Chapter 1
Introduction

1. INTRODUCTION

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.

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. 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 has estimated that there would be about 34,360 new cases of oral cavity and oropharyngeal cancer in the United States in 2007 of whom an estimated 7,550 people will die of these cancers. (www.cancer.org/docroot/cri/content)

Therapies being used to treat oropharyngeal cancer are surgery, radiation therapy and chemotherapy. Chemotherapy is given to shrink the cancer before surgery or radiation treatment. This is called 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. 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).

Most of the anticancer drugs have to be administered parentrally as they have poor bioavailability when administered orally either due to poor permeability or due to significant first pass metabolism (Karasulu et al, 2007).

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). On the other hand, 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 localizing 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 S. C. et al, 2000, Birudaraj et al., 2005).

5-Fluorouracil (FU) has been widely used in the treatment of oropharyngeal cancer. After oral administration, FU is poorly absorbed with significant variation in bioavailability ranging between 0 and 80% due to first pass metabolism and poor membrane permeability (log*P* octanol/water = −0.89) (Umejima et al, 1995). Following parenteral administration of FU, it is rapidly eliminated with an apparent terminal half-life of approximately 8–20 min (Diasio and Harris, 1989). These two problems make FU a suitable candidate for transbuccal delivery.

The oral bioavailability of Methotrexate (MTX) is low (Karasulu et al, 2007). When given orally, MTX is absorbed from GIT via an active transport mechanism. The peak plasma levels occur in 1-5 hours, but at higher doses there is strong evidence of reduced bioavailability (Colin, 1999b). Oral absorption is dose dependent (25-95%). The drug is chosen considering the fact that the patient with oropharyngeal cancer experiences pain and difficulty in swallowing the oral dosage from.

1.1 Aims & Objectives:

Aim of the present project was to develop buccoadhesive formulations of selected drugs for the treatment of oropharyngeal cancer with following objectives:-

- To improve patient compliance by formulating buccoadhesive dosage forms as it need not to be swallowed.

- To prevent presystemic metabolism of drugs (5-Fluorouracil).
- To formulate dosage forms with improved bioadhesion and enhanced contact time which ultimately will increase absorption and hence bioavailability.
- To formulate sustained release formulations which will maintain prolonged drug levels, control therapy, reduce side effects and also drug dose.

In the present investigation, we propose bioadhesive delivery systems (like patch, tablet and gel) for FU and MTX using polymer admixtures to modulate the drug release.

It is envisaged that the proposed delivery systems will overcome first pass metabolism and wastage of drug through gastrointestinal tract which will result in increased bioavailability.

It is expected to provide sustained release of drugs which will reduce the frequency of administration of conventional dosage form and will improve patient compliance as there is no need of swallowing. Delivery system will keep effective control over drug levels; and also reduce the dose of administration and ultimately reduce side effects. Ultimately it will result in improved disease management.

Polymers: Poloxamer 407(P-407), HPMC, and Gantrez® were used in this stduy. Poloxamers are non-ionic surfactants possessing excellent wetting, antifoaming, and solubilizing properties and are commonly used for pharmaceutical and medical purposes. P-407 at concentrations of 20% or higher in aqueous solutions exhibits the unique property of reversible thermal gelation (Schmolka, 1991). It is transformed from a low-viscosity solution to a semisolid gel upon heating from 4°C to room (24°C) or body (37°C) temperature, and the gelation achieved at elevated temperature is reversible upon cooling (Schmolka, 1972).The properties of reversible thermal gelation, the ability to form a clear gel in aqueous media, the high solubilizing capacity, and the low toxicity all make P-407 an attractive vehicle for preparing controlled-release drug-delivery systems (Johnston and Miller,1985; Fults and Johnston,1990; Bhardwaj and Blanchard,1996).

Gantrez® products are a family of synthetic copolymers of methylvinyl ether and maleic

anhydride.Gantrez copolymers are widely utilized in pharmaceutical applications for their excellent film forming properties and high quality bioadhesive performance. They are also used as thickeners, complexing agents and hydrophilic colloids. (Gantrez® Copolymers, 2005).

HPMC (Hydroxy propyl methyl cellulose) is a well known polymer which act as release retardant as well as bioadhesives (Narendra et al, 2005, Shin et al, 2004; Attia et al, 2004). HPMC is widely used to prepare extended-release dosage forms of both water-soluble and water-insoluble drugs because of the drug release rates from HPMC matrix formulations are generally independent of processing variables such as compaction pressure, drug particle size, and the incorporation of a lubricant (Ford et al., 1985; Lahdenpaa et al., 1997; Zuleger and Lippold, 2001; Sako et al., 2002).

1.2 Proposed Plan of Work:

1. Permeation studies of drugs across buccal mucosa.
2. Formulation of buccoadhesive systems for FU and MTX: bilayer patches, bilayer tablets, bioadhesive gels.
3. Optimization of process and formulation variables.
4. *In vitro* characterization and evaluation of formulated buccoadhesive systems.
5. *In vivo* studies of the optimized formulation to study the pharmacokinetic parameters.
6. Histological studies.

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