1.1 BRONCHIAL ASTHMA

Bronchial Asthma is a chronic inflammatory disorder of the airways characterized by bronchial hyper-responsiveness and reversible airflow obstruction causing cough, wheeze, chest tightness and shortness of breath. The various characteristics of Asthma are:

- Air way Obstruction
- Air way inflammation
- Airway Hyper-responsiveness

1.1.1 Patho physiology of Asthma

\[
\text{Phospholipids} \xrightarrow{\text{Phospholipase A}} \text{Arachidonic acid} \xrightarrow{5\text{-lipoxygenase in conjugation with cofactor 5-lipoxygenase activating protein}} \text{Leukotriene A}_4 \xrightarrow{\text{Leukotriene C}_4 \text{ synthase}} \text{Leukotriene C}_4 \xrightarrow{\text{Removal of glutamate and glycine}} \text{Leukotriene D}_4\text{ and E}_4 \xrightarrow{\text{CysLT}_1 \text{ receptor}} \text{Smooth muscle contraction and hyper secretion of mucus.}
\]
1.1.2 **asthma types**\(^{(3-4)}\): Prominent types of Asthma include:

- Exercise Induced Asthma
- Aspirin Induced Asthma
- Nocturnal Asthma

1.1.3 **Role of leukotrienes in asthma pathophysiology**\(^{(5-14)}\):

Leukotrienes (LT) are important pro inflammatory mediators in Asthma\(^{(7-8)}\). These are derived from the metabolism of membrane phospholipids within alveolar macrophages, eosinophils, mast cells and neutrophils. The cysteinyl leukotrienes (LTC\(_4\), LTD\(_4\) and LTE\(_4\)) are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils. Montelukast acts by binding with affinity and selectivity to the CysLT\(_1\) receptor (when compared to other pharmacologically important airway receptors such as the prostanoid, cholinergic, or adrenergic receptor) and inhibits physiological actions of LTC\(_4\), LTD\(_4\) and LTE\(_4\) at the CysLT\(_1\) receptor without agonist activity.

1.2 **ROLE OF INCLUSION COMPLEXES IN ORALLY DISINTEGRATING TABLETS**\(^{(15-22)}\)

Inclusion complexes technique is a unique approach to reduce the particle size and increase the rate of dissolution and absorption. This technique was first demonstrated by Sekiguchi and Obi in 1961. Chiou and Riegelmen (1971) defied solid dispersion as “a dispersion of one or more active ingredients in an inert carrier or matrix at solid state
prepared by the melting (fusion), solvent evaporation or melting-solvent method”.

Solid dosage form  Granules or Aggregates  Fine particles

↓

Dissolution

↓

Drug in solution

↓

(Dissolved drug)

Absorption (Drug in blood, other fluids and tissues)

↓

Elimination

Drug eliminated

1.2.1 Advantages of Inclusion complexes:

1. Formulation of fast release regimen of soluble or insoluble drugs by using soluble or insoluble carriers.

2. Various fast release Inclusion complexes can be prepared by solid dispersion technique. Masking the bitter taste and odor of a drug.

3. To obtain a homogenous distribution of a small quantity of drug in a solid state.
1.2.2 Mechanisms involved in the increased dissolution rates of Inclusion complexes: The increased dissolution rates from solid dispersions were attributed to the reduction of particle size of the drug within the dispersions and increased wettability.

1.2.3 Carriers for Inclusion complexes: A variety of materials belonging to various chemical categories have been examined as potential carriers for solid dispersions. They vary widely in chemical and physiochemical properties.

1.2.4 Ideal requirements of the carrier

1. It should be physically, chemically and physiologically inert
2. It should be soluble in water with intrinsic rapid dissolution properties.
3. It should have thermal stability upto its melting point in case of fusion method.

1.3 TASTE ABATEMENT BY ION EXCHANGE RESINS:

The bitterness of the formulation leads to lack of patient compliance. Two approaches are commonly utilized to overcome bad taste of the drug. The first includes reduction of drug solubility in saliva, where a balance between reduced solubility and bioavailability must be achieved. Another approach is to alter the ability of the drug to interact with the taste receptor.
1.3.1 Factor affecting Resinate Performance:

1. The pH and temperature of the drug solution
2. The molecular weight and charge intensity of the drug and IER
3. Mixing speed
4. Ionic strength of the drug solution
5. Degree of cross linking and particle size of IER
6. Contact time between the drug species and the IER

1.3.2 Properties of ion exchange resin

1) Particle size and form
2) Porosity and Swelling
3) Cross linkage
4) Available Capacity
5) Acid-Base Strength
6) Selectivity of the Resins for the Counter-Ion
7) Stability

1.3.3 Applications of Ion Exchange Resins:

1. Taste
2. Stability
3. Poor Dissolution
4. Deliquescence
5. Polymorphism
6. Tablet Disintegration

1.4 ORALLY DISINTEGRATING DRUG DELIVERY SYSTEM\textsuperscript{(23-37)}:

Oral administration has been considered as one of the most convenient and widely accepted routes of delivery for most therapeutic agents. Traditionally oral dosage forms refer to tablets, capsules and liquid preparations taken orally, swallowed and transiting the gastrointestinal tract (GIT) for post buccal absorption.
The orally disintegrating tablets are synonymous with mouth fast disintegrating tablets, melt in mouth tablets, rapimelts, porous tablets, orodispersible, quick dissolving or rapidly disintegrating tablets. Their growing importance was underlined recently when European pharmacopoeia adopted the term “orodispersible tablet” as a tablet that can be placed in the mouth where it disperses rapidly, before swallowing.

1.4.1 Advantages of orally disintegrating drug delivery system \(^9,10\):

1. Ease of administration for patients who are mentally ill, disabled and uncooperative.
2. Quick disintegration and dissolution of the dosage form.
3. No need of water to swallow the dosage form which is highly convenient feature for patients who are traveling and do not have immediate access to water.
4. Pre gastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects.

1.4.2 Limitations:

1. Limited amount of drug can only be incorporated (For lyophilized dosage forms, the drug dose must be lower than 400mg for insoluble drugs and less than 60 mg for soluble drugs.
2. These are fragile products requiring special unit-dose packaging.

1.4.3 Unsuitable Drug Characteristics:

1. Short half-life and frequent dosing
2. Very bitter or otherwise unacceptable taste because taste masking cannot be achieved.

1.4.4 Role of superdisintegrants in orally disintegrating tablets

A superdisintegrant is an excipient, which is added in lower concentrations to a tablet or capsule blend to aid in breakup of the compacted mass within seconds.

1.4.5 Direct Compression Technique in orally disintegrating Tablets

Direct compression is defined as the process by which tablets are compressed directly from powder blends of the active ingredients and suitable excipients including fillers disintegrating agents and lubricants, which flow uniformly into a die cavity and form into a firm compact.

The main advantages of the direct compression method is that it is cost-effective when compared to all other methods, uses conventional equipment and commonly available excipients, limited number of processing steps and higher doses can be easily accommodated.

1.4.6 Excipients used in ODT formulations: Important ingredients that are used in the formulation of fast-melting tablets should allow quick release of the drug, resulting in faster dissolution. This includes both the actives and the excipients.

1.4.6.1 Bulking materials: These materials contribute the functions of a diluent, filler and cost reducer. Bulking agents improve the textural
characteristics that in turn enhance the disintegration in the mouth. Directly compressible spray dried Mannitol, Sorbitol, xylitol, calcium carbonate, magnesium carbonate, calcium phosphate, calcium sulfate, pregelatinized starch, magnesium trisilicate, aluminium hydroxide.

1.4.6.2 **Emulsifying Agents:** Emulsifying agents aid in rapid disintegration and drug release without chewing, swallowing or drinking water. In addition, incorporating emulsifying agents are useful in stabilizing the immiscible blends and enhancing bioavailability. Alkyl sulfates, propylene glycol esters, lecithin, sucrose esters.

1.4.6.3 **Super disintegrants:** Disintegrants are the agents added to the tablet formulations to break up the tablet into smaller fragments in an aqueous environment thereby increasing the surface area and promoting a more rapid release of the drug substance. Crosspovidone, Microcrystalline cellulose, sodium starch glycolate, sodium carboxy methyl cellulose, pregelatinized starch, calcium carboxy methyl cellulose, and modified corn starch.

1.4.6.4 **Binders and Adhesives:** Binders keep the composition of the orodispersible tablets together during the compression stage. Modified natural polymers the alginates, cellulose derivatives, cocoa butter and hydrogenated vegetable oils.

1.4.6.5 **Lubricants:** Stearic acid, Magnesium stearate, Zinc state, calcium state, talc, polyethylene glycol, colloidal silicon dioxide.
1.4.6.6 **Flavors and Sweeteners:** Flavors and taste-masking agents make the products more palatable and pleasing for patients. The addition of these ingredients assists in overcoming bitterness and undesirable tastes of some active ingredients. Peppermint flavor, cooling flavor and oil of bitter almonds. Flavoring agents include, vanilla, citrus oils, fruit essences. Sugar, Dextrose, Fructose, Non-nutritive sweeteners such as Aspartame, Sugar alcohols and Sucralose.

1.4.7 **Approaches for orally disintegrating tablets:** The orally disintegrating property of the tablet is attributable to a quick ingress of water into the tablet matrix resulting in its rapid disintegration. Hence, the basic approaches to developing orally disintegrating tablets include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent, and using highly water-soluble excipients in the formulation.

1.4.8 **Conventional Techniques Used in the Preparation of Orally Disintegrating Drug Delivery Systems:**

1. Lyophilization
2. Molding:
3. Spray drying
4. Sublimation

1.5. **CHRONOBIOLOGY AND CHRONOTHERAPEUTICS**\(^{44-46}\):

Chronobiology is the study of biological rhythms and the mechanisms of biological time keeping. Humans exhibit endogenous circadian rhythms that are regulated by the master circadian clock of the body.
Chronotherapeutics is the purposeful delivery of medications in unequal amounts over time, for example, during the 24 h.

1.5.1 Chronopathology: The symptom intensity of many medical conditions and the occurrence of life-threatening medical emergencies exhibit rather precise timings. Gout, gallbladder, and peptic ulcer attacks are most frequent at night. Acute pulmonary edema, congestive heart failure, and asthma worsen nocturnally. Migraine headache typically is triggered during rapid eyeball movement (REM) episodes during nighttime sleep or in the early morning hours after awakening.

1.5.2 Chronopharmacology: Chronopharmacology is the study of the manner and extent to which the kinetics and dynamics of medications are directly affected by endogenous biological rhythms, and also how the dosing time of medications affect biological timekeeping and the features (period, level, amplitude, and phase) of biological rhythms.

1.5.3 Chronokinetics: Chronokinetics refers to dosing-time, i.e., rhythm-dependent, differences in the absorption, distribution, metabolism, and elimination of medications. Circadian rhythms in gastrointestinal pH can affect drug dissolution, and circadian rhythms in gastric emptying, motility, and blood flow can affect the rate, and in certain cases the amount, of drug absorption. Moreover, circadian rhythms in hepatic blood flow and enzyme activity can significantly affect drug biotransformation and metabolism, and rhythms in hepatic bile
function and flow as well as renal blood flow, glomerular filtration, and tubular function can affect drug elimination.

1.5.4 Chronodynamics: Chronodynamics refers to dosing-time, i.e., rhythm-dependent, differences in the effects of medications. Such administration-time differences are due to rhythms in the free-to-bound drug fraction, number and conformation of drug-specific receptors, second messenger and ion channel dynamics, and rate limiting step(s) in metabolic pathways.

1.5.5 Pulsatile drug delivery\(^{(47-51)}\): Pulsatile drug delivery \(^{(12-14)}\) is the most interesting time and site specific system. This system is designed for chronotherapy which is based on circadian rhythm. PDDS is defined as the rapid and transient release of certain amount of molecules with in short time period immediately after a predetermined off-release period that is lag time. It can show ideal sigmoidal curve or delayed release after initial lag time.

1.5.6 Conditions that demand PDDS:

1. During the cases of bronchial asthma, myocardial infraction, angina pectoris, rheumatic disease, ulcer, and hypertension where they usually display time dependence. For example asthma attacks show sharp increase during early morning hours.

2. PDDS can give a promising platform for those drugs which produce biological tolerance where usually demands the prevention of drug
continues presence at the biophase which cause decrease in the therapeutic effect.

3. PDDS will comfort to those drugs that undergo extensive first pass metabolism.

1.5.7 Various approaches of PDDS: PDDS are generally classified in to Time Controlled and Site Specific Delivery Systems. The release from the first group is primarily controlled by the system while the release from the next one is controlled by the biological environment i.e., P\text{H} or enzymes in the gastro intestinal tract.

1.5.8 Press coated pulsatile drug delivery:\(^{52-54}\): The main objective of this press coated pulsatile tablets (PCPT)\(^ {17-21}\) is to provide a time pulsed delivery of active agent and to over come first pass effect. It mainly contains

- Centre core with one or more polymers
- Coat for maintaining lag time which contains blend of hydrophilic and hydrophobic polymers with or with out active agent.
- An optional envelope that helps as instant compartment to exceed liver metabolism.

This type of tablet has two parts, internal core and surrounding coat. The core is small porous tablet and prepared on one turret. For preparing final tablet, a bigger die cavity in another turret is used in which first, the coat material is filled to half and then core tablet is mechanically
transferred, again the remaining space is filled with coat material and finally compression force is applied.

Press coating technique can protect hygroscopic (one of the instability of Montelukast sodium), light sensitive oxygen liable drugs most effectively compared to the regular and pan coated techniques. But the disadvantage with this technique is positioning of the core tablet exactly at the centre of the barrier layers which is a great challenge.

![Press coating technique](image)

**Fig. 1.2** Press coating technique

1.5.9 Role of hydrophilic and hydrophobic polymers in press coated compartment of PCPT: The press coated compartment of PCPT contains hydrophilic polymers which dissolve away to weaken the structure of press coated layer where as the hydrophobic polymers retards water penetration and helps to maintain the shape of drug delivery system.

The interaction of polymers with water is of great relevance in many aspects to their biomedical and chemical applications. The water molecule has a strong tendency for hydrogen bond formation in its own
liquid and solid state with other polymer groups. In polar polymers both the solubility and diffusivity are strongly influenced by such interactions.

Hydrophobic polymers mostly used are carbomers, carnauba wax, ethyl cellulose, glyceryl palmitostearate, microcrystalline wax, poly mathacrylates, stearic acid, shellac, zein, polacrilin potassium.
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