# FORMULATION AND EVALUATION OF BUCCAL PATCHES OF PROMETHAZINE HYDROCHLORIDE

**Dissertation**

**Submitted to**

**The Tamil Nadu Dr. M.G. R. Medical University, Chennai.**

**In partial fulfillment for the award of the degree of**

**MASTER OF PHARMACY**

**In**

**PHARMACEUTICS**

**By**

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# CERTIFICATE

This is to certify that, this thesis work entitled "**FORMULATION AND EVALUATION OF BUCCAL PATCHES OF PROMETHAZINE HYDROCHLORIDE"** submitted in partial fulfillment of the requirements for the award of Degree of Master of Pharmacy in Pharmaceutics of The Tamil Nadu Dr. M.G.R Medical University, Chennai is a bonafide work carried out by **Reg.No:26113305** and was guided and supervised by me during the academic year Nov 2012-Oct 2013.

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2.

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## *ACKNOWLEDGEMENT*

*Without the grace of the* ***Almighty*** *and sincere hard work the presentation of this dissertation would not have been possible.*

*It is indeed a moment of great delight and pride to acknowledge with deep sense of gratitude to my guide* ***Dr.C.Vijaya M.Pharm,,Ph.D, Dean and Head of the department, Pharmaceutics, Ultra College of Pharmacy, Madurai,*** *for her invaluable guidance, suggestions and encouragement throughout the course of my dissertation work.*

*With pride and pleasure, I wish to express my thanks to* ***Prof. K.R. Arumugam, M.Pharm, Chairman, Ultra College of Pharmacy, Madurai,*** *for his encouragement, profound knowledge and source of inspiration for my dissertation work. I deem it my privilege in expressing my fidelity to* ***Dr.A.Babu Thandapani M.Pharm, Ph.D, Principal, Ultra College of Pharmacy, Madurai,*** *for providing me the necessary laboratory facilities to carry out this work with great ease and precision.*

*I wish to offer my respectable thanks to the teaching staff* ***Mr.Senthil kumar, Mr. T. Regupathi, Mr. Sivanand, Prof. M. Chandran, Dr. K.G. Lalitha*** *and* ***Mr. R. Sathish*** *for their suggestions and encouragement throughout my dissertation work. I specially thank to Librarian* ***Mr. Sankar Pandian*** *&* ***Ms.Sundaravali,*** *and I must place my record very special thank to* ***Mrs.B.Masila, B.Com., Lab Technician, Department of Pharmaceutics,*** *for her continuous assistance in carrying out the project work.*

*I wish to express my special thanks to my uncle* ***Mr. Biju Philip, Plant Manager, Watson Pharma Pvt.Ltd. Goa,*** *for providing Promethazine hydrochloride as gift sample. I take this opportunity to thank all classmates* ***Vishnuprasad.S, Ratheesh.G, Geethu Susan Georgy*** *&* ***Preetha Francis*** *for their valuable and unforgettable encouragement.*

*I take this opportunity to thank* ***Mr.&Mrs. Saji Abraham*** *for their moral supports and encouragement throughout the entire project time. Finally; I thank and to my parents* ***Kurien*** *&* ***Liciamma,*** *my sisters* ***Dyuthy, Deepa*** *&* ***Daya,*** *and brother in laws* ***Roy Koshy, Roy Abraham*** *&* ***Sherin P Abraham*** *for their Invincible love, spiritual blessings, illimitable sacrifices and their continuous support and motivation throughout my project and I dedicate this dissertation work to my nephews and nieces* ***Rishith, Richu, Salmon, Raya*** *&* ***Sera.***

# DECLARATION

I hereby declare that this thesis work entitled **"FORMULATION AND EVALUATION OF BUCCAL PATCHES OF PROMETHAZINE HYDROCHLORIDE"** submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai was carried out by me in the Department of Pharmaceutics, Ultra College of Pharmacy, Madurai under the valuable and efficient guidance of **Dr.C.VIJAYA M.Pharm. Ph.D,** Department of pharmaceutics, Ultra College of Pharmacy, Madurai during the academic year Nov 2012-Oct 2013. I also declare that the matter embodied in it is a genuine work and the same has not to formed the basis for the award of any degree, diploma, associate ship, fellowship of any other university or institution.

**PLACE:** MADURAI DEEPU THOMAS KURIEN

**DATE:**

## ABBREVIATIONS

| | |
|---|---|
| **Ach** | **: Acetyl choline** |
| **B.P** | **: British Pharmacopoeia** |
| **cm** | **: Centimetre** |
| **Cps** | **: Centi poise** |
| **$^{o}$C** | **: Degree Centigrade** |
| **E.C** | **: Ethyl cellulose** |
| **FTIR** | **: Fourier transfer infrared spectroscopy** |
| **g** | **: Grams** |
| **G.I Tract** | **: Gastro intestinal tract** |
| **hrs** | **: Hour** |
| **HPC** | **: Hydroxy propyl cellulose** |
| **HPMC** | **: Hydroxy Propyl Methyl cellulose** |
| **I.P** | **: Indian Pharmacopoeia** |
| **Kg** | **: Kilogram** |
| **Kg/mm$^2$** | **: Kilogram per millimetre square** |
| **Kg/cm$^2$** | **: kilogram per centimetre square** |
| **L** | **: litre** |
| **λmax** | **: Lambda maximum** |
| **mg** | **: Milligrams** |
| **Mins** | **: Minute** |
| **ml** | **: Milli litre** |
| **µl** | **: Micro litre** |
| **µg/ml** | **: micro gram per millilitre** |
| **µm** | **: micrometer** |

| | |
|---|---|
| **N** | **: Newtons** |
| **nm** | **: Nanometre** |
| **ODT** | **: Orally disintegrating tablet** |
| **PEG** | **: Poly ethylene glycol** |
| **P.G** | **: Propylene glycol** |
| **PVA** | **: Poly Vinyl Alcohol** |
| **PVP** | **: Poly vinyl pyrrolidine** |
| **Q.S** | **: quantity sufficient** |
| **RPM** | **: rotation per minute** |
| **S.D** | **: Standard deviation** |
| **Sec** | **: Second** |
| **%w/w** | **: Percentage weight by weight** |
| **$R^2$** | **: Regression coefficient** |
| **NaCMC** | **: Sodium carboxy methyl cellulose** |
| **U.S.P** | **: United States Pharmacopoeia** |
| **U.V** | **: Ultra violet** |
| **Vd** | **: Volume of distribution** |

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# INTRODUCTION

Oral route is the most preferred route for the delivery of the drugs till date as it bears various advantages over the other route of drug administration.[1] About 60% of all dosage forms available are the oral solid dosage form. The lower bioavailability, delayed onset time and dysphagia in patients turned the manufacturer to the parenterals and liquid orals. But the liquid orals (syrup, suspension, emulsion etc) have the problem of accurate dosing mainly and parenterals are painful drug delivery[2]. Oral drug delivery systems still need some advancements to be made because of their some drawbacks related to particular class of patients which includes geriatric and pediatric patients associated with many medical conditions such as hand tremors, dysphagia in case of geriatric patients, underdeveloped muscular and nervous system in infant and uncooperative patient, the problem of swallowing is common phenomenon which lead to poor patient compliance.[3] The problem of swallowing tablets was more evident in geriatric and pediatric patients, as well as travelling patients who may not have ready access to water. Fast-dissolving dosage technologies are important for patients who have difficulty taking traditional oral dosage forms, as well as those who want the convenience of any-time dosage when water is not available.[4] The oral administrations of many drugs show first-pass metabolism which results in to lower bioavailability. Limitation associated with parenteral delivery and poor oral bioavailability needs alternative route for delivery of such drugs.[5]

So, fast-dissolving drug-delivery systems came into existence in the late 1970's as an alternative to traditional oral solid-dosage forms. These systems consist of the solid dosage forms that disintegrate and dissolve quickly in the oral cavity without the administration of water.[6]

Administration of the drug via the mucosal layer is a novel method that can render treatment more effective and safe, not only for the topical diseases but for systemic ones. These unique dosage forms, which can be applied on a wet tissue, are formulated by utilizing the adhesive properties of some water soluble polymers.[7,8] The distinct problems that are present in the sublingual route like the drug dissolving in the saliva and unpleasant taste, local anaesthetic effect and odour felt by the patient are absent in the buccal mucoadhesive route.[9]

**Advantages of buccal drug delivery systems [10]**

- Excellent accessibility
- Results in rapid absorption and onset of action.
- Results in higher bioavailability thus requiring lower doses of drug
- Direct access to the systemic circulation through the internal jugular vein bypasses drugs from the hepatic first pass metabolism leading to high bioavailability
- Low enzymatic activity
- Suitability for drugs or excipients that mildly and reversibly damages or irritates the mucosa
- Painless administration
- Easy drug withdrawal
- Offers lower risk of overdose
- Facility to include permeation enhancer/enzyme inhibitor or pH modifier in the formulation
- Versatility in designing as multidirectional or unidirectional release systems for local or systemic actions etc.

**Limitations of buccal drug delivery systems [11]**

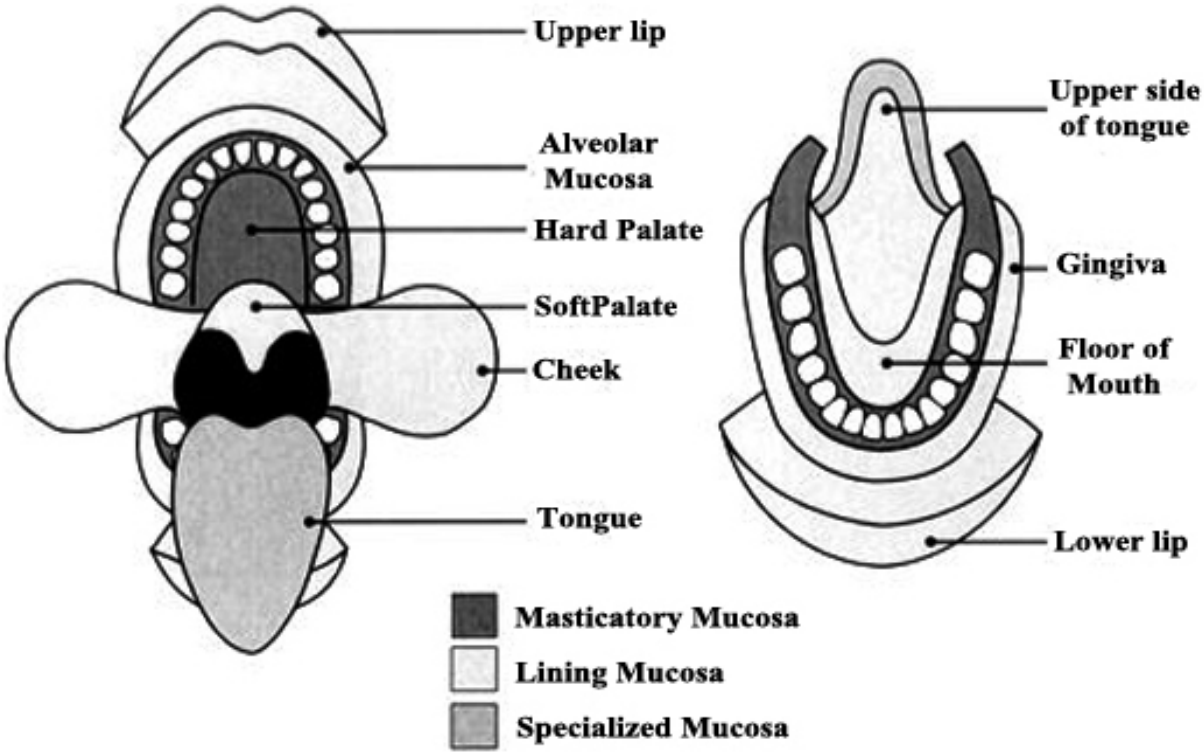
- Drugs, which irritate the oral mucosa, have a bitter or unpleasant taste, odour; cannot be administered by this route.
- Drugs, which are unstable at buccal pH cannot be administered by this route.
- Only drugs with small dose requirements can be administered.
- Drugs may be swallowed with saliva and thus the advantages of buccal route lost
- Only those drugs, which are absorbed by passive diffusion, can be administered by this route.
- Eating and drinking may become restricted.
- Swallowing of the formulation by the patient may be possible.
- Over hydration may lead to the formation of slippery surface and structural integrity of the formulation may get disrupted by the swelling and hydration of the bioadhesive polymers.

**ORAL CAVITY**

The anatomy and physiology of the oral cavity has been well reviewed and will be considered briefly here. The oral cavity consists of two regions,

- the outer oral vestibule which is bounded by the cheeks, lips, teeth and gingiva (gums) and
- the oral cavity proper which extends from the teeth and gums back to the fauces (which lead on to the pharynx) with the roof comprising the hard and soft palates.[12]

**Figure no: 1 Diagram of anatomic locations in the oral cavity**




The tongue projects from the floor of the cavity. The buccal mucosa refers to the membrane lining the inside of the cheek.[12]

Within the oral mucosal cavity, delivery of drugs is classified into three categories, [13]

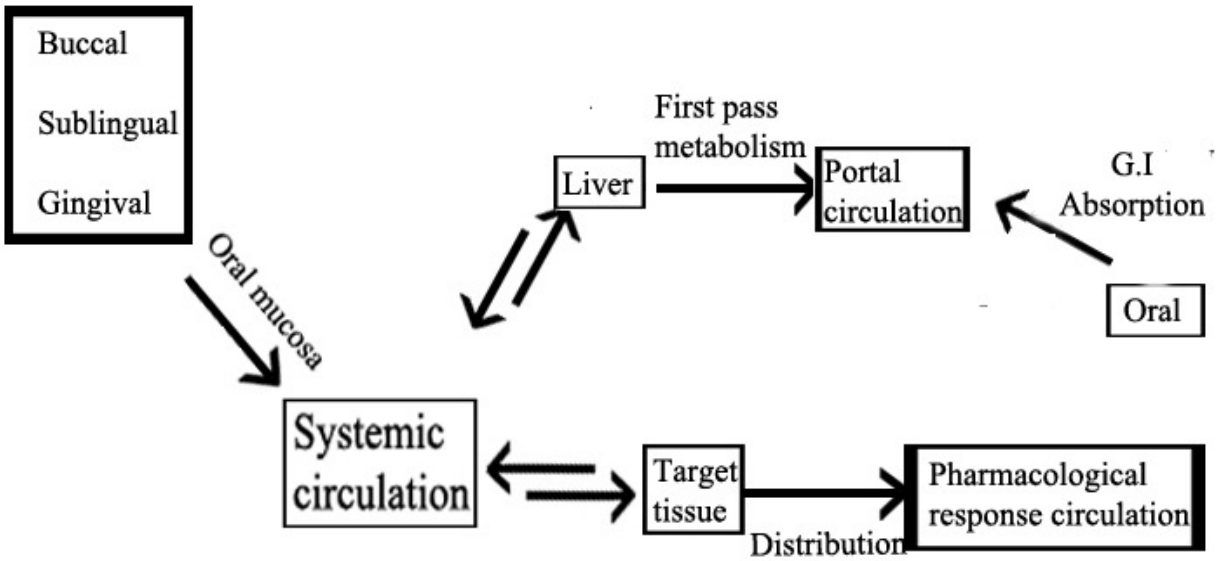
**1) Sublingual delivery**: This is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth

**2) Buccal delivery**: This is drug administration through the mucosal membranes lining the cheeks (buccal mucosa) i.e. when a dosage form is placed in the outer vestibule between the buccal mucosa and gingiva.

**3) Local delivery**: This is drug delivery into the oral cavity

Drugs can be absorbed from the oral cavity through the oral mucosa either sublingually or buccaly. In general, rapid absorption from these routes is observed. The oral cavity is lined by relatively thick, dense and multilayered mucus membrane with high vasculature. Drugs entering into the membrane can find access to the systemic circulation via network of capillaries and arteries. The arterial flow is supplied by branches of external carotid artery. The venous back flow goes via capillaries and the venous network is finally taken up by the jugular vein. The equally developed lymphatic drainage runs more or less parallel to the venous vascularisation and ends up in the jugular ducts. Thus, the buccal and sublingual routes can be used to by-pass hepatic first-pass elimination.[14]

**Figure no: 2 Schematic diagram of drug absorption via oral route**




Drug absorption into the mucosa is mainly via passive diffusion into the lipoidal membrane. Compounds with favourable o/w partition coefficient are readily absorbed through oral mucosa. Compounds administered by either the buccal or sublingual routes include steroids, barbiturates, papain, trypsin and streptokinase, streptoclornase. Besides transcellular diffusion, there is evidence that water soluble molecules with molecular volume

less than 80cm3/mol cross primarily through membrane pores and large water soluble molecules pass paracellularly regardless of polarity, large molecules are poorly absorbed.[14]

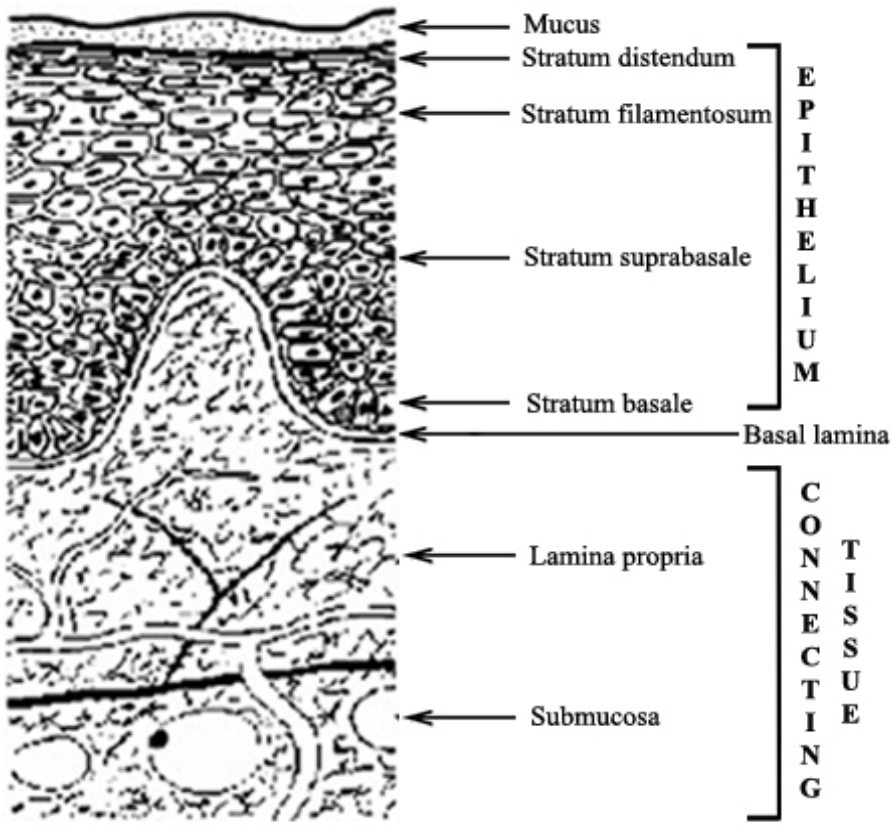
Oral mucosa is a lining tissue that serves to protect the underlying tissues. It consists of two parts; the underlying epithelium and the connective tissues. The epithelium of the oral cavity is in principle similar to that of the skin, with interesting differences regarding keratinization and the protective and lubricant mucus spread across its surface. The total area is about 100 cm; the buccal part with about one third of the total surface is lined with an epithelium of about 0.5 mm thickness and the rest by one of 0.25 mm thickness. The multi-layered structure of the oral mucosa is formed by cell divisions which occur mainly in the basal layer. The mucosa of the oral cavity can be divided into three functional zones. [14]

**Structural Features of Oral Mucosa**

**Structure:** The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer. The epithelium is similar to stratified squamous epithelia found in the rest of the body in that it has a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium.[13]

The turnover time for the buccal epithelium has been estimated at 5-6 days and this is probably representative of the oral mucosa as a whole. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800 μm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue and the gingivae measure at about 100-200 μm. The composition of the epithelium also varies depending on the site in the oral cavity. The mucosae of the gingivae and hard palate are keratinized similar to the epidermis which containe ceramides and acylceramides (neutral lipids) which have been associated with the barrier function. The mucosa of the soft palate, the sublingual and the buccal regions, however, are not keratinized which are relatively impermeable to water and only have small amounts of ceramide.[14] They also contain small amounts of neutral but polar lipids, mainly cholesterol sulfate and glucosyl ceramides. The nonkeratinized epithelia have been found to be considerably more permeable to water than keratinized epithelia.[15]

**Figure no: 3 Structure of Oral mucosal membrane**




**Permeability:** The oral mucosa in general is intermediate between that of the epidermis and intestinal mucosa in terms of permeability. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin.[16] There are considerable differences in permeability between different regions of the oral cavity because of the diverse structures and functions of the different oral mucosa.[14] For the better absorption of APIs in oral region permeation enhancer play important role. So if we want to absorb the drug mostly in mouth as drug released from formulation then there is the need of permeation enhancer.

**Composition of Oromucosal Region**

**Oromucosal Cells:** Are made up of proteins and carbohydrates. It is adhesive in nature and acts as a lubricant, allowing cells to move relative to one another with less friction.[19] The mucus is also believed to play a role in bioadhesion of mucoadhesive drug delivery systems.[17] In other part of body mucus is synthesized and secreted by the goblet cells, however in the oral mucosa, mucus is secreted by the major and minor salivary glands as part of saliva. Up to 70% of the total mucin found in saliva is contributed by the minor salivary glands.[18,19]

**Characteristics of mucus [31]**

The composition of mucus varies widely depending on animal species, anatomical location and whether the tissue is in a normal or pathological state. Native mucin, in addition to mucus, also contains water, electrolytes, sloughed epithelial cells, enzymes, bacteria, bacterial by products and other debris. The glycoprotein fraction of the mucus imparts a viscous gel like characteristic to mucus due to its water retention capacity. Mucus is a glycoprotein, chemically consisting of a large peptide backbone with pendant oligosaccharide side chains whose terminal end is either sialic or sulfonic acid or L–fructose. The oligosaccharide chains are covalently linked to the hydroxy amino acids, serine and threonine, along the polypeptide backbone. About 25% of the polypeptide backbone is without sugars, the so-called 'naked' protein region, which is especially prone to enzymatic cleavage. The remaining 75% of the backbone is heavily glycosylated. The terminal sialic groups have a pKa value of 2.6 so that the mucin molecule should be viewed as a polyelectrolyte under neutral or acid condition. At physiological pH the mucin network may carry a significant negative charge because of the presence of sialic acid and sulfate, residues and this high charge density plays an important role in mucoadhesion.

**Role of Mucus[32]**

- Cell-cell adhesion
- Lubrication
- Bioadhesion of mucoadhesive drug delivery systems

Another feature of the oral cavity is the presence of saliva (digestive secretion) produced by three pairs of salivary glands (parotid, submandibular and sublingual glands). Saliva is mostly water with 1% organic and inorganic materials. The digestive enzyme present in saliva is salivary amylase, which breaks down starch molecules to shorter chains of glucose molecules. Saliva is made from blood plasma and thus contains many of the chemicals that are found in plasma. The major determinant of the salivary composition is the flow rate which in turn depends upon three factors: the time of day, the type of stimulus and the degree of stimulation.[17,19] The salivary pH ranges from 5.5 to 7. The daily salivary volume is between 0.5 to 2 liters and it is this amount of fluid that is available to hydrate oral mucosal dosage forms.

**Role of Saliva [32]**

- Protective fluid for all tissues of the oral cavity.

- Continuous mineralization / demineralization of the tooth enamel.
- To hydrate oral mucosal dosage forms.

A main reason behind the selection of hydrophilic polymeric matrices as vehicles for oral transmucosal drug delivery systems is this water rich environment of the oral cavity.

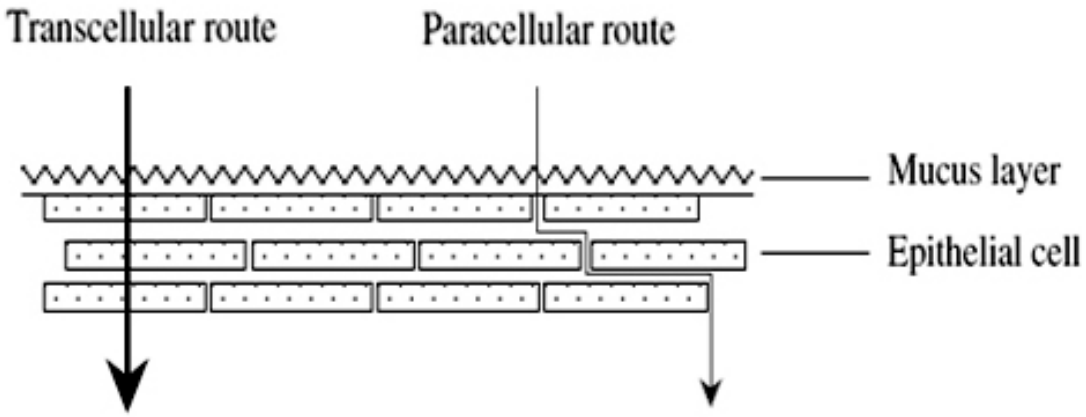
**DRUG ABSORPTION PATHWAYS**

The drug transport mechanism through the buccal mucosa involves two major routes:

I) Transcellular route (intracellular)

2) Para cellular route (intercellular)

**Figure no: 4 Drug absorption pathways through the buccal mucosa**




Studies with microscopically visible tracers such as small proteins and dextrans suggest that the major pathway across stratified epithelium of large molecules is via the intercellular spaces where there is a barrier to penetration as a result of modifications of the intercellular substance in the superficial layers. It is generally recognized that the lipid matrix of the extracellular space plays an important role in the barrier function of the paracellular pathway, especially when the compounds such as peptides are hydrophilic and have a high molecular weight.[20] The absorption potential of the buccal mucosa is influenced by the lipid solubility and molecular weight of the diffusant. Absorption of some drugs via the buccal mucosa is found to increase when carrier pH is lowered and decreased by an increase in pH.[21] In general, for peptide drugs, permeation across the buccal epithelium is thought to be through paracellular route by passive diffusion. Recently, it was reported that the drugs having a monocarboxylic acid residue could be delivered into systemic circulation from the oral mucosa via its carrier.[22] The permeability of oral mucosa and the efficacy of penetration enhancers have been investigated in numerous in vitro and in vivo models. Various kinds of

diffusion cells, including continuous flow perfusion chambers, Ussing chambers, Franz diffusion cells and Grass–Sweetana, have been used to determine the permeability of oral mucosa.[23] Cultured epithelial cell lines have also been developed as an in vitro model to study drug the transport and metabolism at biological barriers as well as to elucidate the possible mechanisms of action of penetration enhancers.[24] Recently, TR146 cell culture model was suggested as a valuable in vitro model of human buccal mucosa for permeability and metabolism studies with enzymatically labile drugs, such as leu-enkefalin, intended for buccal drug delivery.

## FACTORS AFFECTING DRUG ABSORPTION

Besides the biochemical characteristics of the buccal and sublingual membranes, which are responsible for the barrier function and permeability, various factors of the drug molecule influence the extent of permeation through the membranes. The lipid solubility, degree of ionization, pKa of the drug, pH of the drug solution, presence of saliva and the membrane characteristics, molecular weight and size of the drug, various physicochemical properties of the formulation, and the presence or absence of permeation enhancers, all affect the absorption and the permeation of drugs through the oral mucosa.[25]

### Degree of Ionization, pH, and Lipid Solubility

The permeability of unionizable compounds is a function of their lipid solubilities, determined by their oil–water partition coefficients demonstrated this dependence of water permeability on the lipid contents of keratinized and non-keratinized epithelia. The lipids present however contribute to this effect more in the keratinized epithelia (more total lipid content, non-polar lipids, ceramides) than in the non-keratinized epithelia where permeability seems to be related to the amount of glycosylceramides present. The absorption of drug through a membrane depends upon its lipophilicity, which in turndepends on its degree of ionization and partition coefficient. The higher the unionized fraction of a drug, the greater is its lipid solubility. [25]

The degree of ionization in turn depends on the pH of the mucosal membrane and the pKa of the drug. Beckett and Triggs studied the buccal absorption of basic drugs over a range of concentration, pH, and the use of different drug combinations (alone and mixtures). The resultant pH–absorption curves showed that the percentage of drug absorbed increased as the concentration of drug in the unionized form increased. Also, the shapes of the absorption curves were a function of the pKa values and the lipidsolubility of their unionized form. A

study conducted with fentanyl, a weak base with a pKa of 8.2, further demonstrated the relationship between the pH and the absorption across oral mucosa. When the pH of the delivery solution was increased, more of the drug was present in the unionized form, with the drug being 2.45% unionized at pH 6.6, 9.1% unionized at pH 7.2, and 24% unionized at pH 7.7. The fentanyl solutions with a pH range of 6.6 to 7.7 showed a three- to fivefold increase in peak plasma concentration, bioavailability, and permeability coefficients. Similar studies conducted with sublingual administration of opioids such as buprenorphine, methadone, and fentanyl showed increased absorption with increase in pH, where the drug was predominantly present in the unionized form. [25]

However, absorption of other opioids such as levorphanol, hydromorphone, oxycodone, and heroin under similar conditions did not improve. These drugs, however, were more hydrophilic as compared to the earlier set of opioids. Thus, pH modifiers can be used to adjust the pH of the saliva prior to drug administration to increase the absorption of such drugs through the mucosal membranes. However, the nature of the buccal and sublingual membrane complicates the above condition since the pH may vary depending on the area of the membrane and also on the layer of the membrane that is considered. The pH of the mucosal surface may be different from that of buccal and sublingual surfaces throughout the length of the permeation pathway. Thus, the drug in its unionized form may be well absorbed from the surface of the membrane, but the pH in the deeper layers of the membrane may change the ionization and thus the absorption. Also, the extent of ionization of a drug reflects the partitioning into the membrane, but may not reflect the permeation through the lipid layers of the mucosa. [25]

In the buccal absorption study of propranolol followed by repeated rinsing of the mouth with buffer solutions and recovered much of this drug in the rinsing. In addition, the effect of lipophilicity, pH, and pKa will depend on the transport pathway used by the drug. Studies conducted with busiprone showed that the unionized form of the drug used the more lipophilic pathway, the transcellular route, but an increase in the pH increased the ionization of the drug and subsequently the absorption. It was concluded that this transport of the ionized form of the drug was through the more hydrophilic paracellular pathway. Therefore, at neutral pH the preferred transcellular, but at acidic pH, the ionized species of the drug also contributed to the absorption across the membrane.

**Molecular Size and Weight**

The permeability of a molecule through the mucosa is also related to its molecular size and weight, especially for hydrophilic substances. Molecules that are smaller in size

appear to traverse the mucosa rapidly. The smaller hydrophilic molecules are thought to pass through the membrane pores, and larger molecules pass extracellularly. Increases in molar volume to greater than 80 mL/mol produced a sharp decrease in permeability. Due to the advantages offered by the buccal and the sublingual route, delivery of various proteins and peptides through this route has been investigated. It is difficult for the peptide molecules with high molecular weights to make passage through the mucosal membrane. Also, peptides are usually hydrophilic in nature. Thus, they would be traversing the membrane by the paracellular route, between cells through the aqueous regions next to the intercellular lipids. In addition, peptides often have charges associated with their molecules, and thus their absorption would depend on the amount of charge associated with the peptide, pH of the formulation and the membrane, and their isoelectric point.[25]

**Permeability Coefficient**

To compare the permeation of various drugs, a standard equation calculating the permeability coefficient can be used. One form of this equation is,

$$P = \frac{\%\ \text{permeated} \times Vd}{A \times t \times 100}$$

Where P is the permeability coefficient (cm/s), A is the surface area for permeation, Vd is the volume of donor compartment, and t is the time. This equation assumes that the concentration gradient of the drug passing through the membrane remains constant with time, as long as the percent of drug absorbed is small.

**Formulation Factor**

The permeation of drugs across mucosal membranes also depends to an extent on the formulation factors. These will determine the amount and rate of drug released from the formulation, its solubility in saliva, and thus the concentration of drug in the tissues. In addition, the formulation can also influence the time the drug remains in contact with the mucosal membrane. After release from the formulation, the drug dissolves in the surrounding saliva, and then partitions into the membrane, thus the flux of drug permeation through the oral mucosa will depend on the concentration of the drug present in the saliva. This concentration can be manipulated by changing the amount of drug in the formulation, its release rate, and its solubility in the saliva. The first two factors vary in different types of formulations, and the last can be influenced by changing the properties of the saliva that affect the solubility (e.g., pH).

## BIOADHESION

Bioadhesion is an interfacial phenomena in which two materials at least one of which is biological are held together by means of interfacial forces. The attachment could be between an artificial material and biological membrane. In the case of polymer attached to the mucin layer of mucosal tissue, the term mucoadhesion employed.

### Mechanism of Bioadhesion

For bioadhesion to occur, a succession of phenomenon whose role depends on the nature of the bioadhesive is required.[7]

- The first stage involves an intimate contact between a bioadhesive and a membrane, either from a good wetting of the bioadhesive surface or from the swelling of the bioadhesive.
- In the second stage, after contact is established, penetration of the bioadhesive into the tissue surface of inter penetration of the chains of the bioadhesive with those of the mucus, takes place low chemical bonds can then settle.[7]

On a molecular level mucoadhesion can be explained based on molecular interaction. The interactions between two molecules are composed of attraction and repulsion. Attractive interactions arise from Vanderwaal forces, electrostatic attraction, hydrogen bonding and hydrophobic interaction. Repulsive interactions occur based on electrostatic and stearic repulsion. [7]

### Theories of Mucoadhesion [27]

- **The electronic theory** proposes transfer of electrons amongst the surfaces resulting in the formation of an electrical double layer thereby giving rise to attractive forces.
- **The wetting theory** postulates that if the contact angle of liquids on the substrate surface is lower, then there is a greater affinity for the liquid to the substrate surface.
- **The adsorption theory** proposes the presence of intermolecular forces, viz. hydrogen bonding and VanderWaal's forces, for the adhesive interaction amongst the substrate surfaces.
- **The diffusion theory** assumes the diffusion of the polymer chains, present on the substrate surfaces, across the adhesive interface thereby forming a networked structure.

- **The mechanical theory** explains the diffusion of the liquid adhesives into the micro-cracks and irregularities present on the substrate surface thereby forming an interlocked structure which gives rise to adhesion.
- **The cohesive theory** proposes that the phenomena of bioadhesion are mainly due to the intermolecular interactions amongst like-molecules.[27]

**Methods Used To Study Bioadhesion**

Several test methods have been reported for studying bioadhesion. These tests are necessary not only to screen a large number of candidates to mucoadhesives, but also to study their mechanisms. These tests are also important during the design and development of a bioadhesive controlled release system as they ensure compatibility, physical and mechanical liability, surface analysis and bioadhesive bond strength.[8]

The test methods can broadly be classified into two major categories.

I). *In- vitro*/ ex- *vivo* methods

II). *In vivo* methods

**I): *In – vitro* / ex - *vivo* methods:** Most *in- vitro* methods are based on the measurement of either tensile or shear stress, Bioadhesiveness determined by measurement of stress tends to be subjective, since there is no standard test method established for bioadhesion.

**1. Methods based on measurement of tensile strength:**

These methods usually measures the force required to break the adhesive bond between a model membrane and the test polymers. The instruments usually employed are Modified balance or tensile tester. A typical example is the method employed by Robinson and his group. In this method, the force required to separate the bioadhesive sample from freshly excised rabbit stomach tissue was determined using a modified tensiometer.

**2. Methods based on measurement of shear strength:**

The shear strength measures the force that causes the bioadhesive to slide with respect to the mucous layer in a direction parallel to their plane of contact. An example is Wilthemy plate method reported by Smart et al. The method uses a glass plate suspended from a microbalance which is dipped in a temperature controlled mucous sample and the force

required to pull the plate out of the solution is determined under constant experimental conditions.

**3. Other *in- vitro* methods:**

A number of other methods including adhesion weight method, fluorescent probe method, flow channel method, mechanical spectroscopic method, falling liquid film method, colloidal gold staining method, thumb test, adhesion number and electrical conductance method.

**II. *In- vivo* methods**

Various methods for *in-vivo* evaluation of both placebo and drug containing mucoahesive devices in healthy human volunteers have been reported in the literature. Rathbone et al" have discussed several methods to study the rate and extent of drug loss from human oral mucosa.[8]

**FACTORS AFFECTING MUCOADHESION[29]**

The adhesive bond between a bioadhesive system and mucin gel can be investigated in term of contribution of the following factors

**I. Polymer related factors**

- **Concentration of active polymer**

The polymer concentration was dependable on the physical state (solid/liquid) of the mucoadhesive drug delivery systems and an increase in the polymer concentration increases the mucoadhesive strength in solid dosage form while an optimum concentration in liquid system was required for best mucoadhesion. In liquid systems, beyond the threshold concentration the coiled molecules become separated from the medium limiting availability of chain for interpenetration thereby dropping adhesive strength significantly.

- **Hydrophilicity**

Numerous hydrophilic functional groups like hydroxyl and carboxyl, of the bioadhesive polymers; aids swelling in aqueous media leading to maximal exposure of potential anchor sites and subsequent hydrogen bonding with the substrate.

- **Spatial conformation**

Along with molecular weight or chain length; spatial or helical conformation the polymer chain, that may shield many adhesively active groups responsible for adhesion in comparison to that with linear conformation; plays important role in the mucoadhesion.

- **Molecular weight**

Low-molecular-weight of polymer favours interpenetration of molecules while higher molecular weight favours entanglements. Type of the mucoadhesive polymer and the tissue determines the optimum molecular weight for maximum mucoadhesion. The bioadhesive/mucoadhesive force increases with an increase in the molecular weight of polymer up to 100,000 and beyond this level there was not much effect.

- **Flexibility of polymer chains associated with cross-linking and swelling**

Flexibility was important for interpenetration and entanglement. As the cross linking density of water-soluble polymer increases; the mobility of the individual polymer chain decreases; and the effective length of the chain that can penetrate into mucous layer decreases even further consequently mucoadhesive strength decreases. Too great degree of swelling results in slippy mucilage and can be easily removed from the substrate. Polymers grafting onto the preformed network; and the inclusion of adhesion promoters in the formulation (free polymer); enhances mucoadhesion of crosslinked polymers.

**II. Environment related factors**

- **pH of polymer-substrate interface**

The hydrogen ion concentration can influence charge on the surface of mucous, associated with dissociation of functional groups on the carbohydrate moiety and amino acids of polypeptide backbone; as well as certain ionisable mucoadhesive polymers. Studies depicted that the pH of the medium was important for the degree of hydration of cross linked polyacrylic acid that consistently increases from pH 4 through pH 7 and then decrease as alkalinity and ionic strength increases. Polycarbophil shows maximum adhesive strength at pH 3 that gradually decreases with an increase in pH up to 5 and above pH 5 it does not show any mucoadhesive property. Protonated carboxyl groups, rather than the ionised carboxyl

groups, react with mucin molecules, apparently by the concurrent formation of numerous hydrogen bonds.

- **Initial contact time**

Initial contact time between the mucoadhesive and the mucus layer determines the extent of swelling and the interpenetration of polymer chains. An increase in initial contact time increases mucoadhesive strength.

- **Applied strength**

The pressure initially applied on the solid bioadhesive system to apply on mucosal tissue can affect the depth of interpenetration, and the adhesive strength increases with an increase in the applied strength or with the density up to an optimum value.

- **Secretion of the model substrate surface**

Studies on the variability of biological substrate should be confirmed by examining properties like permeability, electro physiology, or histology etc., before and after performing the *in vitro* tests using tissues for the better *in vitro*/*in vivo* correlation.

- **Swelling**

Bioadhesion decreases with too great swelling that depends on the presence of water and on the polymer concentration. In order to achieve sufficient bioadhesion of the system, too early swelling must not occur.

**III. Physiological variables**

- **Mucin turnover**

The natural turnover of mucin molecules from the mucous layer not only limits the residence time of the mucoadhesive on the mucous layer but also released out soluble mucin molecules, insubstantial amount, interacts with mucoadhesives before they have a chance to interact with mucous layer. An increase in mucin turnover decrease mucoadhesion.

- **Disease state**

In diseased conditions; like common colds, gastric ulcers, ulcerative colitis, cystic fibrosis, bacterial and fungal infections of the female reproductive tract, and inflammatory

conditions of the eye; the physicochemical properties of the mucous changes. The mucoadhesive property needs to be evaluated, if mucoadhesives are intended to be used in the diseased state.

## BUCCAL ADHESIVE DOSAGE FORMS

Several buccal adhesive delivery devices were developed at the laboratory scale by many researchers either for local or systemic actions and can be broadly classified in to solid buccal adhesive dosage forms, semi-solid buccal adhesive dosage forms and liquid buccal adhesive dosage forms. Some commercially available buccal adhesive formulations are listed in table no.1.

### ❖ Solid buccal adhesive formulations

Solid buccal adhesive formulations achieve bioadhesion via dehydration of the local mucosal surface. They include tablets, micro particles, wafers, lozenges etc.

#### Tablets

Buccal adhesive tablets that are placed directly onto the mucosal surface for local or systemic drug delivery have been demonstrated to be excellent bioadhesive formulations. Two types of tablets i.e. monolithic and double-layered matrix tablets have been investigated for buccal delivery of drugs. Monolithic tablets consist of a mixture that contains drug and swelling bioadhesive/sustained release polymer. These tablets exhibit a bidirectional release. They can be coated on the outer or on all sides but one face with water impermeable hydrophobic substances to allow a unidirectional drug release for systemic delivery.

Double layered tablets comprise an inner layer based on a bioadhesive polymer and an outer non-bioadhesive layer containing the drug for a bi-directional release but mainly a local action. In the case of systemic action, the drug is loaded into the inner bioadhesive layer whereas the outer layer is inert and acts as a protective layer. Alternatively, the drug is loaded into a controlled release layer and diffuses towards the absorbing mucosa through the bioadhesive layer, whereas a water impermeable layer assures the mono-directional release.

#### Microparticles

Bioadhesive microparticles offer the same advantages as tablets but their physical properties enable them to make intimate contact with a lager mucosal surface area. In addition, they can also be delivered to less accessible sites including the GI tract and upper nasal cavity.[19]

**Wafers**

A conceptually novel periodontal drug delivery system that is intended for the treatment of microbial infections associated with peridontitis was described elsewhere. . The delivery system is a composite wafer with surface layers possessing adhesive properties, while the bulk layer consistsof antimicrobial agents, biodegradable polymers and matrix polymers.[19]

**Lozenges**

Bioadhesive lozenges may be used for the delivery of drugs that act topically within the mouth including antimicrobials, corticosteroids, local anaesthetics, antibiotics and antifungals.[19]

- **Semi-solid dosage forms**

**Gels**

Gel forming bioadhesive polymers include crosslinked polyacrylic acid that has been used to adhere to mucosal surfaces for extended periods of time and provide controlled release of drugs.

**Patches / films.**

Flexible films may be used to deliver drugs directly to a mucosal membrane. They also offer advantages over creams and ointments in that they provide a measured dose of drug to the site. Buccal adhesive films are already in use commercially.[19]

Patch systems are the formulations that have received the greatest attention for buccal delivery of drugs. They present a greater patient compliance compared with tablets owing to their physical flexibility that causes only minor discomfort to the patient. Patches are laminated and generally consist of an impermeable backing layer and a drug-containing layer that has mucoadhesive properties and from which the drug is released in a controlled manner.[19]

❖ **Liquid dosage forms**

Viscous liquids may be used to coat buccal surface either as protectants or as drug vehicles for delivery to the mucosal surface. A novel liquid aerosol formulation (Oralin, Generex Biotechnology) has been recently developed, and it is now in clinical phase II trials.This system allows precise insulin dose delivery via a metered dose inhaler in the form of fine aerosolized droplets directed into the mouth.[19]

**Table no: 1 Commercially available buccal adhesive formulations.**

| Brand Name | Bioadhesive Polymer | Company | Dosage forms |
|---|---|---|---|
| Buccastem | PVP, Xanthum gum, Locust bean gum | Rickitt Benckiser | Tablet |
| Suscard | HPMC | Forest | Tablet |
| Gaviscon Liquid | Sodium alginate | Rickitt Benckiser | Oral liquid |
| Orabase | Pectin,Gelatin | Orabase | Pectin,gelatin |
| Corcodyl gel | HPMC | Glaxosmithkline | Oromucosal Gel |
| Corlan pellets | Acacia | Celltech | Oromucosal Pellets |
| Fentanyl Oralet tm | | Lexicomp | Lozenge |
| Miconaczole Lauriad | | Bioalliance | Tablet |
| Emezine TM | | BDSI's | |

# LITERATURE REVIEW

**Research articles for Promethazine HCl**

1. **Roger Dale Graben (2006)** developed a simple, inexpensive method of manufacturing ODTs. Promethazine HCL was chosen as a model drug. Taste-masking studies were conducted by directly mixing Promethazine with a number of substances. A 1:1 Magnesium Stearate: Promethazine mixture V-blended for one hour was effective in masking the bitter taste of this drug. Rapid disintegration was achieved with Mannitol and Dextrates even with large amount of Magnesium Stearate. Tablets were produced with various combinations of disintegrants with various mechanisms of action. Flavor and sweetener trials were conducted. A combination of Promethazine, Magnesium Stearate, Dextrates, and disintegrants was found to yield robust tablets (Friability < 1.0% with 0 broken at 25 rpm, for 4 minutes) with rapid disintegration (in vitro < 21 seconds, in vivo < one minute). Although the bitter taste was masked, the unpleasant anesthetic effect was not completely eliminated. The addition of 3.0% Menthol with sublimation post-tableting resulted in a visibly more porous tablet with shorter in vitro and in vivo disintegration times. These tablets yielded a pleasant taste without numbing. These tablets met compendial Dissolution and Content Uniformity requirements for conventional Promethazine tablets. These trials indicate an acceptable ODT can be produced using conventional excipients and simple blending followed by direct compression. In the case of Promethazine, the addition of Menthol followed by post-tableting sublimation was required to overcome the unpleasant numbing effect. While the sublimation of Menthol is an additional step, it only required a common laboratory oven and 48 hours.[40]
2. **Sachin et al (2009)** 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 super disintegrants 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.[39]

3. **Ganesh kumar Gudas et al (2010)** prepared fast dissolving tablets of Promethazine.HCl 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.[36]

4. **Sandeep (2011)** made formulations of rapid dissolving tablets of Promethazine HCl by direct compression method with the aid of superdisintegrant addition. Nine formulations were developed using three different superdisintegrants in varying concentrations. All the formulated tablets were subjected for pre and post-compression evaluation parameters. A comparison of *in vitro* drug release of optimized formulation was compared with marketed product (Phenargan). Among the nine formulations, the formulation containing 5% crospovidone showed highest drug release of 98.43% than other formulations. A comparison of *in vitro* drug release was made with marketed product of Promethazine HCl (Phenargan) which shows 93% drug release in 1 hour. That formulated tablets of Promethazine HCl containing crospovidone are better and effective than conventional tablets to meet patient compliance and give fast relief from vomiting and emesis. [34]

5. **Rao et al (2012)** developed mucoadhesive patches for transbuccal delivery of Promethazine hydrochloride to overcome the extensive first-pass metabolism by solvent casting technique with Hydroxy ethyl cellulose and Hydroxylpropyl methyl cellulose as mucoadhesive polymers and propylene glycol as the plasticizer. They evaluated their physicochemical characteristics, in vitro drug release, moisture absorption, surface pH, mechanical properties, in vitro bioadhesion, in vivo residence time, and ex vivo drug permeation through porcine buccal membranes and stability studies. Ex vivo drug permeation through porcine buccal membrane was 83.7% in 6 hours with flux 0.19 mg h–1cm–2. The optimized formulation showed maximum drug release (98%) in 6 hours in

the Higuchi model release profile. In vivo mucoadhesive behaviour was studied in healthy human volunteers and subjective parameters were evaluated. The stability studies showed no significant changes in drug content, in vitro release and ex vivo permeation after 6 months.[33]

**Research works on buccal patches**

6. **Chandra Sekhar et al (2008)** developed and evaluated mucoadhesive buccal patches of prochlorperazine (PCPZ). Permeation of PCPZ was calculated *in vitro* using porcine buccal membrane. Buccal formulations were developed by solvent casting technique using hydroxyl propylmethyl cellulose (HPMC) as mucoadhesive polymer. The patches were evaluated for *in vitro* release, moisture absorption and mechanical properties. The optimized formulation, based on in vitro release and moisture absorption studies, was subjected for bioadhesion studies using porcine buccal membrane. *In vitro* flux of PCPZ was calculated to be 2.14±0.01µg. H-1.cm-2 and buccal absorption was also demonstrated *in-vivo* in human volunteers. *In vitro* drug release and moisture absorbed was governed by HPMC content. Increasing concentration of HPMC delayed the drug release. All the formulations followed Zero order release kinetics whereas the release pattern was non-Fickian. The mechanical properties, tensile strength (10.28±2.27 kg mm-2 for formulation P3) and elongation at break reveal that the formulation to be strong but not brittle. The peak detachment force and work of adhesion for formulation P3 were 0.68±0.15 N and 0.14±0.08 mJ, respectively. The results indicate that suitable bioadhesive buccal patches of PCPZ with desired permeability and suitable mechanical properties could be prepared.[43]

7. **Alagusundaram et al (2009)** prepared mucoadhesive buccal films of ranitidine by solvent casting technique using polymers like hydroxy propyl methyl cellulose-15 cps and poly vinyl pyrrolidone. The formulated films were evaluated for their physiochemical parameters like surface pH, percentage moisture absorption, percentage moisture loss, swelling percentage, water vapour transmission rate, thickness, weight of the films, folding endurance and drug content. *In vitro* release studies were performed with pH 6.8 phosphate buffer solution. Good results were obtained both in physico chemical characteristics and *in vitro* studies. The films exhibited controlled release more than 10 h. The *in vitro* release data were fit to different equations and kinetic models to explain release profiles. The kinetic models used were zero order, Higuchi's and Peppa's. The best mucoadhesive performance and matrix controlled release was exhibited by the

formulation R5 (2 % HPMC and 1 % PVP). The correlation coefficient value (r) indicates the kinetic of drug release was zero order. The formulation was found to be right and suitable candidate for the formulation of ranitidine buccal film for therapeutic use.[46]

8. **Biswajit Basu et al (2010)** prepared buccal mucoadhesive patches for oral mucosal delivery of Pimozide an antipsychotic agent, which is having rapid absorption and less bioavailability due to firstpass metabolism. Different combinations of polymers HPMC (47cPs, 15cPs), PVA, Carbopl-934 and PVP were used with glycerine as plasticizer. In vitro release studies of the patches showed 55.32% to 97.49% drug release in 60min. and in vivo absorption studies for all patches ranged from 47.96% to 83.42% in 60min. in human volunteers. Also in vivo studies in rabbits showed 85.97% of drug absorption from HPMC 15cPs patch in 60min. Good correlation among in vitro release and in vivo absorption of pimozide was observed. [37]
9. **Ananta Choudhury et al (2010)** designed a sustained release film formulation of Ciprofloxacin hydrochloride for the treatment of periodontal diseases and investigated different experimental parameters to conclude in details about its different characteristics. Films were formulated using different concentration HPMC and polyvinyl alcohol. The prepared films were subjected to different evaluation like determination of weight, thickness, surface pH, folding endurance, swelling index, mucoadhesion time, mucoadhesion strength, drug content, *in vitro* drug release study, *ex-vivo* release study and release kinetic behavior. From the results of evaluation it was concluded that all the prepared films having desire flexibility and mucoadhesive properties, along with that they shows good in-vitro and ex-vivo drug release performance. Drug release from the films follows desire sustained release phenomenon as needed in buccoadhesive drug delivery. [38]
10. **Marina et al (2010)** prepared mucoadhesive buccal films of losartan potassium were prepared using hydroxypropyl methyl cellulose (HPMC) and retardant polymers ethyl cellulose (EC) or eudragit RS 100. Thermal analysis by DSC of formulations shows no interaction between drug and polymers. *Ex vivo* permeation studies of losartan potassium solution through porcine buccal mucosa showed 90.2 % absorption at the end of 2 hours. The films were subjected to physical investigations such as uniformity of thickness, weight, drug content, folding endurance, tensile strength, elongation at break, surface pH and mucoadhesive strength. Films were flexible and those formulated from EC were smooth whereas those prepared from Eudragit were slightly rough in texture. The

mucoadhesive force, swelling index, tensile strength and percentage elongation at break was higher for those formulations containing higher percentage of HPMC. *In vitro* drug release studies reveal that all films exhibited sustained release in the range of 90.10 to 97.40 % for a period of 6 hours. The data was subjected to kinetic analysis which indicated non fickian diffusion for all formulations except E2. Ex vivo permeation studies through porcine buccal mucosa indicate that films containing higher percentage of the mucoadhesive polymer HPMC showed slower permeation of the drug for 6-7 hours.[48]

11. **Anuj et al (2011)** prepared Carvedilol buccal mucoadhesive patches using HPMC K15M and Carbopol 940. The patches were evaluated for their thickness, folding endurance, weight and content uniformity, swelling behaviour, mucoadhesive strength and surface pH. In vitro drug release int the range of 77.05 to 97.20% in 8hrs. Data of invitro release from patches were fed into kinetic models (Higuchi and Korsmeyer-Peppas models) to explain release profiles. The optimized formulation showed zero order release.[50]

12. **Raghavendra Rao et al (2011)** have prepared buccal films of Zolmitriptan in order to improve the bioavailability and efficacy using different mucoadhesive polymers by Solvent Casting Technique. Buccal films were characterized for number of parameters like physical appearance and surface texture, weight uniformity, thickness, folding endurance, swelling index, surface pH, drug content uniformity, *in-vitro* residence time, tensile strength, drug excipients interaction study, and *in-vitro* drug release study. All the prepared films were smooth surface and elegant texture and weighed in between 20.66 to 26.66 mg. The thickness of the films was in the range of 0.220 to 0.306 mm. Folding endurance was in the range of 265 to 295. Swelling index was in the range of 29.93 to 40.15 %. Surface pH was in the range of 6.50 to 6.83 pH. Drug content uniformity study showed uniform dispersion of the drug throughout the formulation in the range of 95.66 to 98.54 %. The *in-vitro* residence time for all the films is in between 4.36 to 8.23 hrs. The tensile strength of films is in the range of 6.233 to 4.533 Kg/cm2**.** FT-IR studies revealed that, there was no incompatibility of the drug with the excipients used. *In-vitro* drug release studies in the range of 71.22 to 96.55 in 10 hrs. Formulations like ZBF1 and ZBF3 shows highest drug release at 10th hrs 96.55%, 83.60% respectively. Release of Zolmitriptan from all films followed zero order and mechanism was diffusion rate limited. [35]

13. **Muaadh Mohamed et al (2011)** developed and characterized mucoadhesive drug delivery systems for diltiazem hydrochloride in the form of buccal films for improving bioavailability. Sodium carboxymethyl cellulose (SCMC) and hydroxypropyl cellulose (HPC) were used either alone or in combination for film fabrication. Prepared films were evaluated for various physicochemical characteristics such as weight variation, thickness, drug content uniformity, folding endurance, surface pH, and in vitro drug release. The in vitro mucoadhesive strength and permeation studies were performed using chicken pouch mucosa. Further, in vivo testing of mucoadhesion time and acceptability were performed in human subjects. Results indicated that drug release, swelling index and mucoadhesion performance were found to depend upon polymer type and proportion. The majority of the developed formulations presented suitable adhesion and the mechanism of drug release was found to be non-Fickian diffusion. Good correlation was observed between in vitro drug release and in vitro drug permeation with correlation coefficient ranged between of 0.945 to 0.980. In addition, from healthy human volunteers, bioadhesive behavior was found to be satisfactory. Drug bioavailability of a selected diltiazem hydrochloride adhesive buccal film, F26 (1% HPC and 2%SCMC) was determent and compared with that of a commercial sustained release oral tablet (Altiazem® RS) as a reference formulation. The obtained Cmax and AUC0-$\infty$ values were higher for buccal administration than oral administration and the difference was statistically significant ($p < 0.05$). The percentage relative bioavailability of diltiazem hydrochloride from the selected buccal mucoadhesive film in rabbits was found to be 165.2%.[41]

14. **Mahalaxmi et al (2011)** developed a mucoadhesive buccal film of Betamethasone sodium phosphate by solvent casting method using HPMC E5 LV and carbopol 940P as polymer, PEG 1000 as plasticizer. All the formulations were examined for film thickness, weight variation, drug content, percentage moisture loss, percentage moisture absorption, surface pH, folding endurance, tensile strength, in vitro and in vivo residence time and in vitro release. In vitro and in vivo residence time of all formulations showed above 30 min. Formulation F3 showed optimum tensile strength 7.72±0.41kg/mm$^2$, 88.59 ± 2.74% in vitro drug release at the end of 30 min and showed good stability.[49]

15. **Harshad et al (2011)** prepared Lidocaine HCl patches were prepared using $3^2$ full factorial design by solvent casting technique. Experimental work was carried out using film-forming and mucoadhesive polymer such as HPMC E-15 and

carboxymethylcellulose sodium (NaCMC) alone and successively in combination with mucoadhesive polymers. All the formulations carried drug and Propylene glycol (PG) in water as a solvent. Drug-excipient interaction study was carried out using FTIR technique. Films were evaluated for their weight, thickness, surface pH, swelling index, *in vitro* residence time, folding endurance, *in vitro* release, *in- vitro* permeation and drug content uniformity. The optimized batch showed good mucoadhesion and gave more than 80% drug release within 3hrs and gave maximum release 97%. The release kinetic best fitted to Higuchi model. From Higuchi model we can say the mechanism of drug release is diffusion controlled.[42]

16. **Rani et al (2012)** designed a new formulation Mucoadhesive buccal film of Hydralazine hydrochloride using different polymers like Hydroxy propyl methyl cellulose K4M, Carbopol 934p with different concentrations and plasticizer (poly ethylene glycol4000) by solvent casting method and it is used for treatment of hypertension in the oral cavity and for good retention property on the site. The formulated buccal film of Hydralazine Hydrochloride evaluated for weight and thickness uniformity, folding endurance, swelling index, content uniformity, *Invitro* drug release using Franz- diffusion cell, residence time and mucoadhesive strength. The films containing high concentrations of Hydroxy propyl methyl celluloseK4M shows good swelling and mechanical properties, and *invitro* drug release. Formulation containing similar ratio (1:1) of HPMC and carbopol shows high drug content uniformity and *invitro* drug release. And formulation containing higher concentrations of carbopol shows positive effect on mucoadhesive strength and residence time.[47]

17. **Mamatha et al (2012)** prepared Mucoadhesive buccal patches of Aceclofenac using different polymers like hydroxypropyl methylcellulose, Carbopol 934-P, polyvinyl alcohol, polyvinyl pyrrolidone K-30, Eudragit L-100 in various proportion and combinations by solvent casting method. The prepared patches were smooth, elegant in appearance, uniform in thickness, mass and drug content. All the formulation showed folding endurance of <100. A $3^2$ full factorial design was employed to study the effect of variable polymers like Carbopol 934-P and PVP K-30, hydroxypropyl methylcellulose, which significantly influenced characteristics like swelling index and *ex vivo* residence time of Aceclofenac buccal patches. *In vitro* drug release and *in vitro* drug permeation study showed that, from the formulation F10, the drug is released and permeated fastly. All the formulations were best fitted to Higuchi model. The stability study of selected

patches was done in natural human saliva and it was found that all the patches were stable in human saliva.[44]

18. **Vandana et al (2013)** developed a controlled release drug delivery device of anti-diabetic drug i.e., Glipizide to maintain its bioavailability over an extended period of time and to circumvent the hepatic first pass effect. To achieve this object, Drugcoat and HPMC were used as a polymer for the preparation primary and secondary layer respectively, of controlled release bilayerd buccoadhesive patches of drug. The prepared patches were evaluated for various *in vitro* and *in vivo* studies. From the study it was concluded that the developed bilayered buccoadhesive delivery system bears potential to deliver the drug in a controlled manner over an extended period of time.[45]

# SCOPE, OBJECTIVE AND PLAN OF WORK

**Scope of Work**

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.[51] Nausea, dizziness, fatigue and headache are the most common symptoms of motion sickness.[52] About 30% of people are susceptible to motion sickness.[53] A wide range of drugs have proven to be effective against nausea and vomiting like antihistamines, anticholinergics, dopamine receptor antagonists, 5–$HT_3$ receptor antagonists and gastro prokinetic agent.

Promethazine hydrochloride is the most suitable drug of choice to be used to prevent nausea associated with motion sickness.[52] It is first generation anti-histamine of phenothiazines family.[55] Promethazine hydrochloride competes with free histamine for binding at $H_1$-receptor sites in the GI tract, uterus, large blood vessels, and bronchial muscle.[56] The relief of nausea appears to be related to central anti-cholinergic actions and may implicate activity on the medullary chemoreceptor trigger zone.[54] It acts mainly as a strong antagonist of the $H_1$ receptor (antihistamine) and a moderate mACh 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.[55,57]

Promethazine HCL is highly soluble & highly permeable drug (BCS Class I). It is completely absorbed following oral administration.[54] Peak plasma concentrations have been seen after 2 to 3 hours after a dose by these routes. But its systemic bioavailability after oral doses is very low (about 25%) which is mainly due to extensive first-pass metabolism in the liver.[57]

Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectables and enterable method.[47] It is found that the absorption of the drug from oral mucosa is via passive diffusion into the lipoidal membrane.[14] Buccal absorption is more 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.[47]

Rapid onset of action is of prime importance in patients with nausea and motion sickness.[55]

Promethazine HCl is commercially available as conventional dosage forms such as tablets (12.5, 25, and 50 mg), syrup (6.25 mg/5 ml), suppositories (12.5, 25, and 50 mg), and injections (25 mg/ml and 50 mg/ml).[57]

The present study was undertaken to prepare and to evaluate the buccal patches of Promethazine Hydrochloride for the rapid and effective treatment of the motion sickness.

**Objective of the Work**

The main objectives of the present work are

- To prepare the buccal patches of the Promethazine hydrochloride with the use of film forming polymer hydroxyl propyl methyl cellulose.
- To evaluate the formulated patches for various characteristics and properties.

**PLAN OF THE WORK**

**Plan of work is outlined below:-**

I) Preformulation studies

a. Construction of standard curve of Promethazine hydrochloride by UV spectrophotometry
b. Drug excipients compatibility study.

II) Fabrication of buccal patches

a. Preparation and evaluation of drug loaded patches
    i) Preparation of drug loaded HPMC patches.
    ii) Evaluation of patches for
        a. Thickness
        b. Folding endurance
        c. Weight variation
        d. Drug Content
        e. Surface pH
        f. Swelling index
        g. Tensile strength
        h. Mucoadhesive strength
        i. *In vitro* drug release
        i. *Ex vivo* drug permeation
        k. *In vivo* compatibility.

# MATERIALS AND METHODS

## LIST OF MATERIALS USED

**Table No: 2 List of Materials**

| S.No | Chemicals and reagents | Supplier |
|---|---|---|
| 1 | Promethazine hydrochoride | Gift sample from Watson Pharma, Goa |
| 2 | Hydroxy propyl methyl cellulose K4M | Orchid Healthcare, Chennai |
| 3 | Hydroxy propyl methyl cellulose 15cps | S.D.Fine chem ltd. Mumbai |
| 4 | Glycerin | S.D.Fine chem ltd. Mumbai |
| 5 | P E G 400 | S.D.Fine chem ltd. Mumbai |
| 6 | Propylene glycol | S.D.Fine chem ltd. Mumbai |
| 7 | Potassium dihydrogen ortho-phosphate | Qualigens FineChem. Mumbai |
| 8 | Sodium hydroxide | Merk limited. Mumbai |
| 9 | Fresh Buccal mucosa of Goat | From local Slaughter House |

**LIST OF INSTRUMENT USED**

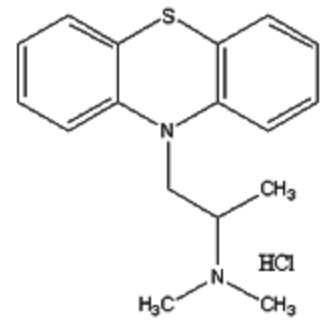
**Table No: 3 List of Instrument Used**

| Sl.no. | Name of instrument/ Equipments | Manufacture |
|---|---|---|
| 1 | Electronic balance (BL-2200H) | Shimadzu corporation |
| 2 | Dissolution apparatus USP VI | Lab India Disso-8000 |
| 3 | UV-Visible double beam spectrophotometer | Systronic 118 |
| 4 | Bath Ultrasonicator | Ultrasonic cleaner C80-4, Confident equipments |
| 5 | FTIR | Perkin Elmer, KMCP Madurai |
| 6 | Desiccator | Qualigens Fine Chem. Mumbai |
| 7 | Dial gauge | Baker Precision measuring instruments |
| 8 | Magnetic stirrer (2MLH) | Remi equipment Pvt Ltd. Mumbai |
| 9 | Microwave oven | Magic cook, Whirlpool |
| 10 | Micropipette variable | Tarson Pvt.Ltd |
| 11 | Vacuum oven | Shavani Scientific Pvt. Mumbai |
| 12 | TA.XT plus Texture analyzer | Stable Microsystems, U.K |
| 13 | Diffusion cell | Modern Scientific, Madurai |

# DRUG PROFILE

## PROMETHAZINE HYDROCHLORIDE[57-59]

**Chemical structure** :




Promethazine Hydrochloride

**Molecular Formula** : $C_{17}H_{20}N_2S$ HCl

**Molecular Weight** : 320.9g/ml

**Chemical Name** : *(RS)*-dimethyl*(2*- phenothiazin-10-ylpropyl) amine hydrochloride.

**Solubility** : very soluble in water, freely soluble in alcohol, chloroform, insoluble in ether

**Melting point** : 220-222°C

**pKa value** : 9.1

**pH** : 5.8

**Log P** : 4.7

**Dose** : 10mg to 25mg and maximum dose per day is 25mg

**Storage** : store in a cool dry place, away from direct heat and light.

**Beer's range** : 1-10µg/ml

**Properties** : Promethazine hydrochloride appears as a white to faint yellow crystalline powder that is practically odourless. Slow oxidation may occur upon prolonged exposure to air usually causing blue discolouration.

**Mechanism of Action** **:** Promethazine hydrochloride is a phenothiazine, is an $H_1$ antagonist with anticholinergic, sedative, antiemetic effects and some local anaesthetic properties. Promethazine competes with free histamine for binding at $H_1$-receptor sites in the GI tract, uterus, large blood vessels, and bronchial muscle. The relief of nausea appears to be related to central anti-cholinergic actions and may implicate activity on the medullary chemoreceptor trigger zone.

**Pharmacokinetics** **:** Following oral absorption, Promethazine HCl is completely absorbed, with absolute bioavailability of 25% due to first pass metabolism. The apparent mean elimination half-life of Promethazine HCl generally ranges from 16 to 20 hours. It is metabolized by the cytochrome P450 2D6 (CYP2D6). Following oral dosing of promethazine an average of 60% and 20% of total metabolites are recovered in the urine and feces, respectively. Promethazine HCl was 30% bound to plasma proteins, primarily with albumin. It is extensively distributed throughout the body with a mean steady state volume of distribution of 2.4 L/kg.

**Contraindications** **:** Promethazine HCl is contraindicated in comatose states, in patients who have received large amounts of central-nervous-system depressants (alcohol, sedatives hypnotics, including barbiturates, general anaesthetics, narcotics, narcotic analgesics, tranquilizers, etc.), and in patients who have demonstrated an idiosyncrasy or hypersensitivity to promethazine. Phenergan tablets and suppositories are contraindicated in comatose states, and in individuals known to be hypersensitive or to have had an idiosyncratic reaction to promethazine or to other phenothiazines.

**Adverse effects** **:** Adverse effects include restlessness, drowsiness and diarrhoea, hypotension. Hypertension, dizziness, headache and depression may occur and there are isolated reports of blood disorders, hypersensitivity reactions (rash, bronchospasm) and neuroleptic malignant syndrome. Promethazine stimulates prolactin secretion and may cause galactorrhoea or related disorders. Transient increase in plasma aldosterone concentrations has been reported.

**Drug interactions** **:** In-vitro studies of cytochrome P450 isoenzymes using human liver microsoms indicate that neither Promethazine nor its metabolites are likely to affect metabolism of other drugs metabolized by cytochrome P450 isoenzymes. The interaction with ciprofloxacin on the pharmacokinetics of a single dose of promethazine was

studied. The Cmax and AUC promethazine increased by 7-fold and 10 fold respectively. These changes leads to decrease in blood pressure, increased drowsiness and increase in psychomotor impairment. Promethazine delayed the Tmax of acetaminophen by 16minutes. Consumption of alcohol with promethazine hydrochloride increases the side effects.

**Indications** **:** Promethazine HCl is used in

- Allergies: Treatment of allergic conditions including some allergic reactions to drugs, urticaria and allergic contact dermatitis, and allergic reactions to insect bites and stings.
- Upper respiratory tract: Relief of excessive secretion in the upper respiratory tract as a result of hay fever and allergic rhinitis.
- Nausea and vomiting: Antiemetic for vomiting from various causes, including postoperative vomiting, irradiation sickness, drug induced nausea and motion sickness.
- Sedation: For short term use under the advice of a doctor or pharmacist. Do not use for more than 7 to 10 consecutive days.
- Other: Promethazine has sedative effects and can be used in the symptomatic management of measles and chicken pox.
- Promethazine can be used as a preanaesthetic medication for the prevention and control of post operative vomiting.

# EXCIPIENT PROFILE

## HYDROXYPROPYL METHYL CELLULOSE[60]

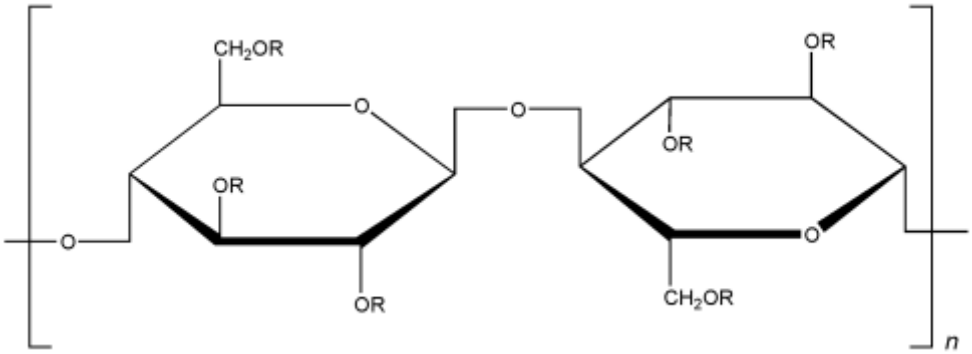
**Non-proprietary Names** **:** BP : Hypromellose
JP : Hydroxypropylmethylcellulose
PhEur : Hypromellosum
USP : Hypromellose

**Synonyms** **:** Cellulose; Hydroxypropylmethyl Ether; Methocel; HPMC; Methylcellulose; Propyleneglycol ether; Pharmacoat, Benecel MHPC; hydroxypropyl methylcellulose;

**Chemical Name** **:** Cellulose, 2-hydroxypropylmethylether.

**Molecular Weight** **:** 10,000 – 15,00,000.

**Structural Formula** **:**




**Description** **:** Hypromellose is an odorless and tasteless, white or creamy white fibrous or granular powder

**Functional Category** **:** Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

**Solubility** **:** Soluble in cold water, insoluble in chloroform, ethanol and ether, soluble in mixtures of ethanol and dichloromethane and mixtures of methanol and dichloromethane.

**Typical Properties**

| | | |
|---|---|---|
| Acidity/Alkalinity | : | pH = 5.5–8.0 for a 1% w/w aqueous solution. |
| Density | : | 0.341 g/cm$^3$ |
| Density (tapped) | : | 0.557 g/cm$^3$ |
| Density (true) | : | 1.326 g/cm$^3$ |
| Melting point | : | browns at 190–200ºC; chars at 225–230ºC. |

**Moisture content** : Hypromellose absorbs moisture from the atmosphere; the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air.

**Stability and Storage** : It is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Increasing temperature reduces the viscosity of solutions. It undergoes a reversible sol–gel transformation upon heating and cooling, respectively. Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

**Safety** : It is generally regarded as a nontoxic and non-irritant material, although excessive oral consumption may have a laxative effect.

**Incompatibilities** : Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

**Applications** : In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended-release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet or dry granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents. Hypromellose is also used as a suspending and thickening agent in topical formulations. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions. Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from

coalescing or agglomerating, thus inhibiting the formation of sediments. In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

**GLYCERIN [60]**

**Non proprietary name** **:** BP : Glycerol
JP : Concentrated glycerin
PhEur : Glycerolum
USP : Glycerin

**Synonyms** **:** Croderol; E422; glycerine; Glycon G-100; Kemstrene; Optim; Pricerine; 1,2,3-propanetriol; trihydroxypropane glycerol.

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

**Empirical Formula** **:** $C_3H_8O_3$

**Molecular Weight** **:** 92.09

**Functional Category** **:**Antimicrobial preservative; emollient; humectants; plasticizer; solvent; sweetening agent; tonicity agent.

**Boiling point** **:** 290$^0$C (with decomposition)

**Density** **:** 1.2656 g/cm3 at 15$^o$C;
1.2636 g/cm3 at 20$^o$C;
1.2620 g/cm3 at 25$^o$C.

**Flash point** **:** 176$^o$C (open cup)

**Hygroscopicity** **:** hygroscopic

**Melting point** **:** 17.8$^o$C

**Osmolarity** **:** a 2.6% v/v aqueous solution is iso osmotic with serum.

**Description** **:** Glycerin is a clear, colorless, odorless, viscous, hygroscopic liquid; it has a sweet taste, approximately 0.6 times as sweet as sucrose.

**Applications** **:** Glycerin is used in a wide variety of pharmaceutical formulations including oral, otic, ophthalmic, topical, and parenteral preparations. In topical pharmaceutical formulations and cosmetics, glycerin is used primarily for its humectant and emollient properties. In parenteral formulations, glycerin is used mainly as a solvent. In oral solutions, glycerin is used as a solvent, sweetening agent, antimicrobial preservative and viscosity-increasing agent. It is also used as a plasticizer and in film coatings. Glycerin is

additionally used in topical formulations such as creams and emulsions. Glycerin is used as a plasticizer of gelatin in the production of soft-gelatin capsules and gelatin suppositories. Glycerin is employed as a therapeutic agent in a variety of clinical applications, and is also used as a food additive.

**Incompatibilities** **:** Glycerin may explode if mixed with strong oxidizing agents such as chromium trioxide, potassium chlorate, or potassium permanganate. In dilute solution, the reaction proceeds at a slower rate with several oxidation products being formed. Black discoloration of glycerin occurs in the presence of light, or on contact with zinc oxide or basic bismuth nitrate. An iron contaminant in glycerin is responsible for the darkening in color of mixtures containing phenols, salicylates, and tannin. Glycerin forms a boric acid complex, glyceroboric acid that is a stronger acid than boric acid.

**Safety** **:** Adverse effects are mainly due to the dehydrating properties of glycerin. Oral doses are demulcent and mildly laxative in action. Large doses may produce headache, thirst, nausea, and hyperglycemia. The therapeutic parenteral administration of very large glycerin doses, 70–80 g over 30–60 minutes in adults to reduce cranial pressure, may induce hemolysis, hemoglobinuria, and renal failure. Slower administration has no deleterious effects. Glycerin may also be used orally in doses of 1.0–1.5 g/kgbody-weight to reduce intraocular pressure. When used as an excipient or food additive, glycerin is not usually associated with any adverse effects and is generally regarded as a non-toxic and non-irritant material.

**Stability and Storage** **:** Glycerin is hygroscopic. Glycerin decomposes on heating, with the evolution of toxic acrolein. Mixtures of glycerin with water, ethanol (95%), and propylene glycol are chemically stable. Glycerin may crystallize if stored at low temperatures; the crystals do not melt until warmed to $20^0$C. Glycerin should be stored in an airtight container, in a cool, dry place.

**POLY ETHYLENE GLYCOL 400** [60]

**Nonproprietary Names** **:** BP : Macrogols
JP : Macrogol 400
PhEur : Macrogola
USPNF : Polyethylene glycol

**Synonyms** **:** Carbowax; Carbowax Sentry; Lipoxol; Lutrol E; PEG; Pluriol E; polyoxyethylene glycol.

**Chemical Name** **:** a-Hydro-o-hydroxypoly(oxy-1,2-ethanediyl)

**Empirical Formula** **:** $HOCH_2$ $(CH_2OCH_2)mCH_2OH$
Where m - averagenumber of oxyethylene groups

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

**Functional Category** and **:** Ointment base; plasticizer; solvent; suppository base; tablet capsule lubricant.

**Density** **:** 1.11–1.14 g/cm3 at 25°C for liquid PEGs;

**Flash point** **:** 238°C for PEG 400.

**Freezing point** **:** 4–8°C for PEG 400;

**Moisture content** **:** liquid polyethylene glycols are very hygroscopic,

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

**Applications** **:** Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral, and rectal preparations. It has been used experimentally in biodegradable polymeric matrices used in controlled-release systems. Polyethylene glycols are stable, hydrophilic substances that are essentially non irritant to the skin. They do not readily penetrate the skin, although the

polyethylene glycols are water-soluble and are easily removed from the skin by washing, making them useful as ointment bases.

Mixtures of polyethylene glycols can be used as suppository bases, for which they have many advantages over fats. Aqueous polyethylene glycol solutions can be used either as suspending agents or to adjust the viscosity and consistency of other suspending vehicles. When used in conjunction with other emulsifiers, polyethylene glycols can act as emulsion stabilizers. Liquid polyethylene glycols are used as water-miscible solvents for the contents of soft gelatin capsules. In concentrations up to approximately 30% v/v, PEG 300 and PEG 400 have been used as the vehicle for parenteral dosage forms.

The presence of polyethylene glycols in film coats, especially of liquid grades, tends to increase their water permeability and may reduce protection against low pH in enteric-coating films. Polyethylene glycols are useful as plasticizers in microencapsulated products to avoid rupture of the coating film when the microcapsules are compressed into tablets.

Polyethylene glycols have been used in the preparation of urethane hydrogels, which are used as controlled-release agents. It has also been used in insulin-loaded microparticles for the oral delivery of insulin; it has been used in inhalation preparations to improve aerosolization; polyethylene glycol nanoparticles have been used to improve the oral bioavailability of cyclosporine; it has been used in selfassembled polymeric nanoparticles as a drug carrier; and copolymer networks of polyethylene glycol grafted with poly (methacrylic acid) have been used as bioadhesive controlled drug delivery formulations.

**Incompatibilities :** The chemical reactivity of polyethylene glycols is mainly confined to the two terminal hydroxyl groups, which can be either esterified or etherified. However, all grades can exhibit some oxidizing activity owing to the presence of peroxide impurities and secondary products formed by autoxidation. Liquid and solid polyethylene glycol grades may be incompatible with some coloring agents. The antibacterial activity of certain antibiotics is reduced in polyethylene glycol bases, particularly that of penicillin and bacitracin.

The preservative efficacy of the parabens may also be impaired owing to binding with polyethylene glycols. Physical effects caused by polyethylene glycol bases include softening and liquefaction in mixtures with phenol, tannic acid, and salicylic acid. Discoloration of sulfonamides and dithranol can also occur and sorbitol may be precipitated from mixtures.

Plastics, such as polyethylene, phenolformaldehyde, polyvinyl chloride, and cellulose-ester membranes (in filters) may be softened or dissolved by polyethylene glycols. Migration of polyethylene glycol can occur from tablet film coatings, leading to interaction with core components.

**Safety** **:** Generally, PEGs are regarded as nontoxic and non-irritant materials. Adverse reactions to polyethylene glycols have been reported, the greatest toxicity being with glycols of low molecular weight. However, the toxicity of glycols is relatively low. Polyethylene glycols administered topically may cause stinging, especially when applied to mucous membranes.

Hypersensitivity reactions to polyethylene glycols applied topically have also been reported, including urticaria and delayed allergic reactions. The most serious adverse effects associated with polyethylene glycols are hyperosmolarity, metabolic acidosis, and renal failure following the topical use of polyethylene glycols in burpatients. Topical preparations containing polyethylene glycols should therefore be used cautiously in patients with renal failure, extensive burns, or open wounds. Oral administration of large quantities of polyethylene glycols can have a laxative effect.

Liquid polyethylene glycols may be absorbed when taken orally. Absorbed polyethylene glycol is excreted largely unchanged in the urine, although polyethylene glycols of low molecular weight may be partially metabolized. In parenteral products, the maximum recommended concentration of PEG 300 is approximately 30% v/v as haemolytic effects have been observed at concentrations greater than about 40% v/v.

**Stability** **:** Polyethylene glycols are chemically stable in air and in solution, although grades with a molecular weight less than 2000 are hygroscopic. Polyethylene glycols do not support microbial growth, and they do not become rancid. Polyethylene glycols and aqueous polyethylene glycol solutions can be sterilized by autoclaving, filtration, or gamma irradiation. Ideally, sterilization should be carried out in an inert atmosphere. Oxidation of polyethylene glycols may also be inhibited by the inclusion of a suitable antioxidant. Oxidation may occur if polyethylene glycols are exposed for long periods to temperatures exceeding 50°C. However, storage under nitrogen reduces the possibility of oxidation.

**Storage Conditions** **:** Polyethylene glycols should be stored in well-closed containers in a cool, dry place. Stainless steel, aluminium, glass, or lined steel containers are preferred for the storage of liquid grades.

**PROPYLENE GLYCOL[60]**

**Nonproprietary Names** **:** BP : Propylene glycol
JP : Propylene glycol
PhEur : Propylenglycolum
USP : Propylene glycol

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

**Chemical Name** **:** b1,2-Propanediol, (þ)-1,2-Propanediol

**Empirical Formula** **:** $C_3H_8O_2$

**Molecular Weight** **:** 76.09

**Typical Properties** **:** Boiling point : 188ºC
Density : 1.038 g/cm3 at 20ºC
Flash point : 99ºC (open cup)
Melting point : -59ºC
Osmolarity : 2.0% v/v aqueous solution is isoosmotic with serum.

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

**Functional Category** **:** Antimicrobial preservative; disinfectant; humectant; plasticizer; solvent; stabilizer for vitamins; water-miscible cosolvent.

**Solubility** **:** miscible with acetone, chloroform, ethanol (95%), glycerin, and water; soluble at 1 in 6 parts of ether; not miscible with light mineral oil or fixed oils, but will dissolve some essential oils.

**Applications** **:** 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.

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

**Safety** **:** Propylene glycol is generally regarded as a relatively nontoxic material. In topical preparations, propylene glycol is regarded as minimally irritant, although it is more irritant than glycerin. Some local irritation is produced upon application to mucous membranes or when it is used under occlusive conditions. Parenteral administration may cause pain or irritation when used in high concentration. Propylene glycol is estimated to be one-third as intoxicating as ethanol, with administration of large volumes being associated with adverse effects most commonly on the central nervous system, especially in neonates and children. Other adverse reactions reported, though generally isolated, include: ototoxicity; cardiovascular effects; seizures; and hyperosmolarity and lactic acidosis, both of which occur most frequently in patients with renal impairment. Adverse effects are more likely to occur following consumption of large quantities of propylene glycol or on adminstration to neonates, children under 4 years of age, pregnant women, and patients with hepatic or renal failure. Adverse events may also occur in patients treated with disulfiram or metronidazole. Formulations containing 35% propylene glycol can cause hemolysis in humans. In animal studies, there has been no evidence that propylene glycol is teratogenic or mutagenic.

**Stability** **:** At cool temperatures, propylene glycol is stable in a well-closed container, but at high temperatures, in the open, it tends to oxidize, giving rise to products such as propionaldehyde, lactic acid, pyruvic acid, and acetic acid. Propylene glycol is chemically stable when mixed with ethanol (95%), glycerin, or water; aqueous solutions may be sterilized by autoclaving. Propylene glycol is hygroscopic and should be stored in a well-closed container, protected from light, in a cool, dry place.

# EXPERIMENTAL METHOD

## ANALYTICAL METHOD DEVELOPMENT

### Identification of λmax for Promethazine Hydrochloride

Promethazine hydrochloride was accurately weighed and dissolved in 6.8 phosphate buffer and sequent dilution was made to get the required concentrations (10µg/ml). The wave length of maximum absorbance (λmax) of this clear solution was determined from 200-400nm. And 6.8 pH buffer was used as blank.

### Construction of Standard Curve for Promethazine Hydrochloride:

### Preparation of reagents:

### Phosphate buffer 6.8:

Placed 0.2 M potassium di hydrogen phosphate in 200 mL volumetric flask, add 16.4 mL of 0.2M sodium hydroxide and make volume up to 200mL with distilled water.[58]

**A) Preparation of 0.2 M potassium dihydrogen phosphate**:

136.09 g of potassium dihydrogen phosphate in 1000 mL of water.[58]

**B) Preparation of 0.2 M sodium hydroxide**:

8g of sodium hydroxide in 1000 mL of water.[58]

### Procedure:

### Preparation of stock solution

Promethazine hydrochloride 50mg was dissolved in water 50 ml. From this solution 1 ml was pipetted and diluted with water up to 10ml, from this solution 5 ml was pipetted and diluted with water up to 50ml mark this solution as stock solution.

### Preparation of sample solution:

Further dilution was carried out taking 2, 4, 6, 8, 10 and made up to 10 ml to obtain the concentration of 2, 4, 6, 8, 10 µg/ml respectively. The absorbance was measured at 249 nm against the respective blank solution using UV visible spectrophotometer Systronics 118.

The standard curves were plotted by putting the known concentration on X- axis and the obtained absorbance on Y- axis.

**In pH 6.8 (Phosphate buffer) and pH 7.4 (Phosphate buffer)**

**Preparation of stock solution**

Promethazine hydrochloride 50mg was dissolved in water 50 ml. From this solution 1 ml was pipetted and diluted with water up to 10ml. From this solution 5 ml was pipetted and diluted with water up to 50ml mark this solution as stock solution.

**Preparation of sample solution:**

Further dilution was carried out taking 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 and made up to 10 ml to obtain the concentration of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 µg/ml respectively. The absorbance was measured at 249nm against the respective blank solution using UV visible spectrophotometer. The standard curves were plotted by putting the known concentration on X- axis and the obtained absorbance on Y- axis.

**DRUG POLYMER COMPATIBILITY STUDIES**

Infrared spectroscopy for pure drug Promethazine hydrochloride and polymers used for formulation were testify to check the intactness of drug and polymer in the formulation using Perkin Elmer model furrier transform infrared spectrometer by KBr disk method.

**FABRICATION OF DOSAGE FORM**

Product optimization was done after the evaluation of polymer and plasticizer combination and concentration by literature studies and drug compatibility studies. Compositions of the formulations given in table no: 4.

**Preparation of Patches:**

Buccal patches of Promethazine hydrochloride were prepared using solvent casting method. The formulation code and their respective composition are given in the table no 4. Accurately weighed quantity of polymers HPMC K4M and HPMC 15cps were added to the specified mentioned amount of double distilled water with continuous stirring until semisolid solution formed. These polymer solutions were kept overnight for completion of swelling and removal of air bubbles. Accurately weighed quantity of drug was dissolved in slurry with

continuous stirring and the specified quantity of plasticizers was added. The prepared thick solution was poured on petriplates of 8cm diameter and dried at 50ºC for 60 min in microwave oven followed by keeping in vacuum oven at 37º for 24hrs. After drying, patches were removed with the help of sharp blade and kept in desiccator overnight. The prepared patches were cut into small circular patches of 2.6 cm diameter containing 10 mg of drug using a die-cutter.

**Table No: 4 Compositions of Formulations**

| INGREDIENTS | | Promethazine HCl (mg) | HPMC K4M (mg) | HPMC 15cps (mg) | Glycerin (mg) | PEG 400 (mg) | Propylene glycol (mg) | Distilled water to makeup to |
|---|---|---|---|---|---|---|---|---|
| FORMULATION CODE | F1 | 100 | 400 | - | 50 | - | - | 20ml |
| | F2 | 100 | 400 | - | 100 | - | - | 20ml |
| | F3 | 100 | 400 | - | 200 | - | - | 20ml |
| | F4 | 100 | 500 | - | 62.5 | - | - | 20ml |
| | F5 | 100 | 500 | - | 125 | - | - | 20ml |
| | F6 | 100 | 500 | - | 250 | - | - | 20ml |
| | F7 | 100 | 400 | - | - | 200 | - | 20ml |
| | F8 | 100 | 400 | - | - | - | 200 | 20ml |
| | F9 | 100 | 500 | - | - | 250 | - | 20ml |
| | F10 | 100 | 500 | - | - | - | 250 | 20ml |
| | F11 | 100 | - | 2000 | 1000 | - | - | 20ml |
| | F12 | 100 | - | 2000 | - | 1000 | - | 20ml |
| | F13 | 100 | - | 2000 | - | - | 1000 | 20ml |

**PHYSICO-CHEMICAL EVALUATION OF PATCHES**

**Thickness**

All the batches were evaluated for thickness by using calibrated Dial gauge. Three samples from all the batches were evaluated for thickness and the average and standard deviation were calculated.

**Uniformity of weight**

Each patch was weighed individually on electronic balance and average weight of three patches was found.

**Drug content estimation**

The unit dose of the prepared patches were dissolved in 100ml of pH 6.8 Phosphate buffer and the amount of Promethazine hydrochloride was determined spectro photometrically at 249 nm.[33]

**Folding endurance**

The folding endurance was measured manually for the prepared patches. A strip of patch was cut and repeatedly folded at the same place till it broke. The number of times the patch could be folded at the same place without breaking gave the value of folding endurance.[35]

**Surface pH**

Patches were left to swell for 10min in Petri-dish containing 1ml of distilled water. The surface pH was measured by means of pH paper placed on the surface of the swollen patches. [35]

**Swelling studies**

The patches were cut into 1×1 $cm^2$ size and weight was noted. The patches were kept on pre weighed cover slips of 1×1$cm^2$ sizes separately and total weight was noted. The patches with cover slips were placed in separate petri-dishes containing 10ml of distilled water. After 30 min. the patches with cover slips were taken out and excess water on the bottom of the cover slips was wiped with tissue paper and weight was noted.

**Swelling index = $W_1 - W_0 / W_0$**

**Where, $W_1$ = final weight $W_0$ = initial weight**

**TENSILE STRENGTH**

Tensile strength of the patch was determined with TA.XT plus texture analyzer. The A/TG consists of two load cell grips (Fig.5). The lower one is fixed and the upper one is movable. The test patch was fixed between the cell grips and the tensile force was gradually applied till the patch broke. The reports of the tests were obtained directly from the software Exponent light.[62-63,66]

**TA Settings :**

| | |
|---|---|
| Accessory | : Tensile Grips (A/TG) using 5kg load cell |
| Mode | : Measure Force in Tension |
| Pre-Test Speed | : 1.0 mm/s |
| Test Speed | : 1.0 mm/s |
| Post-Test Speed | : 10.0 mm/s |
| Distance | : 15mm |
| Trigger Type | : Auto - 5g |

**Sample Preparation :** Cut the patches into strips of 10×20 mm size.

**Test Set-Up :** Upper tensile grip was attached to the load cell carrier and secured the lower tensile grip to the base of the machine. Tensile grips were calibrated to start from a set distance (20mm) apart for each test and saved this as a preset position using the Probe Preset icon in the Project window.

Upper grip moved to a higher sample loading position so that when the sample is attached to the upper grip it is free to hang without contact with the lower grip and the patches were inserted and tighten the grip to secure the sample. Click on T.A. - Move Probe and then Tools - Tare (to zero the weight of the upper grip and sample). Move to the Preset start position by clicking Memory - Location 1 and click on the required position. Sample was attached to the lower grip. The slack in the sample between the jaws should be minimized without stretching the sample when doing this.

**Probe Calibration :** The grips lowered, so that they were close together. Clicked on T.A. then CALIBRATE PROBE and specified the distance that the grips to start apart from each other for each test (20mm).

**Observations :** Clicked OK button to begin test and the graph proceeded to plot the effect on the patches under tension. When the elastic limit is exceeded the patch snaped

(observed as the maximum tension force). The greater the distance at the break point the more extensible the sample.

**Data Analysis** **:** Once tests have been performed, values of particular interest for sample analysis can be automatically obtained by a MACRO.

## MUCOADHESION STUDY

Mucoadhesive strength of the patch was determined with TA.XT plus texture analyzer. Probe A/MUC is used for the test (Fig.6). It consists of two load cell grips. The lower one is fixed and the upper one is movable. The test patch was fixed in the upper moved probe and the goat buccal mucosa was fixed in the lower cell which is moistened with the phosphate buffer pH 6.8. The Mucoadhesion Rig support ring should expose the tissue to the medium, whilst holding the tissue fast during the withdrawal phase of the test. The test patch was stucked to the lower side of the buccal mucosa. The force required to detach the patches from the mucosal surface gave the measure of mucoadhesive strength. [62-64]

**TA Settings** **:**

| | |
|---|---|
| Accessory | : Mucoadhesion Rig (A/MUC) using 50 kg load cell |
| Option | : Adhesive Test |
| Pre-Test Speed | : 0.5 mm/s |
| Test Speed | : 0.1 mm/s |
| Post-Test Speed | : 0.1 mm/s |
| Trigger Type | : Auto - 3g |
| Tare Mode | : Auto |
| Force applied | : 3.5N |
| Contact time | : 120 sec. |

**Test Set-up** **:** The test conditions were maintained i.e, phosphate buffer 6.8 at $37^0$C by use of a thermostatically controlled magnetic heater/stirrer. Prior to testing the tissue was allowed to equilibrate with the medium for 15 minutes. Common probe sizes and dimensions used for bioadhesive testing were acrylic cylinders with a diameter of 10 mm. Patches attached to the underside of the 10mm probe with a double-sided adhesive tape.

**Sample Preparation Alternatives**

A fixed volume of buffer pipetted onto the mucosa to standardise the hydration prior to testing. The force needed to detach the dosage form was recorded as a function of elongation and both maximum strength and area under the force/time curve was usually obtained. The results were converted into work of adhesion and then represented as a mean value with standard deviation.

**Data Analysis** **:** Once tests have been performed sample analysis can be automatically obtained by a MACRO

## *IN-VITRO* DISSOLUTION STUDIES

The release study was carried out in a USP 24 dissolution apparatus type VI (six-station dissolution apparatus, Hanson Research Corp., USA). The dissolution medium was 900 mL. Phosphate buffer, pH 6.8, maintained at $37^0$C and kept in the USP dissolution flask. The patch was fixed to the central axis, which rotated at 50 rpm. Filtered samples (5 ml.) were manually collected at intervals of 30min up to 3hrs. The samples were compensated with an equal volume of phosphate buffer kept at the same temperature. The concentration of drug released in the medium was assayed Spectrophotometrically at 249 nm after suitable dilution with the dissolution medium when necessary.[33]

**Dissolution parameters**

| | |
|---|---|
| Dissolution Medium | : Phosphate buffer pH 6.8 |
| Paddle speed | : 50 rpm |
| Apparatus | : Dissolution apparatus Type USP VI (cylinder Apparatus) (Fig.7) |
| Temperature | : 37ºC ± 0.5ºC |
| Withdrawal time | : 3 hrs with 30 mins interval |
| Volume withdrawn | : 5 ml |

## *EX VIVO* DRUG PERMEATION STUDY

*Ex-vivo* study of Promethazine hydrochloride permeation through goat buccal mucosa was performed using a Diffusion cell. Fresh Goat buccal mucosa was obtained from a local slaughter house .Goat buccal mucosa mounted between the donor compartment and receptor compartment so that the smooth surface of the mucosa faced the donor compartment. The patches were placed on the mucosa and the donor compartment was filled with 15ml of phosphate buffer pH 6.8. The donor compartment fixed such that it touches surface of receptor compartment (15ml capacity). The receptor compartment was filled with phosphate buffer pH 7.4. The assembly was maintained at 37° C and stirred magnetically. 1ml sample was withdrawn at specific time intervals and suitable dilutions were done and analyzed for drug content at 249nm in UV-visible spectrophotometer.[44]

**Diffusion parameters**

| | |
|---|---|
| Donor compartment | : Phosphate buffer pH6.8 |
| Receptor compartment | : Phosphate buffer pH7.4 |
| Apparatus | : Diffusion cell (Fig.8) |
| Withdrawal time | : 3 hrs with 30 mins interval |
| Volume withdrawn | : 1mL |

**Drug release and drug diffusion study was analyse by following method:**

**U.V Spectrophotometry :** The sample withdraw was analyse by U.V Spectrophotometer

***IN VIVO* COMPATIBILITY STUDY**

Informed consent was obtained from all human volunteers before conducting study. The study was conducted on 10 human volunteers. Selected formulation was given to the volunteers and asked them to report for any irritation, discomfort, local anaesthetic effect, heaviness and for the overall acceptance.[33]

**Figure no: 5 Tensile strength analysis** **Figure no: 6 Mucoadhesion study with**

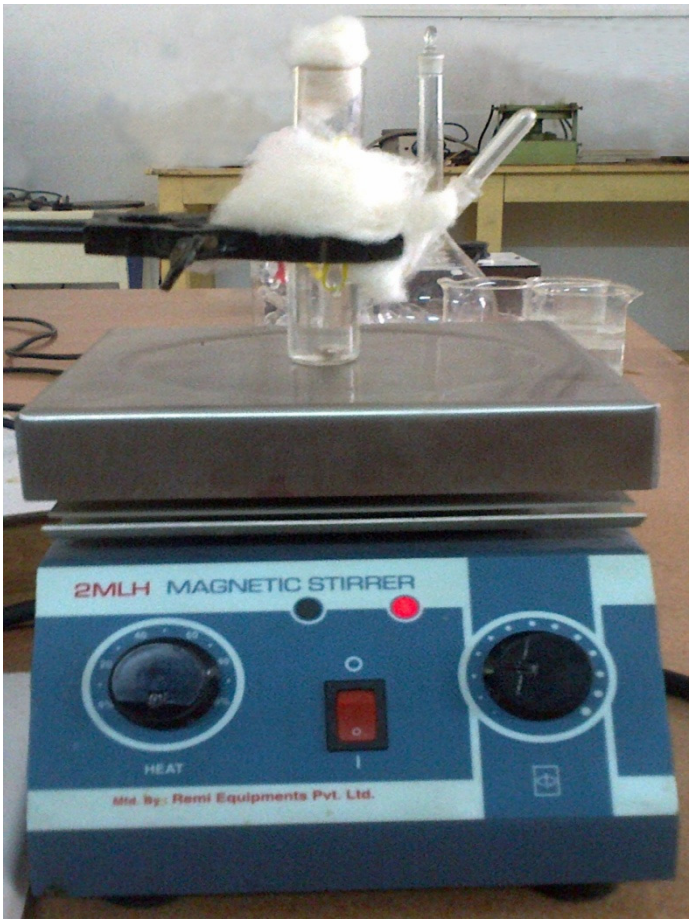
**with Texture analyser.** **Texture analyser.**



**Figure no: 7 *In vitro* Drug release study using Dissolution apparatus USP VI**


**Figure no: 8 *Ex-vivo* drug permeation study through Goat buccal mucosa using**

**Diffusion cell**



# RESULTS AND DISCUSSION

## ANALYTICAL METHOD DEVELOPMENT

### Construction of Standard Curve for Promethazine Hydrochloride

The wave length of maximum absorbance of drug was found to be 249 nm and the drug solution was found to obey Beer's law in the range of 1-10µg/ml at 249 nm against 6.8 pH buffer as blank. The values are given in table no: 5 and standard graphs in figure 9&10**.**

**Table No: 5 Standard Curve of Promethazine hydrochloride Absorbance of Promethazine Hydrochloride at Different pH**

| Sl.no | Concentration(µg/ml) | Absorbance at 249 nm | |
|---|---|---|---|
| | | pH 6.8 | pH 7.4 |
| 1 | 0 | 0 | 0 |
| 2 | 1 | 0.112 | 0.101 |
| 3 | 2 | 0.154 | 0.123 |
| 4 | 3 | 0.268 | 0.214 |
| 5 | 4 | 0.303 | 0.294 |
| 6 | 5 | 0.414 | 0.327 |
| 7 | 6 | 0.486 | 0.421 |
| 8 | 7 | 0.531 | 0.491 |
| 9 | 8 | 0.596 | 0.513 |
| 11 | 10 | 0.711 | 0.697 |

**Figure No: 9 Calibration Curve for Promethazine hydrochloride in pH 6.8**

**Phosphate Buffer at 249nm**

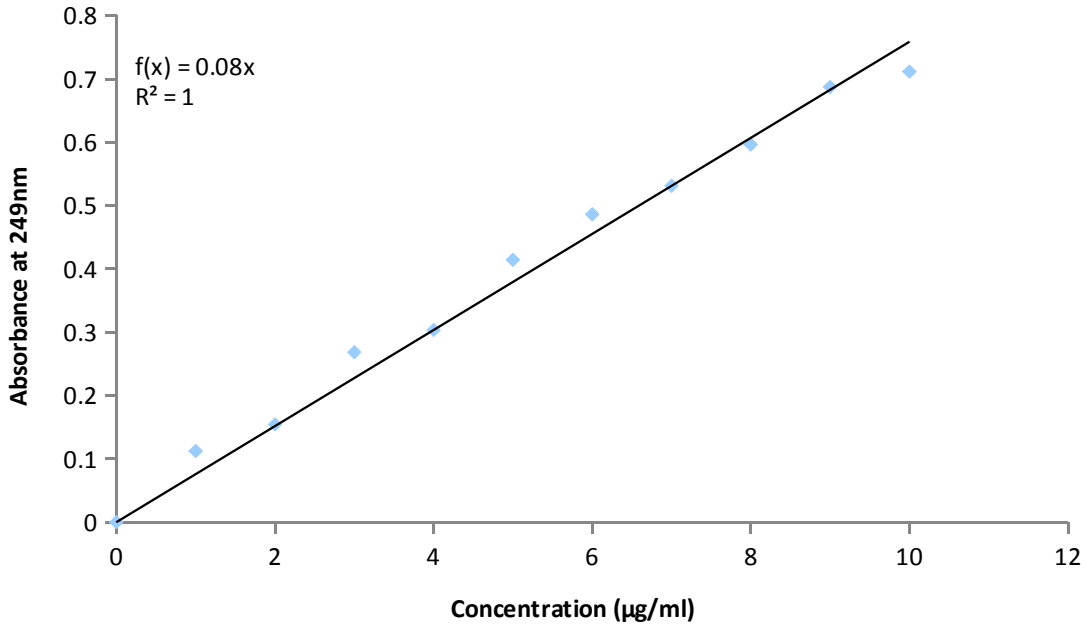
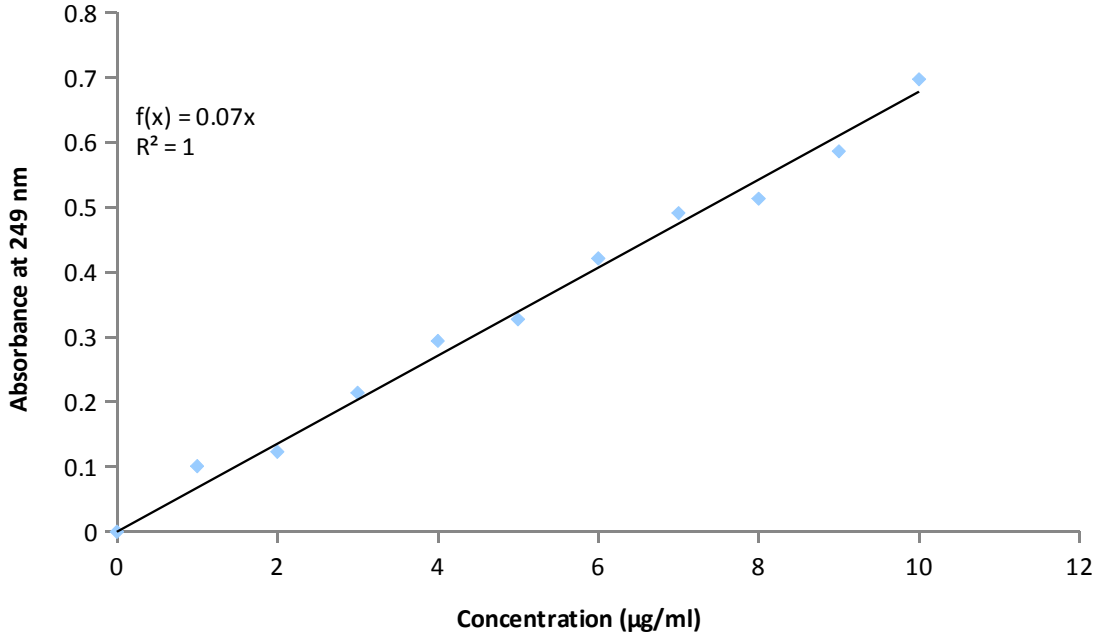



**Figure No: 10 Calibration Curve for Promethazine hydrochloride in pH 7.4 Phosphate buffer at 249nm**



## DRUG-POLYMER COMPATIBILITY STUDY

FTIR analysis for drug, polymers and the drug polymer mixtures were done. The reports were given as figures 11-15 and in tables 6-10.

**Figure No: 11 Promethazine hydrochloride FTIR**

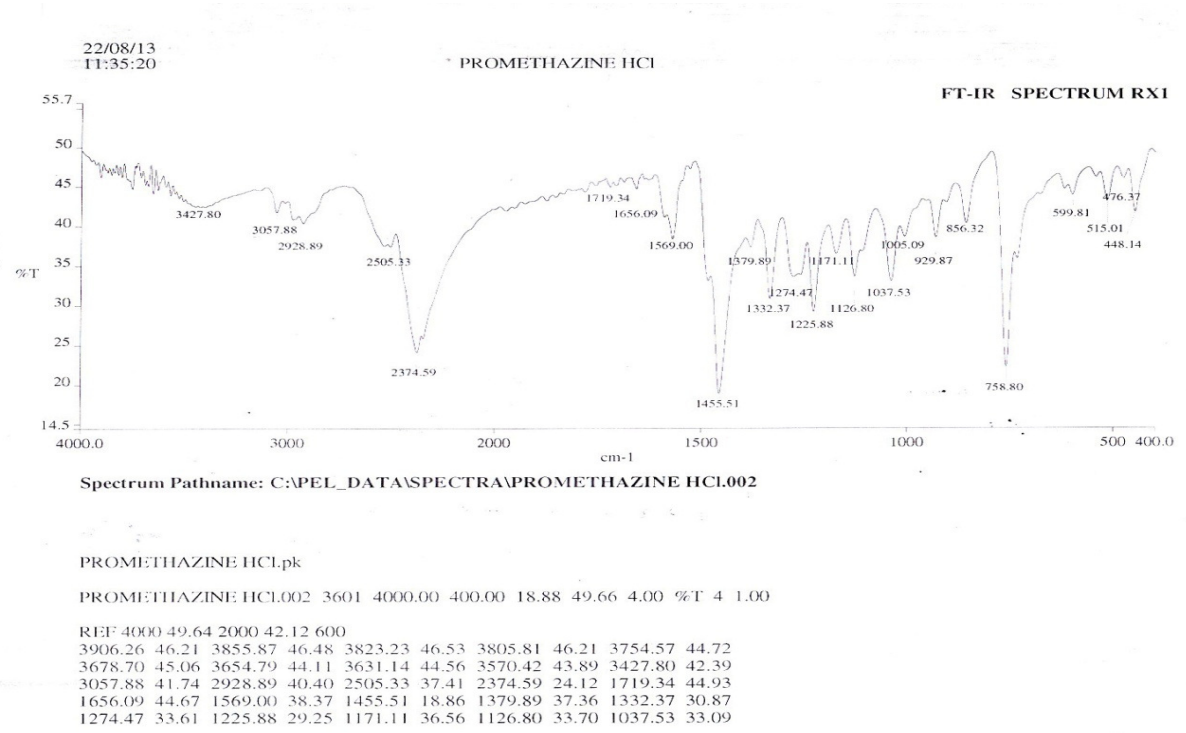



**Table No: 6 Promethazine hydrochloride FTIR**

| Wave number in $cm^{-1}$ | Characteristic band |
|---|---|
| 3426.80 | N-H Stretching |
| 3057.88 | C-H Stretching aromatic |
| 758.80 | C-S deformation |
| 1569.00 | C=C |
| 1455.51 | C=C |
| 1274.47 | C-N Stretching |
| 1225.88 | C-N Stretching |
| 856.32 | C-H deformation |
| 1379 | C-H deformation |
| 1569.00 | N-H deformation |
| 1379.89 | C-S Stretching |

**Figure No: 12 FTIR Studies for HPMC K4M**

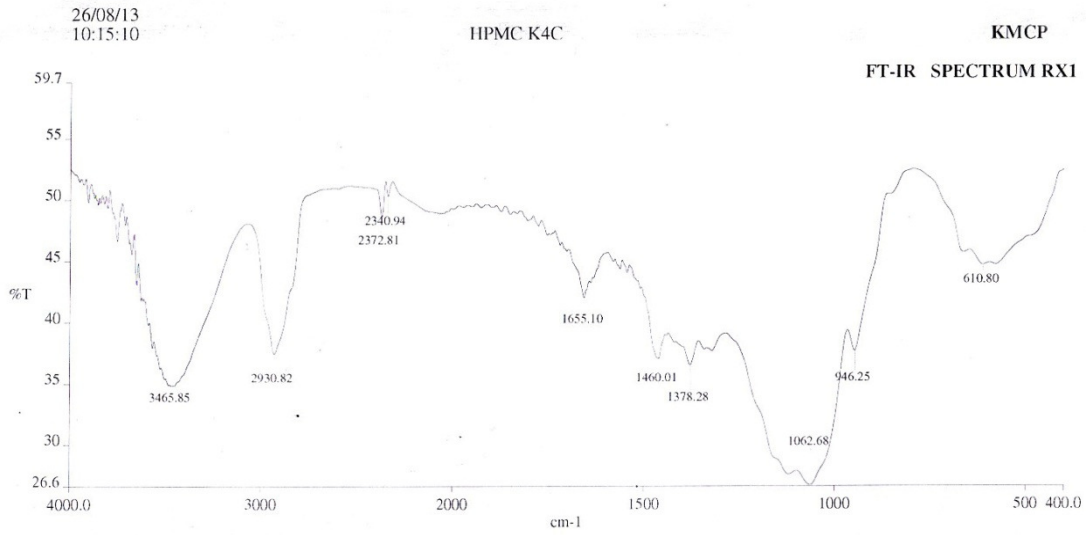
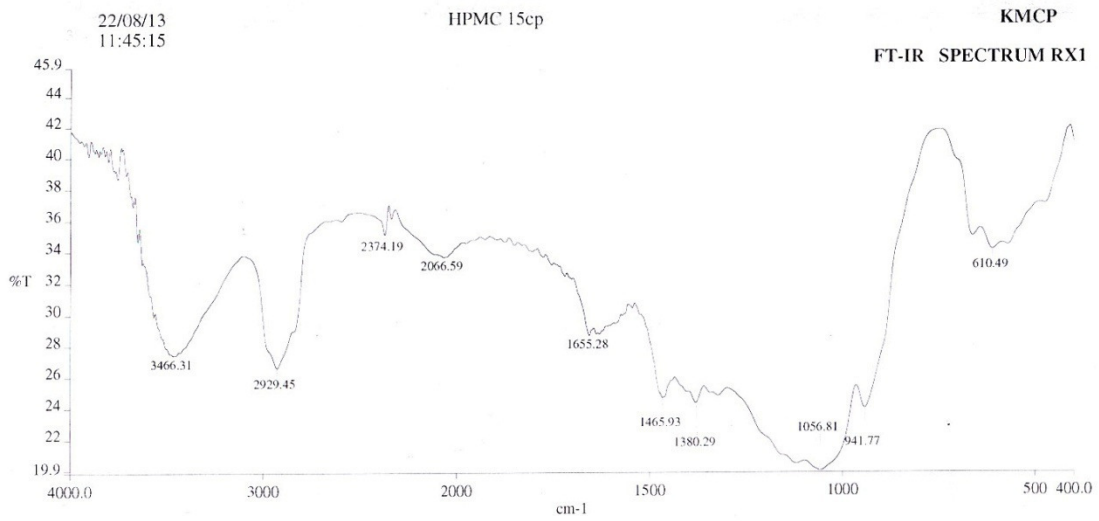



**Table No: 7 FTIR Studies for HPMC K4M**

| Wave number in $cm^{-1}$ | Characteristic band |
|---|---|
| 3465.85 | OH Stretching |
| 2930.82 | C-H Stretching |
| 1062.68 | C-O-C Stretching |
| 1655.10 | C-O Stretching |
| 946.255 | C-H deformation |
| 1460.01 | C-H deformation |

**Figure No: 13 FTIR Studies for HPMC 15cps**




Spectrum Pathname: C:\PEL_DATA\SPECTRA\HPMC 15cp.002

HPMC 15cp.pk

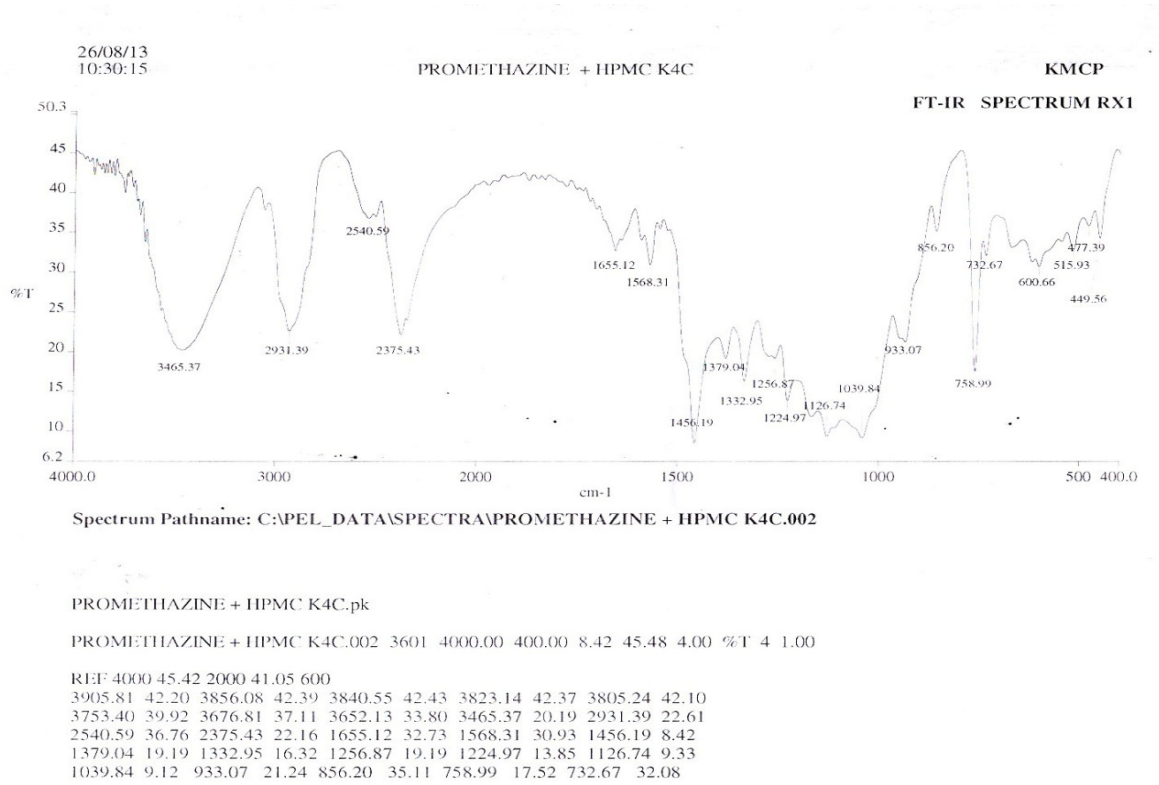
HPMC 15cp.002 3601 4000.00 400.00 19.97 41.98 4.00 %T 4 1.00

REF 4000 41.76 2000 34.34 600
3906.91 40.13 3757.54 38.71 3466.31 27.42 2929.45 26.62 2374.19 35.11
2066.59 33.68 1655.28 28.67 1465.93 24.67 1380.29 24.34 1056.81 19.97
941.77 24.00 610.49 34.13

**Table No: 8 FTIR Studies for HPMC 15cps**

| **Wave number in $cm^{-1}$** | **Characteristic band** |
|---|---|
| 3466.31 | OH Stretching |
| 2929.45 | C-H Stretching |
| 1056.81 | C-O-C Stretching |
| 1655.28 | C-O Stretching |
| 941.77 | C-H deformation |
| 1465.93 | C-H deformation |

**Figure No: 14 FTIR studies for Promethazine hydrochloride and HPMC K4M blend**




PROMETHAZINE + HPMC K4C.pk

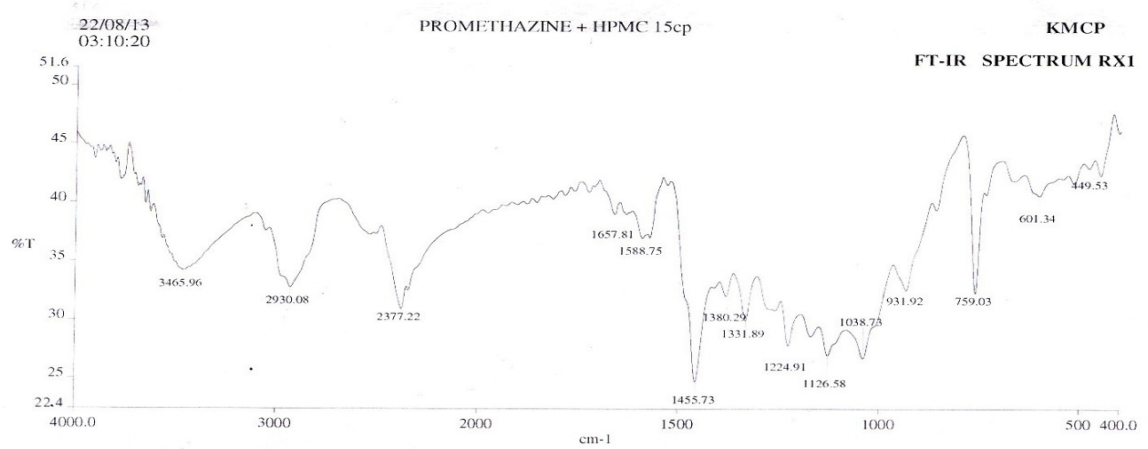
PROMETHAZINE + HPMC K4C.002 3601 4000.00 400.00 8.42 45.48 4.00 %T 4 1.00

REF 4000 45.42 2000 41.05 600
3905.81 42.20 3856.08 42.39 3840.55 42.43 3823.14 42.37 3805.24 42.10
3753.40 39.92 3676.81 37.11 3652.13 33.80 3465.37 20.19 2931.39 22.61
2540.59 36.76 2375.43 22.16 1655.12 32.73 1568.31 30.93 1456.19 8.42
1379.04 19.19 1332.95 16.32 1256.87 19.19 1224.97 13.85 1126.74 9.33
1039.84 9.12 933.07 21.24 856.20 35.11 758.99 17.52 732.67 32.08

**Table No: 9 FTIR studies for Promethazine hydrochloride and HPMC K4M Blend**

| Wave number in $cm^{-1}$ | Characteristic band |
|---|---|
| 3465.37 | O-H Stretching |
| 3465.37 | N-H Stretching |
| 2931.39 | C-H Stretching |
| 1655.12 | C-O Stretching |
| 1126.74 | C-O-C Stretching |
| 1039.84 | C-O-C Stretching |
| 856.20 | C-H deformation |
| 933.07 | C-H deformation |
| 1379.04 | C-S Stretching |
| 758.80 | C-S deformation |
| 1456.19 | C=C Stretching |
| 1568.31 | C=C Stretching |
| 1224.97 | C-N Stretching |
| 1256.87 | C-N Stretching |
| 1568.31 | N-H deformation |

**Figure No: 15 FTIR studies for Promethazine hydrochloride and HPMC 15cps blend**




Spectrum Pathname: C:\PEL_DATA\SPECTRA\PROMETHAZINE + HPMC 15cp.002

PROMETHAZINE + HPMC 15cp.pk

PROMETHAZINE + HPMC 15cp.002 3601 4000.00 400.00 24.73 47.65 4.00 %T 4 1.00

REF 4000 45.93 2000 39.09 600
3908.19 43.71 3779.04 41.92 3655.95 39.89 3465.96 34.21 2930.08 32.76
2377.22 30.95 1657.81 39.00 1588.75 36.99 1455.73 24.73 1380.29 32.04
1331.89 29.95 1224.91 27.80 1126.58 26.95 1038.73 26.72 931.92 32.55
759.03 32.31 601.34 40.57 449.53 42.30

**Table No: 10 FTIR studies for Promethazine hydrochloride and HPMC 15cps Blend**

| Wave number in $cm^{-1}$ | Characteristic band |
|---|---|
| 3465.97 | O-H Stretching |
| 3465.97 | N-H Stretching |
| 2930.08 | C-H Stretching |
| 1657.81 | C-O Stretching |
| 1126.58 | C-O-C Stretching |
| 1038.73 | C-O-C Stretching |
| 856.20 | C-H deformation |
| 931.92 | C-H deformation |
| 1380.29 | C-S Stretching |
| 759.03 | C-S deformation |
| 1455.73 | C=C Stretching |
| 1588.75 | C=C Stretching |
| 1224.91 | C-N Stretching |
| 1256.87 | C-N Stretching |
| 1588.75 | N-H deformation |

The results of FTIR showed that there was no interaction between polymers and drug as all individual peaks for the drug and polymers were obtained in the mixture.

**DEVELOPMENT OF FORMULATIONS:**

The thin films of Promethazine showed unpleasant anaesthetic effect in tongue during preliminary works. The drug content of unit patch (2.6cm diameter) for all the batches were 10 mg Promethazine hydrochloride which was in accordance with amount used in 'Phenergan' (Sanofi aventis). The formulations F1, F2, F3 were prepared with HPMC K4M 2% with glycerine 12.5%, 25% and 50% to the dry weight of polymer respectively. F7 & F8 were prepared using 2% of HPMC K4M with different plasticizers like PEG-400 & Propylene glycol 50% to the dry weight of polymer. The formulations F4, F5, F6 were prepared with HPMC K4M 2.5% with glycerine 12.5%, 25% and 50% to the dry weight of polymer respectively. F9 & F10 were prepared using 2.5% of HPMC K4M with different plasticizers like PEG-400 & Propylene glycol 50% to the dry weight of polymer. Formulations F11, F12, F13 were prepared using 10% of HPMC 15 cps and different plasticizers like glycerine, PEG-400 and Propylene glycol 50% to the dry weight of polymer (Table 4). The drying process was done in microwave oven at 50$^{o}$C to avoid any degradation to drug when subjected to high temperature.

**PHYSICOCHEMICAL EVALUATIONS**

All physicochemical parameters of the prepared buccal patches are given in the Table no.11.

**Weight:**

Weight of patches was ranging from 54.09±0.6 to 311.12±0.6 mg. Weight of patches was found to be increasing proportion of polymer and plasticizer. But there is no much difference in weight of the patches with different plasticizer in same proportion (Table 11).

**Thickness:**

Thickness of the all formulated patches was found to be in the range of 77.67±0.33 to 424.33±2µm. As the total amount of polymer increases the thickness of the patches were found to be increased. Thickness also increased with increase in concentration of plasticizer (Table 11).

**Folding endurance:**

Folding endurance is the index of ease of handling the patches. As the amount of polymer increases the folding endurance was found to be increased. Plasticizer increases the flexibility of the patches so the folding endurance also found to be increased. But there is no marked change in folding endurance with different type of plasticizers. Folding endurance for the patches was found to be 562±2 to 746±3. All patches exhibited folding endurance above 500 proving the flexible nature of the patch (Table 11).

**Surface pH:**

Surface pH for all batches was between 5.5 to 6.0 which were due to pH of the drug solution as well as the polymer, hence no mucosal irritations was expected and ultimately achieves patient compliance (Table 11).

**Drug content:**

All the batches of the patches contain 9.88±0.21 to 10.13±0.01 mg of drug which indicate that there is no loss of drug during preparation of the patch (Table 11). All the batches of the patches exhibit drug content within limit 98.8 to 101.3 % which is within the desirable range due to the equal distribution of drug in the solution (Table 11).

**Swelling studies:**

Swelling index shows the moisture uptake and swelling behavior of buccal patches. All the patches were subjected to swelling studies. The results indicated that all the patches exhibited appreciable swelling nature within 30 min. The buccal patches with 10 % HPMC 15cps showed highest swelling index and also the swelling index increasing with polymer concentration for HPMC K4M. Also it increases with increasing content of glycerine. There is no marked change in swelling nature for patches with 50% of PEG 400 and Propylene glycol when compared with glycerine (Table 11).

**Table No: 11 Physicochemical Evaluations of Buccal Patches.**

| Batch no. | Weight ( mg) (n=3) | Thickness (µm) (n=3) | Folding endurance (n=3) | Surface pH (n=3) | Swelling index | Drug content (mg) (n=3) |
|---|---|---|---|---|---|---|
| F-1 | 54.09±0.6 | 77.67±0.33 | 562±2 | 6 | 20.69 | 10.08±0.09 |
| F-2 | 61.38±0.3 | 91.33±0.89 | 614±2 | 6 | 28.35 | 10.12±0.04 |

| | | | | | | |
|---|---|---|---|---|---|---|
| F-3 | 71.94±0.7 | 107.67±0.57 | 731±3 | 6 | 32.59 | 10.08±0.08 |
| F-4 | 69.57±0.8 | 93.33±0.64 | 628±1 | 6 | 33.99 | 10.05±0.07 |
| F-5 | 74.38±0.2 | 115.67±0.97 | 689±2 | 6 | 32.73 | 10.06±0.08 |
| F-6 | **86.78±0.5** | **129.00±0.85** | **738±3** | **6** | **30.52** | **9.88±0.21** |
| F-7 | 72.26±0.6 | 111.67±0.69 | 725±3 | 5.5 | 33.19 | 10.02±0.04 |
| F-8 | 70.94±0.7 | 114.00±0.83 | 729±2 | 5.5 | 37.42 | 10.02±0.03 |
| F-9 | 84.78±0.5 | 131.33±0.76 | 746±3 | 5.5 | 35.94 | 10.07±0.06 |
| F-10 | 87.78±0.3 | 132.33±0.83 | 741±3 | 5.5 | 38.07 | 10.06±0.05 |
| F-11 | 309.39±0.4 | 380.67±1 | 678±2 | 6 | 47.41 | 9.92±0.03 |
| F-12 | 315.41±0.8 | 372.67±1 | 684±2 | 5.5 | 49.65 | 10.13±0.01 |
| F-13 | 311.12±0.6 | 424.33±2 | 681±2 | 5.5 | 43.76 | 10.08±0.02 |

**Tensile strength**

The tensile strength of the patches was tested in TA.XT plus texture analyser and the results are summarised in table no: 12 and figures 16-20.

**Table no: 12 Tensile strength and Extensibility of the patches.**

| **FORMULATION CODE** | | **EXTENSIBILITY (mm) Elongation at break** | **FORCE (N)** | **TENSILE STRENGTH (MPa)** |
|---|---|---|---|---|
| HPMC K4M 2%, Glycerine 12.5% | **F1** | 5.481 | 23.67 | 30.35 |
| HPMC K4M 2%, Glycerine 25% | **F2** | 5.014 | 19.19 | 21.08 |

| | | | | |
|---|---|---|---|---|
| HPMC K4M 2%, Glycerine 50% | **F3** | 14.588 | 21.51 | 19.91 |
| HPMC K4M 2.5%, Glycerine 12.5% | **F4** | 7.871 | 29.73 | 31.8 |
| HPMC K4M 2.5%, Glycerine 25% | **F5** | 11.218 | 30.23 | 26.06 |
| HPMC K4M 2.5%, Glycerine 50% | **F6** | **14.876** | **35.40** | **27.44** |
| HPMC K4M 2%, PEG400 50% | **F7** | 19.397 | 26.64 | 23.78 |
| HPMC K4M 2%, PG 50% | **F8** | 3.289 | 17.63 | 15.46 |
| HPMC K4M 2.5%, PEG400 50% | **F9** | 22.344 | 39.76 | 30.33 |
| HPMC K4M 2.5%, PG 50% | **F10** | 11.503 | 38.77 | 29.37 |
| HPMC 15cps 2%, Glycerine 50% | **F11** | 17.723 | 72.11 | 18.92 |
| HPMC 15cps 2%, PEG400 50% | **F12** | 4.116 | 49.55 | 13.28 |
| HPMC 15cps 2%, PG 50% | **F13** | 14.803 | 26.50 | 6.25 |

Tensile strength and extensibility of the patches with HPMC K4M is higher compared to patches with HPMC 15cps. Extensibility of the patches increased with increase in polymer concentration and also with increase in the glycerine content. There is no significant effect with PEG 400 and Propylene glycol on extensibility and tensile strength of the patches. The flexibility and tensile strength increases with increasing amount of plasticizer (Table no: 12 and figures 16-20).

**Figure no: 16 Tensile strength of Formulations F1, F2 & F3**

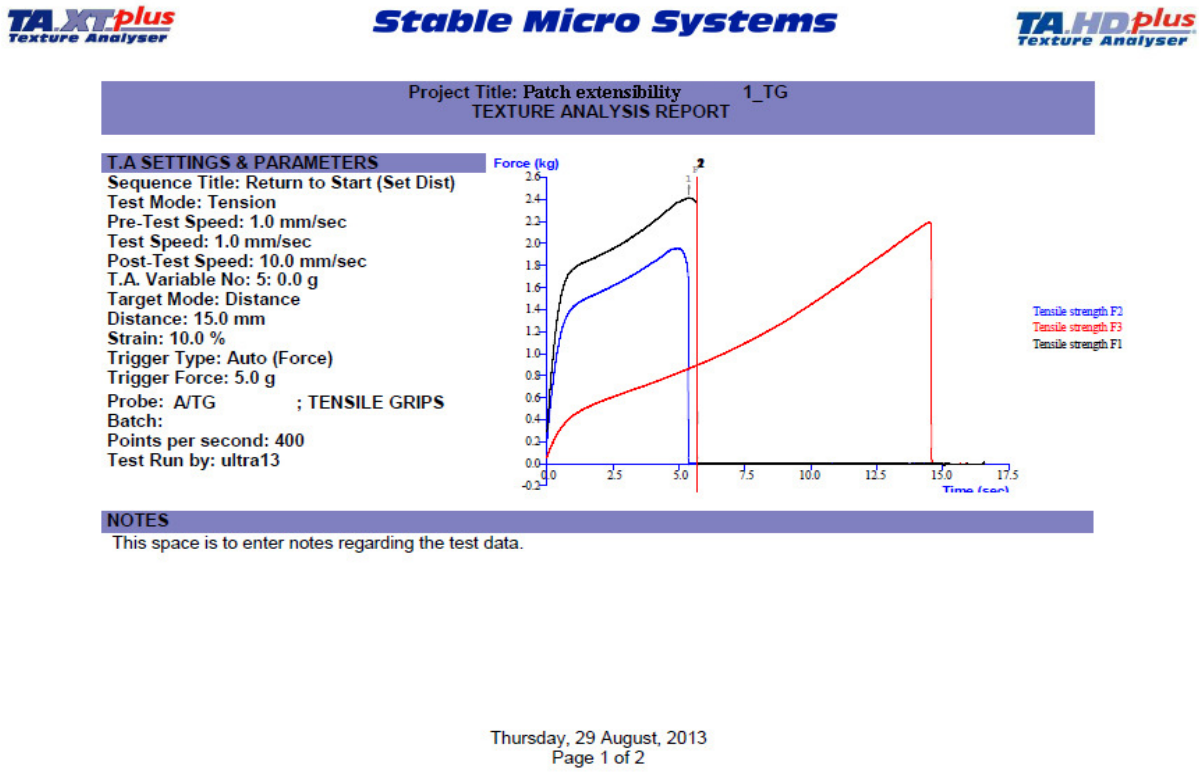



**Figure no: 17 Tensile strength of Formulations F4, F5 & F6**

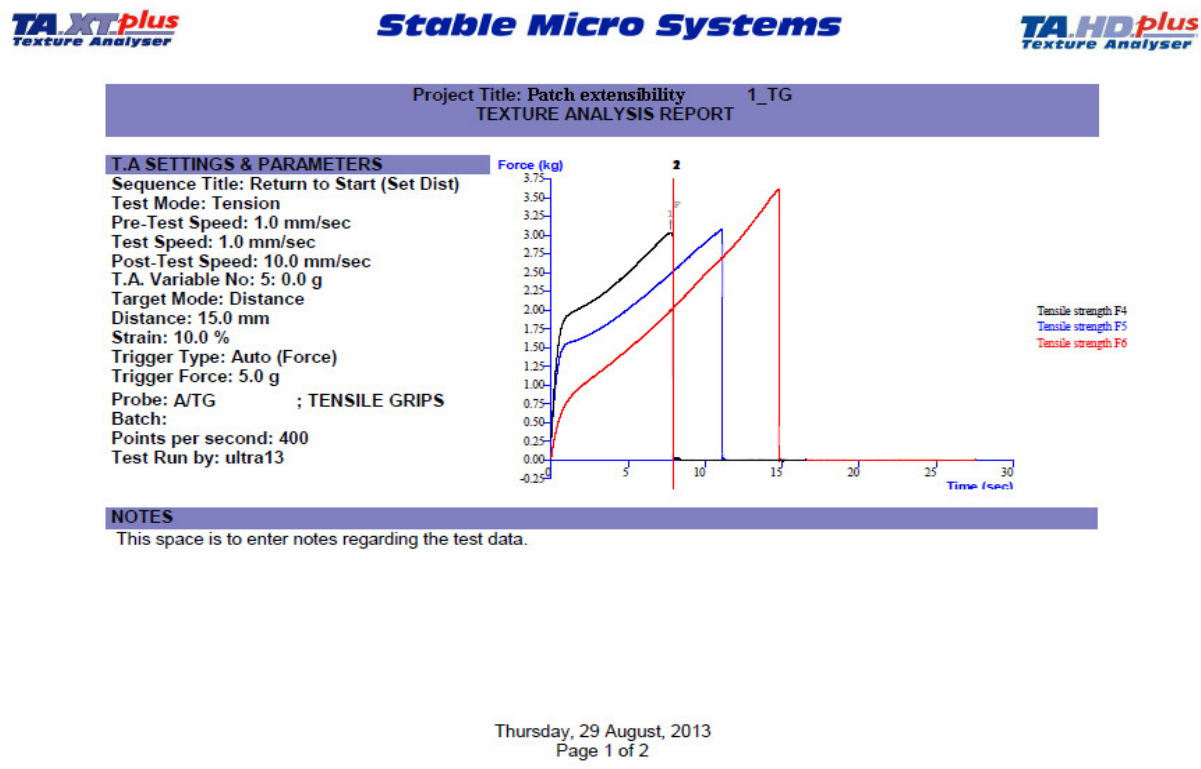



**Figure no: 18 Tensile strength of Formulations F7 & F8**

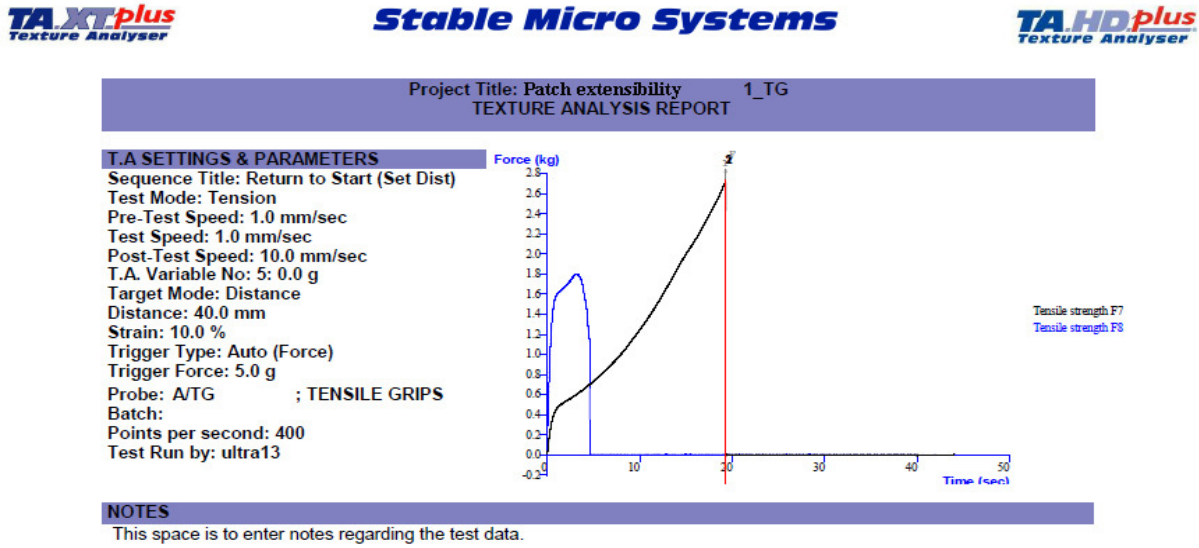



**Figure no: 19 Tensile strength of Formulations F9 & F10**

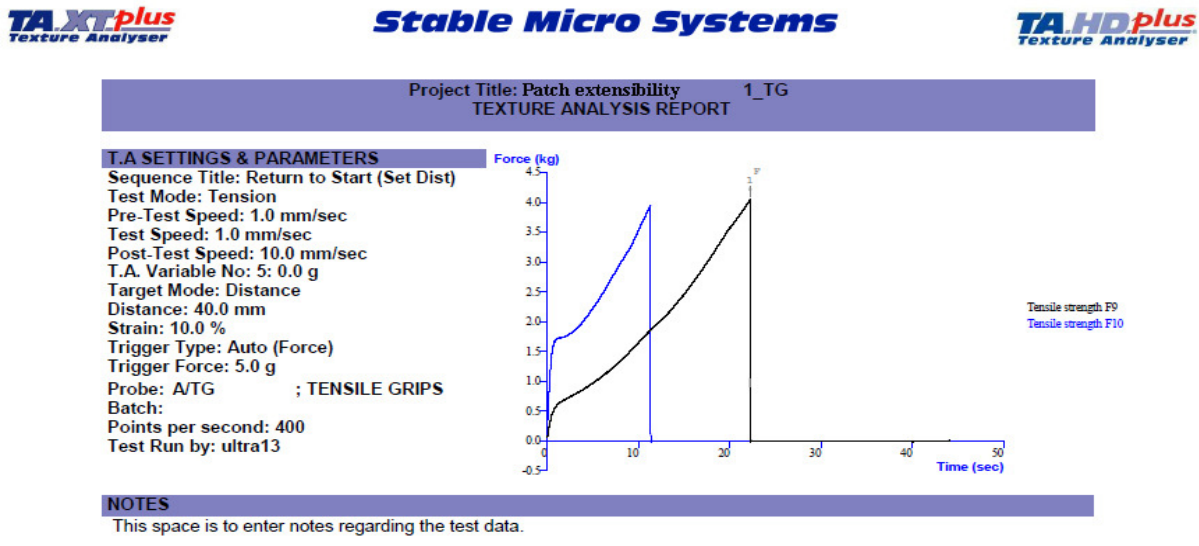



**Figure no: 20 Tensile strength of Formulations F11, F12 & F13**

TA.XT.plus Texture Analyser

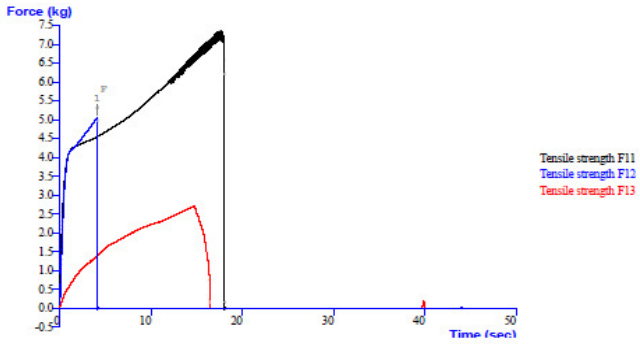
**Stable Micro Systems**

TA.HD.plus Texture Analyser

Project Title: **Patch extensibility** 1_TG
TEXTURE ANALYSIS REPORT

**T.A SETTINGS & PARAMETERS**

Sequence Title: Return to Start (Set Dist)
Test Mode: Tension
Pre-Test Speed: 1.0 mm/sec
Test Speed: 1.0 mm/sec
Post-Test Speed: 10.0 mm/sec
T.A. Variable No: 5: 0.0 g
Target Mode: Distance
Distance: 40.0 mm
Strain: 10.0 %
Trigger Type: Auto (Force)
Trigger Force: 5.0 g
Probe: A/TG ; TENSILE GRIPS
Batch:
Points per second: 400
Test Run by: ultra13




**NOTES**

This space is to enter notes regarding the test data.

Thursday, 29 August, 2013
Page 1 of 2

## EVALUATION OF MUCOADHESION

Mucoadhesive strength for all the prepared batches on Goat buccal mucosa was determined using TA.XT plus Texture analyser and results were given in table no: 13 and figures 21-33.

**Table: 13 Mucoadhesive strength of the buccal patches of Promethazine HCl.**

| BATCH NO: | ADHESIVE FORCE(N)* | WORK OF ADHESION* (N.SEC) | DEBONDING DISTANCE* (mm) |
|---|---|---|---|
| F1 | 0.1951 | 1.667 | 1.688 |
| F2 | 0.0196 | 0.0294 | 0.468 |
| F3 | 0.174 | 0.595 | 1.116 |
| F4 | 1.4562 | 6.251 | 4.340 |
| F5 | 0.1997 | 1.693 | 4.340 |
| F6 | **0.965** | 3.444 | 2.088 |
| F7 | 0.5225 | 1.993 | 3.712 |
| F8 | 0.2113 | 1.335 | 2.696 |
| F9 | 0.0894 | 1.173 | 3.443 |
| F10 | 0.6166 | 2.292 | 1.453 |
| F11 | 0.0848 | 1.744 | 4.641 |
| F12 | 1.238 | 3.550 | 4.926 |
| F13 | 0.459 | 0.664 | 2.431 |

***The functional parameters fixed were 3.5N force applied and 120 sec. contact time.**

The adhesive force of the patches was found to be varying with thickness and swelling of the patches. Patches with PEG 400 and Propylene glycol have poor mucoadhesion. Formulations F3, F6 and F11 i.e, with 50% of glycerine showed good mucoadhesion. Hence glycerine can be used as plasticizer for good mucoadhesion.

Mucoadhesive force increases with an increase in the molecular weight of polymer. Too great degree of swelling results in slippery mucilage and can be easily removed from the substrate. It is a hindrance to the adhesion polymers grafting onto the preformed network; and the inclusion of adhesion promoters in the formulation (freepolymer). Thicker patches remove water from the adhesive joint giving a suboptimal concentration required for effective adhesion with biological substrate. Thinner patches have a lesser capacity for water sequestering and give a more hydrated surface.

**Figure no: 21 Graph of mucoadhesion of F1**

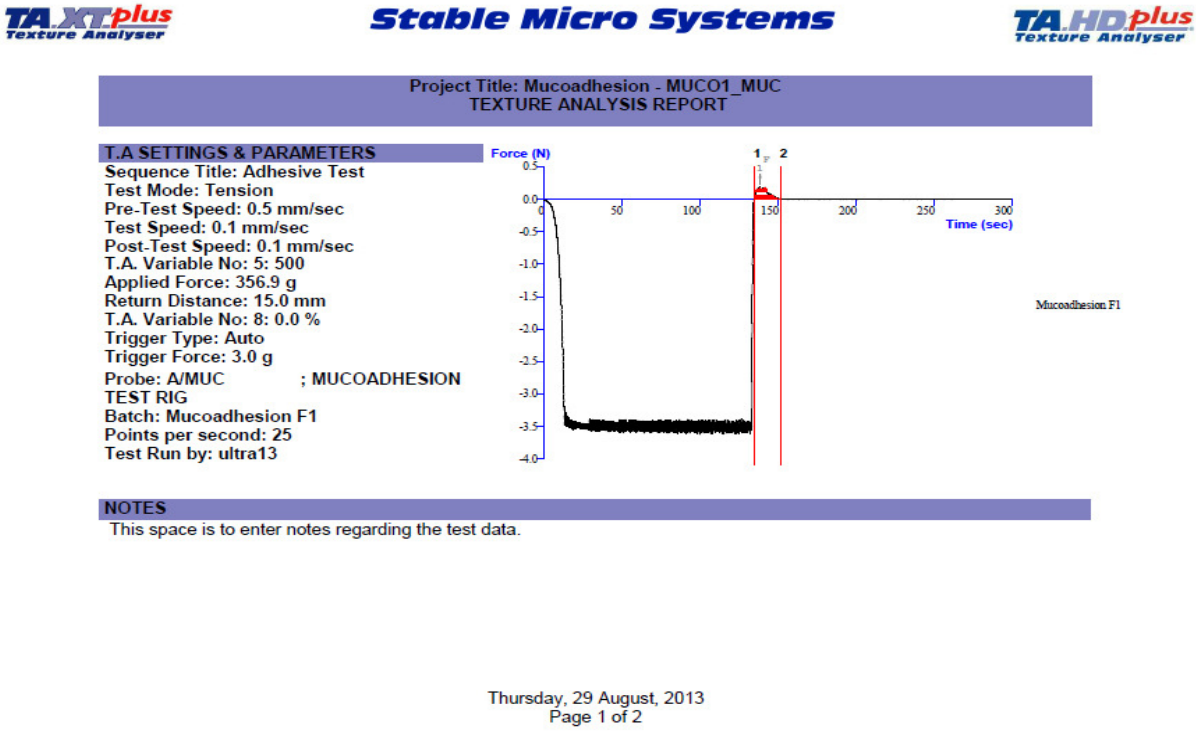



**Figure no: 22 Graph of mucoadhesion of F2**

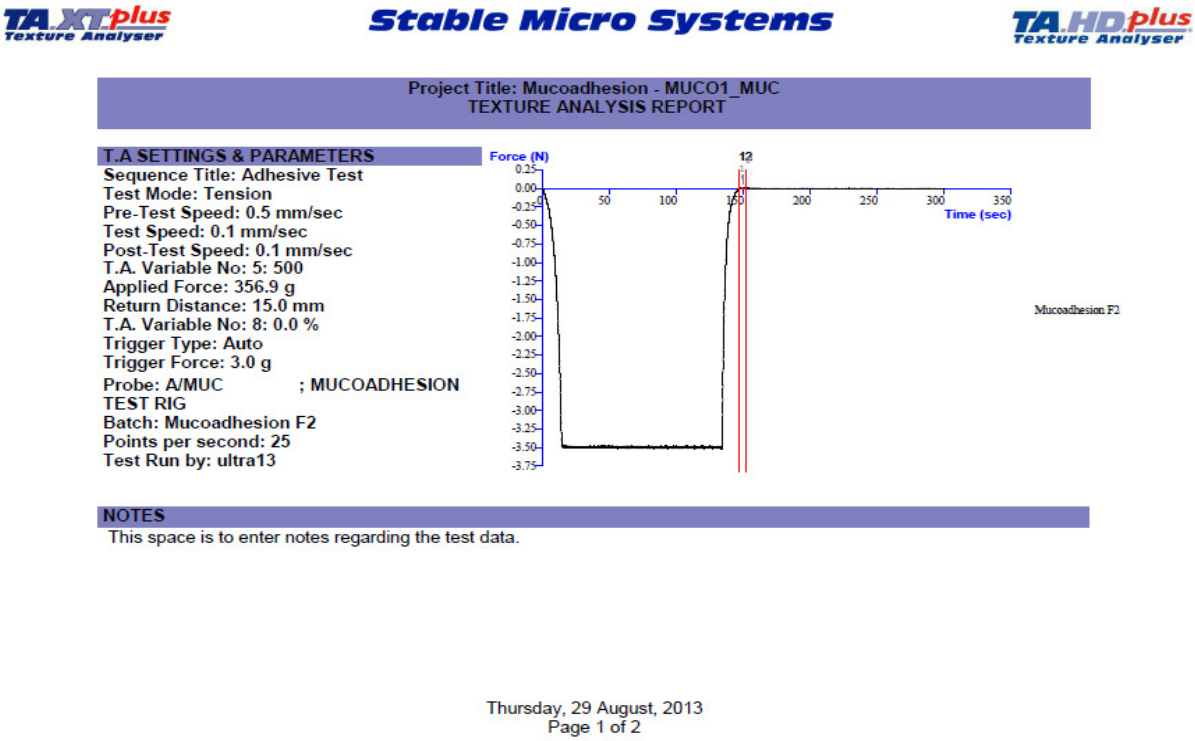



**Figure no: 23 Graph of mucoadhesion of F3**

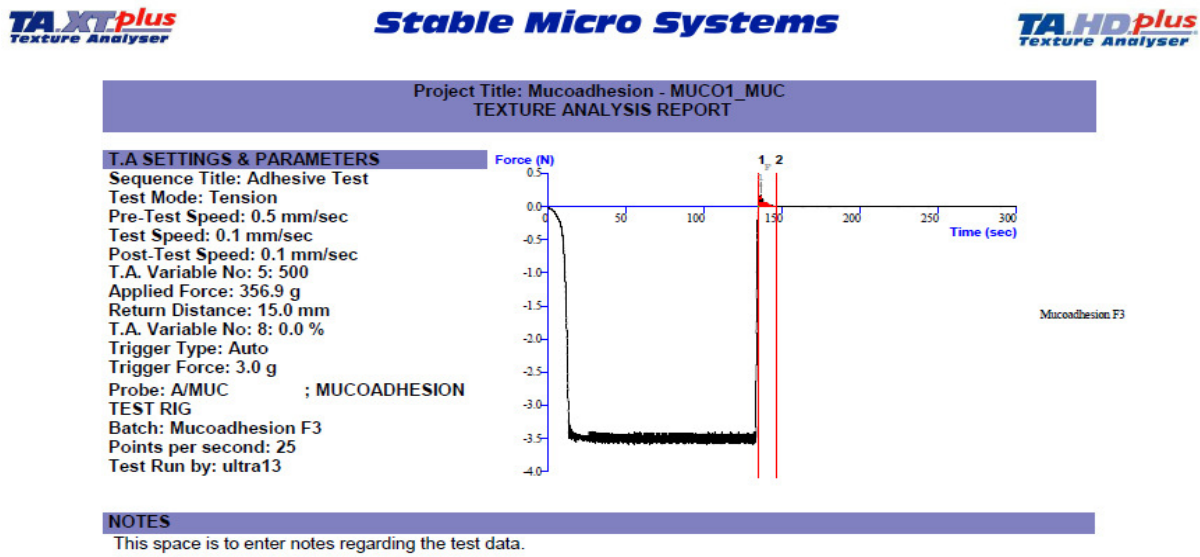



**Figure no: 24 Graph of mucoadhesion of F4**

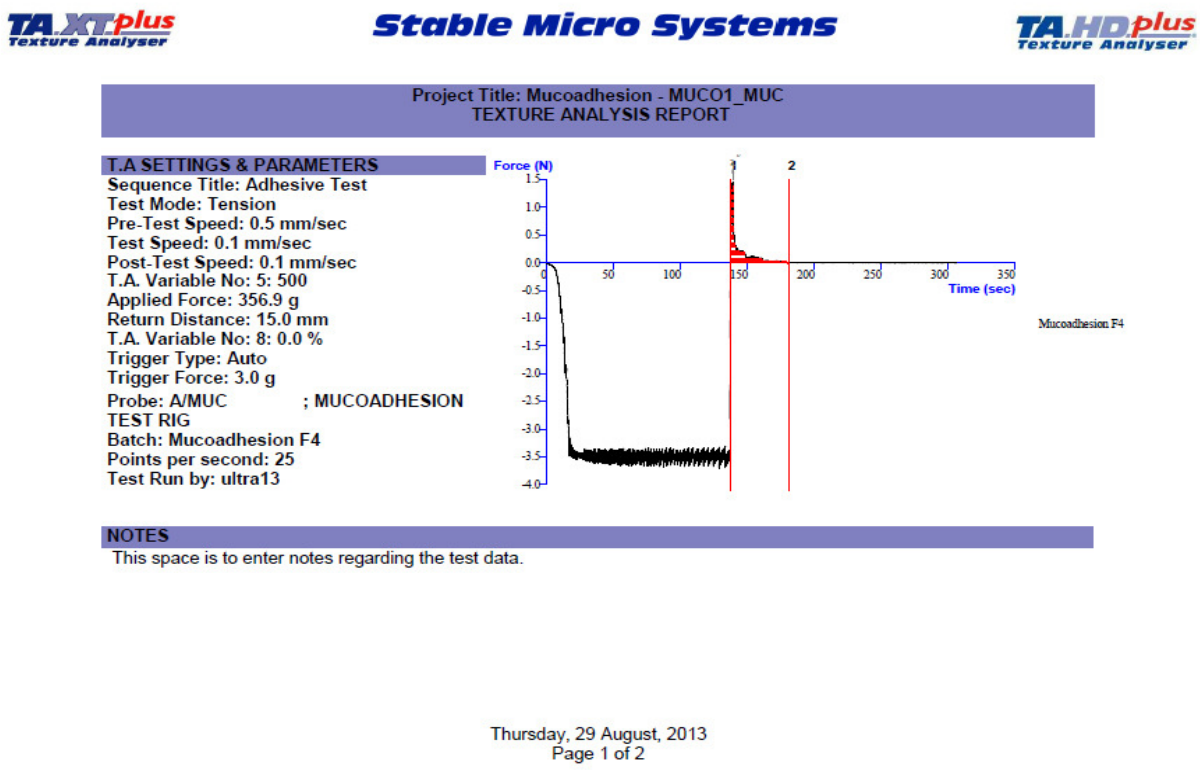



**Figure no: 25 Graph of mucoadhesion of F5**

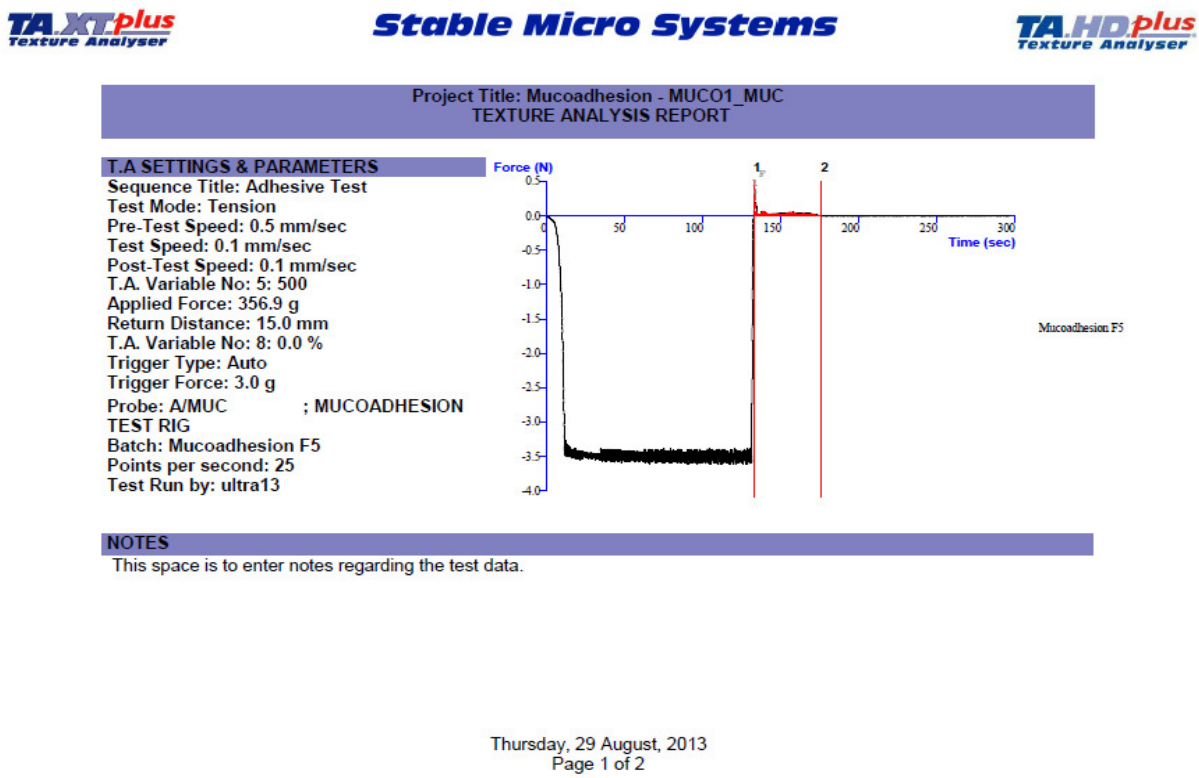



**Figure no: 26 Graph of mucoadhesion of F6**

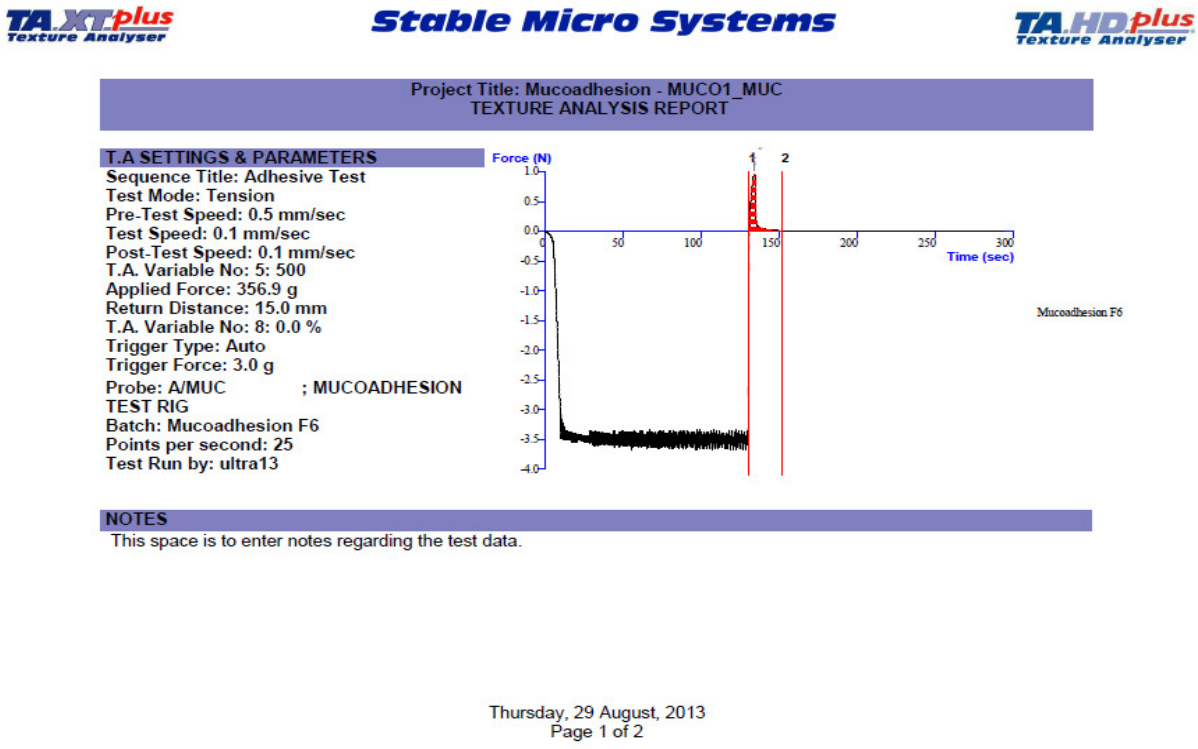



**Figure no: 27 Graph of mucoadhesion of F7**

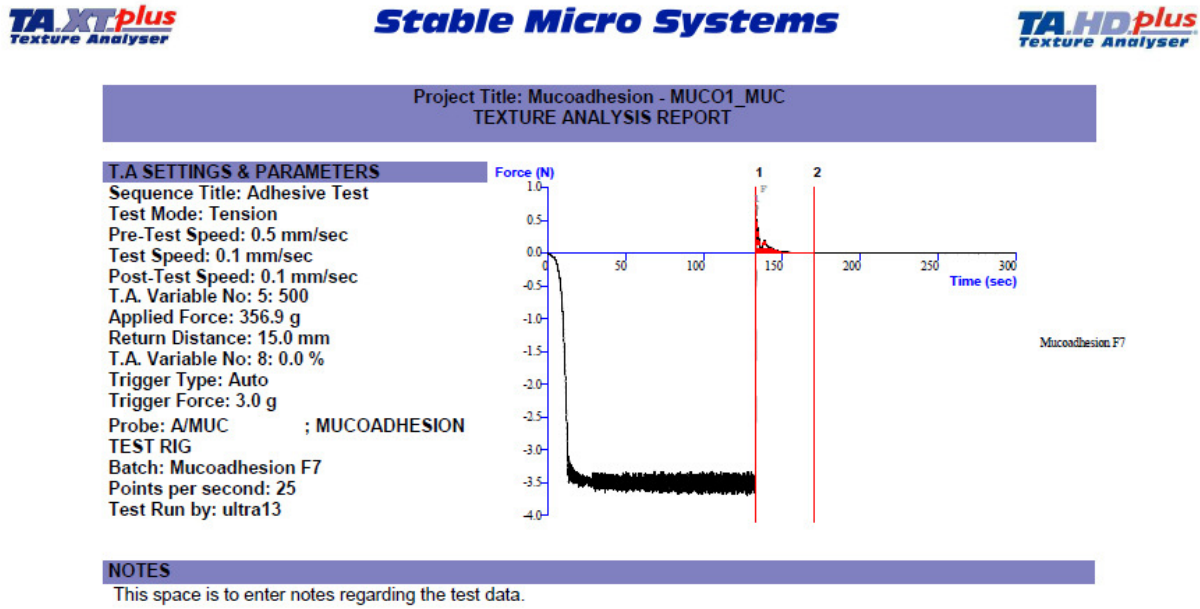



**Figure no: 28 Graph of mucoadhesion of F8**

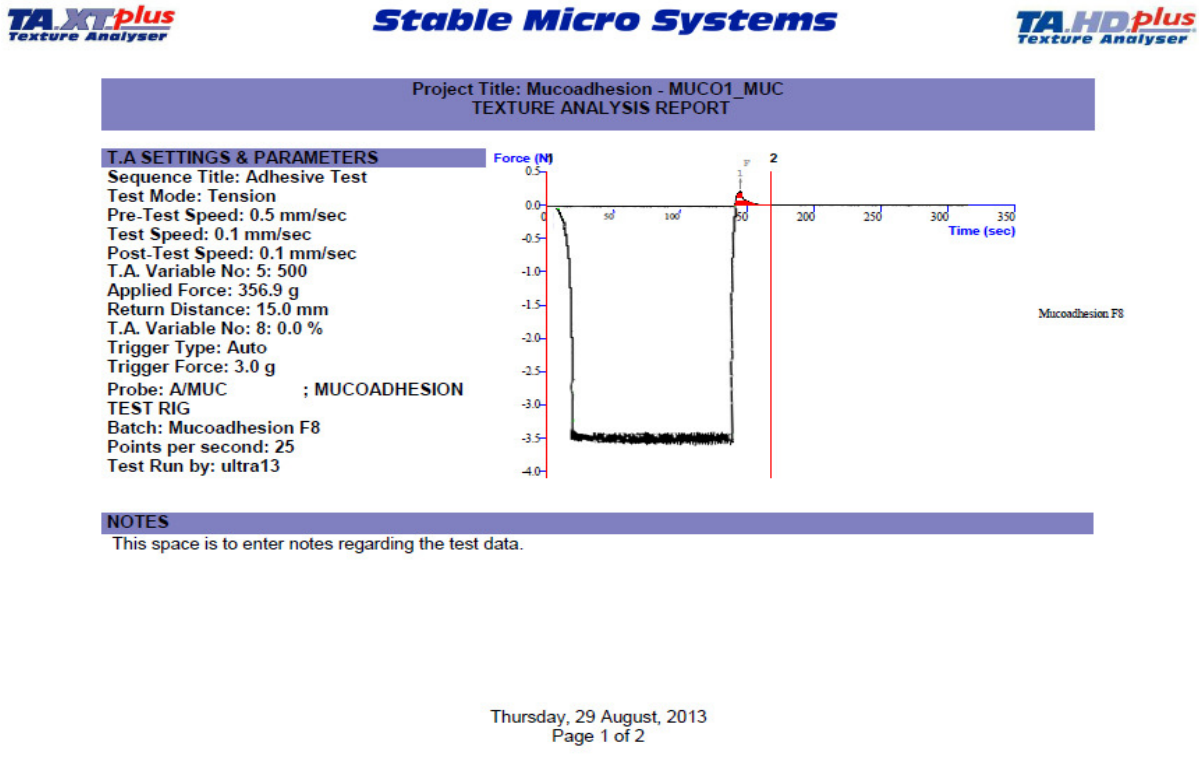


**Figure no: 29 Graph of mucoadhesion of F9**

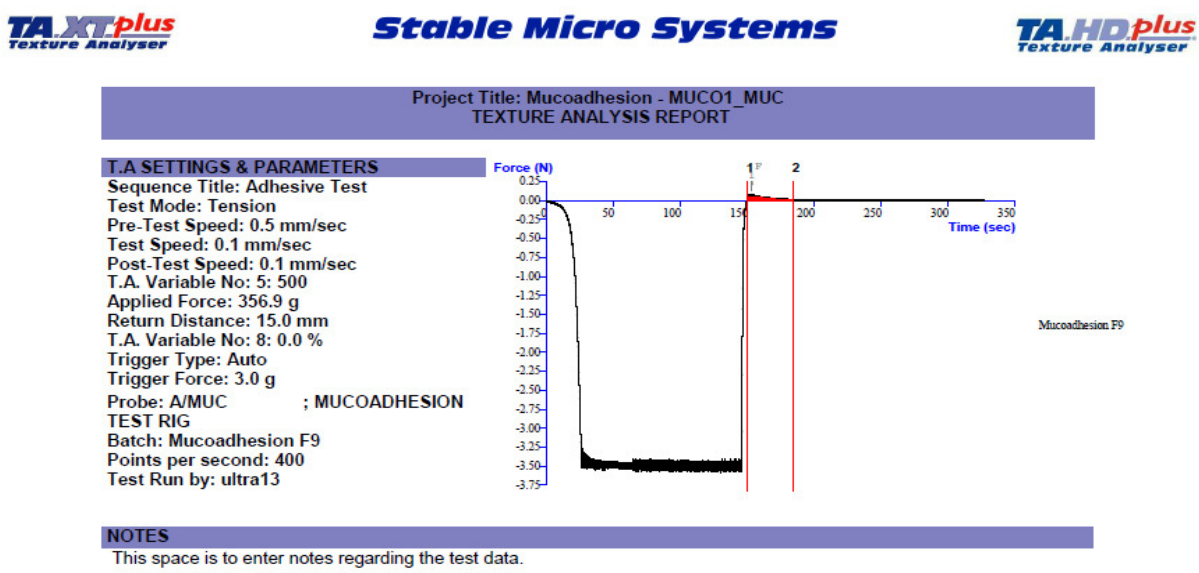



**Figure no: 30 Graph of mucoadhesion of F10**

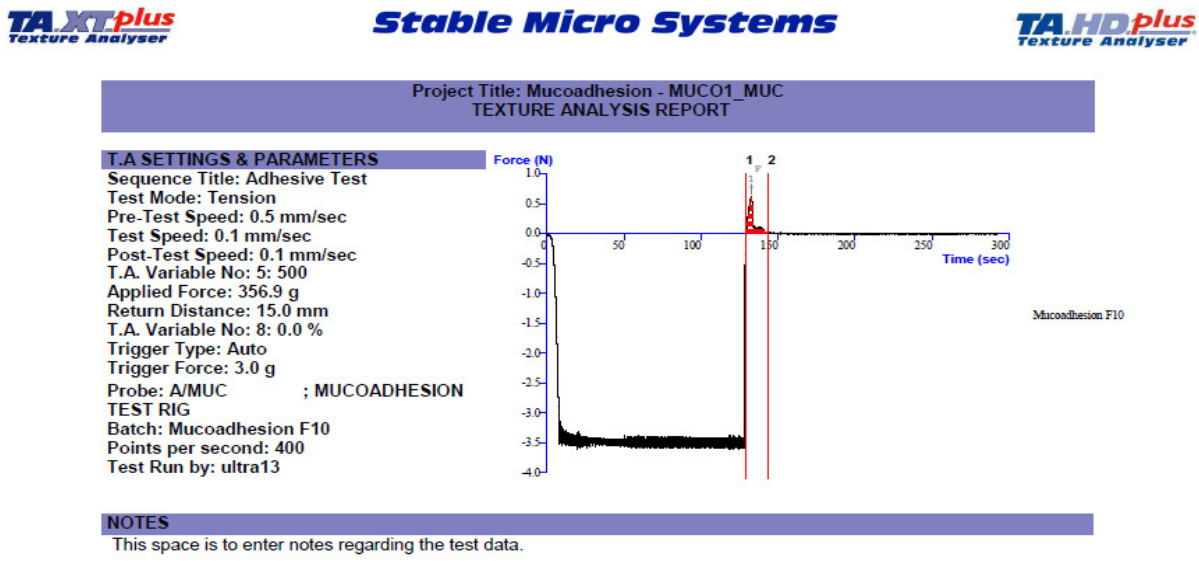



**Figure no: 31 Graph of mucoadhesion of F11**

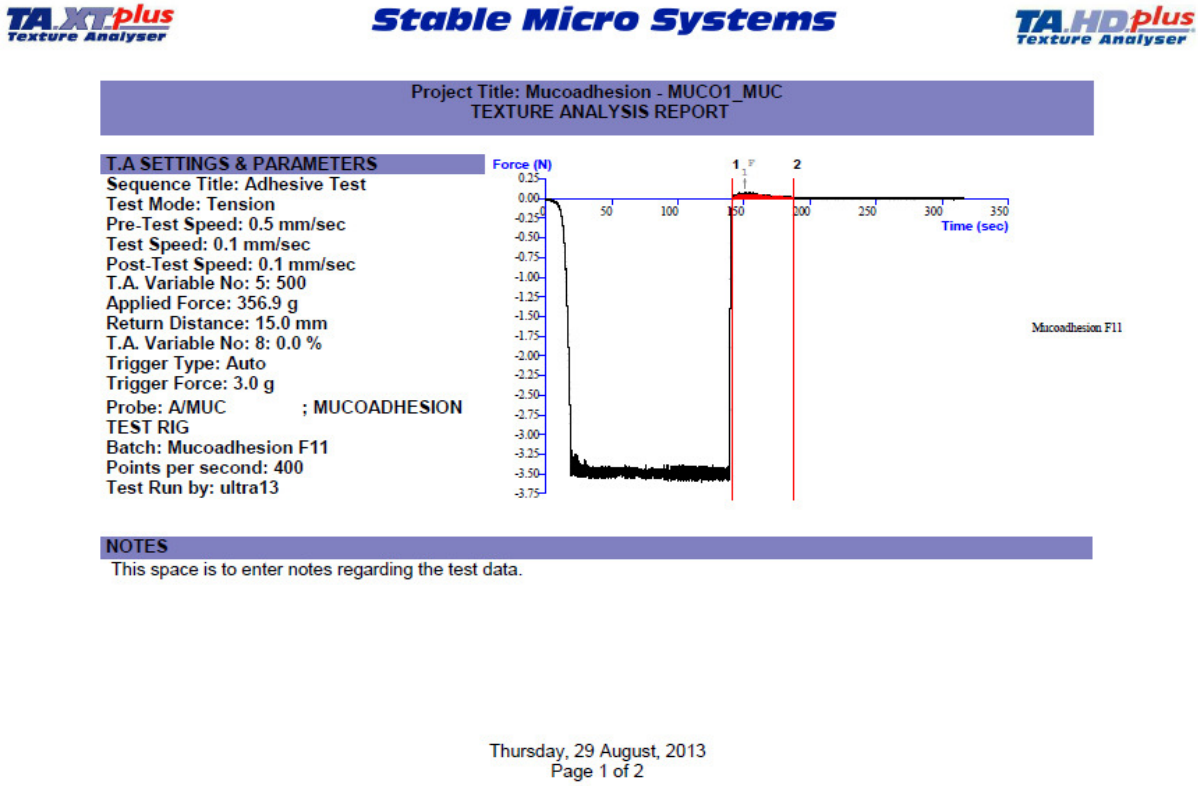



**Figure no: 32 Graph of mucoadhesion of F12**

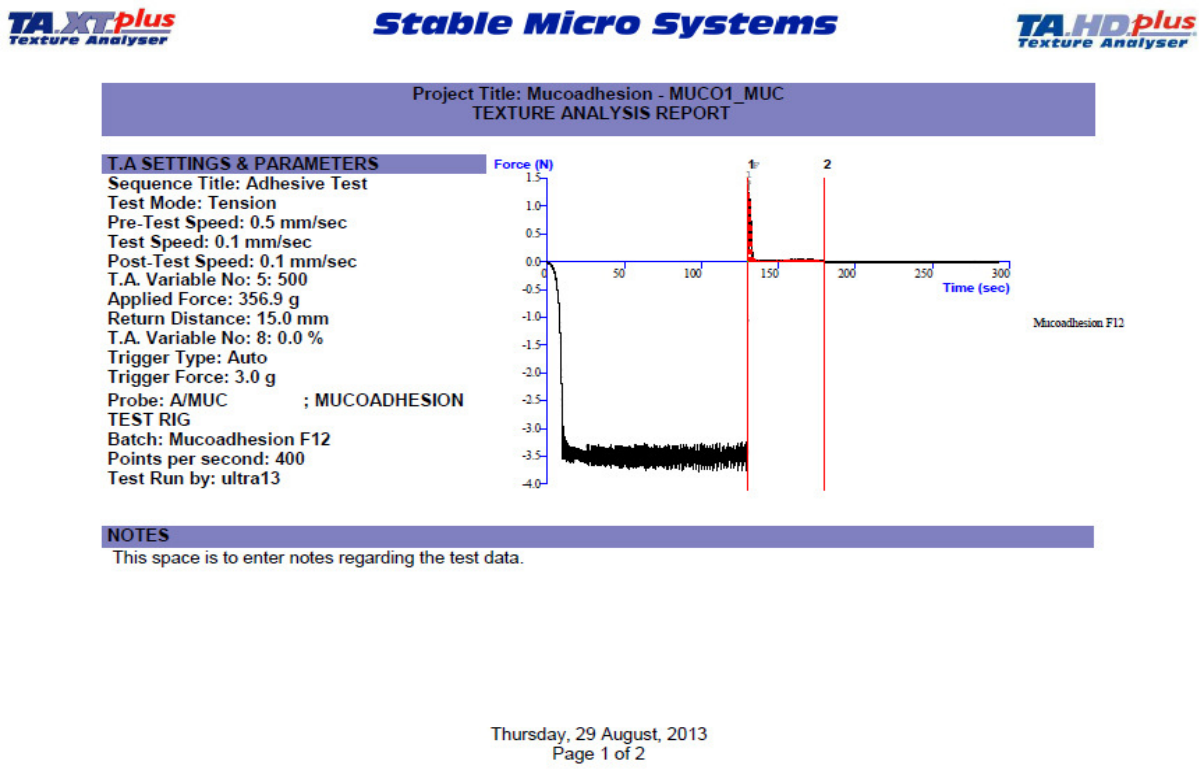


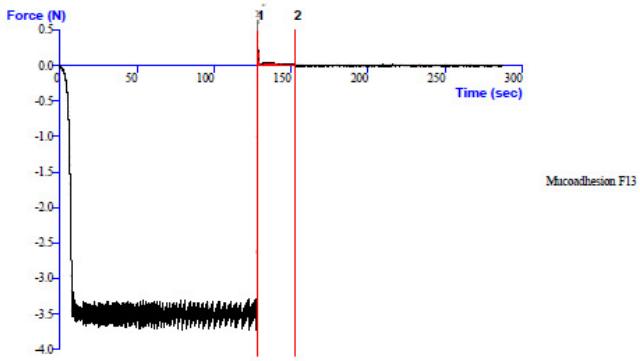

**Figure no: 33 Graph of mucoadhesion of F13**

TA.XT plus Texture Analyser **Stable Micro Systems** TA.HD plus Texture Analyser

Project Title: Mucoadhesion - MUCO1_MUC
TEXTURE ANALYSIS REPORT

**T.A SETTINGS & PARAMETERS**

Sequence Title: Adhesive Test
Test Mode: Tension
Pre-Test Speed: 0.5 mm/sec
Test Speed: 0.1 mm/sec
Post-Test Speed: 0.1 mm/sec
T.A. Variable No: 5: 500
Applied Force: 356.9 g
Return Distance: 15.0 mm
T.A. Variable No: 8: 0.0 %
Trigger Type: Auto
Trigger Force: 3.0 g
Probe: A/MUC ; MUCOADHESION TEST RIG
Batch: Mucoadhesion F13
Points per second: 400
Test Run by: ultra13




**NOTES**

This space is to enter notes regarding the test data.

Thursday, 29 August, 2013
Page 1 of 2

***IN-VITRO* DRUG RELEASE STUDY**

The in vitro drug release studies were done for all the batches in Phosphate buffer pH 6.8 using Dissolution apparatus USP VI (cylinder apparatus). The release data were given in table no: 14 and figures 34-38.

**Dissolution Parameters**

Dissolution Medium : Phosphate buffer pH 6.8

Paddle speed : 50 rpm

Apparatus : Dissolution apparatus Type USP VI (cylinder Apparatus)

Temperature : 37ºC ± 0.5ºC

Withdrawal time : 3hrs with 30min interval

Volume withdraw : 5 ml

**Table no: 14 *In Vitro* Drug Release study**

| Time (min) | Cumulative Percent Drug Released | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 | F13 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 52.06 | 34.58 | 17.34 | 32.27 | 30.68 | 12.98 | 14.45 | 19.20 | 9.02 | 15.66 | 32.16 | 23.36 | 28.09 |
| 15 | 56.07 | 46.75 | 38.41 | 42.27 | 44.58 | 31.49 | 37.25 | 47.16 | 27.98 | 36.70 | 46.75 | 31.86 | 38.30 |
| 30 | 70.44 | 70.46 | 46.75 | 47.95 | 68.19 | 42.78 | 52.14 | 57.12 | 38.61 | 57.26 | 51.20 | 38.42 | 46.19 |
| 60 | 94.94 | 84.59 | 59.92 | 67.49 | 75.26 | 57.92 | 65.01 | 71.33 | 54.80 | 64.74 | 65.30 | 45.95 | 55.25 |
| 90 | **103.89** | 86.77 | 80.33 | **100.9** | 82.10 | 65.14 | 75.17 | 94.56 | 59.66 | 73.16 | 74.70 | 53.29 | 64.07 |
| 120 | | **101.77** | 92.84 | | **99.97** | 74.75 | 89.84 | 95.27 | 75.38 | 85.08 | 77.42 | 71.05 | 85.42 |
| 150 | | | **100.74** | | | 90.13 | **99.10** | **102.62** | 89.95 | 93.72 | 93.75 | 87.07 | 95.17 |
| 180 | | | | | | **100.71** | | | **100.81** | 99.80 | **101.17** | **100.78** | **101.67** |

**Figure No: 34 *In-vitro* drug release of Promethazine HCl from formulations F1, F2&F3.**

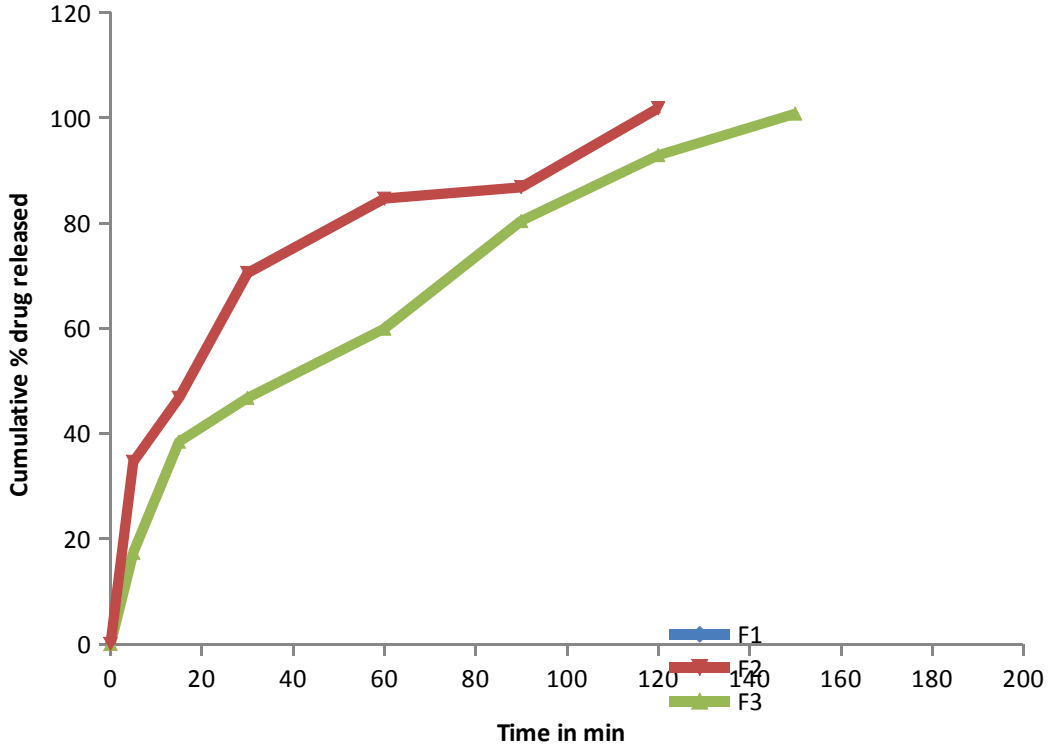



**Figure No: 35 *In-vitro* drug release of Promethazine HCl from formulation F4, F5&F6.**

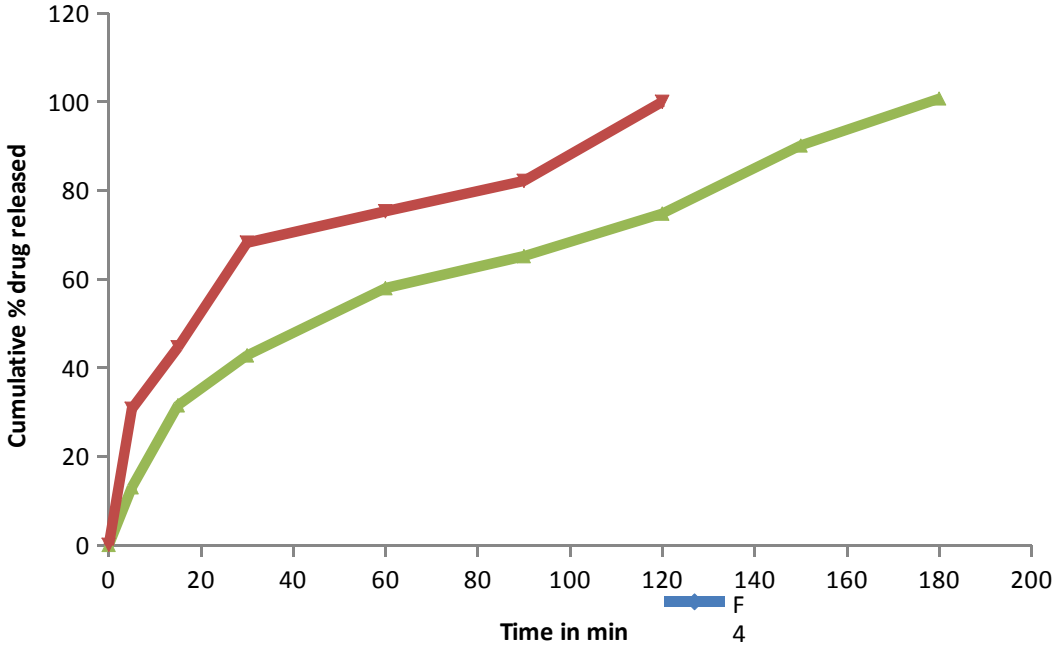


**Figure No: 36 *In-vitro* drug release of Promethazine HCl from formulation F7 & F8.**

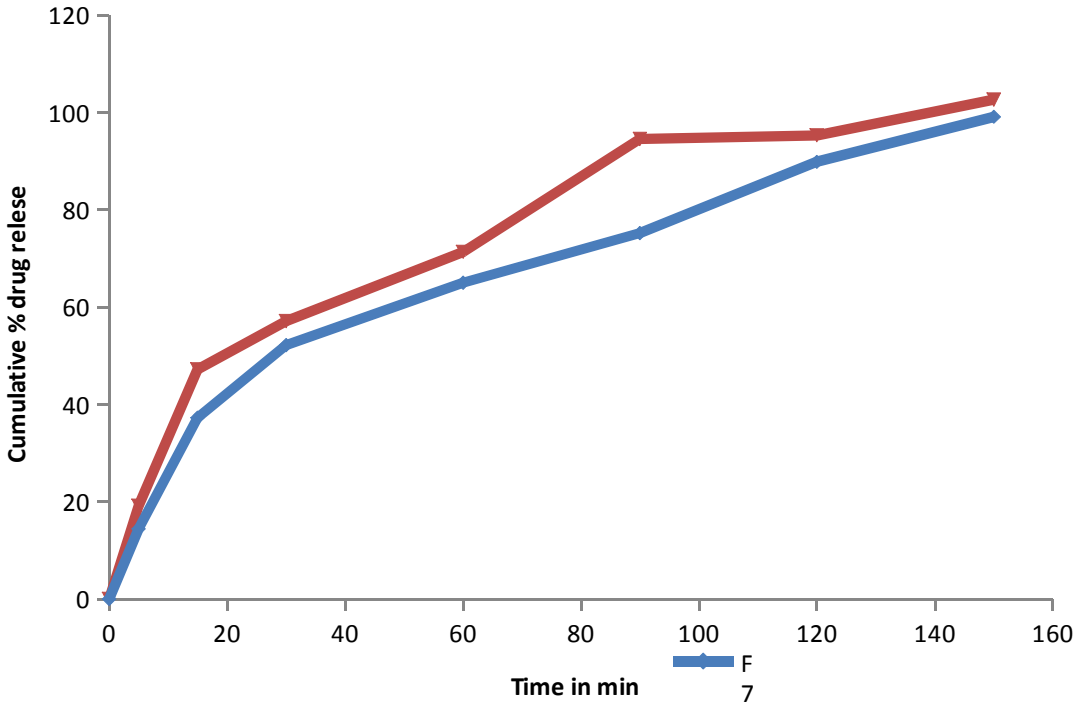



**Figure No: 37 *In-vitro* drug release of Promethazine HCl from formulation F9 & F10.**

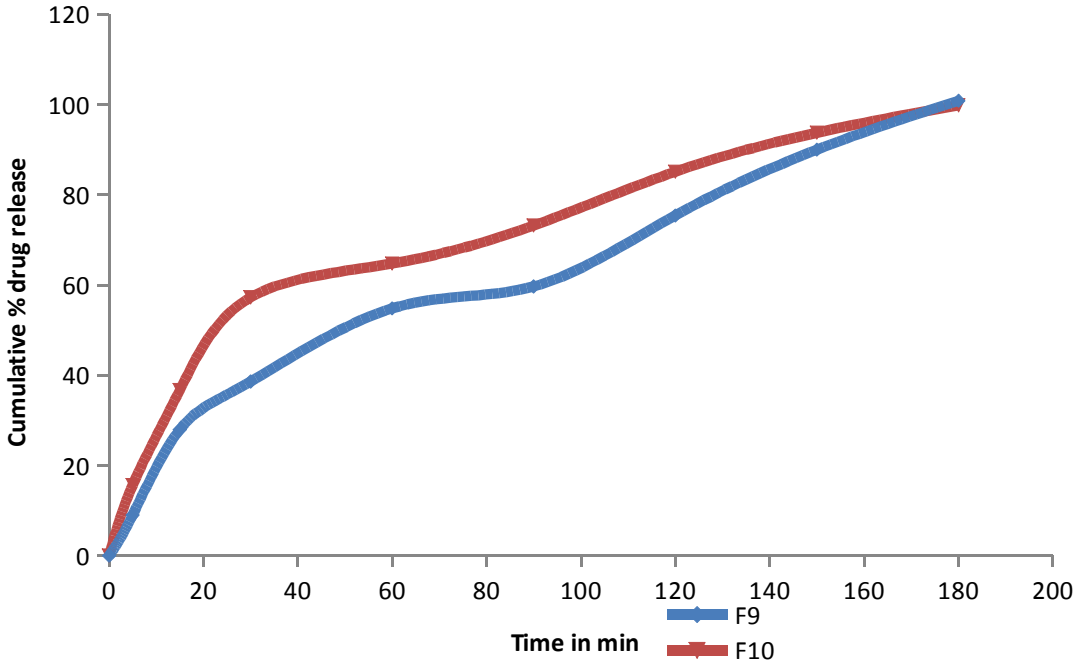
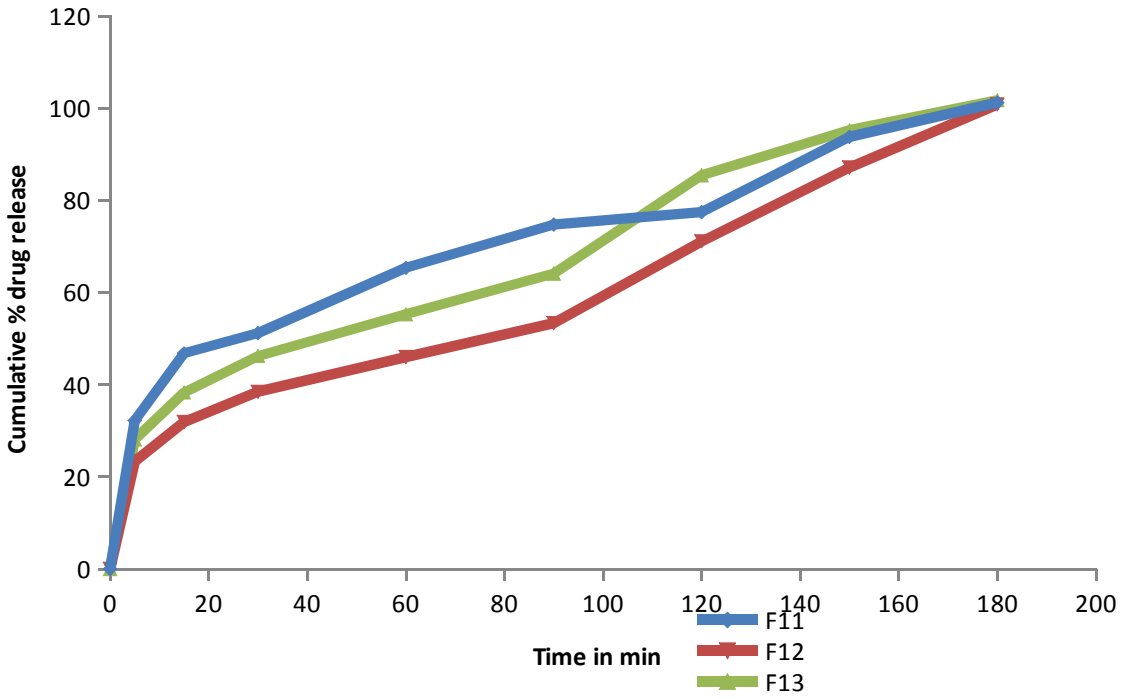


**Figure No: 38 *In-vitro* drug release of Promethazine HCl from formulation F11, F12 & F13.**




From the *in-vitro* release study reports, formulations F1 and F4 showed complete drug release within 90 mins, for F2 and F5 within 120 mins, for F3, F7 and F8 within 150 mins and for F6, F9, F10, F11, F12 and F13 within 180 mins (Table no 14). Drug release within 5 minute was high in F1 (52.09%) and low in F9 (9.02 %).

Drug release was found to be decreasing with increasing polymer content. Also drug release decreased with increasing proportion of glycerine due to increase in thickness. But formulations with different plasticizers have similar drug release and no effect in drug release with different plasticizer type.

The formulation F6 i.e, with HPMC K4M 2.5% and glycerine 50% to the polymer content have 12.98% release within 5min and release completed within 3hrs. The release pattern was linear.

**KINETICS STUDIES**

To understand the order and mechanism of drug release from buccal patches the data was subjected to various kinetic equations and plotted according to first order, Higuchi and Korsemeyer's equations. The kinetic study results were given in table 15 and figures 39&40.

The kinetic studies with Higuchi's equation showed linear plots with high regression co-efficient value 0.9911 indicated that the mechanism of drug release was diffusion controlled.

The release profiles after first 5 minutes was found to follow gel-permeation mediated as the Korsemeyer Peppas plots were linear for all formulations (Fig.40). The release of the drug was through the swollen matrix of the patch after the initial burst release.

**Table no: 15 Kinetic analysis of release data for Higuchi's & Korsemeyer Peppas Model**

| Sl.No: | Formulation Code | $R^2$ values | |
|---|---|---|---|
| | | Higuchi's Equation | Korsemeyer's Equation |
| 1 | F1 | 0.8772 | 0.7582 |
| 2 | F2 | 0.9167 | 0.7825 |
| 3 | F3 | 0.9925 | 0.9184 |
| 4 | F4 | 0.9525 | 0.9019 |
| 5 | F5 | 0.9301 | 0.8042 |
| 6 | F6 | **0.9911** | **0.9275** |
| 7 | F7 | 0.9876 | 08919 |
| 8 | F8 | 0.9631 | 0.8396 |
| 9 | F9 | 0.9844 | 0.9477 |
| 10 | F10 | 0.8973 | 0.8564 |
| 11 | F11 | 0.9170 | 0.8439 |
| 12 | F12 | 0.9523 | 0.9435 |
| 13 | F13 | 0.9652 | 0.9125 |

**Figure no: 39 Higuchi model plot for F6**

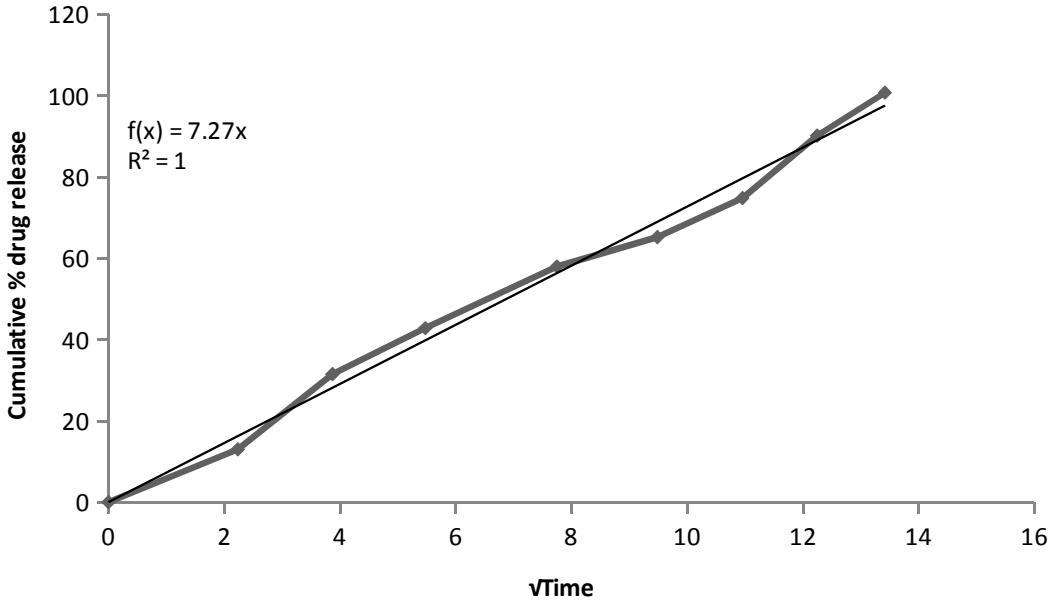
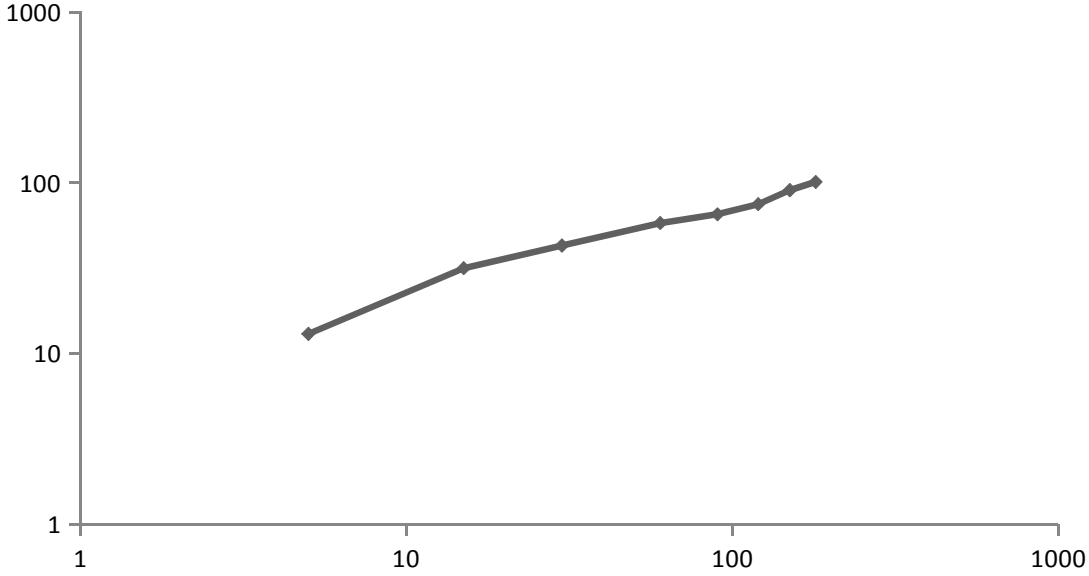



**Figure no: 40 Korsemeyer's plot for F6**



## *EX-VIVO* PERMEATION STUDIES

*Ex vivo* drug permeation through fresh Goat buccal mucosa using Diffusion cell and the results were given in table no 16 and figures 41-45.

**Permeation study parameters**

Donor compartment : Phosphate buffer pH6.8

Receptor compartment : Phosphate buffer pH7.4

Apparatus : Diffusion cell

Withdrawal time : 3 hrs with 30 min interval

Volume withdrawn : 1mL

**Table No: 16 *Ex-vivo* Permeation studies**

| Time (min) | Cumulative Percent Drug Absorbed | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 | F13 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 46.15 | 32.11 | 15.87 | 30.97 | 28.65 | 12.01 | 12.91 | 18.57 | 8.49 | 14.77 | 31.63 | 22.51 | 25.42 |
| 15 | 54.88 | 44.68 | 36.47 | 39.41 | 42.52 | 30.11 | 36.56 | 45.82 | 26.77 | 35.85 | 45.41 | 30.74 | 37.18 |
| 30 | 68.32 | 67.25 | 44.32 | 47.01 | 65.15 | 40.52 | 50.85 | 56.38 | 37.15 | 56.81 | 50.18 | 37.24 | 48.21 |
| 60 | 90.44 | 80.34 | 56.44 | 65.78 | 74.62 | 56.21 | 64.67 | 70.68 | 53.31 | 63.36 | 64.68 | 45.08 | 66.11 |
| 90 | **98.31** | 84.58 | 78.91 | **99.16** | 81.22 | 64.89 | 75.01 | 92.85 | 57.85 | 72.95 | 74.01 | 52.43 | 70.52 |
| 120 | | **98.49** | 90.75 | | **97.87** | 73.68 | 88.67 | 94.54 | 75.11 | 84.05 | 76.39 | 70.28 | 85.96 |
| 150 | | | **98.67** | | | 89.14 | **98.79** | **100.65** | 88.52 | 90.68 | 92.78 | 86.14 | 93.38 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 180 | | | | | | **98.98** | | | **99.89** | **98.73** | **99.81** | **99.76** | **99.75** |

**Figure No: 41 *Ex-vivo* drug permeation of Promethazine HCl from formulation F1, F2 & F3.**

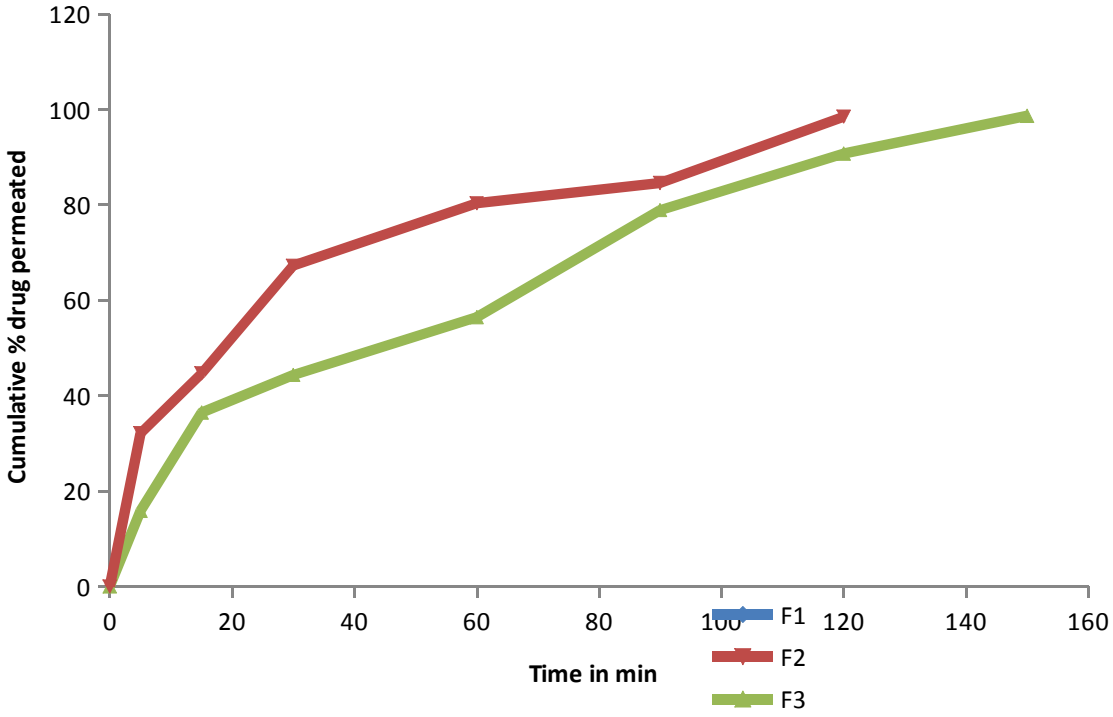



**Figure No: 42 *Ex-vivo* drug permeation of Promethazine HCl from formulation F4, F5 & F6.**

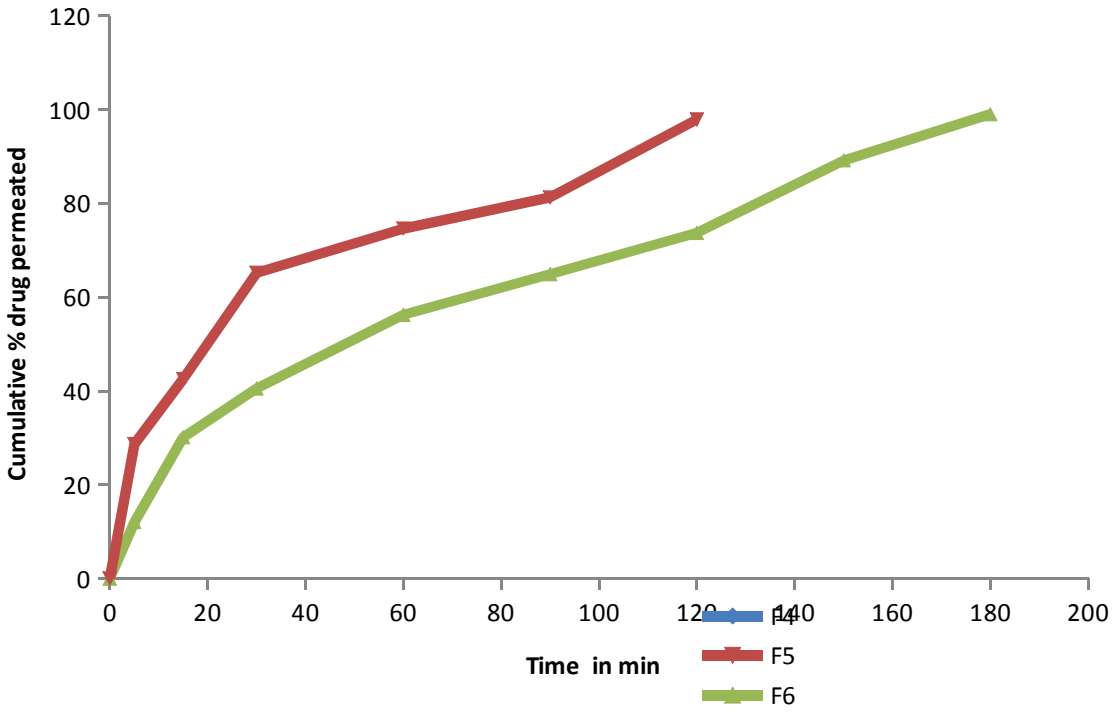



**Figure No: 43 *Ex-vivo* drug permeation of Promethazine HCl from formulation F7&F8.**

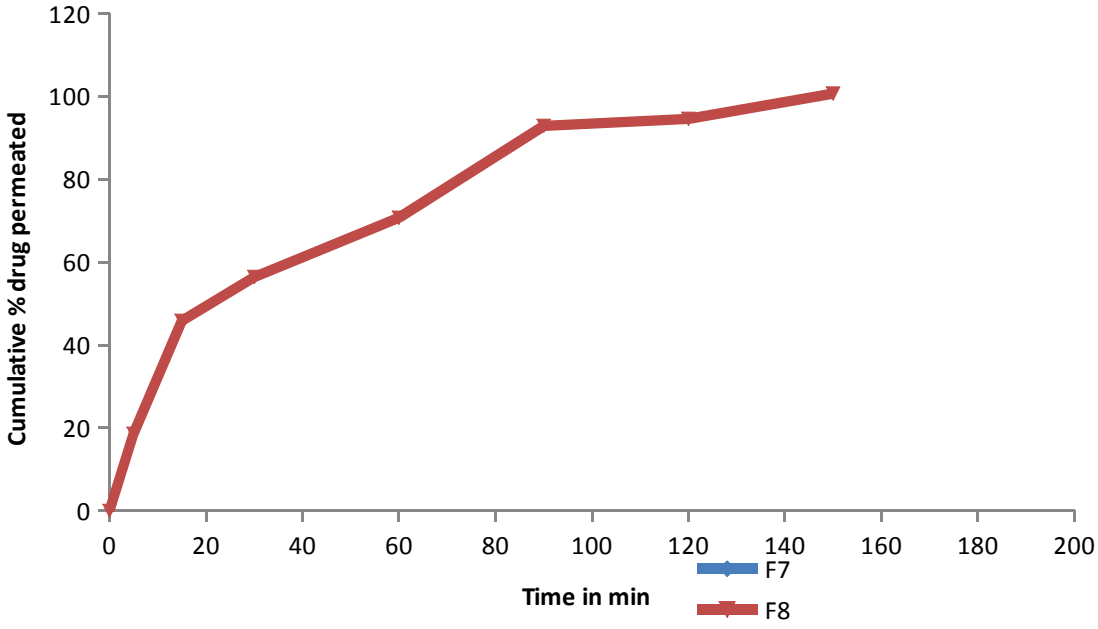



**Figure No: 44 *Ex-vivo* drug permeation of Promethazine HCl from formulation F9 & F10.**

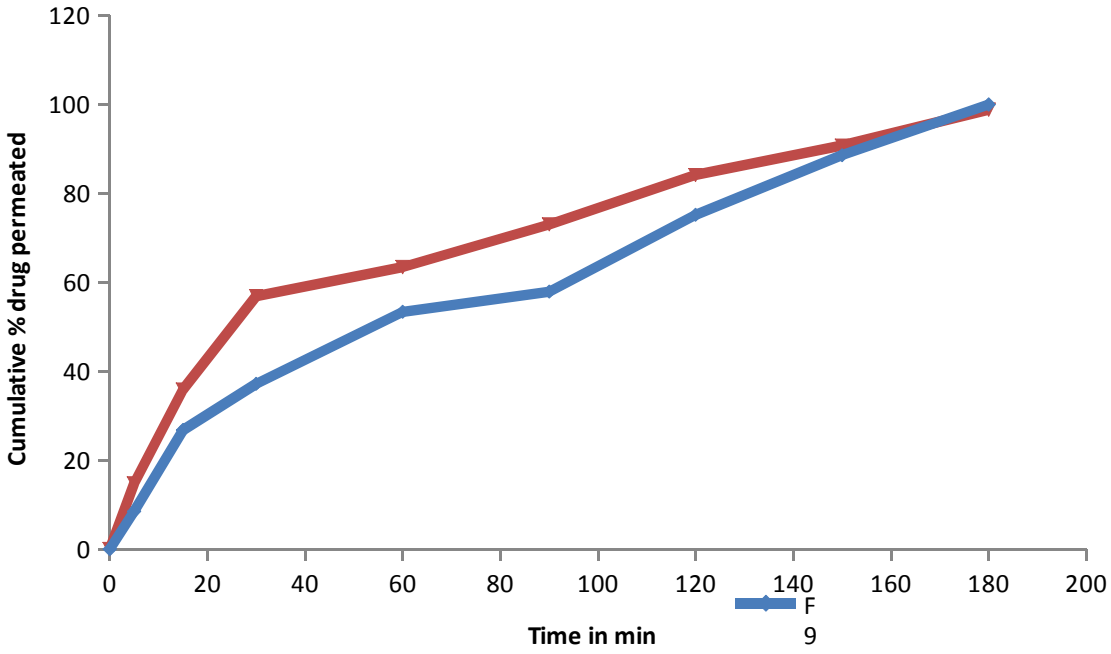
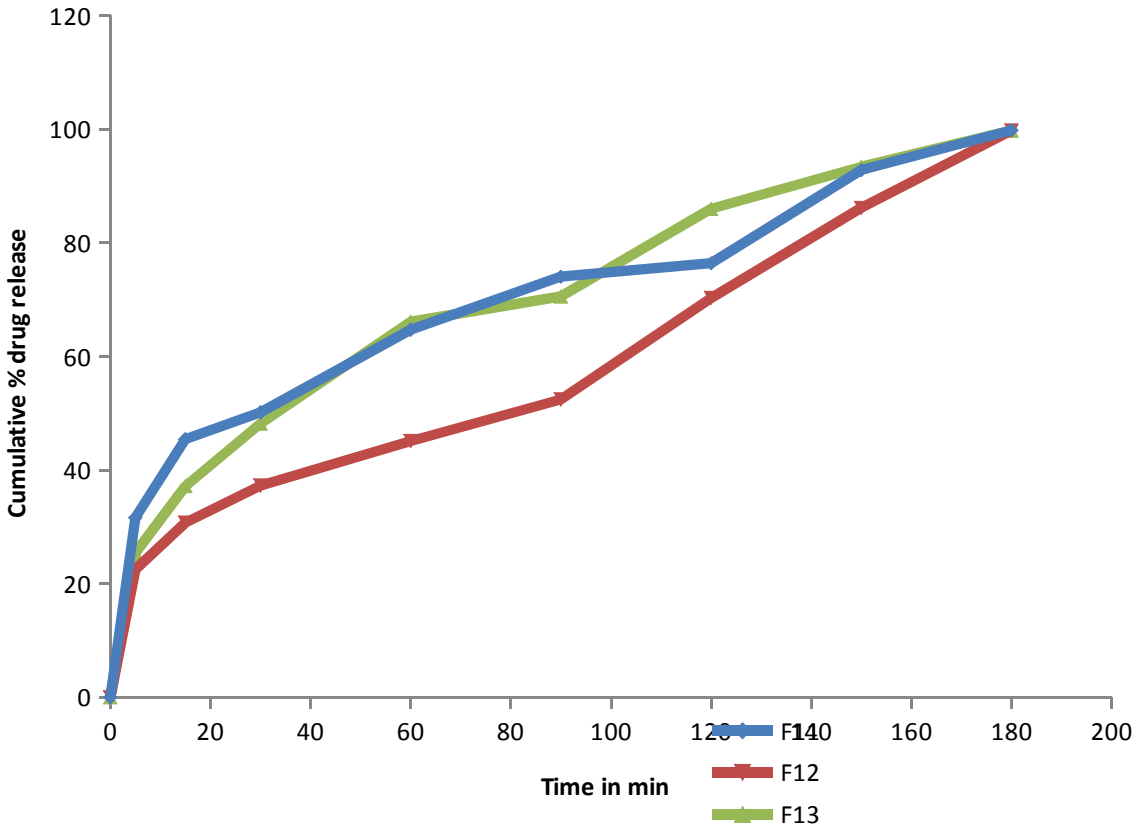



**Figure No: 45 *Ex-vivo* drug permeation of Promethazine HCl from formulation F11, F12&F13.**

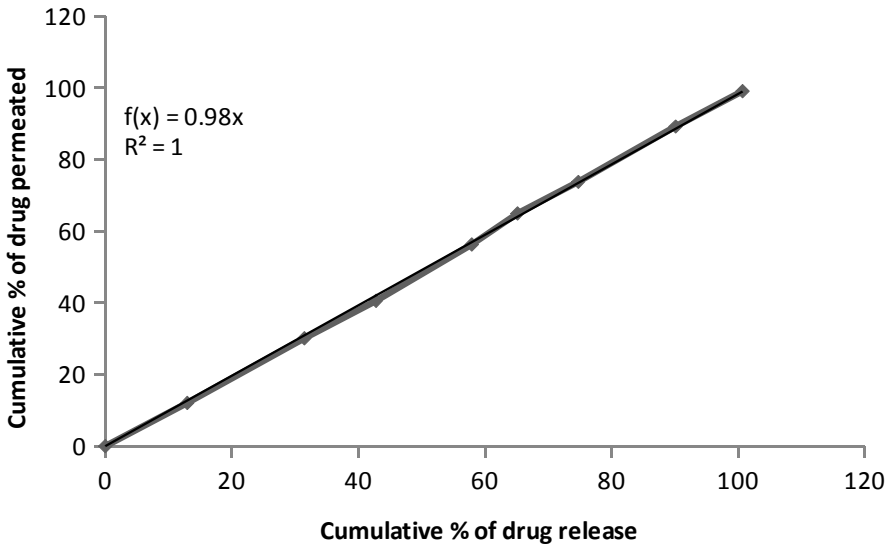


The results indicated that Promethazine hydrochloride can permeate easily across the goat mucosal membrane. This was due to high aqueous and lipid solubility of Promethazine hydrochloride. The cumulative% Promethazine hydrochloride penetrated through the membrane was indicated that the penetration of drug through the Goat cheek membrane was rapid. The comparison profiles of the different patches showed that permeability behavior was same for all the patches. This result reveals that Promethazine hydrochloride could possibly permeate through the human buccal membrane.

**Correlation of *In vitro* drug release and *ex vivo* drug permeation**

A plot between Cumulative % drug release from F6 on X-axis and Cumulative % drug permeation from F6 on Y-axis obtained was a straight line with $R^2$ value of 0.9994 (Figure 46). This shows *in vitro* dissolution performed correlates well (100%) with *ex vivo* permeation study. It further indicates the *in vitro* dissolution study itself is sufficient to evaluate the permeability of the drug from patches in lieu of *ex vivo* permeation study.

**Figure no: 46 Correlation of *In vitro* drug release and *Ex vivo* drug permeation for F6.**




***IN-VIVO* COMPATIBILITY STUDY**

From the *In-vivo* compatibility study of the buccal patches in human healthy volunteers no irritations, no discomfort, no heaviness, no local anaesthetic actions and good mouth feel was observed. This further confirms successful formulation of Promethazine hydrochloride in the form of buccal patch. The tested patches were not detached from the oral mucosa over the study period, which indicated that the bioadhesion values of the formulations were satisfactory to retain the patch on the buccal mucosa.

# SUMMARY AND CONCLUSIONS

Motion sickness is a condition in which there exists a disagreement between visually perceived movement and the vestibular system's sense of movement. Promethazine hydrochloride is the most suitable drug because of its anti-cholinergic effect and reduces the nausea experienced during motion sickness.

Because of the low systemic bioavailability and requirement of rapid onset of action for patients with nausea and motion sickness, buccal mucoadhesive administration dosage form is effective and safe, and unpleasant taste and local anaesthetic effect on tongue can be avoided. This dosage form is convenient for patients those who want any-time dosage especially when travelling.

In the present work successful attempt was made to formulate buccal patches using 10 mg drug loaded in HPMC K4M and HPMC15cps with different plasticizers glycerine, PEG 400 and Propylene glycol in different compositions.

The objectives for the proposed work are given in chapter III. Extensive literature survey was done before the experimental works for collection of theoretical and technical data. The review of literature is presented in chapter II. The materials and equipments used throughout the work are listed in chapter IV followed by Drug profile and excipient profiles.

Methodology for the preparation and characteristic evaluations are included in chapter IV. Drug- excipient compatability was assessed by FTIR spectroscopy. The physicochemical characteristics such as weight, thickness, folding endurance, surface pH, drug content and swelling index were evaluated for all formulations. Tensile strength and mucoadhesion studies were carried out with TA.XT plus texture analyser. *In vitro* drug release studies were carried out in Dissolution apparatus Type VI (cylinder Apparatus). The data was subjected to various kinetic analyses and plotted according to first order, Higuchi and Korsemeyer's equations to understand the order and mechanism of drug release. *Ex-vivo* diffusion study through goat buccal mucosa was carried out in Diffusion cell for all the formulations. In-vitro release ex-vivo correlation study was done. *In-vivo* compatibility study of the buccal patch conducted in 10 healthy human volunteers.

The results obtained are presented in chapter V, in the form of graphs and figures and are explained and discussed in detail

**The following conclusions were drawn from the present investigation:-**

- ❖ Buccal mucoadhesive patches containing Promethazine hydrochloride was prepared with HPMC 15cps and HPMC K4M in different concentrations with different proportions of glycerine and also with PEG 400 and Propylene glycol.
- ❖ The IR spectral data indicates that there was no interaction between drug and the utilized polymers.
- ❖ Each formulation was uniform in their weight (54.09±0.6-311.12±0.6 mg), thickness (77.67±0.33-424.33±2µm) and almost uniform in their drug content with low SD value and all the patches exhibited folding endurance above 500 proving the flexible nature of the patch.
- ❖ The surface pH values were found to be between 5.5 and 6.0 for all the formulations which indicate that all the formulations were compatible with the buccal surface.
- ❖ Swelling index of the patches was increasing with polymer concentration. Also it increases with increasing content of glycerine. There is no marked change in swelling nature for patches with 50% of PEG 400 and Propylene glycol when compared with glycerine.
- ❖ Tensile strength and extensibility of the patches with HPMC K4M is higher compared to patches with HPMC 15cps. Extensibility of the patches increased with increase in polymer concentration. The flexibility and tensile strength increases with increasing amount of plasticizer (Glycerine). There is no significant effect with different plasticizer type on extensibility and tensile strength of the patches.
- ❖ The adhesive force of the patches was found to be varying with thickness and swelling nature of the patches. Patches with PEG 400 and Propylene glycol have poor mucoadhesion. Patches with optimum thickness and swelling nature showed good adhesion (F6). The plasticizer suitable with respect to good mucoadhesion is glycerine.
- ❖ Drug release found to be decreasing with increasing proportions of polymer. Also drug release decreased with increasing proportion of glycerine. But formulations with different plasticizers have similar drug release and no effect in drug release with different plasticizer type.
- ❖ The formulation F6 i.e, with HPMC K4M 2.5% and glycerine 50% to the polymer content have 12.98% release within 5min and release completed within 3hrs. The release pattern is linear.
- ❖ The kinetic studies with Higuchi's equation showed linear plots indicated ($R^2$=0.9911) that the mechanism of drug release was diffusion controlled. The release profiles after first 5 minutes was found to follow gel-permeation mediated as the Korsemeyer Peppas plots were linear for all formulations. The release of the drug was through the swollen matrix of the patch after the initial burst release.

- The permeation across goat mucosal membrane indicated that penetration of Promethazine hydrochloride was rapid due to high aqueous and lipid solubility. This result reveals that Promethazine hydrochloride could possibly permeate through the human buccal membrane.
- *In-vitro* and *Ex-vivo* correlation was carried out for formulation F6 and the correlation co-efficient was found to be 0.9994.
- Results from *In-vivo* compatibility study exhibited good acceptance of the patches.
- Among the various formulations F6 exhibited optimum thickness, swelling, pH, tensile strength, good bioadhesive strength, and the drug release as compared to other formulations. Hence the formulation F6 is selected as optimized formulation.

**ERRATA**

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