INTRODUCTION

Drug of choice

Rationale of selecting anticancer agents

Need for the study

Objectives of the study

Introduction

Oral administration is perhaps the most popular route due to ease of ingestion, pain avoidance, versatility to accommodate various types of drug candidates, do not require sterile conditions and are therefore, less expensive to manufacture and most importantly emphasizes patient compliance. It is probable that at least 90% of all drugs used to produce systemic effects are administered by the oral route. However, certain dosage forms such as tablets, capsules, liquids are found to be difficult to swallow in case of dysphagia patients. The irritation or pain resulting from contact of the solid preparation with the oral cavity or with the larynx and pharynx, or a physical injury caused upon rubbing of the solid preparation against mucous membrane, can give discomfort to a patient and thus do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. It was reported that, the problem of swallowing tablets was more evident in geriatric and pediatric patients, as well as traveling patients who may not have ready access to water.

Dysphagia is a clinical syndrome resulting from a biomechanical disorder defined as “an inability to swallow, or a sensation that solids or liquids do not pass easily from the mouth to the stomach.” Recently clinicians have widened this definition to include, behavioral, sensory, motor acts, cognitive awareness and visual recognition of food. Dysphagia is classified as oropharyngeal or esophageal dysphagia. A patient with
Oropharyngeal dysphagia has difficulty in initiating swallowing or transferring food from the oropharynx to the upper esophagus. Patients with esophageal dysphagia cannot transfer food or other ingested materials from the hypopharynx through the esophagus into the stomach \(^4\). The incidence of swallowing issues and dysphagia correlate with increasing age and morbidity, which are both typical conditions of growing medicinal product usage. Dysphagia can occur at all age groups, preterm babies to the elderly but are most prevalent in elderly individuals and is a growing healthcare concern as geriatric population expands \(^5\). Young students also reported difficulties with swallowing tablets and capsules \(^6\). An estimated six million adults have dysphagia. Swallowing dysfunctions can severely influence patients’ quality of life and social integration. Dysphagia causes potentially compromising nutritional status, complicating the administration of solid medications \(^7\). Researchers reported that an estimated 35% of the general population, and an additional 30 – 40% of elderly institutionalized patients and 18 - 22% of all persons in long-term care facilities, suffer from dysphagia \(^1\).

To ensure safety during oral administration, patients with dysphagia require an appropriate oral dosage form or modification of the dosage form. Crushing tablets and opening capsules are the main alterations of dosage forms and account for up to one third of oral drug administrations in long-term nursing homes. Crushing of enteric-coated or sustained release tablets can lead to adverse events (e.g. choking episodes, adverse drug reactions resulting from the immediate release of drug from a sustained-release product, refusal to take medications) \(^2\). Such alterations may lead to serious adverse effects or severe intoxication of the patients. Crushed tablets are the most frequent cause of obstruction of feeding tubes, which results in increased morbidity and trauma to the patient besides the cost of replacing the tube. This may require surgical intervention \(^1\).

Cancer is a group of diseases characterized by uncontrolled growth and spread of abnormal cells. If the spread is not controlled, it can result in death. Cancer is usually treated with chemotherapy, radiation therapy, surgery and palliative care. The chances of surviving the disease vary greatly by the type and location of the cancer and the extent of disease at the start of treatment. While cancer can affect people of all ages, and a few
types of cancer are more common in children, the risk of developing cancer generally increases with age \(^8\). As the life expectancy at birth increases proportionately the percentage of geriatric population also rises. The World Cancer Report documents that cancer rates are set to increase at an alarming rate globally. Cancer rates could increase by 50 \% new cases for the year 2020 \(^9\). It is predicted that the elderly population of India shall be among the highest in the world by the year 2025, \(i.e\). 177 million (80 \% of them residing in rural areas) \(^10\).

As pediatrics, young adults and aged population are more prone to cancer and dysphagia, hence in the present research work, new pharmaceutical preparation that can be easily taken by patients with dysphagia such as fast disintegrating tablets, fast disintegrating films and eatable dosage forms were prepared and evaluated to ensure safety during oral administration of medications and thereby improving patient compliance.

**Drug of choice**

Many anticancer agents are used for oral delivery for their therapeutic action. Drugs were selected in the present study based on suitability, stability (as solid, semisolid and liquid dosage form) and optimum bioavailability. The following drugs were selected for the study:

1. Anastrozole
2. Cyclophosphamide
3. Methotrexate
4. Imatinib mesylate
5. Capecitabine
Rationale of selecting various anticancer agents in the present study as a dosage form for dysphagia patients.

Anastrozole, Cyclophosphamide, Imatinib Mesylate, Methotrexate and Capecitabine are selected, as they are used as 1st line therapy for various types of cancer.

1. **Anastrozole (ANS)**

   Anastrozole is a potent new-generation nonsteroidal aromatase inhibitor of the triazole class, approved by the United States of Food and Drug Administration (USFDA) for the treatment of advanced breast cancer in post-menopausal women administered as 1 mg conventional tablet by oral route once daily. Breast carcinoma has become a major health problem over the past 50 years, affecting as many as one in eight women. Although there have been substantial developments in its treatment, approximately 25% of women with breast carcinoma will eventually die from the disease. As the conventional tablet are difficult to swallow by dysphagic patients and also considering the disease severity and advantage of anastrozole possessing very good absorption orally, FDFs and FDTs of anastrozole were prepared and evaluated as an alternate dosage form.

2. **Cyclophosphamide (CYP)**

   CYP, an anticancer agent has been used for various malignant types of cancers. The adult dosage for tablets typically is 1 to 5 mg/kg per day for both initial and maintenance treatment of cancer. Cyclophosphamide is marketed as 25 and 50 mg tablets. As the dosage regimen is based on the disease condition, the patient has to consume several tablets (2 - 5) to get desired drug levels. Due to high dose and increased frequency of administration, the conventional tablet may be difficult to swallow by dysphagic patients. Hence in the present research work, FDT’s and FDF’s of CYP were prepared and evaluated that can be easily taken by patients with dysphagia ensuring safety and preventing withdrawal of the medication thereby improving the therapy.

3. **Methotrexate (MTX)**

   Dysphagia is common in patients with advanced Head and Neck Cancer (HNC). The incidence of head and neck cancer increases with age, especially after 50 years of age.
Introduction

Over 2,00,000 cases of head and neck cancer occur each year in India versus 30,000 for the US. Methotrexate (formerly Amethopterin) is an antimetabolite used in the treatment of many neoplastic diseases, one such is HNC. MTX remains the standard of therapy for patients with recurrent or metastatic disease. It has been given in the dosage range of 25 – 50 mg/m². MTX is available in the market as 2.5, 5, 10 and 15 mg tablets strengths. Conventional tablets are difficult to swallow by dysphagic patients which results in withdrawal of the medication and also considering the disease severity; FDFs, FDTs and eatable gels of methotrexate were prepared and evaluated as an alternate dosage form.

4. Imatinib mesylate (IM)

Imatinib (IM), an anti-cancer agent is used for the treatment of many types of cancers in variable dosage range.

- Children greater than 3 years: Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in chronic phase: 260 mg/m² orally once a day or 130 mg/m² twice a day (morning and evening).
- With newly diagnosed, dose is 340 mg/m²/day (not to exceed 600 mg).

Due to variable dose and increased frequency of administration, the conventional dosage forms available may be difficult to swallow by pediatric and geriatric patients suffering from dysphagia and hence nurses tend to dilute the content with juice or water by opening the capsules or breaking the tablet which is potentially risk to humans. Hence in the present study, new pharmaceutical dosage form that can be easily taken by patients with dysphagia such as fast disintegrating film (FDF) was prepared and evaluated to ensure safety during oral administration of medications and thereby improving patient compliance.

Due to the drawback of FDF with high drug loading, fast disintegrating tablets (FDT) were prepared for the following conditions:

- The recommended dose of Imatinib is 600 mg/day for adult patients with relapsed/refractory Ph+ Acute Lymphoblastic Leukemia (ALL).
• The recommended dose of Imatinib is 400 mg/day for adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD).

• The recommended dose of Imatinib is 400 mg/day for adult patients with unresectable and/or metastatic, malignant Gastrointestinal stromal tumors. A dose increase up to 800 mg daily (given as 400 mg twice daily) may be considered, as clinically indicated, in patients showing clear signs or symptoms of disease progression at a lower dose and in the absence of severe adverse drug reactions.

5. Capecitabine (CAP)

Breast carcinoma has become a major health problem over the past 50 years, affecting as many as one in eight women. Colorectal cancer is the second leading cause of cancer deaths in the West and more than 66,000 cases of colon cancer are reported to occur in the Indian subcontinent every year. The oral fluoropyrimidine CAP has been investigated extensively in both metastatic colorectal cancer and metastatic breast cancer. CAP is a pro-drug that is converted to fluorouracil in the body tissues following the oral administration. It is widely used in the treatment of metastatic colorectal cancer and breast cancer, since it is readily absorbed from the gastrointestinal tract. The recommended oral daily dose is large, i.e. 1250 mg/m² administered twice daily for 14 days followed by a 7-day rest period given as 3-week cycles, for as long as needed. Indeed, after oral administration, CAP crosses the gastrointestinal barrier intact and is rapidly and almost completely absorbed. Due to high dose and increased frequency of administration, the conventional tablet may be difficult to swallow by dysphagic patients. Since the dose and frequency is too high, fast disintegrating films of CAP becomes a patient’s compliance and formulation issue. Hence in the present research work, FDT’s of CAP were prepared and evaluated that can be easily taken by patients with dysphagia ensuring safety and preventing withdrawal of the medication thereby improving the therapy.