Issues and current Developments in Biopharmaceutical Oral drug Delivery system.

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***Abstract*— Oral drug delivery remains the most favored route of administration due to its noninvasive nature, high patient compliance, ease of handling, and lack of requirement for specific sterile conditions. Nevertheless, numerous drugs delivered orally encounter various physical, biological, and biochemical obstacles that diminish their therapeutic effectiveness prior to absorption into systemic circulation. The application of nanocarriers in oral drug delivery serves to mitigate these challenges and is regarded as a viable alternative to address the limitations associated with traditional oral drug delivery methods. This chapter provides a summary of recent advancements in the use of nanocarriers for oral drug delivery aimed at treating a range of diseases. Additionally, it discusses how innovative nanocarrier design technologies enhance therapeutic efficacy by overcoming the aforementioned barriers. Although several nanocarrier-based drug delivery technologies have emerged in recent years and demonstrate promising outcomes, they remain distant from widespread clinical application**

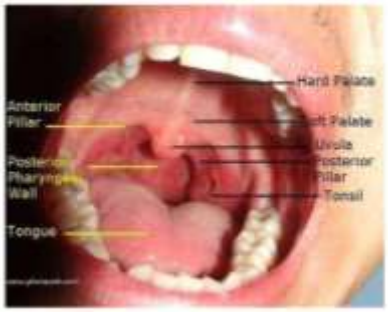
1. INTRODUCTION

The oral route of drug administration is the most important method of administration of drug for systemic effect, despite of tremendous advancement in drug delivery system. Its ease of administration, pain avoidance and various advantages over other routes is the reason that the oral route achieved such popularity. But the most evident drawback of oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patient's incompliance particularly in and films) may show greater patient acceptability and convenience.

Fast-dissolving oral delivery systems are solid dosage forms, which disintegrate or dissolve within 1 min when placed in the mouth without drinking of water. After disintegrating in mouth, enhanced the clinical effect of drug through pre-gastric absorption from mouth pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. More recently, Fast- dissolving drug delivery systems have rapidly gained acceptance as an important new way of administering drugs. They are usually used for pharmaceutical and nutraceutical products. It is the newest frontier in drug delivery technology that provides a very convenient means of taking medications and supplements. Fast dissolving drug delivery system are also applicable when local action in the mouth is desirable such as local anesthetic for toothaches, oral ulcers, cold sores, or teething. This novel drug delivery system can also be beneficial for meeting the current needs of the industry are improved solubility/stability, biological half-life and bioavailability enhancement of drugs. (Kaur et al., 2012)

2. Overview of Oral Mucosa

The oral cavity comprises the lips, cheek, tongue, hard palate, soft palate and floor of the mouth. The lining of the oral cavity is referred to as the oral mucosa, and includes the buccal, sublingual, gingival, palatal and labial mucosa. The buccal, sublingual and the mucosal tissues at the ventral surface of the tongue account for about 60% of the oral mucosal surface area. The top quarter to one-third of the oral mucosa is made up of closely compacted epithelial cells. The primary function of the oral epithelium is to protect the underlying tissue against potentially harmful agents in the oral environment and from fluid loss. Beneath the epithelium are the basement membranes, lamina preppie and sub mucosa. The oral mucosa also contains many sensory receptors including the taste receptors of the tongue. Three types of oral mucosa can be found in the oral cavity; the lining mucosa is found in the outer oral vestibule (the buccal mucosa) and the sublingual region (floor of the mouth). The specialized mucosa is found on the dorsal surface of tongue, while the masticatory mucosa is found on the hard palate (the upper surface of the mouth) and the gingival (gums). The lining mucosa comprises approximately 60%, the masticatory mucosa approximately 25%, and the specialized mucosa approximately 15% of the total surface area of the oral mucosal lining in an adult human. The masticatory mucosa is located in the regions particularly susceptible to the stress and strains resulting from masticatory activity. The superficial cells of the masticatory mucosa are keratinized, and a thick lamina prairie tightly binds the mucosa to the underlying periosteum. Lining mucosa on the other hand is not nearly as subject to masticatory loads and consequently, has a non-keratinized epithelium, which sits on a thin and elastic lamina propria and a sub mucosa. The mucosa of the dorsum of the tongue is a specialized gustatory mucosa, which has well papillae surfaces which are both keratinized and some non-keratinized/



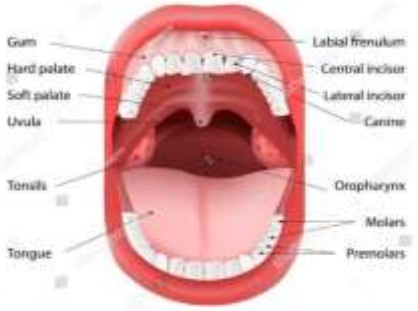


Fig 1.Schematic representation of the different linings of mucosa in mouth

3. Orally Disintegrating Dosage Forms

The concept of orally disintegrating dosage forms has emerged from the desire to provide patients with more conventional means of taking their medication. Interestingly, the demand for ODDFs has enormously increased during the last decade, particularly for geriatric and pediatric patients who experience difficulty in swallowing conventional tablets and capsules. Hence, they do not comply with prescription, which results in high in33cidence of ineffective therapy.

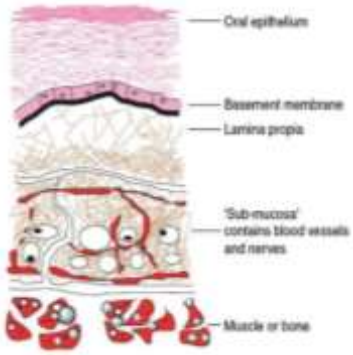


Fig.2: Schematic diagram of buccal mucosa

The advantages and disadvantages associated with utilizing the oral mucosa as a drug delivery site

Tab. 1 Advantages and Disadvantages of Drug Delivery

Advantages	**Disadvantages**
Accessible	Permeability barrier of oral mucosa
Self-administrable	Saliva washes away the drug
Oral mucosa repairs rapidly	Mastication and speech may dislodge
Different areas of the oral cavity have different permeability characteristics	Delivery device
Sustained delivery possible	Highly enzymatic environment
Potential reduction of systemic side Effects	Relatively small surface area
Avoid the hepatic first pass effect	Risk of choking on or swallowing delivery device

In disease conditions such as motion sickness, sudden episodes of attacks of coughingand repeated emesis swallowing conventional solid dosage forms become difficult. Orally disintegrating dosage forms can serve as an effective alternative mode of drug delivery in such situations. When put in the mouth, these dosage forms disintegrate instantly to release the drug, which dissolves or disperses in the saliva. Thereafter, the drug may get absorbed from the pharynx and esophagus or from other sections of GIT as the saliva travels down. In such cases, bioavailability is significantly greater than that observed from conventional tablet dosage form. The novel technology of oral disintegrating dosage forms is known as fast dissolve, rapid dissolve, rapid melt and quick dispersible tablets (Gupta *et al*, 2010). However, the function and concept of all these dosage forms are similar.

- **Different orally disintegrating dosage forms are as follows:**

1. **Orally disintegrating tablets:**

It is a tablet that dissolves or disintegrates in the oral cavity without the need of water or chewing.

2. **Fast dissolving films:**

The fear of taking solid tablets and the risk of choking for certain patient population still exists despite their short dissolution and disintegration time. It consists of very thin oral strip, which releases the active ingredient immediately after uptake in to the oral cavity. It combines all advantages of tablets along with liquid dosage forms. This system is simply placed on patients' tongue or any other mucosal surface, instantly wet by saliva; film rapidly hydrates and dissolves to release the medication.

***3.* Fast Caps:**

A new type of fast disintegrating drug delivery system based on gelatin capsules was developed. In contrast to conventional hard gelatin capsules, the fast caps consist of gelation of low bloom strength and various additives to improve the mechanical and dissolution properties of capsule shell. It includes several advantages like high drug loading, possible solid and liquid filling, and no compression of coated taste masked or extended-release drug particles / pellets, good mechanical properties, simple manufacturing, mechanical stability and requirement of special packaging.

***4.* Medicated chewing gums:**

It is an attractive alternative for drug delivery system with several advantages including convenience for administration, mainly chewing gum is used to promising controlled release drug delivery system. These are mainly available currently for pain relief, smoking cessation, travel illness and freshening of breath.

***5.* Freeze-dried wafer:**

It is a quick-disintegrating, thin matrix that contains a medicinal agent that does not need water for swallowing. This fragile dosage form requires unit-dose packaging to ensure physical stability. The wafer disintegrates instantaneously in the oral cavity and releases drug, which dissolves or disperses in the saliva. The saliva is swallowed and the drug is absorbed across the gastrointestinal tract (GIT). (Priyanka Nagar *et al*., 2011)

4. MOUTH DISSOLVING TABLET

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance. Also, solid oral delivery systems do not require sterile conditions and are therefore, less expensive to manufacture. Patient compliance, high- precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. Excipients and equipment's choices will be significantly affected should solid dosage form technologies change in response to the unprecedented shifts in the drug discovery such as genomics. Should next generation drugs be predominantly protein or peptide based, tablets may no longer be the dominant format give the difficulty of dosing such moiety. Injections generally are not favored for use by patients unless facilitated by sophisticated auto injectors. Inhalation is one good alternative system to deliver these drugs, but the increased research into biopharmaceuticals so far has generate predominantly chemical entities with low molecular weights. The development of enhanced oral protein delivery technology by Fast dissolving Tablets which may release these drugs in the mouth are very promising for the delivery of high molecular weight protein and peptide. The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, manufacturing and ease of administration lead to high levels of patient compliance. (Rajshree Panigrahi *et al*., 2010)

The problem of swallowing is common phenomenon in geriatric patient due to fear of choking, hand tremors, dysphasia and in young individuals due to underdeveloped muscular and nervous systems and in schizophrenic patients which leads to poor patient compliance. Difficulties in swallowing of tablet and capsule are also occurring when water is not available, in diarrhea, coughing during the common cold, allergic condition and bronchial infection. Approximately one-third of the population (mainly pediatric and geriatric) has swallowing difficulties, resulting in poor compliance with oral tablet drug therapy which leads to reduced overall therapy effectiveness. For this reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention (Md. Nehal Siddiqui *et al*., 2010).

United States Food and drug administration (FDA) defined fast dissolving tablet (FDT) as "a solid dosage form containing medicinal substance or active ingredient which disintegrate rapidly usually within a matter of seconds when placed upon the tongue." European pharmacopoeia has used the term "Or dispersible tablet" for tablets that disperses readily and within 3 min in mouth before swallowing. (Johnny Edward Aguilar- Diaz *et al*., 2012)

Desired Characteristics Of Fast Dissolving Tablets

Because administration of FDTs is different from administration of conventional tablets, the FDTs should maintain several unique properties, as listed below (V. Dinesh kumar *et al*., 2011).

a) Fast Disintegration

FDTs should disintegrate in the mouth without additional water or with a very small amount (e.g., 1–2 ml) of water. The disintegration fluid is provided by the saliva of the patient. The disintegrated tablet should become a soft paste or liquid suspension, which can provide good mouth feel and smooth swallowing. The "fast disintegration" usually means disintegration of tablets in less than 1 minute, but it is preferred to have disintegration as soon as possible.

b) Taste of Active Ingredients

Because FDTs dissolve or disintegrate in the patient's mouth, the drug will be partial dissolved in close proximity to the taste buds. After swallowing, there should be minimal or no residue in the mouth. A pleasant taste inside the mouth becomes critical for patient acceptance. An ideal taste-masking technology should provide drugs without grittiness and with good mouth feel. The amount of taste masking materials used in the dosage forms should be kept low to avoid excessive increase in tablet size. The taste- masking technology should

c) Drug Properties

For the ideal FDT technology, the drug properties should not significantly affect the tablet property. Many drug properties could potentially affect the performance of FDTs. For example, the solubility, crystal morphology, particle size, hygroscopicity, compressibility, and bulk density of a drug can significantly affect the final tablets characteristics, such as tablet strength and disintegration. The FDT technology should be versatile enough to accommodate unique properties of each drug.

d) Tablet Strength and Porosity

FDTs are designed to have a quick dissolution/disintegration time, the tablet porosity is usually maximized to ensure fast water absorption into the tablets. The key properties of the tablets are fast absorption or wetting of water into the tablets and disintegration of associated particles into individual components for fast dissolution. This requires that excipients should have high wettability, and the tablet structure should also have a highly porous network. Because the strength of a tablet is related to compression pressure, and porosity is inversely related to compression pressure, it is important to find the porosity that allows fast water absorption while maintaining high mechanical strength. In addition, low compression pressure causes fast dissolving dosage forms to be soft, friable, and unsuitable for packaging in conventional blisters or bottles. A strategy to increase tablet mechanical strength without sacrificing tablet porosity or requiring a special packaging to handle fragile tablets should be provided.

e) Moisture Sensitivity

FDTs should have low sensitivity to humidity. This problem can be especially challenging because many highly water-soluble excipients are used in formulation to enhance fast dissolving properties as well as to create good mouth feel. Those highly water-soluble excipients are susceptible to moisture; some will even deliquesce at high humidity. A good package design or other strategy should be created to protect FDTs from various environmental conditions.

f) Ion Exchange Resin

One of the popular approaches in the taste masking of bitter drugs is based on IER. IER are solid and suitably insoluble high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with the surrounding medium. Being high molecular weight water insoluble polymers, the resins are not absorbed by the body and are therefore inert. The long-term safety of IER, even while ingesting large doses as in the use of cholestyramine to reduce cholesterol is an established unique advantage of IER due to the fixed positively or negatively charged functional groups attached to water insoluble polymer backbone. These groups have an affinity for oppositely charged counter ions, thus absorbing the ions into the polymer matrix. Since most drugs possess ionic sites in their molecule, the resin's charge provides a means to loosely bind such drugs and this complex prevents the drug release in the saliva, thus resulting in taste masking. For taste masking purpose weak cation exchange or weak anion exchange resins are used, depending on the nature of drug. The nature of the drug resin complex formed is such that the average pH of and cation concentration of about 40meq/L in the saliva are not able to break the drug resin complex but it is weak enough to break down by hydrochloric acid present in the stomach. Thus the drug resin complex is absolutely tasteless with no after taste, and at the same time,

- **Requirements of Mouth Dissolving Tablets: -** An ideal FDT should
  1) Have a pleasing mouth feel.
  2) Require no water for oral administration, yet dissolve / disperse/ disintegrate in mouth in a matter of seconds.
  3) Have an acceptable taste masking property.
  4) Be harder and less friable
  5) Exhibit low sensitivity to environmental conditions (temperature and humidity).
  6) Allow the manufacture of tablet using conventional processing and packaging Equipment's. (Bhupendra G Prajapadti *et al*., 2009

- **Advantages of Mouth Dissolving Tablets (MDT)**
  1) MDT can be administered to the patients who cannot swallow tablets/cap., such as the elderly, stroke victims, bedridden patients, patients with esophageal problems & patients who refuse to swallow such as pediatric, geriatric & psychiatric patients and thus improves patient compliance.
  2) It contains the certain studies which concluded increased bioavailability and proved rapid absorption of drugs through pregastric absorption of drugs from mouth, pharynx & esophagus as saliva passes down.
  3) MDT is most convenient for disabled, bedridden patients, travelers and busy people, who do not always have access to water.
  4) Good mouth feel property of MDT helps to change the perception of medication.
  5) As bitter pill particularly in pediatric patients.
  6) The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.
  7) MDT opened new business opportunity like product differentiation, product promotion, patent extension and life cycle management.
  8) Suitable during traveling where water may not be available.
  9) No specific packaging required can be packaged in push through blisters.
  10) Cost effective.
  11) Good chemical stability as conventional oral solid dosage form.
  12) New business opportunity like product differentiation, product promotion, patent extension and life style management.
  13) Allow high drug loading.
  14) Provides rapid drug delivery from dosage forms.
  15) Provide advantage of liquid medication in form of solid Preparation.
  16) Rapid drug therapy intervention.No chewing needed.
  17) Adaptable and amenable to existing processing and packaging Machinery.
  18) Rapid onset of action.

- **Disadvantages of MDTs**

1) MDT is hygroscopic in nature so must be keep in dry place.
2) Some time it possesses mouth feeling.
3) It is also shows the fragile, effervescence granules property.
4) MDT requires special packaging for properly stabilization & safety of stable product. (Priyanka Nagar *et al*., 2011)

5. SELECTION OF FDT DRUG CANDIDATES:

Several factors must be considered when selecting drug candidates for delivery as FDT dosage forms.

1) The drugs which have significantly different pharmacokinetic profiles compared with the same dose administered in a conventional dosage. E.g. selegiline, apomorphine, buspirone etc.
2) The drugs that produce a significant amount of toxic metabolites mediated by first pass liver metabolism and gastric metabolism and for drugs that have a substantial fraction of absorption in the oral cavity and segments of the pre-gastric GIT.
3) Drugs having ability to diffuse and partition into the epithelium of the upper GIT (log P > 1, or preferable > 2); and those able to permeate oral mucosal tissue are considered ideal for FDT formulations
4) Patients who concurrently take anticholinergic medications may not be the best candidates for these drugs.
5) Patients with Sjogren's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for FDT formulations.
6) Drugs with a short half-life and frequent dosing.
7) Drugs which are very bitter or otherwise unacceptable taste because taste masking cannot be achieved.
8) Drugs which require controlled or sustained release are unsuitable candidates of fast dissolving oral dosage forms.
9) Pharmaceutical Companies have formulated FDT for various categories of drugs such as neuroleptics, cardiovascular agents, analgesics, antiallergic, antiepileptics, anxiolytics, sedatives, hypnotics, diuretics, anti-parkinsonism agents, anti-bacterial agents and drugs used for erectile dysfunction (Md. Nehal Siddiqui *et al*., 2010).

1. Mechanisms of ODTs

ODTs involve the following mechanisms to achieve the desired fast dissolving characteristics

1) Water must quickly enter into the tablet matrix to cause rapid disintegration and instantaneous dissolution of the tablet.
2) Incorporation of an appropriate disintegrating agent or highly water-soluble excipients in the tablet's formulation.
3) There are some under mentioned mechanisms by which the tablet is broken down into the smaller particles and then subsequently result a solution or suspension of the drug. (Susijit Sahoo *et al*., 2010)

The mechanisms are-

- ✓ High swell ability of disintegration
- ✓ Chemical reaction
- ✓ Capillary action.

Challenges in Formulating ODTS

1) **Palatability**

As most drugs are unpalatable, orally disintegrating drug delivery systems usually contain the medicament in a taste-masked form. Delivery systems disintegrate or dissolve in patient's oral cavity, thus releasing the active ingredients which come in contact with the taste buds; hence, taste-masking of the drugs becomes critical to patient compliance.

2) **Mechanical strength**

In order to allow ODTs to disintegrate in the oral cavity, they are made of either very porous and soft-molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, difficult to handle, and often requiring specialized peel-off blister packing that may add to the cost.

3) **Hygroscopicity**

Several orally disintegrating dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging.

The application of technologies used for ODTs is limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. This parameter is particularly challenging when formulating a fast-dissolving oral films or wafers.

4) **Aqueous solubility**

Water-soluble drugs pose various formulation challenges because they form eutectic

mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process. Such collapse sometimes can be revented by using various matrix-forming excipients such as mannitol than can induce crystallinity and hence, impart rigidity to the amorphous composite.

5) **Size of tablet**

The degree of ease when taking a tablet depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was one larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve.

6) **Rapid disintegration**

MDT is required to disintegrate rapidly in matter of seconds.

7) **Taste and mouth feel characteristics**

Approved sweeteners and flavors are typically included to achieve a palatable formulation, but additional taste masking strategies may also be required such as ion exchange resin and active pharmaceutical ingredient encapsulation.

8) **Avoid increase in size**

The tablet size of the MDT needs to be monitored and is kept small to maintain the characteristic of rapid disintegration.

9) **Good package design**

requirements need to be considered early in the development process to protect MDTs from moisture and other environmental hazards (Jaysuhk J Hirani *et al*., 2009).

6. Excipients Commonly Used For FDT Preparation

It contains an active principle, mixture of excipients comprising at least one disintegrant, a diluent and optionally a swelling agent, a permeabilizing agent, sweeteners and flavorings. The ingredients used are of food grade and helps to impart desired organoleptic properties and product efficacy (Deshmukh Keshav Ram *et al*., 2011).

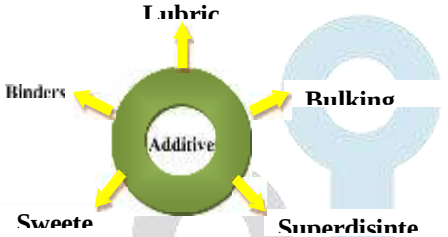


Fig. 3 Additives used in fast dissolving tablet

1. **Super disintegrants**

The basic approach in FDTs is use of disintegrant. Disintegrant play an important role in the disintegration and dissolution of FDT. It is essential to choose a suitable disintegrant, in an optimum concentration, so as to ensure quick disintegration and high dissolution rates. Super disintegrant provide quick disintegration due to combined effect of swelling and water absorption by the formulation. Due to swelling of superdintegrants, the wetted surface of the carrier increases; thus promotes the wettability and dispersibility of the system, thus enhancing the disintegration and dissolution. (Siraj Shaikh *et al*., 2010).

The optimization of tablet disintegration as commonly done by mean of the disintegration critical concentration. Below this concentration the tablet disintegration time is inversely proportional to the disintegrant concentration. Above the critical concentration, the disintegration time remains approximately constant or even increased (Amol V. Patil *et al*., 2011).

Example of some superdintegrants:

1) Croscarmellose sodium (Vivasol, Ac-Di-Sol)
2) Crospovidone (Polyplasdone)
3) Carmellose (NS-300)
4) Sodium starch glycolate (SSG)
5) Indion-414
6) Low substituted Hydroxy propyl cellulose.

2. **Binders**

Proper selection of a binder or combination of binder is essential to maintain integrity and stability of the tablet and to achieve desired sensory and melting characteristics. Binding agent may be liquid**,** semi-solid and slid or mixtures of varying molecules weights. (Deshmukh Keshav Ram et al., 2011)

E.g., cellulosic polymers, povidones, polyvinyl alcohols and acrylic polymers.

3. **Bulking agents**

It improves the textural characteristics that in turn enhance disintegration in mouth. Recommended bulking agents for this delivery system should be more sugar – based such as mannitol, lactitol and starch hydrolysate for higher aqueous solubility and good sensory perception. Bulking agents are added in the range of 10 % to about 90% by weight of the final composition. (Deshmukh Keshav Ram et al., 2011)

4. **Lubricants**

It assists in making tablets palatable and provides quicker disintegration. It removes grittiness and assists in drug transport mechanism from mouth down to stomach.

5. **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 tablets of some active ingredients. Both neutral and synthetic flavors can be used to improve the organoleptic characteristics of FDTs.

Eg: Dextrose, fructose, aspartame, sodium saccharin, sugar alcohols and sucralose.

7. Methodology Employed For Mouth Dissolving Formulations

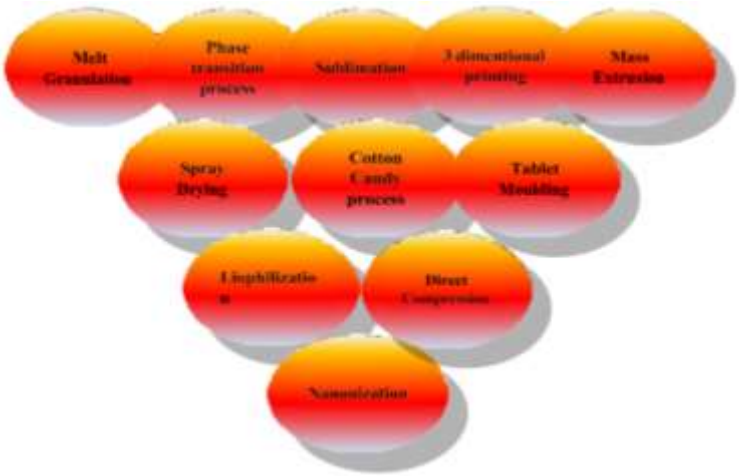


Fig.4 Methodology of Mouth dissolving formulation

1) Melt granulation

Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a meltable binder. The advantage of this technique compared to a conventional granulation is that no water or organic solvents is needed. Because there is no drying step, the process is less time consuming and uses less energy than wet granulation. It is a useful technique to enhance the dissolution rate of poorly water-soluble drugs, such as greseofulvin. This approach to prepare FDT with sufficient mechanical integrity, involves the use of a hydrophilic waxy binder (Superpolystate, PEG - 6 - stearate).

2) Phase transition process

It is concluded that a combination of low and high melting point sugar alcohols, as well as a phase transition in the manufacturing process, are important for making FDTs without any special apparatus. FDT were produced by compressing powder containing erythritol (melting point: 122 °C) and xylitol (melting point: 93 95 °C), and then heating at about 93 °C for 15 min. After heating, the median pore size of the tablets was increased and tablet hardness was also increased. The increase of tablet hardness with heating and storage did not depend on the crystal state of the lower melting point sugar alcohol.

3) *Sublimation*

In this method a subliming material like camphor, is removed by sublimation from compressed tablets and high porosity is achieved due to the formation of many pores where camphor particles previously existed in the compressed tablets prior to sublimation of the camphor. A high porosity was achieved due to the formation of many pores where camphor particles previously existed in the compressed Mannitol tablets prior to sublimation of the camphor. These compressed tablets which have high porosity (approximately 30%) rapidly dissolved within 15 seconds in saliva. Granules containing nimesulide, camphor, Crospovidone, and lactose were prepared by wet granulation technique. Camphor was sublimed from the dried granules by vacuum exposure. Conventional methods like dry granulation, wet granulation and direct compression with highly soluble excipients, superdintegrants and/or effervescent systems can also be used

4) Three-dimensional Printing (3DP)

Three-dimensional printing (3DP) is a rapid prototyping (RP) technology. Prototyping involves constructing specific layers that uses powder processing and liquid binding materials. A novel fast dissolving drug delivery device (DDD) with loose powders in it was fabricated using the three-dimensional printing (3DP) process. Based on computer- aided design models, the DDD containing the drug acetaminophen were prepared automatically by 3DP system. It was found that rapidly disintegrating oral tablets with proper hardness can be prepared using TAG. The rapid disintegration of the TAG tablets seemed due to the rapid water penetration into the tablet resulting from the large pore size and large overall pore volume.

5) Mass Extrusion

This technology involves softening of the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and expulsion of softened mass through the extruder or syringe to get a cylindrical shaped extrude which are finally cut into even segments using heated blade to form tablets. This process can also be used to coat granulesof bitter drugs to mask their taste.

6) Spray Drying

In this technique, gelatin can be used as a supporting agent and as a matrix, Mannitol as a bulking agent and sodium starch glycolate or Croscarmellose or Crospovidone are used as superdisintegrants. Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium. The formulation containedbulking agent like Mannitol and lactose, a superdisintegrants like sodium starch glycolate & Croscarmellose sodium and acidic ingredient (citric acid) and/or alkaline ingredients (e.g. sodium bicarbonate). This spray-dried powder, which compressed into tablets showed rapid disintegration and enhanced dissolution. Maximum drug release and minimumdisintegration time were observed with Kollidon CL excipient base as compared to tablets prepared by direct compression, showing the superiority of the spray dried excipient base technique over direct compression technique.

7) Cotton Candy Process

The Shear form technology is employed in the preparation of a matrix known as ‘floss’, made from a combination of excipients, either alone or with drugs. The floss is a fibrous material similar to cotton-candy fibers, commonly made of saccharides such as sucrose, dextrose, lactose and fructose at temperatures ranging between 180–266 °F. However, other polysaccharides such as polymaltodextrins and polydextrose can be transformed into fibers at 30–40% lower temperature than sucrose.

This modification permits the safe incorporation of thermolabile drugs into the formulation. The tablets manufactured by this process are highly porous in nature and offer very pleasant mouth feel due to fast solubilization of sugars in presence of saliva. The manufacturing process can be divided into four steps as detailed below.

a) Floss Blend

In this step, 80% sucrose in combination with mannitol/dextrose and 1% surfactant is blended to form the floss mix. The surfactant acts as a crystallization enhancer in maintaining the structural integrity of the floss fibers. It also helps in the conversion of amorphous sugar into crystalline form from an outer portion of amorphous sugar mass and subsequently converting the remaining portion of the mass to complete crystalline structure. This process helps to retain the dispersed drug in the matrix, thereby minimizing migration out of the mixture.

b) Floss Processing

The floss formation machine uses flash heat and flash flow processes to produce matrix from the carrier material. The machine is similar to that used in 'cotton-candy' formation which consists of a spinning head and heating elements. In the flash heat process, the heat induces an internal flow condition of the carrier material. This is followed by its exit through the spinning head (2000–3600 rpm) that flings the floss under centrifugal force and draws into long and thin floss fibers, which are usually amorphous in nature.

c) Floss Chopping and Conditioning

This step involves the conversion of fibers into smaller particles in a high shear mixer granulator. The conditioning is performed by partial crystallization through an ethanol treatment (1%) which is sprayed onto the floss and subsequently evaporated to impart improvedflow and cohesive properties to the floss.

d) Blending and Compression

Finally, the chopped and conditioned floss fibers are blended with the drug along with other required excipients and compressed into tablets. In order to improve the mechanical strength of the tablets, a curing step is also carried out which involves the exposure of the dosage forms to elevated temperature and humidity conditions, (40 °C and 85% RH for 15 min). This is expected to cause crystallization of the floss material that results in binding and bridging to improve the structural strength of the dosage form.

8) Tablet Molding

Molding process is of two types' i.e., solvent method and heat method. Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression molding). The solvent is then removed by air-drying. The tablets manufactured in this manner are less compact than compressed tablets and possess a porous structure that hastens dissolution. The heat molding process involves preparation of a suspension that contains a drug, agar and sugar (e.g., mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30°c.

9) Lyophilization or Freeze-Drying

Freeze drying is the process in which water is sublimed from the product after it is frozen.This technique creates an amorphous porous structure that can dissolve rapidly. A typical procedure involved in the manufacturing of ODT using this technique is mentioned here. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. Themixture is done by weight and poured in the walls of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying.

After freeze-drying the aluminum foil backing is applied on a blister-sealing machine. Finally, the blisters are packaged and shipped. The freeze-drying technique has demonstrated improved absorption and increase in bioavailability. The major disadvantages of lyophilization technique are that it is expensive and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions

- **Direct Compression**

Direct compression represents the simplest and most cost-effective tablet manufacturing technique. This technique can now be applied to preparation of ODT because of the availability of improved excipients especially superdisintegrants and sugar-based excipients.

a) Superdisintegrants:

In many orally disintegrating tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration. For the success of fast dissolving tablet, the tablet having quick dissolving property which is achieved by using the super disintegrants,

b) Sugar Based Excipients:

This is another approach to manufacture ODT by direct compression. The use of sugarbased excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing mouthfeel.

- **Nanonization**

Nanonization involves reduction in the particle size of drug to Nano sized by milling thedrug using a proprietary wet-milling technique. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into MDTs. This technique is especially advantageous for poor water-soluble drugs. (A. Guptaet al., 2010).

Tab. 2 : Some of the important patented technologies for preparation of MDTs :

No	*echniques*	*Novelty*	*Advantages*	*Disadvantages*
1	*Zydis*	*First to market, Freeze Dried*	*uick dissolution, Self-preserving and increased bioavailability*	Expensive process, poor stability at higher temperature and humidity
2	*Orasolv*	*Unique taste masking,lightly compressed*	*Taste-masking*	Low mechanicalStrength
3	*Durasolv*	*ompressed dosage form, Proprietary taste*	Dissolution Higher mechanical strength than Oral.e	*Inappropriate withlarger dose*
4	*Flashdose*	Masking Unique spinning mechanism to producea floss- like crystalline structure, much like cotton candy	Good rigidity High surface area for dissolution	High temperature required to melt the matrix can limit the use of heat-sensitive drugs, sensitive to moisture and humidity
5	Flashtab	Compressed dosage form containing drug as microcrystal	Only conventional Tableting Technology	---------
6	Wowtab	Combination of low mouldability and high mouldability saccharides. SMOOTHMELT	Adequate dissolution rate and hardness	significant changein bioavailability
7	Oraquick	ction gives superior mouth feel Uses patented taste	Faster and efficient	-------
8	Ziplet	masking technology Incorporation of water insoluble inorganic excipients for excellent physical performance	production Good mechanical strength satisfactory properties can be obtained at high dose (450 mg) and high weight (850 mg)	As soluble component dissolves, rate of water diffusion in to tablet is decreased because of formation of viscous concentrated solution

- **Materials And Equipments**

Tab. 3 : Material and suppliers

Materials	**Suppliers**
Lomefloxacin HCL	Enaltec Labs, Chennai, India.
Indion-234	Madras Pharmaceuticals, Chennai, India.
Sodium starch glycolate	Octis Research Lab, Uttarkhand, India.
Crospovidone	Octis Research Lab, Uttarkhand, India.
Croscarmellose sodium	Octis Research Lab, Uttarkhand, India.
Microcrystalline cellulose	High purity laboratory chemicals, Mumbai, India.

Mannitol	Universal Scientific Appliances, Madurai, India.
Saccharin sodium	Universal Scientific Appliances, Madurai, India.
Peppermint flavour	Universal Scientific Appliances, Madurai, India.
Magnesium stearate	Universal Scientific Appliances, Madurai, India.

EXPERIMENTAL DETAILS

i. **Calibration Of Lomefloxacin Hcl In Ph5.8**

A) Preparation of pH 5.8 Buffer Solution:

Add 50ml of 0.2M potassium Lomefloxacin HCl in a 200ml of volumetric flask. Add 3.6ml of 0.2M Sodium hydroxide is added and made upto the volume with distilled water.

B) Calibration curve of Lomefloxacin HCl in pH 5.8:

An accurately weighed quantity (100mg) of pure Lomefloxacin HCl is dissolved in sufficient amount of methanol and made upto 100ml with methanol to produce 1mg/ml solution. From this 10ml of the solution is pipetted-out and made upto 100ml with the pH

5.8 buffer solution from this 2-20ml are pipetted-out and diluted to 100ml with the pH 5.8 buffer solution. The solution is scanned within the range of 200-400 nm in UV- Spectrophotometer. The absorbance of the solutions is measured at the λ_{max}. The calibration graph is drawn by taking concentration in X-axis and respective absorbancein Y-axis to get a straight line as per Beers law.

ii. **CALIBRATION OF LOMEFLOXACIN HCL IN 0.1N HYDROCHLORIC ACID**

a) PREPARATION OF 0.1N HYDROCHLORIC ACID BUFFER SOLUTION:

Dilute 8.5ml of hydrochloric acid in distilled water and the volume is made up to 1000 ml.

b) Calibration Curve of Lomefloxacin HCl in 0.1N Hydrochloric Acid:

An accurately weighed quantity (100mg) of pure lomefloxacin is dissolved in sufficient amount of methanol and made upto 100ml with methanol to produce 1mg/ml solution. From this 10ml of the solution is pipetted-out and made upto 100ml with the 0.1N Hydrochloric acid buffer solution. From this 2-20ml are pipetted-out and diluted to 100ml with the 0.1N Hydrochloric acid buffer solution. The solution is scanned withinthe range of 200-400 nm in UV-Spectrophotometer. The absorbances of the solutions are measured at the λ_{max}. The calibration graph is drawn by taking concentration in X- axis and respective absorbance in Y-axis to get a straight line as per Beers law.

iii. **PREPARATION OF DRUG-RESIN COMPLEX(DRC)**

The drug and resin are passed through a #40 mesh screen prior to mixing.The drug Lomefloxacin HCl is dispersed in purified water (100ml) under stirring by using magnetic stirrer at 100rpm in room temperature (25-27˚C).The pH of the drug dispersion is adjusted to pH 6.5 ±0.5 with 2% W/V citric acid solution. The resin is thenadded to the pHadjusted drug dispersion and stirred for 3 hours.The drug resinate dispersion is filtered through whatmann filter paper No;41 and dried at 60˚C.The dried mass is passed through #24 mesh.(Venkata Ramana Retty.S *et al*., 2010)

iv. **SELECTION OF ION-EXCHANGE RESIN(IER)**

The DRC is prepared with two different resins viz INDION-204 and INDION- 234.In each case, 100mg of Lomefloxacin HCl in deionised water is stirred with resin containing various drug-resin ratios(1:1, 1:2, 1:3, 1:4, 1:5) by using magnetic stirrer and stirred for 3 hours at 100 rpm in room temperature.Then the dispersion is filtered through Whatmann filter paper No; 41.The amount of drug loaded is determined indirectly by estimating the amount remaining to be loaded in solution spectrophotometrically at 242 nm in UV-Spectrophotometer. There in to which the drug bound to the maximum percentage is selected for further studies. The following formula is used to calculate the percentage of drug bound to resin.

$$\%Drug\ Bound\ to\ resin = \frac{Total\ amount\ of\ Drug - unbound\ drug}{Total\ amount\ of\ drug}\ X\ 100$$

v. **EVALUATION OF DRUG RESIN COMPLEX**

✓ **Fourier Transform-Infra Red (FT-IR)Studies:**

Lomefloxacin HCl, indion-234 and DRC are subjected to Fourier Transform Infra Red Spectroscopy studies (Shimadzu,Japan).Samples are prepared using KBr disc method and spectra are recorded over the range 400-4000 per cm.Spectra are analyzed for drug-resin interaction and functional groups involved in the complexation process.

✓ **Differential Scanning Colorimetric(DSC) studies:**

A Differential Scanning Calorimeter (DSC Q200 V24.4 Build 116) is used. The equipment is calibrated using indium and zinc. Samples are heated at 10°C per minute in aluminium pans under Nitrogen atmosphere. The onset of the melting points and enthalpies of fusion are calculated. The cell had a nitrogen purge flowing approximately at 30 cube cm per minute. The cell and sample are held isothermally at 79°C for 30 minutes to purge the headspace and sample with nitrogen before heating. The cell and sample are then heated to 400°C while monitoring heat flow.

vi. Formulation Of Fast Dissolving Tablet Of Lomefloxacin Hcl

An accurately weighed quantity of drug-resin complex is mixed with different ratio of (1.5%, 3%, 4.5%, 6%, 7.5%) superdisintegrant (Sodium starch glycolate, Crospovidone, Croscarmellose Sodium). The drug-resin complex along with superdisintegrant is mixed with Microcrystalline cellulose, Mannitol, Saccharin sodium and Peppermint flavour in geometrical dilution. Then Magnesium stearate and Talc are added, mixed and compressed into tablets using single punch tablet punching machine to produce flat faced tablets weighing 200mg each with 8mm diameter. The compositionsof the different formulation are given in Table-14. (Sona P.S. et al., 2011)

vii. Precompression Evaluation For Powder Blend

a) angle of Repose:

The flow characteristics are measured by angle of repose. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane. tan 8=h/r 8=$\tan^{-1}$(h/r)

Where, h=Height of the pile.,r=Radius of the base of the pile,8=Angle of repose.

The angle of repose is determined by fixed funnel method. The powder mass is allowed to flow through the funnel kept on a stand at a fixed height. The powders are carefully poured through the funnel on the piece of paper placed on the horizontal surface until the apex of conical pile just reached the tip of the funnel. The height of the pile and radius of the conical pile is noted and the angle of repose is calculated by the above said formula. (Priyanka Nagar *et al*., 2011)

b) Bulk Density:

Bulk density is defined as the mass of the powder divided by the bulk volume;it is expressed as gm/cm^3. A powder blend (10g) is carefully introduced into a 100ml graduated cylinder. The cylinder is dropped onto a hard wood surface three times from a height of 1 inch at two second interval. The bulk density obtained by dividing the weight of samples in gm by final volume in cm^3 (Mukesh.P.Ratnaparkhi *et al*., 2008).

$$Bulk\ Density = \frac{Mass\ of\ Powder}{Bullk\ Volume}$$

$$a = \frac{m}{Vb}$$

c) Tapped Density:

Tapped density is determined by placing a graduated cylinder, containing a known mass of a drug-resinate excipients blend. The cylinder is allowed to fall under its own weight onto a hard surface from the height of 10cm at 2 second intervals.The tappingis continued until no further change in volume is noted.(Rajashree Panigrahi *et al*., 2010).

The Tapped density (Dt) is calculated in g/ml by the formula

Dt = m/vt

Where, m=Weight of the sample powder taken, Vt =Tapped volume.

d) Carr's Compressibility Index:

The simplex way of measurement of the free flow of powder is compressibility.(Suhas.M.Kakade *et al*., 2010) Which is calculated by the following formula,

$$Carr'sCompressibility = \frac{Tappwed\ Density - Bulk\ Density}{Tapped\ density} X100$$

e) Hausner's Ratio:

Hausner's ratio is an indirect index of ease of powder flow**.** If the Hausner's ratio of the powder is near to 1.25 indicates better powder flow.(Kuldeep V *et al*., 2010). It is calculated by the following formula,

$$Hausner'sRatio = \frac{a}{b}\ x\ 100$$

< 1.25-good flow. 1.25-poor flow.

f) Drug Content:

5mg equivalent of DRC is stirred with 100ml of 0.1N Hydrochloric acid for 60 minutes so as to release the entire drug from DRC. The mixture is filtered and diluted to 100ml using 0.1N Hydrochloric acid. The absorbance of the solution is measured at 242nm using 0.1 N Hydrochloric acid as blank and the content of Lomefloxacin HCl is estimated (Dahima Rashmi *et al*., 2010).

viii. Post Compression Evaluation

a) Thickness and Diameter:

Tablet thickness and diameter is an important characteristic of the tablets.In reproducing appearance and also in counting by using filling equipment. The thickness and diameter of the fast dissolving tablets are determined by using vernier calliper (Magesh Kumar.K *et al*., 2009).

b) Hardness:

The hardness of the tablet is indicative of its tensile strength and is measured in terms of load/pressure required to crush it when placed on its edge.The hardness is a function of physical properties of granules like their hardness and deformation under load, binders and above all the compression force. The hardness has influence on disintegration and dissolution times and is as such a factor that may affect bioavailability. The hardness of the tablet is determined by using Monsanto hardness tester. (Puttewar T.Y *et al*., 2010)

c) Weight Variation Test:

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. First the total weight of 20 tablets from each formulation is determined and the average is calculated. The individual weight of the each tablet is also determined to find out the weight variation. The tablets meets the USP test , If no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limits.(Priyanka Nagar *et al.*, 2011)

d) In-Vitro Dissolution Test:

The release rate of desloratadine from the fast-dissolving tablet is determined using dissolution testing apparatus type -1(paddle method). The dissolution test is performed using 900ml of 0.1N HCL, at 37 ±0.5°Cand 50 rpm.A sample (5ml) of the solution is withdrawn from the dissolution apparatus at 5,10,15,20,25,30 min.The samples are replaced with fresh dissolution medium of same quantity.The absorbance of these solutions is measured at 242 nm in UV-Spectrophotometer(Parmar R.B *et al.*, 2009).

- RESULTS AND DISCUSSION

1. Calibration of Lomefloxacin Hcl In Ph 5.8

The λ_{max} of Lomefloxacin HCl was determined by scanning the 10µg/ml solution of the drug in buffer solution of pH 5.8 using UV-Spectrophotometer and was found to be 242nm. A standard calibration curve for the drug was obtained by measuring absorbance at 242 nm and by plotting the graph of absorbance Vs concentration. The calibration plots of Lomefloxacin HCl were shown in Table-11 and Figure-5. The linear correlation co- efficient was found to be y =0.9997. Lomefloxacin HCl obeys Beer's law within the concentration range of 2-20 µg/ml

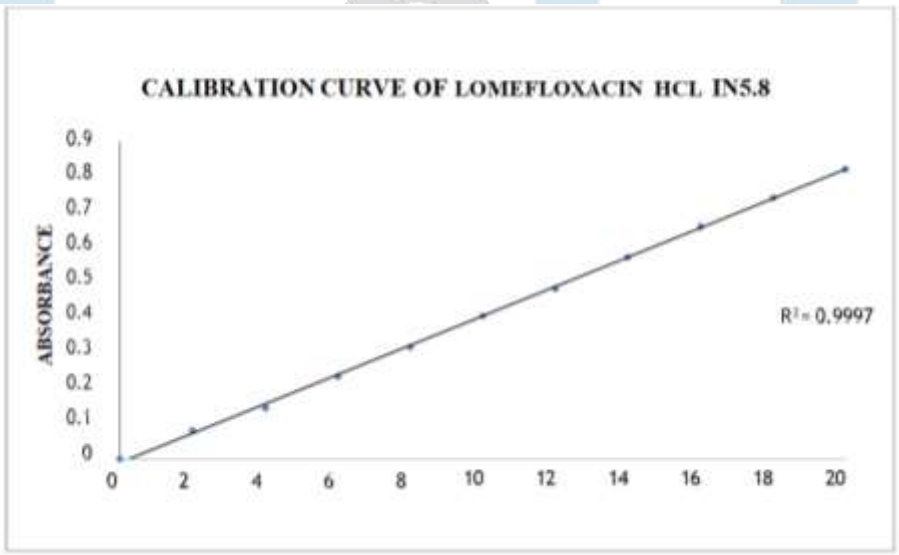


Fig.5 : calibration curve of lomefloxacin HCl in5.8 pH 5.8

2. Calculation Table

Table 4: : Calibrations of Lomefloxacin Hcl In Ph 5.8

Sr. No	Concentration in µgm/ml	Absorbance (Avg ± SD)
1	2	0.081 ± 0.0021
2	4	0.144 ± 0.0018
3	6	0.233 ± 0.0026
4	8	0.317 ± 0.0016
5	10	0.406 ± 0.0038
6	412	0.482 ± 0.0041
7	14	0.573 ± 0.0054
8	16	0.660 ± 0.0024
9	18	0.741 ± 0.0012
10	20	0.823 ± 0.0047
		R^2 0.9997

3. Calibration of Lomefloxacin Hcl In 0.1n Hydrochloric acid

The λ_{max} of Lomefloxacin HCl was determined by scanning the 10µg/ml solution of the drug in buffer solution of 0.1N Hydrochloric acid using UV-Spectrophotometer and was found to be 242 nm. A standard calibration curve for the drug was obtained by measuring absorbance at 242 nm and by plotting the graph of absorbance Vs concentration. The calibration plots of Lomefloxacin HCl were shown in Table- 12 and Figure- 6. The linear correlation co-efficient was found to be y =0.9996. Lomefloxacin HCl obeys Beer's law within the concentration range of 2-20 µg/ml.

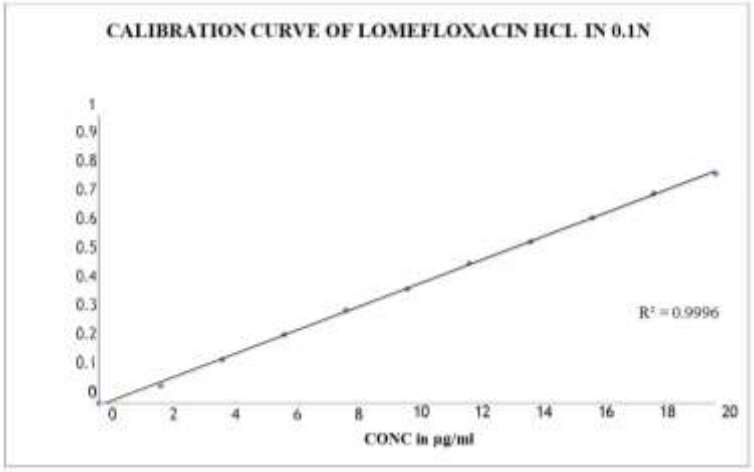


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Fig 6. Calibration curve of lomefloxacin HCl in 0.1N HCl

4. Calibration Of Lomefloxacin

TABLE 5 : CALIBRATION OF LOMEFLOXACIN HCL IN 0.1N HYDROCHLORIC ACID

Sr. No	Concentration in µgm/ml	Absorbance (Avg ± SD)
1	2	0.060 ± 0.0009
2	4	0.152 ± 0.0008
3	6	0.239 ± 0.0006
4	8	0.323 ± 0.0012
5	10	0.397 ± 0.0012
6	12	0.488 ± 0.0008
7	14	0.562 ± 0.0008
8	16	0.643 ± 0.0012
9	18	0.728 ± 0.0004
10	20	0.798 ± 0.0004
		R^2 0.9996

5. Preparation Of Drug Resin Complex (Drc)

The DRC was prepared with two different resins viz Indion-204 and Indion-234.From the trial, it was found that the Indion-234 resin had maximum percentage drug bound to resin. And so, Indion-234 was selected for the preparation of drug resincomplex. The results were shown in Table-13. (Venkada Ramana Retty.S *et al*., 2010)

TABLE 6 : LOMEFLOXACIN HCL -INDION 234, 204 DRUG RESIN COMPLEX 56

Lomefloxacin hcl -indion 234 drug resin complex		
S.No	**Drug-resin ratio**	**% of drug bound to Resin (average ± s.d)**
1	1:1	58.93 ± 1.66
2	1:2	64.89 ± 1.18
3	1:3	61.31 ± 0.32
4	1:4	65.53 ± 2.54
5	1:5	61.59 ± 3.34

Lomefloxacin HCL indion 204 drug- resins complex		
s.no	**drug-resin ratio**	**% of drug bound to resin (average ±s.d)**
1	1:1	76.66 ± 0.68
2	1:2	74.11 ± 0.73
3	1:3	85.25 ± .049
4	1:4	85.96 ± 1.17
5	1:5	88.19 ± 0.68

6. Selection Of Ion Exchange Resin (Ier)

From the trial, the complex which had maximum quantity of drug loading was selected for further studies. It was found that the maximum percentage drug bound to resin for the Indion-204 is 65.53 ± 2.54 % at the ratio of 1:5 and 88.19 ± 0.68 % of drug bound to resin for Indion-234 at the ratio of 1:5. And so, Indion-234 was selected as the best resin for formulating drug-resin complex. The results were shown in Table-13 (Venkata Ramana Retty.S *et al.*, 2010)

7. Evaluation Of Drug Resin Complex

Fourier Transform-Infra Red (FT-IR)Studies:

The Fourier Transform Infra Red Spectroscopy studies were carried out for pure drug, resin, physical mixture of drug-resin and drug-resin complex. The spectra were shown in Figure-7.The spectral analysis of pure drug showed the characteristics peaks at 3423.76cm-^{1} , 3325.39cm-^{1}, 1327.07cm-^{1}, 1292.35cm-^{1}, 844.85 cm-^{1}, 773.48 cm^{-1}.All the above characteristic peaks appear in the spectra of all samples were within the same wavelength number. This indicates that there were no interactions between the drug and resin

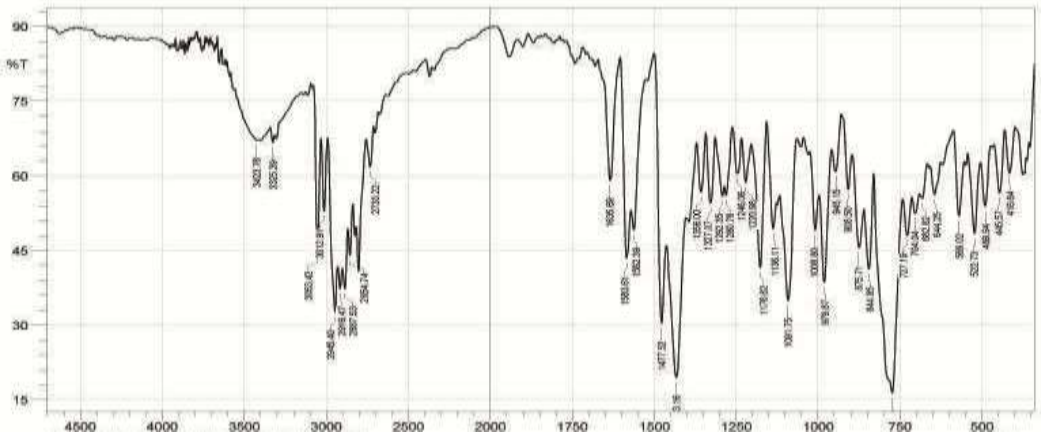

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Fig. 7: ftir spectra drug

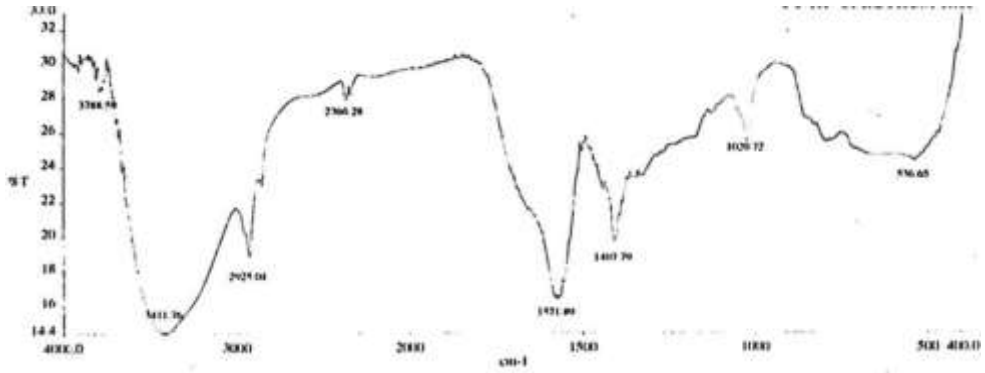

Fig 8.: indion 234

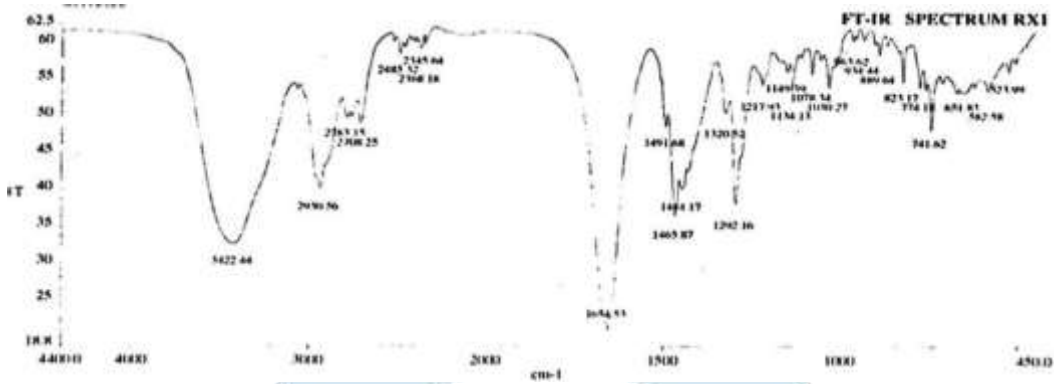

Fig. 9 DRC

Differential Scanning Colorimetric (DSC) Studies:

The DSC thermograms of pure drug, resin, drug-resin complex were shown in the Figure-11. An endothermic peak corresponding to the melting point of pure drug was prominent in the drug-resin complex which suggested clearly that there was no interactionbetween drug, resin and drug-resin complex

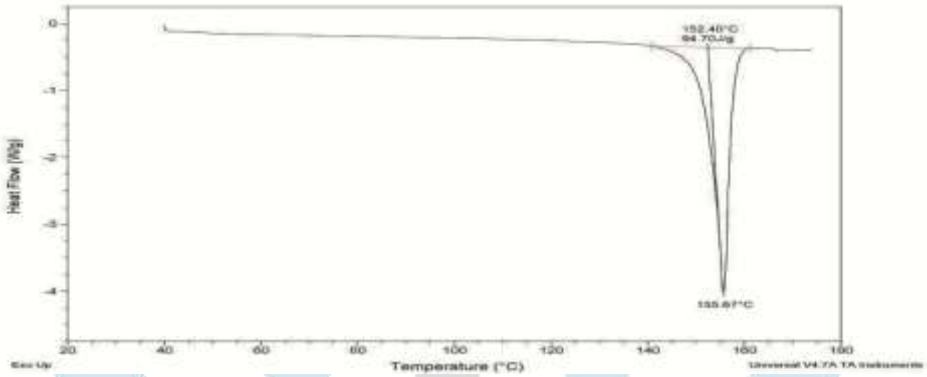

Fig. 10 DSC Thermogram OF Drug

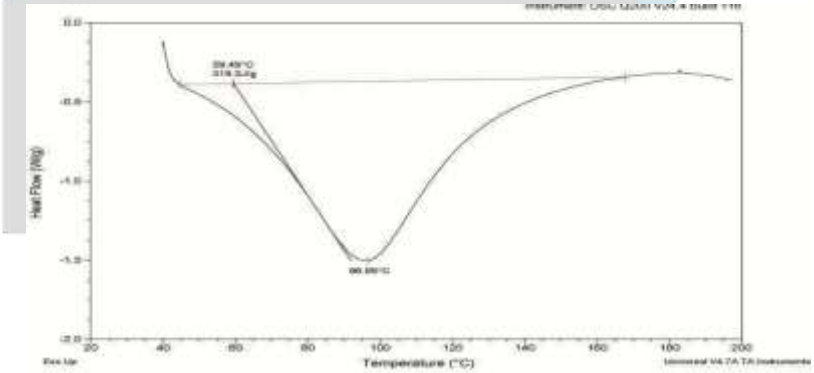

Fig. 11 DSC Thermogram OF INDION 234

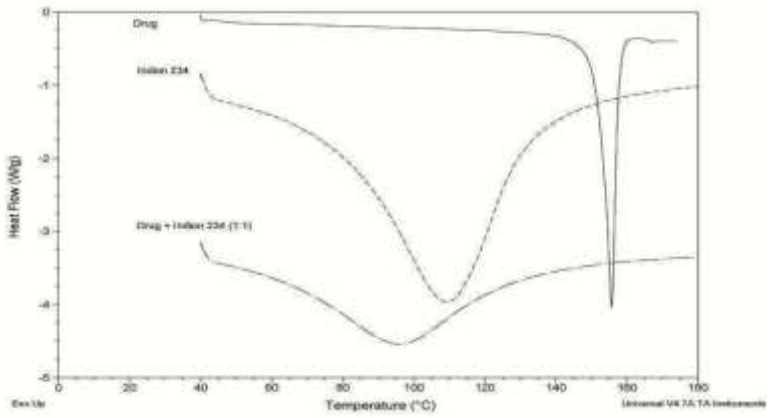

Fig.12 DSC Thermogram of DRC

- Summary **And Conclusion**

Lomefloxacin HCl is a quinolone, a N-arylpiperazine, a quinolinemono carboxylic acid, a quinolone antibiotic and a fluoroquinolone antibitotic. It used to treat bacterial infections including bronchitis and urinary tract infections. Fast mouth dissolving tablets are gaining prominence as a new drug delivery system, which disintegrate or dissolve in the oral cavity within a minute without the need of water or chewing. In the present study, an attempt has been made to prepare bitter less fast dissolving of Lomefloxacin HCl with good mouth feel so as to prepare a "patient- friendly dosage form".

The drug is dispersed in purified water under stirring at 100rpm in room temperature. The pH of the drug dispersion is adjusted to PH 6.5± 0.5 with 2% citric acid solution. The resin is then added to the pH adjusted drug dispersion and stirred for 3 hours. The dispersion is filtered through whatman filter paper NO; 41.

The DRC is formed with two resins (INDION-204, INDION-234). In each case 100mg of drug in deionised water is stirred with resin containing various drug-resin ratio (1:1, 1:2, 1:3, 1:4, 1;5) by using magnetic stirrer. Then the dispersion is filtered through whatman filter paper NO; 41. The amount of drug loaded is determined indirectly by estimating the amount remaining to be loaded in solution spectrometrically at 242 nm in UV-Spectrophotometer. The resin to which the drug bound to maximum percentage is selected for further studies.

An accurately weighed quantity of DRC is mixed with different ratio (1.5%, 3%, 4.5%, 6% and 7.5%) of super disintegrants (CCS, CP, SSG). The drug resin complex along with MCC, Mannitol, Saccharin sodium and Peppermint flavor in geometrical dilution. Then Magnesium stearate and Talc were added, mixed and compressed into tablets using single punch tablet punching machine. Disintegration time is measured in 900ml of artificial Saliva (PH 5.8) at 37± 0.5°C. The disintegration time of 3 tablets are recorded and the average is reported.

Dissolution test is determined by USP dissolution testing apparatus type- 2(paddle method). It is performed using 900ml of 0.1N Hydrochloric acid at 37± 0.5°C and 50 rpm. A 5ml sample solution is withdrawn from the dissolution apparatus at 5, 10, 15, 20, 25 and 30 minutes. The samples are replaced with fresh dissolution medium of same quantity. The absorbance of the solution is measured at 242 nm in UV- Spectrophotometer.

Indion-234 resin was selected for the preparation of DRC (1:5). The maximum drug loading found to be 88.19±0.68%. The disintegration time of the tablets decreased with increase in concentration of super disintegrants. The faster disintegration effect of crospovidone tablets may be attributed to its rapid capillary activity and pronounced hydrating with little tendency to gel formation. The fast-dissolving tablet formulations were subjected to precompression and post compression parameter and the results were found to be within the acceptable limits. *In vitro* dissolution studies of the all formulation showed more than 90% drug release within 10 minutes. The maximum increase in the dissolution rate was observed with 7.5% Crospovidone (F-10) amongst all formulation 97.12 ± 0.37% release was occurring within 10 minutes. F-10 was found to be best formulation as this showed less disintegration time and more drugrelease.

- ***Conclusion:***

Use of cation exchange resins offers good method for preparing bitterless Lomefloxacin HCl formulation using drug-resin complex. Fast mouth dissolving tablets of Lomefloxacin HCl can be successfully prepared by Sublimation method using selected superdisintegrants in order to improve disintegration/dissolution of the drug in oral cavity and hence better patient compliance and effective therapy.

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