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PREPARATION AND EVALUATION OF BENZOCAINE BUCCAL GEL FOR MOUTH ULCER

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ABSTRACT

The formulation and testing of a mucoadhesive buccal gel containing benzocaine for the treatment of mouth ulcers is presented. By using buccal delivery, the drug can avoid first pass metabolism by the liver and acidic degradation once absorbed into the body. Three batches (F1; F2;F3) of gels using a solvent dispersion method (neutralized after the solvent was used) were combined with two different gelling and mucoadhesive polymers (Carbopol 940 and HPMC (K4M)). Formulations produced had similar visual qualities (clear, smooth, etc.), pH (5.1 - 6.7) and spreadability, and had consistent drug quantities (theoretically, each gel contained 5% (w/w) of benzocaine). All the formulated gels also had appropriate viscosity. Also, there have been no changes compared to variations of temperature for both room and accelerated conditions over time and they have been tested as stable. To summarize, the benzocaine buccal gel products have shown excellent mucoadhesive and rheological characteristics; it has been established that they are stable, can be made in the same way each time and therefore are suitable for providing an effective pain relief system for the treatment of oral ulcerative wounds via increasing buccal residence time.

KEYWORDS: Mucoadhesive, benzocaine, solvent dispersion method, rheological characteristics.

INTRODUCTION

Mucoadhesive Drug Delivery System (MDDS)

Biomaterials used in MDDS (Mucoadhesive Drug Delivery Systems) adhere to the stained mucosal surfaces of the body. Thus, MDDS will eventually prolong the time the medication or therapeutic agent remains in the area of application, thereby improving both the stability as well as absorption of the medication. The process of "bioadhesion" occurs when two different substances (at least one of which is a biological substance) are held together for prolonged periods of time by an interfacial force.[1] This process, termed "mucoadhesion," occurs when the mucoadhesive polymer contacts the mucous membrane. The mucoadhesive drug delivery system is the "method of drug delivery" that is associated with a mucoadhesive polymer.[2] The MDDS will bind to the mucus layer of the mucous epithelium located on the surface of the mucous epithelium.

The second type of controlled drug delivery composed of mucoadhesive drug delivery systems; dosage forms can be created to provide increased retention to the intended site of use, yielding better therapeutic effects with a controlled drug release rate. The delivery of medication to its appropriate site of residence is accomplished through an intricate process with the mucoadhesive drug delivery system (MDDS). The type of polymeric material used to create the mucoadhesive drug delivery system, and the mucosal membrane within which it interacts, are both critical components that influence the mucoadhesive characteristics of the system.[3] Mucoadhesive drug delivery systems also help to enhance the therapeutic effect of the drug within the dosage form by aiding in the interaction between the dosage form and the underlying absorption surface. Numerous Mucoadhesive Drug Delivery methodologies have recently appeared; examples include orally, buccally, nasally, vaginally, rectally. Several properties of Mucoadhesive systems have been researched; such as, manufacturing new products, and "smart" polymers and developing innovative ways of reviewing mucoadhesion-related phenomena. Future generations will use the oral mucosa to address numerous ailments ranging from mucosal to global problems if they have appropriate technology, delivery methods and polymers available to them.[4] Another thing is that it could potentially increase the total number of medication products that can be administered via the mucosa. The pharmaceutical industry has shown a great deal of interest in the Concept of Mucoadhesion and continues to apply it as a viable management tool.

BUCCAL DRUG DELIVERY

Buccal administration, a newer way to deliver medications, allows for the distribution of drugs to specific areas of the mouth to treat gum disease and for the treatment of both bacteria and fungi in the mouth.[5] This method provides both the ability to end treatment if side effects or toxicity are experienced, and is a safer option for drug delivery than other methods. Because of the easy accessibility of the buccal mucosa, the drug is able to avoid the liver; as a result, the drug is able to enter the systemic circulation much more readily, allowing it to be delivered directly into the bloodstream via the internal jugular vein. In addition to permitting the direct entry of a drug into the bloodstream, buccal drug delivery also provides a method to bypass elimination prior to entering the bloodstream, which is usually through the gastrointestinal tract.[6] The preferred method of administration for medications that have a high first-pass metabolism and limited bioavailability is to utilize the buccal route. Mucoadhesion refers to two different materials being adhered together via intermolecular force for a prolonged period of time. Mucoadhesion is specifically defined as an interaction between a polymer and an epithelial surface. Buccal patches compared to pills are much more tolerant by the patient because of their high flexibility. Examples of possible adhesion sites for mucoadhesive systems include the buccal cavity, nasal cavity, eye, vagina, rectal area and gastrointestinal area as well as the sublingual route. Buccal films can provide a barrier to the surface of a wound and thus decrease discomfort and improve the treatment of oral diseases.[7]

Buccal Drug Delivery system Advantages

1. This method avoids using medications that may get damaged in an acid environment and would go through liver-first metabolism prior to being absorbed.
2. The intravenous route also allows the body to use passive absorption routes to access the drug without requiring the use of active absorption routes.[8]

Buccal Drug Delivery system Drawbacks

1. Only a very low dose of medications is neededto use the sublingual route.
2. This route allows passive diffusion of drugs into the bloodstream.
3. The buccal mucosa has much less permeability than does the sublingual route. Only a very small amount of drug would therefore be needed to use the buccal route as well.[8]

Oral mucosa

The oral cavity has a total area of 100cm2. Of this, 1/3 makes up the buccal side where the

buccal epithelium (lining of mouth) is approximately 0.5mm thick. The primary purpose of oral mucosa is to protect the underlying tissues. The lipid-based permeability barriers in the epithelial layer provide protection against the loss of fluids as well as from attack by harmful environmental factors such as microbial toxins, antigens, carcinogens, etc. The oral epithelium takes about 5-6 days to proliferate. The oral cavity consists of that part of the mouth which is bounded by the lips, the cheeks, the hard palate, the soft palate and the floor of the mouth.[9] The oral cavity has 2 separate areas, that of the outer oral vestibule and that of the oral cavity proper. The outer vestibule is bounded by the cheeks, lips, teeth and gums while the oral cavity proper extends from the teeth and gums toward the anterior of the head.[10]

FUNCTIONS OF ORAL CAVITY

- Help in chewing food and helping to mix through mastication;
- Assists in the lubrication of a bolus (food mass).
- Helps identify food by taste with the tongue, helping to begin carbohydrates and fat metabolism.[11]

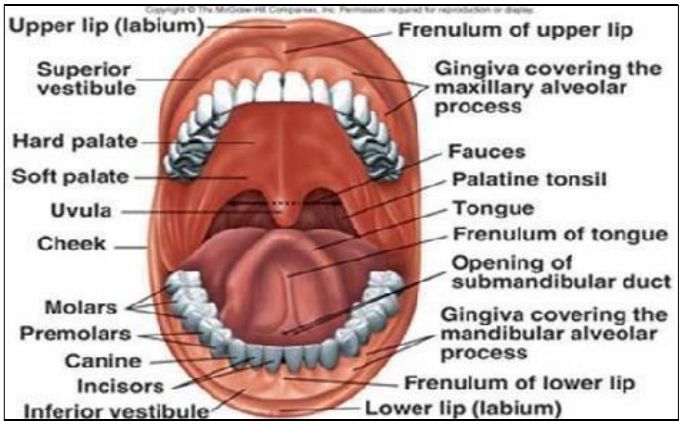


Fig. 1: Oral cavity.

Mechanism

Various mechanisms are attributed to many absorption enhancers that increase permeation. The viscosity (thickness) of being liquid viscous and the ability for a drug to be absorbed; this means that without saliva at the top of the mucous barrier; it will also hinder absorption of drugs across this barrier. Most permeation enhancers reduce mucous viscosity, which will enable saliva to permeate through the thick mucous barrier.[14] Increased lipid bilayer fluidity - the major route for drug absorption across the buccal mucosa appears to be intracellular. Some enhancers will affect intracellular lipid arrangement based on their interactions with the

lipid or protein hydrophilic and hydrophobic nature of the components of the intracellular lipid bilayer.

Gel

The word "gel" and the word "jelly" have their origins in the word "gelatin" and the word "gel." Gel originates from Latin for "frost" and for "freeze" or "to solidify". The important point is that they both ultimately refer to a liquid-like ice crystal structure that does not flow and retains its liquid characteristics because of the way it was formed. As such, the main difference between "gel" and "jelly" continues to be somewhat arbitrary -- depending on the intended purpose of the product. Gels are considered to be a semi-solid (gel) material formed from either an interspersed molecular structure (big molecules intermixed with a liquid) or small inorganic particles that have been suspended in some other liquid.[18] A gel can be defined as a two-phase system because it is comprised of a network of a very large number of tiny, discrete particles. Gelatinous solids, or single-phase gels, create one homogeneous mass of material, with no apparent demarcating boundary between the liquid phase and the dispersed macromolecules. Single-phase gel or jelly material is generally best characterized and identified as a three-dimensional network produced by mixing desirable liquids and macromolecule materials, e.g., proteins, polysaccharides, or synthetic polymers. Water and hydro-alcoholic solutions are commonly used in the pharmaceutical industry as a means of creating polymer gels and many types of polymer gels have a reversible ability to convert to the liquid state or sol, which is a solution that contains approximately the same number of dissolved or dispersed macromolecules as there are in the solid gel. Conversely, due to covalent bonding, some polymer gels cannot be broken apart.[15] Two-phase gelation of three-dimensional networks is a combination of a variety of inorganic colloidal clay materials and a matrix of macromolecules.

TYPES OF GELS

A gel is a gel-like substance that is composed of a solid-like, 3-dimensional structure (a network of gels) that occupies the entire volume of a liquid and creates and holds this volume by surface tension. The 3-dimensional gel structure may be due to a variety of junctions (these are the different types of "gels"), including but not limited to, physical junctions (physical gels); chemical junctions (chemical gels); or various other physical/chemical combinations of junctions together creating an expanded fluid.[19] Any liquid type can be considered as a gel-like medium. Some typical fluids used to create gel-like media are

aqueous (from the use of water, known as hydrogels) fluids, oil and air (from the use of aerogels). Because a gel is primarily composed of a liquid, a gel will usually have a similar density as the liquid that formed it. For instance, edible jelly, which is an example of an aqueous hydrogel, has a density that is very similar to that of water. Gels are divided into 3 Classifications:-

Hydrogels: A hydrogel is a hydrophilic polymer network in which water serves as the liquid phase in a colloidal gel. Hydrogels are composed of over 99% natural or synthetic polymers and have a very large ability to hold water due to their composition. Due to the high volume of water they contain, hydrogels also exhibit an elastic behaviour similar to live tissues. Because of their ability to absorb a significant amount of water, hydrogels are widely used in tissue engineering and other applications as scaffolds.[20]

Xerogels: A xerogel is a solid product formed through the dehydration of a gel. Xerogels typically contain small pore sizes (1-10 nm), possess large surface areas (150-900 m2/g), and have a high degree of porosity (15-50%). The polymer network of the xerogel remains unchanged following the removal of the solvent through hypercritical drying.[21]

Organogel: Organosols are thermos-reversible materials that lack crystalline or glassy structures. Thermoplastic solids consist of a liquid organic medium that is held within the cross-linked (networked) structure (in three dimensions). The liquid component can be a mineral oil, a vegetable oil, or an organic solvent, for example. The structural characteristics (e.g., solubility and particle size) that contribute to the rigidity and elastomeric properties of organosols are dependent on the structural characteristics of the crosslinking agent molecules.[21]

Mucoadhesion

Bioadhesion (also referred to as mucoadhesion) is defined as the attachment of biological (natural) or synthetic (made) macromolecules (large molecules made up of repeating units) to biological tissue. Bioadhesion with respect to mucosal epithelial tissue refers to a bioadhesive interaction made to mucosal epithelial tissue.Bioadhesive interaction of mucosal epithelial tissue usually happens with the mucus layer (layer of secretion covering the epithelial cells).[21]

Mucoadhesion Mechanism

At the first phase mucoadhesion occurs when the mucoadhesive comes into close contact

with the mucus membrane.[22]

At the second stage, when the drug is administered via the mucoadhesive; can be used in unconscious patients; has fast onset of action; carries out a series of physical and chemical reactions to build and bond the mucoadhesive to the mucus membrane ending with prolonged adhesion.[23]

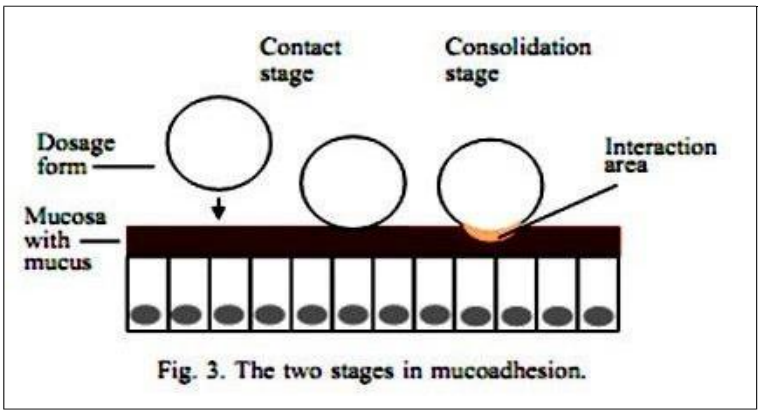
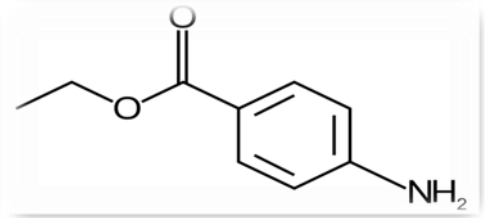


Fig. 3. The two stages in mucoadhesion.

Fig. 2: Stages of mucoadhesion.

Introduction to benzocaine

Benzocaine are the class of local anesthetic, they come under the sub category of amino esters. It prevent the nerve transmission by blocking sodium channel and provide relief from pain for a certain duration of time. They are mostly used in oral pains(toothache, mouth ulcer etc) and also used in skin irritation, throat infections.[25]



IUPAC name- Ethyl 4-aminobenzoate

Molecular formula-$C_9H_{11}NO_2$

Appearance -colorless crystal or white

Solubility -slightly soluble in water but highly soluble in ethanol(90%)

Therapeutic category - local anesthetic, pain relief from mouth ulcer

MOA- It binds to sodium channel and decreases the permeability of sodium ion which causes depolarization of neuronal membrane and inhibiting transmission of nerve impulses which

helps in pain relief.[25]

MATERIAL AND METHODOLOGY

Materials

The model benzocaine local anaesthetic had the api supplied from Shaila Enterprises, And the excipients were carbopol 934/940 (for thickening), hpmc (k4m), (for humectancy), glycerine (for penetration enhancing), propylene glycol (for preservation), and parabens, And triethanolamine (TEA) for pH adjustment, all of which were derived from the college.

Fig. 3: Chemicals and reagents.

Method of the formulation

We can create mucoadhesive Benzocaine gel with a neutralization of solvent dispersion method. This method begins with carefully dissolving the many different types of polymer in the solvent (or base) and completes with a chemical reaction causing the gel to form into solid structure.[27,29,31]

Formulation of benzocaine buccal gel

The gels of local anaesthetic were formulated by neutralization of solvent dispersion method using equal amounts of carbopol and hpmc wet out into their respective vehicles under magnetic stirrer followed by homogenization (300-450 rpm for 15-30 minutes) to achieve a consistent polymer blend. The benzocaine was then incorporated into the gel at this point with continuous stirring for 5 minutes and thereafter all humectants and preservatives are incorporated into the gel prior to the final neutralization of the gel formulation completed to pH 7.[25,29,30]

Fig. 4: HPMC and Carbopol mixture.

Fig. 5: Benzocaine gel.

Formulation Table

S.NO.	Ingredient	(f1)	(f2)	(f3)	Role in formulation
1	Benzocaine	5gm	5gm	5gm	Local Anesthetic(API)
2	Carbopol940	1gm	1.5gm	2gm	Gelling agent
3	HPMC(K4M)	2gm	3gm	4gm	Mucoadhesive polymer
4	Glycerin	10gm	10gm	10gm	Humectant
5	Propylene Glycol	10gm	10gm	10gm	Solvent & penetration enhancer
6	Propyl Paraben	0.1gm	0.1gm	0.1gm	Preservative
7	Triethanolamine (TEA)	1-2gm	1-2gm	1-2gm	Neutralizer
8	Purified water	100gm	100gm	100gm	Vehicle

Evaluation of benzocaine buccal gel

1. Visual Appearance / Color / Clarity / Homogeneity / Texture: Inspect the physical appearance of your gel for properties listed above and the following will be an indication of how well formulated your gels are.[11]

2. pH Determination: Take 1 g of a gel and dilute it with 10 mL of distilled water; mix thoroughly and use a digital pH meter to measure pH of the mixture. Ideal Range: 5.5-7.0 would be acceptable for buccal application products.[12,15]

3. Viscosity Study: Place your gel into a beaker; use a Brookfield or Fungi Lab viscometer at room temperature. Observation: An increase in viscosity will occur as you increase the polymer concentration and/or other factors related to the measurement of viscosity.

4. Spreadability Test: Place a small amount of gel between two glass slides and apply a known weight to the upper slide; measure the time to separate the two slides.

Formula:

$$S = M \times L/T$$

Where S = spreadability

M = mass placed on top slide

L = distance from the bottom edge of top slide to the bottom edge of the bottom slide

T = time measured for slides to separate.

5. Assessment of Uniformity Drug Content: Weigh out 1 g of gel, Dissolve in appropriate solvent (ethanol), Filter solution, Use a UV spectrophotometer to measure the absorbance at 291 nm. (All drug contents should be uniform across each of the different formulations).[11]

6. Stability Study: Store gel at room temperature and acceleration conditions, Observe degree of change in pH, colour, viscosity, and any separation of phases. (If there are no observable changes, the formulation is deemed to be stable).[30]

7. Homogeneity Testing: The gel was placed between my fingers and visually assessed for the uniform consistency of the gel as well as the absence of clumps. (The gel should feel smooth and free from any lumps).[35,36,39]

RESULT AND DISCUSSION

1. **Visual Appearance / Color / Clarity / Homogeneity / Texture:** All three batches (F1, F2 and F3) of prepared benzocaine gel formulations were examined visually for visual appearance, homogeneity and texture. In all cases, each of the three batches of gel formulations exhibited a clear, transparent appearance. All batches of gel formulations were shown to have a uniform consistency when rubbed together using the fingers, with a smooth surface, and no lumps or gritty particles, demonstrating successful homogeneity.
2. **pH Determination**: The pH of gel formulations is a key specification as benzocaine is easily hydrolyzed in strong acidic and alkaline conditions, and both extreme pH values can damage the buccal mucosa. The initial pH of each of the three batches of aqueous dispersions of gels was acidic, and each was then neutralized with triethanolamine. The final pH values of batches F1, F2 and F3 were measured as 5.1, 5.4 and 6.7, respectively.

Table 1: pH of benzocaine gel.

Sr no.	Formulation batches	pH
1.	F1	5.2
2.	F2	5.4
3.	F3	6.5

3. Viscosity Measurements: The rheological properties of gels Were measured at room temperature and found to have measured viscosities of

F1-4700 CPS

F2-3500 CPS

F3-5600 CPS.

In addition, the increase in concentration of carbopol 940 increases the viscosity of gels; however, the increased viscosity after neutralization is due to the ionicization of the carboxylic groups, causing electrostatic repulsion, which, in turn, causes the polymer network to expand, resulting in a stronger gel structure.

4. Spreadability Testing: The ability of a material to spread out is an important factor influencing patient compliance as well as evenly applying the gel on the oral mucosa. each of the formulations (f1, f2 and f3) showed good ability to spread when tested using two glass plates to which they were applied, indicating that each of the formulations will easily allow even application to the intended mucosal target without requiring excessive force.

Table 2: Spreadability of benzocaine gel.

S.No	Formulation batches	Time	Spreadability
1.	F1	6	25.00
2.	F2	8	18.75
3.	F3	11	13.63

5. Assessment of Uniformity Drug Content: Testing for uniformity of drug content for benzocaine the amount of benzocaine present in each dose of gel base was successfully quantified using ultraviolet (UV) spectrophotometric analytical techniques by measuring the absorbance of the filtered solution at the λmax (291.4nm) to determine whether or not there was uniform drug distribution throughout the gel base. All formulations evaluated had an average benzocaine concentration determined to be very similar to the theoretical concentration of 5% (w/w).

Fig. 6: Gel formulation for different batches.

Table 3: Absorbance of benzocaine gel.

S.No	Formulation	Concentration	Absorbance
1	F1	2.5	0.53
2	F2	2.5	0.54
3	F3	2.5	0.56

6. Stability Study: Gels are stored at room temperature and accelerated conditions to check their stability. During the observation we saw no observable changes in their physical appearance (i.e colour, clarity, pH etc). It indicates that our gel formulation is very stable under tested conditions.

7**. Homogeneity Testing:** The gel formulation was placed between the fingers and visually assessed, the formulation have uniform distribution and no lumps formation. The gel is free and smooth without any lumps.

CONCLUSION

With Carbopol940 & HPMC K4M, the developed benzocaine buccal gels exhibited exceptional mucoadhesive and rheological performance. The gels effectively extended the buccal residence time to provide consistent and close-contact of the absorbing mucosal tissue. This optimized formulation method developed a reliable, reproducible, and convenient system for delivering local anesthetic effects or pain relief from oral ulcers.

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