2.0 BACKGROUND

2.1 Introduction of Oral Cavity
The ultimate goal of any drug delivery system is the successful delivery of the drug, in which almost 90% of the drugs are administered to the body for the treatment of various disorders and diseases. Oral route is regarded as the safest, most convenient and most economical method of drug delivery having the highest patient compliance \[^1\]. In the dosage form taken by oral, the drug is dissolved or swallowed and then enters into the systemic circulation to produce the desired effect. Despite of astounding advancement in drug delivery to the oral route of drug administration is considered as the most important method of administration of drug for systemic effect because of self-medication, ease of administration and avoidance of pain compared to parenteral route \[^1\].

Oral cavity offers a unique environment for delivering the drugs. The oral mucosa allows direct access of drug to the systemic circulation and avoids first pass metabolism. The epithelium of the oral cavity is quite similar to that of the skin, with slight differences with regard to keratinization, protective and lubricant mucous which is spread across its surface. The permeability of oral mucosa is 4–1000 times greater than that of the skin. The oral cavity is divided into two regions: outer being the oral vestibule bounded by the lips and cheeks; the hard and soft palates, the floor of the mouth and tonsils \[^2\].

2.2 Challenges and Opportunity in the Medication of Challenging Patients (Pediatric and Geriatric Patients).

What do you mean by challenging patients?
A patient who is troublesome, tedious and/or noncompliant with physician instructions of dosage administration due to different problem like swallowing, palatability, dysphagia etc.

Who are such challenging patients?
Example of such challenging patients are pediatric patients, geriatric patients, patients with swallowing problem (Dysphagia) and nauseous or noncompliant patients.
Challenges for pediatric patients

The pediatric population is divided, by age, into five or six categories, preterm newborns, term newborns (0-1 month), infants and toddlers (1-2 years), children (2-12 years) and adolescents (12-18 years) have been defined. The categorization into these subpopulations has been mainly derived from physiological and pharmacokinetic differences (e.g., metabolic capacity, organ maturation and drug clearance). Differences in the metabolic pattern can be observed, especially in the first 6 months after birth, when compared with older children and adults. Treatment failure and toxicity may result if the drug dose is not adequately adapted. Challenges for pediatric patients are summarized below

- **Diversity of children**
  - Size/weight increases >20-fold from birth to adulthood
  - Dose adjustments of >4-fold often needed
  - Ability to take medicines and dosage form preferences vary greatly with age

- **Taste masking**
  - Taste acceptance can impact patient compliance: Taste perception/preferences are different in children than adults, disease state can also impact taste/smell perception

- **Stability – chemical, physical, microbial**
  - Oral liquids present additional stability challenges due to additional excipients needed for palatability
  - Typically are aqueous based formulations, therefore increasing the importance of microbial control measures
  - Expiration period may be too short to support commercial feasibility

- **Achieving global regulatory acceptability**

- **Providing rapid patient access**

- **Adherence to medical regimen**
  - Individual factors: lack of knowledge, poor skills
  - Healthcare provider: Poor communication Conflicting goals
  - Family factors: Limited problem solving, lack of cohesion, Poor communication
  - Social and material resources: Financial constraints and Lack of social support
Challenges for geriatric patients \[3\]

Not only pediatric patients but also geriatric patients and adults with reduced capability to take conventional solid formulations may benefit from patient-centric approaches to drug delivery. Challenges for geriatric patients are summarized below

- Establishing age classes for drug development is impossible for geriatric patients.
- In contrast to children, the demands of the elderly are not closely related to age, but to the ability of the patient, which is mainly determined by the individual state of health.
- Many geriatric patients suffer from various diseases with multiple-drug treatment. Some of these patients are addicted to alcohol, nicotine and pharmaceuticals. Reduced kidney and liver functions as well as dehydration may dramatically alter the pharmacokinetic properties of a drug.
- Limited audiovisual and ergonomic abilities of geriatric patients must be assumed and considered in drug development.
- Unfortunately, a poor hygienic status can be expected in the domestic environment of some elderly patients, which may also influence the choice of the drug formulation.
- Swallowing Problem of solid medication
- Chocking while taking liquid medication

Dosage form needs for pediatric and geriatric formulation development \[4\]

- Adequate bioavailability
- Safe and minimal numbers of excipients
- Minimal impact on lifestyle Acceptable appearance and taste
- Minimal administration frequency and minimal risk of dosing
- Dose flexibility Acceptability of size/volume Preparation/ administration
- Easily transported and stored low environmental impact
- Age-appropriate oral formulations are expected to meet all the quality attributes of conventional pharmaceutical products as well as specific patient requirements (e.g., higher degree of dose flexibility and ease of swallowing).
- Socio-cultural acceptability
- Precise and clear product information
• Age-appropriate administration devices (e.g., the solid dosage pen, multiparticulate counters and medicated straws) may improve the acceptability of pharmaceutical products.

• A balanced approach between innovation and cost-effectiveness is required to enable high-quality products while not-impairing patient access to better medicines.

Key issues need to be addressed to stimulate the further development of better medicines for children: [4]

• The continued prioritization of unmet formulation needs, particularly drug delivery in neonates and treatment gaps in pediatric cancers and childhood diseases in developing countries

• A better use of existing data to facilitate pediatric formulation development;

• Innovative technologies in adults that can be used to develop new pediatric formulations;

• Clinical feedback and practice-based evidence on the impact of novel formulations;

• Improved access to new pediatric formulations

Different Approach for addressing challenges for pediatric and geriatric patients [5]
The most popular technologies to date have been for the manufacture of small-sized solid oral drug delivery systems. Comprehensive list of different approach available for challenging age appropriate delivery are discussed below.

Commercialized Technology

• Oro-dispersible Tablets
• Oral dispensor coupled to baby bottle
• Pill Swallowing cup
• Medicated dosing straw
• Sustained release suspension
• Medicated spoon that forms oral pulp
• Oral Soluble film
• Chewable soft gel capsules
• Easy to open capsules
• 3D printed oro-dispersible tablets
Non-Commercial Technology

- Orals Soft Gels (Mediated Jam/Jelly)
- Electronic Mini-tablets dispenser
- Segmented easy to score tablets
- Gel forming easy to swallow film
- Multiple score tablets
- Solid dosage pen device
- Milk-based oral liquid formulation
- Nipple shield drug delivery device

The choice of dosage form for challenging patients are totally depend on many factors like type of patients targeted, no of patients affecting that disease (For e.g. Orphan drug), age of patients, type of disease, cost of formulation, robustness of manufacturing technology, dose of drug, dosing frequency, type of action required (onset of action or controlled release action).

Convenience of administration and patient compliance is gaining significant importance in the design of dosage forms. Recently, more stress is laid down on the development of organoleptically elegant and patient friendly drug delivery system for pediatric and geriatric patients. The main problem with oral dosage form is difficulty in swallowing solid dosage form especially pediatric and geriatric patients. The only hurdle for dosage form designing for pediatric and geriatric patients is the patient’s acceptance of the dosage form. Pediatric patients tend to become non co-operative during the administration of oral medication; the most common reason being the taste of the oral formulation administered among the children.

Fast-dissolving drug delivery systems are rapidly gaining interest in the pharmaceutical industry. Rapidly dissolving dosage forms are referred by various names by researchers like quick disintegrating, orally disintegrating, mouth dissolve or melt in mouth dosage forms \[^{6, 7}\]. The introduction of fast-dissolving dosage forms has solved some of the problems encountered in the administration of drugs to the pediatrics, geriatric, bedridden, nauseous or noncompliant patients.
Recently, fast-dissolving films are gaining interest as an alternative to fast-dissolving tablets. The gel dosage form not only overcomes the disadvantages of liquid dosage form, but also of solid dosage forms to increase patient’s compliance. The problem of dose measurement by patients is outweighed as oral medicated gel packaging in a unit dose container. In present work attempt was made to prepare mouth dissolving film (MDF) and oral soft gel (OSG) of granisetron hydrochloride used for nausea and vomiting induced in cancer chemotherapy, linezolid for pneumonia caused by Staphylococcus aureus and memantine Hydrochloride used for childhood behavioral disorder such as autistic spectrum disorder or combined type attention-Deficit/hyperactivity disorder (ADHD) and to treat elderly patients suffering from Alzheimer’s disease.

In the present investigation two dosage form has been selected i.e. mouth dissolving film and oral soft gel. Three different category of drug selected i.e. granisetron hydrochloride, linezolid and memantine hydrochloride. Ration for selection of dosage form and drug candidate is discussed in following section (Section 2.3 and section 2.4).

2.3 Rational for Dosage Form Selection

2.3.1 Mouth dissolving film (MDF)

The films are designed such way that upon contact with the wet surface such as the tongue, it rapidly hydrate on the site of action without the needs of water and rapidly dissolves or disintegrate to release medicament for oro-mucosal absorption and also remaining amount is swallowed orally with saliva and subsequent absorption takes place in the gastro-intestinal tract. Thus mouth dissolving films (MDF) are widely accepted by patients due to ease of administration, portability and accurate dosing. Mouth dissolving film have synonyms like fast dissolving film, rapid dissolving film, quick dissolving film and oral thin film (OTF). Advantages of film over other conventional dosage form involved are listed below. [8, 9].

- Accurate dosing as compare to liquid dosage form.
- Elegant appearance which attracts pediatric patients.
- Increase patient’s compliance due to ease of administration in geriatric, pediatric, bedridden, nauseous or noncompliant and patients having dysphagia (swallowing problem).
• Children cannot spit the drug out because the film adheres to the upper gum after wetting. Therefore, safe administration is increased in children.

• Advantage over orally disintegrating tablet:
  ✓ The fear of taking solid tablets and the risk of choking for certain patient populations still exist despite their short disintegration/dissolution times.
  ✓ The fragility/friability of wafer-like, porous and low-pressure molded tablets fabricated by various manufacturing processes, which require special and expensive packaging to protect the dosage forms, makes them difficult to carry, store and handle.
  ✓ Many ODTs are produced using expensive lyophilization process.

• MDF can be taken without the need of water.

• MDF can easily divide in different dose according to age of children with accuracy as compare to liquid dosage form based on film area without changing formulation technology.

The robustness of the film depends upon the type and amount of polymer used. The properties of the film depend on the characteristics of the film forming polymer as they occupy 20-75% w/w of the total dry weight of the film\(^{[10]}\). Plasticizer is one more component that plays a key role in determining the properties of the film. Additionally, organoleptic characteristics (taste and appearance) are vital parameters that govern patient’s approval and compliance. Flavors, sweeteners and amino acids can reduce or suppress the perception of bitterness of several pharmaceuticals and are generally used in association with other taste-masking techniques \(^{[11]}\).

**Approaches for Preparation of mouth dissolving film** \(^{[12]}\)

• **Solvent casting method**: In this method, firstly the water soluble polymers are dissolved in water at 1,000 rpm and can be heated up to 60°C. All the other excipients like colors, flavoring agent, sweetening agent, etc., are dissolved separately. Then both the solutions obtained are mixed thoroughly stirring at 1,000 rpm. The obtained solution is incorporated with the API dissolved in suitable solvent. The entrapped air is removed by vacuum. The resulting solution is cast as a film and allowed to dry, which is then cut into pieces of the desired size.
• **Hot-melt extrusion:** In hot melt extrusion method, the initial mass is formed with the help of carriers. To form initial mass, the drug is mixed with carriers and a solid mass is obtained and dried. Then dried granular material is introduced into the extruder. The extruder is divided into four zones having following degrees of temperature: 800 (zone 1), 1150 (zone 2), 1000 (zone 3), and 650°C (zone 4). The speed of extruder screw speed should be set at 15 rpm in order to process the granules inside the barrel of extruder for approximately 3-4 min so that mass should be properly melted. The extrudate (T = 650°C) obtained is then pressed into a cylindrical calendar in order to obtain a film. There are certain benefits of hot melt extrusion: Fewer operation units, minimum product wastage, possibility to scale up, an anhydrous process, absence of organic solvents, include shorter temperature and shorter residence time of the drug carrier mix, and better content uniformity.

• **Semisolid casting:** This method is mostly preferred when film ingredient involves acid insoluble polymer. In this firstly, the water soluble polymers are dissolved in water. The obtained solution is added to the acid insoluble polymer solution which is separately formed. Both the solutions are mixed properly. After mixing the two solutions, appropriate amount of plasticizer is added to the obtained final solution so that gel’s mass can be obtained. At last, the gel mass is casted onto the films or ribbons using heat controlled drums. The thickness of the film should be about 0.015-0.05”. The ratio of the acid insoluble polymer to film forming polymer should be 1:4. Examples of acid insoluble polymers are cellulose acetate phthalate and cellulose acetate butyrate.

• **Solid dispersion extrusion:** In this method immiscible components are extrude with drug and then solid dispersions are prepared. Finally the solid dispersions are shaped in to films by means of dies.

• **Rolling Method:** In rolling method a solution or suspension containing drug is rolled on a carrier. The solvent is mainly water and mixture of water and alcohol. The film is dried on the rollers and cut in to desired shapes and size.
2.3.2 Oral soft gel (OSG)

Many patients, elderly people and person with dysphagia find difficulty to swallow tablets and hard gelatin capsules. So, they do not comply with prescription which results in a high incidence of noncompliance and ineffective therapy. Patients with dysphagia can be choked by water while consuming liquid formulation which can be eliminated by administering liquid formulations with high viscosity. Oral soft gel can increase patients compliance by overcome swallowing problems encountered in the administration to the pediatrics, geriatric, bedridden, nauseous or noncompliant patients. Oral soft gel is similar dosage form of available marketed jam used as food. **Hence oral soft gel can also name as "medicated Jam".** Advantages of oral soft gel over conventional dosage form are listed below.

- Oral soft gel is preparation designed to produce a greater patient compliance especially in pediatrics due to its palatability and elegant appearance.
- The hydrophilic gel dosage form can be swallowed easily without water. The oral soft gel dosage for are soft and smooth hence patients will not experience choking of throat.
- The oral soft gel dosage form out passes the liquid dosage form in accurate dosing, the viewpoint of patient compliance and attractive appearance like fruit jam. The problem of dose measurement by patients is outweighed as oral medicated gel is to be packed in unit sachet.
- Oral soft gel can easily divide in different dose according to age of children with accuracy as compare to liquid dosage form based on weight of gel without changing formulation technology.

Oral soft gel is the aqueous colloidal systems with a minimum of two components: the gelling agent and fluid component. Oral soft gel contains a high proportion of water or water-miscible liquid as a fluid component. Gelling agents permitted in the food and confectionary industries can be used for developing medicated gel. Gelling agents such as carrageenan, pectin, sodium alginate, gelatin, gellan gum etc. can be used. The polysaccharide (gellan gum) gel have liquid-like properties because the major constituent is water and solid-like properties due to the formation of the three-dimensional gel network. The pharmaceutically active ingredient is either dissolved or dispersed in the fluid component [13].
2.4 Rational for Selection of Drug

2.4.1. Granisetron hydrochloride

Globally, cancer is increasing at an alarming rate. Chemotherapy is the primary treatment for cancer and in some cases the only resort [14]. Most of the chemotherapeutic drugs have been found to cause release of large amounts of serotonin from enterochromaffin cells in the gut. Serotonin acts on 5-HT₃ receptors in the gut and brain stem and stimulate vagal afferent to initiate the vomiting reflex. Chemotherapy induced nausea and vomiting (CINV) remains a significant problem for cancer patients, having a long lasting effect on their quality of life [15]. 5-HT₃ receptor antagonists or serotonin antagonists suppress nausea and vomiting by inhibiting serotonin binding to the 5-HT3 receptors. Granisetron is a highly selective serotonin (5-HT₃) receptor blocker which inhibits serotonin to bind with serotonin 5-HT3 receptors and hence prevents the vomiting reflex induced by serotonin [16]. In above mentioned condition, rapid and onset of action of the drug is required. The mouth dissolving films/Oral soft gel of granisetron fulfill all the requirements for faster action and also oral absorption of granisetron hydrochloride will help to reduce first pass metabolism. Granisetron is potentially used in preventing nausea and vomiting associated with cancer chemotherapy [17]. Granisetron hydrochloride has half-life of 5-6 hours and undergoes first pass metabolism. Granisetron hydrochloride is classified as Class I drug (highly soluble and highly permeable) according to BCS classification [18]. Brief detail about granisetron hydrochloride like dosage and administration, pharmacokinetics and available market formulation is summarized below.

- **Drug Category**: Antiemetic
- **Mechanism of action**: Granisetron is a selective 5-HT₃ receptor antagonist. Absorption of is rapid and complete though oral.
- **Absorption**: Bioavailability is reduced to about 60% as a result of first pass metabolism.
- **Half Life**: 4-6 hours healthy patients, 9-12 hours in cancer patients
- **Dosage and Administration**
  - **Adult Dose**: 2 mg once daily or 1 mg twice daily
  - **Pediatric Dose**: A dose of 10 – 40 µg/kg body weight
    - Tablets 1mg, 2mg
    - Injection 1mg/ml, 2mg/ml, 3mg/ml
    - Oral Solution (10mL each bottle)
    - Syrup (1mg/ml, 10mL each bottle)
    - Drops (1mg/ml, 10mL each bottle)
    - Suspension (10mL, 30mL each bottle)
- **Available dosage form granisetron in India**
Absorption of Granisetron hydrochloride is rapid and complete through the oral route. Hence oral dosage form is suitable for granisetron hydrochloride. Available dosage forms for pediatric in market are syrup, drops and suspension which having dose accuracy problem as the granisetron hydrochloride is low dose drug. While mouth dissolving film and oral soft gel can be given as different dose with accuracy (film based on area and oral soft gel based on weight). Further syrup contains high amount of sugar which cannot take by diabetic patients but mouth dissolving and oral soft gel can be prepared with low calories sweetener to overcome problem in diabetic patients. In geriatric patients diabetes is very common disease. Other advantages of mouth dissolving film and oral soft gel for geriatric patients has already been discussed earlier.

The present investigation was undertaken with the objective of formulating patient compliance MDF and OSG of granisetron hydrochloride and selection of best dosage form for granisetron hydrochloride to be potentially useful for treatment of CINV to enhance the convenience and compliance by the elderly and pediatric patients (age between 2 to 12 years). In this research mouth dissolving film of granisetron hydrochloride 2mg/film (Dimension: 2cmx2cm) and oral soft gel of granisetron hydrochloride, 2mg/10gm gel was plan for development.

2.4.2 Linezolid

Linezolid is a member of a new structural class of antibiotics, oxazolidinones. The oxazolidinones have a good activity against gram-positive bacteria. They act uniquely by inhibiting the formation of protein synthesis initiation in gram-positive bacteria\textsuperscript{19}. Linezolid is active after oral or intravenous administration. Linezolid is expected to increase the treatment options for severe infections due to Gram positive bacteria, particularly resistant infections (e.g. Methicillin-resistant Staphylococcus aureus (MRSA) and Vancomycin-resistant Enterococci (VRE)). Linezolid is used in Nosocomial pneumonia, Community-acquired pneumonia, complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis, uncomplicated skin and skin structure infections\textsuperscript{19}.

Brief detail about linezolid like dosage and administration, pharmacokinetics and available market formulation is summarized below.
• Drug Category: Antibiotic, Oxazolidinones

• Mechanism of action: It selectively inhibits bacterial protein synthesis via a mechanism of action different from that of other antibacterial agents. Linezolid binds to the 23S ribosomal RNA of the 50S subunit of the bacterial ribosome and prevents the formation of a functional 70S initiation complex which is an essential component of the bacterial translation process.

• Absorption: Linezolid is rapidly and extensively absorbed after oral dosing. Maximum plasma concentrations are reached approximately 1 to 2 hours after dosing, and the absolute bioavailability is approximately 100%

• Half Life: 4.5-5.5 hours

• Dose and administration:
  - Pediatric: 10 mg/kg every 8 hours
  - Adults: 600 mg every 12 hours

• Available dosage form linezolid in India:
  - Tablets, 600mg
  - Injection (600mg/vial)
  - Infusion (200mg/100mL, 600mg/100mL)
  - Syrup (100mg/5mL)
  - Suspension (100mg/5mL) - available in US market
  - Orally Dispersible tablet, 100 mg (for pediatric use)

Absorption of linezolid is rapid after oral administration and absolute bioavailability is about 100% hence oral dosage form is suitable for linezolid. In market for pediatric available dosage forms are syrup, drops and suspension which has problem of dose accuracy. Orally dispersible tablet available for pediatric patients cannot be divided into different dose base on children age. While mouth dissolving film and oral soft gel can be given as different dose with accuracy (film based on area and oral soft gel based on weight). For geriatric patients also mouth dissolving film and oral soft gel has many advantage which already been discussed earlier. Further syrup contains high amount of sugar which cannot take by diabetic but mouth dissolving and oral soft gel can be prepared with low calories sweetener to overcome problem with diabetic as in geriatric patients with diabetes is very common. As discussed earlier moth dissolving film/oral soft gel can overcome swallowing problems encountered in the administration to the pediatrics, geriatric, bedridden, nauseous or noncompliant patients and also increase patients compliance.

The present investigation was undertaken with the objective of formulating patient compliance MDF and OSG of linezolid for pediatric (age between 2 to 12 years) and geriatric patients, selection of best dosage form for linezolid. In this research mouth dissolving film of
linezolid, 100mg (dimension 3cmx3cm) and oral soft gel of linezolid, 100mg/10gm gel was planned for development.

2.4.3 Memantine hydrochloride

Memantine is a systemically-active uncompetitive NMDA receptor antagonist having low to moderate affinity for the receptor and strong voltage dependency and rapid blocking/unblocking kinetics. Memantine hydrochloride is currently available for the treatment of moderate to severe Alzheimer’s disease (AD) in a dose up to 20 mg/day (5-10 mg twice a day). It has been hypothesized that memantine may not only be effective for the treatment of Alzheimer’s disease (as well as Parkinson's and other neurological diseases), but may also be effective for the treatment of autism, Attention-Deficit/Hyperactivity Disorder (ADHD) and other autistic spectrum disorders[19]. Brief detail about memantine hydrochloride like dosage and administration, pharmacokinetics and available market formulation is summarized below.

Drug Category : Anti-Alzheimer’s agent.

Mechanism of action : Persistent activation of central nervous system N-methyl-D-aspartate (NMDA) receptors by the excitatory amino acid glutamate has been hypothesized to contribute to the symptomatology of Alzheimer’s disease. Memantine is postulated to exert its therapeutic effect through its action as a low to moderate affinity uncompetitive (open-channel) NMDA receptor antagonist which binds preferentially to the NMDA receptor-operated cation channels.

Dose : 5-10 mg

Absorption : Following oral administration memantine is highly absorbed with peak concentrations reached in about 3-7 hours. Memantine has linear pharmacokinetics over the therapeutic dose range. Food has no effect on the absorption of memantine.

Dose and administration : The recommended starting dose of memantine hydrochloride is 5 mg once daily.
The dose should be increased in 5mg increments to 10 mg/day

Available dosage form memantine HCL in India.
- Tablets (5mg,10mg)
- Solution (2mg/ml) - available in US market

Current dosing of memantine is twice a day using immediate release tablets. The tablet forms are difficult to swallow and require the tablets to be coated to conceal its bitter taste. Moreover, difficulties associated with tablets result in decreased patient compliance. Mouth
dissolving film/oral soft gel formulations of memantine hydrochloride are beneficial for many reasons. Their characteristic advantages such as administration anywhere without liquid lead to increase their suitability in situations where patients have difficulty in swallowing for such as pedriatic, elderly and patients with neurological disorders.

The present investigation was undertaken with the objective of formulating patient compliance MDF and OSG of memantine hydrochloride and selection of best dosage form for memantine hydrochloride to be potentially useful for treatment of Alzheimer's disease (as well as Parkinson's and other neurological diseases) and treatment of autism, Attention-Deficit/Hyperactivity Disorder (ADHD) and other autistic spectrum disorders to enhance the convenience and compliance by the elderly and pediatric patients (age between 2 to 12 years). In this research mouth dissolving film of memantine hydrochloride, 10mg/film (dimension 2cmx2cm) and oral soft gel of memantine hydrochloride, 10mg/10gm gel was plan for development.