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A Review On Formulation And Estimation Of Buccal Patches Of Ranitidine.

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ABSTRACT

Buccal drug delivery system is been considered as a potential, non-invasive route of drug administration with several advantages viz. Prolonged therapeutic effect, dose reduction, improved bioavailability, lesser side effects than conventional dosage forms etc.

The present investigation involves formulation, evaluation and comparison of formulated polymeric buccal patches using Ranitidine HCl as model drug. The formulations were prepared by solvent evaporation/casting method.

Ranitidine HCl is a competitive inhibitor of histamine H_2-receptors resulting in the inhibition of gastric acid secretion and an effective alternative in the treatment of Duodenal and Peptic ulcers, Pathological hypersecretory conditions (such as Zollinger-Ellison syndrome), Gastroesophageal Reflux Disease (GERD), Erosive Esophagitis and Maintenance of Healing of Erosive Esophagitis. The bioavailability of Ranitidine HCl following oral administration is about 50% which might be due to colonic degradation by colonic bacteria. The bioavailability of Ranitidine HCl is markedly lower from the human colon than the upper part of gastro intestinal tract.

Matrix type buccal patches of Ranitidine HCl were formulated using various concentrations of Carbopol-934K (CP-934K) & Sodium carboxymethylcellulose (SCMC) while glycerol had been used as both plasticizer and penetration enhancer. The patches were casted in 8 cm diameter petridish. The drug-polymer interaction studies were carried out using Fourier Transform Infrared Spectroscopic (FTIR) technique.

The method consisted of two step: addition of calculated amount of drug in half volume of the solvent (distilled water) in a 50ml beaker with continuous stirring till a homogenous and transparent solution was formed, followed by the addition of Sodium carboxymethyl cellulose slowly over time with further stirring till solutes dissolved completely. Simultaneously Carbopol 934k was added to the remaining half volume of the solvent in different beaker waited till swelled and then added slowly in the solution prepared initially. Finally glycerol was added as both plasticizer and penetration enhancer. The formulation was then kept overnight to remove the bubbles formed during stirring. The formulation was then poured on a clean and flat petridish of desired diameter and kept in a hot air oven at a temperature range between 40-45^{o}C for 8 to 10 hours or till the patch dried with continuous in between monitoring.

The prepared buccal patches were evaluated for thickness, drug content uniformity, weight variation, folding endurance, swelling index, surface pH, surface morphology, *in-vitro* & *ex-vivo* drug release.
Five batches of varying polymeric concentrations were prepared (F1, F2, F3, F4 and F5) and were evaluated for aforementioned parameters. For study and evaluation purposes 1 cm^2 area was cut from the patch. The various evaluation parameters of buccal patches revealed that the prepared patches were smooth, flexible and uniform.

In-vitro release studies were performed across cellophane membrane using Franz Diffusion Cell (FDC). The surface morphology of the patch was examined by Scanning Electron Microscopy (SEM). Based on the physicochemical and *in-vitro* release study, formulation F3, F4 and F5 were chosen for further *ex-vivo* release studies. *Ex-vivo* permeation studies were carried out through buccal mucosa of pig using FDC. Drug release data were fitted to various pharmacokinetic model equations such as zero order kinetics, first order kinetics, Higuchi's and Korsmeyer Peppas model in order to find out mechanism of drug release.It was observed from the whole investigation that a successful buccal patch formulation of H_2-receptors antagonist (Ranitidine HCl) could be prepared by solvent evaporation/casting method with a drug content uniformity effective enough to exhibit systemic effect. Thus several side effects caused by high doses of the model drug could best be lowered by a single dose formulation.

Key Words: Buccal, Ranitidine HCl, Patches, *In-vitro*, *Ex-vivo*.

INTRODUCTION

The average development cost of a new chemical entity (NCE) is approximately $150– 350 million. It often costs substantially less to develop new methods of administration for an existing drug, which results in improved efficacy and bioavailability together with reduced dosing frequency to minimize side effects. Therefore, pharmaceutical companies are under constant pressure to maximize the full potential of a drug candidate. This objective can be accomplished by incorporating the drug into various drug delivery systems. This exercise can lead to convenient dosage forms that overcome previously presented administration problems. For the last two decades, there has been an enhanced demand for more patient-compliant dosage forms.

1.1 Ideal attributes of a drug delivery system:

1. Capable in precise control of constant drug delivery rate.
2. Capable of controlled delivery rates to accommodate the pharmacokinetics of various drugs.
3. Applicable to a wide range and varieties of drug.
4. Should not have any effect on drug stability.
5. Capable of high order of drug dispersion.

Since the early 1980s there has been renewed interest in the use of bioadhesive polymers to prolong contact time in the various mucosal routes of drug administration. The ability to maintain a delivery system at a particular location for an extended period of time has great appeal for both local as well as systemic drug bioavailability. Drug absorption through a mucosal surface is efficient because mucosal surfaces are usually rich in blood supply, providing rapid drug transport to the systemic circulation and avoiding degradation by gastrointestinal enzymes and first pass hepatic metabolism.

1.2 Oral Transmucosal Drug Delivery: Within the oral cavity delivery of drug is classified into several categories. Absorption of drug via mucous membranes of the oral cavity was noted as early as 1847 by Sobvero, the discoverer of nitroglycerin, and systemic studies of oral cavity absorption was first reported by Walton in 1935 and 1944. Due to its excellent accessibility and reasonable patient compliance oral mucosal cavity offers attractive route of drug administration. Within the oral mucosal cavity delivery of drug is classified into three categories: [33]

1. **Sublingual delivery**, which is a systemic delivery of drug through the mucosal membrane lining the floor of the mouth
2. **Buccal delivery** &

3. **Local delivery**, for the treatment of conditions of the oral cavity. The oral cavity is foremost part of digestive system of human body. It is also referred to as "buccal cavity". It is accountable for various primary functions of body. The careful examination of various features of oral cavity can help in development of a suitable buccoadhesive drug delivery system.

1.3 Oral Cavity:

1.3.1 Components and structural features of oral cavity:

Oral cavity is that area of mouth which is delineated or surrounded by lips, cheeks, hard palate, soft palate and floor of mouth. The oral cavity consists of two regions, **Outer oral vestibule**, which is bounded by cheeks, lips, teeth and gingival (Gums) and **Oral cavity proper**, which extends from teeth and gums back to the fauces (which lead to pharynx) with the roof comprising the hard and soft palate. The tongue projects from the floor of the cavity. A detailed outline of buccal cavity is been given in Fig.1.

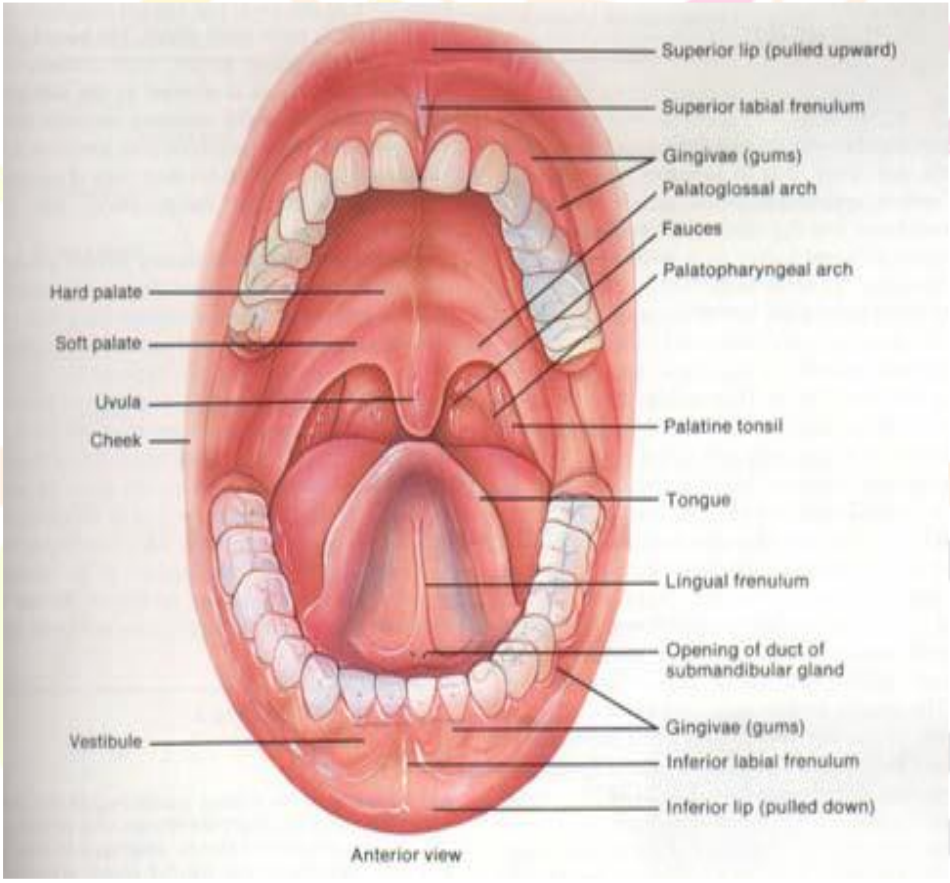

Fig. 1.1 A detailed outline of buccal cavity

1.3.2 Anatomical Features:

The outer surface of the oral cavity is a mucous membrane consisting of an epithelium, basement membrane and lamina propria overlying a submucousa containing blood vessels and nerves. The mucosa can be divided into three

types: Masticatory mucosa, found on the gingiva and hard palate. Lining mucosa, found on the lips, cheeks, floor of mouth, undersurface of the tongue and the soft palate. Specialized mucosa found on the upper surface of the tongue and parts of the lips. All consists of a squamous stratified epithelium, many cell layers (40-50 for buccal mucosa) overlying a connective tissue, layer, the lamina propria. The total surface area of oral cavity = 170 cm^2.

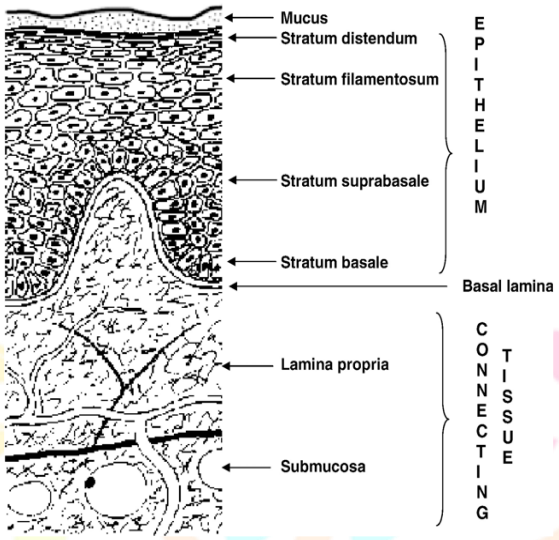

Fig. 1.2 Cross section of buccal mucosa

Thickness and surface area of oral cavity membranes:

Oral cavity membrane	**Thickness (mm)**	**Surface area (cm^2)**
Buccal mucosa	500-600	05.2
Sublingual mucosa	100-20	26.5
Gingival mucosa	200	--
Palatal	250	

Intercellular connection in buccal tissue is characterized by desmosomes and tight junctions and the tissue is a somewhat leaky epithelium. The intercellular material between the superficial epithelial layers is extended by a unique organelle called “membrane coating granule”. It has been shown in rat keratinized epithelium, that the lamella contents of the membrane-coating granules mix with existing material and form broad sheets in the intercellular spaces. These sheets are oriented parallel to the cell membrane and therefore may act as a barrier to permeability. Connective tissue papillae, which penetrate into the epithelia, give the basement membrane an enormous surface area compared to that of the surface of the epithelium.

1.4 Biochemistry of oral mucosa:

All the layers of the oral mucosal membranes contain a large amount of protein in the form of tona filaments, consisting at least seven proteins called "keratins" with molecular sizes of 40-70 Kda. Both keratinized and non keratinized tissues of varying thickness and composition are found in oral cavity. Keratinized and non-keratinized tissue occupies about 50% and 30% respectively of the total surface area of the mouth. The difference between keratinized and non-keratinized epithelia is merely the difference in the molecular size of existing keratins. Cells of non-keratinized epithelia contain lower molecular weight protein while those in keratinized epithelia contain mainly higher-molecular weight keratins. The lipid content of the cells varies between tissues.

Composition and state of keratinization of oral mucosa:

1. Buccal mucosa- Non-keratinized
2. Sublingual mucosa- Non-keratinized, few neutral but mainly polar lipids.
3. Gingiva mucosa- Keratinized
4. Palatal mucosa- Keratinized, Neutral lipids.

Physiological aspects and functions of oral cavity:

The oral cavity is accountable for the following primary functions:

- As a portal for intake of food material and water.
- To bring chewing, mastication and mixing of food stuff.
- Lubrication of food material and formation of bolus.
- Identification of ingested material by taste buds of tongue.
- Initiation of carbohydrate and fat metabolism.
- Absorption of catabolic products thereafter metabolism.
- To aid in speech and breathing process.
- Slight antisepsis of ingested material and within oral cavity by saliva.

1.5 Secretions of Oral Cavity:

The secretion in the oral cavity includes saliva, crevicular fluid and mucus.

1.5.1 Saliva:

Saliva is a complex fluid containing organic and inorganic materials. It is produced by the three pairs of major glands (parotid, submandibular and sublingual) each situated outside the oral cavity and in minor salivary glands situated in the tissues lining most of the oral cavity. The total average volume of saliva produced daily in an adult is around 750 ml. The flow rates of saliva depend upon the type of stimulus used, the time of day, the length of time glands had been stimulated, the age and sex of the individual and by their state of health.

The average resting flow rate for whole saliva is 0.3 ml/ min (range 0.1-0.5 ml/min). For stimulated saliva the average flow rate is 1.7 ml/min (range 1.1 to 3.0 ml/min). Chemically, saliva is 99.5% water and 0.5% solutes. The solutes include ions (sodium, potassium, magnesium, phosphate, bicarbonate and chloride), dissolved gases, urea, uric acid, serum albumin, globulin, mucin and enzymes [lysozyme and amylase (ptyalin)].

The various physiological functions of saliva are:

- Modulation of oral flora.
- Remineralization of the teeth with calcium phosphate salts.
- Neutralization of acid in the oral cavity and esophagus.
- Lubrication and the cleansing of the oral, pharyngeal and esophageal mucosae.
- Assistance in bolus formation.
- Stimulation of epithelial proliferation.
- Initiation of fat and starch digestion.

1.5.2 Crevicular Fluid:

It is a fluid secreted from the gingival glands of oral cavity.

1.5.3 Mucus:

Mucus is a thick secretion composed mainly of water, electrolytes and a mixture of several glycoproteins, which themselves are composed of large polysaccharides bound with smaller quantities of protein. It is secreted over many biological membranes of body for example, throughout the gastrointestinal tract walls. Mucus is secreted by special type of epithelia called mucosa. The mucus secreted in buccal cavity admixtures with saliva of salivary glands in oral cavity to produce whole saliva. Mucus has two main functions:

- Protectant for biological membranes (exposed epithelia).
- Excellent lubricant.

The two main glycoprotein found in buccal mucus or mucin are MG1 and MG2. The mucin glycoprotein MG1 consists of several disulphide-linked subunits containing a protein core with 4-16 oligosaccharide side-chain units. Its molecular size is over 1000 KDa. A small mucin glycoprotein, MG2 has a molecular weight of 200-250 KDa and consists of a single peptide chain with 2-7 oligosaccharide side-chain units.

The important characteristics of mucus are:

- The glycoproteins of mucus have amphoteric properties and are therefore capable of buffering small amounts of either acids or alkalies.

- Mucus is strongly resistant to digestion by proteases.
- Mucus has adherent qualities that make it adhere tightly to the food or other particles and also to spread as a thin film over the surfaces. The mucin film on the surface of oral mucosa provides the pharmaceutical scientist with the opportunity to retain delivery systems in contact with the mucosa for prolonged periods using mucoadhesives. This mucus, however, acts as potential barrier to drug penetration.[61, 72]

1.6 DRUG DELIVERY VIA ORAL CAVITY:

The oral cavity can be used for local and systemic therapy. Examples of local therapy would be the treatment of oral infections, dental caries, mouth ulcers and stomatitis. The buccal route is of particular interest with regard to the systemic delivery of small molecules that are subjected to first pass metabolism or for the administration of proteins and peptides. The two main-routes for administration with oral cavity are:

- Sublingual route
- Buccal route.

1.6.1 Drug Delivery via Sublingual Route:

Sublingual administration implies systemic administration of drugs via the membranes that line the floor of the mouth and ventral surface of the tongue. A rapidly dissolving tablet is generally given by the sublingual route. The sublingual route offers some distinct advantages:

1. The sublingual mucosa is thinner than buccal mucosa and hence has comparatively higher permeability to drugs.
2. Rapid onset of action.
3. Quick termination of drug effect by spitting tablets.

Other advantages associated to this route are common to those of buccal absorption and discussed in later sections. The sublingual region suffers with one major drawback. The two major salivary glands (submandibular and sublingual glands) open their ducts in sublingual area to release saliva. There is constant flushing of saliva in this region because of which it is difficult to retain drugs and delivery system and build or maintain high concentration of drug, in the sublingual region.

1.6.2 Drug delivery via buccal route:

Buccal delivery refers to drug release which can occur when a dosage form is placed in the outer vestibule between the buccal mucosa and gingiva. Various advantages and other aspects of this route are elucidated in latter sections.

1.7 Terminology:

Various terms to be used in theoretical elucidation of buccal absorption are discussed below:

- Oral cavity mucosa: The membranes that line the oral cavity which include the sublingual, buccal mucosa, the gums (gingiva), the palatal mucosa and the labial mucosa.
- Buccal membrane: The membrane inside the mouth that lines the cheek.
- Buccal drug delivery system: A delivery system designed to deliver drugs systemically or locally via or to the buccal mucosa.
- Salivary pellicle: The components of saliva are adsorbed on to the surface of the oral mucosa to form a salivary pellicle. This pellicle coats all surfaces in the mouth and is a multilayered structure.[60, 41]

1.8 BUCCAL ABSORPTION:

Buccal administration involves systemic or local administration via or to the buccal membrane.

1.8.1 Mechanism:

Oral mucosal drug absorption occurs by passive diffusion of the nonionized species, a process governed primarily by a concentration gradient, through the intercellular spaces of the epithelium. The buccal mucosa has been said to behave predominately as a lipoidal barrier to the passage of drugs; as is the case with many other mucosa and (within limits) the more lipophilic (or less ionized) the drug molecule, the more readily it is absorbed. It has been concluded that the passive diffuses in accordance with the pH partition theory of drug absorption is the major route of drug absorption for most drugs. However, it has been reported that certain molecules e.g., some sugars and vitamins may be transported by a specialized transport system capable of saturation. It has been proposed that the intercellular route, rather than the transcellular route, is the predominant route for drug absorption. Large hydrophilic molecules in particular are believed to be transported by the intercellular route and the presence of the contents of membrane-coating granules in the intercellular space may inhibit penetration in both keratinized and nonkeratinized mucosae. [21]

1.8.2 Factors Affecting Buccal Absorption:

The oral cavity is a complex environment for drug delivery as there are many interdependent and independent factors which reduce the absorbable concentration at the site of absorption.

Membrane Factors:

This involves degree of keratinization, surface area available for absorption, mucus layer of salivary pellicle, intercellular lipids of epithelium; basement membrane and lamina propria. In addition, the absorptive membrane thickness, blood supply/ lymph drainage, cell renewal and enzyme content will all contribute to reducing the rate and amount of drug entering the systemic circulation.

Environmental Factors:

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

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

Movement of oral tissues:

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

1.8.3 Absorption pathways:

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 and that there is a barrier to penetration as a result of modifications to the intercellular substance in the superficial layers. However, rate of penetration varies depending on the physicochemical properties of the molecule and the type of tissue being traversed. This has led to the suggestion that materials uses one or more of the following routes simultaneously to cross the barrier region in the process of absorption, but one route is predominant over the other depending on the physicochemical properties of the diffusant.

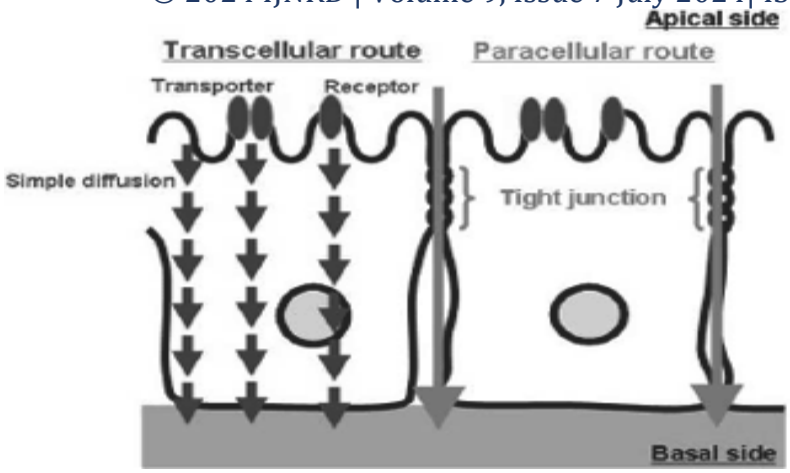

Fig.1.3 Stuructural demonstration of absorption pathways.

a**. Transcellular pathway** (through the epithelial cells).

b**. Paracellular pathway** (in between adjacent cells). Only small (molecular mass < 100–200 Daltons) hydrophilic molecules are absorbed through this pathway. Even in these cases, the absorption is quite limited because the paracellular pathway comprises a very small percentage of the total epithelial surface area. In order to open this pathway to macromolecules, it is necessary to alter or disrupt the tight junctions that exist between cells.

1.9 Buccal Patches: [12, 31]

Buccal patch is a non-dissolving thin matrix modified release dosage form composed of one or more polymer films or layers containing the drug and/or other excipients. The patch may contain a mucoadhesive polymer layer which bonds to the oral mucosa, gingiva, or teeth for controlled release of the drug into the oral mucosa (unidirectional release), oral cavity (unidirectional release), or both (bidirectional release). The patch is removed from the mouth and disposed of after a specified time.

1.9.1 TYPES:

1. **Matrix type (Bi-directional):** The buccal patch designed in a matrix configuration contains drug, adhesive, and additives mixed together. Bi-directional patches release drug in both the mucosa and the mouth.

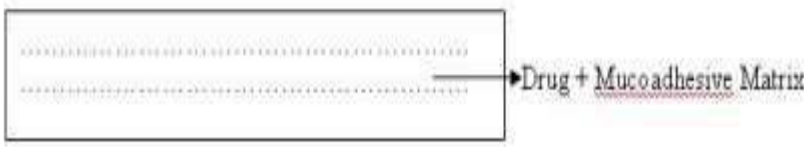

Fig 1.4: Buccal Patch designed for bidirectional drug release.

2. **Reservoir type (Unidirectional):** The buccal patch designed in a reservoir system contains a cavity for the drug and additives separate from the adhesive. An impermeable backing is applied to control the direction

of drug delivery; to reduce patch deformation and disintegration while in the mouth; and to prevent drug loss.

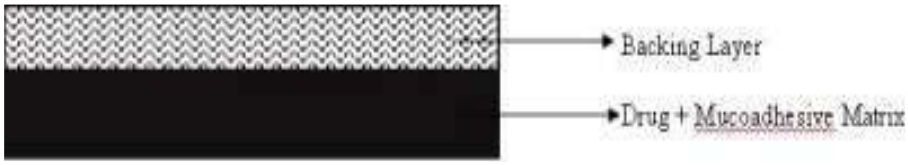

Fig 1.5 Buccal Patch designed for unidirectional drug release.

1.9.2 COMPOSITION:

- **Active ingredient.**
- **Polymers(mucoadhesive layer):** hydroxyethylcellulose, hydroxypropylcellulose and poly (vinylalcohol), Carbomers, PVP, SCMC etc
- **Diluents:** Lactose CD selected as diluent for its high aqueous solubility, its flavouring characteristics, and its physical mechanical properties, which make it suitable for direct compression. MCS, Starch, DCP etc.
- **Sweetening agent:** Sucralose, Aspartame, Mannitol etc.
- **Flavouring agent:** Menthol, Vanillin, Clove Oil etc.
- **Backing layer:** Ethyl Cellulose etc.
- **Penetration enhancer:** EDTA, Sodium Lauryl Sulphate, Cyclodextrins, Dextran, Menthol, Polysorbate 80 etc.
- **Plasticizer:** PEG -.100/400, Propylene Glycol etc.
- **Release liner.**

1.9.3 METHOD(s) OF PREPARATION: [41]

Two methods used to prepare adhesive patches include:-

1. **Solvent Casting:** All patch excipients including the drug co dispersed in a suitable solvent and coated onto a sheet of release liner. After solvent evaporation, a thin layer of the protective backing material is laminated onto the sheet of coated release liner to form a laminate that is die-cut to form patches of the desired size and geometry.

2. **Direct Milling:** Patches are manufactured without the use of solvents (solvent-free). Drug and excipients are mechanically mixed by direct milling or by kneading, usually without the presence of any liquids. After the mixing process, the resultant material is rolled on a release liner until the desired thickness is achieved. The backing material is then laminated as previously described. While there are only minor or even no differences in patch performance between patches fabricated with the two processes, the solvent-free process is preferred because there is no possibility of residual solvents and no associated solvent-related health issues.

1.10 Formulation design:

Buccal adhesive drug delivery systems with the size 1–3 cm^2 and a daily dose of 25-30 mg or less are preferable. The maximal duration of buccal delivery is approximately 8-10 h.

1.10.1 Attributes of a Drug Moiety meant for buccal absorption:

- Half life (3-4 hrs).
- Dose should be ≤30mg.
- Molecular weight (< 500 da).
- Melting point (< 200° C).
- Lipid solubility (Log P) between 1.0 and 4.0.
- Toxicology profile (non-irritating and non-sensitizing).
- Drug must be in its unionic form.

1.10.2 Pharmaceutical considerations:

Great care needs to be exercised while developing a safe and effective buccal adhesive drug delivery device. Factors influencing drug release and penetration through buccal mucosa, organoleptic factors, and effects of additives used to improve drug release pattern and absorption, the effects of local drug irritation caused at the site of application are to be considered while designing a formulation.

Polymers form the backbone of DS, which control the release of the drug from the device. Polymer matrix can be prepared by dispersion of drug in liquid or solid state synthetic polymer base. It should have biocompatibility and chemical compatibility with the drug and other components of the system. Additionally they should provide consistent and effective delivery of a drug throughout the product's intended shelf life

Penetration enhancers are chemical compounds that increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug candidate. It interacts with structural components of stratum corneum *i.e.*, proteins or lipids and subsequently alters the protein and lipid packaging of stratum corneum. It thus chemically modifies the barrier functions leading to increased permeability.

Pressure sensitive adhesive is a material that helps in maintaining an intimate contact between buccal system and the mucosal surface. It should have the following properties:

- Removable from the surface without leaving a residue.
- Physicochemically and biologically compatible.

- Aggressively and permanently tacky .
- Exert a strong holding force.
- Does not alter drug release.

Backing layer must exhibit lowest modulus or high flexibility, it should provide good bond to the drug reservoir and prevent drug from leaving the dosage form through the top.

Release liner is a part of the primary packaging material rather than that of dosage form for delivering the drug. It is protective liner meant to cover the patch that is removed and discharged immediately before its application. As the liner is in intimate contact with the delivery system, it should comply with specific requirements regarding chemical inertness and penetration to the drug, penetration enhancer and water. It is composed of a base layer which may be non-occlusive (*e.g*. paper fabric) or occlusive (*e.g*. polyethylene, polyvinylchloride).

Solvents viz. water, acetone, chloroform, methanol, isopropanol and dichloromethane are used to prepare drug reservoir.

Plasticizers such as dibutylpthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch.

Buccal adhesive polymers:

Polymer is a generic term used to describe a very long molecule consisting of structural units and repeating units connected by covalent chemical bonds. The term is derived from the Greek words: polys meaning many, and meros meaning parts. The key feature that distinguishes polymers from other molecules is the repetition of many identical, similar, or complementary molecular subunits in these chains. These subunits, the monomers, are small molecules of low to moderate molecular weight, and are linked to each other during a chemical reaction called polymerization. Instead of being identical, similar monomers can have varying chemical substituents. The differences between monomers can affect properties such as solubility, flexibility, and strength. The term buccal adhesive polymer covers a large, diverse group of molecules, including substances from natural origin to biodegradable grafted copolymers and thiolated polymers. Bioadhesive formulations use polymers as the adhesive component. These formulations are often water soluble and when in a dry form attract water from the biological surface and this water transfer leads to a strong interaction. These polymers also form viscous liquids when hydrated with water that increases their retention time over mucosal surfaces and may lead to adhesive interactions. Bioadhesive polymers should possess certain physicochemical features including hydrophilicity,

numerous hydrogen bond-forming groups, flexibility for interpenetration with mucus and epithelial tissue, and visco-elastic properties

.

Ideal characteristics:

- Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities.
- Should have good spreadability, wetting, swelling and solubility and biodegradability properties.
- pH should be biocompatible and should possess good viscoelastic properties.
- Should adhere quickly to buccal mucosa and should possess sufficient mechanical strength.
- Should possess peel, tensile and shear strengths at the bioadhesive range.
- Polymer must be easily available and its cost should not be high.
- Should show bioadhesive properties in both dry and liquid state.
- Should demonstrate local enzyme inhibition and penetration enhancement properties.
- Should demonstrate acceptable shelf life.
- Should have optimum molecular weight.
- Should possess adhesively active groups.
- Should have required spatial conformation.
- Should be sufficiently cross-linked but not to the degree of suppression of bond forming groups.
- Should not aid in development of secondary infections such as dental caries.

Factors governing drug release from a polymer:

For a given drug the release kinetics from the polymer matrix could be governed predominantly by the polymer morphology and excipients present in the system. Drug release from a polymeric material takes place either by the diffusion or by polymer degradation or by a combination of the both. Polymer degradation generally takes place by the enzymes or hydrolysis either in the form of bulk erosion or surface erosion.

Polymer morphology:

The polymer matrix could be formulated as macro or nanospheres, gel film or an extruded shape (cylinder, rod etc). Also the shape of the extruded polymer can be important to the drug release kinetics. It has been shown that zero order release kinetics can be achieved using hemispherical polymer form.

Excipients:

The main objective of incorporating excipients in the polymer matrix is to modulate polymer degradation kinetics. Studies carried out have shown that by incorporating basic salts as excipients slow down the degradation and increases the stability of protein polymers. Similarly hydrophilic excipients can accelerate the release of drugs although they may also increase the initial burst effect.

1.10.3 Physiological considerations:

Physiological considerations such as texture of buccal mucosa, thickness of the mucus layer, its turn over time, effect of saliva and other environmental factors are to be considered in designing the dosage forms. Saliva contains moderate levels of esterases, carbohydrases, and phosphatases that may degrade certain drugs. Although saliva secretion facilitates the dissolution of drug, involuntary swallowing of saliva also affects its bioavailability. Hence development of unidirectional release systems with backing layer results high drug bioavailability.

1.10.4 Pharmacological considerations:

Drug absorption depends on the partition coefficient of the drugs. Generally lipophilic drugs absorb through the transcellular route, where as hydrophilic drugs absorb through the paracellular route. Chemical modification may increase drug penetration through buccal mucosa. Increasing nonionized fraction of ionizable drugs increases drug penetration through transcellular route. In weakly basic drugs, the decrease in pH increases the ionic fraction of drug but decreases its permeability through buccal mucosa. Electrostatic interactions of drugs such as tetracycline, hydrogen bonding with drugs like urea and hydrophobic interactions with drugs like testosterone with mucin will decrease rate of absorption. Residence time and local concentration of the drug in the mucosa, the amount of drug transported across the mucosa into the blood are the responsible factors for local or systemic drug delivery. Optimization by a suitable formulation design hastens drug release from the dosage form and taken up by the oral mucosa. Drugs such as buprenorphine, testosterone, fentanyl, nifedipine and several peptides such as insulin, thyrotropin-releasing hormone, and oxytocin have been tried to deliver via the buccal route. However the relative bioavailabilities of peptides by the buccal route were still low due to its poor permeation and enzymatic barrier of buccal mucosa but can be improved by the incorporation of penetration enhancers and/or enzyme inhibitors. Previous drug absorption studies have demonstrated that oral mucosal absoption of amines and acids at constant concentration are proportional to their partition coefficients. Similar dependencies on partition coefficients were obtained from acyclovir, β- adrenoreceptor blocking agents, substituted acetanilide, and others.

Permeation enhancers:

Membrane permeation is the limiting factor for many drugs in the development of buccal adhesive delivery devices. The epithelium that lines the buccal mucosa is a very effective barrier to the absorption of drugs. Substances that facilitate the permeation through buccal mucosa are referred as permeation enhancers. As most of the penetration enhancers were originally designed for purposes other than absorption enhancement, a systemic

search for safe and effective penetration enhancers must be a priority in drug delivery. The goal of designing penetration enhancers, with improved efficacy and reduced toxicity profile is possible by understanding the relationship between enhancer structure and the

effect induced in the membrane and of course, the mechanism of action. However, the selection of enhancer and its efficacy depends on the physicochemical properties of the drug, site of administration, nature of the vehicle and other excipients. In some cases usage of enhancers in combination has shown synergistic effect than the individual enhancers. The efficacy of enhancer in one site is not same in the other site because of differences in cellular morphology, membrane thickness, enzymatic activity, lipid composition and potential protein interactions are structural and functional properties. Penetration enhancement to the buccal membrane is drug specific. Effective penetration enhancers for transdermal or intestinal drug delivery may not have similar effects on buccal drug delivery because of structural differences; however, enhancers used to improve drug permeation in other absorptive mucosae improve drug penetration through buccal mucosa. These permeation enhancers should be safe and non-toxic, pharmacologically and chemically inert, non-irritant, and non-allergenic. However, examination of penetration route for transbuccal delivery is important because it is fundamental to select the proper penetration enhancer to improve the drug permeability. The different permeation enhancers available are

1. Chelators: EDTA, citric acid, sodium salicylate, methoxy salicylates.
2. Surfactants: sodium lauryl sulphate, polyoxyethylene, Polyoxyethylene-9-laurylether, Polyoxythylene-20-cetylether, Benzalkonium chloride, 23-lauryl ether, cetylpyridinium chloride, cetyltrimethyl ammonium bromide.
3. Bile salts: sodium glycocholate, sodium deoxycholate, sodium taurocholate, sodium glycodeoxycholate, sodium taurodeoxycholate.
4. Fatty acids: oleic acid, capric acid, lauric acid, lauric acid/ propylene glycol, methyloleate, lysophosphatidylcholine, phosphatidylcholine.
5. Non-surfactants: unsaturated cyclic ureas.
6. Inclusion complexes: cyclodextrins.
7. Others: aprotinin, azone, cyclodextrin, dextran sulfate, menthol, polysorbate 80, sulfoxides and various alkyl glycosides.

Mechanisms of action:

Mechanisms by which penetration enhancers are thought to improve mucosal absorption are as follows:

1. **Changing mucus rheology**: Mucus forms viscoelastic layer of varying thickness that affects drug absorption. Further, saliva covering the mucus layers also hinders the absorption. Some permeation enhancers act by reducing the viscosity of the mucus and saliva overcomes this barrier.

2. **Increasing the fluidity of lipid bilayer membrane:** The most accepted mechanism of drug absorption through buccal mucosa is intracellular route. Some enhancers disturb the intracellular lipid packing by interaction with either lipid packing by interaction with either lipid or protein components.
3. **Acting on the components at tight junctions:** Some enhancers act on desmosomes, a major component at the tight junctions there by increases drug absorption.

1.11 Advantages of Buccal Absorption: [33, 34]

1. The oral mucosa has a rich blood supply. Drugs are absorbed from the oral cavity through the oral mucosa, and transported through the deep lingual or facial vein, internal jugular vein and braciocephalic vein into the systemic circulation.
2. Following buccal administration, the drug gains direct entry into the systemic circulation thereby bypassing the first pass effect.
3. Contact with the digestive fluids of gastrointestinal tract is avoided which might be unsuitable for stability of many drugs like insulin or other proteins, peptides and steroids. In addition, the rate of drug absorption is not influenced by food or gastric emptying rate.
4. The area of buccal membrane is sufficiently large to allow a delivery system to be placed at different occasions, which may be advantageous if the drug delivery system or other excepients reversibly damage or irritate the mucosa.
5. Additionally, there are two areas of buccal membranes per mouth, which would allow buccal drug delivery systems to be placed, alternatively on the left and right buccal membranes.
6. There is good accessibility to the membranes that line the oral cavity which makes application painless and without discomfort, precise dosage form localization possible and facilitates ease of removal without significant associated pain and discomfort. Thus, patients can control the period of administration or terminate delivery in case of emergencies.
7. The oral mucosal route has in the past exhibited better patient compliance than either the vaginal or rectal route of drug administration thus it would be anticipated that novel buccal dosage forms would be well accepted by patients. In addition, the route is not gender specific as is the case with vaginal route.
8. The oral mucosa is routinely exposed to a multitude of different foreign compounds and physical insult. So it has evolved a robust membrane that is less prone to irreversible damage by drug, dosage form or additives used therein. Thus, it may be feasible to include permeation enhancers in the formulation to increase systemic availability of the drug without observing permanent damaging effects.
9. Due to some therapeutic reasons oral cavity is the only ultimate route for drug delivery, for example, for those patients nil by-mouth, if either nausea or vomiting is a problem, if the patient is unconscious, in patients with an upper gastrointestinal tract disease or surgery, which affects gastrointestinal absorption or patient groups, which have difficulty in swallowing peroral medications e.g., very young and elderly.

10. Additional advantages of the oral cavity as a site for systemic drug delivery include: sterile techniques are not required during manufacture or administration, the oral cavity contains teeth upon which drug delivery systems can be physically attached using dental adhesives, the oral mucosa is low in enzyme activity and enzymatic degradation is relatively slow, hence, from the point of drug inactivation, the oral mucosal route would be preferred to the nasal or rectal routes.

1.12 Limitations in Buccal Absorption:

1. The area of absorptive membrane is relatively smaller. If the effective area for absorption was dictated by the dimensions of a delivery system, this area then becomes even smaller.
2. Saliva is continuously secreted into the oral cavity diluting drugs at the site of absorption resulting in low drug concentrations at the surface of the absorbing membrane. Involuntary swallowing of saliva results in a major part of dissolved or suspended released drug being removed from the site of absorption. Furthermore, there is risk that the delivery system itself would be swallowed.
3. Drug characteristics may limit the use of the oral cavity as a site for drug delivery. Taste, irritancy, allerginicity and adverse properties such as discoloration or erosion of the teeth may limit the drug candidate list for this route. In addition, the drug should not adversely affect the natural microbial flora of the oral cavity.
4. Conventional type of buccal drug delivery systems did not allow the patient to concurrently eat, drink or in some cases, talk.
5. The permeability of the oral mucosa is not great compared to other mucosal membranes.

LITERATURE REVIEW

1. **Alagusundaram M. , 2009,** mucoadhesive buccal films of ranitidine were prepared 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.

2. **Jamrógiewicz. M. (2009),** studied the effects of degradation of Ranitidine hydrochloride exposed to UV radiation (λ=310 nm) and oxygen in a weathering chamber. Effects were studied by Fourier Transform Infrared spectroscopy (FTIR) and Attenuated Total Reflectance Fourier Transform Infrared spectroscopy (ATR-FTIR). ATR-FTIR profile indicated that the degradation was spatially heterogeneous. Significant amounts of photoproducts were detected only in a directly irradiated layer. Major damage/change was reflected in the appearance of broad, extended group of signals near the wavenumber 3600-3200 cm^{-1} or/and 3500-3400 cm^{-1}.

3. **Alagusundaram M. (2009)** prepared buccal films of Ranitidine using polymers of Hydroxypropyl methyl cellulose - 15 cps (HPMC) and Polyvinyl pyrrolidone (PVP) by solvent casting technique employing 'O' shape ring placed on a glass surface as substrate. Polymers were dispersed in ethanol and dichloromethane and 30 % w/w propylene glycol that can be used as plasticizer as well as penetration enhancer. The prepared ranitidine buccal films were evaluated or characterized for surface pH, percentage moisture Absorption (PMA), percentage moisture loss (PML), swelling percentage, water vapour transmission rate, thickness, weight, folding endurance and drug content. During the *in-vitro* release studies, the buccal film of ranitidine showed significant controlled release profile, along with improved bioavailability.

4. **Lohani A. (2011),** Prepared mucoadhesive buccal films of Ranitidine by solvent casting technique using polymers like hydroxyl propyl methyl cellulose E15 (HPMC E15) and carbopol 934P alone or in combination. The formulated films were evaluated for their physiochemical parameters like surface pH, percentage moisture absorption, percentage moisture loss, swelling percentage, water vapor 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. The films exhibited controlled release more than 12 h. The best mucoadhesive performance and matrix controlled release was exhibited by the formulation A2 and A6. The formulation was found to be right and suitable candidate for the formulation of ranitidine buccal film for therapeutic use.

5. **Deshmane S. (2009),** characterized the effect of chitosan with PVP K-30 on water soluble drug by preparing mucoadhesive buccal patch. Each formulated batch was subjected to various evaluation parameters. The swelling percentage was found to be function of solubility of drug and PVP K-30. The mucoadhesive strength, vapour transmission and in-vitro released of water soluble drug through water insoluble chitosan base matrix were found satisfactorily. The physical appearance of buccal patch was examined by scanning electron microscopy. The released kinetic model best to fit for the optimized batch

was Hixson Crowell, indicating that the drug release from systems which there is a change in the surface area and the diameter of particles present in dosage form.

CONCLUSION

Matrix system based Buccal patches of Ranitidine HCl were prepared using different proportions of NaCMC and CP-934k as matrix/film formers and Glycerol as both plasticizer and penetration enhancer. The result of present investigation stated that Sod. Carboxymethyl cellulose and Carbopol 934k have good matrix/film forming characteristics which was confirmed by the visual and physiological characterization of the patches. The in-vitro and ex-vivo studies indicated that successful buccal patches of Ranitidine HCl could be prepared using hydrophilic polymers viz. NaCMC and CP-934k employing solvent casting technique. It was found during investigation that as the concentration of Sod. Carboxymethyl Cellulose was increased the release rate also inclined and the patches showed lesser mucoadhesion time while on the other hand as the concentration of Carbopol 934k was increased the drug release was found to be controlled and the patch also reflected sufficient mucoadhesion time period. Although, a very slight correlation was found between the formulations selected after in-vitro release studies and were studied for ex-vivo permeation studies. Out of the three selected formulations (i.e. F3, F4 & F5), the formulation F5 showed the best permeation release.

In conclusion the present data indicate a confirm reproducibility of developing Ranitidine HCl Buccal Patches that could be used for treating several predicaments. The drug release was found to be sustained and prolonged and thus, multiple dose regimens could be best replaced by single buccal formulation. Further study in respect to in-vivo performance after application of buccal patch is required to substantiate the therapeutic efficiency of these systems.

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