"FORMULATION, OPTIMIZATION AND CHARACTERIZATION OF SUBLINGUAL DOSAGE FORMS OF PROMETHAZINE HYDROCHLORIDE"

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IN

PHARMACEUTICAL TECHNOLOGY AND BIOPHARMACEUTICS

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DECLARATION

*I declare that the thesis "**Formulation, Optimization and Characterization of Sublingual dosage forms of Promethazine Hydrochloride**" has been prepared by me under the guidance of Dr. Jigar N. Shah, Assistant Professor, Department of Pharmaceutics and pharmaceutical technology, Institute of Pharmacy, Nirma University. No part of this thesis has formed the basis for the award of any degree or fellowship previously.*

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Dedicated

To

My Family

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C. LIST OF ABBREVIATIONS

Short name	Abbreviation
°C	Degree centigrade
µg	Microgram
ABS	Absorbance
BP	British Pharmacopoeia
Conc.	Concentration
CPR	Cumulative Percentage Release
DSC	Differential scanning calorimetry
DT	Disintegration Time
ESEM	Enviornment Scanning Electron Microscopy
FDSF	Fast Dissolving Sublingual Film
FDST	Fast Dissolving Sublingual Tablets
FTIR	Fourier Transfer Infra Red
HDPE	High Density Poly Ethylene
HP β-CD	Hydroxy Propyl β cyclodextrin
HPMC	Hydroxy Propyl Methyl Cellulose
IP	India Pharmacopoeia
KBr	Potassium Bromide
L-HPC	Low Hydroxy Propyl Cellulose
MCC	Micro crystalline Cellulose
mg	Milligram
Mg. Stearate	Magnesium Stearate
PEG-400	Poly Ethylene Glycol 400
PG	Propylene Glycol
PhEur	European Pharmacopoeia
PMZ HCl	Promethazine hydrochloride
PVA	Poly Vinyl Alcohol
PVP	Poly vinyl Pyrrolidone
RH	Relative Humidity
SD	Standard Deviation
SSF	Simulated Saliva Fluid
TS	Tensile Strength
USP	United States Pharmacopeia
UV	Ultra Violet
W/v	Weight by volume
W/w	Weight by weight
β-CD	β cyclodextrin

ABSTRACT

Promethazine hydrochloride (PMZ HCl) is a classical anti-motion sickness drug which has oral bioavailability (25%) due to extensive hepatic first pass metabolism. To overcome this drawback, novel, fast dissolving sublingual film (FDSF) and tablet (FDST) of PMZ HCl was developed. FDSF was formulated using pullulan as polymers and propylene glycol as plasticizer by solvent casting method. Complete taste masking was successfully obtained in batch containing PMZ HCl:HP β-CD(1:1) drug: aspartame (1:1) and grape fruit flavour was added to the complex, bitter after-taste of PMZ HCl was successfully masked. Complex of drug was proved using FTIR, DSC and XRD studies. Optimization of concentration of Pullulan and PG was done using 3^2 full factorial design. Optimized Batch F8 was evaluated for the parameters like elongation, tensile strength, in vitro disintegration and in vitro dissolution and where found within acceptable range. Environmental Scanning Electron Microscopy studies also showed uniform drug distribution and integrity of film. FDST were formulated using optimization of different diluents and superdisintegrants. To achieve the desired disintegration time ratio of PMZ HCl:HP β-CD was reduced to 1:0.75 and L-HPC(15%) was used, friability was controlled using PVP K-30. Optimized Batch M25 complies all the pre and post compression parameters. The kinetics of in vivo drug absorbed in human volunteers indicated that about 70.18% of the drug was absorbed from sublingual film and 52.72% from the tablet within 10 min. Comparative drug release, disintegration time and permeation studies indicated that FDSF had more promising result than FDST. The stability studies indicated that label should state “Store at cool, dry place” at temperature 25°C. Thus the developed FDSF formulation was Traveller Friendly.

CHAPTER 1

AIM OF PRESENT INVESTIGATION

AIM OF PRESENT INVESTIGATION

India is one of the rapidly developing country and also undergoing rapid urbanization. Population growth and growing economic activities have contributed to a significant increase in travelling. The increased level of travelling leads to health related issues like motion sickness, traveller's diarrhoea, migraines etc. Motion sickness or kinetosis, also known as travel sickness, is a condition in which there exists a disagreement between visually perceived movement and the vestibular system's sense of movement.

Depending on the mode of travelling and cause it can also be referred to as seasickness, car sickness, simulation sickness or airsickness. Nausea, dizziness, fatigue and headache are the most common symptoms of motion sickness. The prevalence of motion sickness was about 28% in Indian population.

A wide range of drugs have proven to be effective against nausea and vomiting. These include anti- histamines, anti- cholinergics, dopamine receptor antagonists, 5 – HT_3 receptor antagonists and gastro –prokinetic agent. Promethazine hydrochloride is a first generation anti-histamine of the phenothazines family. It acts mainly as a strong antagonist of the H_1 receptor (antihistamine) and a moderate muscarinic acetylcholine receptor antagonist, hence it blocks the action of acetylcholine on the receptors (anticholinergic effect), and this explains its benefit in reducing the nausea experienced during motion sickness.

Promethazine hydrochloride is available in conventional dosage forms such as tablets and syrups, also administered rectally as suppositories, intramuscularly, and intravenously. Onset of action occurs within 15-60 minutes after oral or rectal administration, within 20 minutes after intramuscular administration. Following intravenous administration, onset of action occurs within 3-5 minutes. After an administration of a single dose of 25mg by oral route, absorption was found to be complete, but its systemic bioavailability was very low i.e only 25% and this is consistent with an extensive first-pass effect. Hence an alternative route of administration of this drug should be considered.

Furthermore geriatric patients, unconscious patients, non-compliant patients, non co-operative children experience difficulty in swallowing tablets, intravenous and

intramuscular administration is painful and hence not preferred when repeated administration is required. Rectal suppositories also exhibit inconvenience to the patients.

It is found that the absorption of the drug from oral mucosa is via passive diffusion into the lipoidal membrane. The absorption of the drug through sublingual route is 3 to 10 times greater than oral route. Sublingual absorption is mostly rapid in action. This area is highly perfused and peak blood levels of most drugs can be achieved within 10-15 min by sublingual administration. Also it is possible to bypass the first pass effect and thus bioavailability can be improved significantly.

Among various types of Sublingual formulations such as sublingual spray and tablet and film. Sublingual film and tablet are most preferable for fast dissolving drug delivery because of its advantage like ease of administration for patients who are mentally ill & disabled, no need of water uptake, quick disintegration and dissolution, minimal or no residue in the mouth after administration, improved portability, ease of administration, accurate dosing and cost effectiveness.

The rationale for selection of Promethazine hydrochloride is its physico-chemical properties (low dose, non ionized oral cavity pH, high lipophilicity, low bioavailability), which makes its suitable for the present study.

The objective of the current investigation is development of a novel, fast dissolving taste masked sublingual film and tablet of promethazine hydrochloride using solvent casting and direct compression method respectively. Promethazine hydrochloride is bitter taste drug so to mask the taste, various taste masking techniques like addition of sweeteners, flavours, and cyclodextrins will be tried. The Promethazine hydrochloride sublingual film gets wetted by saliva, followed by hydration which finally results in rapidly dissolving film, when placed sublingually. Various water soluble film forming polymers like HPMC E-5, HPMC E-15, Pullulan, and Polyvinyl alcohol, and plasticizers such as propylene glycol (PG), poly ethylene glycol (PEG-400) etc. will be selected.

The Promethazine hydrochloride sublingual tablet rapidly disintegrate in presence of saliva when place beneath the tongue. Directly compressible excipients like Ludiflash and Microcrystalline cellulose were used along with super disintegrants like Kollidon CL, Ac-Di-Sol and sodium starch glycolate.

In the present research work an attempt will be made to formulate, optimize and evaluate fast dissolving sublingual dosage forms. Bioavailability of Promethazine hydrochloride (25mg) may be enhanced by formulation of fast dissolving sublingual film and tablet, which will disintegrate below the tongue in contact with saliva and should improve therapeutic efficacy. Taste masking will be attempted in order to overcome the bitter taste by using various sweeteners and flavouring agents. Developed formulation was aimed to be “Traveller’s Friendly”.

CHAPTER 2

INTRODUCTION

2. INTRODUCTION

2.1 INTRODUCTION TO ORAL MUCOSAL DRUG DELIVERY [1,2]

Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectable and enteral methods. Because the oral mucosa is highly vascularised, drugs that are absorbed through the oral mucosa directly enter the systemic circulation, bypassing the gastrointestinal tract and first-pass metabolism in the liver. For some drugs, this results in rapid onset of action via a more comfortable and convenient delivery route than the intravenous route. Not all drugs, however, can be administered through the oral mucosa because of the characteristics of the oral mucosa and the physicochemical properties of the drug.

The mucosal lining of the oral cavity are readily accessible, robust, and heal rapidly after local stress or damage. Oral mucosal drug delivery systems can be localized easily and are well accepted by patients. Therefore, it is evident that the oral cavity can serve as a site for systemic drug delivery. The total surface area of the oral cavity is about 100 cm^2. The mucosal membranes of the oral cavity can be divided into five regions: the floor of the mouth (sublingual), the buccal mucosa (cheeks), the gums (gingiva), the palatal mucosa, and the lining of the lips. These oral mucosal regions are different from each other in terms of anatomy, permeability to drug, and their ability to retain a system for a desired length of time.

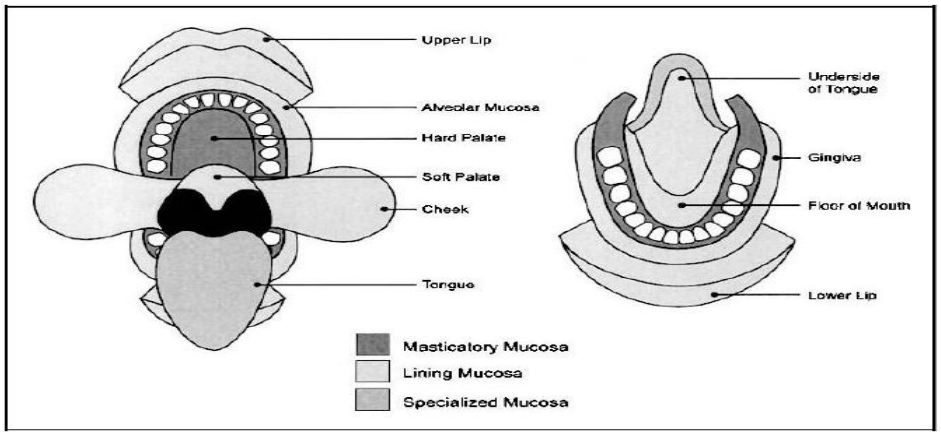


FIGURE 2.1: SCHEMATIC REPRESENTATION OF THE DIFFERENT LININGS OF MUCOSA IN MOUTH[2]

The oral mucosal thickness varies depending on the site as does the composition of the epithelium. The characteristics of the different regions of interest in the oral cavity are shown in Table 2.1

TABLE 2.1 CHARACTERISTICS OF ORAL MUCOSA [2]

Tissue	**Structure**	**Thickness (µm)**	**Surface area (cm^2±SD)**	**Permeability**	**Residence time**	**Blood Flow ml/min/**
Buccal	Non Keratinized	500-600	50.2±2.9	Intermediate	Intermediate	20.3
Sublingual	Non Keratinized	100-200	26.5±4.2	Very good	Poor	12.2
Gingival	Keratinized	200	-	Poor	Intermediate	19.5
Palatal	Keratinized	250	20.1±1.9	Poor	Very good	7.0

The sublingual route has distinct advantage over other routes of administration, as there is a complete absence of absorption rate-limiting barrier stratum corneum; also it has higher blood flow rate. Moreover, the thickness of sublingual mucosa is much lesser than buccal mucosa, due to which faster drug penetration and absorption can occur. Hence sublingual drug delivery will give more promising result than buccal route of administration.

2.2 INTRODUCTION TO SUBLINGUAL DRUG DELIVERY: [1,2,3]

Sublingual mucosa is the membrane of the ventral surface of tongue and the floor of the mouth. Sublingual drug delivery refers to a mode of drug delivery by which the drug substances are placed under the tongue and are directly absorbed via reticulated vein. Systemic drug delivery through the sublingual route had emerged from the desire to provide immediate onset of pharmacological effect. Dysphagia (difficulty in swallowing) is a common problem of all age groups, especially elderly, children, and patients who are mentally restarted, uncooperative, nauseated or on reduced liquid intake/ diets have difficulties in swallowing these dosage forms. The drug solutes are rapidly absorbed into the reticulated vein which lies underneath the oral mucosa, and transported through the facial veins, internal jugular vein, and braciocephalic vein and then drained in to systemic circulation. The main mechanism for the absorption of the drug in to oral mucosa is via passive diffusion into the lipoidal membrane. The absorption of the drug through the sublingual route is 3 to 10 times greater than oral route and is only surpassed by hypodermic injection. For these formulations, the small volume of saliva is usually sufficient to result in tablet disintegration in the oral cavity. Sublingual absorption is mostly rapid in action, but also short acting in duration. In terms of permeability, the sublingual area of the oral cavity is more permeable than the buccal (cheek) area, which in turn is more than the palatal (roof of the mouth) area. The differences in permeability are generally based on the relative thickness, the blood supply, and degree of keratinization of these membranes. In addition to the differences in the permeability of the various mucous membranes, the extent of drug delivery is also affected by the physicochemical properties of the drug to be delivered. Sublingual products have been developed for numerous indications ranging from migraines (for which rapid onset of action is important) to mental illness.

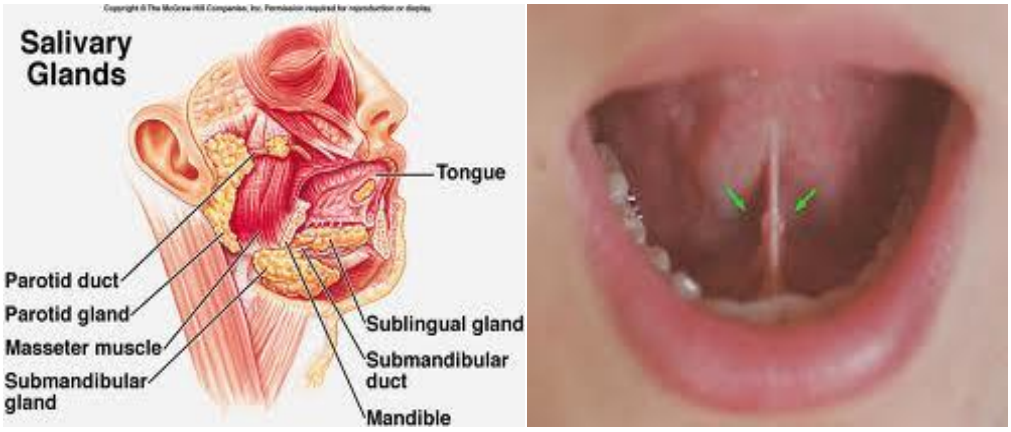


FIGURE 2.2 SCHEMATIC REPRESENTATION OF THE ORAL CAVITY

2.2.1 Anatomical Structure of the Sublingual Mucosa [1,4]

The Sublingual Mucosa can be divided into two layers namely, epithelium and the connective tissue. The Sublingual epithelium is a stratified non keratinized type of squamous epithelium. It consists of a mitotically active basal cell layer which progresses through a number of differentiating intermediate layers to the superficial layers. Sublingual epithelium is relatively thin as compared to the buccal epithelium. The Sublingual epithelium has 8-12 cell layers, while the buccal epithelium is about 40- 50 cell layers thick. The epithelium ends with the basement membrane known as the basal lamina. The connective tissue region which is about 150-500 μm in thickness consists of the lamina propria and submucosa region. The lower layers of the lamina propria are connected to the submucosa. The submucosa is relatively dense connective tissue that contains a few accessory salivary glands.

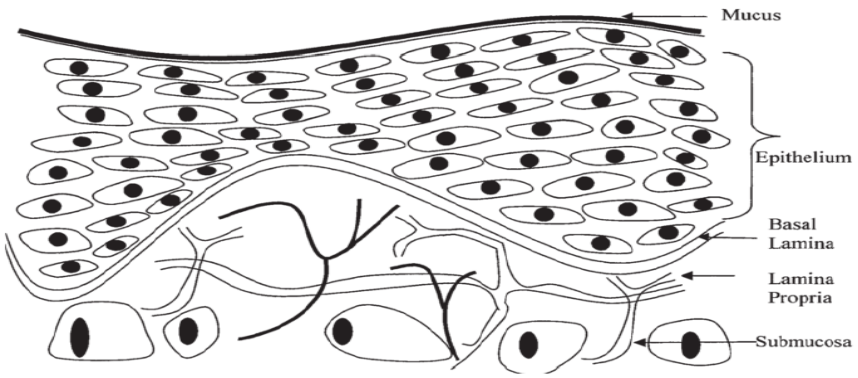


FIGURE 2.3 SCHEMATIC REPRESENTATION OF THE HUMAN SUBLINGUAL MUCOSA [4]

2.2.2 Modes of transport across Sublingual mucosa: [2,3]

Substances can be transported across various epithelial membranes by the mechanisms of simple diffusion, carrier-mediated, active transport, and other specialized mechanism, such as pinocytosis or phagocytosis. Due to the presence of stratified epithelium in the oral cavity, it is unlikely that pinocytosis or phagocytosis occurs. Carrier-mediated and ion-pair transport have not been reported for sublingual drug absorption. Most studies on sublingual point to passive diffusion across the lipid membranes. Passive transport of a drug compound across a molecular barrier is affected by a variety of factors such as distribution coefficient, molecular weight, charge, degree of ionization**.** For drug absorption to take place through the sublingual mucosa of the oral cavity, the dosage form must dissolve in saliva liberating the drug into a solution. Then the drug will partition into the mucus covering the sublingual mucosa at which time it is available for permeation. There are two pathways by which passive drug transport across the sublingual mucosa transcellular and paracellular routes that enable the drug to reach systemic circulation. Drugs can travel through these two routes simultaneously, but one route is preferred over the other depending upon the physicochemical properties of the molecules (i.e. molecular weight, polarity, etc.).

Transcellular Pathway- Drug permeation through the epithelial cells involves transport across the apical cell membrane, the intracellular space, and the basolateral membrane Drug transport through the transcellular pathway, also known as the intracellular pathway, may be by passive transport (diffusion, pH partition). Drug transport through the transcellular pathway is a complex phenomenon that is dependent on various physicochemical parameters of the drug, including molecular weight, lipophilicity, hydrogen bond potential, charge, and conformation. Lipophilic compounds and small hydrophobic molecules predominantly undergo transcellular transport. Transcellular diffusion is inversely proportional to the amount of membrane coating granules present in the intracellular spaces.

Paracellular Pathway-Drug permeation through the epithelial cells also involves transport through the lipids or in-between the epithelial cells. The paracellular pathway (also known as the intercellular pathway) can be of two types: one is an essentially

hydrophobic route, through the lipid bilayer, and the other is a hydrophilic route associated with the narrow aqueous regions adjacent to the polar head groups of the lipid bilayers. For compounds transported through the paracellular route, tortuosity and intercellular space are the main hindrances to permeability. A substance with equal solubility in aqueous and lipid media can permeate by both para and transcellular pathways. However, because the intercellular spaces and cytoplasm are hydrophilic in character, lipophilic compounds would have low solubility in this environment and thus this route will be preferred by hydrophilic compounds.

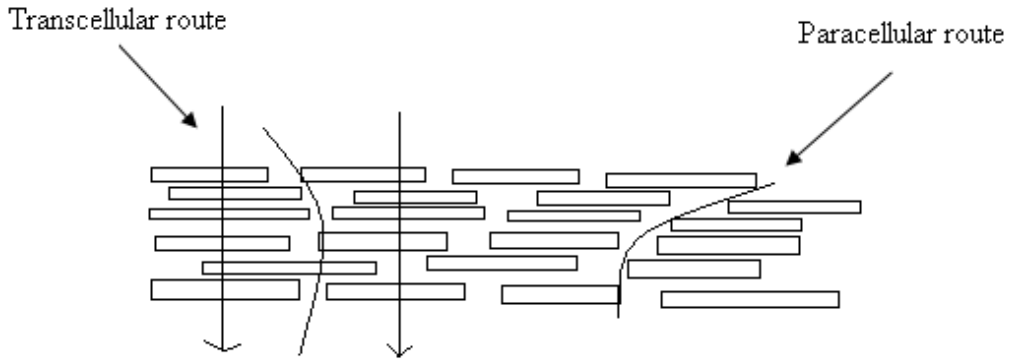


FIGURE NO 2.4 SCHEMATIC REPRESENTATION OF DIFFERENT ROUTE OF DRUG PERMEATION. [2]

2.2.3 Sublingual mucosa Related Physiology: [5]

The sublingual region is kept moist by a film of fluid called saliva that coats the teeth and the mucosal region. Saliva is a complex fluid containing 99% water with organic and inorganic materials constituting the other 1% (Table 2.2). Saliva is produced by the salivary glands and emptied through the salivary ducts. There are three pairs of salivary glands, namely the submandibular, parotid and the sublingual gland in the human oral cavity.

TABLE 2.2- COMPOSITION OF SALIVA [5]

Component	Characteristic
Water	Around 99% of total saliva
Electrolytes	Na^+, K^+, Cl^- , HCO_3^+, Ca^{2+}, Mg^{2+}, HPO_4^{2-}, SCN^- , and F^-

Secretory proteins	Amylase, proline rich proteins, mucins, histatin, cystatin, peroxidise, lysozyme and lactoferrin
Immunoglobulins	Secretory ImmunoglobulinsA, IgG, IgM
Organic materials	Glucose, amino acids, urea, uric acid and lipids
Miscellaneous	Insulin, lingual lipase, proteins and albumin

The pH of the saliva ranges from 5.5 to 7 depending on different factors such as, the food intake and habits. Usually at high flow rates of saliva, higher pH is observed due to the increase in the concentrations of bicarbonate and sodium. Saliva protects the tissues form abrasion, has antibacterial activity, and softens food to form a bolus. The antibacterial activity of saliva is afforded by lysozyme, IgA, and salivary peroxidise. Saliva tents to accumulate in the sublingual region as two major salivary ducts open into this region. The floor of the mouth region and back of the tongue region were found to contain the highest amount of residual saliva suggesting that there is a considerable accumulation of saliva in this region.

The cells of the oral epithelia covered by an intercellular ground substance known as the mucus. Mucus is a complex made up of proteins and carbohydrates. In the other stratified squamous epithelium in the body, mucus is secreted by specialized goblet cells. However, in the oral mucosa, it is synthesized by the salivary glands as a part of saliva. The primary composition of mucus in mucin that is a highly glycosylated peptide containing oligosaccharide chains bound to a protein glycosylated peptide containg oligosaccharide chain bound to a protein core. The peptide backbone consists of repeating sequences rich in serine, threonine and praline amino acids. The oligosaccharide side chain can end with a sialic acid, sulfonic acid or fructose molecule. As result of composition of oligosaccharide molecule, mucins carry a negative charge at the physiological pH. The salivary mucins perform different physiological functions such as, lubrication, softening food, and digestion of food. Two types of mucins exist in the saliva, these include, the high molecular-weight mucin (MG1) with a molecular weight of more than 1000kDa and the low molecular weight mucin glycoprotein 2 (MG2) with a molecular weight of 125kDa. The average rate of saliva secretion is 0.2 to 0.4 ml/min when resting and becomes 2 ml/min when it is stimulated. There is about a 70 μm thick mucus coating

throughout the mouth which is constantly cleared by swallowing. Daily output of saliva in humans is 750 to 1000 ml. Due to this continuous salivary flow, drug solutions are easily cleared from the mouth and thus provide a challenge for designing oral mucosal drug delivery systems.

Advantages

• A relatively rapid onset of action can be achieved compared to the oral route, and the formulation can be removed if therapy is required to be discontinued.
• Liver is bypassed and also drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract
• Improved patient compliance due to the elimination of associated pain with injections; administration of drugs in unconscious or incapacitated patients; convenience of administration as compared to injections or oral medications.
• Low dosage gives high efficacy as hepatic first pass metabolism is avoided and also reduces the risk of side effects.
• The large contact surface of the oral cavity contributes to rapid and extensive drug absorption.
• Due to rapidity in action these sublingual dosage forms are widely used in emergency conditions e.g. asthma.
• Rapid absorption and higher blood levels due to high vascularization of the region and therefore particularly useful for administration of antianginal drugs.
• They also present the advantage of providing fast dissolution or disintegration in the oral cavity, without the need for water or chewing

Disadvantages

• Since sublingual administration of drugs interferes with eating, drinking, and talking, this route is generally considered unsuitable for prolonged administration.
• Although this site is not well suited to sustained-delivery systems.
• Sublingual medication can not be used when a patient is uncooperative or unconscious.
• The patient should not smoke while taking sublingual medication, because smoking causes vasoconstriction of the blood vessels. This will decrease the absorption of the medication.

2.2.4 Factors affecting the sublingual absorption [3]

- Lipophilicity of drug: For a drug to be absorbed completely through sublingual route, the drug must have slightly higher lipid solubility than that required for GI absorption is necessary for passive permeation.
- Solubility in salivary secretion: In addition to high lipid solubility, the drug should be soluble in aqueous buccal fluids i.e. biphasic solubility of drug is necessary for absorption.
- pH and pKa of the saliva: As the mean pH of the saliva is 6.0, this pH favors the absorption of drugs which remain unionized. Also, the absorption of the drugs through the oral mucosa occurs if the pKa is greater than 2 for an acid and less than 10 for a base.
- Thickness of oral epithelium: As the thickness of sublingual epithelium is 100-200 μm which is less as compared to buccal thickness. So the absorption of drugs is faster due to thinner epithelium and also the immersion of drug in smaller volume of saliva.
- Oil to water partition coefficient: Compounds with favourable oil to- water partition coefficients are readily absorbed through the oral mucosa. An oil-water partition coefficient range of 40-2000 is considered optimal for the drugs to be absorbed sublingually.

TABLE 2.3: MARKETED PRODUCT THAT ARE ADMINISTERED BY SUBLINGUAL ROUTE [6]

Drug	Category	Dosage form
Physostigmine salicylate	Anti-Alzheimer's	Tablet
Scopolamine Opioid	Analgesic	Spray
Furosemide	Diuretic	Tablet
Nifedipine	Anti-anginal	Tablet
Nitroglycerine	Anti-anginal	Tablet
Vinpocetine	Neutropic Agent	Tablet
Terbutaline sulphate	Bronchodilator	Tablet
Ondansetron Hydrochloride	Anti emetic	Film
Salbutamol sulphate	Anti-asthmatic	Film

2.3 INTRODUCTION TO SUBLINGUAL FILM [7,8,9,10]

A Fast Dissolving Sublingual Film (FDSF) are dosage form that employs a water-dissolving polymer (generally a hydrocolloid, which may be a bioadhesive polymer), which allows the dosage form to quickly hydrate, adhere, and which rapidly disintegrates and dissolve to release the drug when placed on the tongue or in the oral cavity.

Swallowing a pill is a major difficulty encountered in case of geriatric and paediatric patient which leads to poor patient compliance due to unpalatable taste of drug. To troubleshoot these problems a new dosage form known as oral strip (OS) or FDSF, has been developed which rapidly disintegrate and dissolve in saliva.

FDSF offer fast, accurate dosing in a safe, efficacious format that is convenient and portable, without the need for water or measuring devices. FDSF are user friendly and less fragile form than ODT, allowing easy storage and carry-on during travel.

2.3.1 Salient Features of Fast Dissolving films

Fast dissolving buccal films provide ease of administration for patients who are mentally ill, disabled and uncooperative; requires no water; have quick disintegration and dissolution of the dosage form. They can be unobstructive and can be designed to leave minimal or no residue in the mouth after administration and also provides a pleasant mouth feel. This delivery system has no risk of chocking. It allows high drug loading and has the ability to provide advantages of liquid medication in the form of solid preparation. Fast dissolving films are adaptable and amenable to existing processing and packaging machinery, cost effective and have excellent mucoadhesion. Fast dissolving films can be formulated in various shapes and sizes.

Advantages:

1. Availability of larger surface area that leads to rapid disintegrating and dissolution in the oral cavity.
2. The disadvantage of most ODT is that they are fragile and brittle, which warrants special package for protection during storage and transportation. Since the films

are flexible they are not as fragile as most of the ODTs. Hence, there is ease of transportation and during consumer handling and storage.

3. As compared to drops or syrup formulations, precision in the administered dose is ensured from each of the strips.
4. No need of water has led to better acceptability amongst the dysphagic patients. The difficulty encountered in swallowing tablets or capsules is circumvented. The large surface area available in the strip dosage form allows rapid wetting in the moist buccal environment. The dosage form can be consumed at any place and anytime as per convenience of the individual.
5. The oral or buccal mucosa being highly vascularized, drugs can be absorbed directly and can enter the systemic circulation without undergoing first-pass hepatic metabolism. This advantage can be exploited in preparing products with improved oral bioavailability of molecules that undergo first pass effect.
6. Since the first pass effect can be avoided, there can be reduction in the dose which can lead to reduction in side effects associated with the molecule.
7. Patients suffering from dysphagia, repeated emesis, motion sickness, and mental disorders prefer this dosage form as they are unable to swallow large quantity of water.
8. OS can be administer to the patients who cannot swallow tablets/cap., such as the elderly, stroke victims, bedridden patients, & patients who refuse to swallow such as paediatric, geriatric & psychiatric patients.
9. Rapid drug therapy is possible.
10. Certain studies concluded increased bioavailability/proved rapid absorption of drugs through pregastric absorption of drugs from mouth, pharynx & oesophagus as saliva passes down.
11. OS are convenient for administration and passes good patient compliant for disabled, bedridden patients and for travellers and busy people, who do not always have access to water.
12. Good mouth feel property of OS helps to change the perception of medication as bitter pill particularly in paediatric patients.

13. The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.

2.3.2 Composition of the Formulation

Fast dissolving sublingual film is a thin film with an area of 1-20 cm^2 (depend on dose and drug loading) containing drug. Drugs can be loaded up to a single dose of 30mg. Formulation considerations (plasticizers etc.) have been reported as important factors affecting mechanical properties of the films.

A typical composition contains the following
Drug 1 -25% w/w
Water soluble polymer 40 - 45% w/w
Plasticizers 0 -20% w/w
Fillers, colours, Flavours etc 0 -40% w/w

Film forming polymers:

A variety of polymers are available for preparation of FDSF. The polymers can be used alone or in combination to obtain the desired strip properties. The film obtained should be tough enough so that there won't be any damage while handling or during transportation. The robustness of the strip depends on the type of polymer and the amount in the formulation. The various polymers available, pullulan, PVA and PEO are most commonly used for preparation of FDSF.

Plasticizers:

Plasticizer is a vital ingredient of the FDSF formulation. It helps to improve the flexibility of the strip and reduces the brittleness of the strip. Plasticizer significantly improves the strip properties by reducing the glass transition temperature of the polymer. The selection of plasticizer will depend upon its compatibility with the polymer and also the type of solvent employed in the casting of strip. The flow of polymer will get better with the use of plasticizer and enhances the strength of the polymer. Glycerol, Propylene glycol, low molecular weight polyethylene glycols, phthalate derivatives like dimethyl, diethyl and

dibutyl phthalate, citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin and castor oil are some of the commonly used plasticizer excipients.

Sweetening agents:

Sweeteners have become the important part of the food products as well as pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. The classical source of sweetener is sucrose (derived from cane or beet in the form of liquid or dry state), dextrose, fructose, glucose, liquid glucose and isomaltose. The sweetness of fructose is perceived rapidly in the mouth as compared to sucrose and dextrose. Fructose is sweeter than sorbitol and mannitol and thus used widely as a sweetener. Saccharin, cyclamate and aspartame are the first generation of the artificial sweeteners followed by acesulfame-K , sucralose, alitame and neotame which fall under the second generation artificial sweeteners. Acesulfame-K and sucralose have more than 200 and 600 time sweetness. Neotame and alitame have more than 2000 and 8000 time sweetening power as compared to sucrose.

Flavouring agents:

Flavouring agents can be selected from synthetic flavour oils, oleo resins, extract derived from various parts of the plants like leaves, fruits and flowers. Flavours can be used alone or in the combination. Peppermint oil, cinnamon oil, oil of nutmeg are examples of flavour oils while vanilla, cocoa, coffee, chocolate and citrus are fruity flavours. Apple, raspberry, cherry, pineapple are few examples of fruit essence type. The amount of flavour needed to mask the taste depends on the flavour type and its strength.

Colouring agents:

Pigments such as titanium dioxide or FD & C approved colouring agents are incorporated (not exceeding concentration levels of 1 percent; w/w) in FDF when some of the formulation ingredients or drugs are present in insoluble or suspension form.

2.3.3 Methods of manufacture of fast dissolving films

One (or a combination) of the following processes may be used to manufacture the oral films:

· Solvent casting

· Hot-melt extrusion

· Semisolid casting

· Solid dispersion extrusion

· Rolling

Solvent-casting method:

In this method water-soluble ingredients are dissolved to form a clear viscous solution. The API and other agents are dissolved in smaller amounts of the solution and combined with the bulk. This mixture is then added to the aqueous viscous solution. The entrapped air is removed by vacuum. The resulting solution is cast as a film and allowed to dry, which is then cut into pieces of the desired size.

Advantages:

Better uniformity of thickness and better clarity than extrusion.

Film has fine gloss and freedom from defects such as die lines.

Film has more flexibility and better physical properties. The preferred finished film thickness is typically 12-100 μm, although various thicknesses are possible to meet API loading and dissolution needs.

Disadvantages:

The polymer must be soluble in a volatile solvent or water.

2.3.4 EVALUATION PARAMETER OF SUBLINGUAL FILM

1) Thickness:-

Thickness of the films were measured by Thermonik Tablet Taster, DTH – 250. Films were tested for three different positions by keeping the film in between two jaws of Machine and average thickness was calculated.

2) % Elongation:- [10]

It indicates the elasticity nature of the film. Digital Tensiometer was used to calculate the

% elongation of the film. Elongation was measured when the films breaks. Generally elongation of film increases as the plasticizer content increases.

$$\%\text{elongation} = \frac{\text{Increase in length of strip} \times 100}{\text{Initial length of strip}}$$

3) Tensile strength:- [10]

The mechanical properties of films were evaluated using a QTS Texture Analyzer. The peak load was used to evaluate by the help of probe Dual Grip Jig. The Texture expert software recorded the data when the probe started withdrawing from the film. The peak load and the area under load distance curve obtained from the texture profile were used to assess the tensile strength and % elongation at of the films. Each measurement was repeated three times.

$$\text{Tensile strength} = \frac{\text{Load at failure}}{\text{Strip thickness} \times \text{Strip width}}$$

FIGURE 2.5 ASSEMBLY OF TEXTURE ANALYSER

4) Folding endurance:- [10]

Folding endurance was determined by repeated folding of the film at the same place till it breaks. The number of times the film was folded without breaking was calculated as folding endurance.

5) Drug content:- [10]

A 2.2×1.3 cm2 film was cut into small pieces and put in a 100 ml simulated saliva fluid. It is then shaken in a mechanical shaker for 2 hrs to get a homogenous solution and filtered. Sample solutions were prepared by diluting to different concentrations and determined spectroscopically. The determinations will carry out in triplicates and the average of three readings will be taken.

6) In-vitro dissolution studies:- [11]

The dissolution studies of the optimized film were carried out in a USP basket apparatus, using either 300 ml phosphate buffer pH 6.8. Each film sample was placed in the basket. The basket containing film sample was submerged into the dissolution media and rotated at 50 rpm. Aliquots of 5 ml were withdrawn at predetermined time intervals and fresh medium was used to replace sample volume. The samples were filtered through 0.45µm membrane filter, diluted suitably and analyzed using UV-Spectrophotometer at 250 nm by blank correction method. Dissolution of each sample was performed 6 times and mean of all determinations was used to calculate drug release profile.

7) In-vitro disintegration studies:- [11]

The in vitro disintegration time was determined by a modified method. A glass Petri dish (6.5 cm diameter) was filled with 10 ml of water and the film was carefully placed in the center. The set up was left undisturbed. The time for the film to completely disintegrate into fine particles was noted. The test was performed four times on each formulation and mean value was reported.

8) Taste evaluation:-

Taste acceptability was measured by a taste panel (n=6) with film sample containing 25mg drug held in mouth until disintegration, then spat out and the bitterness level was then recorded.

0: No Bitterness

0.5: Threshold Bitterness

1: Slight Bitterness

2: Moderate Bitterness

3: Strong Bitterness

9) In-vivo sublingual studies in Human:- [47]

The 'buccal absorption test' will be performed on healthy volunteers. Fast dissolving film and tablet containing 25 mg Promethazine hydrochloride will be tested. Before each Sublingual administration, the volunteers are made to wash their mouth with 100 ml of distilled water. Then, the fast dissolving film/tablet will be placed under the tongue for fixed period of time and should not be swallowed. Then if any residue of dosage form is present will be expelled and the mouth will be rinsed with distilled water (3×/20 ml). The residue of dosage form and the washing solutions will be combined and analyzed for the remaining drug content. The amount of Promethazine Hydrochloride absorbed from the mucosa will be determined as difference between initial and re-covered content.

Table 2.4: LIST OF FAST DISSOLVING FILMS AVAILABLE IN MARKET

Product Agent	Manufacturer	Active Pharmaceutical	Strength (mg)
Triaminic	Novartis	Diphenhydramine HCl	12.5
Theraflu	Novartis	Dextromethorphan HBr	15
Gas-X	Novartis	Simethicone	62.5
Sudafed	Pfizer	Phenylephrine HCl	10
Listerene	Pfizer	Cool mint	-
Benadryl	Pfizer	Diphenhydramine HCl	25
Orajel	Del	Menthol/Pectin	2/30

2.4 INTRODUCTION TO SUBLINGUAL TABLET [12,13]

Sublingual tablets (ST) are intended to be placed beneath the tongue and held until absorption has taken place. They must dissolve or disintegrate quickly, without the need of water or chewing, allowing the medicament to be rapidly absorbed.

Advantages of ST

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

17. Rapid drug therapy intervention.
18. No chewing needed.
19. Adaptable and amenable to existing processing and packaging Machinery.
20. Rapid onset of action.

Disadvantages of ST

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

2.4.1 Selection of drugs:

The ideal characteristics of a drug to be selected

- No bitter taste
- Dose lower than 20mg
- Small to moderate molecular weight
- Good stability in water and saliva
- Partially non ionized at the oral cavities pH
- Ability to diffuse and partition into the epithelium of the upper GIT (logp>1, or preferably>2)
- Ability to permeate oral mucosal tissue

2.4.2 MECHANISMS OF ST

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

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

The Mechanisms are:

1. High swellability of disintegration
2. Chemical reaction
3. Capillary action

2.4.3 Various Approaches for manufacturing of Sublingual Tablets

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

Various methods used in the manufacture of Fast dissolving tablets include:

· Freeze –drying or lyophilization

· Tablet Molding

· Direct compression technologies

· Spray drying

· Sublimation

· Phase Transition

· Mass extrusion

Direct Compression

In this method, tablets are directly compressed from the mixture of the drug and excipients without any preliminary treatment. The mixture to be compressed must have adequate flow properties. This Advantage of this method includes easiest way to manufacture tablets, Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression of tablets. Also high doses can be accommodated and final weight of tablet can easily exceed that of other production methods. In Mouth Dissolving Tablets technologies which are based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution. The presence of water-soluble excipients, effervescent agents and sugar based excipients also affect the process.

2.4.4 EVALUATION [12]

1. Bulk Density (D_b):

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It is expressed in gm/ml and is given by

$$\mathbf{D_b = \frac{M}{V_0}}$$

Where, M is the mass of powder

V_0 is the Bulk volume of the powder.

2. Tapped Density (D_t):

It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in gm/ml and is given by

$$\mathbf{D_t = \frac{M}{V_t}}$$

Where, M is the mass of powder

V_t is the tapped volume of the powder.

3. Angle of Repose:

The frictional forces in a loose powder can be measured by the angle of repose, θ. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of powder formed.

$$\mathbf{\tan \theta = \frac{h}{r}}$$

$$\mathbf{\theta = \tan^{-1} \frac{h}{r}}$$

Where, θ is the angle of repose

h is the height in cms

r is the radius.

TABLE 2.5 STANDARD VALUES OF ANGLE OF REPOSE

Sr. No.	Angle of Repose (θ)	Type of Flow
1	<20	Excellent
2	20-30	Good
3	30-34	Passable
4	>34	Very Poor

4. Carr's Index (I):

It indicates the ease with which a material can be induced to flow. It is expressed in percentage and is given by

$$I = \frac{D_t - D_b}{D_t}$$

Where, Dt is the tapped density of the powder.

Db is the bulk density of the powder.

TABLE 2.6 STANDARD VALUES OF CARR'S INDEX

Sr. No.	Carr's Index (I)	Type of Flow
1	5-12	Excellent
2	12-16	Good
3	18-21	Fair to Passable
4	23-35	Poor
5	33-38	Very Poor
6	>40	Very Very Poor

5. Hausner ratio (H):

Hausner ratio is an indirect index of ease of powder flow. It was calculated by the following formula.

$$H = \frac{D_t}{D_b}$$

Where, Dt and Db are tapped density and bulk density respectively.

TABLE2.7 STANDARD VALUES OF HAUSNER'S RATIO

<1.25	Good Flow
>1.25	Poor Flow

6. Hardness:

Hardness of the tablets were measured by Thermonik Tablet Taster, DTH – 250. It is expressed in Kg / cm2.

7. Friability (F):

The friability of the tablet was determined using Roche Friabilator. It is expressed in percentage (%). 10 tablets were initially weighed ($W_{initial}$) and transferred into the friabilator. The friabilator was operated at 25 rpm for four mins. The tablets were weighed again (W_{final}). The percentage friability was then calculated by:

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} X100$$

8. Weight Variation:

Ten tablets were selected randomly from the lot and weighed individually to check for weight variation. IP limit for weight variation in case of tablets weighing upto 250mg is ± 7.5%.

9. Thickness:

The thickness of the tablets were measured by Thermonik Tablet Taster, DTH – 250. It is expressed in mm.

10. *In Vitro* Disintegration Time:

The *In vitro* disintegration time was determined using disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

11. Wetting Time:

A piece of tissue paper folded twice was placed in a small petri plate (internal diameter = 6.5 cm) containing 10ml of water. A tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37^{o} C

12. *In Vitro* Dissolution Study:

In vitro dissolution study was performed by using USP Type II Apparatus (Paddle type) at 50 rpm. Phosphate buffer of pH 7.4, 900 ml was used as dissolution medium which is maintained at 37±0.5ºC. Aliquot of dissolution medium (5ml) was withdrawn at specific time intervals and was filtered. The same volume of dissolution medium is replaced to maintain sink condition. The absorbance of these aliquots was measured at 250 nm using UV-Visible spectrophotometer (Shimadzu). Cumulative percentage release of drug was calculated using an equation obtained from a standard curve

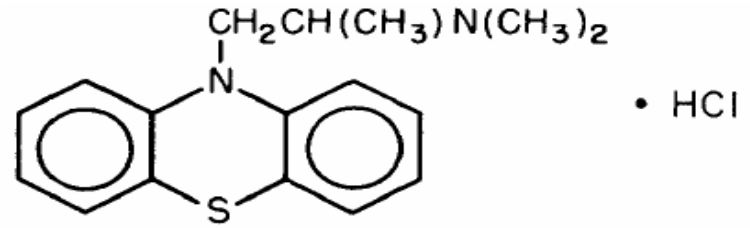
2.5 INTRODUCTION TO PROMETHAZINE HYDROCHLORIDE

[14,15,16,43]

2.5.1 SYNONYMS: Prozamine, Promazinamide

2.5.2 CHEMICAL FORMULA: C17H20N2S•HCl

2.5.3 CHEMICAL STRUCTURE:



2.5.4 CHEMICAL IUPAC NAME: 10H-Phenothiazine-10 ethanamine, N,N,α-trimethyl-, monohydrochloride

2.5.5 PHYSICO CHEMICAL PARAMETERS:

Average Molecular Weight: 320.88

State: White to faint yellow crystalline powder

Melting Point: 220-222^{0}C

Solubility: Freely soluble in water and soluble in alcohol.

Dissociation Constant: pKa 4.12 and 7.32 (20°C)

Partition Coefficient: Log P (octanol/water) – 3.90

Ultraviolet Spectrum: Absorption maxima at 249nm**.**

2.5.6 PHARMACOLOGY:

Antihistaminic, anti-motion sickness, sedative, antiemetic, and anticholinergic effects.

Mechanism of Action:

Antagonise the action of histamine at H1 receptors, reducing histamine-related vasodilation and increased capillary permeability. They also have anticholinergic activity, some have alpha-blocking activity and some have antiserotonin activity.

2.5.7 PHARMACOKINETICS:

Absorption

Well absorbed from the GI tract and after IM administration. Bioavailability is low and variable (approximately25%) due to extensive first pass metabolism. T max is 2 to 3 h (IM).

Distribution

Protein binding is 76% to 93%. Crosses the blood-brain barrier and placenta, and is distributed into breast milk.

Metabolism

Metabolized in the liver; sulfoxides and N-demethylpromethazine are the predominant metabolites.

Half life: 6-12 hours

Elimination

In the urine and bile, chiefly as metabolites. The half-life is approximately 5 to 14 h.

2.5.8 PREGNANCY RISK FACTOR

Category C. Administration within 2 weeks of delivery may inhibit platelet aggregation in the newborn.

2.5.9 CONTRAINDICATIONS

Promethazine Hydrochloride Tablets and Suppositories are contraindicated for use in pediatric patients less than two years of age,and contraindicated in comatose states, and in individuals known to be hypersensitive or to have had an idiosyncratic reaction to promethazine or to other phenothiazines. Antihistamines are contraindicated for use in the treatment of lower respiratory tract symptoms including asthma.

2.5.10 WARNING/PRECAUTIONS

Promethazine hydrochloride should not be used in pediatric patients less than 2 years of age because of the potential for fatal respiratory depression.

2.5.11 DOSAGE AND ADMINSTRATION:

The average adult dose is 25 mg taken twice daily. The initial dose should be taken one-half to one hour before anticipated travel and be repeated 8 to 12 hours later, if necessary. On succeeding days of travel, it is recommended that 25 mg be given on arising and again before the evening meal. For children, Phenergan Tablets, Syrup, or Rectal Suppositories, 12.5 to 25 mg, twice daily, may be administered.

2.5.12 ADVERSE REACTIONS

Cardiovascular: Bradycardia; faintness; increased or decreased blood pressure; tachycardia.

CNS: Catatonic-like states; confusion; convulsive seizures; disorientation; dizziness; drowsiness; euphoria; excitation; extrapyramidal symptoms, including oculogyric crisis, tongue protrusion, and torticollis; fatigue; hallucinations; hysteria; incoordination; insomnia; lassitude; nervousness; NMS (potentially fatal); sedation; somnolence; tremors.

Dermatologic: Dermatitis; photosensitivity; urticaria.

Occular: Blurred vision; diplopia; nasal stuffiness; tinnitus.

GI: Dry mouth; jaundice; nausea; vomiting.

Hematologic-Lymphatic: Agranulocytosis; leukopenia; thrombocytopenia; thrombocytopenic purpura.

Local: Abscess; burning; edema; erythema; gangrene; injection-site phlebitis; pain; swelling; tissue necrosis.

Respiratory: Apnea (potentially fatal); asthma; respiratory depression (potentially fatal).

2.6 INTRODUCTION TO TASTE MASKING TECHNIQUES [17]

Bitterness reduction is important requirements of an ideal oral dosage form. Various methods for bitterness reduction and inhibition have resulted in improved taste acceptability of these formulations.

Various techniques available for masking bitter taste:

1. Taste masking with ingredients such as flavours, sweeteners and amino acids
2. Formation of inclusion complexes with β cyclodextrin
3. Ion exchange resins
4. Spray congealing with lipids
5. Freeze drying process
6. Miscellaneous: Using gelatin, liposomes, lecithin, surfactants and salts.

Taste making with flavors, sweeteners and amino acids

Use of sweeteners and flavours is the simplest and commonest approach for taste masking especially in chewable tablets, paediatric and liquid formulations. But it is not very successful for highly bitter and highly water soluble drugs. Artificial sweeteners and flavours are generally being used along with taste masking techniques for improving characteristics of the dosage form.

TABLE 2.5 SWEETENER LIMIT PER DOSE AS PER FDA IIG GUIDELINE [18]

Sr. No	Sweetener	Sweetness compare to sucrose	Limit per dose as per IIG guideline
1	Neotame	2000-7000	0.0011% (Oral Spray)
2	Sucralose	300-1000	5.75 mg (ODT) 1.5mg (Sublingual Tab)
3	Saccharin sodium	300	1mg (Sublingual Tab) 0.57 mg (Buccal film)
4	Acesulfame K	180-200	3 mg (Sublingual Tab)
5	Aspartame	180-200	36 mg (ODT)
6	Mannitol	0.5	174.78 mg (ODT)

Taste masking by inclusion complexation:

Cyclodextrins are cyclic oligosaccharides containing at least 6 D-(+) glucopyranose units attached by α-(1, 4) glucosidic bonds. The CDs are available in 3 different natural forms as α-,β-, and γ-CDs containing 6, 7, or 8 glucose units respectively. Each CD differs in its ring size and solubility. Of the 3 naturally occurring CD, the cavity size of α-CD is insufficient for many drugs and γ-CD is expensive. β-CD has been widely used in the early stages of pharmaceutical applications because of its ready availability and cavity size suitable for the widest range of drugs. β -cyclodextrin is the most widely used complexing agent for inclusion type complexes. It is a sweet, nontoxic, cyclic oligosaccharide obtained from starch. But it has limited application due to low aqueous solubility and nephrotoxicity.

Chemically modified CD derivatives have been prepared with a view to extend the physicochemical properties and inclusion capacity of parent CDs. Several amorphous, noncrystallizable CD derivatives with enhanced aqueous solubility, physical and microbiological stability, and reduced parenteral toxicity have been developed by chemical modification of parenteral CDs.

Cyclodextrin may be used to form inclusion complex with variety of the molecules, resulting primarily in improvement to dissolution and bioavailability owing to enhanced solubility and improved chemical and physical stability. Cyclodextrin inclusion complexes are also used to mask the unpleasant taste of active materials and to convert a liquid substance to a solid substance.

The drug molecule fits into the cavity of a complexing agent, i.e., the host molecule, forming a stable complex. The complexing agent is capable of masking the bitter taste of drug by either decreasing its oral solubility on ingestion or decreasing the amount of drug particles exposed to taste buds, thereby reducing the perception of bitter taste. β-CD eliminate the bad taste by two theoretical possibilities: β-CD enwraps the bad tasting molecule (inclusion complex formation), impeding its interaction with the taste buds, or the β-CD interacts with the gate-keeper proteins of the taste buds, paralyzing them. In addition, the sweet taste of β-CD may impart an additive effect.

Method of preparation of inclusion complex:

Co-grinding, kneading, solid dispersion, solvent evaporation, co-precipitation, spray drying and freeze drying.

Factors influencing inclusion complex formation:

Degree of Substitution (DS) -It is defined as the average number of substituted hydroxyls per glucopyranose unit of CD ring. The number of reactive hydroxyls per mole of glucopyranose unit is 3, the maximum numbers of substituents possible for α-, β-, and γ-CDs are 18, 21, and 24, respectively.

Average molar degree of substitution (MS) – It is defined as the average number of moles of the substituting agent, e.g, hydroxypropyl, per mole of glucopyranose. The value of MS can be more than 3 for each glycopyranose unit of substituted CDs, or more than 18, 21 and 24 for α-, β-, and γ-CDs, respectively.

Degree of polymerization (DP)-It is defined as the ratio of MS to DS (MS/DS). If no additional reactive sites are produced during the substitution, MS and DS are equal and the DP becomes 1.

Total Degree of Substitution (TDS) - It avoids the confusion between DS and MS and represents the average number of substituted groups (e.g, hydroxypropyl) per CD molecule. Degree of substitution (DS) plays an important role in balancing the CD water solubility and its complexing ability. It was reported that increasing the degree of substitution up to an optimum level improves the CD aqueous solubility, but beyond that, the steric hindrances of the host molecule impair CD complexing capacity.

2.7 INTRODUCTION TO EXCIPIENTS

2.7. 1 INTRODUCTION TO PULLULAN: [19]

1) SYNONYMS INS No. 1204

2) DEFINITION

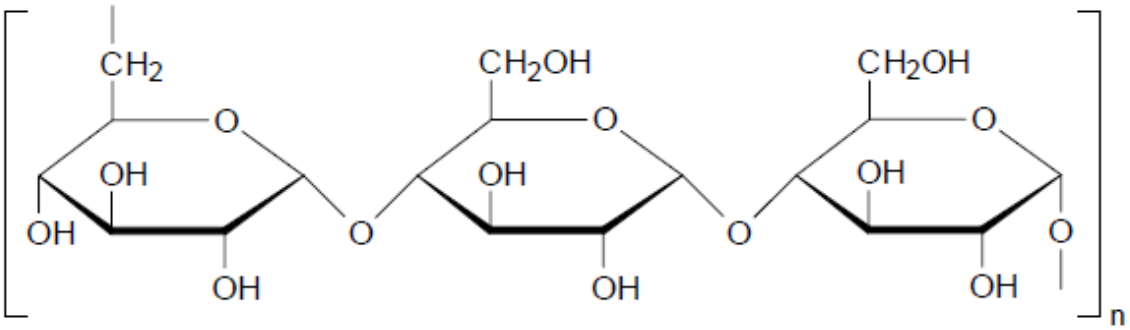
Linear, neutral glucan consisting mainly of maltotriose units connected by α-1,6 glycosidic bonds. It is produced by fermentation from a food grade hydrolysed starch using a non-toxin producing strain of *Aureobasidium pullulans*. After completion of the fermentation, the fungal cells are removed by microfiltration, the filtrate is heat-sterilized and pigments and other impurities are removed by adsorption and ion exchange chromatography.

3) C.A.S. number

9057-02-7

4) Chemical formula

$(C_6H_{10}O_5)_x$



5) Description

A white to off-white tasteless, odourless powder that forms a viscous non-hygroscopic solution when dissolved in water at 5-10%. It can be made into films of high tensile strength and low oxygen permeability. Pullulan starts to decompose at 250°C and chars at 280°C

6) Solubility

Highly soluble in water, dilute alkali, insoluble in alcohol and other organic solvents except dimethylsulphoxide and formamide.

7) pH:

10% w/w solution of PI-20 has a pH between 5 and 7.

8) Viscosity

Pullulan solutions are viscous but do not gel. There is a linear relationship between the viscosity and molecular weight .Viscosity is relatively independent of pH (<2 to >11) and temperature. Heating at 90°C for an hour reduces the viscosity of large polymers (around 300,000 daltons) by about 10% whereas there was little change in the molecular weight of smaller molecules (60,000–100,000 daltons). Viscosity is also unaffected by heating to 100°C for 6 hours in 30% NaCl.

9) Functional uses

Pullulan is used as a glazing agent, as a film forming agent, as a thickener or as a carrier in the production of capsules for dietary supplements (substitute for gelatin), coatings for coated tablets (dietary supplements), for production of edible flavoured films (breath fresheners), jams and jellies, confectionery and some meat and fruit products. It is also used as a texturizer in chewing gum and as a foaming agent in milk based desserts.

10) Stability

The chemical structure and thus the reactivity of pullulan resembles that of maltodextrin and starch, both of which are common constituents of food. Having a large molecular weight, Pullulan PI-20 is essentially non-reducing. It is stable in aqueous solution over a wide pH range (3-8) (Wallenfels *et al*., 1965). Only prolonged heating at pH< 3 leads to a decrease of viscosity which is indicative of hydrolytic depolymerization (Nakamura, 1984). On dry heating, pullulan decomposes and carbonizes at 250-280°C (Tsujisaka & Mitsuhashi, 1993).

2.7.2 INTRODUCTION TO ASPARTAME: [20]

1) Nonproprietary Names

BP: Aspartame

PhEur: Aspartamum

USPNF: Aspartame

2) Synonyms

3-Amino-N-(a-carboxyphenethyl)succinamic acid N-methyl ester; 3-amino-N-(a-methoxycarbonylphenethyl)succinamic acid; APM; aspartyl phenylamine methyl ester; Canderel; E951; Equal; methyl N-a-L-aspartyl-L-phenylalaninate; NutraSweet; Pal Sweet; Pal Sweet Diet; Sanecta; SC-18862; Tri-Sweet.

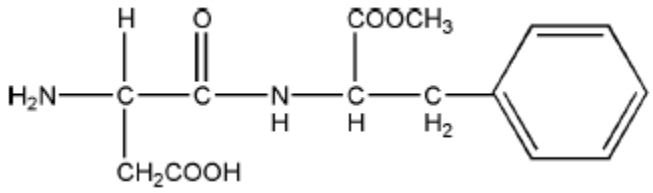
3) Chemical Name and CAS Registry Number

N-a-L-Aspartyl-L-phenylalanine 1-methyl ester [22839-47-0]

4) Empirical Formula and Molecular Weight

$C_{14}H_{18}N_2O_5$ 294.31

5) Structural Formula



6) Functional Category

Sweetening agent.

7) Description

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

8) Applications in Pharmaceutical Formulation or Technology

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 flavor systems and can be used to mask some unpleasant taste characteristics; the approximate sweetening power is 180–200 times that of sucrose. Unlike some other intense sweeteners, aspartame is metabolized in the body and consequently has some nutritive value: 1 g provides approximately 17 kJ (4 kcal). However, in practice, the small quantity of aspartame consumed provides a minimal nutritive effect. Therapeutically, aspartame has also been used in the treatment of sickle cell anemia.

9) Stability and Storage Conditions

Aspartame is stable in dry conditions. In the presence of moisture, hydrolysis occurs to form the degradation products L-aspartyl-L-phenylalanine and 3-benzyl-6-carboxymethyl-2,5- diketopiperazine.

10) Incompatibilities

Differential scanning calorimetry experiments with some directly compressible tablet excipients suggests that aspartame is incompatible with dibasic calcium phosphate and also with the lubricant magnesium stearate.

2.7.3 INTRODUCTION TO 2-HYDROXYPROPYL-B CYCLODEXTRIN: [20]

1) Nonproprietary Names

BP: Betadex

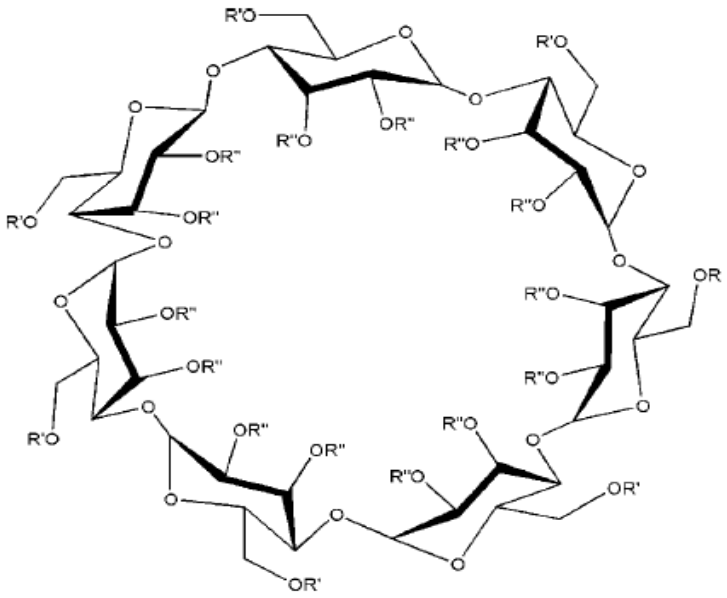
PhEur: Betadexum

USPNF: Betadex

2) CAS number: [128446-35-5]

3) Synonyms: 2-HP-b-CD; Kleptose HPB.

4) Structural Formula and Empirical Formula



R0, R00 = CH2CHOHCH3 for 2-hydroxypropyl cyclodextrins

5) Functional Category

Solubilizing agent; stabilizing agent

6) Description

Cyclodextrins are cyclic oligosaccharides containing at least six D-(þ)-glucopyranose units attached by a(1!4) glucoside bonds. The three natural cyclodextrins, a, b, and g, differ in their ring size and solubility. They contain 6, 7, or 8 glucose units, respectively. Cyclodextrins occur as white, practically odorless, fine crystalline powders, having a slightly sweet taste. Some cyclodextrin derivatives occur as amorphous powders.

Appearance: white crystalline powder.

Solubility: greater than 1 in 2 parts of water at 258C.

Surface tension: 52.0–69.0mN/m (52–69 dynes/cm) at 258C.

7) Applications in Pharmaceutical Formulation or Technology

Cyclodextrins are crystalline, nonhygroscopic, cyclic oligosaccharides derived from starch. Among the most commonly used forms are a-, b-, and g-cyclodextrin, which have respectively 6, 7, and 8 glucose units; see Section 5. Substituted cyclodextrin derivatives are also available; see Section 17. Cyclodextrins are 'bucketlike' or 'conelike' toroid molecules, with a rigid structure and a central cavity, the size of which varies according to the cyclodextrin type; see Section 8. The internal surface of the cavity is hydrophobic and the outside of the torus is hydrophilic; this is due to the arrangement of hydroxyl groups within the molecule. This arrangement permits the cyclodextrin to accommodate a guest molecule within the cavity, forming an inclusion complex. Cyclodextrins may be used to form inclusion complexes with a variety of drug molecules, resulting primarily in improvements to dissolution and bioavailability owing to enhanced solubility and improved chemical and physical stability. Cyclodextrin inclusion complexes have also been used to mask the unpleasant taste of active materials and to convert a liquid substance into a solid material.β-Cyclodextrin is the most commonly used cyclodextrin, although it is the least soluble; see Section 10. It is the least expensive cyclodextrin; is commercially available from a number of sources; and is able to form inclusion complexes with a number of molecules of pharmaceutical interest. However, b-cyclodextrin is nephrotoxic and should not be used in parenteral formulations.b-Cyclodextrin is considered to be nontoxic when administered orally, and is primarily

used in tablet and capsuleformulations. b-Cyclodextrin derivatives tend to be nontoxic when used either orally or parenterally, and the derivatives 2-hydroxypropyl-b-cyclodextrin and 3-hydroxypropyl-b-cyclodextrinare becoming incrasingly important in pharmaceuticalformulations.(1–5)a-Cyclodextrin is used mainly in parenteral formulations.However, as it has the smallest cavity of the cyclodextrins it canform inclusion complexes with only relatively few, small-sizedmolecules. In contrast, g-cyclodextrin has the largest cavity andcan be used to form inclusion complexes with large molecules;it has low toxicity and enhanced water solubility.In oral tablet formulations, b-cyclodextrin may be used in both wet-granulation and direct-compression processes. The physical properties of b-cyclodextrin vary depending on the manufacturer.

8) Stability and Storage Conditions

b-Cyclodextrin and other cyclodextrins are stable in the solid state if protected from high humidity. Cyclodextrins should be stored in a tightly sealed container, in a cool, dry place.

9) Incompatibilities

The activity of some antimicrobial preservatives in aqueous solution can be reduced in the presence of hydroxypropyl-bcyclodextrin.

2.7.4 INTRODUCTION TO PROPYLENE GLYCOL: [20]

1) Nonproprietary Names

BP: Propylene glycol

JP: Propylene glycol

PhEur: Propylenglycolum

USP: Propylene glycol

2) Synonyms

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

3) Chemical Name and CAS Registry Number

1,2-Propanediol [57-55-6]

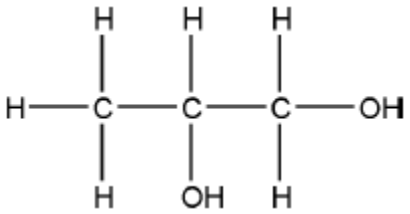
(-)-1,2-Propanediol [4254-14-2]

(+)-1,2-Propanediol [4254-15-3]

4) Empirical Formula and Molecular Weight

C3H8O2 76.09

5) Structural Formula



6) Functional Category

Antimicrobial preservative; disinfectant; humectant; plasticizer; solvent; stabilizer for vitamins; water-miscible cosolvent.

7) Description

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

8) Applications in Pharmaceutical Formulation or Technology

Propylene glycol has become widely used as a solvent, extractant, and preservative in a variety of parenteral and nonparenteral pharmaceutical formulations. It is a better general solvent than glycerin and dissolves a wide variety of materials, such as corticosteroids, phenols, sulfa drugs, barbiturates, vitamins (A and D), most alkaloids, and many local anesthetics. As an antiseptic it is similar to ethanol, and against molds it is similar to glycerin and only slightly less effective than ethanol. Propylene glycol is commonly used as a plasticizer in aqueous film-coating formulations. Propylene glycol is also used in cosmetics and in the food industry as a carrier for emulsifiers and as a vehicle for flavours in preference to ethanol, since its lack of volatility provides a more uniform flavor.

2.7.5 INTRODUCTION TO MICROCRYSTALLINE CELLULOSE: [20]

1 Nonproprietary Names

BP: Microcrystalline cellulose

JP: Microcrystalline cellulose

PhEur: Cellulosum microcristallinum

USPNF: Microcrystalline cellulose

2 Synonyms

Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; Pharmacel; Tabulose; Vivapur.

3 Chemical Name and CAS Registry Number

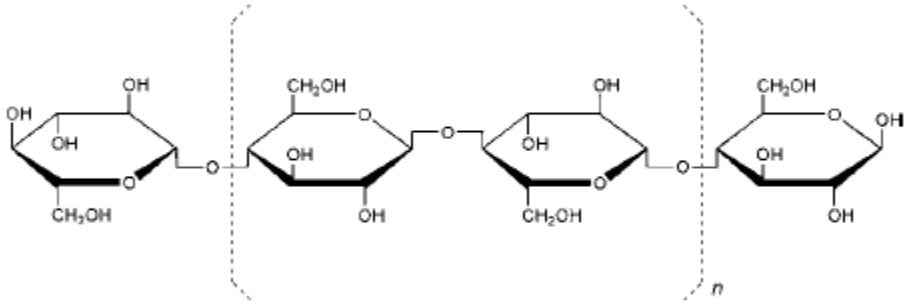
Cellulose [9004-34-6]

4 Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n$ =36 000

where n = 220.

5) Structural formula



6) Solubility

Slightly soluble in 5 % w/v Sodium hydroxide solution, practically insoluble in water, dilute acids and most organic solvents.

7) Functional Category

Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

8) Description

Microcrystalline cellulose is a purified, partially depolymerised cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

9) Applications in Pharmaceutical Formulation or Technology

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes.(1–7) In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.

Microcrystalline cellulose is also used in cosmetics and food products.

10) Stability

It is a stable, though hygroscopic material.

11) Storage conditions

The bulk material should be stored in a well- closed container in a cool, dry, place.

12) Incompatibilities

Incompatible with strong oxidizing agents.

13) Safety

It is generally regarded as a nontoxic and nonirritant material

2.7.6 HYDROXYPROPYL CELLULOSE, LOW-SUBSTITUTED: [20]

1) Nonproprietary Names

JP: Low-substituted hydroxypropylcellulose

USPNF: Low-substituted hydroxypropyl cellulose

2) Synonyms

Hyprolose, low-substituted; L-HPC.

3) Chemical Name and CAS Registry Number

Cellulose, 2-hydroxypropyl ether (low-substituted) [78214-41-2]

4) Empirical Formula and Molecular Weight

The USPNF 23 describes low-substituted hydroxypropyl cellulose as a low-substituted hydroxypropyl ether of cellulose. When dried at 1058C for 1 hour, it contains not less than 5.0% and not more than 16.0% of hydroxypropoxy groups (—OCH2CHOHCH3). Low-substituted hydroxypropyl cellulose is commercially available in a number of different grades that have different particle sizes and substitution levels.

5) Description

Low-substituted hydroxypropyl cellulose occurs as a white to yellowish white powder or granules. It is odorless or has a slight, characteristic odor, and it is tasteless.

6) Functional Category

Tablet and capsule disintegrant; tablet binder.

7) Applications in Pharmaceutical Formulation or Technology

Low-substituted hydroxypropyl cellulose is widely used in oral solid-dosage forms. It is primarily used in tableting as a disintegrant, and as a binder in wet granulation. It has been used in the preparation of rapidly disintegrating tablets produced by direct compression methods. In addition, low-substituted hydroxypropyl cellulose has been used to delay the release of drug from a tablet matrix.

8) Stability and Storage Conditions

Low-substituted hydroxypropyl cellulose is a stable, though hygroscopic, material. The powder should be stored in a wellclosed container.

2.7.7 INTRODUCTION TO CROSPOVIDONE: [20]

1) Synonyms

Cross-linked povidone, *Kollidon CL, Polyplasdone XL*, PVPP, Polyvinylpolypyrrolidone.

2) Functional category

Tablet disintegrant.

3) Applications

It is a water insoluble tablet disintegrant used at 2-5 % concentration in tablets, prepared by wet and dry granulation method.

4) Description

White to creamy-white, finely divided, free-flowing, practically tasteless, odorless, hygroscopic powder.

5) Solubility

Practically insoluble in water and most organic solvents.

6) Stability

Crospovidone is stable

.

7) Storage conditions

Since it is hygroscopic it should be stored in an airtight container in a cool, dry, place.

8) Incompatibilities: When exposed to a high water level it may form molecular adducts with some materials.

9) Safety

It is generally regarded as a nontoxic and nonirritant material.

2.7.8 INTRODUCTION TO CROSS CARMELLOSE SODIUM: [20]

1) Nonproprietary Names

BP: Croscarmellose sodium

PhEur: Carmellosum natricum conexum

USPNF: Croscarmellose sodium

2) Synonyms

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

3) Chemical Name and CAS Registry Number

Cellulose, carboxymethyl ether, sodium salt, crosslinked

[74811-65-7]

4) Empirical Formula and Molecular Weight

Croscarmellose sodium is a crosslinked polymer of carboxymethylcellulose sodium.

See Carboxymethylcellulose sodium.

5) Structural Formula

Cellulose link chain.

6) Functional Category

Tablet and capsule disintegrant.

7) Description

Croscarmellose sodium occurs as an odorless, white or grayishwhite powder.

8) Applications in Pharmaceutical Formulation or Technology

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules,(1,2) tablets,(3–13) and granules. In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes. When used in wet

granulations, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra- and extragranularly) so that the wicking and swelling ability of the disintegrant is best utilized.(11,12) Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

9) Stability and Storage Conditions

Croscarmellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression, with croscarmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at 308C for 14 months. Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

10) Incompatibilities

The efficacy of disintegrants, such as croscarmellose sodium, may be slightly reduced in tablet formulations prepared by either the wet-granulation or direct-compression process that contain hygroscopic excipients such as sorbitol.

2.7.9 INTRODUCTION TO COLLIDOLAL SILICON DIOXIDE [20]

1) Nonproprietary Names

BP: Colloidal anhydrous silica

PhEur: Silica colloidalis anhydrica

USPNF: Colloidal silicon dioxide

2) Synonyms

Aerosil; Cab-O-Sil; Cab-O-Sil M-5P; colloidal silica; fumed silica; light anhydrous silicic acid; silicic anhydride; silicon dioxide fumed; Wacker HDK.

3) Chemical Name and CAS Registry Number

Silica [7631-86-9]

4) Empirical Formula and Molecular Weight

SiO_2 60.08

5) Structural Formula

SiO_2

6) Functional Category

Adsorbent; anticaking agent; emulsion stabilizer; glidant; suspending agent; tablet disintegrant; thermal stabilizer; viscosity-increasing agent.

7) Description

Colloidal silicon dioxide is a submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-whitecolored, odorless, tasteless, nongritty amorphous powder.

8) Applications in Pharmaceutical Formulation or Technology

Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products. Its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tableting. Colloidal silicon dioxide is also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations.With other ingredients of similar refractive index, transparent gels may be formed. The degree of viscosity increase depends on the polarity of the liquid (polar liquids generally require a greater concentration of colloidal silicon dioxide than nonpolar liquids). Viscosity is largely independent of temperature. However, changes to the pH of a system may affect the viscosity. In aerosols, other than those for inhalation, colloidal silicon dioxide is used to promote particulate suspension, eliminate hard settling, and minimize the clogging of spray nozzles. Colloidal silicon dioxide is also used as a tablet disintegrant and as an adsorbent dispersing agent for liquids in powders. Colloidal silicon dioxide is frequently added to suppository formulations containing lipophilic excipients to increase viscosity, prevent sedimentation during molding, and decrease the release rate. Colloidal silicone dioxide is also used as an adsorbent during the preparation of wax microspheres; as a thickening agent for topical preparations; and has been used to aid the freeze-drying of nanocapsules and nanosphere suspensions.

Uses of colloidal silicon dioxide.

Use Concentration (%)

Aerosols 0.5–2.0

Emulsion stabilizer 1.0–5.0

Glidant 0.1–0.5

Suspending and thickening agent 2.0–10.0

2.7.10 INTRODUCTION TO MAGNESIUM STEARATE [20]

1) Synonyms

HyQual, magnesium octadecanoate, stearic acid magnesium salt.

2) Functional category

Tablet and capsule lubricant.

3) Applications

It is primarily used as a lubricant in capsule and Tablet manufacture at concentrations between 0.25-5.0%.

4) Description

It is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint characteristic odor and taste. The powder is greasy to touch and readily adheres to the skin.

5) Solubility

Practically insoluble in ethanol, ethanol (95%), ether and water, slightly soluble in benzene and warm ethanol (95%).

6) Stability

Magnesium stearate is stable.

7) Storage conditions:

It should be stored in a well-closed container in a cool, dry, place.

8) Incompatibilities:

Incompatible with strong acids, alkalis, iron salts and with strong oxidizing materials.

CHAPTER 3

LITERATURE REVIEW

3 LITERATURE REVIEW

3.1 LITERATURE REVIEW ON POLYMERS AND FORMULATION USED FOR SUBLINGUAL FILM

1. **Prasanthi et al.** [21] prepared fast dissolving films by solvent evaporation technique using different water-soluble polymers (hydroxy propyl methylcellulose, hydroxy propyl cellulose and Sodium Alginate) taken through sublingual route. Tween 80 was used as a solubilizing agent and Aspartame as a sweetener. The prepared films were evaluated for thickness, uniformity in drug content, folding endurance, disintegration time, swelling index, moisture loss, in-vitro drug release studies and drug-polymer compatibility studies. The results obtained showed no physical-chemical incompatibility between the drug and the polymers. The prepared films were clear, transparent and smooth surface. Film containing hydroxy propyl methylcellulose (2%w/w), Tween 80 (0.5%w/w) and Aspartame (0.5%w/w) showed optimum performance against all other prepared formulations.

2. **Basani G et al.** [22] reported that oral dissolving film Technology (ODFT) can be administrated in the oro-mucosal cavity, showing the action of the drug within a shorter period of time i.e in seconds and gives better therapeutic action. This technology offers an alternate platform for molecules that undergoes extensive first pass metabolism, by enhancing bioavailability and also improves patient compliance. The aricle provides various advantages of choosing oral mucosa for drug administration like larger surface area, high vascularity, better compliance of drug delivery for geriatric, dysphagic, mental patients, unconcsious patients etc. It also describes various ingredients of commercially available films like drug, polymers, taste maskers, saliva stimulating agents, flavours, colours. The parameters to be tested for like folding eudurance, tensile strength, tear resistance, disintegration time, drug content, percentage elongation test are described. Alist of marketed products is given. Hence, industries and consumers showed good response to this approach making it an attractive means of drug delivery.

3. **Cilurzo F et al.** [23] prepared fast dissolving films made of Maltodextrin by casting and solvent evaporation or hot-melt extrusion by adding sorbitan monoleate (SO) or microcrystalline cellulose (MCC). Flexible films were obtained by using 16-20% w/w glycerine (GLY). A suitable plasticizer and its concentration were selected on basis of flexibility, tensile strength, and stickiness of MDX films, and the MDX plasticizer interaction were investigated by ATR-FTIR spectroscopy. compared to hot-melt extrusion method, the solvent casting method appeared more reliable for the production of films and showed best performance in terms of in-vitro and in-vivo disintegration time.

4. **Sumitha et al.** [24] prepared rapid disintegrating films of intensely bitter Ondansetron HCl using methocel E15. Taste masking was done by complexing Ondansetron HCl with ion exchange resin (Polacriline Potassium) which also has disintegrating property, in different ratios and by using sucralose as a sweetening agent in very low concentrations. Taste was further masked using vanilla flavor in combination with lychee, banana flavor. Fast disintegrating films containing taste-masked ONDCT showed acceptable film properties such as tensile strength, elasticity, percentage elongation and in vitro dissolution characteristics. Thus the objective to accomplish rapid disintegrating films with good mouth feel so as to prepare a "patient friendly dosage form", was accomplished.

5. **Chen et al.** [25] formulated fast dissolving films using water soluble polymers for achieving rapid disintegration, good mouth feel and mechanical properties. Desired fast disintegration and mechanical properties could be tailored with polyethylene oxide and HPMC. Films had good mouth feel and no sticky feeling. Film strength of films containing PEO and HPMC ranged between 3000 kg/m2 to 17000 kg/m2. Increase in glycerine content resulted in marked decrease in film strength.

6. **Mashru et al.** [26] prepared fast dissolving films for sublingual route containing salbutamol sulphate and polyvinyl alcohol as polymer. The films were evaluated

for mechanical properties, in vitro release study and morphology study. A 33 factorial design was applied to study the effect of polyvinyl alcohol, glycerine and mannitol on % drug release and mechanical properties of the films. It was observed that polyvinyl alcohol had positive effect on tensile strength and mannitol had negative effect on tensile strength. Mannitol produced positive effect on drug release where as polyvinyl alcohol produced negative effect on drug release. It was found that the optimum values of the responses for fast release film could be obtained at medium levels of polyvinyl alcohol and glycerol, and a high level of mannitol.

7. **Aditya D et al.** [27] investigated formulation of triclosan (TC) containing fast dissolving films for local delivery to oral cavity. Various film forming agents, film modifiers and polyhydric alcohols were evaluated for optimizing the composition of fast dissolving films. The potential of poloxamer 407 and hydroxypropyl-beta-cyclodextrin (HPBCD) to improve solubility of TC was investigated. Fast dissolving films containing hydroxypropyl methylcellulose (HPMC), xanthan gum, and xylitol were formulated. Use of poloxamer 407 and HPBCD resulted in significant improvement in the solubility of TC. Films containing TC-poloxamer 407 exhibited better in vitro dissolution profile and in vitro antimicrobial activity as compared to films containing TC-HPBCD complex.

8. **Arun A et al.** [28] attempted to introduce orally disintegrating films(ODT) as an innovative form of drug delivery by describing its advantages like rapid dissolution, immediate release, enhanced bioavailability, accurate dosing, taste masking, preference by non compliant patients, geriatric, pediatric, unconscious patients etc. The essential components of ODT are described, they are drug, film forming polymers, plasticizers, surfactants, taste maskers, flavours etc. Different methods of preparation can be used i.e solvent-casting, semi solid casting, hot melt extrusion, rolling. The evaluation parameters like folding endurance, tensile strength, percentage elongation, disintegration time, in- vitro dissolution studies are also described. All these reasons make this system of drug delivery an advantageous and elegant, formulation system6.

9. **Choudhary et al.** [29]A fast-dissolving film containing levocetirizine, a non-sedative antihistamine drug, was developed using pullulan, xanthan gum, propylene glycol, and tween 80 as the base materials. The drug content of the prepared films was within an acceptable limit as prescribed by the USP. These results suggest that the present levocetirizine containing fast-dissolving film is likely to become one of the choices to treat different allergic conditions.

10. **Panchal M S et al.** [30] mouth dissolving films of Ropinirole Hydrochloride with the purpose of developing a dosage form for a very quick onset of action, which is very convenient for administration, without the problem of swallowing and using water. The films of Ropinirole Hydrochloride were prepared by using polymers such as pullulan and PEG 400 as plasticizer, by a solvent casting method. Formulation batches were formulated with the help of 32 full factorial designs. The fast dissolving oral films were designed using optimal design and numerical optimization technique was applied to find out the best formulation. The formulated mouth dissolving films were evaluated for physical characteristics such as uniformity of weight, thickness, folding endurance, drug content uniformity, surface pH, percentage elongation, and tensile strength, and gave satisfactory results.

11. **Choudhary et al**. [31] Ondansetron is a highly selective serotonin (5-HT3) receptor blocker which inhibits serotonin to bind with serotonin 5-HT3 receptors and hence prevent the vomiting reflex induced by serotonin. This work aimed to develop rapid dissolving films of ondansetron for the treatment of chemotherapy induced nausea and vomiting. Rapid dissolving films were prepared by solvent casting method using pullulan PI 20 as film former and PG and tween 80 as plasticizer. Bitterness of Ondansetron was masked by forming inclusion complex with HPβ-CD. The complex was evaluated by XRD, DSC and FT-IR. Optimized films were evaluated for mechanical properties, surface pH and dissolution characteristics. The combination of pullulan PI 20 and PG:tween 80 and xanthan gum exhibited excellent mechanical properties

12. **Avani et al.** [32] Rapidly dissolving films have been introduced in the market recently as they provide convenience and ease of use over other dosage forms such as orally disintegrating tablets. In the present study, rapidly dissolving films of cetirizine hydrochloride were formulated using pullulan as film forming polymer. Pullulan is a water soluble polysaccharide produced from yeast Aureobasidium pullulans. Cetirizine hydrochloride, an antihistamine drug was selected for the study. Solvent casting was the method used for formation of rapidly dissolving films. The rapidly dissolving films were evaluated for the effect of type of casting surface and plasticizer on film separation and taste masking properties. Type of casting surface played a critical role in film formation and separation. Percentage and type of plasticizer affected the formation of rapidly dissolving film. Cetirizine hydrochloride being slightly bitter, taste masking was achieved by use of sweeteners, flavours and citric acid. Type of flavour significantly affected the taste masking property.

3.2 LITERATURE REVIEW ON PROMETHAZINE HYDROCHLORIDE

1. **Fritz M et al.** [33] designed a cross-over study in 6 healthy volunteers to determine if the extent of first pass-effect through rectal absorption occurs to the same extent as it occurs via oral absorption. This was done by measuring plasma concentrations of promethazine by HPLC analysis after administration of micro-enemas and fatty suppositories, and comparing it with orally administered solutions of promethazine (25 mg, 50 mg in 50 ml of water). Suppositories were prepared by mixing promethazine-HCl with a molten base of Witepsol HI5. The release characteristics in vitro from the suppositories were determined by the method of Schoonen et al. (1976). For the in vivo studies, blood samples of 10 ml were taken at specific intervals. The conclusion drawn from the study is rectal and oral administration showed almost same release profiles but suppositories showed local irritation and fatty suppositories showed sustained release profile although first effect was not bypassed by either oral or rectal routes. Thus oral route is preferred.

2. **Sachin BM et al.** [34] prepared fast dissolving tablets of promethazine HCL Taste masked granules were prepared using gastro erodible aminoalkyl methacrylate copolymers (Eudragit E-100) by extrusion method. Fast dissolving tablets were prepared using taste-masked granules and a mixture of excipients containing optimized level of Microcrystalline cellulose (Avicel PH-101) and starch. The effect of various superdisintegrants like crospovidone , Sodium Starch Glycolate (Primogel), Croscarmellose sodium (Ac-Di-Sol) was also studied. The tablets were punched using rotary press tableting machine. The complexation of Promethazine HCl with Eudragit E100 helps to mask its bitter taste as well as it improves the dissolution profile.

3. **Taylor G et al.** [35] measured blood concentrations of promethazine and promethazine sulphoxide following oral and intravenous administration of drug to 7 healthy male volunteers. Pharmacokinetics were consistent with a pronounced first pass effect. There was a marked alteration in the shape of the metabolite curve when oral and IV data were compared. IV doses consisting of 0.5 ml

Phenergan injection (25 mg ml-' promethazine hydrochloride, diluted to 5 ml with saline) were infused during a 5 min period and venous blood was withdrawn at specific intervals. The fraction of the oral dose available to the systemic circulation was calculated from the ratio of the AUCs and the ratio of the cumulative excretion of PMZ for the two routes. The results showed peak metabolite concentrations were lower and were attained at later times through IV route than from oral dosing, thus making oral route an ideal route for the delivery of the drug as fast dissolving films.

4. **Rahul V. Haware et al.** [36] complexation of PM-HCl with Eudragit® E 100 cannot only mask its bitter taste significantly but also improves its dissolution profile. By employing a cost effective direct compression method, fastdissolving tablets of 400 mg total weight with a taste and texture acceptable to patients and sufficient structural integrity could be prepared. From all the superdisintegrants studied, tablets containing 4% Ac-Di-Sol gave the highest improvement in disintegration and dissolution rate of PMHCl.

5. **Ganesh kumar Gudas et al.** [37] Fast dissolving tablets of Promethazine.HCl were prepared using five superdisintegrants viz; sodium starch glycolate, crospovidone, croscarmellose, L-HPC and pregelatinised starch. The precompression blend was tested for angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The tablets were evaluated for weight variation, hardness, friability, disintegration time (1 min), dissolution rate, content uniformity, and were found to be within standard limit. It was concluded that the fast dissolving tablets with proper hardness, rapidly disintegrating with enhanced dissolution can be made using selected superdisintegrants. Among the different formulations of Promethazine.HCl was prepared and studied and the formulation containing crospovidone, mannitol and microcrystalline cellulose combination was found to be the fast dissolving formulation. In the present study an attempt has been made to prepare fast dissolving tablets of Promethazine.HCl, by using different superdisintegrants with enhanced disintegration and dissolution rate.

3.3 LITERATURE REVIEW ON FAST DISSOLVING SUBLINGUAL TABLET

1. **Aleksandra Amelian et al.** [38] studied that disintegration of ODTs is dependent on the nature of disintegrant, and the most effective disintegrant in ODTs manufactured using new ready-to-use excipient Ludiflash® or Parteck® is superfine crospovidone, which enables obtaining pleasant-tasting and pleasant feeling in the mouth tablets that disintegrate rapidly and posses satisfactory physico-mechanical properties.

2. **Bhanja SB et al.** [39] developed perindorpil sublingual tablet using direct compression method and studied the effect of amount of microcrystalline cellulose and crosspovidone had highest effect in disintegration time of ODT.

3. **Patel Kirtan et al.** [40] formulated montelukast sodium sublingual tablet using MCC, Mannitol, Ludiflash and there combination as directly compressible excipients and it it was concluded that combination of superdisintegrants and ludiflash showed better disintegration and drug release. The prepared tablets disintegrate within few seconds without need of water; thereby enhancing the absorption leading to its increased bioavailability.

4. **Vineet bhardwaj et al.** [41] the study shows that the dissolution rate of Amlodipine Besylate can be enhanced to a great extent by direct compression technique with the addition of superdisintegrants. These superdisintegrants accelerate disintegration of tablets by virtue of their ability to absorb a large amount of water when exposed to an aqueous environment. The absorption of water results in breaking of tablets and therefore faster disintegration. This disintegration is reported to have an effect on dissolution characteristics as well. Prepared fast disintegrating tablet gets dispersed in the mouth quickly and releases the drug fast.

CHAPTER 4

EXPERIMENTAL WORK- FAST DISSOLVING SUBLINGUAL FILM

4. FAST DISSOLVING FILM

4.1 MATERIALS AND EQUIPMENT USED

TABLE 4.1 -LIST OF MATERIALS USED

Materials	Company name
Promethazine Hydrochloride	Purchased from Balaji Drug House, Surat
Pullulan	Gifted from Gangwal Chemicals, Mumbai
HPMC E 5	Central Drug House Ltd., New Delhi
HPMC E15	Central Drug House Ltd., New Delhi
Propylene Glycol (PG)	Central Drug House Ltd., New Delhi
Polyethylene Glycol (PEG)	Central Drug House Ltd., New Delhi
β-cyclodextrin	Hi Media lab. Pvt. Ltd. Mumbai
HP β-cyclodextrin	Gifted from Gangwal Chemicals, Mumbai
Aspartame	Hi Media lab. Pvt. Ltd. Mumbai
Sucralose	Gifted from Zydus Research Centre, Ahmedabad
Vanillin flavour	Central Drug House Ltd., New Delhi
Sodium phosphate dibasic	Central Drug House Ltd., New Delhi
Potassium phosphate monobasic	Central Drug House Ltd., New Delhi
Micro crystalline Cellulose	Central Drug House Ltd., New Delhi
Ludiflash	Gift sample from BASF, Mumbai
Kollidon CL	Gift sample from Signet, Mumbai

Low viscosity of Hydroxypropyl Cellulose	Gifted from Torrent Research Centre, Ahmedabad
Cross Carmellose	Gifted from Torrent Research Centre, Ahmedabad
Aerosil	Central Drug House Ltd., New Delhi
Magnesium Stearate	Central Drug House Ltd., New Delhi
Sodium Stearyl Fumarate	Gifted from Evonik Industries, Mumbai

TABLE 4.2 -LIST OF EQUIPMENT USED

EQUIPMENTS	COMPANY NAME
Sonicator Bath	EIE Instruments, Ahmedabad
Q T S Texture Analyser	Brookfield engineering laboratories, Canada
Digital Balance	Citiweigh, Tejas exports, Ahmedabad
Hot air oven	EIE Instruments Pvt. Ltd., Ahmedabad
Thermonik Tablet Tester, DTH – 250	Campbell electronics, Mumbai
Rotary Tablet Machine	Riemek, Karnavati Eng. Pvt Ltd., Ahmedabad
Dissolution test apparatus USP	Electrolab TDT-08L, Mumbai.
Roche Friabilator	Electrolab, Mumbai.
UV/VIS Double beam spectrophotometer	Shimdzu UV 1800 corporation, Japan
FTIR	Jasco FTIR 6100 Type-A, Japan
Humidity chamber	Nova Instruments Pvt. Ltd. Ahmedabad

4.2 IDENTIFICATION OF PROMETHAZINE HYDROCHLORIDE

4.2.1 MELTING POINT DETERMINATION

Melting point is the temperature at which the pure liquid and solid exist in the equilibrium. In the practice it is taken as equilibrium mixture at an external pressure of 1 atmosphere. The thiel's tube method of melting point determination in liquid paraffin was used in the present study.

TABLE 4.3- MELTING POINT DETERMINATION OF PROMETHAZINE HCl

Reported[43]	220-222 ^{0}C
Observed	219-220 ^{0}C

Result: The melting point of Promethazine hydrochloride was found to be 219°C.

Conclusion: The melting point determined is within the range of standard value, hence, it is concluded that the drug sample having intimate physical property as standard drug according to USP.

4.2.2 IR SPECTRA

IR spectra of drug in KBR pellets at moderate scanning speed between 4000-400 cm^{-1} was carried out using FTIR (Jasco FTIR 6100 TYPE A, Japan). All the powder samples were dried under vacuum prior to obtaining any spectra in order to remove the influence of residual moisture.

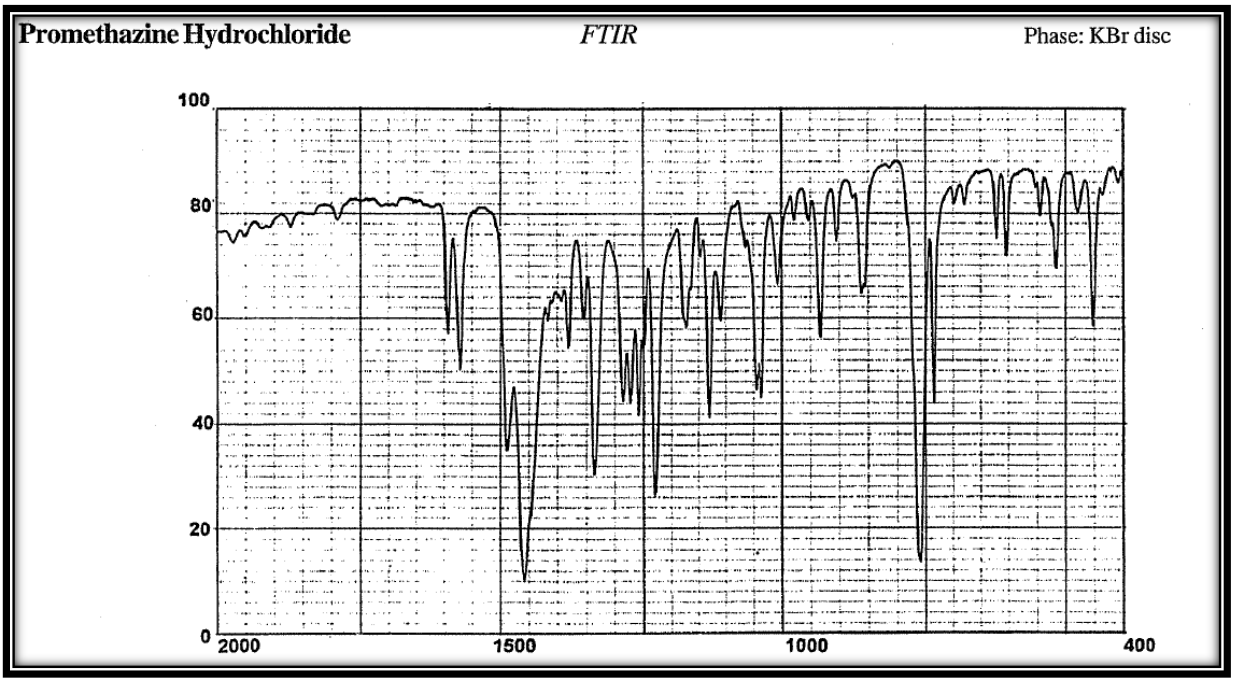


FIGURE 4.1 REFERENCE FTIR SPECTRA OF PROMETHAZINE HCl [16]

FIGURE 4.2 OBSERVED FTIR SPECTRA OF PROMETHAZINE HCl

TABLE 4.4 COMPARISON OF REFERENCE AND TEST IR FREQUENCY OF PROMETHAZINE HCL

Functional Group	Standard frequency (cm^{-1})	Observed frequency (cm^{-1})
C=C Stretching		
CH_3 Bending		
C-N Stretching of tertiary amine		
CH_3 and CH_2 bending		
Out of plane CH bending of distribution of aromatic		

Discussion: The sample spectrum of Promethazine hydrochloride was compared with standard one and both spectra were found similar in peak values representing wave numbers. Thus, it can be concluded that procured Promethazine hydrochloride sample was a pure drug.

4.2.3 UV ABSORPTION MAXIMA OF PROMETHAZINE HYDROCHLORIDE

(A) UV absorption maxima of Promethazine hydrochloride in distilled water:

UV scanning was done for 10 µg/ml drug solution from 200-800 nm in distilled water as a blank using Shimadzu UV 1800 double beam UV/Visible spectrophotometer. The absorption maximum was found to be at 250 nm.

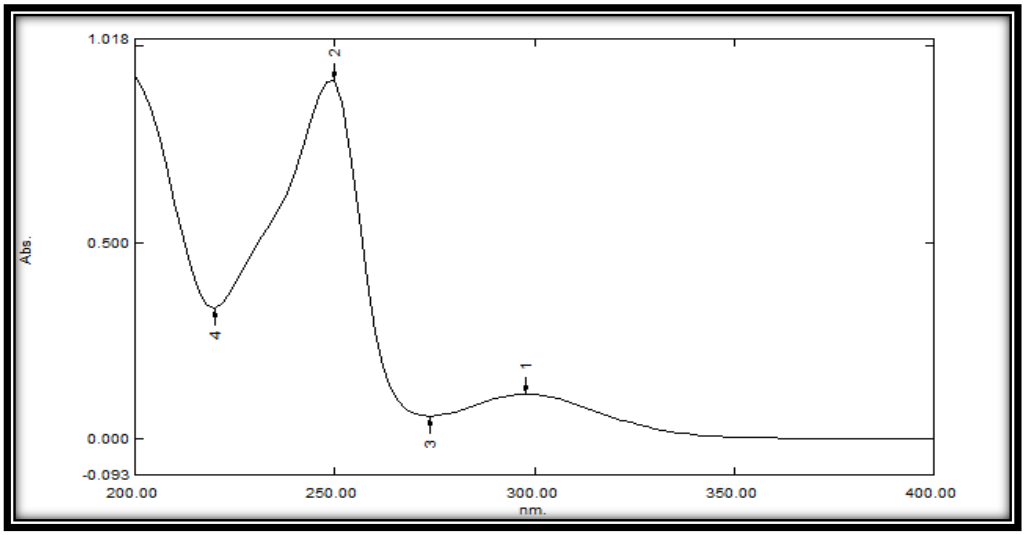


FIGURE 4.3: UV ABSORBANCE SPECTRA OF PROMETHAZINE HCL IN DISTILLED WATER

Result:

The UV spectra of Promethazine HCl shows λmax at 250 nm, which remains constant after dilution and is nearly similar to the reported standard value 249 nm[16]. This also indicates identity and purity of the drug sample.

(B) UV absorption maxima of Promethazine hydrochloride in Simulated Saliva (SS) pH 6.8:

UV scanning was done for 100 µg/ml drug solution from 200-800 nm in SS as a blank

using Shimadzu UV 1800 double beam UV/Visible spectrophotometer. The absorption maxima was found to be at 250 nm.

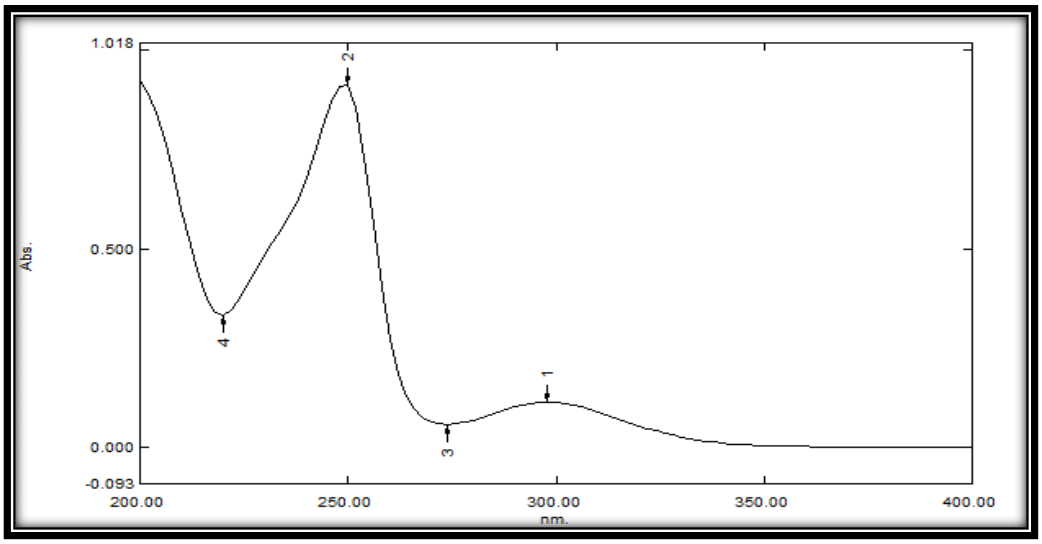


FIGURE 4.4: UV ABSORBANCE SPECTRA OF PROMETHAZINE HCL IN SSF (6.8)

Result:

The UV spectra of Promethazine hydrochloride in simulated saliva showed the λmax at 250 nm. So, this value was utilized for identification and estimation purpose.

4.3 ESTIMATION OF PROMETHAZINE HYDROCHLORIDE

4.3.1 Standard curve of Promethazine HCl in Distilled Water

Preparation of stock solution:

10 mg of Promethazine HCl was accurately weighed and transferred in 100 ml volumetric flask. It was dissolved in Distilled water and volume was made up to the mark with Distilled water. From the resulting solution 10 ml solution was taken in 100 ml volumetric flask to get 10 µg/ml solution.

Preparation of standard curve in Distilled Water:

From the stock solution 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7 0.8, 0.9, 1.0 ml samples were transferred to 10 ml volumetric flask and diluted with the water up to the mark to obtain Promethazine HCl concentration of 1-10µg/ml respectively. The wavelength maxima of Promethazine HCl in water was found to be 250 nm. Absorbance of each solution was measured at 250 nm. The standard curve was performed in triplicate.

Table 4.5: STANDARD CURVE OF PROMETHAZINE HCL IN DISTILLED WATER

SR NO	CONCENTRATION (µg/ml)	ABSORBANCE (nm)			MEAN
		1	2	3	
1	0	0	0	0	0
2	1	0.0987	0.0988	0.0987	0.0987
3	2	0.154	0.156	0.155	0.155
4	3	0.226	0.222	0.225	0.224
5	4	0.286	0.285	0.285	0.285
6	5	0.392	0.390	0.390	0.39
7	6	0.450	0.447	0.448	0.448
8	7	0.517	0.518	0.518	0.516
9	8	0.586	0.585	0.583	0.584
10	9	0.651	0.650	0.651	0.651
11	10	0.732	0.728	0.733	0.73
12	11	0.810	0.810	0.811	0.81
13	12	0.880	0.879	0.880	0.88
14	13	0.929	0.931	0.932	0.93
15	14	0.980	0.981	0.980	0.98

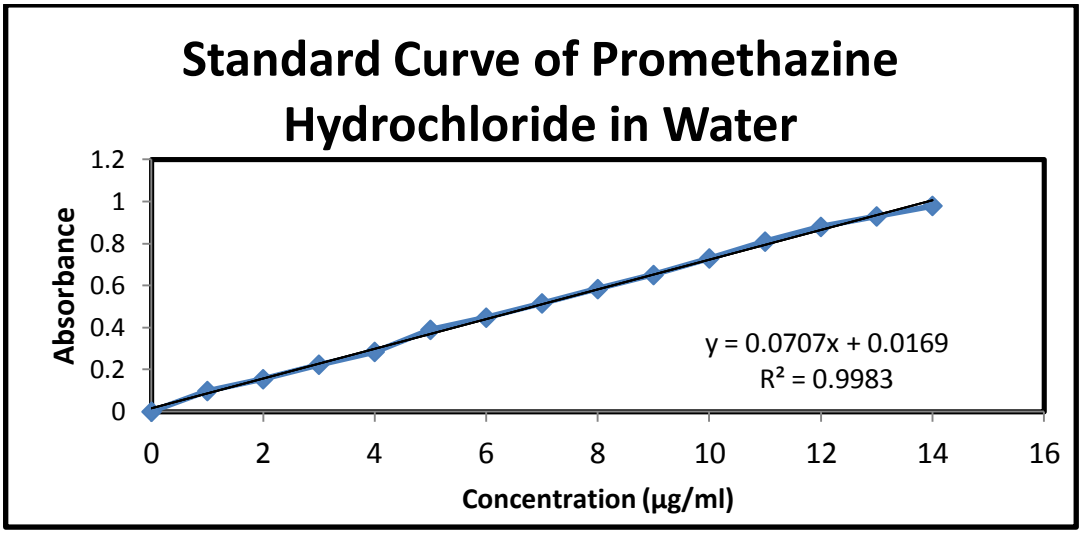


Figure 4.5: STANDARD CURVE OF PROMETHAZINE HCL IN DISTILLED WATER

TABLE 4.6: REGRESSION ANALYSIS FOR STANDARD CURVE OF PROMETHAZINE HYDROCHLORIDE IN DISTILL WATER

Regression Parameter	Value
Correlation Coefficient	0.998
Slope	0.070
Intercept	0.016

4.3.2 Standard curve of Promethazine HCl in simulated saliva (pH 6.8):

Preparation of stock solution:

10 mg of Promethazine HCl was accurately weighed and transferred in 100 ml volumetric flask. It was dissolved in simulated saliva and volume was made up to the mark with simulated saliva. From the resulting solution 10 ml solution was taken in 100 ml volumetric flask to get 10 µg/ml solution.

Preparation of standard curve in simulated saliva pH 6.8:

From the stock solution o.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7 0.8, 0.9, 1.0 ml samples were transferred to 10 ml volumetric flask and diluted with the simulated saliva up to the mark to obtain Promethazine HCl concentration of 1-10µg/ml respectively. The wavelength maxima of Promethazine HCl in simulated saliva were found to be 250 nm. Absorbance of each solution was measured at 250 nm. The standard curve was performed in triplicate.

TABLE 4.7: STANDARD CURVE OF PROMETHAZINE HCL IN SSF (PH 6.8)

SR NO	CONCENTRATION (mcg/ml)	ABSORBANCE (nm)			MEAN
		1	2	3	
1	0	0	0	0	0
2	1	0.129	0.130	0.130	0.13
3	2	0.200	0.202	0.203	0.202
4	3	0.314	0.312	0.314	0.314
5	4	0.390	0.392	0.388	0.388
6	5	0.5	0.501	0.5	0.5
7	6	0.590	0.592	0.589	0.59
8	7	0.691	0.690	0.690	0.69
9	8	0.774	0.773	0.774	0.774
10	9	0.851	0.854	0.852	0.853
11	10	0.923	0.923	0.922	0.923

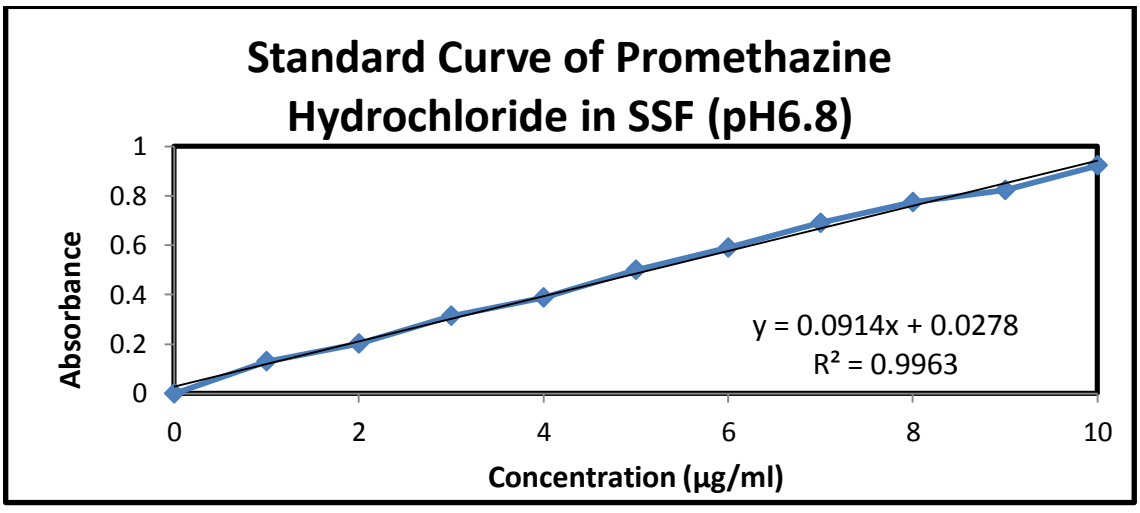


FIGURE 4.6: STANDARD CURVE OF PROMETHAZINE HCL IN SSF

TABLE 4.8: REGRESSION ANALYSIS FOR STANDARD CURVE OF PROMETHAZINE HYDROCHLORIDE IN SIMULATED SALIVA

Regression Parameter	Value
Correlation Coefficient	0.996
Slope	0.091
Intercept	0.027

4.3.3) Standard curve of Promethazine HCl in Hydrochloric acid (0.1N)

Preparation of stock solution:

10 mg of Promethazine HCl was accurately weighed and transferred in 100 ml volumetric flask. It was dissolved in hydrochloric acid and volume was made up to the mark with hydrochloric acid. From the resulting solution 10 ml solution was taken in 100 ml volumetric flask and mark with hydrochloric acid to get 10 µg/ml solution.

Preparation of standard curve in Distilled Water:

From the stock solution 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7 0.8, 0.9, 1.0 ml samples were transferred to 10 ml volumetric flask and diluted with the hydrochloric acid up to the mark to obtain Promethazine HCl concentration of 1-10µg/ml respectively. The wavelength maxima of Promethazine HCl in hydrochloric acid was found to be 250 nm. Absorbance of each solution was measured at 250 nm. The standard curve was performed in triplicate.

TABLE 4.9: STANDARD CURVE OF PROMETHAZINE HYDROCHLORIDE IN HCl

SR NO	CONCENTRATION (mcg/ml)	ABSORBANCE (nm)			MEAN
		1	**2**	**3**	
1	0	0	0	0	0
2	1	0.130	0.131	0.130	0.13
3	2	0.200	0.201	0.204	0.202
4	3	0.314	0.314	0.313	0.314
5	4	0.391	0.390	0.392	0.391
6	5	0.519	0.520	0.520	0.52

7	6	0.612	0.609	0.610	0.61
8	7	0.671	0.673	0.669	0.671
9	8	0.772	0.774	0.774	0.774
10	9	0.910	0.909	0.912	0.911
11	10	0.969	0.970	0.970	0.97

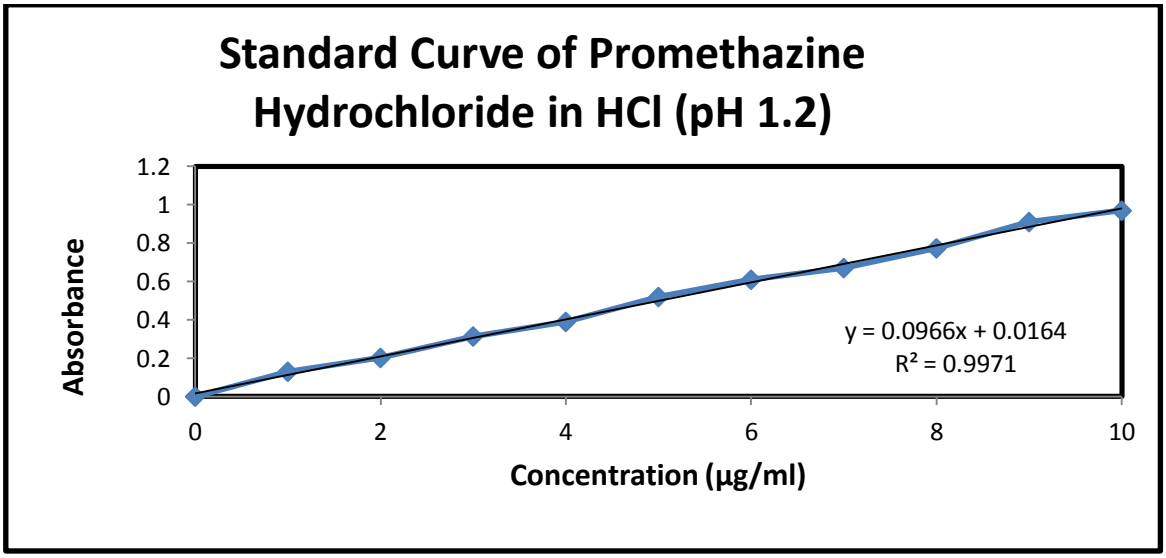


FIGURE 4.7: STANDARD CURVE OF PROMETHAZINE HCL IN HYDROCHLORIC ACID

TABLE 4.10: REGRESSION ANALYSIS FOR STANDARD CURVE OF PROMETHAZINE HYDROCHLORIDE IN HYDROCHLORIC ACID

Regression Parameter	Value
Correlation Coefficient	0.997
Slope	0.096
Intercept	0.016

4.4 PREFORMULATION STUDY

DRUG-EXCIPIENT COMPATIBILITY STUDY:

Compatibility studies were performed using FT-IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied by making a KBr

disc. The characteristic absorption peaks of Promethazine Hydrochloride were obtained at different wave numbers in different samples.

The peaks obtained in the spectra formulation correlates with the peaks of drug spectrum. This indicates that the drug is compatible with the formulation components. The spectra for all formulations are shown below.

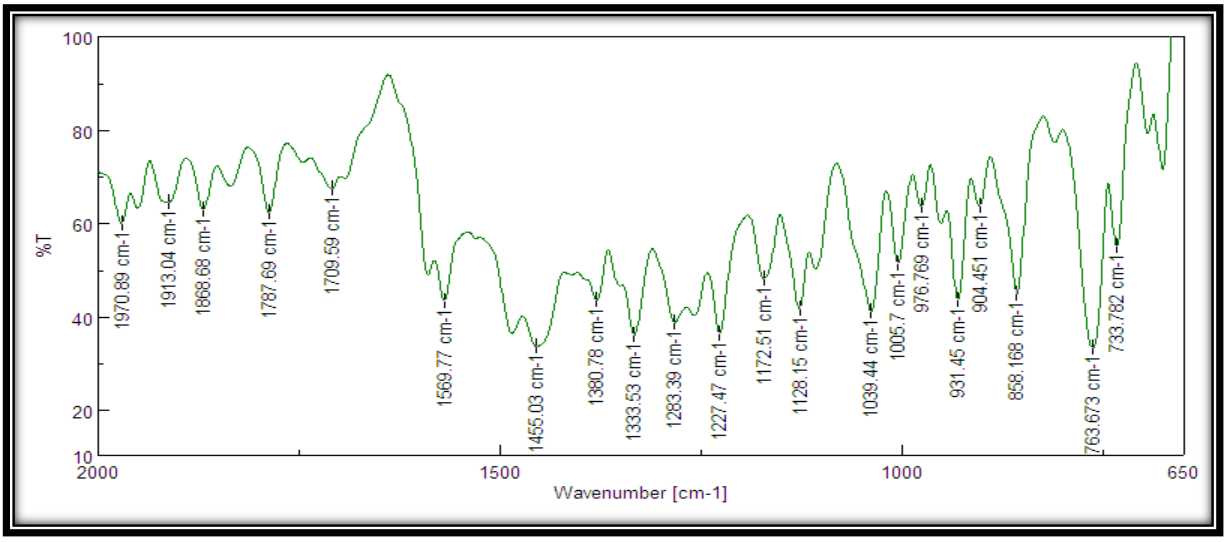


FIGURE 4.8: FTIR OF PROMETHAZINE HYDROCHLORIDE

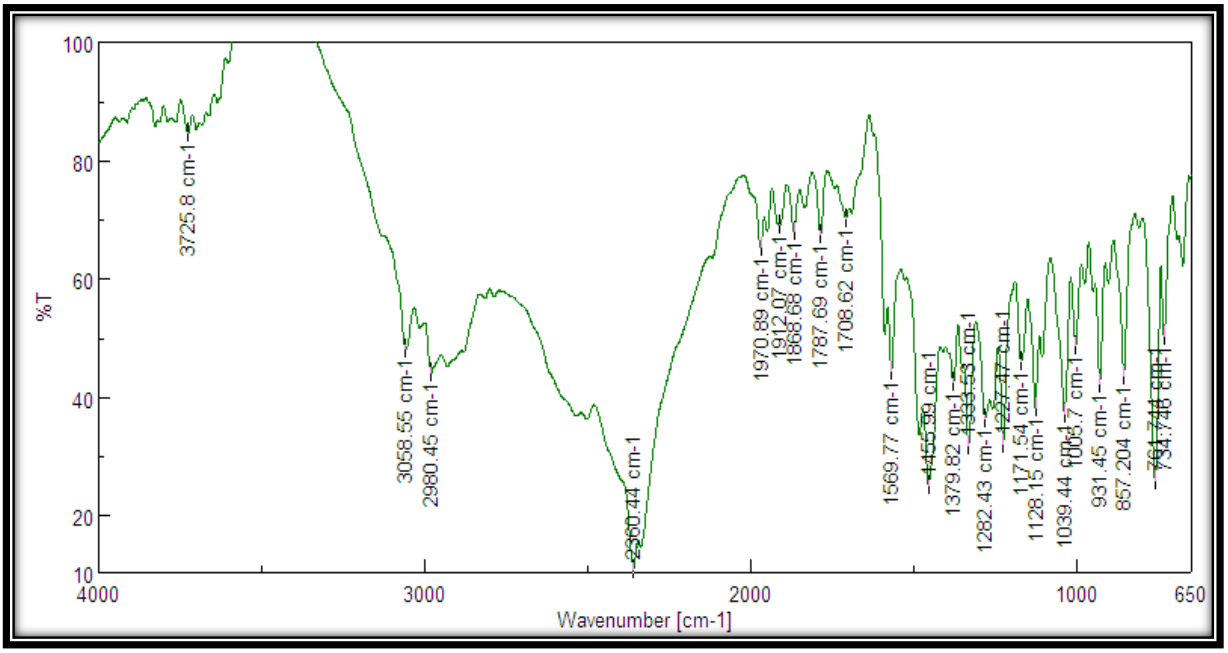


FIGURE 4.9: FTIR OF PMZ HCL + PULLULAN

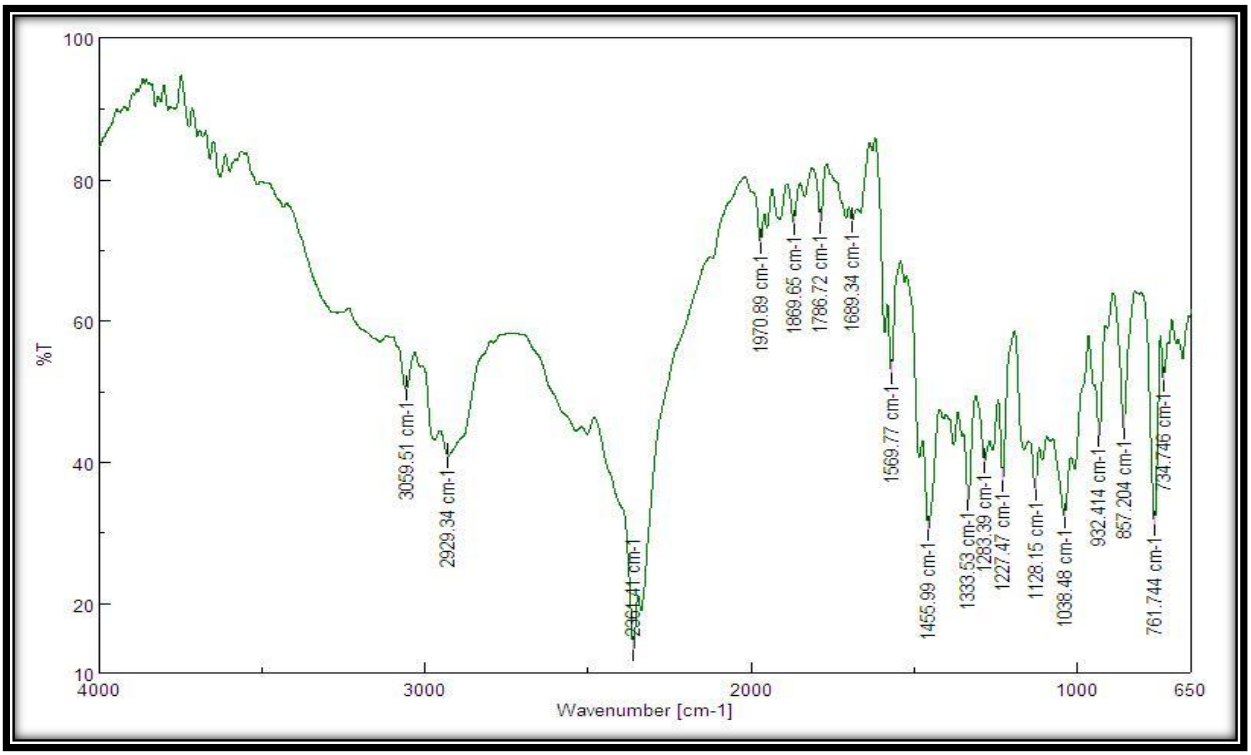


FIGURE 4.10: FTIR OF PMZ HCL + HP β-CD

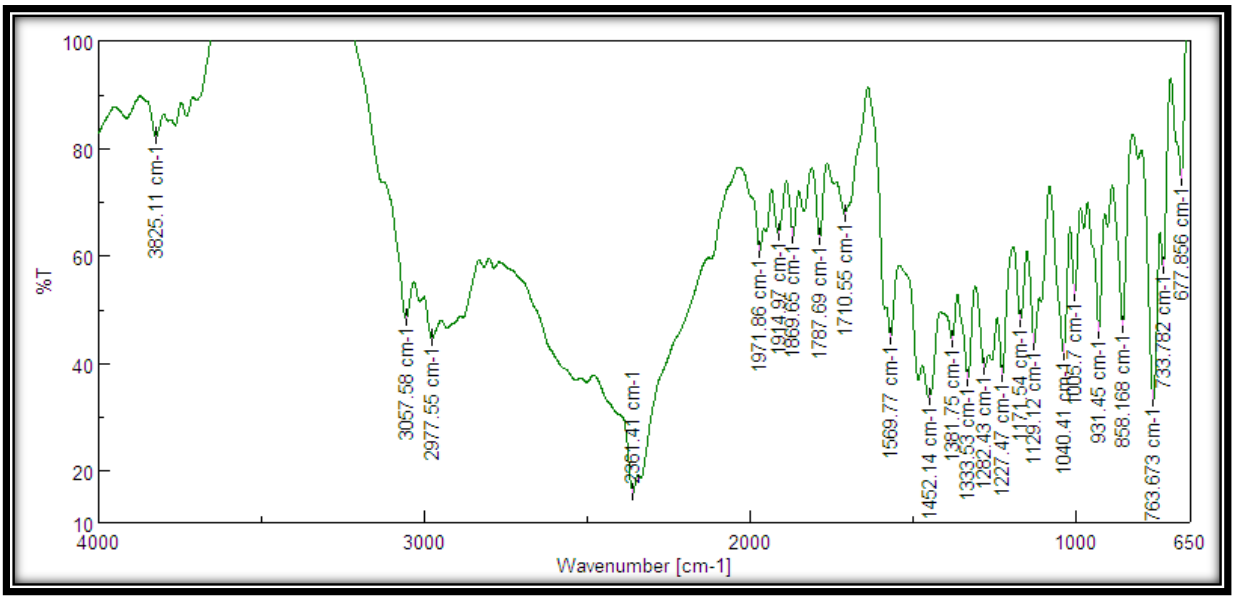


FIGURE 4.11: FTIR OF PMZ HCL + ASPARTAME

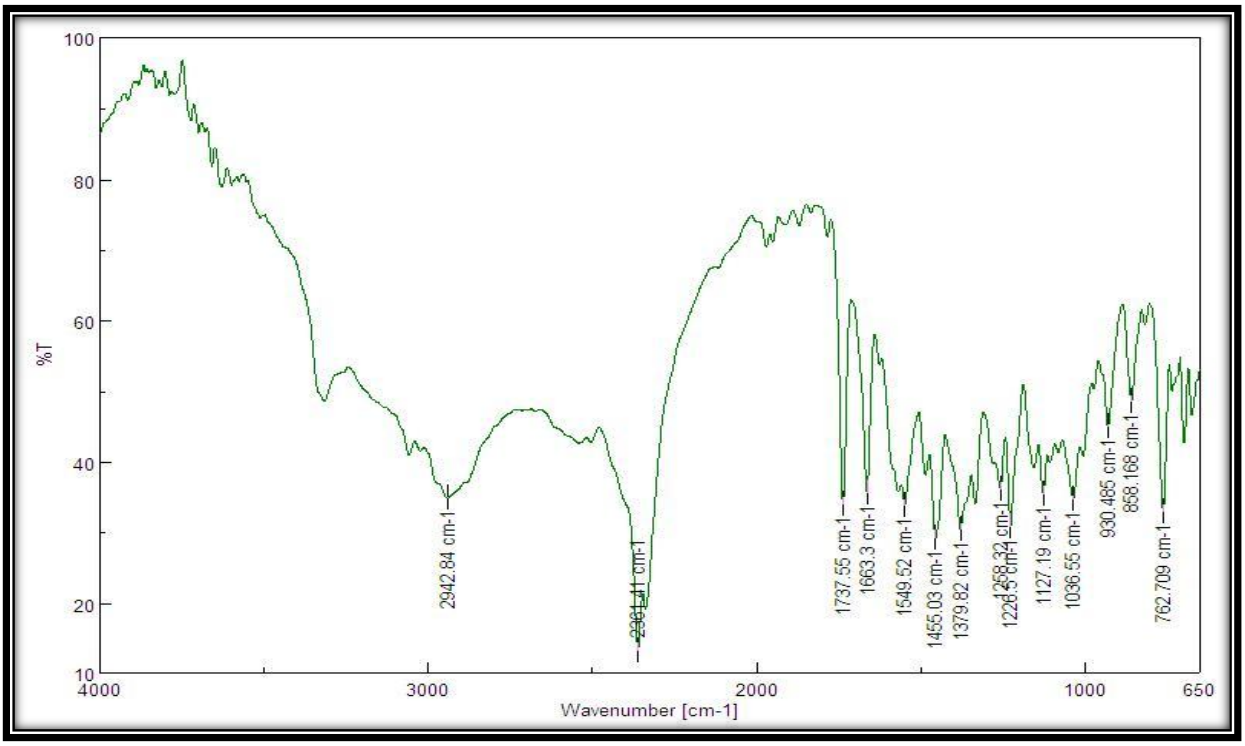


FIGURE 4.12: FTIR OF PMZ HCL + PULLULAN +ASPARTAME+ HP β-CD

TABLE 4.11: FTIR DRUG-EXCIPIENT COMPATIBILITY STUDY

Sample	Sr No.	Peaks at (cm^{-1})	Indications
PMZ HCl	1	1569.77	C=C Stretching
	2	1380.78	CH_3 Bending
	3	1333.33	C-N Stretching of tertiary amine
	4	1430-1470	CH_3 and CH_2 bending
PMZ HCL + Pullulan	1	1569.77	C=C Stretching
	2	1379	CH_3 Bending
	3	133.53	C-N Stretching of tertiary amine
	4	1455	CH_3 and CH_2 bending
	1	1569.77	C=C Stretching
	2	1381.75	CH_3 Bending

PMZ HCL + ASP	3	1333.53	C-N Stretching of tertiary amine
	4	1452	CH_3 and CH_2 bending
PMZ HCL + HP β-CD	1	1569.77	C=C Stretching
	2	1383.78	CH_3 Bending
	3	1333.33	C-N Stretching of tertiary amine
	4	1455.99	CH_3 and CH_2 bending
PMZ HCL + Pullulan+HP β-CD + ASP	1	1559.77	C=C Stretching
	2	1379.78	CH_3 Bending
	3	1328.33	C-N Stretching of tertiary amine
	4	1455.99	CH_3 and CH_2 bending

Conclusion:

Preformulation study for the drug and excipients was conducted using FT-IR spectrophotometer. Promethazine hydrochloride and various polymer mixtures showed the respective characteristic bands of Promethazine Hydrochloride at 1569, 1455, 1379, 1333.53 cm^{-1}. The results confirmed that there was no chemical interaction between drug and excipients.

4.5 PRELIMINARY TRIALS

4.5.1 OPTIMIZATION OF CASTING SURFACE

The initial trials for optimizing casting surface were carried out using 4%w/v of film forming agent like HPMC (5cps and 15 cps), pullulan and PVA, all the formulation were casted on both glass and plastic petridish. And all the casted films were evaluated for the peel ability.

TABLE 4.12: OPTIMIZATION OF CASTING SURFACE

Batch no:	Type Of Casting	Polymers	Peel ability*

	Surface		
P1	Glass	HPMC 5cps	+
P2	Plastic	HPMC 5cps	++
P3	Glass	HPMC 15cps	++
P4	Plastic	HPMC 15cps	++
P5	Glass	Pullulan	+
P6	Plastic	Pullulan	++
P7	Glass	PVA	0
P8	Plastic	PVA	+

*+++ Easily Separable, ++ Partial Separable, + Difficult to separate, 0 Not Separable

Result and Discussion:

From above result it can concluded that plastic as a casting surface has a promising result compare to glass surface, because film comparatively had better peel ability in plastic as a casting surface in all the polymers. Therefore plastic as casting was selected in further trials.

4.5.2 SCREENING OF FILM FORMING AGENTS

Initial trials for film formation were taken using 2%w/v and 4%w/v of HPMC 5cps, HPMC15cps, Pullulan and PVA using plastic as a casting surface & water as a solvent evaluated for the thickness and in-vitro disintegration time.

TABLE 4.13: SCREENING OF FILM FORMING AGENTS

Batch No:	Polymer	Concentration (%w/v)	Film Separation	Thickness (µm)	In –Vitro Disintegration Time (Sec.)

P9	HPMC E5	2	++		
P10		4	++		
P11	HPMC E15	2	++		
P12		4	++		
P13	Pullulan	2	+++		
P14		4	++		
P15	PVA	2	++		
P16		4	+++		

*+++ Easily Separable, ++ Partial Separable, + Difficult to separate, 0 Not Separable

Result and Discussion:

So Pullulan as film forming agent was selected for further studies. But all the film formed lack mechanical integrity hence there was need for addition of plasticizer.

4.5.3 SCREENING OF THE AMOUNT OF PULLULAN

Pullulan was selected as film forming agent as it had a lowest compare to other polymers. Further studies were carried out optimize the amount of pullulan concentration in order to have acceptable mechanical properties and in-vitro disintegration time. Concentration ranging from 1%w/v to 5%w/v of pullulan was selected and subjected to evaluation. Along with it to attain acceptable mechanical strength plasticizer Propylene glycol (PG) and Polyethylene glycol (PEG) (30%w/w) were added.

TABLE 4.14: SCREENING OF THE AMOUNT OF PULLULAN

Batch No:	Concentration of Pullulan (%w/v)	Concentration Of PG	Concentration Of PEG
P17	1	30	-
P18	1	-	30
P19	2	30	-
P20	2	-	30
P21	3	30	-
P22	3	-	30

P23	4	30	-
P24	4	-	30
P25	5	30	-
P26	5	-	30

TABLE 4.15: EVALUATION BATCHES FOR SCREENING AMOUNT OF PULLLULAN

Result and Discussion:

Further studies were carried out for optimization of plasticizer.

4.5.4 OPTIMIZATION OF THE AMOUNT OF PLASTICIZER

Different plasticizer like Propylene Glycol (PG), Polyethylene Glycol (PEG 400) were tried and evaluated for mechanical properties.

TABLE 4.16: OPTIMIZATION OF THE AMOUNT OF PLASTICIZER

Batch No.	Concent-ration of PG	Concent-ration of PEG 400	Thickness (µm)	Tensile strength ($gm/cm^{2)}$	In-vitro disintegration time(sec)	% Elongation	Folding endurance
P27	20	-					
P28	30	-					
P29	40	-					
P30	50	-					
P31	60	-					
P32	-	20					
P33	-	30					
P34	-	40					
P35	-	50					
P36	-	60					

Result and Discussion:

4.6 PREPARATION OF DRUG LOADED FAST DISSOLVING SUBLINGUAL FILM (FDSF)

Drug: Promethazine hydrochloride (25mg)

Polymer: Pullulan

Plasticizer: Propylene Glycol (PG)

Solvent used: Distilled water

Method: Solvent casting method

Diameter of petridish: 9cm

Area of film: 2 × 3 cm

Total number of strips in a batch: 10

Casting surface: Plastic

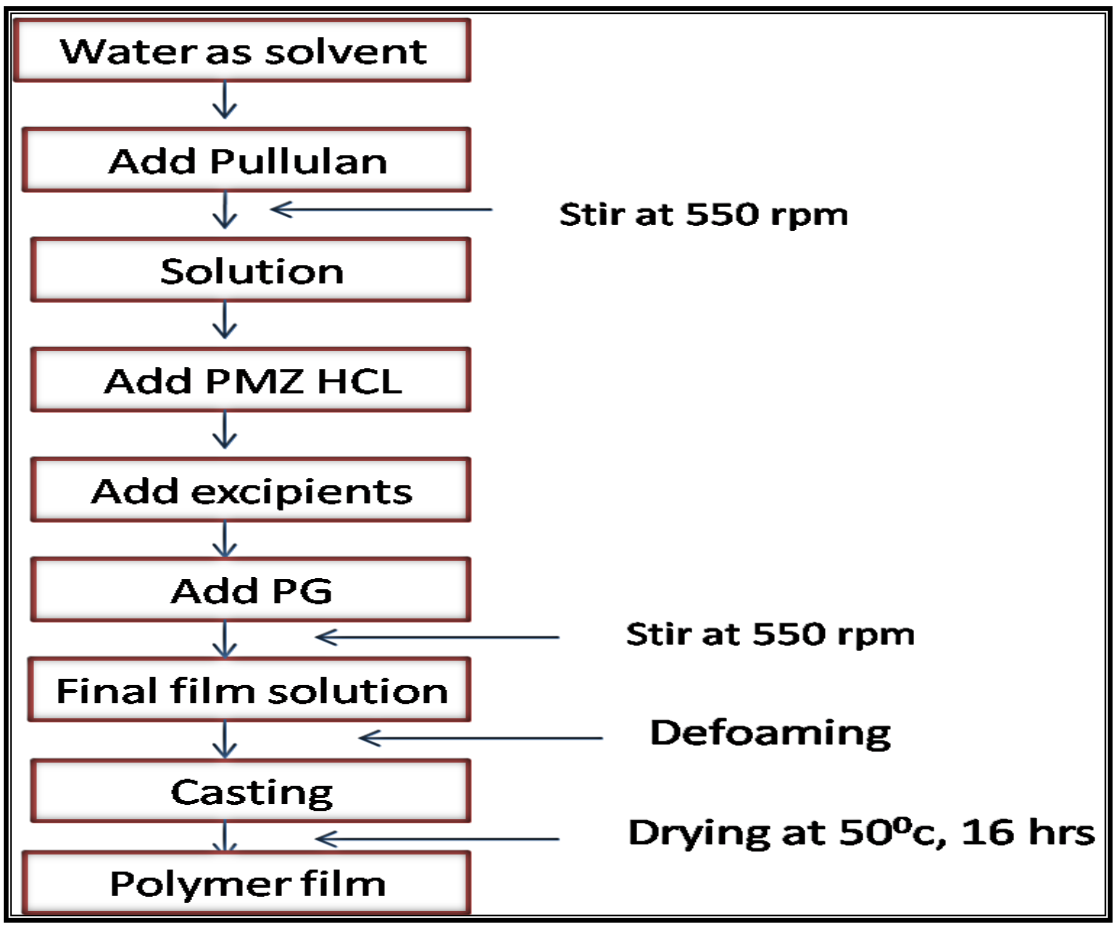


FIGURE 4.13: FORMULATION FLOW CHART OF FAST DISSOLVING SUBLINGUAL FILM

TABLE 4.17: FORMULATION BATCH B1

Ingredient	Quantity
PMZ HCl	
Pullulan	
Propylene Glycol	
Water	

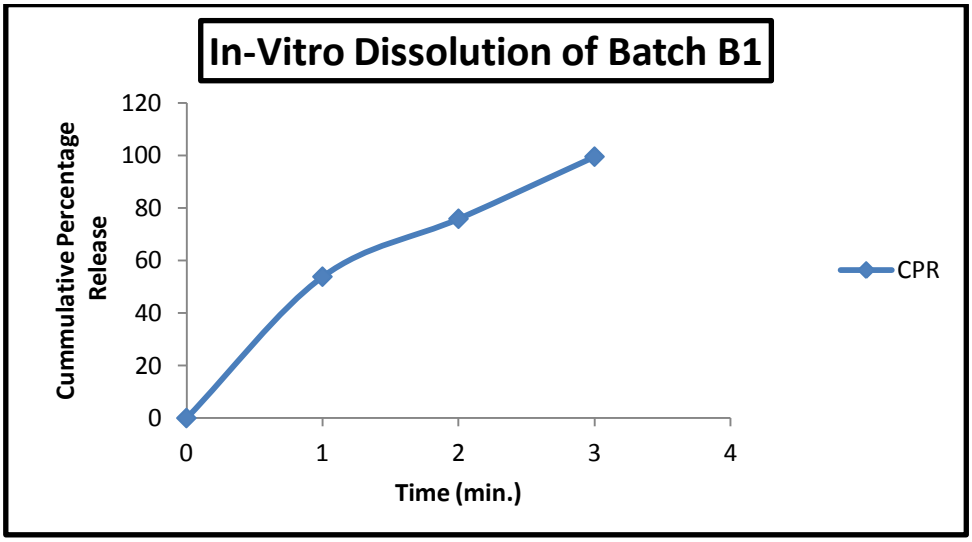


FIGURE 4.14: IN-VITRO DISSOLUTION OF BATCH B1

Result and Discussion:

The in-vitro dissolution study of the drug loaded batch B1 indicated that drug was released in simulated saliva (pH 6.8) in 3 minutes. In-vitro dissolution of Batch B1 indicates that rapid release of drug in short period of time for the fast onset of action. Also tensile strength and in vitro disintegration time was optimum. But the film formed had unacceptable taste. As it was unpalatable there was need of addition of sweetener in further investigation.

4.7 TASTE MASKING APPROACH

4.7.1 SCREENING OF SWEETENER

Promethazine hydrochloride is highly bitter taste drug and hence it was essential to mask the bitter taste, before formulating Fast Dissolving Sublingual Film. Here different types of taste masking agents (aspartame, sucralose) were tried and their effective amounts were optimized. Different batches were prepared and evaluated for taste masking properties. The compositions of the batches are given in the Table 19

TABLE4. 20: OPTIMIZATION OF SWEETENER

Batch No:	Sweetener	Drug: Sweetener	Point Scale*
B2	Sucralose		
B3	Aspartame		
B4	Aspartame		

*0- No Bitterness; 0.5 - Threshold Bitterness; 1-Slight Bitterness; 2- Moderate Bitterness; 3-Strong Bitterness

Result and Discussion:

It was found that addition of sucralose and aspartame alone could not produce desired taste masking effect in Batch B2 to B4. Due to failure of taste masking by selected sweeteners as taste masking agents, incorporation of flavouring agent were tried for their effect on taste masking.

4.7.2 SCREENING OF FLAVOURING AGENTS

As sweetener alone was unable to mask the bitter taste, we decided to evaluate effect of flavouring agent. Flavouring agent like grape fruit, lemon and peppermint were tried for their effect on taste masking.

TABLE 4.21: SCREENING OF FLAVOURING AGENT

Batch No:	Drug: Aspartame	Grape Fruit Flavour	Lemon flavour	Peppermint flavour	Point Scale *
B5	1:1	20 mg	-	-	

B6	1:1	-	20mg	-	
B7	1: 1	-	-	20mg	

*0- No Bitterness; 0.5 - Threshold Bitterness; 1-Slight Bitterness; 2- Moderate Bitterness; 3-Strong Bitterness

Result and Discussion:

Batch B5 to B7 containing different flavouring agent were unable to mask the bitter taste Sweeteners and flavouring agents are unable to mask the bitter taste of drug, so it was decided to try other approaches like inclusion complexation with cyclodextrin etc. for masking bitter taste.

4.7.3 TASTE MASKING USING CYCLODEXTRINS

In spite of trying higher concentration of sweeteners, permissible as per Inactive Ingredient Guideline limit, taste masking was not achieved. Thus, other approaches of taste masking were required to be performed. Taste masking using complexation with β-cyclodextrin (β-CD) and Hydroxy Propyl β- cyclodextrin (HP- β-CD) using physical mixing and kneading approach was carried out. Complexation using physical mixing method was carried out using accurately weighed quantity of Cyclodextrin was mixed with sufficient quantity of PMZ HCl and mixture was mix for 1 hour. In kneading method, accurately weighed quantity of Cyclodextrin was mixed with sufficient quantity of water to obtain a smooth and homogeneous paste. Weighed quantity of PMZ HCl was added slowly by grinding. The mixture was mixed for 1 hour. During this process, appropriate quantity of water was added to maintain suitable consistency. Finally the paste was dried in oven at 40°C for 48 hours. The complex was finally scrapped off from mortar and passed through sieve no. 100.[46]

Various trials were undertaken using different molar ratio PMZ HCl: β-CD and PMZ HCl: HP β-CD namely of 1:0.5, 1:1, 1:1.5 and 1:2 and both physical mixing and kneading method were tried shown in Table 22 and checked their effect on masking the bitter taste of PMZ HCl.

TABLE 4.22: COMPLEXATION USING CYCLODEXTRINS

Batch No:	Drug: β-CD	Drug: HP β-CD	Method
B8	1:0.5	-	Physical
B9	1:1	-	Physical
B10	1:1.5	-	Physical
B11	1:2	-	Physical
B12	1:0.5	-	Kneading
B13	1:1	-	Kneading
B14	1:1.5	-	Kneading
B15	1:2	-	Kneading
B16	-	1:0.5	Physical
B17	-	1:1	Physical
B18	-	1:1.5	Physical
B18	-	1:2	Physical
B19	-	1:0.5	Kneading
B20	-	1:1	Kneading
B21	-	1:1.5	Kneading
B22	-	1:2	Kneading

*0- No Bitterness; 0.5 - Threshold Bitterness; 1-Slight Bitterness; 2- Moderate Bitterness; 3-Strong Bitterness

Result and Discussion:

4.7.4 ADDITION OF SWEETENER AND FLAVOURING AGENT TO THE INCLUSION COMPLEX.

Complexation of drug with HP β-CD was unable to mask the bitter taste completely but kneading method had promising results so it was further combined with aspartame and grape fruit flavour for the taste masking effect as shown in Table 23.

TABLE 4. 23: EFFECT OF ADDITION OF SWEETENER AND FLAVOURING AGENT

*0- No Bitterness; 0.5 - Threshold Bitterness; 1-Slight Bitterness; 2- Moderate Bitterness; 3-Strong Bitterness

Result and Discussion:

TABLE 4.24: EVALUATION OF BATCH B25

Parameters	Result
Appearance	
Thickness	
Tensile Strength	
Folding Endurance	
% Elongation	
In-vitro Disintegration time	

Result and Discussion:

4.8 OPTIMIZATION OF AMOUNT OF POLYMER AND PLASTICIZER

For optimization 3^2 full factorial design was applied to present study as there were only two factors affecting the present formulation that are the concentration of Pullulan and Propylene Glycol. The three- level design is written as a 3^2 factorial design. It means that 2 factors are consider, each at 3 levels which are usually referred to as low, intermediate and high levels. These levels are numerically expressed as -1, 0 and +1. It is a simplest three level design. It has 2 factors each at 3 levels.

The optimization procedure is facilitated by construction of an equation that describes the experimental results as a function of the factor levels. A polynomial equation can be constructed, where the coefficients in the equation are related to the effects and interaction of the factors. The equation constructed form 3^n factorial experiment is in the following form.

$$Y= B_0 +B_1X_1+B_2X_2……B_nX_n + B_{12}X_1X_2+B_1X_1^2+ B_{22}X_2^2….. (1)$$

Concentration of Polymer (X1) and Concentration of Plasticizer (X2) were selected as independent variables and Tensile Strength (TS) and in-vitro disintegration time were selected as the dependent variable as seen in Table 4.25

TABLE 4.25: CODED VALUES OF 3^2 FULL FACTORIAL DESIGN

Concentration of	Coded Value	
Polymer (X1)	-1	
	0	

	+1
Plasticizer (X2)	-1
	0
	+1

TABLE 4.26: 3^2 FULL FACTORIAL DESIGN

BATCH CODE	Variable level in Coded Form		Tensile Strength gm/cm^2	In-vitro Disintegration (Sec.)
	X1	X2		
F1	-1	-1		
F2	-1	0		
F3	-1	+1		
F4	0	-1		
F5	0	0		
F6	0	+1		
F7	+1	-1		
F8	+1	0		
F9	+1	+1		

Result and Discussion:

4.8.1 RESPONSE SURFACE PLOTS

FIGURE 4.15: RESPOSNE SURFACE PLOT FOR IN-VITRO DISINTEGRATION TIME

FIGURE 4.16: RESPONSE SURFACE PLOT FOR TENSILE STRENGTH

Contour plots

FIGURE 4.17: CONTOUR PLOT FOR TENSILE STRENGTH

FIGURE 4.18: CONTOUR PLOT FOR DISINTEGRATION TIME

4.8.2 STASTICAL EVALUATION OF FACTORIAL DESIGN

TABLE 4.27 ANOVA TABLE OF THE TENSILE STRENGTH

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	33695.49	5	6739.10	24.09		
A-Polymer	28571.52	1	28571.52	102.14		
B-Plasticizer	1150.93	1	1150.93	4.11		
AB	132.94	1	132.94	0.48		
A^2	1367.64	1	1367.64	4.89		
B^2	2472.45	1	2472.45	8.84		
Residual	839.21	3	839.21			
Cor Total	34534.70	8				

TABLE 4.28 REGRESSION ANALYSIS OF TS

Std. Dev.	
Mean	
R-Squared	

FINAL EQUATIONOF TS:

TABLE 4.29 ANOVA TABLE OF DISINTEGRATION TIME

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	1074.92	5	214.98	11.30		
A-Polymer	433.50	1	433.50	22.78		
B-Plasticizer	160.17	1	160.17	8.42		

AB	0.25	1	0.25	0.013		
A*2	420.50	1	420.50	22.10		
B*2	60.50	1	60.50	3.18		
Residual	57.08	3	19.03			
Cor Total	1132.00	8				

TABLE 4.30 REGRESSION ANALYSIS OF DT

Std. Dev.	
Mean	
R-Squared	

FINAL EQUATION OF DT:

4.8.3 CHECK POINT BATCH (VALIDATION OF MODEL)

TABLE 31: CHECK POINT BATCHES

Batch Code	**Composition**		**Expected Values**		**Observed Values**	
	Polymer (%w/v)	Plasticizer (%w/w)	Tensile Strength gm/cm^2	In-vitro Disintegration (Sec.)	Tensile Strength gm/cm^2	In-vitro Disintegration (Sec.)
F10			200.19	22.15	204.42	22
F11			200.2	24.2	201.92	24

Result and Discussion:

4.9 TEXTURE ANALYSIS OF THE OPTIMIZED BATCH

BROOKFIELD

TexturePro v2.1

RESULTS SHEET

SELECTED CALCULATIONS

Peak load 3090.00 g

FIGURE 4.19 TEXTURE ANALYSIS OF OPTIMIZED BATCH

TABLE 4.32: OPTIMIZED FORMULA OF FDSF BATCH F8

TABLE 4.33: IN-VITRO DISSOLUTION OF BATCH F8

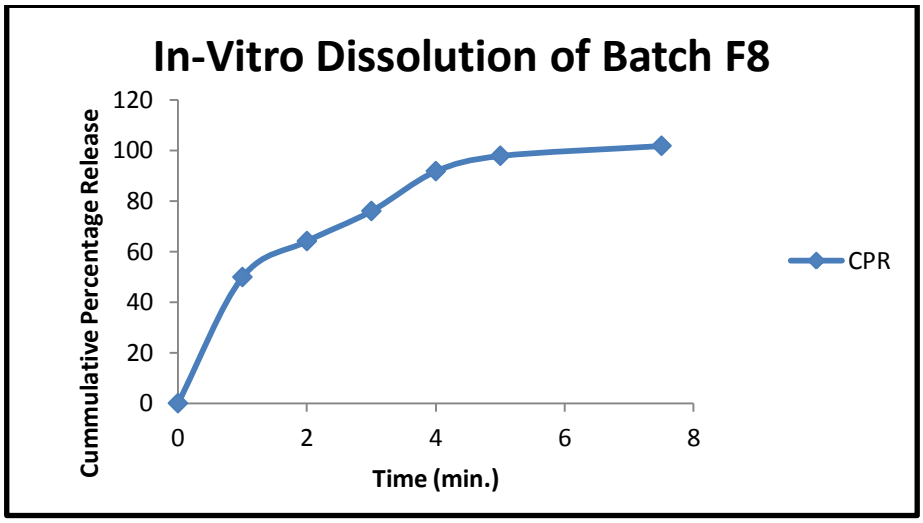


FIGURE4.20: IN-VITRO DISSOLUTION OF BATCH F8

TABLE 4.34: EVALUATION PARAMETERS OF BATCH F8

CONCLUSION

4.10 CHARACTERIZATION OF PMZ HCL AND CYCLODEXTRINS COMPLEX

PMZ HCL and HP-β CD complexation studies were done to study whether the drug has been completed incorporated within the cavity of HP-β CD or not. This will prove the complexation of drug with HP-β CD.

Complex of the PMZ HCl was proved using the FTIR , DSC and XRD studies.

4.10.1 COMPARITIVE FTIR

FIGURE 4.21 COMPARITIVE FTIR OF THE COMPLEX

Discussion:

Figure indicates that all the characteristic peak of the drug were diminished or had lower intensity in the complex of PMZ HCl and HP –β CD, thus it indicates that there is complete incorporation of PMZ HCl within the cavity of HP –β CD

4.10.2 DIFFERENTIAL SCANNING CALORIMETRY

Differential scanning calorimetry (DSC) was performed using a Shimadzu Corporation (DSC-60), Japan The drug, the polymer, and the drug-polymer complex were subjected to the DSC study. Samples were heated at a scanning rate of 20^0Cmin from 50°C to 300°C under air.

FIGURE 4.22: DSC OF PMZ HCL

FIGURE 4.23: DSC OF HP β-CD

FIGURE 4.24: DSC OF PMZ HCL AND HP β-CD

Discussion:

thermogram of PMZ-HCl: HP β-CD complex shows the peak at a higher temperature (249.12°C), indicating that there is complex formed between Promethazine Hydrochloride and Hydroxy Propyl β-Cyclodextrin indicating drug is completely incorporated within the cavity of HP β-CD and therefore it might have contributed to its taste masking.

4.10.3 X-RAY DIFFRACTOMETRY

FIGURE 4.25 XRD OF PMZ HCl

FIGURE 4.26 XRD OF HP-β CD

FIGURE 4.27 XRD OF PMZ HCL AND HP β-CD COMPLEX

Discussion:

From the XRD results it was found that PMZ HCl is highly crystalline form and in the complex there was decrease in peak intensity and decrease in number of peaks therefore it indicates that crystallization of PMZ HCl was reduced using HP β-CD and the complex form was amorphous in state.

4.11 ENVIORNMENT SCANNING ELECTRON MICROSCOPY

The surface morphology of the film was observed using Environment scanning electron microscope. The film sample was placed in the sample holder and the photomicrographs were taken using tungsten filament as electron source and GSE detector at 100x and 1000x magnification. The surface morphology of the film forming excipient pullulan, promethazine hydrochloride and films was observed using Environment scanning electron. The ESEM images are shown FIGURE 4.28.

FIGURE 4.28: ESEM AT 1000X

Discussion:

4.12 *IN VIVO* STUDY ON HUMAN OF BATCH F8 [47]

These studies were approved by Institutional Ethical Committee (IEC) with project Number: IEC/NU/III/IP/02 dated 7th May 2013.

Advantage:

The major benefit of this study was that the absorption kinetics of a drug can be studied in a single subject in just 15–20-min time. Besides the original and modified buccal absorption tests are easy to perform as this study do not require blood sampling, and also the rate and the extent of drug loss from the oral cavity can be easily determined.

Disadvantage:

One of the major disadvantages of this technique is that only the concentration of drug remaining in the oral cavity (swirling solution) can be measured, as blood samples are not determined. The amount of drug which disappears from the swirling solution cannot be equated to the amount entering the systemic circulation, due to other factors including membrane storage, potential metabolism, and swallowing of the drug. Since the solution is swirled around the oral cavity, absorption of compound may also occur through all surfaces within the oral cavity, and so the degree to which absorption occurs across a specific site (e.g., buccal and sublingual) remains unknown.

Procedure:

The 'buccal absorption test' will be performed on healthy volunteers. Fast dissolving film and tablet containing 25 mg Promethazine hydrochloride will be tested. Before each Sublingual administration, the volunteers are made to wash their mouth with 100 ml of distilled water. Then, the fast dissolving film/tablet will be placed under the tongue for fixed period of time and should not be swallowed. Then if any residue of dosage form is present will be expelled and the mouth will be rinsed with distilled water (3×20 ml). The residue of dosage form and the washing solutions will be combined and analyzed for the remaining drug content. The amount of Promethazine Hydrochloride absorbed from the mucosa will be determined as difference between initial and re-covered content.

TABLE 4.35: IN VIVO STUDY ON HUMAN OF BATCH F8

Result and Discussion:

Conclusion:

Volunteers reported that the fast dissolving dosage form, designed to obtain a rapid onset of therapeutic effect, dissolved immediately in the sublingual region. The system claims to have the potential clinical usefulness in delivering the drug. The fast dissolving dosage form, quickly soluble in a small volume of saliva, could rapidly create a high drug concentration in contact with a relatively large absorption surface. The volunteers reported that, in few seconds after deposition of the dosage form in the area under the tongue, the film dissolved thus allowing prompt drug absorption from sublingual mucosa.

However, due to the low residence time of fast dissolving formulation after its administration, it can be supposed that, in practice, only a small amount of drug can be absorbed from sublingual mucosa.

Human study involves ease of sampling and handling of salivary content obtained after the application of the sublingual film and can be easily correlated with the In vivo- In vitro permeation studies.

On the basis of the obtained results, it can be concluded that the delivery of Promethazine hydrochloride via sublingual mucosa has good perspectives in therapeutic application. A future work will concern the study of in vivo Promethazine hydrochloride absorption measuring drug blood levels so that supporting the data presented in this work.

4.13 COMPARATIVE *IN-VITRO* DISSOLUTION STUDIES WITH MARKETED PRODUCT AND PURE DRUG

In vitro dissolution studies were carried out using the simulated saliva fluid pH (6.8)

TABLE 4.36: DISSOLUTION OF PURE DRUG

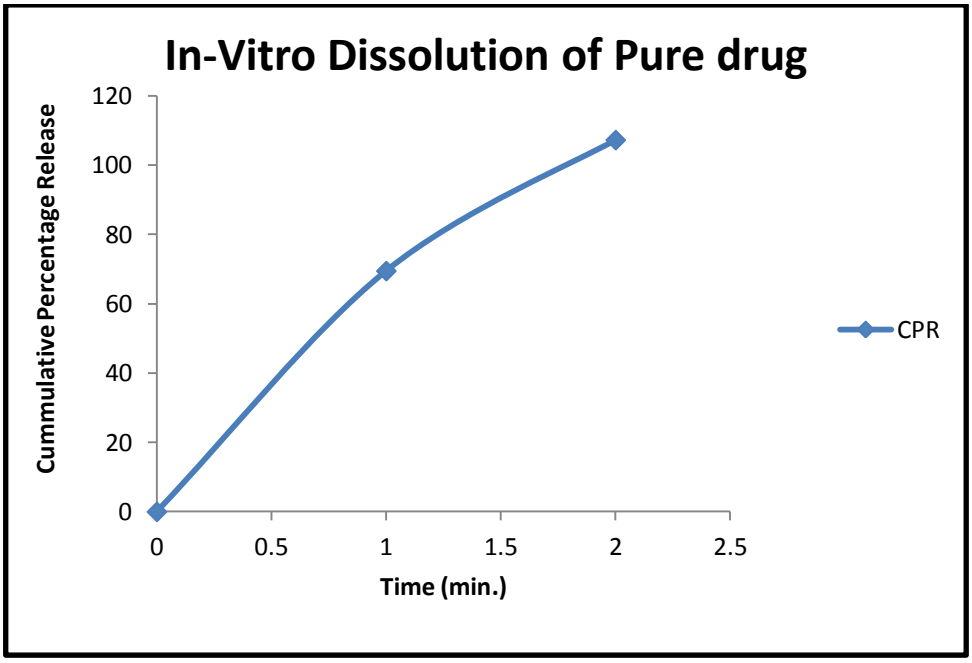


FIGURE 4.29: IN-VITRO DISSOLUTION OF PURE DRUG

TABLE 4.37: IN-VITRO DISSOLUTION OF MARKETED PRODUCT

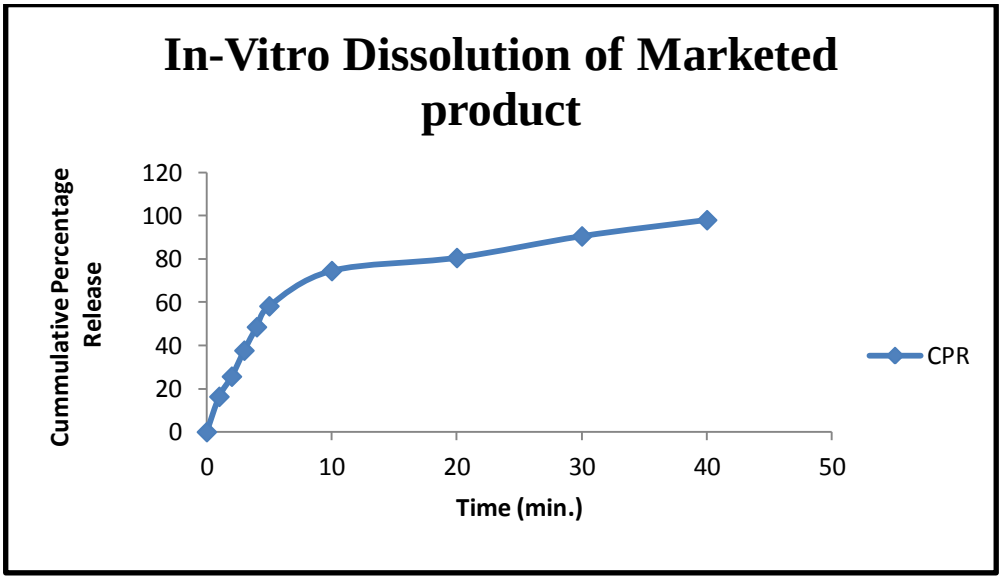


FIGURE 4.30: IN-VITRO DISSOLUTION OF MARKETED PRODUCT

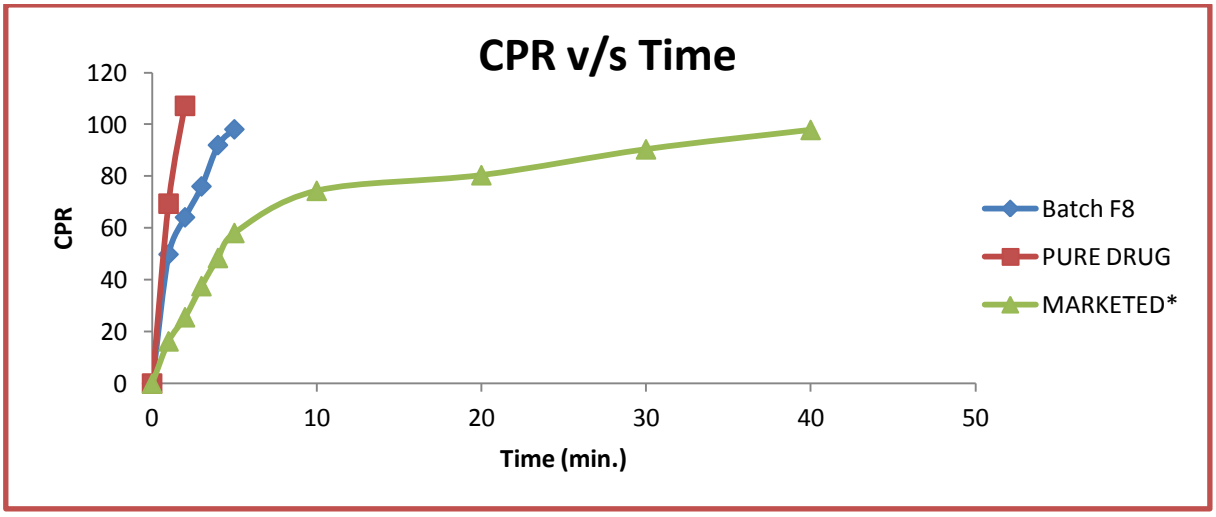


FIGURE 4.31: COMPARITIVE IN-VITRO DISSOLUTION STUDIES (*Phenargan 25)

Conclusion:

4.14 STABILITY STUDY

The stability studies of the optimized batch F8 was carried out in high density polyethylene (HDPE) container in a sealed zip lock bag carried out at 40°C/75% RH and 25°C/60% RH using stability chamber.

TABLE 4.38: STABILITY STUDIES OF BATCH F8

Condition	Time	In-vitro DT (sec.)	In-vivo Dissolution time (min.)	Appearance
40°C/75%RH	Initial			
	1 month			
	2 month			
25°C/60%RH	Initial			
	1month			
	2 month			

Conclusion:

4.15 FUTURE PROSPECTIVE

- In vivo pharmacokinetic parameter (CMax, T Max, T 1/2, AUC) will be determined in rabbit.
- Drying time may be reduced by optimizing the drying process using microwave oven.
- In vivo-in vitro correlation study can be performed.

CHAPTER 5

EXPERIMENTAL WORK- FAST DISSOLVING SUBLINGUAL TABLET

5. FAST DISSOLVING SUBLINGUAL TABLET

In present study the Fast Dissolving Sublingual Tablet (FDST) was formulated using direct compression method. Direct Compression is the process by which tablets are compressed directly from mixtures of the drug and excipients without preliminary treatment such as granulation. In this process, directly compressible diluents like Microcrystalline Cellulose (MCC), Ludiflash are mixed with the drug and other excipients to produce a uniform mixture and compressed into tablet. This is the amount by which they can incorporate substance, which are not directly compressible and yet produce acceptable tablets.

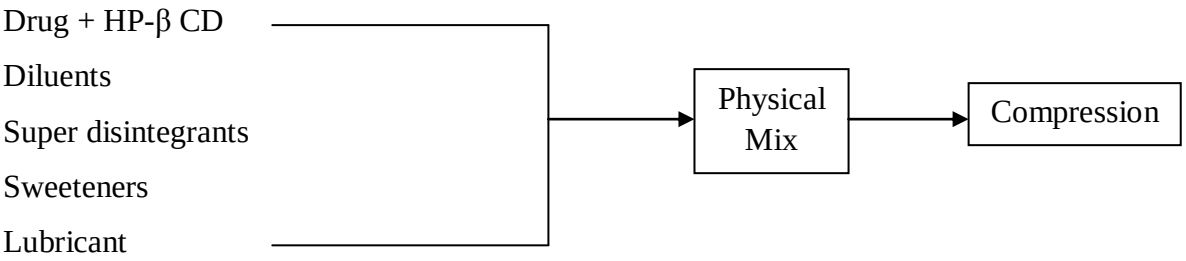


FIGURE 5.1 FLOW CHART OF DIRECT COMPRESSION PROCESS

5.1 SCREENING OF DILUENTS

Promethazine HCl tablet were formulated using Micro crystalline Cellulose (MCC) and Ludiflash as diluents and the average weight of tablet was kept 250mg and 300mg. There effect on compression and disintegration was evaluated as both the diluents have disintegrating property within itself. Drug to HP-βCD complex was kept constant 1:1 as optimized from the FDSF, aspartame as sweetener, vanillin to add flavour, Aerosil and Magnesium Stearate as lubricant. All the formulation was subjected to precompression and post compression evaluation parameters.

TABLE 5.1 SCREENING OF DILUENTS

Ingredients (mg)	S1	S2	S3	S4
Drug:HP-βCD	1:1	1:1	1:1	1:1
MCC				
Ludiflash®				

Aspartame	25	25	25	25
Cross Carmelose	25	30	25	30
Vanillin	5	5	5	5
Aerosil	5	5	5	5
Mg. Stearate	1.25	1.25	1.25	1.25
Total Weight	250	300	250	300

TABLE 5.2 PRECOMPRESSION BLEND CHARACTERIZATION OF DILUENTS

PARAMETERS	S1	S2	S3	S4
Bulk Density (g/ml)	0.393	0.477	0.521	0.453
Tap Density (g/ml)	0.461	0.572	0.611	0.562
Hausner's Ratio	1.17	1.17	1.16	1.16
Carr's Index (%)	13.76	14.41	15.31	13.76
Angle of Repose (θ)	28.1	26.2	29.7	27.3

TABLE 5.3 EVALUATION PARAMETERS OF DILUENTS

Parameters	S1	S2	S3	S4
Hardness (kp)				
Thickness (mm)				
Friability (%)				
Weight variation (%)				
Wetting Time				
In-vitro disintegration time				

Result and Discussion:

5.2 SCREENING OF SUPERDISINTEGRANTS

As the tablet formed using MCC showed high disintegration time there was need of addition of Superdisintegrants like Cross Carmellose, Crosspovidone, Sodium Starch

Glycolate and Low viscosity Hydroxypropyl Cellulose (L-HPC) were tried in concentration of to achieve the disintegration time within 1 minute.

TABLE 5.4 SCREENING OF SUPERDISINTEGRANTS

Ingredients (mg)	M1	M2	M3	M4	M5	M6	M7	M8
Drug	25	25	25	25	25	25	25	25
HP-βCD	110	110	110	110	110	110	110	110
Aspartame	25	25	25	25	25	25	25	25
Kollidon CL								
Cross Carmelose								
SSG								
L-HPC								
Vanillin	5	5	5	5	5	5	5	5
Aerosil	5	5	5	5	5	5	5	5
Mg. Stearate	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
MCC	53.75	41.25	53.75	41.25	53.75	41.25	53.75	41.25
Total Weight	250	250	250	250	250	250	250	250

TABLE 5.5 PRECOMPRESSION BLEND CHARACTERIZATIONOF BAATCH M1-M8

PARAMETERS	M1	M2	M3	M4	M5	M6	M7	M8
Bulk Density (g/ml)	0.508	0.398	0.494	0.385	0.453	0.521	0.477	0.393
Tap Density (g/ml)	0.583	0.477	0.558	0.451	0.562	0.611	0.572	0.461
Hausner's Ratio	1.18	1.18	1.16	1.18	1.16	1.16	1.17	1.17
Carr's Index (%)	13.71	19.5	13.63	15.50	13.76	15.31	14.41	13.76
Angle of Repose (θ)	27.8	30.1	28.9	28.5	27.3	29.7	26.2	26.2

TABLE 5.6 EVALUATION OF BATCH CONTAINING SUPERDISINTEGRANTS

Parameters	M1	M2	M3	M4	M5	M6	M7	M8
Hardness (kp)								
Thickness (mm)								
Friability (%)								
Weight variation (%)								
Wetting Time								
In-vitro disintegration time								

Result and Discussion:

5.3 EFFECT OF HIGHER AMOUNT OF L-HPC

As the 10% of L-HPC was insufficient to get desired disintegration time there was need for increasing the amount of L-HPC, therefore of L-HPC was tried for the effect on Disintegration time.

TABLE5.7 EFFECT OF HIGHER AMOUNT OF L-HPC

Ingredients (mg)	M9	M10
Drug	25	25
HP-β CD	110	110
Aspartame	25	25
L-HPC		
Vanillin	5	5

Aerosil	5	5
Mg. Stearate	1.25	1.25
MCC	47.5	41.25
Total weight	250	250

TABLE 5.8 PRECOMPRESSION BLEND CHARACTERIZATIONOF BATCH M9&M10

PARAMETERS	M9	M10
Bulk Density (g/ml)	0.521	0.453
Tap Density (g/ml)	0.611	0.562
Hausner's Ratio	1.16	1.16
Carr's Index (%)	15.31	13.76
Angle of Repose (θ)	29.7	27.3

TABLE 5.9 EVALUATION OF EFFECT OF HIGHER AMOUNT OF L-HPC

Parameters	M9	M10
Hardness (kp)		
Thickness (mm)		
Friability (%)		
Weight Variation (%)		
Wetting Time		
In-vitro disintegration time		

Result and Discussion:

further trials were taken using decrease amount of HP-β CD with the drug.

5.4 EFFECT OF RATIO OF DRUG TO HP–β CD ON COMPRESSIBILITY OF TABLET

As the high amount of HP–β CD was affecting compressibility there was need of decreasing the ratio of drug to HP–β CD and the taste masking of the drug might be

affected but it was compensated by using the amount of citric acid and high amount of sweetener. And its effect on compressibility and disintegration time was evaluated. ratio of drug: HP- β CD was tried. L-HPC was taken in concentration ranging from 7.5 % to 15%.

TABLE5.10: EFFECT OF RATIO OF DRUG TO HP–B CD

Ingredients (mg)	M11	M12	M13	M14
Drug	25	25	25	25
HP-β CD				
Aspartame	30	30	30	30
L-HPC	18.75	25	31.25	37.5
Vanillin	5	5	5	5
Citric Acid	12.5	12.5	12.5	12.5
Aerosil	5	5	5	5
Mg. Stearate	1.25	1.25	1.25	1.25
MCC	71.5	65.25	59	52.75
Total Weight	250	250	250	250

TABLE 5.11 PRECOMPRESSION BLEND CHARACTERIZATION OF BATCH M11 TO M14

PARAMETERS	M11	M12	M13	M14
Bulk Density (g/ml)	0.423	0.419	0.431	0.381
Tap Density (g/ml)	0.489	0.487	0.499	0.447
Hausner's Ratio	1.15	1.16	1.15	1.17
Carr's Index (%)	13.4	13.9	13.6	14.5
Angle of Repose (θ)	27.2	28.7	28.1	27.9

TABLE5.12 EVALUATION OF EFFECT OF RATIO OF DRUG TO HP–B CD

Parameters	M11	M12	M13	M14

Hardness (kp)				
Thickness (mm)				
Friability (%)				
Weight variation (%)				
Wetting Time (sec.)				
In-vitro disintegration time (sec.)				

Result and Discussion:

Thus there was need of addition of binder to control the friability of tablet.

5.5 USE OF DRY BINDER

As the use of high amount of disintegrating agent was able to decrease disintegration time but the friability was in higher side therefore addition of binder in formulation and evaluated for its effect on disintegration time and friability.

TABLE 5.13 EFFECT OF BINDER ON FRIABILITY

Ingredients (mg)	**M15**	**M16**	**M17**	**M18**	**M19**	**M20**	**M21**	**M22**	**M23**
Drug	25	25	25	25	25	25	25	25	25
HP-β CD									
Aspartame	30	30	30	30	30	30	30	30	30
PVP K-30	1.25	1.25	1.25	2.5	2.5	2.5	3.75	3.75	3.75
L-HPC	25	31.25	37.5	25	31.25	37.5	25	31.25	37.5
Vanillin	5	5	5	5	5	5	5	5	5

Citric Acid	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Aerosil	5	5	5	5	5	5	5	5	5
Mg. Stearate	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
MCC	65.12	59	52.87	65	58.87	52.75	64.87	58.62	52.5
Total Weight	250	250	250	250	250	250	250	250	250

TABLE 5.14 PRECOMPRESSION BLEND CHARACTERIZATIONOF BATCH M15 TO M23

PARAMETERS	M15	M16	M17	M18	M19	M20	M21	M22	M23
Bulk Density (g/ml)	0.372	0.383	0.379	0.381	0.387	0.403	0.409	0.392	0.403
Tap Density (g/ml)	0.441	0.447	0.44	0.451	0.454	0.471	0.475	0.461	0.471
Hausner's Ratio	1.18	1.16	1.16	1.18	1.17	1.16	1.16	1.17	1.16
Carr's Index (%)	15.6	14.3	13.6	15.5	14.7	14.4	13.8	14.9	14.4
Angle of Repose (θ)	28.3	27.7	26.3	28.1	26.9	26.2	25.6	28.1	27.6

TABLE 5.15 EVALUATION OF BINDER

Parameters	M15	M16	M17	M18	M19	M20	M21	M22	M23
Hardness (kp)									
Thickness (mm)									
Friability (%)									
Weight Variation (%)									

Wetting Time (sec.)									
In-vitro disintegration time (sec.)									

Result and Discussion:

5.6 EFFECT OF LUBRICANT

From literature [49] it is shown that Magnesium Stearate contains hydrophobic group which hinders wetting time and disintegration time is increased. Therefore we can decrease disintegration time by substituting Mg. Stearate with some other lubricant. From literature survey it was found that Sodium Stearyl Fumarate (SSF) contains hydrophilic group and has significant effect on disintegration time. Therefore Mg. Stearate was substituted with SSF and evaluated further

TABLE 5.16 EFFECT OF LUBRICATING AGENT

Ingredients (mg)	M 24	M 25
Drug	25	25
HP-βCD		
Aspartame	30	30
PVP K-30		
L-HPC		
Vanillin	5	5
Citric Acid	12.5	12.5
Aerosil	5	5
Mg. Stearate	1.25	-
Sodium Stearyl Fumsarate	-	1.25
MCC	52.75	52.75

Average weight	250	250

TABLE 5.17 PRECOMPRESSION BLEND CHARACTERIZATIONOF BATCH M24 & M25

PARAMETERS	M 24	M 25
Bulk Density (g/ml)	0.477	0.512
Tap Density (g/ml)	0.553	0.577
Hausner's Ratio	1.15	1.12
Carr's Index (%)	13.7	11.2
Angle of Repose (θ)	28.7	23.67

TABLE 5.18 EVALUATION OF LUBRICANT

Parameters	M 24	M 25
Hardness (kp)		
Thickness (mm)		
Friability (%)		
Weight variation (%)		
Wetting Time (sec.)		
In-vitro disintegration time (sec.)		

Result and Discussion:

5.7 IN VITRO DISSOLUTION TIME OF BATCH M25

Dissolution of FDST was taken using SSF (pH 6.8)

TABLE 5.19 IN VITRO DISSOLUTION OF BATCH M25

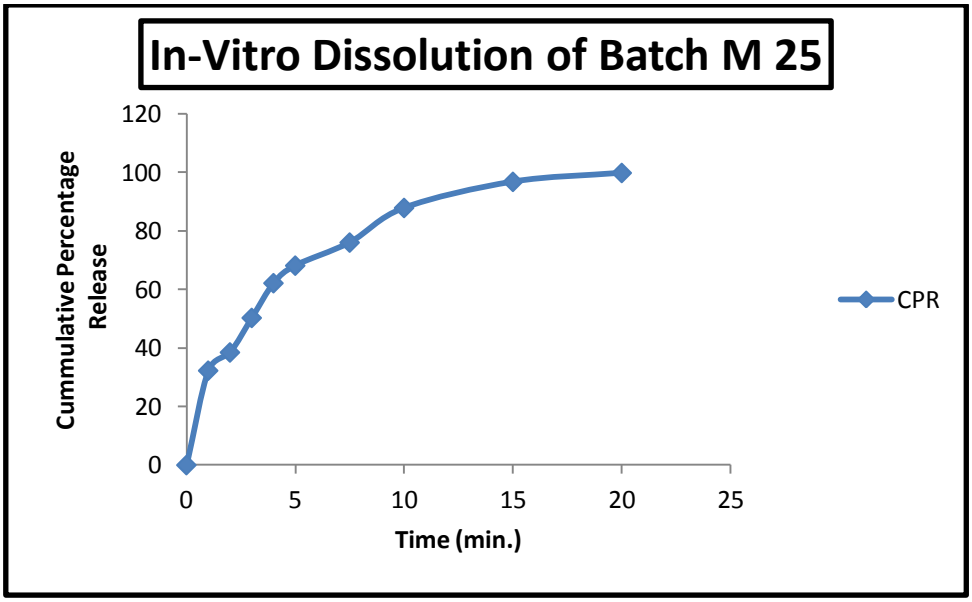


FIGURE 5.2 IN VITRO DISSOLUTION OF BATCH M 25

5.8 IN VIVO HUMAN STUDY OF FDST BATCH M25

Optimized batch was selected for in-vivo human study to check the permeation of drug. Procedure remains the same as mentioned on page no.

TABLE 5.20 IN-VIVO HUMAN STUDY FOR FDST

Result and Discussion:

5.9 OPTIMIZED FDST

TABLE 5.21 OPTIMIZED FORMULA FOR FDST (M25)

TABLE 5.22 EVALUATION OF BATCH M25

5.10 COMPARISON OF FAST DISSOLVING SUBLINGUAL FILM AND FAST DISSOLVING SUBLINGUAL TABLET

FIGURE 5.3: COMPARATIVE IN-VITRO DISSOLUTION STUDIES

FIGURE 5.4: COMPARITIVE IN-VITRO DISSINTEGRATION STUDIES

FIGURE 5.5 COMPARITIVE IN-VIVO PERMEATION STUDIES

CONCLUSION

From the Drug release studies, disintegration time and in-vivo permeation studies it was indicated that the FDSF had more promising result compared to FDST. Moreover there was no problem of friability and no fear of choking in patient's mind when FDSF as dosage form is used. Therefore developed PMZ HCl FDSF achieved all the set objective of present study and hence developed formulation is better option for treatment of patient suffering from the motion sickness. Thus the developed formulation was Traveller's Friendly.

CHAPTER 6

SUMMARY

SUMMARY

Oral route is most acceptable drug delivery route due to its better therapeutic efficacy and high patient compliance. Therefore most of the advances are done in developing new dosage form for the oral route. Oral mucosal drug delivery can be through sublingual or bucccal drug delivery. The sublingual mucosa possess several characteristics that are favourable for drug delivery, such as a rich blood supply that rapidly introduces the drug directly into systemic circulation, avoiding first pass metabolism of drugs in liver and pre-systemic elimination in the gastrointestinal region. Thus, sublingual mucosa is an attractive site for systemic administration of drugs. The objective of this research was to explore sublingual drug delivery routes by formulating fast dissolving taste masking sublingual dosage forms for improved bioavailability of Promethazine hydrochloride.

In the present study, Fast dissolving drug delivery systems of Promethazine hydrochloride were successfully developed in the form of sublingual film and tablet which offers a suitable and practical approach in serving desired objective of taste masking, fast disintegration and dissolution characteristics with increase bioavailability by the administration through sublingual routes.

Film was formulated using Pullulan, HPMC E-5, HPMC E-15, PVA as polymer and Propylene glycol and Polyethylene Glycol as plasticizer. Optimization of polymer, plasticizer and casting surface was done based on the preliminary trials conducted. Taste masking was done using sweeteners, cyclodextrins and flavours. Preformulation study for the drug and excipients was conducted using FT-IR spectrophotometer. No drug-excipients interaction was observed. The batch was evaluated based on parameters like elongation, tensile strength, in vitro disintegration and in vitro dissolution in acceptable range.

Complexation of PMZ HCl: HP β-CD was proved using DSC and FTIR studies. Results indicated that there was no separate peak of drug which indicated complete incorporation of PMZ HCl in cavity of HP β-CD and this might have contributed the taste masking of drug.

SEM results indicated that there was uniform distribution of drug no striations or breaking of film which will contribute to maintain integrity of film and helped to deliver intact film to the patients.

Fast dissolving tablet were formulated using different diluents and super disintegrants but, the disintegration time was not achieved within the acceptable range therefore from the literature review ratio of PMZ HCl: HP β-CD was decreased from 1:1 to and higher concentration of L-HPC was used, disintegration time was achieved within the limit but the friability was posing a problem therefore PVP K-30 as dry binder was used. And the effect of Magnesium stearate and Sodium stearyl fumarate as lubricant was checked on disintegration time.

Comparison of the both developed formulation was done on the basis of in-vitro disintegration time, drug release study and in vivo permeation studies showed that fast dissolving film gave more promising results in all the cases compared to fast dissolving tablet, moreover there was no problem of friability and choking problem in fast dissolving film.

The formulation was subjected to stability studies and it was observed that at 40°C/75% RH the films became brittle and light in colour after 1 month,. The batch was found be acceptable visually, mechanically, with slight change in in-vitro disintegration time. Thus, it was concluded that Pullulan films were sensitive to temperature and humidity. It was found that suitable packaging and storage conditions are required for fast dissolving sublingual films containing Pullulan as film forming polymer & the product should be stored at 25°C or low temperature condition & label should state “Store at cool, dry place at temperature 25°C.

It can be concluded that the sublingual film of Promethazine hydrochloride rapidly soluble in the small volume of saliva underlying the tongue when brought in contact with the sublingual mucosa, the dosage form immediately dissolved allowing the drug penetration across the sublingual mucosa. Hence sublingual film containing Promethazine Hydrochloride provides higher bioavailability as compared to fast dissolving tablet and marketed product. Hence the developed fast dissolving sublingual film was best suited

dosage for the treatment of motion sickness and developed formulation was Traveller friendly.

CHAPTER 7

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