Chapter 4

Drug and Excipient profile
The first step in the design and development of any dosage form is the selection of the quality of drugs and excipients with definite specifications. Before any study can be undertaken, it is important to select the drug and requisite excipients and review literature pertaining to these to understand their physiochemical properties and available methods of analysis. A thorough review of the drug and excipient profiles was carried out prior to conducting research work.

The development of extended release tablets by different technologies, namely, matrix technology, hot melt granulation technology and multiparticulate dosage form were the area of interest. The drug selected was Gliclazide, which is a hypoglycemic agent from sulphonylurea group. It stimulates insulin secretion from functional pancreatic beta cells and increases the sensitivity of the beta cells to a glucose stimulus. It restores the diminished first phase of insulin secretion noted in non insulin dependent diabetes mellitus. Gliclazide is indicated as the drug of choice in Type II diabetes.

Excipients are an integral component of any dosage form. Since they come in intimate contact with the drug and moreover the stability as well as release characteristics of the drug in formulation depends mainly on the quality and quantity of excipients, selection of excipients is crucial step towards developing a stable and successful dosage form. All GRAS excipients were selected for the purpose of the proposed research work.

The drug and excipients were provided by USV ltd. The manufacturer’s certificate of analysis (COA) was considered as the approved standardization for the drug and all the excipients used in the work, however each material was analysed in-house before use. The present chapter highlights the profile of the drug Gliclazide selected for the study. The standardization of the drug as provided by the supplier’s certificate of analysis is also given. The profile and standardization of the drug is followed by the profiles of all excipients used in the entire study and their subsequent standardization as provided by the manufacturer’s certificate of analysis.
Table 4.1: List of drug and excipients used in the development

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Ingredients</th>
<th>Spec.</th>
<th>Brand name</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Gliclazide</td>
<td>Ph. Eur.</td>
<td>NA</td>
<td>Bal Pharma Ltd., Bangalore</td>
</tr>
<tr>
<td>2</td>
<td>Lactose monohydrate</td>
<td>Ph. Eur.</td>
<td>Supertab 30</td>
<td>DMV Fonterra</td>
</tr>
<tr>
<td>3</td>
<td>Dicalcium phosphate Anhydrous</td>
<td>Ph. Eur.</td>
<td>A-Tab granular</td>
<td>Innophos, USA</td>
</tr>
<tr>
<td>4</td>
<td>Microcrystalline cellulose</td>
<td>Ph. Eur.</td>
<td>Avicel PH 101 &amp; Avicel PH102</td>
<td>FMC Biopolymer</td>
</tr>
<tr>
<td>5</td>
<td>Maltodextrin</td>
<td>Ph. Eur.</td>
<td>Glucidex IT 12</td>
<td>Roquette, France</td>
</tr>
<tr>
<td>6</td>
<td>Hydroxypropylmethyl Cellulose</td>
<td>Ph. Eur.</td>
<td>HPMC K 100 LV</td>
<td>DOW Chemicals</td>
</tr>
<tr>
<td>7</td>
<td>Hydroxypropylmethyl Cellulose</td>
<td>Ph. Eur.</td>
<td>HPMC K 4 M</td>
<td>DOW Chemicals</td>
</tr>
<tr>
<td>8</td>
<td>Polyethylene oxide</td>
<td>Ph. Eur.</td>
<td>Polyox WSR coagulant</td>
<td>DOW Chemicals</td>
</tr>
<tr>
<td>9</td>
<td>Xanthan gum</td>
<td>Ph. Eur.</td>
<td>Xanthural 75</td>
<td>C P Kelco</td>
</tr>
<tr>
<td>10</td>
<td>Co-polymer of Polyvinyl alcohol and Povidone</td>
<td>Int. spec.</td>
<td>Kollidone SR</td>
<td>BASF</td>
</tr>
<tr>
<td>11</td>
<td>Ethyl cellulose 7 cps and Ethyl cellulose 20 cps</td>
<td>Ph. Eur.</td>
<td>Ethocel</td>
<td>DOW Chemicals</td>
</tr>
<tr>
<td>12</td>
<td>Hydroxypropyl cellulose</td>
<td>Ph. Eur.</td>
<td>Klucel LF</td>
<td>Hercules</td>
</tr>
<tr>
<td>13</td>
<td>Light magnesium Carbonate</td>
<td>Ph. Eur.</td>
<td>NA</td>
<td>Dead sea, Israel</td>
</tr>
<tr>
<td>14</td>
<td>Magnesium stearate</td>
<td>Ph. Eur.</td>
<td>NA</td>
<td>Ferro, Spain</td>
</tr>
<tr>
<td>15</td>
<td>Colloidal anhydrous Silica</td>
<td>Ph. Eur.</td>
<td>Aerosil 200</td>
<td>Degussa</td>
</tr>
<tr>
<td>16</td>
<td>Hydrogenated castor oil</td>
<td>Ph. Eur.</td>
<td>Cutina HR PH</td>
<td>Cognis</td>
</tr>
<tr>
<td>17</td>
<td>Stearic acid</td>
<td>Ph. Eur.</td>
<td>Stearin</td>
<td>Stearinerie Dubois Fils</td>
</tr>
<tr>
<td>18</td>
<td>Polyethylene glycol 8000 (Macrogol)</td>
<td>Ph. Eur.</td>
<td>NA</td>
<td>DOW chemicals</td>
</tr>
<tr>
<td>19</td>
<td>Aminomethacrylate Copolymer</td>
<td>Int. spec.</td>
<td>Eudragit RS PO</td>
<td>Degussa</td>
</tr>
<tr>
<td>20</td>
<td>Polyacrylate 30% Dispersion</td>
<td>Int. spec.</td>
<td>Eudragit N 30 D</td>
<td>Degussa</td>
</tr>
<tr>
<td>21</td>
<td>Talc</td>
<td>Ph. Eur.</td>
<td>Luzenac</td>
<td>Rio Tinto, Italy</td>
</tr>
<tr>
<td>22</td>
<td>Crospovidone</td>
<td>Ph. Eur.</td>
<td>Kollidone CR</td>
<td>BASF</td>
</tr>
<tr>
<td>23</td>
<td>Sodium Alginate</td>
<td>Ph. Eur.</td>
<td>Keltone HVCR</td>
<td>FMC Biopolymer</td>
</tr>
</tbody>
</table>
4.1 Gliclazide

Source
Gliclazide was sourced from Bal Pharma Ltd., Bangalore, India.

Description
Gliclazide is white to almost white crystalline, odorless powder. It is classified as an anti-diabetic agent of sulphonylurea category.

Physical state
Solid

CAS Registry number
[21187-98-4]

IUPAC name
N - (hexahydrocyclopenta [c] pyrrol-2-ylcarmoyl) -4- methyl benzene sulfonamide.

Molecular formula
C_{15}H_{12}N_{3}O_{3}S

Molecular weight
323.40 g/mol

Molecular structure

![Structure of gliclazide](image)

Brand names
Diamicron tablets, Glimicron tablets and Nordialex tablets

Melting point
163 - 165°C

Log P/ Hydrophobicity
2.6

pH
A saturated solution of gliclazide in water at 25°C shows a pH of 4.7
Hygroscopicity
Gliclazide is non hygroscopic

Clog P\textsuperscript{153}
1.52

pK\textsubscript{a}
Gliclazide is weak acid with pKa value of 6.6 ± 0.1 based on the measurement of half-neutralization point of a methanolic solution of gliclazide due to its very low solubility in water.

Lowest solubility
0.00999 mg/mL, practically insoluble in water, freely soluble in methylene chloride and chloroform, sparingly soluble in acetone and slightly soluble in alcohol and methanol.

Polymorphism
No polymorph reported

BCS classification
BCS class II (log P) and BCS class IV (c log P)

Category
Endocrine and metabolic agents, anti-diabetic agent (Sulphonamide)

Storage
To be stored below 30\textdegree C, in a tight container protected from light.

Stability
Stable under normal storage conditions

Derivative type
Anhydrous

Mechanism of action\textsuperscript{154}
Gliclazide is a sulphonylurea hypoglycemic given orally for non-insulin dependent diabetes mellitus (type 2). Gliclazide stimulates the secretion of insulin from functional pancreatic β-cells, increasing the sensitivity of β-cells to glucose stimulation. Diminished first-phase insulin secretion is increased by gliclazide in type II diabetes mellitus.

Gliclazide may be able to maintain its effect on insulin secretion resulting in long-term hypoglycemic activity and some extra pancreatic effects. Such extra pancreatic effects include potentiation of post-receptor insulin sensitive pathways and improvement of insulin mediated glucose utilization. Gliclazide also reduces platelet adhesiveness and aggregation at normal therapeutic doses in man.
Gliclazide is an oral hypoglycemic (anti-diabetic drug) and is classified as a sulfonylurea which differs from other related compounds. Its classification has been ambiguous, as literature uses it as both first generation and second generation sulfonylurea. It has an N-containing heterocyclic ring with an endocyclic bond. Gliclazide reduces blood glucose levels by stimulating insulin secretion from beta-cells of the islets of langerhans. Gliclazide shows high affinity, strong selectivity and reversible binding to the beta cell K ATP channels with a low affinity for cardiac and vascular K ATP channels. Gliclazide also has extra pancreatic effects and heamovascular.

Gliclazide binds to sulfonylurea receptors on the surface of the beta islets cells found in pancreas. This binding effectively closes the K+ions channels. This decreases the efflux of potassium from the cell which leads to the depolarization of the cells. This causes voltage dependent Ca++ ion channels to open increasing the Ca++ influx. The calcium can then binds to and activate calmodulin which in turn leads to exocystosis of insulin vesicles leading to insulin release.

**Available dosage forms**

Gliclazide is mainly available as tablets. The dosage is 40 to 320 mg depending on the response of the patient. The drug is taken once or twice daily before food, with no more than 160 mg being ingested at a time. It is not available for sale in the United States.

**Pharmacokinetics**

**Absorption**

Absorption of gliclazide occurs in the gastro-intestinal tract reaching peak serum concentrations within 4 to 6 hours. This result in reduction of blood glucose levels by approximately 23% five hours after a single dose is administered. There is extensive binding of gliclazide to plasma proteins. The half-life of gliclazide is approximately 12 hours.

**Distribution**

Gliclazide is distributed in the extracellular fluid, leading to high concentrations in liver, kidneys, skin, lungs, skeletal muscle, intestinal and cardiac tissue when administered to animals. There appears to be negligible penetration into the central nervous system. Gliclazide also crosses placental barrier and circulates in the foetal blood system. A low
The apparent volume of distribution is probably reflected in the high degree of gliclazide binding to proteins (approximately 94% at a plasma concentration of 8 mcg/mL).

**Metabolism**
Gliclazide undergoes extensive metabolism to several inactive metabolites in humans, mainly methylhydroxygliclazide and carboxygliclazide. CYP2C9 is involved in the formation of hydroxygliclazide in human liver microsomes and in a panel of recombinant human P450s *in vitro*. Metabolism of gliclazide occurs in the liver, being metabolised into at least eight metabolites, which have been identified using thin layer and gas-liquid chromatography. The identity of only one metabolite is known (p-toluene sulphonamide). None of the metabolites have any recorded hypoglycemic activity. But the pharmacokinetics of gliclazide MR is affected mainly by CYP2C19 genetic polymorphism instead of CYP2C9 genetic polymorphism. There is no active metabolite reported for gliclazide.

**Elimination**
Approximately 70% of the administered dose is excreted slowly in the urine, reaching a peak 7 to 10 hours after administration. Metabolites are detectable in the urine 120 hours after administration. Faecal elimination accounts for approximately 11% of the administered dose. Gliclazide is usually completely eliminated within 144 hours post dose.

**Elimination half life**
The elimination half life of gliclazide varies between 12 and 20 hours\(^{155}\).

**Volume of distribution**
The volume of distribution is around 30 liters.

**Plasma protein binding**
Plasma protein binding is approximately 95%.

**Food effect**
Food does not affect the rate or degree of absorption.

**Overdosage**
Gliclazide overdose may cause severe hypoglycemia, requiring urgent administration of glucose by IV route and monitoring. Sulphonylurea agent induced hypoglycemia is different to insulin coma. Warning symptoms are often absent, neurological syndromes are frequent and coma is often prolonged. Consciousness should be restored by administration of intravenous glucose or glucagon injection. Care should be taken that hypoglycemia does not reoccur, by constant monitoring of blood sugar levels.
Warning and Precautions
Some acute complications (such as severe trauma, fever, infection or surgery) can occur as a result of metabolic stress. This accentuates the predisposition to hyperglycemia and ketosis. Insulin must be administered to control these situations. An increase in dosage of gliclazide is not appropriate.

Close observation of patients through all stages of administration, particularly in elderly, debilitated, malnourished, and semi-starved or those who have neglected dietary restrictions, are necessary to ensure that hypoglycemia does not occur.

Effects on ability to drive and use machinery
Concentration may be partially impaired if diabetes is not managed well. Therefore, ability to drive or use machinery will be impaired if diabetes is not well managed, including when taking gliclazide.

Use in pregnancy and lactation
Gliclazide is a category C drug, indicating that it may have caused or be suspected of causing harmful effects to the human foetus or neonate without causing malformations. These effects are reversible. Therefore, gliclazide should not be used in pregnancy and should be replaced by insulin. Sulphonylureas may enter the foetus and cause foetal hypoglycemia. Embryo toxicity and/or birth defects have been demonstrated in animal studies. In light of these factors, gliclazide should only be used in women who are likely to become pregnant if the benefits outweigh the potential risk.

Gliclazide should not be used during lactation.

Preclinical safety data
Preclinical data reveal no special hazards for humans based on conventional studies of repeated dose toxicity and genotoxicity. Long term carcinogenicity studies have been done. No teratogenic changes have been shown in animal studies, but lower foetal weight was observed in animals receiving doses 25 fold higher than maximum recommended dose in humans.

Adverse effects
The most notable effects are hypoglycemia; gastrointestinal disturbances such as constipation, nausea, epigastric discomfort and heartburn; dermatological reactions such as rash and transient itching; and biochemical abnormalities such as elevated serum creatinine, increased
serum alkaline phosphatase, raised serum AST, elevated BUN and raised serum bilirubin. Headache, slight disulfiram-like reactions and lassitude have been reported. Although very rare, severe hypoglycemia may occur in patients receiving gliclazide.

**Interactions**

Thiazide diuretics are known to aggravate the diabetic state so caution should be taken when administering thiazide diuretics to patients on gliclazide treatment. Blood sugar control may also be adversely affected where interaction between gliclazide and barbiturates, glucocorticoids or oestrogens occurs.

The hypoglycemic effect of gliclazide may be potentiated by insulin, biguanides, sulphonamides, salicylates, coumarin derivatives, chloramphenicol, monoamine oxidase inhibitors, β-blockers, oxyphenbutazone, phenylbutazone, clofibrate, cimetidine and ethanol. Acute alcohol intoxication potentiates the hypoglycemic action of sulphonylurea agents. Disulfiram-like reactions with characteristic flushing of the face, throbbing headache, giddiness, tachypnoea, tachycardia or angina pectoris may also occur. Chronic alcohol abuse may result in increased metabolism of sulphonylurea drugs, shortening the plasma half-life and duration of action.

**Pharmaceutical precautions**

Gliclazide has a shelf-life of 36 months. It should be stored below 30°C and tablets should not be used if the foil on the blister strip has been punctured. Gliclazide should be protected from heat and moisture.

Patients must be kept under close medical supervision as with all other antidiabetic therapies. Monitoring of patients taking gliclazide should be regular to ensure optimal control of the diabetic state. Dosage should be adjusted where necessary.

Transfer of patients on either single or combination treatment of sulphonylureas or biguanides to gliclazide is permitted. However, careful observation of patients who have previously been on combination therapy is necessary in the transitional phase.

**Indication**

Adult onset of diabetes mellitus (Type II) which cannot be controlled by diet alone.
4.2 Profile of excipients

4.2.1 Diluents

No matter for what purpose diluents are added they must meet certain basic criteria for satisfactory performance in tablet dosage form. Diluent should not react with the drug substance and moreover it should not have any effect on the functions of other excipients, it should not have any physiological or pharmacological activity of its own, it should have consistent physical and chemical characteristics, it should neither promote nor contribute to segregation of the granulation or powder blend to which they are added, it should be able to be milled (size reduced) if necessary in order to match the particle size distribution of the active pharmaceutical ingredient, it should neither support microbiological growth in the dosage form nor contribute to any microbiological load, it should neither adversely affect the dissolution of the product nor interfere with the bioavailability of active pharmaceutical ingredient, it should preferably be colorless or nearly so.

All the excipients were sourced from approved vendors and were available in the development laboratory of USV Ltd. \(^{156,157,158,159}\).

4.2.1.1 Lactose monohydrate

Lactose monohydrate [CAS no. 64044-51-5]. Lactose monohydrate available under the trade name Supertab 30 sourced from DMV-Fonterra Excipients.

The product has approved regulatory status as per USP-NF, Ph.Eur., IP, JP and BP. Lactose monohydrate occurs as white, odourless, free flowing powder slightly sweet in taste. It is a natural disaccharide, obtained from milk, which consists of one glucose and one galactose moiety.

![Structure of Lactose monohydrate](image)

Figure 4.2: Structure of Lactose monohydrate

Lactose monohydrate, spray dried lactose and anhydrous lactose are widely used as diluent in tablets and capsule formulations\(^{160,161}\). It produces a hard tablet and the tablet hardness increases on storage. Disintegrant is usually needed in lactose containing tablets. Drug release rate is usually not affected. It is usually non reactive, except for discoloration when formulated with amines and alkaline materials due to maillard reaction. It contains
approximately 5% water. It needs high compression pressures in order to produce hard tablets. Lactose monohydrate (SuperTab® 30) is produced by fluid bed granulation and has very good flow properties. It shows consistent compaction over a wide range of humidity.

![SEM of SuperTab 30GR.](image)

Figure 4.3: Lactose monohydrate (Supertab 30)

Mould growth may occur under humid conditions. Lactose should be stored in a well closed container and stored in cool dry place\(^{162}\).

### 4.2.1.2 Dicalcium phosphate (anhydrous)

Dibasic calcium phosphate [CAS no. 7757-93-9]. Dicalcium phosphate available under the trade name A-Tab granular was sourced from Innophous, U.S.A – supplied by Signet. The product has approved regulatory status as per USP-NF, Ph.Eur. JP, IP and BP. Dicalcium phosphate, also known as calcium monohydrogen phosphate, is a dicalcium phosphate. It is usually found as the dihydrate, with the chemical formula of \(\text{CaHPO}_4\cdot 2\text{H}_2\text{O}\), but it can be thermally converted to the anhydrous form. It is practically insoluble in water, with a solubility of 0.02 g per 100 mL at 25 °C. It contains about 29.5 percent calcium in its anhydrous form.

![Structure of Dibasic calcium phosphate anhydrous](image)

Figure 4.4: Structure of Dibasic calcium phosphate anhydrous

Dibasic calcium phosphate is a white, odorless, tasteless, powder or crystalline solid with molecular weight of 136.06 and chemical formula as \(\text{CaHPO}_4\). Its main function is as tablet
and capsule diluent. It is also used as a source of calcium in nutritional supplements. It is used in pharmaceutical products because of its good flow and compaction properties. Dibasic calcium phosphate is abrasive and a lubricant 1% is required for tableting such as magnesium stearate or sodium stearyl fumarate. Milled material is typically used in wet granulation or roller compacted formulations whereas unmilled or coarse grade material is used in direct compression formulations. Dibasic calcium phosphate is a non hygroscopic relatively stable material. Under high humidity conditions it does not hydrate to form hydrated salt. The bulk material should be stored in a well closed container in a dry place.

4.2.1.3 Maltodextrin

Maltodextrin has CAS registry no. [9050-36-6]. It is available under the trade name Glucidex IT 12 from Roquette, France.

Maltodextrin is described as a nonsweet, odorless, white powder or granules. It is nutritive saccharide mixture of polymers that consist of D-glucose units, with a dextrose equivalent (DE) less than 20. It is prepared by the partial hydrolysis of a food grade starch with suitable acids and/or alkali. It is freely soluble in water, slightly soluble in ethanol. The solubility, hygroscopicity, sweetness and compressibility of maltodextrin increases as the DE increases.

![Figure 4.5: Structure of maltodextrin](image)

Maltodextrin is used in tablet formulation as a binder and diluent in both direct compression and wet granulation process. Maltodextrin appears to have no adverse effect on the rate of dissolution of tablet and capsule formulations. Magnesium stearate in the range of 0.5-1.0 % may be used as a lubricant. Maltodextrin is stable for atleast 1 year when stored at a cool temperature less than 25°C and 50% relative humidity, may require the addition of an anti-
microbial agent. Maltodextrin should be stored in a well closed container in a cool dry place. Maltodextrin is generally regarded as a non-irritant and non toxic material.

**4.2.1.3 Microcrystalline cellulose**

Microcrystalline cellulose is available under the brand name Avicel PH 101 and Avicel 102 from FMC Biopolymer USA. Microcrystalline cellulose is purified, partially depolymerised cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is GRAS listed excipient. It is commercially available in different particle sizes and moisture grades that have different properties and applications. It has approved regulatory status as per BP, JP, IP, Ph.Eur. and USP NF. It is available in many brand names as Avicel, empirical formula as \((C_6H_{10}O_5)_n \approx 36000\), where \(n\approx 220\).

![Figure 4.6: Structure of microcrystalline cellulose](image)

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet granulation and direct compression processes\(^{168,169}\). Microcrystalline cellulose should be used in the ratio of 20-90% as tablet binder/diluent, 5-15% as tablet disintegrant. Avicel PH 101 has a bulk density of approx. 0.32% and tapped density of 0.45%. Avicel PH 101 has the particle size of 50 μm (60 mesh < 1.0% and 200 mesh < 30%) with moisture content of <5.0% and Avicel PH 102 has nominal mean particles size of 100 μm (60 mesh < 8.0% and 200 mesh < 45%) with moisture content of < 5%. Microcrystalline cellulose is slightly soluble in 5% w/v sodium hydroxide solution, practically insoluble in water, dilute acids and most organic solvents. Avicel PH 101 and 102 have a specific surface area of 1.06 -1.12m\(^2\)/g and 1.21-1.3m\(^2\)/g respectively. Microcrystalline cellulose is a stable though hygroscopic material\(^{170}\). The bulk material should be stored in well closed container in a cool, dry place.
4.2.2 Rate modifying polymers and binders

4.2.2.1 Hydroxypropylmethyl cellulose (HPMC K 4 M and HPMC K 100 LV)

Hydroxypropylmethyl cellulose is available under the trade name Methocel from DOW Chemicals Company.

Hydroxypropylmethyl cellulose also known as hypromellose is white, yellowish-white powder or granules, odorless, tasteless and hygroscopic after drying. It has CAS registry no. [9032-42-2]. the product has approved regulatory status as per USP-NF, Ph.Eur. JP and BP. HPMC is GRAS listed excipient. Hypromellose is soluble in cold water, forming a viscous colloidal solution, practically insoluble in chloroform, ethanol and ether.

![Structure of hydroxypropylmethyl cellulose](image)

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

Figure 4.7: Structure of hydroxypropylmethyl cellulose

Hydroxypropylmethyl cellulose is used as an excipient in a wide range of pharmaceutical products, including oral tablets and suspensions and topical gel preparations. It is available in several grades with viscosity ranging from 3cps to 100000 cps. As tablet binders$^{171}$ is used in concentrations 2-5% w/w, for film coating 2-20% w/w, depending on the type of release required above 20% depending on the grade$^{172,173}$. Hypromellose can be stored with normal precautions of storage.

4.2.2.3 HYDROXYPROPYL CELLULOSE

Hydroxylpropyl cellulose (low substituted HPC) available under the brand name Klucel LF was sourced from Aqualon Division.

Hydroxypropyl cellulose (CAS no. 9004-64-2) is a derivative of cellulose with both water solubility and organic solubility. The product is approved in USPNF, IP, BP, JP and Ph. Eur. Hydroxypropyl cellulose is described as partially substituted poly (hydroxypropyl) ether of cellulose. It is a white to slightly yellow colored odorless and tasteless powder. Commercially available in different grades that has various solution viscosities. Molecular
weight range of 50000-1250000. Hydroxypropyl cellulose is widely used in oral and topical pharmaceutical formulations as binders, film coating and extended release matrix formers. Concentrations of hydroxypropyl cellulose of 2-6% as binder in wet granulation and 15-35% as matrix former in extended release tablets. Hydroxypropyl cellulose is a stable material and is hygroscopic after drying. It should be stored in a well closed container in a cool dry place.

4.2.2.4 Ethyl cellulose

Ethyl cellulose (EC) is available under the brand name Ethocel 7 cps was sourced from DOW Chemicals Company.

The chemical name of ethyl cellulose is Cellulose ethyl ether (CAS no. 9004-57-3). The product has approved regulatory status as per USP-NF, Ph.Eur. JP and BP. It is a derivative of cellulose in which some of the hydroxyl groups on the repeating glucose units are converted into ethyl ether groups.

It is available as free flowing powder, white or light tan in color with a density of 0.4g/cm². It is practically insoluble in water, glycerol and propane-1,2-diol, but soluble in organic solvents. Ethyl cellulose containing 46-48% of ethoxyl group is freely soluble in ethanol, methanol, chloroform and ethyl acetate. Neutral to litmus, with LOD not more than 3%. It is mainly used as a thin-film coating material. In addition to being useful in a variety of pharmaceutical applications. It also features a fine particle (FP) range for use in extended release matrix systems and provides improved lipophilic properties realized by the increased
surface area. This flexibility is further enhanced by the ability to modify release profiles when ETHOCEL™ is used in combination with water-soluble excipients such as Colorcon’s METHOCEL™ premium cellulose ethers\textsuperscript{175,176}.

Ethyl cellulose is a stable, slightly hygroscopic material. It is chemically resistant to alkalies. Ethyl cellulose is prone to oxidative degradation in presence of UV light. Ethyl cellulose should be stored at a temperature not exceeding 32°C in a dry area and away from heat.

### 4.2.2.5 Polyethylene oxide

Polyethylene oxide (PEO) available under the trade name Polywox WSR coagulant was sourced from DOW Chemicals Company. Polyethylene oxide \([\text{CAS no. 25322}-68-3]\), has an approved regulatory status in USPNF. Polyethylene oxide is white to off-white free flowing powder, with slight ammonical odor. It is soluble in water and a number of organic solvents. Polyethylene oxide is described as a non-ionic homopolymer of ethylene oxide, represented by the formula \((\text{CH}_2\text{CH}_2\text{O})_n\) where \(n\) represents the average number of oxyethylene groups. It may contain up to 3\% of silicon dioxide. Polyethylene oxide can be used as a tablet binder at concentration of 5-85\%. The higher molecular weight grades provide delayed drug release via hydrophilic matrix. Polyethylene oxide has been shown to be an excellent mucoadhesive polymer. Lower concentrations are effective thickeners. Polyethylene oxide is available in the viscosity grade of 30-10000 mPas. It should be stored in tightly sealed containers in a cool, dry place. Exposure to high temperatures should be avoided which results in reduction in viscosity.

### 4.2.2.6 Polyethylene glycol

Polyethylene glycol also known as Macrogol was sourced from DOW Chemical Company. Polyethylene glycol is described as addition polymer of ethylene oxide and water. Polyethylene glycol grades 200-600 are liquids and grade 1000 and above are solids. Solid grades are white or off white in color and range in consistency from pastes to waxy flakes. Grades above 6000 are available as free flowing powders. Polyethylene glycol has the chemical name α-hydroxy-ω-hydroxypoly (oxy-1, 2-ethanediyl) with CAS no. 25322-68-3. Polyethylene glycol has the approved regulatory status in BP, JP, and Ph.Eur. and USP-NF. The general formula of polyethylene glycol is H \((\text{OCH}_2\text{CH}_2)_n\) OH where \(n\) are a number of oxyethylene groups. It is available in the molecular wt. from 190-9000. Polyethylene glycols are widely used in variety of pharmaceutical formulations\textsuperscript{177}. Polyethylene glycols are stable, hydrophilic substances. Polyethylene glycol has been used in the preparation of hydrogels,
which are used as controlled release agents. All grades of polyethylene glycol are soluble in water, acetone, dichloromethane, ethanol and methanol. Polyethylene glycols are chemically stable in air and in solution; all grades are hygroscopic in nature. It should be stored in well closed container in a cool dry place.

4.2.2.7 Xanthan gum

Xanthan gum is available under the brand name Xanthural and was sourced commercially from CP Kelco US Inc.

Xanthan gum is a high molecular weight polysaccharide gum. It contains D-glucose and D-mannose along with D–glucoronic acid. It has approved regulatory status in BP, Ph.Eur. and USPNF. Xanthan gum has CAS no. of [11138-66-2] and molecular weight C_{35}H_{49}O_{29} \cdot n.

Xanthan gum is widely used in oral pharmaceutical formulations as suspending and thickening agent. It is non-toxic, compatible with several drugs and has good stability and viscosity properties over a wide range of pH and temperature. Xanthan gum gels show pseudoplastic behavior, the shear thinning being directly proportional to the shear rate. Xanthan gum has been used to prepare sustained release matrix tablets. It has been reported to sustain the drug release in a predictable manner and the drug release profiles of these tablets were not affected by pH and agitation rate. Xanthan gum occurs as a cream to white, odorless, free flowing, fine powder. Various grades with different particle size are available. Xanthan gum is practically insoluble in ethanol and ether and soluble in cold or warm water. Xanthan gum is a stable material. It should be stored in a well closed container in a cool, dry place. Xanthan gum is anionic compound and usually not compatible with cationic surfactants. It is a GRAS listed excipient.

4.2.2.8 Sodium alginate

Sodium alginate is available under the brand name Keltone HVCR sourced from FMC Biopolymer.

Sodium alginate occurs as an odorless and tasteless, white to pale yellowish-brown coloured powder. It is a GRAS listed excipient and has approved regulatory status in BP, Ph.Eur. and USPNF. Sodium alginate CAS registry no. is [9005-38-3]. Sodium alginate consists of sodium salt of alginic acid. It is used in pharmaceutical formulations as both binders and disintegrants. It has also been used in the preparation of sustained release oral formulations since it can delay the dissolution of a drug from tablets in concentrations more than 10%. Sodium alginate is practically insoluble in ethanol and other organic solvents and slowly soluble in water forming a viscous colloidal solution. Various grades of sodium alginate are
commercially available ranging from 20-400 cps. Its viscosity decreases above pH 8.0. Sodium alginate is a hygroscopic material, although stable if stored at low relative humidity’s and cool temperature. It is susceptible on storage to microbial spoilage which may affect the viscosity. The bulk storage is in an air tight container in cool, dry place.

4.2.2.9 Polyvinyl alcohol and Povidone

Polyvinyl alcohol and povidone is available under the brand name Kollidone SR from BASF. Kollidone SR occurs as an odorless and tasteless, white to off white in color. Kollidone SR which is the copolymer of polyvinyl alcohol and povidone used as the rate retarding polymer. It is spray dried physical mixture of the polymers polyvinyl acetate 80% having molecular weight of about 450000 and povidone (Kollidone 30) 19%. About 0.8% of sodium lauryl sulphate and about 0.6% of silica used as stabilizers. It has excellent flowability and compressibility therefore suitable for sustained release tablets by direct compression technology.

4.2.4 Lubricants

4.2.3.1 Magnesium stearate

Magnesium stearate under the brand name Luzenac was sourced from Ferro Ltd. Magnesium stearate [CAS no. 557-04-0] is official in Ph.Eur., USPNF, BP and JP. Magnesium stearate is a white and solid at room temperature. It has the chemical formula Mg(C18H35O2)2. It is the salt containing two equivalents of stearate (the anion of stearic acid) and one magnesium cation (Mg++)

\[
\text{Mg}^{++} + 2\text{C}_{18}\text{H}_{35}\text{O}_{2}^{-} \rightarrow \text{Mg(C}_{18}\text{H}_{35}\text{O}_{2})_{2}
\]

Magnesium stearate melts at about 88°C, is not soluble in water and is generally considered safe for human consumption at levels below 2500 mg/kg.

![Structure of Magnesium stearate](image)

Figure 4.10: Structure of Magnesium stearate

Magnesium stearate is used as a diluent in the manufacture of tablets, capsules and powders. It has lubricating properties, preventing ingredients from sticking to manufacturing equipment during compression into solid tablets. Studies have shown that that magnesium stearate may affect the release time of the active ingredients in the tablets. Magnesium stearate is manufactured from both animals and vegetables.
4.2.3.2 Colloidal anhydrous silica

Colloidal anhydrous silica available under the trade name Aerosil 200 sourced from Evonik. Aerosil® 200 is hydrophilic fumed silica with a specific surface area of 200 m$^2$/g with a particle size of about 15 nm. It is loose, bluish-white colored, odorless, tasteless, non gritty amorphous powder. It is the frequently used pharmaceutical excipient to improve flow properties in tablet and capsule manufacturing. Aerosil 200 is intended specifically for the pharmaceutical industry, having been tested in accordance with European, American and Japanese pharmacopeia and has the CAS registry no. [7631-86-9], empirical formula as SiO$_2$ and molecular weight 60.08. Addition from 0.2 to 1.0% by weight of Aerosil® colloidal silica. In many formulations, hydrophilic Aerosil® colloidal silicon dioxide increases the rate of tablet disintegration and active ingredient release.

4.2.4 Waxes

4.2.4.1 Hydrogenated castor oil

Hydrogenated castor oil available as brand name Cutina HR PH was sourced from Cognis. Hydrogenated castor oil is a hard wax with a high melting point used in oral and topical pharmaceutical formulations. The USPNF 23 describes hydrogenated castor oil as the refined, bleached, hydrogenated, and deodorized castor oil, consisting mainly of the triglyceride of hydroxystearic acid. It is used as extended release agent in tablet formulation. Hydrogenated castor oil is prepared by the hydrogenation of castor oil using a catalyst. Hydrogenated castor oil has approved regulatory status in BP, Ph.Eur. and USPNF with chemical name Glyceryl-tri-(12-hydroxystearate), CAS no. [8001-78-3] and molecule weight of 939.50.

![Figure 4.11: Structure of hydrogenated castor oil](image)

Hydrogenated castor oil has moisture content of < 0.1%, practically insoluble in water, soluble in acetone, chloroform and methylene chloride.
Hydrogenated castor oil is stable at temperature up to 150°C and should be stored in a well closed container in a cool, dry place. It is generally regarded as an essentially nontoxic and non-irritant material.

4.2.4.2 Stearic acid

Stearic acid with the brand name stearin was sourced from Stearrine Ltd. Spain

Stearic acid is described as a mixture of stearic acid and palmitic acid. The content of stearic acid is not less than 40% and sum of two acids is not less than 90%. It has an approved regulatory status in BP, IP, JP, and Ph.Eur. and USPNF, with CAS registry no. [57-11-4] and chemical name Octadecanoic acid. Stearic acid is freely soluble in benzene, carbon tetrachloride and soluble in ethanol and propylene glycol and insoluble in water.

![Figure 4.12: Structure of stearic acid](image)

Stearic acid is widely used in oral and topical pharmaceutical formulations. It is mainly used in formulation as a tablet and capsule. It has been used as a sustained release drug carrier. Stearic acid is a hard, white or faintly yellow-colored, somewhat glossy, crystalline solid or a white or yellowish white powder. It has a slight odor and taste suggesting tallow. Stearic acid is a stable material, should be stored in a well closed container in a cool dry place. Stearic acid is GRAS listed and acceptable in Europe as food additive and is widely used in oral pharmaceutical formulations.

4.2.5 Alkaliser

4.2.5.1 Light magnesium carbonate

Light magnesium carbonate was procured from Deadsea, Israel

Light magnesium carbonate occurs as light, white-coloured friable masses or as a bulky, white colored powder. It has slightly earthy taste and odorless. It is either a basic hydrated magnesium carbonate or a normal hydrated magnesium carbonate with molecular formula as [(MgCO₃)₃,Mg(OH)₂·3H₂O] and molecular weight of 365.30. It has approved regulatory status in BP, JP, and Ph.Eur. and USPNF and CAS registry no. is [546-93-0]. Light magnesium carbonate is an excipient mainly used as a directly compressible material in tablet formulation. It has a bulk density of 0.12 g/cm³ and tapped density of 0.21 g/cm³ and mean particle size distribution of 99.95% passing through #350 mesh. Light magnesium carbonate
is practically insoluble in water containing carbon dioxide. Insoluble in ethanol and other solvents. It is stable in dry air and on exposure to light. The bulk material should be stored in a cool dry place. It is GRAS listed excipient.

4.2.6 Antioxidant

4.2.6.1 Butylatedhydroxy toluene

Butylated hydroxy toluene was procured from Merck Ltd. Butylated hydroxytoluene occurs as a white or pale yellow crystalline solid or powder with a faint characteristic odor.

![Figure 4.13: Structure of butylated hydroxytoluene](image)

Butylated hydroxytoluene has an empirical formula of C₁₅H₂₄O and molecular weight of 220.35. Its chemical name is 2, 6- Di-tert-buty-4-methylphenol and CAS registry no. [128-37-0]. Butylated hydroxytoluene is mainly used as an antioxidant in food and pharmaceutical industry. IIG has given maximum limit of 0.4 mg for BHT. It has a bulk density of 0.48-0.6 gm/cm³, with a melting point of 70°C and moisture content of ≤ 0.05%. It is practically insoluble in water, glycerine, propylene glycol and dilute mineral acids. Freely soluble in acetone, ethanol, methanol etc. Exposure to light, moisture and heat causes discoloration and a loss of activity. Butylated hydroxytoluene should be stored in a well closed container, protected from light, in a cool dry place.