# FORMULATION DEVELOPMENT AND EVALUATION OF METOCLOPRAMIDE HYDROCHLORIDE MEDICATED HARD CANDY LOZENGES

A Dissertation submitted to

THE TAMIL NADU Dr. M.G.R MEDICAL UNIVERSITY

CHENNAI – 600 032

in partial fulfillment of the requirements for the award of degree of

**MASTER OF PHARMACY**
**IN**
**PHARMACEUTICS**


**Submitted by**

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**Under the guidance of**

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**CHENNAI – 600 003**


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**DEPARTMENT OF PHARMACEUTICS**
**COLLEGE OF PHARMACY**
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**CHENNAI-600 003**
**TAMILNADU**


**DATE:**

## CERTIFICATE

This is to certify that the dissertation entitled **"FORMULATION DEVELOPMENT AND EVALUATION OF METOCLOPRAMIDE HYDROCHLORIDE MEDICATED HARD CANDY LOZENGES"** submitted by **S.NITHYA** with **Register No.261711253** to The Tamil Nadu Dr. M.G.R. Medical University examinations is evaluated.

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## ABBREVIATIONS AND SYMBOLS

| | |
|---|---|
| API | Active Pharmaceutical Ingredients |
| FT-IR | Fourier Transform Infra Red |
| IP | Indian Pharmacopoeia |
| Ph.Eur | European Pharmacopoeia |
| NF | National formulary |
| BP | British Pharmacopoeia |
| USP | United states Pharmacopoeia |
| BCS | Biopharmaceutical classification system |
| GIT | Gastro intestinal tract |
| PEG | Poly ethylene glycol |
| PG | Propylene glycol |
| IR | Infra Red |
| NC | No Change |
| NTS | Nucleus tractus solitarius |
| ENS | Enteric nervous system |
| CB1 | Cannabinoid receptors |
| VC | Vomiting centre |
| CTZ | Chemoreceptor trigger zone |
| HT | Hydroxytryptamine receptor |
| D2 | Dopamine 2 receptor |
| NK 1 | Neurokinin receptor 1 |
| PAN | Primary afferent neurons |
| PONV | Postoperative nausea and vomiting |
| H1 | Histamine H1 receptor |
| g | Gram |
| HCL | Hydrochloride |
| RH | Relative Humidity |
| Rpm | Revolution Per Minute |

| | |
|---|---|
| S.D | Standard Deviation |
| % | Percentage |
| $^{0}$ | Degree |
| $^{0}$c | Degree Celsius |
| Cm | Centi Meter |
| Cum. | Cumulative |
| λ | Lambda |
| H | Hours |
| L | Litre |
| M.W | Molecular Weight |
| Mg | Milli Gram |
| Min. | Minutes |
| Mm | Milli Meter |
| Sec. | Seconds |
| µg | Micro gram |

# *INTRODUCTION*

# 1. INTRODUCTION

## 1.1 INTRODUCTION

Oral drug delivery is the most favoured route of administration of various medications and tablets are the most widely accepted dosage form. Solid dosage forms are popular because of the ease of administration, accurate dosage, self medication, pain avoidance, and most importantly patient compliance. [1]

A drug can be administered via a many different routes to produce a systemic pharmacological effect. The most common method of drug administration is via per oral route in which the drug is swallowed and enters the systemic circulation primarily through the membrane of the small intestine. The parenteral route is not routinely used for self-administration of medication. It is probable that at least 90% of all drugs used to produce systemic effects are administered by the oral route.

Absorption of drugs after oral administration may occur at the various body sites between the mouth and rectum. In general, the higher up a drug is absorbed along the alimentary tract, the more rapid will be its action, a desirable feature in most instances. A drug taken orally must withstand large fluctuation in pH as it travels along the gastrointestinal tract, as well as resist the onslaught of the enzymes that digest food and metabolism by micro flora that live there. It is estimated that 25% of the population finds it difficult to swallow tablets and capsules and therefore do not take their medication as prescribed by their doctor resulting in high incidence of non-compliance and ineffective therapy.

Difficulty is experienced in particular by pediatrics and geriatric patients, but it also applies to people who are ill bedridden and to those active working patient who are busy or travelling, especially those who have no access to water. In these cases oral mucosal drug delivery is most preferred [2].

Several mucosal surfaces have been investigated as delivery routes including nasal, rectal, vaginal, ocular and oral. The level of keratinisation in mucous membranes and therefore the permeability barrier is not as extensive as the skin's stratum corneum. The oral mucosa, depending on the site, is between 4 and 4000 times more permeable compared to the skin.

Mucosal delivery sites have the advantage of delivering drugs directly into the systemic circulation and avoiding first pass drug metabolism in the liver and pre-systemic elimination of the drug in the gastrointestinal tract. [3]

## 1.2 ORAL MUCOSAL DRUG DELIVERY

Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectable and enteral methods and also enhances drug bioavailability because the mucosal surfaces are usually rich in blood supply, providing the means for rapid drug transport to the systemic circulation and avoiding, in most cases, degradation by first-pass hepatic metabolism. The systems contact with the absorption surface resulting in a better absorption, and also prolong residence time at the site of application to permit once or twice daily dosing. For some drugs, this results in rapid onset of action via a more comfortable and convenient delivery route than the intravenous route. The clinical need for oral transmucosal delivery of a drug must be high enough to offset the high costs associated with developing this type of product. Transmucosal products are a relatively new drug delivery [4]

Within the oral mucosal cavity, delivery of drugs can be categorised into three classes:

- Buccal delivery
- Sublingual drug delivery
- Local drug delivery

**Buccal drug delivery:** Buccal drug delivery is drug administration over the mucosal membranes lining the cheeks (Buccal mucosa).

**Sublingual drug delivery**: Sublingual drug delivery is systemic delivery of drugs through the mucosal membranes lining the surface of the mouth.

**Local drug delivery:** Local drug delivery is drug delivery among the oral cavity.[5]

### 1.2.1 Structural Features of Oral Mucosa:

**Anatomy and physiology of oral cavity:**

The oral cavity has distinct areas: (Fig.1.1)

- The floor of mouth (sublingual)
- The buccal area (Cheeks)
- The gums (Gingival)
- The palatal region (Hard palate and soft palate) [6]

The buccal and sublingual are commonly used routes for producing local or systemic effects. It has been known that buccal and sublingual administration drug

solutes are rapidly absorbed into the reticulated vein, which lies underneath the oral mucosa and transported through the facial veins, internal juglar vein, and braciocephalic vein and are then drained into the systemic circulation. Therefore the buccal and sublingual routes of administration can be utilized to bypass the hepatic first-pass elimination of drugs. Within the oral mucosal cavity, the buccal region offers an attractive route of administration for systemic drug delivery. The mucosa has a rich blood supply and it is relatively permeable. The oral cavity is highly acceptable by patients, the mucosa is relatively permeable with a rich blood supply and the virtual lack of langerhans cells makes the oral mucosa tolerant to potential allergens.

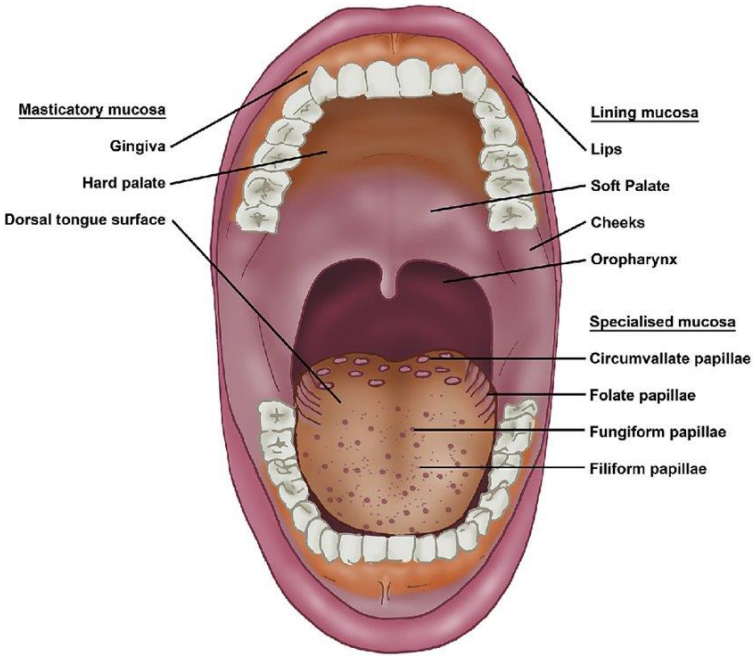



**Fig.1.1.Oral cavity structure**

### 1.2.2 Buccal mucosa Structure:

The total area of the oral cavity is about 100 $cm^2$. Out of this about one third is the buccal surface, which is lined with an epithelium of about 0.5mm thickness. The keratinized and non keratinized regions of the oral epithelium differ from each other in terms of lipid composition of the cells. The keratinized epithelium has predominantly neutral lipids (e.g., Ceramides) while the non keratinized epithelium has few but polar lipids, particularly cholesterol sulphate and glucosylceramides.

Buccal membrane has numerous elastic fibers in the dermis, which is another barrier for diffusion of drug across the buccal membrane. Drug that penetrates this

membrane enters the systemic circulation via network of capillaries and arteries. The lymphatic drainage almost runs parallel to the venous vascularization and ends up in the jugular ducts. The oral mucosal surface is constantly washed by the saliva.

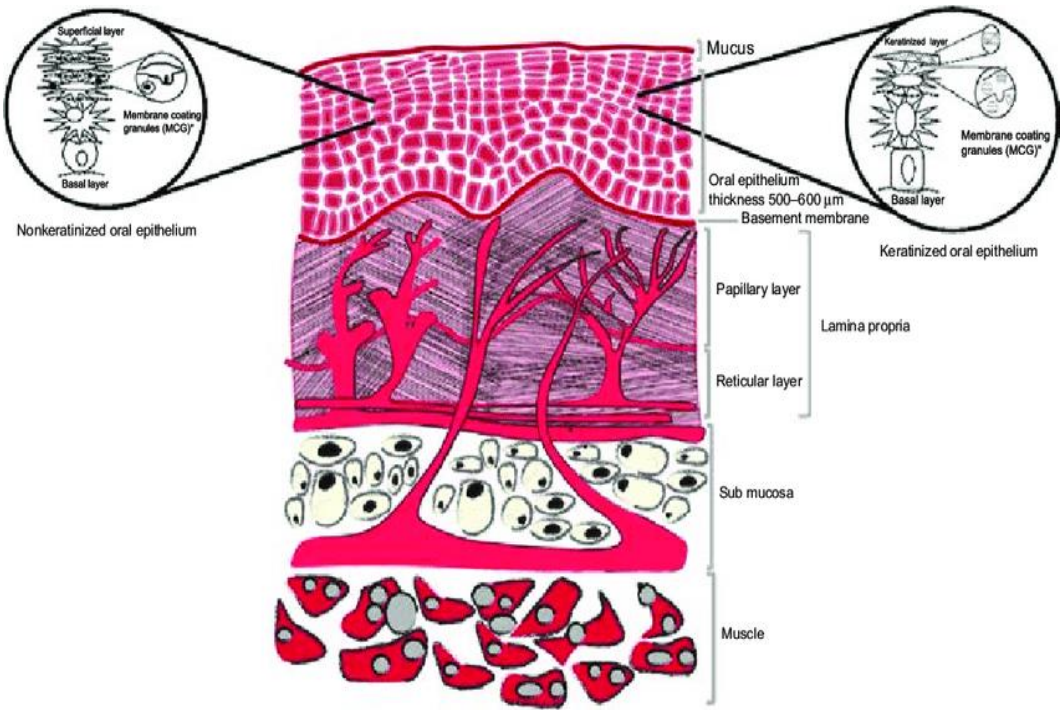



**Fig.1.2. Mucus membrane**

The drug absorption across the oral mucosa occurs in the non-keratinized sections for protein/peptide delivery buccal route offers distinct benefits over other mucosal routes like nasal, vaginal, rectal, etc. [2]

The cells of the oral epithelia are surrounded by an intercellular ground substance, mucus, the principle components of which are complexes made up of proteins and carbohydrates. These complexes may be free of association or some maybe attached to certain regions on the cell surfaces. This matrix may actually play a role in cell-cell adhesion, as well as acting as a lubricant, allowing cells to move relative to one another. [7]

### 1.2.3 Environmental Factors:

**Saliva:**

The thin film of saliva coats throughout the lining of buccal mucosa and is called salivary pellicle or film. The thickness of salivary film is 0.07 to 0.10 mm. The thickness, composition and movement of this film effects buccal absorption.

**Salivary glands:**

The minor salivary glands are located in epithelial or deep epithelial region of buccal mucosa. They constantly secrete mucus on surface of buccal mucosa. Although, mucus helps to retain mucoadhesive dosage forms, it is potential barrier to drug penetration

**Movement of oral tissues:**

Buccal region of oral cavity shows less active movements. The mucoadhesive polymers are to be incorporated to keep dosage form at buccal region for long periods while withstanding tissue movements during talking and if possible during eating food or swallowing. [8]

**Mucus membrane:**

The surface of the mucous membrane is constantly washed by a stream of about 0.5 to 2 L of saliva daily produced in the salivary glands. The chief secretion is supplied by three pairs of glands, namely, the parotid, the sub maxillary, and the sublingual glands. Minor salivary glands are situated in the buccal, palatal, and retro molar regions of the oral cavity.

The presence of saliva in the mouth is important for two main reasons:

a) Drug permeation across moist (mucous) membranes occurs much readily than across non-mucous membranes; compared to drug absorption across the GI tract and skin.

b) Drugs are commonly administered to the mouth in the clinical setting in a solid form. The drug must therefore first dissolve in saliva before it can be absorbed across the oral mucosa.

**1.2.4. Vascular system of the oral mucosa**

**Table No. 1.1 Blood flow in the various regions of the oral mucosa**

| Tissue | Blood flow ml / min / 100 cm2 |
|---|---|
| Buccal | 2.40 |
| Sublingual | 3.14 |
| Floor of mouth | 0.97 |
| Ventral Tongue | 1.17 |
| Frenulum | 1.00 |
| Gingival | 1.47 |
| Palatal | 0.89 |

The mucous membranes of the buccal cavity have a highly vascular nature, and drugs diffusing across the membranes have easy access to the systemic circulation via the internal jugular vein. The blood supply to the mouth is delivered principally via the external carotid artery. The maxillary artery is the major branch, and the two minor branches are the lingual and facial arteries. The lingual artery and its branch, the sublingual artery, supply the tongue, the floor of the mouth, and the gingiva and the facial artery supplies blood to the lips and soft palate. The maxillary artery supplies the main cheek, hard palate, and the maxillary and mandibular gingiva. The internal jugular vein eventually receives almost all the blood derived from the mouth and pharynx.

**Characteristics of mucus**

The composition of mucus varies widely depending on animal species, anatomical location and whether the tissue is in a normal or pathological state. Native mucin, in addition to mucus, also contains water, electrolytes, sloughed epithelial cells, enzymes, bacteria, bacterial by products and other debris. The glycoprotein fraction of the mucus imparts a viscous gel like characteristic to mucus due to its water retention capacity.

Mucus is a glycoprotein, chemically consisting of a large peptide backbone with pendant oligosaccharide side chains whose terminal end is either sialic or sulfonic acid or L–fructose. The oligosaccharide chains are covalently linked to the hydroxy amino acids, serine and threonine, along the polypeptide backbone.

About 25% of the polypeptide backbone is without sugars, the so called ‘naked’ protein region, which is especially prone to enzymatic cleavage. The remaining 75% of the backbone is heavily glycosylated. The terminal sialic groups have a pKa value of 2.6 so that the mucin molecule should be viewed as a polyelectrolyte under neutral or acid condition. At physiological pH the mucin network may carry a significant negative charge because of the presence of a primary function of the oral mucosa is to provide a barrier. At the same time, the oral mucosa shares with the gut the ability to maintain a moist surface. The permeability of the oral mucosa in general is probably intermediate between that of the epidermis and that of the intestinal mucosa. [15]

**Functions of Mucus Layer**

**Protective:** Resulting particularly from its hydrophobicity.

**Adhesion:** Mucus has strong cohesion properties.

**Barrier:** The role of the mucus layer as a barrier in tissue absorption of the drugs and influence the bioavailability.

**Lubrication:** Mucus from the goblet cell is necessary to compensate for the removal of the mucus layer due to digestion, bacterial degradation and solubilization of mucin molecule.[1]

## 1.3 DESIGNING A ORAL MUCOSAL DRUG DELIVERY SYSTEM

### 1.3.1 Permeability of the oral mucosa

The oral mucosa is a squamous cell epithelium comprised of highly proliferating basal keratinocytes which replenish the overlying epithelial cells which differentiate and eventually shed as the cells become more superficial Fig (1.3). The permeability barrier is responsible for preventing exogenous and endogenous materials from entering the body across the oral mucosa and prevents loss of fluid from the underlying tissues to the environment. The permeability barrier is comprised predominantly of the lipid content of the upper layers of the epithelium. As supra-basal cells differentiate they form strong intercellular desmosomal junctions and form membrane coating granules on their apical surfaces. [10, 11]

These membrane coating granules release lipophilic material into the intercellular spaces to ensure epithelial cohesion. This lipophilic material slows the passage of hydrophilic materials across the epithelium.[12] It has also been hypothesised that tight junctions may play a role in permeability barrier function however these are not commonly found in the oral epithelium.

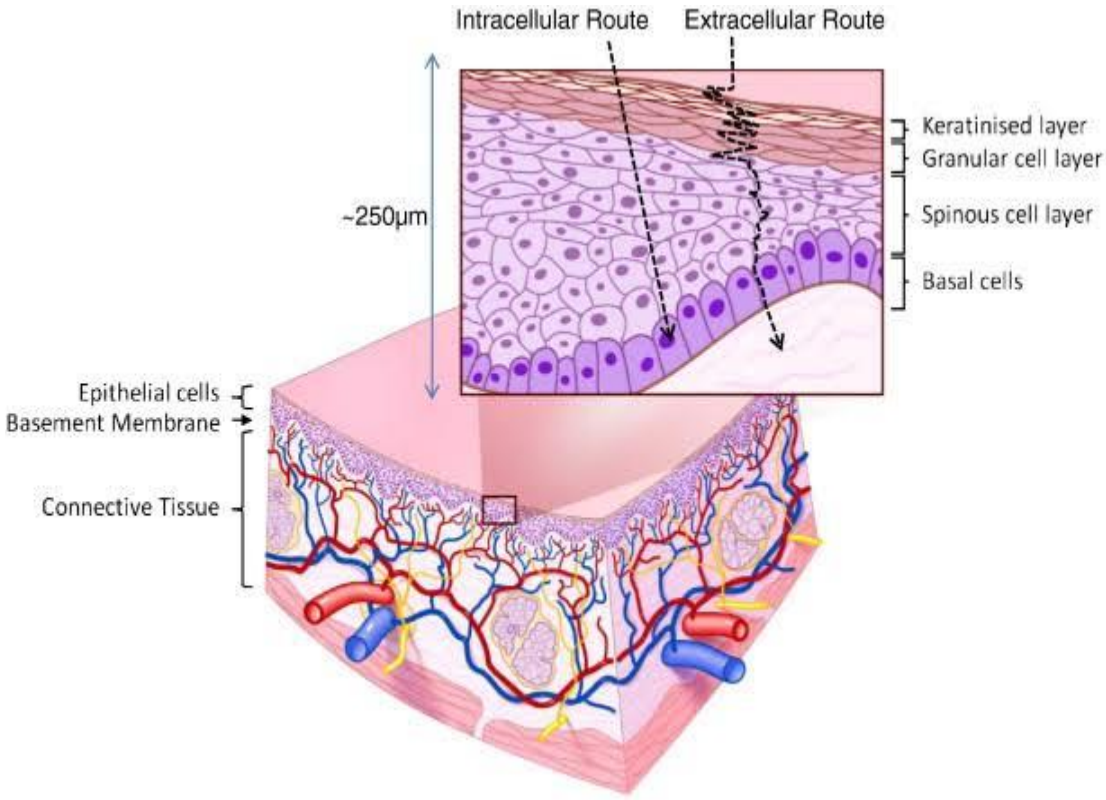



**Fig .1.3 Structure of the Oral Mucosa**

The epithelium is the major barrier to permeability with the connective tissue providing some resistance to lipophilic materials due to the connective tissues high level of hydration. There is variation in permeability across different regions of the oral mucosa due to the differing thickness of the epithelium and degree of keratinisation at different sites. Keratinised tissues display a lower permeability than non-keratinised tissues, this is however due to the lipid composition of the membrane coating granules in the keratinised vs. non-keratinised tissues rather than the presence of keratin itself .The degree of permeability is least in keratinised gingiva followed by the buccal mucosa with the most easily permeated area of the oral mucosa being the sublingual mucosa. [4]

### 1.3.2 Absorption via buccal mucosa:

There are two permeation pathways for passive drug transport across the oral mucosa:

- Para cellular
- Tran cellular

Permeants can use these two routes simultaneously, but one route is usually preferred over the other depending on the physicochemical properties of the diffusant.

Since the intercellular spaces and cytoplasm are hydrophilic in character, lipophilic compounds would have low solubilities in this environment. The cell membrane, however, is rather lipophilic in nature and hydrophilic solutes will have difficulty permeating through the cell membrane due to a low partition coefficient. Therefore, the intercellular spaces pose as the major barrier to permeation of lipophilic compounds and the cell membrane acts as the major transport barrier for hydrophilic compounds. Since the oral epithelium is stratified, solute permeation may involve a combination of these two routes. [9]

Drug absorption via the oral mucosa is a passive diffusion process. By simplifying the oral mucosa into a hydrophobic membrane, Fick's first law can be used to describe the drug absorption process. Parameters such as diffusion coefficient, partition coefficient and thickness of the tissue are inherent properties of the drug and the mucosa. Other parameters, such as surface area, duration of drug delivery and concentration are controlled by the dosage form and formulation. Free drug concentration is a key issue in terms of developing transmucosal drug delivery dosage forms. [13]

## 1.4. ADVANTAGES OF THE ORAL CAVITY AS A SITE FOR DRUG DELIVERY

- **Accessibility**- The different sites in the oral cavity are easily accessible.
- **Administration** -The ease of accessibility referred to above means oral mucosal drug delivery systems are easy to administer.
- **Removal** - The ease of administration is matched by the ease of removal.
- **Patient acceptability**- Highly acceptable site for drug delivery by the patient
- **First-pass effect** - The oral mucosa is a well vascularised tissue and the blood vessels drain directly into the jugular vein.
- **Avoidance of gastrointestinal tract environment**- Drugs absorbed across oral mucosa directly into the systemic circulation.
- **Enzymatic barriers** - The buccal mucosa provides an environment with reduced peptidase and protease activity.
- **Microenvironment**- The microenvironment of a dosage form placed in the oral cavity can directly and easily be modified.

- **Cellular turnover time** - The cellular turnover time of the oral mucosa is estimated to be 4–14 days. This is intermediate between the slow turnover rate of the skin and the fast gastrointestinal rate.

## 1.5. LIMITATIONS:

- **Membrane permeability**- In general, oral cavity mucosa shows low permeability to drugs.
- **Surface area**- The surface area of the oral cavity is small; it is approximately 214 $cm^{2.}$ .
- **Saliva**- Saliva is continually secreted into the oral cavity from major and minor salivary glands.
- **Swallowing** - Salivation leads to swallowing which effectively removes drug from the target site of absorption.
- **Taste receptors** - The tongue contains taste receptors that may present difficulties to patients and decrease compliance with drugs that are bitter.
- **Membrane Flexibility**- Some of the oral mucosa (e.g. sublingual and buccal mucosa) is flexible and flexes as a consequence of normal functions of the mouth (e.g. speaking, chewing or swallowing). This may adversely affect the dosage form.
- **Choking hazard**- Involuntarily swallowing of the delivery system could lead to Choking.
- **Inconvenience**- A buccal delivery system may cause inconvenience to the patient when they are eating or drinking.
- **Tissue irritation**- For some drugs, tissue irritation may arise following the use of an oral mucosal drug delivery System.
- **Drug candidates** - Drug candidate list is small.

## 1.6. INFLUENCE OF DRUG PROPERTIES ON ORAL MUCOSAL DRUG DELIVERY

The physicochemical properties of the drug play a crucial role in the design and formulation of an oral mucosal drug delivery system. It is of paramount importance that the physicochemical properties of the drug are characterized in order to allow for initial selection and subsequent formulation into an oral mucosal drug delivery system.

### 1.6.1. Desirable drug physicochemical properties for formulation of an oral mucosal drug delivery system [14]

**Table No 1.2. Formulation considerations**

| FORMULATION CONSIDERATIONS | IDEAL LIMITS |
|---|---|
| Aqueous solubility | > 1 mg/ml |
| Lipophilicity | 10 < oil: water partition coefficient <1000 |
| Molecular weight | < 500 Da |
| Melting point | < 200°C |
| pH of saturated aqueous solution | pH 5–9 |
| Required dose deliverable | < 10 mg/day |
| Irritation potential, which is the net effect of many physicochemical properties | No irritation to buccal tissue |

## 1.7 MEDICATED LOZENGES

Lozenges are the flavoured medicated dosage forms intended to be dissolved or disintegrate in mouth or pharynx containing one or more medicaments usually in the sweetened base. Lozenges are used for patients who cannot swallow solid oral dosage forms as well as for medications designed to be released slowly to yield a constant level of drug in the oral cavity to bath the throat tissues in a solution of the drug. Lozenges, which may consist of one or more pharmaceuticals into carrier, have been used to deliver medications, either topically within the buccal cavity of the patient or by swallowing the pharmaceutical after it has dissolved in saliva. [18]

Lozenges exert local effect at a particular site in the oral cavity and some systemic effect for which the drug undergoes circulation in the bloodstream and exhibits its pharmacological action.[20] The benefits of the medicated lozenges is they increase the retention time of the dosage form in oral cavity which increases bioavailability, reduces gastric irritation and bypasses first pass metabolism.[18]

Lozenges are placed in oral cavity. Since the sublingual lozenges may be impractical due to their size, buccal lozenges are formulated and have been extensively used and are intended to be placed between the cheek and the gums. Though the lozenge dissolution time is about 30 minutes, this depends on the patient;

as the patient controls the rate of dissolution and absorption by sucking on lozenge until dissolves. The consequence of this can be high variability in amounts of drug delivered each time the lozenge is administered. Depending on the type of lozenge, they may be prepared by moulding or by compression. Moulded lozenges are called pastilles while compressed lozenges are called troches. [19]

Many lozenges have hard candy bases of sugar and syrup and often incorporate an adhesive substance such as acacia. Commercial lozenges (troches) may be made on a tableting machine using high compression pressures. Lozenges are designed to dissolve slowly in the mouth. They are designed to dissolve and not to disintegrate. Ingredients should be heat-stable if they are to be incorporated into extemporaneously-prepared lozenges. [16]

They can deliver drug multi directionally into the oral cavity or to the mucosal surface. Lozenges are better innovative dosage form placed in oral cavity.[1]

**Advantages** [1, 16, 20, 21, 22]

- It is easy to administer to both pediatric and geriatric patients.
- It has a pleasant taste and will extend the time a quantity of drug remains in the oral cavity to elicit local activity.
- Systemic absorption of drugs can be possible through buccal cavity.
- It can be prepared with minimal equipment.
- Taste of the drugs can be masked by sweeteners and flavours used in the formulation.
- Increase the contact time of drug.
- Prolong drug action.
- Do not require water intake form administration.
- It can increase in bioavailability.
- It can reduce dosing frequency.
- It can reduce gastric irritation.
- Avoid first pass metabolism of drugs.
- Lozenges can be withdrawn if dose is not needed.
- Can be given to those patients who have difficulty in swallowing.
- Do not require water intake for administration.
- Technique is non invasive, as is the case with parenteral.
- It extends the time of drug in the oral cavity to elicit a specific effect.

**Disadvantages**

- It could be mistakenly used as candy by children. Parents should be cautioned not to associate medications with candy and to keep the product out of the reach of children. Some drugs may not be suitable with aldehyde candy bases.
- Heat stable drugs are suitable.
- Children having above 6 years of age can use lozenges safely.
- Drugs having minimum bitter taste are suitable.
- Hard candy lozenges the high temperature required for their preparation.
- Hard lozenges become grainy.
- Possible draining of drug into the stomach.
- The non ubiquitous distribution of drug within saliva for local therapy.
- Accidental swallowing of entire dosage form.

**SHAPES OF LOZENGES** [21]

- Flat
- Circular
- Bi convex
- Cylindrical
- Octagonal

**LOZENGES FORMULATIONS** [20]

The lozenges are aimed to formulate into a stable dosage form and to provide a more promising means of administration of variety of drugs.

**Criteria for preparation of medicated lozenges**

a. Selection of drug candidate

b. Selection of drug carrier.

c. Selection of appropriate type of lozenge formulation.

**MEDICAMENTS:** [19]

The type of medicament that can be added to candy base administered to the patient via lozenges is restricted only by flavour, dose limitations, or chemical compatibility. Some materials so unpalatable or irritating to the mucus membrane that they are

unsuitable for this type of administration; some active ingredients must be given at a dosage level sufficiently high to preclude their use in a hard candy lozenge; other medicaments are so reactive with candy base components that the development of a product with a reasonable is impractical.

Drug candidates which can be incorporated in lozenges, belong to one the following categories:

- Local anesthetics
- Antibiotics
- Anti histaminics
- Anti tussives
- Anti emetics
- Analgesic
- Decongestant
- Antifungal

### 1.8 CLASSIFICATION OF LOZENGES: [17]

Lozenges can be classified into various classes based on various methods

**According to the site of action:**

- Local effect. Eg: Antiseptics, Decongestants.
- Systemic effect. Eg: Vitamins, Nicotine.

**According to texture and composition:**

- Chewy or caramel based medicated lozenges
- Compressed tablet lozenges
- Soft lozenges
- Hard lozenges

### 1.8.1. Chewy or caramel based Medicated lozenges [18]

Chewy or Caramel based Medicated Lozenges Chewy or caramel based medicated lozenges are the dosage form in which medicament is incorporated into a caramel base which is chewed instead of being dissolved in mouth. Most formulations are based on the glycerinated gelatine suppository formula which consists of glycerine, gelatine, and water. These lozenges are often highly fruit flavoured and may have a slightly acidic taste to cover the acrid taste of the glycerine. Its constituent ingredients are the candy base, whipping agent, humectants, lubricants, flavour and of course medicaments incorporated into the lozenges.

The candy base consists of a mixture of sugar and corn syrup in a ratio of 50:50 to 75:25 sugars to corn syrup. The whipping agents are used to incorporate air in toffee-based confections to obtain the desired degree of soft chew. These are exemplified by milk protein, egg albumin, gelatin, xanthan gum, starch, pectin, algin and carageenen. The humectants improve chew and mouth feel properties and include glycerin, propylene glycol and sorbitol. Lubricants are added to avoid sticking of candy to the teeth while chewing. It includes vegetable oils and fats.

Medicaments up to 35-40% can be incorporated. Seeding crystal involves addition of fine powdered sugar at 3-10% to warm. Candy mass to speed up the crystallization and allow the base to be formed into tablets in a much shorter time.

**Manufacturing of Chewy or Caramel Based Medicated Lozenges**

The candy base is cooked at 95-125ºc and transferred to planetary or sigma blade mixer. Mass is allowed to cool to 120ºc. This is followed by the addition of whipping agent below 105ºc. The medicaments are then added between 95-105ºc. Colour is dispersed in humectants and added to the above mass at a temperature above 90ºc. Seeding crystals and flavour are then added below 85ºc followed by lubricant addition above 80ºc. Candies are then formed by rope forming.

### 1.8.2. Compressed Tablet Lozenges

If the active ingredient is heat labile, it may be made into lozenge by compression. The granulation is prepared in a manner similar to that used for any compressed tablet. The lozenge tablets differ from conventional tablets in terms of organolepticity, non disintegrating characteristics and slower dissolution profiles. The

lozenge is made using heavy compression equipment to give a tablet that is harder than usual, as it is desirable for the troche to dissolve slowly in mouth. They are usually flat faced with sizes, weight, hardness, and erosion time ranging between, 5/8-3/4 inch, 1.5-4 g, 30-50 kg inch and 5-10 min, respectively. The ingredients for compressed tablet lozenges are tablet based or vehicles which are sugar such as dextrose, sucrose. Other vehicles are sugar free vehicles such as mannitol, sorbitol, polyethylene glycol (PEG) 6000 and 8000. Some commercially available sugar based vehicles include- Emdex, Nu-tab, Sweetrex, Mola-tab, Hony-tab, Sugartab. Other fillers include dicalcium phosphate, calcium sulphate, calcium carbonate, lactose and microcrystalline cellulose. Binders are also included to hold the particles of mass as discrete granules and include acacia, corn syrup, sugar syrup, gelatin, polyvinyl-pyrrolidone, tragacanth and methylcellulose. Lubricants are used to improve flow of final troche mixture and include magnesium stearate, calcium stearate, stearic acid and PEG.

**Manufacturing of Compressed Tablet Lozenges**

Manufacturing of compressed tablet lozenges can either be direct compression and wet granulation. In direct compression, ingredients are thoroughly mixed and then compressed. In wet granulation, sugar content is pulverized by mechanical comminution to a fine powder (40-80 mesh size). Medicament is added and thoroughly blended. The blended mass is subjected to granulation with sugar or corn syrup and screened through 2-8 mesh screen. This is followed by drying and milling to 10-30 mesh size. Flavour and lubricant are then added prior to compression.

### 1.8.3. Soft Lozenges

They are either meant for chewing or for slow drug release in mouth. They can be made from PEG 1000 or 1450, chocolate or sugar-acacia base while some soft candy formulations can also contain acacia and silica gel. Acacia is used to provide texture and smoothness and silica gel is used as a suspending agent to avoid settling of materials to the bottom of the mould cavity during the cooling. The formulation requires heating process at about $50^{o}$c, hence is only suitable to heat resistant ingredients. These are mixtures of sugar and other carbohydrates in an amorphous (non crystalline) or glassy state. They can also be regarded as solid syrups of sugars. The moisture content and weight of hard candy lozenge should be in between, 0.5 - 1.5% and 1.5-4.5 g respectively.

**Manufacturing of Soft Lozenges**

On the account of the soft texture of these lozenges, they can be hand rolled and then cut into pieces or the warm mass can be poured into a plastic mould. Mould cavity should be overfilled if PEG is used, as PEG's contract as they cool. This is not required in case of chocolate as it does not shrink.

**1.8.4. Hard Candy Lozenges**

Hard candy lozenges are mixtures of sugar and other carbohydrates in an amorphous (non crystalline) or glassy state. They can also be regarded as solid syrups of sugars. The moisture content and weight of hard candy lozenge should be between, 0.5 to 1.5% and 1.5-4.5g respectively. These should undergo a slow and uniform dissolution or erosion over 5-10min., and should not disintegrate. The temperature requirements for their preparation is usually high hence heat labile materials cannot be incorporated in them. The ingredients for hard candy lozenges include body agent or base which is corn syrup that is available on Baume basis. A 43° Baume corn syrup is preferred in hard candy lozenges. Sweetening agents such as sucrose, dextrose, maltose and lactose are added.

**Manufacturing of Hard Candy Lozenges**

The candy base is cooked by dissolving desired quantity of sugar in one third amount of water in a candy base cooker. This is continued till the temperature rises to 110ºc. Corn syrup is added and cooked till the temperature reaches 145-156ºc. The candy mass is removed from the cooker and transferred to a lubricated transfer container mounted onto a weight check scale where the weight of the mass is checked. This is followed by colour addition in form of solutions, pastes or colour cubes. The mass is then transferred to a water-jacketed stainless steel cooling table for mixing and the flavour, drug and ground salvage is added. The mass is either poured in mould or pulled into a ribbon while cooling and then cut to desired length. The obtained lozenges are packaged.

## 9.1. INGREDIENTS USED IN THE LOZENGES FORMULATION

**Table.1.3. Ingredients used in the lozenges formulation**

| INGREDIENTS | EXAMPLES |
|---|---|
| **Candy base**<br>**Sugar**<br>**Sugar free vehicles**<br>**Fillers** | <br>Sucrose, Maltose, Dextrose.<br>PEG 600and 800, Mannitol, Sorbitol.<br>Lactose, Calcium sulphate, Calcium carbonate, Dicalcium phosphate, MCC. |
| **Binders** | Acacia, corn syrup, gelatin, polyvinyl pyrollidine, tragacanth and MCC |
| **Lubricants** | Stearic acid, magnesium stearate, calcium, polyethylene glycol, vegetable oils and fats |
| **Flavouring agents** | Menthol, eucalyptus oil, cherry flavour, spearmint. |
| **Colouring agents** | Water soluble and lakolene dyes,orange colour paste, red colour cubes |
| **Whipping agents** | Milk protein, egg albumin, gelatin, xanthan gum, starch, pectin, algin and carrageenan |
| **Humectants** | Glycerin, propylene glycol and Sorbitol |

**Hard Candy Lozenges** [16]

**Raw Materials**

The types of raw materials used in medicated lozenges may vary according to a number of factors.

**Sucrose**

Sucrose, a disaccharide of glucose and fructose, is obtained from sugarcane or beet. The choice of beet or cane sugar is based on availability and geographical considerations. Sucrose and sucrose products are used in medicated lozenges because of their value as neutral sweeteners, their ready solubility, and their function as a ‘‘drier’’ to reduce the weight of the confection through crystallization.

**Corn syrup**

Corn syrup is used in almost every type of confection to control sucrose and dextrose crystallization, which may lead to crumbling. Corn syrup in appropriate proportion with sucrose and dextrose allows the formation of an amorphous glass and produces a candy with the desirable appearance. The following physical properties of corn syrup are extremely important in the preparation of medicated candies: density, dextrose equivalent (DE), hygroscopicity, sugar crystallization, viscosity, freezing point depression, and osmotic pressure.

**Colorants**

Colorants are incorporated into medicated lozenges for appearance, product identification, and masking of physical degradation.

**Dyes and other organic colorants**

Dyes and other organic colorants may degrade by heat or light via oxidation, hydrolysis, photo oxidation, etc., and their compatibility with drug, excipients, and process conditions should be studied before selection. Suppliers of colors are excellent sources of information on current regulatory status of colorants.

**Acidulants**

Acidulants are generally added to medicated lozenges to fortify and strengthen their flavor profile. Organic acids such as citric, malic, fumaric, and tartaric acids are most commonly used. Citric acid alone or in combination with tartaric acid is the most common. Another use of acids in medicated lozenges is to alter the pH to maintain the integrity of the drug. Regular conversion corn syrup has a pH of 5.0–6.0. Addition of a weak organic acid to improve flavor lowers it to 2.5–3.0, a pH at which some medicaments exhibit maximum stability. If necessary, some drugs can be stabilized by adjusting the pH to 7.0–8.0 with a suitable weak base such as calcium carbonate. Some research has shown that excessive use of acidic lozenges could have the potential to enhance existing dental erosion, and that low pH (2.6–3.7) leads to dissolution of calcium and phosphorous from hydroxyapatite. Others have shown that excessive use of citric and tartaric acids may affect bioavailability of zinc in zinc lozenges. Another report indicated that the activity of cetyl pyridinium chloride in candy-base lozenges is influenced by pH, with >5.5 being most desirable. Acceptable taste is necessary to ensure patient acceptability.

**Flavors**

Flavors used in medicated lozenges must be compatible with the drug and excipients and capable of withstanding the rigors of the manufacturing conditions. Flavors consist of numerous chemicals that may interact with excipients or medicaments and that degrade by heat and light. Aldehyde, ketones, and esters may react with drugs. A classic example of flavor–drug interaction is that of a primary amine drug (benzocaine, phenylpropanolamine) with aldehyde containing flavor components like cherry, banana, etc., resulting in the formation of a Schiff base, drug decomposition, and loss of efficacy. Adjustment of lozenge base pH to accentuate certain flavors (e.g., citrus) may also result in incompatibility with some medicaments (e.g., benzocaine).

## 1.10 QUALITY CONTROL OF LOZENGES

### 1.10.1. Evaluation of medicated Lozenges

**(A) Quality Control**

**(1) Candy base** – It has to be check for following parameters-Corn syrup, sugar delivery gears, temperature, steam pressure and cooking speed of pre cookers and temperature, steam pressure, cooking speed and vacuum of candy base cookers.

**(2) Moisture analysis**

**a) Gravimetric method**- 1g of sample is placed in vacuum oven at 60-70ºC for 12-16hrs. After specified period of time, weigh the sample and moisture content is calculated by subtraction of final weight from initial weight.

**(3) Determination of sugar and corn syrup ratios-**This is done by "Dextrose equivalent method: Lane Eynon Titration method".

**(4) Salvage solutions-** Determined using a refractometer.

**(5) Forming checks-** Involves a check on candy rope diameter.

**(6) Cooling checks**- Visual inspection is performed in order to analyze any stress cracking due to rapid cooling, air bubble formation, surface cracking and black specks.

**B) Physical and Chemical Testing**

**(1) Diameter and thickness-** Diameter of the lollipop is important for uniformity of lozenges size. It can be measured using Vernier Calipers.

**(2) Hardness-** The resistance of lozenges to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of lollipops can be measured by using Monsanto hardness tester. The hardness was measured in terms of kg/cm2.

**(3) Weight Variation**-The USP weight variation test is done by weighing 20 lozenges individually, calculating the average weight and comparing the individual weights to the average.

**(4) Drug excipients interaction studies-** Determined by FTIR.

**(5) In-vitro drug release-** This is carried out in USP II paddle type dissolution apparatus.

**(6) Drug content-** Appropriate number of lollipop are crushed and dissolved in an appropriate solvent and the absorbance of the solution is measured spectrophotometrically.

**C) Microbial Check on Lozenges** [19]

In this microbial check, the presence of any bacterial, mold or spore contamination is checked in raw materials, finished products, machinery, cooling tunnels, environmental conditions and storage drums. Laboratory microbial testing should include the following counts: total plate, total coliform, yeast and mold, *E.coli*, *Staphyllococcus, Salmonella.*

**Stability Testing for Lozenges**

Lozenges are subjected to stability testing under following conditions: 2 months at 60 ºC, 3-6months at 45ºC, 9-12 months at 37 ºC, 36-60 months at 25 º C.

Lozenges in their final packs are subjected to the following conditions for stability testing: 25 ºC at 80% relative humidity (RH) for 6-12 months, 3 ºC at 80% RH for 3 months, and 25 º C at 70% RH for 6-12 months. [19]

## 1.11. PACKAGING OF LOZENGES [14]

The lozenges are hygroscopic in nature, a complex and multiple packaging is adopted. The individual unit is wrapped in polymeric moisture barrier material which are then placed in tight or moisture resistant glass, polyvinyl chloride or metal container that is over wrapped by aluminum foil or cellophane membrane.

## 1.12. APPLICATIONS OF LOZENGES [16]

**Antifungal lozenges**: Oral lozenges, such as clotrimazole and nystatin, are used to treat fungal infections.

**Nicotine lozenges**: Nicotine lozenges are used as a method to quit smoking. The lozenges release nicotine into bloodstream when you suck on the lozenges, according to the Mayo clinic.

**Zinc lozenges**: Zinc is used as an antioxidant to help your body fight infections. When contained in lozenges, zinc is thought to help reduce the duration of colds and symptoms.

**Throat/cough lozenges**: Sore throat lozenges contain an anesthetic, such as benzocaine, to soothe your throat. The anesthetic works by numbing the affected area to provide temporary relief. Some throat lozenges also might contain an antibiotic to treat diseases of the throat, including strep throat. Cough lozenges which suppress coughing, can contain ingredients, such as menthol or eucalyptus.

**Morning sickness lozenges**: Prenatal lozenges contain pyridoxine, or vitamin B6 helps to relieve nausea and vomiting symptoms.

**Table.1.4. Marketed products** [16]

| S.No | Brand Name | Active ingredient | Therapeutic use |
|---|---|---|---|
| 1. | **DIFFLAM** | Lignocaine | Anti inflammatory |
| 2. | **STREPSILS** | Antiseptic | Amyl Meta cresol |
| 3. | **NICOTRITE** | Nicotine | Smoking suppressant |
| 4. | **COLD – EEZE** | Zinc Gluconate | Cold |
| 5. | **DURO** | Pholcodine, Cetylpyridinium chloride | Anti tussives |
| 6. | **FUNGILIN** | Anti fungal | Amphotericin B |
| 7. | **LEXCOF** | Dextromethorphan | Cough |

# *REVIEW OF LITERATURE*

**Rao TV et al.** [23] prepared and evaluated the sugar based medicated Tramadol hydrochloride hard lozenges for pediatrics to overcome the administration of dosage forms like tablets, capsules, etc. The lozenges were prepared by heating and congealing method on laboratory scale with corn syrup as base. All the formulations prepared were subjected to various physico-chemical parameters such as hardness, friability, content uniformity, weight variation, thickness, drug content and in vitro dissolution studies. Drug-excipients compatibility studies were conducted by FT-IR spectroscopy and results revealed that no interactions were found between drug and excipients. The results of *in- vitro* drug release studies showed that formulation F9 releases the drug 95.66 percentage using methylcellulose as a polymer at the end of 30 minutes. The result concludes hard lozenge can provide an attractive alternative formulation in the treatment of pain in pediatric patients.

**Yamsani SK et al.** [24] formulated Doxofylline lozenges to provide slow release medicament for the management of asthma for cough and itchy throat. The benefits of these prepared lozenges showed increase in bioavailability, reduction in gastric irritation by passing of first pass metabolism and increase in onset of action. The lozenges were prepared using sucrose as base; liquid glucose in the formulation made the lozenges transparent and smooth; hydroxypropyl methylcellulose (HPMC) and hydroxyethyl cellulose (HEC) are used as polymers. Aspartame and saccharin are used as artificial sweeteners. Sweeteners along with flavours are used to mask the bitter taste of drug. All the formulations prepared were subjected to various physicochemical parameters like hardness, content uniformity, friability, weight variation, moisture content etc. The prepared formulations have a hardness of 8-11 $Kg/cm^2$, non gritty and pleasant mouth feel. Some selected formulations were tested for drug excipients interactions subjecting to infrared (IR) Spectral analysis. *In vitro* drug dissolution studies showed least of 82.7% for FL7 and maximum of 98.8% for FL6.

**Fathima SR et al.** [25] formulated combinations of paracetamol; Diclofenac and Domperidone in the lozenge form to make available the immediate release of the drugs in fever, pain and nausea conditions. Lozenges were prepared by heat

congealing method with varying concentrations of sugar base and polymer. Formulated lozenges were evaluated for various physicochemical parameters like hardness, weight variation, moisture content, friability and *in-vitro* dissolution. The results obtained were compared with pharmacopoeia limits. FTIR studies revealed no signs of incompatibility between the drugs and its excipients. Hardness, friability, moisture content of the prepared lozenges was found within the limits. *In-vitro* dissolution studies showed the drug release of 90% at the end of 30 minutes. Thus, it can be concluded that medicated lozenges are suitable for large doses and immediate drug release requirements with improved bioavailability.

**Manasa A et al.** [26] formulated and evaluated Cetirizine sweetened tablet lozenges were designed for the effective treatment of cough and cold to reduce throat pain. The main interest was for the development of new dosage forms and the effect of different concentration on the *in-vitro* release. At the outset, estimation of drug by UV spectrophotometer was carried out. The possible interaction between the drug and excipient was studied by FTIR spectroscopy which showed that there was no interaction between the selected drug and polymer under study. Lozenges could be successfully prepared by fusion method using sucrose, liquid glucose, aspartame, sucrose, dextrose, mistri, flavor and colour. *In-vitro* release rate studies showed that the drug release for lozenges was maximum in formulation FL2 (98.89±0.5%) which was at 25 minutes.

**Lakshmi MB et al.** [27] formulated and evaluated Domperidone lozenges is a selective serotonin receptor (5-HT3) antagonist and its lozenges are mainly used for the treatment of chemotherapy induced nausea and vomiting. In the study lozenges dosage form is chosen due to their benefits of good patient compliance due to its taste, increased bioavailability, reduced gastric irritation, reduced first pass metabolism and increased onset of action when compared to its tablet dosage form which is in practice conventionally. The preparation process involves mixing of Domperidone with all excipients, used in the formulation in different ratios by using heat congealing technique in which sucrose and dextrose heated separately up to 60ºc fusioned together and reheated upto 160ºc after which polymer HPMC K 100M, HPMC E5 and

all other excipients are added and moulded. The lozenges were subjected to evaluation viz., weight variation test, hardness, friability, drug content and in vitro release studies.

**Jagadeesh P et al.** [28] prepared and evaluated the sugar based Tramadol hydrochloride medicated lollipops for pediatrics to overcome the administration. They were prepared by heating on congealing method on laboratory scale with sugar syrup as base. All the formations were subjected to various physico chemical parameters such as hardness, friability, content uniformity, Wight variation, thickness, drug content and in vitro dissolution studies. Drug excipients compatibility studies were conducted by FT- IR spectroscopy and result release studies showed that formulations F15 release the drug 89.41 percentage at the end of 30 min. The medicated lollipops can provide an attractive alternative formulation in the treatment of pain in paediatric patient.

**Choursiya S et al.** [29] formulated and evaluated Roxithromycin lozenges for oral bacterial infection. In that study, taste is one of the most important parameters of oral formulations so β-Cyclodextrin is used as a good taste masking agent for bitter drug and also enhances the solubility of the drug. Roxithromycin Compressed tablet lozenges were formulated by wet granulation technique with excipients like sucrose, lactose, citric acid, flavour and colour and evaluated for organoleptic properties the test like diameter, thickness, weight variation, hardness, friability, mouth dissolving time, and % drug content. The Optimized formulation of Roxithromycin Compressed tablet lozenges (C6) were sweet in taste, smooth in texture and having a diameter 13.708 ± 0.00 mm , thickness 6.704 ± 0.00 mm, hardness is 12 ± 1kg/cm2 and drug content uniformity is 96 ± 0.02%. The weight variation and friability of lozenges (C6) was passed as per IP and mouth dissolving time is found at 25 ± 2 min. *In vitro* dissolution study for Roxithromycin compressed tablet lozenge was performed in pH 6.8 phosphate buffer wherein 95 % of the drug was released within 30 min.

**Kasar SA et al.**[30] formulation and evaluation of mouth dissolving tablet of Metoclopramide HCl. Metoclopramide HCl is acting through its prokinetic action

increasing gastric emptying. The tablets were prepared by direct compression method using 32 factorial designs. Croscarmellose sodium and crospovidone were used as super disintegrants.

**Lekshmi L et al.** [31]Candy based lozenges of antifungal agent prepared using hydrophilic natural polymers (gelatin, acacia and tragacanth) by heating and congealing method in order to enhance bioavailability, reduce gastric irritation, by-pass first metabolism and increase onset of action. These lozenges were evaluated for various parameters like hardness, friability, thickness, drug content, mouth dissolving time, moisture content and *in vitro* dissolution etc... The optimized formulation was having good transparency and pourability with mouth dissolving time, *in vitro* drug release 98.23% and follows first order release kinetics and the mechanism of drug release was found to be Non fickian. The DSC and FTIR studies indicated that there was no drug-excipients interaction. Accelerated stability study conducted as per ICH guidelines at 45ºC and 75% relative humidity over a period of one month found that there wasn't any substantial interaction between the drugs, flavour and colour and the prepared formulation were stable. The antifungal studies showed that they retained similar antifungal activity of pure drug. It was concluded that development of Ketoconazole loaded gelatin lozenges tablets were successfully formulated cost effectively and has high efficiency in treatment of oral candidiasis.

**Aparna C et al.** [32] medicated hard candy and soft lozenges of Albendazole were formulated to bypass first pass metabolism and increase bioavailability by absorption through oral mucosa. Medicated hard lozenges were prepared by heating and congealing technique using different polymers. Soft lozenges (PEG-base) lozenges were prepared by melting and moulding technique using PEG 1500. Stability studies were carried out according to ICH guidelines. All the formulations were subjected to various physicochemical evaluations like weight variation, hardness, drug content, thickness, disintegration time and moisture content etc. Based on results obtained from hard and soft lozenges, formulation containing methyl cellulose 25mg i.e, hard candy lozenge showed better drug release when compared to soft lozenge. The in-vitro dissolution of Albendazole from the selected formula was found to be 99.37% at 30 min. In case of soft lozenges, a formula containing acacia 300mg formulation was

further optimized and in-vitro dissolution study from the resultant product was found to be 88.92% in 50min. FTIR studies revealed that there were no drug-excipient interactions.

**Majekodunmi SO et al.** [19] reviewed Lozenges are one of the widely used solid dosage forms. They contain medicament and are meant to be in mouth or pharynx. Lozenges provide a palatable means of dosage form administration and possess excellent advantages; though they suffer certain disadvantages too. Lozenges are adopted for both local and systemic administrations and a wide range of active ingredients can be incorporated in them. Buccal lozenges are formulated and have been extensively used and are intended to be placed between the cheek and the gums. Though the lozenge dissolution time is about 30 minutes, this depends on the patient; as the patient controls the rate of dissolution and absorption by sucking on lozenge until dissolves.

**Vidyadhara S et al**. [33] formulated and evaluated the medicated lozenges containing amoxicillin tri hydrate. The benefits of the research work is to increase the retention of the dosage form in oral cavity for increased bioavailability, reduction in gastric irritation and bypassing first pass metabolism. The lozenges were prepared by heating and congealing method employing polyethylene glycol 1500 as matrix base, saccharin sodium (artificial sweetener), stevia (natural sweetener), xanthan gum (polymer), sodium carboxy methyl cellulose (polymer) as other excipients. The prepared medicated lozenges were characterized for drug content uniformity, hardness, thickness, weight variation, friability and dissolution by standard pharmacopeia methods. The results of the evaluation tests obtained were within the limits. Accelerated stability studies were conducted as per ICH guidelines and found that there wasn't any substantial interaction among the drug, flavour and colour and the prepared formulations were found to be stable. Formulations were tested for drug excipients interactions subjecting to IR spectral and DSC analyses. The results revealed that there was no major interaction between the drug and polymers used for the preparation of lozenge .

**Pothu R et al.** [34] formulated Chlorhexidine and Flurbiprofen as lozenges to provide local antiseptic and anti-inflammatory action. The candy based lozenges were prepared by heat and congealing method by sugar as lozenge base, HPC, HPMC as polymers, citric acid artificial flavours and colours and other essential excipients. Some selected formulations were tested for drug excipient interactions subjecting to IR Spectral analysis. Formulated lozenges were evaluated for weight variation, crushing strength, friability, thickness, taste, dissolution time, and %assay. Crushing strength of optimized troches was found between 8-9.50 kg/cm$^2$. The study concludes candies can provide an attractive alternative formulation in the alleviation of pain and Inflammation.

**Bharkad VB et al.** [35] formulated fluconazole lozenges using sucrose as base and gelatin solution as a binder. Lozenges were prepared by wet granulation method using different concentration of maize starch, acacia, HPMC E50.The benefits of these prepared lozenges are increased bioavailability, reduction in gastric irritation by passing first pass metabolism. All the formulations prepared were subjected to various physicochemical parameters like hardness, content uniformity, friability, weight variation etc. The prepared formulations have a hardness of 3.5-10.2 Kg/cm², with good taste.

**Yamsani MR et al.** [36] prepared Lidocaine hard candy lozenges by heat fusion method using sugar as a base. The usage of corn syrup in the formulation made the lozenges transparent and smooth, which helped in improving the elegancy of formulation. The controlled release of medicament from Lozenges was achieved by using polymers like methyl cellulose, locust bean gum, HPMC K4M and xanthan gum. The prepared lozenges were subjected to physico-chemical as well as in vitro drug release study. Among all the formulations of hard candy lozenges FL8 showed the in vitro release of 98.7% at the end of 25 minutes.

**Majumdar S et al.** [37] formulated and evaluated Miconazole medicated lozenges. Miconazole being class II drug has low aqueous solubility and high permeability so in order to increase its solubility, commercial technique for enhancement of drug

release by water soluble carriers like PEG (400,6000,4000) either or in combination were used. Taste masking of bitter drug like Miconazole was done by adding maltodextrin along with sucralose and peppermint flavour. Drug release was calculated by high performance liquid chromatography (HPLC) technique and based on various parameters like disintegration time, drug release and its taste masking efficiency batch was finalized. Drug release from finalized batch was 91% and it gives pleasant mouth feel effect.

**Patel DM et al.** [38] developed the Diphenhydramine hydrochloride as lozenges to provide effective release for the management of cough. Formulated and evaluate lozenges to meet the need of improved bioavailability by avoiding hepatic first pass metabolism of the drug. The lozenges were formulated using various sugars like mannitol, dextrose, sucrose and Isomalt. Polyethylene glycol 200, propylene glycol and glycerine were tested as plasticizer in formulation. The prepared formulations were subjected to various evaluation parameters. After completion of stability study for a period of 1 month, the optimized formulation was subjected to evaluation parameters. Lozenges formulated using isomalt and 0.1 ml glycerine remained as hard candy, while lozenges were not formed with any other sugar. The optimized formulation showed a hardness of around 15 kg/cm²; drug content and content uniformity of 97 % and *in vitro* drug release of more than 99 % within 20 min. After stability study, it was found that the lozenges were not altered in terms of above parameters and were stable. The study concluded that the Isomalt can be successfully used as tooth friendly sugar substitute in the formulation of medicated lozenges and glycerine can be used as a plasticizer to give better appearance.

**Kumar D et al.** [39] formulated and characterized chewable tablets of Paracetamol and Metoclopramide hydrochloride. The investigation was carried out to study the effect of different proportion of Avicel 101, Avicel 102 and moringa gum, which are super disintegrating agents. The chewable tablets of Paracetamol and Metoclopramide hydrochloride were prepared by wet granulation method. Several physicochemical parameters like thickness, diameter, hardness, %weight variation, %loss in weight, drug content, disintegration time, in vitro dissolution studies, kinetics of drug release

and stability studies for all the formulations were studied and were found within the acceptance limits. Formulation F7 (containing moringa gum 1%) showed the best cumulative drug release and disintegration time of 56 secs.

**Aparna C et al.** [40] formulated Itraconazole Compressed tablet lozenges were prepared by wet granulation technique using three different binders, at different concentrations. Soft lozenges (hand-rolled and PEG-base) lozenges were formulated using different excipients. They were evaluated for post-compression parameters by pharmaceutical standard methods. Stability studies were carried out according to ICH guidelines. The optimized formulations were subjected to microbial studies to see their antimycotic activity. The formulated lozenges were evaluated for physical parameters and the results complied with the pharmacopeia limits. In vitro dissolution studies showed 90% drug release by the end of 60 min.

**Renuka P et al.** [41] prepared and evaluated hard candy lozenges of nicotine 2mg for low dependent smokers and 4mg for high dependent smokers. The benefits of these prepared lozenges are increased bioavailability, reduction in gastric irritation and avoiding first pass metabolism. The lozenges were prepared by heat and congealing method in a candy base using sucrose as base. In-vitro drug dissolution studies showed 100% release in 30 minutes for optimized formulations NC11 and NC25.The Hard candy lozenges can provide an attractive alternative formulation in the Nicotine replacement therapy.

**Pundir S et al** [42] prepared and evaluate the medicated lozenges of Ondansetron hydrochloride for the treatment of chemotherapy induced nausea and vomiting. Taste masking was done by complexing Ondansetron HCl with Eudragit E100 in ratio 1:1. The lozenges were prepared by heating and congealing method using sucrose as base; sodium carboxy methyl cellulose (NaCMC), hydroxy propyl methyl cellulose (HPMC K4M) and methyl cellulose (MC) are used as polymers and comparing with lozenges of without hydrocolloids. It was found that the formulation without hydrocolloids (F0) was more stable compare to other formulations. Accelerated stability study conducted as per ICH guidelines (zone IV) at 45°C and 75% relative humidity over a period of

seven weeks found that there wasn't any substantial interaction between the drugs, flavour and colour and the prepared formulations were stable.

**Maheshwari R et al.** [22] reviewed lozenges a unit dosage form of medicament meant to be dissolved in mouth or pharynx. Lozenges currently available in market are of four types: Caramel based soft lozenges, hard candy lozenges and compressed tablet lozenges. The present review covers more or less all aspects associated with lozenge. It includes various researches performed till date, formulation and evaluation parameters adopted for the dosage form. Furthermore, it throws light on the applications of lozenge.

**Purushotham RK et al.** [43] formulated and evaluated the medicated lozenges for paediatrics of Montelukast sodium for the treatment of asthma in paediatric patients. They prepared and evaluated lozenges of Montelukast sodium using hydroxy propyl methyl cellulose as polymer different concentrations to increase retention time. In-vitro drug dissolution studies showed 69.24% for F2, 64.01% for F3 release of drug in 30 min, 97.31% in 10 minutes from F1 formulation. IR spectroscopic studies indicated that there were no drug-excipient interactions. The prepared lozenges of Montelukast sodium could stay in the mouth for a longer period of time, which indicates a potential use of these lozenges for treating asthma.

**Pattanayak D et al.** [44] formulated paracetamol medicated lozenges were using sucrose as base; Sodium Carboxy Methyl Cellulose (NaCMC) and Methylcellulose (MC) are used as polymers. Eudragit is used as taste masking agent. All the formulations prepared were subjected to various physicochemical parameters like hardness, content uniformity, friability, weight variation etc. The prepared formulations have a hardness of 9-10 Kg/cm², not gritty, mouth feel freshness taste. Stability studies of selected formulations were also carried out at 30oC & 40°C for a period of six months. Some selected formulations were tested for drug excipients interactions subjecting to IR Spectral analysis. *In-vitro* drug dissolution studies showed least of 70.012% for PL3 and maximum of 90.648% for PL4 release of drug

in 30 minutes. The moulded lozenges can provide an attractive alternative formulation in the alleviation of pain and fever.

**Kamath J et al**.[45] formulated and evaluated the candy based medicated lollipops of drug Levamisole, a synthetic imidathiazole derivative which acts by targeting the nematode nicotinergic acetylcholine receptor for pediatrics, by heating and congealing technique, using polymers like Sodium carboxy methyl cellulose, Methyl cellulose, Hydroxy propyl methyl cellulose and comparing with lollipops with no hydrocolloids. It was found that the formulation containing methyl cellulose showed better drug release and was more stable.

**Purushotham RK et al.**[46] formulated medicated lollipops of paracetamol for paediatric patients by heating and congealing method using HPMC and HEC as a polymer. The result of phase IV studies revealed that the drug release in 30 minutes under simulated salivary condition was 94.25% from HPMC and 72.14% from HEC based lollipops.

**Bhati R et al.** [47] reviewed Oral mucosal drug delivery system is widely applicable as novel site for administration of drug for immediate and controlled release action by preventing first pass metabolism and enzymatic degradation due to GI microbial flora. Oral mucosal drug delivery system provides local and systemic action. In this review, attention is focused to give regarding physiology of oral mucosal including tissue permeability, barriers to permeation and route of permeation, biopharmaceutics of buccal and sublingual absorption, factors affecting drug absorption, detailed information of penetration enhancers, design of oral mucosal drug delivery system and role of mucoadhesion and various theories of bio adhesion.

**Shivappa NN et al.**[48] prepared and evaluated the medicated candy based tablet lozenges of Clotrimazole for paediatric, geriatric and Dysphagic patients and to investigate the suitability of Isomalt and/or liquid glucose as the sugar substitute in the prepared lozenges. The candy based lozenges were prepared by heating and congealing method in a candy based industry on request with sugar base, Acacia,

citric acid artificial flavours and colours and other essential excipients. The prepared medicated lozenges were characterized for drug content uniformity, hardness, thickness, weight variation, friability, moisture content, in vitro disintegration and dissolution by pharmaceutical standard methods. Accelerated stability study conducted as per ICH guidelines (zone IV) at 45°C and 75% relative humidity over a period of seven weeks found that there wasn't any substantial interaction between the drugs, flavour and colour and the prepared formulations were stable.

**Jaydeep BP et al.**[49] developed buccoadhesive tablets of Metoclopramide hydrochloride (MCP HCl) to release the drug for extended period of time and to bypass the pre systemic metabolism of the drug. The buccal mucosa has been investigated for local and systemic delivery of therapeutic peptides and other drugs that are subjected to first pass metabolism or are unstable within the rest of the gastrointestinal tract. MCP HCl is subjected to first-pass effect; therefore formulation of buccal adhesive dosage form can circumvent this effect. Extended release buccoadhesive hydrophilic matrices containing MCP HCl were prepared using a 32 full factorial design. The study reveals the effect of mucoadhesive polymers on mucoadhesion and drug release characteristics of MCP HCl tablets. Statistical experimental design and data analysis using response surface methodology is also illustrated. Linear regression analysis and model fitting depicted that the formulations followed Higuchi (Matrix) model.

**Nagoba SN et al.**[50] formulated medicated ketoconazole lozenges by heating and congealing technique using sucrose as a base HPMC, HEC as polymers. The study concluded that the polymers used in the formulation shows better drug release and improved bioavailability.

**Kini R et al.**[51] prepared and evaluate the medicated hard candy lozenges of Salbutamol sulphate for paediatric, geriatric and dysphagic patients and to investigate the suitability of Isomalt and/or liquid glucose as the sugar substitute in the prepared lozenges. The candy based lozenges were prepared by heating and congealing method in a candy based industry on request with sugar base, glycerine, citric acid artificial

flavours and colours and other essential excipients. The prepared medicated lozenges were characterized for drug content uniformity, hardness, thickness, weight variation, friability, moisture content, in vitro disintegration and dissolution by pharmaceutical standard methods. Accelerated stability study conducted as per ICH guidelines (zone IV) at 45°C and 75% relative humidity over a period of seven weeks found that there wasn't any substantial interaction between the drugs, flavour and colour and the prepared formulations were stable.

**Phaechamud T et al.** [52] prepared clotrimazole soft lozenges fabricated with melting and mould technique. The soft lozenges prepared by mould technique have potential to improve the solubility of clotrimazole since it was dispersed in PEG system.

**Harri H et al.** [53] formulated zinc medicated lozenges for paediatric using a number of controlled trials have examined the effect of zinc lozenges on the common cold but the findings have diverged. Three trials used zinc acetate in daily doses of over 75 mg, the pooled result indicating a 42% reduction in the duration of colds (95% CI: 35% to 48%). Five trials used zinc salts other than acetate in daily doses of over 75 mg, the pooled result indicating a 20% reduction in the duration of colds (95% CI: 12% to 28%).

# AIM

# AND

# PLAN OF WORK

## 3.1. AIM OF THE WORK

The main objective of the present study is to formulate and evaluate Metoclopramide Hydrochloride using different sugar bases, plasticizers and Methylcellulose as polymer for developing the lozenges to meet the need of improved bioavailability by avoiding hepatic first pass metabolism of the drug.

## 3.2. PLAN OF THE WORK

- Preformulation studies
- Testing of chemical compatibility between drug and excipients by Fourier Transform Infra Red spectrophotometer.
- To prepare calibration curve of Metoclopramide Hydrochloride.
- To formulate and evaluate the hard candy medicated lozenges of Metoclopramide Hydrochloride.
- To evaluate prepared medicated lozenges for physical appearance, hardness, weight variation, thickness, drug content uniformity, moisture content, *in-vitro* drug release, mouth dissolving time.
- Stability studies of the optimized formulation.

# *RATIONALE OF THE STUDY*

# 4. RATIONALE OF THE STUDY

## 4.1. RATIONALE FOR THE SELECTION OF DRUG

Metoclopramide hydrochloride is a potent antiemetic drug, effective in the treatment of nausea and vomiting associated with cancer therapy and pregnancy. Metoclopramide used in the treatment of Gastroparesis by stimulating the stomach activity to hasten the process of gastric emptying. The bioavailability of Metoclopramide Hydrochloride was about 48-80 % it can be reduced by upto 30% as a result of first pass metabolism. Hence by formulating Metoclopramide hydrochloride as medicated lozenges, favors the buccal absorption which overcomes the drug limitations by avoiding the first pass metabolism. Metoclopramide hydrochloride has melting point 180-183$^{o}$ C thus making it an ideal candidate for formulation of lozenges. Molecular weight of the drug is 354.3 which is ideal characteristic for the oral mucosal drug delivery. It is a slightly bitter drug. Taste is masked by formulated as lozenges.

## 4.2. RATIONALE FOR THE SELECTION OF DOSAGE FORM

- Lozenges have a good scope as a patient friendly dosage form for easy administration by oral route. The anatomy of mouth and cheek favours both local and systemic absorption thus ensuring a better patient compliance especially for paediatrics and geriatrics [35]
- Large doses can be incorporated in this dosage form [25]
- Prepared lozenges show increase in bioavailability, reduction in gastric irritation by avoiding first pass metabolism and increase in onset of action. [40]
- Lozenges increase the bioavailability of the drugs together while reducing the frequent dosing.
- Solid dosage forms like tablets and capsules or liquid dosage forms may have unpleasant taste or texture and also difficulty in swallowing which can be overcome by administration of drug in the form of lozenges.
- It extends the time of drug in the oral cavity to elicit a specific effect [25]

# *DISEASE PROFILE*

# 5. DISEASE PROFILE

## 5.1. Definition

Vomiting is the forceful expulsion of stomach contents through the mouth, caused by humoral stimulation of the chemoreceptor trigger zone (CTZ) or neural stimulation of the emetic centre. The CTZ is activated and controlled by neurotransmitter manipulation at the receptor level. [56]

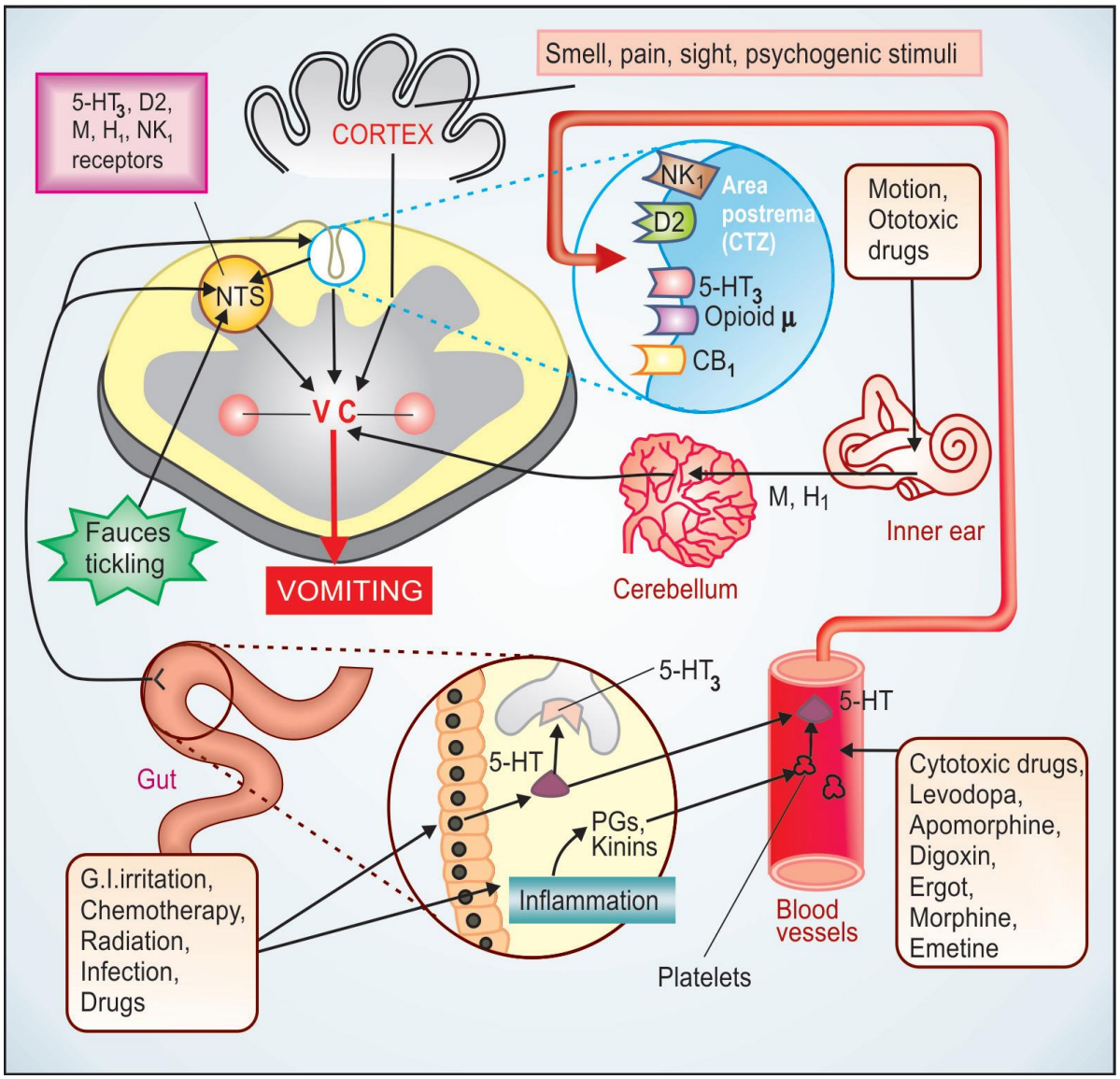
Emesis occurs due to stimulation of the emetic centre situated in the medulla oblongata. Multiple pathways can elicit vomiting. The chemoreceptor trigger zone (CTZ) located in the area postrema and the nucleus tractus solitaries NTS are the most important relay areas for afferent impulses arising the GIT, throat and other viscera. The CTZ is also accessible to blood borne drugs, mediators, hormones, toxins, etc, because it is unprotected by the blood- brain barrier. Cytotoxic drugs, radiation and other GI irritants release 5HT from enterochromaffin cells → acts on 5-HT3 receptors present on extrinsic primary afferent neurones (PAN) of the enteric nervous system (ENS). These neurones connect with vagal and spinal visceral afferents to send impulses to NTS and CTZ. Released in large quantity, 5-HT may also spill into circulation and reach CTZ via the vascular route. 5-HT may as well be released from platelets by inflammatory mediators. However, 5-HT is not the only mediator of such signals: many peptides, e.g. substance P and other messengers are also involved.

The CTZ and NTS express a variety of receptors, e.g. histamine H1, dopamine D2, serotonin 5-HT3, cholinergic M, neurokinin NK1 (activated by substance P), cannabinoid CB1 and opioid receptors through which the emetic signals are relayed and which could be targets of antiemetic drug action.

The vestibular apparatus generates impulses when body is rotated or equilibrium is disturbed or when ototoxic drugs act. These impulses reach the vomiting centre mainly relayed from the cerebellum and utilize muscarinic as well as H1 receptors. Various unpleasant sensory stimuli such as bad odour, ghastly sight, severe pain as well as fear, recall of an obnoxious event, anticipation of emetic stimulus (repeat dose of cisplatin) cause nausea and vomiting through higher centres.

Nausea is accompanied by reduced gastric tone and peristalsis. In the emetic response fundus and body of stomach, esophageal sphincter and esophagus relax, glottis closes, while duodenum and pyloric stomach contract in a retrograde manner. Rhythmic contractions of diaphragm and abdominal muscles then compress the stomach and evacuate its contents via the mouth. Conditions that inhibit gastric emptying predispose to vomiting. [54]

**Fig. 5.1 Major central and visceral structures involved in emesis and the neurohumoral receptors mediating the emetic response.**



## 5.2. PATHOPHYSIOLOGY [56, 57]

The mechanisms involved in nausea are complex and encompass psychological states, the central nervous system, autonomic nervous system, gastric dysrhythmias, and the endocrine system (Figure 5.2).

In order to understand the pathophysiology underlying nausea, it is important to introduce the concept of the dynamic threshold. It is proposed that each individual has a threshold for nausea that changes minute by minute. At any given moment, the threshold depends on the interaction of certain inherent factors of the individual with the more changeable psychological states of anxiety, anticipation, expectation and adaptation. Stimuli giving rise to nausea and vomiting originate from visceral, vestibular, and chemoreceptor trigger zone inputs which are mediated by serotonin/ dopamine, histamine/acetylcholine and serotonin/ dopamine, respectively. These relationships serve as the basis on which current pharmacological therapy for nausea and vomiting is recommended.

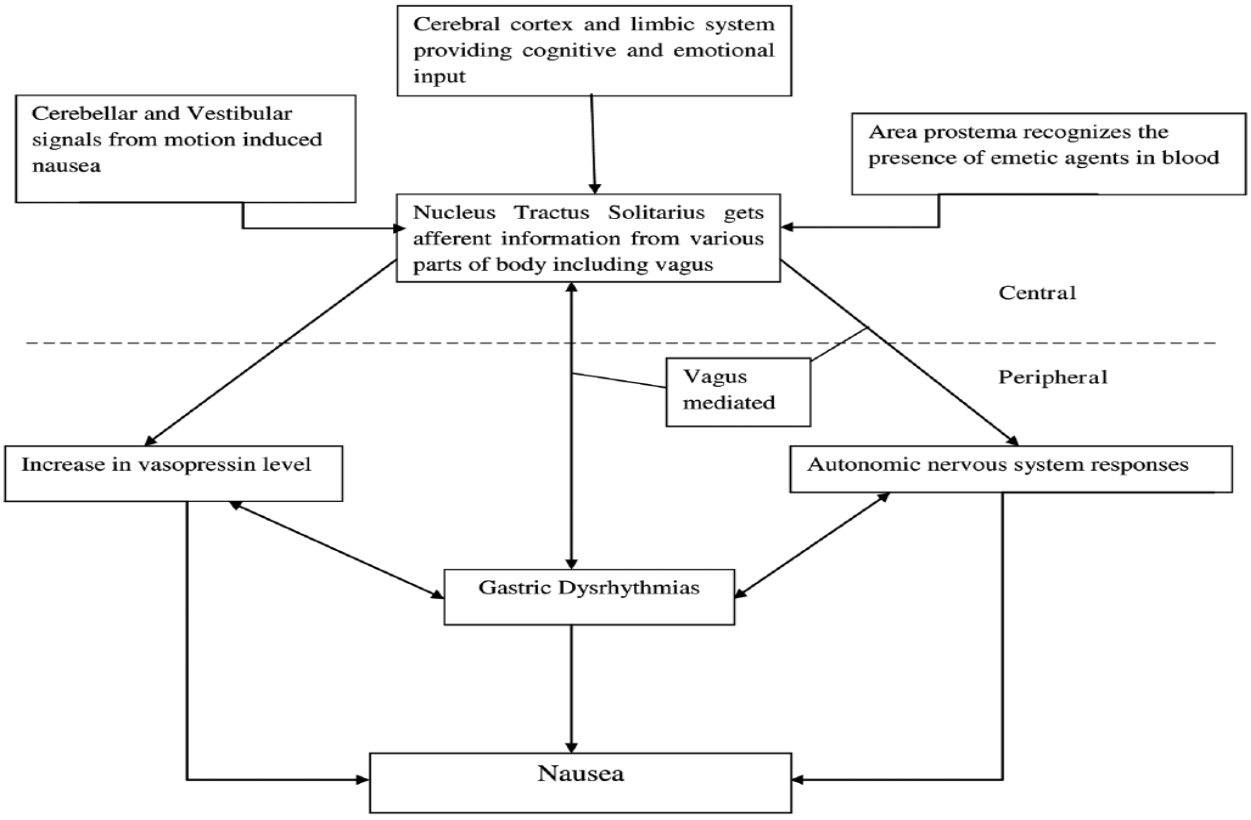



**Fig.5.2 Pathogenesis of Nausea**

## 5.3. MAJOR CAUSES OF EMESIS [58]

### 5.3.1. Gastritis

Gastritis is an inflammation, irritation, or erosion of the lining of the stomach.

### 5.3.2. Pancreatitis

Pancreatitis causes ileus due to intestinal inflammation, resulting in direct afferent input to the vomiting center. Metoclopramide is the most common antiemetic used in these patients because it acts centrally and peripherally.

### 5.3.3. Chemotherapy and Other Drugs

Emesis caused by cancer chemotherapy and other drugs (e.g., digitalis) is mediated by 5-HT3-serotonergic receptors. Nausea and vomiting associated with chemotherapy can be classified as acute, delayed and anticipatory.[62] The chemotherapeutic drugs most commonly associated with vomiting include Cisplatin, Cyclophosphamide, Dacarbazine, and doxorubicin. Metoclopramide is widely used to control chemotherapy-induced vomiting.

### 5.3.4. Motion Sickness

Motion sickness, or kinetosis, is generated from the vestibular apparatus. Motion sickness is caused by three mechanisms:

(1) Conflicting inputs from the visual and vestibular systems

(2) Conflicting inputs from the two vestibular systems

(3) Comparison of input from these systems with the individual's expectations derived from previous experiences. Vomiting caused by motion sickness involves M1-cholinergic and H1-histaminergic receptors and treatment should antagonize both receptors.

### 5.3.5. Uremia

Uremic toxins cause decreased gastrin clearance and irritate the gastrointestinal mucosa, resulting in ulcerative lesions and gastritis. When these toxins cross the blood–brain barrier, they stimulate central and peripheral receptors and activate D2-dopaminergic receptors in the CRTZ. Dopamine antagonists like metoclopramide and chlorpromazine effectively block these receptors.

### 5.3.6. Gastrointestinal Motility Disorders

Prokinetic Cisapride, metoclopramide, and erythromycin should be used to control vomiting due to non obstructive delayed gastric emptying. These drugs exert their effects on different receptors. Cisapride, the most effective prokinetic agent available, lacks direct antiemetic effects but stimulates 5-HT4-serotonergic receptors.

## 5.4. ANTIEMETIC AGENTS [59-61, 63, 64, 65]

The treatment of nausea and vomiting aims to antagonise the afferent supply to the vomiting centre. Antiemetic drugs can be classified according to the receptor at which they act:

- Dopamine antagonists
- Anticholinergics
- Antihistamines
- Serotonin antagonists
- Miscellaneous.

### 5.4.1. DOPAMINE ANTAGONISTS

The CTZ is rich in dopamine receptors; hence most drugs that antagonise $D_2$ receptors have antiemetic properties. The dopamine antagonists used clinically as anti emetics can be divided into three groups: Phenothiazines, butyrophenones and benzamides.

- Phenothiazines –Chlorpromazine, prochlorperazine.
- Butyrophenones- Droperidol, Domperidone.
- Benzamides- Metoclopramide.

### 5.4.2. ANTICHOLINERGICS

Anticholinergics are effective antagonists at the muscarinic receptors; they have minimal activity at the nicotinic acetylcholine (Ach) receptors, found in autonomic ganglia and the neuromuscular junction.

Naturally occurring tertiary amines such as atropine and hyoscine are able to cross the BBB; their central effects include sedation, amnesia, anti emesis and the central Anticholinergics syndrome.

### 5.4.3. ANTIHISTAMINES

**Cyclizine**

Cyclizine is a piperazine derivative, and is available as tablets or as a clear, colourless solution for IV or IM injection. It is used as to treat motion sickness, radiotherapy-induced emesis, PONV and opioid-induced emesis.

### 5.4.4. SEROTONIN (5-HT3) ANTAGONISTS

**Ondansetron**

Ondansetron is a synthetic carbazole, and is available as tablets, a suppository or a clear solution for slow IV injection. It is widely used in the management of nausea and vomiting induced by chemo- or radiotherapy as well as in the preoperative period. It is ineffective for vomiting induced by motion sickness or dopamine agonists.

**Granisetron**

Granisetron is available in tablet form and as a solution for slow IV injection.

### 5.4.5. MISCELLANEOUS

Dexamethasone, propofol, cannabinoids.

# *DRUG PROFILE*

# 6. DRUG PROFILE

## 6.1. METOCLOPRAMIDE HYDROCHLORIDE [66-74]

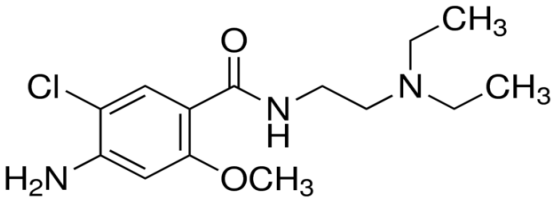
**IUPACNAME:**

4-amino-5-chloro-N-[2-(Diethyl amino) ethyl]-2-methoxybenzamide

**MOLECULAR FORMULA:**

$C_{14}H_{22}ClN_3O_2$, HCL, $H_2O$

**STRUCTURAL FORMULA:**




**MOLECULAR WEIGHT:** 354.3

**MELTING POINT**: 180-183º C

**DESCRIPTION**:

A white or almost white, crystalline powder

**SOLUBILITY:**

Very soluble in water, freely soluble in ethanol (95 percent), sparingly soluble in dichloromethane, practically insoluble in ether.

**CAS NUMBER:** 54143-57-6

**CATEGORY:** Antiemetic

**PHARMACOKINETICS**

**ABSORPTION:**

Metoclopramide is rapidly and completely absorbed in gastrointestinal tract, enters the brain, crosses the placenta and is secreted in milk. Oral Bioavailability-80%.

**VOLUME OF DISTRIBUTION:**

Adults: 2.2 -3.5L/kg, Children: 1.93 -4.4 L/kg.

**PROTEIN BINDING:**

Plasma protein binding 13-30%.

**METABOLISM:**

Hepatic metabolism. About 80% of the drug is excreted in urine in the 24 hours after administration.

**ELIMINATION:**

Approximately 85% of an orally administered dose appears in the urine within 72 hours.

**HALF LIFE:**

Elimination half life: 5 hours.

**MECHANISM OF ACTION:**

Metoclopramide acts through both dopaminergic and seratogenic receptors. The antiemetic action of Metoclopramide is due to its antagonist activity at $D_2$ receptors in chemoreceptor trigger zone in the central nervous system it prevents nausea vomiting triggered by most stimuli. Metoclopramide has a partial 5-$HT_4$ receptor agonist activity that enhances release of acetylcholine in the myenteric plexus and is responsible for its gastrointestinal prokinetic action. Metoclopramide is equipotent to chlorpromazine in preventing vomiting, at one-tenth of chlorpromazine doses.

Metoclopramide is an effective antiemetic that acts both centrally (causing dopamine blockade in the chemoreceptor trigger zone and decreasing sensitivity of the visceral nerves that transmit GI impulses to the central emetic center) and peripherally by stimulating motility of the upper gastrointestinal tract and increasing the lower esophageal sphincter basal tone. Metoclopramide counteracts some of the physiological changes during pregnancy that may lead to nausea or vomiting, such as decreased lower esophageal sphincter tone.

**INDICATIONS:**

Diabetic gastric statis, prevention of cancer chemotherapy induced emesis, prevention of postoperative nausea and vomiting, intubation of small intestine, radiographic examination of the upper GI tract, gastro esophageal reflux, and nausea vomiting in migraine.

**CONTRAINDICATIONS:**

i. Patients having increased gastrointestinal motility might be dangerous. Eg. Presence of gastrointestinal haemorrhage, mechanical obstruction or perforation.
ii. Patients sensitive to procaine and procainamide may be sensitive to metoclopromide.
iii. Patients with porphyria.
iv. Metoclopramide should not be used in patients with epilepsy since it increases the frequency and severity of seizures.
v. Should not be administered to patients receiving other drugs which are likely to cause extra pyramidal reactions.
vi. Pheochromocytoma
vii. Hypersensitivity

**ADVERSE REACTIONS:**

- Sedation
- Dizziness
- Loose stools
- Muscle dystonias
- Parkinsonism
- Galactorrhoea
- Gynaecomastia
- Extra pyramidal symptoms
- Insomnia

**DOSE:**

- The adult dose of metoclopramide 5 or 10 mg three times daily. Child dose 0.2-0.5/kg three times in a day.
    i. 5-14 years : 2.5 mg to 5 mg three times in a day
    ii. 3-5 years 2 mg for three times in a day
    iii. 1-3 years 1 mg for three times in a day

- The total daily dose of metoclopramide should not normally exceed 0.5 mg/kg of bodyweight with maximum of 30 mg daily.

**AVAILABLE DOASAGE FORM:**

i. Oral solution: 5mg/ ml
ii. Tablets: 5 mg, 10 mg
iii. Parenteral injection: 5mg/ml

# *EXCIPIENT PROFILE*

## 7.1 SUCROSE [76]

1. **Non proprietary names:**

   **BP:** Sucrose

   **JP:** Sucrose

   **Ph Eur:** Sucrose

   **USP-NF:** Sucrose

2. **Synonyms:**

   Beet sugar: cane sugar: refined sugar: saccharose: saccharum, sugar.

3. **Chemical name:**

   β-D-fractofuranosyl-α-D- glucopyranoside

4. **Molecular weight:** 342.30

5. **Melting point :**160–186ºC

6. **Functional category:**

   Confectionary base; coating agent; granulation aid; suspending agent; sweetening agent; tablet binder; tablet and capsule diluent; tablet filler; therapeutic agent; viscosity-increasing agent.

7. **Description:**

   Sucrose occurs as colourless crystals, as crystalline masses or blocks, or as a white crystalline powder; it is odourless and has a sweet taste.

8. **Solubility:**

   i. Soluble in ethanol 1in 400 at 20°C

   ii. Soluble in water 1 in 0.5 at 20°C at and 1 in 0.2 at 100°C.

9. **Incompatibility:**

   Powdered sucrose may be contaminated with traces of heavy metals, which can lead to incompatibility with active ingredients, e.g., ascorbic acid. In the presence of dilute or concentrated acids, sucrose is hydrolysed or inverted to dextrose and fructose (invert sugar).

10. **Applications:**

    It is used for oral liquid formulations in the concentration of 67%w/w as syrup and sweetening agent.

## 7.2. MANNITOL

**1. Nonproprietary Names**

**BP:** Mannitol

**JP:** D-Mannitol

**PhEur**: Mannitol

**USP:** Mannitol

**2. Synonyms:**

Cordycepic acid; C PharmMannidex; E421; Emprove; manna sugar; D-mannite; mannite; mannitolum; Mannogem; Pearlitol.

**3. Chemical Name:**

D-Mannitol

**4. CAS Registry Number:**

[69-65-8]

**5. Molecular weight:** 182.17

**6. Functional Category**

Diluents, plasticizer, sweetening agent, tablet capsule diluents, therapeutic agent, and tonicity agent.

**7. Melting point:** 166-168ºC

**8. Description:**

Mannitol is D-mannitol. It is a hexahydric alcohol related to mannose and is isomeric with sorbitol. Mannitol occurs as a white, odourless, crystalline powder, or free flowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth. Microscopically, it appears as orthorhombic needles when crystallized from alcohol. Mannitol shows polymorphism.

**9. Solubility:**

i. Soluble in ethanol 1in 83 at 20°C
ii. Soluble in water 1 in 5.5 at 20°C
iii. Practically insoluble in ether

**9. Incompatibilities**

- Mannitol solutions, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride.
- Mannitol is incompatible with xylitol infusion and may form complexes with some metals such as aluminium, copper, and iron.
- Mannitol was found to reduce the oral bioavailability of cimetidine compared to sucrose.

**10. Applications:**

i. Mannitol is widely used in pharmaceutical formulations and food products.

ii. In pharmaceutical preparations it is primarily used as a diluent (10–90% w/w) in tablet formulations.

iii. Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and 'mouth feel'.

iv. Mannitol has also been used to prevent thickening in aqueous antacid suspensions of aluminium hydroxide (<7% w/v). It has been suggested as a plasticizer in soft-gelatin capsules, as a component of sustained-release tablet formulations.

## 7.3. DEXTROSE

**1. Non proprietary Names:**

**BP:** Glucose

**JP:** Glucose

**PhEur:** Glucose Monohydrate

**USP:** Dextrose2

**2. Synonyms:**

Blood sugar; Caridex; corn sugar; C PharmDex; Dextrofin; D-(þ)-glucopyranose monohydrate; glucosum monohydricum; grape sugar; Lycadex PF; Roferose; starch sugar; Tabfine D-100.

**3. Chemical Name:**

D-(þ)-Glucose monohydrate

**4. CAS Registry Number:**

[5996-10-1]

**5. Empirical Formula**:

$C_6H_{12}O_6.H_2O$

**6. Molecular weight:** 198.17 (for monohydrate)

**7. Melting point:** 146ºC

**8. Description:**

Dextrose occurs as odourless, sweet-tasting, colourless crystals or as a white crystalline or granular powder.

**9. Solubility:**

i. Soluble in water 1 in 1 at 20ºC
ii. Soluble in 95(%) ethanol 1 in 60 at 20ºC
iii. Practically insoluble in chloroform and ether.

**10. Functional Category**

Diluent, therapeutic agent, tonicity agent, sweetening agent.

**!1. Applications**

i. Dextrose is widely used in solutions to adjust tonicity and as a sweetening agent.
ii. Dextrose is also used as a wet granulation diluents and binder, and as a direct-compression tablet diluent and binder.

## 7.4. ISOMALT

**1. Non proprietary Names:**

**BP:** Isomalt

**PhEur:** Isomalt

**USP-NF:** Isomalt

**2. Synonyms:**

C PharmIsomaltidex; E953; galen IQ; hydrogenated isomaltulose; hydrogenated palatinose; Isomaltidex 16500; isomaltum; Palatinit.

**3. Chemical Name:**

Isomalt

**4. CAS Registry Number**:

[64519-82-0]

5**. Empirical Formula and Molecular Weight:**

i. $C_{12}H_24O_{11}$ - 344.32 (for anhydrous)

ii. $C_{12}H2_4O_{11}2H_2O$ -380.32 (for dihydrate)

**6. Melting point:** 168–171ºC

**7. Solubility:**

Soluble in water.

**8. Description:**

Isomalt is a sugar alcohol (polyol) that occurs as a white or almost white powder or granular or crystalline substance. It has a pleasant sugar like taste with a mild sweetness approximately 50–60% of that of sucrose.

**9. Functional Category:**

Coating agent, granulation aid, sweetening agent, tablet and capsule diluent, medicated base.

**10. Applications:**

i. In buccal applications such as chewable tablets it is commonly used because of its negligible negative heat of solution, mild sweetness, and 'mouth feel'.

ii. It is also used widely in lozenges, sugar-free chewing gum, and hard-boiled candies, and as a sweetening agent in confectionery for diabetics.

## 7.5. LIQUID GLUCOSE

**1. Non proprietary Names:**

**BP:** Liquid Glucose

**PhEur:** Glucose, Liquid

**USP-NF:** Liquid Glucose

**2. Synonyms:**

Corn syrup, Pharm Sweet, Flolys, Glucomalt, glucose syrup, glucosum liquidum, Glucosweet, Mylose, Roclys, starch syrup.

**3. Chemical Name:**

Liquid glucose

**4. CAS Registry Number:**

8027-56-3

**5. Empirical Formula:**

$C_6H_{14}O_7$

**6. Molecular Weight:** 198.17

**7. Functional Category:**

Coating agent, sweetening agent, tablet binder.

**8. Description:**

Liquid glucose is an aqueous solution of several compounds, principally dextrose, dextrin, fructose, and maltose, with other oligosaccharides and polysaccharides. It is a colourless, odourless, and viscous sweet-tasting liquid, ranging in colour from colourless to straw-colour.

**9. Solubility:**

Solubility miscible with water, partially miscible with ethanol (90%).

**11. Applications**

i. Liquid glucose is used as a base in oral solutions and syrups and also as a granulating and coating agent in tablet manufacture.

ii. In sugar solutions for tablet coating, liquid glucose is used to retard the crystallization of the sucrose.

iii. Liquid glucose is also used in confectionery products.

## 7.6. PROPYLENE GLYGOL

**1. Non proprietary Names:**

**BP:** Propylene Glycol

**JP:** Propylene Glycol

**PhEur:** Propylene Glycol

**USP:** Propylene Glycol

**2. Synonyms:**

1,2-Dihydroxypropane; E1520; 2-hydroxypropanol; methyl ethylene glycol; methyl glycol; propane-1,2-diol; propylenglycolum.

**3. Chemical Name:**

1, 2-Propanediol

**4. CAS Registry Number:**

[57-55-6]

**5. Empirical Formula:**

$C_3H_8O_2$

**6. Molecular Weight:** 76.09

**7. Description:**

Propylene glycol is a clear, colourless, viscous, practically odourless liquid, with a sweet, slightly acrid taste resembling that of glycerin.

**8. Incompatibilities:**

Propylene glycol is incompatible with oxidizing reagents such as potassium permanganate.

**9. Functional Category:**

Antimicrobial preservative, disinfectant, humectants, plasticizer, solvent, stabilizing agent, water-miscible co solvent.

**10. Application**:

i. As an antiseptic it is similar to ethanol, and against molds it is similar to glycerin and only slightly less effective than ethanol.

ii. Propylene glycol is commonly used as a plasticizer in aqueous film-coating formulations.

iii. Propylene glycol is also used in cosmetics and in the food industry as a carrier for emulsifiers and as a vehicle for flavours.

## 7.7. POLY ETHYLENE GLYGOL 200

**1. Non proprietary Names:**

**BP:** Macrogols

**PhEur:** Macrogols

**USP-NF:** Polyethylene Glycol

**Synonyms:**

1Carbowax; Carbowax Sentry; Lipoxol; Lutrol E; macrogola; PEG; Pluriol E; polyoxyethylene glycol.

**2. Chemical Name:**

A-Hydro-o-hydroxy poly(oxy-1,2-ethanediyl)

**3. CAS Registry Number:**

[25322-68-3]

**4. Empirical Formula:**

HO CH2 (CH2OCH2) mCH2OH where m represents the average number of oxyethylene groups.

**5. Molecular Weight:** 190-210

**6. Functional Category:**

Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

**Description:**

Liquid grades (PEG 200–600) occur as clear, colourless or slightly yellow-colour, viscous liquids. They have a slight but characteristic odour and a bitter, slightly burning taste.

**Solubility:**

All grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols. Liquid polyethylene glycols are soluble in acetone, alcohols, benzene, glycerin, and glycols.

**10. Applications:**

i. Liquid polyethylene glycols are used as water-miscible solvents for the contents of soft gelatin capsules. However, they may cause hardening of the capsule shell by preferential absorption of moisture from gelatin in the shell.

ii. Polyethylene glycols have been used in the preparation of urethane hydrogels, which are used as controlled-release agent.

## 7.8. GLYCERIN

**1. Non-proprietary Names:**

**BP:** Glycerol

**JP:** Concentrated Glycerin

**PhEur:** Glycerol

**USP:** Glycerin

**2. Synonyms:**

Croderol; E422, Glicerol, Glycerine, glycerolum, Glycon G-100,Kemstrene, Optim, Pricerine, 1,2,3-propanetriol, trihydroxypropane, glycerol.

**3. Chemical Name:** Propane-1,2,3-triol

**4. CAS Registry Number:**

[56-81-5]

**5. Empirical Formula:**

$C_3H_8O_3$

**6. Molecular Weight:** 92.09

**7. Functional Category:**

Antimicrobial preservative; co solvent; emollient; humectants; plasticizer; solvent; sweetening agent; tonicity agent.

**8. Description:**

Glycerin is a clear, colourless, odourless, viscous, hygroscopic liquid; it has a sweet taste, approximately 0.6 times as sweet as sucrose.

**9. Incompatibilities:**

Glycerin may explode if mixed with strong oxidizing agents such as chromium trioxide, potassium chlorate, or potassium permanganate.

**10. Applications:**

i. Glycerine is additionally used in aqueous and non aqueous gels and also as an additive in patch applications.

ii. In oral solutions, glycerin is used as a solvent, sweetening agent, antimicrobial preservative and viscosity-increasing agent. It is also used as a plasticizer and in film coatings.

iii. Glycerin is used as a plasticizer of gelatin in the production of soft-gelatin capsules and gelatin suppositories.

## 7.9. CITRIC ACID

**1. Non proprietary Names:**

**BP:** Citric Acid Monohydrate

**JP:** Citric Acid Hydrate

**PhEur:** Citric Acid Monohydrate

**USP:** Citric Acid Monohydrate

**2. Synonyms:**

Acidum citricum monohydricum; E330; 2-hydroxypropane-1,2,3- tricarboxylic acid monohydrate.

**3. Chemical Name:**

2-Hydroxy-1, 2, 3-propanetricarboxylic acid monohydrate

**4. CAS Registry Number:**

[5949-29-1]

**5. Empirical Formula:** $C_6H_8O_7H_2O$

**6. Molecular Weight:** 210.14

**7. Melting point:** 100ºC

**8. Functional Category:**

Acidifying agent, antioxidant, buffering agent, chelating agent, flavour enhancer, preservative.

**9. Description:**

Citric acid monohydrate occurs as colourless or translucent crystals, or as a white crystalline, efflorescent powder. It is odourless and has a strong acidic taste. The crystal structure is orthorhombic.

**10. Solubility:**

Soluble 1 in 1.5 parts of ethanol and 1 in less than 1 part of water.

**12. Applications:**

i. Citric acid (as either the monohydrate or anhydrous material) is widely used in pharmaceutical formulations and food products, primarily to adjust the pH of solutions.

ii. In food products, citric acid is used as a flavour enhancer for its tart, acidic taste.

## 7.10. MENTHOL

**1. Non proprietary Names**

**BP:** Racementhol

**JP:** dl-Menthol

**PhEur:** Menthol, Racemic

**USP:** Menthol

**2. Synonyms:**

Hexahydrothymol,2-isopropyl-5-methylcyclohexanol,4-isopropyl-1-methylcyclohexan-3-ol, 3-p-menthanol, p-menthan-3-ol, d,l menthol, mentholum racemicum, menthomenthol, mentoli, mentolis, peppermint camphor, racemic menthol.

**3. Chemical Name:** (1RS, 2 RS, 5RS)-(±)-5-Methyl-2-(1-methylethyl)cyclohexanol

**4. CAS Registry Number:**

[15356-70-4]

**5. Empirical Formula:**

$C_{10}H_{20}O$

**6. Molecular Weight:** 156.27

**7. Functional Category:**

Flavouring agent, therapeutic agent.

**8. Incompatibilities:**

Incompatible with: butylchloral hydrate; camphor; chloral hydrate; chromium trioxide; b-naphthol; phenol; potassium permanganate; pyrogallol; resorcinol; and thymol.

**9. Applications:**

Menthol is widely used in pharmaceuticals, confectionery, and toiletry products as a flavouring agent or odour enhancer. In addition to its characteristic peppermint flavour, l-menthol, which occurs naturally, also exerts a cooling or refreshing sensation that is exploited in many topical preparations.

## 7.11. METHYLCELLULOSE

**1. Non proprietary Names**

**BP:** Methylcellulose

**JP:** Methylcellulose

**PhEur:** Methylcellulose

**USP:** Methylcellulose

**2. Synonyms:**

Benecel; Cellacol; Culminal MC; E461; Mapolose; Methocel; methylcellulosum; Metolose; Tylose; Viscol.

**3. Chemical Name:**

Cellulose methyl ether

**4. CAS Registry Number:**

[9004-67-5]

**5. Molecular Weight:** 10,000–22000 Da.

**6. Melting point:** 190-200ºC

**7. Functional Category:**

Coating agent, emulsifying agent, suspending agent, tablet and capsule disintegrant, tablet binder, viscosity-increasing agent.

**8. Description:**

Methylcellulose occurs as a white, fibrous powder or granules. It is practically odourless and tasteless. It should be labelled to indicate its viscosity type (viscosity of a 1 in 50 solution).

**9. Applications**

i. Methylcellulose may be added to a tablet formulation to produce sustained-release preparations.

ii. Methylcellulose delays the settling of suspensions and increases the contact time of drugs, such as antacids, in the stomach.

## 7.12. ASPARTAME

**1. Non proprietary Names**

**BP:** Aspartame

**PhEur:** Aspartame

**USP-NF:** Aspartame

**2. Synonyms:**

(3S)-3-Amino-4-[[(1S)-1-benzyl-2-methoxy-2-oxoethyl]amino]-4- oxobutanoic acid; 3-amino-N-(a-carboxyphenethyl) succinamic acid N-methyl ester; 3-amino-N-(a-methoxycarbonylphenethyl)- succinamic acid; APM; aspartamum; aspartyl phenylamine methyl ester; Canderel; E951; Equal; methyl N-L-a-aspartyl-L-phenylalaninate; NatraTaste; NutraSweet; Pal Sweet; Pal Sweet Diet; Sanecta; SC-18862; Tri-Sweet.

**3. Chemical Name:**

N-L-a-Aspartyl-L-phenylalanine 1-methyl ester

**4. CAS Registry Number:**

[22839-47-0]

**5. Empirical Formula:**

$C_{14}H_{18}N_2O_5$

**6. Molecular Weight:** 294.30

**7. Melting point**: 246–2478C

**8. Functional Category:**

Sweetening agent

**9. Description:**

Aspartame occurs as an off white, almost odourless crystalline powder with an intensely sweet taste.

**10. Solubility:**

Slightly soluble in ethanol (95%) sparingly soluble in water. At 208 ºC the solubility is 1% w/v at the iso-electric point (pH 5.2). Solubility increases at higher temperature and at more acidic pH, e.g., at pH 2 and 208ºC solubility is 10% w/v.

**11. Incompatibilities:**

Aspartame is incompatible with dibasic calcium phosphate and also with the lubricant magnesium stearate.

**12. Applications**

Aspartame is used as an intense sweetening agent in beverage products, food products, and table-top sweeteners, and in pharmaceutical preparations including tablets, powder mixes, and vitamin preparations. It enhances flavour systems and can be used to mask some unpleasant taste characteristics; the approximate sweetening power is 180–200 times that of sucrose.

# MATERIALS AND METHODS

## 8.1. MATERIALS USED

**Table.8.1 Materials used in the formulations**

| S.NO | CHEMICALS | SUPPLIERS |
|---|---|---|
| 1. | Metoclopramide HCL | Tablets India Limited, Chennai. |
| 2. | Isomalt | TTK Pharma Ltd, Chennai. |
| 3. | Sucrose | TTK Pharma Ltd, Chennai. |
| 4. | Liquid glucose | TTK Pharma Ltd, Chennai. |
| 5. | Mannitol | Saimirra Innopharm, Chennai. |
| 6. | Dextrose | Pharmafabrikon, Madurai. |
| 7. | Methyl cellulose | Pharmafabrikon, Madurai. |
| 8. | Aspartame | TTK Pharma Ltd, Chennai |
| 9. | Citric acid | Pharmafabrikon, Madurai. |
| 10. | Propylene glycol | Saimirra Innopharm, Chennai |
| 11. | Poly ethylene glycol 200 | Saimirra Innopharm, Chennai |
| 12. | Glycerine | Saimirra Innopharm, Chennai |
| 13. | Menthol | TTK Pharma Ltd, Chennai |

## 8.2. INSTRUMENTS USED

**Table: 8.2 Instruments utilized for formulations**

| INSTRUMENTS | SUPPLIERS |
|---|---|
| UV spectrophotometer | Shimadzu 1800,Japan |
| Weighing balance | Asha Scientific Company |
| Magnetic Stirrer | REMI |
| pH meter | MC Dalal, india |
| Dissolution Apparatus | Campbell Electronics |
| FT-IR | Shimadzu,Japan |
| Vernier caliper | Mitutoyo, Japan |
| Monsanto hardness tester | Campbell Electronics |

## 8.3. PREFORMULATION STUDIES [34]

Preformulation studies were the first step in the rational development of any formulation. It can be defined as "investigation of physical and chemical properties of the drug substance alone and combined with the excipients". These studies focus on those physiochemical properties of the new compound that could affect drug performance and development of an efficacious formulation. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bio available dosage forms that can be

- To establish physical characteristics.
- To establish its compatibility with the excipient.

### 8.3.1. Determination of melting point of Metoclopramide hydrochloride [77]

The electrical melting point apparatus using capillary method measured the melting point of Metoclopramide HCL.

### 8.3.2. Determination of λ max of Metoclopramide hydrochloride [77]

Metoclopramide HCL, solution in phosphate buffer 6.8 was prepared, then the solution was scanned by spectrophotometer from 200-400 nm, and λ max of the drug was determined.

## 8.4. DRUG-EXCIPIENT COMPATIBILITY STUDIES

The proper design and formulation of a dosage form requires consideration for the physical and chemical characteristics of all drug substances and excipients used in fabricating the final product. The successful formulation of a stable and effective dosage forms depends on the careful selection of the excipients that are added in the formulation. The drug and excipients must be compatible with one another to produce a product that is stable, efficacious and easy to administer and safe.

Compatibility study was carried out by recording the sample using Fourier Transform Infra-Red Spectrophotometer (FTIR) in the range of 4000 $cm^{-1}$ to 400 $cm^{-1}$ by Potassium Bromide pellet technique. The spectra was examined and analysed for the study.

## 8.5. PREPARATION OF PHOSPHATE BUFFER pH 6.8 [78]

13.609 g of potassium hydrogen orthophosphate dissolved in 500ml of distilled water to give 0.2M of solution. 4g of sodium hydroxide is dissolved in 500ml of water to give 0.2M of solution. 500 ml of 0.2M of solution potassium hydrogen orthophosphate and 224ml of 0.2M sodium hydroxide solution are mixed together and made up to 2 litres concentration with distilled water.

## 8.6. PREPARATION OF CALIBRATION CURVE FOR METOCLOPRAMIDE HYDROCHLORIDE [79]

10 mg of Metoclopramide hydrochloride was accurately weighed and transfer to 100 ml volumetric flask. The drug is dissolved in phosphate buffer pH 6.8 and the volume was made up to 100 ml to obtain a stock solution of 100µg/ml.3,6,9,12,15,18 ml of this stock solution is again diluted with phosphate buffer pH 6.8 up to 100 ml to obtain a solution with concentrations of 3,6,9,12,15,18 µg/ml. The resulting solution is scanned at 272 nm in a double beam UV-Visible spectrophotometer.

## 8.7. FORMULATION TABLE FOR METOCLOPRAMIDE HYDROCHLORIDE MEDICATED LOZENGES

**Table 8.3 Formulation table**

| Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Metoclopramide hydrochloride (mg) | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Sucrose | 1880 | --- | --- | --- | --- | --- | --- | ---- | --- | --- |
| Dextrose | --- | 1880 | --- | --- | --- | --- | --- | --- | --- | --- |
| Mannitol | --- | --- | 1880 | --- | --- | --- | --- | --- | --- | --- |
| Isomalt | --- | --- | --- | 1880 | 1880 | 1880 | 1880 | 1862 | 1868 | 1874 |
| Liquid glucose | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 |
| Citric acid | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| Aspartame | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 90 |
| Propylene glycol | --- | --- | --- | --- | 0.1ml | --- | --- | --- | --- | --- |
| PEG 200 | --- | --- | --- | --- | --- | 0.1 ml | --- | --- | --- | --- |
| Glycerine | --- | --- | --- | --- | --- | --- | 0.1 ml | 0.1ml | 0.1ml | 0.1ml |
| Menthol | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 |
| Methylcellulose | --- | --- | ---- | --- | --- | --- | --- | 18.5<br>0.75% | 12.5<br>0.50% | 6.25<br>0.25% |
| Colour | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. | q.s |
| Flavour | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. | q.s |
| Purified water | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. | q.s |
| Total (g) | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |

## 8.8. PREPARATION OF METOCLOPRAMIDE HYDROCHLORIDE HARD CANDY MEDICATED LOZENGES [38]

The lozenges were prepared by heating and congealing technique. Syrupy base was prepared in a beaker by dissolving the required amounts of sugar in water and kept for heating on a hotplate. Temperature was maintained at 105-110 ℃ till it became thick. The drug and other excipients (except plasticizer) were added manually and mixed thoroughly after 30 min with continue process of heating. The prepared mass was further heated for 45 min and then plasticizer was added into it. Then above syrupy base was poured into pre-cooled and pre lubricated mould and the mould was kept aside for 10-15 min. Lozenges were removed from mould and were kept for air drying.

## 8.9. EVALUATION PARAMETERS

### 8.9.1. Physical parameters: [24]

The medicated lozenges were examined in terms of clarity, texture and consistency. Texture of lozenges in terms of stickiness was evaluated by visual inspection of the product.

### 8.9.2. Weight Variation Test: [24]

Ten lozenges from each batch were individually weighed in grams on an analytical balance. The average weight and standard deviations are calculated. Individual weight of each lozenge is also calculated using the same and compared with average weight. If any weight variation is there, that should fall within the prescribed limits (generally 10% for lozenge weighing 120 mg or less, 7.5% for lozenge weighing 120 mg to 300 mg and 5% for lozenge weighing more than 300 mg):

$$\% \text{ Deviation} = \left(\frac{\text{Individual weight - Average weight}}{\text{Average weight}}\right) \times 100$$

### 8.9.3. Thickness Test: [24]

The thickness in millimetres (mm) was measured individually for 10 pre weighed lozenges by using a vernier Calipers. The average thickness and standard deviation are reported. The thickness of a lozenge can vary without any change in its weight.

**8.9.4. Hardness Test:** [24]

The hardness of lozenges was measured using a Monsanto Hardness Tester. The crushing strength of the 10 lozenge with known weight and thickness of each batch was recorded in kg/cm2 and the average hardness and the standard deviation is reported.

**8.9.5. Drug Content Uniformity:** [42]

The content uniformity was tested by measuring weight equivalent to one lozenge and dissolving the powder content in 100 ml volumetric flask containing 50 ml of 6.8 phosphate buffers and allowed to stand for 30 min. The mixture was made up to volume with buffer pH 6.8. The diluted samples absorption was recorded at 272 nm. Three replication of each test were analysed for mean and standard deviation. For most of the larger dose drugs in lozenge form, the official potency range permitted is not less than 90% and not more than 110% of the labelled amount.

**8.9.6. Moisture Content:** [25]

By Gravimetric method, one gram sample is weighed and placed in a desiccator at for 24 hrs. Final weight is subtracted from initial and the difference in moisture content is calculated:

% Moisture content = Initial weight – Final weight /Initial weight × 100

**8.9.7. Mouth dissolving Time:** [38]

The mouth dissolving time was determined by in-house method. The time taken by the lozenge to dissolve completely was determined by placing each lozenge in separate beaker containing 100 ml phosphate buffer pH 6.8 at 50 rpm using mechanical stirrer and time was noted at 37°C.

**8.9.8. *In-vitro* Drug Release** [24]

The modified dissolution test apparatus USP type II (paddle) is used and 250 ml of the dissolution medium phosphate buffer pH 6.8 is placed in the beaker containing the lozenge and stirred at 100 rpm. Five ml aliquot samples are withdrawn at 5 min interval and replaced immediately with an equal volume of fresh medium i.e., phosphate buffer pH 6.8. Each aliquot is diluted and analyzed using blank, by UV-Visible spectrophotometer. The amount of drug release is determined from the standard calibration curve of pure drug.

Following parameters were used for the dissolution study

1. Apparatus : USP dissolution apparatus type II (paddle)
2. Speed of the paddle : 100 RPM.
3. Temperature : 37.5ºC ± 0.5ºC.
4. Dissolution medium : Phosphate buffer pH 6.8.
5. Volume of fluid : 250ml

The samples were analysed at 272 nm using UV-Visible spectrophotometer.

## 8.10. EVALUATION OF *IN-VITRO* RELEASE KINETICS OF OPTIMIZED FORMULATION [80]

To study the kinetics, data obtained from *in-vitro* release were plotted in various kinetic models.

### 8.10.1. Zero order equation:

The graph was plotted as percentage drug released Vs time in hours.

$$C = K_0 t$$

Where,

$K_0$ - Zero order constant in Concentration / time

**t** - Time in hours

The graph would yield a straight line with a slope equal to $K_0$ and intercept the origin of the axis. The results were tabulated and graph was shown.

### 8.10.2. First Order Equation:

The graph was plotted as log% cumulative drug remaining Vs Time in hours

$$\mathbf{Log\ C = log\ C_0 - Kt/2.303}$$

Where,

**$C_0$ -** Initial concentration of drug.

**K -** First order constant

**t** – Time

### 8.10.3. Higuchi Kinetics:

The graph was plotted as percentage cumulative drug released Vs square root of time

$$\mathbf{Q = Kt^{1/2}}$$

Where,

**K**=constant reflection design variable systems.

**t** = time in hours

Hence, drug release rate is proportional to the reciprocal of square root of time. If the plot yields as straight line and the slope is one, then the particular dosage form is considered to follow Higuchi Kinetics of drug release. The results were tabulated.

### 8.10.4. Hixson and Crowell Erosion Equation:

To evaluate the drug release with changes in the surface area and the diameter of the particles, the data were plotted using the Hixson and Crowell rate equation. The graph was plotted by cube root of percentage drug remaining Vs time in hours.

$$\mathbf{Q_0^{1/3} - Q_t^{1/3} = K_{HC}\, X_t}$$

Where,

**$Q_t$ -**Amount of drug released in time t.

**$Q_0$** - Initial amount of drug

$K_{HC}$ - Rate constant for Hixson and Crowell equation

### 8.10.5. Korsemeyer – Peppas Equation

To evaluate the mechanism of drug release, it was further plotted in Peppas equation as log cumulative percentage of drug released Vs time.

$$M_t/M_\alpha = Kt^n$$

$$\log M_t/M_\alpha = \log K + n \log t$$

Where,

$M_t/M_\alpha$ - Fraction of drug released at time t.

**t** - Release time

**K**-Kinetic constant (incorporating structural and geometric characteristics of preparation)

**α** – Diffusional exponent indicative of the mechanism of drug release.

If the value is 0.5 or less, the release mechanism follows "Fickian Diffusion" and higher values of $0.5 < n < 1$for mass transfer follow a non-fickian model (anomalous transport). The drug release follows zero-order drug release and case-II transport if the value is 1. For the values of n higher than 1, the mechanism of drug release is regarded as super case II transport. This model is used to analyse the release of pharmaceutical polymeric dosage forms when the release mechanism is not known or more than one type of release phenomenon was involved. The n value could be obtained from slope of the plot of long cumulative percentage of drug release Vs log time. The results were tabulated.

**Table.8.4. Diffusion exponent and solute release mechanism**

| Release exponent (n) | Drug transport mechanism | Rate as a function of time |
|---|---|---|
| 0.5 | Fickian diffusion | $t^{-0.5}$ |
| 0.45< n=0.89 | Non- fickian diffusion | $t^{n-1}$ |
| 0.89 | Case II transport | Zero order release |
| Higher than 0.89 | Super case II transport | $t^{n-1}$ |

## 8.11. STABILITY STUDIES: [81]

The optimized formulations were subjected to stability studies at temperature i.e. 40ºC /75% RH for a period of one month. All the evaluations were performed and tabulated.

# RESULTS AND DISCUSSION

## 9.1. PREFORMULATION STUDIES

### 9.1.1. CHARACTERIZATION OF THE DRUG

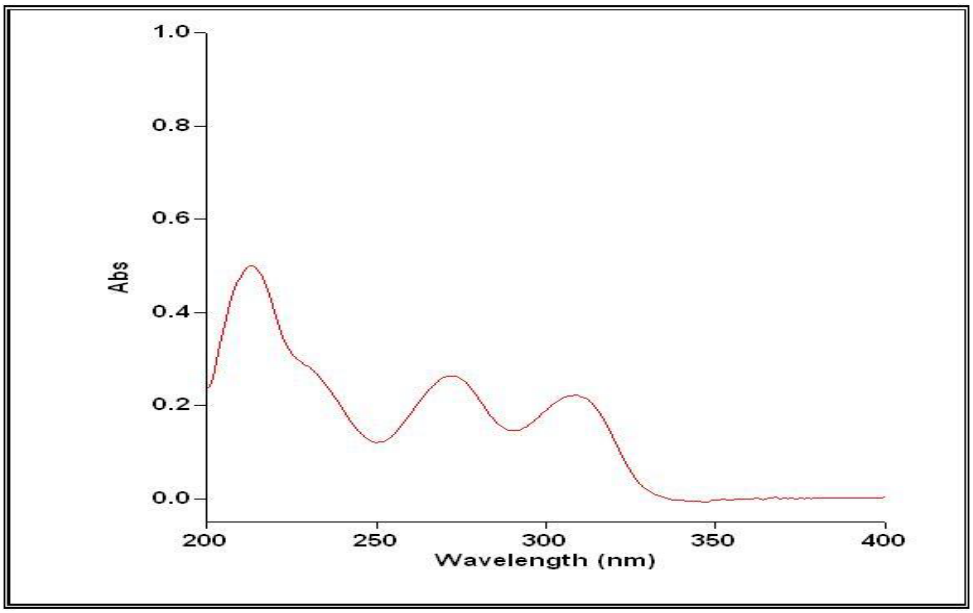
#### 9.1.1.1. Melting point of Metoclopramide Hydrochloride

Melting point was measured by the capillary method and it was found to be 182ºC.

#### 9.1.1.2. Determination of λ max of Metoclopramide hydrochloride

The maximum absorbance of the Metoclopramide hydrochloride was studied and found to be 272 nm. Hence the wavelength of 272 nm was selected for the analysis of the drug in dissolution media.

**Fig.9.1.The UV spectrum of Metoclopramide HCL in phosphate buffer 6.8**



### 9.1.2. DRUG-EXCIPIENT COMPATIBILITY STUDY

The drug excipient study was conducted to reveal the excipient compatibility with the drug.

**Table.9.1. Physical Compatibility of Drug and Excipients**

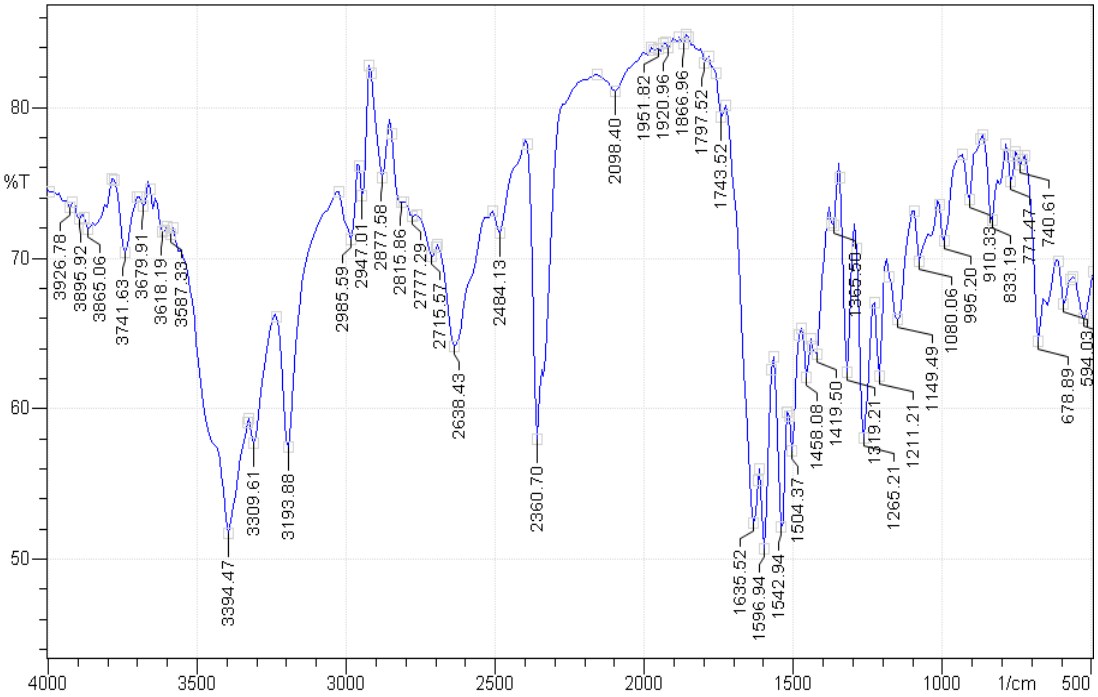
| S. No. | Drug+Excipients | Description and Condition | Room Temperature and 40ºC/75% RH in days | | |
|---|---|---|---|---|---|
| | | | $10^{th}$ | $20^{th}$ | $30^{th}$ |
| 1. | Metoclopramide hydrochloride | White crystalline Powder | NC | NC | NC |
| 2. | Sucrose | White crystalline Powder | NC | NC | NC |
| 3. | Mannitol | White crystalline powder | NC | NC | NC |
| 4. | Dextrose | White powder | NC | NC | NC |
| 5. | Isomalt | White powder | NC | NC | NC |
| 6. | Citric Acid | White crystalline powder | NC | NC | NC |
| 7. | Aspartame | White powder | NC | NC | NC |
| 8. | Methyl Cellulose | White powder | NC | NC | NC |

**NC**-No Change

The physical compatibility was observed visually. The study reveals that the drug and the excipients were physically compatible with each other as there was no change of colour. The excipients are compatible with the drug selected for the formulation.

### 9.1.2. CHEMICAL COMPATIBILITY STUDY:

**Fig.9.2. IR SPECTRA OF METOCLOPRAMIDE HYDROCHLORIDE**



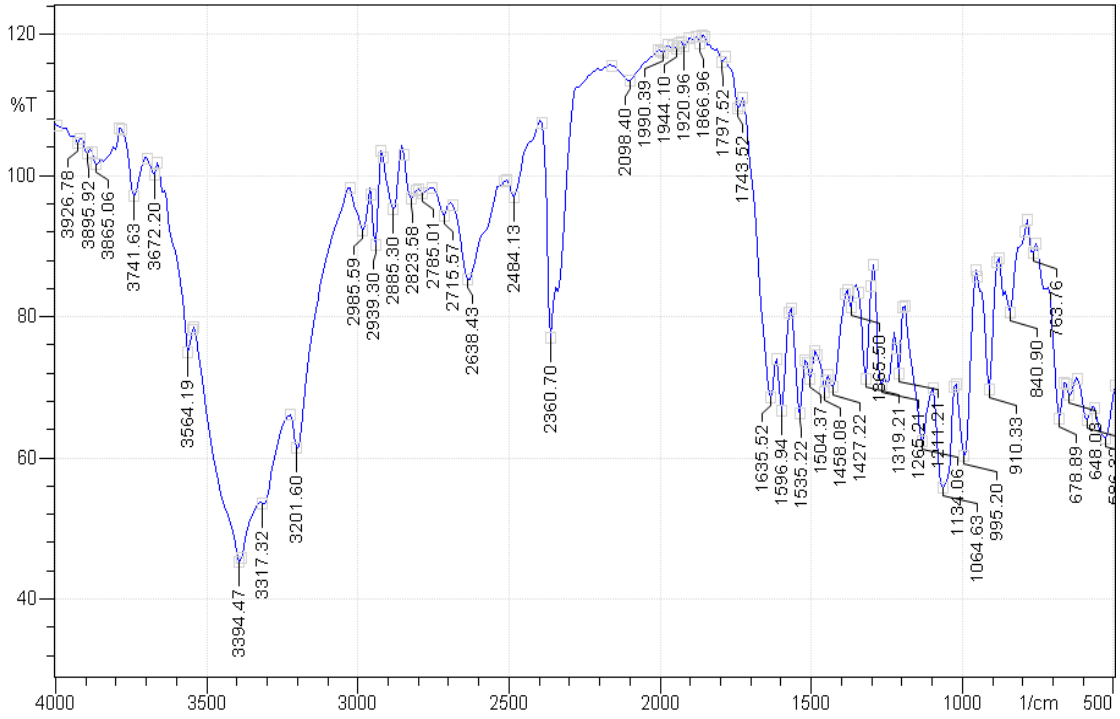

**Observation:**

**Table: 9.2. FTIR spectral interpretation of Metoclopramide hydrochloride**

| S. No | Functional group | Characteristic peak | | Observed peak | |
|---|---|---|---|---|---|
| | | Stretching | Bending | Stretching | Bending |
| 1 | Ar-$NH_2$ | 3500-3350 | - | 3394.4 | - |
| 2 | CO-NH | 1700-1500 | - | 1635.5 | - |
| 3 | Ar-C=C | 1600-1400 | - | 1596.9 | - |
| 4 | C-O-C | 1250-1050 | - | 1265.2 | - |
| 5 | C-$Cl_3$ | 800-600 | - | 678.8 | - |

There is no disappearance of characteristic peaks of drug in FT-IR Spectra. Hence there is no interaction.

**Fig.9.3. IR SPECTRA OF DRUG + SUCROSE**



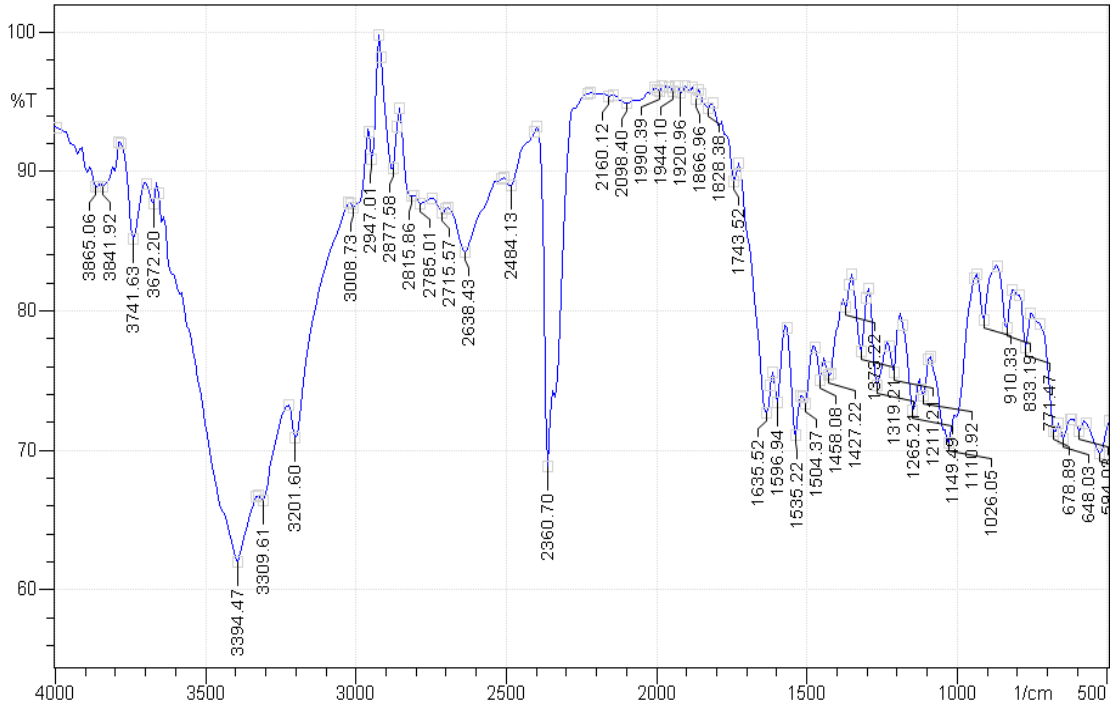

**Observation:**

**Table: 9.3. FTIR spectral interpretation of Metoclopramide hydrochloride with Sucrose**

| S. No | Functional group | Characteristic peak | | Observed peak | |
|---|---|---|---|---|---|
| | | Stretching | Bending | Stretching | Bending |
| 1 | Ar-$NH_2$ | 3500-3350 | - | 3394.4 | - |
| 2 | CO-NH | 1700-1500 | - | 1635.5 | - |
| 3 | Ar-C=C | 1600-1400 | - | 1535.2 | - |
| 4 | C-O-C | 1250-1050 | - | 1265.2 | - |
| 5 | C-$Cl_3$ | 800-600 | - | 678.8 | - |

There is no disappearance of characteristic peaks of drug in FT-IR Spectra. Hence there is no interaction.

**Fig.9.4. IR SPECTRA OF DRUG + DEXTROSE**



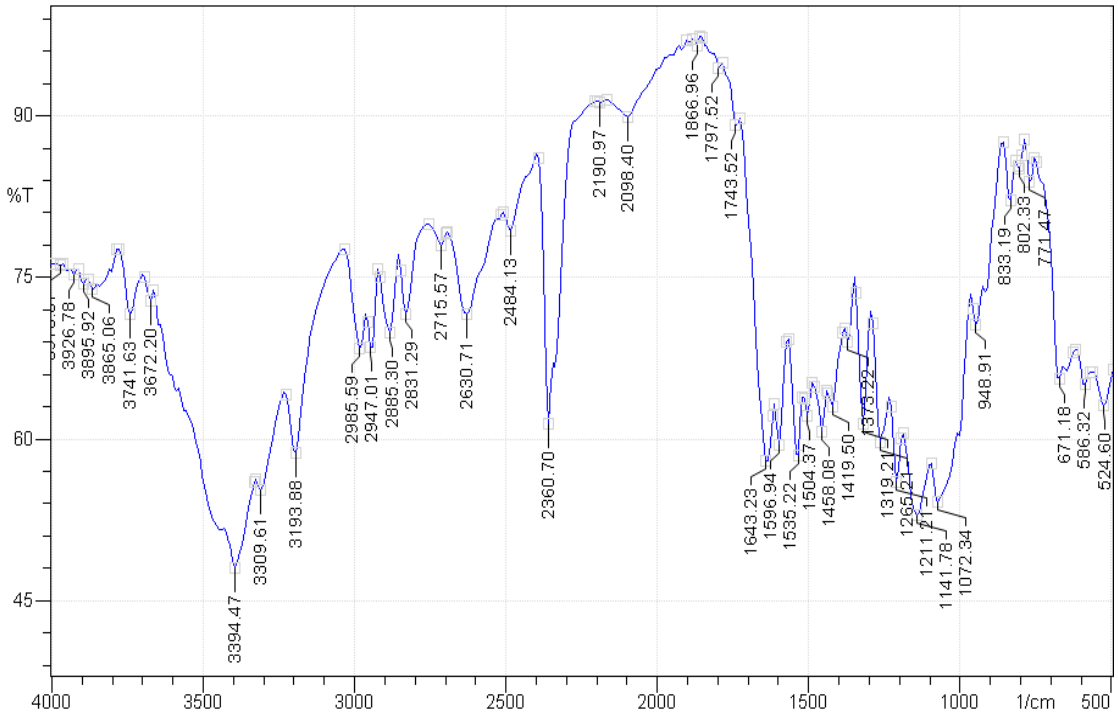

**Observation:**

**Table: 9.4. FTIR spectral interpretation of Metoclopramide hydrochloride with Dextrose**

| S. No | Functional group | Characteristic peak | | Observed peak | |
|---|---|---|---|---|---|
| | | Stretching | Bending | Stretching | Bending |
| 1 | Ar-$NH_2$ | 3500-3350 | - | 3394.4 | - |
| 2 | CO-NH | 1700-1500 | - | 1635.5 | - |
| 3 | Ar-C=C | 1600-1400 | - | 1535.2 | - |
| 4 | C-O-C | 1250-1050 | - | 1149.4 | - |
| 5 | C-$Cl_3$ | 800-600 | - | 678.8 | - |

There is no disappearance of characteristic peaks of drug in FT-IR Spectra. Hence there is no interaction.

**Fig.9.5. IR SPECTRA OF DRUG + MANNITOL**



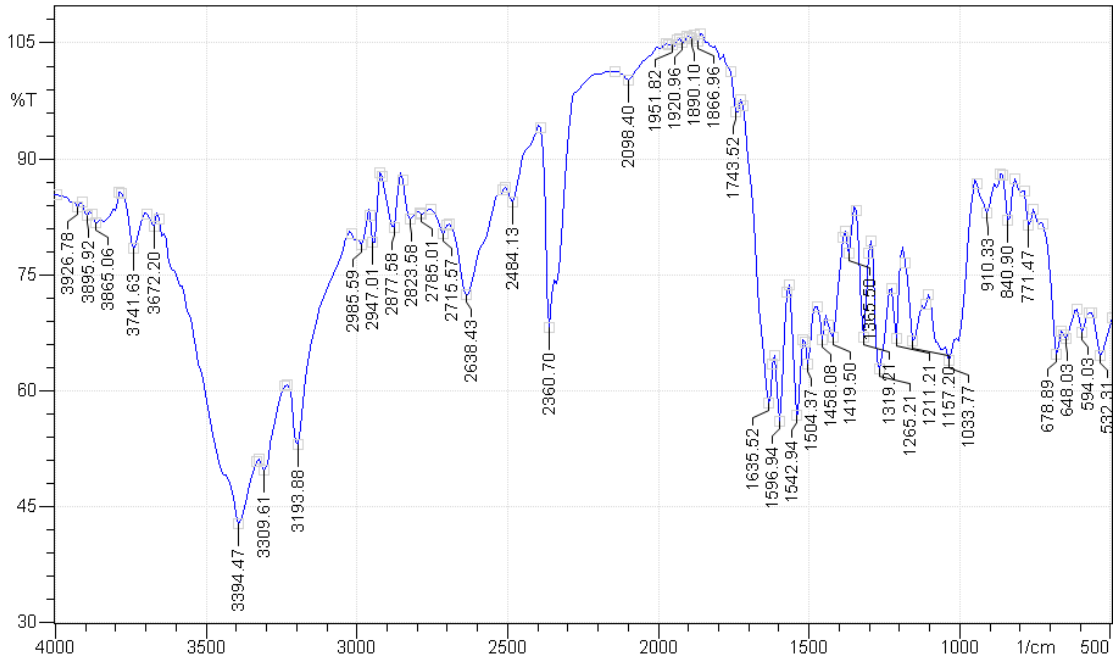

**Observation:**

**Table: 9.5. FTIR spectral interpretation of Metoclopramide hydrochloride with Mannitol**

| S. No | Functional group | Characteristic peak | | Observed peak | |
|---|---|---|---|---|---|
| | | Stretching | Bending | Stretching | Bending |
| 1 | Ar-$NH_2$ | 3500-3350 | - | 3394.4 | - |
| 2 | CO-NH | 1700-1500 | - | 1635.5 | - |
| 3 | Ar-C=C | 1600-1400 | - | 1535.2 | - |
| 4 | C-O-C | 1250-1050 | - | 1149.4 | - |
| 5 | C-$Cl_3$ | 800-600 | - | 678.8 | - |

There is no disappearance of characteristic peaks of drug in FT-IR Spectra. Hence there is no interaction

**Fig.9.6. IR SPECTRA OF DRUG + ISOMALT**



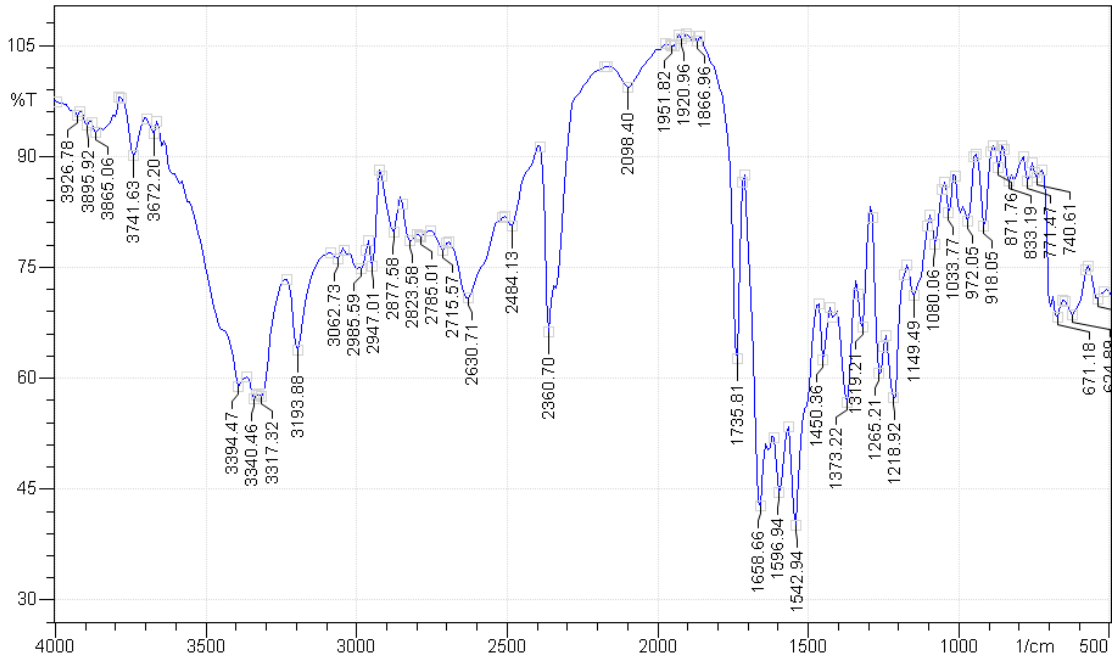

**Observation:**

**Table: 9.6. FTIR spectral interpretation of Metoclopramide hydrochloride with Isomalt**

| S. No | Functional group | Characteristic peak | | Observed peak | |
|---|---|---|---|---|---|
| | | Stretching | Bending | Stretching | Bending |
| 1 | Ar-$NH_2$ | 3500-3350 | - | 3394.4 | - |
| 2 | CO-NH | 1700-1500 | - | 1635.5 | - |
| 3 | Ar-C=C | 1600-1400 | - | 1596.9 | - |
| 4 | C-O-C | 1250-1050 | - | 1265.2 | - |
| 5 | C-$Cl_3$ | 800-600 | - | 678.8 | - |

There is no disappearance of characteristic peaks of drug in FT-IR Spectra. Hence there is no interaction

**Fig.9.7. IR SPECTRA OF DRUG + ASPARTAME**



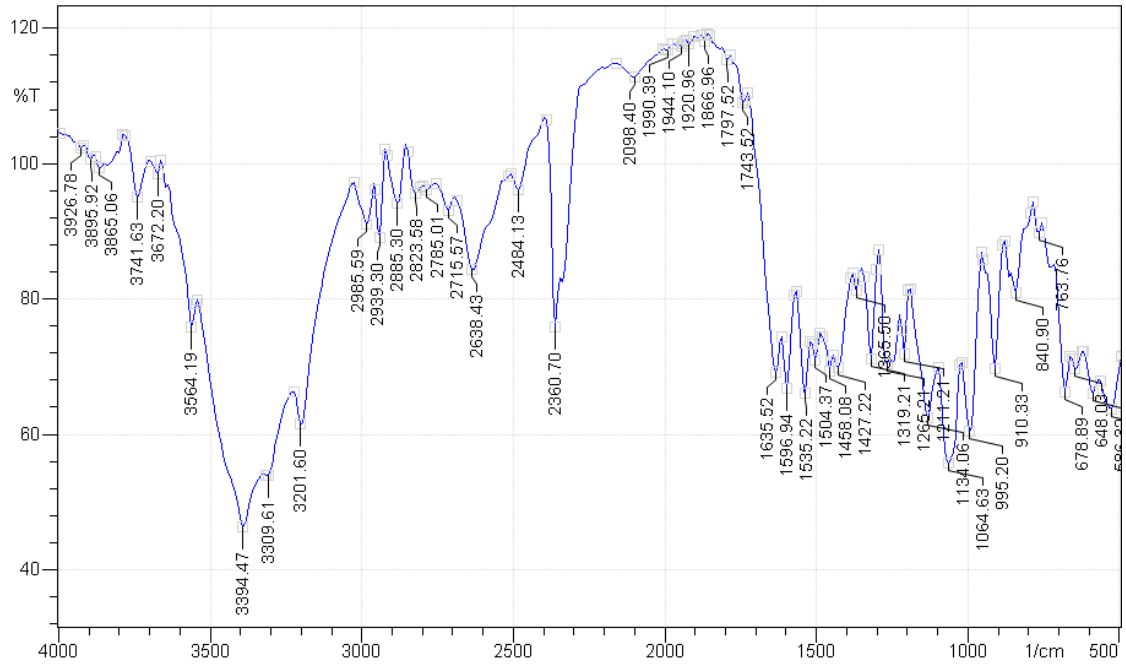

**Observation:**

**Table: 9.7. FTIR spectral interpretation of Metoclopramide hydrochloride with Aspartame**

| S. No | Functional group | Characteristic peak | | Observed peak | |
|---|---|---|---|---|---|
| | | Stretching | Bending | Stretching | Bending |
| 1 | Ar-$NH_2$ | 3500-3350 | - | 3394.4 | - |
| 2 | CO-NH | 1700-1500 | - | 1658.6 | - |
| 3 | Ar-C=C | 1600-1400 | - | 1596.9 | - |
| 4 | C-O-C | 1250-1050 | - | 1265.2 | - |
| 5 | C-$Cl_3$ | 800-600 | - | 671.1 | - |

There is no disappearance of characteristic peaks of drug in FT-IR Spectra. Hence there is no interaction.

**Fig.9.8. IR SPECTRA OF DRUG + CITRIC ACID**



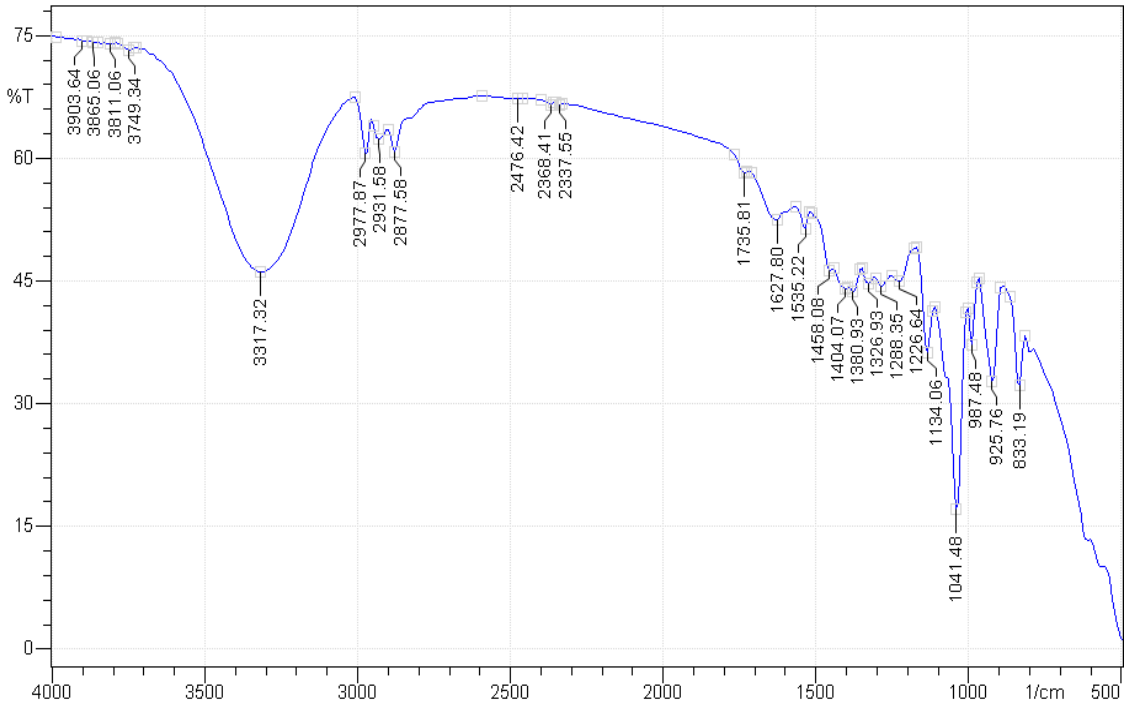

**Observation:**

**Table: 9.8. FTIR spectral interpretation of Metoclopramide hydrochloride with Citric acid**

| S. No | Functional group | Characteristic peak | | Observed peak | |
|---|---|---|---|---|---|
| | | Stretching | Bending | Stretching | Bending |
| 1 | Ar-$NH_2$ | 3500-3350 | - | 3394.4 | - |
| 2 | CO-NH | 1700-1500 | - | 1635.5 | - |
| 3 | Ar-C=C | 1600-1400 | - | 1596.9 | - |
| 4 | C-O-C | 1250-1050 | - | 1265.2 | - |
| 5 | C-$Cl_3$ | 800-600 | - | 678.8 | - |

There is no disappearance of characteristic peaks of drug in FT-IR Spectra. Hence there is no interaction.

**Fig.9.9. IR SPECTRA OF DRUG + PROPYLENE GLYCOL**



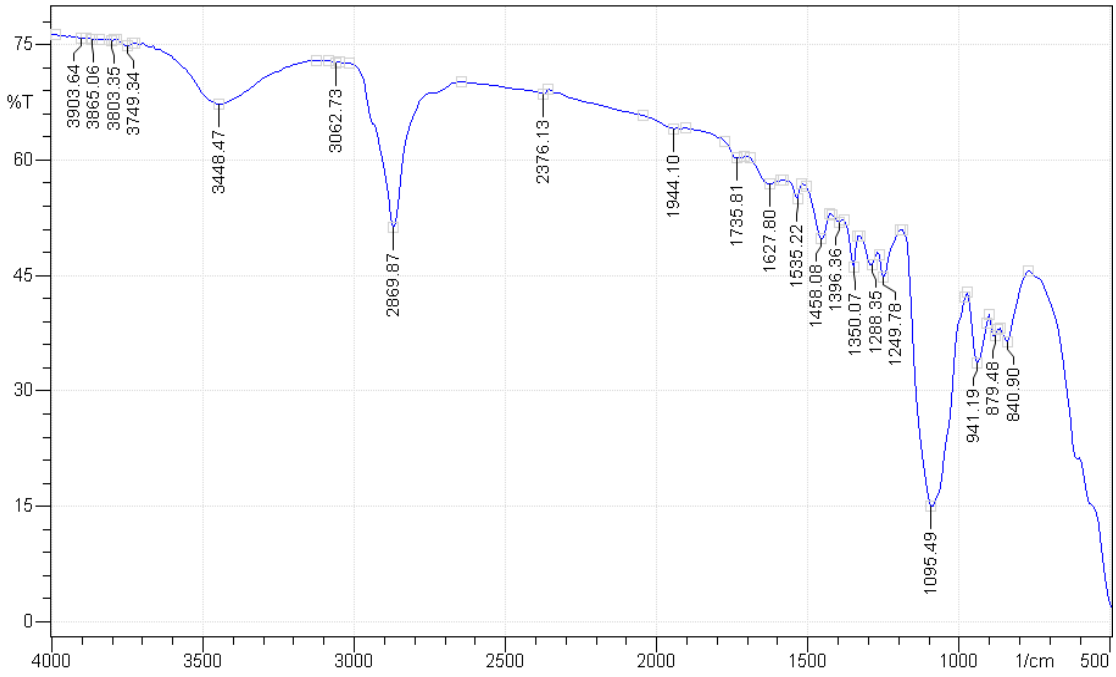

**Observation:**

**Table: 9.9. FTIR spectral interpretation of Metoclopramide hydrochloride with Propylene glycol**

| S. No | Functional group | Characteristic peak | | Observed peak | |
|---|---|---|---|---|---|
| | | Stretching | Bending | Stretching | Bending |
| 1 | Ar-$NH_2$ | 3500-3350 | - | 3317.3 | - |
| 2 | CO-NH | 1700-1500 | - | 1627.8 | - |
| 3 | Ar-C=C | 1600-1400 | - | 1535.2 | - |
| 4 | C-O-C | 1250-1050 | - | 1134.0 | - |

There is no disappearance of characteristic peaks of drug in FT-IR Spectra. Hence there is no interaction.

**Fig.9.10. IR SPECTRA OF DRUG + PEG 200**



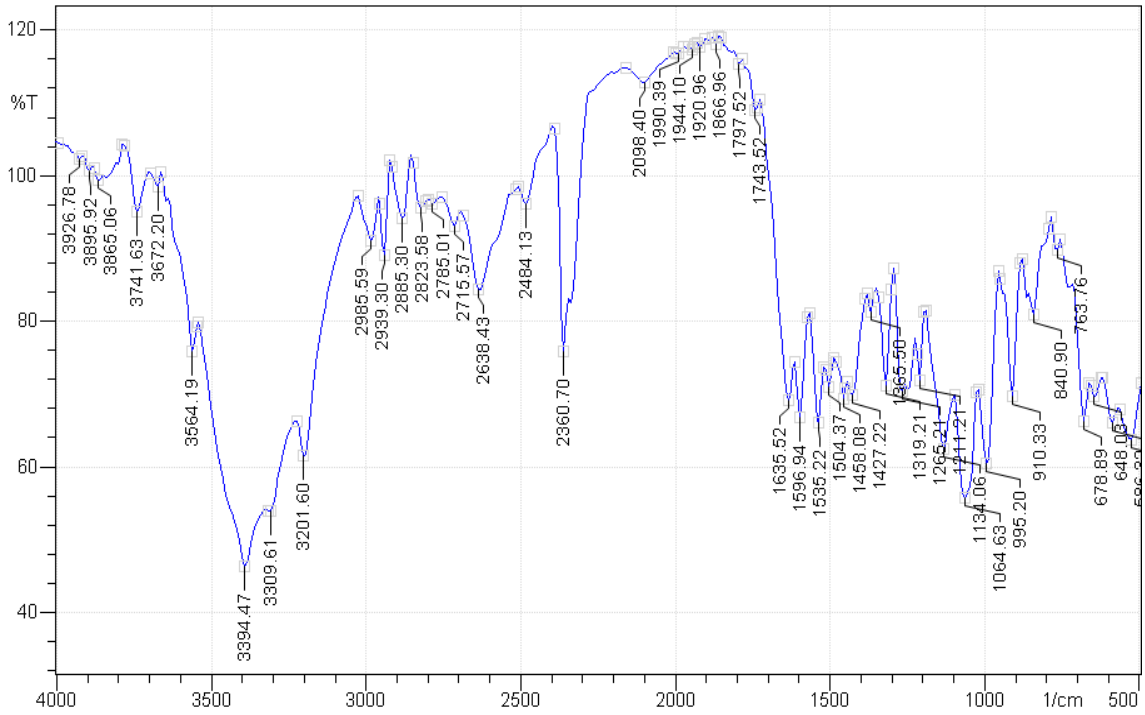

**Observation:**

**Table: 9.10. FTIR spectral interpretation of Metoclopramide hydrochloride with PEG 200**

| S. No | Functional group | Characteristic peak | | Observed peak | |
|---|---|---|---|---|---|
| | | Stretching | Bending | Stretching | Bending |
| 1 | Ar-$NH_2$ | 3500-3350 | - | 3448.4 | - |
| 2 | CO-NH | 1700-1500 | - | 1635.5 | - |
| 3 | Ar-C=C | 1600-1400 | - | 1535.2 | - |
| 4 | C-O-C | 1250-1050 | - | 1095.4 | - |

There is no disappearance of characteristic peaks of drug in FT-IR Spectra. Hence there is no interaction.

**Fig.9.11. IR SPECTRA OF DRUG + GLYCERIN**



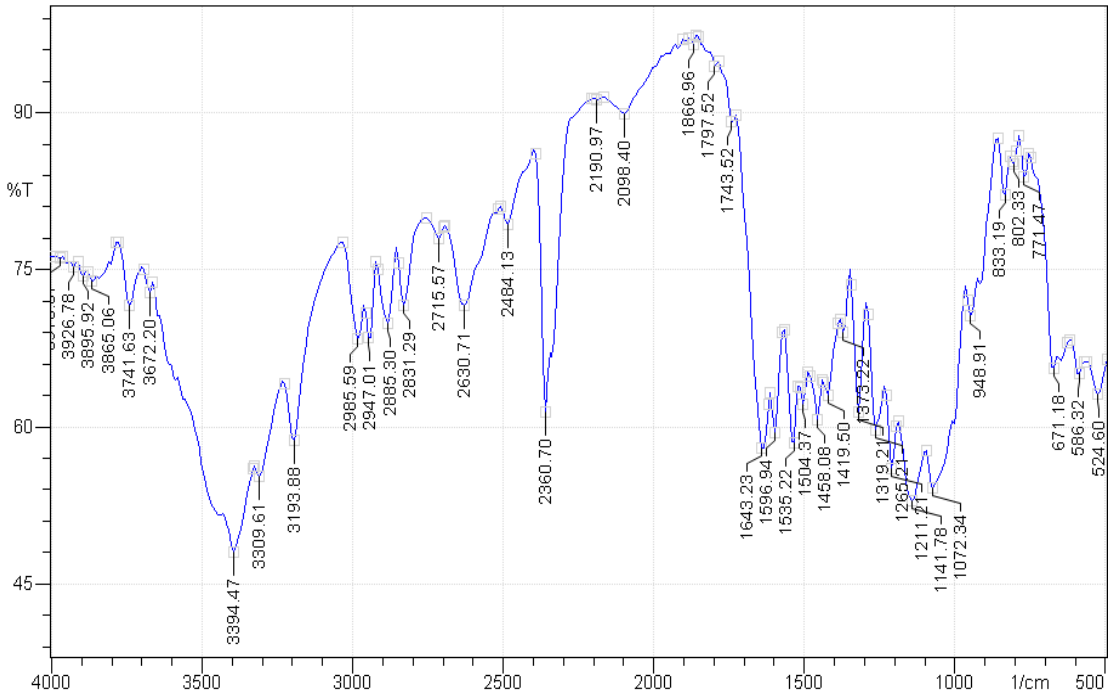

**OBSERVATION:**

**Table: 9.11. FTIR spectral interpretation of Metoclopramide hydrochloride with Glycerin**

| S. No | Functional group | Characteristic peak | | Observed peak | |
|---|---|---|---|---|---|
| | | Stretching | Bending | Stretching | Bending |
| 1 | Ar-$NH_2$ | 3500-3350 | - | 3394.4 | - |
| 2 | CO-NH | 1700-1500 | - | 1635.5 | - |
| 3 | Ar-C=C | 1600-1400 | - | 1596.9 | - |
| 4 | C-O-C | 1250-1050 | - | 1265.2 | - |
| 5 | C-$Cl_3$ | 800-600 | - | 678.8 | - |

There is no disappearance of characteristic peaks of drug in FT-IR Spectra. Hence there is no interaction.

**Fig.9.12. IR SPECTRA OF DRUG + LIQUID GLUCOSE**



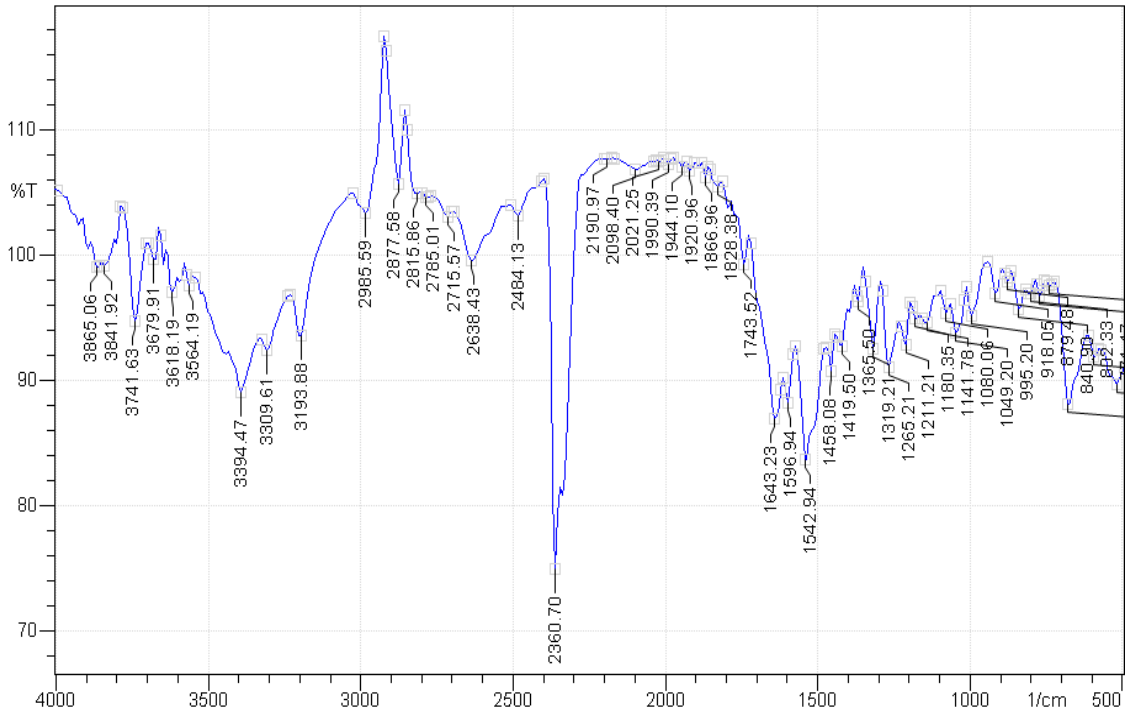

**Observation:**

**Table: 9.12. FTIR spectral interpretation of Metoclopramide hydrochloride with Liquid glucose**

| S. No | Functional group | Characteristic peak | | Observed peak | |
|---|---|---|---|---|---|
| | | Stretching | Bending | Stretching | Bending |
| 1 | Ar-$NH_2$ | 3500-3350 | - | 3394.4 | - |
| 2 | CO-NH | 1700-1500 | - | 1643.3 | - |
| 3 | Ar-C=C | 1600-1400 | - | 1596.9 | - |
| 4 | C-O-C | 1250-1050 | - | 1265.2 | - |
| 5 | C-$Cl_3$ | 800-600 | - | 671.1 | - |

There is no disappearance of characteristic peaks of drug in FT-IR Spectra. Hence there is no interaction.

**Fig.9.13. IR SPECTRA OF DRUG + MENTHOL**



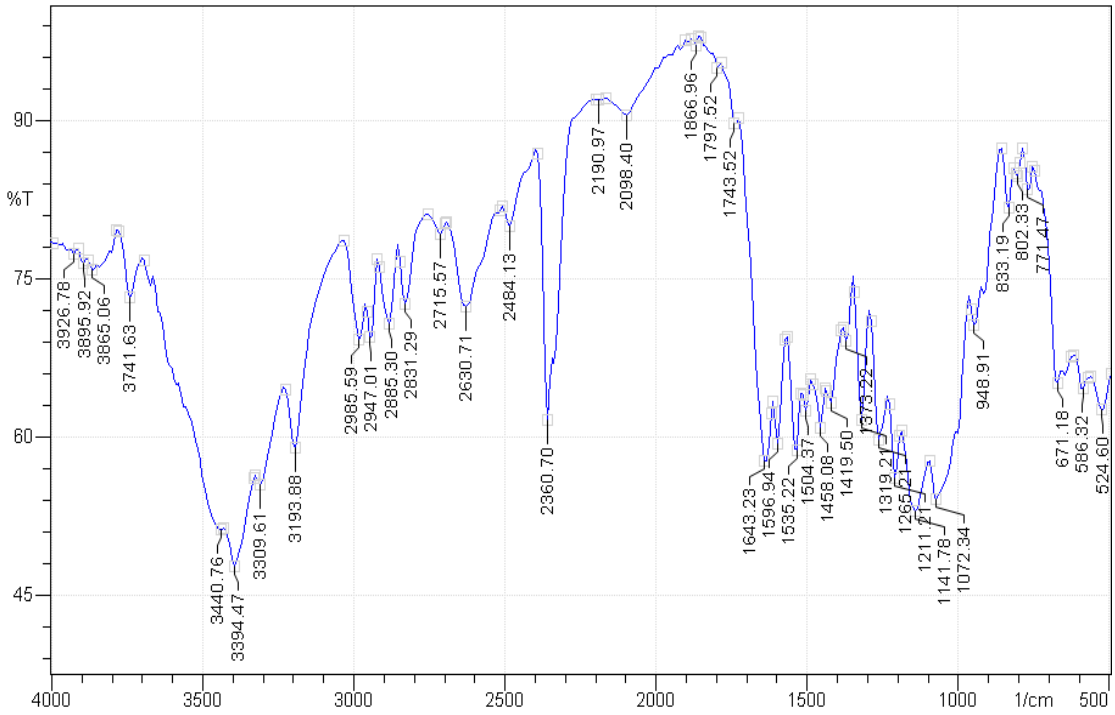

**Observation:**

**Table: 9.13. FTIR spectral interpretation of Metoclopramide hydrochloride with Menthol**

| S. No | Functional group | Characteristic peak | | Observed peak | |
|---|---|---|---|---|---|
| | | Stretching | Bending | Stretching | Bending |
| 1 | Ar-$NH_2$ | 3500-3350 | - | 3394.4 | - |
| 2 | CO-NH | 1700-1500 | - | 1643.3 | - |
| 3 | Ar-C=C | 1600-1400 | - | 1596.9 | - |
| 4 | C-O-C | 1250-1050 | - | 1265.2 | - |

There is no disappearance of characteristic peaks of drug in FT-IR Spectra. Hence there is no interaction.

**Fig.9.14. IR SPECTRA OF DRUG + METHYL CELLULOSE**



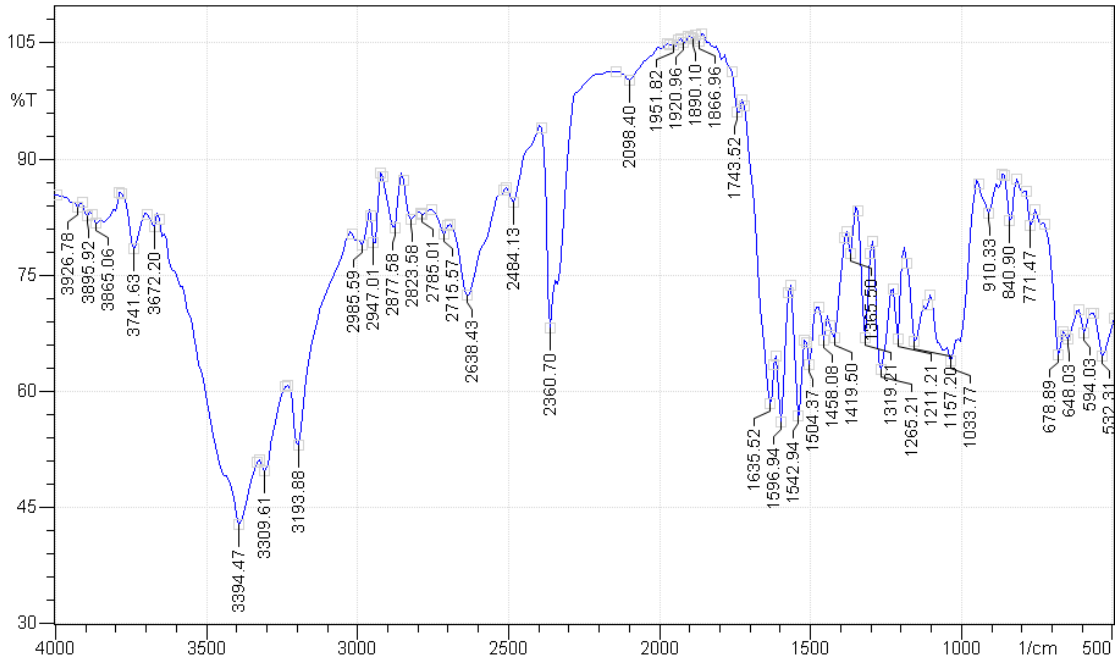

**Observation:**

**Table: 9.14. FTIR spectral interpretation of Metoclopramide hydrochloride with Methyl cellulose**

| S. No | Functional group | Characteristic peak | | Observed peak | |
|---|---|---|---|---|---|
| | | Stretching | Bending | Stretching | Bending |
| 1 | Ar-$NH_2$ | 3500-3350 | - | 3394.4 | - |
| 2 | CO-NH | 1700-1500 | - | 1643.2 | - |
| 3 | Ar-C=C | 1600-1400 | - | 1596.9 | - |
| 4 | C-O-C | 1250-1050 | - | 1265.2 | - |
| 5 | C-$Cl_3$ | 800-600 | - | 671.1 | - |

There is no disappearance of characteristic peaks of drug in FT-IR Spectra. Hence there is no interaction.

**Fig.9.15. IR FOR THE OPTIMIZED FORMULATION**




**Observation:**

**Table: 9.15. FTIR spectral interpretation of the Optimized formulation**

| S. No | Functional group | Characteristic peak | | Observed peak | |
|---|---|---|---|---|---|
| | | Stretching | Bending | Stretching | Bending |
| 1 | Ar-$NH_2$ | 3500-3350 | - | 3394.4 | - |
| 2 | CO-NH | 1700-1500 | - | 1635.5 | - |
| 3 | Ar-C=C | 1600-1400 | - | 1596.9 | - |
| 4 | C-O-C | 1250-1050 | - | 1265.2 | - |
| 5 | C-$Cl_3$ | 800-600 | - | 678.8 | - |

There is no disappearance of characteristic peaks of drug in FT-IR Spectra. Hence there is no interaction

## 9.2. DATA FOR CALIBRATION CURVE:

**Fig.9.21. Calibration curve for Metoclopramide Hydrochloride**

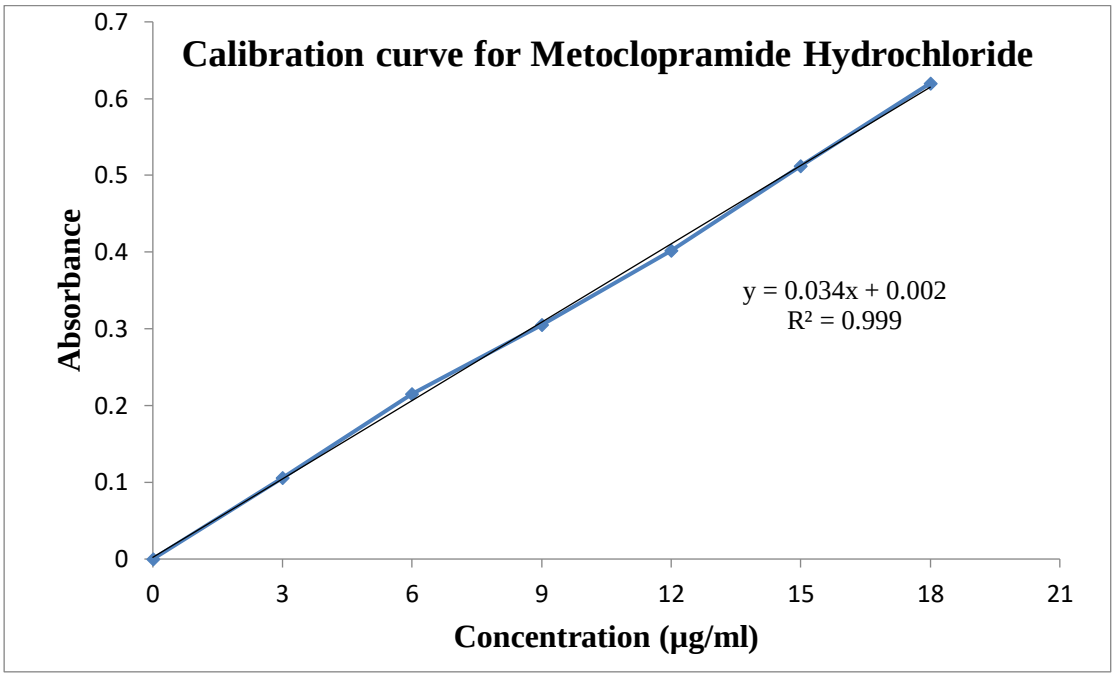



**Table.9.21. Concentration and absorbance of Metoclopramide Hydrochloride**

| Concentration (µg/ml) | Absorbance at λ 272 nm |
|---|---|
| 0 | 0 |
| 3 | 0.106±0.005 |
| 6 | 0.215±0.005 |
| 9 | 0.305±0.003 |
| 12 | 0.402±0.005 |
| 15 | 0.512±0.004 |
| 18 | 0.620±0.005 |
| $R^2$ | 0.9995 |

n=3

It was found that the solutions Metoclopramide hydrochloride in phosphate buffer pH 6.8 showed linearity $r^2$=0.9999) in absorbance at concentrations of 3 to 18µg /ml and obey Beer Lambert's Law

## 9.3. PHYSICAL APPEARANCE OF METOCLOPRAMIDE HYDROCHLORIDE MEDICATED LOZENGES

**Table.9.22. Physical appearance of formulated lozenges**

| S.No. | F Code | Clarity | Texture | Consistency | Stickiness |
|---|---|---|---|---|---|
| 1 | F1 | Translucent | Smooth | Slightly Thick | Sticky |
| 2 | F2 | Translucent | Smooth | Thick | Non-sticky |
| 3 | F3 | Translucent | Smooth | Thick | Non-sticky |
| 4 | F4 | Translucent | Smooth | Thick | Non-sticky |
| 5 | F5 | Translucent | Smooth | Slightly Thick | Sticky |
| 6 | F6 | Translucent | Smooth | Slightly Thick | Sticky |
| 7 | F7 | Translucent | Smooth | Thick | Non-sticky |
| 8 | F8 | Translucent | Smooth | Thick | Non-sticky |
| 9 | F9 | Translucent | Smooth | Thick | Non-sticky |
| 10 | F10 | Translucent | Smooth | Thick | Non-sticky |

In physical appearance evaluation all the formulations were translucent smooth nature. F1, F5, F6 formulations shows slightly thick and sticky in nature. All other formulations were good and acceptable.

## 9.4. WEIGHT VARIATION OF METOCLOPRAMIDE HYDROCHLORIDE HARD CANDY LOZENGES

**Table.9.23. Weight Variation of formulated Medicated Lozenges**

| S. No. | Formulation Code | Weight of lozenges |
|---|---|---|
| 1 | F1 | 2.5035±0.032 |
| 2 | F2 | 2.493±0.039 |
| 3 | F3 | 2.488±0.059 |
| 4 | F4 | 2.515±0.023 |
| 5 | F5 | 2.507±0.030 |
| 6 | F6 | 2.508±0.036 |
| 7 | F7 | 2.518±0.041 |
| 8 | F8 | 2.511±0.038 |
| 9 | F9 | 2.519±0.040 |
| 10 | F10 | 2.503±0.029 |

**Mean±SD (n=20)**

The average weight of 20 lozenges was taken to determine weight variation from each formulated lozenges. There was no specified deviation in the weight of lozenges, comparing each formulation. This indicates the uniform weight of the prepared lozenges.

## 9.5. HARDNESS OF MEDICATED LOZENGES

**Table.9.24. Hardness of formulated Medicated Lozenges Mean±SD (n=3)**

| S.No. | Formulation Code | Hardness of lozenges (Kg/cm$^2$) |
|---|---|---|
| 1 | F1 | 10.5 ±0.57 |
| 2 | F2 | 10.75 ±0.92 |
| 3 | F3 | 7.3 ±0.42 |
| 4 | F4 | 13.6±0.64 |
| 5 | F5 | 10.65±0.57 |
| 6 | F6 | 9.65±0.56 |
| 7 | F7 | 15.25±0.63 |
| 8 | F8 | 15.45±0.43 |
| 9 | F9 | 15.50±0.74 |
| 10 | F10 | 15.30±0.74 |

The hardness of all formulated lozenges was found within the range up to 7.3 kg/cm$^2$ to 15.50 kg/cm$^2$.Among the ten formulations of lozenges, the lowest value for hardness was noted for F3 (i.e., 7.3 kg/cm$^2$) and highest i.e., 15.50 kg/cm$^2$ for F9. The hardness of the lozenges is due to the presence of methyl cellulose.

## 9.6. THICKNESS OF MEDICATED LOZENGES

**Table.9.25. Thickness of formulated Medicated Lozenges**

| S.No. | Formulation Code | Thickness of lozenges (mm) |
|---|---|---|
| 1 | F1 | 12.25 ±0.051 |
| 2 | F2 | 12.23 ±0.044 |
| 3 | F3 | 12.02 ±0.043 |
| 4 | F4 | 12.24±0.054 |
| 5 | F5 | 12.24±0.057 |
| 6 | F6 | 12.25±0.054 |
| 7 | F7 | 12.26±0.054 |
| 8 | F8 | 12.25±0.054 |
| 9 | F9 | 12.24±0.041 |
| 10 | F10 | 12.24±0.054 |

Thickness of the lozenges was found to be in the uniform range of 12-12.26mm.

## 9.7. MOUTH DISSOLVING TIME OF MEDICATED LOZENGES

### 9.26. Mouth dissolving time of the formulated Medicated lozenges

| Formulation Code | Mouth dissolving time(mins) | Average |
|---|---|---|
| F1 | 10:58 | 10.16±0.51 |
| | 10:32 | |
| | 9:59 | |
| F2 | 11:02 | 11.00±0.3 |
| | 10:52 | |
| | 11:48 | |
| F3 | 7:16 | 7.06±0.43 |
| | 7:54 | |
| | 6:49 | |
| F4 | 12:53 | 12:50±0.19 |
| | 12:17 | |
| | 12:08 | |
| F5 | 15:42 | 15:61±0.45 |
| | 16:14 | |
| | 15:29 | |
| F6 | 12:08 | 13.47±1.25 |
| | 13:23 | |
| | 15:12 | |
| F7 | 16:48 | 16:65±0.36 |
| | 17:16 | |
| | 16:33 | |
| F8 | 25:26 | 24:20±0.56 |
| | 24:02 | |
| | 22:14 | |
| F9 | 28.26 | 29:05±0.31 |
| | 27.58 | |
| | 30.12 | |
| F10 | 30:25 | 30:28±0.75 |
| | 29:52 | |
| | 31:08 | |

Mouth dissolving time of medicated lozenges was found to be within the range upto 7:06 to 30:28 minutes. The addition of plasticizer was increases the mouth dissolving time of the formulations. F10 formulation shows the highest mouth dissolving time.

## 9.8. MOISTURE CONTENT OF MEDICATED LOZENGES

**Table.9.27. Moisture Content of formulated Medicated Lozenges**

| S.No. | Formulation Code | Moisture content of lozenges (%) |
|---|---|---|
| 1 | F1 | 1.19 |
| 2 | F2 | 1.44 |
| 3 | F3 | 2.10 |
| 4 | F4 | 1.02 |
| 5 | F5 | 1.15 |
| 6 | F6 | 0.94 |
| 7 | F7 | 0.69 |
| 8 | F8 | 0.93 |
| 9 | F9 | 0.84 |
| 10 | F10 | 0.83 |

Moisture content determination is a critical parameter of lozenges quality. It influences lozenges manufacturing and packaging. The standard limits of moisture content should be in the range of 0.5 to 1.5 %.

As per the result obtained that moisture content in the prepared lozenges was found in the range 0.5 to 1.5 % which is within the standard limits.

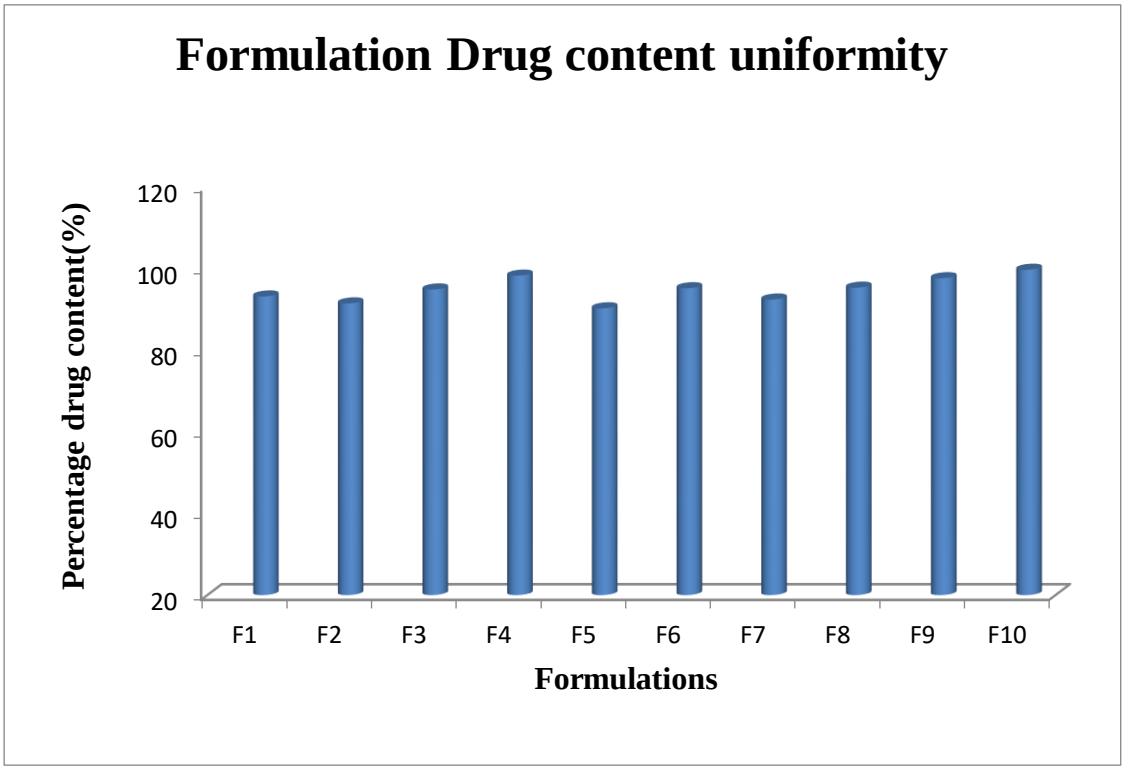
## 9.9. DRUG CONTENT UNIFORMITY OF METOCLOPRAMIDE HYDROCHLORIDE MEDICATED LOZENGES

### 9.28. Percentage drug content uniformity of formulated Medicated lozenges

| Formulation Code | Drug content (%) |
|---|---|
| F1 | 93.13±2.32 |
| F2 | 91.43±3.31 |
| F3 | 94.84±3.85 |
| F4 | 98.24±3.5 |
| F5 | 90.22±2.50 |
| F6 | 95.15±2.65 |
| F7 | 92.38±3.52 |
| F8 | 95.29±2.53 |
| F9 | 97.60±2.96 |
| F10 | 99.68±1.50 |

**Mean±SD (n=3)**

**Fig.9.22.Percentage drug content uniformity of formulated medicated lozenges**



The drug content of all lozenges (F1 to F10) is within 90% to 110% as per specification when compared with the Metoclopramide Hydrochloride tablets (IP 2018), Volume II).

## 9.10. FORMULATED METOCLOPRAMIDE HYDROCHLORIDE MEDICATED LOZENGES

**Fig.9.29. Optimized formulation of Medicated lozenges**

## 9.10. *In-vitro* DISSOLUTION STUDY OF FORMULATED MEDICATED LOZENGES OF METOCLOPRAMIDE HYDROCHLORIDE

**Table.9.30. In-vitro drug release study of Medicated lozenges**

| Time (min.) | PERCENTAGE DRUG RELEASE (%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 53 | 73.2 | 84.5 | 71.5 | 51.5 | 63 | 23 | 23 | 31.4 | 25.5 |
| 10 | 74.2 | 92.4 | 96.38 | 96.86 | 88.06 | 82.02 | 41.92 | 33.8 | 40.2 | 38.4 |
| 15 | 99.4 | -- | -- | 101.1 | 96.5 | 97.7 | 79.4 | 51.48 | 62.2 | 71 |
| 20 | -- | -- | -- | -- | 100.14 | --- | 92.14 | 80.6 | 82.0 | 83.6 |
| 25 | -- | -- | -- | -- | -- | --- | 99.6 | 88.6 | 94.2 | 91.4 |
| 30 | -- | -- | -- | -- | --- | --- | --- | 95.02 | 98.6 | 100.6 |

**Fig.9.24. *In- vitro* release profile of the formulations F1 to F4 containing varying sugar bases**

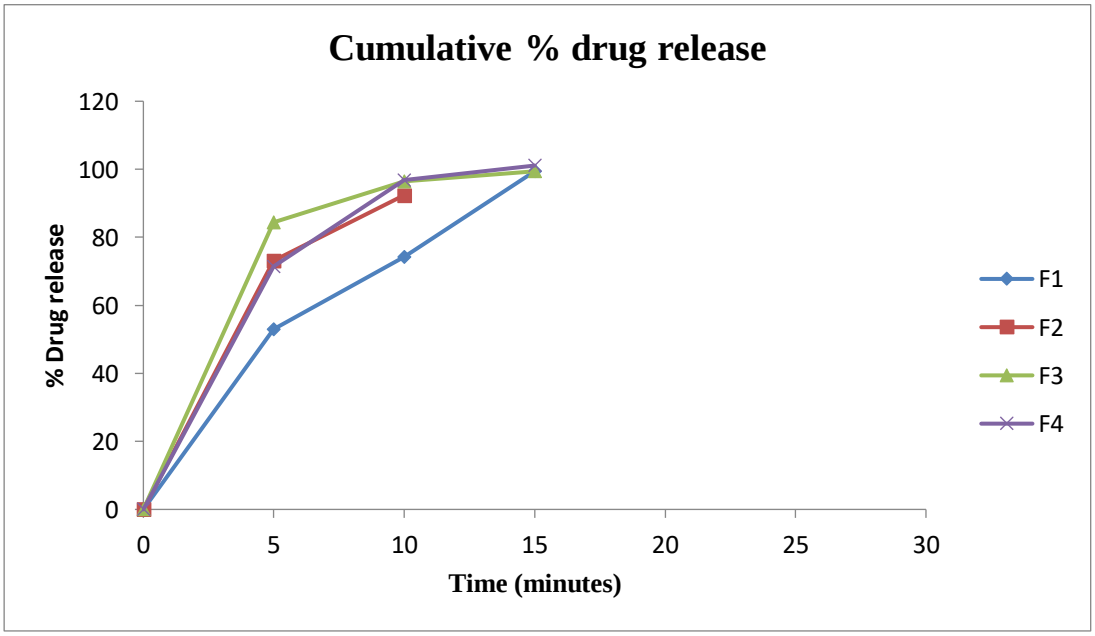


**Fig.9.25. *In-vitro* release profile of the formulations F5 to F7 containing varying plasticizers**

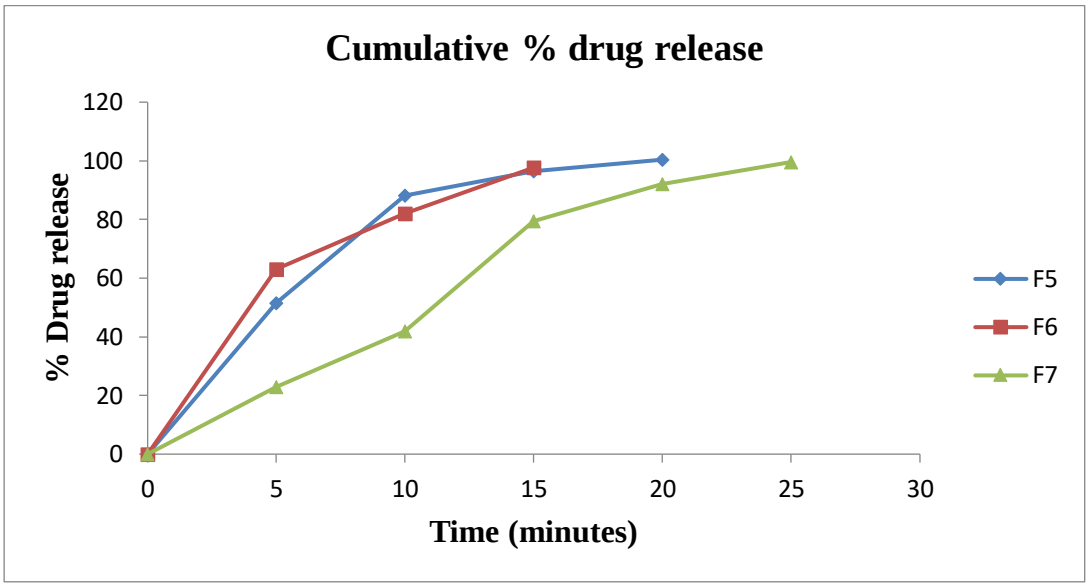
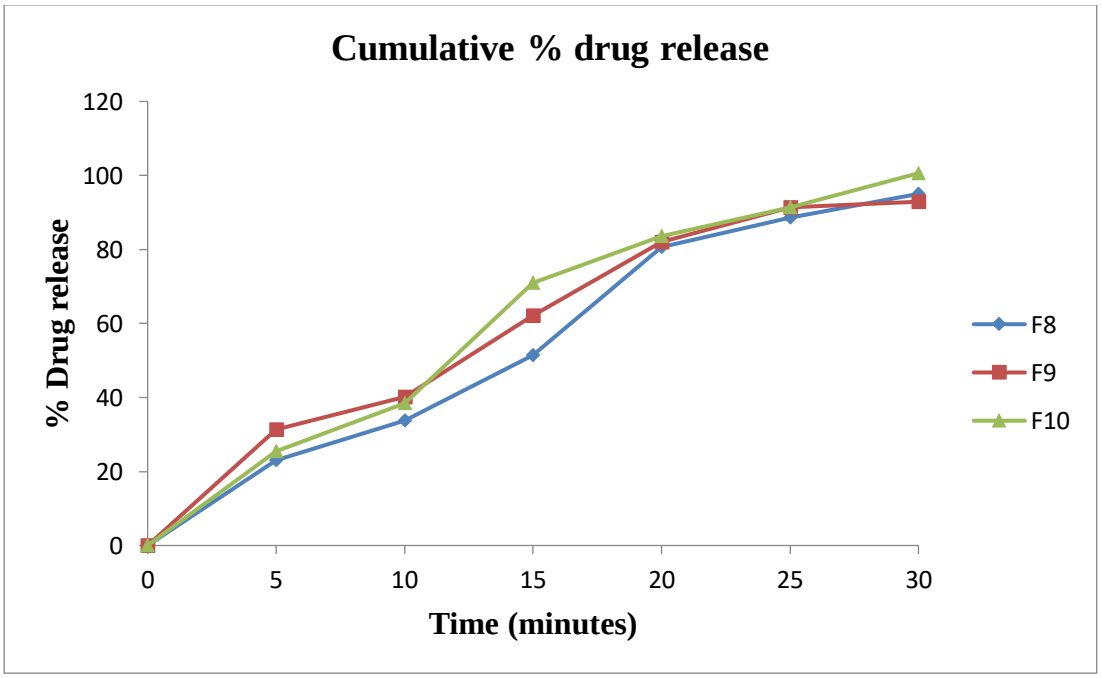



**Fig.9.26. *In-vitro* release profile of the formulations F8 to 10 containing varying concentration of Methylcellulose**



The cumulative percentage of drug release for the F1 which contains the sucrose as sugar showed 99.4 % at 15 minutes. F2, F3 formulations containing dextrose and mannitol as a base showed the drug release 92.4 %, 96.8 % respectively within 10 minutes.

In F4 formulation isomalt as a sugar base it showed the drug release 101 % at 15 minutes. The addition of plasticizers in F5, F6, F7 formulations showed the increase in time for the drug release. F5 formulation showed the release rate at 100.4% within 20 minutes. For F6 cumulative drug release 97.7% at 15 minutes and for F7 99.6 % in 25 minutes.

The formulations F8, F9, F10 contains 0.75%, 0.5% ,0.25% of methylcellulose as polymer showed the cumulative drug release of Metoclopramide hydrochloride 95.02 %, 98.6 %, 100.6 % respectively in 30 minutes. Hence the formulation F10 containing 0.25% Methyl cellulose which showed 100.6% drug release at the end of 30 minutes was considered as the optimized formulation.

### 9.11. *In-vitro* RELEASE KINETICS

**Table: 9.31. *In-vitro* release kinetics of optimized formulation**

| Time in mins | Square root of time | Log time | % Cum. Drug release | % Cum. Drug remaining | Log % Cum. Drug remaining | Log % Cum. Drug release | Cube root of % drug remaining |
|---|---|---|---|---|---|---|---|
| 0 | 0 | ∞ | 0 | 100 | 2 | ∞ | 4.64159 |
| 5 | 2.23607 | 0.69897 | 25.5 | 74.5 | 1.87216 | 1.40654 | 4.20777 |
| 10 | 3.16228 | 1 | 38.4 | 61.6 | 1.78958 | 1.58433 | 3.94936 |
| 15 | 3.87298 | 1.17609 | 71 | 29 | 1.4624 | 1.85126 | 3.07232 |
| 20 | 4.47214 | 1.30103 | 83.6 | 16.4 | 1.21484 | 1.92221 | 2.54067 |
| 25 | 5 | 1.39794 | 91.4 | 8.6 | 0.9345 | 1.96095 | 2.0488 |
| 30 | 5.4772 | 1.47712 | 100.6 | -0.6 | - | 2.0026 | -0.8434 |

**Fig.9.27. Zero order Kinetics**

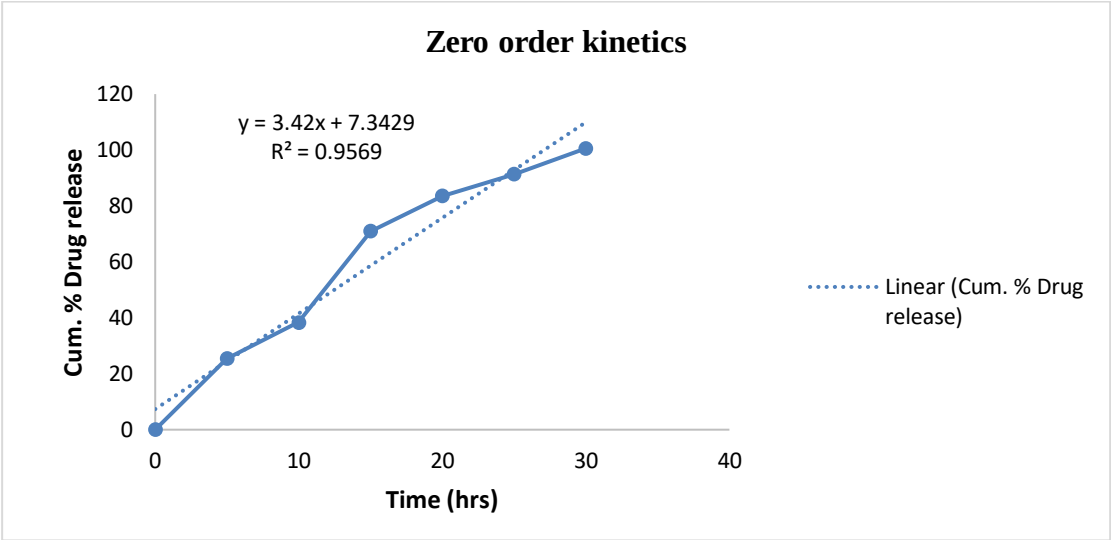



**Fig.9.28. First order kinetics**

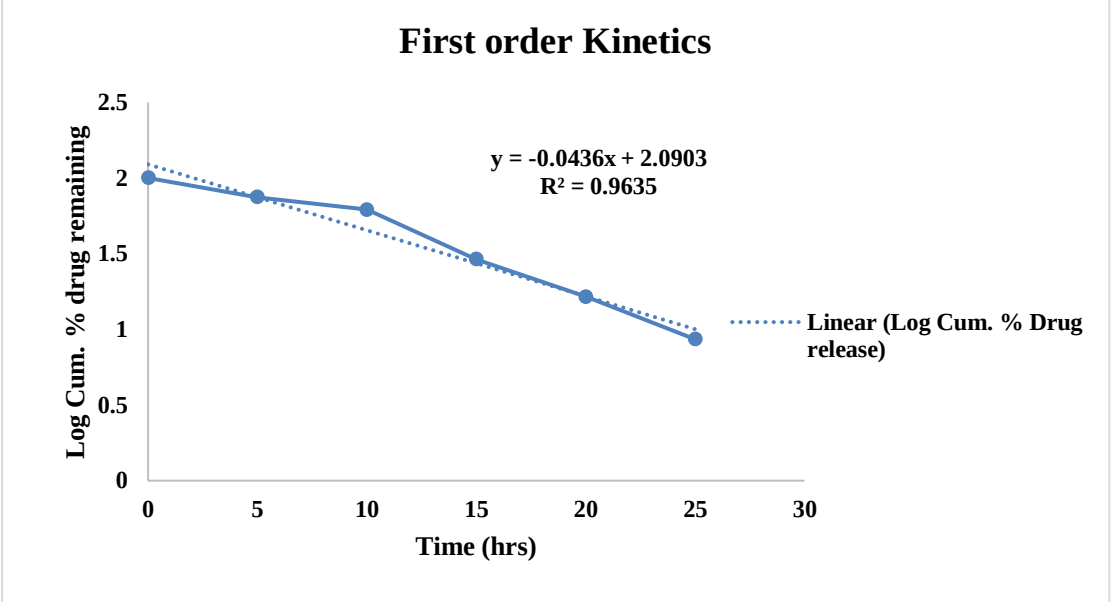


**Fig.9.29. Higuchi kinetics**

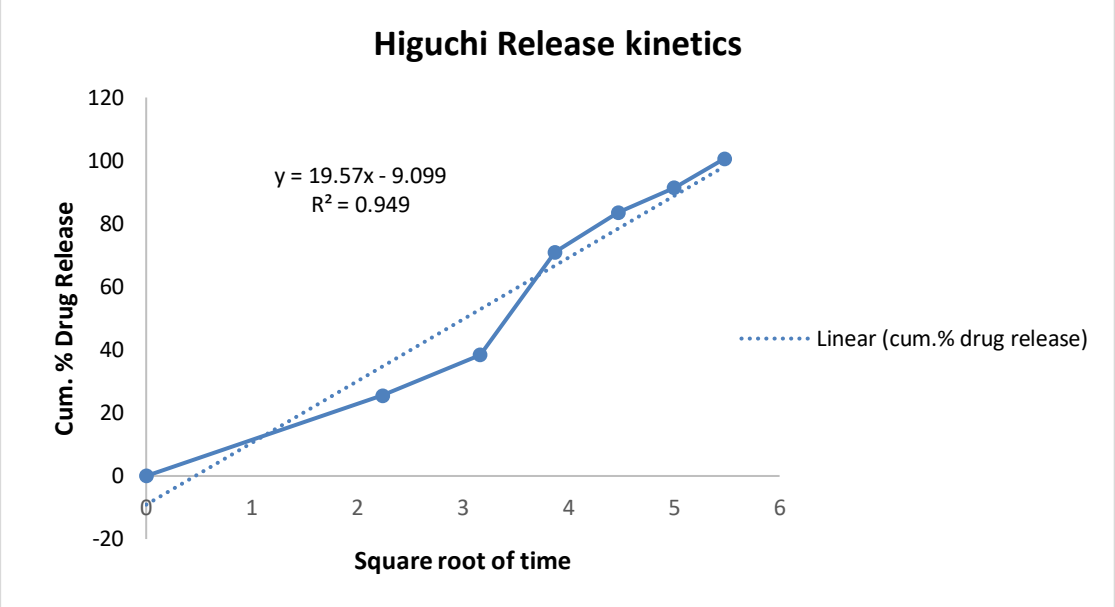



**Fig.9.30.Hixon-crowell kinetics**

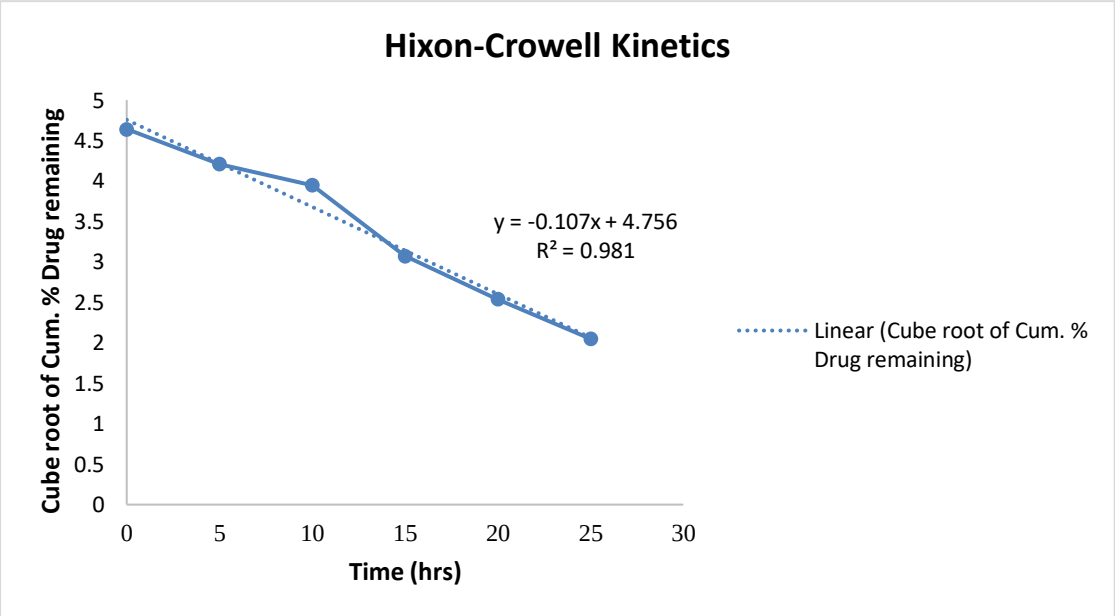


**Fig.9.31. Korsemeyer- Peppas kinetics**

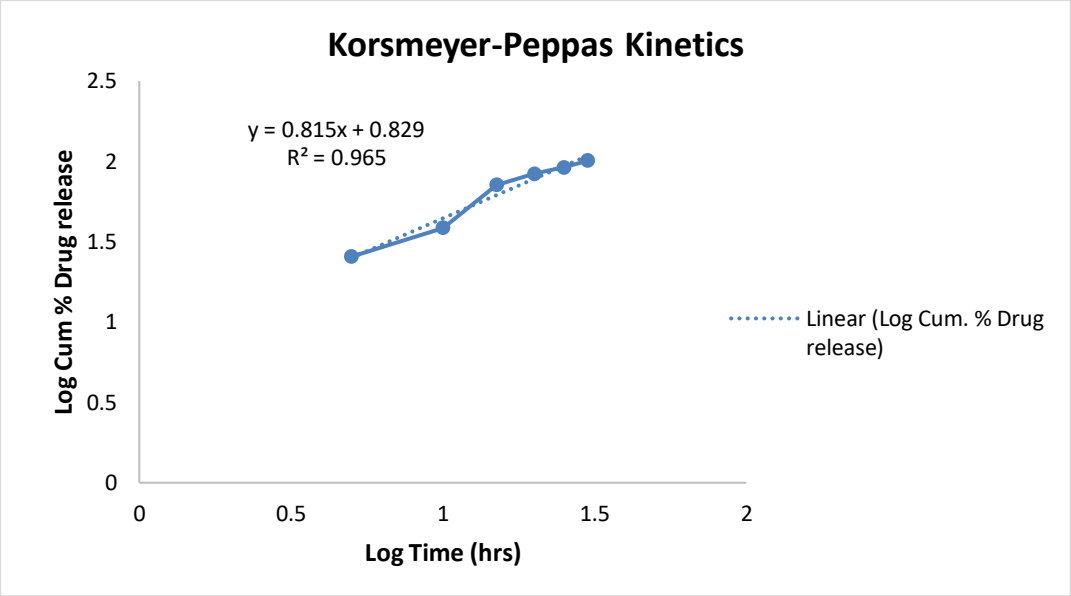


**Table.9.32.The summarized data of the *In vitro* release kinetics**

| S.No | Data fitted in | X-axis | Y-axis | Slope | Intercept | $R^2$ | Linear equation |
|---|---|---|---|---|---|---|---|
| 1 | Zero -order equation | Time in hours | Cumulative % drug Release | 3.42 | 9.757 | 0.956 | y = 3.42x + 7.342 |
| 2 | First -order equation | Time in hours | Log cumulative drug remaining | 0.043 | 2.090 | 0.963 | y=-0.043x+ 2.090 |
| 3 | Higuchi | Square root of time | Cumulative % drug Release | 19.57 | 9.099 | 0.949 | y =19.57x - 9.099 |
| 4 | Hixon-Crowell | Time in hours | Cube root of drug remaining | 0.107 | 4.756 | 0.981 | y=-0.107x+ 4.756 |
| 5 | Korsemeyer Peppas equation | Log time | Log cumulative % dug released | 0.815 | 0.829 | 0.965 | y=0.815x + 0.829 |

The order of release of the drug was found to be first -order, in which $R^2$ value was close to 1 than the value compared to $R^2$ of the zero order equation.

The slope of the regression line from the Higuchi plot ($R^2$ =0.949) and Hixon – Crowell plot $R^2$ = (0.981), which indicates the rate of drug release follows the both diffusion and dissolution mechanism.

The n value, an exponent of Korsemeyer-Peppas equation was 0.815 indicating that mass transfers follows the Non- Fickian diffusion.

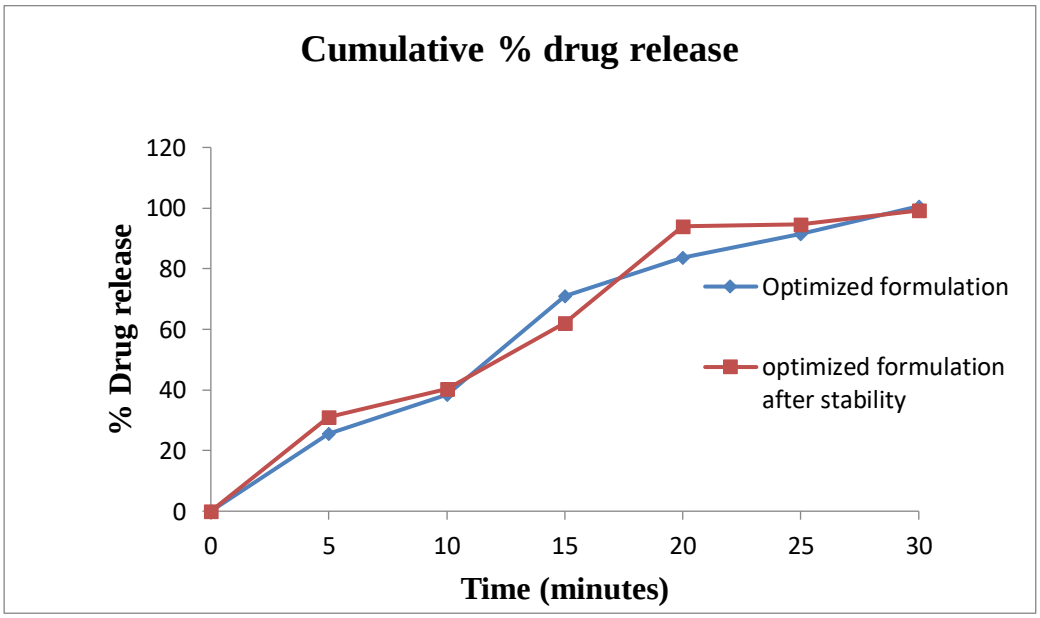
Thus the release kinetics of the optimized formulation showed first order release with Non-fickian diffusion.

## 9.12. STABILITY STUDIES

**Table.9.33. Evaluation parameters after the stability studies**

| EVALUATION PARAMETER | OPTIMIZED FORMULATION(F 10) | AFTER STABILITY STUDY OF 1 MONTH |
|---|---|---|
| Weight variation | 2.503± 0.0290 | 2.507 ± 0.030 |
| Hardness | 15.30±0.74 | 15 ±0.08 |
| Thickness | 12.26± 0.054 | 12.18 ± 0.16 |
| Moisture Content | 0.83% | 0.69 % |
| Mouth dissolving Time | 30:28±0.75 | 29:61±0.98 |
| Content uniformity | 99.68%±1.50 | 96.48±1.20 |
| Drug release | 100.6% | 99.2% |

**Fig .9.32.Comparative cumulative % drug release curve for the optimized formulation (F10)**




The optimized formulations were subjected to stability studies at temperature i.e. 45ºC /75% RH for a period of one month. There is no change in physicochemical properties after performing stability studies. There is no relative change in the release kinetics of the formulation F10 after stability studies.

# SUMMARY AND CONCLUSION

# 10. SUMMARY AND CONCLUSION

The present study was aimed to formulate and evaluate Metoclopramide hydrochloride medicated lozenges to provide the antiemetic action through the buccal absorption by the addition of polymer.

- Physical compatibility study showed that the drug and excipients are physically compatible with each other.
- Chemical compatibility study was performed using FT-IR spectroscopy and FT-IR studies revealed that there was no change in major peaks, thus confirming no interaction between the drug and excipients.
- Liquid glucose 20 % is used in the formulation to improve the appearance, smoothness and prevent the crystallisation of the sugar base.
- After performing formulation of batches for sugar selection (F1 to F4), the observations were reported. Mannitol was easily dissolved in water, but the mass formulated with mannitol was stuck on the wall of beaker while heating and thick viscous mass was not obtained. The batches formulated with dextrose and sucrose showed re-crystallization of sugars. Batch formulated with isomalt showed hard candy type lozenges, but the appearance was not good. Due to lack of physical appearance, it was decided to add plasticizer in further formulations.
- Formulations were prepared by incorporating a plasticizer i.e. PG and PEG 200 showed soft lozenges while those formulated with glycerine formed hard candy lozenges after keeping aside for half an hour. Also, Formulations with PG, PEG 200 was in sticky nature. So, glycerine was selected for further batches and its quantity was varied to check the effect on the quality of lozenges.
- With lower concentration of glycerine, the lozenges remained as hard candy type with good appearance. Further addition of methylcellulose increased the buccal retention time.
- All formulations were prepared and evaluated for *in-vitro* drug release, physical appearance, weight variation, thickness, hardness, moisture content, mouth dissolving time and drug content.
- The formulated lozenges showed the uniformity in weight and thickness.
- The hardness of all formulated lozenges was found within the standard range up to 7.3 $kg/cm^2$ to 15.50 $kg/cm^2$.

- Mouth dissolving time of medicated lozenges was found to be within the range upto 7:06 to 30:28 minutes. F10 formulation showed the maximum time to dissolve in a medium.
- The standard limits of moisture content should be in the range of 0.5 to 1.5 %.
- As per the result obtained that moisture content in the prepared lozenges was found in the range 0.5 to 1.5 % which is within the standard limits.
- The drug content of all formulated lozenges (F1 to F10) was within the acceptable limits (90% -110%).
- From the *in-vitro* drug release study, it was found that the formulations, Metoclopramide hydrochloride lozenges containing Methyl cellulose in the concentrations of 0.75%, 0.5%, 0.25% showed the maximum drug release at 30 minutes. Among those formulations formulation F10 showed 100.6% of drug release.
- The *in-vitro* release kinetic study of the optimized formulation (F10) was found to be first order. The release of the dosage form follows the diffusion and dissolution mechanism and Non- Fickian diffusion mechanism.
- Metoclopramide lozenges by utilizing Isomalt as a vehicle which dissolve slowly in the mouth which prevail over the problem of dysphagia which is commonly associated with paediatric, geriatric patients suffering from nausea (in cancer patients) and other patients having a problem in swallowing tablets.
- From the present work, it can be concluded that Isomalt can be successfully used as the tooth friendly sugar substitute in the formulation of medicated lozenges and owing to its low caloric value and its ability to withstand formation of plaques, it could be used safely for diabetic and paediatric patient concerns.
- It is found that candy based medicated lozenges will be an alternative dosage forms. These will have additional advantages of patient compliance, convenience and comfortness for efficient treatment including low dose, immediate onset of action, reduced dosage regimen and economy.

**FUTURE PLAN**

- Scale-up studies of the optimized formulation.
- *In-vivo* studies and *in-vivo-in-vitro* correlation studies.

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# *ANNEXURE*

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## Certificate of Participation

*This is to certify that* S.Nithya *has participated as Delegate/Speaker in the CME on "BIOAVAILABILITY - BIOEQUIVALENCE STUDIES" conducted by the Department of Pharmacology, Govt. Kilpauk Medical College. Chennai in association with CDSCO, Chennai on 1st September,2017.*

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## "PHARMKINETIKOS"

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This is to certify that.....Mrs. Nithya. S..... has participated as Delegate/Speaker in the CME on " PHARMACOKINETICS" conducted by the Department of Pharmacology, Govt. Kilpauk Medical College, Chennai on 17th August, 2018.

*This CME is accredited within 10 credit points under Category II by The TN.Dr.M.G.R Medical University, Guindy, Chennai.*

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*This is to certify that ~~Mr.~~/Ms./~~Prof.~~/~~Dr.~~* NITHYA.S *of* SECOND M. PHARMACY *has actively participated as a Delegate in the National Seminar on* **"Impact of Intellectual Property Rights in Formulation and Development"** *organized by* ***Department of Pharmaceutics*** *on 23.02.2019 at* ***Arulmigu Kalasalingam College of Pharmacy,*** *Krishnankoil, Tamil Nadu.*

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