REVIEW OF LITERATURE

Cancer
Swallowing
Dysphagia
Fast disintegrating films
Fast disintegrating tablets
Eatable gels
Drug used in the Study
Polymers and excipients of Interest
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\(^\text{21}\).

In cancer, cells divide and grow uncontrollably, forming malignant tumors, and invade nearby parts of the body. The cancer may also spread to more distant parts of the body through the lymphatic system or bloodstream. Cells from malignant tumors can invade and damage nearby tissues and organs\(^\text{21}\). In particular, malignant cells may have altered shapes and cell-surface characteristics that contribute to their rapid proliferation. Many malignant cells also have abnormal chromosomes or altered genes, and they manufacture abnormal proteins. When a tumor successfully spreads to other parts of the body and grows, invading and destroying other healthy tissues, it is said to have metastasized. This process itself is called metastasis, and the result is a serious condition that is very difficult to treat\(^\text{22, 23}\).

Not all tumors are cancerous. Benign tumors do not grow uncontrollably, do not invade neighboring tissues, and do not spread throughout the body. Benign tumors, such
as cysts, warts, moles, and polyps, do not spread to other parts of the body. Benign tumors usually can be removed surgically and generally are not a threat to life. There are over 200 different known cancers that afflict humans. There are over 100 different types of cancer, and each is classified by the type of cell that is initially affected. Cancer cells are more autonomous than normal cells and are independent of growth-control pathways and regulatory mechanisms.

**Symptoms of cancer**

Cancer symptoms are quite varied and depend on where the cancer is located, where it has spread, and how big the tumor is? Some cancers can be felt or seen through the skin - a lump on the breast or testicle can be an indicator of cancer in those locations. Skin cancer (melanoma) is often noted by a change in a wart or mole on the skin. Some oral cancers present white patches inside the mouth or white spots on the tongue. Other cancers have symptoms that are less physically apparent. Some brain tumors tend to present symptoms early in the disease as they affect important cognitive functions. Pancreatic cancers are usually too small to cause symptoms until they cause pain by pushing against nearby nerves or interfere with liver function to cause a yellowing of the skin and eyes called jaundice. Colon cancers lead to symptoms such as constipation, diarrhea and changes in stool size. Bladder or prostate cancers cause changes in bladder function such as more frequent or infrequent urination. When cancer spreads, or metastasizes, additional symptoms can present themselves in the newly affected area. Swollen or enlarged lymph nodes are common and likely to be present early. Symptoms of metastasis ultimately depend on the location to which the cancer has spread.

**Causes of cancer**

The vast majority of cancers are sporadic. There is no clear cause why one person gets cancer and another does not. These are the most common risk factors for cancer such as:

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**Dept of Pharmaceutics, ISSCP, Mysore**
Review of Literature

1. Tobacco
2. Diet
3. Alcohol
4. Physical activity
5. Occupational exposures
6. Hormones
7. Viruses and other biological agents
8. Radiation
9. Drugs
10. Host characteristics influencing cancer
   a. Age
   b. Sex
   c. Socioeconomic factors
   e. Hereditary
   f. Ethnicity and race
11. Psychoneuroimmunology and cancer risk
   a. Nocturnal light exposure
   b. Biobehavioral factors and stress

Prevention of cancer\textsuperscript{25-27}

At least one-third of all cancer cases are preventable. Prevention offers the most cost-effective long-term strategy for the control of cancer.
1. **Lifestyle interventions**

   Regular physical activity, decreased alcohol intake, limited intake of processed foods and maintenance of a healthy body weight.

   Tobacco use is the single greatest avoidable risk factor for cancer mortality worldwide, causing an estimated 22% of cancer deaths per year. Smoking avoidance and smoking cessation result in decreased incidence and mortality from cancer.

2. **Medical interventions**

   Chemoprevention refers to the use of natural or synthetic compounds to interfere with early stages of carcinogenesis, before invasive cancer appears. Chemoprevention trials have some positive results. Daily use of selective estrogen receptor modulators (tamoxifen or raloxifene) for up to 5 years reduces the incidence of breast cancer by about 50% in high-risk women. Finasteride (an alpha-reductase inhibitor) lowers the incidence of prostate cancer; this finding was complicated by a greater cumulative incidence of high-grade cancers in the finasteride-versus-placebo-group.

3. **Infections**

   Globally, infectious agents have been estimated to cause 18% of all cancer cases. The burden of cancers caused by infections is much greater in developing nations (26%) than in developed nations (8%). If an infectious agent is truly a cause of cancer, then efficacious anti-infective interventions would be expected in most instances to be effective cancer prevention interventions. Administration of vaccines to protect against cancer-causing viruses is a relatively new medical approach in cancer prevention.

4. **Radiation**

   Exposure to radiation, primarily ultraviolet radiation and ionizing radiation, is a clearly established cause of cancer. Limiting unnecessary CT scans and reducing radiation exposure doses is an important prevention strategy. Avoiding excessive exposure, use of sunscreen and protective clothing are effective preventive measures.
UV-emitting tanning devices are now also classified as carcinogenic to humans based on their association with skin and ocular melanoma cancers.

**Diagnosis of cancer**

There is no single test that can accurately diagnose cancer. The complete evaluation of a patient usually requires a thorough history and physical examination along with diagnostic testing. Many tests are needed to determine whether a person has cancer, or if another condition (such as an infection) is mimicking the symptoms of cancer. Effective diagnostic testing is used to confirm or eliminate the presence of disease, monitor the disease process, and to plan for and evaluate the effectiveness of treatment.

1. Physical exam and history
2. Laboratory analysis
3. Analytical techniques
4. Genetic testing
5. Tumor imaging
6. Invasive diagnostic techniques

**Treatment of cancer**

A. Setting treatment goals
   - Patient perspective
   - Medical perspective

B. Choice of cancer treatment modality
   - Surgery
   - Radiotherapy
   - Chemotherapy
Biological response modifiers and molecular targeted therapy

Combined-modality therapy

C. Palliative care

Chemotherapeutic agents and its classification

The purpose of treating cancer with chemotherapeutic agents is to prevent cancer cells from multiplying, invading, metastasizing and ultimately killing the host (patient). In the most effective chemotherapeutic regimens, the drugs are capable not only of inhibiting but also of completely eradicating all neoplastic cells while sufficiently preventing normal marrow and other target organs to permit the patient to return to normal, or at least satisfactory function and quality of life. Most agents currently in use, with the exception of immunotherapeutic agents, other biologic response modifiers and molecular targeted therapies appear to have their primary effect on either macromolecular synthesis or function. This effect means that they interfere with the synthesis of DNA, RNA or proteins or with the appropriate functioning of the preformed molecule. When interference in macromolecular synthesis or function in the neoplastic cell population is sufficiently great, a proportion of the cells die. Some cells die because of the direct effect of the chemotherapeutic agent. In other instance, the chemotherapy may trigger differentiation, senescence, or apoptosis, the cell’s own mechanism of programmed death.

Classification

Classification of classical and molecular targeted agents is summarized in Table 1.
Table 1. Classification of classical and molecular targeted agents

<table>
<thead>
<tr>
<th>Class and type</th>
<th>Agents</th>
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<tbody>
<tr>
<td><strong>Alkylating agents</strong></td>
<td></td>
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<tr>
<td>Alkyl sulfonate</td>
<td>Busulfan</td>
</tr>
<tr>
<td>Ethylenimine derivatives</td>
<td>Thiotepa (triethylenethiophosphoramide)</td>
</tr>
<tr>
<td>Metal salt</td>
<td>Carboplatin, cisplatin, oxaliplatin</td>
</tr>
<tr>
<td>Nitrogen mustard</td>
<td>Bendamustine, chlorambucil, cyclophosphamide, estramustine, ifosfamide, mechlorethamine, melphalan</td>
</tr>
<tr>
<td>Riazene-imidazole</td>
<td>Dacarbazine, temozolamide</td>
</tr>
<tr>
<td><strong>Antimetabolites</strong></td>
<td></td>
</tr>
<tr>
<td>Antifolates</td>
<td>Methotrexate, pemetrexed, pralatrexate</td>
</tr>
<tr>
<td>Purine analogs</td>
<td>Cladribine, fludarabine, mercaptopurine, nelarabine, pentostatin, thioguanine</td>
</tr>
<tr>
<td>Pyrimidine analogs</td>
<td>Azacitidine, capecitabine, cytarabine, doxorubicin, epirubicin, idarubicin, mitomycin, mitoxantrone, valrubicin</td>
</tr>
<tr>
<td><strong>Natural products</strong></td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Bleomycin, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, mitomycin, mitoxantrone, valrubicine</td>
</tr>
<tr>
<td>Enzyme</td>
<td>Asparaginase</td>
</tr>
<tr>
<td>Microtubule polymer stabilizer</td>
<td>Cabazitaxel, docetaxel, paclitaxel</td>
</tr>
<tr>
<td>Mitoticinhibitor</td>
<td>Eribulin, ixabepilone, vinblastine, vincristine, vindesine, vinorelbine</td>
</tr>
<tr>
<td>Topoisomerase I inhibitors</td>
<td>Irinotecan, topotecan</td>
</tr>
<tr>
<td>Topoisomerase II inhibitors</td>
<td>Etoposide, teiposide</td>
</tr>
<tr>
<td><strong>Hormones and hormone antagonist</strong></td>
<td></td>
</tr>
<tr>
<td>Androgen</td>
<td>Fluoxymesterone and others</td>
</tr>
<tr>
<td>Androgen antagonist</td>
<td>Bicalutamide, flutamide, nilutamide</td>
</tr>
<tr>
<td>Aromatase inhibitor</td>
<td>Aminogluthethimide, anastraazole, letrozole, exemestane</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>Dexamethasone, prednisone</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Diethylstilbestrol</td>
</tr>
<tr>
<td>GNRH receptor antagonist</td>
<td>Degarelix</td>
</tr>
<tr>
<td>LNRH agonist</td>
<td>Goserelin, leuprolide, triptorelin</td>
</tr>
<tr>
<td>Polypeptide hormone release suppression</td>
<td>Octreotide</td>
</tr>
<tr>
<td>Progestin</td>
<td>Megestrol acetate, medroxypregesterone</td>
</tr>
<tr>
<td><strong>Selective estrogen-receptor-modulator (estrogen antagonist)</strong></td>
<td>acetate</td>
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<tr>
<td>-----------------</td>
<td>---------</td>
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<tr>
<td>Fulvestrant, raloxifene, tamoxifen, toremifene</td>
<td></td>
</tr>
<tr>
<td><strong>Somtostatin analog</strong></td>
<td>Octreotide</td>
</tr>
<tr>
<td><strong>Thyroid hormones</strong></td>
<td>Levothyroxine, liothyronine</td>
</tr>
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**Molecularily targeted agents**

<table>
<thead>
<tr>
<th>Cyclin-dependent kinase inhibitor</th>
<th>Flavopiridol</th>
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<tbody>
<tr>
<td><strong>Geneexpression modulators</strong></td>
<td>Retinoids, rexinoids, romidepsin</td>
</tr>
<tr>
<td><strong>IL-2 receptor toxin</strong></td>
<td>Denileukindiftitox</td>
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<tr>
<td><strong>Monoclonal antibody</strong></td>
<td>Alemtuzumab, cetuximab, getuzumab, ibritumomabtiuxetan, ibrutinomab, ofatumumab, pantitumumab, trastuzumab, rituximab, iodine-131 tositumomab</td>
</tr>
<tr>
<td><strong>mTor kinase inhibitor</strong></td>
<td>Everolimus, temsirolimus</td>
</tr>
<tr>
<td><strong>PARP1 inhibitor</strong></td>
<td>Olaparib</td>
</tr>
<tr>
<td><strong>Proteasome inhibitor</strong></td>
<td>Bortezomib</td>
</tr>
<tr>
<td><strong>Receptor tyrosine kinase inhibitors, multikinaseinhibitors</strong></td>
<td>Dasatinib, erlotinib, gefitinib, imatinibmesylate, lapatinib, midostaurin, pazopanib, semaxanib, sorafenib, sunitinib, vandetanib</td>
</tr>
<tr>
<td><strong>Retinoic acid receptor expression modification</strong></td>
<td>Tretinoin (all-\textit{trans}-retinoic acid)</td>
</tr>
</tbody>
</table>

**Biologic response modifiers**

<table>
<thead>
<tr>
<th>Interferons</th>
<th>Interferon-\textit{α}<em>{2a}, interferon-\textit{α}</em>{2b}</th>
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</thead>
<tbody>
<tr>
<td>Interleukins</td>
<td>Aldesleukin (IL-2), oprelvekin, denileukindiftitox</td>
</tr>
<tr>
<td><strong>Myeloid- and erythroid-stimulating factors</strong></td>
<td>Epoetin, filgrastim, sargramostim</td>
</tr>
<tr>
<td><strong>Nonspecific immunomodulation</strong></td>
<td>Thalidomide, lenalidomide</td>
</tr>
<tr>
<td><strong>Vaccine (autologous)</strong></td>
<td>Sipuleucel-T</td>
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</tbody>
</table>

**Miscellaneous agents**

<table>
<thead>
<tr>
<th>Adrenocortical suppressant</th>
<th>Mitotane</th>
</tr>
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<tbody>
<tr>
<td>Bisphosphonates</td>
<td>Pamidronate, zoledronic acid</td>
</tr>
<tr>
<td>Cytoprotector (reactive aspeciesanagonist)</td>
<td>Amifostine, dextrazoxane, mesna</td>
</tr>
<tr>
<td>Methylhydrazine derivative</td>
<td>Procarbazine</td>
</tr>
<tr>
<td>Photosensitizing agents</td>
<td>Porphine</td>
</tr>
<tr>
<td>Platelet-reducing agent</td>
<td>Anagrelide</td>
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<tr>
<td>Salt</td>
<td>Arsenic trioxide</td>
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<tr>
<td>Substituted melamne</td>
<td>Altretamine (hexamethylmelamine)</td>
</tr>
<tr>
<td>Substituted urea</td>
<td>Hydroxycarbamide (hydroxyurea)</td>
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**SWALLOWING**

Deglutition is the act of swallowing, through which a food or liquid bolus is transported from the mouth through the pharynx and esophagus into the stomach. Normal deglutition is a smooth coordinated process that involves a complex series of voluntary and involuntary neuromuscular contractions. Total swallow time from oral cavity to stomach is no more than 20 s. Swallowing uses both skeletal muscle (tongue) and smooth muscles of the pharynx and esophagus. The autonomic nervous system coordinates this process in the pharyngeal and esophageal phases. Understanding the normal physiology and pathophysiology of eating and swallowing is fundamental to evaluating and treating disorders of eating and swallowing. Swallowing can be divided into three phases such as the oral phase, the pharyngeal phase and the esophageal Phase \(^{15,29,30}\).
DYSPHAGIA

Types

Common causes

Consequences

Diagnosis

Management

Difficulty in swallowing (dysphagia) happens when a person has trouble in getting food or liquid to pass down the throat. Dysphagia can occur at any time during the lifespan.

Types of dysphagia

1. Esophageal dysphagia: arises from the body of the esophagus, lower esophageal sphincter, or cardia of the stomach, usually due to mechanical causes or motility problems. Patients usually complain of dysphagia (the feeling of food getting stuck several seconds after swallowing), and will point to the suprasternal notch or behind the sternum as the site of obstruction. If there is dysphagia to both solids and liquids, then it is most likely a motility problem. If there is dysphagia initially to solids but progresses to also involve liquids, then it is most likely a mechanical obstruction.

2. Oropharyngeal dysphagia: is defined as difficulty swallowing resulting from abnormalities of structure or movement of the oral cavity, (including lips, jaw and tongue), the oropharynx, velopharynx, hypopharynx, larynx and upper oesophageal sphincter. Some signs and symptoms of swallowing difficulties include difficulty controlling food in the mouth, inability to control food or saliva in the mouth,
difficulty initiating a swallow, coughing, choking, frequent pneumonia, unexplained weight loss, gurgly or wet voice after swallowing, nasal regurgitation, and dysphagia (patient complaint of swallowing difficulty) \(^{32}\).

3. **Functional dysphagia**: when there is no organic cause for dysphagia that can be found, then these patients are defined as having functional dysphagia \(^{32}\).

**Common Causes of dysphagia**

Swallowing disorders can occur in all age groups, resulting from congenital abnormalities, structural damage, and/or medical conditions \(^{32}\). Dysphagia occurs in patients with neurologic or muscular disorders that affect the patient’s ability to swallow (e.g., a patient with muscular dystrophy). Dysphagia also occurs in patients with upper esophageal sphincter or anatomic abnormalities. The most common etiologies of dysphagia are stroke, burns, trauma, Parkinson’s disease, oropharyngeal tumors, gastroesophageal reflux disease (GERD), blunt throat injury, surgery-caused impairment, multiple sclerosis, Asperger syndrome, esophageal cancer, laryngeal cancer, chagas disease, celiac, cystic fibrosis, Huntington's disease, Niemann-Pick disease, cervical osteophytes, Zenker’s diverticulum, upper esophageal sphincter or anatomic abnormalities, cervical osteophytes, Myasthenia gravis, Achalasia, Eosinophilic esophagitis, Scleroderma and AIDS. Patients with amyotrophic lateral sclerosis (ALS), Alzheimer’s disease, spinal cord or other trauma, poor dentition or poor fitting dentures can also develop dysphagia \(^{2,4,33}\). People who have been treated for head and neck cancer, such as laryngeal cancer or oral cancer, often experience swallowing problems (dysphagia). The seriousness of the swallowing problem depends on the type and nature of the treatment, the size and location of the tumor, and the nature of any reconstruction. Medications can be the cause of dysphagia or may exacerbate an existing dysphagia. Medications with central nervous system sedating properties that overly sedate or impair cognition may affect swallowing. Medications that cause xerostomia, such as those with anticholinergic or diuretic properties can result in a decreased ability to wet food making it uncomfortable to chew or difficult to transfer food within the oral cavity, thus making it
difficult to swallow. Patients with drug-induced mouth ulcers or other oral pathologic disorders may find it difficult to chew, transfer, or swallow. Medications that can result in esophageal injury when not taken properly or when esophageal motility is impaired include Non steroidal anti-inflammatory drugs (NSAIDs), aspirin, vitamin C tablets, bisphosphonates, potassium chloride, quinidine, tetracycline’s, clindamycin, doxycycline and iron products such as FeoSol, Feratab, Fer-Iron etc. Older patients are at a greater risk for medication injuries since they take more medications, have slowed swallowing, spend more time in a recumbent position, have decreased saliva production, and are more likely to have motility or anatomic disorders of the esophagus.

Consequences of dysphagia

Aspiration and resulting pneumonia, choking, poor or malnutrition, and dehydration are the most serious and potentially life threatening consequences of dysphagia. Other consequences include physical discomfort, anxiety about eating or drinking, social isolation, medication-induced esophageal injury, emotional well being and quality of life issues. Aspiration of food by dysphagic patients is considered one of the factors causing pneumonia among the aged. Dysphagia affects the quality of life (QOL) of the patients. Ekberg et al. provide evidence of dysphagia’s assault on QOL. Their study of 360 dysphagic patients from five European countries is informative. Only 45 % found eating pleasurable, 41 % were anxious while eating and 36 % avoided eating with others. One of the conclusions is that formal measures of these QOL related conditions are mandatory and that treatment should be directed toward their amelioration.

Diagnosis of dysphagia

A. History of the patients
B. Clinical and physical examination
C. Tests
Barium swallow, CT scanning, magnetic resonance imaging, or direct endoscopy, Fiberoptic endoscopic evaluation of swallowing (FEES), modified barium swallow (MBS), or scintigraphic evaluation of swallowing, Pulse oximetry, ultrasound, rapid sequence magnetic resonance imaging also assess swallow function.

D. Functional evaluation of swallowing

   a) Bedside swallowing evaluation
   b) Modified barium swallow
   c) Fiberoptic endoscopic evaluation of swallowing
   d) Scintigraphy
   e) Ultrasonography
   f) Pulse oximetry

Management of dysphagia

A. Nonsurgical therapy

   The nonsurgical treatment of swallowing disorders focuses on swallow safety and nutrition. The susceptibility of the elderly population to dysphagia and its relation to malnutrition and its consequences are subject to greater attention. Clinicians rely on multiple approaches to enhance swallowing safety, including prostheses, diet modification, direct swallowing therapy, indirect swallowing therapy, and modification of utensils to improve and control feeding\(^3\)\(^8\).

   Diet modifications:

   Speech pathologists make specific recommendations regarding the type of diet (\textit{e.g.} pureed), fluid thickness, and other techniques to aid the patient in swallowing and
decrease the risk of aspiration, choking or gagging. Pharmacists should note these recommendations, particularly those regarding fluid thickness and type of diet since these may affect how medications are administered.

Fluid thickness is usually described as one of the following:

- **Thin** – regular fluids, no change is required
- **Nectar-like** – thin enough to sip through a straw, but still spillable (e.g. eggnog)
- **Honey-like** – thick enough to require a spoon and too thick for a straw; will not hold its shape independently (e.g. yogurt or honey)
- **Spoon-thick** – must be eaten with a spoon; pudding-like (e.g. thickened apple sauce).

Diet alterations and food presentation strategies also can be used therapeutically to improve efficiency and safety of swallowing. Thickening liquids may slow the rate of bolus flow through the pharynx for patients with a delayed swallow. A puree diet can be used if surgical resection or trismus prevents chewing. Foods prepared with sauces and gravies may be useful for a xerostomic patient. Alternating solids and liquids can reduce pharyngeal stasis.²

In 2002, the American Dietetic Association established the National Dysphagia Diet (NDD) guidelines for thickened dietary supplements. This Task Force proposed viscosity ranges for thin, nectar-, and honey-thick and spoon thick liquids (Table 2).³⁹

**Table 2. Proposed Terms and Viscosity Ranges for Dysphagia Diet Task Force (DDF).**

<table>
<thead>
<tr>
<th>Liquid</th>
<th>Viscosity Range *</th>
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<tbody>
<tr>
<td></td>
<td>Pas</td>
</tr>
<tr>
<td>Thin</td>
<td>0.001-0.05</td>
</tr>
<tr>
<td>Nectar-like</td>
<td>0.051-0.350</td>
</tr>
<tr>
<td>Honey-like</td>
<td>0.351-1.75</td>
</tr>
<tr>
<td>Spoon-thick</td>
<td>&gt;1.751</td>
</tr>
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* At a shear rate of 50 s⁻¹ at 25°C.
B. Surgical therapy

i. Vocal cord medialization         V. Surgical closure of the larynx

ii. Medialization laryngoplasty     Vi. Gastrostomy tubes

iii. Cricopharyngeal myotomy        Vii. Tracheotomy

iv. Palatopexy

Robbins J and Hind J \(^{40}\) presented an overview of largest randomized clinical trial in dysphagia. The two-part sequential randomized clinical trial studied the effect of two common dysphagia interventions (chin tuck and thickened liquids) for immediate prevention of aspiration during videofluorographic assessment and also for the incidence of pneumonia at 3-months for patients with Parkinson's disease and/or dementia. Results indicated that thickened liquids (nectar-thick or honey-thick) prevented aspiration during the radiographic study more frequently than chin-down posture; however, both interventions were equally successful at preventing pneumonia. Median length of hospital stay due to pneumonia was three times longer for patients drinking honey-thick liquids compared to nectar-thick and chin-tuck arms of the study.

Germain I et al. \(^{41}\) conducted a randomized controlled trial in a Canadian residential aged care facility to examine the effectiveness of a novel dysphagia diet (which included thickened fluids) compared to the standard facility diet. This study found that a reformed diet of minced/pureed foods and thickened fluids can demonstrate a significant change in dietary intake resulting in weight gain for an undernourished, elderly group with dysphagia and some cognitive decline when compared to a traditional modified-textured diet. It also demonstrated that a change in thickened fluid (type and range offered) may be beneficial for residents with dementia who require thickened fluids.
Many pharmaceutical firms have directed their research activity in reformulating existing drugs into new dosage forms. One such relatively new dosage form is the fast disintegrating films (FDF), a thin film that is prepared using hydrophilic polymers. When quick dissolving films/ fast disintegrating films are placed on the tongue, the dosage form disintegrates instantaneously or within few seconds releasing the drugs, which dissolve or disperse in saliva. The saliva containing drug is swallowed and the drug is absorbed in normal way. Some fraction of the drug may be absorbed from pregastric sites such as mouth, pharynx and esophagus as the saliva passes down into gastro retentive platforms. They can be unobstructive and can be designed to leave minimal or no residue in the mouth after administration and also provides a pleasant mouth feel.

**Properties**

Oral fast disintegrating films are thin, elegant, printable, low moisture, non-tacky film that is convenient for dosing, suitable for labeling and flexible for easy packing, handling and application. The thickness of the typical films ranges from 1 to 10 mil and its surface area can be 1 to 20 cm$^2$ for any geometry. The flexibility and strength of the film may be selected/ modified to facilitate automatic rewinding, die cutting and packing.
during manufacturing. The flexibility and strength are reflected by the tensile strength, elongation, young modulus, bending length and tear resistance of the film.

Advantages

- FDF’s are unit dosage forms which provide accurate dosing, easy to manufacture and small packing size.

- Administration to patients who cannot swallow such as dysphagic, elderly, stroke victim and bedridden patients and patients who refuse to swallow such as pediatric, geriatric and psychiatric patients prefer FDF as these dosage forms are unobstructive, easy to administer and handle, prevents choking and provides better patient compliance.

- Convenience and patient compliance for travelling and busy people who do not have ready access to water.

- The difficulty encountered in swallowing tablets or capsules is circumvented. The large surface area available in this dosage form allows rapid wetting in the moist buccal environment. The dosage form can be consumed at anyplace and anytime as per convenience of the individual.

- Since the films are flexible in nature and not fragile, hence, there is ease of consumer handling, transportation and storage.

- FDF provides both site specific and systemic action. The oral or buccal mucosa being highly vascularized, drugs can be absorbed directly and can enter the systemic circulation without undergoing first-pass hepatic metabolism. This advantage can be exploited in preparing products with improved oral bioavailability of molecules that undergo first pass effect. Since the first pass effect can be avoided, there can be reduction in the dose which can lead to reduction in side effects associated with the molecule.
• Patients suffering from repeated emesis and motion sickness prefer this dosage form as they are unable to swallow large quantity of water.

• Availability of larger surface area in these dosage forms leads to rapid disintegrating and dissolution in the oral cavity which in turn results in rapid absorption which can provide rapid onset of action.

Disadvantage

• The disadvantage of FDF is that high dose cannot be incorporated into the strip. However, research has proven that the concentration level of active can be improved up to 50 % per dose weight.

Manufacturing Methods

There are five methods to prepare films i.e.

1. Solvent casting
2. Semisolid casting
3. Hot melt extrusion
4. Solid dispersion extrusion
5. Rolling

But the most commonly used industrial methods are solvent-casting method and hot melt extrusion

1. Solvent casting method

    Aqueous solution (I) is prepared by dissolving the required quantities of polymer and plasticizer in distilled water. The solution is stirred until it forms a clear viscous solution. The viscous solution is kept aside to remove all the air bubbles entrapped.
Another aqueous solution (II) is prepared by dissolving specified quantities of drug, sweetener and flavors in specific proportion in a suitable solvent system. Aqueous solution I is added to solution II and stirred. After removal of air bubble the polymeric solution containing drug is casted into glass petridish of specified dimension and dried in the vacuum oven. The film was carefully removed from the petridish, observed for any imperfections and cut according to the size required for testing.

The selection of solvent essentially depends on the API to be incorporated into the strip. The physicochemical properties of the Active Pharmaceutical Ingredient (API) like heat sensitivity, shear sensitivity, the polymorphic form of the API used, compatibility of the API with solvent and other strip excipients are to be critically studied. The significant elements in this are liquid rheology, desired mass to be cast and content or dosage uniformity. Solvents used for the preparation of solution or suspension should ideally be selected from ICH Class 3 solvent list. Entrapped air may tend to produce uneven strips. Deaeration step is imperative to get a strip with uniform thickness. Vacuum assisted machines can be employed to remove the entrapped air. Many firms adopt bubble-free mixing using suitable type of specialized stirring systems. Another important aspect is the moisture present in the solution. It is observed that moisture can cause changes in the mechanical properties of the strips such as tensile strength, flexibility, folding endurance, Young's modulus, elongation etc. Hence care should be exercised by using suitable humidity controls in the manufacturing production area. The solution is subjected to continuous mixing process in order to keep the viscosity and concentration unchanged. The solution or suspension may be kept under controlled temperature condition to achieve the desired viscosity of the material.

El-Setouhy DA and El-Malak NSA 50 formulated orodispersible film (s) of tianeptine sodium to enhance the convenience and compliance by the elderly and pediatric patients by solvent casting method. The novel film former, lycoat NG73 (granular hydroxypropyl starch), along with different film-forming agents (hydroxypropyl methyl cellulose, hydroxyethyl cellulose, and polyvinyl alcohol), in addition to three film modifiers; namely, maltodextrin, polyvinyl pyrrolidone K90 and lycoat RS780 (pregelatinized
hydroxypropyl starch) were evaluated. The prepared formulations were evaluated for their in vitro dissolution characteristics, in vitro disintegration time, and their physico-mechanical properties. The promising orodispersible film based on lycoat NG73 (F1); showing the greatest drug dissolution, satisfactory in vitro disintegration time and physico-mechanical properties that are suitable for orodispersible films, was evaluated for its bioavailability compared with a reference marketed product (Stablon® tablets) in rabbits. Statistical analysis revealed no significant difference between the bioavailability parameters of the test film (F1) and the reference product. These findings suggest that the fast orodispersible film containing tianeptine is likely to become one of choices for acute treatment of depression.

2. Hot Melt Extrusion

The drug-excipient mixture is filled in the hopper and is conveyed, mixed, and melted by the extruder. The die then shapes the melt in the required film form. The equipment used for hot melt extrusion consists of extruder, downstream auxiliary equipment and monitoring tools. Extruder is composed of a feeding hopper, barrel, screw, die, screw-driving unit and heating/cooling device. Hot-melt extrusion include lower temperature and shorter residence time of the drug carrier mix (< 2 min), absence of organic solvents, continuous operation possibility, minimum product wastage, good control of operating parameters, and possibility to scale up.

Cilurzo et al. prepared films using both solvent casting and hot-melt extrusion. It was reported that the solvent casting method is more reliable for the production of fast dissolving films compared to the hot-melt extrusion method. Moreover, films produced from solvent casting method exhibited the highest patient’s compliance and best performances in terms of in vitro and in vivo disintegration time.
Advantages:

- Without use of any solvent or water.
- Fewer processing steps.
- Compressibility properties of the API may not be of importance.
- Better alternative for poorly soluble drugs.
- More uniform dispersion because of intense mixing and agitation.
- Less energy compared with high shear methods.

Disadvantages:

- Thermal degradation due to use of high temperature
- Flow properties of the polymer are essential to processing
- Limited number of available polymers
- All excipients must be devoid of water or any other volatile solvent

3. Semisolid casting method

Solution of water soluble film forming polymer is prepared. Resulting solution was added to a solution of acid insoluble polymer (e.g. cellulose acetate phthalate, cellulose acetate butyrate) to form homogenous viscous solution. Appropriate amount of plasticizer is added so that gels mass is obtained. Finally the gel mass is casted in to the films or ribbons using heat controlled drums. The thickness of the film should be about 0.015 - 0.05 inches. The ratio of the acid insoluble polymer to film forming polymer should be 1:4. 43
4. Solid dispersion extrusion

The term “solid dispersions” refers to the dispersion of one or more active ingredients in an inert carrier in a solid state in the presence of amorphous hydrophilic polymers and also using methods such as melt extrusion. Solid dispersions are prepared by immiscible components and drug. Finally the solid dispersions are shaped into films by means of dies.

5. Rolling method

In this method, the film is prepared by preparation of a pre-mix, addition of an active and subsequent formation of a film. The pre-mix or master batch which includes the film-forming polymer, polar solvent, and any other additives except a drug active is added to the master batch feed tank. Then a pre-determined amount of the master batch is controllably fed via a first metering pump and control valve to either or both of the first and second mixers. The required amount of the drug is added to the desired mixer through an opening in each of the mixers. After the drug has been blended with the master batch pre-mix for a sufficient time to provide a uniform matrix, a specific amount of the uniform matrix is then fed to the pan through the second metering pumps. The metering roller determines the thickness of the film and applies it to the application roller. The film is finally formed on the substrate and carried away via the support roller. The wet film is then dried using controlled bottom drying, desirably in the absence of external air currents or heat on the top (exposed) surface of the film.

Film forming polymers \(^{43, 44, 46, 52}\)

Film is prepared using hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity, delivering the drug to the systemic circulation via dissolution when contact with liquid is made. A variety of polymers are available for preparation of fast dissolving oral films. The use of film forming polymers in oral films has attracted
considerable attention in medical and nutraceutical applications. The selection of polymer, is one of the most important and critical parameter for the successful development of the film formulation. The polymers can be used alone or in combination to obtain the desired film properties. The film obtained should be tough enough so that there won't be any damage while handling or during transportation. The robustness of the strip depends on the type and amount of polymer in the formulation. In order to remain intact against the internal and external stresses developed during storage and especially when exposed to environmental conditions, a film should have high mechanical strength with sufficient elongation and elasticity properties. On the other hand, fast dissolving strip dosage forms should have the property to disintegrate in seconds when placed in mouth and deliver the drug to the oral cavity instantaneously.

The polymers employed in the oral film preparation should be:

- Non-Toxic and Non-Irritant.
- Devoid of leachable impurities.
- Should not retard disintegration time of film.
- Tasteless.
- Should have good wetting and spread ability property.
- Should exhibit sufficient peel, shear and tensile strength.
- Readily available.
- Inexpensive.
- Should have sufficient shelf life.
- Should not aid in causing secondary infections in the oral mucosa or dental regions.
These properties of films developed from the polymers are dominated by polymer chemistry, solvent effects, and additives such as plasticizer, sugars, and humectants. The polymers used in the films can be cellulose derivatives (hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose), synthetic polymers (polyvinyl alcohol, polyethylene glycol, polyacrylic acid, methylmethacrylate copolymer, polyvinyl pyrrolidone, carboxyvinyl polymer), natural gums (xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum), starch derivatives (amylose, high amylose starch, hydroxypropylated high amylose starch), polysaccharides (dextrin, pectin, chitin, chitosan, levan, sodium alginate) and peptides (elsinan, collagen, gelatin, zein, gluten, soy protein isolate, whey protein isolate, casein) and others.

Dinge A and Nagarsenker M formulated fast dissolving films containing triclosan for delivery into oral cavity. Various film forming agents, film modifiers and polyhydric alcohols were evaluated for optimizing the composition of fast dissolving films. Fast dissolving films containing hydroxypropyl methyl cellulose (HPMC), xanthum gum, and xylitol were formulated. Fast dissolving films containing hydroxypropyl-b-cyclodextrin (HPBCD) complex and TC-Poloxamer 407 were formulated and were evaluated for the in vitro dissolution profile and in vitro microbiological assay. Films containing TC-Poloxamer 407 exhibited better in vitro dissolution profile and in vitro antimicrobial activity as compared to films containing TC-HPBCD complex.

Hiroyoshi S et al. formulated fast dissolving oral thin film that contains dexamethasone and base materials, including microcrystalline cellulose, polyethylene glycol, hydroxypropylmethyl cellulose, polysorbate 80 and low-substituted hydroxypropyl cellulose. This preparation showed excellent uniformity and stability, when stored at 40 °C and 75 % in humidity for up to 24 weeks. The film was disintegrated within 15 s after immersion into distilled water. The dissolution test showed that approximately 90 % of dexamethasone was dissolved within 5 min.

Nishimura M et al. developed an Oral disintegrating film containing prochlorperazine using microcrystalline cellulose, polyethylene glycol and hydroxypropylmethyl cellulose.
as the base materials. The film showed an excellent stability at least for 8 weeks when stored at 40 °C and 75 % in humidity. The dissolution test revealed a rapid disintegration property, in which most of prochlorperazine dissolved within 2 min after insertion into the medium. Subsequently, rats were used to compare pharmacokinetic properties of the film preparation applied topically into the oral cavity with those of oral administration of prochlorperazine solution. None of the parameters, including Tmax, Cmax, area under curves, clearance and steady-state distribution volume was significantly different between oral disintegrating film and oral solution.

_Cilurzo F et al._ 51 Aimed to study maltodextrins (MDX) with a low dextrose equivalent as film forming material and their application in the design of oral fast-dissolving films. The suitable plasticizer and its concentration were selected on the basis of flexibility, tensile strength and stickiness of MDX films, and the MDX/plasticizer interactions were investigated by ATR-FTIR spectroscopy. Main production technologies such as casting and solvent evaporation (Series C) or hot-melt extrusion (Series E), by adding sorbitan monoleate (SO) or cellulose microcrystalline (MCC), respectively were used. MCC decreased the film ductility and significantly affected the film disintegration time both _in vitro_ and _in vivo_ (Series C < 10 s; Series E ~ 1 min). To assess the film loading capacity, piroxicam (PRX), a water insoluble drug, was selected. The loading of a drug as a powder decreased the film ductility, but the formulation maintained satisfactory flexibility and resistance to elongation for production and packaging procedures. The films present a high loading capacity, up to 25 mg for a surface of 6 cm$^2$. The PRX dissolution rate significantly improved in Series C films independently of the PRX/MDX ratio.
FAST DISINTEGRATING TABLETS

Advantages

Disadvantages

Techniques/methods to prepare FDT

Superdisintegrants

Patented Technologies for FDT’s

Tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness, and ease in manufacturing. Orally disintegrating tablets are also called as orodispersible tablets, quick-disintegrating tablets, mouth-dissolving tablets, fast-disintegrating tablets, fast dissolving tablets, rapid-dissolving tablets, porous tablets, and rapimelts. However, of all the above terms, the United States Pharmacopoeia (USP) approved these dosage forms as orodispersible tablets (ODT’s). Recently, the European Pharmacopoeia has used the term orodispersible tablets for tablets that disperse readily and within 3 min in the mouth before swallowing. The United States Food and Drug Administration define ODT as “a solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue.” The disintegration time for ODTs generally ranges from several seconds to about a minute.

Advantages

The advantages of mouth dissolving dosage form are increasingly being recognized in both industry and academia.
Improved patient compliance is the primary benefit of this technology.

Administration to patients who cannot swallow such as dysphagic, elderly, stroke victim and bedridden patients, patients who should not swallow such as those affected by renal failure and patients who refuse to swallow such as pediatric, geriatric and psychiatric patients prefer FDT as these dosage forms are unobstructive and prevents choking.

No need of water for swallowing the dosage forms. This is highly convenient feature for the patients who are traveling or do not have immediate access to water.

Superior taste of the tablet helps to change the basic view of medications as the “bitter pill” particularly for pediatric patients.

Added benefits of convenience and accurate dosing as compared to liquids.

Rapid drug therapy intervention is possible.

Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach; in such cases bioavailability of drugs is increased.

Easily portable and suitable for transportation by patients.

Can be produced at industrial scale more simply and more efficiently.

The fast dissolving dosage forms combines the benefit of liquid formulation with those of solid oral dosage forms.

Leave minimal or no residue in the mouth after oral administration and also provide a pleasant mouth feel.

Allows high capacity of drug loading.

New business opportunities: product differentiation, line extension and life-cycle management, exclusivity of product promotion, and patent-life extension.
Disadvantages

- Drugs absorbed at specific site cannot be given in these dosage forms.
- These tablets show high friability, less hardness than conventional tablets.

Techniques/methods used in the preparation of FDT

1. Tablet molding

   In this technique, the tablet is prepared using water-soluble additives. These water-soluble additives dissolve rapidly and completely in mouth. All ingredients of the formulation are passed through fine mesh. Then this dry blend is wetted with a hydro-alcoholic solvent and then compressed into tablets using low compression forces. The solvent present inside the tablets is removed by air-drying. Thus so formed molded tablets contain a porous structure, which enhances the dissolution. The molded tablets prepared by this method possess low mechanical strength. To improve mechanical strength, binding agent like sucrose, polyvinyl pyrrolidone, cellulosic polymers like hydroxylpropyl methylcellulose may be added to the solvent system. The scope of taste masking in molded tablets is very limited. To mask the unpalatable taste of the medicament, the drug to be incorporated has to be pretreated with different techniques available like spray congealing or flavor addition, micro-particulate system of the drug etc.

2. Spray Drying

   Spray drying can be used to prepare rapidly dissolving tablets. This technique is based upon a particulate support matrix that is prepared by spray drying an aqueous composition containing support matrix and other components to form a highly porous and fine powder. This is then mixed with active ingredient and compressed into tablet.
Allen and Wang \(^{64}\) have employed spray-drying technique to prepare fast dissolving tablets. They developed formulation by using mannitol as bulking agent, hydrolyzed and non-hydrolyzed gelatin as support matrix, sodium starch glycolate as disintegrant and acidic material (citric acid) and /or alkali material (e.g. NaHCO\(_3\)) to enhance disintegration and dissolution. Tablets manufactured from this powder disintegrated in less than 20 s in an aqueous medium.

3. Lyophilization

Freeze drying (lyophilisation) is a process in which solvent is removed from a frozen drug solution or suspension containing structure forming excipients. Freeze-dried forms offer more rapid dissolution than other available solid products as process imparts glossy amorphous structure to the bulking agent and sometimes to the drugs. Lyophilization results in preparations, which are highly porous, with a very high surface area, which dissolve rapidly and show improved absorption and bioavailability. Lyophilization technique is generally used for heat sensitive drugs and biologicals. Tablets prepared by lyophilization, are fragile and possess low mechanical strength, which makes difficult to handle and they also exhibit poor stability on storage under stressed conditions.

4. Sublimation

Compressed tablets composed of highly water-insoluble excipients do not dissolve rapidly in the water because of its low porosity, so porous tablets that exhibit good mechanical strength and dissolve quickly is the best remedy for above problem.

The basic principle involved in preparing FDT by sublimation technique is addition of a sublime salt (e.g. ammonium carbonate, ammonium bicarbonate and ammonium acetate) to the tablett ing components. Mixing the components to obtain a substantially homogenous mixture and volatilizing the sublime salt. The removal of sublime salt creates pores in the tablet, which help in achieving rapid disintegration when tablet come in contact with saliva.
5. Mass Extrusion

Hot melt extrusion enhances solubility by producing an increased-energy form of the drug through a combination of the process and the chemical properties of the excipient. The resulting product, called the extrudate, is then further processed and converted into a final dose form to achieve the final drug delivery profile desired.

Sherry et al. 65 patented the preparation of ODTs of NSAID and paracetamol by melt extrusion method. The method involved dry blending of sugar alcohol and drugs with other excipients that may be present in the granular component. This powder mixture was heated at a temperature of 100 to 165 °C in an extruder in order to completely melt the sugar alcohol. This resultant mass consisting of fully or partially molten sugar alcohol (xylitol, sorbitol, mannitol, etc.) and non-molten (NSAID (ibuprofen, naproxen, diclofenac) or paracetamol) and other optional excipients was poured on cooled stainless steel trays or a cooled moving belt (10 °C) and allowed to cool. The molten mixture typically solidified within 60 s. The solid mass thus formed was milled by passing through a cone mill fitted with a screen with a round hole of 1 mm diameter. The resulting granules were blended with extra-granular components namely, colloidal silicon dioxide, magnesium stearate, stearic acid, lactose, dicalcium phosphate and microcrystalline cellulose in a blender. The blended material was fed to a rotary tableting machine and compressed into tablets under compaction force ranging from 4 kN to 14 kN. It was reported that tablets obtained from fully melted xylitol were more robust than tablets produced by conventional dry blending process.

6. Effervescent Disintegration System

In this process, an effervescent disintegrating agent is employed. The effervescent excipient (known as effervescent couple) is prepared by coating the organic acid crystals with a stoichiometrically lesser amount of material that is alkaline in nature. The particle size of the organic acid crystals is carefully chosen to be larger than the alkaline excipient to ensure uniform coating of the alkaline excipient on the acid crystals. The coating
process is initiated by the addition of a reaction initiator (water). The reaction is allowed to proceed only to the extent of completing the coating of alkaline material on organic acid crystals. The required end point for reaction termination is determined by measuring carbon dioxide evolution. Then, the excipient is mixed with the active ingredient or its micro particles along with other standard tableting excipients and finally compressed into tablets. Saliva activates the effervescent agent, causing the tablet to disintegrate.

7. Direct Compression

It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of tablet can easily exceed that of other production method. Directly compressed tablet disintegration and solubilization depends on single or combined action of disintegrants and water-soluble excipients. Disintegrant efficacy is strongly affected by tablet size and hardness. Large and hard tablets have disintegration time more than that usually required. As consequences, products with optimal disintegration properties often have medium to small size and/or high friability and low hardness. Breakage of tablet edges during handling and opening of blister alveolus, all results from insufficient physical resistance.

Superdisintegrants

Disintegration starts when a small amount of water or saliva contacts the dosage form (wetting) and penetrates the tablet matrix by capillary action. Therefore, the material properties of pharmaceutical excipients and also the matrix structure including pore size and distribution need to be considered for successful formulation development. Since most disintegrants swell to some extent, swelling pressure is generally considered the main factor for tablet disintegration. Depending on the level and characteristics of the active pharmaceutical ingredient (API) and the desired release profile, the levels of superdisintegrant used can be 1 - 10 wt % of the formulation, and it can be higher or
lower in some cases. Thus, in developing an ODT formulation for direct compression, choosing the optimal superdisintegrant is critical.

Superdisintegrants are another version of superabsorbing materials with tailor-made swelling properties. These materials are not intended to absorb significant amounts of water or aqueous fluids, but intended to swell very fast. Superdisintegrants are used as a structural weakener for the disintegrable solid dosage forms. They are physically dispersed within the matrix of the dosage form and will expand when the dosage form is exposed to the wet environment. Swelling pressure and isotropic swelling of the particles create stress concentrated areas where a gradient of mechanical properties will exist. In fact, a mild explosion occurs at the stress-concentrated area by which the whole structure will break apart.

**Selection of superdisintegrant:**

Although the superdisintegrant primarily affects the rate of disintegration, when used at high levels it can also affect mouth feel, tablet hardness, and friability. Thus, several factors must be considered when selecting a superdisintegrant.

- **Disintegration:** The disintegrant must quickly wick saliva into the tablet to generate the volume expansion and hydrostatic pressures necessary to provide rapid disintegration in the mouth.

- **Compactibility:** When manufacturing an ODT, it is desirable to have tablets with acceptable hardness at a given compression force to produce robust tablets that avoid the need to use specialized packaging while maximizing production speed. Thus, a more compactable disintegrant will produce stronger, less-friable tablets.

- **Mouth feel:** To achieve patient compliance, ODTs must provide a palatable experience to the patient. Large particles can result in a gritty feeling in the mouth. Thus, small particles are preferred. If the tablet forms a gel-like consistency on
contact with water, however, it produces a gummy texture that many consumers find objectionable.

- Flow: As with all direct compression tablet formulations, attaining good flow and content uniformity is important to achieving the required dosage per unit. In typical tablet formulations, superdisintegrants are used at 2 - 5 wt % of the tablet formulation. With ODT formulations, disintegrant levels can be significantly higher. At these higher use levels, the flow properties of the disintegrant are more important because it makes a greater contribution to the flow characteristics of the total blend. The selection of the optimal disintegrant for a formulation depends on a consideration of the combined effects of all of these factors.

**Mechanism of superdisintegrants:**

The four major mechanisms for tablets disintegration are as follows:

- **Swelling**

  Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration gets slow down.

- **Porosity and capillary action (Wicking)**

  Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug/excipient and on tableting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.
Due to disintegrating particle/particle repulsive forces

Another mechanism of disintegration attempts to explain the swelling of tablet made with ‘nonswellable’ disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that non-swelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

Due to deformation

During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet. This may be a mechanism of starch and has only recently begun to be studied.

**Types of superdisintegrants**

Croscarmellose sodium, Crospovidone, Sodium starch glycolate, Alginic acid NF, Soy polysaccharides, Calcium silicate, Low-substituted hydroxypropyl cellulose (L-HPC) etc.

**Patented technologies for mouth dissolving tablets**

Zydis Technology

Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped or dissolved within the matrix of fast dissolving carrier material. When Zydis units are put into the mouth, the freeze-dried structure disintegrates instantaneously and
does not require water to for swallowing. The Zydis technology is an example of a technology platform for lyophilized ODT products. The basic formulation and process for lyophilized ODTs are all similar, but there are some important differences between each lyophilized ODT technology, which result in significant variation in performance.

To create FDTs using the Zydis lyophilization technology, the active pharmaceutical ingredient (API) is dispersed in a matrix consisting of a polymeric structure former (e.g. gelatin) and a saccharide (typically mannitol) dissolved in water. In the finished product, the glassy amorphous structure of the polymeric component imparts strength and resilience while retaining some flexibility. Depending on its solubility, the API may be dissolved in the matrix or dispersed to form a homogenous suspension for dosing. In addition to the basic structure-forming components and API, other excipients may be included in the formulation such as pH-modifying agents for optimal stability or taste-masking effect, and flavors and sweeteners for palatability. The active mix is dispensed into preformed blister packs, which travel through a tunnel cooled with liquid nitrogen to freeze the product rapidly. After freezing, the product is lyophilized, and the dried blisters are sealed. Following administration and rapid dispersion on the tongue, the Zydis formulation effectively reverts to the original API solution/suspension. Therefore, the Zydis ODT provides all the convenience of a solid oral-dose form with the advantages of a solution/suspension product.

- Orasolv Technology

CIMA labs have developed Orasolv Technology. OraSolv product combines taste-masked active drug ingredients with a low-effervescence system. On contact with saliva, the effervescent system promotes disintegration of the tablet. The Ora-Solv process typically involves blending the microencapsulated API with magnesium oxide and mannitol to aid in the release of the drug from the polymeric coating. These microparticles are further blended with other excipients and loosely compressed to maintain some degree of tablet porosity to aid dispersion. Compression forces need to be kept to a minimum so as not to disrupt the API taste-masking coating. The resultant tablet
is relatively weak and friable and requires specific patented packaging technology (PakSolv, CIMA Labs) and use of aluminum blisters to protect the drug from moisture. Disintegration times are typically less than 40 s.

- Durasolv Technology

Durasolv is second-generation fast dissolving/disintegrating tablet formulation. Durasolv is the patented technology of CIMA labs (USA). The DuraSolv (CIMA Labs) technology is similar to OraSolv technology but uses increased compression forces during tableting such that the product is sufficiently robust to be packaged into traditional push-through blister packs or bottles. Durasolv technology incorporates the taste-masked active drug ingredients but may or may not contain the low-effervesence system. A consequence of increasing compression to improve robustness is a compromise in drug loading, which limits the product to fairly small doses. Both OraSolv and DuraSolv products are sensitive to moisture due to the presence of the effervescent system and must be packaged appropriately.

- FlashTab and Pharmaburst

FlashTab (Ethypharm, Saint Cloud, France) and Pharmaburst (SPI Pharma, Wilmington, DE) technologies rely on the use of super disintegrants. FlashTab is a combination of wet and dry granulation before compression. Microparticles of taste-masked API are blended with conventional tableting aids and disintegrants such as polyvinyl polypyrrolidone or crospovidone (cross-linked PVP), cross-linked sodium carboxymethyl cellulose (cross-linked CMC) and swelling agents such as starches or microcrystalline cellulose. Disintegration times are typically less than 1 min. The Pharmaburst ODT uses a proprietary disintegrant (Pharmaburst) that is based on mannitol blended with conventional tableting aids. The excipient system is claimed to be of good flow characteristics and highly compressible such that robust tablets can be produced while maintaining disintegration times of 30 s or less depending on the drug loading.
- **AdvaTab**

The AdvaTab (Eurand Pharmaceuticals, Dayton, OH) system incorporates the microencapsulated API (Microcaps, Eurand Pharmaceuticals) for taste-masking purposes. This ODT platform relies on the fact that AdvaTab tablets are compressed using a patented external lubrication system in which the lubricant is only applied to the tablet surface. AdvaTab tablets can be manufactured using low-compression forces and permit ingress of moisture on contact with saliva. AdvaTab tablets are claimed to be robust and to disintegrate rapidly in the oral cavity. The tablet-compression step does not lead to breakage of the drug particles. The advantage of the compressed tablet ODT platforms is that they are able to accommodate taste-masked APIs, either by microencapsulation or within a taste-mask matrix, with relative ease. However, the compression forces used need to be carefully balanced to avoid compromising the taste-masking coat or rapid disintegration time while still achieving sufficient cohesion within the tablets for adequate handling robustness.

- **Sugar-floss systems**

Biovail’s (Mississauga, Canada) Flashdose system is an example of a sugar-floss system. This system involves producing fibers from molten sacharrides (sucrose, dextrose, or lactose) or polysacharrides. The floss fibers are blended with API and other excipients and compressed into tablets. There is usually a conditioning step at elevated temperature and humidity to ensure complete conversion of amorphous sugar fibers to crystalline material. This system relies on the highly soluble nature of the sugar components as well as the formulation porosity to achieve rapid disintegration.

- **Molded tablets**

Molded tablets are based on a technology platform that uses water-soluble ingredients such as sacharrides (lactose, mannitol, or maltose) that cause the tablets to disintegrate and dissolve rapidly. Typically, the powder blend is moistened with a hydroalcoholic solvent and molded into a tablet using low-compression pressure. The
wet-compressed mass is air dried. The manufacturing process for the WOWTAB (Astellas Pharma, Yamanouchi, Japan) product involves granulating highly soluble low-moldable sugars (e.g. mannitol, lactose, glucose, sucrose) with high moldable sugars (e.g. maltose, maltitol and sorbitol). Following compression, there is a humidity conditioning step to increase product robustness.

**Jagdale SC et al.** studied the optimum concentration of superdisintegrants and effect of hardness on disintegration time (DT). 2, 4 and 6 % w/w concentration of superdisintegrants (sodium starch glycollate, crospovidone, croscarmellose sodium and Methacrylic copolymer with divinyl benzene) were used for this purpose. Famotidine which belongs to a class of medications called *H2-antagonists* was selected as a suitable candidate. 4 % Crospovidone was most effective as a superdisintegrant for Famotidine. It was seen that as hardness increased, the DT increased with all concentration of superdisintegrant. Superdisintegrants when used in combination did not show that much remarkable decrease in disintegration time as compared to the individual. Stability studies of the formulation suggest that there was no degradation with respect to time. IR data indicated no interaction of drug with the excipients.

**Patel HA et al.** developed and characterized fast dissolving tablets of domperidone using direct compression and wet granulation technique. The formulations containing croscarmellose sodium, crospovidone, and sodium starch glycolate as superdisintegrants, disintegrated faster compared to the formulation containing microcrystalline Cellulose. Pre compression and post compression parameters were evaluated for all ten formulations (D1 - D10). *In vitro* drug release showed that almost drug was release in the range of 94 – 97 % range in 10 min. Depending upon cumulative drug release, *in vitro* disintegration time, wetting time, there was found that direct compression method is better than wet granulation method. Depending upon cumulative drug release, *in vitro* disintegration time, wetting time results, one formulation D1 was selected for stability studies and subjected to stability studies at 250 ºC, 300 ºC and 400 ºC for 2 month. Overall, formulation D1 was found to be the best formulation in direct compression method.
Jeong SH et al. \textsuperscript{70} prepared fast dissolving tablets (FDTs) by several different methods including crystalline transition, phase transition, sublimation, spray drying, and direct compression. Of these approaches, a conventional tablet compression method is used most widely because of its low cost and ease of manufacturing. Research on FDTs prepared by the compression method has focused on decreasing the dissolution (or disintegration) time of the tablets in the mouth, while maintaining sufficiently high mechanical strength to withstand handling during manufacturing, packaging, and transportation. The key to developing a successful FDT formulation by the compression method is to select the right excipients and the right processing techniques. In general, FDTs are made of highly hydrophilic materials and possess highly porous structures for fast water absorption into the tablet matrix. The excipients that are currently used as well as those that are expected to be used for the future development of improved FDTs are described.

Fu Y et al. \textsuperscript{56} reviewed on fast disintegrating tablets (FDTs) which have received ever-increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical industry. Upon introduction into the mouth, these tablets dissolve or disintegrate in the mouth in the absence of additional water for easy administration of active pharmaceutical ingredients. The popularity and usefulness of the formulation resulted in development of several FDT technologies. This review describes various formulations and technologies developed to achieve fast dissolution/dispersion of tablets in the oral cavity. In particular, this review describes in detail FDT technologies based on lyophilization, molding, sublimation, and compaction, as well as approaches to enhancing the FDT properties, such as spraydrying, moisture treatment, sintering, and use of sugar-based disintegrants. In addition, taste-masking technologies, experimental measurements of disintegration times and clinical studies are also discussed.

Setty M C et al. \textsuperscript{72} formulated an aceclofenac fast dispersible tablets prepared by direct compression method. Effect of superdisintegrants (croscarmellose sodium, sodium starch glycolate and crospovidone) on wetting time, disintegrating time, drug content, \textit{in vitro}
release and stability parameters were studied. Disintegrating time and dissolution parameters decreased with increase in the level of croscarmellose sodium. Disintegrating time and dissolution parameters increased with increase in the level of croscarmellose sodium in tablets. However the disintegration time values did not reflect in the dissolution parameter values of crospovidone tablets and release was dependent on the aggregate size in the dissolution medium. Stability studies indicated that tablets containing superdisintegrants were sensitive to high humidity conditions. Stability studies indicated that tablets containing superdisintegrants were sensitive to high humidity conditions. It was concluded that fast dispersible aceclofenac tablets could be prepared by direct compression using superdisintegrants.
EATABLE GELS

Gels

Advantages

Disadvantages

Ideal properties

Classification

Formulation considerations

Gels

Gels can also be defined as semisolid systems in which a liquid phase is constrained within a 3-D polymeric matrix (consisting of natural or synthetic gum) having a high degree of physical (or sometimes chemical) cross-linking. Some are as transparent as water itself, an aesthetically pleasing state, other are turbid, as the polymer is present in colloidal aggregates that disperse light. Gels are generally classified as a two phase system, if the particle size of the dispersed phase is large; or as single phase gels, when the organic macromolecules are uniformly distributed throughout a liquid such that no apparent boundaries exist between the dispersed macromolecules and the liquid. Single-phase gels can be described as three dimensional networks formed by adding macromolecules such as proteins, polysaccharides and synthetic macromolecules to appropriate liquids. The three dimensional networks formed in two phase gels are formed by several inorganic colloidal clays. Formation of these inorganic gels is reversible. Gels are generally considered to be more rigid. Gels contain more covalent crosslink’s, a higher density of physical bonds, or simply less liquid.
Gels are also defined as semi-rigid systems in which the movement of the dispersion medium is restricted by an interlacing three dimensional network of particles or solvated macromolecules in the dispersed phase. Physical and/or chemical crosslinking may be involved. The interlacing and consequential internal friction is responsible for increased viscosity and the semi-solid state. Gels are made using substances (called gelling agent) that undergo a high degree of cross-linking or association when hydrated and dispersed in the dispersion medium, or when dissolved in the dispersion medium.

The United States of Pharmacopoeia (USP) defines gels (sometimes called jellies) as semisolids systems consisting of either suspensions made up of small inorganic particles or large organic molecules interpenetrated with liquid.

**Advantages of gels**

- Gels can be administered to dysphagia patients, stroke victims, bedridden patients, pediatrics, geriatric and psychiatric patients who cannot intake tablets, capsules, solutions, syrups and suspensions.
- It provides convenience and patient compliance especially for travelling and busy people who do not have ready access to water.
- Allow high drug loading.
- No risks of choking or suffocation, as the gels are soft and smooth; hence physical obstruction is avoided, thus providing improved safety.
- Improved taste masking and good mouth feel property which helps to change the perception of medication.
- Ability to provide advantages of liquid medication in the form of semi-solid preparation.
- Cost-effective dosage form.
- It stimulates salivation through positive enhancement of taste, smell and/or texture, which further facilitates swallowing.

- No chewing, non-invasive hence better patient compliance.

- Can be used for both immediate and sustained release of drugs.

**Disadvantages of gels**

- Stability of the dosage form is the main drawback, since it contains mainly water, there may be chance of microbial contamination. Hence addition of preservatives and other excipients is necessary.

- Dose uniformity is a problem.

- Packing of these dosage forms has to be done properly to prevent exposure from light, spillage during travelling.

**Ideal properties required for oral gel dosage form**

- Stability – It should be physically and chemically stable. Should prevent the formulation form microbial contamination, hence a suitable preservative has to be added to prevent from contamination.

- Viscosity – Sufficient viscosity has to be adjusted so that it can easily pass from mouth without any problem of difficulty in swallowing, choking *etc*\(^76\).

- Taste – It is a vital factor for this type of dosage form which masks the taste of bitter drugs and also thereby increases patient compliance. Inclusion of proper sweeteners and flavors overcome the problem of decreased compliance.
• pH – pH has to be adjusted such that it is not irritant to oral cavity and also to keep the formulation stable.

• Texture – Texture should be such that it should be smooth, free from stickiness and grittiness.

• Polymer concentration – If the polymer concentration is not adjusted properly it causes syneresis (separation of water from gels upon storage). Hence proper optimization of the formulation has to be done to prevent from syneresis. Syneresis occurs when the interaction between particles of the dispersed phase becomes so great that on standing the dispersing medium is squeezed out in droplets and the gel shrinks. Syneresis is a form of instability in aqueous and non-aqueous gels. Separation of a solvent phase is thought to occur because of the elastic contraction of the polymeric molecules; In the swelling processes during the gel formation the macromolecules becomes stretched, and the elastic forces increase as the swelling proceeds. At equilibrium the restoring force of macromolecules is balanced by the swelling forces, determined by the osmotic pressure. If the osmotic pressure decreases, as on cooling, water may be squeezed out of the gel. pH as a marked effect on suppression of water. At low pH marked syneresis occurs, possibly as a result of suppression of ionization of carboxylic acid groups, loss of hydrating water, and the formation of intramolecular hydrogen bonds. This would reduce the attraction of the solvent for the macromolecule.

Classification

Gels are divided into organic and inorganic gels on the basis of the nature of the colloidal phase. The nature of the solvent is also useful in classifying gels. Aqueous gels are, of course water based. The term hydrogel has evolved to refer specifically to aqueous gels containing an insoluble polymer. Organogels contain a nonaqueous solvent as the continuous phase. Solid gels with low solvent concentration are known as xerogels.
Substances that form aqueous gels are usually hydrophilic polymers capable of extensive solvation. At certain temperatures and polymer concentration and in some cases with the addition of ions, a three dimensional network is formed. Although polymer gels vary considerably in chemical structure, they all behave as elastic solids at low applied stress, even though they primarily consist of liquid.

**Formulation considerations**

Formulation of gels involves intricate application of aesthetic and performance characteristics such as taste masking, pH, viscosity, mouth feel, physical appearance, stability etc. From the regulatory perspectives, all the excipients used in the formulation should be generally considered as safe (*i.e.* GRAS-listed) and should be approved for use in oral pharmaceutical dosage form. Preparation of gels include drugs, viscosity imparting agents, solvent, preservatives, emulsifiers, pH modulating agents, antioxidants, sweeteners, flavors and coloring agents ¹.

**Gohel M C et al.** ⁷⁶ developed soft paracetamol gel using gellan gum as a gelling agent and sodium citrate as a source of cation. Different batches were prepared using three different concentrations of gellan gum (0.1, 0.3 and 0.5 %), each with two different sodium citrate concentrations (0.3 and 0.5 %). The consistency of the paracetamol gel was dependent on the concentration of gellan gum, sodium citrate and co-solute. The results of dissolution study of soft gel containing 0.3 % gellan gum and 0.3 % sodium citrate revealed that paracetamol was completely released in 30 min. Polyethylene glycol 400 worked as a solubilizer for paracetamol. All the gels possessed acceptable sensory characteristics when evaluated by human volunteers. Short term stability study carried out for four weeks at different temperatures revealed no considerable changes in performance characteristics of developed optimized formulation.

**Dabhi et al.** ⁷⁸ developed ambroxol hydrochloride soft gel formulation with the application of statistical experimental design and response surface methodology (RSM).
The prepared formulations were evaluated for pH, viscosity, rheological properties, gelation time, drug content, \textit{in vitro} drug release, appearance, and taste. All the formulations showed a gelation time in the range of 6 to 48 min. The drug content in all the formulations was within limit (99.6 ± 1.56 %). The viscosity of all the formulations was found in the range of 1872 – 12,182 cps. Dissolution studies of the formulations showed drug release in the range of 40.56 – 72.46 % within 10 min and 80.2 – 100.5 % within 30 min. Human evaluation tests revealed that all the gels possessed acceptable characteristics. This study showed that the soft gel formulation GA5, containing 0.3 % of gellan gum and 0.4 % of sodium citrate, has potential use as an immediate release soft gel for oral drug delivery.

\textbf{Mohapatra A et al.} \textsuperscript{79} formulated oral soft gel batches of metformin using hydrophilic polymer gellan gum at concentrations ranging from 0.2 - 0.4 % w/v and sodium citrate at two different concentrations (0.3 % and 0.5 %). The prepared batches were evaluated for appearance, viscosity, pH, drug content, syneresis, \textit{in vitro} drug release, and taste masking. The batch with 0.4 % w/v gellan gum and 0.5 % sodium citrate not only showed 85 % drug release at 15 min, but all the desired organoleptic properties. The taste masking was carried out using nonnutritive sugar and flavors. The optimized batch showed substantial stability when subjected to short term stability study (0 – 8 °C and Room temperature). The problem of dose measurement by patients was outweighed as oral medicated gels are to be packed in unit dose container.

\textbf{Miyazaki S et al.} \textsuperscript{80} Designed gel formulations for the oral administration of paracetamol with suitable rheological characteristics for ease of administration to patients with swallowing difficulties and sufficient integrity in the acidic environment of the stomach to achieve a sustained release of this drug. Gels formed by gelatin, agar, gellan, pectin, and xyloglucan were assessed for suitable gel strength and \textit{in vitro} and \textit{in vivo} release characteristics. Gellan (1.5 % w/v) and xyloglucan gels (1.5 % w/w) had acceptable gel strengths for ease of swallowing and retained their integrity in the rat stomach sufficiently well to sustain the release of paracetamol over a period of 6 h. Comparison of
1.5 % xyloglucan gels with a commercially available preparation with identical paracetamol concentrations demonstrated improved sustained release properties of the xyloglucan gels. Gels formed by gellan and xyloglucan have suitable rheological and sustained release characteristics for potential use as vehicles for oral delivery of drugs to dysphagic patients.

Hanawa et al. 81 prepared a new dosage form for elderly patients containing benfotiamine (BTMP) in silk fibroin gel (SFG) to ease handling and swallowing. The release behavior of BTMP from SFG was studied as a function of silk fibroin content and glycerol content and the influence of the existence of β-cyclodextrin on the physiochemical properties of SFG were investigated. It was found that the release profile of BTMP from SFG was inversely proportional to the SFG firmness.
DRUG USED IN THE STUDY

METHOTREXATE

Chemical structure of Methotrexate

Molecular formula: $\text{C}_{20}\text{H}_{22}\text{N}_8\text{O}_5$

Molecular weight: 454.45 g/ml.

Description: Orange-brown, odorless, crystalline powder.

Solubility: Practically insoluble in water, alcohol, chloroform and diethyl ether; slightly soluble in dilute hydrochloric acid; soluble in dilute solutions of alkali hydroxides and carbonates.

Oral dose range: 25 - 50 mg/m$^2$ (for head and neck cancer).

Bioavailability: Mean bioavailability is 60 %.

Absorption, distribution, metabolism and excretion: In adults, oral absorption of methotrexate appears to be dose dependent. Peak serum levels are reached within one to five hours. At doses of 30 mg/m$^2$ or less, methotrexate is generally well absorbed with a mean bioavailability of about 60 %. The absorption of doses greater than 80 mg/m$^2$ is significantly less, possibly due to a saturation effect. Methotrexate is metabolized by intestinal bacteria to the inactive metabolite 4-amino-4-deoxy-N-methylpteroid acid (DAMPA), which accounts for less than 5 % loss of the oral dose. Methotrexate is actively transported across cell membranes. The drug is widely distributed into body
tissues with highest concentrations in the kidneys, gallbladder, spleen, liver, and skin. Renal excretion is the primary route of elimination, and is dependent upon dosage and route of administration. The majority of a dose is excreted unchanged in the urine within 24 h and up to 10 % may appear in the bile although because of reabsorption less may be excreted in the faeces.

**Half life:** Terminal: Low doses: 3 to 10 h. High doses: 8 to 15 h.

**Therapeutic uses:** Used to treat various types of cancer such as breast, head and neck, lung, blood, bone, lymph, uterus, bladder, brain(lymphoma), cervix, colon and rectum, esophagus, ovaries, pancreas, penis, stomach, acute non lymphocytic leukemia(a type of cancer of the blood and lymph system), Cancer in the membranes that cover and protect the brain and spinal cord (the meninges), Cancers of the soft tissues of the body, including the muscles, connective tissues (tendons), Hodgkin's lymphoma (a cancer of the lymph system, a part of the body's immune system), gestational choriocarcinoma, chorioadenoma destruens and hydatidiform mole.

**Preparations:** Methotrexate tablets, methotrexate sodium injection, methotrexate syrup, methotrexate injection.

**Storage:** Store in an air tight container protected from light.

**Chandak AR and Verma PR**[^83] evaluated the possibility of using different concentrations and polymeric grades of hydroxypropyl methylcellulose (K4M, K15M and K100M) for transdermal delivery of methotrexate for rheumatoid arthritis. The matrix films were evaluated for their physicochemical characterization followed by *in vitro* and *in vivo* evaluation. Selected formulations were subjected for their *in vivo* studies on healthy rabbits. The relevance of difference in the *in vitro* dissolution rate profile and pharmacokinetic parameters (Cmax, tmax, AUC, t1/2, Kcl, and MRT) were evaluated statistically. The thickness and weight of the patch increased with the increase in polymeric grade and content. FT-IR spectroscopy and DSC results confirm that there is no interaction between drug and polymer used. X-ray diffraction study reveals an

[^83]: Chandak AR and Verma PR, 1983
amorphous state of drug in the matrix films. The in vitro drug release followed Higuchi kinetics ($r = 0.972 - 997; p < 0.001$) as its coefficient of correlation values predominates over zero order and first order release kinetics. In vitro dissolution profiles and pharmacokinetic parameters showed a significant difference between test products ($p < 0.01$), but not within test products. A quantitatively good correlation was found between per cent of drug absorbed from the transdermal patches and AUC. A significant in vitro/in vivo correlation was observed when per cent drug released was correlated with serum drug concentration. Out of the various formulations made, the selected formulations are better in their in vitro dissolution and pharmacokinetic characteristics and thus hold potential for transdermal delivery.

**Wang X M et al.** 84 prepared the methotrexate gel. The content of methotrexate was determined by UV spectrophotometer. Its quality standard was established. The linear range of methotrexate was 2 to 20 mcg/ml, $r^2 = 0.9999$. The quality of the preparation was stable and the determination method had a recovery rate of 100.65 %. It was concluded that preparation of methotrexate gel is simple and its quality can be controlled.

**CYCLOPHOSPHAMIDE** 82

![Chemical structure of cyclophosphamide](image)

**Molecular Formula:** C$_7$H$_{15}$Cl$_2$N$_2$O$_2$P

**Molecular Weight:** 261.10
Color/Form: Fine, white, crystalline powder; odorless or almost odorless

Taste: Slightly bitter

Melting Point: 49.5 - 53 °C

Octanol/Water Partition Coefficient: \( \log K_{o/w} = 0.63 \)

Solubility: 1 in 25 parts water, 1 in 1 parts alcohol, Slightly soluble in benzene, carbon tetrachloride; very slightly soluble in ether and acetone, Soluble in chloroform, dioxane and glycols and insoluble in carbon tetrachloride and carbon disulfide.

Bioavailability: ~ 100 %

Absorption, metabolism, Distribution and Elimination: Cyclophosphamide is well absorbed orally; absorption must be activated in liver by microsomal enzymes to active compounds & toxic metabolites. Cyclophosphamide is converted by mixed-function oxidase enzymes in the liver to active metabolites. The main active metabolite is 4-hydroxycyclophosphamide. Cyclophosphamide is distributed with a volume of distribution of 30 - 50 l, which approximates to the total body water. It is eliminated primarily in the form of metabolites, but from 5 to 25 % of the dose is excreted in urine as unchanged drug. Several cytotoxic and noncytotoxic metabolites have been identified in urine and in plasma. It has not been demonstrated that any single metabolite is responsible for either the therapeutic or toxic effects of cyclophosphamide.

Biological Half-Life: Maximal concentration in plasma is achieved 1 h after oral admin, & the half-life in plasma is about 3 - 10 h (parent).

Oral dose range: The usual oral dose is 1 - 5 mg/kg daily. Subsequent maintenance doses are adjusted based on the response of the tumor to treatment and the side effects.

Uses: It is used to treat cancer of the ovaries, breast, blood and lymph system, nerves (found primarily in children), retinoblastoma (a cancer of the eye found primarily in children), multiple myeloma (cancer in the bone marrow), and mycosis fungoides (tumors on the skin). Cancer of the bladder, bones, cervix, endometrium , lungs, prostate,
Cancer of the testicles, adrenal cortex (the outside layer of the adrenal gland), Ewing's sarcoma (a certain type of bone cancer), Germ cell tumors in the ovaries (a cancer in the egg-making cells in the ovary), Gestational trophoblastic tumors (a certain type of tumor in the uterus/womb), Soft tissue sarcomas (a cancer of the muscles, tendons, vessels that carry blood or lymph, joints, and fat), Thymoma (a cancer in the thymus, a small organ beneath the breastbone), Tumors in the brain, Waldenström's macroglobulinemia (a certain type of cancer of the blood), Wilms' tumor (a cancer of the kidney found primarily in children).

**Preparations:** Cyclophosphamide is supplied as 25 & 50 mg tablets and as a powder in sterile vials for parenteral administration.

**Storage:** Cyclophosphamide reacts with strong oxidizing agents, is sensitive to moisture and light, and is hydrolyzed in aqueous solutions above 30 °C.

**Wagner T and Fenneberg K**[^1] determined the bioavailability of cyclophosphamide from oral formulations. Cyclophosphamide (CYP) is an alkylating cytostatic compound, which is activated to its cytotoxic form in the liver. Since the therapeutic range of CYP in the treatment of human tumours, is small like other cytostatics, a constant high bioavailability is essential for its oral administration. Although CYP has become one of the most widely used cytostatics, there do not appear to have been any bioavailability investigations providing the necessary information. The development of a very sensitive gas chromatographic analytical method has now permitted investigation of the pharmacokinetics of oral CYP in conventional clinical doses.

[^1]: Wagner T and Fenneberg K
ANASTROZOLE

Chemical structure of anastrozole

Molecular Formula: C_{17}H_{19}N_{5}

Molecular Weight: 293.37

Color/Form: Crystals from ethyl acetate/cyclohexane; Off-white powder

Melting Point: 81 - 82 °C

Dissociation Constants: pKa = 2.01 (est)

Octanol/Water Partition Coefficient: log Kow = 2.37 (est)

Solubility: Freely soluble in methanol, acetone, ethanol, tetrahydrofuran; very soluble in acetonitrile. In water, 0.5 mg/ml at 25 °C.

Absorption, Distribution, Metabolism and Elimination: Anastrozole is well absorbed into systemic circulation following oral administration. Plasma concentrations approach steady-state at about 7 days of once-daily dosing, and steady-state concentrations are approximately 3 - 4 times higher than concentrations achieved after a single dose of the drug. Food does not affect the extent of oral absorption of anastrozole. Metabolism of Anastrozole occurs by N-dealkylation, hydroxylation and glucuronidation. Three metabolites of Anastrozole (triazole, a glucuronide conjugate of hydroxy-Anastrozole, and a glucuronide conjugate of Anastrozole itself) have been identified in human plasma and urine. Anastrozole has been shown to cross the placenta in rats and rabbits receiving oral doses of 0.1 mg/kg. It is not known whether anastrozole is distributed into milk in
humans. Hepatic metabolism accounts for about 85% of the elimination of anastrozole, with renal excretion accounting for only about 11%. Studies with radiolabeled drug have shown that 83 – 85% of an orally administered dose is recovered in urine and feces. Studies in postmenopausal women indicate that about 10% of an oral dose is excreted in urine as unchanged drug within 72 h of dosing, and about 60% of the dose is excreted in urine as metabolites.

**Biological Half-Life:** Following oral administration of anastrozole in postmenopausal women, a mean terminal elimination half-life of approximately 50 h has been reported.

**Uses:** It is indicated for the first-line treatment of postmenopausal woman with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer. It is also indicated for treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy.

**Formulations/Preparations:** Available as 1 mg Tablets

**Storage:** Commercially available anastrozole tablets should be stored at a controlled room temperature of 20 - 25 °C.

Shavi GV et al. 86 developed sustained release formulation of anastrozole-loaded chitosan microspheres for treatment of breast cancer. Chitosan microspheres cross-linked with two different cross-linking agents viz, tripolyphosphate (TPP) and glutaraldehyde (GA) were prepared using single emulsion (w/o) method. Formulations were characterized for various parameters. Encapsulation efficiency varied from 30.4 ± 1.2 to 69.2 ± 3.2% and mean particle size distribution ranged from 72.5 ± 0.5 to 157.9 ± 1.5 μm. SEM analysis revealed smooth and spherical nature of microspheres. TPP microspheres exhibited higher swelling capacity, percentage erosion and drug release compared to GA microspheres. Release of anastrozole (ANS) was rapid up to 4 h followed by slow release status. FTIR analysis revealed no chemical interaction between drug and polymer. DSC analysis indicated ANS trapped in the microspheres existed in amorphous form in polymer matrix. The highest correlation coefficients (R) were obtained for Higuchi model, suggesting a diffusion controlled mechanism. There was significant difference in the pharmacokinetic parameters when ANS was formulated in
the form of microspheres compared to pure drug. This may be attributed to slow release rate of ANS from chitosan microspheres and was detectable in rat plasma up to 48 h which correlates well with the in vitro release data.

CAPECITABINE

Chemical structure of capecitabine

**Molecular Formula:** C₁₅-H₂₂-F-N₃-O₆

**Molecular Weight:** 359.35

**Color/Form:** White to off-white crystalline powder

**Melting Point:** 110 - 121 °C

**Octanol/Water Partition Coefficient:** log Ko/w = 0.56 (est)

**Solubility:** In water, 26 mg/ml at 20 °C

**Absorption, metabolism and excretion:** Capecitabine is designed as a 'pro-drug' to the cytotoxic agent 5-fluorouracil (5-FU) and to be administered orally. The gastrointestinal absorption of capecitabine is nearly complete. Capecitabine is absorbed as unchanged parent substance but is subsequently substrate of enzymes and thus is nearly completely metabolized (5'-DFCR and 5'-DFUR). Following oral administration of capecitabine the time to peak plasma concentrations will be obtained within 2 h. Capecitabine and its
metabolites are predominantly excreted in urine; 95.5 % of administered capecitabine dose is recovered in urine and 2.6 % in feces.

**Biological Half-Life:** The plasma elimination half-life of capecitabine and its metabolites, including the active drug, fluorouracil, is about 38 - 45 min.

**Uses:** It is widely used in the treatment of metastatic colorectal cancer and breast cancer, since it is readily absorbed from the gastrointestinal tract.

**Dose:** The recommended oral daily dose is large, *i.e.* 1250 mg/m$^2$ administered twice daily for 14 days followed by a 7-day rest period given as 3-week cycles, for as long as needed.

**Formulations/Preparations:** Tablets (150 and 500 mg)

**Storage:** Capecitabine tablets should be stored in tightly closed containers at 25 °C but may be exposed to temperatures of 15 - 30 °C.

Agnihotri SA *et al.* Synthesized capecitabine-loaded semi-interpenetrating network hydrogel microspheres of chitosan-poly(ethylene oxide-g-acrylamide) by emulsion crosslinking using glutaraldehyde. Capecitabine, an anticancer drug, was successfully loaded into microspheres by changing experimental variables such as grafting ratio of the graft copolymer, ratio of the graft copolymer to chitosan, amount of crosslinking agent and percentage of drug loading in order to optimize process variables on drug encapsulation efficiency, release rates, size and morphology of the microspheres. Grafting, interpenetrating network formation and chemical stability of the capecitabine after encapsulation into microspheres was confirmed by Fourier infrared spectra. Differential scanning calorimetry and X-ray diffractometry studies were made on drug-loaded microspheres to investigate the crystalline nature of drug after encapsulation. Results indicated amorphous dispersion of capecitabine in the polymer matrix. Scanning electron microscope confirmed spherical shapes and smooth surface morphology of the microspheres. Mean particle size of the microspheres as measured by the laser light scattering technique ranged between 82 and 168 µm. Capecitabine was successfully encapsulated into semi-IPN microspheres and percentage of encapsulation efficiency
varied from 79 to 87. In vitro release studies were performed in simulated gastric fluid (pH 1.2) for the initial 2 h, followed by simulated intestinal fluid (pH 7.4) until complete dissolution. The release of capecitabine was continued up to 10 h. In conclusion, this work demonstrates the feasibility of preparing semi-IPN hydrogel matrices by physical blending of the biocompatible polymers such as chitosan and poly(ethylene oxide)-grafted polyacrylamide that are crosslinked with GA.

Srinivas P et al., 88 prepared and evaluated capecitabine matrix tablets for colon-specific drug delivery using a novel polymer, Polymethylacrylate-co-methylmethacrylate-co-methacrylic acid (Eudragit® FS 30D). The tablets were prepared by wet granulation technique and evaluated for colon-specificity by in vitro and in vivo studies. The polymer used here has threshold dissolution at about pH 7.2 and exhibits control release properties. Various concentrations of the polymer were used to optimize the formulation. The in vitro drug release study revealed that the polymer at a concentration of 25 % was able to control the drug release up to 9 h. Drug-excipient interaction studies were also carried out using FT-IR Spectroscopy and no interaction was found between the drug and the polymer. In vivo X-ray studies in rabbit indicated that the optimized polymer concentration was effective in delivering the required concentration of capecitabine to the proximal colon. In conclusion, orally administered colon-specific of capecitabine is a promising candidate for use in colorectal cancer. This could be beneficial in reducing the dose dependent side-effects thus improving the patient compliance.
IMATINIB MESYLATE

Molecular Formula: C_{29}\text{-H}_{31}\text{-N}_{7}\text{-O}\text{-C}\text{-H}_{4}\text{-O}_{3}\text{-S}

Molecular Weight: 589.72

Color/Form: White to off white to brownish or yellowish tinged crystalline powder

Solubility: Freely soluble in water

Melting point: 227 °C

Bioavailability: Mean absolute bioavailability is 98 %.

Absorption, Distribution, metabolism & Excretion: Imatinib is rapidly absorbed when given by mouth, and is highly bioavailable: 98 % of an oral dose reaches the bloodstream achieved within 2 - 4 h post-dose. Metabolism of imatinib occurs in the liver and is mediated by several isozymes of the cytochrome P450 system, including CYP3A4 and, to a lesser extent, CYP1A2, CYP2D6, CYP2C9, and CYP2C19. The main metabolite, N-demethylated piperazine derivative, is also active. The major route of elimination is in the bile and feces; only a small portion of the drug is excreted in the urine. Most of imatinib is eliminated as metabolites, only 25 % is eliminated unchanged.

Biological Half-Life: Following oral administration in healthy volunteers, the elimination half-lives of imatinib and its major active metabolite, the N-desmethyl derivative, were approximately 18 and 40 h, respectively.

Uses: (a) Newly diagnosed adult and pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase; (b) Ph+ CML in blast
cancer, accelerated phase, or chronic phase after failure of interferon-alpha therapy; (c) Adult patients with relapsed or refractory Philadelphia chromosome + Acute Lymphoblastic Leukemia (Ph+ ALL); (d) Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with PDGFR gene rearrangements; Gastrointestinal stromal tumors that are C-kit positive.

**Dose:**

**Adult Patients with Ph+ CML in chronic phase, acute phase and blast phase.**

The recommended dose of imatinib is 400 mg/day for adult patients in chronic phase CML and 600 mg/day for adult patients in accelerated phase or blast crisis.

**Pediatric Patients with Ph+ CML**

- 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).

**Ph+ ALL**

The recommended dose of imatinib is 600 mg/day for adult patients with relapsed/refractory Ph+ ALL.

**MDS/MPD**

The recommended dose of imatinib is 400 mg/day for adult patients with MDS/MPD.

**GIST**

The recommended dose of imatinib is 400 mg/day for adult patients with unresectable and/or metastatic, malignant GIST. 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.
Formulations/Preparations: Tablets (100 and 400 mg), capsules (50 and 100 mg).

Storage: Store at room temperature at 77 °F (25 °C) away from light and moisture. Brief storage between 59 - 86 °F (15 - 30 °C) is permitted.

Leveque D and Maloisel F et al. 89 reviewed on clinical pharmacokinetics of imatinib. Imatinib (formerly known as STI 571 or CGP 57148B) is a recent oral anticancer agent currently approved in the treatment of Philadelphia chromosome- positive chronic myelogenous leukemia (CML) and metastatic gastrointestinal stromal tumors (GIST). The rational and quite rapid development of imatinib (3 years between the first clinical trial in patients with CML and the approval in 2001 in the United States), combined with the promising clinical results observed in the treatments of these two rare cancers, has led to extensive literature including several comprehensive reviews.
POLYMERS AND EXCIPIENTS PROFILE

XANTHAN GUM

Nonproprietary Names: BP: Xanthan Gum, PhEur: Xanthan Gum, USP-NF: Xanthan Gum

Synonyms: Corn sugar gum; E415; Grindsted; Keldent; Keltrol; polysaccharide B-1459; Rhodicare S; Rhodigel; Vanzan NF; xanthani gummi; Xantural.

Chemical Name: Xanthan gum

Functional Category: Gelling agent; stabilizing agent; suspending agent; sustained-release agent; viscosity-increasing agent.

Description: Xanthan gum occurs as a cream or white-colored, odorless, free flowing, fine powder.

Solubility: Practically insoluble in ethanol and ether; soluble in cold or warm water.

Viscosity: 1 % solution - 1340 cps.

Applications in Pharmaceutical Formulation or Technology: Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and foods as a suspending and stabilizing agent. It is also used as a thickening and emulsifying agent. It is nontoxic, compatible with most other pharmaceutical ingredients, and has good stability and viscosity properties over a wide pH and temperature range; Xanthan gum gels show pseudoplastic behavior, the shear thinning being directly proportional to the shear rate. The viscosity returns to normal immediately on release of shear stress.
POLYVINYL ALCOHOL

Nonproprietary Names: PhEur: Poly(Vinyl Alcohol), USP: Polyvinyl Alcohol.

Synonyms: Airvol; Alcotex; Celvol; Elvanol; Gelvatol; Gohsenol; Lemol; Mowiol; poly(alcohol vinylicus); Polyvinol; PVA; vinyl alcohol polymer.

Chemical Name: Ethenol, homopolymer

Functional Category: Coating agent; lubricant; stabilizing agent; viscosity-increasing agent.

Description: Polyvinyl alcohol occurs as an odorless, white to cream-colored granular powder.

Viscosity: 1% solution – 25 to 32 cps

Solubility: Soluble in water; slightly soluble in ethanol (95 %); insoluble in organic solvents. Dissolution requires dispersion (wetting) of the solid in water at room temperature followed by heating the mixture to about 90 °C for approximately 5 min. Mixing should be continued while the heated solution is cooled to room temperature.

Applications in Pharmaceutical Formulation or Technology: Polyvinyl alcohol is used primarily in topical pharmaceutical and ophthalmic formulations; it is used as a stabilizing agent for emulsions (0.25 – 3.0 % w/v). Polyvinyl alcohol is also used as a viscosity-increasing agent for viscous formulations such as ophthalmic products. It is used in artificial tears and contact lens solutions for lubrication purposes, in sustained-release formulations for oral administration, and in transdermal patches. Polyvinyl alcohol may be made into microspheres when mixed with a glutaraldehyde solution.
HYDROXY PROPYL METHYL CELLULOSE (HPMC)

USP: Hypromellose.

Synonyms: Cellulose, hydroxyl propyl methyl ether, HPMC, methocel, metolose.

Description: HPMC is an odorless and tasteless; white or creamy white colored fibrous or granular powder.

Functional Category: Coating agent, film-former, stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent.

Viscosity (2 % w/v solution at 20 °C): Methocel E5 Premium LV: 5 cps, Methocel K4M Premium: 4000 cps.

Solubility: Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol, and ether, but soluble in mixture of ethanol and dichloromethane, and mixture of methanol and dichloromethane.

Application in Pharmaceutical Formulation: HPMC is widely used as suspending agent and thickening agent in topical formulations, particularly ophthalmic preparations. Compared with methylcellulose, hydroxypropylmethyl cellulose produces solution of greater clarity, with fewer undispersed fibres present, and is therefore preferred in formulations for ophthalmic use. Concentration of between 0.45 - 1.0 % w/w may be added as thickening agent to vehicles for eye drops and artificial tear solutions. HPMC is also used as an emulsifier, suspending agent and stabilizing agent in topical gels and ointment.
HYDROXYPROPYL CELLULOSE

**Nonproprietary Names:** BP: Hydroxypropylcellulose, JP: Hydroxypropylcellulose, PhEur: Hydroxypropylcellulose, USP-NF: Hydroxypropyl Cellulose

**Synonyms:** Cellulose, hydroxypropyl ether; E463; hydroxypropylcellulosum; hyprolose; Klucel; Nisso HPC; oxypropylated cellulose.

**Functional Category:** Coating agent; emulsifying agent; stabilizing agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.

**Description:** Hydroxypropyl cellulose is a white to slightly yellow-colored, odorless and tasteless powder.

**Solubility:** Soluble 1 in 10 parts dichloromethane; 1 in 2.5 parts ethanol (95 %); 1 in 2 parts methanol; 1 in 5 parts propan-2-ol; 1 in 5 parts propylene glycol; and 1 in 2 parts water. Practically insoluble in aliphatic hydrocarbons; aromatic hydrocarbons; carbon tetrachloride; petroleum distillates; glycerin; and oils. Hydroxypropyl cellulose is freely soluble in water below 38 °C, forming a smooth, clear, colloidal solution. In hot water, it is insoluble and is precipitated as a highly swollen floc at a temperature between 40 and 45 °C. Hydroxypropyl cellulose is soluble in many cold or hot polar organic solvents such as dimethyl formamide; dimethyl sulfoxide; dioxane; ethanol (95 %); methanol; propan-2-ol (95 %); and propylene glycol.

**Applications in Pharmaceutical Formulation or Technology:** Hydroxypropyl cellulose is widely used in oral and topical pharmaceutical formulations. In topical formulations, hydroxypropyl cellulose is used in transdermal patches and ophthalmic preparations. The release rate of a drug increases with decreasing viscosity of hydroxypropyl cellulose.
SODUM CARBOXY METHYL CELLULOSE (Na CMC)

Nonproprietary Names: BP: Carmellose Sodium, JP: Carmellose Sodium, PhEur: Carmellose Sodium, USP: Carboxymethylcellulose Sodium

Synonyms: Akucell; Blanose; Cekol; Cellulose gum; SCMC; CMC sodium.

Chemical Name: Cellulose, carboxymethyl ether, sodium salt

Functional category: Coating agent; disintegrant; binding agent; stabilizing agent; suspending agent; viscosity increasing agents.

Description: White to almost white colored, odorless, granular powder.

Solubility: Practically insoluble in acetone, ethanol (95 %), ether and toluene. It is easily dispersed in water forming clear colloidal solution

Application in pharmaceutical formulation or technology: Carboxymethylcellulose sodium is widely used in oral and topical pharmaceutical formulations, primarily for its viscosity-increasing properties. Viscous aqueous solutions are used to suspend powders intended for either topical application or oral and parenteral administration.
SODIUM ALGINATE

Nonproprietary Names:  BP: Sodium Alginate, PhEur: Sodium Alginate, USP-NF: Sodium Alginate

Synonyms:  Alginato sodico; algin; alginic acid, sodium salt; E401; Kelcosol; Keltone; natrii alginas; Protanal; sodium polymannuronate.

Chemical Name:  Sodium alginate

Functional Category:  Stabilizing agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity increasing agent.

Description:  Sodium alginate occurs as an odorless and tasteless, white to pale yellowish-brown colored powder.

Solubility:  Practically insoluble in ethanol (95 %), ether, chloroform, and ethanol/water mixtures in which the ethanol content is greater than 30 %. Also, practically insoluble in other organic solvents and aqueous acidic solutions in which the pH is less than 3. Slowly soluble in water, forming a viscous colloidal solution.

Applications in Pharmaceutical Formulation or Technology:  Sodium alginate is used in a variety of oral and topical pharmaceutical formulations. It is used in the preparation of buccal gels, vaginal tablets and oral mucosal adhesive tablets.
SUCRALOSE

Synonyms: Splenda, TGS.

Description: Sucralose is a white to off-white colored, free-flowing, crystalline powder

Solubility: Freely soluble in ethanol (95 %), methanol and water; slightly soluble in ethyl acetate.

Functional Category: Sweetening agent.

Applications: Sucralose is used as a sweetening agent in beverages, foods, and pharmaceutical applications. It has a sweetening power approximately 300 – 1000 times that of sucrose and has no aftertaste. It has no nutritional value, is noncariogenic, does not promote dental caries, and produces no glycemic response.

MANNITOL

Synonyms: Cordycepic acid; E421; Manna sugar; D-mannite; Pearlitol.

Chemical Name: D-Mannitol.

Nonproprietary Name: BP – Mannitol, PhEur – Mannitolum, USP NF – Mannitol.

Description: Mannitol occurs as a white, odorless, crystalline powder, or free-flowing granules. It has sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth.

Solubility: Practically insoluble in ether, in water it has solubility of 1 part in 5.5 parts.

Functional Category: Tablet diluent/sweetener.

Application in Pharmaceutical Formulation: In pharmaceutical preparations it is primarily used as diluents (10 – 90 % w/w) in tablet formulations, where it is of particular value since it not hygroscopic and may thus be used with moisture sensitive active ingredients. Mannitol may be used in direct-compression tablet applications, for which
granular and spray dried forms are available. Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and mouthfeel.

MAGNESIUM STEARATE

**Synonyms:** Magnesium octadecanoate; Octadecanoic acid; Magnesium salt; Stearic acid; Magnesium salt.

**Chemical Name:** Octadecanoic acid magnesium salt.

**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.

**Application in Pharmaceutical Formulation:** Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. In pharmaceutical preparations it is primarily used as a lubricant in tablet and capsule manufacture at concentrations between 0.25 % and 5.0 % w/w. It is also used in barrier creams.
MICROCRYSTALLINE CELLULOSE

**Synonyms:** Avicel PH; Cellets; Celex; cellulose gel; hellulosum microcristallinum; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; MCC Sanaq; Pharmacel; Tabulose; Vivapur.

**Chemical Name:** Cellulose

**Functional Category:** Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

**Description:** Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles.

**Solubility:** Slightly soluble in 5 % w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

**Applications in Pharmaceutical Formulation or Technology:** Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.
CROSPVIDONE

Nonproprietary Names: BP: Crospovidone, PhEur: Crospovidone, USP-NF: Crospovidone.

Synonyms: Crospovidonum; Cospopharm; crosslinked povidone; E1202; Kollidon CL; Kollidon CL-M; Polyplasdone XL; Polyplasdone XL-10; polyvinylpolypyrrolidone; PVPP; 1-vinyl-2-pyrrolidinone homopolymer.

Chemical Name: 1-Ethenyl-2-pyrrolidinone

Functional Category: Tablet disintegrant.

Description: Crospovidone is a white to creamy-white, finely divided, free flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

Typical Properties: Acidity/alkalinity pH = 5.0 – 8.0 (1 % w/v aqueous slurry), Density (bulk) of polyplasdone XL-10 = 0.323 g/cm$^3$, Density (tapped) of polyplasdone XL-10 = 0.461 g/cm$^3$

Solubility: Practically insoluble in water and most common organic solvents.

Applications in Pharmaceutical Formulation or Technology: Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2 – 5 % concentration in tablets prepared by direct compression or wet and dry-granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels.
CROSCARMELLOSE SODIUM


Synonyms: Ac-Di-Sol; carmellosum natricum conexum; crosslinked carboxymethylcellulose sodium; Explocel; modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol.

Chemical Name: Cellulose, carboxymethyl ether, sodium salt, crosslinked.

Functional Category: Tablet and capsule disintegrant.

Description: Croscarmellose sodium occurs as an odorless, white or grayish white powder.

Solubility: Insoluble in water, although croscarmellose sodium rapidly swells to 4 – 8 times its original volume on contact with water. Practically insoluble in acetone, ethanol and toluene.

Applications in Pharmaceutical Formulation or Technology: Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets and granules. In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes. When used in wet granulations, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra- and extragranularly) so that the wicking and swelling ability of the disintegrant is best utilized. Croscarmellose sodium at concentrations 0.5 – 5 % w/w may be used as a tablet disintegrant.
SODIUM STARCH GLYCOLATE

**Nonproprietary Names:** BP: Sodium Starch Glycolate, PhEur: Sodium Starch Glycolate
USP-NF: Sodium Starch Glycolate.

**Synonyms:** Carboxymethyl starch, sodium salt; carboxymethylamylum natricum; Explosol; Explotab; Glycolys; Primojel; starch carboxymethyl ether, sodium salt; Tablo.

**Chemical Name:** Sodium carboxymethyl starch.

**Functional Category:** Tablet and capsule disintegrant.

**Description:** Sodium starch glycolate is a white or almost white free-flowing very hygroscopic powder.

**Solubility:** Practically insoluble in methylene chloride. It gives a translucent suspension in water.

**Applications in Pharmaceutical Formulation or Technology:** Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct-compression or wet-granulation processes. The usual concentration employed in a formulation is between 2 % and 8 %, with the optimum concentration about 4 %, although in many cases 2 % is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling. Although the effectiveness of many disintegrants is affected by the presence of hydrophobic excipients such as lubricants, the disintegrant efficiency of sodium starch glycolate is unimpaired. Increasing the tablet compression pressure also appears to have no effect on disintegration time.
NEUSILIN® US2

Chemical formula: Al₂O₃.MgO.1.7SiO₂. x H₂O

Description and functional category: It is a fine ultra light granule of magnesium aluminometasilicate and is widely accepted as a multifunctional excipient that improves the quality of pharmaceuticals. Due to its large surface area and porous nature, US2 adsorbs high loads of oils or water and can be mechanically compacted into high quality tablets. Furthermore, it is a synthetic, amorphous form with a neutral pH that can be used in both direct compression and wet granulation of solid dosage forms. Neusilin makes hard tablets at low compression forces compared to similar binders. Neusilin is stable against heat and has a long shelf life.

Dosage and Safety: Neusilin® is extremely safe with no reports of adverse reactions and is listed in the US Pharmacopeia/National Formulary and Japanese Pharmaceutical Codex.