat ECD, Ethocel (Rowe et al., 2009).

**CAS registry number and Chemical name**

[9004-57-3]; Cellulose ethyl ether

**Structural formula**

![Structure of Ethyl Cellulose]

Figure 4.12 Structure of Ethyl cellulose

**Molecular weight and Empirical formula**

\[ C_{12}H_{23}O_6(C_{12}H_{22}O_5)_nC_{12}H_{23}O_5 \]

Where, \( n \) can vary to provide a wide variety of molecular weights.

**Functional category**

* flavoring fixative
* Coating agent
* viscosity increasing agent
* tablet filler
* tablet binder
Description

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

Typical properties (Rowe et al., 2009).

- **Density (bulk):** 0.4 g/cm$^3$

Moisture content

It is hydrophobic in nature and engrosses very slight H2O from damp air or during involvement, and as due to small amount present it evaporates freely.

- **Glass transition temperature:** 129–133°C

- **Specific gravity:** 1.12–1.15 g/cm$^3$

Solubility

EC is basically insoluble in propylene glycol (PG), glycerin, and water.

The ethoxyl groups of EC contains NLT 46.5% of R-O-CH$_3$ is freely soluble in ethanol (95%), chloroform, methanol, ethyl acetate, and toluene.

Viscosity

Various Grades of EC with different viscosities ranges are available in market. Usually 5% w/v solutions prepared in organic solvent blends used to measure viscosity. It is measured usually at 25°C with 5%w/v EC dissolved in a solvent-blend of 80:20 toluene:ethanol in %w/w. Viscosities technically in range from 7-100 mPa.s or 7–100 cP. Higher viscosity with longer chains polymer of gives durable and strong films. Higher EC concentration will definitly increase viscosity. Further it also depends on amount of volatile solvent.
Applications

✓ To cover an disagreeable taste of medicament,
✓ As a coating agent, for granules and tablets. These coatings provide hydrophobicity and are used to modify the release,
✓ To improve the stability of formulation; For ex, oxidation of granules will be prevented if coated with EC.
✓ Modified release of tablet can be achieved using EC as a matrix former.
✓ EC is widely used in topical and oral formulations with different concentration are shown in Table 4.7.

Table 4.7: Ethylcellulose usage (Rowe et al., 2009).

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microencapsulation</td>
<td>10.0–20.0</td>
</tr>
<tr>
<td>SR tablet coating</td>
<td>3.0–20.0</td>
</tr>
<tr>
<td>Tablet coating</td>
<td>1.0–3.0</td>
</tr>
<tr>
<td>Tablet granulation</td>
<td>1.0–3.0</td>
</tr>
</tbody>
</table>

EC solution in an organic liquids or Liquid mixture used to produce hydrophobic films. Greater viscosity EC, more durable and stronger will be the hydrophobic films. By the addition of plasticizer or hypromellose, EC films can be modified to modify its solubility.

In EC coated dosage formulations, API release can be Sustain by film coating on formulation. EC coated granules and beads have also confirmed the skill to withstand pressure and can defend the coating from breakage while tablet compression.

Grater viscosity grades of EC are also used in API microencapsulation. In API release from an EC-microcapsule, microcapsule wall thickness and surface area acts as basic release-mechanism.
As binder, in solid formulations, direct compression may create mechanical strength problem; EC as in wet or dry granulated with a solvent such as ethanol (95%) can solve the problem. Thus produced EC tablets will be with good hardness with least friability, although dissolution will be poor.

As in topical formulations like gels, lotions or creams, EC is used as a solidifying agent with suitable solvent.

EC also used in cosmetics and food products and has been used as a stabilizer for emulsions.

**Stability and Storage conditions**

EC is generally a stable polymer, and very slightly hygroscopic in nature. It is chemically tough with concentrated as well as with dilute alkalis, and also with salt solutions, though it is sensitive to acidic materials than are cellulose esters.

EC is prone to oxidative deterioration in the UV light or presence of sunlight at high temperatures. This can be prevented or reduced by the use of chemical agent that can engross UV light and antioxidant. While storing ethyl cellulose, temperature should not hike more than 90°F (32°C).It should be stored in a dry area and keeping away from any kind of heat sources. It should never be stored next to any oxidizing agents or peroxides.

**Incompatibilities**

Incompatible with microcrystalline wax and paraffin wax
4.2.8 Povidone

Nonproprietary Names

BP, USPNF, PhEur: Povidone (Rowe et al., 2009).

**Synonyms:** Polyvinylpyrrolidone, E1201; Kollidon; Plasdone; poly [1-(2-oxo-1-pyrrolidinyl) ethylene]; Polyvidone

**CAS no/ Chemical name:** [9003-39-8]/1-Ethenyl-2-pyrrolidione homopolymer

![Figure 4.13: Structure of Povidone](image)

**Empirical Formula:** \((C_6H_9NO)_n\)

Povidone is linear 1-vinyl-2-pyrolidinone, synthetic group polymer, its different polymerization differentiate polymers to different molecular weights. It is categorized by its aqueous solution viscosity, relative to that viscosity of water, stated as a K-value.

**Molecular weight:**

<table>
<thead>
<tr>
<th>K</th>
<th>Mol. Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>8000</td>
</tr>
<tr>
<td>25</td>
<td>30000</td>
</tr>
<tr>
<td>30</td>
<td>50000</td>
</tr>
<tr>
<td>90</td>
<td>1000000</td>
</tr>
<tr>
<td>120</td>
<td>3000000</td>
</tr>
</tbody>
</table>

**Description:** Povidone is a white to creamy-white fine, colored, hygroscopic almost odorless, powder.
Functional category:

- Disintigrant,
- Suspending agent,
- Dissolution aid,
- Tablet binder

- **Solubility:** Freely soluble in ethanol, acids, methanol, ketones, chloroform and water. Practically insoluble in mineral oil, hydrocarbons, and ether

- **Incompatibility:** The effectiveness of some preservatives may be unpleasantly affected by the creation of complexes with povidone. It forms molecular incompatibilities, in solution with sodium salicylate, sulfathiazole, Phenobarbital, salicylic acid, tannin etc. In solution, it is well-matched with almost all synthetic and natural resins inorganic salts, and other chemicals.

- **Stability and Storage Conditions:** On extreme heating at 150°C, it get dark with a lowing value of water solubility. If short heat exposure cycle of around 110-130°C are given, it is stable. Sterilization by steam does not alter properties of its aqueous solution. Can be stored under normal conditions without any degradation or decomposition. But as it is hygroscopic, stored in a sealed container in adry, cool, place.

- **Safety:** Widely used in food products, oral pharmaceutical and generally regarded as a nonirritant material and nontoxic material.

**Applications**

- Primarily povidone is used for solid dosage form like tablets.
- As binders, Povidone’s solutions are used in granulation processes.
- It is also be used as coating agent.
- It can be added in dry form to powder blends and insitu granulated by the addition of alcohol, water, or mixture of them.
4.2.9 STARCH

**Empirical formula and molecular weight**

\[(C_6H_{10}O_5)n \approx 50000 - 160000\]

Where \(n = 300 - 1000\)

**Structural formula**

![Starch Structural Formula](image)

**Figure 4.14 Structure of Starch**

**Description**

Starch is tasteless, odorless, white colored, fine powder made up of ovoid or spherical granules. The shape and size are important properties vary from its botanical species to species (Rowe et al., 2009).

**Functional category**

* As capsule and tablet disintegrate
* As a tablet binder.
* Glidant,
* As diluent for capsule and tablet,
Density

* Density will be different for different starch. For e.g. for corn starch
* Bulk density – 0.462 g/cm³
* Tap density – 0.658 g/cm³

Moisture content

Table 4.9 Moisture content at 50 % relative humidity

<table>
<thead>
<tr>
<th>Starch</th>
<th>Moisture content (approx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corn starch</td>
<td>11 %</td>
</tr>
<tr>
<td>Rice starch</td>
<td>14 %</td>
</tr>
<tr>
<td>Wheat starch</td>
<td>13 %</td>
</tr>
</tbody>
</table>

Starch is normally hygroscopic in nature and in damp atmosphere, rapidly absorbs H2O.

Particle size distribution

* Rice starch: 2–20 µm;
* Corn starch: 2–32 µm; Median: 17 µm
* Tapioca starch: 5–35 µm
* Potato starch: 10–100 µm;
* Wheat starch: 2–45 µm. Median: 23 µm.

Solubility

Not soluble practically in cold water and in (95%) cold ethanol. Swell immediately in water at 5–10% con. at 37°C.

Specific surface area

* 0.27–0.31 m²/g for wheat starch.
* 0.12 m²/g for potato starch;
* 0.41–0.43 m²/g for corn starch;
- **Swelling temperature**
  
  * 55°C for wheat starch.
  * 64°C for potato starch;
  * 65°C for corn starch;

- **Viscosity (dynamic)**

  13.0 cP (13.0 mPa.s) for a 2% w/v solution of corn starch in water at 25°C.

**Stability and storage conditions**

Storing in dry place and away from heat, starch will be stable. It is inert in normal storage condition. It should be kept safe from high moisture. Although previously heated starch or starch paste or solution is physically unstable and prone to microbial growth.
4.2.10 AVICEL

**Microcrystalline cellulose**

BP, USPNF, JP,

**Cellulosum microcristallinum**

Ph Eur

**Synonyms**

Pharmacel; Avicel PH; cellulose gel; Celex; Celphere; crystalline cellulose; Ceolus KG; Emcocel; E460; Fibrocel; Tabulose; Ethispheres; Vivapur (Rowe et al., 2009).

**Chemical name and CAS registry number**

Cellulose & [9004-34-6]

**Structural formula**

![Structural formula of microcrystalline cellulose](image)

**Figure 4.15 Structural formula of microcrystalline cellulose**

**Empirical formula and molecular weight**

\[(C_6H_{10}O_5)n \approx 36,000\]

Where \(n = 220\).

**Description**

MCC is partially depolymerized, purified, cellulose that occurs as a tasteless, odorless, white, crystalline powder made up of porous particles. It is available
commercially in different moisture grades and particle sizes that have dissimilar applications and properties (Rowe et al., 2009).

- **Density (bulk)** 0.347 g/cm³
- **Density (tapped)** 0.488 g/cm³
- **Density (true)** 1.522–1.678 g/cm³

**Solubility**

- 5% w/v NaOH solution: Slightly soluble
- In dilute acids, water, and organic solvents: practically insoluble

**Melting point**: 260–271 °C

**Moisture content**

- Usually <5% w/w. Different grades may have moisture content in varying amounts. MCC is hygroscopic.

**Functional category**

- * Suspending agent
- * Adsorbent
- * Tablet disintegrant.
- * Diluent for tablet and capsule

**Applications**

- MCC is extensively used in pharmaceutical products, mainly as a diluent/binder in oral capsule and tablet where it is used for direct-compression; Dry-granulation or wet-granulation processes.
- MCC is also used in food products and in cosmetics
MCC also used as disintegrant and lubricant in tableting as it possess both properties which fall it in unique excipient

**Table 4.10 Use of microcrystalline cellulose** (Rowe et al., 2009).

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adsorbant</td>
<td>20 – 90</td>
</tr>
<tr>
<td>Capsule binder / Diluent</td>
<td>20 – 90</td>
</tr>
<tr>
<td>Antiadherent</td>
<td>5 – 20</td>
</tr>
<tr>
<td>Tablet binder / Diluent</td>
<td>20 – 90</td>
</tr>
<tr>
<td>Tablet disintegrants</td>
<td>5 – 15</td>
</tr>
</tbody>
</table>

**Incompatibilities**

Keep away MCC from strong oxidizing substance, they are incompatible with MCC

**Stability and Storage**

MCC is hygroscopic material though stable material. The MCC in bulk should be warehoused in a cool, dry place in a well-closed vessel.
4.2.11 LACTOSE

<table>
<thead>
<tr>
<th>BP</th>
<th>Lactose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PhEur, USP-NF</strong></td>
<td>Lactose Monohydrate</td>
</tr>
<tr>
<td><strong>JP</strong></td>
<td>Lactose Hydrate</td>
</tr>
</tbody>
</table>

**Synonyms**

Tablettose, GranuLac; CapsuLac; lactosum Lactochem; monohydricum; Pharmatose; Monohydrate; SacheLac; PrismaLac; SpheroLac; SorboLac; 30GR; SuperTab (Rowe et al., 2009).

**Chemical name**

✓ O-b-D-Galactopyranosyl-(1\4)-a-D-glucopyranose monohydrate

**Empirical formula and molecular weight**

✓ C_{12}H_{22}O_{11} H_{2}O, 360.31

**Structural formula**

![Figure 4.16 Structure of Lactose](image)

**Functional category**

* Capsule and Tablet diluent
* Capsule and Tablet filler
* Dry powder inhaler carrier
* Tablet binder
* Lyophilization aid
Description

- Lactose is odorless, white to off-white, slightly sweet-tasting, crystalline powder. α-lactose is 20% while β-lactose is 40% as sweet as sucrose approximately (Rowe et al., 2009).

Solubility

- Lactose is aqueous insoluble almost and also with most other liquids.

Properties

- **Melting point** 200-202°C
- **Moisture content** It contains 5% w/w water of crystallization approx.

Applications

- Lactose is used as a diluent in dry-powder inhalation. In limited amount used to support lyophilized formulation and infant formulas. Lactose is widely used as a diluent and filler in capsule and tablet.
- Lactose is also used in the manufacture of liquid-solids for use as solid suspensions or solutions.
- Generally very well grades of lactose are being used for the formulation of tablets usually by the wet-granulation.
- Few grades are sometimes used to prepare direct-compression formulation for lower dose formulation without wet or dry-granulation. directly compressible grade are anhydrous lactose and spray-dried lactose
- The mixture of sucrose with Lactose is used to prepare sugar-coating solutions. It may also be used in IV injections.