CHAPTER 3
3. DRUG AND POLYMER PROFILE

3.1 Glipizide

3.1.1 Description

A whitish, odorless powder with PKₐ of 5.9.

3.1.2 Nomenclature

- Chemical name

- Generic Name
  Glucotrol

3.1.3 Chemical formula

C₂₁H₂₇N₅O₄S

3.1.4 Molecular weight

445.54

3.1.5 Chemical structure

3.1.6 Category
Antidiabetic

3.1.7 Solubility

Insoluble in water and ethanol; soluble in alkali hydroxides, freely soluble in dimethylformamide, and sparingly soluble in acetone.

3.1.8 Pharmacokinetics

Glipizide is rapidly absorbed ensuring prompt and constant activity. Peak plasma concentrations are attained within 1.5 to 2.0 hrs after a single oral dose. The half-life of elimination ranges from 2 to 3 hrs. The drug is excreted in the urine as virtually inactive metabolites. When taken before each meal, glynase controls post-prandial hyperglycaemia without the risk of delayed episodes of hypoglycaemia1.

3.1.9 Mechanism of action

The primary mode of action of glipizide in experimental animals appears to be the stimulation of insulin secretion from the beta cells of pancreatic islets tissue and is thus dependent on functioning beta cells in the pancreatic islets. In human glipizide appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islet. In man stimulation of insulin secretion by glipizide in response to a meal is undoubtedly of major importance. Fasting insulin levels are not elevated even on long term glipizide administration, but the post-prandial insulin response continues to be enhanced after at least six months of treatment. The insulinotopic response to a meal occurs within 30 min after an oral dose of glipizide in diabetic patients, but elevated insulin levels do not persist beyond the time of the meal challenge. Extrapancreatic effects may play a part in
the mechanism of action of oral sulfonylurea hypoglycemic drugs. Beginning 2 to 3 hrs after the administration of glipizide sustained release, plasma concentrations of glipizide gradually rise reaching to a maximum concentration within 3 to 8 hrs after dosing. With subsequent once daily dosing of glipizide sustained release, effective plasma concentrations are maintained throughout 24 hrs period with fewer peaks to trough fluctuations. In view of the time required to reach an optimal concentration in plasma, drug may be more effective when given 30 min before eating. Drug in plasma 98.3 % bound to plasma protein especially with albumin. Drug is metabolized in liver, and the metabolites are excreted in the urine. Less than 5 % drug excreted unchanged in urine.

3.1.10 Indication and dosage

Management of Type 2 diabetes (Non insuine Dependent Diabetes mellitus) where diet control alone is not effective in controlling the hyperglycemia. Dosage should be adapted to patients individually, on basis of periodic tests of glycosuria and blood sugar. The maximum daily dose should not exceed 10 mg.

3.1.11 Contraindications

Like other sulfonylurea, glipizide is contraindicated in: Insulin dependent diabetes mellitus, diabetic-keto-acidosis, diabetic coma, pregnancy, subjects with severely impaired kidney or liver function, adrenal insufficiency and cases of confirmed individual hypersensitivity to the drug. In latent diabetes or prediabetic states, the use of sulfonylurea is not advisable.

3.1.12 Drug interaction
The hypoglycemic actions of sulfonylurea may be potentiated by certain drugs including nonsteroidal anti-inflammatory drugs and other drugs that are highly protein bound salicylates, sulphonamides, and chloramphenicol. When such drugs are administered to a patient receiving Glipizide, the patient should be observed for hypoglycemia.

3.1.13 Side effect

Hypoglycemia, gastrointestinal disturbances, allergic reactions including erythema urticaria.

3.1.14 Precaution

Patients should be instructed to closely follow their physician's prescription as regards diet, dosage and schedule for taking the drug, and should be taught to recognize promptly the early symptoms of hypoglycemia, that generally are headache, irritability, sleep disorders, tremor and heavy sweating, so they can contact a doctor in good time.

3.2 Carbopol

3.2.1 Nonproprietary name

Carbopol 934P, Carbomer, Carbomera.

3.2.2 Synonyms

Carboxy polymethylene; carboxyvinyl polymer; acrylic acid polymer, carbopol.

3.2.3 Chemical name

Carboxy polymethylene.

3.2.4 Structural formula
3.2.5 Method of manufacture

A synthetic, high molecular weight, cross-linked polymer of acrylic acid co polymerized with approximately 0.75-2.0 % w/w of polyalkylsucrose. The end product contains 56-68% carboxylic acid groups.

3.2.6 Description

A white, fluffy, acidic, hygroscopic powder with a slight characteristic odor.

3.2.7 Functional category

Bioadhesive, suspending and/or viscosity-increasing agent, release-modifying agent, tablet binder.

3.2.8 Typical properties

Carbopol is soluble in water, alcohol and glycerin. Agents that can neutralize carbopol include sodium hydroxide; potassium hydroxide; sodium bicarbonate; borax; amino acids; polar organic amines.

Specific gravity: 1.41

Density (bulk): 5 g/cm³

Density (tapped): 1.4 g/cm³

Viscosity (0.2%): 20.5-54.5 poise and (0.5%): 305-394 poise.
Acidity/ alkalinity: pH = 2.7-3.5 for a 0.5 % w/v aqueous dispersion, pH = 2.5-3.0 for a 1 % w/v aqueous dispersion.

Glass transition temperature: 100-105 °C.

Moisture content: normal water content is up to 2 % w/w. Carbomers are hydroscopic and typical equilibrium moisture content at 25 °C and 50 % relative humidity is 8-10 % w/w.

3.2.9 Applications in pharmaceutical formulation or technology\(^4\)-\(^7\)

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 only of ethyl acetate, such as carbomer 971P or 974P, may be used in oral preparations, in suspensions, tablets or sustain release tablet formulation. Carbomer resins have also been investigated in the preparation of sustained-release matrix beads as enzyme inhibitors of intestinal proteases in peptide containing dosage forms, as a bioadhesive for a cervical patch and for intranasally administrated microspheres and magnetic granules for site specific drug delivery to the esophagus.

3.2.10 Stability and storage conditions

Dry powder forms of carbopol do not support the growth of molds and fungi; however, microorganisms grow well in unpreserved aqueous dispersions. Dispersions maintain their viscosity on storage during prolonged periods at room temperature or elevated temperature when stored away from light or with the addition of an antioxidant. Store in an airtight or well-closed container.
3.2.11 Incompatibilities

Carbopol is incompatible with phenol, cationic polymers, strong acids and high concentrations of electrolytes, and is discolored by resorcinol. Exposure to light causes oxidation, which is reflected in a decrease in viscosity.

3.2.12 Safety

Acute oral doses of Carbopol 934P to rats, mice and guinea pigs produce LD$_{50}$ values of 4.3, 4.6 and 2.5 g/kg, respectively. In dogs, no fatalities were noted with doses as high as 8g/kg. No primary irritation or any evidence of sensitivity or allergic reaction in humans following topical application of dispersions containing Carbopol 934P has been observed. Carbopol 934P in contact with the eye is very irritating.

3.3 Hydroxypropyl methyl cellulose

3.3.1 Nonproprietary names

BP/USP: Hypromellose

PhEur: Hypromellossum

3.3.2 Synonyms

Methyl hydroxypropyl cellulose, propylene glycol ether of methyl cellulose, methyl cellulose propylene glycol ether, methocel, HPMC.

3.3.3 Chemical names

Cellulose, 2-hydroxy propyl methyl ether.

3.3.4 Structural formula
3.3.5 Functional category

Suspending and/or viscosity increasing agent, tablet binder, coating agent, Viscosity increasing agent, adhesive anhydrous ointment ingredient, film former, emulsion stabilizer, rate-controlling polymer for sustain release.

3.3.6 Method of manufacture

A purified form of cellulose fibers obtained from cotton linters or wood pulp, are treated with caustic (sodium hydroxide) solution. The alkali cellulose thus obtained is in turn treated with methyl chloride and propylene oxide to provide methylhydroxypropyl ethers of cellulose. The fibrous reaction product is then purified and ground to a fine, uniform powder or granules.

3.3.7 Description

An odorless, tasteless, white or creamy-white fibrous or granular powder.

3.3.8 Applications in pharmaceutical formulation or technology\textsuperscript{9,10}

Hypromellose is widely used in oral and topical pharmaceutical formulations. In oral products, primarily used as a tablet binder, in film-coating and as an extended-release tablet matrix. Concentrations between 2 % and 5 % w/w may be used as a binder in either wet or dry granulation. Depending upon the viscosity grade, concentrations of 2-20 %
w/w are used for film-forming solutions to film-coat tablets. Hypromellose is also used as a suspending and thickening agent in topical formulations, particularly ophthalmic preparations. Concentrations between 0.45-0.1 % w/w may be added as a thinking agent to vehicles for eye drops and artificial tear solutions. It is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. It is used as an adhesive in plastic bandages and wetting agent for hard contact lenses.

3.3.9 Typical properties

Acidity/ alkalinity: pH = 5.5-8.0 for a 1 % w/w aqueous solution.

Autoignition temperature: 360 °C

Density (bulk): 0.341 g/cm³

Density (tapped): 0.557 g/cm³

Density (true): 1.326 g/cm³

Melting point: browns at 190-200 °C, chars at 225-230 °C, glass transition temperature is 170-180 °C.

Moisture content: hypromellose absorb moisture from the atmosphere, the water absorbed depending upon the initial moisture content and temperature and relative humidity of the surrounding air.

Specific gravity: approximately 1.3

3.3.10 Solubility

Soluble in cold water, forming a viscous colloidal solution; insoluble in alcohol, ether and chloroform, but soluble in mixtures of methyl alcohol and methylene chloride.
Certain grades are soluble in aqueous acetone, mixtures of methylene chloride and isopropyl alcohol and other organic solvents.

3.3.11 Stability and storage conditions

Very stable in dry condition. Solutions are stable at pH 3-11. Aqueous solution is liable to be affected by microorganisms when used as a viscosity-increasing agent in ophthalmic solutions and anti-microbial agent. Hypromellose powder should be store in a well-closed container, cool place and dry place.

3.3.12 Incompatibilities

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

3.4 Chitosan

Chitosan are biodegradable, high molecular weight cationic polysaccharides. Industrially they are produced from chitin, the world's second most abundant biopolymer, by deactivation process involving alkaline hydrolysis. The term chitosan refers to a family of polymers, individually characterized by their ratio of acetylated to deactivated units and molecular weight, both parameters being equally responsible for the properties of the polymer. Chitosan has been used for a range of applications as diverse as for water purification, as a food ingredient and as a pharmaceutical excipient. Braconnot first described chitin in 1811. A good deal of fundamental research on chitin occurred in the next century and a half but most of the information available today had been obtained since 1950. Chitin is the major polysaccharide of the shells of crustacean and
exoskeletons of insects. It is also found in the cell walls of many fungi, yeast and algae. Chitosan was discovered by Rouget\textsuperscript{12} in 1859 and was prepared by Hope Seylar\textsuperscript{12}. Chitosan is deacivated chitin derivative. It is found naturally in fungal cell walls but can also be produced by alkaline treatment of chitin.

3.4.1 Structure and properties of chitosan\textsuperscript{13}

Chitosan is (1-4)-2-amino-2-deoxy-B-D glucosan. It has similar structural characteristics as that of glucosaminoglycans. It is tough, biodegradable and nontoxic.

![Chemical Structure of Chitosan]

\[ R = -NH_2 - \text{Chitosan} \]

Chitin, poly-B-(1-4) linked N acetyl -D- glucosamine is a highly hydrophobic material that is insoluble in water and most ordinary solvents. This property of chitin restricts its use to application that do not require solubilization of the polymer. Considering chitosan as a weak base, a certain minimum amount of acid is required to transform the glucosamine units into the positively charged, water soluble form. At neutral pH most chitosan molecules will lose their charge and precipitate from solution. Chitosan is soluble in dilute organic acids like formic, acetic, propionic, oxalic, malonic, succinic, adipic, lactic, pyruvic, malic, tartaric and citric.

Chitosan is also soluble in dilute nitric and hydrochloric acids, marginally soluble in 0.5% phosphoric acid and insoluble in sulfuric acid at room temperature. Formic acid is
the best solvent, overall good solutions being obtained in aqueous systems containing 0.2 to 100% of this acid. Acetic acid has been selected as the standard solvent for solution property measurement. Chitosan readily dissolves is 3:1 glycerol water when the mixture contains 1% acetic acid, resulting in clear colorless and very viscous solution.

Solutions of Chitosan in 10% w/v aqueous oxalic acid show thermo reversible gel property. A solution containing more than 7% chitosan will gel in less than a day and 3% solution will gel in about 3 weeks. The chitosan films were cross-linked by glutaraldehyde vapors in a closed chamber for 24 hrs at ambient temperature. This process was done to retard the chitosan degradation rate. The decrease in degradation rate of cross linked chitosan was probably due to the retarded hydrolysis of Schiff’s bases induced by the glutaraldehyde cross linked of chitosan’s amino groups. Chitosan a linear polyelectrolyte at acidic pH, is soluble in variety of acids and interacts with polyanionic counter ions. It forms gels with a number of multivalent anions and also with glutaraldehyde. It has a high charge density i.e. one charge per glucosamine unit. Since many minerals carry negative charges, the positive charge of chitosan interacts strongly with negative surfaces.

Chitosan is a linear polyamine where amino groups are readily available for chemical reactions and salt formation with acids. The important characteristics of chitosan are its molecular weight, viscosity, deacetylation degree (DA) crystallinity index, number of monomeric units (n), water retention value, pka and energy of hydration.

3.4.2 Pharmaceutical requirements of chitosan

Particle size < 30 μm, density between 1.35 and 1.40 g/cc, pH 6.5-7.5, insoluble in water, and partially soluble in acids. Chitosan can also be characterized in terms of its
quality, intrinsic properties and physical forms. The quality characteristics of chitosan are levels of heavy metals and proteins, pyrogenicity and degree of deacetylation are the intrinsic properties.

3.4.3 Biological and chemical properties of chitosan

Biocompatibility (e.g. Nontoxic, biodegradable, natural), bioactivity, wound healing acceleration, reduced blood cholesterol levels, and immune system stimulant effect. Biomedical properties biological activity and biodegradation of chitosan are stated by Knapczyk et al. Muzzarell gives the chemical behavior of chitosan and modified chitosan. Sanford summarized the chemical and biological properties of chitosan that relate to applications. Tables 3.1 and 3.2.

3.4.4 Mucoadhesive properties of chitosan

Lehr et al. first evaluated mucoadhesive properties of chitosan. A number of characteristics are necessary for mucoadhesion (a) strong hydrogen bonding groups (-OH, -COOH), (b) strong anionic charges, (c) high molecular weight, (d) sufficient chain flexibility, and (e) surface energy properties favoring spreading on to mucus. However, chitosan is a poly-cationic polymer and does not have any anionic charge. Instead, a positively charged hydrogel is formed in acidic environment that could develop additional molecular attractive forces by electrostatic interactions with negatively charged mucosal surfaces or the negatively charged sialic acid groups of the mucus network. High molecular weight chitosan gave the best mucoadhesive properties.

3.4.5 Toxicological studies of chitosan

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In vivo toxicity tests indicated that chitosan is non toxic, inert and sterilized films was free of pyrogens. LD_{50} and oral toxicity levels of chitosan were estimated in both rats and mice. Lack of cute oral toxicity to chitosan was noticed as evidenced by an oral LD_{50}, 10g/ kg in mice. Acute systemic toxicity tests in mice did not show any significant toxic effects of chitosan.

3.5 References


Table 3.1 Chemical properties of chitosan

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<th>Property</th>
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<tbody>
<tr>
<td>Cationic polyamine</td>
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<td>High charge density at pH &lt; 6.5</td>
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<tr>
<td>Adheres to negatively charged surfaces</td>
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<tr>
<td>Forms gels with poly anions</td>
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<tr>
<td>High molecular weight linear polyelectrolyte</td>
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<tr>
<td>Viscosity, high to low</td>
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<tr>
<td>Chelates certain transitional metal</td>
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Table 3.2 Biological properties of chitosan

<table>
<thead>
<tr>
<th>Property</th>
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<tbody>
<tr>
<td>Biocompatibility</td>
</tr>
<tr>
<td>Natural Polymer</td>
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<tr>
<td>Biodegradable to normal body constituents</td>
</tr>
<tr>
<td>Safe and non – toxic</td>
</tr>
<tr>
<td>Haemostatic</td>
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<tr>
<td>Bacteriostatic</td>
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<td>Fungistatic</td>
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