Chapter 2
Literature Review

2.1 INTRODUCTION TO CANCER:

Cancer is the second leading cause of death in the United States. Half of all men and one third of all women in the United States will develop cancer during their lifetimes. Today, millions of people are living with cancer or have had cancer. The risk of developing most types of cancer can be reduced by changes in a person's lifestyle, for example, by quitting smoking and eating a better diet. The sooner a cancer is found and treatment begins, the better are the chances for living for many years (http://www.cancer.org/docroot/CRI/content/).

Cancer develops when cells in a part of the body begin to grow out of control. Although there are many kinds of cancer, they all start because of out-of-control growth of abnormal cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide more rapidly until the person becomes an adult. After that, cells in most parts of the body divide only to replace worn-out or dying cells and to repair injuries. Because cancer cells continue to grow and divide, they are different from normal cells. Instead of dying, they outlive normal cells and continue to form new abnormal cells.

Cancer cells develop because of damage to DNA. People can inherit damaged DNA, which accounts for inherited cancers. More often, though, a person's DNA becomes damaged by exposure to something in the environment, like smoking.

Cancer usually forms as a tumor. Some cancers, like leukemia, do not form tumors. Instead, these cancer cells involve the blood and blood-forming organs and circulate through other tissues where they grow. Often, cancer cells travel to other parts of the body where they begin to grow and replace normal tissue. This process is called metastasis.

Oropharyngeal cancer develops in the part of throat just behind mouth, called the oropharynx. Oropharynx includes the base of tongue, soft palate, tonsils and tonsillar pillars and back wall of the throat. As oropharynx helps in breathing, eating and talking, patients suffering from oropharyngeal cancer need special help adjusting to the side effects of cancer and its treatment (www.cancer.gov). Signs and symptoms of oropharyngeal cancer are:

- a sore throat or a feeling that something is caught in the throat that doesn't go away
- voice changes
- a lump or mass in the neck
- weight loss
- Persistent bad breath.
- Trouble swallowing
- A dull pain behind the breastbone.
- Cough.

Tumors of the head and neck have been clearly related to tobacco consumption, heavy ingestion of alcohol, and chewing of tobacco. Poor oral hygiene, mechanical irritation, and the Plummer-Vinson syndrome have been implicated in the etiology of head and neck cancer.

Risk factors include the following:

- Smoking and chewing tobacco.
- Heavy alcohol use.
- A diet low in fruits and vegetables.
- Drinking maté, a stimulant drink common in South America.
- Chewing betel quid, a stimulant commonly used in parts of Asia.
- Being infected with human papillomavirus (HPV) (www.cancer.gov).

A case-control study has found that use of mouthwash with high alcohol content is associated with a 40% to 60% increase in oropharyngeal malignancy after correction for known etiologic factors (Winn et al, 1991).

In India, squamous cell carcinoma of the head and neck region accounts for 12% of all malignancies (http://www.doctorndtv.com/topicsh/Oral).The American Cancer Society estimates about 34,360 new cases (24,180 in men and 10,180 in women) of oral cavity and oropharyngeal cancer will be diagnosed in the United States in 2007. An estimated 7,550 people (5,180 men and 2,370 women) will die of these cancers in 2007. Head and neck cancers account for about 3% of all cancers in the United States. About 84% of patients survive at least one year after diagnosis. The survival rates for patients living at least five and ten years after diagnosis are 57% and 45%, respectively (www.peoplelivingwithcancer.org).

2.2 TREATMENT OF OROPHARYNGEAL CANCER:

Therapies being used to treat oropharyngeal cancer are surgery, radiation therapy and chemotherapy.

2.2.1 Surgery:

Depending on the exact location and stage of cancer, one or more operations may be used to remove the cancer, and to help restore the appearance and function of the tissues affected by the cancer or its treatment.

2.2.2 Radiation therapy:

It uses high energy rays or particles to destroy cancer cells or slow their rate of growth. It can be used as main treatment for small cancers. Patients with larger cancers may need both surgery and radiation therapy. After surgery, radiation therapy can be used as an additional (adjuvant) treatment to kill very small deposits of cancer that can not be seen and removed during surgery. Also, radiation therapy can be used to relieve symptoms of cancer, such as pain, bleeding, difficulty swallowing, and problems caused by metastasis to bones.

2.2.3 Chemotherapy:

Chemotherapy is the use of anticancer drugs given to shrink the cancer before surgery or radiation treatment. This is called as neoadjuvant therapy. Chemotherapy has also been used for palliation for cancers of head and neck that are too large to be completely removed surgically and which can not be controlled by radiation therapy.

The two chemotherapy drugs used most often for cancers of oropharynx are **Cisplatin** and **5-Fluorouracil (5-FU)**. Other drugs that may be used include **Methotrexate, Bleomycin, Carboplatin.** Several other drugs are being studied, but are not often used. Newer drugs that are being used include **paclitaxel, docetaxel, and ifosfamide.**

Side effects of Chemotherapy:

Chemotherapy drugs kill the cancer cells but also damage some normal cells. Therefore, careful attention must be given to avoid or minimize side effects. The side effects to chemotherapy depend on the type of drug used, the amount taken, and the length of treatment. Temporary side effects include nausea and vomiting, loss of appetite, loss of hair and mouth sores. There may be fall in blood cell counts.

Most of the anticancer drugs have to be administered parentrally as they have poor bioavailability when administered orally either due to poor absorption or due to significant first pass metabolism.

However, this route is associated with pain on administration, formulations need to be sterile, and it is time consuming for doctors and patients. In addition, certain health risks are associated with this route (including psychological distress, occasional allergies, hypertrophy or atropy of the subcutaneous fat at the injection site, especially on chronic administration) (Nair and Chien, 1993). ***A recent study concerning patient preference showed that the large majority, approximately 90%, of cancer patients preferred oral administration to intravenous administration*** (Liu et al, 1997).

However, patients suffering from oropharyngeal cancer have difficulty in swallowing. Systemic delivery of drugs through mucosal membranes presents a possible solution to the problems of hepatic and gastrointestinal metabolism associated with oral delivery and the health risks associated with the parenteral route (Rathbone et al., 1994).

The buccal region appears to be an attractive site for administration of drugs due to good accessibility, smooth and relatively immobile surface, avoidance of possible degradation in the gastrointestinal tract, and avoidance of the first-pass metabolism in the liver. There are some therapeutic reasons why the oral cavity may be a useful route for drug delivery; for example, for those patients nil-by-mouth, if either nausea or vomiting is a problem, if the patient is unconscious, in patients with an upper gastrointestinal tract disease or surgery which affects oral drug absorption, or in patient groups which have difficulty swallowing peroral medications, e.g., the very young and the elderly.

Additional advantages of the oral cavity as a site for systemic drug delivery include: sterile techniques are not required during manufacture or administration, the oral cavity contains teeth upon which drug delivery systems can be physically attached using dental adhesives, the oral mucosa is low in enzyme activity and enzymatic degradation is relatively slow, hence from the point of drug inactivation, it would be preferred to the nasal or rectal routes (de Vries et al., 1991). Also the buccal membrane, with its expanse of accessible, smooth surface, offers a platform for localising prolonged drug delivery systems (Tucker, 1988).

However, continuous saliva excretion and swallowing may lead to a very short residence time in the oral cavity (Rathbone et al., 1994). To overcome this problem, bioadhesive dosage forms have been developed, such as bioadhesive tablets, patches, gels and ointments, and medicated chewing gums (Gandhi and Robinson, 1994; Hao and Heng, 2003; Shin et al, 2000, Birudaraj et al., 2005).

2.3 BUCCAL DRUG DELIVERY:

Sobero in 1847 noted that drugs could be absorbed through mucous membranes. In 1877, Brunton stated that glyceryl trinitrate was absorbed sublingually. In the early 1980s, academic research groups working in the ophthalmic field pioneered the concept of mucoadhesion as a new strategy to improve the efficacy of various drug delivery systems (Harris D, et al, 1992).

The buccal mucosa is generally considered to be that lining the inner cheek, buccal formulations typically being placed in the mouth between the upper gingivae (gums) and cheek. In some texts, however the whole oral cavity is referred to as the buccal cavity. (Smart, 2004)

Owing to the ease of the administration, the oral cavity is an attractive site for the delivery of drugs. Through this route it is possible to realize mucosal (local effect) and transmucosal (systemic effect) drug administration. In the first case, the aim is to achieve a site-specific release of the drug on the mucosa, whereas the second case involves drug absorption through the mucosal barrier to reach the systemic circulation. The oral mucosa is highly vascularized and presents a reduced enzymatic activity with respect to intestinal, rectal and nasal mucosa and is less sensitive to damage and irritation than the nasal epithelium. The transmucosal route utilizes sublingual and buccal mucosa as absorption sites with two different therapeutic goals. In particular, the sublingual route is generally employed for the delivery of drugs characterized by a high permeability across the mucosa and used in the treatment of acute disorders, whereas the buccal route is generally used in the treatment of chronic disorders when a prolonged release of the active substance is required.

Although the sublingual route has been extensively investigated in the past, the interest on buccal drug delivery is comparatively more recent and coincides with the advances in biotechnology that have made peptides readily available for therapeutic use. Hydrophilic high molecular weight drugs, such as peptides that cannot be administered by the oral route due to degradation and poor absorption, are favorable candidates for administration via the buccal route. (Rossi et al, 2005).

Systemic delivery of drugs through mucosal membranes presents a possible solution to the problems of hepatic and gastrointestinal metabolism associated with oral delivery and the health risks associated with the parenteral route.

Transdermal and Transmucosal routes offer attractive alternatives routes for drug administration and may avoid significant drawbacks of peroral and parentral administration. These routes of administration bypass first pass metabolism by delivering drug directly into systemic circulation. Low permeability due to skin's stratum cormeum limits transdermal delivery of pharmacological agents, leaving transmucosal routes with greater permeabilities as the only significant alternative. Transmucosal delivery of drugs can be achieved from different administration sites such as mouth, nose, vagina and rectum. Vaginal and rectal routes have poor patient compliance; moreover vaginal delivery is obviously restricted to females. In case of nasal administration, ciliary cells are injured by chronic administration of drugs and the area of nasal mucosa is small. Compared to the other routes of drug administration, buccal route has larger surface area for drug application, better patient compliance, ease of dosage forms in case of emergencies, robustness and good accessibility. These advantages make this route of administration very attractive for systemic delivery.

Table 2.1 suggests that as a site for drug delivery, the oral cavity offers several advantages over the gastrointestinal route and other alternative routes of drug administration.

Table 2.1 Comparison of some routes for systemic delivery

Feature	Gasrtointestinal	Dermal	Nasal	Oral Mucosal	Vaginal
Accessibility	+	+++	++	++	+
Surface area	+++	+++	+	++	+++
Surface environment	+	++	++	+++	+
Permeability	+++	+	+++	++	+++
Reactivity	++	++	+	+++	++
Vascular drainage	+++	+	+++	++	+++
First pass clearance	+	+++	+++	+++	+
Patient acceptibility	++	+++	++	+++	++

+ Poor; +++Excellent

2.3.1 Anatomy and physiology of oral mucosa:

The oral mucosa is a complex series of tissues with a range of permeabilities. As shown in Figure 2.1, the mucosae in the oral cavity may be divided as follows: (1) sublingual mucosa, the membrane of the ventral surface of the tongue and the floor of the mouth; (2) buccal mucosa, the lining of the cheek and the upper and lower lips; and (3) gingival mucosa, the membrane lining the roof of the mouth. The mucosal lining of the oral cavity differ in their thickness, presence of keratinization, polarity of the lipid, and blood flow to the membranes, as summarized in Table 2.2.

The oral mucosal membrane comprises of a superficial layer, epithelium, covered with mucus. The turnover time of the buccal epithelium has been estimated to be 5-6 days. The buccal epithelium is composed of 40-50 cell layers. Oral epithelium has a well-defined layer of cuboidal basal cells succeeded by several layers of flattened cells-the prickle cell layer, which is also referred to as spinous cell layer. Below the epithelium lies the connective tissue referred to as lamina propria. The lamina propria consists of collagen fibrils, a supporting layer of connective tissue, blood vessels, and smooth muscle. A schematic representation of the tissue components of the oral mucosa is shown in Figure 2.2

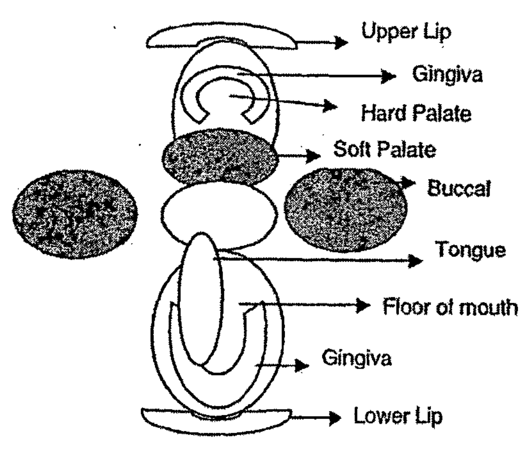


Fig. 2.1. Schematic representation of the oral cavity, showing keratinized (white) and non-keratinized (grey) regions (Rathbone et al.,1994)

.The intercellular spaces in basal cells are even in width. In the spinous layer, they increase in width and reach a maximum in upper spinous layers. A fine granular or filamentous material in an amorphous background is present in the intercellular spaces throughout the epithelium. This material is denser in the superficial layer than in the spinous and basal cell layers. Desmosomes and hemidesmosomes are found in the basal, upper, and lower prickle cell layers. Tight junctions are rare throughout the buccal epithelium.

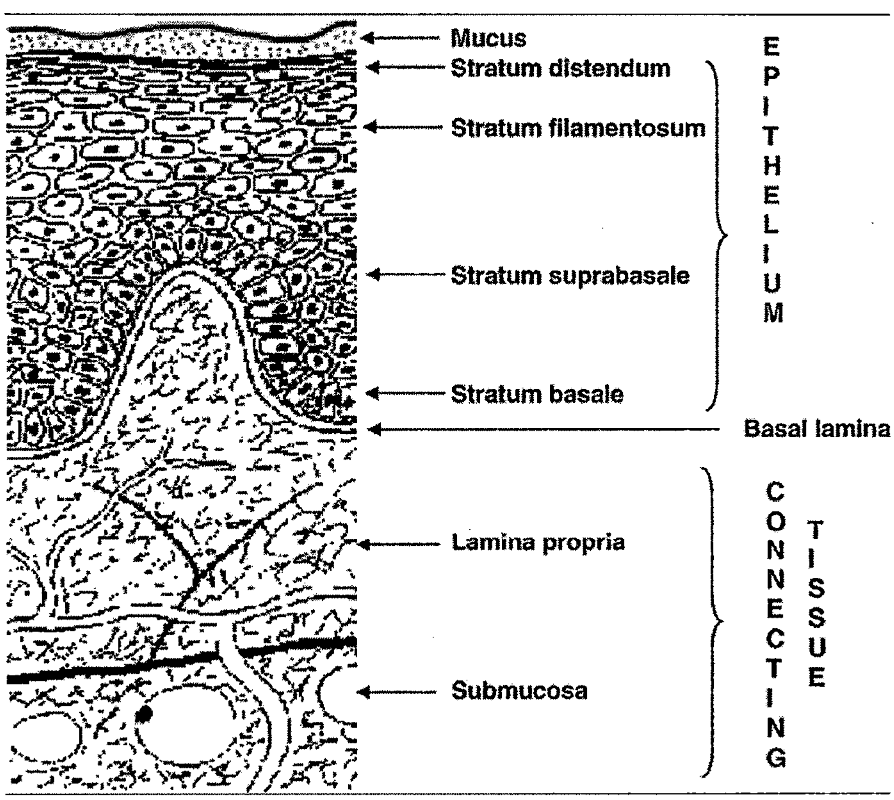


Fig 2.2 Schematic representation of the main tissue components of the oral mucosa

Table 2.2 Characteristics of Different Regions of Oral Mucosa and Their Suitability for Buccal Delivery

Tissue	Keratinization	Thickness (μm)	Lipid polarity	Permeability	Blood flow	Salivary flow
Sublingual	No	100-200	Polar	++	+	---
Gingival	Yes	200	Non-polar	---	+	+
Palatal	Yes	250	Non-polar	---	-	

++ indicates very suitable; + indicates suitable; - indicates not suitable; --- indicate least suitable; + and – signs indicate degree of suitability for buccal delivery

2.3.2 Absorption pathways

Substances can be transported across epithelial membranes by passive diffusion, carrier mediated, active transport or specialized mechanisms such as pinocytosis or phagocytosis. Because of the stratified epithelium in the oral cavity, phagocytosis or pinocytosis are not relevant.

Across transcellular route, the absorption of drug is limited by magnitude of partition coefficient. Permeation of polar molecules, such as peptide-based pharmaceuticals, may be by way of paracellular route (Fig 2.3). Carrier mediated transport has been reported for monocarboxylic acids acroos the rabbit buccal mucosa (Utoguchi et al., 1997).

The flux of drug through the membrane under sink condition for paracellular route can be written as Eq. (1)

$$Jp=Dp\ \varepsilon / hp \times Cd- \qquad \text{-----(2.1)}$$

Where, Dp is diffusion coefficient of the permeate in the intercellular spaces, hp is the path length of the paracellular route, ε is the area fraction of the paracellular route and Cd is the donor drug concentration.

Similarly, flux of drug through the membrane under sink condition for transcellular route can be written as Eq. (2).

$$Jc = \frac{(1-\varepsilon)DcKc}{hc}\,Cd \qquad \text{-----(2.2)}$$

Where, Kc is partition coefficient between lipophilic cell membrane and the aqueous phase, Dc is the diffusion coefficient of the drug in the transcellular spaces and hc is the path length of the transcellular route (Shojaei et al., 1997).

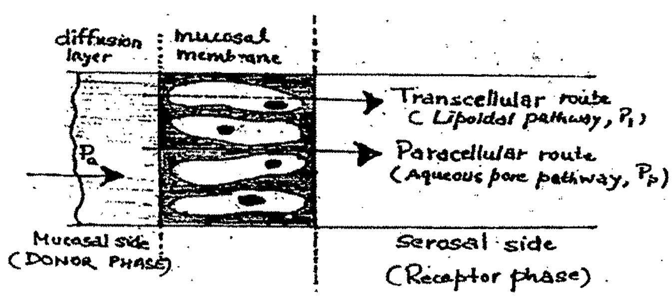


Fig .2.3. Permeation across mucosal membrane

2.3.3 Barriers to penetration across buccal mucosa

The barriers such as saliva, mucus, membrane coating granules, basement membrane etc retard the rate and extent of drug absorption through the buccal mucosa. The main penetration barrier exists in the outermost quarter to one third of the epithelium (Gandhi and Robinson, 1988).

2.3.3.1 Membrane coating granules or cored granules

In nonkeratinized epithelia, the accumulation of lipids and cytokeratins in the keratinocytes is less evident and the change in morphology is far less marked than in keratinized epithelia. The mature cells in the outer portion of nonkeratinized epithelia become large and flat, retain nuclei and other organelles and the cytokeratins do not aggregate to form bundles of filaments as seen in keratinizing epithelia. As cells reach the upper third to quarter of the epithelium,membrane-coating granules become evident at the superficial aspect of the cells and appear to fuse with the plasma membrane so as to extrude their contents into the intercellular space. The membrane-coating granules found in nonkeratinizing epithelia are spherical in shape, membrane-bounded and measure about 0.2 μm in diameter (Squier, 1977).

However, current studies employing ruthenium tetroxide as a post-fixative indicate that in addition to cored granules, a small proportion of the granules in nonkeratinized epithelium do contain lamellae, which may be the source of short stacks of lamellar lipid scattered throughout the intercellular spaces in the outer portion of the epithelium. In contrast to the intercellular spaces of stratumcorneum, those of the superficial layer of nonkeratinizing epithelia contain electron lucent material, which may represent nonlamellar phase lipid, with only occasional short stacks of lipid lamellae (Sudhakar et al., 2006).

2.3.3.2 ***Basement membrane***

Although the superficial layers of the oral epithelium represent the primary barrier to the entry of substances from the exterior, it is evident that the basement membrane also plays a role in limiting the passage of materials across the junction between epithelium and connective tissue. A similar mechanism appears to operate in the opposite direction. The charge on the constituents of the basal lamina may limit the rate of penetration of lipophilic compounds that can traverse the superficial epithelial barrier relatively easily.

2.3.3.3 ***Mucus***

The epithelial cells of buccal mucosa are surrounded by the intercellular ground substance called mucus with the thickness varies from 40 μm to 300 μm (Allen, 1989). Though the sublingual glands and minor salivary glands contribute only about 10% of all saliva, together they produce the majority of mucus and are critical in maintaining the mucin layer over the oral mucosa (Sudhakar et al., 2006). It serves as an effective delivery vehicle by acting as a lubricant allowing cells to move relative to one another and is believed to play a major role in adhesion of mucoadhesive drug delivery systems (Peppas and Buri, 1985). At buccal pH, mucus can form a strongly cohesive gel structure that binds to the epithelial cell surface as a gelatinous layer (Gandhi and Robinson, 1988). Mucus molecules are able to join together to make polymers or an extended three-dimensional network Mucus is composed chiefly of mucins and inorganic salts suspended in water. Mucins are a family of large, heavily glycosylated proteins composed of oligosaccharide chains attached to a protein core (Fig 2.4). Three quarters of the protein core are heavily glycosylated and impart a gel like characteristic tomucus.Mucins contain approximately 70–80% carbohydrate, 12–25% protein and up to 5% ester sulphate (Harding et al., 1983). Mucins are secreted as massive aggregates by prostaglandins withmolecularmasses of roughly 1 to 10million Da.Within these aggregates, monomers are linked to one another mostly by noncovalent interactions, although intermolecular disulphide bonds also play a role in this process. Oligosaccharide side chains contain an average of about 8–10 monosaccharide residues of five different types namely L-fucose, D-galactose, N-acetyl-D-glucosamine, N-acetyl-D-galactosamine and sialic acid. Amino acids present are serine, threonine and proline (Jimmenez et al., 1993). Because of the presence of sialic acids and ester sulfates, mucus is negatively charged at physiological salivary pH of 5.8–7.4 (Gandhi and Robinson, 1988).

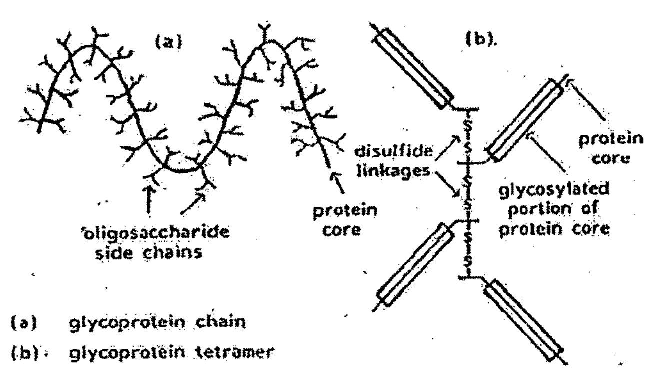


Fig 2.4 Structure of mucus

2.3.3.4 Saliva

Saliva is the protective fluid for all the tissues of the oral cavity and its necessity for oral health generally only becomes significant when either the amount of saliva is reduced or its quality changes. Saliva protects the soft tissues from abrasion by rough materials and from some chemicals. It allows the continuing mineralisation of the enamel of teeth after they erupt and aids remineralisation of the enamel in the early stages of dental caries. It also plays an important antibacterial role by either aiding or preventing the attachment of bacteria to the surfaces of the oral cavity (Rathbone et al., 1994).

Disappearance of drugs from the oral cavity has been shown to be by passive diffusion of the nonionised species (Beckett and Triggs,1967; Barsuhn et al, 1988; Rathbone,1991a, Rathbone, 1991b; Beckett and Moffat, 1968) Hence the absorption of drugs from the oral cavity is pH dependent and the variations in saliva pH will influence drug absorption (Beckett and Triggs, 1967; Barsuhn et al., 1988; Al Sayed et al, 1987) however, it may be possible to adjust the pH of whole saliva or at a localised region to promote the presence of nonionised drug species and facilitate absorption.

Several independent lines of evidence suggest that saliva and salivary mucin contribute to the barrier properties of oral mucosa (Schenkels et.al., 1996). The major salivary glands consist of lobules of cells that secrete saliva; parotids through salivary ducts near the upper teeth, submandibular under the tongue, and the sublingual through many ducts in the floor of the mouth. Besides these glands, there are 600–1000 tiny glands called minor salivary glands located in the lips, inner cheek area (buccal mucosa), and extensively in other linings of the mouth and throat (Kontis and Johns, 1998). Total output from the major and minor salivary glands is termed as whole saliva, which at normal conditions has flow rate of 1–2 ml/min (Mattes, 1997). With stimulation of salivary secretion, oxygen is consumed and vasodilator substances are produced; and the glandular blood flow increases, due to increased glandular metabolism (Sinha, 1999). The thickness of the salivary film was reported by Collins and Dawes (Collins and Dawes, 1987) as being between 0.07 and 0.10 mm.

The stimulation of saliva production is under parasympathetic and sympathetic control. Parasympathetic stimulation produces serous watery saliva, while sympathetic stimulation produces much thicker saliva which is higher in organic content and lower in volume (Baum, 1987). The total average volume of saliva produced daily in an adult is around 750 ml (Edgar, 1992; Mandel and Wotman, 1976). This is made up of 60% from the submandibular glands, 30% from the parotids, less than 5% from the sublingual glands and between 5% and 7% from the minor salivary glands. Saliva is composed of 99.5% water in addition to proteins, glycoproteins and electrolytes. It is high in potassium (7×plasma), bicarbonate (3×plasma), calcium, phosphorous, chloride, thiocyanate and urea and low in sodium (1/10×plasma).

The pH of whole saliva varies between 6.5 and 7.5 and will depend on how the pH is measured - particularly whether the carbon dioxide is driven off first. The pH of saliva as it leaves the ducts is different to that when it is measured in whole saliva and varies markedly depending on the flow rate. The pH of saliva as it leaves the salivary ducts can be a low as 5.5 but increase to over pH 7 at high flow rates (Edgar, 1992; Mandel and Wotman, 1976). This is mainly due to the increase in bicarbonate and sodium concentrations which also occur with increasing flow. The main buffering system is the bicarbonate system, however, phosphate and protein buffers also play a role. Saliva contains enzymes namely α-amylase (breaks 1–4 glycosidic bonds), lysozyme (protective, digests bacterial cell walls) and lingual lipase (break down the fats) (Silvers and Som, 1998).

2.4 ADVANTAGES OF BUCCAL DRUG DELIVERY

The oral mucosa has a rich blood supply. Drugs are absorbed from the oral cavity through the oral mucosa, and transported through the deep lingual or facial vein, internal jugular vein, and braciocephalic vein into the systemic circulation. Lymphatic uptake of drug also occurs but is less common (Gibaldi and Kanig, 1965). Following buccal or sublingual administration the drug gains direct entry into the systemic circulation thereby avoiding the hepatic first-pass effect. Contact with the digestive fluids of the upper gastrointestinal tract is avoided. In addition the rate of drug absorption is not influenced by food or gastric emptying rate. The mucosal lining of the oral cavity is generally more permeable to drugs than the skin (Galey et al., 1976; Lesch et al, 1989), but in contrast has a much smaller surface area available for absorption.

However, the area of the buccal membrane is sufficiently large to allow a delivery system to be placed at different sites on the same region of the oral cavity on different occasions which may be advantageous if the drug, delivery system or other excipients reversibly damage or irritate the mucosa. Additionally, there are two areas of buccal membranes per mouth which would allow buccal drug delivery systems to be placed alternatively on the left and right buccal membranes. There is good accessibility to the membranes that line the oral cavity which makes application painless and without discomfort, precise dosage form localization possible and facilitates ease of removal without significant associated pain and discomfort. Thus patients could conceivably control the period of administration or terminate delivery in cases of emergencies. ***The oral mucosal route has in the past exhibited better patient compliance than either the vaginal or rectal route of drug administration thus it would be anticipated that novel buccal or sublingual dosage forms would be well accepted by patients.*** In addition the route is not gender specific as is the case with the vaginal route. Merkle et al (1990) surmise that since the oral mucosa is routinely exposed to a multitude of different foreign compounds and physical insult it has evolved as a robust membrane that is less prone to irriversible damage by the drug, dosage form or additives used therein (Merkle et al., 1990). **Thus it may be feasible to include permeation enhancers in the formulation to increase systemic availability of the drug without observing permanent damaging effects.**

2.5 LIMITATIONS OF BUCCAL DRUG DELIVERY

2.5.1 The oral cavity

The oral cavity has restrictions that limit its use as a site for systemic drug delivery. The absorption rate into, and the elimination rate from, the blood dictate the plasma concentration - time profile of a drug administered via this route. The absorption rate is a function of the surface area, permeability coefficient and the concentration of drug at the surface of the absorbing membrane. The available surface area for absorption in the oral cavity is relatively small (total surface area of oral cavity membranes ~ 170 cm ^{2} (Collins and Dawes, 1987). The area of each specific membrane in the oral cavity is considerably smaller. If the effective area for absorption was dictated by the dimensions of a delivery system this area then becomes even smaller.

The oral cavity is a complex environment for drug delivery as there are many interdependent and independent factors which reduce the absorbable concentration at the site of absorption (Fig. 2.5). Saliva is continuously secreted into the oral cavity diluting drugs at the site of absorption resulting in low drug concentrations at the surface of the absorbing membrane. Involuntary swallowing of saliva results in a major part of the dissolved or suspended released drug being removed from the site of absorption; furthermore, there is a risk that the delivery system itself could be swallowed. Saliva is a particular problem for the sublingual route where saliva pools before swallowing and two major salivary ducts enter this area. In this region high concentrations of drug in contact with the sublingual mucosa are sustained for a relatively short period of time (probably in the order of minutes) and both drug and delivery system are rapidly flushed away by saliva (Harris and Robinson, 1992). Substances dissolved or suspended in saliva are distributed to and cleared from different parts of the oral cavity at different rates (Dawes and Weatherell, 1990); Weatherell et al., 1984; Jenkins and Krebsbach, 1985; Weatherell et al., 1989). Released drug will not only be distributed to less permeable regions of the oral cavity but also localized drug concentrations in the mouth may occur which may or may not be of a sufficiently high concentration for effective plasma concentrations. The mobility of some of the oral mucosal membranes may affect the retention of delivery system. The sublingual area moves freely during talking and swallowing which makes it unsuitable for attachment of a retentive delivery system (Harris and Robinson, 1991). The tongue is a highly innervated area and any delivery system administered to the oral cavity is likely to be explored by this organ which may affect release rates or retention times. Eating and drinking may also present limitations for this route. If the delivery system is not designed to overcome these limitations, then delivery will have to be terminated while these activities take place.

2.5.2. *Drugs*

Drug characteristics may limit the use of the oral cavity as a site for drug delivery. Taste, irritancy, allergenicity and adverse properties such as discolouration or erosion of the teeth may limit the drug candidate list for this route. In addition the drug should not adversely affect the natural microbial flora - the oral cavity has a complex microflora whose composition and variability is essential for its health and appearance. Both drug (and excipients) may act as irritants, cause allergic reactions or be keratinolytic. There is therefore the need for careful evaluation of the potential for mucosal irritation with new delivery systems and their components. Place et al. applied aqueous formulations to the buccal mucosa of normal volunteers to assess for the irritancy potential of drugs (Place et al., 1988).They found that the noninvasive system was capable of assessing the contact irritation of drugs under varying formulation conditions. It is important during preformulation studies that all additives should be critically evaluated for there irritancy, allergenic response and effect on the natural microbial flora.

The problems of taste, discoloration of teeth and erosion of teeth may be overcome using unidirectional delivery systems; however, the potential for lateral diffusion during penetration followed by back partitioning of the drug into the oral cavity may mean that this problem is not overcome in all cases. In such circumstances, however, the concentration of drug in the oral cavity will be reduced.

2.5.3. *Delivery systems*

Traditionally, oral mucosal drug delivery systems for systemic delivery have been adapted from those used for other routes (e.g., conventional tablets). With these systems retention of the drug and the delivery system at the chosen site of absorption has been poorly addressed, drug concentrations have failed to build up at the absorbing membrane and delivery systems have dislodged, causing the patient to expel the delivery system or choke on it. In addition, they do not allow the patient to concurrently eat, drink or, in some cases, talk. Pharmaceutical scientists have failed to address the limitations of the oral cavity and environmental issues which influence the successful development of an oral mucosal drug delivery system.

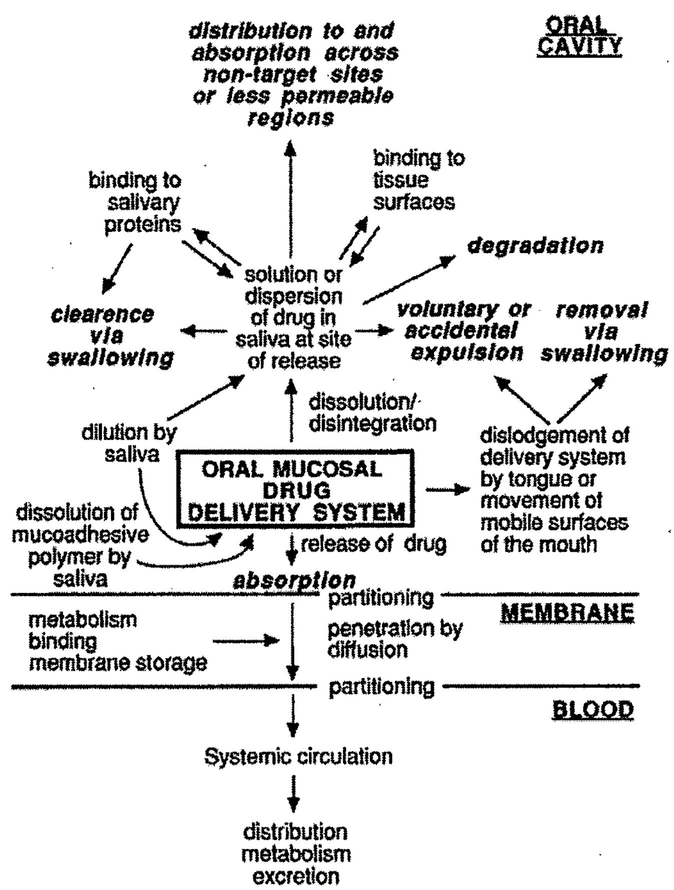


Fig. 2.5. Problems associated with the oral cavity as a site for systemic drug delivery

2.6 PENETRATION ENHANCERS

Membrane permeation is the limiting factor for many drugs in the development of buccal adhesive delivery devices. The epithelium that lines the buccal mucosa is a very effective barrier to the absorption of drugs. Penetration enhancers are the substances added to pharmaceutical formulations to increase membrane permeation rate or absorption rate of a co administered drug. Different types of penetration enhancers are listed below in Table 2.3 (Birudaraj et al., 2005; Sudhakar et al, 2006). Table 2.4 gives summary of studies carried out on buccal permeation enhancement.

Table 2.3. Buccal penetration enhancers

Bile salts	Sodium glycocholate, sodium deoxycholate, sodium taurocholate, sodium glycodeoxycholate, sodium taurodeoxycholate.
Fatty acids:	Oleic acid, capric acid, lauric acid, lauric acid/propylene glycol, methyloleate, lysophosphatidylcholine, phosphatidylcholine
Fatty acid esters:	Glyceryl monostearate, sodium caprate, sodium laurate, sodium fusidate, lauranth-9, diethylene glycol monoethyl ether, sucrose laurate, sucrose oleate, sucrose palmitate, sucrose stearate.
Surfactants	Sodium lauryl sulphate, polyoxyethylene, Polyoxyethylene-9-laurylether, Polyoxythylene-20-cetylether, Benzalkonium chloride, 23-lauryl ether, cetylpyridinium chloride, cetyltrimethyl ammonium bromide.
Alcohols/Cosolvents	Ethanol, Polyethylene glycols
Complexing agents	Cyclodextrin, EDTA
Chitosan	
Thiolated polymers:	Chitosan-4-thiobutylamide,chitosan-4-thiobutylamide/GSH, chitosan-cysteine, Poly (acrylic acid)-homocysteine, polycarbophil-cysteine, polycarbophil- cysteine/GSH, chitosan-4-thioethylamide/GSH, chitosan-4-thioglycholic acid.
Lecithins:	Lecithin, lysolecithin
Amides	Urea
Azones	Laurocapram
Miscellaneous	Menthol, dextran sulfate, dihydrofusidates, alkyl glycosides, aprotinin, labrafil, limonene(d), sodium salicylate, sulfoxides

Table 2.4 Reports citing use of enhancers in buccal permeation enhancement

Drug	Enhancer	Results	Reference
Piroxicam	3% Sodium deoxycholate	Increase in Flux value and enhancement factor	Attia et al, 2004
Lidocaine hydrochloride	Sucrose esters	Increased flux	Ganem-Quintanar et al, 1998
Myristoylated dipeptide	Ethanol/Phosphate buffer (30/70 pH 7.4)	Enhanced permeation	Veuillez et al, 2002
Flecainide, Sotalol	1.0% (w/v) Sodium glycocholate	Effective penetration enhancement of flecainide in but no improvement in the transport of sotalol across buccal mucosa.	Deneer et al, 2002
Triamcinolone acetonide	Azone	Increased tissue concentrations of drug , which may be of clinical benefit	Nicolazzo et al, 2005
Acyclovir	5-Methyl-pyrrolidinone chitosan	Significant penetration enhancement	Sandri et al, 2004
Buserelin	10 mM Sodium glycodeoxycholate	Significant improvement in Bioavailability	Junginger et al, 1999
Caffeine, Estradiol	Sodium dodecyl Sulfate	Enhnaced permeation of Caffeine but reduced permeation of estradiol.	Nicolazzo. et al, 2004,
Buspirone	5% Oleic acid, 40% propylene glycol in buffer	Enhanced flux	Birudaraj et al, 2005
Triamcinolone acetonide	Sodium deoxycholate	1.5 times enhanced bioavailabilty	Shin et al, 2000.

2.7 BIOADHESION

Bioadhesion is the phenomenon between two materials,which are held together for extended periods of time by interfacial forces (Longer and Robinson, 1986). It is generally referred as Bioadhesion when .interaction occurs between polymer and epithelial surface; mucoadhesion when occurs with the mucus layer covering a tissue. Generally bioadhesion is deeper than the mucoadhesion. However, these two terms seem to be used interchangeably.

2.7.1 Mechanism and theories of bioadhesion

The mechanisms by which mucoadhesive bonds form are not completely clear. It is generally accepted that the process involves three steps (Duchene et al., 1988).

1. Wetting and swelling of polymer to permit intimate contact with biological tissue.

2. Interpenetration of bioadhesive polymer chains and entanglement of polymer and mucin chains (Fig 2.6).

3. Formation of weak chemical bonds between entangled chains.

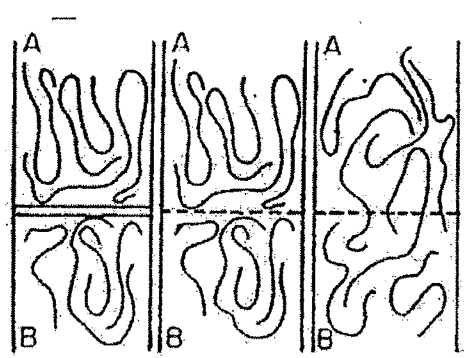


Fig. 2.6 Chain interpenetration during bioadhesion of polymer (A) with the mucus (B)

Five theories of adhesion have been developed to explain the properties of a wide range of materials including glues, adhesives and paint (Chickering and Mathiowitz, 1999).

(i) The **electronic theory** assumes that the different electronic structures of the mucoadhesive and the biological material result in electron transfer upon contact.

(ii) The **adsorption theory** states that the bioadhesive bond is due to van der Waals interactions and hydrogen bonds. This is the most widely accepted theory of adhesion.

(iii) The **wetting theory** uses interfacial tension to predict the degree of spreading of, for example, a gel formulation on the mucosa, which can then be used to predict the degree of mucoadhesion.

(iv) The **diffusion theory** states that interpenetration and entanglement of polymer chains are responsible for mucoadhesion. The more structurally similar a mucoadhesive is to the mucosa, the greater the mucoadhesion will be. It is believed that an interpenetration layer of 0.2-0.5μm is required to produce an effective bond.

(v) The **fracture theory** analyzes the force required to separate two surfaces after adhesion. It is often used for calculating fracture strengths of adhesive bonds during detachment.

2.7.2 Factors affecting oral mucosal drug delivery system design

Many factors affect the successful delivery of a drug molecule to the systemic circulation via oral mucosa (Table 2.5). There are numerous important considerations that include biocompatibility (both the drug/device and device/environment interfaces), reliability, durability; environmental stability,accuracy, delivery scalability and permeability are to be considered while developing such formulations. While biocompatibility is always an important consideration, other considerations vary in importance depending on the device application. Bioadhesive formulations designed for buccal application should exhibit suitable rheological and mechanical properties, including **pseudoplastic or plastic flow with thixotrophy**, ease of application, good spreadability, appropriate hardness, and prolonged residence time in the oral cavity. These properties may affect the ultimate performance of the preparations and their acceptance by patients (Jones et al., 1997; Sudhakar et.al, 2006)

Table 2.5. Drug and formulation factors affecting systemic absorption of drugs via the oral mucosa. (Rathbone et.al, 1996)

Biological Factors	
	Area
	Thickness (Effective diffusional pathlength)
	Composition of oral mucosa
	Structure of oral mucosa
	pH of environment
	Saliva flow rates
	Composition of saliva
Drug Factors	
	Taste
	Discoloration of teeth
	Solubility
	Partition coefficient
	pKa
	Biological half life
	Retention
	Rate of absorption
	Irritation potential
	Allergenicity
	Diffusion coefficient in the epithelium
	Drug stability
Delivery system factors	
	Feel of delivery system
	Taste,color,staining etc., of excipient
	Visibility
	Release characteristics
	Retentive properties
	Protection from saliva
	Mobility of backing layer or delivery system
	Size, Shape and Texture
	Irritational potential
	Allergenicity

2.7.3 Developments in buccal adhesive drug delivery

Retentive buccal mucoadhesive formulations may prove to be an alternative to the conventional oral medications as they can be readily attached to the buccal cavity retained for a longer period of time and removed at any time. Buccal adhesive drug delivery systems using matrix tablets, films, layered systems, discs, micro spheres, ointments and hydrogel systems has been studied and reported by several research groups.

However, limited studies exist on novel devices that are superior to those of conventional buccal adhesive systems for the delivery of therapeutic agents through buccal mucosa.

An ideal buccal adhesive system must have the following properties:

- Should adhere to the site of attachment for a few hours,
- Should release the drug in a controlled fashion,
- Should provide drug release in an unidirectional way toward the mucosa,
- Should facilitate the rate and extent of drug absorption,
- Should not cause any irritation or inconvenience to the patient and
- Should not interfere with the normal functions such as talking, drinking etc.

Recent reports suggest that the market share of buccal adhesive drug delivery systems are increasing in the American and European market with the steady growth rate of above 10%. Some of the commercially available buccal adhesive formulations are listed in Table 2.6.

2.7.4 Ongoing Research on buccal adhesive drug delivery systems

2.7.4.1 Tablets

Several bioadhesive tablet formulations were developed in recent years either for local or systemic drug delivery. Tablets that are placed directly onto the mucosal surface have been demonstrated to be excellent bioadhesive formulations. However, size is a limitation for tablets due to the requirement for the dosage form to have intimate contact with the mucosal surface. These tablets adhere to the buccal mucosa in presence of saliva. They are designed to release the drug either unidirectionally targeting buccal mucosa or mutidirectionally in to the saliva. Table 2.7 represents some of the research done so far in the development of buccal adhesive tablets.

Table 2.6 Commercial buccal adhesive drug delivery systems:

Commercial name	Drug	Dosage form	Company
Buccastem	Prochlorperazine	Tablet	Reckitt Benckiser
Suscard	Glyceryl Trinitrate	Tablet	Forest Labs
Miconaczole Lauriad	Miconazole	Tablet	BioAlliance Pharma
Tibozole	Miconazole Nitrate	Tablet	Tibotec
Luborant	--	Artificial Saliva	Antigen
Saliveze	--	Artificial Saliva	Wyvern Medical Ltd
Corcodyl gel	Chlorhexidine Gluconate	Oromucosal Gel	GlaxoSmithKline
Corlan pellets	Hydrocortisone Sodium Succinate (pellets).	Oromucosal Pellets	Celltech
Gaviscon liquid	Sodium Alginate, Sodium Bicarbonate, Calcium Carbonate	Oral liquid (Used in heart burn)	Reckitt Benckiser
Orabase	Gelatin, Pectin and Sodium CMC	Oral Paste	ConvaTec

Table 2.7. Summary of research work on buccal adhesive tablets

Drug	Bioadhesive polymer	References
Omeprazole	Sodium alginate, HPMC, CMC	Yong et.al.,2001; Choi et.al.,2000
Calcitonin	Hakea gum	Alur et al,1999a
Chlorpheneramine	Hakea gum	Alur et al,1999b
Clotrimazole	CP 974P, HPMC K4M	K. Rajesh et al, 1996.
Ergotamine tartrate	PVA	Tsutsumi et al,2002
Hydralazine HCl	CP 934P and CMC	T. Dinesh et al.,1997
Prednisolone	Polycarbophil and CP934P	Tehrani et al., 2002
Morphine Sulphate	Carbomer and HPMC	Anlar et al., 1994
Nimesulide	--	Ceschel, G.C, 2004
Thiocolchicoside	--	Artusi et al.,2003
Propranolol	CP-934P, HPMC K4M	Desai et al., 2004
Nicotine	HPC, CP-934P, PVP	Park and Munday, 2002
Pentazocine	CP-934P, HPMC	Agarwal and Mishra,1999
Nystatin	Carbomer, HPMC	Labot et al., 2002; Bouckaert ,1992
Metaclopromide	CP, HPMC, PC, SCMC, PAA	Taylan et.al., 1996
Verapamil	HPC, CP 934	Gupta et al., 1994
Nifedipine	Chitosan, polycarbophil, sodium alginate, gellan gum	Lopez et al.,1998
Ketoprofen	Chitosan and sodium alginate	Miyazaki et al., 1994

Abbrevations: CP: carbapol, HPMC: hydroxypropylmethylcellulose, PC:polycarbophil, SCMC: sodium carboxymethylcellulose, PAA: polyacrylic acid, HPC: hydroxypropyl cellulose, PVP: poly (vinylpyrrolidone),

2.7.4.2 Gels

The term "gels" is braod, encompassing solids of a wide range of characteristics- from fairly rigid gelatin slabs, to suspensions of colloidal clays, to certain greases. Gels can be looked on as being composed of two interpenetrating phases. The united states pharmacopeia (USP) defines gels as semisolids, being either suspensions of small inorganic particles or large organic molecules interpenetrated with liquid.

Gels have been widely used in the delivery of drugs to the oral cavity as well as systemic delivery. Advantages of gel formulations include their ability to form intimate contact with the mucosal membrane and their rapid release of drug at the absorption site. As a result of their soft structure, gel dosage forms are able to undergo the stretching and contraction strains of the underlying mucosa and. thus, their bioadhesive joint is less prone to premature rupture than the one of tablets and patches. A limitation of gel formulations lies on their inability to deliver a measured dose of drug to the site. Gels find use as delivery systems for oral administration as gels proper or as capsule shells made from gelatin.

Table 2.8 represents some of the research done so far in the development of buccal adhesive gels.

Table 2.8. Summary of research work on buccal bioadhesive gels

Drug	**Polymer**	**Reference**
Triamcinolone Acetonide	CP 934, Poloxamer 407	Shin et al, 2000
Chlorhexidine	HEC, PVP K- 90, PC	Jones et al, 1997
Piroxicam	Sodium alginate, HEC, SodiumCMC, Methyl cellulose, HPMC, Poloxamer 407	Attia et al, 2004
Sucralfate and Lidocaine	Palstibase, SCMC,Chitosan, PC	Jacque et al, 1997

Abbrevations: CP: carbopol, HPMC: hydroxypropylmethylcellulose, PC:polycarbophil, SCMC: sodium carboxymethylcellulose, PVP: poly (vinylpyrrolidone), HEC: hydroxyethylcellulose.

2.7.4.3 Patches/films

Flexible films may be used to deliver drugs directly to a mucosal membrane. They also offer advantages over creams and ointments in that they provide a measured dose of drug to the site. Buccal adhesive films are already in use commercially for example, Zilactin used for the therapy of canker sores, cold sores and lip sores. These are represented in Table 2.9.

Table 2.9 Summary of research work on buccal adhesive patches/films

Drugs	Polymers	References
Chlorhexidine gluconate	Chitosan	Senel et.al.,2000
Ipriflavone	PLGA, chitosan	Perugini et al, 2003
Chlorpheneramine maleate	Polyoxyethylene	Tiwari et al , 1999
Buprenorphine	CP-934, PIB and PIP	Guo et al., 1994
Isosorbide dinitrate	HPC, HPMCP	Danjo et al, 1994
Lidocaine	HPC, CP	Ishida et al, 1982
Miconazole nitrate	SCMC, chitosan, PVA, HEC and HPMC	Nafee et al, 2003.
Acyclovir	[P (AA-co-PEG)]	Shojaei and Li, 1997.
Nifedipine	Sodium alginate	Save et al., 1994.
Plasmid DNA	Noveon, eudragit S-100	Cui and Mumper, 2002
B-galactosidase	Noveon, eudragit S-100	Cui and Mumper, 2002
Protirelin	HEC, HPC, PVP, PVA	Anders et al, 1983; Anders and Merckle 1989.

Abbrevations: CP: carbopol, HPMC: hydroxypropylmethylcellulose, PC:polycarbophil, SCMC: sodium carboxymethylcellulose, PVP: poly (vinylpyrrolidone), PLGA: poly (D,L-lactide co-glycolide), HPMCP: hydroxypropylmethyl cellulosephthalate, PIB: polyisobutylene, PIP: polyisoprene, [P (AA-co-PEG)]: copolymers of polyacrylic acid and polyethylene glycol monomethylether monomethacrylate, HPC: hydroxypropylcellulose, HEC: hydroxyethylcellulose, PVA: polyvinylalcohol.

2.7.4.4 Liquid dosage forms

Viscous liquids may be used to coat buccal surface either as protectants or as drug vehicles for delivery to the mucosal surface. Traditionally, pharmaceutically acceptable polymers are used to enhance the viscosity of products to aid their retention in the oral cavity. Dry mouth is treated with artificial saliva solutions that are retained on mucosal surfaces to provide lubrication. These solutions contain sodium CMC as bioadhesive polymer (Sudhakar et.al, 2006)

2.8 OPTIMIZATION : BRIEF CONCEPTS

2.8.1 Introduction

In the traditional approach of design and development of drug dosage form the primary aim of the formulator may not be in designing the best formulation, but finding a suitable solution under the given set of restrictions. Thus conventional approach of drug formulation development suffers from several pitfalls (Schwartz and Connors, 1996). The said approach not only utilizes much greater magnitudes of time, money, energy but is also inconducive to plug errors, unpredictable, ill-suited to reveal interactions, yields only workable solutions and at times is even unsuccessful.

Now a days, systematic optimization techniques are being widely practiced to alleviate such inconsistencies. These encompass the use of experimental designs, mathematical equations and graphic outcomes, thus depicting a complete picture of variation of the response(s) as a function of the factor(s). The systematic approaches possess greater benefits and surmount various pitfalls inherent in the traditional approaches, as these require fewer experiments to achieve an optimum formulation, reveal interactions (Doornbas and Haan, 1995), give best solution in the presence of competing objectives, make problem tracing and rectification quite easier and simulate the product or process performance using model equation.

Therefore, optimization techniques have globally become a regular practice in design and development of diverse kinds of dosage forms (Schwartz and Connors, 1996).

2.8.2 Methodologies

Broadly, optimization methodology can be categorized into two classes, i.e., ***simultaneous optimization***, where the experimentation is completed before the optimization takes place and ***sequential optimization*** where experimentation continues as the optimization study proceeds. The entire optimization program is attempted in several stages. The whole endeavour encompasses various steps commencing from the screening for the influential factors, factor influence studies followed by implementation of various techniques to reach an optimum (Doornbas and Haan, 1995; Lewis et al., 2000).

The process of investigating the possible input variables as factors is called screening of influential variables.

2.8.2.1 Simultaneous (model-dependent) methods

In simultaneous methods, usually called as ***response surface methodology (RSM)***, one or more selected experimental responses are recorded for a set of experiments, carried out in a systematic way, to predict the optimum and the interaction effects. These approaches involve the postulation of empirical mathematical model, for each response, which adequately represents changes in the response within the zone of interest. Rather than estimating the effects of each variable directly, fitting the coefficients in the model equation to the response and mapping of the response over the whole of the experimental domain in the form of a surface is done (Schwartz and Connors, 1996).

For implementation of the simultaneous optimization, one or more of the following statistical designs can be adopted i.e., factorial designs and their modification, central composite design and their modification, mixture designs, artificial neural networks, etc. Factorial designs (FD), where all the factors are studied in all possible combinations, are considered to be the most efficient in estimating the influence of individual variables (main effects) and their interactions using minimum experimentation. An FD for two factors at three levels each (3^2) is considered identical to a two-factor composite design, and has the added advantage of determining a quadratic response surface (Ahuja et al, 2002).

2.8.2.2 *Sequential (model-independent) methods*

In sequential approach, the optimization is attempted in a step wise fashion, experimentation started at an arbitrary point in experimental domain, responses evaluated and the subsequent experiments are designed based on the results of these studies obtained according to an algorithm that directs these new experiments towards the optimum. Whether the chosen optimum is maximum or minimum, the general term used for this approach is "hill climbing". An important aspect of sequential designs is to know when the procedure has finished. There are many different stopping rules, but sometimes the best method involves the experimenter's skill in judging the true optimum, which is generally a local maximum and minimum. Various statistical designs adopted for sequential optimization are, Evolutionary operations (EVOP), Sequential simplex and its modifications, steepest ascent (or descent) methods (Lewis et al., 2000).

The overall approach for conduct of an optimization studies in pharmaceutical dosage forms can be described by an optimization strategy. The salient steps involved in an optimization strategy are (Doornbas and Haan, 1995):

Problem definition: The optimization problem (e.g., release of a drug from dosage form) should be clearly understood and defined.

Selection of factors and levels: The independent variables selected should be quantifiable and easily controllable. The levels of each variable are either established from the prior experience or pilot studies. Factor and level selection should be judicious enough to gather a maximum of information with a minimum of experimental effort. If a large number of independent variables are involved, a preliminary screening study for the influential variables should be carried out. The levels for each factor should neither are too narrow nor too wide.

Design of experimental protocol: Based on the choice of independent variables and the type of response expected a suitable statistical method is selected. A choice has to be made between the simultaneous and sequential methods and further choice has to be exercised between the designs amongst the chosen method. If no information is available on the type of response a quadratic model is chosen. The number of experiments required is dictated by the selected design. To measure the inherent variability, a sufficient number of replicates should also be determined.

Formulating and evaluating the dosage form: The dosage form is formulated corresponding to the requisite number of experiments and evaluated for the desired response(s).

Prediction of optimum formula: The experimental data is used for generation of a mathematical model and an optimum formula is determined using search methods and/or mathematical optimization methods. This is usually facilitated with the help of computer software.

Verification of results: The predicted optimal formulation is formulated and the responses evaluated. The results are implemented in the process/product development cycle.

Computer use is considered essential in the design and evaluation of optimization methods as good amount of statistical and mathematical calculations are involved. Use of suitable software can make the optimization task a lot easier, faster, more elegant and economical (Schwartz & Flamholz, 1973). Many commercial software packages are available which are either dedicated to experimental design or are of a more general statistical nature with modules for experimental design (Huang et al, 2005), e.g., Sigmastat, Design Ease etc.

2.8.3 Graphic presentation of optimization results

Usually, the results of an optimization are graphically depicted using one or more of the following plots:

Contour plots are the geometric illustration of responses, obtained by plotting one independent variable *versus* another while holding the magnitude of response level and other variables constant (Doornbos and Haan, 1995; Schwartz and Connor, 1996; Harris et al, 1985; Bolton, 1990). The resulting curves are called ***contour lines***. Fig. 2.7 depicts different types of contour plots:

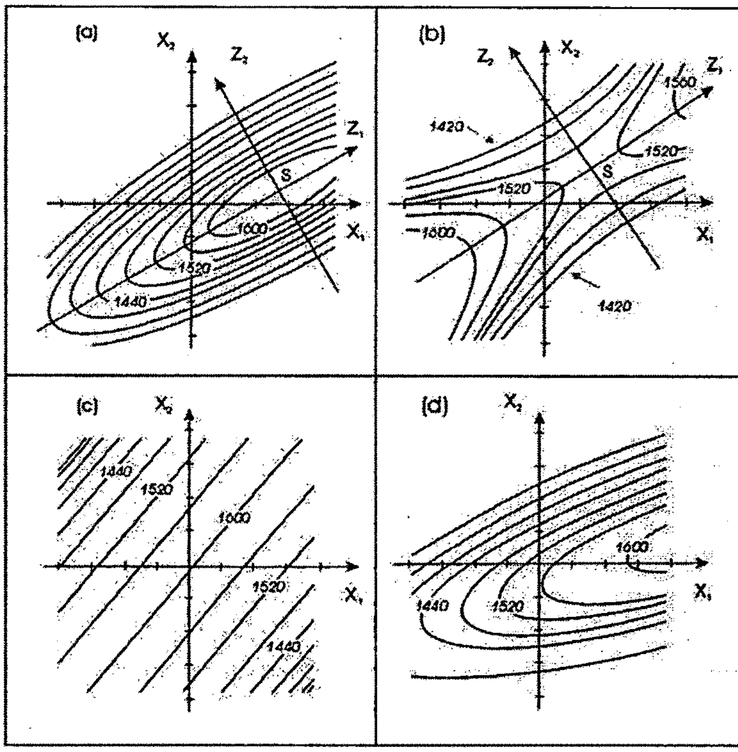


Fig. 2.7. Contour lines (a) maximum; (b) saddle point; (c) ridge; and (d) rising ridge.

Response surface plots are three dimensional (3-D) graphical representation of a response plotted between two independent variables and one response variable (Wehrle et al, 2002). The use of 3-D response surface plots allows understanding of the behaviour of the system by demonstrating the contribution of the independent variables. The slices of response surface are represented by the contour plots.

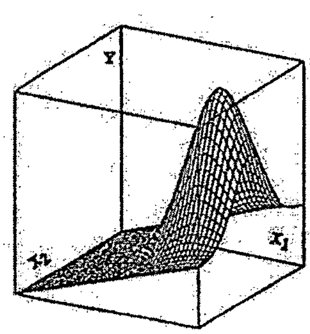


Fig. 2.8. A typical response surface plotted between two factors X_1 and X_2 and a response variable Y.

Normalized plots are the graphical representation of a response plotted between normalized factor levels (N) and a response variable. These are usually plotted only when the levels of the factors are not equidistant, i.e., the central level is not the mean of the high and the low levels. Normalization in such cases tends to make data amenable to further specialized mathematical treatment (Harris et al, 1985). Normalized factor levels can be calculated using equation. 2.1

$$\mathbf{N = (X\text{-}L)/(H\text{-}L) \times 100} \qquad \text{---- (2.3)}$$

where, X is unnormalized factor level, L is the lowest factor level and H is the highest factor level, respectively.

2.8.4 Search for an optimum

The experimental designs used for optimization enables one to generate a mathematical model by careful planning of the experimentation. The mathematical model so generated is further analyzed for generating response surfaces, contour maps and finally, predict an optimum composition for the desired product using ***search methods*** and/or ***mathematical optimization methods*** (Doornbos and Haan, 1995; Schwartz and Connor, 1996)

Search methods

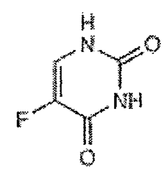
Search methods do not require continuity or differentiability of the function, but only computability (Schwartz and Connor, 1995; Bohidar et al, 1986). In these methods, the response surfaces, as defined by the appropriate equations, are searched by various methods to find the combination of independent variables yielding the optimum. Two major steps are used *viz.* ***feasibility search*** and the ***grid search***. The feasibility search method is used to locate a set of response constraints that are just at the limit of possibility. One selects the several values for the responses of interest (i.e., the responses one wishes to constrain) and a search of the response surface is made to determine whether a solution is feasible. The feasibility search method yields the possibilities satisfying the constraints. The exhaustive grid-search method is later applied in which the experimental range is divided into a grid of specific size and methodically searched (Takayama et al, 1990). Grid search method can provide a list of possible formulations and the corresponding response values. At this point, the experimenter can trade off one response for another and the most acceptable formulation is selected from the results to complete the optimization objective.

Mathematical optimization methods

Desirability functions: This method is used to achieve an optimum formula based on desirability functions. In this approach, each response (i) is associated with its own partial desirability function (d_i).This value varies from 0 to1, according to the closeness of the response to its target value. The target for drug entrapment in microcapsules, e.g., is generally 100%; the desirability at this point, therefore, is 1. If no formulation is acceptable below 75% drug entrapment, then the desirability is equal to 0 at this point. Between, 75% and 100%, the desirability decreases linearly or non linearly in a convex or concave form. Similar to response variables, the desirability functions can also be calculated over the entire the experimental domain. The desirability function is a guide to optimize the process or a formulation using multiple response data from a staiatically planned experiment (Lewis et al, 2000).

2.9 DRUG PROFILE

2.9.1. 5-Fluorouracil (FU)



A white to practically white, practically odourless, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether. 1% solution in water has a pH of 4.5 to 5.0.Store in airtight containers. Protect from light(USP, 25, 2002) .

Melting point : M.p. lies between 282 -283 ° C with decomposition (Bayomi et al, 1989).

Dissociation Constant. pK_a8.0, 13.0.

Partition Coefficient. Log P(octanol/pH 7.4), -1.0.

Ultraviolet Spectrum.: The UV spectrum of FU in methanol is depicted in Fig 2.9.

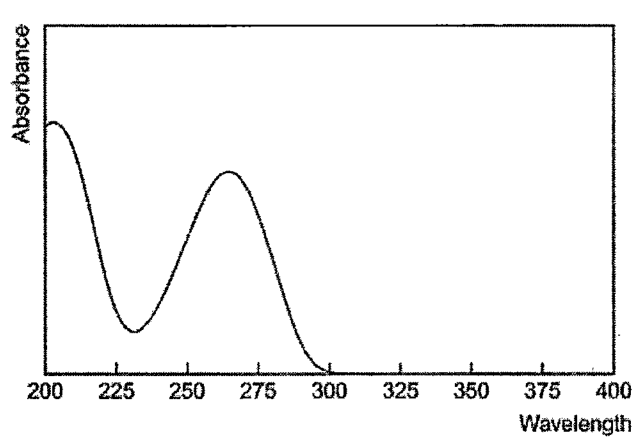


Fig 2.9. Ultraviolet spectrum of FU (Solvent methanol).

Infra-red Spectrum.

Principal peaks at wavenumbers 1653, 1242, 1718, 816, 1220, 1495 cm^{-1} (KBr disk)**(Bayomi et al, 1989).**

FU estimation in plasma: Different HPLC methods for the detection of FU in plasma have been previously described with extraction yields ranging from 34 to 92% (Joulia et al., 1997; Smith et al., 1991). The lower limits of detection of these published methods have also been found to vary from 3 ng/ml to 70 µg/ml (Ackland et al., 1997a; Ackland et al., 1997a; Gamelin et al., 1997). A review of the published methods for the detection of 5-FU by HPLC reveals that highly sensitive methods are typically disadvantaged by a low extraction yield (Smith et al., 1991; Ackland et al., 1997; Gamelin et al., 1997).

Mechanism of Action: Fluorouracil, an analogue of the pyrimidine uracil, is an antineoplastic that acts as an antimetabolite. After intracellular conversion to the active deoxynucleotide it interferes with the synthesis of DNA by blocking the conversion of deoxyuridylic acid to thymidylic acid by the cellular enzyme thymidylate synthetase. It can also interfere with RNA synthesis.

Pharmacokinetics

FU is given orally or by parentral route. The drug undergoes first pass metabolism (presystemic metabolism). After oral administration, FU is poorly absorbed with significant variation in bioavailability ranging between 0 and 80% (Diasio et al, 1989). Absorption of fluorouracil from the gastrointestinal tract is unpredictable and fluorouracil is usually given intravenously. Little is absorbed when fluorouracil is applied to healthy skin (Singh et al, 2005).

After intravenous injection fluorouracil is cleared rapidly from plasma with a mean half-life of about 16 minutes. It is distributed throughout body tissues and fluids including crossing the blood-brain barrier to appear in the CSF, and disappears from the plasma within about 3 hours. Within the target cell fluorouracil is converted to 5-fluorouridine monophosphate and floxuridine monophosphate (5-fluorodeoxyuridine monophosphate), the former undergoing conversion to the triphosphate which can be incorporated into RNA while the latter inhibits thymidylate synthetase. About 15% of an intravenous dose is excreted unchanged in the urine within 6 hours. The remainder is inactivated primarily in the liver and is catabolised via dihydropyrimidine dehydrogenase similarly to endogenous uracil. A large amount is excreted as respiratory carbon dioxide; urea and other metabolites are also produced. The extent of first pass metabolism is dose dependent. Since the liver enzyme system is saturable, an increase in dose will increase oral bioavailability.There is an additional first pass effect owing to the relatively high gut mucosal activity of dihydrouracil dehydrogenase. This combination of effects causes the substantial variability of the bioavailability of FU. FU crosses the placenta and is contraindicated in pregnancy (Colin, 1999a ; Sweetman, 2005a) .

Oral Absorption	28%
Presystemic metabolism	First pass but saturable with dose increment
Plasma half life	11±4 min
V_d	0.25±0.12 L/kg
Plasma protein binding	8 – 12%

Therapeutic uses:

Indications

1. Carcinoma of colon and rectum
2. Carcinoma of head and neck
3. Carcinoma of stomach and exocrine pancreas.
4. Carcinoma of breast
5. Carcinoma of liver
6. Carcinoma of bladder
7. Carcinoma of lung
8. Cervical Carcinoma .
9. Epethelial ovarian Carcinoma.

Contraindications:

Pregnancy.

Mode of use: 5-Fluorouracil formulations are available in market for oral (capsules), parenteral (Injections) and topical (Cream, solution) administration.

Dose: By intravenous injection, 3 to 12 mg per kg daily for 4 days followed by 6 mg per kg on alternate days, to a maximum of 800 mg daily (Indian Pharmacopoeia, 1996). When the dose of 5-FU exceeds 1 g daily, toxic effects are seen more frequently (Colin, 1999a).

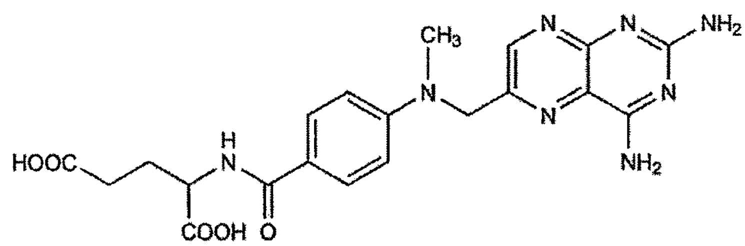
Adverse Effects

The main adverse effects of fluorouracil are on the bone marrow and the gastrointestinal tract, and may be dose-limiting. Toxicity is schedule dependent: reducing the rate of injection to a slow infusion is associated with less haematological toxicity but does not decrease gastrointestinal toxicity. With protracted continuous infusion in particular, the palmar-plantar erythrodysesthesia syndrome (erythema and painful desquamation of the hands and feet) may occur. Gastrointestinal toxicity may be exacerbated if fluorouracil is given with folinic acid.

Leucopenia, thrombocytopenia, stomatitis, gastrointestinal ulceration and bleeding, diarrhoea, or haemorrhage from any site, are signs that treatment should be stopped. The nadir of the white cell count may occur from 7 to 20 days after a dose, and counts usually return to normal after about 30 days. Thrombocytopenia is usually at a maximum 7 to 17 days after a dose. Anaemia may also occur. Nausea and vomiting, rashes, and alopecia are common. Ocular irritation, central neurotoxicity (notably cerebellar ataxia), and myocardial ischaemia have occurred. Local inflammatory and photosensitivity reactions have occurred after topical use. Dermatitis and, rarely, erythema multiforme have been reported (Sweetman, 2005a; Colin, 1999a)

2.9.2 METHOTREXATE (MTX)

Synonym(s): Amethopterin



Methotrexate or *N*-[4-[[(2,4-Diamino-6-pteridinyl)methyl]methylamino]benzoyl]-L-glutamic acid ; $C_{20}H_{22}N_8O_5$=454.4

MTX is an analog of foilc acid and is widely used antimetabolite anticancer drug, with a role in the treatment of both hematological malignancies and solid tumors. It is also used commonly as an immunosuppressive agent in the treatment of a number of autoimmune and inflammatory disorders (e.g. severe psoriasis and rheumatoid arithritis).

MTX is a yellow or orange-brown crystalline powder. It contains not more than 12% of water. Practically insoluble in water, in alcohol, in chloroform, and in ether; freely soluble in dilute solutions of alkali hydroxides and carbonates; slightly soluble in 6N hydrochloric acid. Store in airtight containers. Protect from light.

M.P.	:	182° to 189°.
Dissociation Constant.	:	pK_a3.8, 4.8, 5.6.
Partition Coefficient	:	Log P(octanol/water), −1.8.

Analytical Methods:

Ultraviolet Spectrum.

In the UV spectrum of methotrexate in 0.1N NaOH, the longest wavelength maximum appears at 372 nm and is ascribable to the diaminopteridine moiety. The intermediate wavelength maximum occurs at 303 nm and is due primarily to the aminobenzoyl group. The short wavelength maximum is at 258 nm and attributed to both chromophores. In 0.1 N HCl methotrexate experiences a hypsochromic shiftresulting in a UV spectrum (Fig 2.10) that exhibits maxima at 307 and 243 nm. The UV data are summarized in table 2.10.

Table2.10. Absorption spectra of Methotrexate.

Solvent	**λ_{max} nm (ϵ_{max} x 10^{-3})**		
0.1 N HCl	-	307 (21.6)	243 (18.1)
0.1 M pH 6.7 Tris Buffer	370 (7.45)	302 (24.8)	257 (23.3)
0.1 N NaOH	372 (8.05)	303 (24.8)	258 (24.7)

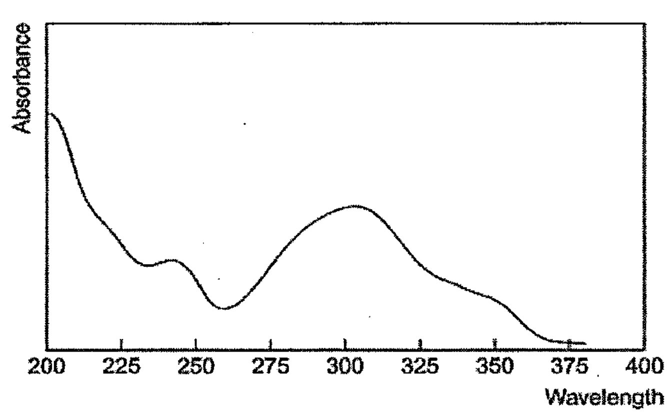


Fig. 2.10. Ultraviolet spectrum of Methotrexate (Solvent 0.1N NaOH).

Infra-red Spectrum.

Principal peaks at wavenumbers 1600, 1511, 1634, 1305, 1200, 1538 cm^{-1} (Nujol mull) (Chamberlin et al, 1976).

Methods for determination of MTX Plasma: Different methods have been described for the determination of Methotrexate in plasma and other biological fluids including enzyme inhibition methods, radiometry and radio immunoassay, enzyme multiple immunoassay technique (EMIT), fluorescence polarization immunoassay (FPIA) (Fleisher,1993; Schilsky, 1983), and high performance liquid chromatography (Assadullahi et.al, 1991; Breithaupt et al., 1982; Brimmed and Sams, 1987; Cosolo et al., 1986; Farid et al., 1983; Lawson and Dixon, 1981; Najjar et al., 1991; Salamoun and Frantsiek, 1986; Skoglund et al, 1994).

Mechanism of Action

Methotrexate has been in clinical use since 1948. It and its active metabolites compete for the folate binding site of the enzyme dihydrofolate reductase. Folic acid must be reduced to tetrahydrofolic acid by this enzyme for DNA synthesis and cellular replication to occur. Competitive inhibition of the enzyme leads to blockage of tetrahydrofolate synthesis, depletion of nucleotide precursors, and inhibition of DNA, RNA and protein synthesis. Methotrexate also inhibits thymidylate synthetase and the transport of reduced folates into the cell. Methotrexate is cell cycle phase-specific (S phase).

Therapeutic uses:

MTX has antitumor activity against a wide variety of tumors. However, the drug is used most often in combination chemotherapy regimns. It is also used in the treatment of severe psoriasis and with increasing frequency in other immunologically mediated disease states.

Indications:

- Acute leukemias
- High grade non- Hodgkin's lymphomas
- Breast carcinoma
- Gastric carcinoma
- Choriocarcinoma
- Head and neck carcinoma
- Severe psoriasis
- Rheumatoid arthritis
- Severe juvenile chronic arthritis.

Other uses

Deematomyositis, Reitger's disease, Chrohn's disease, systemic lupus erythematosus, polymyalgia rheumatica, giant cell arteritis.

Contraindications:

Caution should be taken while admonistering the drug to patients with renal or hematological failure. If clearance is likely to be impaired, then leucoverin rescue should be administered and plasma methotrexate concentrations should be monitored as for high dose regimens.

Pharmacokinetics

When given in low doses, methotrexate is rapidly absorbed from the gastrointestinal tract, but higher doses are less well absorbed. At higher doses there is strong evidence of reduced bioavailability (Smith et al, 1980). It is also rapidly and completely absorbed after intramuscular doses. Peak serum concentrations are achieved in 1 to 5 hours after an oral dose, and 30 to 60 minutes after an intramuscular one (Colin, 1999b; Sweetman, 2005b).

Methotrexate is distributed to tissues and extracellular fluid with a steady-state volume of distribution of 0.4 to 0.8 litres/kg; it penetrates ascitic fluid and effusions, which may act as a depot and thus enhance toxicity. Clearance from plasma is reported to be triphasic, with a terminal elimination half-life of between 3 and 10 hours after doses less than 30 mg/m^2 or 8 to 15 hours after high-dose parenteral therapy. It is about 50% bound to plasma protein. Methotrexate enters the cells in part by an active transport mechanism and is bound as polyglutamate conjugates: bound drug may remain in the body for several months, particularly in the liver. Only small or insignificant amounts cross the blood-brain barrier and enter the CSF after oral or parenteral doses although this may be increased by giving higher doses; however, after intrathecal doses there is significant passage into the systemic circulation. Methotrexate has been detected in very small amounts in saliva and breast milk. It crosses the placenta. Methotrexate does not appear to undergo significant metabolism at low doses; following high-dose therapy the 7-hydroxy metabolite (7-OHMTX) has been detected. Methotrexate may be partly metabolised by the intestinal flora after oral doses. It is excreted primarily in the urine, by glomerular filtration and active tubular secretion. Small amounts are excreted in bile and found in faeces; there is some evidence for enterohepatic recirculation. Considerable interindividual variation exists in the pharmacokinetics of methotrexate: those patients in whom clearance is delayed are at increased risk of toxicity (Shen and Azarnoff, 1978; Balis et al, 1983; Wang and Fujimoto, 1984; Witter, 1993; Grim et al, 2003).

Adverse Effects

The most common dose-related toxic effects of methotrexate are on the bone marrow and gastrointestinal tract. Bone-marrow depression can occur abruptly, and leucopenia, thrombocytopenia, and anaemia may all occur. The nadir of the platelet and white-blood cell counts is usually around 5 to 10 days after a bolus dose, with recovery between about 14 to 28 days, but some sources suggest that leucocytes may exhibit an early fall and rise, followed by a second nadir and recovery, within this period. Ulceration of the mouth and gastrointestinal disturbances are also early signs of toxicity: stomatitis and diarrhoea during treatment indicate that it may need to be interrupted, otherwise haemorrhagic enteritis, intestinal perforation, and death may follow.

Severe or Irreversible adverse effects

Hepatotoxicity: Methotrexate is associated with liver damage, both acute (notably after high doses) and, more seriously, chronic (generally after long-term use). Hepatic fibrosis and cirrhosis may develop without obvious signs of hepatotoxicity, and have led to eventual death.

Neurotoxicity: Neurotoxic reactions to intrathecal MTX have been observed. The most common is acute chemical arachnoiditis (severe headache, nuchal rigidity, vomiting, fever and inflammatory cell pleocytosis of the spinal fluid.).

Symptometic adverse effecxts: Nausea, vomiting, ocular irritation, pleuritis, vsculitis, self limiting pneumonitis with fever.

Interference with clinical pathology tests: The drug may cause falsly high readings in tests for measuring protein in CSF.

Miscellaneous: Methotrexate may cause defective oogenesis and spermatogenesis, and fertility may be impaired (this may be reversible) (Colin, 1999b).

Pharmaceutics: Methotrexate is available in the market for oral, intravenous, intrathecal, intra-arterial, or intraventricular administration (Colin, 1999b).

Dose: For adults, 2.5 to 10 mg; for children, 2.5 to 5 mg (Indian Pharmacopoeia, 1996).

2.10 EXCIPIENTS

2.10.1 Hydroxypropylmethyl cellulose (HPMC):

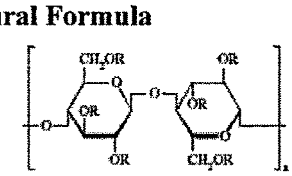
Hydroxypropyl methylcellulose is an odorless and tasteless, white or creamy-white colored fibrous or granular powder.

Synonyms

Benecel MHPC; Cellulose, hydroxypropyl methyl ether; E464; HPMC; *Methocel*; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; *Metolose*; *Pharmacoat.*

The PhEur describes hydroxypropyl methylcellulose as a partly *O*-methylated and *O*-(2-hydroxypropylated) cellulose. It is available in several grades which vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 20°C. Hydroxypropyl methylcellulose defined in the USP specifies the substitution type by appending a four digit number to the nonproprietary name, e.g., hydroxypropyl methylcellulose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH_3). The second two digits refer to the approximate percentage content of the hydroxypropoxy group ($OCH_2CHOHCH_3$), calculated on a dried basis. Molecular weight is approximately 10 000-1 500 000.

Structural Formula



Where R is H, CH_3, or [$CH_3CH(OH)CH_2$]

Functional Category

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

Hydroxypropyl methylcellulose is widely used in oral and topical pharmaceutical formulations.

In oral products, hydroxypropyl methylcellulose is primarily used as a tablet binder (Chowhan, 1980) in film-coating (Rowe, 1977; Rowe, 1980; Banker et al., 1981; Okhamafe and York, 1982) and as an extended-release tablet matrix. (Hardy et al, 1982; Hogan, 1989; Shah et al, 1989, Wilson and Cuff, 1989; Dahl, et al, 1990). Concentrations of between 2-5% w/w may be used as a binder in either wet- or dry-granulation processes. High viscosity grades may be used to retard the release of drugs from a matrix at levels 10-80% w/w in tablets and capsules.

Depending upon the viscosity grade, concentrations between 2-20% w/w are used as film-forming solutions to film-coat tablets. Lower viscosity grades are used in aqueous film-coating solutions while higher viscosity grades are used with organic solvents.

Hydroxypropyl methylcellulose is also used as a suspending and thickening agent in topical formulations, particularly ophthalmic preparations. Compared with methylcellulose, hydroxypropyl methylcellulose produces solutions of greater clarity, with fewer undispersed fibers present, and is therefore preferred in formulations for ophthalmic use. Concentrations of between 0.45-1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions.

Hydroxypropyl methylcellulose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.

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

Incompatibilities

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

Safety

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

Hydroxypropyl methylcellulose is generally regarded as a nontoxic and nonirritant material although excessive oral consumption may have a laxative effect. (Anomynous, 1986). The WHO has not specified an acceptable daily intake for hydroxypropyl methylcellulose since the levels consumed were not considered to represent a hazard to health (FAO/WHO, 1990)

LD_{50} (mouse, IP): 5 g/kg (Harwood, 2003)

LD_{50} (rat, IP): 5.2 g/kg

2.10.2 Poloxamer

Description

Poloxamers generally occur as white-colored, waxy, free flowing prilled granules, or as cast solids. They are practically odorless and tasteless. At room temperature, poloxamer 124 occurs as a colorless liquid.

Synonyms

Lutrol; *Monolan*; *Pluronic*; poloxalkol; polyethylene-propylene glycol copolymer; polyoxyethylene-polyoxypropylene copolymer; *Supronic*; *Synperonic*

The poloxamer polyols are a series of closely related block copolymers of ethylene oxide and propylene oxide conforming to the general formula:

$$\mathbf{HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH}$$

The grades included in the USP are shown below:

Table 2. 11 Typical Poloxamer grades

Poloxamer (Commercial grade)	Physical form	a	b	Average molecular weight
124 (L-44)	Liquid	12	20	2090-2360
188 (F-68)	Solid	80	27	7680-9510
237 (F-87)	Solid	64	37	6840-8830
338 (F-108)	Solid	141	44	12 700-17 400
407 (F-127)	Solid	101	56	9840-14 600

Functional Category

Dispersing agent; emulsifying and coemulsifying agent; solubilizing agent; tablet lubricant; wetting agent.

Applications in Pharmaceutical Formulation or Technology

Poloxamers are nonionic polyoxyethylene- polyoxypropylene copolymers used primarily in pharmaceutical formulations as emulsifying or solubilizing agents. (Reddy et al, 1976; Pandit and Wang, 1998; Suh and Jun, 1996; Collett and Tobin, 1979; El Shaboury, 1989; Wang and Johnston, 1993). The polyoxyethylene segment is hydrophilic while the polyoxypropylene segment is hydrophobic. All of the poloxamers are chemically similar in composition, differing only in the relative amounts of propylene and ethylene oxides added during manufacture. Their physical and surface-active properties vary over a wide range and a number of different types are commercially available.

Poloxamers are used as emulsifying agents in intravenous fat emulsions, and as solubilizing and stabilizing agents to maintain the clarity of elixirs and syrups. Poloxamers may also be used as wetting agents, in ointments, suppository bases, gels, (Gilbert et al, 1986; Tomida et al, 1987) and as tablet binders and coatings. Poloxamer 188 has also been used as an emulsifying agent for fluorocarbons used as artificial blood substitutes and in the preparation of solid dispersion systems. More recently, poloxamers have found use in drug delivery systems (Zhang et al, 2002; Bhardwaj and Blanchard, 1996; Fults and Johnston, 1990; Johnston and Miller, 1985).

Therapeutically, poloxamer 188 is administered orally as a wetting agent and stool lubricant in the treatment of constipation; it is usually used in combination with a laxative such as danthron. Poloxamers may also be used therapeutically as wetting agents in eye drop formulations, in the treatment of kidney stones, and as skin wound cleansers. Poloxamer 338 and 407 are used in solutions for contact lens care.

Table 2.12. Uses of Poloxamer

Use	Concentration (%)
Fat emulsifier	0.3
Flavor solubilizer	0.3
Fluorocarbon emulsifier	2.5
Gelling agent	15-50
Spreading agent	1
Stabilizing agent	1-5
Suppository base	4-6 or 90
Tablet coating	10
Tablet excipients	5-10
Wetting agent	0.01-5

Stability and Storage Conditions

Poloxamers are stable materials. Aqueous solutions are stable in the presence of acids, alkalis, and metal ions. However, aqueous solutions do support mold growth.The bulk material should be stored in a well-closed container in a cool, dry, place.

Incompatibilities

Depending on the relative concentrations, poloxamer 188 is incompatible with phenols and parabens.

Table.2.13. Solubility at 25°C for various types of poloxamer in different solvents.

Type	Solvent				
	Ethanol (95%)	Propan-2-ol	Propylene glycol	Water	Xylene
Poloxamer 124	Freely soluble	Freely soluble	Freely soluble	Freely soluble	Freely soluble
Poloxamer 188	Freely soluble	—	—	Freely soluble	—
Poloxamer 237	Freely soluble	Sparingly soluble	—	Freely soluble	Sparingly soluble
Poloxamer 338	Freely soluble	—	Sparingly soluble	Freely soluble	—
Poloxamer 407	Freely soluble	Freely soluble	—	Freely soluble	—

Safety

Poloxamers are used in a variety of oral, parenteral, and topical pharmaceutical formulations and are generally regarded as nontoxic and nonirritant materials. Poloxamers are not metabolized in the body. Animal toxicity studies, with dogs and rabbits, have shown poloxamers to be nonirritating and nonsensitizing when applied, in 5% w/v and 10% w/v concentration, to the eyes, gums, and skin.

In a 14-day study of intravenous administration to rabbits, at concentrations up to 0.5 g/kg/day, no overt adverse effects were noted. A similar study with dogs also showed no adverse effects at dosage levels up to 0.5 g/kg/day. In a longer term study, rats fed 3% w/w or 5% w/w of poloxamer in food, for up to 2 years, did not exhibit any significant symptoms of toxicity. However, rats receiving 7.5% w/w of poloxamer in their diet showed some decrease in growth rate.No hemolysis of human blood cells was observed over 18 hours at 25°C, with 0.001-10% w/v poloxamer solutions (Collett, 2003).

Handling Precautions

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

2.10.3 Ethylcellulose

Description

Ethylcellulose is a tasteless, free-flowing, white to light tan colored powder

Functional Category

Coating agent; flavoring fixative tablet binder; tablet filler; viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology

Ethylcellulose is widely used in oral and topical pharmaceutical formulations, *see* Table 2.14

Table 2.14. Uses and typical concentrations of ethylcellulose.

Use	Concentration (%)
Microencapsulation	10.0-20.0
Sustained-release tablet coating	3.0-20.0
Tablet coating	1.0-3.0
Tablet granulation	1.0-3.0

The main use of ethylcellulose in oral formulations is as a hydrophobic coating agent for tablets and granules (Ozturk ,et al , 1990; Narisawa, 1994; Bodmeier and Paeratakul, 1994; Dressman, et al., 1995; Sarisuta and Sirithunyalug, 1988; Porter, 1989). Ethylcellulose coatings are used to modify the release of a drug, (Porter, 1989; Goracinova, 1996; Lin, 1987) to mask an unpleasant taste, or to improve the stability of a formulation, as is the case where granules are coated with ethylcellulose to inhibit oxidation. Modified-release tablet formulations may also be produced using ethylcellulose as a matrix former (Pollock and Sheskey, 1996; Klinger, 1990; Katikaneni et al, 1995).

Ethylcellulose, dissolved in an organic solvent, or solvent mixture, can be used on its own to produce water-insoluble films. Higher viscosity ethylcellulose grades tend to produce stronger and more durable films. Ethylcellulose films may be modified to alter their solubility, (Kent and Rowe, 1978) by the addition of hydroxypropylmethylcellulose (Rowe, 1986) or a plasticizer (Saettone et al., 1995; Beck and Tomka, 1996).An aqueous polymer dispersion (or latex) of ethylcellulose such as *Aquacoat* (FMC Corp) or *Surelease* (Colorcon) may also be used to produce ethylcellulose films without the need for organic solvents. Drug release through ethylcellulose-coated dosage forms can be controlled by diffusion through the film coat. This can be a slow process unless a large surface area (e.g., pellets or granules vs. tablets) is utilized. In those instances, aqueous ethylcellulose dispersions tend therefore to be used to coat granules or pellets. Ethylcellulose-coated beads/granules have also demonstrated the ability to absorb pressure and hence protect the coating from fracture during compression (Celik, 1994).

High viscosity grades of ethylcellulose are used in drug microencapsulation. (Lavasanifar et al, 1997; Moldenhauer and Nairn, 1992).Release of a drug from an ethylcellulose microcapsule is a function of the microcapsule wall thickness and surface area.In tablet formulations, ethylcellulose may additionally be employed as a binder, the ethylcellulose being blended dry or wet-granulated with a solvent such as ethanol (95%). Ethylcellulose produces hard tablets with low friability; however, they may demonstrate poor dissolution.Ethylcellulose has also been used as an agent for delivering therapeutic agents from oral (e.g., dental) appliances (Friedman et al, 1988). In topical formulations, ethylcellulose is used as a thickening agent in creams, lotions, or gels, provided an appropriate solvent is used. Ethylcellulose is additionally used in cosmetics and food products.

Solubility: ethylcellulose is practically insoluble in glycerin, propylene glycol, and water. Ethylcellulose that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform, methyl acetate, tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%). Ethylcellulose that contains not less than 46.5%

of ethoxyl groups is freely soluble in chloroform, ethanol (95%), ethyl acetate, methanol, and toluene.

Stability and Storage Conditions

Ethylcellulose is a stable, slightly hygroscopic material. It is chemically resistant to alkalis, both dilute and concentrated, and to salt solutions. It is, however, more sensitive to acidic materials than cellulose esters. Ethylcellulose is subject to oxidative degradation in the presence of sunlight or UV light at elevated temperatures. This may be prevented by the use of an antioxidant and chemical additives which absorb light in the 230-340 nm range. Ethylcellulose should be stored at a temperature not exceeding 90°F (32°C) in a dry area away from all sources of heat. Do not store next to peroxides or other oxidizing agents.

Incompatibilities

Incompatible with paraffin wax and microcrystalline wax (Dahl, 2003).

Safety

Ethylcellulose is widely used in oral and topical pharmaceutical formulations. It is also used in food products. Ethylcellulose is not metabolized following oral consumption and is therefore a noncaloric substance. It is generally regarded as a nontoxic, nonallergenic, and nonirritating material. Ethylcellulose is not metabolized and therefore is not recommended for parenteral products; parenteral use may be harmful to the kidneys.

Since ethylcellulose is not considered to be a health hazard, the WHO has not specified an acceptable daily intake (Dahl, 2003).

Handling Precautions

It is important to prevent fine dust clouds of ethylcellulose from reaching potentially explosive levels in the air. Ethylcellulose is combustible. Ethylcellulose powder may be an irritant to the eyes and therefore eye protection should be worn.

2.10.4 Gantrez

Gantrez® products are a family of synthetic copolymers of methylvinyl ether and maleic anhydride. They are supplied as the anhydride powder or in various other chemical forms derived from the anhydride

Description: In the solid state, Gnatrez copolymers are a white to off-white free flowing, odorless, hygroscopic powders. In solution, it is a slightly hazy, odorless, viscous liquid.

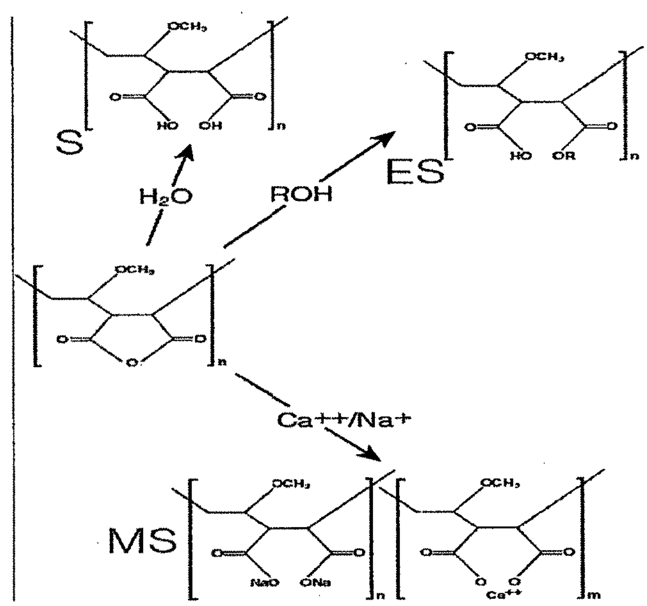


Fig 2.11 Gantrez Anhydride Conversion to the Various Forms

Functional Category:

Bioadhesive, color dispersant, emulsion stabilizer, film former, viscosity increasing agent.

Applications in Pharmaceutical Formulation

Poly(methylvinylether maleic anhydride) copolymers are used in denture adhesive bases **(Shay, 1997)** Controlled release coatings, enteric coatings, ostomy adhesives

(Scalf and Fowler, 2000), transdermal patches (Woolfson et al, 1998), toothpastes (Busscher et al, 2004), mouthwashes (Kockisch et al, 2001) and transdermal gels (Jones et al., 2002, Jones et al, 2003). Gantrez have been utilized to develop novel polyethylene surface modified medical devices with enhanced hydrophobocity and wettability (Kuzuya et al, 2003).

Table 2.15. Chemical name for poly(methylvinyl ether/maleic anhydride) copolymers and derivatives.

Chemical name	Trade name
Poly(methylvinyl ether/maleic anhydride)	*Gantrez AN-119*
	Gantrez AN-903
	Gantrez AN-139
	Gantrez AN-149
	Gantrez AN-169
	Gantrez AN-179
Poly(methylvinyl ether/maleic acid)	*Gantrez S-95*
	Gantrez S-96
	Gantrez S-97
Monoethyl ester of poly(methylvinyl ether/maleic acid) (48–52%) in ethanol (48–52%)	*Gantrez ES-225 50% Alcoholic Solution*
Mixture of monoethyl ester of poly(methylvinyl ether/maleic acid) and monobutyl ester of poly(methylvinyl ether/maleic acid) (48–52%) in ethanol (43–47%) and *n*-butyl alcohol (≈5%)	*Gantrez ES-425 50% Alcoholic Solution*
Mixed sodium/calcium salts of poly(methylvinyl ether/maleic anhydride)	*Gantrez MS-955*

Table 2.16. Molecular weights of selected commercially available copolymers of poly(methylvinyl ether/maleic anhydride)

Grade	Approximate molecular weight
Gantrez AN-119	200 000
Gantrez AN-903	800 000
Gantrez AN-139	1 000 000
Gantrez AN-169	2 000 000
Gantrez S-96	700 000
Gantrez S-97 (powder)	1 200 000
Gantrez S-97 (solution)	1 500 000
Gantrez MS-995	1 000 000
Gantrez ES-225	100 000–150 000
Gantrez ES-425	90 000–150 000

Table 2.17. Gantrez Copolymers Typical Applications (ISP Technical literature, 2003)

Gantrez AN Series	• Thickening and suspending agents • Denture adhesive base • Buccal/transmucosal tablets • Transdermal patches
Gantrez S Series	• Toothpastes • Mouthwashes
Gantrez MS Series	• Denture adhesives • Ostomy adhesives • Topical carriers for mucosal applications
Gantrez ES Series	• Enteric film coating agents • Ostomy adhesives

Stability and Storage Conditions

Poly(methylvinyl ether/maleic anhydride) {PVMA} and related free acids are hygroscopic powders and therefore excessive exposure to moisture should be avoided. Aqueous solutions exhibit decrease in viscosity upon exposure to UV light. These should be stored in a cool, dry place out of direct sunlight.

Incompatibilities

PVMA and copolymers are incompatible with strong oxidizing and reducing agents, concentrated nitric acid, sulfuric acid, notrofoam, oleum, aluminium. In addition, the anhydride will hydrolyze in water to form a water soluble free acid that can subsequently be ionized to form salts in the presence of cations (Zn^{2+}, Na^{+}, Ca^{2+}, and Al^{3+}).

Safety:

Poly(methylvinyl ether/maleic anhydride) and copolymers are widely used in a diverse range of topical and oral pharmaceutical formulations. (Sharma et al, 1999). These copolymers are generally regarded as nontoxic and nonirritant. Moreover, the dry powders and aqueous solutions are nonirritating with the exception of ES, MS, and A grades, which are irritating to the eye and may cause tissue damage.

LD50 (rat, oral): 8 g/kg (Gantrez AN-130 Powder)10

LD50 (rat, oral): 40 ml/kg (Gantrez AN-139 20% w/w aqueous solution)

LD50 (rat, oral): <25.6 g/kg (Gantrez ES-225)

LD50 (rat, oral): 25.6 g/kg (Gantrez ES-425 40% w/v corn oil solution)

LD50 (rat, oral): 25.6 g/kg (Gantrez MS-955 20% aqueous solution)

Gantrez copolymers are regarded relatively non-toxic and non irritant. Furthermore, neither the dry powder nor its aqueous solutions have been shown to be primary irritants or sensitizers. However, as is common in the handling of powders, the use of a dust mask is recommended.

Handling Precautions

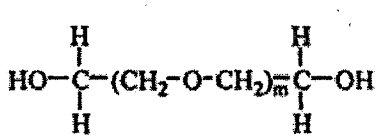
Observe normal precautions appropriate to the circumstances and quantity of material handled. Exceesive dust genetration should be avoided when using powders and an appropriate ventilation area and dust mask are recommended. Hand and eye protection are also recommended.

2.10.5 Polyethylene glycol

Description

The USP describes polyethylene glycol as being an addition polymer of ethylene oxide and water. Polyethylene glycol grades 200-600 are liquids; grades 1000 and above are solids at ambient temperatures.Liquid grades (PEG 200-600) occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight, but characteristic odor and a bitter, slightly burning taste. PEG 600 can occur as a solid at ambient temperatures.Solid grades (PEG >1000) are white or off-white in color, and range in consistency from pastes to waxy flakes. They have a faint, sweet odor. Grades of PEG 6000 and above are available as free-flowing milled powders.

Structural Formula



Empirical Formula

$HOCH_2(CH_2OCH_2)_mCH_2OH$; Where m represents the average number of oxyethylene groups.

Alternatively, the general formula $H(OCH2CH2)_nOH$ may be used to represent polyethylene glycol, where n is a number one more than the value of m in the previous formula. Table 2.17 shows for the average molecular weights of typical polyethylene glycols. Note that the number which follows PEG indicates the average molecular weight of the polymer.

Table 2.18. Structural formula and molecular weight of polyethylene glycol polymers.

Grade	m	Average molecular weight
PEG 200	4.2	190-210
PEG 300	6.4	285-315
PEG 400	8.7	380-420
PEG 540 (blend)	—	500-600
PEG 600	13.2	570-613
PEG 900	15.3	855-900
PEG 1000	22.3	950-1050
PEG 1450	32.5	1300-1600
PEG 1540	28-36	1300-1600
PEG 2000	40-50	1800-2200
PEG 3000	60-75	2700-3300
PEG 3350	75.7	3000-3700
PEG 4000	69-84	3000-4800
PEG 4600	104.1	4400-4800
PEG 8000	181.4	7000-9000

Functional Category

Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology

Polyethylene glycols are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral, and rectal preparations.Polyethylene glycols are stable, hydrophilic substances that are essentially nonirritant to the skin, .Although they do not readily penetrate the skin, polyethylene glycols are water soluble and as such are easily removed from the skin by washing; they are therefore useful as ointment bases (Hadia et al, 1989). Solid grades are generally employed in topical ointments with the consistency of the base being adjusted by the addition of liquid grades of polyethylene glycol.

Mixtures of polyethylene glycols can be used as suppository bases (Kellaway and Marriott, 1975). Aqueous polyethylene glycol solutions can be used either as suspending agents or to adjust the viscosity and consistency of other suspending vehicles. When used in conjunction with other emulsifiers, polyethylene glycols can act as emulsion stabilizers.

Liquid polyethylene glycols are used as water-miscible solvents for the contents of soft gelatin capsules. However, they may cause hardening of the capsule shell by preferential absorption of moisture from gelatin in the shell.

In concentrations up to approximately 30% v/v, PEG 300 and PEG 400 have been used as the vehicle for parenteral dosage forms.

In solid-dosage formulations, higher molecular weight polyethylene glycols can enhance the effectiveness of tablet binders and impart plasticity to granules (Wells et al, 1982). However, they have only limited binding action when used alone, and can prolong disintegration if present in concentrations greater than 5% w/w. When used for thermoplastic granulations, (Chiou and Riegelman, 1971; Ford and Rubinstein, 1980; Vila-Jato et al, 1986) a mixture of the powdered constituents with 10-15% w/w PEG 6000 is heated to 70-75°C. The mass becomes paste-like and forms granules if stirred while cooling. This technique is useful for the preparation of dosage forms such as lozenges when prolonged disintegration is required.

Polyethylene glycols can also be used to enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds by making solid dispersions with an appropriate polyethylene glycol (Miralles et al, 1982).

In film coatings, solid grades of polyethylene glycol can be used alone for the film coating of tablets or can be useful as hydrophilic polishing materials. Solid grades are also widely used as plasticizers in conjunction with film-forming polymers (Miralles et al, 1982). Polyethylene glycol grades with molecular weights of 6000 and above can be used as lubricants, particularly for soluble tablets.

Stability and Storage Conditions

Polyethylene glycols are chemically stable in air and in solution although grades with a molecular weight less than 2000 are hygroscopic. Polyethylene glycols do not support microbial growth, nor do they become rancid.

Polyethylene glycols should be stored in well-closed containers in a cool, dry, place.

Incompatibilities

The chemical reactivity of polyethylene glycols is mainly confined to the two terminal hydroxyl groups, which can be either esterified or etherified. However, all grades can exhibit some oxidizing activity due to the presence of peroxide impurities and secondary products formed by autoxidation.

Liquid and solid polyethylene glycol grades may be incompatible with some colors.

The antibacterial activity of certain antibiotics, particularly penicillin and bacitracin, is reduced in polyethylene glycol bases. The preservative efficacy of the parabens may also be impaired due to binding with polyethylene glycols.

Physical effects caused by polyethylene glycol bases include softening and liquefaction in mixtures with phenol, tannic acid, and salicylic acid. Plastics, such as polyethylene, phenolformaldehyde, polyvinyl chloride, and cellulose-ester membranes (in filters) may be softened or dissolved by polyethylene glycols. Migration of polyethylene glycol can occur from tablet-film coatings, leading to interaction with core components.

Safety

Polyethylene glycols are widely used in a variety of pharmaceutical formulations. Generally, they are regarded as nontoxic and nonirritant materials (Smyth et al, 1950; Tusing et al, 1954; Smyth et al, 1955). However, adverse reactions to polyethylene glycols have been reported and although of relatively low toxicity, any toxicity appears to be greatest with polyethylene glycols of low molecular weight.

The WHO has set an estimated acceptable daily intake of polyethylene glycols at up to 10 mg/kg body-weight (FAO/WHO, 1980). In parenteral products, the maximum recommended concentration of PEG 300 is approximately 30% v/v since hemolytic effects have been observed at concentrations greater than about 40% v/v.

Handling Precautions

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

2.10.6 Lactose

Description

White to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-tasting; α-lactose is approximately 15% as sweet as sucrose, while β-lactose is sweeter than the α -form.

Solubility: Table 2.19 gives solubility of lactose in different solvents.

Table 2.19. Solubility of Lactose

Solvent Solvent	Solubility at 25°C unless otherwise stated at 25°C Unless otherwise stated
Chloroform	Practically insoluble
Ethanol	Practically insoluble
Ether	Practically insoluble
Water	1 in 4.63
	1 in 3.14 at 40°C
	1 in 2.04 at 50°C
	1 in 1.68 at 60°C
	1 in 1.07 at 80°C

Functional Category

Tablet and capsule diluent.

Applications in Pharmaceutical Formulation or Technology

Lactose is widely used as a filler or diluent in tablets, capsules, and to a more limited extent in lyophilized products and infant feed formulas (Çelik and Okutgen, 1993; Lerk, 1993; Otsuka et al., 1993; Kibbe and Weller, 2003).

Various lactose grades are commercially available which have different physical properties such as particle size distribution and flow characteristics. This permits the selection of the most suitable material for a particular application, e.g., the particle size range selected for capsules is often dependent upon the type of encapsulating machine used. Usually, fine grades of lactose are used in the preparation of tablets by the wet-granulation method or when milling during processing is carried out, since the fine size permits better mixing with other formulation ingredients and utilizes the binder more efficiently.

Other applications of lactose include as a carrier/diluent for inhalation products and in lyophilized products, where lactose is added to freeze-dried solutions to increase plug size and aid caking. Lactose is also used in combination with sucrose (approximately 1:3) to prepare sugar-coating solutions.

Generally, the grade of lactose chosen is dependent on the type of dosage form being developed. Direct-compression grades are often used to carry small quantities of drug and this permits tablets to be made without granulating.

Direct-compression grades of lactose are more fluid and more compressible than crystalline or powdered lactose and are generally composed of spray-dried lactoses which contain specially prepared pure ά-lactose monohydrate along with a small amount of amorphous lactose. The amorphous lactose improves the compression force/hardness profile of the lactose. Other specially produced direct-compression grades of lactose do not contain amorphous material but may contain glassy or vitreous areas which impart improved compressibility.

Stability and Storage Conditions

Under humid conditions (80% relative humidity and above), mold growth may occur. Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions. The purity of different lactoses can vary and color evaluation may thus be important, particularly if white tablets are being formulated. The color stability of various lactoses also differ. Lactose should be stored in a well-closed container in a cool, dry, place

Incompatibilities

A Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown-colored products.(20) This reaction occurs more readily with the amorphous material rather than with crystalline lactose. The spray-dried material, which contains about 10% amorphous lactose, is also prone to discoloration. The 'browning reaction' is base-catalyzed and may therefore be accelerated if alkaline lubricants are used. Lactose may also develop a yellow-brown color, in the absence of amines, with browning again occurring most rapidly in the spray-dried material, possibly due to the formation of 5-hydroxymethyl-2-furfural.Lactose is incompatible with amino acids, aminophylline (Hartauer and Guillory, 1991) and amphetamines (Blaug and Huang, 1972).

Safety

Lower doses of lactose produce fewer adverse effects, and lactose is better tolerated if taken with other foods. As a result, there is a significant population with lactose malabsorption who can still ingest normal amounts of lactose, such as that in milk, without the development of significant adverse effects.

2.10.7 Magnesium stearate

Description

Magnesium stearate is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Solubility: practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Functional Category

Tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25-5.0%. It is also used in barrier creams (Allen and Luner, 2003).

Stability and Storage Conditions

Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

Incompatibilities

Incompatible with strong acids, alkalis and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

Safety

Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being nontoxic following oral administration. However, oral consumption of large quantities may result in some laxative effect or mucosal irritation (Chowhan et al., 1982).

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